The Associations between Poor Sleep in Pregnancy and Obstetric, Perinatal and Neonatal Outcomes

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1. **Scientific contribution that was based on material from Chapter 3**

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Alghamdi, A., Law, G., Scott, E. and Ellison, G. 2015. *Latent class analysis reveals six distinct sleeping patterns that are associated with key sociodemographic and health characteristics in both Wave 1 and Wave 4 of Understanding Society.* Understanding Society Scientific Conference, 21-23 July. University of Essex – Colchester.

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4. Scientific contribution that was based on material from Chapter 6

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Abstract

Background

Sleep has a complex nature that is thought to make it a risk factor for many health concerns, which have recently included poor pregnancy outcomes.

Aim

Studying the association between sleep and poor pregnancy outcomes in pregnant women.

Methods

To achieve this aim, several studies were done. First, the literature was searched to examine and critically evaluate the quality of current evidence in regards to sleep and pregnancy outcomes. Second, the latent complex nature of sleep was defined using latent class analysis and the UKHLS data set before examining the association between the generated patterns and socio-demographic features and health. Third, sleep events present in the UKHLS sleep module and the generated latent sleep patterns were examined in women from the UK population who were presented in the UKHLS study, and in women at risk of gestational diabetes (GDM) presented in the Scott/Ciantar study, in relation to poor pregnancy outcomes.

Results

In the literature there was ‘positive’ evidence of an association between sleep and poor pregnancy outcomes. However, the evidence suffered from limitations, and the complex nature of sleep was not considered. Our definition of sleep as a latent variable revealed six latent sleep patterns which were associated with individual socio-demographic features and health. Sleep events and latent patterns did not always elevate the risk of poor pregnancy outcomes in women from the UK population or women at risk of GDM, as sleep lowered the risk on some occasions.

Conclusion

Sleep might increase the risk of poor pregnancy outcomes, according to evidence from the literature review and the two empirical studies. However, the current evidence had many limitations, and further research is required in this area.

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List of Abbreviations

AIC	Akaike information criterion
BHP	British Household Panel
BIC	Bayesian information criterion
BMI	Body mass index
CHF	Congestive heart failure
CI	Confidence interval
CS	Caesarean section
DAG	Directed acyclic graph
DM	Diabetes mellitus
ES	Effect size
ESS	Epworth Sleepiness Scale
g	Gram
GA	Gestational age
GCSE	General Certificate of Secondary Education
GDM	Gestational diabetes
GSDS	General sleep disturbance scale
hr	Hour
HTN	Hypertension
Hz	Hertz
I^2	I –squared
Kg	Kilogram
KQ	Key question
LBW	Low birth weight
LCA	Latent class analysis
LGA	Large for gestational age
m	Mean
m^2	Metre squared
mg	Milligram
M-H	Mantel-Haenszel test
min.	Minute
ml	Millilitre
Mmol/l	Millimole per litre
MSAS	Minimum sufficient adjustment set
n	Number
NICU	Neonatal intensive care unit

NREM	Non-rapid eye movement
OGTT	Oral glucose tolerance test
OR	Odds ratio
OSA	Obstructive sleep apnea
PE	Pre-eclampsia
PIH	Pregnancy induced hypertension
PPB	Post-partum blood loss
PSG	Polysomnography
PSQI	Pittsburgh sleep quality index
R^2	R-squared
RCT	Randomized control trials
REM	Rapid eye movement
RLS	Restless leg syndrome
SBD	Sleep breathing disorders
SD	Standard deviation
SES	Socioeconomic status
SF12	12-item health survey
SGA	Small for gestational age
T	Time point
TFG	Temporal functional group
UKHLS	UK household longitudinal study
WASO	Wakeup time after sleep onset
X^2	Chi-square test

Chapter 1 Introduction

1.1 The growing interest in sleep research

In contemporary high- (and many low-) income societies, a number of new health challenges have emerged, particularly a suite of cardiometabolic 'chronic' diseases and a range of mental health disorders, which have elicited renewed interest in potential causes and potentially modifiable risk factors (McMichael and Butler, 2006, Egger and Dixon, 2014). Amongst these has emerged growing interest in sleep, particularly as a candidate risk factor for chronic metabolic disorders, such as diabetes. Such interest began started when it was found that various sleep-related characteristics (most notably, sleep duration) were associated with obesity, itself a major risk factor for numerous chronic health issues (Agborsangaya et al., 2013, Flegal et al., 2013, Egger and Dixon, 2014, St-Onge and Shechter, 2014). The association between obesity and sleep was initially considered to reflect the lack of energy poor sleep appears to cause, together with lower activity and exercise levels. At the same time, several commentators postulated that less time spent asleep would mean more time in which food could be consumed, particularly during the night (University of Chan Harvard:School of Public Health, 2017, St-Onge and Shechter, 2014). Endocrinological studies seemed to support these hypotheses, demonstrating that unfavourable sleep might affect the secretory mechanisms of hormones that increase appetite (leptin and ghrelin, Taheri et al., 2004).

Interest in sleep as a potential risk factor for weight gain went beyond a preoccupation with obesity and soon linked sleep itself to hormones that affect the synthesis and metabolism of both lipids and glucose (particularly insulin; Meslier et al., 2003, Spiegel et al., 2005; and cortisol; Leproult et al., 1997, Omisade et al., 2010). This, more direct, link between sleep and hormone levels led to further attention towards sleep as a possible risk factor for the development of diabetes and hyperlipidaemia, both of which form part of more a complicated condition (dubbed the 'metabolic syndrome' or 'syndrome X'), characterised by the presence of all or some of the following: diabetes, hyperlipidaemia, obesity and hypertension (Coughlin et al., 2004, Spiegel et al., 2005, Hall et al., 2008). Researchers examining cross-sectional observational data sets found that short sleep duration was associated with higher blood levels of triglyceride and low-density lipoprotein, both of which were considered risk factors for coronary

heart disease and hypertension (BjØrn et al., 2007). Thus, both heart disease and hypertension were thought to be susceptible to sleep deprivation and sleep apnoea (a condition characterised by ‘disordered breathing’ whilst asleep), since both were found to be associated with increased levels of inflammatory factors. These factors can, in turn, cause defects in the regeneration of endothelial tissues, which might precipitate vascular damage and lead to inflammatory vascular disease and atherosclerosis, important precursors to cardiovascular disease and stroke (Irwin et al., 2006, Jelic et al., 2008).

Yet interest in sleep has not stopped there, as it has been further linked to a wider range of emerging health challenges including such as immunological function (Lange et al., 2010), cancer (Stepanski and Burgess, 2007) and mental health, for each of which ‘less favourable’ sleep is increasingly viewed as both a predictor and an early indicator of their presence and severity (Reid et al., 2006, Kaneita et al., 2007). More recently, consideration has been made of the potential role that sleep problems may have on the well-being of pregnant women and their foetuses. This has included the suggestion that sleep might influence the development of gestational diabetes, pregnancy-induced hypertension and excessive gestational weight gain in a similar fashion to its effect on diabetes, hypertension and obesity in non-pregnant women and men (Qiu et al., 2010, Reutrakul et al., 2011, Benediktsdottir et al., 2012). At the same time, the possible impact of unfavourable sleep on vascular regeneration has been postulated as a potential cause of dysfunctional placental circulation, thereby affecting foetal growth and well-being (He et al., 2012).

1.2 Sleep concept

Regardless of the developments in knowledge of sleep and sleep medicine over the past 50 years (Pelayo and Dement, 2017), the true biological nature of sleep remains unclear (Prinz, 2004). Sleep scientists have developed several theories to explain the mechanistic functions of sleep at the cellular and molecular level (Silber et al., 2016); sleep being viewed as instrumental in the process of protein synthesis and cell division, and thereby important for growth and body repair (Horne, 1985). Yet the principal challenge facing such hypotheses, and in further developing our understanding of sleep is in large part due to the substantial challenge of evaluating sleep states by observation alone, since sleeping individuals appear both inactive and resting (Moorcroft, 2013). Yet sleep-resting states differ from unconscious comas by the ability that sleeping individuals retain to respond to external stimuli (Moorcroft,

2013). It was nonetheless the middle of the 20th century before scientists fully grasped that sleep was essentially an ‘active’ state instead of an inactive or inert one; and that sleep had several stages, each of which is characterised by a unique EEG brainwave, respiratory rhythm and muscular tone (Carskadon and Dement, 2017). These advances required the development of objective techniques for evaluating sleep states, and for measuring the accompanying brain and body activity using a device known as a polysomnography (Moorcroft, 2013). Today, researchers now suggest that some areas of the brain remain active during sleep, whilst others become less active, and that which parts of the brain these are depend upon the specific stage of what is widely acknowledged to be the ‘sleep cycle’ (Moorcroft, 2013).

At its simplest, the sleep cycle can be divided into two broad stages: rapid eye movement (REM) and non-rapid eye movement (NREM), each defined according to the presence or absence of REM (Carskadon and Dement, 2017). NREM sleep can be further subdivided into four stages depending on the depth of sleep and accompanying EEG brain activity (Carskadon and Dement, 2017). All five stages of sleep alternate with one another in a specific sequence to create the cycle (Mary and William, 1980) – the first four stages of the cycle comprising the NREM stages whilst the final stage comprising REM. The characteristics of sleep during each of these stages have been summarised in Table 1-1 (after Silber et al., 2016 and Siegel, 2017).

Table 1-1 Summary of sleep stages

	Wakefulness	NREM Stage 1	NREM Stage 2	NREM Stages 3 and 4[1]	REM
Common name	-	Drowsy sleep	Light sleep	Deep sleep or slow wave sleep	-
Eye movement	Present	No movement	No movement	No movement	Rapid
EEG brain wave frequencies	Alpha wave (8-13Hz), Beta wave (>13Hz) and Gamma wave (average ≥ 40Hz); Highest wave in frequency and lowest wave in amplitude	Theta wave (4-7 Hz)	Theta wave with Sleep spindle (11-16 Hz) and K-complex	Delta wave (0.5-4 Hz); slowest frequency and deepest amplitude	Mixture of Alpha and Beta waves
Length (% in a single cycle)	-	5%	50%	20%	25% of the cycle
External environment	Fully aware	Aware of external stimuli	Disappearance of external environment awareness	External environment awareness disappeared	External environment awareness disappeared
Events	-	Hypnagogic hallucination[2]	-	Sleep walking and talking; involuntary urination	Memorable dream
Muscle tone	Full tone strength	Loss of some muscle tone; muscle twitch and sudden jerks	Decreased muscle tone	Decreased muscle tone	Atonia or muscle paralysis

[1] Stage 3 consists of 20-50% delta wave whilst Stage 4 consists of more than 50% delta wave, so some authors suggested that they could be combined and named stage 3 as transitional stage that transits into stage 4.

[2] Hypnagogic hallucination is a mental phenomenon that is accrued during transition from wakefulness to sleep and might cause dreams, paralysis and hallucination.

1.3 Measurement of sleep

Limited knowledge about the biology of sleep, and the true nature of sleep, have made it difficult for scientists to measure this phenomenon with any degree of certainty (Prinz, 2004). For this reason, scientists have traditionally measured sleep by recording several ostensibly discrete sleep characteristics which, together or independently, were considered key indicators of 'healthy' sleep (Silber et al., 2016, Buysse, 2014). These characteristics included the presence and duration of discrete sleep stages (i.e. REM and Non-REM sleep; Silber et al., 2016), as well as the presence and frequency of several (ostensibly) 'unfavourable' sleep events (e.g. prolonged latency, disturbance, and symptoms of SBD; Buysse et al.,1989). Researchers have also evaluated sleep health by assessing individual perceptions of (subjective) sleep quality, together with self-reported use of medication to improve sleep and perceived next day sleepiness (Soldatos et al., 1999, Lee et al, 1992, Buysse et al.,1989,). Finally, sleep position and the sleep environment (for instance; room temperature and the amount of ambient light and noise) have also been included as important considerations when evaluating sleep (Bartel et al., 2015., Dorrian et al., 2013, Stacey and Mitchell, 2012). Nonetheless, scientists are still uncertain as to how best to measure sleep, not least because there remain a number of challenges to sleep measurement:

First, it seems unlikely that sleep can be defined solely on the basis of a single sleep characteristic, simply because sleep manifests as a complex, multidimensional concept (Buysse, 2014). Attempts to achieve more holistic, multidimensional measures of sleep have been dogged by the use of different indicators by different researchers, and the lack of a unified definition of sleep, leading to a lack of comparability amongst studies using different sets of indicators (Buysse, 2014, Alghamdi, 2013, Babson et al., 2012, Casement et al., 2012, Wu et al., 2012).

Second, because sleep varies markedly between different individuals and within the same individual on different nights (Bei et al., 2016), the inherent variability of sleep has made it difficult to measure without substantial measurement error, especially when such measurements require the use of one or more reference points for defining what constitutes 'normal', 'healthy' sleep (Hirshkowitz et al., 2015). During the searches of the literature conducted for the present thesis, it became apparent that several authors have used very different reference points to define 'normal/healthy' sleep, whilst few appear to have considered the possibility of considering sleep as a

continuous spectrum of phenomena, in which there might exist (one or more) a ‘normal’ range or a range that is flexible enough to accommodate a variety of reference points (Buysse, 2014, Alghamdi, 2013). At the same time, the inherent (within- and between-subject) variability of sleep militates for multiple measurements (over more than one night) – an approach that is likely to be challenging given the cost and effort required (Buysse et al., 1989).

Third, the absence of consensus on what ‘standard’ test might accurately measure sleep (as a multidimensional construct) has required the use of a range of different measurement tools, each measuring several sleep characteristics simultaneously, to thereby achieve a sufficient level of comprehensive assessment and precision (Silber et al., 2016). There are also epistemological issues regarding the correct measurement of sleep in terms of whether the most accurate measures should be subjective (i.e. using a sleep diary and/or sleep questionnaires) or objective (i.e. using polysomnography [PSG] and/or actigraphy; Silber et al., 2016). Some claim that objective measures are more accurate (i.e. less prone to bias), yet not all sleep characteristics can be measured using PSG or actigraphy (Kushida et al., 2005, Ancoli-Israel et al., 2003). For instance, PSG might be considered the ‘golden standard’ for diagnosing SBD due its ability in detecting changes in oxygen saturation, respiratory movement and airflow limitations simultaneously. However, PSG cannot generate information about perceived sleep quality, daytime sleepiness, or the use of sleep medication - these important characteristics making subjective tools appear superior in this regard (Kushida et al., 2005).

Finally, as alluded to earlier, there are a number of challenges to measuring sleep related to the cost, time and the resources/intrusiveness required. These challenges have made studies that use subjective sleep measurements much commoner (particularly at the population level) than those studies using objective measurements – simply because subjective measurements are cheaper and easier to apply on a large scale (Barclay and Gregory, 2013). Furthermore, when used repeatedly for patient follow up, objective measurements are expensive and time consuming (Gliklich and Wang, 2002), and may adversely affect the ‘natural’ sleeping habits of research/clinical study participants. These somewhat intractable issues aside, amongst subjective measurements of sleep, sleep diaries might appear superior to sleep questionnaires in their ability to detect day to day fluctuation in sleep measures. However, sleep diaries do place extensive burdens of time, effort and responsibility on the study participants, making them difficult to employ in larger scale samples or

for lengthy periods of time (Silber et al., 2016, Carney et al., 2012). In addition, the analysis of data from sleep diaries can prove difficult to analyze, or to compare with the results of other studies due to lack of data coding standardization (Carney et al., 2012) and the role of subjective biases (including awareness of previous diary entries) by the participants involved. Indeed, unlike the many sleep questionnaires that use multiple choice/polytomous answer formats, free-text diary responses coded using numerical or ordinal coding systems can severely undermine the validity and reliability of the data they produce (Spruyt and Gozal, 2011). As such, in the main, researchers examining population-based variation in sleep have tended to use questionnaires as their principal data collection tool, and this tendency has over time resulted in both the proliferation of tools, and the emergence of popular (and, by implication, 'standard') tools. One such questionnaire is the Pittsburg Sleep Quality Index (PSQI; Buysse et al., 1988), the psychometric properties of which have been validated in a range of studies in different sittings, in different languages and different populations (including pregnant women: Qiu et al. 2016; Zhong et al. 2015; Van Ravesteyn et al. 2014; and Skouteris et al. 2009). In pregnant women, PSQI is thought to be a particularly useful tool to assess sleep subjectively as it displays good construct validity and internal reliability amongst pregnant participants (Qiu et al., 2016, Zhong et al., 2015), though it has only moderate temporal stability in this population (Skouteris et al., 2009). For this reason, the PSQI remains the most commonly used multiple item-based instrument for assessing the self-reported sleep of pregnant women, and as such is arguably considered the 'gold standard' for such measurements in this context.

1.4 Populations at risk of developing unfavourable sleep events

While sleep remains challenging to measure, and the measures available (particularly through self-report) continue to diversify, the available evidence suggests that the prevalence of sleep problems is increasing, particularly in modern, industrialised settings. In the UK for example, it has been claimed that around two thirds of the adult population report having at least one 'unfavourable sleep event' (such as short duration or daytime sleepiness; Mental health Foundation, 2011). At the same time, a growing number of studies suggest that some populations are at higher risk of developing (or, at least, reporting) such events, a risk associated with several factors thought to alter their sleep cycle and/or trigger unfavourable sleep events:

I. Participants from poorer socioeconomic backgrounds (such as those with lower educational achievement, those who are unemployed and those on lower

incomes) are all considered at elevated risk of ‘unfavourable’ sleep events (Bonke , 2015, Felden et al., 2015). Some suggest this risk is mediated by the anxiety and concerns associated with their day-to-day circumstances (Okun et al., 2014, Moore et al., 2002) or is simply the direct effect of their material circumstances (Okun et al., 2014, Mezick et al, 2008).

II. Participants employed in jobs requiring shift work, or traveling between time zones (e.g. airline staff) are considered at elevated risk since their occupations seem likely to affect the synchronization of their internal ‘sleep clock’ (Waterhouse et al., 2013, Åkerstedt, 2003).

III. Participants form non- ‘White’ ethnic (minority) backgrounds are also considered at elevated risk of ‘unfavourable’ sleep as a result of a combination of psychosocial and economic/structural factors and, though currently based on little if any evidence, potential genetic factors (Whinnery et al., 2014, Lichstein et al., 2013).

IV. Older participants, especially those older than 60 years (Ohayon et al., 2004), whose elevated risk of ‘unfavourable’ sleep is considered likely if only as a result of their elevated risk of health-related medical and psychological conditions such as breathing disorders, dementia and depression (Smagula et a., 2016, Lichstein et al., 2013).

V. Participants with poor health – particularly those with conditions having a direct bearing on sleep – are thought likely to have an elevated risk of ‘unfavourable’ sleep events, particularly with regard to SBD, RLS and insomnia (Trenkwalder et al., 2016, Franklin and Lindberg, 2015, Kyle et al., 2010).

VI. Participants with adverse psychological disorders – particularly those such as anxiety or depression in which sleep disruption is considered a key symptom/mechanism – are also considered at increased risk of ‘unfavourable’ sleep (Alvaro et al., 2013).

VII. Participants with certain specified behavioral risk factors (i.e. unhealthy diets, inactive life styles, those who smoke and/or consume excessive alcohol or caffeine or drugs) are all considered at increased risk of ‘unfavourable’ sleep, though primarily as a direct or indirect consequence of these behaviours (Clark and Landolt, 2017, Araghi et al., 2013, Kaneita et al., 2005).

VIII. Participants who are women (as compared to men) are also considered at increased risk of ‘unfavourable’ sleep, partly as a result of gender-imposed differences in lifestyle, responsibility and stress, partly as a result of sex-based differences in hormonal and metabolic patterns (Arber et al., 2009). There is

> also substantial evidence that pregnant women, especially in their first or third trimesters, are even more susceptible to 'unfavourable' sleep as a result of hormonal, anatomical and physiological changes that occur even during otherwise 'normal' pregnancies (Al Afif, 2016).

Given the focus of the present thesis, sex- and gender-based disparities in sleep, both self-reported and objectively measured, are of particular interest. It is believed that women tend to experience more variation in their sleep cycles, which some authors suggest reflect changes in female sex hormone levels occurring during the menstrual cycle (Manber and Armitage, 1999). However, others have argued that women are often under social influences that force them to wake or sleep at non-desirable times (such as those amenable to running a household and, of course, when taking the brunt of responsibility for nocturnal child care) and that this might be what is responsible for interrupting, and thereby varying, their sleep cycles (Silber et al., 2016). Certainly, during pregnancy, women undergo a host of psychological, anatomical and physiological changes including mental preparation for motherhood, the enlargement of the uterus, and variation in hormone levels, as well as nocturnal foetal movement during the later stages of pregnancy (Silber et al., 2016). Clearly, these changes seem likely to alter pregnant women's sleep cycle rhythms since they are likely to make it difficult to asleep, find a comfortable sleeping position or maintain sleep without waking up (several times a night) to urinate (Brunner et al., 1994). However, there is as yet only a modest amount of information available about how the REM and NREM stages of the sleep cycle might vary during pregnancy, though there is some evidence to suggest that REM sleep and stages 3 and 4 of NREM sleep tend to be shorter in pregnant women (Ursavaş and Karadag, 2009). Indeed, it is known that the shortening of REM sleep and NREM stages 3 and 4 increases as pregnancy progresses, although this shortening can also display substantial night-to-night fluctuations (Brunner et al., 1994). These physiological phenomena aside, novel psychological stressors that emerge as a result of and/or during pregnancy (such as anticipation, excitement, exhaustion or anxiety) are also likely to affect the sleep cycle in pregnant women, possibly as a result of nightmares and/or light, easily disturbed sleep (Van et al., 2004).

1.5 The impact of pregnancy on sleep

Sleep disturbance is a commonly reported problem during pregnancy, especially during the final, third trimester (Naud et al., 2010). Several factors may be responsible

for such disturbances, such as: an increased uterus size (Silber et al., 2016); alteration in hormonal levels (especially of progesterone; Sloan, 2008); increased frequency of nocturnal urination (Sloan, 2008); uncomfortable foetal movements (Silber et al., 2016); backache (Wang et al., 2004); restless leg syndrome (RLS – a neurological condition causing leg pain and discomfort, and associated sleep disturbance; Neau et al., 2009); heartburn; and feeling overly cold or hot (Naud et al., 2010). As a result, pregnant women usually suffer from increased sleep latency (Lee et al., 2000, Mindell and Jacobson, 2000), snoring (Miri et al., 2012) and symptoms associated with sleep disordered breathing (SDB; Mindell and Jacobson, 2000; see Figure 1-1[3]).

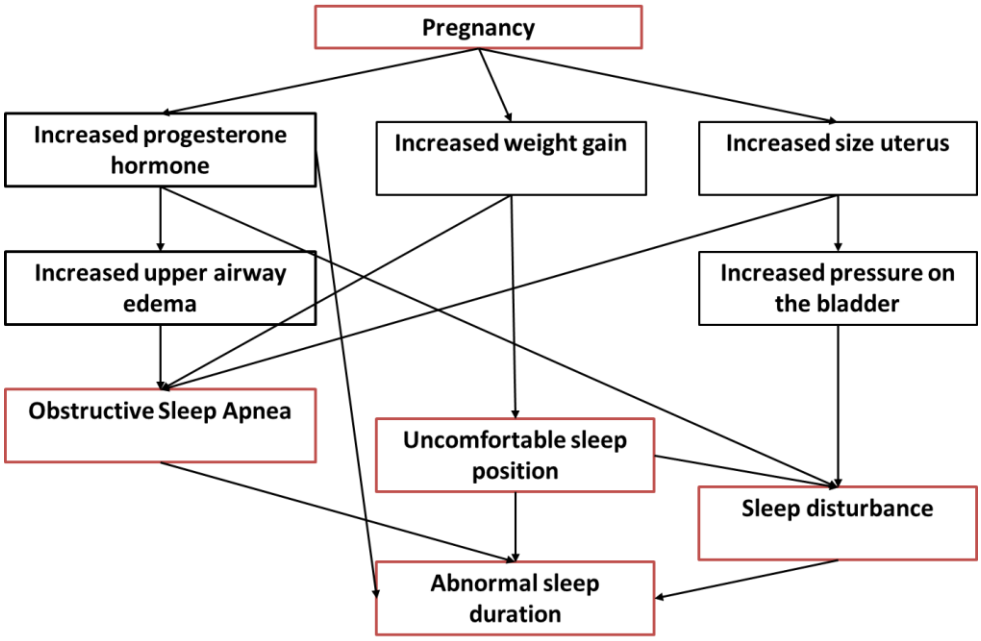

Figure 1-1 Summary of theorised risk factors for pregnancy-induced sleep disorders, as proposed in published studies, reviews and opinion pieces

Sleep duration – the total time spent in *actual* sleep during the night (and not time spent in bed awake; Stenholm et al., 2011) – is generally thought to be longer in the first trimester as compared to pre-conception (Kennelly et al., 2011). However, it is claimed that the duration of sleep returns to its pre-pregnancy length in the second trimester (Kennelly et al., 2011). Empirical studies suggest that the mean sleep duration of pregnant women in the first trimester is around 8hrs/night, and that it only

[3] **Note:** Figures 1-1 to 1-6 reflect hypothesised pathways generated (by this thesis author) as visually simplified diagrams that aim to summarise the complex interactions between factors cited as potential/likely causes of 'unfavourable' sleep in the literature (as summarised and discussed in the text).

reaches its minimum length (of around 6hrs/night) in the third trimester (Kennelly et al., 2011, Paine et al., 2012).

Night-time sleep is important to maintain functional energy levels the following day (Vgontzas et al., 2007), so it may not be surprising that some pregnant women who suffer from night sleep problems are believed to compensate for shorter, disturbed sleep by frequent napping or short periods of sleep during the day (Tsai et al., 2011). However, since longer naps can interfere with the subsequent night's sleep, causing it to become shorter and with prolonged latency, there is also a possibility that daytime napping can itself play a role in shorter disturbed sleep at night (Tsai et al., 2011), though this has received somewhat equivocal support from studies designed to examine this – some studies failing to find any reason why daytime sleepiness might not be successfully resolved through frequent napping without any subsequent risk to the following night's sleep duration (Signal et al., 2012).

Meanwhile, snoring is thought to be almost "universal" amongst pregnant women, particularly during their third trimester (Bourjeily et al., 2013). Ironically, since snoring is seen as commonplace it has not, until recently, received much attention from clinicians. However, since snoring can reflect the presence of serious underlying sleep disorders (particularly obstructive sleep apnoea, which is known to have pronounced cardio-metabolic effects; Ursavaş and Karadag, 2009), there has been growing interest in the potential risk that widespread snoring might pose to the health of pregnant women and their developing baby. Some clinicians have therefore proposed that pronounced snoring (as well as full-blown sleep apnoea) require greater vigilance during pregnancy, and may require or benefit from clinical intervention to prevent subsequent maternal and foetal complications, such as gestational hypertension (GHTN) and low birth weight (LBW), both of which might occur as a result of lowered oxygen saturation (Sahin et al., 2008).

1.6 The potential influence of sleep on pregnancy outcomes

Arguably, any undesirable maternal or foetal morbidity that arises during pregnancy or the perinatal period can be considered an "unfavourable" or "poor" pregnancy outcome. These include, for example: pregnancy-induced hypertension (occurring during the antenatal period); preterm delivery (a feature of the perinatal period); and low birth weight (LBW, a feature of the neonate). In extreme cases, miscarriage, foetal death or still birth can occur; and, likewise, maternal death. Yet poor pregnancy

outcomes tend to manifest as consecutive events each of which can lead into, or facilitate the development of, another. In this way, for example, gestational hypertension can lead to preterm delivery and thereby to LBW. At the same time, poor pregnancy outcomes can accumulate or interact with one another to produce even worse outcomes. For example, an otherwise term and 'normal' birth weight infant might nonetheless be admitted to the neonatal intensive care unit (NICU) after several maternal and foetal complications developing during pregnancy.

During the preparatory phase of the present thesis, a detailed search of the literature revealed that little is known about how variation in sleep characteristics might influence the risk of poor pregnancy outcomes – though there are plenty of opinion pieces and some dedicated empirical studies which claim that such risks are real (and may be substantial). On this somewhat tentative and speculative basis, various theories have been proposed regarding the different types of mechanisms involved – some involving specific characteristics of sleep (including sleep duration, latency and daytime sleepiness), though most focussing on obstructive sleep apnoea (OSA), with a modest number on sleep quality and some on sleeping position. However, to-date there has been little consideration as to how these mechanisms might interact with one another, and there remains little interest in viewing 'sleep' in a more holistic fashion as a phenomenon characterised by a mixture of separate yet interdependent and interacting characteristics.

Predominant theories regarding the potential role of sleep on pregnancy outcomes have thus far focussed (as mentioned earlier) on pregnant women who suffer from SDB, who are thought to be at a higher risk of developing pre-eclampsia and/or delivering LBW babies (Reutrakul et al., 2011, Chen et al., 2012). In this scenario, it is believed that pre-eclampsia develops secondarily to arterial inflammation resulting from a lack of tissue oxygenation and the build-up of circulatory inflammatory factors (Figure 1-2; Edwards et al., 2000). At the same time, it has been postulated that a lack of placental oxygenation or hypoxemia might interfere with infant growth, leading to LBW (Figure 1-3; Reutrakul et al., 2011).

Other theories include the suggestion that poor perceived sleep quality and short sleep duration might both influence foetal growth (though precisely how remains unclear), leading to excessive foetal weight gain and macrosmia (Keeffe and St-Onge, 2013). One proposed mechanism involves the development of macrosomia as a consequence of the effect of short sleep duration (<6hrs/night) on maternal glucose metabolism and increased insulin secretion (Reutrakul et al., 2011, Keeffe and St-

Onge, 2013). High insulin levels would be likely to lead to lipid deposition in the foetus and thereby cause excessive weight gain and large birth weight neonates (Keeffe and St-Onge, 2013; Figure 1-1).

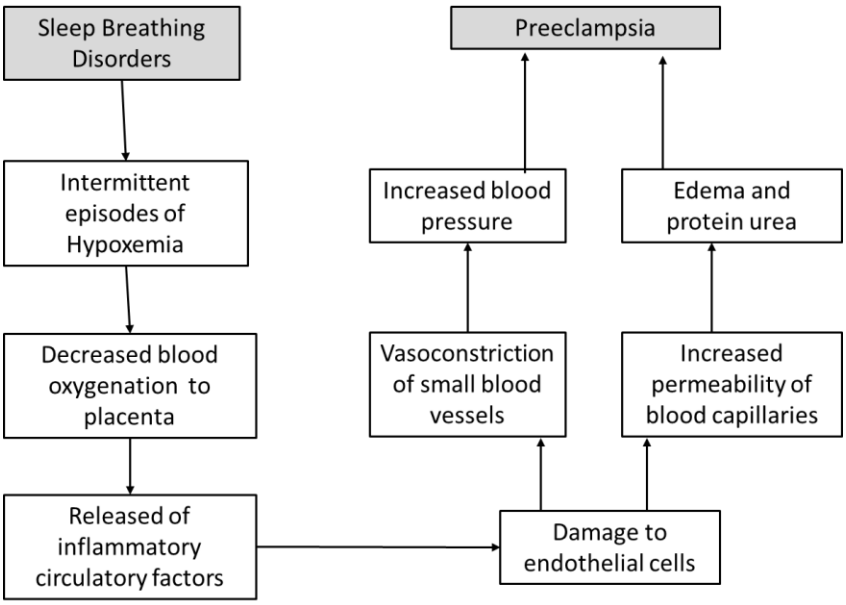

Figure 1-2 Summary of proposed pathophysiology of pre-eclampsia secondary to sleep disordered breathing.

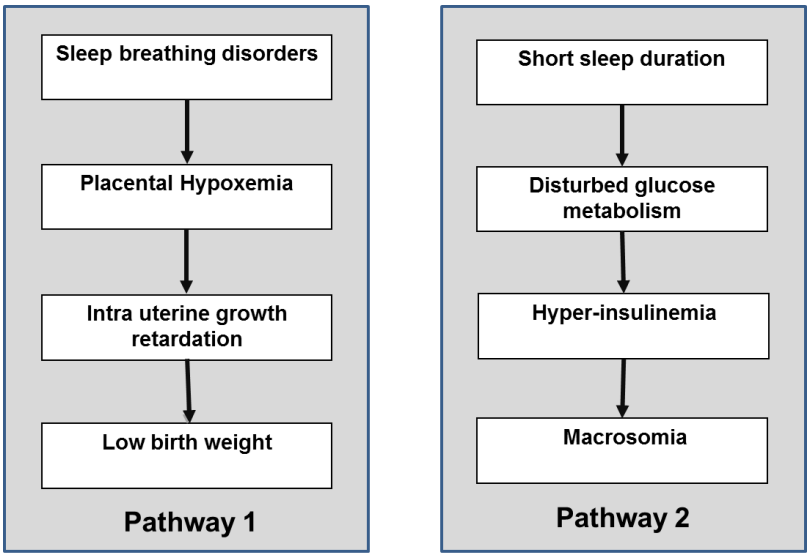

Figure 1-3 Summary of proposed pathophysiology of abnormal neonatal birth weight secondary to short sleep duration and sleep disordered breathing.

As regards the theories that have emerged surrounding sleeping positions during pregnancy, it has been suggested that adopting the supine sleep position in early pregnancy may affect the location of the placenta (Edwards et al., 2001), while in late pregnancy, abnormal placentation may decrease the blood supply to, and oxygenation of, the placenta due to pressure from the enlarged uterus on the placental blood vessels, leading to the release of inflammatory factors and, eventually, pre-eclampsia (Figure 1-4; Edwards et al., 2001).

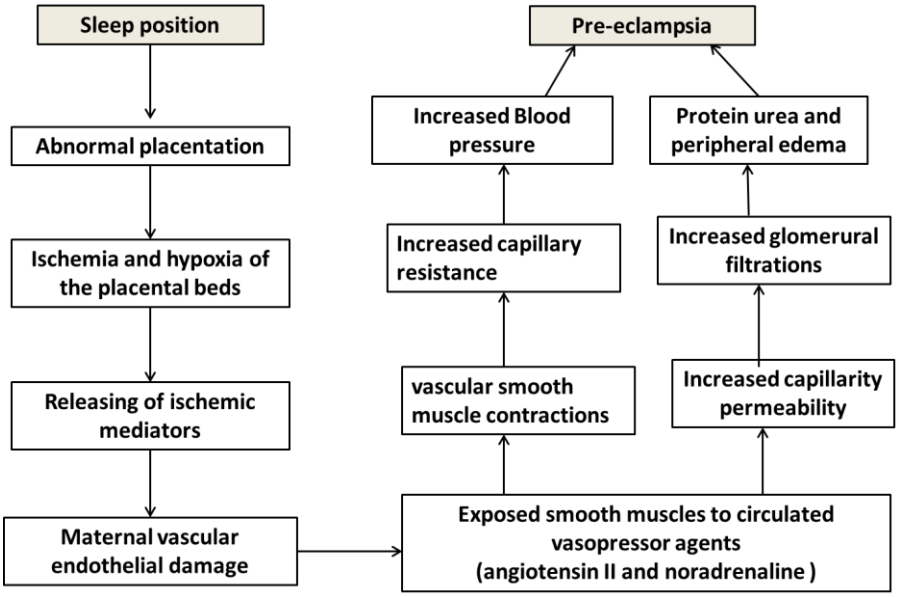

Figure 1-4 Summary of proposed pathophysiology of pre-eclampsia secondary to abdnormal sleep position in early pregnancy.

At the same time, sleeping in the supine position late in pregnancy is also thought to affect placental blood supply, as (again) the enlarged uterus would press on the large blood vessels supplying the placenta, causing a reduction in the delivery of oxygen and nutrients to the foetus (Stacey et al., 2011, Stacey and Mitchell, 2012). Dorrian and Warland (2013) proposed that this might then result in restricted foetal growth and, in severe cases, in stillbirth. In a similar fashion, it has been proposed that SDB might itself cause placental hypoxemia severe enough to cause foetal death or stillbirth (Stacey and Mitchell, 2012).

Meanwhile, excessive gestational weight gain by the mother is thought to be a key risk factor for SDB during pregnancy, simply as a result of the additional mechanical load caused by central adiposity, which in turn narrows the upper airway *and* reduces

maternal lung capacity (Schwartz et al., 2008) - a phenomenon that may further exaggerate the pressure-related effects of an enlarged uterus and supine sleeping position, especially in late pregnancy (Schwartz et al., 2008, Louis et al., 2012, Stacey and Mitchell, 2012; Figure 1-5)

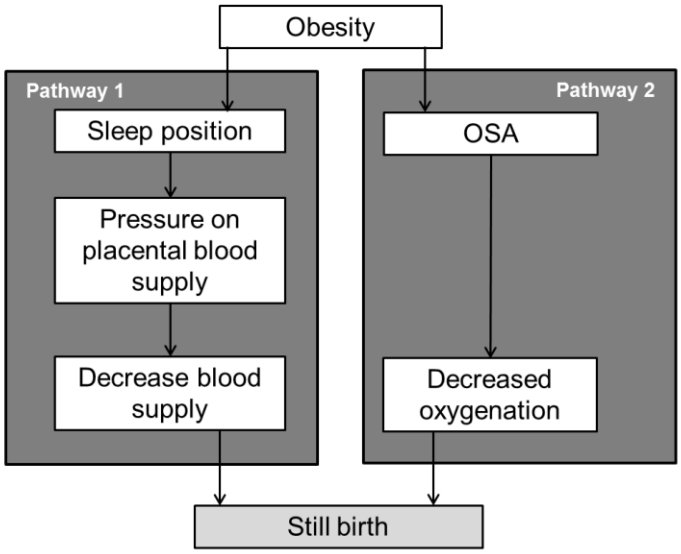

Figure 1-5 Summary of proposed pathophysiology of stillbirth secondary to SDB/OSA and sleep position

1.7 Risk factors of poor pregnancy outcomes and sleep events

Poor pregnancy outcomes can arise as a result of a large number of very different risk factors which can be developmental/ontogenetic (or environmental) in origin (Bernabe et al., 2004). However, ontogenetic and environmental factors interact with one another making it difficult to separate them analytically (Fuller, 2000). These factors may also influence the risk of unfavourable sleep events, and might therefore act as potential confounders in any apparent relationship between sleep and poor pregnancy outcomes (primarily because these factors would then predispose the women concerned to be less “healthy”; Alvarez and Ayas, 2004, Gallicchio and Kalesan, 2009).

Some of the sociodemographic (‘environmental’) features that have been considered risk factors for poor pregnancy outcomes (and less favourable sleep) include: the ethnic origin of the mother and her socioeconomic status. For example, Rowe and Garcia (2003) and Connor et al. (2003) argue that there is substantial empirical

evidence that women from white ethnic backgrounds (i.e. backgrounds that reflect higher social position and autonomy within ethnocentric and discriminatory contexts) tended to have fewer 'poor' pregnancy outcomes and less unfavourable sleep events than women from other ethnic backgrounds. At the same time, social class is known to affect the level of care pregnant women receive (even in contexts where antenatal and obstetric care are free at the point of use; Rowe and Garcia, 2003), and low social class is known to be associated with poorer maternal nutrition and with anxiety-related disorders capable of affecting sleep (Moore et al., 2002).

As regards maternal health and behavioural risk factors, a maternal pre-pregnant body mass index (BMI) of >30kg/m^2) and excessive gestational weight gain during pregnancy are both considered putative risk factors for sleep disorders, just as they are among non-pregnant female and male populations (Tremblay et al., 2009,Facco et al., 2012). Indeed, obesity is perhaps the most widely accepted risk factor for poor pregnancy outcomes (King, 2006, Cappuccio et al., 2008).

Elsewhere, pre-existing maternal health conditions (such as chronic hypertension, diabetes mellitus and asthma) and a maternal age below 18 years or above 35 years are also widely thought to be associated with an increased risk of poor pregnancy and neonatal outcomes (such as caesarean delivery and preterm birth; and LBW and birth trauma, respectively); as well as a range of less favourable sleep characteristics such as disturbed sleep, extended sleep latency and SDB (Olausson et al., 1997, Gilbert et al., 1999, Floyd et al., 2000, Seoud et al., 2002). While multiple pregnancies often affect the rate of growth amongst each of the individual foetuses (especially during the third trimester), and can increase the risk of complications at delivery (including prematurity and caesarean delivery; Rao et al., 2004); multiple pregnancies are also thought to increase the risk of interrupted and poor-quality sleep (Eeva Nikkola et al., 1996). Finally, iron and vitamin deficiency, together with low haemoglobin concentration are also thought to be associated with RLS (Tunç et al., 2007) as well as with foetal growth retardation (Scholl and Reilly, 2000).

Likewise, while a range of maternal 'health' behaviours, such as alcohol, smoking and drug abuse, are known to increase the risk of foetal growth retardation, preterm labour and (in severe cases) foetal loss due to congenital anomalies and complications (Floyd et al., 1993, Greenfield et al., 2007, Henderson et al., 2007); these can also lead to less favourable sleep. For example, smoking can aggravate SDB symptoms (Young et al., 2004), whilst alcohol and drug abuse can affect sleep quality and interfere with next-day alertness and function (Vitiello, 1997).

1.8 Gestational diabetes, pregnancy outcomes and the role of sleep as a potentially modifiable risk factor

Gestational diabetes (GDM) is a growing medical problem affecting around 2-7% of pregnant women in the UK (National Institute for Clinical Excellence, 2008). Women are considered to have GDM if their fasting blood glucose levels fall ≥ 7 mmol/l (i.e. recorded before receiving the OGTT); or/and their blood glucose reading after 2 hours following a 75 mg oral does of glucose falls ≥ 7.8 mmol/l (as defined by the National Institute for Clinical Excellence, 2008).

Several risk factors are believed to increase the risk of GDM in pregnant women, including: elevated BMI (≥ 30 kg/m^2); previous history of GDM; previous history of macrosomia; family history of DM in a first degree relative (e.g. mother or brother); and ethnic minority backgrounds that have a high prevalence of GDM (e.g. those from Arab or Black African backgrounds; National Institute for Clinical Excellence, 2015). These risk factors are thought to elevate the risk of developing cellular insulin resistance and a subsequent decrease in cellular utilization of glucose leading into hyperglycaemia in the mother (Kaaja and Rönnemaa, 2008).

GDM, if left untreated, can lead to a range of poor pregnancy outcomes (such as macrosomia - believed to be one of the commonest poor pregnancy outcomes; Reutrakul et al., 2011; Figure 1-6). Of particular concern is that the prevalence of macrosomia is projected to reach 45% amongst the newborns of women with GDM (Kamana et al., 2015), and that this poses immediate risks during delivery and the perinatal period, and potentially for the infant in later life.

Macrosomia, defined as a neonatal birth weight exceeding 4000 gm at birth (Kamana et al., 2015, Chatfield et al., 2001), is considered to be a consequence of increased foetal insulin production resulting from maternal hyperglycaemia (Kamana et al., 2015). Macromsomia, either on its own or together with GDM, is believed to increase the risk of preterm birth (i.e. birth before or during 37 weeks of gestation) and caesarean delivery, which can in turn cause a range of maternal and neonatal complications including postpartum maternal blood loss and/or the need for admission to the neonatal intensive unit (Yogev and Langer, 2007, Yang et al., 2002). Regardless of the possible maternal complications of caesarean delivery, such interventions are often considered appropriate to reduce the possibility of shoulder dystoica (i.e. the obstruction of the infant shoulder in the birth canal during delivery) which is also thought to be more prevalent amongst macrosomic babies and to be a direct cause of

excessive maternal postpartum bleeding (Wang et al, 2015). Meanwhile, the elevated risk of caesarean delivery and preterm delivery might also be related to preeclampsia which is also more prevalent amongst women with GDM, although the precise mechanisms behind this relationship remain unclear (Wu et al., 2016). Whatever the mechanism, preterm delivery secondary to preeclampsia or GDM is also likely to be associated with an elevated risk of low birth weight which might, in and of itself, increase the risk of NICU admission (World Health Organization, 2015). In the worst case scenario, GDM has been linked to third trimester stillbirth, either as a result of maternal and/or foetal comorbidities associated with GDM (such as maternal obesity or pre-eclampsia), or simply due to the possible effect of maternal hyperglycaemia on foetal metabolism, leading into foetal acidosis and hypoxemia and thereby stillbirth (Dudley, 2007, Silver et al., 2007). In order to reduce the risk of macrosomia and//or still birth, medical intervention commonly results in efforts to induce labour in women with GDM at around 38 weeks of gestation, regardless of the risks that might then ensue (such as an increased risk of caesarean delivery; Witkop et al., 2009).

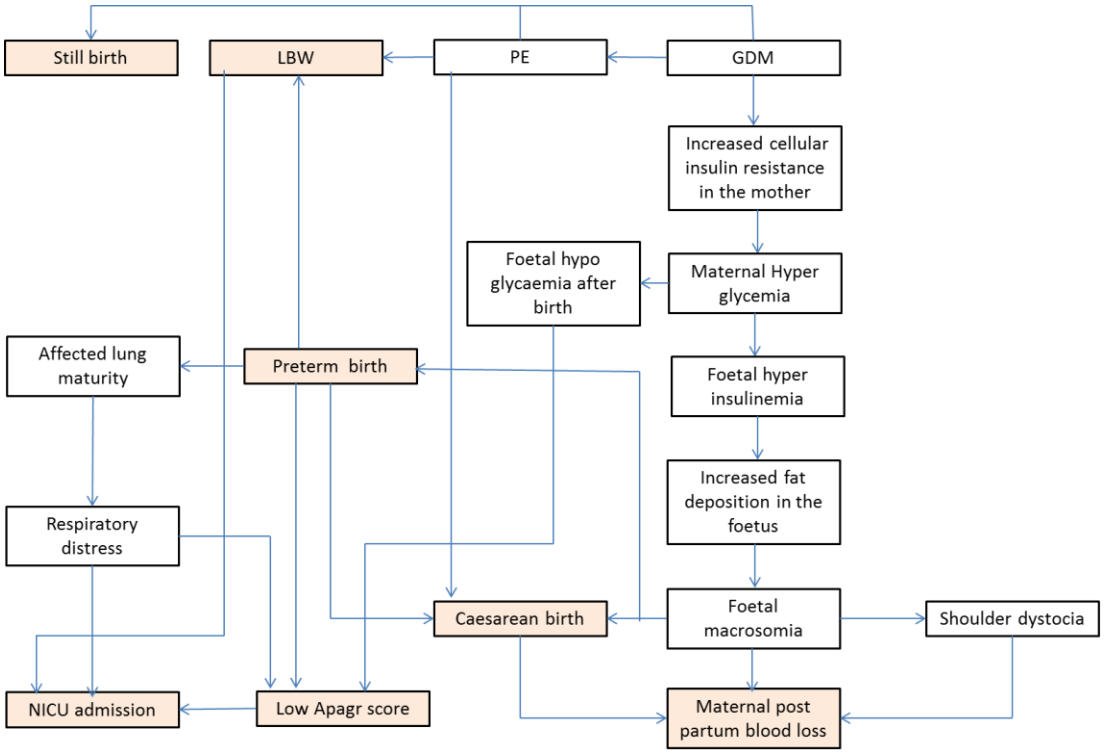

Figure 1-6 Summary of the proposed pathophysiology of poor pregnancy outcomes secondary to GDM and/or comorbid pre-eclampsia.

GDM has also been linked to less favourable sleep, including both short sleep duration (<7hrs), OSA (Reutrakul et al., 2011) and habitual snoring (O'Brien et al., 2013). Unfortunaly the pathophysiological mechanisms behind any potential effect of GDM on sleep has yet to be described (at least within the litreature examined for the present thesis), not least because there remain limited puplished studies examining sleep in women with GDM. Of the evidence that is available, it appears that 'unfavourable' sleep may be linked to impaired glucose control in women with GDM, perhaps as a result of increased insulin resistance, impaired glucose metabolism and abnormal maternal weight gain (Twedt et al., 2015). Indeed, it is for this reason that these sleep characteristics are themselves considered prognostic factors for poor pregnancy outcomes (Pamidi et al., 2014).

Despite improvements in the care available and provided to women with GDM, there remains substantial evidence that, by the final (third) trimester of pregnancy, it can be very challenging to prevent poor pregnancy outcomes (Kerssen et al., 2007). Moreover, clinical interventions to control blood glucose levels in pregnant women with GDM can risk causing hypoglycaemia, which itself can compromise the well-being of both the mother and her foetus (Nielsen et al., 2008).

Perhaps most commonly, the period from late in the second to early in the third trimester of pregnancy seems likely to be the time during which dramatic physiological and metabolic changes take place that affect blood glucose levels; and it is therefore likely that this is also the time when GDM most commonly develops (Kühl, 1991, Murphy et al., 2008). If, then, appropriate clinical intervention takes place before these metabolic changes begin, improvements in pregnancy outcomes may be possible (Berk et al., 1989). In addition, where healthier lifestyle interventions succeed in improving these aspects of the 'environmental' exposures pregnant women face (not least when these achieve healthier lifestyles *prior* to pregnancy, through exercise [Tobias et al., 2011, Nobles et al., 2015] and/or healthier diets [Zhang et al., 2014, Tryggvadottir et al., 2016]), then this too might reduce the risk of GDM and any subsequent need for metformin and/or insulin in late pregnancy (the latter being linked to both hypoglycaemia [Rosenn et al., 1995, Nielsen et al., 2008 *and* macrosomia [Berk et al., 1989]).

In this context (of using a healthier lifestyle to prevent, treat or mitigate the effects of GDM) sleep is increasingly presented as a key (potential) modifiable risk factor, not least because sleep is widely thought to worsen during later pregnancy (Mindell et al., 2015) and to be worse still amongst mothers with GDM (Qiu et al., 2010).

Unfortunately, there remains substantial uncertainty (as already discussed, above) regarding what role sleep might play as a risk factor for poor pregnancy outcomes in the presence of GDM (be sleep a correlate, determinant or consequence thereof). Nonetheless, it is plausible to postulate three specific theories in this regard, each of which are worthy of closer examination. The first of these is that less favourable sleep might compromise the homeostatic mechanisms involved in glucose control and thereby lead to poor pregnancy outcomes. The second is that abnormal glucose might itself *cause* disturbed sleep, which then itself causes poor pregnancy outcomes. The third is that both of these 'effects' operate in a more or less continuous cycle in which sleep and blood glucose affect one another and thereafter affect the outcome of pregnancy. Ideally then, repeated measurements of sleep (and glucose control) are required to assess which of these theories might be correct, preferably using an intervention-based experimental study design that might, for example, examine the effect of improved sleep quality on glucose control and thereafter macrosomia, in women with GDM (Facco et al., 2013). However, where repeated measures of blood glucose control and sleep are neither feasible nor practicable, then perhaps the preferred time to conduct such a study would be in the late second to early third trimester of pregnancy – i.e. the period preceding clinical intervention to stabilise blood glucose (National Institute for Clinical Excellence, 2008) yet when the development of anatomical (i.e. enlarged uterus and central adiposity) and hormonal factors (i.e. high progesterone and oestrogen) are still likely to be affecting sleep (Mindell et al., 2015, Silber et al., 2016). Since foetal growth also starts to accelerate around this time, following the formation of the foetus' internal organs, this is also the period in which screening for foetal abnormalities that can be detected by variation (such as intrauterine growth retardation [IUGR] and foetuses that are small for their gestational age [SGA]) takes place whether through the measurement of fundal height and/or ultrasound imaging (American College of Obstetricians and Gynecologists, 2013). It therefore seems likely that, were no relationship to be observed between sleep and pregnancy outcome at around this time, particularly in women with GDM, it seems likely that the relationship is most likely to be absent (since any apparent relationship might actually simply reflect confounding due to clinical intervention or some other, latent, confounders).

1.9 Summary

In conclusion, the present thesis recognises that sleep medicine remains an emerging (albeit, more recently, a rapidly emerging) research field. Nonetheless, the thesis also recognises that sleep is a complex phenomenon and there is much still to learn about its function, mechanism and biological effects. Much of our current understanding of these effects relies on descriptive and observational studies, and theories. These claim that less favourable sleep is likely to increase the risk of poor pregnancy outcomes, even though unfavourable sleep is a common experience of otherwise normal pregnancies (i.e. pregnancies that do *not* experience poor pregnancy outcomes). Nonetheless, the role of unfavourable sleep on pregnancy outcomes is theorised as having a number of different pathophysiological mechanisms, occasionally with a separate mechanism for each sleep characteristic and each pregnancy outcome; yet with little consensus (or attention) on how these hypothesised (pathophysiological) pathways might accumulate or interact.

While gestational diabetes (GDM) predisposes both the mother and her foetus to the risk of a range of poor outcomes, in addition to less favourable sleep, little is known about whether 'less favourable' sleep might *independently* predict pregnancy outcomes in women who are at risk of/already have GDM.

1.10 Research aim

The overarching aim of the present thesis was therefore to study the association between sleep and poor maternal and foetal pregnancy outcomes in pregnant women, and to extend this to pregnant women at risk of GDM (amongst whom the risk of both unfavourable sleep *and* poor pregnancy outcomes are likely to be higher).

1.11 Research questions

To achieve this overarching aim four key research questions were proposed

KQ1: What might be learnt from the methods and findings of previous empirical studies exploring the relationship between sleep and pregnancy outcomes regarding: the challenges and potential flaws of such studies; the strength of the evidence these studies provide; and priorities for strengthening the evidence generated from existing data sources?

KQ2: What, if any, sleep patterns exist amongst the UK population; are any of these stable over time and/or associated with sociodemographic and health characteristics that might provide evidence of reliability and criterion-based validity?

KQ3: Is there any evidence that self-reported sleep characteristics predict subsequent pregnancy outcomes amongst pregnant women who are broadly representative of the UK population? And to what extent might 'sleep patterns', identified using a range of self-reported sleep characteristics, predict subsequent pregnancy outcomes amongst them?

KQ4: Is there any evidence that self-reported sleep characteristics predict subsequent pregnancy outcomes amongst pregnant women at increased risk of developing gestational diabetes? And to what extent might 'sleep patterns', identified using a range of self-reported sleep characteristics, predict subsequent pregnancy outcomes amongst them?

Each question will be answered in consecutive Chapters of the present thesis, these four Chapters being preceded by a dedicated 'methodology chapter' (containing the rationale for study designs, data and analytical techniques used) and followed by a dedicated Discussion Chapter (in which the results of the four preceding Chapters will be interpreted and applied within the context of recommendations for further research). To enhance the readability of the thesis, much of the supporting detail (particularly regarding data collection, categorisation and preliminary/exploratory analysis) has been located in an extended Appendix, to which specific references are made, where appropriate, throughout the text that follows.

Chapter 2 Methodology

The principal aim of this thesis is to examine the association between sleep and pregnancy outcomes in pregnant women, including those at increased risk of GDM. In order to achieve this goal, a total of four separate studies were conducted. In the present chapter, each of these studies will be described in terms of the data sources used; the analytical tests applied, and related theoretical concepts underpinning the selection of these data and tests.

2.1 Research design

As discussed in Chapter 1 (Section 1.11, page 44), this Doctoral thesis addresses four separate objectives. To achieve each of these objectives, the following studies were performed:

2.1.1 Systematic review and meta-analysis

A systematic review and meta-analysis was undertaken to provide a comprehensive overview of the current extent of knowledge on the subject matter in hand. Within the so-called 'hierarchy of evidence', systematic reviews and related meta-analyses are generally considered the highest 'level' of evidence attainable (albeit, particularly so when generated from multiple primary experimental studies), and it is for this reason that this was the first analytical chapter to be undertaken for inclusion in the present thesis, providing (as this should) a critical evaluation of the current evidence regarding the possible association between sleep and pregnancy outcomes. This required a systematic search of the published scientific literature to optimise the identification of relevant primary studies (initially, at least), regardless of their study design (be this experimental or observational). Similarly, a careful process of critical appraisal and data extraction was required to evaluate possible reporting gaps and likely limitations or flaws in the data and analytical techniques these primary studies used – limitations and flaws that might then be addressed or mitigated in the design and conduct of the *de novo* studies conducted for inclusion in the present thesis.

2.1.2 Empirical *de novo* primary studies

These *de novo* studies comprised three separate observational analytical studies, each study with its own specific objective (as described in Chapter 1), which together contributed towards addressing the principal aim of the thesis (Figure 2-2). Each of these studies is briefly described below:

2.1.2.1 UKHLS (UK Household Longitudinal Study) latent class analysis

This study was performed to carefully examine the complex nature of sleep and any unmeasured ('latent') sleep patterns evident therein, using the seven self-reported sleep characteristics collected during the first and fourth Waves of the UK Household Longitudinal Study (UKHLS). As discussed in the introductory chapter, there is still much to learn and understand about sleep and the biology of sleep, though there is substantial consensus on a number of sleep features or 'characteristics' that can be reasonably reliably evaluated using both subjective and objective tools. However, these characteristics seem likely to interact with one another in a complex way to shape an individual's sleep pattern, yet very little is known about their inter-item associations (be these, for example: cumulative, permissive or multiplicative).Studying each sleep characteristic at a time (as many primary studies do) might therefore introduce a number of biases (not least if some characteristics act as confounders or mediators for others) and cause the loss of substantial valuable information. Instead, treating 'sleep' (as a 'whole') as a latent structure (i.e. one that cannot not be directly measured but is nonetheless present) might warrant further attention, not least if it were then possible to limit the necessity of estimating and evaluating complicated inter-characteristic associations by combining and considering all available characteristics simultaneously using a single latent variable. This would then result in allocating individuals to latent 'sleep pattern' clusters on the basis of their measured sleep characteristics (see Figure 2-1).

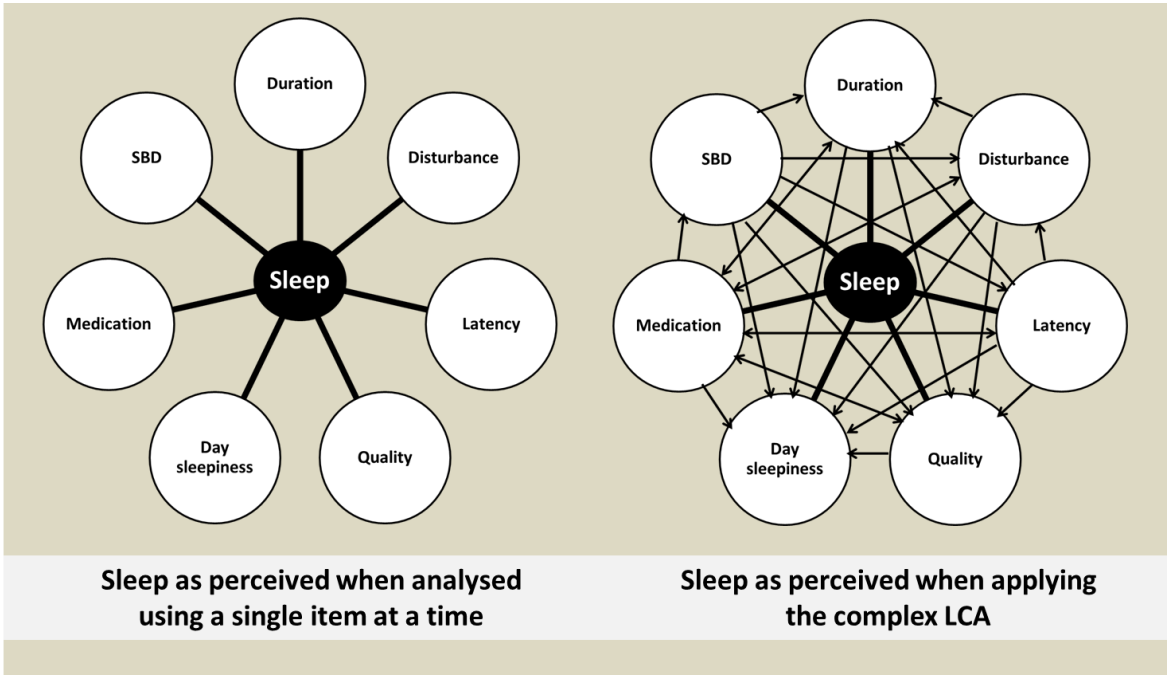

Figure 2-1 Sleep as perceived when treating it as a latent structure (to which each component contributes, though in a potentially complex, interactive fashion)

2.1.2.2 Sleep and pregnancy outcomes amongst UKHLS participants

The second of the *de novo* primary observational analytical studies was performed to examine the association between sleep and pregnancy outcomes in pregnant women from the UK population using both the 7 separate sleep characteristics available within the UKHLS and any latent 'sleep patterns' identified in the preceding chapter. The source of the data used (i.e. the UKHLS) was chosen to enhance the external validity of these analyses, albeit at the cost of not having access to comprehensive clinical information on UKHLS participants who were pregnant to permit the adjustment of all potential, salient confounding variables considered plausible for such analyses. Nonetheless, despite the relatively modest proportion of UKHLS participants who were pregnant at the time the seven sleep characteristics were measured (i.e. during Wave 1 and Wave 4), because the UKHLS was a large-scale study, there were still several hundred participants available for inclusion in these analyses (as described in more detail, below).

2.1.2.3 Sleep and pregnancy outcomes amongst women at risk of GDM in the Scott/Ciantar study

The final *de novo* primary observational analytical study was performed to examine the association between sleep and pregnancy outcomes in pregnant women likely to have an enhanced risk of *both* less favourable sleep *and* poor pregnancy outcomes; again, using both 7 separate sleep characteristics available within the UKHLS and any 'latent' sleep patterns identified in Chapter 4 (see Section 2.1.2.1 page 47). The rationale for using data from the Scott/Ciantar study (which had already commenced the recruitment of participants and the collection of sleep data by the time the present Doctoral thesis began), was the ready availability of clinical data within participants' medical records – data that might help to address a potential weakness in the analyses undertaken in the preceding chapter (which used a population-based sample, with limited clinical information, drawn from the UKHLS). The Scott/Ciantar study dataset thereby offered: the possibility of developing better analytical models, that had been more comprehensively adjusted using a minimally sufficient adjustment set of (clinical and non-clinical) covariates identified once more using a directed acyclic graph (or 'DAG' – as described later in the present Chapter); the better understanding required (from this prospective study) on the temporal sequences of the events and characteristics measured by each of the available variables to permit the confident specification of the DAG (again, see Chapter 2, Section 2.4, page 60 for further details); and a larger number and greater variety of pregnancy outcomes to examine. Meanwhile, the larger

prevalence of poor pregnancy outcomes expected in this dataset (given it comprised women at increased risk of GDM, and therefore at increased risk of poor pregnancy outcomes) was also expected to be somewhat higher that that observed in the population sample drawn from the UKHLS; and this was also viewed as helpful for improving the analytical power of analyses examining the association between sleep and pregnancy outcomes.

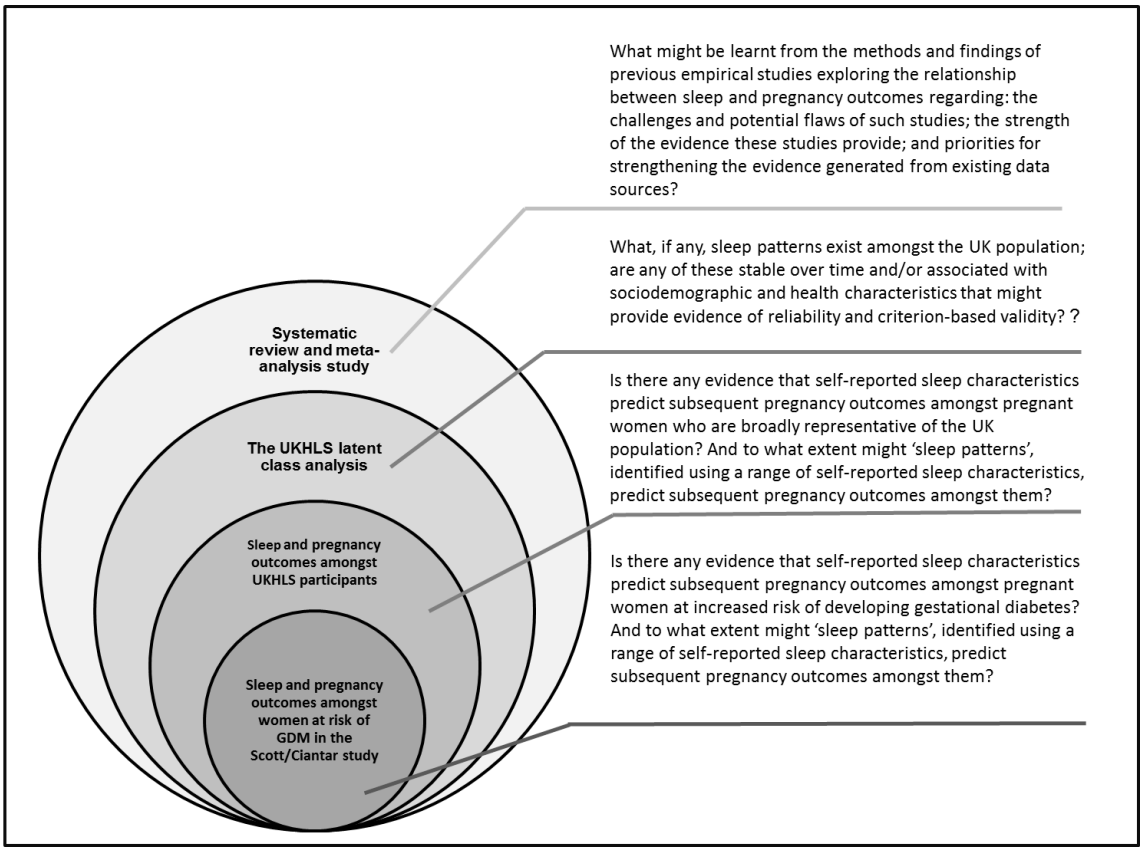

Figure 2-2 Graphical illustration of the way in which each of the thesis' *de novo* primary observational analytical studies built upon one another to address each of the objectives these set, and thereby achieve the overall aim of the thesis.

2.2 Data sources

For Chapters 4 and 5 (comprising the assessment of latent sleep classes and of the association between sleep and pregnancy outcomes using data from the UKHLS), the variables and sample available were determined by what had been collected by the UKHLS latent sleep study (University of Essex. Institute for Social and Economic Research and NatCen Social Research, 2015). For the Scott/Ciantar study, comprising women at risk of GDM, a study that had already been initiated by Dr Eleanor Scott and Dr Etienne Ciantar provided the sleep data and participant sample available, and made it possible (under the ethical and governance approvals this study had obtained) to access additional data from each

participant's medical records. Thus, whilst accessing the UKHLS dataset simply required downloading the study's publicly available datasets, substantial additional work was required to locate, examine, extract and evaluate data from the medical records of participants in the Scott/Ciantar study (a lengthy process taking more than 18 months, albeit with support from clinical colleagues and conducted in partnership with a fellow Doctoral student [Nora Al Afif] whose PhD focussed on determinants of variation in sleep during pregnancy). Further details regarding the data extraction techniques developed and used can be found in the Appendix (Chapter 8, Section 8.5.2, page 352)

2.2.1 UK Household Longitudinal Study (UKHLS) dataset

The UKHLS datasets available for use in Chapters 4 and 5 of the present thesis came from the mainstage dataset (though data from the innovation panel were also examined to assess the comparability of the seven separate sleep characteristics generated using bespoke sleep module items in the mainstage questionnaire, with answers generated from the validated Pittsburgh Sleep Quality Index [PSQI], on which the UKHLS sleep items were based, and which participants in the innovation panel also completed; see Appendix, Section 8.1.2, page 284). The mainstage dataset of the UKHLS was chosen as the basis from which to study sleep patterns in the UK for three broad reasons;

First of all, the mainstage study's sampling frame was specifically designed to be broadly representative of the UK population; comprising participants in more than 50,000 households from England, Scotland, Wales and Northern Ireland. So to begin with, the mainstage study comprised four separate sub-samples of UKHLS participants: the general population sub-sample; the general population comparison sub-sample; the ethnic minority boost sub-sample; and the (original) British Household Panel (BHP) survey sub-sample. The proportions and sizes of these sub-samples were, however, different. Nonetheless, to ensure the generalisability of the mainstage study (i.e. the ability of the final sample to represent the UK population, considering the different probability of: selection experienced by participants between, and within, the several smaller subsamples; and having a selection bias; Gundi, 2016) a special weighting variable was

developed by the UKHLS research team for researchers to include in their analysis (i.e. n_indpxub_lw and n_indpxub_xw) [4].

In summarising the sub-sampling technique of the main stage UKHLS design it should be emphasised that the 'general population' sub-sample was designed to be representative of the UK population by stratifying the UK on the basis of postcode sectors, with household addresses chosen randomly with multi staging technique within each of the postcode sectors. The general population *comparison* sub-sample was a smaller sample, randomly selected from within the larger general population sample; while the ethnic minority boost sub-sample was designed to elevate the numbers of participants from key ethnic minority groups, specifically from the: Indian, Pakistani, Bangladeshi, Caribbean and African communities. This approach aimed to ensure that the UKHLS had access to data from at least 1,000 households in each of these ethnic groups. To this end, the postcode sectors with the highest proportion of addresses where ethnic minorities were known to reside were identified, and these sectors were combined to generate sampling strata. Finally, households within these strata were selected through multistage random selection to ensure a similar number of participants were recruited from each ethnic group. Thereafter, the 'original' BHP sub-sample included participants who had already been enrolled in the final wave of the BHP study (in many respects, the precursor to the UKHLS), and comprised BHP participants who had agreed to participate in the UKHLS, these participants being incorporated into the UKHLS from Wave 2 of the UKHLS onwards (University of Essex. Institute for Social and Economic Research and NatCen, 2015). The use of random, complex and multi-staging sampling (a technique that covered the majority of the UK post code sectors) by the UKHLS was viewed as a distinct advantage for the analysis of latent sleep patterns in the present thesis (i.e. for use in Chapter 4), since it ensured that these analyses were likely to be broadly representative of any such sleep patterns across the UK's population as a whole. In addition, the inclusion of an ethnic minority boost sample was felt to be helpful (and important) for the analysis of sleep and pregnancy outcomes (in Chapter 5), since ethnicity is considered a clinically relevant predictor for pregnancy outcomes, and having sufficient numbers of participants from the ethnic minority populations

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[4] **Note:** The results of the analyses using UKHLS dataset (as presented in Chapter 4 of the present thesis) did *not* include a weighting variable, since the results of these analyses were found to be the same with or without the inclusion of the weighting variable. Therefore, it was decided that all subsequent analyses would be undertaken without the use of these weights, though solely to facilitate greater simplicity in the presentation and interpretation of these analyses' results.

helped to ensure that ethnicity could be included as a potential confounder in these analyses.

The second reason for choosing the UKHLS data was that the UKHLS remains one of the few large-scale surveys to have included items on sleep (and, importantly, on far more than just sleep duration alone); though the UKHLS also collected extensive additional data on the sociodemographic, economic, cultural and behavioural background and circumstances of its participants; and included adult (>16yrs) participants across all age groups and from both sexes, including women who were pregnant at the time of questionnaire completion.

The final reason for choosing the UKHLS was that the this was designed as a powerful, prospective, longitudinal study, carried out in a series of interconnected cross-sectional waves. Each wave of data collection commenced on an annual basis, and each wave lasted for 24 months, with a 12-month period of overlap between consecutive waves. Data collection for the first wave ('Wave 1') commenced in January 2009, and the last of the current rounds of completed waves used in the present thesis (Wave 6) concluded in late 2015 - the data from which being released in November 2016. Waves 1 and 4 included the complete UKHLS sleep module (each comprising items designed to collect data on 7 different, individual sleep characteristics). For this reason, data from these two waves were used to:

I. examine the nature of latent sleep patterns amongst all UKHLS participants (Chapter 4); and
II. identify pregnant women with complete sleep data, and analyse the association between sleep and pregnancy outcomes (in Chapter 5).

The longitudinal design of the UKHLS was particularly beneficial to the analyses undertaken in the present thesis, as this made it possible to examine the stability of any latent sleep patterns over time (i.e. between Waves 1 and 4), and to specify the DAGs used to inform the covariate adjustment sets used in the multivariable statistical analyses used to examine the association between sleep and pregnancy outcomes (since the longitudinal nature of data collection helped to identify the temporal sequence with which potential confounders and likely mediators had occurred/were recorded – a crucial issue in the specification of DAGs, as explained later in this chapter).

UKHLS data from modules relevant to pregnancy-related issues were also examined, including those generated from other Waves (particularly Waves 2 and 5), since these had information about *previous* pregnancies that had occurred during, or shortly after, the preceding Wave. Thus, any birth outcomes and

pregnancy-related data of any participants who were pregnant in Waves 1 or 4 were carefully traced in the datasets for Waves 2 and 5. These pregnancy-related data were then used in the UKHLS pregnancy study (i.e. Chapter 5; see Figure 2-3).

The UKHLS is primarily funded by the UK's Economic and Social Research Council, with additional support from multiple other government departments. The UKHLS is coordinated and directed by Institute for Social and Economic Research at the University of Essex with collaborators at the University of Warwick and the London School of Economics and Political Science (University of London). The experienced National Centre for Social Research (NatCen; based at City University in London) conducted the data collection field work (University of Essex. Institute for Social and Economic Research and NatCen, 2015).

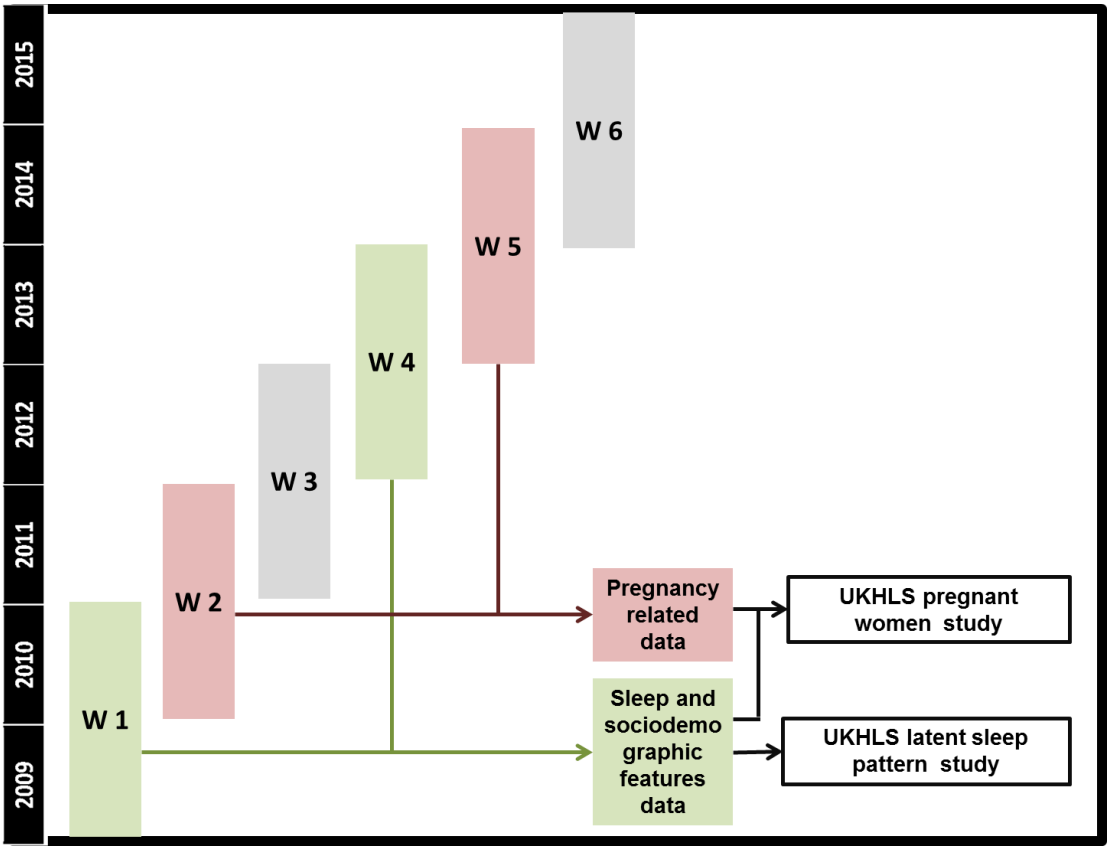

Figure 2-3 Diagram showing how data from successive Waves of the UKHLS provided data on pregnancy and sociodemographic, health, and behavioural variables for use in analysing the association between sleep and pregnancy outcomes in Chapter 5 of this thesis.

2.2.2 Scott/Ciantar study data

The Scott/Ciantar study was initiated in 2012–2015, and was designed to be conducted in Leeds on pregnant women with GDM and those identified as at increased risk of GDM. The study adopted a prospective longitudinal design, with sleep measurements made during pregnancy and with access to pregnancy outcomes data within medical records that could be examined after delivery. In contrast to the UKHLS (as described earlier), the Scott/Ciantar study generated a range of data about: sleep in pregnancy, pre-existing/pre-pregnant maternal health, and pregnancy-related characteristics, procedures and events – but it had limited data on the sociodemographic and economic background of study participants. However, the benefit of access to clinical data, extracted directly from participants' original medical records, offered a much more comprehensive assessment of participants' clinical characteristics (including a wider range of directly observed/recorded pregnancy outcomes) as well as greater understanding of data quality issues therewith (i.e. the absence, precision, accuracy and reliability of the data - information critical to a fuller assessment of the potential limitations and temporal sequence of such data).

The key source of variability within the participants recruited into this study stemmed from variability in the results of the oral glucose tolerance tests (OGTT) which were performed on all participants once they had been classified as being at increased risk of GDM. These OGTT results independently affected both the (possible) presence of unfavourable sleep events and the current (and future) presence of GDM – the latter then determining the clinical treatment provided and the subsequent risk of poor (or better) pregnancy outcomes (as described in the flow chart in Figure 2-4). It was anticipated that from every ten women at risk of GDM who had been screened (using OGTTs), at least one woman would then go on to develop the condition, and since the original sampling frame was stratified so as to include n=100 women at risk of GDM and n=100 diagnosed with GDM, it was anticipated that the final sample of participants would comprise n=90 (i.e. 100 minus 10%) without GDM, and n=110 with GDM, while all n=200 women would have (at some stage in the study) simply been classified as 'at increased risk of' GDM.

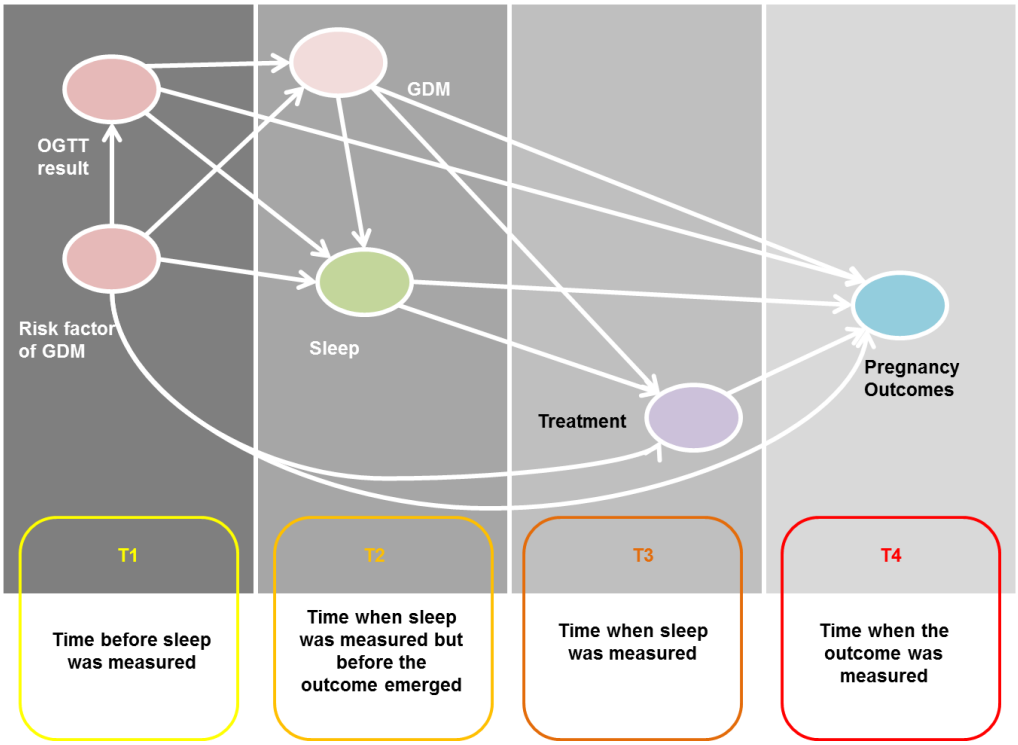

Figure 2-4: Simplified flowchart, drawn in the form on a directed acyclic graph (or 'DAG') showing the hypothesised temporal relationships between preceding risks for GDM, OGTT assessments, the development of GDM and pregnancy outcomes.

2.3 Variables selected for analysis

2.3.1 Sleep

In the present thesis, the sleep variables used comprised two separate types. The first were simply the initial measurements of each of the seven individual sleep characteristics. The second comprised a single latent categorical variable in which each of its constituent categories represented a distinct sleep pattern that had been identified using latent class analysis involving all seven of the original, individual sleep characteristics as integral constituents/components (this latent variable being generated using analyses presented in Chapter 4).

In the Scott/Ciantar study, sleep was measured using the Pittsburgh Sleep Quality Index (PSQI – a validated, self-completed psychometric instrument; Buysse et al., 1989); whilst in the UKHLS, sleep was measured using seven items in the UKHLS sleep module, each of which had been developed with direct reference to the PSQI (on which this module's items were deliberately, if somewhat broadly, based).

The PSQI contains a total of 19 items/questions and was originally designed to provide a 'global score' of sleep quality. This 'global' score consists of seven sub-scores (or 'components'), each calculated from groups of questions presented

within a common theme. These seven sub-scores are: sleep duration, sleep efficiency, sleep disturbance, sleep latency, daytime sleepiness, use of sleep-related medication and a subjective assessment of perceived sleep quality. Each of these components draws on answers to a number of questions, most of which involve multiple-choice responses that measure the weekly frequency of unfavourable sleep events per week over the preceding month, as follows: none during the past month, less than once a week, once or twice a week, and more than three times a week. Sleep duration is measured using an open-ended question with an answer format of hours and minutes (generating data that were then categorised as short, normal or long on the basis of specified criteria). Each of the PSQI's components has a total (sub)score ranging from 0 to 2, each of which is calculated using a dedicated algorithm, whereas the total ('global') score is simply the sum of each of the sub-scores. The lower each of the component's (sub)scores or the total ('global') score itself, the better the sleep; with a score of 5 being the cut-off point between good and poor PSQI-derived quality (its 'global' score; see also the Appendix; Chapter 8, Section 8.1.2, page 284).

In contrast, the items contained in the UKHLS sleep module were developed by the UKHLS research team (University of Essex. Institute for Social and Economic Research and NatCen, 2015). The module comprised seven questions which closely resembled those contained in the PSQI, each question representing an individual sleep characteristic. However, the key departure from the PSQI was that the UKHLS sleep module did not include a question on sleep efficiency; and instead included a question on coughing/snoring whilst asleep. In summary, then, the seven sleep characteristics measured by the questions in the UKHLS sleep module generated data on: sleep duration, sleep disturbance, sleep latency, coughing/snoring , daytime sleepiness, use of sleep-relevant medication, and a subjective assessment of perceived sleep quality (see Figure 2-5).

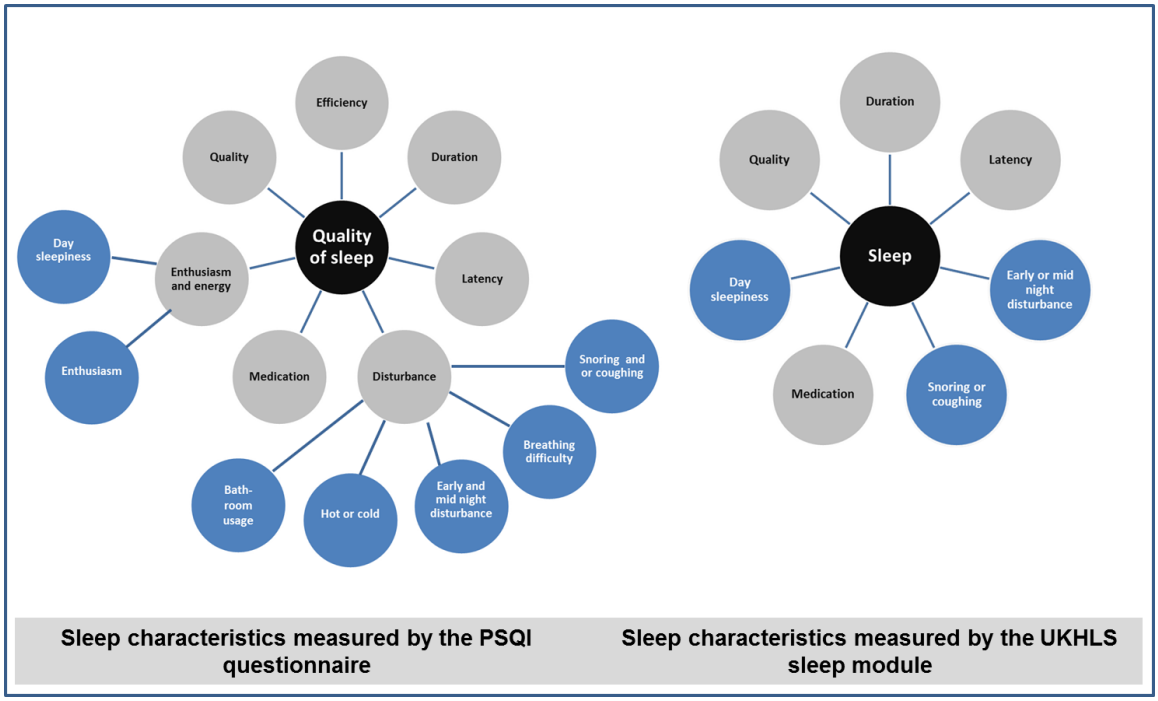

Figure 2-5 A comparison of the individual sleep characteristics measured by the PSQI and by questions contained in the UKHLS sleep module.

When the present thesis was initially envisaged, the main focus of interest was the PSQI, since this was a well-known, widely used and comprehensively validated sleep questionnaire – albeit one that is long and potentially unwieldy to use in large scale surveys. The PSQI also uses a somewhat poorly justified and conceptualised scoring system that, though widely used, remains under-examined in terms of its parametric properties and potential biases (not least in the way it considers quite different aspects of sleep to be independent and equivalent in their contribution to 'global' sleep quality). The UKHLS sleep module was therefore designed by the UKHLS research team to provide a briefer, modified version of the PSQI though, unlike the PSQI, the UKHLS sleep module questions have yet to be validated and offer no prescriptive scoring system. To address the first of these issues (i.e. the lack of validation), a detailed sub-study was performed as part of the present thesis to compare the UKHLS sleep module with the PSQI and thereby assess its validity as a shorter version of the longer PSQI. Undertaking this comparative sub-study was considered an important step because it facilitated (and justified) the desired application of sleep patterns (generated using data from the UKHLS sleep module questions in Chapter 4) to data generated using the PSQI (in Chapter 5). At the same time, the (sub)study also helped to enhance understanding of sleep as a potentially complex, latent variable, likely to be somewhat insensitive to the original source of its constituent components.

The sleep patterns identified in Chapter 4 could then be confidently applied to sleep data of pregnant participants in the Scott/Ciantar study (Chapter 6; which used the PSQI to collect these data) *and* the analysis of sleep and pregnancy outcomes amongst pregnant UKHLS participants (Chapter 5; which, like Chapter 4, had used sleep data generated using the UKHLS sleep module questions). Further details regarding the (sub)study can be found in the Appendix (Chapter 8, Section 8.1.2, page 284); where it was concluded that the UKHLS sleep module questions provide an acceptable, comprehensive screening tool for sleep that can be used as a shortened version of the PSQI (albeit without the associated component and 'global' scores) .

Based on the results of this (sub)study, it was considered defensible to use the seven individual sleep characteristics covered by the UKHLS sleep module questions to evaluate sleep in the present thesis, first on pragmatic grounds since these were all that were available within a valuable, broadly representative dataset (the UKHLS) that was readily accessible for analysis; and second (given the findings presented in Chapter 4), since these seven sleep characteristics proved sufficient to differentiate between several sleep patterns and thereby facilitate the creation of a more holistic latent sleep variable.

To this end, the seven equivalent sleep questions from the UKHLS sleep module and PSQI have been presented in Table 2-1, alongside the categorisations imposed on the answers generated by these to make these two sources of sleep data broadly comparable and ostensibly interoperable.

Table 2-1 The questions used by the UKHLS sleep module and PSQI to generate data on seven individual sleep characteristics, together with the modified response categories developed to enhance their interoperability.

The seven sleep questions	Original responses	Responses used in generating sleep clusters	Responses used in running the regression analysis
Q1: "How many hours of actual sleep did you usually get at night during the last month"? Note: This may be different than the actual number of hours you spent in bed.	*Reported in hours and minutes*	*1. Reference (≥ 6 and ≤ 9 hours)* *2. Long sleep (>9 hours)* *3. Short sleep (<6 hours)*	*1. Reference (≥ 6 and ≤ 9 hours)* *2. Long sleep (>9 hours)* *3. Short sleep (<6 hours)*
Q2: During the past month, how often have you had trouble sleeping because you "Cannot get to sleep within 30 minutes"?	*1. Not during the past month* *2. Less than once a week* *3. Once or twice a week* *4. Three or more times a week* *5. More than once most nights*	1. *Absent (1)* 2. *Less than three times a week (2,3)* 3. *Three or more times a week (4&5)*	*1. Absent (1)* *2. Present (2,3,4&5)*
Q3: During the past month, how often have you had trouble sleeping because you "Wake up in the middle of the night or early in the morning"? **7	*1. Not during the past month* *2. Less than once a week* *3. Once or twice a week* *4. Three or more times a week* *5. More than once most nights*	1. *Absent (1)* 2. *Less than three times a week (2,3)* 3. *Three or more times a week (4&5)*	*1. Absent (1)* *2. Present (2,3,4&5)*
Q4: During the past month, how often have you had trouble sleeping because you "Cough or snore loudly"?	*1. Not during the past month* *2. Less than once a week* *3. Once or twice a week* *4. Three or more times a week* *5. More than once most nights*	1. *Absent (1)* 2. *Less than three times a week (2,3)* 3. *Three or more times a week (4&5)*	*1. Absent (1)* *2. Present (2,3,4&5)*
Q5:"During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep"?	1. *Not during the past month* 2. *Less than once a week* 3. *Once or twice a week* 4. *Three or more times a week*	1. *Absent (1)* 2. *Less than three times a week (2,3)* 3. *Three or more times a week (4)*	*1. Absent (1)* *2. Present (2,3 & 4)*
Q6:"During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity"?	1. *Not during the past month* 2. *Less than once a week* 3. *Once or twice a week* 4. *Three or more times a week*	1. *Absent (1)* 2. *Less than three times a week (2,3)* 4. *Three or more times a week (4)*	*1. Absent (1)* *2. Present (2,3 & 4)*
Q7:"During the past month, how would you rate your sleep quality overall"?	1. *Very good* 2. *Fairly good* 3. *Very bad* 4. *Fairly bad*	*1. Good (1&2)* *2. Bad (3&4)*	*1. Good (1&2)* *2. Bad (3&4)*

2.3.2 Pregnancy outcomes

Any unfavourable event/condition occurring during pregnancy and/or the perinatal period which affected the mother or her baby, was considered a poor pregnancy outcome. Some such outcomes, as used by previous studies of similar events/conditions, can rely on detailed laboratory-based assessments (e.g. blood levels of maternal inflammatory factors) or specific psychological investigations (e.g. postpartum depression) – both of which were beyond the scope of this Doctoral project, and for which insufficient data were available in either the UKHLS or Scott/Ciantar study datasets. Indeed, in those UKHLS modules that were relevant to participants' pregnancies and in the Scott/Ciantar study, there were four common pregnancy outcomes: birth weight (and thereby an assessment of macrosomia and LBW), caesarean delivery (CS) and preterm delivery. The Scott/Ciantar study, based as this was on a clinical sample and with access to clinical records, there were a number of additional outcomes available, including: an assessment of postpartum blood loss (PPB), admission of the baby to the neonatal intensive care unit (NICU), and Apgar scores recorded five minutes after birth. Ideally it would have been informative to have been able to compare the outcomes of women at risk of GDM (i.e. those in the Scott/Ciantar study) with those of pregnant women from the UK population as a whole (i.e. those in the UKHLS), since this comparison would have helped to facilitate a comparison of the direction and strength of any associations observed between sleep and pregnancy outcomes amongst these two contrasting samples. However, such a comparison was limited by the fact that there were only four (of the available) pregnancy outcomes in common between the two studies' datasets, and any comparison of associations between these and sleep were further weakened by the very different covariates that were available in each (the UKHLS offering substantial detail on sociodemographic and economic circumstances; the Scott/Ciantar study having greater emphasis on the clinical history of participants therein).

2.4 Directed acyclic graph and casual pathways

2.4.1 Basic Knowledge

This thesis adopted causal path diagrams (in the form of directed acyclic graphs, or 'DAGs') as visual aids in the identification of (and subsequent multivariable adjustment for) potential confounders. Potential confounders are variables that precede, and can therefore affect, both the outcome and exposure of interest; thereby weakening ('suppressing') or strengthening ('enhancing') the apparent causal relationship between exposure and outcome (McNamee, 2003). However,

it was important to correctly identify potential confounders, to distinguish these from likely mediators, Mediators are those variables that precede and can therefore cause the outcome, but which fall after (and can therefore be affected by) the exposure – their name relating to the manner in which they can mediate the effect of the exposure on the outcome (Tu and Greenwood, 2012).

Directed a cyclic graph (DAG) is a graphical representation that summarises the causal relationships between each of the known and measured (i.e. 'manifest') and unknown/unmeasured (i.e. 'latent') variables considered relevant to the topic of interest (Tu and Greenwood, 2012). As seen in Figure 2-6, variables are represented by circles (or 'nodes') and causal pathways by unidirectional arrows (or 'arcs'; Shrier and Platt, 2008). If two variables have a causal link, the temporal sequence (i.e. the sequence when each variable occurs or 'crystalizes', as measured) guides the direction of the causal pathway involved, and ensures that only a unidirectional arrow is drawn. All of the DAG graphs presented in the present thesis were examined using the open source software DAGitty (Textor et al., 2017), which is capable of analysing such diagrams and identifying any 'minimally sufficient' sets of covariates which, if adjusted for, will address all of the known confounding represented therein. Whilst this approach to the specification of multivariable statistical modelling helps to avoid inappropriate and under-adjustment for potential confounding, it remains vulnerable to the mis-specification of DAGs (i.e. incorrectly identifying which variables are confounders and mediators) and to the absence of measurements for key known yet unmeasured and unknown and therefore unmeasured (i.e. 'latent' confounders).

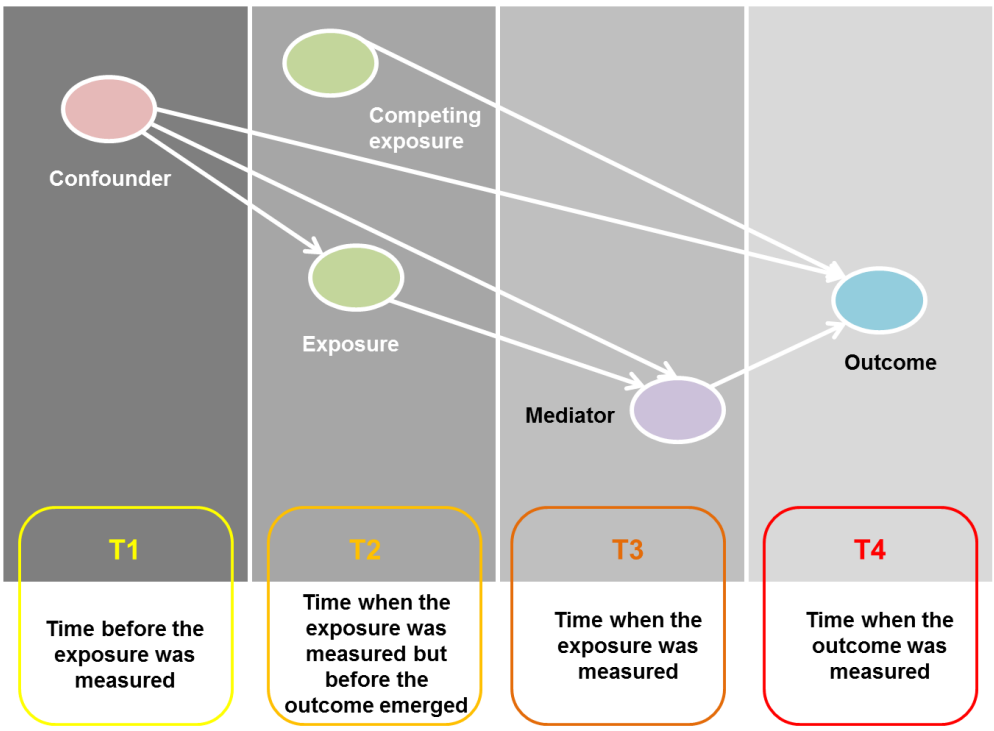

Figure 2-6 A generic directed acyclic graph drawn to illustrate the principal casual pathways between variables occurring/crystallizing at four specific time points.

2.4.2 Drawing DAGs

Once all of the relevant covariates used by the published studies reviewed in Chapter 3 had been extracted from the articles summarising the analytical models used, these variables were arranged within a directed acyclic graph (DAG), according to the temporal sequence in which the events, characteristics or processes associated with each variable had occurred/crystalised – a time point that could, in some instances, differ markedly from the time point at which they were measured (for example, height/stature is a characteristic that crystallizes shortly after puberty and remains more or less constant throughout adult life; thus regardless of when measured in adults height is a variable that is situated in early adult life). After arranging the variables in the DAG in this fashion, it was then possible to draw causal paths (unidirectional arrows or 'arcs') from preceding variables to all subsequent variables, and thereby generate a DAG from which variables acting as potential confounders (i.e. those causing both the exposure and the outcome of interest) could be easily distinguished from likely mediators (i.e. those caused by the exposure but then causing the outcome).

DAGs proved to be invaluable tools for anchoring the timing at which characteristics, processes and events occurred – the key ingredient required to decide the direction of potential causal relationships between variables available

for analysis. In the present thesis, the following considerations (regarding the timing of variables) were taken into account when drawing the many different DAGs used:

I. The likely temporal sequences of variables considered ‘events’.
II. The presence of potential (temporally) bi-directional relationship.
III. The availability of multiple measurements for individual variables (recorded at different points in time).
IV. The gestational age at which specific events occurred and/or variables were measured.

2.4.2.1 Likely temporal sequences

Temporal sequences refer to the order of ‘events’ (be these the occurrence, emergence or ‘crystallization’ of an event, process or characteristic) and their measurements in relation to time. Four suggested time points were identified during the specification of DAGs in the present thesis, each of which were considered to have an important impact in determining the likely role of the variables ‘occurring’ or ‘crystallizing’ therein (see Figure 2-6 and Figure 2-9):

T1: the time period preceding the time of sleep measurement;

T2: the time period around/within which sleep measurements were (also) made;

T3: the time period that *followed* the period in which sleep measurements were made, *but* that *preceded* the time at which pregnancy outcomes developed; and

T4: the time at which pregnancy outcomes were measured.

The temporal sequence of these ‘events’ and measurements played a crucial role in differentiating between likely mediators and potential confounders, especially when the relationship between the exposure and the covariate of interest was potentially (temporally) bidirectional; or when there were multiple readings for the covariate(s) and/or the exposure(s) concerned.

Temporal sequence was also an important consideration when dealing with pregnancy outcomes during the analyses that followed, since it was theorised that pregnancy outcomes were all *consequences* of events (i.e. the preceding event precipitating the other and mediating the effect of sleep as ‘exposure’). This meant that it was necessary to generate several analytical models, each measuring one outcome at a time – each with different sets of potential confounders and likely mediators (Figure 2-7).

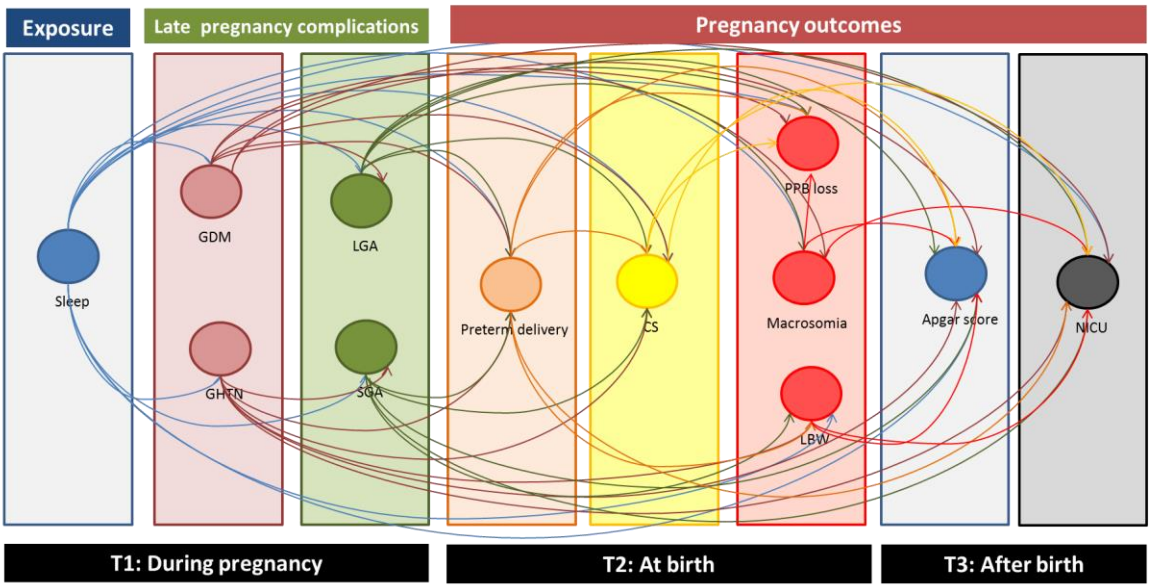

Figure 2-7 Directed cyclic graph arranged in a temporal sequence in which the possible causal relationships between sleep, pregnancy outcomes, and other measured covariates) is dependent upon where in the sequence these 'occurred' and/or 'crystallized'.

2.4.2.2 Bidirectional relationships

Within the temporal framework used to specify DAGs in the present thesis, bidirectional relationships are likely to exist whenever variables occurred (or crystallized) at exactly the same time. Although these might appear to require bidirectional arcs/arrows (something that is explicitly *not* permitted *directed* acyclic graphs), they can be operationalised within DAGs by assuming that the two (or more) variables involved are both causally linked by at least one preceding variable – such that if no such variable exists, a new (hitherto unknown) 'latent' variable can be specified acting as the common cause of the two (or more) variables concerned. An example of these sorts of 'simultaneously crystallizing' variables in the present thesis might be sleep and behavioural risks, each of which were assessed at a single point in time, and both of which seem (very) likely to have caused one another (on the basis of temporal logic and theoretical understanding of how these variables functionally relate to one another; see Figure 2-8). In the present thesis, whenever such measurements of simultaneously crystallising variables preceded the measurement of others, the former were considered likely causes of the latter. Often this approach can make it challenging to be sure which variable preceded another, particularly in datasets collected cross-sectionally (such as the data available for each wave of the UKHLS. Under these circumstances, when the time of 'occurrence' or 'crystallization' measurement was uncertain or unknown, the covariates concerned were not included in the analytical statistical models to avoid

the risk of adjusting for covariates acting as mediators and thereby generating an estimation bias – in effect, the risk of under adjustment for confounding was deemed less worrisome (given other confounders had been adjusted for) than the risk of inappropriate adjustment for mediators.

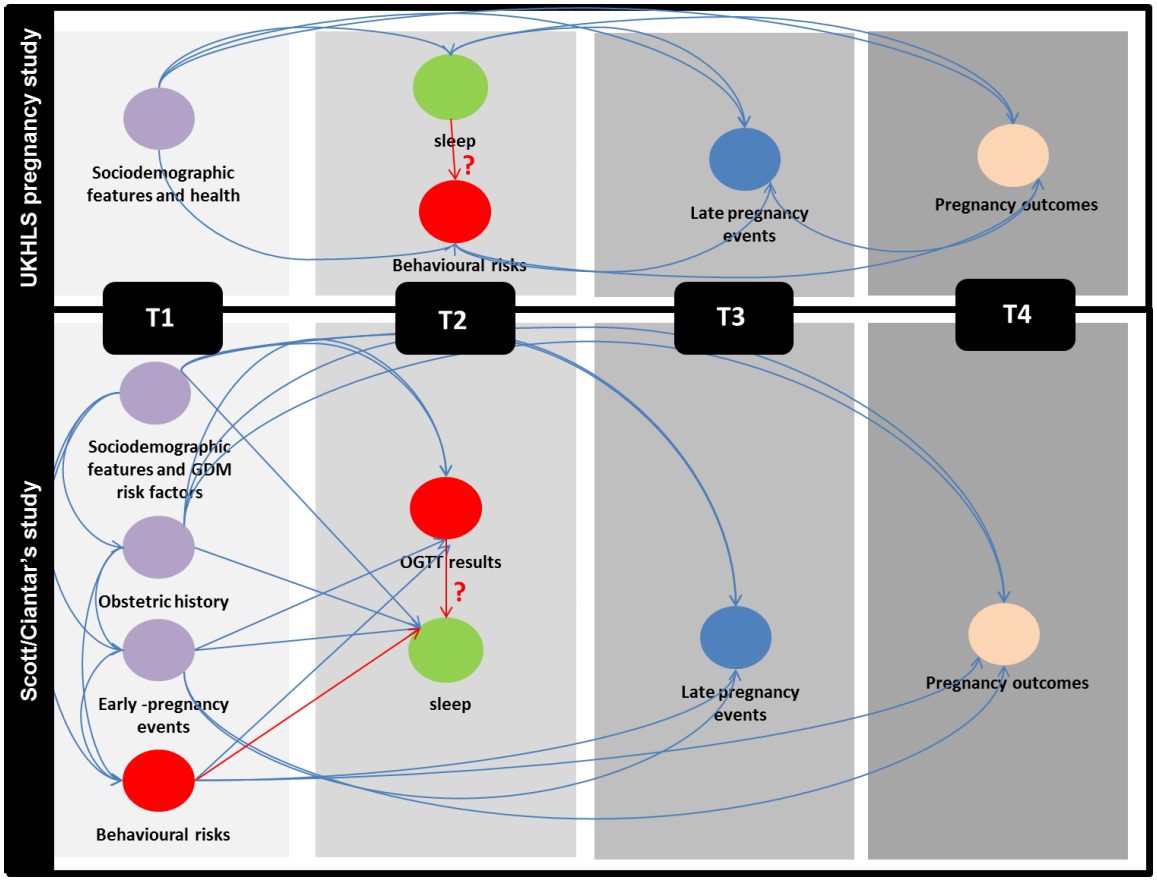

Figure 2-8 DAG displaying the hypothesised temporal sequence of variables available for use in the UKHLS (above) and Scott/Ciantar study (below) datasets.

2.4.2.3 Use of multiple readings for individual variables

For some of the variables of interest that were available in the UKHLS and Scott/Ciantar study datasets (i.e. variables relating to sleep, potential confounders, likely mediators and/or pregnancy outcomes), measures were available at more than one-time point. To address how best to use such data, the first step was to identify the time point at which sleep had been measured and the time point at which when the pregnancy outcomes occurred. Once these time points had been set, it was possible to select only those measurements of covariates acting as confounders one of whose (multiple) readings had preceded the measurement of sleep (and could therefore be safely assumed to represent a potential confounder). Meanwhile, for covariates with multiple readings that were believed to act as likely

mediators, the only consideration was whether one of the multiple measurements available might actually precede the measurement of sleep and might therefore be used as a potential confounder rather than a likely mediator. The frequency of variables with multiple readings was most common in the Scott/Ciantar study dataset, where the clinical context facilitated (and, on occasion, required) the repeated measurement of some key variables. One such variable was BMI, this being measured at the very first antennal visit, at the first diabetic clinic visit and additionally prior to delivery. In order to adjust for BMI as a confounder, the BMI measured at the first antenatal clinic would have had to have been considered as 'crystallizing' prior to the measurement of sleep, which it was – hence, in this instance, it was this measurement of BMI that was included in the covariate adjustment sets used.

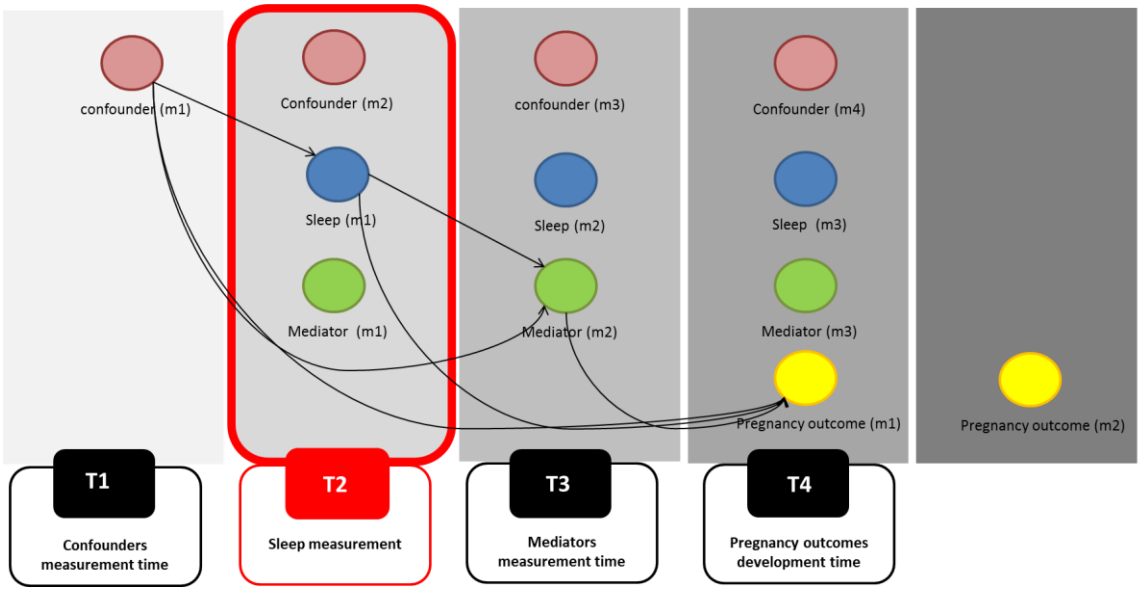

Figure 2-9 A DAG summarising the treatment of multiple readings for confounders, mediators, exposures and outcomes indicating how the temporal sequence of these measurements influences the choice of reading to include in the analytical models based thereon.

2.4.2.4 Gestational age

The gestational age at which sleep was measured had substantial importance to the analyses presented in Chapters 5 and 6 of the present thesis (Figure 2-10), not least because it determined the temporal sequences of variables before and after the sleep measurements were made, and therefore which covariates would act as a likely mediators or potential confounders. If, for example, sleep was measured in the first trimester, then the vast majority of pregnancy-related variables that

followed thereafter (e.g. GDM or PIH) could only act as mediators or outcomes. In contrast, where sleep was measured in late pregnancy, then all of the preceding pregnancy-related variables would act as potential confounders (e.g. GDM, PIH or SGA). The principal difficulty encountered (particularly with regard to specifying the DAG) was therefore where sleep was measured in the late second or early third trimester, since it was then often challenging to determine which of the pregnancy-related variables were measures of phenomena that had occurred/crystallized prior to or after the measurement of sleep. The approach adopted under these circumstances was that, whenever the precise timing of the 'late pregnancy' events were unknown in relation to the measurement of sleep, the former were assumed to act as likely mediators and were therefore excluded from the covariate adjustment sets used (a consequence of which might be that the estimates generated by these multivariable, adjusted models might have suffered from unadjusted confounding even from confounders for which measurements were available).

In the UKHLS, there were insufficient numbers of participants with data on gestational age at the point of sleep measurement, and for this reason it was unclear when the sleep of most participants had actually been measured. For this reason, it was decided that none of the variables relating to pregnancy-relevant phenomena (such as GDM) should be included in the covariate adjustment sets used (again, eliminating the risk of inappropriate mediator adjustment whilst accepting the risk of incomplete adjustment for potential confounding).

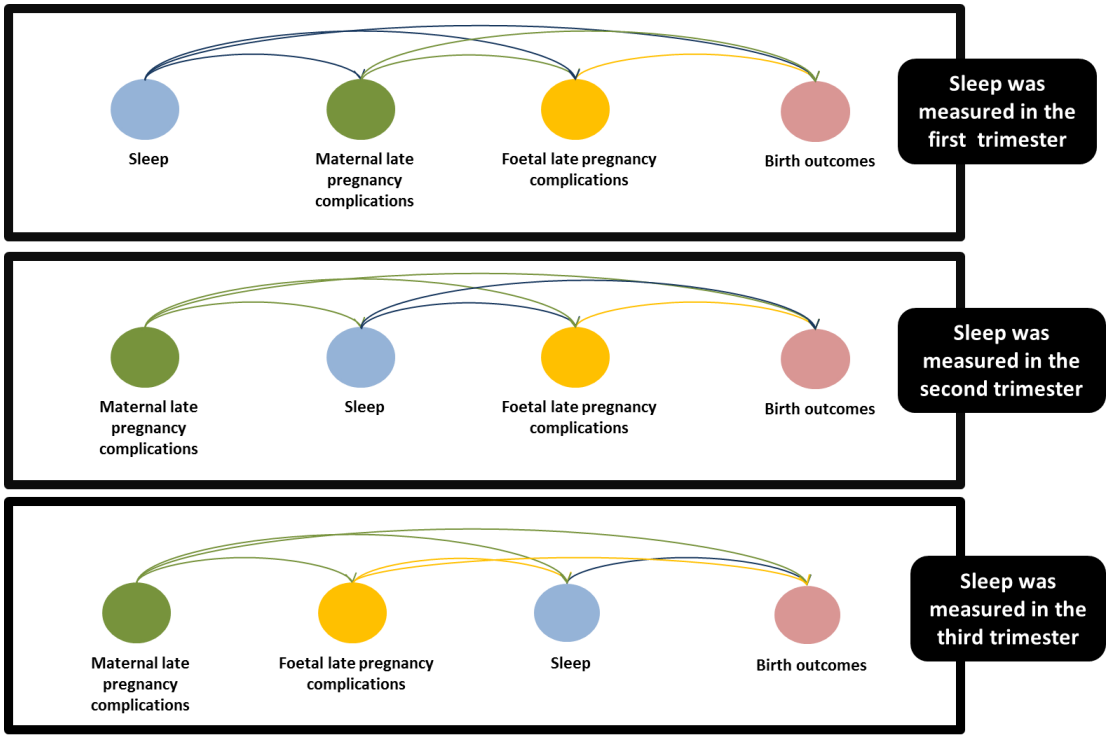

Figure 2-10 Three alternative DAGs intended to illustrate the changes in casual pathways observed amongst the study's variables where the measurement of sleep occurred in each of the three trimesters of pregnancy.

2.4.3 Application of DAGs

During the critical appraisal of primary studies identified during the systematic review and meta-analyses presented in Chapter 3 of the present thesis, each of the primary studies examined was individually assessed with regard to the choice of covariates included in any adjustment sets used. This involved compiling a complete list of all covariates that had been included in adjustment sets by any of these studies, and using these to construct a theoretical causal path diagram (in the form of a DAG) using known (or hypothesised) temporal relationships between the covariates, exposure(s) and outcome(s), from which it was then possible to identify any covariates likely to have acted as potential confounders and any that were likely to have been mediators. In addition, the very same temporal rules adopted when drawing DAGs to inform the design of statistical models used in later chapters (i.e. Chapter 5 &6) were also used to carefully consider whether inappropriate adjustment might have occurred in any of the models reported by the primary studies reviewed. This involved only including estimates derived from models adjusting for no possible mediators in the synthesis of evidence and/or meta-analyses presented in this chapter.

In the course of the two observational analytical studies (in Chapters 5 and 6; as well as in the latter part of Chapter 4) a wide range of measured (and therefore 'manifest) covariates were identified as potential confounders. However, in the UKHLS dataset, there were limited data on the health of study participants (such as pre-pregnancy BMI) or on the gestational age at questionnaire completion (i.e. when sleep, and other covariates, were actually measured). In contrast, in the Scott/Ciantar study's dataset, there were limited data on some potentially important sociodemographic characteristics (such as education and employment), though substantial data on a wide range of health and clinical factors. Both pregnancy studies nonetheless had (as already described, see Table 2-2) only modest numbers of participants and this meant it was likely that (at least from a parametric point of view) the scope for including large numbers of covariates in the adjustment sets used was likely to be limited. To address the latter concern, the covariates considered potential confounders were, wherever possible, recoded as binary variables to reduce the number of categories involved (and the number of degrees of freedom required), thereby permitting the inclusion of as many covariates (i.e. those acting as potential confounders) as possible.

2.4.4 Limitations of the 'DAG approach'

Although DAGs are considered a very useful tool when modelling multivariable systems, they nonetheless retain a number of substantive limitations, especially when the relation between the exposure and the outcome is complicated (as is the case for the relation between sleep and pregnancy outcomes; Shrier and Platt, 2008).

First of all, DAGs only permit unidirectional relationships between variables – an assumption that is difficult to justify in real life since many variables are 'time-variant' and can affect one another in a sequence that would be evident were a sequence of measurements on each to be available (Textor et al, 2011). However, this limitation was mitigated by applying the temporal sequences of *measured* events as hypothesised in terms of the likely consequences of any tendency for bidirectional relationships between two variables to move, primarily, in one direction over time.

Furthermore, DAGs cannot improve the inherent uncertainty in casual inference relating to a study's inherent design and data measurement limitations (such as selection bias or measurement error, respectively; Shrier and Platt, 2008, Greenland and Morgenstern,1999) 2001). Likewise, DAGs cannot help identifying the reference point of each included covariate that is necessary/optimal for optimally addressing any effect of that covariate on the casual relation between

exposure and outcome (for instance, whether ‘obese’ or ‘overweight’ should be the reference point against which to adjust for the effect of excessive body weight/weight gain on snoring in pregnant women; Greenland and Morgenstern, 2001). At the same time, DAGs cannot inform what conditions//circumstances are required amongst each of the covariates in order to actually elicit an effect on the casual pathway between exposure and outcome (e.g. whether, for instance, treatment for GDM is required to be taken consistently over time in order to lower blood sugar levels and, thereby, prevent poor pregnancy outcomes; Greenland and Morgenstern, 2001). For these reasons, in regard to sleep characteristics, it was decided that the presence versus the absence of each such characteristic should be chosen as the ‘cut off’ point for these variables, though it may well be that this decision will have influenced the relations that could (and were) observed in the present thesis’ analyses. However, to ensure the reference points chosen for the polytomous latent sleep variables appeared appropriate, multiple tests were run to investigate the validity of each potential reference point and their likely utility in facilitating the interpretation of the results from multivariable statistical analyses. In a similar vein, the reference points for each of the pregnancy outcomes were chosen based on their clinical importance (i.e. the need for medical intervention), potential interpretability and subsequent comparability (i.e. as evident elsewhere in the medical literature). As for the remaining covariates (i.e. those included in one or more of the ‘adjustment sets’), it was rarely possible to assess the appropriateness of alternative reference points since in the main it was necessary to consider both the distribution of events/characteristics amongst the study population and a cut-off point that was considered most likely (on the basis of prior empirical claims in the literature reviewed) to have a substantive impact on sleep, OGTT readings and pregnancy outcomes.

Above and beyond these limitations, in a more general sense it is important to acknowledge/reiterate that DAGs cannot address the issue of unmeasured (and therefore unadjusted/un adjustable) confounding (i.e. confounding due to variables that have an influence on the casual relation between exposure and outcome but could not be included in the covariate adjustment set because they were either ‘unknown’ or had not been measured; Suttorp et al., 2014). This issue was problematic during adjustment for covariates in both the UKHLS-based pregnancy study and Scott//Ciantar study. Not all hypothesised confounders were available in either of these datasets, and for this reason the adjusted multivariable models are likely to have under adjusted for important potential confounders (e.g. BMI in UKHLS and employment status in the Scott//Ciantar study).

Finally, using DAGs cannot deal with the risk of harmful (inappropriate) adjustment where sample stratification occurred prior to analysis (Suttorp et al., 2014, Greenland et al.,1999). This effect can occur when the stratification applied drew on an event/phenomenon that occurred between the time sleep was measured and the time that the pregnancy outcomes developed – such that the events/phenomena concerned either mediated the effect of sleep on pregnancy outcomes (i.e. acted as likely mediators) or were influenced by *both* sleep *and* pregnancy outcomes (i.e. acted as a 'collider'; Cole et al., 2009). In such circumstances, although the hypothesised DAG will be correct, the estimation of casual inference will be biased as a direct result of the faulty stratification (Suttorp et al., 2014, Cole et al., 2009). While, in the present thesis, stratification for adjustment was avoided, , it appeared to have been commonly used in many of the studies identified in the literature, and this is likely to limit the validity and subsequent analytical utility of the estimates produced by these studies – an issue that required careful assessment when evaluating the quality of study results over and above issues of (in)appropriate adjustment.

In summary, then, each of the following limitations cannot be addressed (or improved upon) by using DAGs, and remain a key challenge to unbiased casual inference – contributing to residual uncertainty as to whether the estimates generated are accurate/useful irrespective of DAG-assisted assessments of the appropriateness of adjustment:

I. limitations in study design and data quality;
II. ensuring the required circumstances/conditions are met by each of the covariates (to reflect their optimal effects on the casual pathway);
III. the presence of unadjusted confounding; and
IV. the faulty stratification of data.

2.5 Data analysis

2.5.1 Logistic regression analysis

Multivariable logistic regression analyses, with covariate adjustment sets informed by theoretical causal path diagrams (in the form of a DAG), specified *a priori,* was the principal statistical technique used by the two *de novo* observational analytical studies conducted for the present thesis (i.e. those analyses presented in Chapters 5 and 6). Logistic regression is a statistical technique that assesses the association between one or more independent variables and a dependent binary variable. Unlike t-tests, chi-square tests and correlation analyses, logistic regression permits the inclusion of additional variables (i.e. covariates) so that the analyses are able

to adjust for those covariates acting as confounders (Peng et al., 2002). This technique was deemed a suitable choice for the analysis of data in Chapters 5 and 6 of the present thesis since the poor pregnancy outcomes were amenable to (re)coding as either “absent” or “present.” Likewise, the presence of many potential confounders in any such analyses of the association between sleep and pregnancy outcomes necessitated careful covariate adjustment – another key issue in the choice of logistic regression as the principal analytical technique used in the present thesis.

For similar reasons, multivariable logistic regression analysis was also used in analyses of UKHLS data to assess the criterion-based validity of latent sleep patterns identified using latent class analysis (LCA, see Section 2.5.2, page 79). This involved examining the associations between a range of sociodemographic and health characteristics considered likely determinants/predictors of latent sleep patterns. However, the estimation methods used in these analyses (i.e. in Chapters 4, 5 and 6) varied somewhat depending upon the sample size available and the distribution of the exposure and outcome variables.

2.5.1.1 Estimation method

In the analysis of latent sleep patterns using UKHLS data (Chapter 4), the estimation method used for its logistic regression analyses was the maximum likelihood estimation – the standard estimation method used within logistic regression and the default estimation available within the STATA statistical analysis software used. By contrast, when analysing the association between sleep and pregnancy outcomes using data from the UKHLS and Scott/Ciantar studies (i.e. Chapters 5 and 6, respectively), the estimation method used was the penalised maximum likelihood estimation (Firth, 1993). The reason why this alternative estimation method was chosen was because of the small sample sizes available for analysis in each of these analyses, and the limited number of participants in each who had poor pregnancy outcomes.

Logistic regression analyses using the maximum likelihood estimation method is limited for small sample sizes (< 200) (Hirji et al., 1987, Firth, 1993, Mehta and Patel, 1995, King and Zeng, 2001) because it underestimates the probability of rare events (King and Zeng, 2001), leading to an inflated estimate with a larger standard error. An alternative to maximum likelihood estimation is the exact logistic regression (Hirji et al., 1987, Mehta and Patel, 1995), which works with both unbalanced and small sample sizes (< 200). However, this method has a number of additional limitations: first, the number of covariates permitted in the model is (or should be) limited, and each must be dichotomous; and second, substantial

computing power is required to generate the estimation. In the present thesis, the estimation method used was therefore exact logistic regression – chosen because the sample size available was less than n=200 and there were relatively few covariates. However, an initial trial of using this method failed due to a hardware memory shortage. Instead, the present thesis considered using a new estimation method, proposed by King and Zeng (2001) – a method that is mainly used with large sample sizes and rare events, and seems to over-correct the maximum likelihood estimation when applied to small sample sizes (such as those used in the present study). As a result, the present thesis used a method first described by Firth (1993), the penalised maximum likelihood estimation, which prevents estimation bias and works well with small sample sizes; allowing for the use of many covariates, even those that are not dichotomous; and without the need for excessive computer memory. The STATA software provides this estimation method as the 'Firthlogit' command, and this was the command used to enact this estimation method in Chapters 5 and 6 of the present thesis.

2.5.1.2 Estimated statistical power of the regression analyses

The achieved statistical power of the regression analyses included in Chapters 4, 5 and 6 of the present thesis was calculated *post hoc*, after the sample size and odds ratio-based estimates that had been achieved. As there were a range of different values for the odds ratios generated by Chapter 4-6's logistic regression analyses, the estimation of statistical power was carried out using a range of different odds ratio values (see Table 2-2). The level of alpha selected was 0.05 and the sample sizes available were n=294 for the analysis of sleep and pregnancy outcomes using UKHLS data, and n=108 using data from the Scott/Ciantar study; while the probability of a positive outcome when the exposure was present was assumed to be 0.5. Based on these criteria, in order to be able to detect a 10% change in risk with a power of 0.8, the sample size required would have had to have been ~n=3,500 – 15-30 times larger than that actually available in the analyses summarised in Chapters 5 and 6; making both sets of analyses extensively underpowered (and therefore at risk of type I and II error, and of a substantial loss of precision). The software used for these estimations was 'Gpower' (Faul et al., 2009), which was based on research undertaken by Demidenko (2006).

While these power calculations identify a sobering limitation of the analyses conducted within Chapters 5 and 6 of the present thesis, they are also important for screening the literature included in the systematic review and meta-analyses presented in Chapter 3. This is because *a priori* knowledge of the likely statistical

power required, and the sample sizes needed to achieve this, can help to reduce the possibility of type I and type II errors. However, in Chapter 3, the *post hoc* power estimation analyses conducted for each of the studies included in the review were conducted on the basis of assumptions that were similar to those applied to the two empirical datasets examined *de novo* in the present thesis.

Table 2-2 The statistical power achieved by regression analyses across a range of odds ratio values with alpha set at 0.05; focussing specifically on the final sample size available for analysis using data from the UKHLS (n=294) and the Scott/Ciantar study (n=108).[1]

	Odds ratios																
	0.3	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**	**2.00**
UKHLS (n=294)			**1.00**	**0.97**	0.78	0.45	0.18	0.16	0.34	0.55	0.74	**0.87**	**0.93**	**0.98**	**0.99**	**1.00**	
Scott/Ciantar (n=108)	**1.00**	**0.98**	**0.87**	0.66	0.42	0.23	0.11	0.11	0.18	0.28	0.39	0.50	0.60	0.70	0.76	**0.83**	**0.87**

[1] **Bold text indicates the acceptable level of power (i.e. 0.8 and above).**

2.5.1.3 Multiple testing

Multiple testing (or examining multiple hypothesis using a single data set) can be problematic since it can increase the possibility of type I error/false positive results (i.e. in this instance suggesting an association between sleep and poor pregnancy outcomes exists when, in fact, the association is absent). To address this it is considered necessary to adjust the alpha level so that this is then appropriate for the total number of tested hypotheses (Benjamini and Hochberg, 1995). To illustrate this further, at a 5% level of significance, were a single test to be conducted and the null hypothesis were true, there would be a 5% chance of falsely rejecting the null hypothesis. However, were 20 tests to be conducted simultaneously, using exactly the same data and the same level of significance there would be 64% chance of falsely rejecting one of the null hypotheses even if *all* of the null hypotheses tested were actually true (Bender and Lange, 2001). The chance of rejecting the null hypothesis as a result of a 'statistically significant' result therefore tends to increase as the number of tested hypotheses (i.e. regression models) increases. For this reason, the alpha level set should be adjusted according to the number of hypotheses tested, thereby reducing the possibility of detecting a false positive association. Such adjustments (generally labelled 'corrections') can be achieved done using a range of different techniques such as the Bonferroni method, in which the alpha level is simply dividing by the number of tested hypotheses (Bonferroni, 1936).

Multiple testing and the elevated risk of a type I error associated therewith, was actually a more problematic issue for the systematic review and meta-analyses conducted in Chapter 3 of the present thesis. This is because many authors commonly overlook the fact that they have run multiple, simultaneous tests and publish the results of these as if they were independent. In the empirical analyses undertaken for this thesis (i.e. in Chapters 4-6), the presence of multiple testing was carefully examined and, where evident, the alpha level was corrected using the Bonferroni method. Whilst this approach may be of particular interest to those analysts focusing on the statistical significance and precision of the estimates generated in these analyses, the main focus of the present thesis was on the *clinical* significance (i.e. the direction and strength) of the estimates and only secondarily on the levels of precision (i.e. statistical significance) achieved. For this reason, odds ratios with higher magnitudes (with or without narrower confident intervals) formed the principal basis for assessing the clinical significance of these analyses' findings, and such findings formed the basis upon which theoretical speculation and interpretation was then

undertaken, for the most part regardless of the statistical *p*-value these estimates attained.

For a number of related reasons, the *p*-values calculated by analyses in the present thesis were felt to be potentially misleading:

I. First, these *p*-values relate to an examination of the null hypothesis rather than a chosen alternative hypothesis, since it remains uncertain whether the alternative hypothesis chosen or another (alternative) hypothesis are likely to be be true (Goodman, 1999)
II. Second, the presence of multiple testing is likely to have elevated the risk of rejecting the null hypothesis even though the null hypothesis might actually be true (Bonferroni, 1936).
III. Third, the small sample sizes available for the *de novo* analyses are likely to have increased the risk of accepting the null hypothesis even though/when the null hypothesis might actually be false (Akobeng, 2016)

For these reasons, it was considered better (if not best) practice not to report *p*-values for the *de novo* analyses presented in the present thesis. Nonetheless, although *p*-values were not reported in these results, estimates with confidence intervals indicating these exceeded a null based on 'no effect' (i.e. at a *p*-value <0.05) were highlighted in bold text in the Tables that follow, in order to draw the attention of the reader to these while signaling that the 'significant' *p*-values concerned are at increased risk of occurring simply by chance (especially where these analyses involved multiple testing) and indicating that careful circumspection was warranted when interpreting these results. Thus, instead of reporting the precise *p*-value, and commenting on its relevance as a potential indicator of certainty (and/or precision), 95% CIs were used throughout the present thesis to offer a clearer indication of the precision achieved (even though it was expected that the level of precision achieved would, for the most part, be modest as a result of the small sample size of participants, and the impact of this on the limited power of these analyses; Akobeng, 2016, Button, 2013, Poole, 2001)

2.5.1.4 Identification and adjustment for potential confounders

The majority of confounders identified in the analyses presented in this thesis were adjusted for by including these in the covariate adjustments sets of the multivariable regression models used. This approach (adjustment) was chosen in preference to alternatives (particularly stratification) due to the small numbers of participants

available for the analysis of sleep and pregnancy outcomes (in Chapters 5 and 6), the presence of (at least some) continuous confounders, and the comparatively large number of potential confounders – since stratification, for example, would have substantially reduced the statistical power of these tests (Weinberg, 1993).

However, it was important to correctly identify potential confounders, to distinguish these from likely mediators, and not to under-adjust for any available/measured (so-called 'manifest') confounders, since inappropriate and under-adjustment can both lead to biased causal inference (Textor et al., 2017). While under-adjustment (including an insufficient number of confounders), might lead to *either* an underestimation *or* an overestimation of the causal relationship, the inclusion of more covariates in the adjustment sets used, particularly when the number of discrete observations (such as study participants) is low, can decrease the parametric stability of the statistical model used (Vittinghoff and McCulloch, 2006) or decrease its power (Textor and Li´skiewicz, 2017). In terms of the latter, some authors have suggested that a useful rule of thumb is that the number of covariates included in multivariable adjustment sets should not exceed one for every 10 to 20 observations/participants (Concato et al., 1995, Peduzzi et al., 1996, Vittinghoff and McCulloch, 2006). Yet this concern is largely secondary to correctly identifying potential confounders and including these (and *not* mediators), in the adjustment sets used (since adjusting for mediators might can cause estimation bias; VanderWeele, 2009).

Variables related to each of the exposures and outcomes were identified within the UKHLS and Scott/Ciantar studies datasets, and the choice of which were subsequently used was based on their availability, likely/actual levels of acuity/missingness, clinical expertise and empirical evidence from the literature. The variables selected in this fashion were then mapped onto a directed acyclic graph (DAG), where all of the potential causal relationships between the variables could be drawn. Using a DAG in this way was felt to be an important step, since a substantial number of potential variables were related to both the exposure (sleep) and the outcomes (pregnancy outcomes), especially in the large UKHLS dataset. However, given the limited knowledge/certainty regarding the temporal sequences of (and thereby potential causal relationships between) events/variables in the UKHLS dataset, together with the limited number of pregnant participants in both datasets, it was necessary to limit the number of variables/covariates included in the analyses' covariate adjustment sets, and include only those considered definitive confounders, and those considered likely to exert string (causal) effects on both exposure and

outcome. At the same time, wherever possible, the covariates selected as likely to be (strong) confounders were recoded as binary variables to reduce the number of categories involved (and the number of degrees of freedom required), thereby permitting the inclusion of as many covariates (i.e. those acting as potential confounders) as *parametrically* possible/plausible.

Meanwhile, it is important to point out that, in Chapter 5 and 6, different covariate adjustment sets (of confounders) were included in different multivariable un/adjusted models, including those that were; unadjusted; 'maximally-adjusted' models (i.e. with as many potentially 'important' confounders as could be included, parametrically); and models that were ostensibly 'under-adjusted' (but similar covariate adjustment sets with both datasets, to facilitate comparability). In other words, models considered 'under-adjusted' included covariates (identified as potential confounders) in their adjustment sets which were available in both the UKHLS and Scott/Ciantar datasets) – the aim being to facilitate comparison between the results of analyses on each of these two studies' datasets (which keeping in mind that the two studies had very different source populations, and very different methodological designs).

2.5.2 Latent class analysis

In addition to the multivariable logistic regression analyses used to assess the criterion-related validity of latent sleep patterns (in Chapter 4) and the association between sleep and pregnancy outcomes (in Chapters 5 and 6), the present thesis used a second advanced statistical technique - latent class analysis (LCA) – to establish whether participants in the UKHLS might be classified into groups based on common sleep patterns identified using the seven individual sleep characteristics measured by the UKHLS sleep module questions. In contrast to each of the regression analyses which included a single sleep variable (as the exposure of interest) in each model, the LCA analyses included data on all seven sleep characteristics simultaneously to identify any unobserved (i.e. 'latent') patterns, and thereby generate a more holistic assessment of sleep as a complex latent variable in which there might be (extensive) interaction between each of the individual sleep characteristics.

To identify any latent sleep patterns amongst UKHLS participants representative of the wider UK population, data on the individual sleep characteristics of both male and female participants were used. The resulting patterns observed were then applied to pregnant participants in the UKHLS (in Chapter 5) and Scott/Ciantar study (Chapter

6), amongst whom the relationship between these latent sleep patterns and each of the pregnancy outcomes were then investigated.

2.5.2.1 LCA estimation method

Latent Gold 4.5 software (Statistical Innovations Inc., 2009) was used to conduct the LCA analyses. This software calculates the posterior probability of each participant's 'membership' within each latent class, and these probabilities can then be used to assign that class to the individual concerned which achieves the highest probability (using the maximum likelihood as the key estimation method; Vermunt and Magidson, 2005).

2.5.2.2 Identifying the best-fitting latent model

At first, exploratory LCA analyses were conducted to generate models with a wide range of (sleep) clusters; after which two key information criteria (i.e. the Bayesian information criterion [BIC] and the Akaike information criterion [AIC]), together with two entropy statistics (i.e. R^2 and model estimation error), were used to compare different models with varying numbers of clusters. In each case, the lower the information criteria and the higher R^2 the more robust the model was assumed to be, after 'penalising' the statistics by the number of variables included therein (as recommended by Vermunt and Magidson, 2005). However, although these four statistical parameters were used to assist in the identification of the 'best-fitting' models, two further 'stability' sub-analyses were also conducted to verify the consistency of cluster classifications- the first over time and the second within the population examined. These stability sub-studies were important to ensure that the UKHLS sleep module data were capable of detecting/generating similar clusters that were stable over time and place (see Section 2.5.2.3).

2.5.2.3 Stability of the chosen latent class model

The two 'stability' sub-studies assessed whether similar clusters were produced using LCA applied to data collected (by the UKHLS) at different points in time or in different (sub)populations; though this assessment did not evaluate whether the participants allocated to each sleep cluster remained within these over time (i.e. what might be termed 'membership stability' rather than 'cluster classificatory' stability). Each of these 'stability' sub-studies were conducted as follows:

1) Stability within sub-samples

This first stability study compared the classification of sleep clusters between:

I. a sub-sample of participants who participated in Wave 1 only;
II. a sub-sample of participants who participated in Wave 4 only; and
III. all participants who participated either in Wave 1 and/or Wave 4.

This study assessed whether the sleep clusters that were identified among all participants (i.e. sample III) were the largest-size sleep clusters identified in the two sub-samples (i.e. samples I and II).

2) Stability of sleep clusters over time

This sub-study examined exactly the same UKHLS participants over two discrete time points (i.e. using data they provided at Wave 1 and again at Wave 4). The aim was to assess whether the same (number and classification of) sleep clusters would be generated using LCA on data from the same participants (regardless of any changes in the membership of individuals to any given sleep cluster) over time.

2.5.2.4 LCA power assessment

During the literature searches conducted in the course of the present thesis, no appropriate “rule of thumb” emerged for conducting LCA power estimation, although several authors have made related recommendations. One of these suggested that there should, ideally, be 10-15 observations per parameter, which implies that in the present thesis’ LCA analyses, at least 210 to 315 participants would be required for the 21 discrete sleep parameters assessed using the UKHLS sleep module (i.e. those that were used in generating the latent sleep models; Comrey and Lee, 1992). An alternative recommendation was that no latent class analysis should be conducted on samples smaller than 100 participants (Gorsuch,1983, Kline,1979); while a sample of 1000 participants was felt sufficient to generate ‘excellent’ analytical power (Comrey and Lee, 1992). Likewise, a sample of 200-250 was felt to afford ‘fair’ estimation power (Comrey and Lee, 1992, Cattell, 1978, Guilford, 1954). Meanwhile, on the basis of several *Monto Carlo* studies simulations, some authors suggest that a larger sample size can be required when the aim of the LCA analyses is to detect small-sized clusters or a larger number of clusters, and when larger numbers of indicators with limited variability across the sample are used (Dziak et al., 2014, Tein et al., 2013, Nylund et al., 2007). As such, all of these (somewhat eclectic) recommendations suggest that the analyses undertaken for this part of the present thesis had ample

power, since the UKHLS dataset drew on a population-based study with a very large sample size (>50,000 households) – a sample that was more than large and variable enough to ensure a sufficient level of power to estimate cluster-based classifications using LCA analysis.

2.5.3 The treatment of missing data

Prior to the exclusion of missing data, these data were examined for the "missing at random" assumption. Missing completely at random means that the missing data do not systematically differ from the observed data, since the cause of missingness is unrelated to the data (van Buuren, 2012). However, missing completely at random is extremely difficult to assess, thus a broader assumption – missing at random – was examined instead (Van Buuren, 2012, Cattle et al., 2011). The missing at random assumption means that any possible systematic difference between the missing data and the observed data could be explained by differences in the characteristics of the observed data (Van Buuren, 2012, Sterne at al., 2009). For example, missing blood pressure measurements might be lower than reported blood pressure measurements but only because women in their very early pregnancy may be more likely to have missing blood pressure measurements (Sterne at al., 2009). It was important to assess the "missing not at random" assumption, as this would bias the estimates generated by analyses in which variables and/or participants were excluded on the basis of missing data (Allison, 2002). Missing *not* at random simply means that the missing data are systematically different from the observed data for reasons that can not be explained by the observed characteristics of the data (Van Buuren, 2012, Cattle et al., 2011). For instance, participants with low socioeconomic status might avoid reporting their income because of their hidden worries (Cattle et al., 2011) or pregnant women with GHTN might not attend their antenatal care clinic because they have headache (Sterne et al., 2009).

In the present thesis, it was originally considered worthwhile using multiple imputation to deal with missing data, since multiple imputation is considered superior to all other method for treating missing data (Van Buuren, 2012, Rubin, 2004). However, rather than imputing values for missing data, the variables and/or participants with any missing data were instead simply excluded (i.e.listwise deletion) – a technique that deals with missingness but only at the risk of creating biased analytical samples, and decreasing the statistical power of the sample available for analysis. However, this approach (variable or participant deletion) may still be superior to most other imputation techniques (particularly simple ones), as it is capable of generating a

sample on which an unbiased estimate can be calculated *provided* the “missing at random” assumption can be upheld (Allison, 2002). That said, multiple imputation (a complex, multistage imputation method, recommended by many authors including Rubin, 1996), would not have biased the estimate, and would have improved the standard error of the estimate and preserved the power of the analyses (Van Buuren, 2012, Rubin, 2004). However, Sterne et al. (2009) have pointed out that a lack of experience in multiple imputation can often generate misleading results and incorrect conclusions (Sterne et al., 2009). In the event, multiple imputations could not be used to address problems with missing data in the UKHLS dataset due to computational limitations, many of which resulted from the sheer size and complexity of the UKHLS dataset (i.e. a very large dataset containing some variables with a very large number of response categories). On the other hand, the power of the analyses in the Scott/Ciantar study would have remained severely underpowered even were multiple imputation to have been applied. Likewise, the number of auxiliary variables (i.e. variables which are included in the imputation model but not in the main regression model of the analysis; Thoemmes and Rose, 2014, Little and Rubin, 2002) required to impute values for missing sleep and medical variables with sufficient certainty were severely limited by the small number of such variables with complete data (i.e. n=108) – a substantive problem given a minimum of 10 participants per variable were required for inclusion in the imputation model and given that the number of auxiliary variables included should not be more than one third of the cases with complete data (i.e. all participants excluding those with missing data, Hardt et al., 2012).

Finally, some of the variables that would have been important to include in any imputation models (particularly those required to impute missing sleep and/or pregnancy outcome data) were unavailable within either of the two datasets: in the UKHLS there was insufficient information on pregnancy-related variables (e.g. gestational age and BMI) to use as predictors in the imputation model; whilst in the Scott/Ciantar study there were insufficient sociodemographic and psychological measures to include in the imputation model for missing sleep variables. Multiple imputation would nonetheless remain an aspiration for future research in this field (see Discussion, Chapter 7), not least because most of the studies reviewed in the present thesis appeared to have avoided using multiple imputation and instead chose to delete cases with (any, relevant) missing data. That said, the best solution to the challenge of missing data is to avoid this during data collection, or by including more cases and variables so that these are available to inform subsequent multiple imputation (e.g.

larger studies with data on a greater variety of sociodemographic and medical-related variables, and with better data quality/completeness).

2.6 Conclusion

The present chapter aimed to briefly describe the rationale behind the samples, data and analytical techniques used in the analytical chapters that follow. These involved two principal, advanced statistical techniques (latent class analysis, or LCA; and multivariable logistic regression) the latter informed by recent advances in causal inference techniques (particularly the use of directed acyclic graphs, or DAGs, to identify suitable covariate adjustment sets for inclusion in multivariable statistical models). Some of these methods were used in the systematic review and meta-analyses undertaken in Chapter 3, which helped to strengthen the choice of analytical methods in the present thesis. Further detail on many of the methodological decisions made when planning and conducting the present thesis can be found in the Appendix – detail collated therein to ensure that the remainder of the thesis was clear and easy to read and assimilate.

Chapter 3 Systematic review and meta-analysis

3.1 Introduction

As described earlier, in the introductory chapter to the present thesis, there appears to be a reasonable amount of evidence of various associations across a range of sleep characteristics and pregnancy outcomes in the published scientific literature; much of this evidence suggesting that unfavourable sleep is associated with an increased risk of poor pregnancy outcomes (Ding et al., 2014). Unfavourable sleep (including shortened sleep duration and disturbed sleep) are reportedly common during pregnancy, these phenomena often being attributed to the effects of the many physiological, anatomical and psychological changes that occur during each successive trimester of pregnancy. Indeed, since there are different bio-social phenomena involved during each trimester of pregnancy these also appear to display differing frequencies of unfavourable sleep events.

Meanwhile, some poor pregnancy outcomes (such as low birth weight and preterm delivery) can be determined early in pregnancy by genetic, phenotypic or environmental factors including maternal health, height and socioeconomic position. Such factors may be resistant to clinical modification, whilst others (including sleep) might be more amenable to improvement or optimisation through educational and/or behavioural intervention. As such, the potential importance of sleep (and other, ostensibly modifiable 'lifestyle' factors) warrant careful examination; not least because of the evidence provided by previous studies which (appears, at first sight, to) indicate an association between (less favourable) sleep and (poor) pregnancy outcomes.

Sleep in pregnancy remains a relatively under-researched topic that faces many unusual challenges due to the sensitive nature of pregnancy; the rapid maternal changes and foetal development that occurs therein; the complex nature of sleep; and much that is still unknown about the biological basis (and consequences) of sleep. For this reason it might therefore be expected that research in this area is somewhat limited, particularly that adopting experimental/intervention-based study designs since these are likely to be considered high risk for mothers and their unborn child, and therefore subject to levels of ethical scrutiny, participant resistance and/or lack of compliance that make them very challenging to conduct.

In this chapter of the present thesis, a systematic review will be undertaken to summarise *and* evaluate the research evidence available of an association

between sleep and pregnancy outcomes, and thereby highlight the possible gaps (flaws and limitations) in this evidence. This is considered an important first step in the analyses presented later in the present thesis, since it aims to avoid repetition (except where replication might add novel insights or confirmation of existing findings) and avoid (m)any of the flaws and errors that may have undermined the quality of the evidence currently available.

3.2 Methods

3.2.1 Systematic review

3.2.1.1 Time scale

The systematic search undertaken for the present chapter's review and meta-analysis took place at the beginning of the period of Doctoral study, and the initial search therefore focussed on publications up until January, 2014. However, to update the results of these searches, towards the end of the period of study, the same search was undertaken to identify any articles papers that had been published between January 2014 (the date of the original search) and March 2017 (the date of the second search).

3.2.1.2 Search terms and engines

Dedicated search terms were used to identify articles that included a focus on sleep and pregnancy, by applying these terms in the EMBASE and Medline databases. These terms had been developed by NA Al Afif (a fellow doctoral student at the University of Leeds, whose thesis examined the impact of pregnancy on sleep), using terms collated from published systematic reviews that had used these to review topics in which sleep and/or pregnancy had been involved. Subsequent pilot tests using these terms found them to display high sensitivity in detecting references to sleep in articles examining pregnancy or pregnancy-related issues (Al Afif, 2016). To maintain the highest possible level of sensitivity, terms within each group (i.e. with those synonyms for 'sleep' and for 'pregnancy') were linked with "or", while the two groups were then linked with "and".

Group one: sleep-related terms

Central sleep apnea, sleep apnea, apnea, obstructive sleep apnea, obstructive sleep, sleep-related breathing, insomnia, sleep*, sleep time, sleep duration, sleep hours, time in bed, sleep quality, sleep disorder, sleep disorders, sleep disordered, time spent asleep, time spent sleeping, time asleep, sleep length, dysomnia, parasomnia, hypersomnia, sleep disturbance, sleeplessness, sleep efficiency,

sleep latency, sleep problem, sleep disturbance, sleep difficulties, nightmare, sleep deprivation, and sleep terror

Group two: terms related to pregnancy outcomes (obstetric, perinatal, and neonatal)

Pregnancy, pregnan*, pregnant women, pregnancy complication, pregnancy trimester, obstetric complication, maternal, obstetric, maternal age, maternal complication, pregnancy outcome, pregnancy in adolescence, pregnancy rate, maternity care, paternal, antenatal, gestational outcome, and gestation.

3.2.1.3 Search inclusion criteria and screening strategies

Using the options available in each of the databases searched, the search was limited to include only the following types of studies;

I. human studies
II. female studies
III. adult studies.

In a later step, the titles, abstracts, and full texts of the resulted studies were screened manually; those whose content did not match the topic (sleep in pregnancy) or the limits intended (as at I, II and III, above) were excluded using each of the following exclusion criteria:

I. animal studies
II. studies irrelevant to sleep
III. studies relevant to sleep but not related to pregnancy
IV. studies relevant to sleep in pregnancy that did not examine the relationship between sleep and pregnancy outcomes
V. non-primary studies such as meta-analyses, reviews, opinion/consensus documents/pieces, and non-quantitative studies

Screening was performed twice by two independent reviewers: the candidate (AA Alghamdi) and a Doctoral colleague (NA Al Afif. The screening results of each reviewer were compared, and any disagreements were discussed and resolved.

3.2.2 Data extraction method

After reading the full text of each article screened for inclusion in the review, five sets of Tables were created.

The first table summarises pertinent general information about each article, including the author, year of publication, relevant study inclusion and exclusion criteria, the study setting, and any reported characteristics of the population studied.

The second table summarises information about the exposure examined, including its timing, the measurement tools used, the definition thereof and/or reference point used, and any available descriptive statistics.

The third table adopts a similar structure to the second table, but focusses on the pregnancy outcomes examined rather than the sleep exposures of interest.

The fourth table contains information about any covariates measured in each of the studies reviewed, including similar details to those contained in the second and third tables.

The fifth table includes details of any regression models used by each of the studies, including the exposure and outcome used, any covariate adjustment sets used, a narrative regarding any justification given for the adjustment set(s) used, and the results of these analyses expressed as logistic odds ratios (OR) with 95% confidence intervals in parentheses.

At this stage of data extraction, any articles that had not used multivariable regression models to analyse their data were excluded from the review – the principal rationale for this was simply that in the absence of any adjustment for potential confounding the results of these studies' analyses are likely to have suffered from confounding bias.

A directed acyclic graph (DAG) was drawn for each article to represent the temporal sequence and potential causal relationships between each of the measured covariates, and the exposure and outcome of interest. These, separate, DAGs were then combined into a single DAG summarising the theoretical causal relationships between all of the covariates (exposures and outcomes) measured across all of the studies included. Variables for which each studies' analyses were judged to have adjusted included not only those included in the covariate adjustment sets of any multivariable statistical models, but also any variable for which the study was restricted during sampling or stratified during analysis.

3.2.3 Quality assessment of the studies

Each of the articles that included at least one regression model were assessed for the quality of the models used. The focus of these quality assessments were the analytical validity of the published results and the absence/presence of any potential biases, rather than the overall quality of the published articles. Biases were considered deviations from the true value of the estimate, arising as a result of flaws in study design or analysis, so that the resulting estimate(s) would be greater or smaller than their actual, true value (Attia, 2005).

What follows comprises a summary of the key aspects that were examined during quality assessments. Further detail on these issues are provided in the extended Appendix (Chapter 8, Section 8.2.1, page 304).

First, each outcome and/or exposure of interest was carefully examined to establish whether this had been the study's main outcome or exposure. If these were assessed as being the main outcome/exposure, then the study's design was examined to identify its type (i.e. longitudinal versus case-control or cross-sectional). If the outcome or exposure had not been considered during the development of the study's design and when the intended/achieved sample size was known (and had, instead, been published only once the statistical significance of any results was known), then each such study was carefully examined for each of the following: the possible presence of selection bias or unadjusted confounders; the prevalence of the exposure and the outcome (i.e. rare events; King and Zeng, 2001); the presence of potential type II errors (as evident from the power of the test; Freiman et al., 1978); and the correction of alpha values to account for any multiple testing (type I error; Cronbach, 1951, Bonferroni, 1936). As no power and/or sample size calculation was reported in most of the observational primary studies included in this review, the assessment of power for each of the primary studies included was done *post hoc* (i.e. following the same approach as those conducted for this thesis' empirical, *de novo* primary studies – as discussed in the Methodology Chapter under Section 2.5.1.2). The level of power that was considered acceptable was 0.8 although that meant that there was still a 20% chance of type II errors.

Second, the measurement tool used to record sleep was examined for the possibility of measurement error, and to ensure it was clear when these measurements had occurred (i.e., the gestational age when sleep was measured). In addition, the precise manner in which sleep characteristics, pregnancy outcomes, and any study covariates had been defined and measured were carefully considered with regard to any reference point used and related diagnostic criteria chosen.

Studies were then carefully evaluated for the presence of confounding bias. To this end, any covariate adjustment sets used in the regression models were evaluated with regard to the choice of covariates included therein (i.e. whether these would have been classified as potential confounders or likely mediators in the DAG developed specifically for this purpose [see Chapter 2, Section 2.4, page 60]). In addition, the inclusion and exclusion characteristics of the included participants were evaluated, since stratifying or restricting study samples based on one or more

characteristics might have also achieved ‘adjustment’, while also affecting the generalisability (i.e. the external validity) of their results (Bossuyt et al., 2003).

3.2.4 Meta-analysis

3.2.4.1 Pooled estimates

The logistic odds ratios (OR) and 95% confidence intervals (CI) of estimates generated by regression models examining the association between sleep and pregnancy outcomes were pooled to calculate composite, summary estimates. Due to a huge variety of differently measured (and defined) pregnancy outcomes and sleep-related exposures, several small meta-analyses were performed rather than a single large meta-analysis, since the latter would have suffered from extensive heterogeneity simply on the basis of the exposures and outcomes used (making any such meta-analysis extraordinarily difficult to interpret).

Meta-analysis was conducted if the number of pooled logistic ORs with a matching outcome and exposure was three or more. When there were fewer than three, the pooled results were reported without any further analysis, since when using a fixed-effect model, the resulting summary effect is unlikely to be generalisable to other populations, since the characteristics of the studies included therein are inevitably very limited.

Each of the meta-analyses undertaken used only those estimates from logistic regression models in which the covariates included in the adjustment sets performed similar causal roles within the hypothesised, combined DAG. As such there were models in which:

i. no covariates were included in any adjustment sets (i.e. un-adjusted models);
ii. *only* adjusted for covariates acting as potential confounders were included in the adjustment sets used (i.e. appropriately adjusted models); and
iii. that adjusted for any covariates acting as likely mediators (i.e. inappropriately adjusted models).

3.2.4.2 Analytical tests

The Mantel-Haenszel (M-H) test (the default test used by the STATA software employed in the present thesis; Statistical Innovations Inc., 2009), was chosen as the estimation test used. It has a number of advantages over alternatives (such as the inverse-variance test) since it is more robust to meta-analyses with smaller numbers of studies and those with comparatively rare outcomes.

A random-effects meta-analytical model was chosen as the initial analytical method used, since there was a prior assumption of considerable heterogeneity amongst the studies reviewed, given these had examined different populations of pregnant women studied by different authors in different countries and different healthcare and non-healthcare settings. However, whenever the heterogeneity statistics were statistically non-significant (i.e. when I^2 was 0% and the *p*-value was >0.05); a fixed-effect model was used, since no benefit would then be gained from using a random effects model (Borenstein et al., 2009, Glasziou et al., 2004). A forest plot, which offers a visual summary of the pooled study estimates and their summary/combined estimate, was then used to examine the results of each of the meta-analyses conducted in this review.

Finally, to test for heterogeneity, I-square ($\boldsymbol{I^2}$) and chi-square ($\boldsymbol{X^2}$) tests were used. $\boldsymbol{I^2}$ measures the variance between studies and uses the same units as the summary effect, making it easy to interpret (Glasziou et al., 2004). $\boldsymbol{X^2}$ was estimated by running a random-effect model to test if there was a significant difference between the random- and fixed-effects models. Tests of heterogeneity, in general, can suffer from weak power; and for this reason investigating sources of heterogeneity can be very important in meta-analyses (Glasziou et al., 2004). Statistical heterogeneity (i.e. a high $\boldsymbol{I^2}$ value and a significant $\boldsymbol{X^2}$) can occur secondarily to each of the following: study design, specific characteristics of the study population, inclusion and exclusion criteria used when sampling participants, the definitions of exposures and outcomes of interest, the measurements tools used, the gestational age when sleep was measured, and definition of follow-up period (Monroe, 2007). Additionally, statistical heterogeneity may also occur as a result of the limited number of model estimates available for inclusion in a given meta-analysis (Thompson, 1994)

3.3 Results

3.3.1 Number of articles examined

The total number of articles found in the first search (conducted in January 2014) was n=10,875, of which most were excluded after reading the title, leaving n=319. After then scanning the abstracts and/or full texts of these articles, only 71 remained at the data extraction stage – all of which had studied the association between sleep and pregnancy outcomes. However, only 27 articles were included in the systematic review and/or meta-analyses, as only these contained at least one regression model that had examined the association between sleep and pregnancy outcomes (Figure 3-1)

The second search (conducted in March 2017) found n=1,412 additional articles, of which only 167 were retained after screening their titles; while, after reading their abstracts, only 29 references were retained from which only 7 references went on to be included in the systematic review (see Figure 3-1). Figure 3-2 and Figure 3-3 summarise the number of articles included based on the topic of the published articles therein.

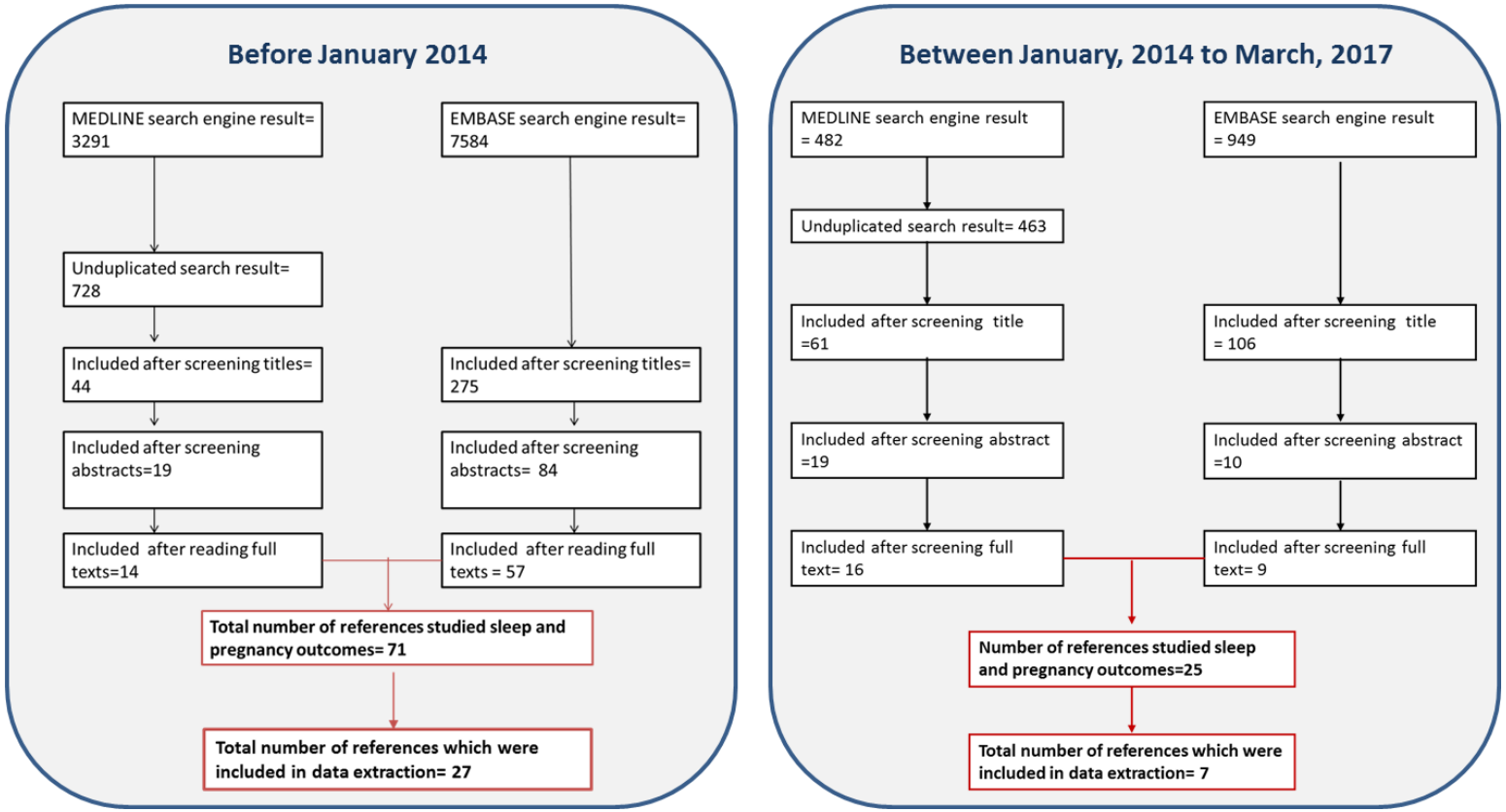

Figure 3-1 Flow chart summarising the number of articles identified and retained at each stage of the searching and screening process.

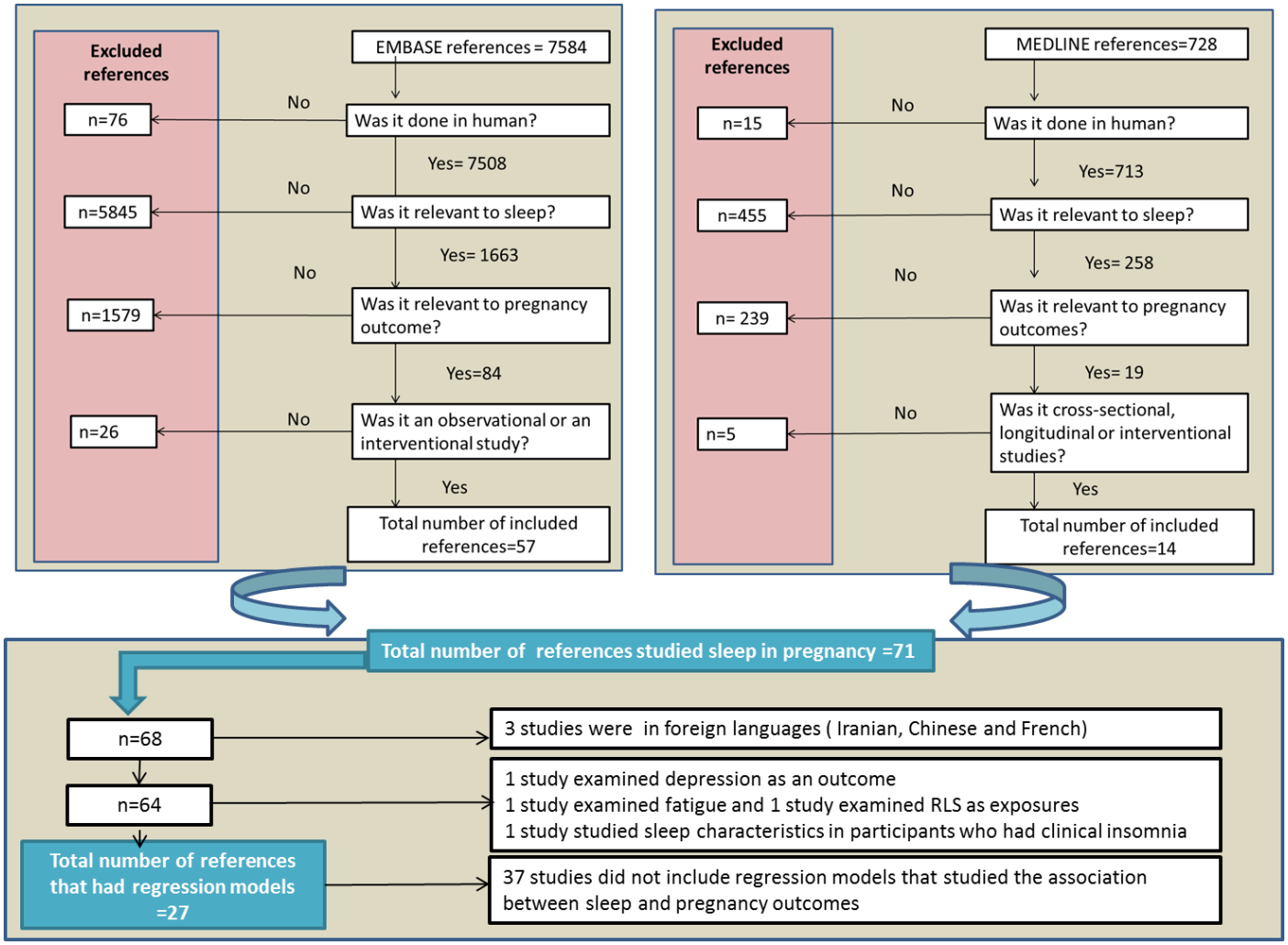

Figure 3-2 Flow chart summarising the number of articles included and excluded from the first search (conducted in January, 2014), based on the topic of the published articles.

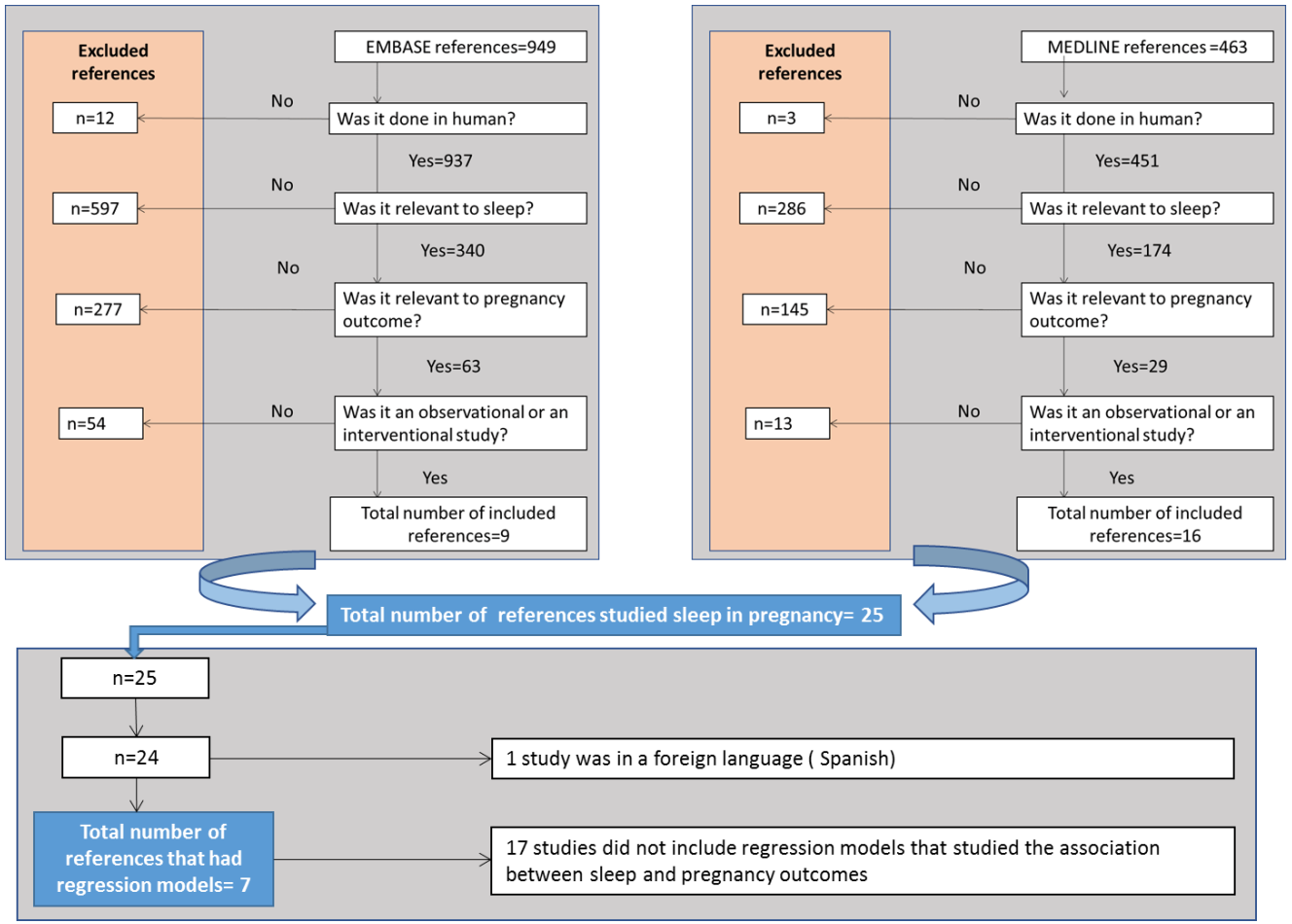

Figure 3-3 Flow chart summarising the number of articles included and excluded from the second search (conducted in March, 2017) based on the topic of the published articles

3.3.1.1 Study settings and sample sizes

Most of the studies described in the articles included in this review had been conducted in outpatient antenatal clinics (n = 17), the remainder taking place in hospital wards (n = 10), national registries (n = 6), and antepartum educational sessions (n = 1). Approximately 55.88% (n = 19) of the studies included were conducted in one setting, 11.76% (n = 4) in two settings, and 14.71% (n =5) in three or more settings; while the remainder 17.65% (n = 6) were those using data from national registries. The sample sizes of these studies ranged from n=45 to n=12,506 participants, with an average sample size of n=359 (SD=869) participants and a total of n=21,911 participants overall. Based on our *post hoc* power assessments, the sample size of the majority of studies was insufficient to achieve an acceptable level of power (as defined at 0.8).

3.3.1.2 Participant characteristics

A complete summary of the key characteristics of each of the studies included in the systematic review and meta-analyses is presented in Table 3-2.

3.3.1.2.1 Sociodemographic features

The average age of the women examined in these studies was 29.6 years (SD = 5.2, range = 18–47). Their average BMI (at booking) was 27.9 kg/m^2 (SD = 5.5, range = 21–46).

3.3.1.2.2 Inclusion and exclusion criteria

Multiple pregnancy was the most common exclusion criterion, and 52.94% (n=18) of the studies explicitly included only singleton pregnancies. The second most common exclusion criterion was previous or current obstetric complication(s), and 47.06% (n = 16) of the studies included only women with a current and/or previous pregnancy considered healthy (Table 3-1).

Table 3-1 Summary of the commonest inclusion and exclusion criteria for studies included in the systematic review.

Common excluded criteria	(Total number =34)	%
Multiparous	2	5.88
Multiple pregnancy	18	52.94
Neonatal death and/or severe neonatal complications	9	26.47
Current or previous obstetric complications	16	47.06
Maternal history of chronic disease	13	38.24
Psychiatric disease or medication	4	11.76
Sleep disorders, travelling across time zones and /or shift work	5	14.71
Obese [pre-pregnancy BMI >30 kg/m^2]	3	8.82
Behavioural risks (smoking, caffeine, drug, alcohol)	4	11.76
Can't speak and/or write in English	8	23.53

Table 3-2 Summary of key characteristics for each of the studies included in the systematic review and the meta-analysis.

References	Location	Sample size	Setting	Population of interest	Inclusion criteria	Exclusion criteria
Retrospective longitudinal studies (n=8)						
(Bourjeily et al., 2010)	USA	1000	Delivery ward	Women in the 48 hours postpartum period	1. English speakers 2. With or without bed-partner	1. Women with a neonatal death
(Bourjeily et al., 2013)	USA	1000	University hospital delivery ward	Women in the 48 hours postpartum period	English speakers	1. Women who cannot speak English 2. Women with neonatal death
(Franklin et al., 2000)	Sweden	502	University hospital OB/GYN ward	Not reported	Singleton pregnancy	1. Caesarean delivery 2. Women with a neonatal death
(Louis et al., 2010)	USA	Women with OSA =57 Women without OSA =114 Total=171	The Urban tertiary care center Prenatal ward	Women diagnosed with and without OSA who delivered in the urban tertiary care center	Obese (pregnancy BMI $\geq$ 30 kg/m^2) or normal weight (pregnancy BMI between18 and 24 kg/m^2)	1. No PSG confirmation of OSA 2. Multiple gestation
(Owusu et al., 2013)	Ghana	234	Korle Bu University Hospital postpartum ward	Women in the 48 hours post-partum period	Women delivered after the 28 week of gestation	Not reported
(Perez-Chada et al., 2007)	Argentina	456	Hospital 'Donacio n f Santojanni' Obstetric ward	Pregnant women who came for delivery	Singleton pregnancy	Not reported
(Reid et al., 2011)	Canada	219	Royal university hospital fetal assessment and ante partum ward	Pregnant women with PIH with or without protein urea compared with healthy singleton pregnant women in similar gestational age	Singleton pregnancy	1. Multiple pregnancy 2. Sever underlying maternal or fetal complications 3. Poorly controlled HTN 4. Diabetes 5. Premature delivery
Chen et al., 2012)	Taiwan	**Total**=4786 Women with OSA=791 Women without OSA=3995	National health insurance database	Women diagnosed as OSA by PSG twice and women never diagnosed with OSA	Singleton pregnancy	Not reported

References	Location	Sample size	Setting	Population of interest	Inclusion criteria	Exclusion criteria
Case control studies (n=6)						
(Champagne et al., 2009)	Canada	**Total**=50 **Cases**=17 **Control**=33	**Cases:** antenatal admission ward in a tertiary hospital **Control:** antenatal clinics, ultrasound clinics, antenatal word	**Cases**: pregnant women with gestational hypertension **Controls**: pregnant women without gestational hypertension	**Controls:** 1. ≥20 week of gestation or a prior month history of delivery 2. Singleton pregnancy	1. Women with pre-gravid hypertension 2. Treated obstructive sleep apnea 3. Neuromuscular disease 4. Previous stroke 5. Women lived >30 Km from the center 6. Women Lacking English communication 7. Unstable (intensive care admission or foetal loss)
(Gordon et al., 2015)	Sydnee	**Total=**295 Cases=103 Controls=192	**Cases and controls:** maternity hospitals in metropolitan Sydney (9 hospitals)	**Cases:** Pregnant women with GA greater than or equal to 32 weeks **Control**: matched with cases for booking hospital and GA	**Cases:** 1. Singleton 2. Still birth was in or after the 32 weeks of gestation **Controls:** 1. Singleton 2. In the 32 weeks of gestation or greater	**Cases and controls**; 1. Multiple gestation 2. Fetal with chromosomal abnormalities or fatal pre-diagnosed condition 3. Terminated pregnancies 4. Women identified as Aboriginal or Torres Strait Islander,
(Kajeepeta et al., 2014)	Peru	**Total=959** Cases=479 Controls=480	**Cases and controls:** Hospital Nacional Dos de Mayo, the Instituto Nacional Materno Perinatal de Lima, and The Hospital Edgardo Rebagliati Martins	**Cases:** women with spontaneous preterm delivery **Controls:** women with full term delivery	**Cases:** 1. Singleton pregnancies 2. spontaneous births <,37 weeks (22–36 weeks). Controls: **Controls**: singleton term (≥37 weeks of gestation) selected from the same hospital of delivery.	**Cases:** 1. Medically indicated premature births
(Reutrakul et al., 2013)	USA	**Total**=45 **Cases**=15	**Cases:** University of Chicago obstetric clinic	**Cases**: pregnant women with GD	Singleton pregnancy	1. Multiple pregnancy

References	Location	Sample size	Setting	Population of interest	Inclusion criteria	Exclusion criteria
		Controls=30	**Controls:** Advertisement via fliers distributed in university of Chicago medical center	**Controls**: non-diabetic pregnant women with normal blood glucose level		2. Pre-existing chronic diseases (DM, sleep disorders, neurological disorders, psychiatric disorders, sever pulmonary, cardiac or renal diseases) 3. Usage of (steroid, medication which may affect sleep or glucose metabolisms, significant alcohol ≥ 7 drinks/wk, caffeine consumption ≥ 400 mg/d, smoking, durgs) 4. Shift work 5. Recent travel over time zone
(Stacey et al., 2011)	New Zealand	**Total**=467 **Cases**=155 **Controls**=312	**Cases:** all maternity units in Auckland region **Controls:** pregnancy registration list from regions where the still birth happened	**Cases:** pregnant women Women with a history of still birth **controls:** healthy pregnant women	Not reported	1. Still birth due to congenital anomalies 2. Multiple pregnancy
(Samaraweera and Abeysena, 2010)	Sri Lanka	**Cases**=230 **Controls**=504 **Total**=734	**Cases**: gynecological ward in De Soysa Maternity Hospital in Sri Lanka **Controls**: antenatal clinics in De Soysa Maternity Hospital in Sri Lanka	**Cases**: mothers with a confirmed miscarriage **Controls**: healthy pregnant ladies in the > 28 weeks of gestation	1. Confirmed partial or complete miscarriage 2. < 28 weeks of gestation	1. Thyroid disease 2. Major psychiatric disease **3.** HTN
Prospective longitudinal studies (n=15)						
(Abeysena et al., 2009)	Sri Lanka	690	2 primary health care antenatal clinic in Sri Lanka district	Not reported	Not reported	1. Women with GDM or PIH 2. Twin pregnancy
(Abeysena et al., 2010)	Sri Lanka	885	2 primary health care antenatal clinic in the Sri Lanka district	Not reported	Not reported	1. Pre-existing DM 2. Pre-existing HTN 3. Epilepsy 4. Psychiatric diseases

References	Location	Sample size	Setting	Population of interest	Inclusion criteria	Exclusion criteria
(Facco et al., 2010)	USA	189	Outpatient clinic in Northwestern Memorial Hospital affiliated practices.	Not reported	1. Nulliparous 2. Singleton pregnancy	1. chronic hypertension 2. Heart disease 3. Chronic lung disease 4. Chronic renal disease 5. Autoimmune disease
(Herring et al., 2014)	USA	63	Five university outpatient antenatal clinics	Urban and low-income pregnant women	1. < 16 weeks' gestation 2. Fluency in English or 3. Spanish 4. Currently lives in Philadelphia	Not reported
(Howe et al., 2015)	New Zealand	633	Data from Maternal Sleep and Health Study in New Zeland	Women in the third trimester of pregnancy (35–37 weeks)	1. Single term 2. Third trimester	Preterm birth
(Ko et al., 2013)	Korea	276	Obstetric outpatient clinics in 2 private hospitals and 3 secondary located hospitals in Soul and its surrounding area	Pregnant women aged 20-45 years	Not reported	Not reported
(Lee and Gay, 2004)	USA	131	Child birth educational classes	Not reported	1. First pregnancy 2. Read and write English	1. Diagnosed sleep disorder 2. Work the night shift 3. Previous involuntary pregnancy lost
Louis et al., 2012)	USA	175	General health and high risk clinics	Obese pregnant women (Pre-pregnancy BMI ≥ 30 kg/m^2)	Pre-pregnancy BMI was ≥ 30 kg/m^2	1. Miscarriage 2. Language barrier 3. Usage of narcotic drugs 4. Usage of any medication that may affect sleep **5.** Non- attendance to three antenatal visits
(Na-rungsri et al., 2016)	Thailand	1345	Five prenatal care clinics affiliated with Maharat Nakhon Ratchasima Hospital, which is a large tertiary hospital	Pregnant women in the second trimester	1. Singleton pregnancy 2. Started antenatal care before 20 weeks. 3. Had intention to keep the pregnancy to term	1. Had asthma 2. Had chronic renal disease 3. Had chronic hypertension 4. Had miscarriages 5. lost on follow-up

References	Location	Sample size	Setting	Population of interest	Inclusion criteria	Exclusion criteria
					and to deliver at the study hospitals were recruited	
(O'Brien et al., 2012)	USA	1719	University of Michigan prenatal clinics	Pregnant women who are in the>28 week	≥ 28 week of gestation Single foetus	Not reported
(O'Brien et al., 2013)	USA	1673	Large tertiary medical center	Pregnant women who were in the third trimester	Not reported	Not reported
(Okun et al., 2011)	USA	166	University medical center	Pregnant women in the first trimester	1. Singleton pregnancy 2. Non-smoker 3. Do not use any substance or medication 4. Do not have any medical condition that may interfere with their neuro-endocrine regularity 5. English speakers	Not reported
(Qiu et al., 2010)	USA	1290	Prenatal medical care clinic at Swedish medical center in Seattle	Healthy Pregnant ladies	1. Started their antenatal care before the 20th week of gestation 2. English speaker 3. Planning to complete her pregnancy period	1. GDM before the study 2. Pregnancy loss
(Reutrakul et al., 2011)	USA	169	(Chicago)	Adult pregnant women in the 2nd trimester	Not reported	1. Previous history of GDM 2. Sever diseases (pulmonary, renal, cardiac) 3. Current neurological disorders 4. Current psychiatric disorders 5. Recent travel over the time zone 6. Shift work 7. Usage of (steroid, drugs, smoking, significant alcohol or caffeine consumptions)

References	Location	Sample size	Setting	Population of interest	Inclusion criteria	Exclusion criteria
						8. Medication that may affect glucose level)
(Sharma et al., 2016)	India	273	All India Institute of Medical Sciences (AIIMS) which is a tertiary-level referral center	Pregnant women in the first trimester attending AIIMS OPD	1. Singleton 2. Aged 20 to 40 years 3. First trimester	4. Trophoblastic disease 5. Multifetal gestation 6. Lost to follow-up 7. Had abortions 8. With incomplete data about perinatal outcomes
(Strange et al., 2009)	USA	220	Antenatal clinics in 15 obstetrical practices	20-29 weeks	1. 20- 29 week of gestation 2. 20-40 years old 3. Reading and understanding English	1. History of drug abuse 2. History of alcohol abuse 3. History of a diagnosed sleep disorder 4. History of a psychiatric disorder 5. History of an acute illness 6. History of a chronic illness
(Stinson and Lee, 2003)	359	USA	Antenatal care clinics located in 4 military hospitals	Pregnant military women	Singleton gestation	1. History of previous preterm labor or un intentional miscarriage 2. History of previous obstetric complications 3. History of chronic illness 4. History of recently treated vaginal or urinary tract infection 5. Diagnosed as being in a preterm labor
(Ugur et al., 2012)	Turkey	465	In-patient obstetric ward or delivery ward in seven hospitals in seven distinct regions (Ankara, Istanbul, Sanliurfa, Erzurum, Rize, Gaziantep)	admitted pregnant women for follow or labor	Not reported	Not reported
(Wang et al., 2017)	China	12 506	antenatal care system of the urban districts of Tianjin	Pregnant women attended antenatal care in Tianjin	-	1. Women who did not take GCT 2. Women with a positive GCT but did not take OGTT

References	Location	Sample size	Setting	Population of interest	Inclusion criteria	Exclusion criteria
						3. 3. Women with missing sleepinformation
(Williams et al., 2010)	Sweden	1272	Prenatal medical care clinics at Swedish medical center in Seattle	Healthy pregnant women	1. Started their antenatal care before the 20th week of gestation 2. English speaker 3. Planning to complete her pregnancy period	1. GDM before the study 2. Pregnancy loss

3.3.2 Measured variables

3.3.2.1 Sleep characteristics

3.3.2.1.1 Sleep disordered breathing (SDB)

The most commonly studied sleep characteristic was SDB, a characteristic studied in 22 of the studies reviewed. Snoring and OSA were the two key SDBs covered therein. Snoring, which was studied in 14 studies, was assessed subjectively using questionnaires; whilst obstructive sleep apnoea (OSA), which was studied also in 14 studies, was measured either objectively using polysomnography (PSG) or subjectively using a dedicated OSA-relevant questionnaire.

Various aspects of snoring were considered when studying the relationship between these and pregnancy outcomes. These included: the onset of snoring (before vs. during pregnancy), the frequency of snoring, and the presence or absence of snoring. The effect of chronic snoring (defined as snoring before 28 weeks of pregnancy) was studied in comparison to 'pregnancy-induced' snoring (i.e. snoring after 28 weeks of gestation). In four such studies, the authors suggested that chronic snoring might be expected to lead to a greater risk of poor pregnancy outcomes than pregnancy-induced snoring.

The effect of habitual snoring (i.e. snoring that occurred ≥ 3 times per week) was studied in comparison to non-habitual snoring (< 3 times per week) in no fewer than 12 studies. The authors of these studies postulated that the effect of snoring on pregnancy outcomes is likely to become clinically significant once snoring becomes an 'habitual' sleep behaviour – others suggesting that regardless of the frequency of snoring or its time of onset, the mere presence of snoring could influences pregnancy outcomes (n= 3). These authors suggested that participants might over- or underestimate the frequency of their snoring, especially the latter if they did not have a sleeping partner complaining about their snoring. A participant's awareness of their own snoring is therefore likely to be the key indicator of underlying SDB that achieves a certain (i.e. a noticeable/reportable) degree of severity.

In a similar vein, obstructive sleep apnoea was considered a severe and advanced-stage form of SDB when compared to snoring which, in contrast, was considered merely an indicator of underlying SDB (and *not necessarily* a severe presentation or form thereof). Indeed, not all of these studies examined the effect of both snoring and OSA; some concentrated on one and some on the other. Those studies that examined OSA primarily concentrated on the presence of OSA rather than its frequency, as it was suggested that (regardless the frequency of apnoeic attacks)

the mere presence of apnoea was likely to be sufficient to cause poor pregnancy outcomes.

Table 3-3 and Table 3-4 summarise the definitions of SDB used by the studies included in the present review, together with some summary descriptive statistics of the study participants therein.

Table 3-3 Summary of snoring-related characteristics operationalised as exposures by the studies examined in the review.

Reference	Gestational age	Measurement	Onset of snoring	Reference range	Descriptive statistics
Retrospective longitudinal design					
(Bourjeily et al., 2010)	Third trimester	***Questionnaire (MAPI);*** "In the last 3 months of your pregnancy, how often have you experienced (or were you told) about the following symptoms" "snoring loudly"	Not specified	Never or rarely (less than once a week) **[*reference*]** Sometimes (1–2 times a week). Frequently (3–4 times a week) or always (5–7 Times a week).	Total participants = 1000 Never\ rarely =483(51%) Sometimes=133(14%) Frequently\ always=333(35%)
(Franklin et al., 2000)	Third trimester	***Bespoke questionnaire***	Not specified	Non-habitual (often, or always) **[*reference*]** Habitual (never, seldom, sometimes)	Total participants=502 Habitual snoring in the last week of pregnancy 23% Occasional snoring during the last week of pregnancy 25%
(Owusu et al., 2013)	Third trimester	***Bespoke questionnaire*** "Do you snore loudly?" regardless if it was witnessed or self-noticed	Not specified	Absent **[*reference*]** Present	Snoring presented in 54 out of 216 (24.0%)
(Perez-Chada et al., 2007)	Not specified	***Bespoke questionnaire*** How much have you snored during your pregnancy?	Not specified	Non-habitual (Never, seldom or sometimes) **[*reference*]** Habitual (often or almost always)	156 out of 456 participants reported habitual snoring (35%).
Prospective longitudinal design					
(Howe et al., 2015)	Not specified	***GSDS questionnaire***	Chronic snoring vs. pregnancy induced snoring	Non-habitual (<3 times/week) **[*reference*]** Habitual snoring (3-4 times /week)	Total participants=633 Number of snorers= 151(23.85%) Number of women started snoring during pregnancy = 104(68.87%) Number of women started snoring before pregnancy = 50(33.11%)
(O'Brien et al., 2012)	Chronic snoring; before the 3rd trimester Pregnancy induced snoring; snoring induced in the third trimester	***Pregnancy sleep questionnaire***	Chronic snoring vs. pregnancy induced snoring	Non-habitual (<3 times/week) **[*reference*]** Habitual snoring (3-4 times /week)	Total participants=1712 Snoring rate was =34.1% 25% started snoring during pregnancy 9% reported chronic snoring
(Qiu et al., 2010)	Not specified	***Bespoke questionnaire*** "Since becoming pregnant, when you are asleep, to the	Not specified	Non-snorer (some of the time, a little of the time or none of the time)	89 women out of 1290 pregnant women (6.90%) reported snoring in pregnancy

Reference	Gestational age	Measurement	Onset of snoring	Reference range	Descriptive statistics
		best of your knowledge, have you snored?"		Snorer (all of the time or most of the time)	
(Reutrakul et al., 2011)	2nd trimester	***Berlin Questionnaire***	Not specified	Non-frequent snorer (< 3 times a week) **[*reference*]** Frequent snorer (≥3-4 times a week)	41 out of 169 participants (25%) were identified as frequent snorers
(Sharma et al., 2016)	Not specified	***Berlin Questionnaire***	Not specified	Negative **[*reference*]** Once per week Twice per week Three or more tines per week	Total participants= 273 Number of snorers = 53 (19.41%) Number of women snored once per week=15 (28.30%) Number of women snored twice per week=20 (37.74%) Number of women snored three times per week or more=18 (33.96%)
(Facco et al.,2010)	2nd trimester	***Bespoke questionnaire***	Not specified	Non-frequent snorer: < 3 times a week **[*reference*]** Frequent snorer (≥3 times a week)	Total participants=189 Frequent snoring in early pregnancy=11% (21) Frequent snoring in late pregnancy=16% (31) P<0.03
O'Brien et al., 2013b)	Chronic snoring; before the 3rd trimester Pregnancy induced snoring; snoring induced in the third trimester	***Bespoke questionnaire***	Chronic vs. acute	Non-habitual (<3 times/week) **[*reference*]** Habitual snoring (3-4 times a week)	117 out of 362 pregnant women (32%) reported snoring
(O'Brien et al., 2013a)	Third trimester	***Bespoke questionnaire***	Chronic vs. acute	Non-habitual (<3 times/week) **[*reference*]** Habitual snoring (≥3 times /week)	Total participants= 1673 Pregnant women reported snoring= 35%. Women who were non-snorers at both pre-pregnancy and in the 3rd trimester = 65%. Women started snoring during pregnancy= 26% Women reported chronic snoring before and during pregnancy= 9%
Case control studies					
(Gordon et al., 2015)	Third trimester	***Berlin Questionnaire***	Not specified	Not specified	Total participants= 295 Total snorers= 138 (46.78%) Snorers women with still birth = 51 of 103 (49%),

Reference	Gestational age	Measurement	Onset of snoring	Reference range	Descriptive statistics
					Snorer women with viable birth= 87 of 192 (45%)
(Stacey et al., 2011)	Not specified	Not specified	Not specified	Not specified	Number of snorer women who had still birth= 69/155 (45%) Number of snorer women who had live birth= 130/310 (42%)

Table 3-4 Summary of OSA-related characteristics operationalised as exposures by the studies examined in the review.

Reference	Gestational age	Measurement	Type of apnoea	Reference range	Descriptive statistics
Retrospective longitudinal studies					
(Bourjeily et al., 2010)	Third trimester	***Questionnaire (MAPI);*** "In the last 3 months of your pregnancy, how often have you experienced (or were you told) about the following symptoms" "stopped breathing"	Self-reported	Never or rarely (less than once a week) **[*reference*]** Sometimes (1–2 times a week). Frequently (3–4 times a week) or always (5–7 Times a week).	50 participants out of 362 (13.8%) had OSA
(Perez-Chada et al., 2007)	Not specified	***Bespoke questionnaire*** Did your partner notice sleep apnoea during your pregnancy?	witnessed apnea	Presence of apnoea Absence of apnoea **[*reference*]**	15 out of 447 pregnant women (3.4%) reported witnessed apnoea
(Reid et al., 2011	Third trimester	Full- night polysomnography in sleep laboratory	Measured sleep apnea	Absence of apnoea (respiratory disturbing index(RDI)< 5 events per hour) **[*reference*]** Presence of apnoea (RDI ≥ 5 events per hour)	Mean RDI in women with PIH=11.5 (SD=11.2) Mean RDI in women without PIH= 2.3 (SD=3.1) p<0.0002
(Louis et al., 2010)	Not specified	PSG	Measured sleep apnea	Absence of apnoea (apnoea hypopnea index (AHI) < 5%) **[*reference*]** Presence of apnoea ((AHI)≥ 5%)	Total participants=171 Women without OSA = 114 Women with OSA = 57 Diagnosis of OSA amongst women with OSA: Before pregnancy=33 (58%) During pregnancy= 24 (42%)
(Ugur et al., 2012)	Not specified	Berlin questionnaire	Risk of OSA	Not reported	69 women out of 465 women had positive risk of OSA (14.4%)
Case control studies					
(Champagne et al., 2009)	>20 weeks	Unattended over one night PSG Done at home or hospital	Pregnancy induced apnea Measured sleep apnea	Absence of apnoea (apnoea hypopnea index (AHI) < 15%) **[*reference*]** Presence of apnoea (AHI)≥ 15%	Total participants=50 The rate of OSA was 14 out of 17 (82%) among the hypertensive pregnant women compared with 15 out of 33 (45%) among the normotensive pregnant women.
(Gordon et al., 2015)	≥32 weeks	Berlin Questionnaire	Subjective OSA	Not defined	Total participants = Total number of women with apnea symptoms=34 13 out of 192 women with no still birth had OSA symptoms (11%) 21 out of 103 women with still birth had OSA symptoms (12%)

Reference	Gestational age	Measurement	Type of apnoea	Reference range	Descriptive statistics
(Reutrakul et al., 2013)	Late second to early third trimester	PSG over night	Measured OSA	Absence of apnoea (apnoea hypopnea index (AHI) < 5%) **[*reference*]** Presence of apnoea ((AHI)≥ 5%)	Total participants=45 15 out of 30 women had OSA (50%) 11 from the 15 GDM women (73%) were diagnosed with OSA, 4 from the 15 pregnant without GDM (27%) were diagnosed with OSA P<0.01
Prospective longitudinal studies					
(Chen et al., 2012)	Not specified	Polysomnography	Measured OSA	Absence of apnoea **[*reference*]** Presence of apnoea	Total participants=4786 Women without OSA= 3955 Women with OSA =791
(Ko et al., 2013)	Not specified	Berlin Questionnaire	Self-reported OSA	Absence of apnoea risk **[*reference*]** Presence of apnoea risk	Total participants=276 Total prevelence of OSA = 32.6% Prevelence of OSA in non- obese women = 43.6% Prevelence of OSA in obese women= 28.3% P=0.001
(Louis et al., 2012)	Not specified	In home portable PSG overnight	Measured OSA	Absence of apnoea (apnoea hypopnea index (AHI) < 5%) **[*reference*]** Presence of apnoea ((AHI)≥ 5%)	AHI median=12.9 events/hour Total participants=175 OSA rate=15.4% CI 95%= 10.4–21.6%
(Na-rungsri et al., 2016)	2nd trimester	Berlin Questionnaire	Subjective OSA	Not reported	Rate of women with high risk OSA =10.1% (n = 136)
(Reutrakul et al., 2011)	2nd trimester	Berlin Questionnaire	Subjective OSA	Not reported	29% 48/169 women had an increased risk of SDB
(O'Brien et al., 2013)	Third trimester	***Bespoke questionnaire*** "had stopped breathing/gasped for air at night."	Subjective OSA	Absence of apnoea (never) **[*reference*]** Presence of apnoea (often, usually, always, almost always)	Total participants=1673 Total women had either stopped breathing or air gasping= 3.1%

3.3.2.1.2 Sleep duration

Sleep duration was the second most-commonly studied sleep characteristic, and was examined in 10 of the studies reviewed.

'Normal' sleep duration was defined using a range of different cut-off points by the authors of different studies (Table 3-5). In general, the range of the 'normal' sleep duration considered suitable as a reference value was between 6 and 10 hours, as measured at different gestational ages of pregnancy, and primarily using subjective questionnaires – except in the studies by Lee and Gay (2004) and Herring et al (2014) in which wrist-worn actigraphs were used.

3.3.2.1.3 Sleep quality

Sleep quality was examined by a total of 6 studies, all of which used subjective measurement tools. Sleep quality was either assessed by using a single question or measured by the frequency of unfavourable sleep phenomena. For example, two studies measured sleep quality using the Pittsburgh Sleep Quality Index (PSQI), which defined sleep quality based on seven sleep characteristics: duration, efficiency, latency, disturbance, daytime dysfunction, usage of medication, and subjective sleep quality (Okun et al., 2011, Reutrakul et al., 2011). Three studies used the general sleep disturbance scale (GSDS), designed to measure the level of sleep disturbance by concentrating on how frequently respondents had difficulty of falling sleep, the duration of sleep latency, the frequency of waking in the middle of the night, the frequency of waking early in the morning, the use of sleep-related medication, and the subjective assessment of sleep quality (Sharma et al., 2016; O'Brien et al., 2013, Stinson and Lee, 2003) – i.e. in a very similar fashion to the PSQI. Finally, two studies used a bespoke question to assess the subjective quality of sleep without measuring any of the other sleep characteristics' contributions to 'quality' (Wang et al., 2017, Lee and Gay, 2004; Table 3-6).

3.3.2.1.4 Sleep disturbance

Two studies included in the systematic search examined the association between sleep disturbance and pregnancy outcomes (Table 3-7). Sleep disturbance was measured subjectively in the first (by Stacey et al. 2011), in which it was defined as fragmented sleep secondary to toilet use during the night. The second, by Lee and Gay (2004), examined sleep disturbance using an wrist-worn actigraph and defined disturbance as a wakeup time after sleep onset (WASO) that exceeded 15% of the total sleep time (Table 3-7).

3.3.2.1.5 Excessive daytime sleepiness

Three studies examined the association between daytime sleepiness and pregnancy outcomes (Table 3-8). Daytime sleepiness was measured using the Epworth sleepiness scale (ESS) in two studies (Bourjeily et al., 2013, Reutrakul et al., 2011), though these studies used different reference points to define excessive daytime sleepiness (Table 3-8). The third study, by Stacey et al. (2011) measured daytime sleepiness using a bespoke questionnaire, but did not define the reference point they used to characterise excessive daytime sleepiness (Table 3-8).

3.3.2.1.6 Sleep position

Three studies examined the association between sleep position and pregnancy outcomes (

Table 3-9). Stacey et al. (2011) used the left-side sleep position as the referent for lower risk, while Owusu et al. (2013) and Gordon et al. (2015) examined the risk of the supine position against all other positions (

Table 3-9).

Table 3-5 Summary of sleep duration-related characteristics operationalised as exposures by studies examined in the review.

Reference	Measurement tool	Trimesters	Sleep deprivation (hours/night)	Short sleep (hours/night)	Normal sleep (hours/night)	Long sleep (hours/night)	Descriptive results
Case control studies							
(Kajeepeta et al., 2014)	"During the first 6 months of your pregnancy, how many hours per night did you sleep?"	The first 6 months of pregnancy		<6	7-8	>9	Short sleep duration rate= 22.3% among preterm cases and 16.5% among term controls long duration rate= 18.4% among preterm cases and 15.8% in terms controls.
(Stacey et al., 2011)	"the usual duration of sleep at night during the last month"	After second trimester	-	< 6	6-8	> 8	-
(Reutrakul et al., 2011)	PSQI	Not specified		<7	-	-	-
(Samaraweera and Abeysena, 2010)	"the total hours of sleep per day"	Not specified	-		< 8	≥ 8	-
Prospective longitudinal studies							
(Abeysena et al., 2009)	Physical activity questionnaire	Not specified	-	≤8	-	-	-
(Abeysena et al., 2010)	Physical activity questionnaire	Not specified	-	≤8	> 8	-	-
(Facco et al., 2010)	"During the past month, how many hours of actual sleep did you get at night?"	Not specified	-	< 7	-	-	-
(Howe et al., 2015)	Bespoke questionnaire	Third trimester	-	≤6	7-8	≥9	-
(Herring et al., 2014)	Actigraph watch	2nd trimester	-	-	-	-	Mean sleep duration=6h 09 min (SD = 09 min)
(Lee and Gay, 2004)	Actigraph watch	Third trimester	< 6	< 7	7-8	> 8	Mean sleep duration= 7h10min (SD = 1h10min).

Reference	Measurement tool	Trimesters	Sleep deprivation (hours/night)	Short sleep (hours/night)	Normal sleep (hours/night)	Long sleep (hours/night)	Descriptive results
(Qiu et al., 2010)	"Since becoming pregnant, how many hours per night do you sleep?"	First trimester	≤ 4	5-8	9	≥ 10	
(Wang et al., 2017)	“How many hours of sleep did you get every day during the index pregnancy, including both day and night time?”	Not specified	-	<7	7-8	≥9	The median sleep duration was 9 h.
(Williams et al., 2010)	“Since becoming pregnant, how many hours per night do you sleep?”	First trimester	< 6	5-6	9	≥ 10	

Table 3-6 Summary of sleep quality-related characteristics operationalised as exposures by studies examined in the review.

	Gestational age	Sleep quality measurement tool	Used question	Reference point	Measured component of sleep quality	Descriptive statistics
Prospective longitudinal studies						
(Howe et al., 2015)	Third trimester	GSDS	Global score	Good sleep quality=global score <3	Duration, latency, disturbance, day sleepiness, medication, subjective quality	86.6% (n=380) of mother identifies as Māori (N=194) had poor quality 86.1% (n=167) of mother identifies as non-Māori (N=439) had poor quality
			Single question	Non-problematic quality <3 nights per week	Subjective quality	82.9% (n=364) of mother identifies as Māori (N=194) had poor quality 84% (n=163) of mother identifies as non-Māori (N=439) had poor quality
(Lee and Gay, 2004)	Third trimester	A bespoke question	The question formula was not mentioned	was not defined	subjective sleep quality assessment	Not reported
(Okun et al., 2011)	Third trimester	PSQI	Global score	Good quality sleep= global score ≤5	Duration, efficiency, latency, disturbance, day-dysfunction, medication, subjective quality	**Mean PSQ according to trimesters** In women with preterm delivery 1st =7.8(SD=4.9) 2nd=6.2(SD=4.0) 3rd=7.8(SD=4.1) In women with term delivery 1st=5.0(SD=2.7) 2nd=5.0(SD=2.6) 3rd=5.3(SD=2.7) P<0.03
(Reutrakul et al., 2011)	Second trimester	PSQI	Global score	Good quality sleep= global score ≤5	Duration, efficiency, latency, disturbance, day dysfunction, medication, subjective quality	64% of 169 women had poor sleep quality Mean PSQI = 7.4 ± 4.0
(Stinson and Lee, 2003)	Second trimester	GSDS	Global score	Good sleep quality=global score <3	Duration, latency, disturbance, day sleepiness, medication, subjective quality	**Mean GSDS** In women with preterm delivery 43.7(SD=16.5)

	Gestational age	Sleep quality measurement tool	Used question	Reference point	Measured component of sleep quality	Descriptive statistics
Prospective longitudinal studies						
						In women with term delivery 49.8(SD=15.5
(Wang et al., 2017)	Not specified	'How did you feel about your sleep quality during the index pregnancy: good, moderate or poor?'	Good Moderate Poor	Good	Subjective quality	37.9% of women reported good quality, 59.9% of women reported moderate quality 2.2% of women reported poor quality

Table 3-7 Summary of sleep disturbance-related characteristics operationalised as exposures by the studies examined in the review.

	Gestational age	measurement tool	Reference point	Measured component of sleep	Descriptive results
Case control studies					
(Stacey et al., 2011)	Third trimester	A bespoke question	Not defined	"Frequency of getting up to the toilet" over the last month"	Not mentioned
Prospective longitudinal studies					
(Lee and Gay, 2004)	Third trimester	Actigraph watch	WASO ≥ 15%	WASO	Women with WASO≥ 15%=41 (31.30%)

Table 3-8 Summary of daytime sleepiness-related characteristics operationalised as exposures by the studies examined in the review.

	Gestational age	measurement tool	Reference point	Descriptive results
Retrospective longitudinal studies				
(Bourjeily et al., 2013)	Not specified	ESS	Excessive day time sleepiness >10	Total participants= 1000 **ESS mean score** (p< 0.0001) Women with snoring= 6.6 Women without snoring = 7.9 **ESS > 10** (p<0.0002). 25.5 % of women had snoring, (n=329) 15.3 % of women did not have snoring (n=610)
Case control studies				
(Stacey et al., 2011)	Third trimester	Bespoke questionnaire	Not defined	Total participants=467 78 of women with still birth (n=155) reported regular day sleepiness whilst 116 women from the 310 women who did not had still birth reported regular day sleepiness p<0.006
Prospective longitudinal studies				
(Reutrakul et al., 2011)	Second trimester	ESS	Normal score ≤8	41% of 169 women had excessive day time sleepiness

Table 3-9 Summary of sleep position-related characteristics operationalised as exposures by the studies examined in the review.

Reference	Gestational age	Measurement tool	Reference sleep position	High risk sleep position	Descriptive results
Retrospective longitudinal studies					
(Owusu et al., 2013)	Not specified	***Bespoke questionnaire*** While pregnant, what is your most common sleep position?	Not defined	Supine position	21 out of 216 (9.7%) reported supine sleep position
Case control studies					
(Stacey et al., 2011)	Last night of pregnancy	***Bespoke questionnaire***	Left side	All others positions	From the 287 pregnant women 61% (n=174) women slept on their left side, 46% (n=133) on their right side and 10% (n=30) on their back.
(Gordon et al., 2015)	≥ 32 weeks	***Bespoke questionnaire***	Not defined	Supine position	Supine position rate was 9.71% (10 of 103) in women with still birth 2.08% (4 of 192) in women viable birth

3.3.2.2 Measured birth outcomes

3.3.2.2.1 Neonatal pregnancy outcomes

Foetal growth was studied by studies included in the review using two different though related concepts: small for gestational age (SGA) being examined in six studies and low birth weight (LBW) in four. Newborn health and well-being were measured in three studies using Apgar scores and by admission to the neonatal intensive care unit (NICU) in two.

SGA was defined by Franklin et al. (2000) as a birth weight below 2 standard deviations of the median value in the Sweden infant weight reference charts; whilst it was defined by Howe et al. (2015), Ko et al. (2013), Bourjeily et al. (2010) and Abeysena et al. (2009) as simply a birth weight <10th percentile after adjusting for foetal sex and gestational age at birth. O'Brien et al. (2013) further scaled the birth weight to maternal height, weight, ethnic origin, and parity (essentially adjusting birth weight by each of these preceding maternal covariates). Low birth weight (LBW) was examined by the studies authored by Sharma et al. (2016), Owusu et al. (2013), Chen et al. (2012) and Abeysena et al. (2010). In all of these studies LBW was defined as a birth weight below 2500g as measured immediately after birth without adjusting for gestational age at birth or the sex of the newborn. The Apgar scores used were those measured immediately after birth (Bourjeily et al., 2010) and those measured 5 minutes thereafter (Sharma et al., 2016, Chen et al., 2012, Bourjeily et al., 2010). These two measurements were studied in relation to sleep using a value of ≥7 as the reference cut-off score.
NICU admission was reported regardless of the reason for admission or the length of stay, though only in two of the studies reviewed (Reutrakul et al., 2011, Louis et al., 2010).

Finally, fatal foetal outcomes were assessed using reports of miscarriage and stillbirth; miscarriage being defined by Samaraweera and Abeysena (2010) as partial or full expulsion of the foetus during the first 28 weeks of gestation.

Gordon et al. (2015), Owusu et al. (2013) and Stacey et al. (2011) examined the association between stillbirth and several unfavourable sleep events. Stacey et al. (2011) defined stillbirth as the birth of a baby that had died in utero during the antenatal or intrapartum periods during/or after 28 weeks gestation, and did not suffer from congenital anomalies. In contrast, Gordon et al. (2015) included only those neonatal deaths that occurred during/or after 32 weeks gestation.

Since stillbirth and miscarriage are both extremely traumatic to mothers, a few of the studies explicitly excluded women with histories of these phenomena (Champagne et al., 2009).

3.3.2.2.2 Maternal pregnancy outcomes

The following maternal pregnancy outcomes were examined in relation to sleep by studies included in the review: gestational diabetes (GDM), pregnancy-induced hypertension (PIH), pre-eclampsia (PE), preterm delivery, and caesarean delivery (Table 3-10 and Table 3-11).

Eight references studied GDM as the outcome of interest, diagnosed using the 100g OGTT test. However, not all of these studies reported their GDM criteria (Table 3-10). Indeed, one study (Wang et al. 2017) used a 75g OGTT test to diagnose GDM in their study, whilst Herring et al. (2014) used a 50g non-fasting OGTT to diagnose hyperglycaemia rather than GDM.

Preterm delivery was defined as delivery before 37 weeks of gestation and was examined by 4 separate studies.

As for complications with delivery, the risk of elective and/or emergency caesarean delivery was examined in comparison to spontaneous or assisted vaginal delivery. Emergency caesarean delivery was examined separately (i.e. not in conjunction with elective caesarean delivery) in just one reference (Bourjeily et al., 2013). Elective caesareans are important to examine separately since these may be likely to be decisions taken due to causes that occurred prior to the measurement of sleep – such as uterine abnormalities or a previous history of caesarean delivery. In addition, elective caesarean delivery may be secondary to causes that follow sleep measurement (such as excessive foetal growth or breech position). However, examining caesarean deliveries alongside emergency caesareans would not necessarily cause confounding bias, but it might cause measurement error or mediation bias.

Pregnancy-induced hypertension (also known as gestational hypertension), which is a key component of pre-eclampsia, was examined in relation to sleep in a total of 12 different studies (Table 3-10), 5 of which distinguished PIH from PE (Ko et al., 2013, Owusu et al., 2013, Ugur et al., 2012, Louis et al., 2012, Williams et al., 2010). In these studies, pre-eclampsia was defined as elevated blood pressure after 20 weeks of gestation with a diastolic reading >90 mmHg or a systolic reading >140 mmHg *plus* proteinuria of >300 mg/24 hr. In contrast, PIH was defined as elevated blood pressure after 20 weeks of gestation *with or without* proteinuria.

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Table 3-10 Summary of pregnancy outcomes examined by studies included in the review.

	Reference	Used definition	Descriptive statistics
Small for gestational age			
Retrospective longitudinal	(Bourjeily et al., 2010)	Birth weight "<10th percentile for gestational age"	Not reported
	(Franklin et al., 2000)	"Birth weight below two standards deviation in the Sweden infant weight charts"	Total participants=502 7% of 113 habitual snorers gave a birth to SGA infant 2.6% of 389 non- habitual snorers gave a birth for SGA (p<0.05
Prospective longitudinal study	(Abeysena et al., 2009)	Birth weight < 10th percentile adjusted for maternal height, feeding requirement, foetal sex, GA, ethnicity and maternal weight	Mean birth weight= 2946 g
	(Howe et al., 2015)	Birth weight "<10th percentile for gestational age"	Total participants=633 Rate of SGA was 8.85% (n=56) Rate of SGA in mother identifies as Māori (N=194) was 6.7% (n=13) Rate of SGA in mother identifies as non-Māori (N=439) was 9.8% (n=43)
	(Ko et al., 2013)	"<10th percentile adjusting for foetal sex and gestational age"	17 participants of 276 total participants (6.16%) give a birth to SGA neonates
	(O'Brien et al., 2013)	Birth weight < 10th centile adjusted for maternal height, maternal weight, ethnic origin, parity, infant sex, gestational age	Birth weight < 10th centile =12.5% of total 1673 participants
Low birth weight			
Retrospective longitudinal study	(Owusu et al., 2013)	Birth weight< 2500 g at birth	Total participants=234 6 out of 53 snorers had low birth babies (11.3%) 21 out of 167 non-snorers had low birth weight babies (12.6%) :
Prospective longitudinal study	(Abeysena et al., 2010)	Birth weight< 2500 g at birth	Mean= 2946± 473 g 87 LBW babies (11.8%) from 885 babies
	(Chen et al., 2012)	Birth weight< 2500 g at birth	**Mean birth weight** Women with OSA= 306 (SD=584) g Women without OSA=3147(SD=418) g 233 women from the 4746 (4.91%) had LBW babies
	(Sharma et al., 2016)	Birth weight< 2500 g at birth	**Total participants= 273** Rate of LBW was 31.14 % (n=85)
Apgar score			
Retrospective longitudinal study	(Bourjeily et al., 2010)	1-min. and 5-min. low Apgar scores (<7)	Not reported

	Reference	Used definition	Descriptive statistics
Prospective longitudinal study	(Chen et al., 2012)	5-min. low Apgar scores (<7)	Total participants=4786 Women with OSA=10 (1.3%) Women without OSA= 5(0.1%) P<0.001
	(Sharma et al., 2016)	5-min. low Apgar scores (<7)	Not reported
NICU admission			
Prospective longitudinal study	(Reutrakul et al., 2011)	Not reported	Not reported
	(Louis et al., 2012)	Not reported	12 (46.1%) women with OSA reported NICU admission 24 (17.8%) women without OSA reported NICU admission
Still birth and miscarriage			
Retrospective longitudinal studies	(Owusu et al., 2013)	Not reported	2 out of 53 snorers had a still birth delivery (3.8%) 7 out of 53 non –snorers had a still birth delivery
Case control study	(Samaraweera and Abeysena, 2010)	"partial or full expulsion of the foetus during the first 28 weeks of gestation"	Women with miscarriage 230 Women without miscarriage 501 Amongst women with miscarriage: 1st trimester miscarriage= 91/230 women (39.5%) 2nd trimester miscarriage= 139/230 women (60.4%)
	(Stacey et al., 2011)	"Stillbirth was defined as the birth of a baby that died in utero during the antenatal or intrapartum periods" GA= ≥ 28 week	Pregnant women experienced late still birth = 215 Prevalence of still birth = 3.09/1000 births The absolute risk of late stillbirth = 3.09/1000 95% CI= 2.70 to 3.53/1000
	(Gordon et al., 2015)	Late still birth during or after 32 weeks of gestation	Women with still birth =103 Women with viable birth= 192
Gestational diabetes			
Prospective longitudinal study	(Qiu et al., 2010)	If one of the following results was positive using 100 grams, 3-hour OGTT • fasting ≥ 95 mg/dl • 1-hour ≥ 180 mg/dl • 2-hour ≥ 155 mg/dl • 3-hour ≥140 mg/dl.	68 /1290 women (5.3%) developed GDM
	(Reutrakul et al., 2011)	The test was done using 100-g OGTT But no cut off point was reported	26 women (15%) had GDM
	(Facco et al., 2010)	The test was done using 100-g OGTT But no cut off point was reported	9 out of the 88 women With short sleep duration (10.2%) and 1 out of the 94 women Without short sleep duration (1.1%) were diagnosed with GDM P<0.008

	Reference	Used definition	Descriptive statistics
	(Chen et al., 2012)	Not reported	Women with OSA=37 (4.7%) Women without OSA=130 (3.3%) P<0.053
	(Herring et al., 2014)	Hyperglycemia was identified if the blood glucose level was ≥130 mg/dL using 50-g non-fasting OGTT with 1 hour sample	From the 63 participants 7 women (11%) were classified with hyperglycemia
	(O'Brien et al., 2012)	Not reported	19%women from 584 women with snoring had GDM 15 %women from the1128 non- snorer women had GDM
	(Reutrakul et al., 2013)	Using 100-g OGTT Two abnormal readings Using 1- hour glucose tolerance test with 50 g OGTT Blood glucose=≤ 140 mg/dl Blood glucose =≥ 200 mg/dl	Pregnant women with GDM= 15 Pregnant women without GDM= 15
	(Sharma et al., 2016)	American Diabetes Association criteria	Total participants= 273 Rate of women diagnosed of GDM= 14.65 % (n=40)
	(Wang et al., 2017)	Using 75-g OGTT GDM was diagnosed if one of the following Fasting glucose ≥ 5.1 mmol/l 1-h plasma glucose ≥ 10.0 mmol/l 2-h plasma glucose ≥ 8.5 mmol/l	7.3% (n=919) women had gestational diabetes
Retrospective longitudinal	(Bourjeily et al., 2013)	American Diabetes Association criteria	94 (10%) women had GDM
	(Bourjeily et al., 2010)	Not reported	98 (9.8%) of women had GDM
Mode of delivery			
Prospective longitudinal study	(Lee and Gay, 2004)	Both Elective and emergency caesarean	General vaginal birth= 62% Assisted vaginal birth=17% Caesarean section=21%
	(O'Brien et al., 2013)	Emergency caesarean or Elective caesarean	Emergency CS= 19.4% Elective CS= 18.2%
	(Chen et al., 2012)	Both Elective and emergency caesarean	Women with OSA=399 (50.4%) Women without OSA=1475(37.3%) P<0.01
	(Ko et al., 2013)	Both Elective and emergency caesarean	From 89 women with OSA 32 had caesarean delivery (36%) From187 women without OSA 42 (22.5%) caesarean delivery
	(Louis et al., 2012)	Both Elective and emergency caesarean	Total Caesarean delivery= 64 women 38% Elective caesarean=40%
	(Sharma et al., 2016)	Both Elective and emergency caesarean	Total participants= 273 Rate of CS was 28.57 % (n=78)
Retrospective longitudinal	(Bourjeily et al., 2013)	Elective caesarean	498 (53%) women had vaginal delivery 305 (32.5%) women had Caesarean delivery

	Reference	Used definition	Descriptive statistics
	(Bourjeily et al., 2010)	Emergency caesarean	5.4% had Caesarean delivery
Preterm delivery			
Prospective longitudinal study	(Louis et al., 2012)	Delivery before 37 weeks	From the 89 women with OSA 5 (17.6%) had preterm delivery From the 187 women without OSA 26 (18.5 %) had preterm delivery
	(Louis et al., 2010)	Not defined	From the 57 women with OSA 17 (29.8%) had preterm delivery From the 114 obese women11 (9.6 %) had preterm delivery From the 114 normal weight women 14 (12.3%) had preterm delivery
	(Stinson and Lee, 2003)	Not reported	50 participants had preterm delivery (13.9%)
	(Okun et al., 2011)	Delivery before 37 weeks	Preterm delivery= 15 (9.0%) Term delivery= 151 (91%)
	(Na-rungsri et al., 2016)	Delivery before 37 weeks and was divided into	Total participants= 1345 Preterm delivery= 143 (10.63%) Term delivery= 1197(88.99%)
	(Reutrakul et al., 2011)	Not reported	Not reported
	(Strange et al., 2009)	Not reported	Total preterm birth= 14.6%
Retrospective longitudinal	(Bourjeily et al., 2010)	Delivery before 37 weeks	12% women from 1000 participants had preterm delivery
Case control	(Kajeepeta et al., 2014)	Spontaneous and not medically indicated delivery that happened before 37 weeks and after 22 weeks of gestation	Women with preterm delivery =479 Women with term delivery =480
Pre-eclampsia			
Prospective longitudinal	(Williams et al., 2010)	Not reported	Not reported
	(O'Brien et al., 2012)	Not reported	12.9% from 584 snorers had PE 8.2% from 1128 non-snorers had PE
	(Ko et al., 2013)	Systolic BP>140 mmHg or diastolic BP>90mmHg Measured 2 times within 4-14 days apart plus protein urea >300gm/dl	3 of 89 women with OSA had PE 6 of 187 women without OSA had PE
	(Louis et al., 2012)	New onset HTN (GA >20 week) in previously normal women Bp>140/90 mmHg Proteinuria> 300 mg/24 hours	23 (16.9%) women without OSA had PE 11 (42.3%) women with OSA had PE
	(Ugur et al., 2012)	Not reported	18 (5%) women without OSA (n=396) had PE 19 (23%) women with OSA (n=69) had PE
Retrospective longitudinal	(Franklin et al., 2000)	pregnancy-induced hypertension with proteinuria ≥ 300 mg/24 hour	Total 26 cases of PE 10% in habitual snorer 4% in non habitual snorer p<0.05

	Reference	Used definition	Descriptive statistics
	(Owusu et al., 2013)	Not reported	26 (11.8%) 12 out of 53 snorers developed PE (22.6%) 13 out of 167 non- snorers developed PE (7.8%), p<0.0065
	(Chen et al., 2012)	Not reported	Women with OSA=11(1.4%) Women without OSA=18 (0.5%) P<0.002
Gestational Hypertension			
Retrospective longitudinal	(Bourjeily et al., 2010)		13% of 1000 participants had gestational hypertension
	(Franklin et al., 2000)	Not reported	Total 40 cases of HTN 14 % in habitual snorer 6 % in non-habitual snorer p<0.01
	(Perez-Chada et al., 2007).	Blood pressure ≥140/90 mmHg, regardless of proteinuria.	Pregnancy-induced hypertensive disease occurred in 42% snoring women compared to 27% of the women who had never snored (p<0.001)
	(Reid et al., 2011)	After 20 weeks of Gestation With or without proteinuria	422 out of 8651 deliveries between 2/2006 and 2/2008 were diagnosed with PIH 216 included in the study
	(Chen et al., 2012)	Not reported	Women with OSA=53 (6.7%) Women without OSA=85 (2.2%) P<0.001
Case control	(Champagne et al., 2009)	-New onset -Diastolic Bp= ≥90 mmHg -Measured 2 times -≥ 4 hours apart	Women with PIH =135 Women without PIH =150
Prospective longitudinal	(O'Brien et al., 2012)	Not reported	9.8% of the 584 the snorers participants had PIH 8.2% the 584 the non-snorers participants had PIH
	(Sharma et al., 2016)	(a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg)	The rate of women with PIH= 27.11% (n=74)

Table 3-11 Summary of the studies included in the review together with the (sleep-related) exposures and (pregnancy outcome-related) outcomes examined.

	Sleep duration	Sleep quality	Sleep disturbance	Day sleepiness	Latency	Sleep Position	Snoring	OSA
Neonatal outcomes								
SGA	(Abeysena et al., 2009) (Howe et al., 2015)	(Howe et al., 2015)					(Franklin et al., 2000) (Bourjeily et al., 2010) (Howe et al., 2015)	(Ko et al., 2013) (O'Brien et al., 2013)
LBW	(Abeysena et al., 2010)					(Owusu et al., 2013).	(Sharma et al., 2016)	(Chen et al., 2012)
Apgar Score							(Sharma et al., 2016)	(Bourjeily et al., 2010) (Chen et al., 2012)
NICU admission				(Reutrakul et al., 2011)				(Louis et al., 2012)
Miscarriage	(Samaraweera and Abeysena, 2010)							
Still birth	(Stacey et al., 2011).		(Stacey et al., 2011).	(Stacey et al., 2011)		(Owusu et al., 2013) (Stacey et al., 2011) (Gordon et al., 2015)	(Stacey et al., 2011) (Gordon et al., 2015**)**	(Gordon et al., 2015)
Maternal and perinatal outcomes								
GDM	(Qiu et al., 2010) (Reutrakul et al., 2011) (Facco et al., 2010) (Wang et al., 2017) (Herring et al., 2014)	(Wang et al., 2017)					(Qiu et al., 2010) (Reutrakul et al., 2011) (O'Brien et al., 2012) (Facco et al., 2010) (Bourjeily et al., 2010)	(Reutrakul et al., 2011) (Chen et al., 2012) (Reutrakul et al., 2013) (Bourjeily et al., 2010)

	Sleep duration	Sleep quality	Sleep disturbance	Day sleepiness	Latency	Sleep Position	Snoring	OSA
Mode of delivery	(Lee and Gay, 2004)	(Lee and Gay, 2004)	(Lee and Gay, 2004)	(Bourjeily et al., 2013)			(O'Brien et al., 2013) (Bourjeily et al., 2010) (Sharma et al., 2016)	(Chen et al., 2012) (Ko et al., 2013) (Louis et al., 2012) (Bourjeily et al., 2010)
Preterm delivery	(Kajeepeta et al., 2014)	(Stinson and Lee, 2003) (Okun et al., 2011) (Reutrakul et al., 2011)		(Reutrakul et al., 2011)	(Strange et al., 2009)			(Bourjeily et al., 2010) (Louis et al., 2012) (Louis et al., 2010) (Na-rungsri et al., 2016
PE	(Williams et al.,2010)						(Franklin et al., 2000) (Owusu et al., 2013) (O'Brien et al., 2012) (Sharma et al., 2016)	(Ko et al., 2013) (Louise et al., 2012) (Chen et al, 2012) (Ugur et al., 2012)
PIH							(Bourjel ly et al., 2010) (Franklin et al., 2000) (Perez-Chada et al., 2007) (O'Brien et al., 2012) (Sharma et al., 2016)	(Bourjelly et al., 2010) (Perez-Chada et al., 2007) (Reid et al., 2011) (Champagn et al., 2009) (Chen et al., 2012)

3.3.2.3 Measured covariates

Table 3-12 summarises all of the many covariates that were measured by one or more of the different studies examined in the present review. Many of these were then included in the covariate adjustment sets used in the adjusted multivariable statistical models some of these studies used. Any covariates that were measured prior to the measurement of sleep, can only have operated as either confounders or competing exposures in any causal relationship between sleep and pregnancy outcomes. In contrast, any covariates that were measured *after* sleep measurements could only act as potential confounders if the characteristics, events or processes these describe had occurred or 'crystallized' prior to the measurement of sleep. If not, these covariates are likely to have acted as mediators in the relationship between sleep and pregnancy outcomes. Since adjustment for mediators in causal inference analyses introduces a bias known as the 'reversal paradox' (Tu et al., 2005) including such covariates in the covariate adjustment sets used means that the models involved are potentially biased. However, whether or not covariates *can* act as confounders or mediators inevitably depends upon when the exposure variable(s) (i.e. sleep) were recorded – those studies measuring sleep in the third trimester (whether using retrospective or prospective longitudinal designs) might be able to consider adjusting for late pregnancy events as confounders where these occurred or crystallized at a time that *preceded* sleep measurement; while, for those measuring sleep early/ier in pregnancy, it would not be appropriate to include covariates occurring later in pregnancy in their covariate adjustment sets (Table 3-12).

According to these rules, covariates that shared similar functions and temporal positions (as a result of their occurrence, crystallization and/or measurement) in relation to the point at which sleep was measured were grouped together and two DAGs were drawn, one for each possible study design (see Figure 3-4 and Figure 3-5). These Figures illustrate the effect of differences in gestational age at which sleep was measured(GA) on the appropriate (and inappropriate) choice of covariates for inclusion in covariate adjustment sets. Variables that were measured before or during pregnancy (T2) and before the sleep measurement time (T3), and which might therefore affect both sleep and pregnancy outcomes were considered definitive potential confounders. Yet the same variables were considered mediators If they had been measured after the point at which sleep was measured and might then have mediated the effect of sleep on pregnancy outcomes.

Table 3-12 Summary of covariates used in the covariate adjustment sets of the multivariable regression models in the studies included in the review.

Temporal functional group	Reported variables	Assigned variable number	Time of events in regard to pregnancy	Temporal sequence in regard to sleep	Temporal sequence in regard to pregnancy outcomes	Functional role in DAG
Maternal characteristics						
Sociodemographic features	**Maternal age**	**1.**	Pre-pregnancy events	Precede sleep measurement	Precede pregnancy outcomes measurement	Confounders
	Ethnicity	**2.**				
	Socioeconomic status	**3.**				
	Health insurance	**4.**				
	Maternal education	**5.**				
	Marital status	**6.**				
	The geographic region which a pregnant participant lives in	**7.**				
	Deprivation index	**8.**				
	Maternal income	**9.**				
	Paternal age	**10.**				
Maternal health risk factors						
Anthropometric features	**Pre-pregnancy weight**	**11.**	Pre-pregnancy event	Preceded sleep measurement	Precede pregnancy outcomes measurement	Confounders
	Pre-pregnancy BMI	**12.**				
	Pre-pregnancy obesity	**13.**				
	Maternal height	**14.**				
	Weight gain	**15.**	Mid or late pregnancy event	Depending on the study design 1-Cross-sectional studies and retrospective studies; Late pregnancy events preceded sleep measurement 2-prosective longitudinal studies; sleep measurement	Precede pregnancy outcomes measurement	Confounders if they precede sleep measurement and mediators if they follow it
	Current weight	**16.**				
	Current pregnancy BMI	**17.**				
	Current neck circumference	**18.**				

Temporal functional group	Reported variables	Assigned variable number	Time of events in regard to pregnancy	Temporal sequence in regard to sleep	Temporal sequence in regard to pregnancy outcomes	Functional role in DAG
				preceded late events		
Chronic maternal diseases	**Chronic hypertension**	**19.**	Pre-pregnancy or early pregnancy events	Precede sleep measurement	Precede pregnancy outcomes measurement	Confounders
	Diabetes mellitus	**20.**				
	Anaemia	**21.**				
	Coronary heart disease	**22.**				
	Hyperlipidaemia	**23.**				
Pregnancy related maternal complications	**Pre-eclampsia**	**24.**	Mid or late pregnancy events	Depending on the study design 1-Cross-sectional studies and retrospective studies; Late pregnancy events preceded sleep measurement 2-prosective longitudinal studies; sleep measurement preceded late events	Depending on the timing of the outcome 1-Might precede the outcome if the outcome was late pregnancy event or after birth event 2- Might precede or follow the outcome if the outcome was mid pregnancy event	Confounders if they preceded sleep measurement and mediators if they follow it
	Gestational diabetes	**25.**				
	Gestational hypertension	**26.**				
Psychological disorders	**Pre-existing Depression**	**27.**	Pre-pregnancy or early pregnancy	Precede sleep	Precede the outcome	Confounders
Maternal behavioural risks	**Smoking**	**28.**	Pre-pregnancy, early, mid or late pregnancy event	Might precede or follow sleep	Precede the outcome	Confounders or mediators depending on their measurement time with regard to sleep
	Alcohol	**29.**				
	Vitamin supplement during pregnancy	**30.**				
Maternal obstetric history						
Previous obstetric History	**Parity**	**31.**	Pre-pregnancy event	Preceded sleep measurement	Precede the outcome	Confounders
	Gravidity	**32.**				
	Prior preterm delivery	**33.**	Pre-pregnancy event	Preceded sleep measurement	Precede the outcome	Confounders

Temporal functional group	Reported variables	Assigned variable number	Time of events in regard to pregnancy	Temporal sequence in regard to sleep	Temporal sequence in regard to pregnancy outcomes	Functional role in DAG
	Previous caesarean birth	**34.**				
	Previous abortion	**35.**				
	History of PIH	**36.**				
	History of PE	**37.**				
Maternal family history						
Family history of chronic diseases	**Family history of DM**	**38.**	Pre-pregnancy event	Preceded sleep measurement	Precede the outcome	Confounder
Family history of obstetric complications	**Family history of PIH**	**39.**	Pre-pregnancy event	Preceded sleep measurement	Precede the outcome	Confounders
	Family history of PE	**40.**				
Pregnancy related factors						
	Infant sex	**41.**	Early pregnancy event	Preceded sleep measurement	Precede the outcome	Confounders
	Multifetal pregnancy	**42.**				
Pregnancy outcomes						
	Infant birth weight	**43.**	After birth events	Follow sleep measurement	Might precede the outcome if the outcome was after birth event	Mediators
	Gestational age at delivery	**44.**				
Sleep related events						
Pre-pregnancy sleep characteristics	**Pre-pregnancy short sleep duration**	**45.**	Pre-pregnancy event	Preceded current sleep measurement	Precede the outcome	Confounders
Current pregnancy sleep characteristics	**Sleep efficiency**	**46.**	*Mid or late pregnancy event	Up to date little is known about which sleep characteristic precedes the other	Precede the outcome	Up to date little is known about how each sleep characteristic affect the other
	Sleep quality	**47.**				
	Number of nights with poor sleep quality	**48.**				

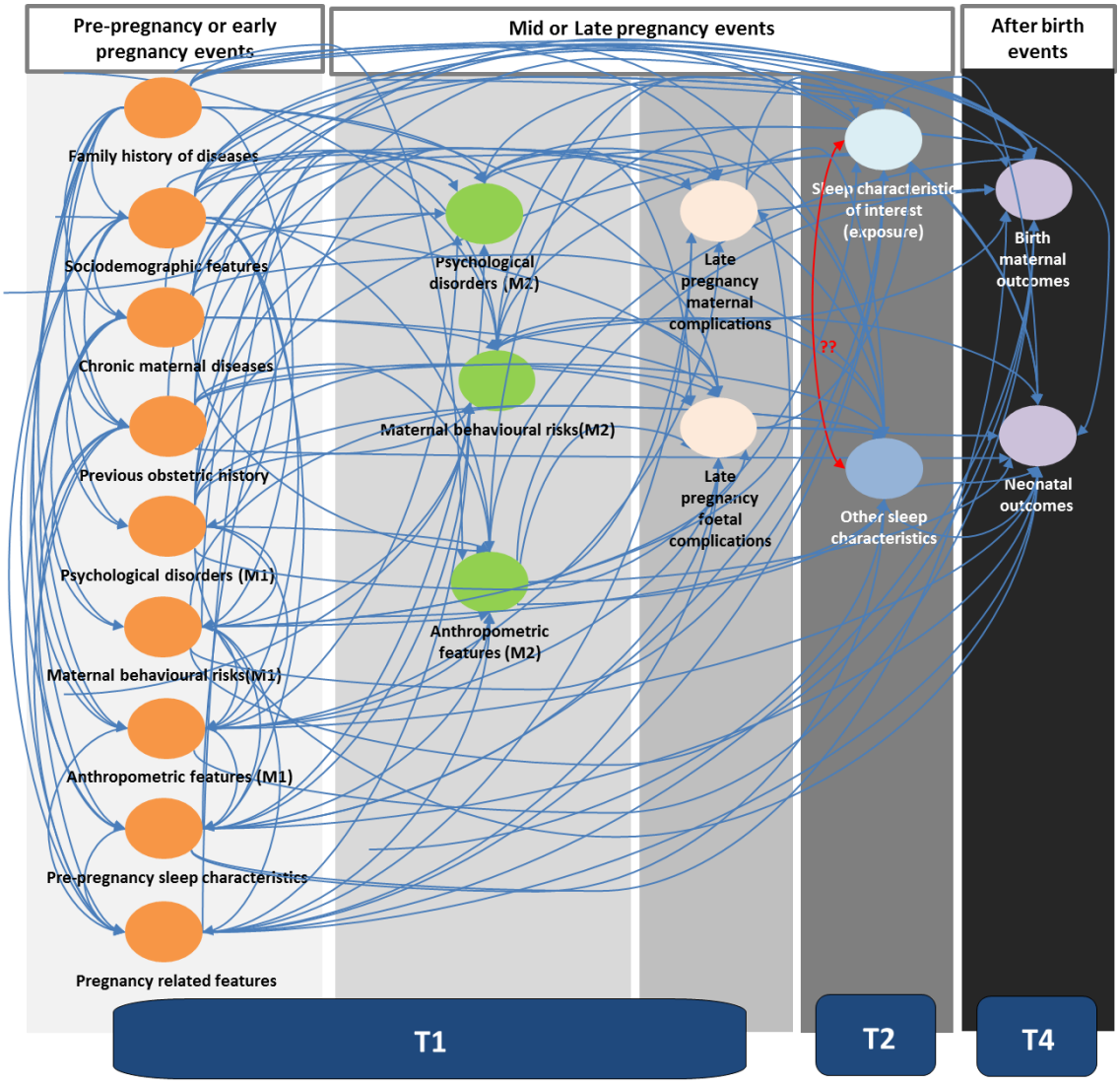

Figure 3-4 Directed acyclic graph showing the temporal positions of each of the covariates included in the covariate adjustment sets of the regression models in the studies included in the review – including those using retrospective longitudinal study designs or prospective study designs with sleep measurements recorded later in pregnancy.

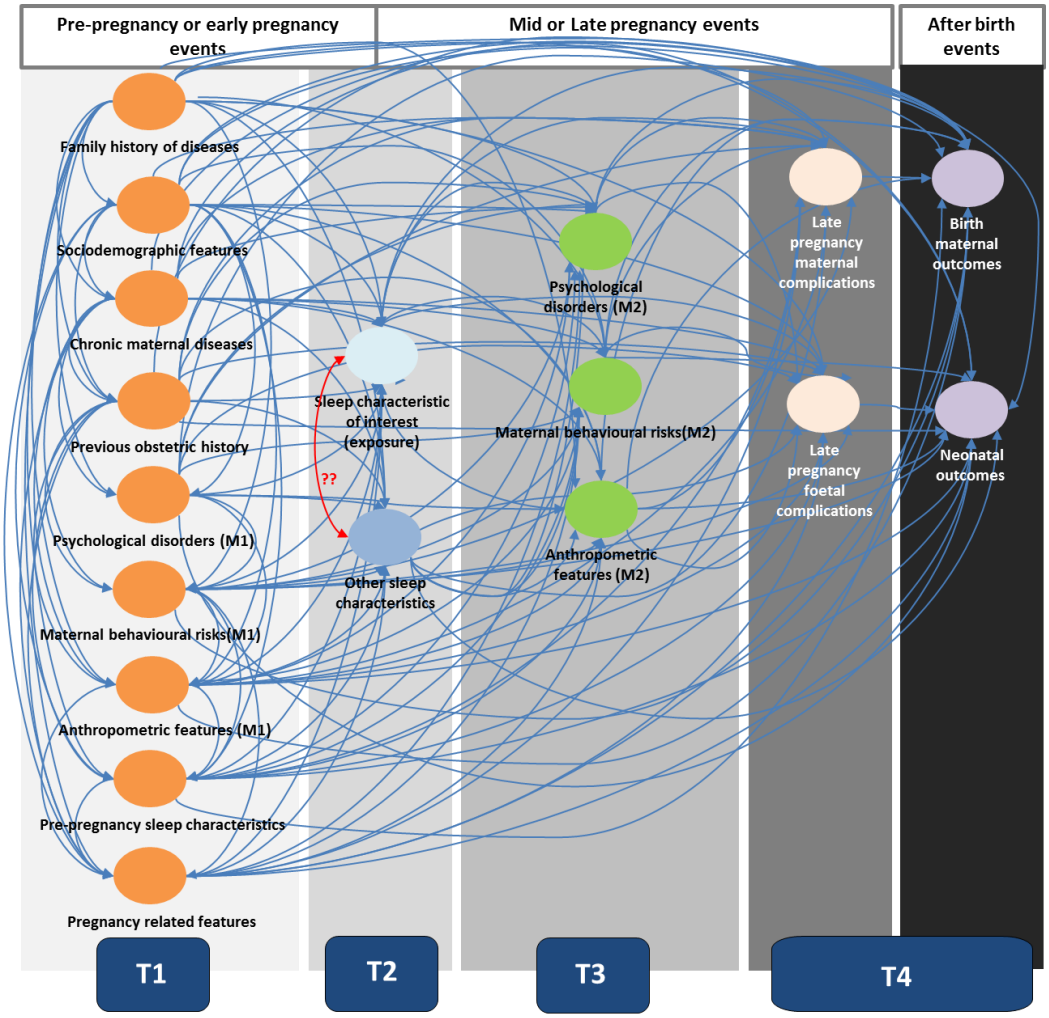

Figure 3-5 Directed acyclic graph showing the temporal positions of each of the covariates included in the covariate adjustment sets of the regression models in the studies included in the review – including those using in the prospective study designs with sleep measurements recorded earlier in pregnancy.

3.3.3 The association between sleep characteristics and pregnancy outcomes

When considering the direction of any associations observed between unfavourable sleep events and the risk of poor pregnancy outcomes, it was found that, with the exception of three adjusted models, *all* of the unfavourable sleep events (as described in Tables 3-13 to 3-18) examined in each of the unadjusted and adjusted models increased the risk of all of the poor pregnancy outcomes examined (as described in Table 3-10). In the first of the models that constituted exceptions to this rule, OSA was found to be associated with a lower the risk of PIH (adjusted Log OR= 0.9; CI=0.30 to 2.04; Table 3-13). The second model found that an inverse association between short sleep duration and SGA (adjusted OR=0.90; CI=0.40 to 1.80; Table 3-14). However, both of these models included

covariates that were judged to be mediators in their covariate adjustment sets. Meanwhile, the third and final model examined the association between sleep duration (as a continuous variable) and hyperglycemia and found an inverse relationship though without considering the possibility that this might have resulted from an imbalanced U-shaped relationship (where an increased odds of hyperglycaemia might have been caused by short or long duration sleep; adjusted OR= 0.2; 0.1 to 0.8; Table 3-14).

In regard to the magnitude of the associations observed between unfavourable sleep events and pregnancy outcomes, it was found that this tended to vary primarily as a result of the following factors:

I. The type of unfavourable sleep events - it being evident that SDB-related sleep characteristics symptoms had the strongest associations with poor pregnancy outcomes, regardless of the poor pregnancy outcomes involved (Table 3-13).
II. The type of pregnancy outcomes – it being evident that late pregnancy maternal events (i.e. GDM, PE and PIH) had the strongest associations with unfavourable sleep characteristics regardless of the specific unfavourable sleep events involved.
III. The categorisation of the unfavourable sleep characteristic used – this was clearly evident when sleep duration was examined as a continuous variable. Ignoring the possibility of a U-shaped relationship between sleep duration and pregnancy outcomes appeared to reverse the direction of any association between sleep duration and pregnancy outcomes (Table 3-15)
IV. The gestational age at which sleep was measured – it being evident sleep measurements recorded earlier or later in pregnancy affected the strength of any association between sleep and pregnancy outcomes, though without affecting the direction of these associations. For instance O'Brien et al. (2013) reported a far stronger association between snoring which developed (and was measured) during the 3rd trimester and PIH (adjusted OR=2.36; CI=1.48 to 3.77; Table 3-13) compared to snoring that developed prior to the 3rd trimester (adjusted OR= 1.72; CI= 0.80 to 3.71; Table 3-13).
V. The choice of covariates included in the covariate adjustment sets used – it being evident that including covariates likely to operate as mediators within the covariate adjustment sets altered the direction of association between OSA and PIH as well as that between SSD and SGA, whilst only affecting the magnitude of the associations in the remainder of the inappropriately adjusted models.

A detailed summary of the ORs extracted from the studies included in the review, together with lists of the covariates included in these studies covariate adjustment sets are listed in Table 3-13 through to Table 3-18.

Considering the number of pregnancy outcomes examined, it was clear that only 11 separate maternal/perinatal and neonatal outcomes have thus far been examined by studies examining the relationship between sleep and pregnancy outcomes. Furthermore, 3 of these have only been examined by a single study each and few of the remainder have been studied with much consistency in either the definition or categorisation of the variables examined, or in the study designs adopted or the gestational age at which the sleep exposure variables were measured.

At the same time, a total of (only) 8 separate/distinct sleep characteristics have thus far been examined by such studies; and three of these characteristics have only been examined, to-date, by a single study each; whilst for the others there was, once more, little evidence of consistency in the definition, categorisation, measurement tool/point or covariate adjustment sets used.

By far the most attention has been paid to maternal/perinatal characteristics than to neonatal characteristics; and to snoring, OSA and (to a lesser extent) sleep duration. Yet many of the studies failed to present either unadjusted and/or adjusted coefficient estimates (which, together with the lack of consistency in terms of methods, further reduces the scope for meta-analysis). Much of what is known about the relationship between sleep and pregnancy outcomes is therefore based on very little evidence (for most sleep characteristics and most pregnancy outcomes), and appears to be sensitive to difference in sampling, measurement, categorisation and analysis.

Table 3-13 Summary of adjusted and unadjusted ORs of studies that examined the relationship between SDB symptoms and poor pregnancy outcomes.

Study design	Reference	SDB component	Trimester	Sample size	Unadjusted OR	95% confidante interval	Adjusted OR	95% confidante interval	Temporal functional groups (TFG)			
									Adjusted variables	Number of TFGs	Number of mediators	Number of confounders
Small for gestational age												
Retrospective longitudinal study	**(Bourjeily et al., 2010)**	Snoring	3rd	1000	1.90	0.80 to 4.30	-	-	Un-adjusted	0	0	0
	(Franklin et al., 2000)	Snoring	3rd	502	-	-	2.03	1.01 to 4.10	1,11, 28	3	0	3
Prospective longitudinal	**(Howe et al., 2015)**	Snoring	Not specified	633	-	-	1.20	0.60 to 2.40	1,2, 3,12,16,18, 27, 31, 41, 44	6	1	5
	(Ko et al., 2013)	OSA	Not specified	276	-	-	2.56	0.56 to 11.68	1,32, 44,	3	0	3
	(O'Brien et al., 2013)	OSA	3rd	1673	1.60	0.70 to 3.90	-	-	Un-adjusted	0	0	0
Low birth weight												
Retrospective longitudinal study	**(Chen et al., 2012)**	OSA	Not specified	4786	2.16	1.61 to 2.90	1.72	1.42 to 2.40	1, 5, 6, 7,10,21, 22, 28,32,41	7	1	6
Prospective longitudinal	**(Sharma et al., 2016)**	Habitual snoring	Not specified	273	-	-	2.70	1.00 to 7.20	Not reported	Not reported	Not reported	Not reported
Apgar score												
Retrospective longitudinal	**(Bourjeily et al., 2010)**	OSA and 1 min Apgar	3rd	1000	-	-	1.90	1.00 to 3.40	1,28,42	3	0	3
		OSA and 5 min Apgar	3rd		-	-	3.70	1.10 to 11.90	1,28,42	3	0	3
	(Chen et al., 2012)	OSA and 5 min Apgar	Not specified	4786	-	-	10.11	3.45 to 29.67	1	1	0	1
Prospective longitudinal	**(Sharma et al., 2016)**	Habitual snoring and 5 min Apgar	Not specified	273			1.30	0.40 to 4.10	Not reported	Not reported	Not reported	Not reported
NICU ddmissiom												
Prospective longitudinal	**Louis et al., 2012)**	OSA	Not specified	171	3.39	1.23 to 9.32	3.96	1.63 to 9.63	1, 2, 12	2	0	2
Still birth												
Case control	**(Stacey et al., 2011)**	Snoring	Not specified	467	-	-	1.12	0.75 to 1.67	1, 2,3, 12,28, 31	3	1	3
	(Gordon et al., 2015)	Snoring	3rd	295	1.20	0.70 to 1.90	-	-	Un-adjusted	0	0	0

Study design	Reference	SDB component	Trimester	Sample size	Unadjusted OR	95% confidante interval	Adjusted OR	95% confidante interval	Temporal functional groups (TFG)			
									Adjusted variables	Number of TFGs	Number of mediators	Number of confounders
	(Gordon et al., 2015)	Apnea	3rd	295	1.20	0.60 to 2.10	1.60	0.65 to 4.20	Not reported	Not reported	Not reported	Not reported
Preterm delivery												
Retrospective longitudinal	**(Bourjeily et al., 2010)**	OSA	3rd	1000	-	-	1.90	1.10 to 3.30	1,28,42	3	0	3
	(Louis et al., 2010)	OSA	Not specified	171	-	-	2.60	1.00 to 6.60	1,2,4,13, 19,20,28, 33	5	2	3
Prospective longitudinal	**(Louis et al., 2012)**	OSA	Not specified	175	1.07	0.37 to 3.08	0.63	0.18 to 2.24	1, 2, 12	2	0	2
	(Na-rungsri et al., 2016)	OSA	2nd	959	2.10	1.32 to 3.36	2.00	1.20 to 3.34	1, 12, 28,33,35	4	1	3
Caesarean delivery												
Retrospective longitudinal	**(Bourjeily et al., 2010)**	Snoring	3rd	1000	2.10	1.40 to 3.20	2.10	1.40 to 3.20	28, 42, 43	3	0	3
		OSA	3rd	1000	1.8	0.80 to 4.10	1.80	0.80 to 4.20	28, 42, 43	3	0	3
	(Chen et al., 2012)	OSA	Not specified	4786	1.73	1.48 to 2.02	1.74	1.48 to 2.04	1, 5, 6, 7,10, 21, 22, 28, 32, 41	7	1	6
Prospective longitudinal	**(Ko et al., 2013)**	OSA	Not specified	276	-	-	1.53	0.79 to 2.96	1,32, 44,	3	0	3
	(Louis et al., 2012)	OSA	Not specified	175	3.86	1.6 to 9.33	3.04	1.14 to 8.10	1, 2, 12	2	0	2
	(O'Brien et al., 2013)	Chronic snoring	1st and 2nd	1673	2.00	1.33 to 3.04	2.25	1.22 to 4.18	5, 24, 25, 34,43	4	0	4
		Pregnancy onset snoring	3rd	1673	1.43	1.06 to 1.92	1.70	1.13 to 2.57	5, 24, 25, 34,43	4	0	4
	(Sharma et al., 2016)	Habitual snoring	Not specified	273	-	-	2.90	1.00 to 8.20	Not reported	Not reported	Not reported	Not reported
GDM												
Prospective longitudinal	**(Qiu et al., 2010)**	Snoring	Not specified	1290	-	-	6.91	2.87 to 16.60	1, 2, 12	2	0	2
	(Reutrakul et al., 2011)	Snoring	2nd	169	-	-	3.40	1.30 to 8.80	12	1	0	1
		OSA	2nd		3.00	1.20 to 7.40	-	-	Un-adjusted	0	0	0
	(O'Brien et al., 2012)	Pregnancy onset snoring	3rd	1719	1.29	0.96 to1.74	-	-	Un-adjusted	0	0	0
		Chronic snoring	1st and 2nd		1.67	1.10 to 2.52	-	-	Un-adjusted	0	0	0

Study design	Reference	SDB component	Trimester	Sample size	Unadjusted OR	95% confidante interval	Adjusted OR	95% confidante interval	Temporal functional groups (TFG)			
									Adjusted variables	Number of TFGs	Number of mediators	Number of confounders
Prospective longitudinal	**(Facco et al., 2010)**	Snoring	2nd	189	4.90	1.30 to 18.10	6.90	1.40 to 33.90	1, 2,45	2	0	2
Retrospective longitudinal	**(Bourjeily et al., 2010)**	Snoring	3rd	1000	2.70	1.70 to 4.30	2.10	1.30 to 3.40	28, 42,43	3	0	3
Retrospective longitudinal	**Bourjeily et al., 2010)**	OSA	3rd	1000	2.60	1.30 to 5.50	2.00	0.90 to 4.30	3, 16, 28	3	0	3
	Chen et al., 2012)	OSA	Not specified	4786	1.45	0.99 to 2.11	1.63	1.07 to 2.48	1, 5, 6, 7,10, 21, 22, 28, 32,41	7	1	6
Case control	**(Reutrakul et al., 2013)**	OSA	Late 2nd to 3rd	45	-	-	6.60	1.15 to 37.96	12	1	0	1
Pre-eclampsia												
Retrospective longitudinal	**(Franklin et al, 2000)**	Snoring	3rd	502	-	-	2.18	0.50 to 2.68	1, 12, 16, 42	4	0	4
	(Owusu et al, 2013)	Snoring	3rd	234	-	-	3.50	1.40 to 8.50	1, 31, 44	3	0	3
Prospective longitudinal	**(O'Brien et al, 2012)**	Pregnancy onset snoring	3rd	1719	1.71	1.20 to 2.44	1.59	1.06 to 2.37	1, 2, 5, 12, 15, 28, 32, 36, 37, 40	7	2	5
		Chronic snoring	1st to 2nd	1719	-	-	1.12	0.58 to 2.14	1, 2, 5, 12, 15, 28, 32, 36, 37, 40	7	2	5
	(Sharma et al., 2016)	Habitual snoring	Not specified	273	-	-	1.50	0.50 to 4.90	Not reported	Not reported	Not reported	Not reported
	(Ko et al, 2013)	OSA	Not specified	276	-	-	1.99	0.23 to 17.70	1,32, 44,	3	0	3
	(Louis et al, 2012)	OSA	Not specified	175	3.60	1.47 to 8.84	3.54	1.26 to 9.92	1, 2, 12	2	0	2
	(Ugur et al., 2012)	OSA	Not specified	465	-	-	12.40	4.90 to 13.90	32, 44	2	0	2
Retrospective longitudinal	**(Chen et al, 2010)**	OSA	Not specified	4786	1.60	1.45 to 6.55	3.08	2.16 to 11.26	1, 5,6, 7,10, 21, 22, 28, 32, 41	7	1	6
Gestational hypertension												
Retrospective longitudinal	**(Bourjeily et al., 2010)**	Snoring	3rd	1000	4.00	2.40 to 6.50	2.30	1.40 to 4.00	1,12, 19, 24, 25, 28, 42	6	1	5
		OSA	3rd	1000	1.30	0.60 to 3.20	0.90	0.30 to 2.40	1,12, 19, 24, 25, 28, 42	6	1	5

Study design	Reference	SDB component	Trimester	Sample size	Unadjusted OR	95% confidante interval	Adjusted OR	95% confidante interval	Temporal functional groups (TFG)			
									Adjusted variables	Number of TFGs	Number of mediators	Number of confounders
Retrospective longitudinal	**(Franklin et al., 2000)**	Snoring	3rd	502	-	-	2.03	1.01 to 4.10	1,16, 28	3	0	3
	(Perez-Chada et al., 2007)	Snoring	Not specified	456	-	-	1.82	1.16 to 2.84	1, 12, 15, 18, 28, 29	4	2	2
		OSA	Not specified	456	-	-	3.15	1.50 to 6.61	1, 12, 15, 18, 28, 29	4	2	2
Prospective longitudinal	**(O'Brien et al, 2012)**	Pregnancy onset snoring	3rd	1719	2.57	1.69 to 3.53	2.36	1.48 to 3.77	1, 2, 5, 12, 15, 28, 32, 36, 37, 40	7	2	5
		Chronic snoring	1st	1719	-	-	1.72	0.80 to 3.71	1, 2, 5, 12, 15, 28, 32, 36, 37, 40	7	2	5
	(Sharma et al., 2016)	Habitual snoring	Not specified	273	-	-	2.90	1.00 to 8.20	Not reported	Not reported	Not reported	Not reported
Retrospective longitudinal	**(Reid et al., 2011)**	OSA	3rd	219	8.30	2.10 to 33.40	-	-	Un-adjusted	0	0	0
	(Chen et al, 2010)	OSA	Not specified	4786	1.45	0.99 to 2.11	1.63	1.07 to 2.48	1, 3, 4, 12, 19, 20, 31, 32, 33, 44	8	0	8
Case control	**(Champagne et al., 2009)**	OSA	>20 weeks	50	5.60	1.40 to 23.20	7.50	3.50 to 16.20	1, 12, 31, 44	4	0	4

Table 3-14 Summary of adjusted and unadjusted ORs of studies that examined the relationship between sleep duration and poor pregnancy outcomes

Study design	Reference	Pregnancy outcomes	Sleep duration risk group	Sample size	Trimester	Unadjusted OR	95% CI	Adjusted OR	95% CI	Functional temporal groups (TFG)			
										Adjusted variables	Number of TFGs	Number of mediators	Number of confounders
Neonatal outcomes													
Case control	**Stacey et al. (2011)**	Still birth	>8 hr/night	467	> 2nd	1.83	1.14 to 2.94	-	-	Unadjusted	0	0	0
Prospective longitudinal	**Abeysena et al. (2009)**	Small for gestational age	≤ 8 hr/night	690	1st	1.14	0.75 to 1.74	-	-	Unadjusted	0	0	0
		Small for gestational age	≤ 8 hr/night	690	2nd	1.50	0.96 to 2.34	-	-	Unadjusted	0	0	0
		Small for gestational age	≤ 8 hr/night	690	3rd	1.23	0.77 to 1.89	-	-	Unadjusted	0	0	0
	(Howe et al., 2015)	Small for gestational age	<6 hr/night	633	3rd	-	-	0.90	0.40 to 1.80	1, 2, 5, 14, 15, 17, 19, 31, 38, 42	7	1	6
		Small for gestational age	9 hr/night	633	3rd	-	-	1.60	0.80 to 32.00	1, 2, 5, 14, 15, 17, 19, 31, 38, 42	7	1	6
	(Abeysena et al., 2010)	Low birth weight	> 8 hr/night	885	Not specified	1.87	1.16 to 3.02	-	-	Unadjusted	0	0	0
Case control	**Samaraweera and Abeysena (2010)**	Miscarriage	>8 hr/night	734	Not specified	-	-	3.80	1.01 to 14.30	44	1	0	1
Maternal outcomes													
Prospective longitudinal	**Qiu et al. (2010)**	GDM	<4 hr/night	1290	1st	-	-	5.50	1.31 to 23.69	1, 2, 12	2	0	2
		GDM	>9 hr/night	1290	1st	-	-	4.18	0.94 to 18.60	1, 2, 12	2	0	2
	Facco et al. (2010)	GDM	<7 hr/night	189	Not specified	2.6	1.3 to 5.5	2.40	1.10 to 5.30	1, 2, 12, 20	3	0	3

Study design	Reference	Pregnancy outcomes	Sleep duration risk group	Sample size	Trimester	Unadjusted OR	95% CI	Adjusted OR	95% CI	Functional temporal groups (TFG)			
										Adjusted variables	Number of TFGs	Number of mediators	Number of confounders
Prospective longitudinal	**Reutrakul et al. (2011)**	GDM	<7 hr/night	169	Not specified	2.40	1.00 to 5.90	-	-	Unadjusted	0	0	0
	Wang et al, 2017)	GDM	<7 hr/night	12,506	Not specified	1.36	0.87 to 2.14	1.12	0.69 to 1.81	1	1	0	1
		GDM	≥ 9 hr/night	12,506	Not specified	1.21	1.013 to 1.42	1.29	1.09 to 1.52	1	1	0	1
	Herring et al., (2014)	Hyperglycaemia	None	63	2nd	0.30	0.10 to 0.80	0.20	0.10 to 0.80	1, 2, 5, 12, 14, 19, 31, 38, 42.	7	0	7
	Lee and Gay (2004)	Caesarean delivery	< 6 hr/night	63	2nd	-	-	4.54	1.36 to 15.21	43	1	0	1
		Caesarean delivery	6 to 6.9 hr/night	131	3rd	-	-	3.67	1.33 to 10.18	43	1	0	1
	Williams et al. (2010)	Preeclampsia	≤ 6 hr/night	1272	1st	2.64	0.82 to 8.56	2.36	0.72 to 7.72	1, 12, 31	3	0	1
Case control	**Kajeepeta et al., (2014)**	Preterm delivery	< 6 hr/night	959	1st and 2nd	1.55	1.11 to 2.16	1.56	1.11 to 2.19	1, 11, 30	3	0	3
		Preterm delivery	≥ 9 hr/night	959	1st and 2nd	1.33	0.94 to 1.87	1.34	1.04 to 2.16	1, 11, 30	3	1	2

Table 3-15 Summary of adjusted and unadjusted ORs of studies that examined the relationship between sleep quality and poor pregnancy outcomes.

Study design	Reference	Pregnancy outcomes	Trimester	Sample size	Unadjusted OR	95% CI	Adjusted OR	95% CI	Adjustment	Temporal functional group		
										Number of TFGs	Number of mediators	Number of confounders
Maternal outcomes												
Prospective longitudinal	**(Lee and Gay, 2004)**	Caesarean delivery	3rd	131	-	-	4.30	1.05 to16.93	12	1	0	1
	(Reutrakul et al., 2011)a	Preterm delivery	2nd	169	1.20	1.00 to 1.30	-	-	Unadjusted	0	0	0
	(Okun et al., 2011)	Preterm delivery	3rd	166	1.10	1.03 to 1.18	1.25	1.04 to1.5	9	1	0	1
	(Stinson and Lee, 2003)	Preterm delivery	2nd	359	2.36	1.09 to 5.07	-	-	Unadjusted	0	0	0
	(Wang et al., 2017)	GDM and moderately poor quality	Not specified	12,506	1.62	1.20 to 2.17	1.19	1.01 to 1.41	1, 2, 5, 14, 15, 17, 19, 31, 38, 42	7	1	6
Neonatal outcomes												
Prospective longitudinal	**(Howe et al., 2015)**	Small for gestational age	3rd trimester	633	-	-	1.00	0.40 to 2.00	1, 2, 8, 17, 27, 28, 31, 41, 45, 48	7	1	6
		Small for gestational age	3rd trimester	633	-	-	1.10	0.50 to 2.70	1, 2, 8, 17, 27, 28, 31, 41, 45, 48	7	1	6

Table 3-16 Summary of adjusted and unadjusted ORs of studies that examined the relationship between sleep disturbance, latency and poor pregnancy outcomes.

Study design	Reference	Pregnancy outcomes and sleep	Trimester	Sample size	Unadjusted OR	95% CI	Adjusted OR	95% CI	Temporal functional group (TFG)			
									Adjusted variables	Number of TFGs	Number of confounders	Number of mediators
Maternal outcomes												
Prospective longitudinal	**(Lee and Gay, 2004)**	Caesarean delivery and disturbance	3rd	131	-	-	5.19	1.77 to 15.18	43	1	0	1
Neonatal outcomes												
Case control	**(Stacey et al., 2011)**	Still birth and disturbance	3rd	467	-	-	2.42	1.46 to 4.00	1, 2, 3, 12, 28	4	0	4
Prospective longitudinal	**(Strange et al., 2009)**	Preterm delivery and latency	2nd	220	-	-	1.04	1.01 to 1.07	33, 46, 47,48,	2	0	2

Table 3-17 Summary of adjusted and unadjusted ORs of studies that examined the relationship between daytime sleepiness and poor pregnancy outcomes.

Study design	Reference	Pregnancy outcomes	Trimester	Sample size	Unadjusted OR	95% CI	Adjusted OR	95% CI	Temporal functional group (TFG)			
									Adjusted variables	Number of FTGs	Number of mediators	Number of confounders
Maternal outcomes												
Retrospective longitudinal	**(Bourjeily et al., 2013)**	Elective caesarean section	Not specified	1000	1.80	1.03 to 3.11	1.76	0.99 to 3.10	42, 43	2	0	2
	(Bourjeily et al., 2013)	Vaginal delivery	Not specified	1000	1.09	1.02 to 1.16	1.08	1.01 to 1.15	42, 43	2	0	2
Neonatal outcomes												
Case control	**(Stacey et al., 2011)**	Still birth	3rd	467	1.78	1.18 to 2.68	2.04	1.26 to 3.30	1, 12, 2, 31, 28, 3	4	0	4
Prospective longitudinal	**(Reutrakul et al., 2011)**	NICU admission	2nd	169	1.10	1.00 to1.30	-	-	Unadjusted	0	0	0

Table 3-18 Summary of adjusted and unadjusted ORs of studies that examined the relationship between sleep position and poor pregnancy outcomes.

	Reference	Pregnancy outcomes	Trimester	Sample size	Sleep position	Unadjusted OR	95% CI	Adjusted OR	95% CI	Adjustment	Temporal functional group		
											Number of TFGs	Number of mediators	Number of confounders
Maternal outcomes													
No studies were resulted													
Neonatal outcomes													
Case control	**(Stacey et al., 2011)**	Still birth	3rd	467	Supine	3.28	1.46 to 7.34	-	-	Unadjusted	0	0	0
			3rd	467	Right side	1.88	1.14 to 3.10,	-	-	Unadjusted	0	0	0
			3rd	467	Other positions	2.00	1.20 to 3.33	-	-	Unadjusted	0	0	0
	(Gordon et al., 2015)	Still birth	3rd	295	Supine	5.00	1.50 to 16.5	6.26	1.20 to 34	Not reported	Not reported	Not reported	Not reported
Retrospective longitudinal	**(Owusu et al., 2013)**	Still birth	Not specified	234	Supine	-	-	8.00	1.50 to 43.20	1, 31, 44	3	0	3
		Low birth weight		234	Supine	-	-	2.00	1.20 to 3.33	1, 31, 44	3	0	3

3.3.4 Meta-analysis results

Because of the limited number of studies that examined similar exposure-outcome pairs using similarly sound analytical techniques (Table 3-11) it was only possible to generate just 4 sets of meta-analyses, each containing the results of three or more comparable analytical models. These were those examining the relationships between:

1- short sleep duration and GDM using adjusted models with covariate adjustment sets that did not include likely mediators (3 models; Figure 3-6)
2- OSA and CS using adjusted models with covariate adjustment sets that did not include likely mediators (3 models; Figure 3-7)
3- OSA and PE using adjusted models with covariate adjustment sets that did not include likely mediators (3 models; Figure 3-8)
4- snoring and GDM using (only) un-adjusted models (3 models) or only adjusted models with covariate adjustment sets that did not include any likely mediators (4 models; Figure 3-9)

These meta-analyses confirmed that short sleep duration was associated with an increased risk of GDM (summary ES= 2.07; CI= 1, 06 to 4.04; Figure 3-6). A very similar association was observed between snoring and GDM in the meta-analysis of unadjusted models (summary ES= 2.31; CI= 1.44 to 3.70; Figure 3-9a), although this strengthened considerably when using models that had adjusted (only) for covariates likely to have operated as potential confounders (summary ES= 3.72; CI= 1.92 to 7.18; Figure 3-9b).

As for OSA, this was found to be associated with an increased risk of both CS and PE. OSA was associated with an increased risk of CS of 1.87 (CI=1.18 to 2.95; Figure 3-7) and an increased risk of PE of 5.73 (CI= 1.87 to 17.56; Figure 3-8) in meta-analyses that only included models in which the covariate adjustment sets contained only confounders (and no mediators).

In addition, it was also clear that there was substantial heterogeneity amongst the models included in most of these meta-analyses (Figure 3-6, Figure 3-8, Figure 3-9 and Figure 3-10), the exception being in the meta-analysis examining the relation between OSA and CS, in which heterogeneity was not detected (Figure 3-7). The heterogeneity between studies included in each of the former meta-analysis was primarily due to differences in the study design (prospective vs retrospective longitudinal), the studies' inclusion and exclusion criteria (such as multiple pregnancies, maternal health conditions/risk factors and the gestational age at which participants were recruited), the measurement tool used to assess the sleep characteristic of interest (be that objective vs subjective) and the referent

categories used for these sleep characteristics (short vs long duration or habitual vs non habitual events).

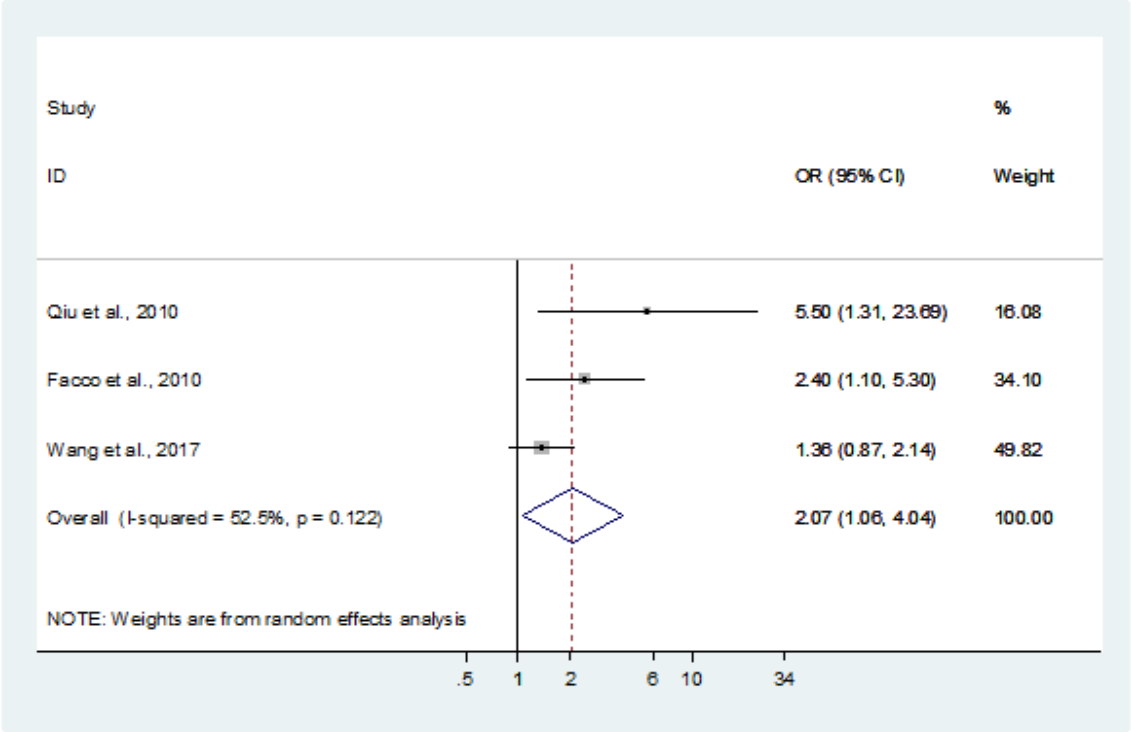

Figure 3-6 Forest plot summarising the ORs of studies that examined the relationship between short sleep duration and GDM using adjusted models that did not include possible mediators

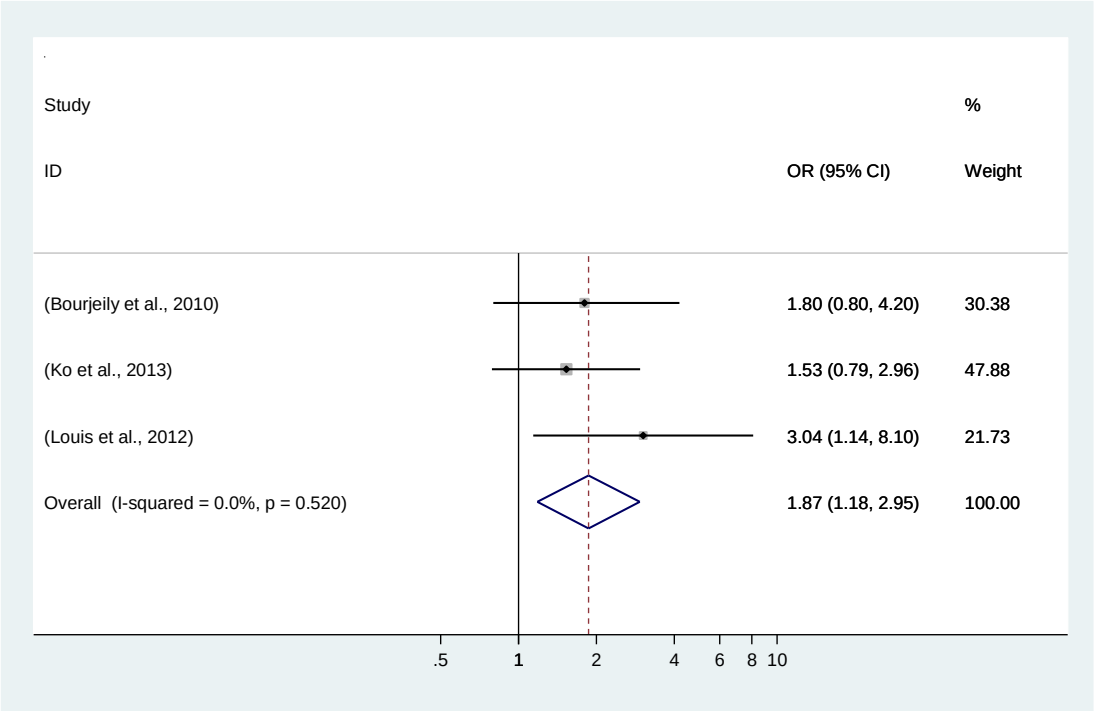

Figure 3-7 Forest plot summarising the ORs of studies that examined the relationship between OSA and caesarean delivery using adjusted models that did not have any possible mediators

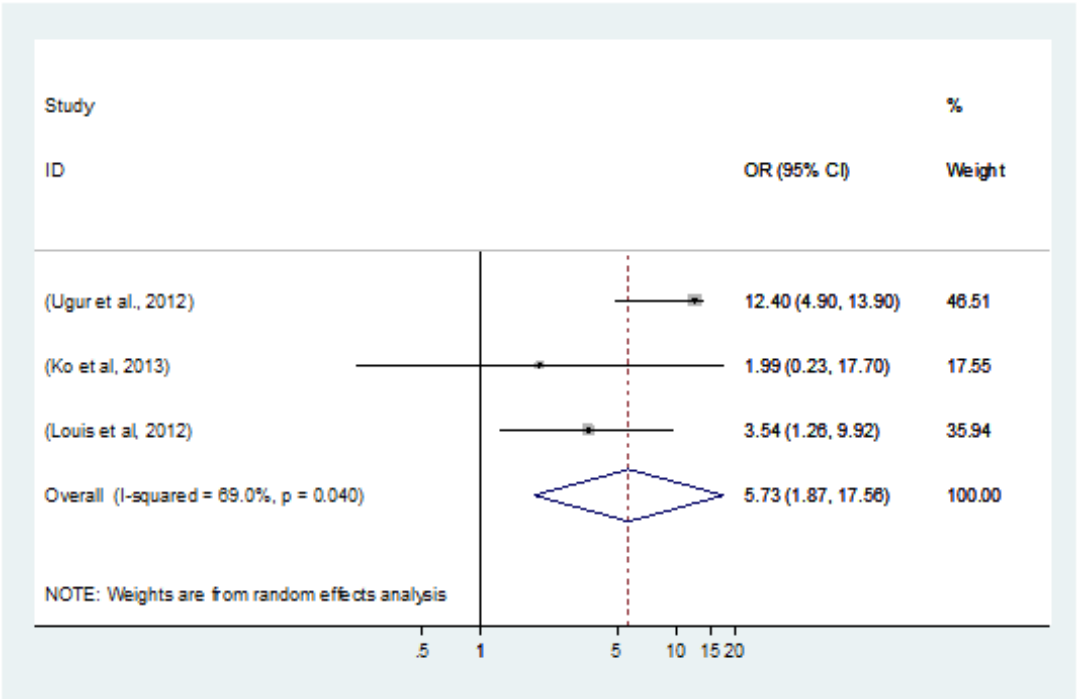

Figure 3-8 Forest plot summarising the ORs of studies that examined the relationship between OSA and pre-eclampsia adjusted models that did not have any possible mediators

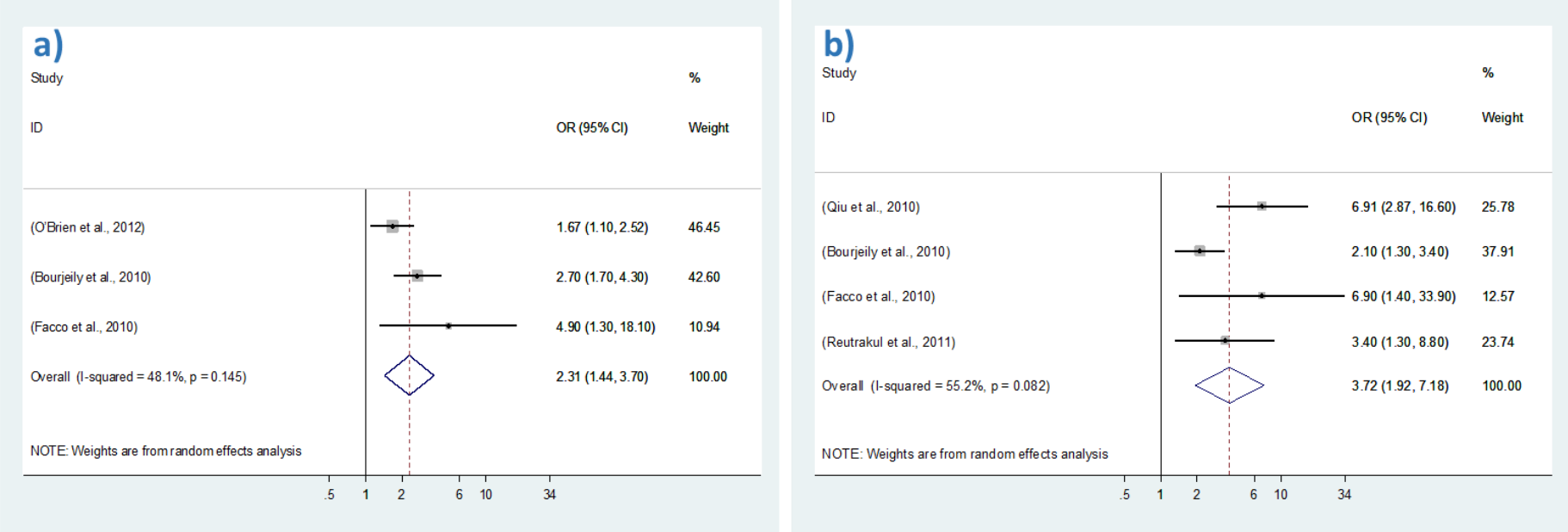

Figure 3-9 Forest plot summarising the ORs of studies that examined the relationship between snoring and GDM using un-adjusted (a) and adjusted models that had no mediators (b).

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3.4 Discussion

3.4.1 Limitations

By far, the most serious limitations of the review described in the present chapter were as follows:

First, the limited numbers of studies on (some) unfavourable sleep events and (some) pregnancy outcomes. Unfortunately, as seen in Table 3-11 many of the pregnancy outcomes have not yet been fully examined in relation to all of the unfavourable sleep events examined. Indeed, since sleep is likely to be a multifactorial, complex phenomenon, in order to understand its full effect on pregnancy outcome this will require examining all measurable sleep characteristics in relation to each of the outcomes of interest concerned.

Second, the extensive evidence of methodological heterogeneity in the studies (and their models) observed/as extracted and summarised. The extent of this heterogeneity amongst studies limited the number of models that could be combined in subsequent meta-analyses, and required substantial care to be taken to examine in great detail the range of different study designs used; the range of exposures, outcomes and covariates measured; the range of different measures used for each cognate exposure and outcome, the timing of such measurements, and the treatment of such data (e.g. if and how categorical variables were derived from the raw data); and the range of different analytical techniques and covariates included in the covariate adjustment sets used by each analytical model.

In addition, this review was prone to a number of limitations that remain commonplace for all such reviews, including:

I. The potential risk of not identifying or including all available studies due to possible limitations in the search protocol or the search inclusion criteria used;
II. The inappropriate classification of covariates acting as confounders vs. mediators during the design and/or analysis of each primary study;
III. The limited external validity (generalizability) of results due to limitations in the study's exclusion/inclusion criteria, its setting and/or design;
IV. The insufficient information available about the quality of the data used and how (if at all) missing data were treated in any of the primary studies included.
V. The small sample sizes of many of the primary studies (as well as the lack of power/sample size calculations to assess the impact of this) which would

increase the chance of type II errors (finding the absence of an association between sleep and poor pregnancy outcomes when an association exists) and decrease the power of any analyses as well as the precision of their estimates.

VI. The absence of adequate adjustment for multiple testing which might increase the chance of type I errors (finding, in this instance, the presence of an association between sleep and poor pregnancy outcomes when no such association actually exists).

VII. The possibility of publication bias, especially considering that *only* papers describing at least one statistically significant finding were found in the review's search of the literature, even though their designs/methods suffered at least one of the limitations mentioned earlier.

In the forest plots summarized below (Figure 3-10), studies with smaller samples of participants commonly had effect sizes/coefficient estimates situated towards the right hand extremes of the graphs, as their ORs tended to be much larger than the null with 95% CIs that did not include 1.0 (i.e., indicative of a 'statistically significant' finding). In contrast, most of the studies with larger sample sizes tended to report at least one regression model in which the effect size/coefficient estimate did *not* achieve formal 'statistical significance' and were aggregated closer to (or either side of) the null, 1.0. This is likely to reflect the fact that studies with smaller sample sizes usually have less statistical power and a higher chance of type II errors than studies with larger sample sizes, particularly in the absence of *a priori* sample size/power calculations used to inform sampling. Hence, one would expected to find more of the studies with smaller sample sizes reporting findings that did not achieve formal 'statistical significance', and fewer such studies with larger sample sizes. However, in this review, approximately two-thirds of the articles examined (n= 17) had relatively modest sample sizes (of ≤500 participants) yet reported 'statistically significant' estimates with large ORs. As sample sizes increased, fewer of the reported models achieved formal 'statistical significance' – which constitutes *prima facie* evidence of publication bias.

Whilst the failure to access unpublished studies (or *all* published studies) and to include foreign language studies may have contributed to the appearance publication bias (Dickersin, 1990); approximately 63% of the articles included had been published in English-speaking countries, and only three articles included in the search were written in a non-English language. The latter suggests that restricting the search to English language articles had, at most, only a very minor influence on the magnitude of potential publication bias, since only a small number

of published studies on this topic had been performed in non-English-speaking countries (and fewer still had been published in a language other than English).

With regard to the generalisability of the results (whether from each specific study or from the meta-analyses undertaken), limited information was generally available about the socioeconomic status of many of the studies' participants, and most of the studies applied exclusion criteria (including for social characteristics, such as English language proficiency) that are likely to have limited the external validity/generalizability of their findings. This is because, for example, language proficiency might reflect both ethnicity and/or socioeconomic status, so that excluding participants with limited English language proficiency might inevitably lead to selection bias. Furthermore, it is notable that more than two-thirds of the published studies took place in the USA, and that none had been conducted in the UK. The disproportionate geographical distribution of studies might therefore limit the wider, international generalisability of the results reviewed due simply to the influence of environmental factors on sleep events and pregnancy outcomes that differ internationally.

Finally, in the vast majority of the studies reviewed insufficient information was provided concerning current and pre-pregnancy medical health conditions of the participants included. In some studies participants with specific health conditions, such as gestational diabetes (GDM), were excluded from the sample. Some such conditions, not least GDM, affect a substantial proportion of pregnant women and are displaying a gradual increase over time (e.g. GDM affects about 2–7% of pregnant women and has increased substantially over the last 20 years; Lawrence et al., 2008, Ben-Haroush et al., 2004). Excluding women with such conditions from any given study sample means that it may not be appropriate to apply the research findings of that study to them, especially when (as is the case for conditions such as GDM) the conditions themselves increase the risk of *both* unfavorable sleep events *and* poor pregnancy outcomes (albeit depending upon the time at which sleep and the conditions concerned are measured). One would therefore expect to find potentially different results amongst currently published studies and pregnant women experiencing such conditions, and knowledge in this regard remains scarce.

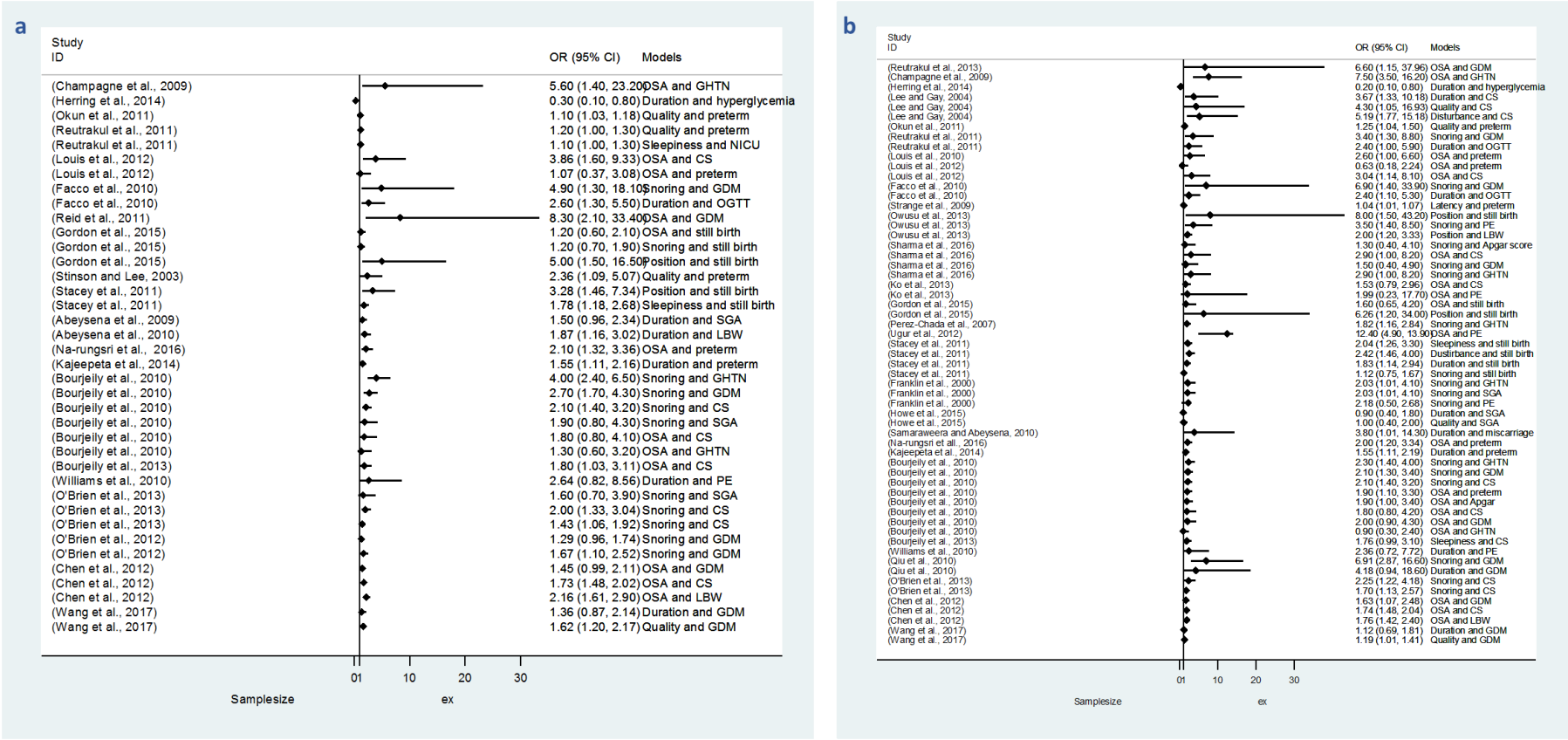

Figure 3-10 Forest plot summarising the un-adjusted (a) and adjusted (b) ORs of the regression models reported in the included references

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3.4.2 Key findings

The aim of this review was to evaluate the findings of published studies examining the association between sleep and pregnancy outcomes. It found that only a very limited number of studies had examined the association between unfavourable sleep events and pregnancy outcomes; and that not all unfavourable sleep characteristics and pregnancy outcomes had received an equal level of attention in the literature. Indeed, some sleep events (i.e. latency, disturbance and daytime sleepiness) and some pregnancy outcomes (i.e. Apgar score, birth weight and late maternal pregnancy events) have not been examined at all to-date. Nonetheless, despite the relatively few sleep characteristics and pregnancy outcomes examined, there was still evidence of a general tendency towards positive associations between unfavorable sleep and poor pregnancy outcomes in which unfavorable sleep characteristics were associated with an increased risk of poor pregnancy outcomes. However, much of this evidence had multiple methodological flaws, and there was some evidence of publication bias. These methodological flaws decreased the certainty offered by the current evidence available, and undermined the level of precision available – so that the summarized findings cannot be interpreted with substantial confidence and should be applied with circumspection and a degree of scepticism.

The review also found that the magnitude of the increased risk of poor pregnancy outcomes associated with unfavourable sleep characteristics varied according to the pregnancy outcome and/or sleep characteristic examined. This also varied in relation to a range of specific study design criteria, including: the design of the primary studies; the inclusion and exclusion criteria used in the recruitment of study participants; the gestational age at which sleep was measured; the choice of covariates included in any covariate adjustment sets; the appropriateness of any adjustment achieved; and the use of various reference points for what were considered ‘normal’ sleep characteristics as well as variation in the measurement tools used – all of which appeared to have affected the magnitude of the estimated risks, causing either an increase or decrease in the estimated ORs, and (in a few instances) appeared to have reversed the direction of the association observed. Although our assumptions regarding the possible impact(s) of these aspects of study design and analysis on the magnitude and direction of the estimated ORs might be true, the lack of the precisely estimated ORs made it difficult to assess or confirm with any degree of confidence whether these aspects were *actually* the reasons why substantial differences were evident amongst the estimated results.

However, considering these aspects of study design, data measurement and analysis, and their likely impact on the estimation of any casual pathway between sleep and pregnancy outcomes (while *also* considering the potential bidirectional nature of any relationship between sleep and the majority of covariates included in the regression models examined in this review), it is sensible to consider each of the following issues (each of which were discussed previously in the methodology chapter [Chapter 2, Section 2.4, page 60] when the original 'hypothesized' DAG was first presented and explained):

I. First, the importance of considering each study's design when specifying the relationship between sleep and pregnancy outcomes (particularly whether the design is retrospective or prospective).
II. Second, the importance of the temporal sequence of events, since this can be crucial when specifying the direction of any causal arc when dealing with potentially bidirectional relationships.
III. Third, the importance of reporting/knowing the time (i.e. the gestational age) at which sleep and other covariates were measured (to help avoid the inclusion of mediators in the covariate adjustment sets used).
IV. Fourth, the importance of carefully considering the timing of measurements when repeated measurements of sleep and/or other covariates are available (again, to help avoid the inclusion of mediators in the covariate adjustment sets used).

In addition to the covariates included in the hypothesized DAG described earlier in the present thesis, this was further elaborated by the inclusion of variables that had been adjusted for by one or more of the studies included in this chapter's review– each of which were carefully categorised as: sociodemographic indicators; behavioral risk indicators; current (and/or previous) maternal health indicators; current (and/or previous) obstetric-related variables; psychological indicators; and fetal health indicators. However, some of these (additional) variables were also considered likely to have had bidirectional relationships with sleep, and as such might have been likely to behave as mediators (rather than confounders) according to their position in the DAG.

3.4.3 Conclusion

In conclusion, this review of previous studies examining the association between (a range of) sleep (characteristics) and (a range of) pregnancy outcomes found some evidence that such associations do indeed exist. However, this evidence is limited in scope since not all measurable sleep characteristic and not all available pregnancy outcomes were examined by these studies; while sleep was never

‘holistically’ defined (an important consideration given its complex nature and substantial variability between each of the different trimesters of pregnancy). Additionally, the evidence summarized and appraised in the present review is highly variable in quality both in terms of data (quality) and the presence of a number of potential biases (most importantly selection bias and confounding bias). Finally, many of the evidence summarized herein came from studies that appear severely underpowered.

Meanwhile, the possibility of publication bias may indicate that much of the currently published evidence is prone to type I and type II error – not least because the majority of published results are nominally ‘statistically significant’ even though many of the studies involved appear underpowered. As such, it seems likely that the currently available/published evidence overestimates the strength of the relationship between sleep and pregnancy outcomes.

3.4.4 Recommendations

Further research is needed in this area with: greater consistency in the measurement of sleep and pregnancy outcomes (particularly with regard to the reference point used, the measurement tool used, and the gestational age when sleep was measured); more evidence from less commonly examined sleep characteristics and pregnancy outcomes (particularly sleep latency and macrosomia, respectively); and more robust study designs and analytical techniques (particularly as regards sampling, power estimation and adjustment for confounding). There is also scope for extending the research undertaken to include more participants with additional risks of poor pregnancy outcome (such as those with gestational diabetes or those at risk of diabetes), who are often excluded from existing study populations. Improving the conceptualization of sleep (beyond the definition and measurement of its many disparate, yet inherently related, characteristics and components), would also be worth pursuing (using, for example, latent class analysis).

Chapter 4 Sleep Patterns in the United Kingdom Population: a latent class analysis of the UKHLS

4.1 Introduction

Sleep is a complex phenomenon which, though amenable to objective study (in most detail using polysomnography), also has important experiential characteristics that are cognitive and subjective (Carskadon and Dement, 2017). While there remains substantial debate on how best to measure sleep, and how best to distinguish the specific components and characteristics these measurements generate, it remains clear that: different measurements offer different perspectives on these different components and characteristics (Kryger et al, 2011, Van Den Berg et al, 2008); some components and characteristics are associated with sociodemographic, behavioural and clinical factors (Arber et al, 2009) . These associations include evidence that sleep may cause, and be caused by, a variety of disease states – evidence that has led to a resurgence of interest in the role of sleep in the aetiology of disease, and the potential role that sleep-enhancing interventions might play in disease prevention and treatment (Cappuccio et al, 2010, Alvarez and Ayas, 2004). However, despite growing acceptance that sleep plays a significant role in memory consolidation and mental health, and mounting evidence that sleep is likely to be both a cause and a consequence of poor somatic health, there remain few non-pharmacological interventions (beyond 'sleep hygiene' advice) that are amenable to experimentation, and limited experimental evidence that 'enhancing' sleep may have therapeutic benefits in non-clinical populations (Reid et al, 2006, Montgomery and Dennis, 2004). For this reason, much of the current evidence base linking variation in sleep to variation in health is based on studies adopting observational designs and dependent upon observational data (Cappuccio et al, 2010, Alvarez and Ayas, 2004). These studies face a theoretical and methodological challenge that is common to many analyses of observational data where there are multiple measureable characteristics of a single phenomenon, yet little firm knowledge of the functional causal relationships between these. In the absence of such knowledge it is difficult to apply recent developments in causal path modelling to design statistical models capable of confidently adjusting for confounders (variables causing both the exposure and outcome of interest) while avoiding inappropriate adjustment for mediators (variables forming part of the causal path between the exposure and the outcome).

As summarised in the previous chapter, in the literature sleep has tended to be examined as a potential determinant of pregnancy outcomes using one single sleep characteristic at a time. Occasionally, multiple characteristics have been included in a single analytical model, though without a proper understanding of how these characteristics might be functionally or causally related to a more 'holistic' concept of sleep *per se*, or how these characteristics might interact with one another. Indeed, it seems most likely that sleep is a complex phenomenon, best described in quantitative terms as a latent variable, measured using multiple indicators rather than any single characteristic.

Notwithstanding this 'holistic' view of sleep, it is important to recognise that what might constitute 'normal' sleep is likely to vary dramatically between individuals – such that what is considered 'normal' for one individual may be experienced as 'abnormal' for another. Furthermore, because sleep varies from one night to the next, it is likely to be challenging to measure sleep using rigid cut-off points for 'normal' vs. 'abnormal' sleep without incurring substantial measurement error.

The present chapter aimed to address these issues by applying Latent Class Analysis (LCA) to a large contemporary dataset with data on a range of different sleep characteristics, and thereby establish whether these characteristics might (when considered together, in a more 'holistic' fashion) reflect any hitherto hidden sleep 'patterns'. The present Chapter also aimed to assess the temporal stability of any LCA-identified sleep patterns (using data on sleep characteristics collected twice from the same individuals) and to assess whether any such patterns are associated with sociodemographic and/or clinical variables. As such the present Chapter aimed not only to establish whether sleep patterns might be identified from data on multiple sleep characteristics, but also whether these patterns display temporal stability and appear sensitive to sociodemographic, behavioural and clinical characteristics thought to influence (and/or to be influenced by) sleep.

4.2 Methods

4.2.1 Data source

The data used in the present chapter were taken from Waves 1 and 4 of the UK Household Longitudinal Study (UKHLS) which was accessed through the UK Data Archive website during 2014 -2016 (Chapter 2, Section 2.2.1, page 17). These data were originally gathered by the National Centre for Social Research (NatCen) and the Central Survey Unit (CSU) under the direction of the UK Longitudinal Studies Centre (University of Essex. Institute for Social and Economic Research and NatCen Social Research, 2015).

The UKHLS is a large ongoing study covering most of the UK's geographical area, and has a sampling design that aims to generate participants who are representative of the UK population as a whole. The study includes questionnaire items covering many of the most commonly studied sleep components (i.e. as evident in the literature on sleep reviewed earlier in this thesis), as well as items generating data on sociodemographic, behavioural and health-related clinical features which permit further examination of their relationships with sleep using latent class analysis (see: Chapter 2, Section 2.1.2.1, page 47).

4.2.2 Study design

4.2.2.1 'Temporal stability' study

A cross-sectional design was initially used to generate the latent class sleep models for both Waves 1 and 4 separately, first using participants who had participated in both Waves. Thereafter, a longitudinal study design was used to compare the stability of the resulting latent sleep models from each Waves (i.e. at Wave 1 vs. Wave 4) over time.

4.2.2.2 'Correlates of latent sleep classes' study

After assessing the stability of sleep models over time, a third sample of participants (comprising all those offering responses to the survey's questionnaire sleep items; and based on the very first time each participant answered these items [be that in Wave 1 or in Wave 4]) was analysed to identify latent sleep classes from the largest possible sample of participants available. For assessing the sociodemographic, behavioural and clinical correlates of latent sleep classes, relevant data were extracted from responses given to items in the same wave as that providing the sleep data used. (i.e. the sociodemographic/behavioural/clinical data generated from the questionnaire in which participants first gave responses to the sleep items).

4.2.3 Participants

As sleep data were only available from the questionnaires used in Waves 1 and 4 of the UKHLS, only participants providing responses to from these two UKHLS Waves were eligible for inclusion in the present chapter.

Male participants as well as female participants were included in the present chapter's analyses to identify the latent sleep patterns amongst the UK population, while analyses of their relationship(s) with pregnancy outcomes necessarily include only (pregnant) women. This two-stage process was considered necessary for the following reasons;

First, the aim was to discover all possible, stable sleep patterns amongst UKHLS participants, and since women might share similar pattern with men we aimed to maximize the number of participants involved.

Second, since the aim was then to describe the distribution of sleep in women as compared to men, subsequent analyses were *then* conducted to establish which patterns were more/less commonly associated with female participants.

Finally, the aim of these (gender-disaggregated) analyses was to examine whether pregnant women's sleep patterns differed in comparison to those of the general population (i.e. male and female), since the literature contained claims that pregnant women's sleep was substantively less 'favourable' than the population as a whole (claims that therefore required conducting latent class analyses not only in pregnant women, but also amongst female participants separately and male and female participants combined).

4.2.3.1 Temporal stability study

Male and female participants who participated in both Waves 1 and 4 of the UKHLS and had complete sets of sleep data were included in the the sub-studies that examined the stability of the latent class analysis approach over time when using the UKHLS sleep module.

4.2.3.2 'Correlates of latent sleep classes study'

Male and female participants who participated in Wave 1 and/or Wave 4 and had complete sets of sleep data were included in the latent class analysis to generate the UK population sleep clusters .

4.2.4 Measurements

4.2.4.1 Sleep variables

To generate the sleep clusters in the temporal stability and correlates of sleep classes studies, all seven sleep variables generated by items in the UKHLS sleep module were used: sleep duration, latency, sleep disturbances due to snoring or coughing, use of medication to help with sleep, next-day sleepiness, sleep disturbance, and perceived sleep quality.

4.2.4.2 Coding of sleep variables

The sleep variables, which include latency, disturbance, snoring and/or coughing, usage of medication and next-day sleepiness, were re-categorized using fewer categories (3 ordinal categories) to make it easier to visualise more distinguished patterns of variations between the generated clusters when conducting the latent analysis (Table 4-1). The following classification was carried when categorising the

variables; absent, non-habitual (< 3 events a week) and habitual (≥ 3 times a week), as it was the classification most often used in the literature and the classification of insomnia symptoms used by the DSMVI (Amarican Psychiatric Association, 2013). Sleep duration was categorised into four categories, using similar to the Pittsburgh Sleep Quality Index (PSQI; Buysse et al, 1989) scoring categories (Table 4-1; the sleep questionnaire most commonly used by sleep researchers). This categorisation was chosen to facilitate comparison of any sleep patterns identified in the present chapter with those described in the literature.

Table 4-1 The seven items in the Understanding Society Sleep Questionnaire, together with the original response categories and the categories adopted to facilitate comparison with studies using the PSQI.

Sleep questions	Original responses	Responses after reducing the numbers of categories
Q1: "How many hours of actual sleep did you usually get at night during the last month? Note: This may be different than the actual number of hours you spent in bed".	*Reported in hours and minutes*	Reference: *≥7 hours* *Short: ≥6 and <7 hours* *Restricted: ≥5 and <6 hours* *Severely restricted: <5 hours*
Q2: During the past month, how often have you had trouble sleeping because you "Cannot get to sleep within 30 minutes"?	*1. Not during the past month* 2. *Less than once a week* 3. *Once or twice a week* 4. *Three or more times a week* 5. *More than once most nights*	*1. Not during the past month (1)* *2. less than three times a week (2&3)* *3. Three or more times a week (4&5)*
Q3: During the past month, how often have you had trouble sleeping because you "Wake up in the middle of the night or early in the morning"?	*1. Not during the past month* 2. *Less than once a week* 3. *Once or twice a week* 4. *Three or more times a week* 5. *More than once most nights*	*1. Not during the past month (1)* *2. less than three times a week (2&3)* *3. Three or more times a week (4&5)*
Q4: During the past month, how often have you had trouble sleeping because you "Cough or snore loudly"?	*1. Not during the past month* 2. *Less than once a week* 3. *Once or twice a week* 4. *Three or more times a week* 5. *More than once most nights*	*1. Not during the past month (1)* *2. less than three times a week (2&3)* *3. Three or more times a week (4&5)*
Q5: During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	1. *Not during the past month* 2. *Less than once a week* 3. *Once or twice a week* 4. *Three or more times a week*	*1. Not during the past month (1)* *2. less than three times a week (2&3)* *3. Three or more times a week (4)*
Q6: During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	1. *Not during the past month* 2. *Less than once a week* 3. *Once or twice a week* 4. *Three or more times a week*	*1. Not during the past month (1)* *2. less than three times a week (2&3)* *3. Three or more times a week (4)*
Q7: During the past month, how would you rate your sleep quality overall?	1. *Very good* 2. *Fairly good* 3. *Fairly bad* 4. *Very bad*	*1. Good (1&2)* *2. Bad (3&4)*

4.2.4.3 The coding of sleep variables included in the exploratory regression analyses

When running the regression analyses to evaluate the association between each of the seven self-reported sleep characteristics and each of the sociodemographic, and health characteristics, all of the sleep variables were re-categorised as binary variables. The rationale for using binary variables was to permit comparison of the logistic odd ratios generated for analyses of each sleep characteristic with those generated for analyses of any/each LCA-derived sleep cluster.

Sleep duration was categorized as ≥7 hours and < 7 hours, while sleep latency, disturbance, snoring and/or coughing, next-day sleepiness and sleep medication was categorised as 'ever versus never'. Sleep quality was categorised as very/fairly good vs. fairly/very bad.

Sociodemographic features (i.e. age, gender, current employment status, household composition and highest educational qualification achieved) were used to study the associations between each of the seven sleep characteristics and each/any sleep cluster. Data on each of the sociodemographic variables used were extracted from the same wave as that providing the self-reported sleep data. Most of the sociodemographic variables were re-categorised to simplify those with large numbers of response categories, thereby ensuring that there were likely to be sufficient numbers of participants in each of the reduced categories to permit robust analysis.

A full description of how each of the sociodemographic variables were categorised (before and after re-categorisation) is available in the appendices. A brief summary is provided below:

I. Age was re-categorised into: ≤19 years, 20-39years, 40-59 years and ≥60 years.
II. Education was re-categorised into: 'A' level or above vs. GCSE level or 'other'
III. Occupation was categorised into: employed, unemployed, sick or disabled, in training/education, and retired
IV. Household structure was categorised into: Single without children, Single with children, Couple without children, and Couple with children

4.2.4.4 Health indicators

Three indicators were chosen to provide measures of participant health, including the physical and mental components of the eight items of the SF12v (a shorter version of the SF36v developed by Quality Metric Incorporate; Quality Metric Inc.,

2007). These were used to subjectively evaluate each participant's well-being and functional health, including the first item of the SF12v (which provides a general subjective evaluation of an individual's overall health). The physical and mental components of the SF12v were originally rated from 0 to 100, where the higher the score, the 'healthier' the participant. The components were re-categorised into three equal categories (i.e. 66, <66 and ≥ 32, <32) using 'norm scoring' (i.e. based on the mean [M=50] and standard deviation [SD=16]; see Table 8-12). Likewise, the general health variable was re-categorised into a binary variable: 'excellent to good' and 'fair to poor'. For further detail with regard to the SF12v questionnaire please refer to the appendices (see Chapter 8, Section 8.3.1, page 314).

4.2.5 Ethical considerations

Ethical approval for the main survey of the UKHLS was obtained from the Ethics Committee of the University of Essex on 6 July 2007 for Wave 1, and on 17 December 2010 for Wave 4 (Gundi, 2016).

4.3 Analysis

4.3.1 Descriptive analysis

4.3.1.1 Missing data

The following responses were recorded as missing: 'I do not know', 'proxy', 'refused' and 'inapplicable'. The patterns of missing data observed suggested that where data for one variable was missing, data for many/most of the other variables were also missing. In these instances case-wise deletion (i.e. excluding participants with missing data on any of the variables of interest) was applied.

In this way, cases/participants with missing sleep data were excluded from the latent class analyses used to identify/generate 'sleep clusters'. At the same time, cases with missing sociodemographic data (age, gender, education, household composition, employment) and/or missing health data (i.e. SF12v mental and physical components, general health) were also excluded case-wise, prior to conducting the regression analyses.

4.3.1.2 Participants characteristics

Frequencies and percentages were used to describe the distribution of the seven sleep characteristics and each of the sociodemographic and health variables amongst participants included in the analyses conducted in the present chapter.

4.3.2 Latent class analyses (LCA)

In the LCA the seven sleep variables were used as indictors of a complex latent structure that was envisaged as having multiple categories (or 'clusters') within which participants could be placed/classified. These classifications were based on the principal of identifying participants who shared common patterns in their responses to the sleep questions, and calculating the probability of each participant being classified within each sleep cluster (Lazarsfeld and Henry, 1968, Goodman, 1974)

A latent class analysis was used to generate sleep clusters for both the temporal stability and correlates of sleep classes studies. First, exploratory analyses were conducted to generate models with a range of different numbers of clusters. Each of the information criteria (i.e. BIC and AIC) statistics as well as measurement of entropy statistics (i.e. R^2 and estimation error) were used to compare different latent models with differing numbers of clusters. In each case, the lower the information criteria and the higher the R^2 statistic the more robust the model was considered to be, after considering the number of parameters included (since this penalises the statistics; Vermunt and Magidson, 2005).

Latent Gold 4.5 software (Statistical Innovations Inc., 2009) was used to generate the latent sleep clusters. It calculated the posterior probability of a participant being a member of each cluster, and it then assigned each individual to the cluster with the highest probability using the maximum likelihood (Vermunt and Magidson, 2005).

4.3.3 Regression analysis

For participants with complete sleep, sociodemographic and health indicator data who also participated in Wave 1 and/or Wave 4, logistic regression analysis was used to examine the association between each of the socio-demographic characteristics, the health indicators and: the seven sleep variables; or the sleep clusters assigned to participants generated using LCA.

After generating the latent sleep clusters using Latent Gold these were later transferred to STATA-v13 software (StataCorp., 2013) as multinomial variables before separating the categories into 6 binary variables with 'yes' or 'no' coding. At this stage the multinomial regression was not considered ideal for the following reasons:

1- The multinomial regression estimated the risk of several categories relative to a single referent category yet, at this stage, it was not clear which category should be chosen as the referent.

2- The multinomial regression approach would not estimate the risk for participants classified within any given referent category, and this was suboptimal given the intention was to estimate the risk for each category.
3- By coding the latent sleep variable that had six categories into six binary variables with six different referents, it would be possible to understand the risk relationship of each category by estimating their ORs and comparing these with the OR of each sleep characteristic. This approach was intended to assist in deciding which reference point might be used when running the regression models in the next two chapters using the latent sleep variable.

The minimal sufficient adjustment sets in these regression models were specified using a directed cyclic graph (DAG) - a graphical tool in which the relation between the variables of interest are presented using unidirectional arrows that symbolise the direction of potential causal effects between variables. It was generated using open source software DAGitty (Textor et al., 2017).

4.4 Results

As illustrated in Figure 4-1, the total number of participants who participated in both Waves 1 and 4 and who had complete sleep data in both waves (and thus were included in the temporal stability study) was n=19,442. In contrast, the number of participants who participated in *either* Waves 1 and/or 4 and had complete sleep data (and were therefore in the correlates of sleep classes study) was n=45,141.

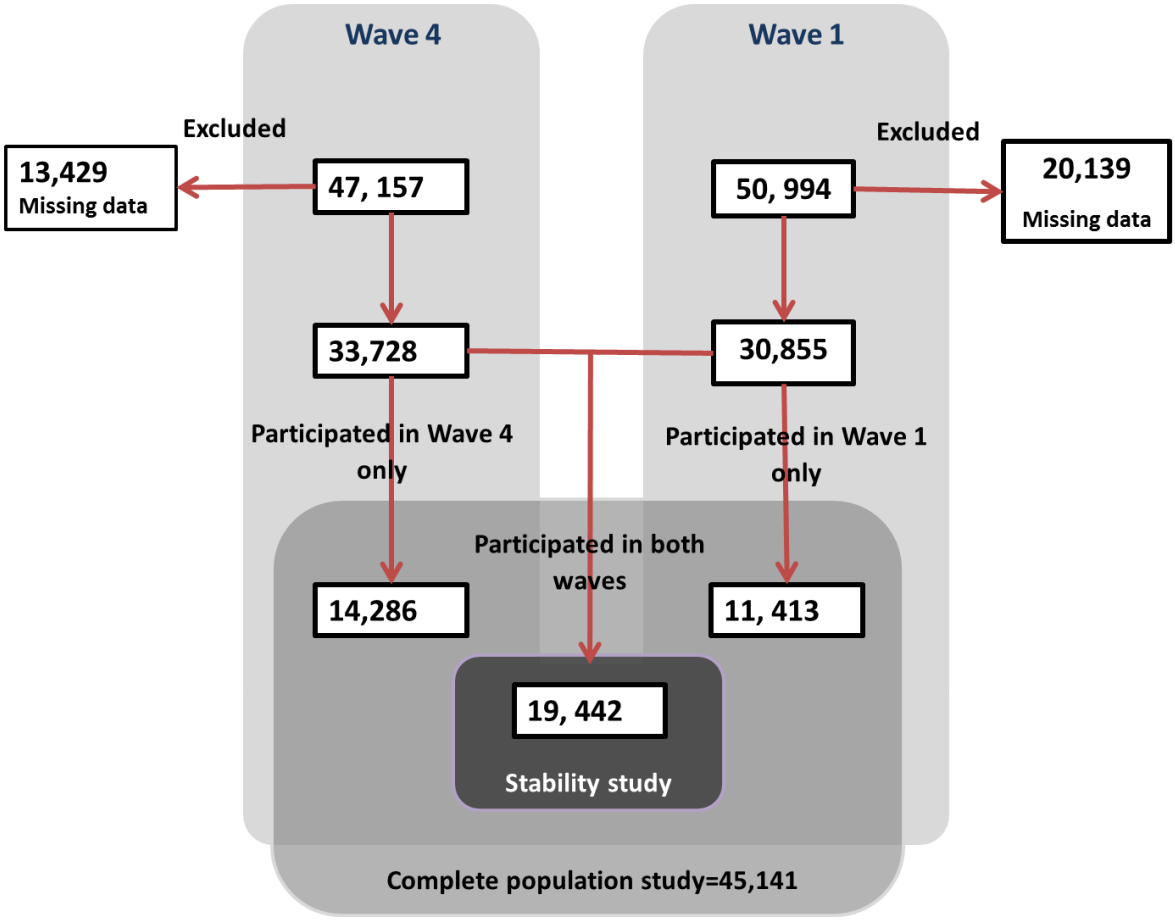

Figure 4-1 Flow chart of participants who participated in Waves 1 and/or 4 of the UKHLS and were involved in the temporal stability study and/or the correlates of sleep classes study.

4.4.1 Results of the descriptive analysis

4.4.1.1 Missing data

4.4.1.1.1 Mechanism of missing data

In Wave 1, the majority of missing data was secondary to a 'failure to collect data' (i.e. data missing or unattainable from proxy respondents). Indeed, only 19 of the participants who were contacted refused to answer the sleep questions, the majority of these being female (n=15), who did not appear to belong to any specific age, employment or household composition group. Indeed, their education was equivalent to GCSE or other in 11 out of 15 (see Table 4-2).

Likewise, the majority of missing data in Wave 4 was due to an inability to contact participants (i.e. proxy, missing). Only seven participants refused to answer any of the sleep questions. These were mostly males (n=5) who, again, did not appear to belong to any specific age, education, employment or household composition group.

Elsewhere, the majority of the ‘I do not know’ responses were recorded under the ‘snoring or coughing’ sleep item. These participants were primarily female (n=280) and tended to be aged 70 or older (n=129). In addition, the majority of these also had missing data on many of their sociodemographic characteristics.

Based on Table 4-2 and Table 4-3, it can be observed that where data on any one sleep item were missing, then the data for other sleep items also tended to be missing.

4.4.1.1.2 Characteristics of missing data

The distribution of missing data amongst each of the sociodemographic characteristics was comparable to the distribution of participants with incomplete sleep data (Table 4-4). Indeed, the distribution of missing data did not appear to be dependent on particular sociodemographic features or clustered amongst groups with specific characteristics.

Table 4-2 Known mechanisms underlying the (non)reporting of missing data for sleep items in Wave 1 of the UKHLS.

	Wave 1										
	Missing		Proxy		Refused		Inapplicable		I don't know		Total number
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	
Duration	9,339	74.00	3,262	25.85	19	0.15	0	0.00	0	0.00	12,620
Latency	10,631	76.52	3,262	23.48	0	0.00	0	0.00	0	0.00	13,893
Disturbance	9,968	75.34	3,262	24.66	0	0.00	0	0.00	0	0.00	13,230
Snoring	13,735	80.81	3,262	19.19	0	0.00	0	0.00	0	0.00	16,997
Sleepiness	8,007	71.05	3,262	28.95	0	0.00	0	0.00	0	0.00	11,269
Medication	7,953	70.91	3,262	29.09	0	0.00	0	0.00	0	0.00	11,215
Quality	7,511	69.72	3,262	30.28	0	0.00	0	0.00	0	0.00	10,773
Total number	15,877	82.87	3,262	17.03	19	0.10	0	0.00	0	0.00	19,158

Table 4-3 Known mechanisms underlying the (non)reporting of missing data for sleep items in Wave 4 of the UKHLS.

	Wave 4										
	Missing		Proxy		Refused		Inapplicable		I don't know		Total number
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	
Duration	15	0.37	3,940	98.01	2	0.05	0	0.00	65	1.62	4,020
Latency	14	0.35	3,940	98.99	2	0.05	0	0.00	24	0.60	3,980
Disturbance	14	0.35	3,940	99.14	2	0.05	0	0.00	18	0.45	3,974
Snoring	14	0.32	3,940	99.24	2	0.05	0	0.00	485	10.92	4,441
Sleepiness	13	0.33	3,940	99.24	1	0.03	0	0.00	17	0.43	3,970
Medication	14	0.35	3,940	99.42	2	0.05	0	0.00	7	0.18	3,963
Quality	14	0.35	3,940	98.80	2	0.05	0	0.00	32	0.80	3,988
Total number	15	0.33	3,940	86.25	7	0.15	0	0.00	606	13.27	4,568

Table 4-4 Sociodemographic characteristics of missing and complete sleep data in Waves 1 and 4 of the UKHLS.

	Wave 1 (n=50,994)				Wave 4 (n=47,157)			
	Complete sleep items		Missing sleep items		Complete sleep items		Missing sleep items	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Gender								
Male	14,397	45.22	8,811	45.99	18,883	44.34	2,903	63.55
Female	17,439	54.78	10,347	54.01	23,706	55.66	1,665	36.45
Missing	0	0	0	0	0	0	0	0
Age								
≤19 years	2,332	7.33	1,054	5.50	2,752	6.46	462	10.11
20-39years	11,806	37.08	5,666	29.58	12,255	28.78	1,669	36.54
40-59 years	11,083	34.81	6,313	32.95	15,253	35.81	1,468	32.14
≥ 60 years	6,615	20.78	6,125	31.97	12,329	28.95	969	21.21
Missing	0	0	0	0	0	0	0	0
Education								
A level and above	18,256	57.34	7,826	40.85	23,297	54.70	2,205	48.27
GCSE level and others	13,569	42.62	11,251	58.73	18,520	43.49	2,157	47.22
Missing	11	0.03	81	0.42	772	1.81	206	4.51
Occupation								
Employed	18,600	58.42	8,881	46.36	23,257	54.61	2,648	57.97
Unemployed	4,080	12.82	2,990	15.61	4,661	10.94	471	10.31
Sick or disabled	1,226	3.85	1,132	5.91	1,726	4.05	238	5.21
Full time training or education	2,694	8.46	1,208	6.31	2,907	6.83	506	11.08
Retired	5,230	16.43	4,941	25.79	10,036	23.56	702	15.37
Missing	6	0.02	6	0.03	2	0	3	0.07
Household composition								
Single with children	2,938	9.23	1,857	9.69	3,434	8.06	334	7.31
Single without children	6,460	20.29	4,756	24.83	8,876	20.84	734	16.07
Couple with children	10,465	32.87	5,496	28.69	13,154	30.89	1,607	35.18
Couple without children	11,973	37.61	7,049	36.79	17,125	40.21	1,893	41.44
Missing	0	0	0	0	0	0	0	0
General health								
Excellent to good	25,987	81.63	13,916	72.64	33,758	79.26	3,526	77.19
Fair to poor	5,837	18.33	5,160	26.93	8,827	20.73	1,019	22.31
Missing	12	0.04	82	0.43	4	0.01	23	0.50
Physical wellbeing								
≥ 66	167	0.52	95	0.50	163	0.38	4	0.09
<66 and ≥ 32	29,021	91.16	13,101	68.38	34,938	82.04	398	8.71
<32	2,560	8.04	2,456	12.82	3,712	8.72	94	2.06
Missing	88	0.28	3,506	18.30	3,776	8.87	4,072	89.14
Mental wellbeing								
≥ 66	270	0.85	233	1.22	304	0.71	3	0.07
<66 and ≥ 32	29,716	93.34	14,117	73.69	35,980	84.48	444	9.72
<32	1,762	5.53	1,299	6.78	2,529	5.94	49	1.07
Missing	88	0.28	3,509	18.32	3,776	8.87	4,072	89.14

4.4.1.2 Sociodemographic features and health

A very similar distribution of sociodemographic and health characteristics was evident within each of the samples selected for examination in the present chapter (i.e. Wave 1, Wave 4, temporal stability study and correlates of sleep classes study samples). Overall, the ratio of male to female participants was very similar, whilst the majority of participants were between 20 to 60 years of age, employed, had a partner, and were in good mental and physical health (Table 4-5).

4.4.1.3 Sleep characteristics

The sleep data of participants included in the temporal stability study displayed a very similar distribution as that from participants in Wave 1 or Wave 4 (see Table 4-6).However, in the correlates of sleep classes study (i.e. which data generated from the first response to the sleep questions was of key interest), there was an increase in the rate of the following events: next-day sleepiness (44.2%), habitual snoring or coughing (49.1%), habitual disturbance (62.1%), habitual latency (54.8%) and restricted sleep duration (45.8%; Table 4-6)

Table 4-5 Sociodemographic features of UKHLS participants included in each of the samples used to generate latent sleep clusters.

	Wave 1 Matched population		Wave 4 Matched population		Waves 1 and or 4 First time response		All Wave 1 participants		All Wave4 Participants	
	Frequency (n=19,442)	Percent (%=100)	Frequency (n=19,442)	Percent (%=100)	Frequency (n=45,121)	Percent (%=100)	Frequency (n=50,994)	Percent (%=100)	Frequency (n=47,157)	Percent (%=100)
Gender										
Male	8,479	43.61	8,479	43.61	20,456	45.32	23,208	45.51	21,786	46.20
Female	10,963	56.39	10,963	56.39	24,685	54.68	27,786	54.49	25,371	53.80
Missing	0	0	0	0	0	0	0	0	0	0
Age										
≤19 years	1,047	5.39	309	1.59	4,514	10	2,450	4.80	3,214	6.82
20-39years	6,505	33.46	5,977	30.74	15,742	34.87	17,470	34.26	13,924	29.53
40-59 years	7,473	38.44	7,823	40.24	15,043	33.32	17,396	34.11	16,721	35.46
≥ 60 years	4,417	22.72	5,333	27.43	9,842	21.80	12,740	24.98	13,298	28.20
Missing	0	0	0	0	0	0	0	0	0	0
Education										
A level and above	11,505	59.18	12,053	61.99	24,953	55.28	26,082	51.15	25,502	54.08
GCSE level and others	7,931	40.79	7,389	38.01	19,429	43.04	24,820	48.67	20,677	43.85
Missing	6	0.03	0	0	759	1.68	92	0.18	978	2.07
Occupation										
Employed	11,82	60.84	11,855	60.98	23,957	53.07	27,481	53.89	25,905	54.93
Unemployed	2,231	11.48	1,986	10.21	5,647	12.51	7,070	13.86	5,132	10.88
Sick or disabled	742	3.82	709	3.65	1,917	4.25	2,358	4.62	1,964	4.16
Full time training or education	1,154	5.94	585	3.01	4,835	10.71	3,902	7.65	3,413	7.24
Retired	3,483	17.91	4,307	22.15	8,782	19.45	10,171	19.95	10,738	22.77
Missing	3	0.02	0	0	3	0.01	12	0.02	5	0.01
Household condition										
Single with children	1,623	8.35	1,425	7.33	4,153	9.20	4,795	9.40	3,768	7.99
Single without children	3,541	18.21	3,935	20.24	8,782	19.45	11,216	21.99	9,610	20.38
Couple with children	6,562	33.75	6,074	31.24	14,962	33.15	15,961	31.30	14,761	31.30
Couple without children	7,716	39.69	8,008	41.19	17,244	38.20	19,022	37.30	19,018	40.33
[;pl/.'k;0Missing	0	0	0	0	0	0	0	0	3,768	7.99
General health										
Excellent to good	15,983	82.21	15,856	81.56	36,807	81.54	39,903	78.25	37,284	79.06
Fair to poor	3,453	17.76	3,586	18.44	8,328	18.45	10,997	21.57	9,846	20.88
Missing	6	0.03	0	0	6	0.01	94	0.18	27	0.06
Physical wellbeing										
≥ 66	92	0.47	78	0.40	216	0.48	262	0.51	167	0.35
<66 and ≥ 32	17,862	91.87	16,625	85.51	39,967	88.54	42,122	82.60	35,336	74.93
<32	1,488	7.65	2,739	14.09	3,558	7.88	5,016	9.84	3,806	8.07
Missing	0	0	0	0	1,400	3.1	3,594	7.05	7,848	16.64
Mental wellbeing										
≥ 66	158	0.81	124	0.64	363	0.80	503	0.99	307	0.65
<66 and ≥ 32	18,221	93.72	16,985	87.36	40,818	90.42	43,833	85.96	36,424	77.24
<32	1,063	5.47	2,333	12.00	2,560	5.67	3,064	6.01	2,578	5.47
Missing	0	0	0	0	1,400	3.1	3,594	7.05	7,848	16.64

Table 4-6 Sleep characteristics of UKHLS participants included in the samples used to generate latent sleep clusters

	Wave 1 Matched population		Wave 4 Matched population		Waves 1 and or 4 First time response		All Wave 1 participants		All Wave4 Participants	
	Frequency (n=19,442)	Percent (%=100)	Frequency (n=19,442)	Percent (%=100)	Frequency (n=45,121)	Percent (%=100)	Frequency (n=50,994)	Percent (%=100)	Frequency (n=47,157)	Percent (%=100)
Sleep duration										
≥7 hours	12,628	64.95	11,210	57.66	16,561	36.69	24,671	48.38	24,861	52.72
≥ 6 and < 7 hours	5,230	26.90	5,133	26.40	5,764	12.77	8,987	17.62	11,014	23.36
≥ 5 hours and <6 hours	901	4.63	1,974	10.15	2,164	4.79	3,091	6.06	4,516	9.58
<5 hours	683	3.51	1,125	5.79	20,652	45.75	1,625	3.19	2,745	5.82
Missing	0	0	0	0	0	0	12,620	24.75	4,021	8.53
Sleep latency										
Never	8,263	42.50	9,326	47.97	11,549	25.58	15,228	29.86	20,426	43.31
Non-habitual (<3nights a week)	7,568	38.93	6,419	33.02	8,848	19.60	14,063	27.58	13,769	29.20
Habitual (≥ nights a week)	3,611	18.57	3,697	19.02	24,744	54.81	7,810	15.32	8,982	19.05
Missing	0	0	0	0	0	0	13,893	27.24	3,980	8.44
Sleep disturbance										
Never	4,426	22.77	6,136	31.56	8,194	18.15	8,538	16.74	13,921	29.52
Non-habitual (<3nights a week)	7,678	39.49	6,535	33.61	8,898	19.71	14,270	27.98	13,847	29.36
Habitual (≥ nights a week)	7,338	37.74	6,771	34.83	28,049	62.14	14,956	29.33	15,415	32.69
Missing	0	0	0	0	0	0	13,230	25.94	3,974	8.43
Snoring or coughing										
Never	12,384	63.70	15,540	79.93	18,976	42.04	21,378	41.92	34,185	72.49
Non-habitual (<3nights a week)	4,200	21.60	2,241	11.53	3,989	8.84	7,393	14.5	4,894	10.38
Habitual (≥ nights a week)	2,858	14.70	1,661	8.54	22,176	49.13	5,226	10.25	3,637	7.71
Missing	0	0	0	0	0	0	16,997	33.33	4,441	9.42
Next day sleepiness										
Never	16,434	84.53	17,397	89.48	22,249	49.29	33,469	65.63	38,394	81.42
Non-habitual (<3nights a week)	2,711	13.94	1,701	8.75	2,940	6.51	5,516	10.82	3,841	8.15
Habitual (≥ nights a week)	297	1.53	344	1.77	19,952	44.20	740	1.45	951	2.02
Missing	0	0	0	0	0	0	11,269	22.10	3,971	8.42
Usage of sleep medication										
Never	16,452	84.62	17,981	92.49	22,764	50.43	32,827	64.37	39,651	84.08
Non-habitual (<3nights a week)	1,369	7.04	723	3.72	1,400	3.10	3,149	6.18	1,603	3.40
Habitual (≥ nights a week)	1,621	8.34	738	3.80	20,977	46.47	3,803	7.46	1,940	4.11
Missing	0	0	0	0	0	0	11,215	21.99	3,963	8.40
Sleep quality										
Good	15,299	78.69	15,547	79.97	20,594	45.62	31,124	61.03	34,343	72.83
Poor	4,143	21.31	3,895	20.03	24,547	54.38	9,097	17.84	8,826	18.72
Missing	0	0	0	0	0	0	10,773	21.13	3,988	8.46

4.4.2 Results of generating the sleep clusters

4.4.2.1 Choosing the best-fit model

In the temporal stability study, the best fitting model included six clusters in data from both Wave 1 and Wave 4. Both of these models were the simplest models, with the lowest BIC, AIC and estimation error as well as the highest R^2 (after accounting for the number of parameters examined). Similarly, the models with six clusters were chosen as the simplest models with the lowest BIC, AIC and estimation error as well as the highest R^2 (again, when considering the number of parameters used) in the subsequent 'correlates of sleep classes' sub-study (see Appendix, Section 8.3.2, page 316).

It is important to note, however, that when binary coding was used for the seven sleep indicators to generate the clusters (instead of the original categorisation), the temporal stability of the sleep clusters over time was lost. This loss of stability was evident in number of the differences in the patterns of sleep clusters that emerged between data from Wave 1 and 4, despite the fact that the number of clusters remained the same (see Appendix, Section 8.3.4, page 317).

4.4.2.2 Description of sleep patterns and clusters

In the temporal stability study, the best fitting models in both Waves (1 and 4) were models containing six clusters, with a number of similarities in patterns therein. Three clusters displayed essentially identical patterns (clusters 1, 3 and 6), whilst the remaining three clusters differed in the severity of restriction of sleep duration and/or the frequency of sleep latency. Inconsistencies in the contribution that sleep duration made was observed in clusters 2 and 4. In cluster 2, the relevant sleep duration changed from normal to short, while in cluster 4, the duration changed from short to restricted (i.e. one-hour difference). Likewise, in cluster 2, the frequency of sleep latency changed from non-habitual to habitual, while in cluster 5 this changed from non-habitual to no event (i.e. a change of just one adjacent category; Table 4-7 and Table 4-8).

Regardless of the stability of the six clusters between data generated in Wave 1 and Wave 4, there was also some evidence that participants 'moved' between sleep clusters from Wave 1 to Wave and 4 (i.e. their membership of sleep cluster changed over time; Table 4-9). Most such movements involved participants who moved from cluster 2 in Wave 1 to cluster 1 in Wave 4 (n=2,244, 58.4%), whilst the least number of participants moved from cluster 3 in Wave 1 to cluster 2 in Wave 4 (n=61, 2%). The most stable cluster was cluster 1, since 61% of participants who were members of this cluster remained in that cluster in both Wave 1 and Wave 2. At the other extreme,

cluster 2 had the least stability, since only 296 (7.7%) of the participants in that cluster remained therein.

In the correlates of sleep classes study, the best fitting model was the model that had six clusters, as it was the simplest model with the lowest BIC (taking account of the number of parameters examined (Table 4-10). These clusters were named on the basis of the patterns observed there in, paying particular attention to the following sleep items: sleep duration, subjective assessment of sleep quality and the most dominant sleep-related event. In this way the six clusters were referred to as short bad sleeper, long moderate sleeper, long good sleeper, disturbed bad sleeper, struggle-to-sleep sleeper and snoring good sleeper. The majority of participants were in cluster 1 (n=19464, 43.1%), and the minority were in cluster 6 (n=1,591, 3.5%). Cluster 1 had the highest prevalence of unfavourable sleep events, whilst cluster 3 had a complete absence of unfavourable sleep events. Clusters 4 and 5 shared similar patterns of unfavourable sleep events, except that cluster 5 had a poor level of sleep quality. Cluster 6 included participants with habitual (i.e. frequently occurring) snoring and habitual disturbances but with normal quality and duration. Cluster 2 contained participants exhibiting non-habitual sleep disturbances in the absence of other sleep-related events.

Table 4-7 Patterns of sleep clusters based on the latent class analysis for participants from Wave 1 who also participated in Wave 4 (n=19,442). The patterns described are based on the probabilities of the mean event within each cluster.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6
Duration	**Normal**	**Normal**	**Normal**	**Short**	**Short**	**Short**
	0.846	0.604	0.788	0.421	0.462	0.447
Latency	**No event**	**Non-habitual**	**No event**	**Habitual**	**Non-habitual**	**Non-habitual**
	0.467	0.545	0.964	0.986	0.531	0.557
Snoring	**No event**	**No event**	**No event**	**No event**	**No event**	**No event**
	0.708	0.483	0.904	0.404	0.538	0.616
Disturbance	**Non-habitual**	**Habitual**	**No event**	**Habitual**	**Habitual**	**Non-habitual**
	0.671	0.655	0.999	0.968	0.998	0.668
Sleepiness	**No event**	**No event**	**No event**	**No event**	**No event**	**No event**
	0.904	0.858	0.929	0.676	0.728	0.671
Medication	**No event**	**No event**	**No event**	**No event**	**No event**	**No event**
	0.905	0.826	0.911	0.643	0.783	0.797
Quality	**Good**	**Good**	**Good**	**Bad**	**Bad**	**Bad**
	1.000	0.999	0.991	0.876	0.989	0.705

Table 4-8 Patterns of sleep clusters based on the latent class analysis for participants from Wave 4 who had previously participated in Wave 1 (n=19,442). The patterns described are based on the probabilities of the mean event within each cluster.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6
Duration	**Normal**	**Short**	**Normal**	**Restricted**	**Short**	**Short**
	0.723	0.397	0.769	0.411	0.370	0.394
Latency	**No event**	**Habitual**	**No event**	**Habitual**	**No event**	**Non-habitual**
	0.473	0.923	0.988	0.942	0.719	0.553
Snoring	**No event**	**No event**	**No event**	**No event**	**No event**	**No event**
	0.809	0.673	0.946	0.653	0.721	0.748
Disturbance	**Non-habitual**	**Habitual**	**No event**	**Habitual**	**Habitual**	**Non-habitual**
	0.524	0.992	0.999	0.959	0.997	0.524
Sleepiness	**No event**	**No event**	**No event**	**No event**	**No event**	**No event**
	0.919	0.907	0.966	0.755	0.823	0.803
Medication	**No event**	**No event**	**No event**	**No event**	**No event**	**No event**
	0.951	0.858	1.000	0.723	0.882	0.887
Quality	**Good**	**Good**	**Good**	**Bad**	**Bad**	**Bad**
	1.000	0.600	0.991	0.998	**0.604**	0.575

Table 4-9 The distribution of participants amongst clusters in Waves 1 and 4 presented as percentages and frequencies.[1]

			Wave 4						
			Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**	**Cluster 6**	**Total**
Wave 1	**Cluster 1**	*(n)*	**5,137**	275	1,805	285	352	309	8,163
		(%)	**62.93**	3.37	22.11	3.49	4.31	3.79	100.00
	Cluster 2	*(n)*	2,244	**296**	509	305	329	157	3,840
		(%)	58.44	**7.71**	13.26	7.94	8.57	4.09	100.00
	Cluster 3	*(n)*	1,431	61	**1,351**	64	82	95	3,084
		(%)	46.40	1.98	**43.81**	2.08	2.66	3.08	100.00
	Cluster 4	*(n)*	528	228	111	**801**	209	177	2,054
		(%)	25.71	11.10	5.40	**39.00**	10.18	8.62	100.00
	Cluster 5	*(n)*	539	78	112	215	**320**	107	1,371
		(%)	39.31	5.69	8.17	15.68	**23.34**	7.80	100.00
	Cluster 6	*(n)*	416	45	119	115	76	**159**	930
		(%)	44.73	4.84	12.80	12.37	8.17	**17.10**	100.00
	Total	*(n)*	10,295	983	4,007	1,785	1,368	1,004	**19,442**
		(%)	52.95	5.06	20.61	9.18	7.04	5.16	**100.00**

[1] Bold text indicates the percentages of participants who remained within their clusters between Wave 1 and 4.

Table 4-10 Patterns of sleep clusters based on the latent class analysis for participants from Wave 1and/or Wave 4 (n=45, 141). The patterns described are based on the probabilities of the mean event within each cluster.

	Cluster1	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**	**Cluster 6**
Cluster name	Short Bad sleeper	Long Moderate sleeper	Long good sleeper	Disturbed bad sleeper	Struggle to sleep-er	Snoring good sleeper
Cluster size n (%)	19,464 (43.12)	13,343 (29.56)	3,186 (7.06)	5,186 (11.49)	2,371 (5.25)	1,591 (3.52)
Duration	**Severely restricted** 0.9998	**Normal** 0.778	**Normal** 0.820	Short 0.349	Restricted 0.301	**Normal** 0.587
Latency	**Habitual** 0.9999	**No event** 0.446	**No event** 0.963	**Non-habitual** 0.498	**Habitual** 0.999	**Non-habitual** 0.493
Coughing or snoring	**Habitual** 0.9999	**No event** 0.751	**No event** 0.981	**No event** 0.722	**No event** 0.557	**Habitual** 0.229
Disturbance	**Habitual** 1.000	**Non-habitual** 0.503	**No event** 0.999	**Habitual** 0.530	**Habitual** 0.981	**Habitual** 0.709
Sleepiness	**Habitual** 0.9998	**No event** 0.906	**No event** 0.960	**No event** 0.776	**No event** 0.738	**No event** 0.643
Medication	**Habitual** 0.9999	**No event** 0.929	**No event** 0.957	**No event** 0.853	**No event** 0.697	**No event** 0.647
Quality	**Bad** 1.000	**Good** 0.999	**Good** 0.993	**Bad** 0.646	**Good** 0.863	**Good** 0.673

4.4.3 Results of the regression analysis

4.4.3.1 Adjustment for confounding

Based on the DAG presented in Figure 4-2, the following adjustments were applied when conducting each of the linear regression models: age was adjusted for gender; education was adjusted for age and gender; employment was adjusted for age, gender and education; household structure was adjusted for gender, age, education and employment; and mental and physical health were both adjusted for age, gender, education, household structure and employment.

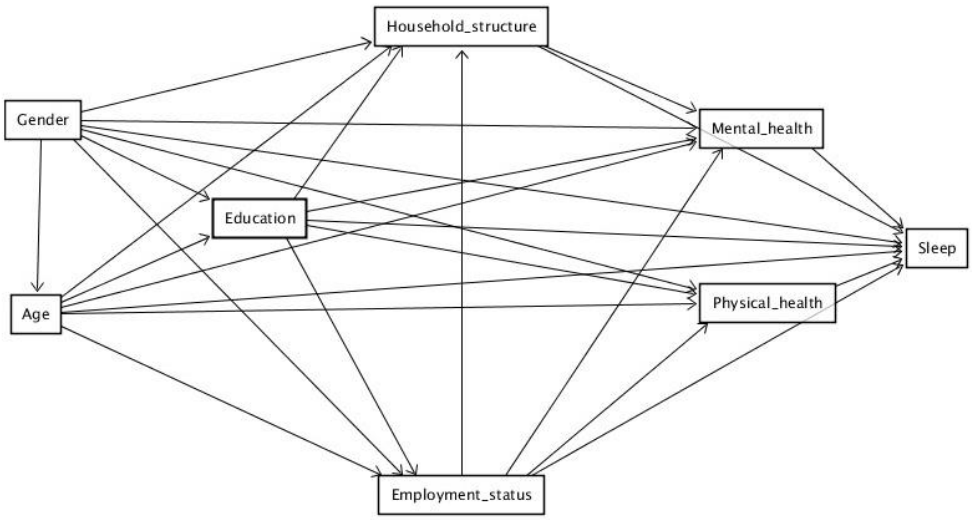

Figure 4-2 DAG representing the association between sleep, sociodemographic features and health indicators. The variables are represented by rectangles squares, and the direction of potential causal influence between variables are represented by unidirectional arrows.

4.4.3.2 The association between sociodemographic, health features and sleep

In comparison to the six sleep patterns, the seven individual sleep characteristics displayed far less variability in their associations with sociodemographic and health features. (Table 4-11, Table 4-12, Table 4-13 and Table 4-14)

Female participants were more likely to display sleep latency, sleep disturbance and poorer sleep quality, and to report using sleep-related medication than men. In addition, female participants were far less likely to be associated with cluster 3 ‘good long sleeper’ compared to men and this might in part reflect the effect of hormonal differences and hormonal variability (i.e. during menstruation, menopause and pregnancy as well as postpartum). In addition, older participants were less likely to report sleep latency and daytime sleepiness than younger participants. Participants who were older and female were significantly more likely to have particular sleep patterns, such that: compared to those aged less than 20 years, people aged between 20–39 years tended to be found within cluster 1 (“short bad sleeper”), and those between 40–69 years tended to be found in either cluster 1 or 6 (“snoring good sleeper”); while participants who were older than 70 years had a six times higher odds of being snorers with a good perceived sleep quality.

Participants with lower educational attainment were more likely to exhibit all of the unfavourable sleep examined (with the exception of disturbance). Participants who were unemployed also had a higher risk of experiencing unfavourable sleep events,

while participants with poor health indicators (i.e. unemployment due to sickness, a lower score in the mental and physical component of the SF12V and poor reported subjective health) were more likely to report unfavourable sleep events across all seven individual sleep characteristics. These trends in the association between individual sleep characteristics and health was noticeably absent when the association between health and latent sleep clusters was examined. Instead, health displayed a range of different relationships (positive and negative, strong and weak) with the six sleep pattern clusters/classes.

Full-time trainees/students had the lowest risk of being associated with ostensibly unfavourable sleep patterns compared to those who were employed or on leave. This might in part be related to an age effect. Meanwhile, educational attainment was associated with a range of different sleep pattern clusters: participants with postgraduate qualifications had twice the odds of being in cluster 5 (“struggle-to-sleep-er”) compared to those with a degree. Having no qualifications increased the risk of being classified in cluster 6 (“snoring good sleeper”) as well as in cluster 5.

Household structure, in terms of presence of children or living as couples, had a range of different associations with different sleep pattern clusters. For example, in comparison to single participants without children, being single *with* children decreased the risk of being associated with cluster 6 (“snorers, good sleepers”), perhaps because snorers are usually not aware of their snoring unless informed by a bed partner (i.e. acting as a witness). Being a couple without children significantly decreased the odds of being in cluster 5 (“struggle-to-sleep-er”) – as such it was associated with a lower odds of experiencing sleep latency, or disturbance or protracted sleep duration. Perhaps caring for young children might cause some degree of sleep disturbance as parents often awake to settle, change or feed their children if these wake in the night. Living with others, either as couples or not, and with/without children, decreased the odds of being associated with sleep patterns that had unfavourable events (as compared with living alone). However, this finding should not be mistaken with the likely effects of overcrowding or cohabitation with extended families on the availability of sleeping space/accommodation as the latter had a higher odds of being associated with bad sleep quality and shorter duration sleep (Fowler et al., 2014).

4.4.3.2.1 Sociodemographic features and sleep

In regards to the seven sleep characteristics, when compared to participants younger than 20 years of age, those who were older than 40 years of age had an odds of short sleep duration that was three times higher (OR= 3.31, CI = 3.03, 3.61), while the odds of disturbance (OR=2.30, CI=2.14, 2.47) and snoring (OR=2.75, CI=2.52, 3.00) were

both over twice as high. In participants older than 60 years of age, the odds of using medication to help with sleep was two times higher (OR=2.52, CI=2.21, 2.88). Female participants displayed a higher tendency towards unfavourable sleep events than males, excluding snoring or coughing (OR=0.66, CI=0.64, 0.69) and short sleep duration (OR=0.95, CI=0.913, 0.98) where females had a substantially and modestly lower odds thereof, respectively. In general, participants with lower education attainment had a modestly higher odds of unfavourable sleep events, except the odds of disturbance, which was marginally lower amongst participants with lower educational attainment (OR=0.95, CI=0.91, 0.99). Compared to employed individuals, participants who were unemployed or undergoing training displayed a higher odds of unfavourable sleep events. On the other hand, the odds of reporting poor sleep quality (OR=0.90, CI=0.82, 0.99), short sleep (OR=0.72, CI=0.681, 0.76) and snoring or coughing (OR=0.76, CI=0.70, 0.82) were all lower amongst participants who were retired. The association between each of the categories of household structure and the risk of unfavourable sleep events varied, but in general it appeared that: a those participants living alone without any children had a higher odds of unfavourable sleep events, except snoring or coughing. Having children increased these odds to OR=1.18 (CI=1.08, 1.29), having a partner increased the odds to OR=1.36 (CI=1.29, 1.45) and having a partner plus children increased the odds to OR= 1.20 (CI=1.13, 1.28).

In regards to sleep clusters, female participants were more likely to be in clusters 1, 5 and 6 than males. The highest odds for females was to be in cluster 5 (OR =1.61, CI=1.47, 1.31). Being older than 20 years of age increased the odds of being included in clusters 1 and 5. The odds of being in cluster 1 was three times higher in the age group 40-59 years (OR=3.07, CI=2.84, 3.32), two times higher in the age group 20 to 39 years (OR=2.14, CI=1.98, 2.31) and more than two times higher for the age group older than 60 (OR=2.67, CI=2.46, 2.90).Lower education was associated with a higher odds of being included in clusters 4, 5 and 6 with the highest odds being membership of cluster 5 (OR=1.75, CI=1.60, 1.91).

The association between employment and cluster membership varied. Participants who were enrolled in education or training programs had a higher odds of being in cluster 2 (OR=1.35, CI=1.23, 1.48) and cluster 4 (OR=1.26, CI=1.11, 1.42). Unemployed participants had a higher odds of being in cluster 5 (OR=1.86, CI=1.64, 2.11) and cluster 6 (OR=1.77, CI=1.52, 2.07). Similarly, more retired participants tended to be in cluster 5 (OR=1.59, CI=1.30, 1.94) and cluster 6 (OR=1.53, CI=1.19, 1.97).

Compared to single participants without children, having children increased the odds of being in cluster 1 by OR= 1.26 (1.16, 1.37). In addition, having a partner increased

the odds of being in cluster 1 by OR=1.13 (CI=1.07, 1.19) and being in cluster 3 by OR=1.24 (CI=1.12, 1.38). In a very similar fashion, having a partner and children increased the odds of being in cluster 1 by OR=1.31 (CI=1.24, 1.39).

4.4.3.2.2 Health indicators and sleep

Overall, participants with low scores for the mental and physical components of the SF12v (i.e. total score < 32), and participants who reported a bad to poor level of perceived general health, showed an elevated risk of developing unfavourable sleep events. A low score on the SF12v physical component increased the odds of reporting poor sleep quality by more than six times (OR=6.19, CI=5.67, 6.76) and by more than two times for using sleep-related medication (OR=2.64, CI=2.41, 2.89) and reporting next-day sleepiness (OR=2.40, CI=2.14, 2.70). A low score for the mental components of the SF12v was also associated with an increase of three times the odds of reporting poor sleep quality (OR=3.03, CI=2.77, 3.83) and daytime sleepiness (OR=3.07, CI=2.77, 3.41), and of almost twofold for each the remaining sleep characteristics. Likewise, poor general health was associated with an increased odds of reporting poor quality sleep by over three times (OR=3.61, CI=3.40, 3.83) and an elevated odds of daytime sleepiness by over two times (OR=2.39, CI=2.21, 2.88).

Participants who reported current unemployment secondary to sickness or disability also reported an increased odds of developing unfavourable sleep. For example, the odds of reporting poor quality sleep was 4 times higher (OR=4.56, CI=4.11, 5.07), and the odds of using sleep-related medication was more than three and a half times higher (OR=3.75, CI=3.36, 4.20). Elsewhere, the odds of other unfavourable sleep characteristics amongst participants who were unemployed due to sickness or disability was almost doubled (Table 4-12).

Unlike the associations between health indicators and individual sleep characteristics items, which tended to reflect the ill-effect of illness on sleep (and/or vice versa), the odds of being included in a sleep cluster varied substantially according to the sociodemographic and health characteristics examined (Table 4-13 and Table 4-14). Participants with poor mental and physical health scores were only more likely to be included in clusters 5 and 6; while reporting a poor subjective general health increased the odds of being in cluster 5 by over three times (OR=3.24, CI= 3.24, 3.94) and was also associated with a more modestly elevated odds of being in cluster 6 (OR=1.54, CI=1.35, 1.75). Participants with a low physical health score for the SF12v had three times the odds of being in cluster 5 (OR=3.11, CI=2.70, 3.53) as well as a higher odds of being in cluster 6 (OR=1.75, CI=1.47, 2.09). Participants with a low score in the mental health components of the SF12v had over four times the odds of being in cluster 5 (OR=4.75, CI=4.24, 5.33).

4.4.3.2.3 Choosing a reference point for the latent sleep variable

'Long good sleeper' was chosen as the referent for the latent sleep variable (with six separate categories) for each of the following reasons:

1- The pattern of the 'long good sleeper' category was characterised by the absence of any unfavourable sleep events; hence it was easier and theoretically more plausible to use this category as the referent for 'good'/'favourable' sleep.
2- Participants who had a lower probability of displaying a 'long good sleeper' pattern were those who were mentioned in the literature (Chapter 1, Section 1.4, page 29) as groups at high risk of sleep complications, these groups were:
    I. older participants
    II. participants who were currently not working because they were unemployed, sick /disabled or retired
    III. participants with children or couples living with children in the same household
    IV. participants with poor physical health
    V. participants with poor psychological health
3- The pattern of the relationships between participants classified as 'long good sleepers' and available health indicators was similar to the inverse of the pattern observed between unfavourable individual sleep characteristics and health (i.e. poor health was associated with an increased the risk of unfavourable individual sleep characteristics).

4.4.4 Results to-date and the associated DAG

The results presented in this chapter indicate that sociodemographic and health features had substantive relationships with individual sleep characteristics as well as with each of the latent sleep clusters. These findings supported the specification of the hypothesised DAG (see Chapter 2, Section 2.4, page 59), which hypothesised that casual pathways were likely to exist between sociodemographic characteristics, health features and sleep. However, the causal nature of such relationships remains tentative (given the cross-sectional nature of these analyses), and definitive evidence of causality will need to be confirmed by further (ideally longitudinal and/or experimental) research. Meanwhile, the specific relationship(s) between sleep and pregnancy outcomes will now be examined in the next two chapters (Figure 4-3).

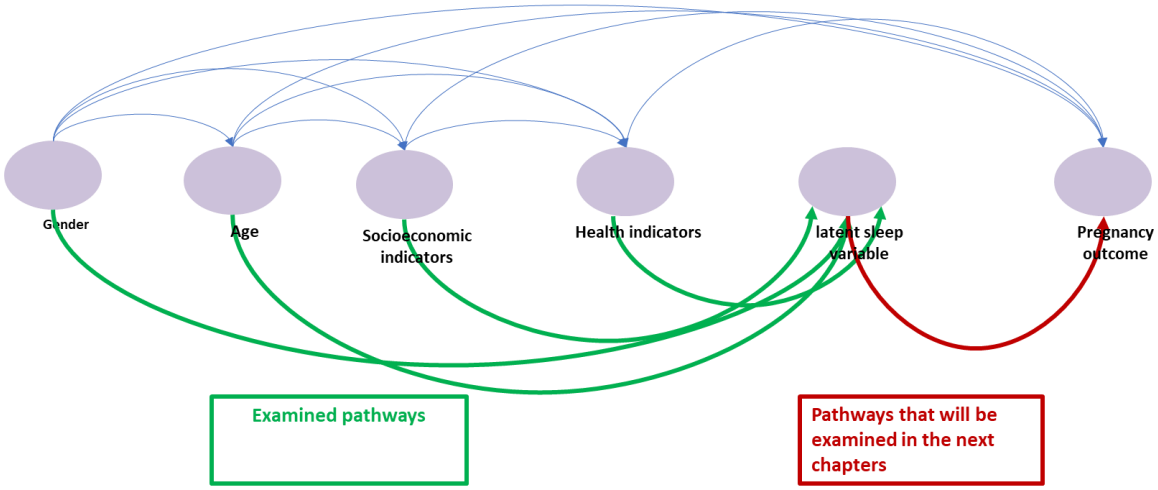

Figure 4-3 DAG representing the association between sleep, sociodemographic features and health indicators. The green pathways are the ones that have been examined in the present chapter, whilst those in red ones will be examined later in the following two chapters.

Table 4-11 Logistic regression analyses examining the unadjusted association between seven separate sleep characteristics and a range of sociodemographic and health factors (n= 43,211).[1,2]

	Latency		Disturbance		Snoring and/or coughing		Sleepiness		Medication		Quality		Duration	
	OR	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**
Gender														
Male	Ref.													
Female	1.38	**1.33, 1.44**	1.44	**1.38, 1.50**	0.66	**0.64, 0.69**	0.88	**0.82, 0.94**	1.316	**1.24, 1.39**	1.47	**1.40, 1.54**	0.95	**0.92, 0.99**
Age categories														
≤19 years	Ref													
20-39years	0.87	**0.81, 0.93**	1.68	**1.56, 1.80**	1.71	**1.56, 1.86**	0.72	**0.65, 0.80**	1.81	**1.59, 2.06**	1.46	**1.33, 1.60**	2.33	**2.13, 2.54**
40-59 years	0.72	**0.68, 0.78**	2.30	**2.14, 2.48**	2.70	**2.48, 2.95**	0.57	**0.51, 0.63**	2.24	**1.97, 2.55**	1.58	**1.44, 1.73**	3.30	**3.02, 3.61**
≥ 60 years	0.67	**0.62, 0.72**	2.84	**2.62, 3.08**	2.69	**2.45, 2.94**	0.45	**0.40, 0.51**	2.51	**2.20, 2.86**	1.06	0.96, 1.17	3.31	**3.31, 3.63**
Education														
A level and above	Ref.													
GSCE level and others	1.11	**1.07, 1.16**	1.07	**1.02, 1.11**	1.38	**1.33, 1.44**	0.95	0.89, 1.01	1.34	**1.27, 1.42**	1.23	**1.17, 1.29**	1.18	**1.13, 1.23**
Employment														
Employed	Ref.													
Unemployed	1.39	**1.31, 1.48**	1.11	**1.04, 1.19**	1.11	**1.04, 1.19**	1.24	**1.12, 1.38**	1.54	**1.42, 1.67**	1.68	**1.57, 1.80**	1.01	0.95, 1.08
Sick or disabled	2.17	**1.94, 2.42**	2.58	**2.23, 2.98**	1.83	**1.65, 2.02**	2.56	**2.24, 2.92**	4.20	**3.76, 4.69**	4.93	**4.45, 5.46**	2.44	**2.20, 2.70**
Training or education	1.43	**1.34, 1.53**	0.57	**0.53, 0.60**	0.48	**0.44, 0.52**	1.84	**1.67, 2.02**	0.72	**0.65, 0.81**	0.81	**0.74, 0.88**	0.44	**0.41, 0.48**
Retired	1.01	0.96, 1.06	1.65	**1.54, 1.75**	1.23	**1.16, 1.30**	0.77	**0.70, 0.86**	1.56	**1.45, 1.68**	0.90	**0.84, 0.97**	1.21	**1.15, 1.28**
Household														
Single without children	Ref.													
Single with children	1.03	0.95, 1.11	0.79	**0.73, 0.86**	0.89	**0.82, 0.97**	0.99	0.88, 1.12	1.00	0.90, 1.11	1.25	**1.14, 1.36**	0.71	**0.66, 0.77**
Couple with children	0.80	**0.76, 0.85**	0.79	**0.74, 0.84**	1.04	0.98, 1.10	0.81	**0.75, 0.89**	0.65	**0.60, 0.70**	0.89	**0.83, 0.94**	0.73	**0.69, 0.77**
Couple without children	0 .86	**0.82, 0.91**	1.07	**1.01, 1.14**	1.40	**1.32, 1.48**	0.70	**0.64, 0.77**	0.86	**0.80, 0.92**	0.78	**0.73, 0.83**	0.75	**0.71, 0.80**
Physical wellbeing														
≥ 66	2.14	**1.58, 2.89**	1.36	0.99, 1.87	0.80	0.59, 1.09	1.78	**1.20, 2.61**	1.89	**1.35, 2.65**	4.92	**3.76, 6.45**	1.79	**1.37, 2.35**
≥ 32 and <66	Ref.													
<32	1.85	**1.72, 1.99**	2.75	**2.48, 3.04**	1.95	**1.82, 2.09**	2.02	**1.83, 2.22**	3.71	**3.44, 4.01**	3.32	**3.09, 3.56**	2.45	**2.29, 2.63**
Mental wellbeing														
≥ 66	0 .70	**0.57, 0.86**	0.68	**0.55, 0.85**	1.04	0.83, 1.30	0.56	**0.34, 0.91**	1.42	**1.07, 1.88**	0.92	0.70, 1.22	1.18	0.95, 1.46
≥ 32 and <66	Ref.													
<32	3.36	**3.04, 3.71**	2.78	**2.47, 3.14**	1.72	**1.58, 1.87**	3.38	**3.07, 3.74**	3.55	**3.25, 3.88**	7.73	**7.10, 8.42**	3.02	**2.78, 3.28**
General health														
Excellent to good	Ref.													
Fair to poor	1.88	**1.79, 1.98**	2.22	**2.09, 2.37**	2.13	**2.03, 2.24**	2.18	**1.98, 2.29**	3.32	**3.12, 3.53**	3.69	**3.50, 3.89**	2.20	**2.09, 2.31**

[1] The rows represent the postulated 'predictors' and the columns represent the outcomes; while the generated ORs are for several models based on the exposure and the outcome.

[2] Bold fonts indicate statistically significant *p*-values ($p<0.05$).

Table 4-12 Logistic regression analyses examining the confounder-adjusted association between seven separate sleep characteristics and a range of sociodemographic and health factors (n= 43,211).[1, 2]

	Latency		Disturbance		Snoring and/or coughing		Sleepiness		Medication		Quality		Duration	
	OR	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**
Gender														
Male	Ref.													
Female	1.38	**1.33, 1.44**	1.46	**1.40, 1.53**	0.66	**0.64, 0.69**	0.87	**0.82, 0.93**	1.32	**1.25, 1.40**	1.46	**1.39, 1.53**	0.95	**0.91, 0.99**
Age categories														
≤19 years	Ref.													
20-39years	0.86	**0.80, 0.92**	1.66	**1.55, 1.78**	1.74	**1.59, 1.90**	0.72	**0.65, 0.80**	1.80	**1.58, 2.04**	1.45	**1.32, 1.59**	2.33	**2.13, 2.54**
40-59 years	0.72	**0.67, 0.77**	2.30	**2.13, 2.47**	2.75	**2.52, 3.00**	0.57	**0.51, 0.63**	2.23	**1.96, 2.54**	1.57	**1.43, 1.72**	3.31	**3.03, 3.61**
≥ 60 years	0.67	**0.62, 0.73**	2.88	**2.66, 3.12**	2.69	**2.45, 2.95**	0.45	**0.40,0.51**	2.52	**2.21, 2.88**	1.06	0.96, 1.17	3.31	**3.02, 3.63**
Education														
A level and above	Ref.													
GSCE level and others	1.16	**1.11, 1.20**	0.95	**0.91, 0.99**	1.31	**1.25, 1.36**	1.03	0.96, 1.10	1.23	**1.16, 1.30**	1.23	**1.18, 1.29**	1.07	**1.03, 1.12**
Employment														
Employed	Ref.													
Unemployed	1.26	**1.18, 1.34**	1.14	**1.06, 1.22**	1.23	**1.15, 1.32**	1.24	**1.11, 1.37**	1.47	**1.34, 1.60**	1.47	**1.37, 1.58**	1.05	0.98, 1.12
Sick or disabled	2.12	**1.89, 2.37**	2.40	**2.07, 2.78**	1.77	**1.59, 1.96**	2.66	**2.32, 3.05**	3.75	**3.36, 4.20**	4.56	**4.11, 5.07**	2.19	**1.98, 2.43**
Training or education	1.12	**1.04, 1.21**	0.76	**0.70, 0.82**	0.67	**0.61, 0.74**	1.45	**1.29, 1.63**	0.85	**0.75, 0.97**	0.72	**0.65, 0.80**	0.61	**0.55, 0.66**
Retired	1.27	**1.18, 1.36**	1.07	0.98, 1.17	0.76	**0.70, 0.82**	1.04	**0.90, 1.19**	1.07	0 .97, 1.19	0.90	**0.82, 0.99**	0.72	**0.67, 0 .78**
Household														
Single without children	Ref.													
Single with children	0.78	0.71, 0.84	0.96	0.88, 1.05	1.18	**1.08, 1.29**	0.81	**0.71, 0.92**	1.12	0.99, 1.25	1.10	0.99, 1.21	0.97	0.89, 1.05
Couple with children	0.72	**0.68, 0.76**	0.95	0.89, 1.01	1.20	**1.13, 1.28**	0.72	**0.66, 0.79**	0.77	**0.70, 0.84**	0.86	**0.81, 0.93**	0.88	**0.83, 0.93**
Couple without children	0.92	**0.87, 0.97**	1.04	0.98, 1.11	1.36	**1.29, 1.44**	0.77	**0.70, 0.85**	0.89	**0.83, 0.96**	0.82	**0.76, 0.87**	0.72	**0.68, 0.76**
Physical wellbeing														
≥ 66	1.91	**1.41, 2.58**	1.49	**1.08, 2.06**	0.88	0.64, 1.21	1.53	**1.04, 2.27**	1.82	**1.30, 2.60**	0.86	0.65, 1.15	1.94	**1.47, 2.55**
≥ 32 and <66	Ref.													
<32	1.90	**1.75, 2.07**	1.86	**1.67, 2.08**	1.55	**1.43, 1.67**	2.40	**2.14, 2.70**	2.64	**2.41, 2.89**	6.19	**5.67, 6.76**	1.80	**1.67, 1.95**
Mental wellbeing														
≥ 66	0.70	**0.57, 0.87**	0.52	**0.42, 0.65**	0.86	0.68, 1.08	0.60	**0.37, 0.99**	1.08	0.81, 1.43	4.48	**3.45, 5.90**	0.94	0.78, 1.17
≥ 32 and <66	Ref.													
<32	2.89	**2.61, 3.20**	2.52	**2.23, 2.86**	1.74	**1.60, 1.90**	3.07	**2.77, 3.41**	2.81	**2.56, 3.08**	3.03	**2.79, 3.30**	2.87	**2.64, 3.13**
General health														
Excellent to good														
Fair to poor	1.95	**1.84, 2.06**	1.83	**1.71, 1.96**	1.87	**1.77, 1.98**	2.39	**2.21, 2.60**	2.69	**2.52, 2.88**	3.61	**3.40, 3.83**	1.84	**1.74, 1.94**

[1] The rows represent the postulated 'predictors' and the columns represent the outcomes; while the generated ORs are for several models based on the exposure and the outcome.

[2] Bold fonts indicate statistically significant *p*-values ($p<0.05$).

Table 4-13 Logistic regression analyses examining the unadjusted association a range of sociodemographic and health factors and six LCA-generated sleep clusters (n= 43,211).[1,2,3]

	Latent sleep model 1		Latent sleep model 2		Latent sleep model 3		Latent sleep model 4		Latent sleep model 5		Latent sleep model 6	
	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI
Gender												
Male	Ref.											
Female	1.12	**1.08, 1.166**	0.85	0.81, 0 .88	0.93	**0.86, 0.99**	0.74	**0.80, 0 .79**	1.60	**1.46, 1.75**	1.30	**1.17, 1.44**
Age categories												
≤19 years	Ref											
20-39years	2.15	**1.99, 2.32**	0.63	**0.59, 0.68**	0.89	0.78, 1.02	0.60	0.54, 0.66	1.37	**1.14, 1.65**	0.65	**0.55, 0.76**
40-59 years	3.08	**2.85, 3.32**	0.47	**0.44, 0.51**	0.95	0.83, 1.10	0.45	0.41, 0.49	1.65	**1.38, 1.98**	0.49	**0.42, 0.59**
≥ 60 years	2.66	**2.46, 2.89**	0.54	**0.50, 0.58**	0.86	**0.74, 0.99**	0.41	0.37, 0.46	1.62	**1.34, 1.96**	0.68	**0.58, 0 .81**
Education												
A level and above	Ref.											
GSCE level and others	0 .83	**0.80, 0.86**	0.97	0.93, 1.02	0.87	**0.81, 0.94**	1.05	0.99, 1.12	1.75	**1.60,1.90**	1.40	**1.26, 1.55**
Employment												
Employed	Ref.											
Unemployed	0.83	**0.78, 0.88**	0 .89	**0.83, 0.95**	0.83	**0.74, 0.93**	0.95	0.86, 1.05	2.14	**1.89, 0.42**	2.02	**1.75, 2.34**
Sick or disabled	0.92	0.83, 1.01	0.50	**0.44, 0.57**	0.51	**0.44, 0.60**	0.34	**0.26, 0.43**	5.67	**4.92, 6.54**	1.56	**1.21, 2.02**
Training or education	0.39	**0.36, 0.42**	1.77	**1.66, 1.89**	0.99	0.87, 1.13	1.76	**1.62, 1.92**	0.90	0.75, 1.07	1.81	**1.54, 2.13**
Retired	0.98	0.93, 1.03	0 .95	0 .89, 1.01	0.84	**0.76, 0.93**	0.71	**0.65, 0.78**	1.59	**1.42, 1.79**	1.52	**1.32, 1.75**
Household												
Single without children	Ref.											
Single with children	0.95	0.88, 1.03	0.96	0.88, 1.04	1.05	0.91, 1.21	1.22	**1.08, 1.37**	1.00	0.86, 1.17	1.11	0.92, 1.33
Couple with children	1.16	**1.10, 1.23**	0.98	0.93, 1.04	1.13	**1.02, 1.25**	1.14	**1.04, 1.24**	0.59	**0.52, 0.66**	0.71	**0.61, 0 .82**
Couple without children	1.20	**1.14, 1.27**	1.00	0.95, 1.06	1.27	**1.15, 1.41**	0.92	0 .85, 1.00	0.74	**0.66, 0.83**	0.82	**0.72, 0.94**
Physical wellbeing												
≥ 66	0.92	0.70, 1.21	0.53	**0.38, 0.75**	0.57	**0.37, 0.87**	0.85	0.54, 1.33	2.44	**1.54, 3.88**	2.79	**1.72, 4.54**
≥ 32 and <66	Ref.											
<32	0.84	**0.78, 0.90**	0.62	**0.57, 0 .67**	0.51	**0.45, 0.57**	0.41	**0 .35, 0.48**	4.40	**3.97, 4.88**	1.82	**1.56, 2.12**
Mental wellbeing												
≥ 66	0.96	0.78, 1.19	0.80	0.63, 1.02	1.06	0.69, 1.64	1.52	**1.15, 2.02**	1.12	0.68, 1.86	1.10	0.63, 1.92
≥ 32 and <66	Ref.											
<32	0.84	**0.77, 0.91**	0.44	**0.39, 0.49**	0.47	**0 .41, 0.53**	0.30	0 .24, 0.37	6.60	**5.93, 7.35**	1.65	**1.37, 1.97**
General health												
Excellent to good	Ref.											
Fair to poor	0.96	0.92, 1.01	0.59	0.56, 0.63	0.46	**0.42, 0.50**	0.41	**0.37, 0.46**	4.47	**4.09, 4.88**	1.62	**1.44, 1.82**

[1] The rows represent the 'predictors' and the columns represent the 'outcomes'; and the generated ORs are for several models based on the exposure and the outcome.

[2] The latent sleep models had the following categorisations of their binary latent sleep variables: **Model 1**= cluster 1 and the other clusters, **Model 2 =** cluster 2 and the other clusters, **Model 3=** cluster 3 and the other clusters, **Model 4=** cluster 4 and the other clusters, **Model 5=** cluster 5 and the other clusters, **Model 6=** cluster 6 and the other clusters.

[3] Bold fonts indicate statistically significant *p*-values ($p<0.05$).

Table 4-14 Logistic regression analyses examining the confounder-adjusted association a range of sociodemographic and health factors and six LCA-generated sleep clusters (n= 43,211).[1,2,3]

	Latent sleep model 1		Latent sleep model 2		Latent sleep model 3		Latent sleep model 4		Latent sleep model 5		Latent sleep model 6	
	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI	OR	CI
Gender												
Male			Ref.									
Female	1.12	**1.08, 1.17**	0.85	**0.82, 0.88**	0.93	**0.86, 0.99**	0.74	**0.69, 0.78**	1.61	**1.47, 1.76**	1.31	**1.18, 1.46**
Age categories												
≤19 years			Ref.									
20-39years	2.14	**1.98, 2.31**	0.64	**0.59, 0.68**	0.89	0.78, 1.03	0.60	**0.55, 0.66**	1.35	**1.13, 1.62**	0.64	**0.55, 0.76**
40-59 years	3.07	**2.84, 3.32**	0.47	**0.44, 0.51**	0.95	0.83, 1.10	0.45	**0.41, 0.50**	1.64	**1.36, 1.96**	0.49	**0.41, 0.58**
≥ 60 years	2.67	**2.46, 2.90**	0.54	**0.50, 0.58**	0.85	**0.74, 0.99**	0.41	**0.37, 0.46**	1.63	**1.35, 1.97**	0.69	**0.58, 0.82**
Education												
A level and above			Ref.									
GSCE level and others	0.81	**0.78, 0 .84**	0.98	0.94, 1.02	0.87	**0.81, 0.94**	1.09	**1.03, 1.17**	1.75	**1.60, 1.91**	1.36	**1.22, 1.52**
Employment												
Employed			Ref.									
Unemployed	0.89	**0.84, 0.95**	0.89	**0.83, 0.95**	0.89	0.79, 1.00	0.91	0.82, 1.01	1.86	**1.64, 2.11**	1.77	**1.52, 2.07**
Sick or disabled	0.94	0.85, 1.04	0.52	**0.46, 0.60**	0.54	**0.46, 0.63**	0.34	**0.27, 0.44**	4.76	**4.11, 5.51**	1.45	**1.45, 1.12**
Training or education	0.63	**0.57, 0.69**	1.35	**1.23, 1.48**	1.01	0.84, 1.20	1.26	**1.11, 1.42**	1.03	0.82, 1.30	1.22	0.98, 1.52
Retired	0 .93	0.85, 1.01	0.98	0.89, 1.08	0.84	**0.70, 0.99**	0.76	**0.65, 0.89**	1.59	**1.30, 1.94**	1.53	**1.19, 1.97**
Household												
Single without children			Ref.									
Single with children	1.26	**1.16, 1.37**	0.81	**0.74, 0.88**	1.01	0.86, 1.17	0 .99	0.87, 1.12	0.90	0.76, 1.06	0.80	**0.65, 0.98**
Couple with children	1.31	**1.24, 1.39**	0.89	**0.83, 0.94**	1.05	0.94, 1.17	0.96,	0.88, 1.05	0.63	**0.56, 0.72**	0.66	**0 .56, 0.77**
Couple without children	1.13	**1.07, 1.19**	1.03	0.97, 1.09	1.24	**1.12, 1.38**	0.94	0.86, 1.03	0.81	**0.73, 0.91**	0.88	0.77, 1.01
Physical wellbeing												
≥ 66	1.04	0.79, 1.38	0.51	**0.36, 0.72**	0.59	**0.38, 0.91**	0.79	0.50, 1.24	2.13	**1.33, 3.39**	2.41	**1.48, 3.94**
≥ 32 and <66			Ref.									
<32	0 .74	**0.68, 0.79**	0.75	**0.68, 0.82**	0.55	**0.49, 0.63**	0.57	**0.48, 0.67**	3.11	**2.74, 3.53**	1.75	**1.47, 2.09**
Mental wellbeing												
≥ 66	0.94	0.76, 1.16	0.86	0.68, 1.10	1.16	0.75, 1.80	1.83	**1.37, 2.43**	0.86	0.52, 1.43	0.99	0.56, 1.73
≥ 32 and <66			Ref.									
<32	0 .86	**0.79, 0.93**	0.48	**0.43, 0.54**	0.52	**0 .46, 0.59**	0.33	**0.33, 0.41**	4.75	**4.24, 5.33**	1.40	**1.16, 1.70**
General health												
Excellent to good			Ref.									
Fair to poor	0.91	**0.86, 0.96**	0.66	**0.61, 0.70**	0.50	**0.43, 0.51**	0.48	**0.43, 0.53**	3.57	**3.24, 3.94**	1.54	**1.35, 1.75**

[1] The rows represent the 'predictors' and the columns represent the 'outcomes'; and the generated ORs are for several models based on the exposure and the outcome.

[2] The latent sleep models had the following categorisations of their binary latent sleep variables: **Model 1**= cluster 1 and the other clusters, **Model 2 =** cluster 2 and the other clusters, **Model 3=** cluster 3 and the other clusters, **Model 4=** cluster 4 and the other clusters, **Model 5=** cluster 5 and the other clusters, **Model 6=** cluster 6 and the other clusters.

[3] Bold fonts indicate statistically significant *p*-values ($p<0.05$).

4.5 Discussion

4.5.1 Limitations

In the temporal stability study, the differences in patterns observed between Waves 1 and 4 were evident for only two of the component sleep characteristics: sleep duration and latency. These differences might simply reflect inherent variability in either/both of these two sleep characteristics, or higher levels of respondent error/reporting bias for these (as compared to the other separate) sleep characteristics (Collins and Lanza, 2013, Lazarsfeld and Henry 1968). Certainly, external environmental and contextual factors such as household structure (Fowler et al, 2014), shift work (Åkerstedt, 2003) and/or day of the week/season of the year (Anderson et al, 1994) are likely to affect both sleep duration and sleep latency, and given these are both highly sensitive to changes in individual socio-demographic circumstances (Arber et al, 2009), which themselves are prone to vary over time and between Wave 1 and 4, such changes may indeed be responsible for the three sleep pattern clusters with less than *exactly* the same characteristics/composition in both Waves 1 and 4 of the UKHLS.

There is also the possibility that recall bias and/or classification error (i.e. the error involved when categorising the continuous variable 'sleep duration') might have undermined the accuracy of both of these sleep characteristics – not least because estimating an 'average' sleep duration and sleep latency for the month preceding questionnaire completion may prove rather more difficult than reporting the frequency of disturbances or medication use etc (Van Den Berg et al, 2008, Lockley et al, 1999). While this may well be true for sleep duration, the format of the sleep latency question was actually very similar to that for the other 'sleep event' questions (e.g. disturbances, coughing/snoring, and medication use). It is therefore unlikely that recall bias or classification differentially affected sleep latency alone. Instead, it may simply be that responses provided by UKHLS participants who provided sleep data in both Waves 1 and 4 may have been influenced by their prior exposure (in Wave 1) to sleep questionnaire items (i.e. items with which they were initially unfamiliar; Backhaus et al, 2002, Buysse et al, 1989). However, the last of these possibilities also appears (un)likely given the lack of an exact match between the six clusters identified in the analysis of Wave 1 data (for the 'temporal stability study) and the analysis of Wave 1 and 4 data (for the 'correlates of sleep classes study), given that in both these instances the data involved were provided *only* by respondents answering these sleep questions for the very first time.

The LCA analyses used in the present chapter generated a total of six latent sleep models using sleep data from n=45,141 participants in Wave 1 and /or Wave 4 who would have been broadly representative of the UK population. However, adding additional participants over and beyond those included in the temporal stability study population (i.e. adding those who participated in Wave 1 or Wave 4 but not both) resulted in the identification of new sleep patterns that had not been identified earlier in the temporal stability study participants. These new patterns were labelled: “short bad sleeper” (43.1%), “struggle-to-sleep-er” (6.2%) and “snoring good sleeper” (1.7%). These additions might suggest the underlying presence of (even) more sleep patterns amongst other populations, not least those younger than 16 years (the youngest age of UKHLS participants) or those living in different locations/contexts.

Nonetheless, the substantial temporal stability of sleep clusters over time was clearly evident in the temporal stability study in the movement of participants between classes/clusters rather than in any radical changes in the composition/derivation of the classes themselves. This inter-class/cluster mobility may, of course, reflect participants’ changing socio-demographic features or environmental living conditions. Importantly, such changes of sleep patterns, resulting primarily as a result of changes in an individual participant’s characteristics over time, might lead one to conclude that the stability of sleep might similarly differ amongst other populations were these to be subjected to changes in their sociodemographic and health circumstances (such as that occurring during pregnancy, where gestational age plays an important role in predicting sleep).

In addition, it is clear from analyses conducted in the correlates of sleep classes study that it is also likely that more (as yet ‘undiscovered’) sleep patterns are likely to exist amongst those participants with missing data and/or those coming from different populations/contexts (again, such as those who are younger or those living in different latitudes/time zones and in contexts with very different environmental and sociocultural characteristics).

4.5.2 Key findings

The analyses conducted in the present chapter examined both the presence and temporal stability latent sleep patterns using data from Waves 1 and 4 of the UKHLS. Latent class analysis of sleep data provided by exactly the same respondents in both Waves 1 and 4 of the UKHLS demonstrated substantial stability of sleep pattern classes/clusters over time – both in respect of the number of classes (or ‘types’ of sleep patterns) and the specific characteristics of each of

these classes (i.e. the key features that distinguished one class from another). However, sleep duration and sleep latency appeared to display slightly higher rates of measurement/classification error than the five other sleep characteristics. The importance of both for health (as evident in the literature) suggests that they need to be measured with great (and perhaps more) care to address and ameliorate the possibility of measurement error.

Meanwhile, it is worth pointing out that the vast majority of UKHLS participants were members of cluster one – a class characterised by short sleep duration, poor quality sleep and unfavourable sleep events. In contrast, the cluster that appeared to characterise the least unfavourable sleep pattern (cluster three – which characterised by long sleep duration, good quality sleep and absence of unfavourable events) was only the third most common sleep pattern amongst UKHLS participants. The low prevalence of a 'favourable' sleep pattern is not only an interesting finding (given current interest in sleep and its relationship with health).

This variability in the associations between sleep patterns and health suggests that these clusters/classes might have substantial utility in determining any relationship between sleep in pregnancy and pregnancy outcomes. This is because pregnancy represents a stressful physiological condition that causes many women to describe their perceived health as poor even in the absence of clinical disease or infirmity.

Meanwhile, the somewhat different directions of associations between individual sleep characteristics, LCA-derived sleep patterns and sociodemographic/health features might best be explained by the nature of sleep patterns themselves. Thus, while individual sleep characteristics measure only one aspect of sleep, LCA-derived sleep patterns are likely to offer more 'holistic' and comprehensive assessments of sleep across more than simply one individual sleep characteristic.

The 'long good sleeper' category was considered the referent for the latent sleep variable that will (also) be used in the analyses contained in the next two chapters. This choice was made due to the similarity between 'long good sleeper' patterns and individual sleep characteristic with respect to their relationship with health indicators; as well as the fact that participants with a lower probability of displaying 'long good sleeper' sleep patterns were those individuals with a higher risk of displaying sleep problems.

Compared to men, women were more likely to display 'struggle to sleep-er', 'snoring good sleeper' and 'short bad sleeper' sleep patterns. However, this relation between sleep patterns and female gender might be under the influence of other sociodemographic and health features not examined in the present chapter

(including pregnancy, which will be studied in the next two chapters). Unfortunately, then, it remains unclear why women (particularly those who were not pregnant, as will become clear later) were prone to these less 'favourable' sleep patterns and further investigations are warranted to better understand this.

Knowing that the latent sleep variable generated using LCA of UKHLS sleep module data was significantly associated with sociodemographic and health features confirmed the usefulness of the hypothesised DAG (originally postulated in Chapter 2; Section 2.4, page 59). Likewise, the association between sleep and sociodemographic/health confirmed the possibility that the latter might act as potential confounders in the relation between sleep and pregnancy outcomes (not least because many of these sociodemographic/health variables are also known to be risk factors for poorer pregnancy outcomes). However, the second half of the DAG (i.e. to the right hand side of 'sleep') which summarised the hypothesised association between sleep and pregnancy outcomes still requires closer examination – an issue that will be examined in the next chapters.

Although the findings presented in the present chapter are 'powerful' (based as they are on a large sample size and the number of individual sleep characteristics available for analysis), these findings remain constrained by the subjective measurement of sleep, the (somewhat uncertain) choice of referent sleep categories, and the presence of substantial missing data. Therefore, better data with better measurement, and better specification of referent sleep categories might further improve the value of these analyses, and may (for example) identify other sleep patterns that were not evident with the data available for the present chapter's analyses. As such it is important to stress that these results might not be generalizable to other populations (with contrasting sociodemographic and health features) or to studies using alternative sources of sleep data. Nonetheless, by including as many participants as possible the analyses presented in this chapter ensured that these were able to discover a substantial number and variety of sleep patterns; and these patterns suggest a similar approach may have utility for further studies examining sleep amongst UKHLS participants (or other, similar datasets)

4.5.3 Conclusion

Latent class analysis generated 6 clusters with distinct patterns and different sizes as the membership of some sleep clusters was more common than others. The latent sleep clusters were quite stable over time except, to a modest extent, with respect to the relative contributions made by sleep duration and sleep latency in some of the clusters – variation that might suggest a role for more objective measures of these variables in future studies of this nature. However, over time,

some participants' sleep patterns changed (and that such changes were more common from/to some sleep patterns than others – suggesting that some might be more 'transitory states' and others more 'stable', perhaps due to their varying sensitivity to changes in the sociodemographic and health circumstances prevailing at different time points. Both these clusters and each the individual sleep characteristic display important associations with sociodemographic and health variables, even after adjustment for potential confounding, although these associations are different for sleep clusters and individual sleep characteristics, suggesting that clusters and characteristics capture distinct aspects of sleep, and supporting the possibility that latent sleep clusters represent more holistic assessments of overall 'sleep patterns'. However, this suggestion would not change the hypothesized DAG (in which 'sleep' is represented by a single variable), since the association between latent sleep, sociodemographic characteristics and health still exist. In the chapters that follow, the distribution of sleep clusters identified in the present chapter are examined in populations of pregnant women, and are then compared to sleep characteristics as potential correlates of/precursors to a range of pregnancy outcomes.

4.5.4 Recommendation

Further research is required in this area to describe sleep patterns using LCA because, at the time of this study (and as far as is evident from the literature examined during the course of the present thesis), no research has previously described sleep using LCA to describe 'sleep patterns' in this way before. However, the analyses presented in the present chapter do suggest that adopting a 'latent sleep approach' may be more useful in defining sleep than the classic approach (using separate, individual sleep characteristics, or composite scores such as the PSQI 'sleep quality index'); and that the latent sleep categories generated can (and did) have very different patterns of association with sociodemographic and health-related characteristics when compared to analyses using separate, individual sleep characteristics .

Additional sleep research using LCA would also facilitate the comparison of sleep patterns observed between different populations, as well as furthering understanding as to which covariates might influence which of these sleep patterns. Meanwhile, the measurement of sleep clearly requires careful consideration, particularly when choosing the measurement tool used, and especially regarding sleep duration and latency (both of which displayed some variation in their contributions to sleep patterns over time). Moreover, thoughtful consideration should be given when choosing the referent categories for both

individual sleep variables and LCA-derived sleep clusters, since the results showed that the choice of the referent category can affect the pattern of association(s) observed between sleep, sociodemographic characteristics and health-related features. Finally, as ever, better quality data is required for such studies, particularly regarding the missingness of data. These considerations, together with wider acceptance amongst researchers regarding the quality of their data, the power of their sample sizes, and the number of hypotheses examined, might be required to temper the number of clusters derived, and the certainty with which the best-fitting number of clusters are selected for subsequent analytical use.

Chapter 5 The relationship between sleep and birth outcomes in the UK pregnant women: UKHLS

5.1 Introduction

A few UK-based sleep studies have reported higher rates of sleep 'problems' in women than men (Arber et al., 2009, Hislop and Arber, 2003), attributing these to possible hormonal and/or psychosocial causes. However, amongst pregnant women, sleep is widely considered to become more problematic due to changing hormone levels, and anatomical consequences of an enlarged uterus (Hedman et al., 2002, Hertz et al., 1992). Some authors have also suggested that the increase in sleep problems during pregnancy are often associated with poorer pregnancy outcomes. Nonetheless, little is known about the pathophysiology of how sleep problems might affect the mother and her foetus or might correlate with poor pregnancy outcomes (albeit with the exception of SBD, which is known to affect cardiovascular and respiratory functions). If a broader relationship between the sleep and poor pregnancy outcomes were to be established, this might identify potential interventions for preventing or attenuating some potentially serious pregnancy complications simply by improving (or otherwise modifying) maternal sleep.

As discussed in the preceding chapter which reviewed previous studies of this topic, despite the broad consensus these suggest of a link between less favourable sleep and poor pregnancy outcomes – few of these studies examined the full breadth of sleep-related measures available (i.e. few had measured more than a few sleep characteristics). Moreover, none had attempted to examine sleep more 'holistically' using a combination of sleep characteristics to identify latent 'sleep patterns' (as the present thesis has done). Furthermore, the present thesis could find no information in the literature regarding pregnant women in the UK and any possible association between sleep and pregnancy outcome – most of the published studies having been conducted in the US.

The aim of this study was therefore to examine both a wide range of sleep characteristics (i.e. the 7 discrete sleep characteristics generated within the UKHLS sleep module) *and* the LCA sleep patterns identified in the preceding chapter, in a population-based sample of pregnant women from the UK population, and thereafter to examine their relationship with poor pregnancy outcomes.

5.2 Materials and method

5.2.1 Data source

The sample used in the present chapter's analyses included pregnant participants from Waves 1 and 4 of the UKHLS, both of which included the collection of sleep data. Birth outcomes and pregnancy-related events data were extracted from subsequent Waves, as these were recorded retrospectively after the participants gave birth – thus data were extracted from Wave 2 for participants who were pregnant in Wave1 and from Wave 5 for participants who were pregnant in Wave 4; Figure 5-1)

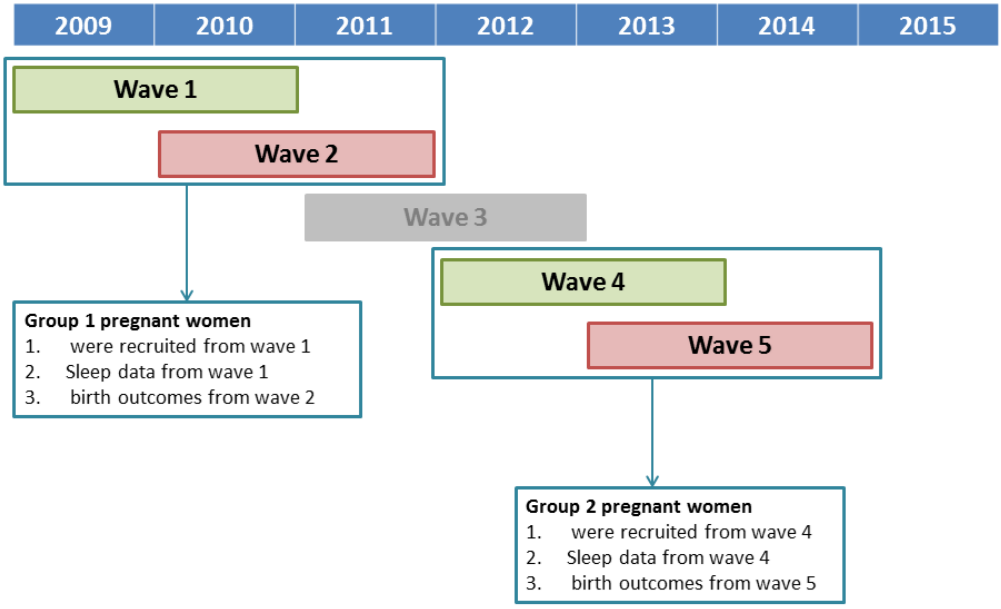

Figure 5-1 Data sources for pregnant participants in the UKHLS

5.2.2 Study design

The present chapter therefore adopted a prospective longitudinal design since the collection of data on sleep characteristics preceded the collection of pregnancy-related outcomes data.

5.2.3 Participants

The following criteria were used to select the participants:

I. the participant had complete sleep and pregnancy data
II. the pregnancy resulted in a singleton birth
III. the pregnancy ended with a live birth

Women with multiple pregnancy were excluded because their number was small (n=3) hence it was not possible to adjust for them in the analytical models (it being likely that multiple pregnancy would affect both the risk of poor sleep and poor pregnancy outcomes). Additionally, the sample was restricted to women whose pregnancies ended in a live birth simply because there were no pregnancy- related data for any pregnant women who subsequently suffered a termination or still birth.

Pregnant participants were identified in both Waves (i.e. 1 & 4) using each of the steps shown in the following sub-section, though only those for whom sleep data were available were included in the analyses that follow.

5.2.3.1 Identifying pregnant participants in Wave 1

The pregnant women in Wave 1 were identified according to their responses to the following questions:

I. The first question used was in Wave1, and stated: **"Do you think you will have *[any more/any]* children?"** The selected participants responded as follows: **"Self/partner currently pregnant" [included only females].**

II. The second question was in Wave 2, and stated: **"Since [ff_Int_Date] have you been pregnant at all, even if this did not result in a live birth?"** The selected participants responded as follows: **"Pregnant at last interview".**

5.2.3.2 Identifying pregnant participants in Wave 4

The participants in Wave 4 were also identified based on their responses to two questions:

I. The first question was from the Wave 4 questionnaire, and stated: **"Last time we interviewed you, you were pregnant. Did this/your next pregnancy result in a live birth with a normal delivery or by caesarean section?"** Currently pregnant women selected the response **"current pregnancy".**

II. The second question was from the Wave 5 questionnaire, and stated: **"The next questions are about any children you may have had. Since [ff_Int_Date], have you been pregnant at all, even if this did not result in a live birth?"** Women who had been pregnant in the preceding Wave (Wave 4) selected the response "**pregnant at last interview".**

5.2.4 Measurements

5.2.4.1 Sleep characteristics

Sleep data were gathered using the self-completed UKHLS Sleep Module. In the analysis presented in the present chapter, sleep duration was categorised into the

following: long sleep (>9 hours), short sleep (<6 hours) and reference range (≥6 and ≤9 hours) to ensure that these analyses were capable of assessing the possibility of a U-shaped relationship between sleep duration and (poor) pregnancy outcomes. For items relevant to different sleep 'events' (i.e. latency, disturbance, snoring or coughing, daytime sleepiness, use of sleep-related medication), these were each categorised as binary variables based on the absence or presence of the events in question. Finally, sleep quality was simply categorised as good vs. bad.

Reducing each of these polytomous variables to binary categorical variables was needed to ensure that the analyses could accommodate the limited number of pregnant UKHLS participants in some instances. For similar reasons, an 'absence vs. presence' cut off point was chosen rather than an 'habitual' versus 'non-habitual' cut off to ensure there were sufficient numbers of participants in both categories and to minimise the possible effect of measurement error in the reporting of the frequency of the events.

5.2.4.2 Sleep clusters

Sleep clusters were assigned to participants from the UKHLS using the algorithm generated from the latent class analysis study which was discussed in detail previously in Chapter 4. The algorithm used (Appendix, Section 8.3.5, page 319) was generated in table format using Latent Gold Software (Statistical Innovations Inc., 2009) and the table was then transformed into commands within STATA (StataCorp., 2013). The STATA commands were then applied to the responses of study participants to the seven sleep questions (the answers to each of which had been recoded so as to be the same as that categorised for the analyses in which the sleep clusters were generated in Chapter 4). As described earlier in the thesis, these six sleep clusters were labelled: short bad sleeper, long moderate sleeper, long good sleeper, disturbed bad sleeper, struggle-to-sleep-er, and snoring good sleeper.

5.2.4.3 Birth outcomes

In the UKHLS, the birth outcomes on which data were available were: birth weight, mode of delivery and preterm delivery. The birth outcomes of women who were pregnant in Wave 1 were obtained from responses presented in Wave 2, and the outcomes of pregnant women in Wave 4 were obtained from responses presented in Wave 5 (see Figure 5-1). Each of these outcome variables were re-categorised into binary categorical variables so that these were amenable for analytical techniques that generated the OR associated with the risk of developing poor pregnancy outcomes.

For birth weight this first involved some standardisation of units, since this was recorded in two different units (i.e. grams, ounces and pounds), all of which were standardised into grams. For the analyses that follow, birth weight was then categorised as low birth weight (<2500 grams), macrosomia (>4000 gram) or normal weight (≥2500 and ≤4000 grams). The cut-off points were chosen based on the WHO criteria for 'abnormal' birth weight (United Nations Children's Fund and World Health Organization, 2004).

Caesarean delivery was categorized as caesarean delivery (which included both elective and emergency delivery) vs. vaginal delivery (which included both assessed and non-assessed vaginal delivery). This categorisation was chosen due to the absence of any further information regarding the reasons for caesarean delivery or any other difficulties encountered with the natural birth.

Preterm delivery was defined as any delivery prior to 37 weeks of gestation, again based on the WHO definition (World Health Organization, 2015). Preterm delivery was thereby categorised into preterm delivery and term delivery (which included both date and post-date deliveries).

For further details about the extraction of variables from the UKHLS data set and the coding of these, please refer to the Appendix (Chapter 8, Section 8.4, page 343).

5.2.4.4 Covariates

Confounders were identified from amongst those covariates that were available within the UKHLS data set. In the first instance, a simple Directed Acyclic Graph (DAG) was drawn to generate a visual guide for selecting those covariates acting as confounders from amongst the large number of covariates available (Figure 5-2). The covariates selected included sociodemographic features, pre-pregnant maternal health conditions and parity – all of which were judged to have preceded the exposures examined in the present chapter's analysis (i.e. sleep during pregnancy).

In regard to the potential role of behavioural risk factors for poor pregnancy outcomes (i.e. smoking and alcohol), some of which may have become established prior to the measurement of the exposure, the decision was taken not to adjust for these in the multivariable analyses that follow primarily because they were collected retrospectively (i.e. after birth), and it was therefore not known if their measurement preceded or followed the measurement of sleep.

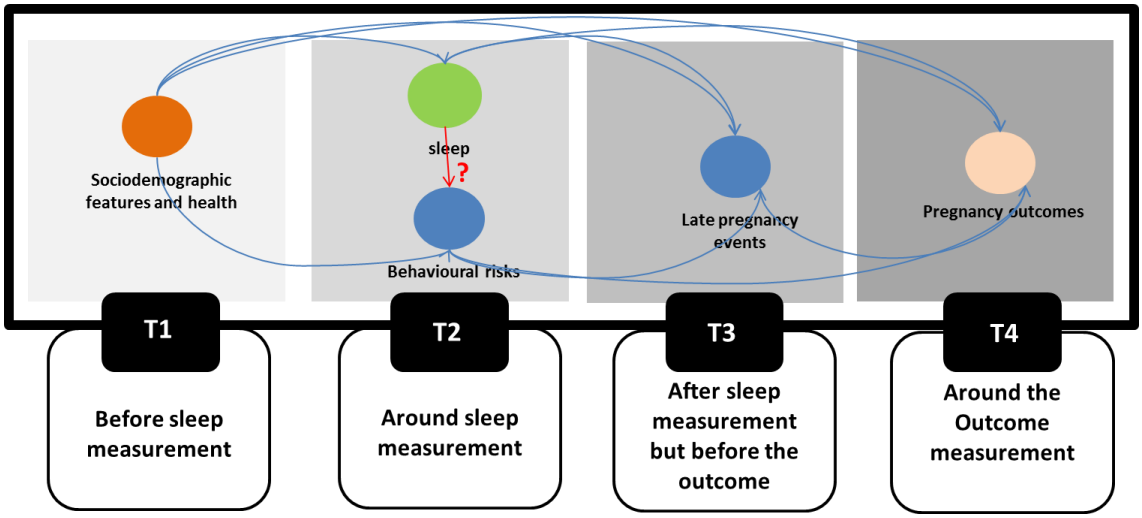

Figure 5-2 Simplified DAG illustrating shows the temporal relationship between the covariates available in the UKHLS dataset.

Sociodemographic features and the data on maternal health condition were extracted from the same UKHLS wave as that providing the sleep data (that is, in Waves 1 and 4, respectively).

As before, the number of categories for each of the covariates included in these analyses was reduced into two (i.e. each were re-categorised as binary variables) to facilitate the inclusion of as many confounders as possible (given the modest sample sizes available). In each instance, the cut-off points chosen were based on the distribution of the data, although a secondary (yet equally important consideration) was to also try to reduce the loss of meaning and the risk of (further) categorisation error. Indeed, for this reason, maternal (participant) age was retained for use as a continuous variable.

Elsewhere, ethnicity was categorised based on its classification within the NICE-generated GDM risk scoring, in which women classified as having a 'White' ethnicity is considered to be at 'low risk' (of GDM) whilst those classified as having other (black and minority ethnic group ethnicities - such as South Asian and Black) are considered to be at higher risk.

Employment status was included in the analyses after re-categorisation into 'currently working' vs. 'currently not working'. Likewise, education was categorised into 'lower' vs. 'higher' educational attainment. Cohabitation was also categorised into a binary variable as being either 'had' or 'did not have' a partner. Meanwhile, pregnant women who reported having any of the following health conditions were coded as having poor(er) pre-pregnant health: asthma, arthritis, congestive heart failure, coronary heart disease, angina, heart attack or myocardial infarction, stroke, emphysema, hypothyroidism or under-active thyroid, chronic bronchitis,

any liver condition, cancer or malignancy, diabetes mellitus (but not GDM), epilepsy, high blood pressure, clinical depression, hyperthyroidism or an over-active thyroid. Finally, parity was simply categorised into nulliparous vs. multiparous.

For further details about the extraction and (re)coding of covariates from the UKHLS data sets, please refer to the Appendix (Chapter 8, Section 8.4.3, page 344).

5.2.5 Ethical considerations

Ethical approval for the main survey of the UKHLS was obtained from the Ethics Committee of the University of Essex on 6 July 2007 for Wave 1 and on 17 December 2010 for Wave 4 (Gundi, 2016).

Access to the 'special license version' of the UKHLS dataset was obtained in March 2015 by the candidate and their supervisors. However, data released under the special license version were not used due to the very poor quality of data for each of the variables of interest examined (in particular, those variables that might have helped to generate estimates of the gestational age at which participants in Wave 1 responded to the items on sleep [and other covariate characteristics]).

5.3 Analyses

5.3.1 Descriptive analysis

5.3.1.1 Missing data

The distributions of missing data, as compared to the distribution of complete data, were tabulated to facilitate closer inspection. Missing data were examined for the possibility that these were missing at randomand were then treated by listwise deletion.

5.3.1.2 Participant's characteristics

Frequency and percentage tables were used to display the distribution of each of the characteristics examined for participants included in the present chapter's analyses.

5.3.2 Regression analysis

Adjusted and unadjusted logistic regression models were used to assess the relationship between sleep and pregnancy outcomes. As mentioned in Section 5.2.4.2, the latent sleep variable that was included in the present chapter's analysis comprised the six categories of the latent sleep variable that had 'long good

sleeper' as the referent, and in which participants were allocated membership to one of the six sleep clusters by applying the LCA-generated algorithm (as discussed in Chapter 4) using participants' responses to the seven sleep questions presented in the UKHLS sleep module.

The estimation method used in the logistic regression analysis was the penalized maximum likelihood estimation (Firth, 1993; see Chapter 2, Section 2.5.1.1, page 72). STATA.13 software was used for all of these analyses (StataCorp., 2013).

A dedicated DAG was used to assist in identifying the minimal sufficient set of covariates necessary to adjustment for any confounding associated therewith. This DAG was drawn using the open-source software DAGitty (see Textor et al., 2017).

5.4 Results

5.4.1 Included participants

The number of pregnant UKHLS participants identified from Wave 1 was 532 and from Wave 4 was 408 (Figure 5-3 and Figure 5-4). However, the final number of participants included in the study was only 294 since many had missing data on the selected exposures, outcomes and/or covariates. This final number was achieved by merging data from each wave and thereafter excluding data from any duplicate participants occurring (not only in Wave 1 but also) in Wave 4 (- meaning that these participants' first responses to the sleep questionnaire, from Wave 1, remained in the analyses that follow, see: Figure 5-5).

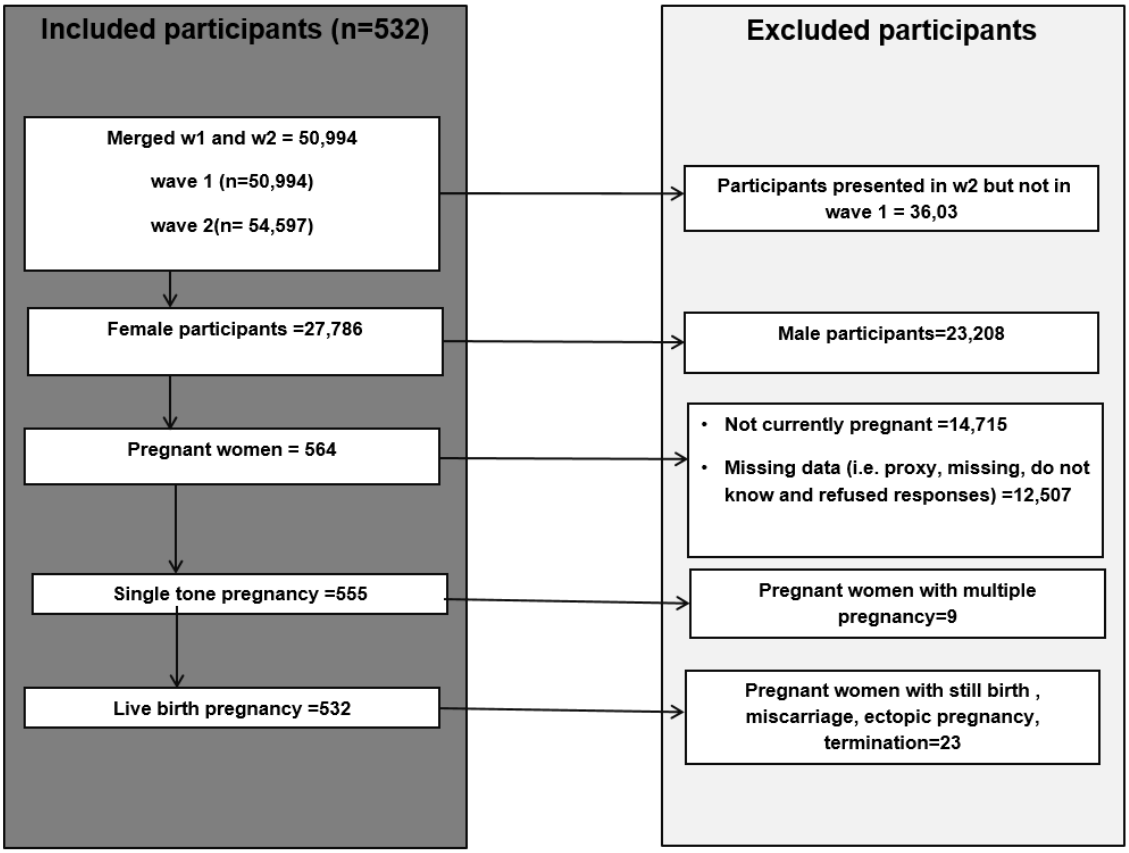

Figure 5-3 Flowchart showing how pregnant women were included or excluded from data generated during Waves 1 and 2 of the UKHLS

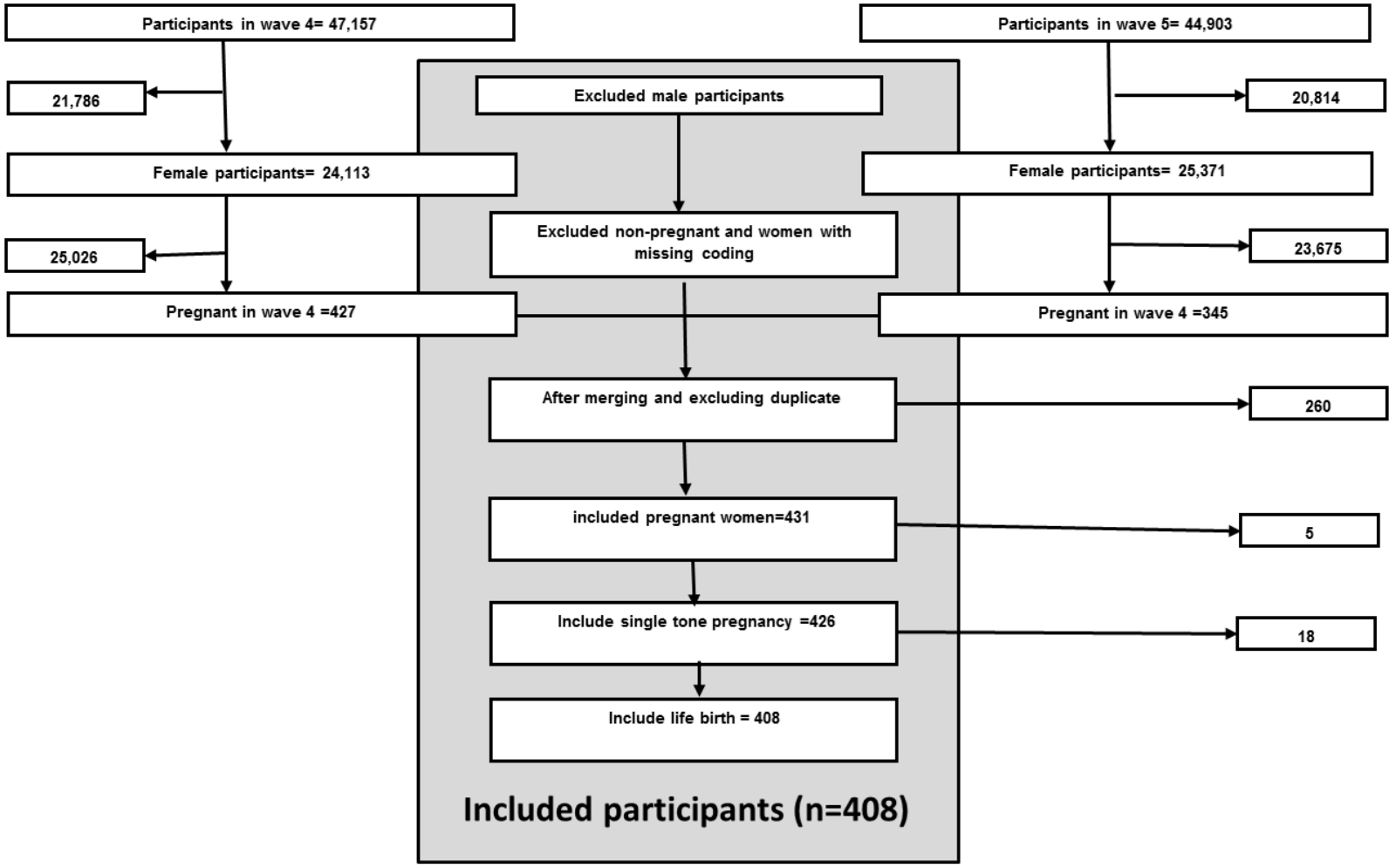

Figure 5-4 Flowchart showing how data from pregnant women were included and excluded from the datasets generated during Waves 4 and 5 of the UKHLS

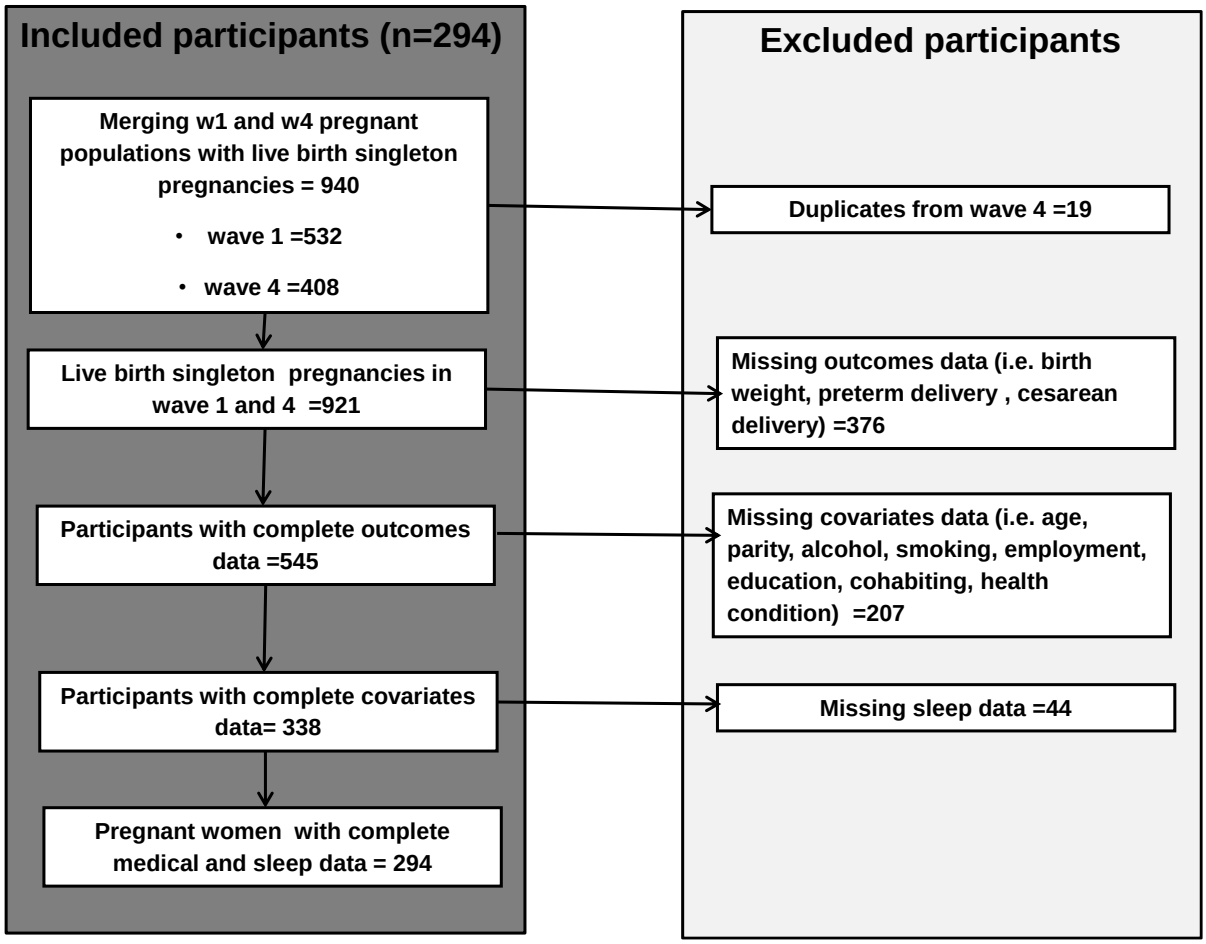

Figure 5-5 Flowchart showing pregnant women included or excluded after samples and data from Waves 1 and 4 of the UKHLS were merged

5.4.2 Descriptive analysis results

5.4.2.1 Missing data

There was no visible association between missingness amongst the sleep and pregnancy outcomes variables, and the distribution of sleep characteristics in the women with missing data on birth outcomes was similar to the distribution of sleep characteristics amongst women with complete data on birth outcomes (Appendix, Section 8.4.4, page 346, Table 8-22). Similarly, women with missing sleep data had birth outcome distributions that appeared broadly similar to those of women with complete sleep data (Appendix, Section 8.4.4, page 346, Table 8-23). In addition, there did not appear to be any clustering of missing data amongst particular groups of participants, since women with missing data on sleep or health had a very similar distribution of sociodemographic characteristics to those women with complete data on sleep and health (Appendix, Section 8.4.4, page 346, Table 8-24).

5.4.2.2 Sleep characteristics

As evident in Table 5-1, the distribution of sleep characteristics amongst women with complete data on each of the sleep and health variables followed a distribution that was similar to the sleep characteristics of all eligible pregnant women. Overall, the pregnant women were more likely to display sleep durations falling between 6 and 9 hours a day. In addition, they reported low rates of the following events: snoring, daytime sleepiness and (particularly) use of sleep-related medication. In contrast, they reported higher rates of sleep latency and disturbance.

As regards the latent sleep clusters, the commonest sleep pattern was 'short bad sleeper' whilst the least common was 'disturbed bad sleeper'. Only 12.9% (n=38) of the pregnant UKHLS participants reported an absence of unfavourable sleep events and had sleep patterns characterised as long good (Table 5-1).

Table 5-1 Distribution of sleep characteristics amongst pregnant UKHLS participants

		Singleton livebirth pregnant women with complete data		All singleton livebirth pregnant population	
		n=294	**%**	**n=921**	**%**
Sleep duration	*Short sleep (<6)*	37	12.59	106	11.51
	Reference range (6-9)	229	77.89	659	71.55
	Long sleep (>9)	28	9.52	55	5.97
	Missing	0	0	101	10.97
Latency	*Absent*	113	38.44	313	33.98
	Present	181	61.56	509	55.27
	Missing	0	0	99	10.75
Disturbance	*Absent*	41	13.95	128	13.9
	Present	253	86.05	698	75.79
	Missing	0	0	95	10.31
Snoring or coughing	*Absent*	226	76.87	626	67.97
	Present	68	23.13	181	19.65
	Missing	0	0	114	12.38
Day sleepiness	*Absent*	247	84.01	692	75.14
	Present	47	15.99	125	13.57
	Missing	0	0	104	11.29
Medication	*Absent*	282	95.92	786	85.34
	Present	12	4.08	50	5.43
	Missing	0	0	85	9.23
Quality	*Good*	217	73.81	589	63.95
	Bad	77	26.19	249	27.04
	Missing	0	0	83	9.01
Sleep clusters	*Short bad sleeper*	162	55.1	393	42.67
	Long moderate sleeper	27	9.18	87	9.45
	Long good sleeper	38	12.93	95	10.31
	Disturbed bad sleeper	11	3.74	32	3.47
	Struggle to sleep-er	36	12.24	106	11.51
	Snoring good sleeper	20	6.8	66	7.17
	Missing	0	0	142	15.42

5.4.2.3 Birth outcomes

The mean birth weight of pregnant women in the present analyses was 3,439 g (SD=597, minimum=1,814, maximum=4,320). Only 19.4% (n=15) of the pregnant women with macrosomic babies delivered via CS, while 88.2% (n=15) of low birth weight babies were born premature. Nonetheless, the rate of term deliveries was around 75% (n=221), one quarter of which were caesarean deliveries (n=55, 24.9%).

Unfortunately, only 113 women in the UKHLS study with complete data reported their gestational age: 23 of these women participated while they were in their first trimester of pregnancy, 43 were in their second trimester, and 47 women were in their third trimester.

A summary of the distribution of birth outcomes amongst pregnant UKHLS participants is presented in Table 5-2.

Table 5-2 Distribution of birth outcomes amongst pregnant UKHLS participants

		Singleton livebirth pregnant with complete data		All singleton livebirth pregnant population	
		n=294	**%**	**n=921**	**%**
Macrosomia	*≤ 4000 gm*	252	85.71	426	46.25
	>4000 gm	42	14.29	119	12.92
	Missing	**0**	**0**	376	40.83
Low birth weight	*Birth weight ≥ 2500 gm*	277	94.22	292	31.7
	Birth weight <2500 gm	17	5.78	253	27.47
	Missing	**0**	**0**	376	40.83
Preterm labour	*Term*	221	75.17	672	72.96
	Preterm	73	24.83	121	13.14
	Missing	**0**	**0**	128	13.9
Mode of delivery	*Vaginal*	217	73.81	594	64.5
	Caesarean	77	26.19	192	20.85
	Missing	0	0	135	14.66

5.4.2.4 Sociodemographic features and health

As summarised in Table 5-3, the majority of the participants examined were in their twenties and thirties, were nulliparous and had a partner. From the 34 participants who did not work around the time sleep was measured; 31 were on maternity leave and three were on long-term sickness or disability leave.

Nearly 13% of the participants reported smoking during pregnancy, whereas around 25% of the non-smokers were ex-smokers (n= 61). Twelve participants smoked more than 10 cigarettes a day during their first trimester, and 6 participants smoked more than 10 cigarettes during their second and third trimesters. Approximately 75% of the participants did not consume alcohol during their pregnancy, and around half of those who consumed alcohol (n= 47) consumed two or less units of alcohol per week.

Around 12% of the participants had a pre-existing (chronic) health condition (n= 38), 23 of whom had a respiratory condition, 5 had arthritis, 3 had a heart condition, 6 had thyroid disease, 2 had diabetes, 1 had epilepsy, 4 had hypertension (HTN), and 5 had clinical depression.

Table 5-3 Distribution of sociodemographic features and health of pregnant UKHLS participants

		Singleton livebirth pregnant with complete data		All singleton livebirth pregnant population	
		n=294	%	n=921	%
Age	*≤ 19 years*	9	3.06	42	4.56
	20-29 years	120	40.82	382	41.48
	30-39 years	151	51.36	441	47.88
	≥ 40 years	14	4.76	56	6.08
	Missing	0	0	0	0
Parity	*Nulliparous*	214	72.79	573	62.21
	Multiparous	80	27.21	348	37.79
	Missing	0	0	0	0
Ethnicity	*Lower risk of GDM*	247	84.01	693	75.24
	Higher risk of GDM	47	15.99	223	24.21
	Missing	**0**	**0**	5	0.54
Cohabitation	*Not cohabited*	55	18.71	174	18.89
	Cohabited	239	81.29	746	81
	Missing	0	0	1	0.11
Smoking	*Not current smoker*	254	86.39	688	74.7
	current smoker	40	13.61	122	13.25
	Missing	**0**	**0**	111	12.05
Alcohol	*No alcohol consumption*	210	71.43	632	68.62
	Alcohol consumption	84	28.57	179	19.44
	Missing	**0**	**0**	110	11.94
Employment	*Currently working*	260	88.44	57	6.19
	Currently not working	34	11.56	548	59.5
	Missing	**0**	**0**	316	34.31
Education	*Degree and higher*	131	44.56	453	49.19
	A level and Lower	163	55.44	392	42.56
	Missing	**0**	**0**	76	8.25
Health condition	*No*	256	87.07	801	86.97
	Yes	38	12.93	120	13.03
	Missing	**0**	**0**	0	0

5.4.3 Regression results

5.4.3.1 Adjustment of the regression models

The minimal sufficient adjustment sets of covariates identified as confounders (albeit amongst the covariates available for analysis) were: age, education, employment, ethnicity, cohabitation, household structure, and medical condition (Figure 5-6). Smoking and alcohol were considered likely to have a bidirectional relationship with sleep, but since there was not enough information about the precise time at which

these variables were measured (particularly in relation to the measurement of sleep), both were considered potential mediators and were therefore not included in the covariate adjustment sets used.

An additional covariate adjustment set was included that only had those variables available in both the Scott/Ciantar study and UKHLS. Although this analysis was considered under-adjusted (since it lacked confounders available in one, though not both, of these datasets), it was nonetheless conducted to permit a direct comparison of the regression analyses' results between these two studies. The common adjustment set included the following confounders: age, ethnicity, education, cohabiting and health.

Unfortunately, it was not possible to include BMI in the covariate adjustment sets because so few participants had data (only those who had participated in Wave1 where weight and height were recorded). Late pregnancy complications were also not available in the UKHLS data set, though these were likely to have been mediators in the relationship between sleep and pregnancy outcomes.

As for gestational age at questionnaire completion and BMI, it was not possible to consider the inclusion of neonatal sex in the multivariable analyses since this information was rarely available.

With regard to the various pregnancy outcomes used, it was clear that preterm delivery was likely to have affected birth weight. However, because preterm delivery was also considered a mediator for any relation between sleep and birth weight it was not included in the analyses of these relationships.

Given there was little detail about previous obstetric history (e.g. previous macrosomia or caesarean section), and no data on late pregnancy complications (e.g. pregnancy induced hypertension) neither could be considered for inclusion in the multivariable analyses undertaken in the present chapter.

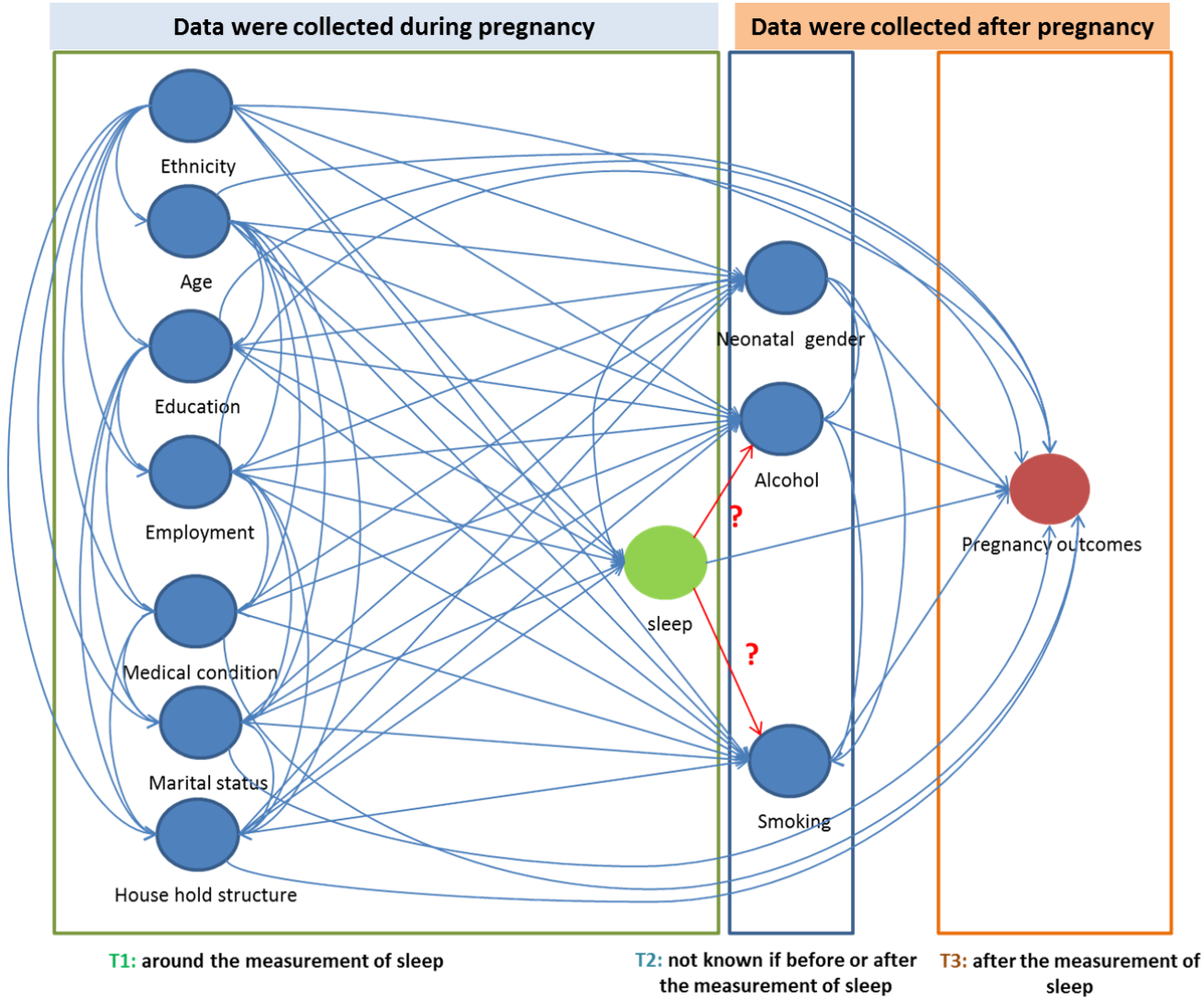

Figure 5-6 Directed acyclic graph summarizing the minimal sufficient covariate adjustment set required to adjust for confounding in regression models examining the relationship between sleep and maternal outcomes.

5.4.3.2 The relation between sleep and birth outcomes

In general when examining each of the seven specific sleep characteristics, the odds of macrosomia was higher amongst pregnant women with short sleep, coughing/snoring and disturbed sleep (Table 5-6); whilst, the odds of LBW neonates was higher amongst women who coughed/snored, used medication to assist with sleep, and who experienced protracted sleep latency (Table 5-7). In contrast, the odds of preterm delivery exhibited a relationship with unfavourable sleep amongst all of the individual sleep characteristics, with the exception of daytime sleepiness (Table 5-5). A heightened odds of caesarean section, however, was only associated with sleep latency and coughing/snoring (Table 5-4). That said, it is important to note that the estimated risk of pregnancy outcomes lacked precision, as reflected by a wide 95% confidence interval, as a result of the underpowered analysis. At the same time, some of the 95% CIs were wider than others due to the difference in the distribution of the unfavourable sleep events and pregnancy outcomes amongst the study's participants.

As regards the LCA-derived sleep patterns, the odds of preterm delivery was higher amongst women classified as long good sleepers (Table 5-5), whilst the odds of caesarean section was higher amongst women classified as short bad sleepers, long moderate sleepers, disturbed bad sleepers, and struggle-to-sleep-ers (Table 5-4). Meanwhile, the odds of macrosomia was higher in struggle to-sleep-ers and snoring good sleepers (Table 5-6), in contrast to the elevated odds of low birth weight amongst long good sleepers (Table 5-7).). Again, these estimated ORs lacked precision which made it difficult to interpret the results with a preferred level of confidence and certainty.

Nonetheless, it is possible to claim that coughing/snoring had the most (and strongest) relation with an elevated odds of *all* poor pregnancy outcomes – while daytime sleepiness was generally accompanied by a *lower* odds of poor pregnancy outcomes. The odds of preterm delivery was lower amongst women with less favourable sleep patterns, except for those who were short bad sleepers; whilst the risk of caesarean delivery was higher across all sleep patterns with the exception of those labelled snoring good sleepers.

In the following sections of this results section, the relation between sleep and pregnancy outcomes will be presented using ORs as well as 95% CIs to reflect the level of confidence and precision of the OR estimates. The associated *p*-values will not be presented since multiple testing was involved, and might therefore increase the chance of type I error (reflected by a significant *p*-value). However, there were occasionally statistically 'significant' findings which have been highlighted using bold

text in the results tables that follow, though once again these should be interpreted with caution since they might merely be due to chance.

5.4.3.2.1 Mode of delivery

Latency (OR=1.25, CI=0.72, 2.17) and snoring (OR=1.61, CI=0.89, 2.90) were accompanied by an elevated risk of caesarean delivery. In contrast, long duration (OR= 0.56, CI= 0.19, 1.60) and disturbance (OR=0.69, CI=0.33, 1.43) were accompanied by a reduced risk of caesarean delivery. Short duration (OR=1.02, CI= 0.47, 2.47) and usage of medication (OR = 1.09, CI = 0.30, 3.89) showed a modest relation with caesarean delivery (Table 5-4).

In regards to LCA-derived sleep patterns, the risk of caesarean delivery increased with all sleep patterns except snoring good sleep pattern (OR=0.88, CI=0.24, 3.25) when compared to participants who had long good sleep pattern (Table 5-4).

5.4.3.2.2 Preterm delivery

After adjustment of possible confounders, an elevated risk of preterm delivery was accompanied by all unfavourable sleep characteristics except next day sleepiness (OR=0.40, CI=0.17, 0.96; Table 5-5)

In regards to LCA-derived sleep patterns, short bad sleepers (OR=0.79, CI=0.36, 1.72), long moderate sleepers (OR=0.50, CI=0.15, 1.69) and disturbed bad sleepers (OR=0.34, CI=0.05, 2.17) had a lower risk of preterm delivery compared to participants who had absent unfavourable events (i.e. long good sleepers) whilst, struggle to sleep-ers and snoring good sleepers had almost similar odds of preterm delivery compared to long good sleepers.

5.4.3.2.3 Macrosomia

Latency was accompanied by a reduced risk of macrosomia (OR=0.76, CI=0.39, 1.48) in contrast to snoring, which had a higher risk of macrosomia (OR= 2.12, CI=1.02, 4.41). The other sleep characteristics showed modest effect on the risk of macrosomia; their ORs were almost 1.0 (Table 5-6)

Compared to long good sleepers, the risk of macrosomia in the UKHLS pregnant participants was higher in the struggler to sleep-ers (OR=1.26, CI=0.36, 4.40) and snoring good sleepers (OR=1.59, CI=0.39, 6.38); whereas, it was lower in the Long moderate sleepers (OR=0.97, CI=0.23, 4.19) and disturbed bad sleepers (OR=0.28, CI=0.14, 5.49).

5.4.3.2.4 Low birth weight

Short (OR=0.61, CI=0.11, 3.43) and long (OR=0.79, CI=0.13, 4.66) duration and quality (OR=0.67, CI=0.20, 2.24) were accompanied by a small risk of low birth weight. Snoring (OR=2.02, CI=0.73, 5.55) and medication (OR=3.70, CI=0.80, 17.25) were accompanied by an elevated risk of low birth weight (Table 5-7).

In regards to sleep patterns, the risk of low birth weight was lower for all five sleep patterns compared to long good sleep patterns (Table 5-7)

Table 5-4 Logistic regression model examining the relationship between caesarean delivery and each of the seven specific sleep characteristics and six sleep patterns. All results are presented as odds ratios (OR) with 95% confidence intervals (CI). [1,2]

Cesarean Delivery Models	Level of Adjustment					
	Unadjusted model		Adjusted model[1]		Adjusted model[2]	
	OR	CI	OR	CI	OR	CI
Caesarean delivery model 1: caesarean delivery and short sleep duration						
≥ 6 hours	Referent					
< 6 hours	0.91	0.50, 1.65	1.10	0.51, 2.40	1.02	0.47, 2.47
Caesarean delivery model 2: caesarean delivery and long sleep duration						
≤ 9 hours	Referent					
> 9 hours	0.48	0.17, 1.37	0.56	0.19, 1.65	0 .56	0 .19, 1.60
Caesarean delivery model 3: caesarean delivery and sleep duration						
Continuous	0.88	0.72, 1.07	0.93	0.76, 1.14	0.94	0.77, 1.16
Caesarean delivery model 4: caesarean delivery and sleep latency						
Absent	Referent					
Present	1.21	0.71, 0.71	1.27	0.73, 2.20	1.25	0.72, 2.17
Caesarean delivery model 5: caesarean delivery and sleep disturbance						
Absent	Referent					
Present	0.72	0.36, 1.46	0.66	0.32, 1.38	0.69	0.33, 1.43
Caesarean delivery model 6: caesarean delivery and snoring (and/or coughing)						
Absent	Referent					
Present	1.64	0.91, 2.93	1.61	0.89, 2.93	1.61	0.89, 2.90
Caesarean delivery model 7: caesarean delivery and sleep medication						
Absent	Referent					
Present	1.03	0.29, 3.61	1.02	0.29, 3.63	1.09	0.31, 3.89
Caesarean delivery model 8: caesarean delivery and next day sleepiness						
Absent	Referent					
Present	0.55	0.25, 1.22	0.59	0.26, 1.31	0.57	0.26, 1.27
Caesarean delivery model 9: caesarean delivery and sleep quality						
Good	Referent					
Poor	1.03	0.49, 2.16	0.94	0.44, 2.09	0.99	0.47, 2.00
Caesarean delivery model 10: caesarean delivery and polytomous latent sleep variable						
Short bad sleeper	1.35	0.59, 3.11	1.38	0 .58, 3.28	1.40	0.60, 3.27
Long moderate sleeper	1.56	0.52, 4.74	1.81	0 .57, 5.71	1.65	0.53, 5.12
Long good sleeper	Referent					
Disturbed bad sleeper	2.15	0.53, 8.68	2.07	0.49, 8.77	1.91	0.46, 7.96
Struggle to sleep-er	1.24	0.43, 3.58	1.26	0.42, 3.74	1.14	0.39, 3.31
Snoring good sleeper	0.98	0.27, 3.56	0.98	0.26, 3.73	0.88	0 .24, 3.25

[1] Minimal sufficient adjustment for: age, ethnicity, employment, education, parity, cohabiting status and health.

[2] Adjusted for age, ethnicity, parity, cohabiting status and health. Although this model was under-adjusted, it was included in this table to compare its results with the results of a comparable model using data from the Scott/Ciantar study (Table 6-4).

Table 5-5 Logistic regression model examining the relationship between preterm delivery and each of the seven specific sleep characteristics and six sleep patterns. All results are presented as odds ratios (OR) with 95% confidence intervals (CI).[1,2,3]

Preterm Delivery Models	Level of Adjustment					
	Unadjusted model		Adjusted model[1]		Adjusted model[2]	
	OR	CI	OR	CI	OR	CI
Preterm delivery model 1: preterm delivery and short sleep duration						
≥ 6 hours	Referent					
< 6 hours	1.17	0.54, 2.51	0.99	0.45, 2.20	1.09	0.50, 2.38
Preterm delivery model 2: preterm delivery and long sleep duration						
≤ 9 hours	Referent					
> 9 hours	1.53	0.67, 3.49	1.48	0.63, 3.51	1.51	0.65, 3.52
Preterm delivery model 3: preterm delivery and sleep duration						
Continuous	0.99	0.82, 1.22	1.03	0.83, 1.26	1.01	0 .82, 1.24
Preterm delivery model 4: preterm delivery and sleep latency						
Absent	Referent					
Present	**1.89**	**1.07, 3.37**	1.78	0.96, 3.10	1.74	0.97, 3.13
Preterm delivery model 5: preterm delivery and sleep disturbance						
Absent	Referent					
Present	1.00	0.47, 2.13	1.06	0.48, 2.30	0.96	0.45, 2.07
Preterm delivery model 6: preterm delivery and snoring (and/or coughing)						
Absent	Referent					
Present	1.37	0.75, 2.50	1.34	0.73, 2.47	1.40	0.77, 2.56
Preterm delivery model 7: preterm delivery and sleep medication						
Absent	Referent					
Present	1.11	0.32, 3.89	1.34	0.37, 4.83	1.23	0.34, 4.40
Preterm delivery model 8: preterm delivery and next day sleepiness						
Absent	Referent					
Present	0.42	0.18, 1.00	**0.38**	**0.16, 0.93**	**0.40**	**0.17, 0.96**
Preterm delivery model 9: preterm delivery and sleep quality						
Good	Referent					
Poor	1.20	0.67, 2.16	1.03	0.56, 1.90	1.20	0.66, 2.17
Preterm delivery model 10: preterm delivery and polytomous latent sleep variable						
Short bad sleeper	0.79	0.36, 1.72	0.87	0.39, 1.92	0.79	0.36, 1.72
Long moderate sleeper	0.46	0.14, 1.55	0.43	0.12, 1.50	0.50	0.15, 1.69
Long good sleeper	Referent					
Disturbed bad sleeper	0.34	0.05, 2.14	0.24	0.04, 1.62	0.34	0.05, 2.17
Struggle to sleep-er	1.08	0.41, 2.87	0.94	0.34, 2.59	1.06	0.40, 2.85
Snoring good sleeper	1.07	0.34, 3.40	1.22	0.37, 4.06	1.07	0.34, 3.42

[1]Mininmal sufficient adjustment for: age, ethnicity, employment, education, parity, cohabiting status and health.

[2] Adjusted for age, ethnicity, parity, cohabiting status and health. Although this model was under-adjusted, it was included in this table to compare its results with the results of a comparable model using data from the Scott/Ciantar study (Table 6-5).

[3] Bold font Bold fonts indicate statistically significant *p*-values (p<0.05).

Table 5-6 Logistic regression model examining the relationship between macrosomia and each of the seven specific sleep characteristics and six sleep patterns. All results are presented as odds ratios (OR) with 95% confidence intervals (CI).[1,2,3]

Macrosomia Models	Level of Adjustment					
	Unadjusted model		Adjusted model[1]		Adjusted model[2]	
	OR	CI	OR	CI	OR	CI
Macrosomia model 1: macrosomia and short sleep duration						
≥ 6 hours	Referent					
< 6 hours	1.25	0.50, 3.12	1.21	0.46, 3.17	1.02	0.35, 3.00
Macrosomia model 2: macrosomia and long sleep duration						
≤ 9 hours	Referent					
> 9 hours	1.09	0.38, 3.15	0.87	0.29, 2.61	0.87	0.29, 2.61
Macrosomia model 3: macrosomia and sleep duration						
Continuous	1.03	0.80, 1.32	0.99	0.78, 1.28	1.03	0.80, 1.32
Macrosomia model 4: macrosomia and sleep latency						
Absent	Referent					
Present	0.72	0.37, 1.38	0.89	0.40, 1.54	0.76	0.39, 1.48
Macrosomia model 5: macrosomia and sleep disturbance						
Absent	Referent					
Present	1.15	0.44, 3.01	1.21	0.45, 3.27	1.13	0.43, 3.00
Macrosomia model 6: macrosomia and snoring (and/or coughing)						
Absent	Referent					
Present	1.85	0.92, 3.73	**2.10**	**1.01, 3.36**	**2.12**	**1.02, 4.41**
Macrosomia model 7: macrosomia and sleep medication						
Absent	Referent					
Present	0.76	0.13, 4.30	0.81	0.14, 4.85	0.92	0.16, 5.39
Macrosomia model 8: macrosomia and next day sleepiness						
Absent	Referent					
Present	1.11	0.47, 2.61	1.11	0.46, 2.68	1.08	0 .46, 2.58
Macrosomia model 9: macrosomia and sleep quality						
Good	Referent					
Poor	1.02	0.49, 2.13	1.10	0.50, 2.43	1.14	0.53, 2.45
Macrosomia model 10: macrosomia and polytomous latent sleep variable						
Short bad sleeper	1.08	0 .40, 2.93	0.90	0.32, 2.51	1.07	0.39, 2.93
Long moderate sleeper	0.87	0.21, 3.67	0.98	0.20, 3.94	0.97	0.23, 4.19
Long good sleeper	Referent					
Disturbed bad sleeper	0.27	0.01, 5.17	0.26	0.01, 5.42	0.28	0.01, 5.49
Struggle to sleep-er	1.30	0.38, 4.47	1.18	0.33, 4.25	1.26	0.36, 4.40
Snoring good sleeper	1.66	0.42, 6.59	1.38	0.33, 5.87	1.59	0.39, 6.38

[1]Mininmal sufficient adjustment for: age, ethnicity, employment, education, parity, cohabiting status and health.

[2] Adjusted for age, ethnicity, parity, cohabiting status and health. Although this model was under-adjusted, it was included in this table to compare its results with the results of a comparable model using data from the Scott/Ciantar study (Table 6-4).

[3] Bold font Bold fonts indicate statistically significant *p*-values (p<0.05).

Table 5-7 Logistic regression model examining the relationship between low birth weight and each of the seven specific sleep characteristics and six sleep patterns. All results are presented as odds ratios (OR) with 95% confidence intervals (CI).[1,2]

Low Birth Weight Models	Level of Adjustment					
	Unadjusted model		Adjusted model[1]		Adjusted model[2]	
	OR	CI	OR	CI	OR	CI
LBW model 1: LBW and short sleep duration						
≥ 6 hours	Referent					
< 6 hours	0.60	0.11, 3.30	0.43	0.07, 2.62	0.61	0.11, 3.43
LBW model 2: LBW and long sleep duration						
≤ 9 hours	Referent					
> 9 hours	0.83	0.15, 4.61	0.78	0.13, 4.73	0.79	0.13, 4.66
LBW model 3: LBW and sleep duration						
Continuous	1.03	0.71, 1.50	1.09	0.74, 1.60	1.06	0.72, 1.55
LBW model 4: LBW and sleep latency						
Absent	Referent					
Present	1.46	0.52, 4.08	1.23	0.43, 3.51	1.32	0.46, 3.79
LBW model 5: LBW and sleep disturbance						
Absent	Referent					
Present	0.67	0.20, 2.25	0.89	0.25, 3.22	0.72	0.21, 2.47
LBW model 6: LBW and snoring (and/or coughing)						
Absent	Referent					
Present	1.95	0.72, 5.31	1.84	0.66, 5.12	2.02	0.73, 5.55
LBW model 7: LBW and sleep medication						
Absent	Referent					
Present	4.11	0.94, 17.89	4.04	0.84, 19.55	3.70	0.80, 17.25
LBW model 8: LBW and next day sleepiness						
Absent	Referent					
Present	0.45	0.08, 2.48	0.51	0.09, 2.83	0.45	0.08, 2.49
LBW model 9: LBW and sleep quality						
Good	Referent					
Poor	0.66	0.20, 2.18	0.51	015, 1.80	0.67	0.20, 2.24
LBW model 10: LBW and polytomous latent sleep variable						
Short bad sleeper	0.70	0.20, 2.47	0.95	0.26, 3.51	0.75	0.21, 2.71
Long moderate sleeper	0.99	0.18, 5.45	0.87	0.16, 4.91	0.97	0.17, 5.50
Long good sleeper	Referent					
Disturbed bad sleeper	0.44	0.02, 9.19	0.35	0.02, 7.68	0.45	0 .02, 9.87
Struggle to sleep-er	0.43	0.06, 3.07	0.41	0.05, 3.21	0.46	0.06, 3.33
Snoring good sleeper	0.78	0.11, 5.71	0.90	0.11, 7.67	0.80	0.11, 5.99

[1]Mininmal sufficient adjustment for: age, ethnicity, employment, education, parity, cohabiting status and health.

[2] Adjusted for age, ethnicity, parity, cohabiting status and health. Although this model was under-adjusted, it was included in this table to compare its results with the results of a comparable model using data from the Scott/Ciantar study (Table 6-4).

5.5 Discussion

5.5.1 Limitations

There were number of limitations encountered in the present chapter's study. The first of these was that there was likely to have been substantial error in the measurement of sleep since this was measured only once during the gestational period (though at a gestational age that was not known for most of the women), and used a subjective and retrospective sleep questionnaire (Manconi et al, 2010, Lauderdale et al, 2008, Rotenberg et al, 2000, Lee, 1998). The absence of data on gestational age at questionnaire response is likely to have introduced substantial heterogeneity since several studies including the comprehensive work of Al Afif (2016) suggest that sleep often varies during the course of pregnancy. However, the use of a subjective questionnaire was necessary within the UKHLS since this was a large household study which meant that measuring sleep objectively (using, for example, polysomnography) would have been prohibitively expensive in terms of time and effort. Indeed, it can be argued that subjective (i.e. self-reported) sleep offers a more precise indication of key sleep characteristics *as these are experienced* by participants, and avoid undue reliance on objective measures which might be insensitive to the more cognitive, experiential aspects of sleep (Buysse et al, 1989). There might also be an advantage in using a retrospective questionnaire (i.e. a questionnaire asking about sleep during the preceding week[s], as the UKHLS Sleep Module did), since day-to-day variation in sleep might be better contained by assessing sleep over (several nights in) the preceding weeks/months – in effect, generating an estimate of 'average sleep' (Libman et al, 2000, Buysse et al, 1989). The second key limitation also relates to the lack of data on gestational age when the sleep questionnaire was completed, since this would improve the identification of covariates acting as mediators or confounders (since an earlier measure of sleep might mean that some within-pregnancy covariates were likely to have acted as mediators, while a later measure of sleep might mean that these covariates would have acted as mediators). For example, if sleep was measured late in pregnancy late pregnancy, some of the behavioural traits on which data were available (e.g. smoking during pregnancy) might have acted as potential confounders. In the absence of complete data on gestational age, the analyses presented in the present chapter are therefore likely to be less precise (as a result of the heterogeneity of sleep during the different trimesters of pregnancy) and be biased by unadjusted confounding (as a result of the mis-specification of some within pregnancy covariates as mediators rather than confounders).

Meanwhile, the third limitation related to the use of a population-level sample (which was intended to strengthen the study's external validity), but involved substantial levels of missing data. This limited the number of participants who could be included in the analysis and reduced both the external validity of the results and the precision of any estimates generated (since the lower samples available for analysis following list-wise deletion would have reduced the statistical power of these analyses; Sterne et al, 2009, Allison, 2002). While list-wise deletion may is not the only way of dealing with missing data, and may not always be the best way of doing so (Allison,2001, Rubin, 1996), after investigating the potential mechanisms underlying missingness in the present chapter's study, it was concluded that missing data primarily occurred for multiple variables where, for example, a missing participant had some (though far from all) of their data provided by a nominated 'proxy' respondent.

A fourth, and somewhat inevitable, limitation involved the likelihood that the estimates generated in the present chapter's analyses were biased due to unadjusted and residual confounding (Attia, 2005, Psaty et al, 1999). Unadjusted confounding would have resulted from the absence of some potentially important possible determinants of sleep and pregnancy outcome (such as a range of behaviours/practices established prior to pregnancy), while residual confounding would have been exacerbated by the need to reduce many of the covariates to binary categorical variables in order to optimise the statistical power achieved given the modest sample size of participants achieved (i.e. those without missing data on the covariates selected for inclusion in the multivariable statistical models). Notwithstanding the effort taken to include sufficient numbers of potential confounders in these models, some important confounders were not available in the dataset, most notably BMI. BMI has an important influence on both sleep events and poor pregnancy outcomes (Kennelly et al, 2011, Doherty et al, 2006). Therefore, failing to adjust for BMI is likely to have affected the estimate generated, its impact varying depending upon the birth outcome and sleep event examined. Finally, the fifth limitation related to the lack of detail available in the definitions of each of the UKHLS study's variables. For instance, a history of previous caesarean delivery included both elective and emergency caesareans – two very different phenomena (Mylonas et al, 2015, Lavender et al, 2000, Wilkinson et al, 1998). Elective caesareans might occur for: causes that are unrelated to sleep (for instance uterine abnormalities; Hua et al, 2011); causes that precede sleep as measured (for instance previous history of emergency caesareans; Lydon-Rochelle et al, 2001); or causes that occurred *after* sleep was measured (for instance breech presentations; Gilbert et al, 2003). Likewise, in the present study parity was defined on the basis of the information available in the UKHLS dataset (i.e. the number of livebirths), yet the more sensitive, medical definition, would be the number of any prior

pregnancies that continued until the fetus was viable (widely considered to be ≥ 23 weeks; Creinin and Simhan, 2009). Both of these, and other, somewhat simplistically defined variables will have also introduced heterogeneity and error to the estimates generated by the present chapter's analyses.

Notwithstanding these limitations, the study presented in this chapter is the first study that has treated sleep in pregnancy as a latent variable and studied the possible effect of differences in 'sleep patterns' on pregnancy outcomes. Treating sleep as a latent variable means that the resulting variable is capable of considering more than one sleep characteristic at the same time/simultaneously, and therefore offers a more holistic assessment of the role that sleep might play as compared to any single sleep characteristic. Incidentally, this chapter's analyses are also the only study to-date to have included participants from the UK population to study the possible impact of variation in sleep on pregnancy outcomes, and it therefore helps to extend the contexts in which this phenomenon has been examined (to include one in which the vast majority of pregnant women receive care from a single, state-controlled healthcare provider – the NHS).

5.5.2 Key findings

The main finding of the present chapter was that ostensibly unfavourable sleep characteristics (such as short sleep or daytime sleepiness) and ostensibly less favourable (latent) sleeping patterns are not always accompanied by an *elevated* risk of poor pregnancy outcome. Indeed, in some instances, poorer sleep was accompanied by lower odds of such outcomes. Elsewhere, there remained some evidence that sleep characteristics and particular sleep patterns *were* consistently accompanied by poorer pregnancy outcomes, though the outcomes involved varied amongst the characteristics and patterns examined. However, these somewhat variable findings lacked precision due to the underpowered analysis and the presence of measurement error as a result of using retrospective subjective measurements of sleep and pregnancy outcomes. Therefore, it might not be possible to conclude with much certainty whether these findings are robust/valid. Instead, these findings might be considered as testable hypotheses for future research with better quality data and sample sizes. These findings have been summarised below:

First, a number of sleep characteristics had very similar relationships with pregnancy outcomes – suggesting that these (and perhaps sleep more generally) might be causes, mediators of preceding causes or share similar pathophysiology pathways. This finding again suggests that it might be more meaningful to combine sleep characteristics into a single latent variable.

Second, latent sleep patterns and individual sleep characteristics often had a different direction in their relationships with pregnancy outcomes, which is likely to indicate that each functioned differently as predictors/correlates/determinants. Indeed, in contrast to the relationships observed for the individual sleep characteristics, the direction of relationships between sleep patterns and several of the pregnancy outcomes examined supported the suggestion that poor pregnancy outcomes constituted a series of events (e.g. preterm birth leading to LBW and to caesarean delivery). This would have occurred had each sleep characteristic influenced each pregnancy outcome through its own, unique pathophysiological pathway, while the latent sleep variable combined these pathways so that the estimate generated was the 'net effect' of each of these combined (individual sleep characteristic-related) pathways. However, due to the limited precision of the estimates generated, the net effects of the hypothetical sleep clusters were not precise and cannot be compared with the seven individual sleep characteristics' estimates. As such it is not possible to conclude with any degree of certainty which of these sleep characteristics influenced the net effect and which may have reduced it.

Third, when sleep patterns that included (one or more) unfavourable sleep characteristics were compared to the pattern with none (i.e. long good sleep), it was evident that not *all* of these 'unfavourable' patterns were accompanied by a higher odds of poor pregnancy outcomes. This might indicate that some degree of unfavourable sleep might benefit pregnancy or, perhaps more realistically, that some degree of unfavourable sleep might be a normal consequence of a healthy pregnancy.

These three issues aside, perhaps the strongest finding from the present chapter's analyses was that coughing/snoring had the strongest relation with poor pregnancy outcomes although this finding also lacked quality and precision, regardless of the specific outcome examined – a consequence perhaps of the well-established link between coughing/snoring and cardiovascular and respiratory dysfunction.

Finally, as these all of these findings were influenced by the underpowered nature of the analyses (as well as by the choice of model adjustment sets used, and the definition of sleep referents), these findings are somewhat speculative; such that altering any of these analytical aspects might alter the results obtained, not least considering the extensive lack of precision in most of the models' estimates.

5.5.3 Conclusion

In conclusion, notwithstanding the limitations discussed above, it is clear that defining sleep using LCA-derived sleep patterns offers not only a more convenient and holistic approach to assessing the potential role of sleep on pregnancy outcomes than sleep characteristics, but it was also arguably more meaningful. Nonetheless, neither LCA-

derived sleep patterns nor individual sleep characteristics explained the subsequent odds of all poor pregnancy outcomes well, and in many instances ostensibly 'unfavourable' sleep was accompanied by *better* pregnancy outcomes – suggesting that any relationship between the two is complex, and requires better powered studies with better defined (and a more comprehensive selection of) covariates and outcomes, as well as better knowledge concerning the likely temporal sequence of events/variables and the gestational age at which sleep was measured .

5.5.4 Recommendations

As it proved challenging to estimate the associations examined by the present chapter's underpowered analyses with anything approaching sufficient certainty/ precision (as a result of inherent to design limitations), it is recommended that additional research is required in this field to establish firmer evidence concerning the relation between sleep and pregnancy outcomes. Such studies are required to have better quality data (especially regarding the measurement of sleep) and less missing data. Additionally, it will be necessary for researchers to use sufficiently large sample sizes to achieve an appropriate level of analytical power and thereby minimise type II error. It will also be necessary to carefully interpret any 'statistically significant' results, especially where multiple testing is involved, to minimise the risk of type I error.

As regards the study design of such studies, researchers should aim to deploy longitudinal designs that carefully consider the temporal sequence of events/measurements, as well as the gestational age at which sleep is measured (again, particularly were multiple measurements of the study's covariates are recorded). Furthermore, future studies should consider examining high risk populations (such as women with multiple pregnancies, or women with maternal health complications) as both of these groups were under-represented in in the present chapter's analyses, and elsewhere in the literature. Finally, it is also recommended that sufficient data should be collected regarding a wider range of covariates likely to act as powerful confounders (such as previous obstetric history and current early-pregnancy/pre-sleep measurement events). This will help to ensure that these studies achieve a greater level of certainty/precision regarding the possible causal association as hypothesised by the hypothetical DAG proposed in the present thesis.

In the chapter that follows, the last of these issues will be addressed by examining the relationship between sleep and poor pregnancy outcomes amongst pregnant women at risk of GDM (for whom there should be a greater prevalence of unfavourable sleep and poor pregnancy outcomes), using clinical data with a more comprehensive suite of better defined and better measured covariates.

Chapter 6 The relationship between sleep and pregnancy outcomes in women at risk of GDM

6.1 Introduction

Gestational diabetes is a known risk factor for a number of serious maternal and foetal complications. In the UK, the prevalence of GDM rose from around 2% in 1998 to 9% in 2013 in part due to increasing rates of obesity (Torloni et al., 2009); an increase in the proportion of pregnancies amongst ethnic minority communities (Farrar et al., 2016); and changes in the definition and screening protocols for GDM (Agarwal, 2015). Substantial efforts have been made to mitigate the risk of GDM on poor pregnancy outcomes through the early detection of GDM and by controlling blood glucose levels throughout pregnancy (American Diabetes Association, 2003). However, in many cases, physicians are unable to control blood glucose levels during GDM, and thereby fail to prevent many of the resulting effects on poor pregnancy outcome.

Recent research has suggested that sleep (both before and during pregnancy) might act as an independent risk factor for GDM. This is because sleep is known to influence, and to be influenced by, the blood glucose levels, and to be sensitive to treatments for GDM – making sleep a potentially important risk factor albeit one that is difficult to measure or control (not least in the presence of elevated blood sugar levels).

In women with GDM it is still not known if problematic or ‘less favourable’ sleep might manifest similarly or in a very different way to that observed in ostensibly normoglycaemic women (amongst whom, as was observed in the previous chapter of this thesis, there is some evidence that some aspects ostensibly ‘poor’ sleep may be a characteristic of pregnancies with good outcomes as well as of those with poor outcomes). However, since there is essentially a continuum between the blood glucose levels observed amongst women diagnosed with GDM and the blood glucose levels of women who are free of GDM but at risk of developing GDM later in their pregnancy; it is very likely that many of the latter may approach (or dip into) GDM unnoticed especially if they did not attend their antenatal visits regularly. Therefore, it might be logical to consider women at risk of GDM as having, essentially a milder form of GDM (World Health Orgnization, 2013, Hezelgrave et al., 2012), not least because the GDM has recently been reconceptualised as a continuum of elevated blood glucose levels with diagnostic cut-off points for GDM

that are subject to change dependent upon the risks identified for different levels in different clinical and population contexts (Hezelgrave et al., 2012).

As evident from the studies examined in this thesis' systemic review (see Chapter 3), many previous studies examining the relation between sleep and pregnancy outcomes considered GDM an important exclusion criterion, while others included women with GDM but without adjusting for the potential impact that established risk factors for GDM (or a diagnosis of GDM itself) might have on the relationship observed. This means that there is currently only limited evidence about sleep as a predictor of poor pregnancy outcomes in those women who experience abnormal blood glucose levels.

Unfortunately, in the UKHLS study (which provided data for the analyses conducted in the preceding chapter), there was insufficient data of GDM (or on a prior history of GDM) to permit these to be adjusted for in the multivariable analyses conducted. There were also too few pregnant UKHLS participants diagnosed with GDM to permit investigation of any associated differences in the relationship between sleep and outcomes in these women. The focus of the present Chapter's analyses is therefore on women at risk of GDM, and the Chapter aims to examine the relationship between individual 'sleep characteristics', 'sleep patterns' and poor pregnancy outcomes, before and after DAG-assisted covariate adjustment.

6.2 Materials and methods

6.2.1 Data source

The data used in the present chapter's analyses were derived from the Scott/Ciantar clinical study, initiated in 2012 to examine the association between sleep, GDM and pregnancy outcomes. The clinical data used were extracted from medical records by the candidate, and with the assistance of other members of the research team. Further detail of the data extraction and coding procedures can be found in the Appendix (Chapter 8, Section 8.5.2, page 352).

6.2.2 Study setting

The study setting comprised the (specialist) gestational diabetes antenatal clinic and the regular antenatal clinic at Leeds General Infirmary and St James Hospitals (both of which are integral parts of the Leeds Teaching Hospitals NHS Trust).

6.2.3 Study design

The present chapter used a study with a prospective longitudinal design in which the exposure (sleep) was measured during pregnancy and the (pregnancy) outcomes were measured postpartum (from medical records).

6.2.4 Participants

6.2.4.1 Inclusion and exclusion criteria

6.2.4.1.1 Inclusion criteria

The participants comprised pregnant women who were at risk of gestational diabetes mellitus, all of whom received an OGTT during antenatal care. These women were diagnosed to be 'at risk' of GDM if they met at least one of the following criteria (set by the National Institute for Clinical Excellence, 2008):

I. a history of GDM in a previous pregnancy;
II. a family history of diabetes mellitus (DM) in a first degree relative;
III. a body mass index greater than 30 kg/m^2;
IV. a history of delivering a macrosomic baby (birth weight > 4,000 g); [5]
V. a "minority ethnic family origin with a high prevalence of diabetes" (National Institute for Clinical Excellence, 2008)

As mentioned previously (in this thesis' Methodology Chapter; Chapter 2, Section 2.1.2.3, page 48), to ensure a suitable degree of variability across the sample, some of the participants were recruited *after* their OGTT findings indicated that they would achieve a formal clinical diagnosis of GDM. According to the National Institute for Clinical Excellence (2008), pregnant women are diagnosed with GDM following OGTT (i.e. after receiving 75 g oral glucose tolerance test) if one of the following criteria are met:[6]

I. a fasting blood glucose level ≥ 7 mmol/l (recorded before receiving the OGTT); or
II. a blood glucose reading after 2 hours of 75 mg oral glucose ≥ 7.8 mmol/l.

6.2.4.1.2 Exclusion criteria

Potential participants with pre-existing type I or type II diabetes were not included in the analyses that follow because they did not require an OGTT screening test, and would have had early access to the diabetic antenatal clinic. As a result, such

[5] In 2015, the birth weight cut-off point used in the definition of macrosomia changed from > 4000 g into > 4500 g (National Institute for Clinical Excellence, 2015)

[6] These criteria were updated in 2015. At the present time, women who have fasting blood glucose levels ≥5.6 mmol/l or blood glucose levels 2 hours postprandial (using 75 g oral glucose) of ≥ 7.8 mmol/l, are considered 'to be positive for GDM (National Institute for Clinical Excellence, 2015)

women would have already started receiving medical treatment to prevent poor pregnancy outcomes *before* the measurement of sleep took place.

Meanwhile, potential participants with multiple pregnancies (i.e. twins or triplets, etc) were excluded from the analyses that follow simply because their very small numbers made it unfeasible to adjust for multiple pregnancies in the analytical models used (or to evaluate any differential relationships between sleep and pregnancy outcome in such pregnancies).

6.2.5 Recruitment

The recruitment of women took place at the time the OGTTs were administered (i.e. during routine antenatal care for women judged to be at elevated risk of GDM). These women received the OGTT at 24–28 weeks gestation and, if they failed this test, they were considered to have a positive diagnosis for GDM. Women with a history of GDM in a previous pregnancy were tested both <16 weeks gestation and, in cases where the previous test result was normal or inconclusive, again at 24–28 weeks.

Nonetheless, all of the participants in the present chapter's study were recruited after 26 weeks gestation, this recruitment taking place in two waves. The first wave ran from late 2012 until early 2013 when most of participants were recruited, with a second wave taking place in late 2014 (Figure 6-1).

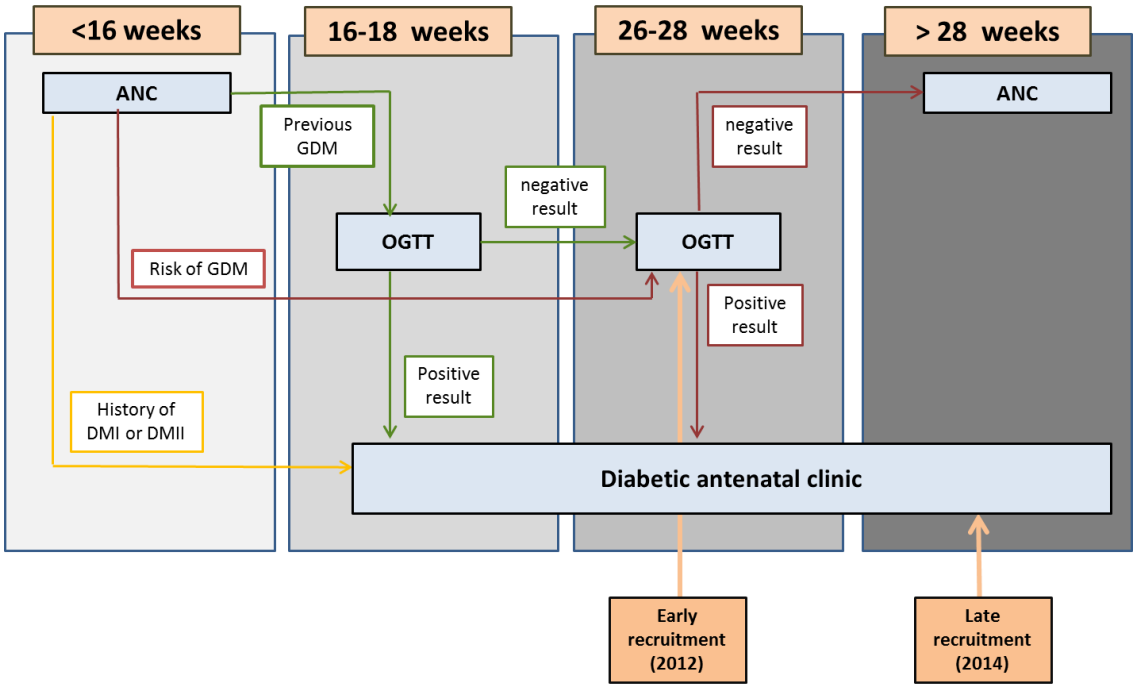

Figure 6-1 Flow chart summarising recruitment into the Scott/Ciantar study.

6.2.6 Measurements

6.2.6.1 Sleep characteristics

The assessment of sleep was recorded immediately after the OGTT results had been received (i.e. >24 weeks gestation for women at risk of GDM or for women recruited from the diabetic clinic; see Figure 6-1).In the present chapter, sleep was measured using the PSQI questionnaire (see Chapter 2, Section 2.3.1, page 55), seven key items from which were then used to study the association between sleep and pregnancy outcomes. These items were those that mapped onto the seven sleep questions in the UKHLS Sleep Module (i.e. the same seven sleep characteristics that had been used in generating the six latent 'sleep pattern clusters'). The seven measured sleep characteristics were: sleep duration, latency, disturbance, medication, daytime sleepiness, coughing/snoring and quality. Neither the PSQI's 'global score' nor the 'compartments scores' were used (both of which use combinations of two or more items to generate the main and sub-indices) since either were likely to cause the loss of valuable information about each of the individual sleep characteristics.

However, in line with the preceding chapters in the present thesis, sleep duration was categorised into three categories: long sleep (>9 hours), short sleep (<6 hours) and reference range (≥ 6 and ≤ 9 hours). Once again, sleep duration was categorised in this way to permit exploration of any possible 'U-shaped' the relationship between sleep duration and poor pregnancy outcomes.

Sleep events (i.e. latency, disturbance, coughing/snoring, daytime sleepiness, and use of sleep-related medication) were also, once again, re-categorised into two categories based on the absence or presence of each of these events; while sleep quality was again categorised simply as good or bad. Reducing the number of categories to just two was once more deemed sensible given the small sample size of participants (particularly the small number with complete data), and the limited number of participants in some of the sub-categories. However, the rationale for choosing an 'absence vs. presence' cut off rather than 'habitual vs. non-habitual' was to ensure not only that sufficient numbers of participants were included both categories, but also to minimise the possibility of measurement error in the reporting of these events' frequencies.

6.2.6.2 Sleep clusters

The six sleep clusters were generated using the same criteria as those generated from the analysis of UKHLS population data in Chapter 4. These six clusters were again labelled: short bad sleeper, long moderate sleeper, long good sleeper,

disturbed bad sleeper, struggle-to-sleeper, and snoring good sleeper. As in Chapter 5, these six sleep clusters were therefore assigned to participants using the algorithm generated from the latent class analysis (see Appendix, Section 8.3.5, page 319). This algorithm was applied to the responses participants gave to each of the seven sleep items (i.e. those contained in the UKHLS sleep questionnaire) as mapped to questions in the PSQI (i.e. equivalent items on sleep: duration, latency, disturbance, daytime sleepiness, use of medication, coughing/snoring, and quality). This required responses to the PSQI sleep items to be recoded so that these were equivalent to the categorization of the UKHLS questionnaire's sleep items used when generating the sleep clusters in the first place (i.e. in Chapter 5 of the present thesis).

6.2.6.3 Pregnancy outcomes

Data on birth outcomes were extracted from participant medical records after each participant had given birth. The principal outcomes of interest were type of delivery, preterm delivery, low birth weight and macrosomia. The secondary outcomes of interest were: estimated blood loss at delivery, ≥third degree tear, 5-minute Apgar score, and admission to the neonatal intensive care unit (NICU).

Type of delivery was categorised as either vaginal or caesarean. The latter included all caesarean deliveries (i.e. elective or emergency) as these were imprecisely reported in the medical notes. Preterm delivery was defined as any delivery <37 weeks gestation, based on the WHO's definition (World Health Organization, 2015). A birth weight < 2,500g was considered 'low', and a birth weight >4,000g was considered 'macrosomic' - both as defined by the WHO and the American Society of Obstetrics and Gynecology (Chatfield, 2001). Clinically significant blood loss postpartum blood was defined as a blood loss that exceeded 500 ml (Gordon, 2007). A clinically significant 'low' 5-minute Apgar score was defined as < 7 (Apgar, 1953; as this is considered the level at which serious neonatal complications occur that require medical intervention).

6.2.6.4 Covariates

Additional data on a range of covariates were extracted from the medical records of participants after the birth of their child, and these were considered for inclusion in the multivariable analyses based, initially, on their availability and their data quality/precision. Prior to extraction, in order to enhance efficiency, a simple directed acyclic graph (DAG) was drawn to inform the selection of suitable covariates (see Figure 6-2; where only those covariates considered likely to operate as potential confounders were considered necessary/useful to extract from the medical records). Further detail on the extraction, coding and quality

assessment of covariates from participant medical records can be found in the Appendix (see Chapter 8, Section 8.5.3, page 360). As a result, the covariates included as confounders in the multivariable analyses that follow were: fasting and two hours post-prandial OGTT results (as continuous variables); socioeconomic status (SES; categorised into lower and higher); parity (categorised into nulliparous vs. multiparous); ethnicity (categorised into those considered at risk vs. not at risk of GDM); cohabitation (categorised as cohabiting vs. not cohabiting); current or previous medical condition (categorised as present or absent); current smoking (categorised as smoker vs. non-smoker); alcohol consumption (categorised as consumer vs. non-consumer); body mass index (BMI) at booking (as a continuous variable); and age (as a continuous variable). As such, and as described earlier with regard to the sleep characteristics, the number of categories for many of these covariates was reduced to permit adjustment for a larger number of covariates than might otherwise have been possible given the modest sample size of participants available for inclusion in these analyses. For each of these re-categorised covariates, the categorical splits chosen were based primarily on their distribution across participants, though great care was taken to avoid altering the functional meaning of each variable (to support the subsequent interpretation of the analyses)

Figure 6-2 Hypothetical directed acyclic graph showing temporal consequences of the suggested variables for the Scott/Ciantar study.

6.2.7 Ethical considerations

Ethical approval for the study was obtained by Dr Eleanor Scott and Dr Etienne Ciantar in May 2012 from the National Research Ethics Service. The approval included the administration of sleep questionnaires to n=200 participants and subsequent access to their medical records from which the necessary clinical data could then be obtained (Appendix8.5, page 349). Each participant was provided with a written informed consent form to complete, and a detailed information leaflet explaining their (potential) role in the study and requesting their consent to take part. All participants were informed that they were able to withdraw from the study at any time without any effect on their care plan or the level of care they might then receive. Each participant who consented to take part in the study was then given a unique study ID number, which was used to pseudo-anonymise all of the datasets subsequently used in the study's analyses. Finally, all of the data recorded by the study were stored on the University of Leeds' encrypted and password-protected hard drive, to which only authorised members of the research team had access.

6.3 Analysis

6.3.1 Descriptive analysis

6.3.1.1 Data quality

The quality of the data for each of the variables included in the analyses that follow is examined with regard to precision, accuracy, consistency and missingness. This examination of the data is intended to ensure that any potential impact of any lack of data quality on the reliability of the analyses' results can be considered prior to the interpretation of these results.

6.3.1.2 Missing data

The likely mechanism and pattern of missingness of data for each of the variables included in the present chapter's analyses was carefully examined to assess whether this missingness was 'at random'. This involved using flowcharts to summarise the likely steps involved in each mechanism of missingness, and using tables of frequencies and percentages to describe and compare participants with missing sleep and outcome data and to assess any abnormal patterns (such as pairing or clustering) therein.

6.3.1.3 Participants characteristics

Contingency tables with frequencies and percentages were used to describe each of the following population samples: participants with complete medical and sleep data; and all (potential) participants included in the Scott/Ciantar study.

6.3.2 Regression analysis

Unadjusted and confounder-adjusted logistic regression models were used to examine the relation between pregnancy outcomes and each of the sleep variables (i.e. both the individual sleep characteristics and the LCA-derived sleep patterns). Again, as mentioned in Section 6.2.6.2, the latent sleep variable which was used in the present chapter's analysis was the latent sleep variable with six categories and with the 'long good sleeper' cluster as referent. Participants were allocated their membership of one of the six clusters by applying the same LCA-derived algorithm as that discussed in Chapter 4 (generated using participants' response to the seven individual sleep questions presented in the PSQI, which mirror those sleep questions included in the UKHLS sleep module).

The logistic regression estimation method used was penalized maximum likelihood (Firth, 1993; Methodology, Section 2.5.1.1, page 72). STATA13 software was used in the analysis (StataCorp., 2013).

The minimal sufficient covariate adjustment set was determined using a DAG drawn using the open source software DAGitty (Textor et al., 2017). Several regression models with multiple levels of adjustment were run in order to compare estimates generated with the results of the UKHLS analyses (see Chapter 5, Section 5.3.2, page 198), since not all of the covariates used were available in both the UKHLS and Scott/Ciantar study data sets. In addition, the readings of the OGTT were adjusted for in a separate model to examine their effect on the association estimate.

6.4 Results

6.4.1 Included participants

The original recruitment target for the Scott/Ciantar study was n=200 women at risk of GDM; 100 of whom were to have already been diagnosed with gestational diabetes; and 100 of whom were at risk of GDM, but not yet formally diagnosed with GDM. Unfortunately, the study only managed to recruit 193 participants (89 of whom did not have GDM, while the remaining 104 had been diagnosed with GDM). Three of these participants were excluded because they had multiple pregnancies; 3 had pre-gestational diabetes (either type I or type II DM); and more than a third

(n=79) had missing data on one or more of the exposure, outcome or potential confounder variables (see Figure 6-3).

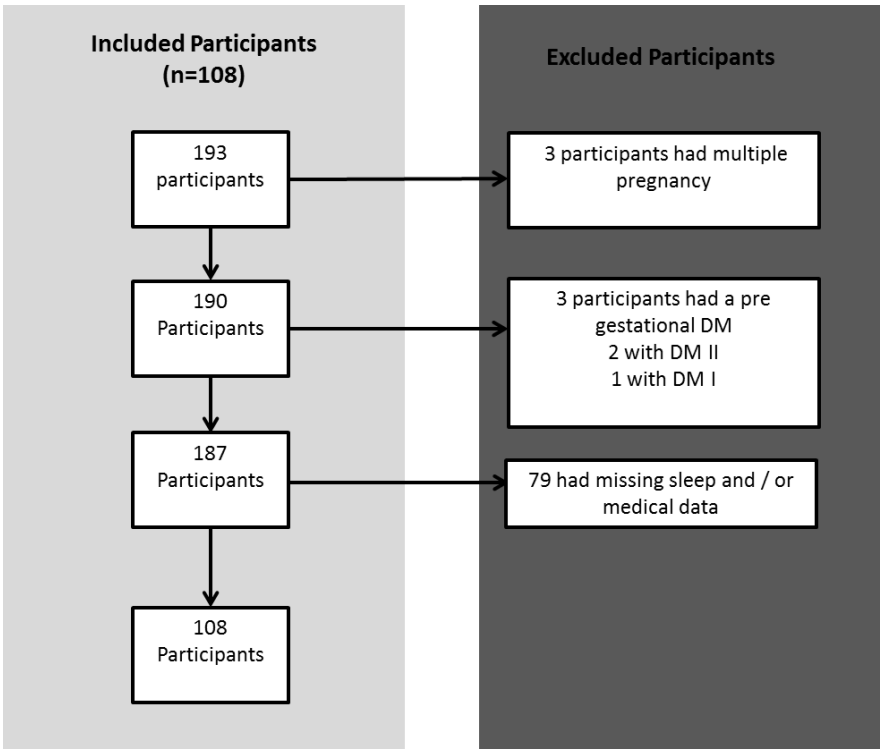

Figure 6-3 Flow chart of participants included and excluded from the Scott/Ciantar study, following recruitment.

6.4.2 Descriptive analysis results

6.4.2.1 Data quality

6.4.2.1.1 Data precision, consistency and accuracy

All of the variables selected for inclusion in the present chapter's analyses were considered consistent with one another (i.e. data of a medical variable of interest were repeatedly the same throughout a participant's medical record regardless the sections they were reported under or the health personal who reported them), with the exception of two variables: previous obstetric history and parity. This is because the variables that had been used to generate parity and previous obstetric history (i.e., number of miscarriages, number of still births, number of caesarean deliveries, number of low birth weights, previous pregnancy complications, previous birth complications and previous after birth complications) were themselves not consistently recorded in the medical records, and therefore

substantial efforts were required to unify and reach consensus amongst these (see Appendix, Section 8.5.3, page 360 for further details).

Likewise, all of the variables extracted from the medical records were considered to be within an acceptable degree of accuracy, with the exception of estimated blood loss at delivery and SES. This is because estimated blood loss at delivery was determined based upon a visual estimation of the amount of blood lost, as assessed by the midwife and/or physician attending the delivery. As for the derived SES variable, this lacked both accuracy and precision since it was derived from postcode-based area-level assessments of deprivation. Relying on postcode to estimate SES from measures of deprivation attributed to neighbourhood characteristics which are then applied to each constituent household involves a number of assumptions, and as such perhaps better reflects the 'neighbourhood SES' than that pertaining to each individual participant.

As a result of the deliberate reduction in the number of categories for many of the variables selected for inclusion in the present chapter's analyses, there was inevitably some loss of accuracy and/or precision (Appendix, Section 8.5.3, page 360; Table 8-26).

6.4.2.1.2 Completeness of data

Of the 193 participants successfully recruited into the Scott/Ciantar study, the files of 15 participants could not be found at the end of the study, and it was therefore not possible to extract data from these records for these participants. Only 127 of the remaining 178 participants with accessible medical records had complete medical records of the outcomes of interest and the covariates – such that, as mentioned previously, more than a third of recruited participants had to be excluded from the analyses due to missing data.

At the same time, of the 193 participants who were recruited into the study, 9 failed to complete their sleep questionnaires; while 19 of the 180 women who completed these did not respond to all of the questions therein. Together with missing or incomplete medical records, the loss of key exposure data played an important role in the loss of participants due to missing/incomplete data. Taken together, the number of participants who completed the sleep questionnaire and who had complete data available within their medical records, was just n=108, which means that the retention rate post-recruitment was (108/187) x 100 = 57.4%.

For further detail on the collection, extraction and evaluation of data for the present chapter, please refer to the Appendix (Chapter 8, Section 8.5.4, page 365).

6.4.2.1.3 Missing data

By carefully tracing the mechanisms likely to have been involved in missing data it was clear that, in general, where one sleep variable had missing data the other variables also tended to be missing. The same applied to data on the antenatal variables and birth outcomes extracted from medical records. In both instances this suggested that the mechanisms of missingness involved were as described earlier (i.e. mislaid medical records and/or non-completed sleep questionnaires). For this reason, missing data were excluded from the analysis through list-wise deletion.

Meanwhile, the distribution of socio-demographic characteristics and birth outcomes amongst participants with missing sleep data was very similar to that of participants with complete data. For example, approximately half of the missing sleep data were from women in their thirties (48%, n = 12), with at least one birth experience (60%, n = 15), a low (neighbourhood) SES (68%, n = 17) and a minority ethnic identity (64%, n = 16). Missingness was more frequent amongst women with partners (76%, n = 19) and with a BMI>30 kg/m^2. Women with significant postpartum blood loss also had higher rates of missingness (60%, n = 16), as did women with vaginal deliveries (64%, n = 16), and those who delivered 'normal' birth weight babies (100%, n = 25).

At the same time, the frequency distribution of sleep characteristics amongst participants with (some/any) missing data was also similar to that observed amongst those with complete data. For example, the sleep duration of participants with (some/any) missing data was primarily within the reference range (75%, n = 45); while sleep latency (71%, n = 44) and sleep disturbance (93.6%, n = 58) was very common; whereas the use of sleep-related medication (3.2%, n=2) and the prevalence of snoring (25.8%, n=116) were almost absent. Sleep quality was reported as good to fairly good in just over half of such participants (54.8%, n = 34), as was daytime sleepiness (59.7%, n = 37).

For further details of the apparent similarities between participants with and without complete data on all of the variables selected for inclusion in the present chapter's analyses, please refer to the Appendix (Chapter 8, Section 8.5.4, page 365; Table 8-27, Table 8-28 and Table 8-29).

6.4.2.2 Sleep characteristics

The most common sleep duration reported in the Scott/Ciantar study was from six to nine hours per night, though the majority of participants suffered from difficulty in falling sleep or from interrupted/disturbed sleep. Approximately two thirds of the participants reported that they did not cough/snore, and had little daytime

sleepiness and generally good to very good sleep quality. Only three participants reported that they used medication to help them sleep, and only one of these reported using it on a daily basis (Table 6-1).

The commonest LCA-derived sleep pattern amongst the participants in the present study was short bad sleeper, whilst the least common was disturbed bad sleeper. Indeed, only 15.7% (n=17) of the study participants reported an absence of unfavourable sleep events and were classified as having a long good sleep pattern (Table 6-1).

Table 6-1 Frequency distribution of sleep characteristics amongst participants in the Scott/Ciantar study (N = 187)

		Participants with complete medical and sleep data		All participants included in the study	
		n=108	%	n=187	%
Sleep duration	*Short sleep (<6)*	22	20.37	33	17.65
	Reference range (6-9)	68	62.96	119	63.64
	Long sleep (>9)	18	16.67	24	12.83
	Missing	0	0	11	5.88
Latency	*Absent*	34	31.48	51	27.27
	Present	74	68.52	125	66.84
	Missing	0	0	11	5.88
Disturbance	*Absent*	11	10.19	13	6.95
	Present	97	89.81	163	87.17
	Missing	0	0	11	5.88
Snoring or coughing	*Absent*	71	65.74	117	62.57
	Present	37	34.26	58	31.02
	Missing	0	0	12	6.42
Day sleepiness	*Absent*	72	66.67	115	61.5
	Present	36	33.33	58	31.02
	Missing	0	0	14	7.49
Medication	*Absent*	105	97.22	169	90.37
	Present	3	2.78	5	2.67
	Missing	0	0	13	6.95
Quality	*Good*	69	63.89	106	56.68
	Bad	39	36.11	65	34.76
	Missing	0	0	16	8.56
Clusters	*Short bad sleeper*	51	47.22	74	39.57
	Long moderate sleeper	7	6.48	7	3.74
	Long good sleeper	17	15.74	24	12.83
	Disturbed bad sleeper	2	1.85	3	1.6
	Sleeper struggle-to-sleeper	19	17.59	35	18.72
	Snoring good sleeper	12	11.11	19	10.16
	Missing	0	0	25	13.37

6.4.2.3 Pregnancy outcomes

Of the 108 women included in the present chapter's analyses, 58 did not develop GDM and 50 developed it. The mean fasting OGTT results of all 108 women were

4.37 mmol/l (SD=0.843, range= 3.6, 8.5) and the mean two hours post-prandial was 7.22 mmol/l (SD=2.01, range=3.2, 14). There was a prior history of GDM (alone) in one participant, two risk factors in 32 participants and multiple risk factors in the remaining women (Table 6-2).

The mean birth weight of term babies (n = 102) was 3449 g (SD = 542g, range = 2465g, 5210g). Approximately 10% (n = 11) of term babies had a birth weight >4000g, five of whom had a birth weight >4500 g. Seven macrosomia babies were delivered via caesarean section and one of these had a mother diagnosed with GDM. At the other extreme, only 3.7% (n = 4) of the neonates had a birth weight <2,500 g, two of whom were delivered prematurely via caesarean section and who were then admitted to the NICU (Table 6-2).

These two (premature) babies were amongst 9 (8.3%) neonates admitted to the intensive care unit. One had a low Apgar score after 5 minutes of birth, 2 more (i.e. 4 in total) were premature, while the remainder were admitted for unknown/less clear reasons (Table 6-2).

Ten new-borns (9.3%) had Apgar scores less than 7, 1 of which (as described earlier) was premature; 2 were delivered via caesarean section; and 3 were admitted to the NICU. Only 1 of the babies with an Apgar score less than 7 after 5 minutes of birth had been delivered vaginally at term with a normal birth weight, though this baby was one of those admitted to the NICU (Table 6-2).

Overall, 34 (31.5%) women delivered via caesarean section, 18 of whom had an elective caesarean for each the following reasons: a history of previous (emergency) caesarean (n=15), macrocosmic babies (n = 2), and for unknown reasons (n=1). Thirty-two women (29.63%) had reported blood losses of >500ml after delivery, 17 of whom delivered via caesarean delivery (51.5 %). Of the 74 women who delivered via vaginal birth, 18 nonetheless had an ‘assisted’ delivery, three experienced had a ≥third degree tear and one delivered a neonate suffering from shoulder dystocia (Table 6-2).

Table 6-2 Frequency distribution of pregnancy outcomes amongst participants of the Scott/Ciantar study (n=187)

		Participants with complete medical and sleep data		All participants included in the study	
		n=108	**%**	**n=187**	**%**
EBL	*<500 ml*	76	70.37	120	64.17
	≥ 500 ml	32	29.63	53	28.34
	Missing	0	0	14	7.49
Macrosomia	*≤ 4000 gm*	97	89.81	157	83.96
	>4000 gm	11	10.19	17	9.09
	Missing	0	0	13	6.95
Low birth weight	*Birth weight ≥ 2500 gm*	104	96.30	167	89.3
	Birth weight <2500 gm	4	3.70	7	3.74
	Missing	0	0	13	6.95
Apgar1 min.	*≥ 7*	98	90.74	150	80.21
	<7	10	9.26	17	9.09
	Missing	0	0	20	10.7
Preterm labour	*Term*	102	94.44	170	90.91
	Preterm	6	5.56	8	4.28
	Missing	0	0	9	4.81
Mode of delivery	*Vaginal*	74	68.52	119	63.64
	Caesarean	34	31.48	57	30.48
	Missing	0	0	11	5.88
NICU admission	*No admission*	100	91.67	160	85.56
	Admission	9	8.33	10	5.35
	Missing	0	0	17	9.09

6.4.2.4 Sociodemographic features

At first glance, the distribution of sociodemographic characteristics amongst participants with complete sleep and outcome data were very similar to those of all participants recruited into the study. The mean age was 30.407 (SD= 5.059, range= 17 to 41), whereas the commonest age spanned from 30–39 years. The majority of participants had partners, and 57.6% (n = 57) of these were married. Of the participants who did not have partners, two were divorced, three were separated and the remainder were single. With regard to ethnicity, the majority of participants were not from an ethnic minority community, and only 18.5% were from minority ethnic groups (most, 20 participants, being South Asian; 10 being were Black African; and 5 from other ethnic minorities). Of the participants who smoked during their current pregnancy (n=13), seven admitted that they smoked more than 10 cigarettes a day. Among the participants who did not smoke (n=93), 17 participants nonetheless had a partner who smoked, 19 were ex-smokers and 11 of them had (only recently) quit smoking (i.e. within the last year). Around 85% of the participants did not consume any alcohol during their current pregnancy, and those participants who did (n = 8) were recorded as having kept their consumption below 2 units per week (Table 6-3).

Table 6-3 Frequency distribution of sociodemographic characteristics amongst participants from the Scott/Ciantar study participants who had complete and incomplete data derived from medical records (n=187).

		Women at risk of GDM with Complete sleep and medical data		All participants included in the study	
		n=108	%	n=187	%
Age	*≤ 19 years*	4	3.7	5	2.67
	20-29 years	38	35.19	68	36.36
	30-39 years	64	59.26	103	55.08
	≥ 40 years	2	1.85	3	1.6
	Missing	0	0	8	4.28
Parity	*Nulliparous*	49	45.37	75	40.11
	Multiparous	59	54.63	99	52.94
	Missing	0	0	13	6.95
Ethnicity	*Lower risk of GDM*	73	67.59	106	56.68
	Higher risk of GDM	35	32.41	61	32.62
	Missing	**0**	**0**	20	10.7
Cohabitation	*Not cohabited*	9	8.33	14	7.49
	Cohabited	99	91.67	157	83.96
	Missing	0	0	16	8.56
Smoking	*Not current smoker*	93	86.11	134	71.66
	current smoker	15	13.89	20	10.7
	Missing	0	0	33	17.65
Alcohol	*No alcohol consumption*	92	85.19	133	71.12
	Alcohol consumption	16	14.81	25	13.37
	Missing	0	0	29	15.51

6.4.3 Regression analysis results

6.4.3.1 Adjustment of the regression models

Once all potential variables of interest that had an acceptable level of quality had been identified, a more detailed DAG was generated where all of these variables were arranged in their hypothesised temporal sequence (see Figure 6-4).According to this DAG, the minimal sufficient adjustment set of covariates necessary to address potential confounding included; ethnicity, alcohol consumption, smoking, booking BMI, age, postcode-derived SES, parity, sex of the neonate, pre-existing maternal health conditions and cohabitation. This list did not, amongst other variables, include employment status because the data available were judged to be of too poor quality to use in the analyses.

Several regression models with differing levels of adjustment were evaluated in order to compare the present chapter's ORs with those generated from analyses of data from the UKHLS. Since not all the same variables were available in both data sets, only those variables common to both datasets were included, these being: age, ethnicity, education, cohabiting and health condition.

Elsewhere, as mentioned earlier, women with multiple pregnancies were excluded from the analysis because only three participants with multiple pregnancies were recruited, which was insufficient to adjust for this characteristic (or examine its potential effects) in the analyses. For this reason, the analyses that follow are, in the first instance, only likely to be applicable to singleton pregnancies.

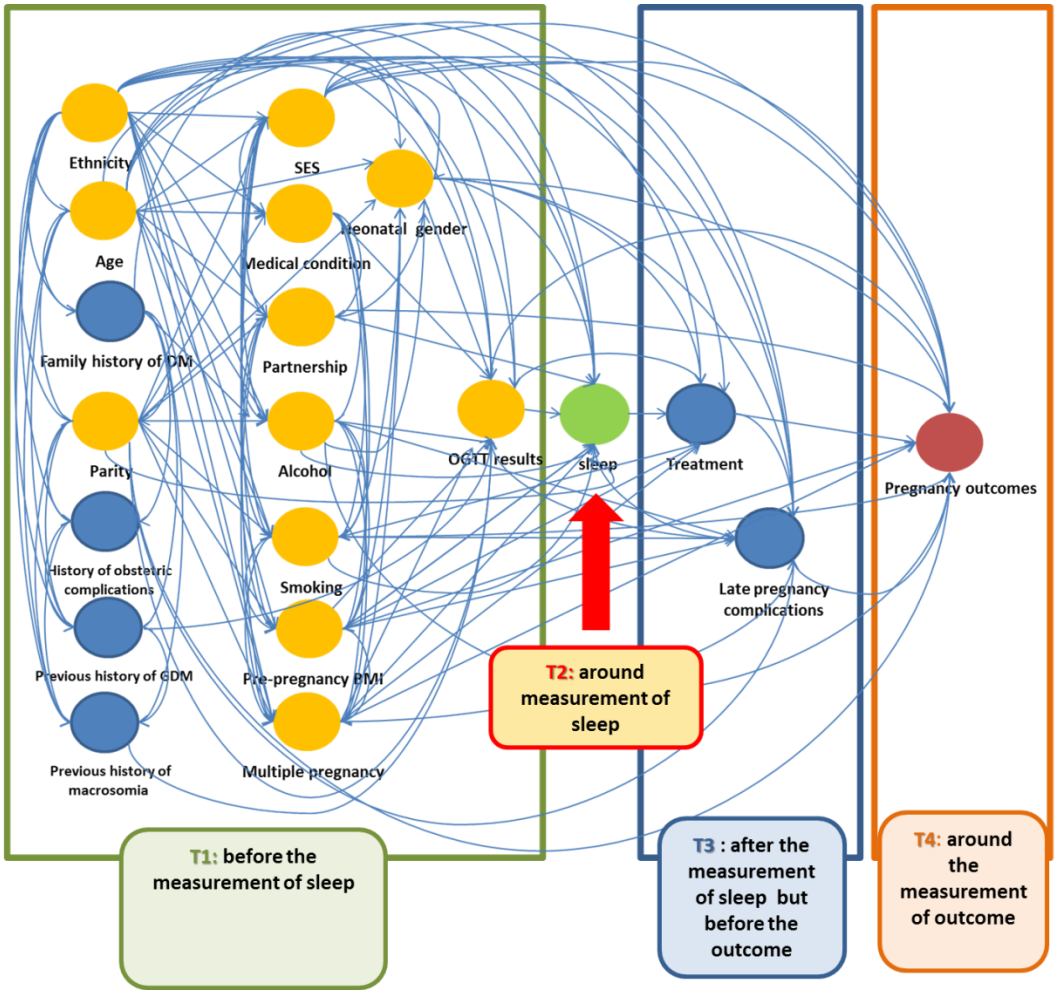

Figure 6-4 Directed acyclic graph showing the hypothesised relationships between sleep, pregnancy outcomes and possible confounders extracted from participants' medical records in the Scott/Ciantar study.

6.4.3.2 The relation between sleep characteristics and birth outcomes

A cursory examination of the associations observed between different pregnancy outcomes and each of the seven individual sleep characteristics indicated that the strength and direction of these associations varied considerably. What was ostensibly considered 'less favourable' sleep appeared to both increase and decrease the odds of poor pregnancy outcomes, depending on the characteristics and outcomes involved. For example, as suggested by evidence of a U-shaped relation between sleep duration and health, both short and long sleep were accompanied by an increased odds of caesarean delivery (Table 6-4), postpartum blood loss (Table 6-8). Coughing/snoring and sleep disturbance displayed very similar trends to sleep duration, except that disturbance was related with an increased odds of preterm delivery (Table 6-5) and NICU admission (Table 6-10). Sleep latency also increased the odds of preterm delivery (Table 6-5), a low Apgar score at birth (Table 6-9) and admission to the NICU (Table 6-10), while poor quality sleep and the use of sleep-related medication increased the odds of: macrosomia, low birth weight, caesarean delivery and low Apgar score.

Somewhat unexpectedly (given the tendency for less favourable sleep characteristics to be associated with poor pregnancy outcomes), daytime sleepiness was accompanied by a lower odd of developing all of the poor pregnancy outcomes examined, except macrosomia. In addition, it was noticed that sleep quality and the use of sleep medication shared similar relationships with pregnancy outcomes, as did snoring and duration. However, the estimated risk of poor pregnancy outcomes lacked precision, as reflected by the wide 95% confidence intervals (caused, in no small part, by the underpowered analyses). Additionally, some of the 95 % CIs were wider than the others due to differences in the distribution of unfavourable sleep events and pregnancy outcomes amongst the study's participants.

To compare these relationships (between individual sleep characteristics and pregnancy outcomes) to the sleep patterns identified using LCA, long good sleeper was chosen as the referent category. Compared to pregnant women who were long good sleepers, the odds of preterm delivery was elevated amongst short bad sleepers (Table 6-5) whilst the odds of caesarean section was higher in both snoring good sleepers and struggle-to-sleepers (Table 6-4). Meanwhile, the odds of macrosomia was higher in snoring good sleepers and disturbed bad sleepers (Table 6-6), although the odds of low birth weight was only higher in disturbed bad sleepers (Table 6-7); and the odds of elevated post-partum haemorrhage was higher in long moderate sleepers (Table 6-8), while whilst the odds of a lower Apgar

score was higher in both struggle-to-sleepers and snoring good sleepers (Table 6-9). Finally, the odds of NICU admission was higher in both short bad sleeper and struggle-to-sleeper (Table 6-10). Again, these estimated ORs lacked precision, making it challenging to interpret the results with anything approaching an appropriate level of confidence and certainty.

However, none of sleep patterns exhibited exactly the same relationship with pregnancy outcomes (i.e. each pattern appeared somewhat unique/specific in the way each was linked with a higher or lower odds of each of the outcomes examined). Participants classified as long moderate sleepers tended to have a lower odds of all of the pregnancy outcomes examined, except caesarean delivery; even though caesarean delivery and low Apgar scores were the only two pregnancy outcomes that were higher across most unfavourable sleep characteristics and less favourable sleep patterns.

The following sections of the present chapter examining the relationships between sleep and pregnancy outcomes will be presented using ORs as well as 95% CIs to reflect the level of confidence and precision of the estimates generated. The associated *p*-values will not be presented because these analyses involved multiple testing, and as such might increase the chance of type I error (which would then be reflected by 'statistically significant' *p*-values). However, there were occasionally 'significant' findings which were highlighted using bold text in each of the results tables, even though (once again), these significant findings might simply reflect chance associations and should be interpreted with caution.

6.4.3.2.1 Caesarean delivery

Short sleep (OR=1.72, CI=0.65, 4.59), long sleep (OR=1.53, CI=0.51, 4.59)., snoring (OR=1.36, CI=0.61, 3.01), usage of medication (OR=2.32, CI=0.25, 21.84) and poor quality (OR=1.40, CI=0.91, 2.13) increased the risk of CS. Whilst, Sleep latency (OR=0.60, CI=0.26, 1.37) and day sleepiness (OR=0.76, CI=0.32, 1.82) were associated with a reduced risk of CS. Considering the LCA- derived sleep clusters, the risk of caesarean delivery was reduced in short bad sleepers (OR=0.52, CI=0.16, 1.72), in long moderate sleepers (OR=0.45, CI=0.07, 2.97), and in disturbed bad sleepers (OR=0.23, CI=0.01, 5.92). This is in contrast to sleepers struggle to sleep (OR=1.27, CI=0.32, 5.05) and snoring good sleepers (OR=1.18, CI=0.26, 5.44), whom had an elevated risk of caesarean delivery (Table 6-4).

6.4.3.2.2 Preterm delivery

Unlike birth weight, long sleep (OR=0.26, CI=0.01, 8.74) and short sleep (OR=0.40, CI=0.01, 16.79) duration were accompanied by a decreased risk of preterm delivery. Similar to duration, subjective quality (OR=0.84, CI=0.12, 5.84), day sleepiness (OR=0.73, 0.02, 27.29), usage of medication (OR=0.23, CI=0.00, 66.84) and snoring (OR=0.63, CI=0.02, 15.90) were accompanied by a reduced risk of preterm delivery. Latency (OR=1.78, CI=0.05, 61.60) and disturbance (OR=5.00, CI=0.09, 268.64) were both related to an elevated risk of preterm delivery (Table 6-5). In regards to the LCA derived sleep patterns, short bad sleepers (OR=2.31, CI=0.05, 98.03) and sleepers struggle to sleep (OR=1.12, CI=0.02, 76.72) had a lower risk of developing preterm delivery compared to long good sleepers. Conversely, participants who had disturbed bad sleep pattern (OR= 0.38, CI=0.00, 138.74) and snoring good sleep pattern (OR=0.79, CI=0.02, 38.40) had a reduced risk of preterm delivery

6.4.3.2.3 Macrosomia

As shown in Table 6-6, long sleep (OR=0.99, CI=0.16, 5.97), short sleep (OR = 0.54, CI=0.09, 1.97), disturbance (OR=0.41, CI=0.09, 1.91) and snoring (OR=0.73, CI=0.20, 2.70) were accompanied by a small risk of having a macrosomic baby. In contrast, reported day sleepiness (OR=1.89, CI=0.56, 6.32), poor quality (OR=1.29, CI=0.70, 2.35) and usage of medication (OR=1.29, CI=0.70, 2.35) were accompanied by an elevated risk of macrosomia. When compared to the risk of developing macrosomia in long good sleepers, the risk of macrosomia was lower in sleepers struggle to sleep (OR=0.58, CI=0.07, 4.90) and short bad sleepers (OR=0.60, CI=0.12, 3.12). Conversely, it was higher in long moderate sleepers (OR=1.43, CI=0.16, 13.20), disturbed bad sleep-ers (OR=1.24, CI=0.05, 34.20), and snoring good sleepers (OR=2.28, CI=0.37, 13.99).

6.4.3.2.4 Low birth weight

Unlike long sleep (OR=0.44, CI=0.02, 11.88), short sleep (OR=1.34, CI=0.17, 10.72) was related with a higher risk of having a low birth baby. Similar to long sleep were snoring (OR=0.83, CI=0.11, 6.21), disturbance (OR=0.60, CI=0.03, 14.74) and daytime sleepiness (CI=0.29, OR=0.02, 5.39) were all associated with a reduced odds of developing LBW. Poor quality (OR=1.36, CI=0.53, 3.48) and medication (OR=10.55, CI=0.24¸469.57) showed an increased risk of developing LBW. The risk of low birth weight was elevated in long moderate sleepers (OR=1.51, CI=0.04, 51.75), disturbed bad sleepers (OR=1.56, CI=0.03, 71.01), and snoring good sleepers (OR=3.56, CI=0.28, 44.64); whereas, the risk was

reduced in short bad sleepers and sleepers struggle to sleep (OR=0.32, CI=0.01, 8.13)

6.4.3.2.5 Other pregnancy outcomes

Postpartum blood loss

All sleep characteristics except latency (OR=0.42, CI=0.18, 1.00) were accompanied by an elevated risk of postpartum blood loss. On the other side, the risk of postpartum blood loss decreased with all the sleep clusters except long moderate sleeper (OR= 1.51, CI=0.04, 51.75) when compared to long good sleeper (Table 6-8).

Apgar score at birth

As shown in (Table 6-9), all unfavourable sleep characteristics except day sleepiness, (OR=0.63, CI=0.15, 2.63) were related with increased risk of low Apgar score. The risk of lower Apgar score was higher in sleeper struggle to sleep (OR=1.15, CI=0.13, 10.13) and snoring good sleeper clusters whilst it was lower in the rest compared to good long sleep-er cluster.

Neonatal intensive care admission

Disturbance (OR=4.60, 0.09, 238.02) was the only unfavourable sleep characteristics which was accompanied by an increased risk of neonatal admission. Additionally, the risk of NICU admission was higher in short bad sleepers (OR=2.52, CI=0.06, 115.09) and struggle to sleep-ers (OR=1.13, CI=0.03, 48.31) compared to long good sleep-ers (Table 6-10)

Table 6-4 Logistic regression analyses examining the relationship between caesarean delivery, individual sleep characteristics and sleep patterns; before and after adjusting for potential confounders.[1,2,3]

Cesarean Delivery Models	Level of Adjustment							
	Unadjusted model		Adjusted model[1]		Adjusted model[2]		Adjusted model[3]	
	OR	CI	OR	CI	OR	CI	OR	CI
Caesarean delivery model 1: caesarean delivery and short sleep duration								
≥ 6 hours	Referent							
< 6 hours	1.78	0.71, 4.44	1.55	0.58, 4.14	1.55	0.59, 0.12	1.72	0.65, 4.59
Caesarean delivery model 2: caesarean delivery and long sleep duration								
≤ 9 hours	Referent							
> 9 hours	1.43	0.49, 4.19	1.55	0.50, 4.83	1.52	0.49, 4.75	1.53	0.51, 4.59
Caesarean delivery model 3: caesarean delivery and sleep duration								
Continuous	0.89	0.69, 1.14	0.93	0 .71, 1.22	0.93	0.70, 1.22	0.92	0.70, 1.22
Caesarean delivery model 4: caesarean delivery and sleep latency								
Absent	Referent							
Present	0.61	0.27, 1.35	0.59	0.25, 1.39	0.60	0.26, 1.42	0.60	0.26, 1.37
Caesarean delivery model 5: caesarean delivery and sleep disturbance								
Absent	Referent							
Present	0.96	0.29, 3.23	1.18	0.31, 4.39	1.18	0.32, 4.31	1.42	0.40, 5.03
Caesarean delivery model 6: caesarean delivery and snoring (and/or coughing)								
Absent	Referent							
Present	1.23	0.56, 2.69	1.43	0.63, 3.27	1.44	0.63, 3.29	1.36	0.61, 3.01
Caesarean delivery model 7: caesarean delivery and sleep medication								
Absent	Referent							
Present	3.53	0.45, 27.75	2.38	0.23, 24.21	2.31	0.24, 22.39	2.32	0.25, 21.83
Caesarean delivery model 8: caesarean delivery and next day sleepiness								
Absent	Referent							
Present	0.95	0.42, 2.16	0.69	0.28, 1.74	0.70	0.28, 1.73	0.76	0.32, 1.82
Caesarean delivery model 9: caesarean delivery and sleep quality								
Good	Referent							
Poor	1.34	0.90, 2.00	1.25	0.81, 1.93	1.24	0.80, 1.92	1.40	0.91, 2.13
Caesarean delivery model 10: caesarean delivery and polytomous latent sleep variable								
Short bad sleeper	0.62	0.20, 1.95	0.55	0.16, 1.97	0.50	0.14, 1.80	0.52	0.16, 1.72
Long moderate sleeper	0.80	0.14, 4.76	0.53	0.08, 3.74	0.44	0.06, 3.33	0.45	0.07, 2.97
Long good sleeper	Referent							
Disturbed bad sleeper	0.35	0.02, 8.55	0.25	0.01, 7.71	0 .23	0.01, 6.98	0.23	0.01, 5.92
Struggle to sleep-er	1.31	0.35, 4.84	0.98	0.23, 4.08	0.89	0.21, 3.74	1.27	0.32, 5.05
Snoring good sleeper	1.30	0.30, 5.60	1.21	0 .25, 5.89	1.04	0.21, 5.17	1.18	0.26, 5.44

[1] Adjusted for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, health and cohabiting status. This model was presented to examine the effect of not including the OGTT reading in the covariate adjustment set.

[2] Minimal sufficient adjustment set for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, fasting OGTT, 2 hours postprandial OGTT, health and cohabiting status.

[3] Adjusted for ethnicity, age, cohabiting, parity and health. Although this model was under adjusted, it was included in this table to compare its results with the results of a comparable model based on data from the UKHLS (Table 5-4).

Table 6-5 Logistic regression analyses examining the relationship between preterm delivery, individual sleep characteristics and sleep patterns; before and after adjusting for potential confounders.1,2,3

Preterm Delivery Models	Level of Adjustment							
	Unadjusted model		Adjusted model[1]		Adjusted model[2]		Adjusted model[3]	
	OR	CI	OR	CI	OR	CI	OR	CI
Preterm delivery model 1: preterm delivery and short sleep duration								
≥ 6 hours	Referent							
< 6 hours	0.24	0.01, 12.59	0.56	0.02, 16.36	0.65	0.03, 16.20	0.40	0 .01, 16.79
Preterm delivery model 2: preterm delivery and long sleep duration								
≤ 9 hours	Referent							
> 9 hours	0.14	0.00, 7.20	0.40	0 .02, 10.49	0.45	0.02, 10.04	0.26	0.01, 8.74
Preterm delivery model 3: preterm delivery and sleep duration								
Continuous	0.53	0.08, 3.41	1.04	0.33, 3.27	1.01	0.35, 2.89	0.82	0.13, 5.01
Preterm delivery model 4: preterm delivery and sleep latency								
Absent	Referent							
Present	2.29	0.05, 117.53	1.27	0.06, 26.84	1.33	0.07, 24.42	1.78	0.05, 61.60
Preterm delivery model 5: preterm delivery and sleep disturbance								
Absent	Referent							
Present	8.60	0.16, 452.69	2.78	0.07, 103.73	2.76	0.08, 91.99	5.00	0.09, 268.64
Preterm delivery model 6: preterm delivery and snoring (and/or coughing)								
Absent	Referent							
Present	0.53	0.01, 27.13	0.76	0.04, 13.62	0 .85	0.05, 14.44	0.63	0 .02, 15.90
Preterm delivery model 7: preterm delivery and sleep medication								
Absent	Referent							
Present	0.03	0.00, 1.74	0.31	0.00, 46.52	0.30	0.00, 30.49	0.23	0.00, 66.84
Preterm delivery model 8: preterm delivery and next day sleepiness								
Absent	Referent							
Present	0.48	0.01, 24.87	0.64	0 .02, 17.22	0 .67	0.03, 13.69	0.73	0.02, 27.29
Preterm delivery model 9: preterm delivery and sleep quality								
Good	Referent							
Poor	0.74	0.10, 5.28	0.88	0.18, 4.25	0.92	0.21, 4.02	0.84	0.12, 5.84
Preterm delivery model 10: preterm delivery and polytomous latent sleep variable								
Short bad sleeper	2.94	0.06, 153.95	2.05	0.08, 53.49	2.18	0.09, 52.42	2.31	0.05, 98.03
Long moderate sleeper	0.43	0.01, 023.69	0.63	0.01, 35.48	0.66	0.01, 32.17	0.49	0.01, 30.84
Long good sleeper	Referent							
Disturbed bad sleeper	0.14	0.00, 8.95	0.52	0.01, 46.19	0.57	0.01, 45.53	0.38	0.00, 138.74
Struggle to sleep-er	1.11	0.02, 59.20	1.24	0 .03, 53.02	1.39	0.04, 46.08	1.12	0.02, 76.72
Snoring good sleeper	0.71	0.01, 38.48	0.84	0.02, 35.08	0.85	0.02, 30.07	0.79	0.02, 38.40

[1] Adjusted for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, health and cohabiting status. This model was presented to examine the effect of not including the OGTT reading in the covariate adjustment set.

[2] Minimal sufficient adjustment set for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, fasting OGTT, 2 hours postprandial OGTT, health and cohabiting status.

[3] Adjusted for ethnicity, age, cohabiting, parity and health. Although this model was under-adjusted, it was included in this table to compare its results with the results of a comparable model based on data from the UKHLS (Table 5-4).

Table 6-6 Logistic regression analyses examining the relationship between macrosomia, individual sleep characteristics and sleep patterns; before and after adjusting for potential confounders.[1,2,3,4]

Macrosomia Models	Level of Adjustment							
	Unadjusted model		Adjusted model[1]		Adjusted model[2]		Adjusted model[3]	
	OR	CI	OR	CI	OR	CI	OR	CI
Macrosomia model 1: macrosomia and short sleep duration								
≥ 6 hours	Referent							
< 6 hours	0.54	0.09, 3.16	0.80	0.13, 4.91	1.05	0 .17, 6.31	0.54	0.09, 1.97
Macrosomia model 2: macrosomia and long sleep duration								
≤ 9 hours	Referent							
> 9 hours	0.99	0.16, 5.97	0.80	0.13, 4.93	0.70	0.10, 4.95	0.99	0.16, 5.97
Macrosomia model 3: macrosomia and sleep duration								
Continuous	1.34	0.99, 1.97	1.19	0.89, 1.89	1.05	0.70, 1.57	1.34	0.91, 1.97
Macrosomia model 4: macrosomia and sleep latency								
Absent	Referent							
Present	0.73	0.21, 2.51	0.75	0.21, 2.68	0.78	0.21, 2.85	0.73	0.21, 2.51
Macrosomia model 5: macrosomia and sleep disturbance								
Absent	Referent							
Present	0.41	0.09, 1.91	0.62	0.12, 3.16	0.61	0.12, 3.11	0.41	0.09, 1.91
Macrosomia model 6: macrosomia and snoring (and/or coughing)								
Absent	Referent							
Present	0.73	0.20, 2.70	0.64	0.17, 2.41	0.73	0.18, 2.94	0.73	0.20, 2.70
Macrosomia model 7: macrosomia and sleep medication								
Absent	Referent							
Present	5.97	0.72, 49.82	69.66	0.71, 6871.77	**44.05**	**1.06, 1831.89**	5.97	0.72, 49.82
Macrosomia model 8: macrosomia and next day sleepiness								
Absent	Referent							
Present	1.89	0.57, 6.32	1.86	0.56, 6.22	1.95	0 .57, 6.69	1.89	0.56, 6.32
Macrosomia model 9: macrosomia and sleep quality								
Good	Referent							
Poor	1.29	0.70, 2.35	1.64	0.83, 3.25	1.77	0.89, 3.55	1.29	0.70, 2.35
Macrosomia model 10: macrosomia and polytomous latent sleep variable								
Short bad sleeper	0 .60	0.11, 3.12	0.49	0.09, 2.69	0.62	0.10, 3.64	0.60	0.12, 3.12
Long moderate sleeper	1.43	0.16,13.197	0.94	0.09, 10.05	1.59	0.14, 17.88	1.43	0.16, 13.20
Long good sleeper	Referent							
Disturbed bad sleeper	1.24	0.05, 34.20	2.26	0.06, 91.17	1.39	0.14, 13.56	1.24	0.05, 34.20
Struggle to sleep-er	0.53	0.06, 4.50	0.78	0 .09, 6.61	0.78	0.09, 6.61	0.58	0.07, 4.91
Snoring good sleeper	2.28	0.37, 13.99	2.31	0.35, 15.35	3.14	0.41, 24.18	2.28	0.37, 13.99

[1] Adjusted for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, health and cohabiting status. This model was presented to examine the effect of not including the OGTT reading in the covariate adjustment set.

[2] Minimal sufficient adjustment set for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, fasting OGTT, 2 hours postprandial OGTT, health and cohabiting status.

[3] Adjusted for ethnicity, age, cohabiting, parity and health. Although this model was under adjusted, it was included in this table to compare its results with the results of a comparable model based on data from the UKHLS (Table 5-4).

[4] Figures in bold type are statistically significant ($p<0.05$)

Table 6-7 Logistic regression analyses examining the relationship between low birth weight, individual sleep characteristics and sleep patterns; before and after adjusting for potential confounders.[1,2,3]

Low Birth Weight Models	Level of Adjustment							
	Unadjusted model		Adjusted model[1]		Adjusted model[2]		Adjusted model[3]	
	OR	CI	OR	CI	OR	CI	OR	CI
LBW model 1: LBW and short sleep duration								
≥ 6 hours	Referent							
< 6 hours	1.74	0.24, 12.467	1.15	0.14, 9.37	0.62	0.02, 17.51	1.34	0.17, 10.72
LBW model 2: LBW and long sleep duration								
≤ 9 hours	Referent							
> 9 hours	0 .76	0.04, 14.88	0.62	0.04, 10.69	0.88	0.04, 21.23	0.44	0.02, 11.88
LBW model 3: LBW and sleep duration								
Continuous	0.72	0.36, 1.41	0.81	0.45, 1.46	0.78	0.34, 1.84	0.76	0.44, 1.32
LBW model 4: LBW and sleep latency								
Absent	Referent							
Present	1.06	0.15, 7.44	0.88	0.12, 6.72	1.38	0.12, 16.40	0.96	0.13, 6.97
LBW model 5: LBW and sleep disturbance								
Absent	Referent							
Present	1.11	0.06, 21.83	0.96	0.04, 21.67	0.22	0.00, 13.01	0.60	0.03, 14.74
LBW model 6: LBW and snoring (and/or coughing)								
Absent	Referent							
Present	0.78	0.11, 5.47	0.78	0.10, 5.83	1.19	0.10, 14.61	0.83	0.11, 6.21
LBW model 7: LBW and sleep medication								
Absent	Referent							
Present	3.51	0.16, 78.61	3.73	0.10, 135.34	4.21	0.03, 574.95	10.55	0.24,469.57
LBW model 8: LBW and next day sleepiness								
Absent	Referent							
Present	0.22	0.01, 4.21	0.14	0.01, 3.72	0.15	0.01, 3.17	0.29	0.02, 5.39
LBW model 9: LBW and sleep quality								
Good	Referent							
Poor	1.38	0.56, 3.39	1.17	0.45, 3.03	1.45	0.42, 4.93	1.36	0.53, 3.48
LBW model 10: LBW and polytomous latent sleep variable								
Short bad sleeper	0.33	0.03, 3.43	0.21	0.01, 8.41	0.18	0.01, 3.78	0.35	0.03, 3.86
Long moderate sleeper	0.73	0.03, 20.18	1.65	0.04, 75.87	1.88	0.03, 136.48	1.51	0.04, 51.75
Long good sleeper	Referent							
Disturbed bad sleeper	2.20	0.07, 70.42	0.01	0.00, 41.61	0.04	0.00, 55.92	1.56	0.03, 71.01
Struggle to sleep-er	0.30	0.01, 7.81	0.14	0.00, 8.98	0.31	0.01, 9.03	0.32	0.01, 8.13
Snoring good sleeper	2.62	0.30, 22.87	4.64	0.32, 68.32	3.84	0.13, 111.36	3.56	0.28, 44.64

[1] Adjusted for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, health and cohabiting status. This model was presented to examine the effect of not including the OGTT reading in the covariate adjustment set.

[2] Minimal sufficient adjustment set for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, fasting OGTT, 2 hours postprandial OGTT, health and cohabiting status.

[3] Adjusted for ethnicity, age, cohabiting, parity and health. Although this model was under adjusted, it was included in this table to compare its results with the results of a comparable model based on data from the UKHLS (Table 5-4).

Table 6-8 Logistic regression analyses examining the relationship between postpartum blood loss, individual sleep characteristics and sleep patterns; before and after adjusting for potential confounders.[1,2,3,4]

Postpartum Blood Loss (PBL) Models	Level of Adjustment							
	Unadjusted model		Adjusted model[1]		Adjusted model[2]		Adjusted model[3]	
	OR	CI	OR	CI	OR	CI	OR	CI
PBL model 1: PBL and short sleep duration								
≥ 6 hours	Referent							
< 6 hours	1.95	0.76, 5.01	1.24	0.40, 3.80	1.32	0.43, 4.05	1.42	0.47, 4.27
PBL model 2: PBL and long sleep duration								
≤ 9 hours	Referent							
> 9 hours	**3.86**	**1.31, 11.37**	**5.61**	**1.71, 18.34**	**5.38**	**1.65, 17.47**	**5.20**	**1.66, 16.29**
PBL model 3: PBL and sleep duration								
Continuous	0.98	0.76, 1.27	1.11	0.82, 1.50	1.07	0.80, 1.50	1.09	0.81, 1.47
PBL model 4: PBL and sleep latency								
Absent	Referent							
Present	**0.41**	**0.18, 0.18**	0.50	0.21, 1.22	0.50	0.21, 1.21	0.42	0.18, 1.00
PBL model 5: PBL and sleep disturbance								
Absent	Referent							
Present	1.20	0.33, 4.37	1.87	0.47, 7.53	1.84	0.46, 7.32	1.26	0.33, 4.81
PBL model 6: PBL and snoring (and/or coughing)								
Absent	Referent							
Present	1.21	0.54, 2.74	1.21	0.50, 2.92	1.25	0.52, 3.02	1.31	0.55, 3.11
LBW model 7: LBW and sleep medication								
Absent	Referent							
Present	1.40	0.18, 11.02	0.10	0.01, 1.77	0.11	0.01, 1.93	0.18	0.01, 2.79
PBL model 8: PBL and next day sleepiness								
Absent	Referent							
Present	1.49	0.66, 3.35	1.25	0.51, 3.10	1.28	0.52, 3.15	1.13	0.47, 2.74
PBL model 9: PBL and sleep quality								
Good	Referent							
Poor	1.08	0.71, 1.65	0.99	0.62, 1.59	0.99	0.62, 1.58	1.02	0.65, 1.60
PBL model 10: PBL and polytomous latent sleep variable								
Short bad sleeper	0.33	0.03, 3.43	0.21	0.01, 8.41	0.18	0.01, 3.78	0.35	0.03, 3.86
Long moderate sleeper	0.73	0.03, 20.18	1.65	0.04, 75.87	1.88	0.03, 136.48	1.51	0.04, 51.75
Long good sleeper	Referent							
Disturbed bad sleeper	2.20	0.07, 70.42	0.01	0.00, 41.61	0.04	0.00, 55.92	1.56	0.03, 71.01
Struggle to sleep-er	0.30	0.01, 7.81	0.14	0.00, 8.98	0.31	0.01, 9.03	0.32	0.01, 8.13
Snoring good sleeper	1.69	0.33, 7.58	1.25	0.22, 6.96	1.31	0.23, 7.53	1.51	0.28, 8.22

[1] Adjusted for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, health and cohabiting status. This model was presented to examine the effect of not including the OGTT reading in the covariate adjustment set.

[2] Minimal sufficient adjustment set for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, fasting OGTT, 2 hours postprandial OGTT, health and cohabiting status.

[3] Adjusted for ethnicity, age, cohabiting, parity and health. Although this model was under-adjusted, it was included in this table to compare its results with the results of a comparable model based on data from the UKHLS (Table 5-4).

[4] Figures in bold type are statistically significant ($p<0.05$).

Table 6-9 Logistic regression model ORs that showed the relationship between Apgar score at birth and sleep characteristics; before and after adjusting for potential confounders.[1,2,3]

Low Birth Weight Models	Level of Adjustment							
	Unadjusted model		Adjusted model[1]		Adjusted model[2]		Adjusted model[3]	
	OR	CI	OR	CI	OR	CI	OR	CI
LBW model 1: LBW and short sleep duration								
≥ 6 hours	Referent							
< 6 hours	1.72	0.45, 6.53	1.86	0.44, 7.86	1.88	0.41, 8.77	1.88	0.45, 7.88
LBW model 2: LBW and long sleep duration								
≤ 9 hours	Referent							
> 9 hours	2.14	0.47, 9.69	2.60	0 .51, 13.09	2.36	0.47, 11.74	2.90	0.59, 14.23
LBW model 3: LBW and sleep duration								
Continuous	1.19	0.80, 1.76	1.13	0.76, 1.70	1.13	0.74, 1.73	1.19	0.80, 1.78
LBW model 4: LBW and sleep latency								
Absent	Referent							
Present	1.76	0.41, 7.50	1.58	0.37, 6.85	1.42	0.33, 6.12	1.40	0.33, 5.97
LBW model 5: LBW and sleep disturbance								
Absent	Referent							
Present	1.10	0.32, 3.77	1.11	0.32, 3.84	1.03	0.29, 3.71	1.07	0.31, 3.68
LBW model 6: LBW and snoring (and/or coughing)								
Absent	Referent							
Present	1.10	0.32, 3.77	1.11	0.32, 3.84	1.03	0.29, 3.71	1.07	0.31, 3.68
LBW model 7: LBW and sleep medication								
Absent	Referent							
Present	6.60	0.78, 55.56	19.50	0.61, 623.41	21.75	0.60, 794.74	22.66	0.69, 744.55
LBW model 8: LBW and next day sleepiness								
Absent	Referent							
Present	0.93	0.25, 3.51	0.68	0.16, 2.93	0.73	0.18, 2.99	0 .63	0.15, 2.63
LBW model 9: LBW and sleep quality								
Good	Referent							
Poor	1.37	0.73, 2.56	1.41	0.71, 2.79	1.52	0.74, 3.11	1.35	0.70, 2.58
LBW model 10: LBW and polytomous latent sleep variable								
Short bad sleeper	1.36	0.21, 9.02	0.93	0.13, 6.66	1.03	0.14, 7.69	0.88	0.13, 6.15
Long moderate sleeper	0.73	0.03, 20.18	0.24	0.01, 8.29	0.30	0.01, 11.58	0.37	0.01, 11.96
Long good sleeper	Referent							
Disturbed bad sleeper	2.20	0.07, 70.42	0.89	0.01, 131.81	1.45	0.01, 149.39	0.86	0.01, 53.66
Struggle to sleep-er	1.57	0.19, 13.26	1.21	0.12, 12.18	1.36	0.12, 14.86	1.15	0.13, 10.13
Snoring good sleeper	2.62	0.30, 22.87	1.82	0.19, 17.05	2.08	0.22, 19.87	2.09	0.22, 19.53

[1] Adjusted for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, health and cohabiting status. This model was presented to examine the effect of not including the OGTT reading in the covariate adjustment set.

[2] Minimal sufficient adjustment set for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, fasting OGTT, 2 hours postprandial OGTT, health and cohabiting status.

[3] Adjusted for ethnicity, age, cohabiting, parity and health. Although this model was under-adjusted, it was included in this table to compare its results with the results of a comparable model based on data from the UKHLS (Table 5-4).

Table 6-10 Logistic regression analyses examining the relationship between NICU admission at birth, individual sleep characteristics and sleep patterns; before and after adjusting for potential confounders.[1,2,3]

NICU Admission Models	Level of Adjustment							
	Unadjusted model		Adjusted model[1]		Adjusted model[2]		Adjusted model[3]	
	OR	CI	OR	CI	OR	CI	OR	CI
NICU model 1: NICU and short sleep duration								
≥ 6 hours	Referent							
< 6 hours	0.24	0.01, 12.33	0.55	0.02, 14.79	0.61	0.03, 14.95	0 .47	0.01, 20.63
NICU model 2: NICU and long sleep duration								
≤ 9 hours	Referent							
> 9 hours	0.13	0.00, 6.87	0.42	0.02, 10.60	0.46	0.02, 10.23	0.24	0.01, 11.22
NICU model 3: NICU and sleep duration								
Continuous	0.52	0.09, 3.01	1.06	0.34, 3.27	1.01	0.36, 2.82	1.04	0.19, 5.64
NICU model 4: NICU and sleep latency								
Absent	Referent							
Present	2.39	0.05, 122.96	1.28	0.06, 26.86	1.34	0.07, 24.53	1.50	0.04, 52.31
NICU model 5: NICU and sleep disturbance								
Absent	Referent							
Present	8.36	0.159, 440.11	2.77	0.08, 99.56	2.78	0.09, 85.13	4.60	0.09, 238.02
NICU model 6: NICU and snoring (and/or coughing)								
Absent	Referent							
Present	0.55	0.01, 28.21	0.77	0.04, 14.57	0.80	0.05, 13.33	0.63	0.02, 18.59
NICU model 7: NICU and sleep medication								
Absent	Referent							
Present	0.02	0.00, 1.34	0 .26	0.00, 48.92	0.29	0.00, 43.19	0.14	0.00, 16.09
NICU model 8: NICU and next day sleepiness								
Absent	Referent							
Present	0.48	0.01, 24.86	0.60	0.03, 14.09	0.63	0.03, 11.68	0.61	0.01, 30.70
NICU model 9: NICU and sleep quality								
Good	Referent							
Poor	0.74	0.10, 5.29	0.85	0.19, 3.93	0.90	0.22, 3.79	0.80	0.12, 5.14
NICU model 10: NICU and polytomous latent sleep variable								
Short bad sleeper	2.83	0.05, 148.03	1.91	0.07, 49.31	2.15	0.09, 50.78	2.52	0.06, 115.09
Long moderate sleeper	0.43	0.01, 23.69	0.58	0.01, 31.94	0.63	0.01, 28.81	0.42	0.01, 22.67
Long good sleeper	Referent							
Disturbed bad sleeper	0.14	0.00, 8.95	0.46	0.01, 42.13	0.52	0.01, 39.35	0.25	0.00, 16.16
Struggle to sleep-er	1.11	0.02, 59.20	1.14	0.03, 44.84	1.34	0.04, 0 .04	1.13	0.03, 48.31
Snoring good sleeper	0.66	0.01, 35.52	0.73	0.02, 28.88	0.79	0.02, 25.84	0.74	0.02, 36.67

[1] Adjusted for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, health and cohabiting status. This model was presented to examine the effect of not including the OGTT reading in the covariate adjustment set.

[2] Minimal sufficient adjustment set for ethnicity, alcohol consumption, smoking, booking BMI, age, SES, parity, sex of the neonate, fasting OGTT, 2 hours postprandial OGTT, health and cohabiting status.

[3] Adjusted for ethnicity, age, cohabiting, parity and health. Although this model was under-adjusted, it was included in this table to compare its results with the results of a comparable model based on data from the UKHLS (Table 5-4).

6.5 Discussion

6.5.1 Limitations

The Scott/Ciantar study had a number of limitations, though these should not diminish the relative importance of this study for enhancing understanding of the possible association between sleep and pregnancy outcomes in women at risk of GDM. Quite simply, this is because this remains the only study to-date that has concentrated on this important high-risk group, whose prevalence appears to be growing year on year (Farrar et al., 2016).

Nonetheless, since the study only examined women recruited from two clinical contexts within the same UK-based NHS Trust will inevitably limit the potential generalisability of the analyses and the external variability of the present chapter's findings (Hedt and Pagano, 2011, Bellomo et al., 2009). However, generalisability might not have been severely compromised given that the Leeds General Infirmary and St James Hospital are the only two referral hospitals in Leeds that accept patients from all over Leeds (and further afield) – a geographical area in which there resides varied multiethnic populations experiencing substantial variation in socioeconomic status.

A more critical limitation stems from the fact that sleep was measured only once during the study period. This is likely to have introduced a degree of measurement error, since night-by-night variation in sleep is common (not least amongst pregnant women; Al Afif, 2017, Lee, 1998). The risk of measurement error would have nevertheless been mitigated by the fact that:

I. the questions included in the PSQI were originally (and specifically) designed to measure sleep over a period of month, and thereby seek to accommodate a degree of varation/fluctuation in sleep (Carpenter et al., 1998, Buysse et al., 1989);
II. the relation between unfavourable sleep and the physiological changes which usually develop in the second trimester of otherwise healthy pregnancy is likely to be a bidirectional relationship (Wang et al., 2017, Aurora and Punjabi, 2013, Qiu et al., 2010), though poor sleep was primarily considered the 'exposure of interest' (rather than the 'outcome of interest') in the present thesis and the decision to record sleep during the second trimester (i.e. before any *abnormal* physiological/anatomical changes developed) therefore ensured that 'sleep', as measured, could be examined as the potential cause of (subsequent) pregnancy outcomes.

Meanwhile, it is important to consider the potential impact of categorising not only the individual sleep characteristics and pregnancy outcomes as binary variables, but also the covariates identified as potential confounders. The decision to reduce the number of categories in most variables was taken to deal with the comparatively small number of participants with adequate data to permit their inclusion in the analyses, merging/reducing categorical data in this way can lead to or exacerbate cause categorisation error (Vittinghoff et al., 2006).

Somewhat unexpectedly, the criteria used for diagnosing GDM within the UK NHS were updated in 2015 (National Institute for Clinical Excellence, 2015), just as recruitment into the Scott/Ciantar study ceased. According to revised criteria, pregnant women with fasting OGTT results of $\leq$5.6 mmol/l are now to be diagnosed with GDM (National Institute for Clinical Excellence, 2015). Five women from the Scott/Ciantar study sample were diagnosed with GDM using these revised criteria, as one had a fasting OGTT equal to 5.6, and 4 had a fasting 0GTT >5.6. Fortunately, however, this change in practice should not have radically affected the results presented in the present chapter, since this focussed on the risk of GDM and on the OGTT reading itself, rather than on a formal clinical diagnosis of GDM.

Perhaps the most important limitation of the analyses conducted in the present Chapter relate to the small sample size available (which, as already mentioned, required most of the variables to be reduced to binary categorical variables in order to address the possible loss of statistical power; Vittinghoff et al., 2006, Demidenko , 2006, Freiman et al., 1978). While the sample size proposed in the original Scott/Ciantar study protocol was already optimistically small, the substantial proportion of participants lacking data on one or more of the variables of interest had a substantial impact on the numbers of participants on which the present chapter's analyses could be conducted. On the one hand, the completion rates of sleep questionnaires (85.6%, n=162) and the availability of data from medical records (71.3%, n=125) both appeared acceptable. However, when combined, the numbers of participants with complete data fell to almost 50% (57.4 %, n=108), and thereby substantially reduced the sample of participants with complete data that could be included in the analyses.

This, substantively reduced sample size inevitably affected the statistical power of these analyses and will have also increased the risk of type II error (Demidenko, 2006, Freiman et al., 1978). Yet, since this is the first such study of its type (focusing primarily on women at risk of GDM), and since many of the limited number of studies in this field had similarly modest sample sizes (the smallest being n=45, and most being around n=300), the present chapter is still considered

to have made a credible and important contribution to this potentially important topic.

Meanwhile, it is important to stress that the present chapter went to some lengths to carefully evaluate the potential impact of missingness on the sample and data available for analysis. In particular it is important to reiterate that missing data were excluded in two stages. The first was undertaken only after examining the likely causes of missing data and confirming that this involved the loss of all data due to missing records or uncompleted sleep questionnaires. The second comprised carefully examining the distribution of missing data against other variables. This approach meant that missing data could be excluded after verifying that the missing data were missing at random. Indeed, this process established that the pregnancy outcomes of participants with missing sleep data were similar to those with complete sleep data, and that there did not appear to be any peculiar/unusual aggregation of outcomes amongst participants with/without missing data. In a similar fashion, close examination was able to establish that the sleep characteristics/patterns and sociodemographic and health characteristics of participants with/without missing data were broadly very similar. In particular, there was no evidence of 'dependency' between the exposures and outcomes, nor were there abnormal patterns (such as clustering or pairing) in the distribution of missing data amongst any of the key variables of interest.

Nonetheless, excluding participants with (any) missing data will have inevitably caused a loss of information, since the rate of missing data varied from 0% to 10% in the variables of interest. Nonetheless, the majority of participants with (any) missing data had missing data for more than one variable, indicating either the loss of entire medical records, non-completion of sleep questionnaires, or both. In these instances, the modest missingness overlap would have minimized the amount of information lost and the number of excluded participants. So, even though listwise deletion might have decreased the statistical power of the analyses and might have increased the standard errors (SE) of any estimates generated, these estimates (and their SEs) are likely to have been unbiased, making listwise deletion more "honest", and therefore ostensibly superior when compared to many other conventional methods of estimation (Allison, 2001).

A final limitation worth consideration is that the analyses conducted in the present chapter might have been at risk of sampling bias, since as women who were *already* interested in sleep and/or concerned about their pregnancy were more likely to have been recruited. At the same time, (more) frequent medical intervention (particularly for women considered 'at risk' of GDM – as all of the

participants here were – and those subsequently diagnosed with GDM) might have influenced the precision of any (preceding) sleep measurements as potential predictors of poor pregnancy outcome. In other words, for example, this might have occurred had there been a latent confounder – say 'anxiety' – that influenced both self-reported sleep and the likelihood of medical intervention; or any later pregnancy complications, such as the early detection of abnormal fundal height which might have then caused an early induction of labour by the medical team before the baby grew too large.

6.5.2 Key findings

The key finding of the analyses conducted in the present chapter was that unfavourable sleep events and less favourable (LCA-derived) sleep patterns were not always accompanied by an elevated risk of poor pregnancy outcome. Instead, these were sometimes accompanied by a lower risk of poor outcomes, varying amongst the different outcomes examined and the different sleep characteristics observed. However, this key finding was subject to all of the limitations discussed earlier, which affected both the precision and the quality of this evidence and limited its generalisability to other populations.

Beyond this key finding, there were several more minor, secondary findings evident from a closer inspection of the direction and strength of the relationships observed. In the main, these findings support the theoretical basis of the present thesis, although the estimates generated had wide 95% confidence intervals which mean it is not possible to be certain concerning the precision of the interpretations based thereon. Additionally, as a result of the underpowered analysis, the poor data quality and the limited generatability of the results, these findings will need to be confirmed by better quality future studies:

First, the direction and magnitude of the relationship observed between individual sleep characteristics and pregnancy outcomes were somewhat different to those observed between LCA-derived sleep patterns and pregnancy outcomes. These differences might suggest that both of these somewhat different approaches to defining sleep successfully detected very different aspects of their role in the development of poor pregnancy outcomes. Additionally, while some of the individual sleep characteristics displayed similar patterns of relationships with pregnancy outcomes, this was not the case for the LCA-derived sleep pattern clusters, each of which had a unique suite of relationships with the pregnancy outcomes examined. This observation might support the notion that some of the individual sleep characteristics (e.g. sleep duration and latency) share similar pathophysiological pathways; whilst each of the LCA-derived sleep patterns had

their own unique relationships with pregnancy outcomes, and as such detected more specific/sensitive ‘net’ effects on potential pathophysiological pathways.

Second, unfavourable sleep characteristics were not always accompanied by an elevated risk of poor pregnancy outcomes. Indeed, some were occasionally accompanied by a *lower* odds of poor pregnancy outcome – something that was most evident with daytime sleepiness, long moderate sleeper pattern, LBW and preterm delivery. This finding perhaps suggests that unfavourable/less favourable sleep may often simply be a symptom of pregnancy and/or the growing foetus rather than operating as a risk factor for poor pregnancy outcomes. However, this was not true for caesarean delivery or Apgar score, perhaps because both of these outcomes are less a reflection of the growing foetus and more a marker for unfavourable pregnancy complications.

Finally, the use of alternative covariate adjustment sets (to address the uncertainty as to where, temporally and within the DAG, OGTT results might ‘occur’), was able to demonstrate that neither the direction nor the magnitude of the relationships observed differed markedly before or after the adjustment for the OGTT results. This would have occurred had the ‘direct backdoor path’ between OGTT results (as a cofounder) and pregnancy outcomes was mediated by subsequent GDM treatment and glucose monitoring whilst receiving enhanced clinical care. It might therefore be advisable were future studies to adopt a prospective longitudinal study design in which there are frequent sleep measurements/assessments *and* blood glucose measurements.

Arguably, these findings were inevitably influenced by choices made regarding the covariates included in each of the regression models. These choices were justified using the hypothesised DAG, even though this DAG was built on the basis of theory rather than firm knowledge (and therefore still requires empirical testing). Hence, changing the covariate adjustment sets would likely alter the estimates generated. Meanwhile, the referent for sleep used, and the possibility of measurement error due to the variable nature of sleep (together with the reliance on subjective sleep measurements), are also likely to have influenced the results obtained. For these reasons, using a different measurement tool and/or a different sleep referent, might lead to substantively different findings. Finally, being underpowered and imprecise the analyses conducted in the present chapter offers less confidence concerning the magnitude of the estimates generated *and* the direction of the relationships observed between sleep and pregnancy outcomes. Nonetheless, given similar findings were obtained from analyses of the Scott/Ciantar dataset and those based on the UKHLS dataset might mean that there is a high possibility that these

estimates reflected the true direction of the relationships observed between sleep and pregnancy outcomes (even if their strength might be less certain as a result of the previously discussed limitations).

6.5.3 Conclusion

The relation between sleep on a range of pregnancy outcomes (some maternal, some perinatal, and some neonatal) varied according to the type of outcomes and sleep characteristics/patterns examined. However, unfavourable sleep events and sleep patterns did not *always* elevate the odds of poor pregnancy outcomes, and instead, occasionally lowered these odds. However, these findings lack a sufficient level of statistical confidence (or functional understanding) and remain somewhat speculative and imprecise. Importantly, they may reflect the influence of the medical interventions allocated to women at high risk of developing pregnancy complications in this group. Nonetheless, since the findings of the present chapter's analyses and those based on the UKHLS dataset were very largely the same regarding the relationship(s) observed between sleep characteristics and pregnancy outcomes, the replicability of these suggests their findings are likely to be broadly valid (shared methodological limitations notwithstanding). Indeed, the very similar findings suggest that there should be less certainty concerning the (very different) results published elsewhere in the literature, not least given the concerns raised earlier in the present thesis regarding the apparent evidence of publication bias. Finally, it is worth adding that the differences between the two datasets analysed in the present thesis, particularly with respect to the relationships between latent sleep clusters and pregnancy outcomes, tend to confirm the thesis' supposition that sleep clusters are potentially more sensitive to changes in health (and, possibly GDM treatment) than individual sleep characteristics; albeit that further research are required to confirm this possibility.

6.5.4 Recommendations

Future studies will be required to address each of the (substantial) limitations affecting the present chapter's analyses, so that more precise results and more certain conclusions can be drawn. Unfortunately, the present chapter's analyses, like those using the UKHLS dataset, are the only studies to-date that have used sleep in the form of a latent sleep variable. For this reason, future studies are encouraged to adopt the conceptualisation of sleep as a latent variable to generate and evaluate similar sleep patterns. Additionally, researchers are highly encouraged to consider the sleep measurement used with great care (and, potentially more importantly) to choose their 'normal' sleep referent category with great care, since 'normal' sleep is likely to represent a broad spectrum of sleep-

related phenomena. Until such studies have been performed, understanding of the relation between sleep and pregnancy outcomes will remain limited, and to a large extent determined (and undermined) by the quality and quantity of data available, and each of the key analytical decisions required.

Medical intervention should also be considered with great care when designing any future studies since such interventions are likely to have a substantial impact on the results obtained. This will be particularly relevant when sleep is operationalised as a latent concept; in which multiple measurements of sleep, as well as of any covariates acting as potential confounders, will help in correctly specifying the temporal sequence of events and the most appropriate adjustment for any such interventions. Indeed, although the effect of adjustment for OGTT readings on the estimates obtained for the relation between sleep and pregnancy outcomes was minor, appropriate adjustment for OGTT readings will still be required in order to appropriately reduce any confounding effect associated with medical intervention (such as the treatment of GDM, prior to the measurement of sleep). Therefore, perhaps, a better structured study, comparing the effect of sleep on pregnancy outcomes in women at risk of GDM who either did or did not require and receive medical intervention, with women who had low risk pregnancies, might highlight how treatment (before *or* after the measurement of sleep) might influence any effect of sleep on pregnancy outcomes.

Chapter 7 Discussion

There have been a growing number of studies exploring the potential relationship between sleep and poor pregnancy outcomes (Ding et al., 2014, Pamidi et al.,2014, August et al., 2013), especially over the last 10 years (Pelayo and Dement, 2017). The evidence these studies have generated suggests that there might well be an association between (what appear to be) 'less favourable' sleep characteristics and a range of pregnancy outcomes (August et al., 2013, Ibrahim and Foldvary-Schaefer, 2012), However, this evidence is beset by a number of limitations in relation to both its internal and external validity (Pamidi et al, 2014, Khan et al, 1999, Lee, 1998). Indeed, the 'science' behind the potential pathophysiological mechanisms through which sleep might affect pregnancy outcomes is largely built on theoretical extrapolation from studies of non-pregnant populations, and the likely impact of experimental effects of sleep deprivation on physiological and metabolic processes during pregnancy (Irish et al., 2015, Ibrahim and Foldvary-Schaefer, 2012). To some extent this reflects the ethical challenges of experimentation during pregnancy and the limited number of interventions capable of improving sleep (Blyton et al, 2013, Reid et al, 2013); and for these reasons, the bulk of what we know about sleep and pregnancy outcome (as presented in the literature) is based on the findings of observational studies (Pamidi et al, 2014, Khan et al, 1999, Lee, 1998).

In these studies, sleep was primarily measured by assessing individual perceptions of one (or more) sleep characteristics events (e.g. duration, latency and disturbance), rather than using more objective measures (such as polysomnography or actigraphy; Silber et al.,2016, Prinz, 2004). The aim of the present thesis was therefore to carefully evaluate the evidence available in the literature before identifying (and filling) the key gaps in current knowledge by examining both a population sample of pregnant women (drawn from the UKHLS – a representative study of the UK population that offers substantial external validity) and a clinical population of pregnant women considered to be at elevated risk of the sorts of metabolic conditions (in this instance, GDM; Sisira et al., 2017, Bjørn et al., 2007) considered to be particularly susceptible to less favourable sleep. To address the possibility that any effects of sleep on pregnancy outcomes might be the result of variation in individual sleep characteristics and/or variation in sleep 'patterns' (i.e. a combination of, and interactions between, individual sleep characteristics), the operationalization of sleep in the analyses of both samples of pregnant women compared the relationship between sleep and pregnancy

outcomes with sleep defined as multiple individual characteristics *and* as a single, more complex, 'pattern based' phenomenon.

7.1 Summary of findings and limitations

To achieve the main aim of the thesis, four key questions (KQ) were addressed. Each question was examined in successive chapters in the present thesis using a series of studies, each with different designs, data and/or analyses in the following order;

KQ1: What might be learnt from the methods and findings of previous empirical studies exploring the relationship between sleep and pregnancy outcomes regarding: the challenges and potential flaws of such studies; the strength of the evidence these studies provide; and priorities for strengthening the evidence generated from existing data sources?

Chapter 3 answered KQ1 using a systematic review and meta-analysis of published observational studies examining the association between sleep and pregnancy outcomes. From the systematic review of previous observational studies (i.e. Chapter 3) it was evident that, few of these studies had examined more than one (or, at best, a handful) of 'self-reported' sleep characteristics; and that none had sought to examine sleep more 'holistically' (i.e. used more than one sleep characteristic simultaneously to characterise any multifactorial 'sleep patterns'; Babson et al., 2012, Casement et al., 2012). There were also a number of potential biases in many of the analyses reported by these studies, both in terms of sampling (particularly for some of the rarer pregnancy outcomes), but also in terms of: sample size/power; multiple testing; and inappropriate covariate adjustment (King and Zeng, 2001, Khan et al.,1999). There was also some evidence to support the likelihood of publication bias – the tendency for studies that observe strong and/or precise associations to be published in comparison to those with null findings (Song et al., 2013, Rothstein et al., 2006, Easterbrook et al., 1999).

Given these limitations, especially the high likelihood of publication bias, it remains difficult to conclude with any certainty whether poor pregnancy outcomes are associated (whether causally, or not) with unfavourable sleep. Indeed, it is entirely possible (as well as causally plausible) that (some) unfavourable sleep characteristics are related to a *lower* risk of some pregnancy outcomes. As such, these 'unfavourable' sleep characteristics might present as symptoms of healthy pregnancies. This is possible since only a limited range of sleep characteristics and a limited range of pregnancy outcomes have thus far been adequately examined (or examined at all) in the literature; while the odds reported in the

literature tend to lack precision and the methods involved in generating these seem affected by a number of potentially problematic errors and flaws. Added to this, the vast majority of previously published findings based their interpretations on findings assessed using *p*-values to examine 'the' null hypothesis rather than the 'alternative' hypothesis.

KQ2: What, if any, sleep patterns exist amongst the UK population; and are any of these stable over time and/or associated with socio-demographic and health characteristics that might provide evidence of reliability and criterion-based validity?

Chapter 4 answered KQ2 using the UKHLS data set and complex LCA to examine the presence, temporal stability and criterion based validity of any distinct multifactorial sleep 'patterns'. Using latent class analysis of the seven discrete self-reported sleep characteristics recorded by the UKHLS, the present thesis (in Chapter 4) was able to identify six distinct 'sleep patterns' amongst adults within the UK population – patterns that were stable over time (i.e. that were present in a very similar form in two successive Waves of data from the UKHLS) and were strongly associated with variation in a range of socio-demographic and health characteristics (these characteristics being chosen on the basis that they were likely to be determinants and/or consequences of unfavourable sleep; Arber et al., 2009, Bjørn et al., 2007, Kaneita et al, 2007). The analyses undertaken in this Chapter (4) found that the associations observed between these six 'sleep patterns' and health and sociodemographic characteristics was more variable than those observed amongst each of the seven individual sleep characteristics. It seems likely that these differences indicate that 'sleep patterns' are more sensitive to variation in health and sociodemographic characteristics because they provide a more holistic measure of sleep overall as compared to each of the individual sleep characteristics (Alghamdi, 2013, Babson et al., 2012, Casement et al., 2012, Vermunt, and Magidson, 2004). These findings went some way towards confirming the plausibility of the present thesis' so-called 'hypothesised' DAG – drawn using knowledge (and supposition) regarding the timing of measured events/variables to visualise the likely causal relationships between sleep, pregnancy outcomes and a range of likely mediators and potential confounders. These findings also helped justify the use of the 'long good sleeper' category as an appropriate referent category in the analyses undertaken in the two chapters that followed.

For the most part there were only modest concerns regarding the suitability of data from the UKHLS, albeit that the data on sleep were generated using a subjective retrospective sleep questionnaire (Abrishami et al, 2010, Coughlin, 1990) based

on (but somewhat different to) the validated PSQI (Zhong et al., 2015, Beaudreau et al., 2012, Buysse et al., 1989), and there were a modest number of participants with missing data (Little and Rubin, 2014) for one or more of the individual sleep characteristics and/or sociodemographic and health variables.

KQ3: Is there any evidence that self-reported sleep characteristics predict subsequent pregnancy outcomes amongst pregnant women who are broadly representative of the UK population? And to what extent might 'sleep patterns', identified using a range of self-reported sleep characteristics, predict subsequent pregnancy outcomes amongst them?

Chapter 5 answered KQ3 using the UKHLS population-based dataset and multivariable regression analyses to assess the relationship between individual sleep characteristics, LCA-generated sleep patterns and a range of pregnancy outcomes, before and after adjusting for potential confounders identified using a directed acyclic graph (DAG).

The six latent sleep patterns identified using LCA on the UKHLS sleep dataset, together with the 7 individual sleep characteristics measured in the UKHLS sleep module, were then examined amongst UKHLS participants who had been pregnant at questionnaire completion during Waves 1 or 4 (see Chapter 5). These measures of sleep were then examined as potential determinants of a range of self-reported pregnancy outcomes, using data on the latter provided in the same or subsequent Waves, and using multivariable logistic regression analyses before and after adjustment for covariates identified as potential confounders using a directed acyclic graph (DAG). In general, the results of these analyses provided precious little evidence of any strong relationships between sleep and poor pregnancy outcome, regardless of whether these used individual sleep characteristics or LCA-derived sleep patterns as the exposure of interest. Moreover, where such relationships were observed, it was clear that unfavourable sleep characteristics and patterns were *not* always accompanied by increased odds of poor pregnancy outcome. Instead, on occasion, less favourable sleep was accompanied with a lower odds of (some) poor pregnancy outcomes. Meanwhile, the direction and magnitude of relationships between individual sleep characteristics and pregnancy outcomes were also somewhat different to that observed for the LCA-derived sleep patterns – suggesting that individual characteristics and composite patterns captured different pathways of these relationships or causes to one another (Buysse, 2014, Alghamdi, 2013, Babson et al., 2012, Casement et al., 2012), evidence that both may be helpful in better understanding the potential role of sleep in the development of poor pregnancy outcomes. Unfortunately, these findings may

also have been affected by a number of substantive data and sample quality issues, particularly those stemming from: the paucity of pregnancy outcomes data (with limited numbers of outcomes reported; and all of these based on maternal self-reports, which many previous studies have suggested can be rather imprecise; Schmidt et al., 2015, Herring et al., 2013, Harris et al., 1997); the inclusion of pregnant women who completed the UKHLS questionnaires at different times during their pregnancy (i.e. some in the first, some in the second and some in the third trimester of pregnancy; Al Afif, 2016, Facco et al., 2010); and the use of multiple testing (of 8 sleep variables and multiple pregnancy outcomes; Sullivan and Feinn, 2012) and the concomitant risk of type II errors due the underpowered analyses and inadequate sample size (Freiman et al., 1978).

KQ4: Is there any evidence that self-reported sleep characteristics predict subsequent pregnancy outcomes amongst pregnant women at increased risk of developing gestational diabetes? And to what extent might 'sleep patterns', identified using a range of self-reported sleep characteristics, predict subsequent pregnancy outcomes amongst them?

Chapter 6 answered KQ3 using the Scott/Ciantar study clinical dataset (of women at elevated risk of GDM) and multivariable regression analyses to assess the relationship between individual sleep characteristics, LCA-generated sleep patterns and a range of pregnancy outcomes, before and after adjusting for potential confounders identified using a directed acyclic graph (DAG). Subsequent analyses, using similar techniques to those applied to pregnant women from the UKHLS to women at risk of GDM, nonetheless found very similar results with regard to unfavourable sleep characteristics (see Chapter 6). However, in this instance the LCA-derived sleep patterns had very variable relationships with poor pregnancy outcomes and these were not always accompanied by an elevated risk of poor pregnancy outcomes. Moreover, there were additional limitations with the Scott/Ciantar study data which make a direct comparison between analyses of these data and those of the UKHLS data (in Chapter 5) challenging. In particular there: were much poorer quality data on covariates acting as potential confounders (Schmidt et al., 2015, Harris et al., 1997); was a potential risk of sampling bias (since this study may have only succeeded in recruiting women who were already interested in sleep and/or were worried about their pregnancy; Hedt and Pagano, 2011); was the likelihood that more frequent medical attention/intervention may have influenced the precision of any (preceding) sleep measurements as predictors of (subsequent) poor pregnancy outcomes (if, for example, there had been a latent confounder – say 'anxiety' – that had influenced *both* self-reported sleep *and* the likelihood of medical intervention and its effect[s] on pregnancy

outcomes (Crowther et al., 2005, Maxwell et al., 2011). However, while in the UKHLS analyses (Chapter 5), variation in the gestational age at which sleep data were recorded was viewed seen as an important potential limitation, in the Scott/Ciantar study the much tighter period of time over which sleep was recorded might also be seen as a limitation (not least if this period had been when sleep was less important or a weaker predictor/determinant of subsequent pregnancy outcomes; Al Afif , 2016, Facco et al., 2011). In general then, the results of these analyses revealed no strong associations between sleep characteristics or patterns and the subsequent odds of poor pregnancy outcome(s) amongst women zwat increased risk of GDM.

7.2 Evidence of associations between sleep and poor pregnancy outcomes

Given the limitations of the *de novo* analyses contained in the present thesis (and those of previously published studies examined in Chapter 3), perhaps the most important evidence from Chapters 5 and 6 was that the empirical data did not always support the claim made in the literature that less favourable sleep was associated with an increased risk of poor pregnancy outcomes as discussed comprehensively in Chapter 3. In Chapters 5 and 6 it was clear that while less favourable sleep predominantly *increased* the risk of poor pregnancy outcomes amongst women from the wider UK population or women at risk of GDM; on a number of occasions less favourable sleep was actually accompanied by a *lower* risk of poor pregnancy outcomes. While all of these associations lacked precision (i.e. had wide confidence intervals, primarily as a result of measurement error and the modest sample sizes involved; Borenstein et al., 2009, Montori et al., 2004), it was also clear that whether positive or negative, there usually existed a relationship of some sort between sleep and pregnancy outcome, and there were very few occasions where no relationship whatsoever was apparent.

These results contrast quite markedly with those reported in the literature (Pamidi et al., 2013, Chang et al., 2010, Pien et al., 2004). Indeed there remain, to-date, limited numbers of studies (particularly considering that *some* outcomes in relation to *some* sleep events have only been examined once thus far; August et al, 2013, Pamidi et al., 2013); which means that these studies have only examined a limited range of (clinical and non-clinical) populations (Chang et al., 2010, Pien et al., 2004), and makes it challenging to compare their findings to those generated in Chapters 5 and 6, and particularly so for Chapter 6 since many of the studies reviewed in Chapter 3 had specifically and deliberately excluded pregnancies

considered to be ‘high risk’ (including those affected by GDM). And since many of these studies failed to report many of the more important social and biological characteristics of their participants (such as socioeconomic status or health conditions), it remains somewhat unclear whether comparisons between any of these studies might not be undermined by inter-study heterogeneity (August et al, 2013, Pamidi et al., 2013, Borenstein et al., 2009).

At the same time, the modest number of previous studies, and the fact that most of these had reported ‘positive’ findings, seems likely to indicate that there may be numerous unpublished studies (and related datasets; Borenstein et al., 2009, Dickersin, 1990) which found no evidence of any association between sleep and pregnancy outcomes, or which might have actually shown the sorts of inverse relationships between ‘unfavourable sleep’ and ‘good’ pregnancy outcomes that were observed in Chapters 5 and 6, here (Louis et al., 2012). If, as the published literature suggests, the overwhelming theoretical hypothesis driving such analyses is that ‘unfavourable’ sleep characteristics and patterns are likely to pose substantive risks of ‘poor’ pregnancy outcomes (as a result of the ill-effects of sleep deprivation on cardio-metabolic health evident in experimental studies of non-pregnant populations; Cappuccio et al., 2010, Coughlin et al., 2004), then the tendency for published studies of pregnant women to report ‘positive’ associations between sleep and pregnancy outcomes, together with the apparent strength/statistical significance of many of the smaller (and therefore more underpowered) studies, presents a strong *prima facie* case for publication bias at work (see Chapter 3; Rothstein et al., 2006). This impression is further strengthened by the fact that so few of these published studies recognized and cited many potential limitations that might have affected their internal validity (again, see Chapter 3; Grimes and Schulz, 2002, Stroup et al., 2000).

That is not to say that either of the two *de* novo studies conducted for the present thesis (i.e. Chapters 5 and 6) were unaffected by potential challenges to their internal validity - particularly as regards sample size, statistical power, multiple testing and the risk of type I and type II errors (Demidenko et al., 2006, Grimes and Schulz, 2002, Freiman et al., 1978). Hence, it cannot be concluded with a substantive degree of certainty (nor with traditional levels of confidence or statistical precision) that either of these studies found clear evidence of positive, inverse or null associations between sleep and pregnancy outcomes. In particular, these studies do not permit the absence of any association between sleep and pregnancy outcomes to be rejected with much level of certainty. Yet, in a similar fashion to that observed in the literature, Chapters 5 and 6 found a number of statistically significant associations between sleep and poor pregnancy outcomes

– associations that are consistent with type I errors, especially were alpha to have been corrected to account for multiple testing (Bender and Lange, 2001, Benjamini and Hochberg, 1995, Bonferroni, 1936). Somewhat paradoxically, then, these 'occasional', statistically significant (and therefore more precise) findings seem likely to support the view that the evidence presented in the published literature are also primarily the result of type I errors (Borenstein et al., 2009, Stroup et al., 2000) . Such 'occasional' findings can be found in many of the studies in which multiple (ostensibly exploratory) tests were likely to have been applied to more sleep characteristics than that reported (Keppel and Wickens, 2004, Grove and Andreasen, 1982) – not least since most of these studies reported that they had used sleep questionnaires that would have generated data on more than just the one sleep characteristic on which the published study's findings hinged.

Nonetheless, and this is perhaps an equally important point, given the findings from a growing number of published studies, it seems unlikely that there is (as yet) sufficient evidence to completely reject the possibility or plausibility of an association between sleep and pregnancy outcomes – though this may, in the main, simply be the result not only of publication bias, but also the many substantive limitations of the sampling, sample size, data measurement and analysis techniques that affect most of these previously published studies (Monroe, 2007, Grimes and Schulz, 2002, Stroup et al., 2000). However, at best, it seems likely that any true effect present (such as an increased risk of hypertension-mediated prematurity or low birth weight, or of obesity and GDM-mediated macrosomia amongst women with sleep disordered breathing Reutrakul et al., 2013, Benediktsdottir et al., 2012 Micheli et al., 2011, Qiu et al., 2010) might still be too modest to detect with any degree of certainty or precision in the sample sizes used and with such extensive reliance on self-reported (sleep and other) data and data extracted from clinical records (Maxwell et al., 2011, Fritz and MacKinnon, 2007, Harris et al., 1997, Coughlin, 1990). Under these circumstances, and for all of these reasons, the present thesis would argue that previously published studies seem likely to have exaggerated the strength of any relationships between sleep and pregnancy outcomes. For this reason alone, better quality studies will be required to provide the evidence necessary to generate any definitive conclusions regarding the potential relationship between sleep and pregnancy outcomes.

7.3 Sleep in pregnancy

Several empirical studies, and a wealth of theoretical conjecture, suggest that sleep is likely to be more 'problematic' during pregnancy (Naud et al., 2010) –

simply as a result of the effects of the many physical, hormonal and psychological factors that militate against more favourable sleep (Silber et al., 2016, Sloan, 2008, Wang et al., 2004). Yet, closer examination of more descriptive studies of sleep in pregnancy (published elsewhere in the literature) and neither of the two empirical *de novo* studies included in the present thesis (Chapters 5 and 6) appear to not support this. For example, the descriptive summary statistics from published studies suggest that the reported mean sleep duration of the pregnant women examined ranged from 6 to 9 hrs/night (Lee and Gay, 2004, Dorheim et al., 2012, Herring et al., 2014, Wang et al., 2017) – a range that is thought to be within the 'normal' length of sleep duration as reviewed in Chapter 3. Likewise, in terms of overall sleep quality, the majority (60%) of pregnant women in more than one study reported poor quality PSQI-derived scores (i.e. a PSQI global score of >5; Okun et al., 2011, Reutrakul et al., 2011), yet when a single question was used to assess subjective sleep quality only a small minority of pregnant women appear to report poor sleep quality (2.2%), whilst the remainder tend to report 'good' to 'moderate' sleep quality (Wang et al., 2017). Such differences in findings generated using two different tools/approaches to the evaluation of overall sleep quality might indicate: differential measurement error (Manconi et al, 2010, Elsenbruch et al, 1999); or differential sensitivity (of the PSQI and individual sleep quality questions) when detecting sleep problems (Mollayeva et al., 2016). The last of these possibilities was supported by the comparison of UKHLS sleep module questions and data from UKHLS participants in the dedicated subsample (who, as part of the methods development and testing procedures used by the UKHLS, had additionally completed the PSQI; see Chapter 2 and Appendix), which showed that the PSQI data failed to identify an important group of women who *did not* have unfavourable sleep events.

These summary findings can be interpreted as evidence that the majority of pregnant women do not appear to display less favourable sleep – an interpretation that is largely supported by both of the empirical studies presented in this thesis (Chapters 5 and 6). In these studies, around 70% of pregnant women (from the UKHLS) and 64% of women at risk of GDM (from the Scott/Ciantar study) reported that their sleep duration over the month preceding data collection had been within the reference range (i.e. 6 to 9 hrs/night); while two thirds of pregnant women in both samples reported 'good' sleep quality and an 'absence' of disturbed sleep. At the same time, when the sleep patterns identified on the UKHLS study population (old and young, male and female, healthy and unhealthy) were applied to the self-reported sleep characteristics of pregnant women, far more of these women were found to display long good sleep patterns (12.9%) as compared to other

participants in the UKHLS (7.1%). Indeed, the prevalence of LCA-derived good sleep patterns was even higher amongst women at risk of GDM (15.7 %) than that observed amongst pregnant women from the wider population (as sampled by the UKHLS).

While pregnancy is widely considered (and experienced as) a risk factor for developing some unfavourable sleep events (Ward, B. 2017, Al Afif, 2016); unfavourable sleep events should not necessarily be considered characteristic of (all) pregnancy *per se*, and their presence may (or may not) indicate the existence of pregnancy complications (Ward, 2017). Comparisons with pre-pregnancy sleep patterns would be required before drawing such a conclusion (Al Afif, 2016), although careful consideration should also be given to the possibility that subjective sleep measurement might (in and of itself) cause substantial measurement errors which might themselves be susceptible to changes in affect, mood and perception during pregnancy (Sedov et al., 2017). Of particular relevance in this regard (given that most previous studies examining the relationship between sleep and pregnancy examined just one sleep characteristics), using a single sleep characteristic, be that duration or perceived quality, to argue/demonstrate that unfavourable sleep is common in pregnancy, would be far from satisfactory (Sedov et al., 2017, Pamidi et al., 2014). For instance, in Chapter 3, both male and non-pregnant female UKHLS participants had similar rates of ‘long moderate’ – a pattern characterised by long hours of sleep, good perceived quality, and an absence of unfavourable sleep characteristics (except disturbance). Disturbance was therefore the single individual sleep characteristic that differentiated between ‘long good’ sleepers and ‘long moderate’ sleepers, both of which had a very different distribution across sociodemographic and health variables. Therefore, arguing that sleep is ‘worse’ or ‘better’ based solely on the presence (or absence) of ‘disturbance’ alone might offer a balanced assessment of good vs. bad sleep, and additional, alternative measures of (other) sleep-related characteristics are required to do so.

7.4 Sleep as a complex latent variable

Given the likely multifactorial nature of ‘sleep’ and the potential for error were just one sleep characteristic to be used as a marker/measure thereof, the present thesis theorised that sleep might be better (and more holistically) described as a latent variable (Alghamdi et al., 2014, Babson et al., 2012, Casement et al., 2012). This has not been attempted by any of the previously published studies reviewed as discussed in (Chapter 3 and although, on a few occasions, the seven different

sleep characteristics available within the UKHLS and Scott/Ciantar study had been examined by studies exploring the association between sleep and health, these studies (and others) tended to construct separate theories around the findings generated for each aspect of sleep and (in the studies reviewed in Chapter 3) how this might then influence poor pregnancy outcome(s).

In the UKHLS and the Scott/Ciantar study, the 7 sleep individual characteristics, which were measured using the UKHLS sleep module or PSQI, displayed very different patterns amongst the study participants to those evident when using the 6 LCA-derived sleep patterns – patterns that differed in both the direction and magnitude of their relationships with pregnancy outcomes. In particular, while the strength and precision of the relationships between unfavourable sleep characteristics and poor pregnancy outcomes varied, each of the 7 individual sleep characteristics examined were consistently accompanied by an elevated odds of poor pregnancy outcomes. In contrast, only those pregnant women with sleep patterns characteristic of LCA-derived clusters 5 and 6 displayed an elevated risk of poor pregnancy outcomes, and the risk of these was actually lower amongst women with sleep patterns characterized by clusters 1, 2, 3 and 4 (only one, or perhaps two, of which might reasonably be considered 'favourable' sleep patterns). Clearly then, amongst pregnant women, the magnitude, precision *and* direction of relationships between sleep and pregnancy outcomes was different for individual sleep characteristics and sleep patterns overall. There are a number of different possible reasons for this novel and potentially important finding. First, LCA-derived sleep patterns may suffer from different specification errors to those experienced by individual sleep characteristics (in particular, that any individual measurement errors associated by the use of self-reported retrospective questionnaire items might become conflated when each of the individual characteristics are combined in the LCA; Collins and Lanza, 2013, Hagenaars et al., 2002). Second, measurement error might have also been exacerbated by the imposition of rigid cutoff points to demarcate sleep duration, sleep events or the perception of sleep quality (Buysse, 2014, Buysse et al., 2008, Buysseet al., 1989), also might be from relying on recall when collecting birth outcomes data from the UKHLS participants or during reporting medical data in the medical records by several health personal (Biemer and Lyberg, 2003, Thiru et al., 2003, Harris et al.,1997). Yet, these somewhat obvious sources of heterogeneity and error aside, the third possibility is that the two approaches to characterizing sleep actually measured very different things – the first measuring separate characteristics/dimensions of sleep; the second offering a more integrated assessment of sleep which took into account the inter-dependence and conditional equivalence of different individual sleep

characteristics ((Babson et al., 2012, Casement et al., 2012, Wu et al., 2002). Indeed, the last of these possibilities appears an attractive prospect, considering so little is still known about the biology of sleep (Prinz, 2004) and what each of the salient (and therefore measureable/manifest) sleep characteristics might represent in terms of the physiology of sleep and how these might interact with one another and with the physiological and biochemical processes involved in the etiology of disease (Silber et al., 2016). The fact that this, more holistic approach to the operationalization of 'sleep' (i.e. the use of LCA-derived, ostensibly latent sleep 'patterns') displayed more variable relationships with both health (in Chapter 4) and pregnancy outcomes (in Chapters 5 and 6) is *prima facie* evidence that this was more sensitive (and therefore a more nuanced assessment of the potential role of sleep as a consequence, correlate or determinant of poor pregnancy poutcomes) than the use of individual sleep characteristics (Alghamdi, 2013, Casement et al., 2012). This is because the more variable relationships observed are likely to be more useful when trying to identify, design and apply interventions to address 'less favourable' sleep in pregnant women (Vézina-Im et al, 2017, Dorrian and Warland, 2013. Blyton et al, 2013, Kaneita et al., 2005)– essentially knowing to which sleep pattern women might benefit from thereby concentrating on improving the specific individual sleep characteristics required to 'shift' or 'nudge' them into sleep patterns that are associated with far fewer unfavourable pregnancy outcomes (Vézina-Im et al., 2017, Irish et al., 2015, Stepanski and Wyatt, 2003. This might prove rather counter-intuitive given, for example, the finding that long good sleepers (ostensibly the least unfavourable of the sleep patterns observed) were not those who displayed the lowest risk of poor pregnancy outcomes.

7.5 Pregnant women at risk of GDM

Women at risk of GDM are considered to (also) be at higher risk of poor pregnancy outcomes (National Institute For Clinical Excellence, 2015, Wendland et al., 2012) and of less favourable sleep (Wang et al, 2017, Reutrakul et al, 2013, Qiu et al, 2010) – both, primarily, because many of these women go on to develop gestational diabetes, a condition that has a well-established increased risk of poor pregnancy outcomes (particularly macrosomia and caesarean section; National Institute For Clinical Excellence, 2015, Kamana et al., 2015, Alberico et al., 2014). Somewhat unsurprisingly, some of the GDM risk factors (notably high BMI) are also thought to predict poor pregnancy outcomes and unfavourable sleep, regardless of the development of GDM (Kennelly et al, 2011, Lawrence et al, 2008, Torloni et al, 2008, Bjørn et al, 2007). However, because blood glucose levels constitute a continuum (and the cutoff point used to define GDM is arguably

somewhat arbitrary; World Health Organization, 2013, Hezelgrave et al, 2012), women 'at risk of GDM' are likely to be at risk of poor pregnancy outcomes and unfavourable sleep regardless of whether they actually go on to develop GDM.

Amongst the background papers reviewed in Chapter 1, and the specific studies reviewed in Chapter 3, there was little empirical evidence available concerning the sleep of pregnant women who were at risk of GDM or who had GDM. Instead, in most instances, women with GDM were actually excluded from the sample, or included there in without adjustment for their condition, which made it challenging to generalise between the results generated from these published studies to the analyses presented in this thesis' Chapter 6. These analyses therefore offer novel insights into the sleep and pregnancy outcomes of women at risk of GDM – insights that are amenable to comparisons with the analyses presented in Chapter 5 (based on the population sample of pregnant women from the UKHLS), not least because both sets of analyses used similarly measured sleep and pregnancy outcome variables, identical categorisations of these variables, and multivariable logistic regression analyses informed by comparable causal path diagrams (the directed acyclic graphs specified in line with the likely temporal sequence of the variables available for inclusion in the analyses). In the analysis of UKHLS (Chapter 5) and Scott/Ciantar study data (Chapter 6), the distribution of individual sleep characteristics and pregnancy outcomes participants was very similar amongst participants in both samples. However, this was not true with regard to the distribution of LCA-derived sleep patterns – these patterns displayed very different distributions in each case.

Since GDM is considered likely to be (potentially causally) linked with unfavourable sleep events (Wang et al, 2017, Pamidi et al., 2014, Reutrakul et al, 2013, Qiu et al, 2010), it might have been expected that pregnant women with GDM (or with an elevated risk of GDM), were more likely to display a higher prevalence of short bad sleep patterns (Pamidi et al., 2014). Yet in fact, pregnant women from the UKHLS population sample, most of whom are unlikely to have been at increased risk of GDM, were even *more* likely to display short bad sleep patterns, albeit in the absence of appropriate data on a number of key potential confounders (most notably BMI; Louis et al, 2012), than those participants in the Scott/Ciantar study. All potential confounders require careful identification and adjustment when examining the potential total causal effect of sleep on pregnancy outcomes, and the lack of data on key covariates likely to have acted as (powerful) potential confounders is a key weakness and limitation of the analyses present in Chapter 5 (Williamson et al., 2013, McNamee, R. 2003). It is likewise possible that the paucity of data on gestational age at questionnaire completion in the UKHLS, and

the lack of adjustment for gestational age, may have been responsible for the very different distribution of sleep patterns observed in these participants (from the UKHLS, who completed the sleep module questionnaire in different trimesters of pregnancy) and those from the Scott/Ciantar study (who all provided self-reports of sleep during the second trimester; Mindell et al, 2015, Lee et al, 1998). In effect, the distribution of LCA-derived sleep patterns of participants in Chapter 5 may have reflected the patterning of sleep at a very different period in pregnancy to that seen in Chapter 6. Given the substantial evidence that sleep does vary during the course of pregnancy (Al Afif, 2016, Mindell et al, 2015), being least 'favourable' in the third trimester, and least 'unfavourable' (indeed, somewhat comparable to pre-pregnant sleep) in the second trimester, with first trimester sleep falling somewhere between the two (Al Afif, 2016, Mindell et al, 2015, Pien and Schwab, 2004), this factor alone may suffice to explain the differential distribution of sleep patterns amongst pregnant women in the UKHLS and Scott/Ciantar studies. Not withstanding the impact of differences in gestational age at sleep assessment on the sleep patterns observed in Chapters 5 and 6, it is nonetheless of some interest that the *directions* of relationships between *individual* sleep characteristics and pregnancy outcomes were very similar in both studies, and that it was only the directions of relationships between sleep *patterns* and pregnancy outcomes that differed substantially between the two groups (just as the distribution of these LCA-derived sleep patterns had varied between them). It is not immediately clear what might have made the relationships between sleep patterns and pregnancy outcomes so different in these two samples (beyond that is, the key difference in population vs. clinical sample, and [presumed] lower vs. higher risk of GDM; Von Elm et al., 2014, Monroe, 2007, Stroup et al., 2000). However, these different relationships were all independent of pre-existing health, suggesting that they were likely to be evidence of differential affects amongst (ostensibly) 'healthy' UKHLS participants and 'at higher risk' Scott/Ciantar participants. Further (and better quality) research, paying particular attention to greater standardisation in the availability of covariates and/or the timing of sleep measurement, will be required to confirm that these very different relationships are indicative of different aetiological pathways linking sleep to pregnancy outcomes in women at (presumably) negligible risk of GDM (i.e. participants from the UKHLS) and those at elevated risk of GDM (i.e. the Scott/Ciantar study participants).

7.6 Recommendations

This thesis purposely appraised evidence available from previously published studies and evaluated this before designing *de novo* empirical observational

studies that dealt with many of the limitations and flaws evident in the literature. Although this approach aimed to address weaknesses in the design and analysis of most previous studies exploring the relationship between sleep and pregnancy outcomes, there were a number of flaws that could not be addressed (or could only be incompletely addressed); and for this reason the present thesis would make a number of recommendations for further research in this area.

7.6.1 Study design

First and foremost, it is recommended that researchers undertake interventional studies to assess the potential influence of sleep on different samples of pregnant women experiencing with different metabolic (and other) risk profiles. Such intervention-based experimental studies would allow researchers to control sleep independently of health, and thereby assess the independent effect of sleep *per se.* Although this might prove difficult to achieve, particularly considering the vulnerability of both mother and foetus during pregnancy (and the special protections placed on experimentation with pregnant women), and the absence of non-pharmacological interventions with proven efficacy for addressing unfavourable sleep, such studies (not least focussing on the use of continuous positive airway pressure [CPAP], an effective treatment for sleep disturbed breathing and obstructive sleep apnoea [OSA]) will nonetheless be crucial for strengthening evidence of cause-and-effect in this context (Reid et al., 2013, Guilleminault et al., 2007, Poyares et al., 2007). Unfortunately, the cost of such studies may prove prohibitive, particularly when studying rare pregnancy outcomes that might require large numbers of participants to achieve sufficient statistical power.

In the meantime, a more cost-effective contribution might be made by more, and better, population level observational studies. To improve the quality of these (given the many flaws and limitations of the studies examined in Chapter 3), further consideration should be given to: the prevalence of the pregnancy outcomes selected; the sample sizes required to meet the needs of statistical analyses (and the level of precision desired); the measurement of (all known) covariates likely to act as powerful, potential confounders and/or competing exposures; and (perhaps) the inclusion of additional sleep measures (beyond the seven ‘core’ sleep characteristics included in the UKHLS and PSQI instruments), including those capable of recording objective assessments of sleep from ‘free living’ populations (such as actigraphy). Careful consideration of (potentially) rare pregnancy outcomes can help to improve the choice of study design to ensure the design chosen can accommodate the possibility of rare events.

Wherever possible, cross-sectional and retrospective longitudinal designs should be avoided unless these are the only choice available. This is because, with both classes of design, the temporal sequence(s) of events can be unclear, making it very challenging to distinguish between covariates acting as mediators or confounders. Similarly, careful consideration should also be given when applying a prospective longitudinal design, especially where there are multiple measurements of study covariates or when sleep measurements are available in different gestational trimesters. In both instances, multiple regression models with different covariate adjustment sets are likely to be required for each sleep measurement using sets assigned dependent on the time at which covariate measurements are made and the gestational age at which these and sleep measurements are recorded.

7.6.2 Sample size

Sample size estimations and power calculations conducted prior to sampling would help ensure the analyses based thereon have sufficient power to generate estimates of association with a lower chance of type II error and better precision than that achieved by many published studies to-date (and the two *de* novo studies presented in Chapters 5 and 6 of this thesis). However, not only are sufficient sample sizes required, but special consideration should also be given to the variability of important events amongst study participants (i.e. the prevalence of unfavourable sleep events, poor pregnancy outcomes and/or important study covariates). With insufficient observations of such events regression models will struggle to generate clear findings, and even more so with variables that have multiple categories (Irala et al, 1997). Such concerns can interfere with the appropriate adjustment for confounding as, for example, was the case in the present thesis, when women with multiple pregnancies were excluded from the UKHLS and Scott/Ciantar studies because there were insufficient participants to estimate (with any degree of precision) the differential effect of sleep on pregnancy outcomes – an important issue given that multiple pregnancy, in this instance, was considered an important potential confounder. At the same time, excluding such participants also undermines the generalisability of the studies, and this is an important consideration in its own right (Bossuyt et al., 2003).

Unfortunately, small sample sizes together with a limited number of ‘positive’ exposure or outcome ‘events’ might require researchers to reduce the number of categories examined; and this may also be necessary to optimise the numbers of confounders that can be included in underpowered samples by collapsing/reducing the categorisations of these variables in their analytical models. In the present

thesis, the latter was a strategy employed in analyses of both the UKHLS and Scott/Ciantar datasets - polytomous categorical variables being reduced to binary variables to reduce the numbers of degrees of freedom available in the multivariable regression models used. Although, reducing the number of the categories in this way might allow for better confounder adjustment (by increasing the number of categorical confounders that can be included in models applied to smaller sized samples), it is also likely to interfere with the precision of the variables concerned, and thereby the benefit of adjusting for these (Andrich,1995).

7.6.3 Study participants and setting

All researchers need to consider the risk of selection bias when choosing study participants (Nilsen et al., 2009), especially when recruitment was done within specified/restrictive contexts (such as hospital wards), rather than contexts in which a wider distribution of participants is available (e.g., in antenatal care clinics – since, in this instance, hospitalized pregnant women are much more likely to have concurrent medical conditions, better access to health care and/or worse sleep, if only as a result of staying in a working hospital). Additionally, women who are hospitalized (whether from pregnancy complications or issues with the foetus) are potentially more likely to participate in the study (due to their elevated risk of poor pregnancy outcomes), avoid participation (due to anxieties regarding their or their babies' health) or provide biased responses (whether deliberately or subconsciously, to present/understand their circumstances in terms of the issue – in this instance sleep – placed before them by the researcher).

Most published studies examining sleep and pregnancy outcomes appear to have used so-called 'convenience' samples from just one or two settings, rather than spelling out a sampling strategy and carefully considering the potential limitations of the sampling approach taken. For this reason, sampling strategies and techniques need careful consideration to address potential challenges to both external and internal validity (Rothwell, 2005; Calder et al., 1982). Furthermore, to enhance external validity, researchers might benefit from using 'general population registries' (Calder et al., 1982), albeit notwithstanding the importance of being able to determine the sequences of measured events (particularly when using DAGs to assist in the identification of confounders and mediators when using cross-sectional or retrospective longitudinal designs). Either way, researchers need to carefully focus on inclusion and exclusion criteria applied to their sampling frames (such as excluding women who cannot speak English or only including primigravida), as these are central to ensuring the intended generalizability of their studies' results (Rothwell, 2005). Descriptions of sampling strategies and

inclusion/exclusion criteria rarely were provided in adequate detail by the studies included in the systematic review conducted for the present thesis, and this, together with the limited information on the conceptualization and operationalization of key covariates (such as maternal health conditions and socioeconomic status), means that it can be extremely challenging to compare and combine estimates generated by different studies in meta-analyses capable of assessing the extent (and potential sources of) heterogeneity.

Finally, researchers are advised to study women at risk of poor pregnancy outcomes (such as women with chronic health conditions, women with multiple pregnancies and/or obese women), as these groups have thus far been neglected in the literature to date. This means that, due to their health status and any concurrent medical interventions, the evidence currently available (i.e., within published studies) cannot be generalized to them, so further research will be required.

7.6.4 Measurement of sleep and other covariates

This thesis also highlighted the potential importance of recording sleep on more than one occasion, and throughout pregnancy - especially for those participants that suffered late pregnancy events such as GDM or GHTN and/or received treatment *after* the measurement of sleep. In future, researchers should be encouraged to make multiple measurements of sleep to assess (and then make provision for) its variability, *and* to take measurements of sleep much closer to the time of outcome measurement. However, researchers will need to be careful when assessing relationships that might actually manifest as bidirectional (where sleep causes poor pregnancy effects that, in turn affect sleep) and, for this reason, avoid retrospective designs as far as is possible since the likely bidirectionality of sleep-related causal/correlational pathways make it difficult to address which variables predicts, and which mediates, the potential effect of each casual pathway. Such bidirectionality may be a particularly important consideration where researchers adopt recent advances in the specification of theoretical models (such as DAGs) prior to statistical analysis, and within the context of sleep and pregnancy outcomes, it is recommended that researchers carefully consider the gestational age(s) at which any measurements of sleep are recorded, as this inevitably determines the likely sequence of events, and thereby the choice of covariate adjustment sets and the adjustment technique that best suits the analyses (be that multivariable adjustment, stratification or restriction).

Meanwhile, since this study appears to be the first to treat sleep as a complex latent variable, it is recommended that future research examining the complex

nature and extensive variability of sleep, might want to consider using LCA-derived ‘sleep patterns’ (along the lines of Chapter 4). This may make substantial novel inroads into our understanding sleep (and its effects) since little is still known about the true nature (and function[s]) of sleep and, since the LCA-derived sleep patterns examined in the present study behaved in tantalisingly different ways in a number of analyses, as compared to analyses of individual sleep characteristics; and these differences may reflect hitherto hidden processes at play. Additionally, researchers might benefit from improving the measurement of sleep by developing, validating and extending the scope of self-reported sleep instruments, and/or augmenting these with objective measurement tools (if only for use with those aspects of sleep that are amenable to actigraphic assessment – such as the timing of sleep, sleep duration, and sleep efficiency; Van Den Berg et al., 2008, Lockley et al., 1999).

Meanwhile, special attention should be given to the referent chosen for binary or polytomous sleep variables, as results might vary depending on such variables therein (especially sleep duration). Indeed, in the literature, various studies used a variety of reference points, although the researchers involved rarely (if ever) reported why they chose their referent categories or what theories were behind their choices – and they should be encouraged to disclose these decisions explicitly. Moreover, because only a limited number of individual sleep characteristics had been measured/employed in the studies reviewed, more effort is required to ensure that hitherto under-researched characteristics (such as sleep position, latency and daytime sleepiness) receive additional attention in the future.

Likewise, attention should be paid to the measurement of study outcomes, as occasionally, two distinct variables have very similar definitions, though measurements are taken at very different time points (e.g., maternal BMI upon booking and at different time points throughout the pregnancy). As a result, the analysis of these might require different covariate adjustment sets depending on the time at which the outcome was measured and when it (had) actually/previously developed. Equally important are the measurement tools used to measure the specified outcome (e.g., the type of OGTT test used and how post-partum blood loss was measured/estimated). The categorization of outcome variables also might affect precision and accuracy (e.g., when elective and emergency caesarean section were combined in a single variable), as might the time point at which the outcome was reported/measured (e.g., a premature vs. a term birth weight.

7.6.5 Covariates adjustment and DAG

Standardising the inclusion criteria and measurement protocols for covariates would also help to tackle some of the key problems faced by the analyses

conducted in Chapters 5 (the absence of data on gestational age at questionnaire completion and on key salient confounders, not least BMI) and 6 (the focus only on sleep in the second trimester of pregnancy, and the poor quality of many of the variables extracted from medical records, not least the employment status of the pregnant woman herself).

As by far, the majority of regression models used by published studies were inappropriately adjusted (i.e. did not adjust for all measured/measurable confounders, and/or adjusted for likely mediators), the apparent associations these analyses report between sleep and pregnancy outcomes might simply be the result of unadjusted confounding and/or the influence of the reversal paradox. There is therefore still substantial need for improvements in the specification of multivariable analytical models, to ensure that such analyses are appropriately adjusted for all potential/measurable confounders (including, for example, pre-existing maternal health indicators) and no covariates likely to act as mediators. Improving covariate

Adjustment would, therefore, benefit from each of the following:

I. To reach a minimal, sufficient level of confounder adjustment, it is suggested that sufficient data be collected (with quality measurements and/or reports) so that at least one variable from each of the following temporo-functional groups can be included in the multivariable analyses: age, ethnicity, socioeconomic status, anthropometric features, mental-health indicators, maternal-health indicators, previous obstetric history, current maternal health status, current foetal health status and pre/early-pregnancy maternal behavioral risks.
II. The temporal sequence of events should be reified as pre-eminent, to allow for the identification of confounders – an important consideration given that the direction between sleep and many of the available study covariates is likely to be (potentially) or temporally bidirectional.
III. The gestational age at which sleep was measured should be carefully considered when drawing DAGs and, when needed, several DAGs (one for each gestational age-dependent sleep measurement) might need to be specified.
IV. It is important to recognize that prospective study designs might require a different DAG to those developed for retrospective study designs, for each of which, the sequence of events/measures can vary substantively.
V. When using multiple measurements of sleep, careful consideration particularly should be given to the specific sequence of events, as multiple

DAGs might be required to support the correct specification of several models (and for each ‘sleep measurement time’, as needed).

VI. Pregnancy outcomes might be better conceptualized as the consequences of events that interact *between* them, so that greater attention is given when including *any* poor pregnancy outcome as a potential predictor/covariate in the analytical models used (as is the case, e.g., when caesarean sectiondelivery as a poor pregnancy outcome might best be conceptualized as a mediator in the relation between sleep and postpartum hemorrhage).

Finally, it should be remembered that while DAGs are (or at least, can be) useful visual tools for helping researchers pre-specify their hypothesized casual pathways, and thereby correctly identify a suitable, minimally sufficient covariate adjustment set, unless these can include sufficient numbers of confounding covariates in the subsequent statistical models (and thereby be appropriately adjusted for these variables), DAGs offer little substantive improvements. Added to that, a poorly specified DAG that mis-specifies covariates acting as confounders cannot support appropriately adjusted multivariable analyses. Nonetheless, because DAGs can be drawn with variables included that have not been measured/recorded (and are, therefore, ‘latent’ and unavailable for inclusion in any subsequent multivariable statistical models), DAGs can still be ‘correctly’ specified and yet be of little ultimate use to the analyses (simply because some/all of the variables identified as potential confounders have not been measured/recorded; see Chapter 2, Section 2.4.469).

7.6.6 Analysis and data quality

During the systematic review and meta-analysis conducted for the present thesis, a good many papers were excluded because the analyses only involved unadjusted t-tests and/or chi square tests. In the future, researchers are urged to consider the power of multivariable analyses in adjusting for potential confounders (albeit when supported by well-powered samples capable of sustaining the inclusion of all necessary confounders in the multivariable statistical models used).

In the present thesis’s primary/*de novo* analyses, multivariable logistic regression was chosen as the statistical-analysis tool of choice (primarily to facilitate comparison). However, several difficulties were faced due to the small sample sizes available and the limited number of ‘positive’ events among the participants included in each study’s dataset. Researchers might, therefore, benefit from using other types of statistical-analysis models capable of estimating risk, despite the limited number of ‘events’ observed. Researchers also might benefit from using multilevel analyses to make the most of any multiple measures of sleep and/or covariates. Indeed, they might even consider using more complicated analyses,

such as structural equation models capable of estimating the additive effect of separate arcs within each causal pathway and including latent variables.

Regardless of the type of analysis chosen, each of the following issues should be carefully considered, and the results must be interpreted accordingly:

I. Power should be examined (preferably *a priori*), as many of the published estimates lack precision and were prone to type II error (Dziak et al., 2014, Freiman et al., 1978).
II. The sample size available is also of substantial importance when adjusting for confounders or running complicated analyses, since smaller (underpowered) sample sizes can undermine model stability, as well as the models' capacity to include all necessary potential confounders (Vittinghoff et al., 2006)
III. When multiple-theory testing is conducted, the *p*-value used (if it is used) might require correction before interpretation, given the increased risk of type I error (Bender and Lange, 2001).

Finally, more effort should be made to produce data of better quality (concerning not only the accuracy, but also the precision and completeness of the data), and to report data-quality limitations when publishing study findings. Although this thesis failed to use multiple imputation due to computing difficulties and a shortage of appropriate covariates, researchers might want to consider imputing any missing data using multiple imputation (to enhance the completeness of their data) and/or carefully investigating the missingness pattern as needed (before dealing with their missing data) (Van Burren, 2012; Rubin, 1996). However, researchers should do their best to prevent losing data at the point of collection, and, in the case of extracting data from medical records (in which the quality of data might be varied and vulnerable to missingness), researchers would benefit from planning any potential imputation *before* extracting their data, if only to ensure that they utilize sufficient numbers of participants (and data on a sufficient range of covariates required for imputation) to run such imputations successfully.

7.7 Contribution to the Knowledge

On 21 November 2017, while watching the ITV lunchtime news, I was surprised to hear about a health campaign to prevent still-births by educating pregnant women **not** to sleep on their backs (Lunchtime News, 2017), a recommendation based on a single study that recently had been conducted in the UK that found a two-fold elevated risk of still-births amongst pregnant women from sleeping on their back (Heazell et al., 2017). Unfortunately, this study, like so many other studies on sleep

and pregnancy outcomes, suffered multiple flaws that are likely to have interfered with the quality of the evidence collected. Nevertheless, perhaps the single largest contribution made by the present thesis was in highlighting the uncertainty of the evidence currently available and pointing out that more studies of (far) better quality are needed before we can be certain about the nature of the relationship between sleep and poor-pregnancy outcomes (as well as before designing interventions to prevent poor-pregnancy outcomes by altering pregnant women's sleep habits).

Indeed, contrary to the published literature, the present thesis found evidence to suggest that (some) unfavourable sleep events might not always be accompanied by poor pregnancy outcomes, but that occasionally, they might simply be considered symptoms of healthy pregnancy. While these findings were (like others in the underpowered analyses undertaken for this thesis) uncertain and lacked precision, the findings were evident in analyses of *both* the UKHLS pregnancy study and Scott/Ciantar study, even though these two studies comprised data from two very different populations experiencing very different levels of medical intervention. This finding supported the thesis's claim about the possibility of publication bias within the current evidence and that researchers might have published their results based on *p*-value, which examined the null hypothesis, rather than the other hypotheses, one of which might suggest that sleep sometimes was accompanied by a lower risk of pregnancy outcomes, as this thesis proposed.

Regarding a *sleep* definition, this thesis was the first to examine sleep in pregnancy as a latent variable, and interestingly, each pattern of sleep predicted poor pregnancy outcomes differently and independently of the other patterns, suggesting that little is known still about sleep and that further effort should be made to approach sleep holistically. Conveniently, this thesis created an algorithm to generate the six latent sleep patterns using participants' responses to the seven sleep questions presented in the UKHLS, then made the algorithm available for interested researchers to use in their own future analyses. Additionally, this thesis highlighted the importance of carefully choosing the reference point of sleep and the time of sleep measurements (i.e. gestational age) as both might alter the results.

Finally, this thesis was the first to examine sleep in relation to pregnancy outcomes in a high-risk population. This aspect made our thesis valuable for future researchers, who might develop a similar interest in this field, especially after knowing that this thesis highlighted most possible limitations and suggested several comprehensive recommendations to avoid these limitations, which concerned the study design, covariate adjustment, analytical models and data quality. Since this thesis proudly covered many sleep events and poor-pregnancy

outcomes, either by applying thoughtful systematic review and meta-analysis research, or by applying several *de novo* empirical studies, it might be considered a rich source of knowledge for future research, especially considering that this thesis emphasized that some unfavourable sleep events might be symptoms of a healthy progressing pregnancy.

7.8 Future steps and knowledge sharing/dissemination

At the end of this thesis, we had more questions than answers, so we hope to initiate an 'ideal' study that might answer the uncertainty of the relation between sleep and pregnancy outcomes, although one study cannot answer that, as multiple, high-quality studies are needed before reaching certainty. This proposed study should be free of the flaws and limitations of this thesis, such as being large enough to be well-powered and having a prospective longitudinal (preferably interventional) design that has multiple measurements of sleep and pregnancy outcomes over several pregnancy trimesters, although we suggest that the first sleep measurement should be taken before pregnancy to establish a baseline measurement. We proposed using different measurement tools to assess sleep to better gauge accuracy in sleep measurements (i.e., subjective, as well as objective, sleep measurements depending on the nature of the sleep characteristics, e.g., subjective measurement for quality and objective measurement for duration). Additionally, there should be a sufficient number of clinical and sociodemographic covariates with known temporal sequences to adjust for in the analysis, preferably multilevel to spot variations in sleep over various gestational ages. However, this proposed study might require long durations and plenty of resources, but as the Scott/Ciantar study started as a pilot study, we might suggest improvements and enhancements in their study for future research.

In Chapter 3, our systematic review and meta-analysis critically appraised the quality of evidence presented in the literature, highlighted possible limitations in the current knowledge about sleep and pregnancy outcomes and (cautiously) suggested the possibility of publication bias for the first time in this field. Therefore, we aim to publish our review results (while considering the possible limitations) to reflect the uncertainty in current evidence and encourage further and better research in this area.

In Chapter 4, we generated six latent sleep patterns and suggested that they were valid and stable by running several investigatory sub-studies. Later, we aim to make these generated latent-sleep cluster membership algorithms available to

other researchers to use in their own research, as this might encourage them to adopt (conveniently) the complex concept of latent sleep in their future analysis.

In Chapter 5, we examined the relationship between sleep and pregnancy outcomes, but our analyses were limited by data-quality issues and a lack of important pregnancy-related variables. Thus, the next step will be to contact the UKHLS research group to draw their attention toward the importance of reporting the gestational age when sleep is measured. Additionally, we would like to draw their attention to the importance of reporting temporal sequences of events related to pregnancy and (perhaps) suggest including further data in their pregnancy module about previous obstetric events, pre-pregnancy weight (or weight gain before sleep measurement), and current maternal and/or foetal complications. Finally, we hope to highlight the difficulties in imputing UKHLS data using multiple imputation (due to the considerable number of categories and the large number of participants), as well as advise them on the crucial importance of multiple imputation (especially when using a smaller sub-sample from the UKHLS main dataset), as the amount of missing data reduced the power of our UKHLS pregnancy study dramatically.

In Chapter 6, we examined the relationship between sleep and pregnancy outcomes in women at risk of GDM using the Scott/Ciantar study. During data extraction from medical records, accessing requested medical files was very difficult as well as time consuming, and a significant effort was made to trace missing charts. Therefore, we plan to contact the research authority in the Leeds NHS Trust to highlight the difficulties that researchers experienced trying to access data and (perhaps) to suggest creating an electronic database that might facilitate easy data access. Additionally, the quality of data presented in the medical records was lacking; thus, an effort will be made to contact health personnel, including Dr. Scott and Dr. Ciantar, regarding data quality to highlight the limitations in some variables. Finally, we aim to publish some methodological papers about strategies in data collection and suggest some methods to improve the quality of pregnancy-related data (such as collecting data from notes made during multiple visits to examine data consistency).

Last, but definitely not least, we aim to publish the results of the UKHLS pregnancy study and Scott/Ciantar study to share the fact that an alternative hypothesis exists and that researchers should make more of an effort to examine this hypothesis, rather than focus on rejecting the null hypothesis.

7.9 Conclusion

In conclusion, the present thesis found that there is only weak evidence of a relationship between unfavourable sleep events and poor pregnancy outcomes, and that all of these results lack precisions. Moreover, less favourable sleep is not always accompanied with an increased risk of poor pregnancy outcomes and, in some instances less favourable sleep has a modestly strong relation with good pregnancy outcomes. Further research using better (larger) samples, better (quality) data, and better (specified) analyses is therefore required in this area before it will be possible to achieve a degree of certainty and confidence regarding the potential role that sleep might play in the aetiology of poor pregnancy outcomes. Such research seems likely to demonstrate that many of the claims and much of the hyperbole surrounding the (apparent) association between sleep and pregnancy outcomes simply reflects publication bias.

Chapter 8 Appendix

The present chapter contains substantial additional detail relevant to each of the preceding chapters

8.1 Methodology

8.1.1 Pittsburgh sleep Quality index (Buysse et al., 1989)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

Please answer all questions. During the past month,

1. When have you usually gone to bed? _____

2. How long (in minutes) has it taken you to fall asleep each night? _____

3. When have you usually gotten up in the morning? _____

4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed) _____

	Not during the past month	Less than Once a week	Once or twice a week	Three or more times a week
5-During the past month, how often have you had rouble sleeping because you…				
a. Cannot get to sleep within 30 minutes	()	()	()	()
b. Wake up in the middle of the night or early morning	()	()	()	()
c. Have to get up to use the bathroom	()	()	()	()
d. Cannot breathe comfortably	()	()	()	()
e. Cough or snore loudly	()	()	()	()

	Not during the past month	Less than Once a week	Once or twice a week	Three or more times a week
f. Feel too cold	()	()	()	()
g. Feel too hot	()	()	()	()
h. Have bad dreams	()	()	()	()
i. Have pain	()	()	()	()
j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s):	()	()	()	()
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	()	()	()	()
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	()	()	()	()
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?	()	()	()	()
9. During the past month, how would you rate your sleep quality overall?	Very good	Fairly good	Very bad	Fairly bad

8.1.2 Comparing the UKHLS sleep module questions with the PSQI sub-study

8.1.2.1 Rationale

The UKHLS sleep module could be considered a short version of the PSQI, as it consists of questions presented in the PSQI. However, it is unknown how valid this might be. This issue will be addressed in the following section of the Appendix because this was not the main purpose of this thesis (although it was an important step in using the UKHLS sleep module questions to measure sleep).

8.1.2.2 Method

8.1.2.2.1 Data source

The UKHLS innovation panel households were selected by postcodes using a complex, multistage, random selection process. The innovation panel was designed to conduct methods testing for the mainstage component of the study, and involved a group of households randomly assigned to receive an alternative (test) survey instrument or procedure. For the comparison of UKHLS sleep module questions and those from the PSQI, the data collection method and data content were similar to those of the mainstage study discussed previously. Sleep data were available in three Waves; Waves 1, 2 and 3. The first wave of the innovation panel started 12 months prior to the first wave of the mainstage study. The third Wave was completed in 2010 and the fourth wave in 2011 (Figure 8-1).

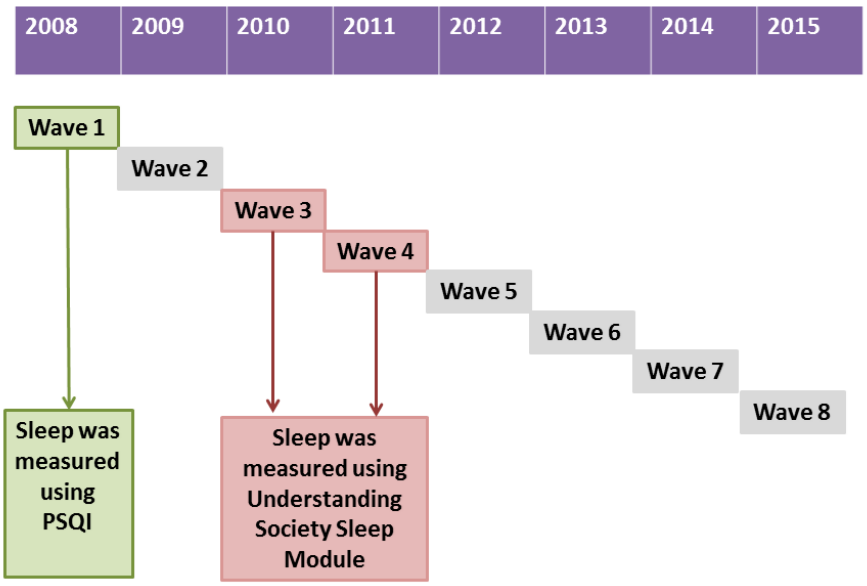

Figure 8-1 Waves of the Innovation panel data publication years and the sleep measurement tools used in the Waves of interest

8.1.2.2.2 Participants

The participants included in this comparison study were all of the adult males and females (age > 16 years) who participated in the three Waves (Waves 1, 3 and 4) of the UKHLS innovation panel , and had therefore completed each of the sleep modules and had complete data from these (n= 733; Figure 8-2; University of Essex; Institute for Social and Economic Research, 2016).

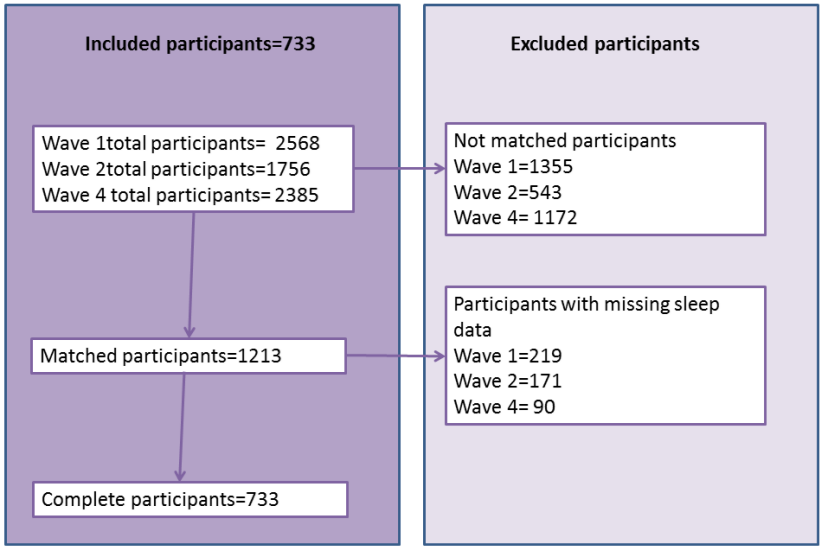

Figure 8-2 Flow chart showing the included and excluded participants in the UKHLS sleep module/PSQI comparison study

8.1.2.2.3 Sleep measurement

Sleep was measured three times during the first four Waves. The first measurement made use of the PSQI during Wave 1 of the panel; the second and third measurements used the UKHLS sleep module questions, during Waves 3 and 4 (Figure 8-1).

As summarised in Table 8-1, each question in the UKHLS sleep module was similar to a question in one of the components of the PSQI. Therefore, in the comparison study, each question in the UKHLS sleep module was compared to its equivalent component in the PSQI. However, there was no question in the UKHLS sleep module to represent sleep efficiency, and there was no equivalent component in the PSQI to evaluate sleep disordered breathing. For the comparison, it was therefore necessary to simulate a new component from questions available within the PSQI to identify participants with possible sleep-related breathing disorders. This was constructed this using two questions extracted from the ‘sleep disturbance’ component of the PSQI. These concerned

trouble with sleeping due to coughing or snoring loudly, and trouble with sleeping due to an inability to breathe comfortably. Scoring was undertaken in a similar process to that used in the original scoring of the next-day dysfunction and latency components of the PSQI (Table 8-1). In regards to the efficiency component in the PSQI, since sleep efficiency was not included in the LCAs conducted in Chapter 4 of the present thesis (since this was not available in the UKHLS sleep module) and it was not possible to construct a similar component using sleep questions present in the UKHLS sleep module.

During the LCA stage, the response categories of both the PSQI questionnaire and the UKHLS sleep module questions were standardised. Following the PSQI scoring guidelines, sleep duration was categorised as ≥ 7 hours, ≥ 6 hours but < 7 hours, ≥ 5 hours but < 6 hours, and < 5 hours. The following responses were then combined and renamed as “less than three times a week,” “less than once a week” and “once or twice a week.” By choosing this frequency of events, the intention was to match these to the International Statistical Classification of Diseases (ICD 10) diagnostic frequency for insomnia, which comprises: the frequency of an event of more than three times per week or at least once a month (World Organization Health, 1992). Quality was coded as “good” if the response to that question was good or fairly good, and “bad” if the response was bad or fairly bad.

Table 8-1 Questions present in the PSQI, and the corresponding questions present in the UKHLS sleep module

Sleep	**PSQI Sleep Questions**		**UKHLS sleep module Questions**	
Duration	**During the last month How many hours of actual sleep did you usually get at night? (This may be different than the number of hours you spend in bed)**		**How many hours of actual sleep did you usually get at night? (This may be different than the number of hours you spend in bed)**	
Coding	***Before***	***After***	***Before***	***After***
	Hours of sleep per night (hours: min)	*≥ 7 hours* *< 7 hours and ≥ 6 hours* *< 6 hours and ≥ 5hours* *< 5 hours*	*Hours of sleep per night (hours: min)*	*≥ 7 hours* *< 7 hours and ≥ 6 hours* *< 6 hours and ≥ 5hours* *< 5 hours*
Efficiency	**1. When have you usually gone to bed?** **2. How long (in minutes) has it taken you to fall asleep each night?** **3. When have you usually gotten up in the morning?** **4. How many hours of actual sleep do you get at night?**		***Was not measured in the module***	
Coding	***Before***		***After***	
	Efficiency=number of hour slept/number of	*Did not include in the LCA*		

Sleep	PSQI Sleep Questions		UKHLS sleep module Questions	
	hours spent in bed *x 100= %* *>85%=0* *75-84%=1* *65-74%=2* *<65%=3*			
Disturbance	**During the past month, how often have you had trouble sleeping because you……** 1- Wake up in the middle of the night or early in the morning? 2- Have to get up to use the bathroom? 3- Cannot breathe comfortably? 4- Cough or snore loudly? 5- Feel too cold? 6- Feel too hot? 7- Have bad dreams? 8- Have pain? 9- For some other reason? **Responses:** *a) Not during the past month (0 point)* *b) Less than once a week (1 point)* *c) Once or twice a week (2 points)* *d) Three or more times a week (3 points)* e) *More than once most night (4 points)*		**During the past month, how often have you had trouble sleeping because you……** Wake up in the middle of the night or early in the morning?	
Coding	***Before***	***After***	***Before***	***After***
	Sum of points of each question: Total =0, disturbance =0 Total =≥ 1 and ≤9, disturbance= 1 Total >9 and ≤ 18, disturbance= 2 Total>18, disturbance =3	The total was categorized into three instead of four: 0=0 1 or 2 =1 3=2	*a) Not during the past month* *b) Less than once a week* *c) Once or twice a week* *d) Three or more times a week* *e) More than once most night*	*a) Not during the past month* *b) Less than twice a week* *c) Three or more times a week*
Latency	**1-During the past month, how often have you had trouble sleeping because you……** **2-Cannot get to sleep within 30 min.? How long did it take you to fall asleep each night?** *a) Not during the past month (0 point)* *b) Less than once a week (1 point)* *c) Once or twice a week (2 points)* *d) Three or more times a week (3 points)*		**During the past month, how often have you had trouble sleeping because you……** **Cannot get to sleep within 30 min.?**	

Sleep	PSQI Sleep Questions		UKHLS sleep module Questions	
	e) *More than once most night (4 points)*			
Coding	***Before***	***After***	***Before***	***After***
	STEP 1 Q1 score: ≥ 0 and ≤ 15=0 > 15 and ≤ 30=1 > 30 and ≤ 60=2 > 60=3 **STEP2** Sum of Q1+Q2 0=0 ≥ 1 and ≤ 2=1 ≥ 3 and ≤ 4=2 ≥ 5 and ≤ 6 =3	The total was categorized into three instead of four: 0=0 1 or 2 =1 3=2	*a) Not during the past month* *b) Less than once a week* *c) Once or twice a week* *d) Three or more times a week* *e) More than once most night*	*a) Not during the past month* *b) Less than twice a week* *c) Three or more times a week*
Breathing Sleep disorders	**During the past month, how often have you had trouble sleeping because you……** **Cough or snore loudly?** **Cannot breathe comfortably?**		**During the past month, how often have you had trouble sleeping because you……** **Cough or snore loudly?**	
Coding	***Before***	***After***	***Before***	***After***
	Sum of Q1+Q2 0=0 ≥ 1 and ≤ 2=1 ≥ 3 and ≤ 4=2 ≥ 5 and ≤ 6 =3	The total was categorized into three instead of four: 0=0 1 or 2 =1 3=2	*a) Not during the past month* *b) Less than once a week* *c) Once or twice a week* *d) Three or more times a week* *e) More than once most night*	*a) Not during the past month* *b) Less than twice a week* *c) Three or more times a week*
Medication	**During the past month, how often have you taken medicine (prescribe or "over the counter") to help you sleep?**		**During the past month, how often have you taken medicine (prescribe or "over the counter") to help you sleep?**	
Coding	***Before***	***After***	***Before***	***After***
	a) Not during the past month *b) Less than once a week* *c) Once or twice a week* *d) Three or more times a week*	*a) Not during the past month* *b) Less than twice a week* *c) Three or more times a week*	*a) Not during the past month* *b) Less than once a week* *c) Once or twice a week* *d) Three or more times a week*	*a) Not during the past month* *b) Less than twice a week* *c) Three or more times a week*

Sleep	PSQI Sleep Questions		UKHLS sleep module Questions	
Sleepiness	**During the past month, how often have you had trouble staying awake while driving, eating meals or engaging in social activity?** **During the past month, how much of a problem has it been for you to keep up enthusiasm to get things?**		**During the past month, how often have you had trouble staying awake while driving, eating meals or engaging in social activity?**	
Coding	***Before***	***After***	***Before***	***After***
	Sum of Q1+Q2 0=0 ≥ 1 and ≤ 2=1 ≥ 3 and ≤ 4=2 ≥ 5 and ≤ 6 =3	The total was categorized into three instead of four: 0=0 1 or 2 =1 3=2	*a) Not during the past month* *b) Less than once a week* *c) Once or twice a week* *d) Three or more times a week*	*a) Not during the past month* *b) Less than twice a week* *c) Three or more times a week*
Subjective sleep quality	**During the past month, how would you rate your sleep quality overall?**		**During the past month, how would you rate your sleep quality overall?**	
Coding	***Before***	***After***	***Before***	***After***
	a) Very good b) Fairly good c) Fairly bad d) Very bad	a) Good b) Bad	a) Very good b) Fairly good c) Fairly bad d) Very bad	a) Good b) Bad

8.1.2.3 Analysis

First, descriptive frequency and percentage tables were used to describe the sociodemographic features and sleep characteristics of the innovation panel participants. In addition, missing data were examined for any pattern of missingness before excluding these prior to the analysis.

Second, the UKHLS sleep module and PSQI were each examined for internal consistency using Cronbach's alpha (Cronbach, 1951). Cronbach's alpha is a widely used test to measure the internal consistency of such questionnaire. The magnitude of Cronbach's alpha increases as the correlation between questionnaire items increases, since the questionnaire items measure the same construct.

Third, the Spearman correlation, which is a non-parametric test capable of assessing the monotonic relation between two ranked variables (Spearman, 1904), was chosen to examine the association between the PSQI questions and sleep component scores, as both of these were ranked variables. For the questions in the UKHLS sleep module to be substituted for the relevant PSQI components, they

should have the highest correlation with each of the relevant components and should have a low correlation with all other components.

Later, LCAs were run using Wave 1 sleep data measured by the PSQI and Wave 3 sleep data measured using the UKHLS sleep module questions, separately. In addition, these LCAs were applied twice using Wave 1 sleep data measured using the PSQI and that before and after modifying the sleep disturbance score. These LCAs were used to determine if the UKHLS sleep module and PSQI would differentiate the group of participants who were free of unfavourable sleep events from those who had them, and would describe similar numbers of clusters with a variety of different levels of severity.

Finally, the longitudinal validity of the UKHLS sleep module or the stability of sleep patterns over time was examined by repeating the LCA over Waves 3 and 4. Unfortunately, it was not possible to measure the longitudinal validity of the PSQI using LCA to compare this with the UKHLS sleep module, since the PSQI was used only once in Wave 1 of the innovation panel.

The Bayesian information criterion (BIC) was used to compare LCA models, with the model having with the lowest BIC considered to be the best-fitting model. All LCAs were performed using Latent Gold 4.5 software (Statistical Innovations Inc., 2009).

8.1.2.4 Results

8.1.2.4.1 Sociodemographic features

As seen in Table 8-2, the distribution of the participants' sociodemographic characteristics among each of the three Waves were similar. The majority of participants were females, almost 54% of whom were in all three Waves. Nearly 43% of the participants were in their forties or fifties. Around 40% had a GCSE-level of education or lower, and around 96% were white. In regard to economic status, nearly 62% of the participants were working at the time of the interview.

Sleep characteristics

Table 8-3 summaries the distribution of sleep characteristics among each of the three Waves. Sleep duration, medication use and sleep quality shared a similar distribution amongst all three Waves. More than half of the participants had a sleep duration longer, or equal, to 7 hours per day. More than 80% of the participants in the three Waves did not use medication and reported good sleep quality.

However, sleep latency, disturbance and snoring were substantially different in Wave 1, as these were measured using the PSQI component score instead of a single question. In Wave 1, around 56% of the participants reported non-habitual sleep latency using the PSQI latency component, compared to 42% in Wave 3 and 45% in Wave 4 (the latter using the UKHLS sleep module questions). When using the PSQI component to measure disturbance in Wave 1, around 90% of the participants reported non-habitual disturbance, compared to 42% in Waves 3 and 4 (when the UKHLS sleep module was used). Meanwhile, using the UKHLS sleep module to measure snoring detected around a quarter of the participants as having non-habitual snoring, while using the PSQI component score resulted in 34% with non-habitual snoring (Table 8-3). Missing data were excluded prior to the analysis after confirming that the distribution of missing data was “missing at random”. Missing at random means that there was no clustering of missing data amongst participants with certain sociodemographic features, and no dependency on missing data between any specific variables, such as age and missing data on sleep items.

Table 8-2 Sociodemographic features of subjects who participated in w1, w3 and w4 of UKHLS innovation panel

	Wave 1				Wave 3				Wave 4			
	All participants		Matched participants with complete sleep data		All participants		Matched participants with complete sleep data		All participants		Matched participants sleep with complete data	
	n=2,568	%	n=733	%	n=1,756		n=733	%	n=2,385	%	n=733	%
Gender												
Male	1,186	46.18	331	45.16	806	45.9	331	45.16	1,081	45.32	331	45.16
Female	1,382	53.82	402	54.84	950	54.1	402	54.84	1,304	54.68	402	54.84
Missing	0	0	0	0	0	0	0	0	0	0	0	0
Age												
≤19 years	139	5.41	18	2.46	94	5.35	8	1.09	149	6.25	5	0.68
20-39years	732	28.5	206	28.1	439	25	176	24.01	627	26.29	166	22.65
40-59 years	918	35.75	312	42.56	645	36.73	320	43.66	892	37.4	321	43.79
≥ 60 years	779	30.33	197	26.88	578	32.92	229	31.24	717	30.06	241	32.88
Missing	0	0	0	0	0	0	0	0	0	0	0	0
Education												
A level and above	985	38.36	336	45.84	721	41.06	349	47.61	1,145	48.01	353	48.16
GCSE level and others	1,080	42.06	307	41.88	705	40.15	301	41.06	909	38.11	299	40.79
Missing	503	19.59	0	0	330	18.79	83	11.32	331	13.88	81	11.05
Ethnicity												
White	2,269	88.36	705	96.18	1,575	89.69	705	96.18	2,091	87.67	705	96.18
Other	175	6.81	28	3.82	111	6.32	28	3.82	171	7.17	28	3.82
Missing ‘	124	4.83	0	0	70	3.99	0	0	123	5.16	0	0
Occupation												
Currently working	1,448	56.39	475	64.8	933	53.13	455	62.07	1,336	56.02	456	62.21
Currently not working	1,108	43.15	255	34.79	811	46.18	277	37.79	1,034	43.35	272	37.11
Missing	12	0.47	0	0	12	0.68	1	0.14	15	0.63	5	0.68
General health												
Excellent to good	2,029	79.01	607	82.81	1,347	76.71	589	80.35	1,835	76.94	584	79.67
Fair to poor	537	20.91	126	17.19	407	23.18	144	19.65	546	22.89	149	20.33
Missing	2	0.08	0	0	2	0.11	0	0	4	0.17	0	0

Table 8-3 Sleep characteristics of subjects who participated in w1, w3 and w4 of UKHLS innovation panel

	Wave 1				Wave 3				Wave 4			
	All participants		Matched participants with complete sleep data		All participants		Matched participants with complete sleep data		All participants		Matched participants sleep with complete data	
	n=2,568	%	n=733	%	n=1,756		n=733	%	n=2,385	%	n=733	%
Duration												
≥7 hours	1,435	55.88	488	66.58	789	44.93	442	60.3	1,118	46.88	434	59.21
≥ 6 and < 7 hours	491	19.12	184	25.1	366	20.84	201	27.42	494	20.71	202	27.56
≥ 5 hours and <6 hours	156	6.07	42	5.73	115	6.55	57	7.78	183	7.67	69	9.41
<5 hours	73	2.84	19	2.59	67	3.82	33	4.5	103	4.32	28	3.82
Missing	413	16.08	0	0	419	23.86	0	0	487	20.42	0	0
Latency												
Never	667	25.97	245	34.08	529	30.13	294	40.11	739	30.99	277	37.79
Non-habitual	1,186	46.18	406	56.47	552	31.44	309	42.16	786	32.96	331	45.16
Habitual	197	7.67	68	9.46	277	15.77	130	17.74	384	16.1	125	17.05
Missing	518	20.17	0	0	398	22.67	0	0	476	19.96	0	0
Disturbance												
Never	102	3.97	30	4.09	230	13.1	126	17.19	423	17.74	151	20.6
Non-habitual	1,735	67.56	689	94	561	31.95	315	42.97	799	33.5	312	42.56
Habitual	19	0.74	14	1.91	576	32.8	292	39.84	688	28.85	270	36.83
Missing	712	27.73	0	0	389	22.15	0	0	475	19.92	0	0
Snoring												
Never	1,249	48.64	453	61.8	795	45.27	445	60.71	1,258	52.75	499	68.08
Non-habitual	682	26.56	252	34.38	310	17.65	177	24.15	390	16.35	163	22.24
Habitual	127	4.95	28	3.82	212	12.07	111	15.14	218	9.14	71	9.69
Missing	510	19.86	9	0	439	25	0	0	519	21.76	0	0
Medication												
Never	1,726	67.21	605	82.54	1,177	67.03	644	87.86	1,658	69.52	651	88.81
Non-habitual	164	6.39	42	5.73	83	4.73	39	5.32	135	5.66	45	6.14
Habitual	256	9.97	86	11.73	106	6.04	50	6.82	127	5.32	37	5.05
Missing	422	16.43	0	0	390	22.21	0	0	465	19.5	0	0
Sleepiness												
Never	980	38.16	338	46.11	1,116	63.55	601	81.99	1,606	67.34	616	84.04
Non-habitual	1,087	42.33	380	51.84	215	12.24	114	15.55	281	11.78	106	14.46
Habitual	47	1.83	15	2.05	28	1.59	18	2.46	34	1.43	11	1.5
Missing	454	17.68	0	0	397	22.61	0	0	464	19.45	0	0
Quality												
Good	1,707	66.47	587	80.08	1,053	59.97	570	77.76	1,447	60.67	567	77.35
Poor	464	18.07	146	19.92	325	18.51	163	22.24	478	20.04	166	22.65
Missing	397	15.46	0	0	378	21.53	0	0	460	19.29	0	0

8.1.2.4.2 Results of internal consistency analysis

The internal consistency of the UKHLS sleep module questions, as measured by the Cronbach's alpha coefficient, was 0.936 using Wave 3 data and 0.980 using Wave 4 data. The Cronbach's alpha of the PSQI was 0.54. The inter-item correlation between the PSQI items and each of their respective components is presented in Table 8-4. The sleep latency component had the highest correlation with "the length of sleep latency in minutes" question (r = 0.81). Sleep disturbance had its highest correlation with "Wake up in the middle of the night or early in the morning?" (r = 0.54). The "next-day sleepiness" component had its highest correlation with "How much of a problem has it been for you to keep up enthusiasm to get things done?" (r = 0.89). The breathing-related sleep disorders component had the highest association with "cough or snore loudly" (r = 0.89).

Table 8-4 Spearman correlation coefficients between each of the PSQI components and questions used to collect sleep data in Wave1 of the UKHLS innovation panel.[1]

		Sleep duration	Sleep latency	Sleep disturbance	Breathing sleep disorders	Next day dysfunction	Sleep medication	Subjective quality
Sleep duration	Sleep duration in hours and minutes	**-0.834**	-0.178	-0.066	-0.096	-0.113	-0.058	-0.344
Sleep latency	a) Minutes of latency	0.277	0.807	0.243	0.010	0.139	0.1047	0.379
	b) Frequency of latency	0.293	**0.909**	0.336	0.138	0.236	0.142	0.484
Sleep disturbance	a) Early or mid night disturbance	0.273	0.318	**0.542**	0.154	0.175	0.104	0.477
	b) Usage of bathroom	0.091	0172	0.513	0.211	0.088	0.045	0.197
	c) Breathing difficulty	0.091	0.141	0.300	0.661	0.223	0.147	0.263
	d) Snoring or coughing	0.051	0.033	0.249	**0.892**	0.136	0.142	0.120
	e) Feeling too cold	0.060	0.134	0.399	0.163	0.214	0.123	0.142
	f) Feeling too hot	0.070	0.198	0.503	0.277	0.242	0.094	0.214
	g) Dream	0.078	0.196	0.388	0.188	0.238	0.116	0.217
	h) Pain	0.148	0.220	0.527	0.299	0.225	0.269	0.289
	i) Other reason	0.140	0.187	0.399	0.099	0.256	0.093	0.311
Day dysfunction	a) Day sleepiness	0.119	0.061	0.224	0.151	0.667	0.140	0.202
	b) Enthusiasm	0.194	0.472	0.321	0.213	**0.886**	0.129	0.338
Sleep medication	Sleep medication	0.078	0.107	0.076	0.125	0.086	**1.000**	0.179
Subjective quality	Subjective quality	0.386	0.306	0.128	0.125	0.246	0.179	**1.000**

[1] Bold text highlights the highest correlation levels between the PSQI indicators and their components

8.1.2.4.3 Results of latent class analysis

The latent sleep model with four clusters was chosen as the best-fit model when using sleep data collected using the UKHLS sleep module from participants in Waves 3 and 4 (Table 8-5). Both latent models that resulted from running the LCA using the UKHLS sleep module and data from Waves 3 and 4 had similar cluster patterns; and in two of these clusters (1 and 3) the patterns were identical. However, the two latent models differed in the subjective sleep quality pattern in cluster 2; its pattern changing from "good" to "bad" from Wave 3 to Wave 4. In addition, they differed in terms of sleep duration, which changed from 5–6 hours to 6–7 hours from Wave 3 to Wave 4 (Table 8-6 and Table 8-7).

Table 8-5 BIC of latent sleep models with different numbers of clusters resulting from exploratory latent class analyses of data from Waves 1, 3 and 4 of the UKHLS innovation panel.

		W1 PSQI original disturbance score	W1 PSQI modified disturbance score	W3 UKHLS sleep module	W4 UKHLS sleep module
Clusters	**Number of parameters**	**BIC**	**BIC**	**BIC**	**BIC**
1	14	10079	10025	10573	10754
2	22	**9631**	9576	9908	10001
3	30	9637	9585	9851	9955
4	38	9656	**9564**	**9827**	**9933**
5	46	9667	9598	9839	9978
6	54	9704	9632	9882	10002
7	62	9741	9667	9902	10039

Bold text indicates the chosen value for BIC after considering the number of parameters

Table 8-6 Latent sleep model with four clusters using data from Wave 3 of the innovation panel (i.e. sleep data collected using the UKHLS sleep module questions).

	Cluster 1 47.30%	Cluster2 31.27%	Cluster 3 12.74%	Cluster4 8.69%
Duration	≥ 7 hours 0.8344	6-7 hours 0.4460	≥ 7 hours 0.6977	5-6 hours 0.3423
Latency	<3 nights/week 0.4838	<3 nights/week 0.5722	No events/week 0.9008	≥ 3 events/week 0.9642
Snoring and coughing	No events/week 0.6413	No events/week 0.5229	No events/week 0.8475	No events/week 0.3386
Disturbance	<3 nights/week 0.7030	≥ 3 events/week 0.7257	No events/week 0.9828	≥ 3 events/week 0.9661
Sleepiness	No events/week 0.8868	No events/week 0.7652	No events/week 0.8698	No events/week 0.5941
Medication	No events/week 0.9207	No events/week 0.8408	No events/week 0.9634	No events/week 0.6217
Quality	Good 0.9994	Good 0.5646	Good 0.9462	Bad 0.9930

Table 8-7 Latent sleep model with four clusters using data from Wave 4 of the innovation panel (i.e sleep data collected using the UKHLS sleep module questions).

	Cluster1 56.87%	**Cluster2 16.19%**	**Cluster3 15.58%**	**Cluster4 11.36%**
Duration	≥ 7 hours 0.7270	≥ 7 hours 0.7554	6-7 hours 0.3443	6-7 hours 0.3714
Latency	< 3 nights/week 0.6075	No events/week 0.9668	≥ 3 nights/week 0.8591	< 3 nights/week 0.5876
Snoring and coughing	No events/week 0.6591	No events/week 0.9351	No events/week 0.5229	No events/week 0.5373
Disturbance	< 3 nights/week 0.6039	No events/week 0.8048	≥ 3 nights/week 0.8864	≥ 3 nights/week 0.6041
Sleepiness	No events/week 0.8958	No events/week 0.9097	No events/week 0.7421	No events/week 0.6579
Medication	No events/week 0.9088	No events/week 0.9528	No events/week 0.7421	No events/week 0.8097
Quality	Good 0.9903	Good 0.9885	Bad 0.8295	Bad 0.7801

After using the PSQI with a modified disturbance scoring to generate sleep patterns in Wave 1 (i.e., after excluding questions related to sleep-related breathing disorders), the latent sleep model with four clusters was chosen as the best-fitting sleep model (see Table 8-8). On the other hand, when we used the PSQI with the original sleep disturbance scoring, the best-fitting model was that with two clusters (Table 8-9). These two clusters were similar to clusters 1 and 3, resulting from the latent analysis of PSQI-derived data with a modified disturbance score. The first cluster of the two clusters common to the modified and original PSQI was characterised by prolonged latency and increased disturbance, while the second cluster was characterised by shorter sleep duration, prolonged latency, the presence of snoring, next-day sleepiness, increased disturbance, and bad subjective sleep quality. None of the clusters in either version of PSQI were therefore free from unfavourable sleep events.

The sleep clusters generated using the PSQI data were different to those resulting from the UKHLS sleep module questions, except for cluster 1, which was characterised by the presence of sleep latency and sleep disturbance, with a frequency of less than three nights per week. This common cluster represented more than half of the population across each of the Waves.

Table 8-8 Latent sleep model with four clusters using data from Wave 1 of the innovation panel (i.e. sleep data generated using the PSQI with modified disturbance component scores).

	Cluster 1 54.54 %	**Cluster2 37.46 %**	**Cluster3 62.10 %**	**Cluster4 17.90 %**
Duration	≥ 7 hours 0.8553	≥ 7 hours 0.4631	6-7 hours 0.3220	≥ 7 hours 0.4986
Latency	<3 nights/week 0.5213	<3 nights/week 0.7175	≥ 3 nights/week 0.8475	< 3 nights/week 0.6661
Snoring and breathing	No events/week 0.7430	No events/week 0.4917	<3 nights/week 0.5289	<3 nights/week 0.6975
Disturbance	<3 nights/week 0.8978	<3 nights/week 0.8568	<3 nights/week 0.7432	≥ 3 nights/week 0.9192
Sleepiness and enthusiasm	No events/week 0.6462	<3 nights/week 0.7249	<3 nights/week 0.7137	<3 nights/week 0.6611
Medication	No events/week 0.8920	No events/week 0.7683	No events/week 0.5937	≥ 3 nights/week 0.6371
Quality	Good 0.9997	Good 0.6512	Bad 1.9787	Bad 0.8165

Table 8-9 Latent sleep model with four clusters using data from Wave 1 of the innovation panel (i.e. sleep data generated using the PSQI with original disturbance component scores).

	Cluster 1 68.58%	**Cluster 2 31.42%**
Duration	≥ 7 hours 0.8045	6-7 hours 0.4026
Latency	< 3 nights/week 0.5396	< 3 nights/week 0.6505
Snoring and coughing	No events/week 0.7052	< 3 nights/week 0.4986
Disturbance	< 3 nights/week 0.8819	< 3 nights/week 0.7774
Sleepiness	No events/week 0.5729	< 3 nights/week 0.7341
Medication	No events/week 0.8821	No events/week 0.6713
Quality	Good 0.9963	Bad 0.6485

8.1.2.5 Discussion

In this study, the UKHLS sleep module was examined as a shorter version of the PSQI, in order to enhance our understanding of sleep behaviours when generating latent sleep patterns from data in the UKHLS, and how these might be applied to pregnant participants in the UKHLS and Scott/Ciantar study. The relevance of examining the PSQI in this was stemmed from its widespread use as perhaps the most used sleep quality questionnaire, but which has proven to be unwieldy for use in large population surveys due to the presence of several items with a long, poorly

justified and poorly conceptualised score algorithm. Unlike the PSQI, no scoring system had been developed for the UKHLS sleep module questions, and this is what led to studying this using LCA.

The internal consistency of the UKHLS sleep module questions was also examined and found to be excellent; in contrast to the PSQI, which showed only moderate internal consistency. The PSQI was reported by other researches to have an internal consistency ranging from anywhere between 0.5 to 0.8 (Carpenter and Andrykowski, 2016, Beck et al., 2004, Carpenter and Andrykowski, 1998). With a higher internal consistency evident in the UKHLS sleep module questions, this might reflect that its questions were better correlated and perhaps better on measuring just one construct/characteristic at a time – suggesting that the UKHLS sleep module questions offered a stronger basis with which to detect sleep patterns once each of these constructs/characteristics were considered.

In this sub-study the correlation between each of the PSQI items and their respective components were examined to verify if the UKHLS sleep module questions were similar to those in the PSQI. The high correlations obtained indicate the strength of associations between variables from each of these 'questionnaires, meaning that as the level of the first variable changes, the second will change accordingly and, as a result, one of these variables can be substituted for the other (notwithstanding the linguistic validity of the substituted item to represent the relevant component in the other).

In the following section the linguistic validity of the UKHLS sleep module questions will be discussed with regard to their representation of the relevant PSQI components and their subsequent diagnostic value. The question, "How many hours of actual sleep did you usually get at night during the last month?" from the UKHLS sleep module is identical to question 4 in the PSQI, which aims to measure subjective sleep length. Yet there were other questions in the PSQI for calculating actual sleeping time. Actual sleeping time differs from the time spent in bed, which many participants appeared to have usually recorded instead. Time spent in bed included the actual time spent in bed, time needed to fall asleep (latency), and time wasted in disturbed sleep (Olds et al., 2010). Although the UKHLS sleep module questions do not measure the actual time spent sleeping, it has questions to estimate the frequency of sleep latency and disturbance, which facilitate greater understanding of the sleep patterns involved. That said, the lack of accuracy in the measurement of actual sleeping hours appeared to have had an effect in the form of measurement error when generating the latent sleep clusters and examining their stability over time. Sleep duration had a low mean probability in the allocated

cluster (i.e., the certainty that the mean length of sleep duration of participants belonging to a certain cluster was within that reported category). In addition, the measurement error of sleep duration might be reflected in the instability of a sleep duration pattern within clusters over Waves. Even so, the stability was a matter of one to two hours, which was the difference between adjacent categories.

The question to determine if participants “cannot go to sleep within 30 min” is identical to question 5 from the PSQI, which identifies the frequency of sleep latency and is used to calculate the latency component after adding the score of the question concerning “the length of sleep latency in minutes”. Delayed Phase Circadian Rhythms Disorder patients differed from primary insomnia patients by their recurrent or chronic sleep difficulties in sociable acceptable time. Delayed Phase Circadian Rhythms Disorder patients developed sleep latency whenever they were requested to sleep in time that mismatch their endogenous regulatory cycle (Barion and Zee, 2007). This difference between the two conditions may be difficult to spot thorough the UKHLS sleep module or PSQI questionnaires. People who suffer from jet lag disorder have a misalignment between their endogenous clock and their new environmental exogenous clock as a result of travelling. This misalignment causes them to suffer from sleep latency (Bjorvatn and Pallesen, 2008). However, this cause of latency cannot be diagnosed using the two questionnaires. The PSQI scoring for the latency component seems to overestimate the severity of latency (sensitive), as the cluster with no abnormal latency pattern was absent among the latent sleep clusters.

The question concerning sleep disturbance, by which the participant “wake[s] up in the middle of the night or early in the morning,” is identical to Q5b in the PSQI, which seeks, in addition to other questions, to define sleep disturbance. Unfortunately, this question joins two different aspects of sleep disorders: early waking and interrupted sleep. The early waking after uninterrupted sleep is a symptom of Advanced Phase Disorder that is one of a circadian rhythm disorders (Bjorvatn and Pallesen, 2008, Barion and Zee, 2007). Whereas early waking after disturbed sleep may reflect primary insomnia (American Psychiatric Association, 2000). By contrast, disturbed sleep without early waking is seen in breath sleep disorders and neurological sleep disorders patients (Kryger et al., 2011, American Psychiatric Association, 2000). Similar to the latency score, the PSQI scoring for the disturbance component seems to overestimate the severity of the disturbance (sensitive), given that the cluster with a normal disturbance pattern was absent among the latent sleep clusters.

The question concerning those participants who “cough or snore loudly” is identical to Q5c in the PSQI, which, in addition to the question concerning the “presence of breathing difficulty,” seeks to discover sleep disturbances secondary to Obstructive Sleep Apnoea (OSA). Although not included in the PSQI score, the PSQI had several questions evaluating the bed-partner’s attitude in regards their partner’s snoring, as an individual may not be aware of his or her sleeping behaviour. Snoring may be a symptom of OSA, which is occasionally linked with serious diseases like heart and lung diseases (Kryger et al., 2011, American Psychiatric Association, 2000). Snorers usually distinguished from the OSA patients by the absence of interrupted sleep and daytime sleepiness (American Psychiatric Association, 2000). Coughing is a symptom of respiratory or cardiovascular diseases in addition to OSA, so including it in the question might decrease the specificity to those with OSA (i.e., a false positive would result).

The question “During the past month how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?” is identical to Q8 from the PSQI, which is designed, in addition to the question concerning “the level of enthusiasm,” to evaluate daytime dysfunction. Daytime sleepiness may be a symptom of either fragmented nocturnal sleep or narcolepsy. Fragmented nocturnal sleep is seen in primary insomnia and OSA patients (American Psychiatric Association, 2000). Narcolepsy patients have prolonged and undisturbed nocturnal sleep, while they have day time that is unexpected and accompanied with hallucinations and catalepsy or muscle paralysis (American Psychiatric Association, 2000). The day time sleep in narcolepsy is refreshing and differentiates narcolepsy from other reasons of daytime sleepiness. However, refreshing day sleepiness of narcolepsy should not be mistaken with normal daily naps (American Psychiatric Association, 2000). Falling asleep during daily activities indicates an advanced state of sleep deprivation or the presence of a sleep disorder, thus falling asleep during activities might be used to differentiate between those with and those without a severe form of sleep disturbance.

The question “During the last month how often have you taken medicine (prescribed or over the counter) to help you sleep?” is identical to Q6 from the PSQI. A limited number of questionnaires cover sleep medication. Usage of sleep medications decrease sleep latency and improve quality but decrease morning alertness and may alter behaviour (Parrott and Hindmarch, 1980). Knowing about the usage of sleep medication explains the severity of the associated unfavourable sleep events and allows the researchers to adjust for the effect of sleep medications on sleep quality. However, this question might mislead by including

an “over the counter” in the question, as participants might interpret herbs, such as chamomile taken in tea, as medicine.

The question “During the past month how would you rate your sleep quality overall?” is identical to Q6 in the PSQI, which aims to evaluate a person’s attitude toward his or her sleep quality. Poor sleep quality is a complaint in patients with OSA, neurological sleep disorders, primary insomnia (American Psychiatric Association, 2000) and in night-shift workers. Night shift worker’s poor sleep quality appears in the form of “shortened sleep, fatigue, decreased alertness” (Bjorvatn and Pallesen, 2008).

As indicated from the foregoing discussion, the ability of the two questionnaires to describe sleep patterns differed. The PSQI was more sensitive to detecting sleep disturbance and latency than the UKHLS sleep module. The sensitivity of PSQI might be reflected in the LCA by the absence of a sleep pattern without latency or disturbance. Day sleepiness and usage of medication indicated severe sleep abnormalities that, unlike the UKHLS sleep module, the PSQI was able to detect. This might be due to its sensitivity in detecting sleep disturbance and latency; thus, as the number of participants with sleep disturbance and latency increased, the probability of detecting and describing those participants who suffered from day sleepiness and who used medication increased as well. However, due to the small sample size, there might not be enough participants who shared severe forms of sleep abnormalities in all components, so no cluster that had all abnormal sleep characteristics was identified. Unfortunately, neither the PSQI nor the UKHLS sleep module were able to diagnose sleep disorders, as both lack diagnostics questions that are required to differentiate between sleep disorders that share similar characteristics. However, the UKHLS sleep module showed a greater range of patterns and less sensitivity than the PSQI, which might be useful in surveys that are interested in depicting the variations in sleep patterns, rather than in clinical sittings that require a diagnosis of sleep disorders.

In considering how much the included items in the UKHLS sleep module represent the corresponding components in the PSQI, we examined the correlation between the included items and the relevant component. The PSQI items that were included in the UKHLS sleep module had higher correlations with their relevant component scores than the items that were not included in the UKHLS sleep module. In addition to the correlation, the included items in the UKHLS sleep module should be comprehensive and serve the lingual and diagnostic purposes of the components they will substitute.

The correlation value between the “frequency of the latency” question and the latency component was very close to the correlation between the “minutes of sleep latency” question and the latency component score. However, the former question was more comprehensive, as it covered both the presence of prolonged latency (> 30 min.) and the frequency of latency. The correlation between the frequency of mid-night or early-morning disturbances and the disturbance component was very close to the correlation between the frequency of the disturbance secondary to using the bathroom or pain. However, the frequency of mid-night or early-morning disturbances was more representative and comprehensive of the disturbance component than disturbance secondary to bathroom usage or pain, as the latter appears in special occasions, such as pregnancy or old age. Including these two questions in the UKHLS sleep module to cover latency and disturbance components rather than the other questions that had almost similar correlations was a better choice, as those two questions had more comprehensive information than the other questions in the same components.

The next-day sleepiness (level of alertness) item was related more to sleep than next-day dysfunction or enthusiasm, as the latter might be secondary to many causes, such as mood disorders or poor health. We generated a component relating to breathing disorders, for which we used two questions that were part of the disturbance component. These questions concerned disturbance due to breathing difficulty and disturbance secondary to snoring. The snoring item had the highest correlation among the two questions with the calculated component score. In addition, it was more sensitive than the “breathing difficulty” item in screening for sleep breathing disorders. The use of the two questions was a specific method by which to identify those with sleeping disorders who could not be identified through assessment for snoring alone.

Considering the result of the latent class analysis, we find that the cluster patterns resulting from the PSQI and the UKHLS sleep module were different except for one cluster, which included more than half of the participants. The PSQI was very sensitive to the presence of disturbance and latency, and perhaps overestimated their presence, as there is no cluster that has an absence of unwanted sleep events. By examining the variability of the sample, the percentage of participants who reported unfavourable sleep events with a frequency of more than 3 nights per week was limited. As a result, it would be expected from the LCA based on the UKHLS sleep module that the cluster that is characterised by restricted sleep duration (< 5 hours), bad quality, and unfavourable sleep events with a frequency ≥ 3 night per week would not be observed, due to the expected small size of that cluster.

In summary, the UKHLS sleep module provides an acceptable comprehensive screening for sleep and can be used as a short version of the PSQI, especially in large-scale surveys. However, the UKHLS sleep module cannot be used as a diagnostic tool for causes of poor sleep, as it lacks many diagnostic questions needed to differentiate between several sleep disorders.

8.2 Systematic review and meta-analysis

8.2.1 Aspects of quality assessment of results

The focus of these quality assessments was the analytical validity of the published results and the absence/presence of any potential biases, rather than the overall quality of the published articles. However, as most of the current published studies were designed to assess the quality of published papers, we decided to generate guidelines that focused on the quality of the results instead of the quality of the publication. Thus, we designed the guidelines based on other published checklists, although we included only aspects that might interfere with the internal and/or external validity of the results.

8.2.1.1 Generating a bespoke biases assessment guideline

8.2.1.1.1 Searching for current quality assessment tool

During our quality assessment of resultant observational studies, we generated bespoke guidelines. The aim of the guidelines was to ensure that we covered all issues that might bias the final estimates, instead of focusing on the quality of the published papers. To achieve this, Google Scholar and Medline searches were undertaken to look for any observational study-quality assessment tool that was published before the end of 2014 (i.e., the beginning of our doctoral studies)[7]. In the beginning, 32 tools were found, but 20 were excluded for not being validated. Seven also were excluded, as they were designed for specific types of studies other than medical observational studies (e.g., RCT). In the end, five were chosen: ‘Quality of reporting of observational longitudinal research checklist’ (Tooth et al., 2005), ‘EPHPP statement’ (Thomas et al., 2004), ‘STROBE statement’ (Von Elm et al., 2014), ‘Scottish Intercollegiate Guidelines Network (SIGN) checklists’ (SIGN, 2012) and ‘MOOSE statement’ (Stroup et al., 2000; Figure 8-3)

[7] Please note that this search was not a typical systematic search as the aim was not to generate a validated assessment tool instead the aim was to generate a simple useful guideline that will help in assessing the biases in the published results (instead of the quality of published papers) to use in this thesis.

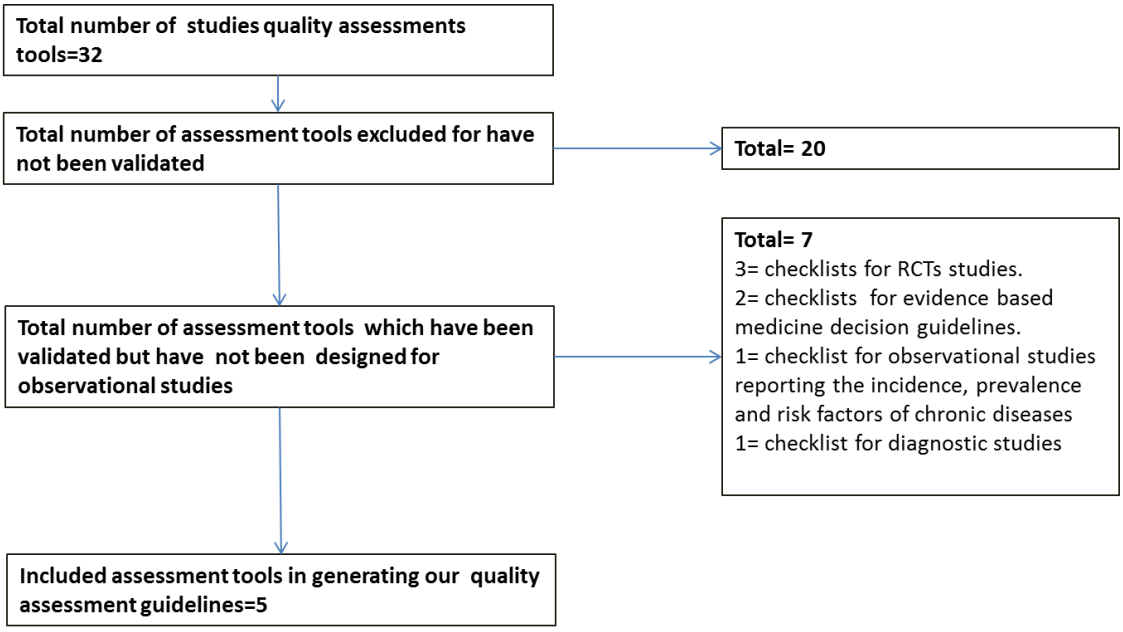

Figure 8-3. Flow chart showing the number of included assessment tools

8.2.1.1.2 Application of the bespoke guideline in the assessment of biases

The 34 sleep and pregnancy studies found through a systematic search were all included in the review, but not all regression models were included in the meta-analysis, as each extracted regression model was evaluated carefully for the possibility of adjustment bias before being considered for inclusion in the final adjusted meta-analysis (Figure 8-4). Although all the resultant sleep and pregnancy-outcome studies were included in the review, the results of the review were determined after considering limitations and biases inherited from primary studies. These limitations and biases were highlighted based on the bespoke guidelines generated from the five quality-assessment checklists. The six aspects we focused on were:

1) measurement bias;
2) confounding bias;
3) selection bias and generalizability of results;
4) multiple testing and type I errors;
5) sample size and type II errors; and
6) quality of results.

Finally, the results of the review were assessed for publication bias after examining the quality of the included sleep and pregnancy outcomes' primary studies. A summary of the bespoke guidelines is presented in (Table 8-10)

8.2.1.2 Illustration of the bespoke bias assessment guideline

The bespoke bias-assessment guidelines covered six aspects of biases and considered publication bias. The list of guidelines could be found in Table 8-10, and in the following section, an illustration is provided on the aspects that were considered during quality assessments.

Each outcome and/or exposure of interest was evaluated to see if it was the main outcome or exposure of the assessed study. The power of the analysis and the strategy of the study design depended on the rate of the main outcome and/or exposure of the study (Faul et al., 2009, Demidenko, 2006). If the outcome or exposure was the main one, the study design was assessed for its type, as randomized controlled trial (RCT) studies were the most favorable, followed by cohort studies, case control studies, and cross-sectional studies. However, an RCT can be difficult to perform due to ethical reasons, especially during pregnancy (Khan et al., 1999). For that reason, it might be expected that there would be limited numbers of RCT studies in regard to pregnancy outcomes. However, if the outcome or exposure of interest were a secondary outcome or exposure that was published due to its statistical significance (i.e., the outcome or exposure was not considered when developing the study design and choosing the sample size), the result was examined for the following: presence of selection bias or unadjusted confounders; prevalence of the exposure and the outcome (rare events); presence of type II errors (the power of the test); and the correction of the *p*-value for multiple testing (type I error). Selection bias may have been a factor in choosing the study population based on a characteristic of interest—for instance, high pregnancy BMI. High pregnancy BMI is a mediator for early trimester sleep breathing disorders (SBD), and adjusting for high BMI or excluding women with high BMI from the analysis might bias the estimate. In contrast, late pregnancy SBD can be precipitated by high BMI, and not adjusting for high BMI can lead to confounding bias. In the case of rare events such as stillbirth, the study should be designed to ensure a sufficient number of events to detect the association with sufficient power—for example, by using a case control study design or by increasing the length of the study period in the prospective longitudinal study. Not considering the limited number of positive events in the design or the analysis can bias the estimate, cause a wide confidence interval regardless of the sample size, and increase the possibility of type II errors (Abeysena et al., 2009). Calculating the sample size is very important for providing sufficient power to reject the null hypothesis (Freiman et al., 1978) or to reduce type II errors. In the case of multiple testing, due to the presence of more than one exposure and/or outcome,

consideration should be given to the alpha level, to reduce the chance of type I errors (Cronbach, 1951, Bonferroni, 1936).

Inclusion and exclusion characteristics of the included participants were evaluated, as restricting a study to one group can affect the generalisability of the result; for instance, restricting the sample to snoring women could prevent generalising the results to non-snoring women (Bossuyt et al., 2003).

The measurement tool used was examined for the possibility of measurement error and the feasibility and timing of the measurement (i.e., the gestational age when the measurement was taken). Objective measurements (such as polysomnography (PSG)) may have less measurement error than subjective measurements (such as sleep questionnaires), when considering sleep quantity or the presence of SBD. On the other hand, subjective measurements are more comprehensive and informative when measuring other sleep characteristics, such as usage of sleep medication, lack of day refreshment, and sleep satisfaction. However, accuracy and usage of subjective measurements can vary as well—for instance, sleep diaries. Unlike questionnaires, sleep diaries can measure daily fluctuations in sleep characteristics. Nevertheless, sleep questionnaires are easier to analyze than sleep diaries, as the responses in the questionnaires are linked with numbers that can be utilised in analysis.

With regard to feasibility of the measurement tool, PSG—which is considered superior to other measurements of sleep duration—is difficult to apply over a long period of time. Because of that, it could be difficult to find many prospective longitudinal studies using PSG, especially when recurrent measurements of sleep were taken. In addition, a PSG device can be uncomfortable to wear during sleep, which might lead to shortened and fragmented sleep, especially in heavily pregnant women who already find it difficult to sleep with an enlarged uterus. It was important to consider the timing of measurements of sleep characteristics. Variables that precipitate unfavorable sleep events in the late trimester can work as mediators for unfavorable sleep events developed in the early trimester, such as high pregnancy BMI and gestational diabetes. In addition, considering the variability of sleep during pregnancy, it could be recommended to measure sleep more than once during pregnancy, depending on the study design and duration. However, that might not be feasible or easy to achieve, especially for a large population sample with objective sleep measurements or in high-risk groups whose study compliance might be a concern.

The definitions of sleep characteristics used, pregnancy outcomes, and included study covariates were considered when comparing the results of studies. Several

studies used different cut-off points to define normal and abnormal sleep events. For instance, a sleep duration longer than 9 hours per night was considered abnormally long in some papers, and a duration longer than 8 hours was abnormal in others. Similarly, pregnancy outcomes such macrosomia and Apgar scores were defined using different reference points. In some papers, different variables were considered to be similar; for instance, low birth weight and small for gestational age as references to low birth weight are equally applicable for term and preterm babies, while small for gestational age, premature, and term babies had different reference weights. In addition, it was noticed that two outcomes with different mechanisms were combined under one title—for example, preeclampsia and pregnancy-induced hypertension. With regard to covariates, the single most important factor in the definition was the timing—for instance, gestational age and late pregnancy events. Gestational age when sleep was measured could be a possible competing exposure, while gestational age when the outcome was measured might be a possible mediator, depending on the study hypothesis and design.

Studies were evaluated for the presence of a confounding bias. Confounders can be adjusted during the study design or the analysis. Adjustment can be achieved by restricting the study to a certain population, stratifying the study population into sub-groups based on a character of interest, or by using multivariable regression analysis. Study design can affect the amount of confounders present. Observational studies—either cross sectional studies or longitudinal studies—may have many unadjusted confounders in the study design, and careful adjustment is required. Randomized controlled trials adjust for confounders in the design by randomly assigning individuals to groups; however, unconsidered confounders could affect the subsequent study estimate (for instance, participants' height and BMI; (Attia, 2005); for instance, limiting stratification of the data based on obesity might limit the generalisability of the results to women of normal weight. In addition, stratifying the sample could affect the power and the level confidence in the estimate.

Adjustments of the regression models were evaluated with regard to the choice of the adjusted confounders and the level of adjustment. Adjustment can be classified as suitable, under-adjusted, unadjusted, and over-adjusted. Suitable adjustment was defined as including the minimum acceptable number of confounders; however, it might be difficult to cover all confounders, due to several limitations (e.g., a limited number of participants or unavailable measurements in the data registry). The regression models in the majority of the studies, especially cross-sectional studies or studies without a control group, were considered under-

adjusted. Under-adjusted models were those that did not have all the minimum acceptable confounders. Unadjusted or under-adjusted models might have a confounding bias that overestimates or underestimates the association between the exposure and the outcome of interest (Psaty et al., 1999). In over-adjusted models (which include variables that are not confounders, such as competing exposures or mediators), the unnecessary adjustment of variables might bias the estimate when the model contains mediators (intermediate variables between the exposure and the outcome that mediate the effect of the exposure on the outcome; (Schisterman et al., 2009). However, including competing exposures (variables that affect the outcome but are not related to the main exposure of interest), should not bias the estimate but might narrow the CI level of the estimate and improve precision (Textor and Li´skiewicz, 2017). The number of adjusted confounders should be in proportion to the sample size, as including too many confounders might affect the stability of the regression models and lead into inaccurate estimation (Vittinghoff and McCulloch, 2006, Peduzzi, 1995). Finally, data were evaluated for quality, ability to answer the research question, and presence and treatment of missing data

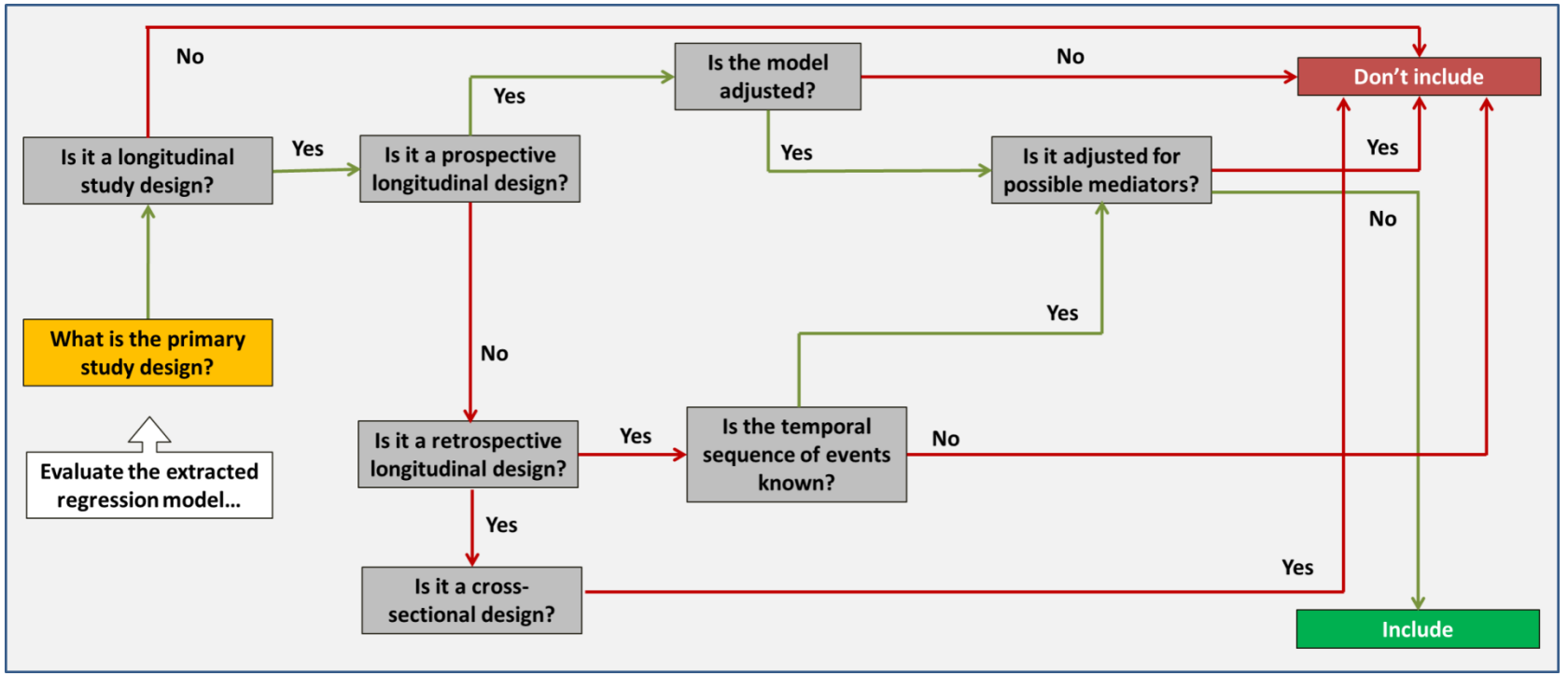

Figure 8-4. Flow chart that illustrates the guidelines used in assessing the regression models before including them in the meta-analysis

Table 8-10 summary of bias-assessment guidelines, which was generated based on the quality-assessment checklist

	How might this aspect increase bias?	Recommendations to minimize bias
1- Evaluating for measurement error		
Retrospective or prospective study design	Retrospective design might increase the risk of recall bias if the exposure and confounders were measured retrospectively at the time when the outcome was measured.	Avoid the usage of retrospective longitudinal study design.
Measurement tool (i.e., subjective or objective)	1. Subjective tools might increase the risk of recall bias. 2. Subjective tools might increase the risk of measurement error, especially for some variables such as sleep duration or post-partum blood loss.	Use objective measurements as needed.
Collection method (i.e., extracting data from the medical record or collecting via interview)	Collecting medical data from participants, rather than extracting the data from medical records, might increase the risk of recall bias and/or measurement error.	Extract medical data from medical records as needed, rather than interviewing participants.
2- Evaluating for confounding bias		
Stratification of analysis	Stratifying the sample based on mediators might bias the results while stratifying the sample based on how confounders might affect the generalizability of results.	Avoid stratification as much as possible.
Study design (i.e., known or unknown temporal sequence of events)	Not knowing the temporal sequence of events might increase the risk of adjusting for mediators, rather than adjusting for confounders, because most relationships between sleep and other covariates were bidirectional relationships, considering that the longitudinal temporal sequences of events will change the bidirectional relationship into a unidirectional relationship under the influence of time. However, when using cross-sectional design rather than longitudinal design, the risk of adjusting for a mediator might increase. Similarly, using a retrospective design without knowledge of the temporal sequence might increase the risk of adjusting for a mediator.	Use longitudinal design rather than cross-sectional, and if the retrospective design was used, ensure the legitimacy of the knowledge about the temporal sequence of events to minimize the risk of adjusting for mediators.
Gestational age when sleep was measured (multiple measurement of sleep or a single measurement without the knowledge about gestational age)	1. If sleep was measured once, however, without specifying the gestational age when sleep or other adjusted covariates were measured (regardless of having a prospective longitudinal study design), it might increase the risk of adjusting for mediators, as it will not be clear which covariate preceded the other one. 2. The risk of adjusting for mediators might rise when measuring sleep and other covariates repeatedly without ensuring that the measurement of the adjusted covariates preceded the measurement of sleep.	1-Report the gestational age when each sleep and/or covariate measurement is taken. 2-Consider several adjustments if sleep was measured repeatedly in different gestational ages while the covariates were measured only once during pregnancy. 3-Consider using different covariate measurements to include in the adjusted models if the covariates were measured repeatedly depending on the gestational age when sleep was measured to avoid adjusting for mediators.

	How might this aspect increase bias?	Recommendations to minimize bias
Multiple testing and Type I errors		
A questionnaire or a bespoke question	If a questionnaire was used rather than a single question. However, only one sleep characteristic was considered when presenting the result, which might raise the possibility of Type I errors or, in the final stage of the review, a publication bias.	Avoid reporting only significant results while neglecting insignificant results.
multiple outcomes or exposures	If the authors did not adjust for the α level of multiple testing and presented their results using *p*-value (especially with a wide CI), this might raise the possibility of Type I errors.	1- Adjust the α level for multiple testing. 2- Avoid presenting the results based on *p*-value and neglecting the precision of the results.
3- Sample size and Type II errors		
Sample size and power calculation	Not including a priori sample-size estimation or post hoc power calculation might increase the chances for type II errors.	A priori sample size estimation or post hoc power calculation should be included to estimate the magnitude of type II errors.
Stratification	Stratification might reduce the power of the test and increase the chances for type II errors.	Carefully consider stratification to avoid affecting the power of the analysis.
4- Selection bias and generalizability of results		
Inclusion and exclusion criteria	Excluding participants due to a characteristic that might be defined as a confounder (e.g., GDM, ethnicity) might interfere with the generalisability of results.	Carefully consider exclusion criteria.
Stratification of the sample	Stratification of the results based on covariates that are thought to be confounders (e.g., BMI) might interfere with generalizability of results.	Avoid stratification by running multivariable analysis as needed.
Study settings	**Number:** Including only one clinical setting might cause selection bias and affect the generalizability of results. **Type:** Running the study in a specific clinical setting, such as a high-risk antenatal care clinic, might affect the generalizability of results, as well as cause selection bias.	
5- Quality of result		
Missing data	Missing data might cause a loss of information and bias the estimate (especially if the missing data were not missing randomly), as well as decrease the power of the analysis and elevate the chances for type II errors if they were excluded, rather than imputed.	Carefully evaluate missing data for missing at random assumption and apply multiple imputation as needed.
6- Publication bias		
	Signs of publication bias:	Carefully consider publication bias.

	How might this aspect increase bias?	Recommendations to minimize bias
	1- Most results were significant. 2- Most of the study used a small sample size with underpowered regression models. 3- Most of the reported OR were large, and the CI lacked precision. 4- Multiple flaws in the design of the published primary studies 5- Severe heterogeneity between the results or in the other extreme repeated studies with similar results	

8.2.2 Descriptive results of the systematic review

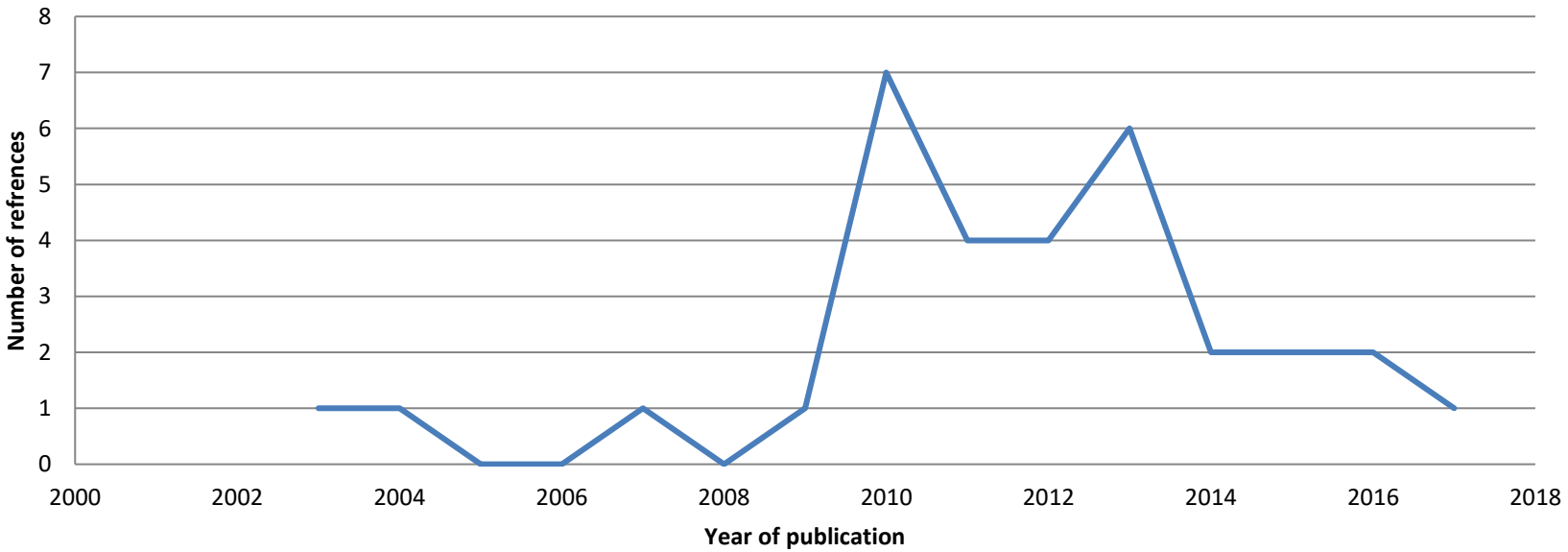

Figure 8-5 Line graph showing the number of articles in the searches conducted per year of publication.

8.3 Sleep Patterns in the United Kingdom Population: a latent class analysis of the UKHLS

8.3.1 Coding sociodemographic features and health indicators

Table 8-11 Sociodemographic features of interest together with their original and new categorisations.

Variable	Original categorization	New categorization
Gender		
Gender	Male Female	Male Female
Age		
Q: Age at the time of interview	10-19 years old	≤19 years
	20-29 years old 30-39 years old	20-39years
	40-49 years old 50-59 years old	40-59 years
	60-69 years old 70 years or older	≥ 60 years
Education		
Q: Current status of highest educational or vocational qualification	Degree Other higher A level and others	A level and above
	GCSE and others Other qualification No qualification	GCSE level and others
Occupation		
Q: Current employment situation	Self employed Unpaid family business Doing something else Paid employment(ft/pt)	Employed
	Unemployed Family care or home	Unemployed
	On maternity leave Sick or disabled	Sick or disabled
	Government training scheme Full-time student On apprenticeship	Training or education
	Retired	Retired
Household structure		
Q: This was a derived variable generated from several questions in regards to age , presence of couple and number of adult and children in the household	1 male, aged 65+, no children 1 female, age 60+, no children 1 adult under pensionable age, no children 2 adults, not a couple, both under pensionable age, no children 2 adults, not a couple, one or more over pensionable age, no children 3 or more adults, no children, excl. any couples	Single without children
	1 adult, 1 child 1 adult, 2 or more children 2 adults, not a couple, 1 or more children	Single with children
	Couple both under pensionable age, no children Couple 1 or more over pensionable age, no children 3 or more adults, 1 or more children excl. any couples	Couple without children
	Couple with 1 child Couple with 2 children Couple with 3 or more children 3 or more adults, no children, incl. at least one couple 3 or more adults, 1-2 children, incl. at least one couple	Couple with children

Table 8-12 SF12v questionnaire used in the UKHLS. The questions and responses were a modified combination of both the SF12v1 and SF12v2.

Subdomain	Question	Response
General health	**1-In general, would you say your health is...**	*1-Excellent* *2-Very good* *3-Good* *4-Fair* *5-Poor*
Physical health	**2-The following questions are about activities you might do during a typical day.** **a- Does your health now limit you in these activities? If so, how much?** Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf **b- Does your health now limit you in these activities? If so, how much?)** Climbing several flights of stairs	*1-Yes, limited a lot* *2-Yes, limited a little* *3-No, not limited at all*
Physical health (role functioning)	**3a--During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?** Accomplished less than you would like **3b-During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?)** Were limited in the kind of work or other activities	*1-All of the time* *2-Most of the time* *3-Some of the time* *4-A little of the time* *5-None of the time*
Emotional (role functioning)	**4a-During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?** Accomplished less than you would like **4b-(During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?) Did work or other activities less carefully than usual**	*1-All of the time* *2-Most of the time* *3-Some of the time* *4-A little of the time* *5-None of the time*
Bodily pain	**5-During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**	*1-Not at all* *2-A little bit* *3-Moderately* *4-Quite a bit* *5-Extremely*
	6-These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.	*1-All of the time* *2-Most of the time* *3-Some of the time* *4-A little of the time* *5-None of the time*
Mental health	a- Have you felt calm and peaceful? b- Did you have a lot of energy?	
Mental health	c- Have you felt downhearted and depressed?	
Social health	d- How much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends or relatives)?	

8.3.2 Choosing best fit model

Table 8-13 the iteration criteria observed for latent models generated using LCA to UKHLS sleep module data.

	Stability study										Complete population study				
	Wave 1					Wave 4									
	Goodness of fit			Entropy measurements		Goodness of fit			Entropy measurements		Goodness of fit			Entropy measurements	
Model	**BIC**	**AIC**	**Number of parameters**	**R^2**	**CE**	**BIC**	**AIC**	**Number of parameters**	**R^2**	**CE**	**BIC**	**AIC**	**Number of parameters**	**R^2**	**CE**
Model1	213405	213295	14	1.00	0.00	202112	202001	14	1.00	0.00	575342	575220	14	1.00	0.00
Model2	198887	198713	22	0.79	0.06	186782	186608	22	0.78	0.04	331168	330970	22	0.78	0.06
Model3	197069	196833	30	0.69	0.11	185479	185242	30	0.67	0.13	312114	311853	30	0.71	0.11
Model4	196340	196040	38	0.67	0.15	184506	184206	38	0.71	0.13	309722	309391	38	0.68	0.15
Model5	196115	195753	46	0.68	0.17	184099	183753	46	0.68	0.17	308702	308301	46	0.69	0.15
Model6	**195502**	**195328**	**54**	**0.68**	**0.14**	**183819**	183364	**54**	0.74	0.15	**307816**	307620	**54**	**0.73**	**0.14**
Model7	195626	195430	62	0.66	0.18	183861	183371	62	0.72	0.17	307864	307696	62	0.68	0.17
Model8	195753	195551	70	0.66	0.18	183672	183318	70	0.69	0.17	307745	307585	70	0.66	0.18
Model9	195429	195315	78	0.66	0.19	183515	183298	78	0.65	0.19	307574	307472	78	0.66	0.19
Model10	195481	195254	86	0.63	0.27	183534	183154	86	0.68	0.21	307489	307339	86	0.63	0.27

The Bold text indicates the chosen iteration criteria values

8.3.3 Choosing best fit model (binary coding of data)

Table 8-14 BIC values and the number of parameters observed for latent sleep models generated using exploratory latent class analyses using binary coding for each of the sleep variables.

	Stability study (n=19,442)				Complete population study (n=45, 141)	
	Wave 1		Wave 4			
	Number of parameters	BIC	Number of parameters	BIC	Number of parameters	BIC
1 Cluster	7	151509.3	7	139987.9	7	338323.2
2 Clusters	15	142591.1	15	130987.4	15	316944
3 Clusters	23	140624.4	23	129700.6	23	312662.9
4 Clusters	31	140497	31	129654.4	31	312294.9
5 Clusters	**39**	**140499.5**	**39**	**129703.1**	39	312082.5
6 Clusters	47	140543.9	47	129753.5	**47**	**312128.5**
7 Clusters	55	140541.2	55	129789.3	55	312143.8
8 Clusters	63	140611.4	63	129861.1	63	312178.9
9 Clusters	71	140671.4	71	129927.7	71	312234.4
10 Clusters	79	140734.2	79	130005.5	79	312348.6

The Bold text indicates the chosen BIC values after considering the number of parameters

8.3.4 Latent sleep pattern models (using binary coded of data)

Table 8-15 Wave 1 matched population (n=19,442) cluster patterns using binary variables.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Duration	**≥ 7 hours** 0.252	**≥ 7 hours** **0.174**	**< 7 hours** **0.7868**	**< 7 hours** **0.715**	**≥ 7 hours** **0.096**
Latency	**Present** 0.633	**Absent** 0.169	**Present** 0.922	**Present** **0.697**	**Present** **0.801**
Snoring	**Absent** **0.399**	**Absent** **0.126**	**Present** **0.649**	**Absent** **0.210**	**Present** **0.610**
Disturbance	**Present** **0.952**	**Absent** **0.246**	**Present** **0.995**	**Present** **0.878**	**Present** **0.927**
Sleepiness	**Absent** **0.108**	**Absent** **0.072**	**Absent** **0.345**	**Absent** **0.260**	**Absent** **0.215**
Medication	**Absent** **0.071**	**Absent** **0.0812**	**Absent** **0.367**	**Absent** **0.129**	**Present** **0.689**
Quality	**Absent** **0.012**	**Absent** **0.001**	**Present** **0.790**	**Present** **0.889**	**Absent** **0.099**

Table 8-16 UKHLS Wave 4 matched population (n=19,442) sleep cluster patterns generated using binary variables.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Duration	≥ 7 hours 0.200	≥ 7 hours **0.265**	< 7 hours **0.863**	≥ 7 hours **0.425**	< 7 hours **0.789**
Latency	Absent 0.176	Present 0.664	Present 0.860	Present **0.718**	Absent **0.484**
Snoring	Absent **0.082**	Absent **0.296**	Absent 0.313	Absent **0.226**	Absent 0.169
Disturbance	Absent **0.303**	Present **0.854**	Present **0.980**	Present **0.946**	Present **0.698**
Sleepiness	Absent **0.035**	Absent **0.162**	Absent **0.206**	Absent **0.008**	Absent **0.217**
Medication	Absent **0.012**	Absent **0.118**	Absent **0.236**	Absent **0.015**	Present **0.011**
Quality	Absent **0.001**	Absent **0.012**	Present **0.885**	Absent **0.027**	Absent **0.381**

Table 8-17 UKHLS Wave 1 and 4 (n=45,141) sleep cluster patterns generated using binary variables.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6
Duration	≥ 7 hours 0.264	≥ 7 hours **0.177**	< 7 hours **0.807**	≥ 7 hours **0.179**	< 7 hours **0.865**	≥ 7 hours 0.192
Latency	Present 0.627	Absent 0.172	Present 0.932	Present **0.777**	Present 0.626	Present 0.768
Snoring	Absent **0.383**	Absent **0.100**	Present **0.544**	Absent **0.059**	Absent 0.181	Present **0.858**
Disturbance	Present **0.957**	Absent **0.223**	Present **0.999**	Present **0.805**	Present **0.844**	Present **0.888**
Sleepiness	Absent **0.031**	Absent **0.038**	Absent **0.198**	Absent **0.142**	Absent **0.159**	Absent **0.275**
Medication	Absent **0.071**	Absent 0.056	Absent **0.330**	Absent **0.113**	Absent **0.120**	Absent **0.388**
Quality	Absent **0.008**	Absent 0.001	Present **0.822**	Absent **0.154**	Present **0.706**	Absent **0.174**

8.3.5 Algorithm of generated latent sleep patterns

Table 8-18 Latent sleep patterns coding algorithm generated using latent class analysis.

Q= quality, SL= sleepiness, M= medication, SN= snoring and/or coughing, D= disturbance, L= latency, SD= sleep duration, FO= frequency of observations, LSP= latent sleep pattern.

Q	SL	M	SN	D	L	SD	FO	LSP
1	0	1	1	2	1	2	8	3
1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
1	0	1	2	0	0	2	1	1
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1	0	1	2	0	1	1	2	1
1	0	1	2	0	2	0	1	1
1	0	1	2	1	0	0	18	1
1	0	1	2	1	0	1	3	1
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1	0	1	2	1	1	1	7	1
1	0	1	2	1	1	2	2	1
1	0	1	2	1	2	0	5	1
1	0	1	2	1	2	1	1	1
1	0	1	2	2	0	0	15	1
1	0	1	2	2	0	1	1	1
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1	0	1	2	2	1	1	5	3
1	0	1	2	2	2	0	16	3
1	0	1	2	2	2	1	14	3
1	0	1	2	2	2	2	4	3
1	0	2	0	0	0	0	166	2
1	0	2	0	0	0	1	22	2
1	0	2	0	0	0	2	5	2
1	0	2	0	0	0	3	2	2
1	0	2	0	0	1	0	28	1
1	0	2	0	0	1	1	3	1
1	0	2	0	0	2	0	6	1
1	0	2	0	1	0	0	82	1
1	0	2	0	1	0	1	14	1
1	0	2	0	1	0	2	3	1
1	0	2	0	1	1	0	121	1
1	0	2	0	1	1	1	17	1
1	0	2	0	1	1	2	2	4
1	0	2	0	1	1	3	2	4
1	0	2	0	1	2	0	19	1
1	0	2	0	1	2	1	6	1
1	0	2	0	2	0	0	67	1

Q	SL	M	SN	D	L	SD	FO	LSP
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1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
1	0	2	0	2	0	1	23	1
1	0	2	0	2	0	2	5	6
1	0	2	0	2	0	3	1	6
1	0	2	0	2	1	0	51	1
1	0	2	0	2	1	1	27	3
1	0	2	0	2	1	2	2	3
1	0	2	0	2	2	0	27	3
1	0	2	0	2	2	1	17	3
1	0	2	0	2	2	2	10	3
1	0	2	0	2	2	3	4	3
1	0	2	1	0	0	0	22	1
1	0	2	1	0	0	1	1	1
1	0	2	1	0	0	2	2	1
1	0	2	1	0	1	0	7	1
1	0	2	1	0	2	0	1	1
1	0	2	1	1	0	0	39	1
1	0	2	1	1	0	1	5	1
1	0	2	1	1	1	0	64	1
1	0	2	1	1	1	1	13	1
1	0	2	1	1	1	2	2	4
1	0	2	1	1	1	3	2	4
1	0	2	1	1	2	0	8	1
1	0	2	1	1	2	1	2	4
1	0	2	1	1	2	2	1	4
1	0	2	1	1	2	3	1	4
1	0	2	1	2	0	0	14	1
1	0	2	1	2	0	1	1	6
1	0	2	1	2	1	0	40	1
1	0	2	1	2	1	1	8	3
1	0	2	1	2	2	0	16	3
1	0	2	1	2	2	1	9	3
1	0	2	1	2	2	2	1	3
1	0	2	1	2	2	3	1	3
1	0	2	2	0	0	0	16	1
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1	0	2	2	1	0	0	29	1
1	0	2	2	1	0	1	7	1
1	0	2	2	1	0	2	1	1
1	0	2	2	1	1	0	37	1
1	0	2	2	1	1	1	9	1

Q	SL	M	SN	D	L	SD	FO	LSP
1	0	1	1	2	1	2	8	3
1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
1	0	2	2	1	1	2	2	4
1	0	2	2	1	2	0	3	1
1	0	2	2	1	2	1	3	4
1	0	2	2	2	0	0	30	1
1	0	2	2	2	0	1	7	6
1	0	2	2	2	0	3	1	6
1	0	2	2	2	1	0	39	3
1	0	2	2	2	1	1	21	3
1	0	2	2	2	1	2	2	3
1	0	2	2	2	1	3	1	3
1	0	2	2	2	2	0	32	3
1	0	2	2	2	2	1	16	3
1	0	2	2	2	2	2	6	3
1	0	2	2	2	2	3	1	3
1	1	0	0	0	0	0	182	2
1	1	0	0	0	0	1	59	2
1	1	0	0	0	0	2	12	2
1	1	0	0	0	0	3	4	2
1	1	0	0	0	1	0	69	1
1	1	0	0	0	1	1	19	1
1	1	0	0	0	1	2	1	4
1	1	0	0	0	1	3	1	4
1	1	0	0	0	2	0	11	1
1	1	0	0	0	2	1	5	4
1	1	0	0	0	2	2	1	4
1	1	0	0	0	2	3	1	4
1	1	0	0	1	0	0	165	1
1	1	0	0	1	0	1	46	1
1	1	0	0	1	0	2	13	1
1	1	0	0	1	1	0	299	1
1	1	0	0	1	1	1	85	1
1	1	0	0	1	1	2	10	4
1	1	0	0	1	1	3	5	4
1	1	0	0	1	2	0	53	1
1	1	0	0	1	2	1	9	4
1	1	0	0	1	2	2	4	4
1	1	0	0	1	2	3	1	4
1	1	0	0	2	0	0	60	1
1	1	0	0	2	0	1	39	1
1	1	0	0	2	0	2	9	6
1	1	0	0	2	0	3	1	6
1	1	0	0	2	1	0	85	1
1	1	0	0	2	1	1	40	1
1	1	0	0	2	1	2	5	6

Q	SL	M	SN	D	L	SD	FO	LSP
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1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
1	1	0	0	2	1	3	1	6
1	1	0	0	2	2	0	27	3
1	1	0	0	2	2	1	15	3
1	1	0	0	2	2	2	2	3
1	1	0	0	2	2	3	2	3
1	1	0	1	0	0	0	24	1
1	1	0	1	0	0	1	7	1
1	1	0	1	0	0	2	3	1
1	1	0	1	0	1	0	21	1
1	1	0	1	0	1	1	5	1
1	1	0	1	0	2	0	2	1
1	1	0	1	0	2	1	1	4
1	1	0	1	1	0	0	61	1
1	1	0	1	1	0	1	27	1
1	1	0	1	1	0	2	4	1
1	1	0	1	1	1	0	168	1
1	1	0	1	1	1	1	50	1
1	1	0	1	1	1	2	12	4
1	1	0	1	1	1	3	1	4
1	1	0	1	1	2	0	14	1
1	1	0	1	1	2	1	8	4
1	1	0	1	1	2	2	1	4
1	1	0	1	2	0	0	32	1
1	1	0	1	2	0	1	9	6
1	1	0	1	2	0	2	3	6
1	1	0	1	2	1	0	56	1
1	1	0	1	2	1	1	36	3
1	1	0	1	2	1	2	2	3
1	1	0	1	2	1	3	1	6
1	1	0	1	2	2	0	21	3
1	1	0	1	2	2	1	10	3
1	1	0	1	2	2	2	3	3
1	1	0	2	0	0	0	18	1
1	1	0	2	0	0	1	5	1
1	1	0	2	0	0	3	2	4
1	1	0	2	0	1	0	8	1
1	1	0	2	0	1	1	6	1
1	1	0	2	0	2	1	1	4
1	1	0	2	0	2	2	1	4
1	1	0	2	1	0	0	19	1
1	1	0	2	1	0	1	4	1
1	1	0	2	1	0	2	2	1
1	1	0	2	1	1	0	39	1
1	1	0	2	1	1	1	19	1

Q	SL	M	SN	D	L	SD	FO	LSP
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1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
1	1	0	2	1	1	2	3	4
1	1	0	2	1	2	0	6	1
1	1	0	2	1	2	1	3	4
1	1	0	2	1	2	3	1	4
1	1	0	2	2	0	0	21	1
1	1	0	2	2	0	1	9	6
1	1	0	2	2	0	2	1	6
1	1	0	2	2	0	3	1	6
1	1	0	2	2	1	0	33	1
1	1	0	2	2	1	1	22	3
1	1	0	2	2	1	2	3	3
1	1	0	2	2	2	0	16	3
1	1	0	2	2	2	1	9	3
1	1	0	2	2	2	2	1	3
1	1	0	2	2	2	3	2	3
1	1	1	0	0	0	0	40	2
1	1	1	0	0	0	1	6	2
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1	1	1	0	0	2	0	1	1
1	1	1	0	0	2	1	1	4
1	1	1	0	1	0	0	9	1
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1	1	1	0	1	1	1	6	1
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1	1	1	0	2	1	0	11	1
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1	1	1	1	0	1	2	2	4
1	1	1	1	0	2	0	1	1
1	1	1	1	1	0	0	10	1
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Q	SL	M	SN	D	L	SD	FO	LSP
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1	0	1	1	2	1	3	2	3
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1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
1	1	1	1	1	0	3	1	4
1	1	1	1	1	1	0	37	1
1	1	1	1	1	1	1	20	1
1	1	1	1	1	1	2	6	4
1	1	1	1	1	1	3	1	4
1	1	1	1	1	2	0	3	1
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1	1	1	1	2	0	1	1	6
1	1	1	1	2	1	0	20	1
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1	1	1	1	2	1	2	1	3
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1	1	1	1	2	2	0	6	3
1	1	1	1	2	2	1	5	3
1	1	1	2	0	0	1	1	1
1	1	1	2	0	1	0	1	1
1	1	1	2	1	0	0	4	1
1	1	1	2	1	0	2	1	1
1	1	1	2	1	1	0	13	1
1	1	1	2	1	1	1	6	1
1	1	1	2	1	2	0	2	1
1	1	1	2	1	2	1	3	4
1	1	1	2	1	2	2	1	4
1	1	1	2	2	0	0	1	1
1	1	1	2	2	0	1	3	6
1	1	1	2	2	1	0	6	3
1	1	1	2	2	1	1	5	3
1	1	1	2	2	1	2	1	3
1	1	1	2	2	1	3	1	3
1	1	1	2	2	2	0	7	3
1	1	1	2	2	2	1	4	3
1	1	1	2	2	2	2	1	3
1	1	2	0	0	0	0	13	2
1	1	2	0	0	0	1	4	2
1	1	2	0	0	1	0	4	1
1	1	2	0	1	0	0	12	1
1	1	2	0	1	0	1	2	1
1	1	2	0	1	0	2	1	4
1	1	2	0	1	1	0	19	1
1	1	2	0	1	1	1	5	1
1	1	2	0	1	1	3	1	4
1	1	2	0	1	2	0	3	1
1	1	2	0	1	2	1	3	4
1	1	2	0	2	0	0	4	1

Q	SL	M	SN	D	L	SD	FO	LSP
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1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
1	1	2	0	2	0	1	1	6
1	1	2	0	2	1	0	8	1
1	1	2	0	2	1	1	2	3
1	1	2	0	2	1	2	1	3
1	1	2	0	2	2	0	1	3
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1	1	2	1	1	1	3	1	4
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1	1	2	1	1	2	1	1	4
1	1	2	1	2	0	0	2	1
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1	1	2	2	1	0	1	2	1
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1	1	2	2	1	1	0	5	1
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1	1	2	2	1	1	2	1	4
1	1	2	2	1	2	0	6	4
1	1	2	2	1	2	1	1	4
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1	1	2	2	2	0	2	1	6
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1	1	2	2	2	2	0	4	3
1	1	2	2	2	2	1	2	3
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1	1	2	2	2	2	3	1	3

Q	SL	M	SN	D	L	SD	FO	LSP
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1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
1	2	0	0	0	0	0	10	2
1	2	0	0	0	0	1	3	2
1	2	0	0	0	0	2	4	4
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1	2	0	0	0	2	1	1	4
1	2	0	0	1	0	0	5	1
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1	2	0	0	2	0	0	4	1
1	2	0	0	2	0	1	1	6
1	2	0	0	2	0	3	1	6
1	2	0	0	2	1	0	6	1
1	2	0	0	2	1	1	1	6
1	2	0	0	2	2	0	4	3
1	2	0	0	2	2	1	3	3
1	2	0	0	2	2	3	1	3
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1	2	0	1	0	0	1	2	1
1	2	0	1	0	1	1	1	4
1	2	0	1	1	0	0	3	1
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1	2	0	1	2	0	0	2	1
1	2	0	1	2	0	1	1	6
1	2	0	1	2	1	0	1	1
1	2	0	1	2	1	1	1	3
1	2	0	1	2	1	2	1	6
1	2	0	1	2	2	0	3	3
1	2	0	2	0	0	0	2	1
1	2	0	2	0	1	0	2	1
1	2	0	2	0	2	0	1	4
1	2	0	2	1	0	1	1	1
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1	2	0	2	1	1	0	4	1
1	2	0	2	1	2	0	1	4
1	2	0	2	1	2	1	1	4
1	2	0	2	1	2	2	1	4
1	2	0	2	2	0	0	3	1
1	2	0	2	2	0	2	3	6

Q	SL	M	SN	D	L	SD	FO	LSP
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1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
1	2	0	2	2	1	0	1	3
1	2	0	2	2	1	1	1	3
1	2	0	2	2	2	0	5	3
1	2	0	2	2	2	3	2	3
1	2	1	0	0	0	0	1	2
1	2	1	0	1	0	0	1	1
1	2	1	0	2	1	0	1	1
1	2	1	0	2	2	0	1	3
1	2	1	1	0	0	0	1	1
1	2	1	1	0	2	1	1	4
1	2	1	1	1	0	0	1	1
1	2	1	1	1	0	1	1	1
1	2	1	1	1	1	1	1	4
1	2	1	2	1	0	0	1	1
1	2	1	2	2	2	0	4	3
1	2	1	2	2	2	1	1	3
1	2	1	2	2	2	3	1	5
1	2	2	0	0	0	0	1	2
1	2	2	0	0	0	1	1	4
1	2	2	0	1	0	0	1	1
1	2	2	0	1	2	0	1	4
1	2	2	0	2	0	0	1	6
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1	2	2	0	2	0	3	1	6
1	2	2	0	2	1	0	2	1
1	2	2	0	2	1	1	1	6
1	2	2	0	2	2	0	2	3
1	2	2	0	2	2	1	1	3
1	2	2	1	1	0	1	1	4
1	2	2	1	1	1	1	1	4
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1	2	2	1	2	1	0	1	3
1	2	2	2	0	0	0	1	1
1	2	2	2	1	1	0	2	4
1	2	2	2	1	2	0	1	4
1	2	2	2	2	0	0	2	6
1	2	2	2	2	0	1	1	6
1	2	2	2	2	1	0	4	3
1	2	2	2	2	1	1	2	3
1	2	2	2	2	2	0	2	3
1	2	2	2	2	2	1	2	3
2	0	0	0	0	0	0	21	2
2	0	0	0	0	0	1	26	4
2	0	0	0	0	0	2	14	4

Q	SL	M	SN	D	L	SD	FO	LSP
1	0	1	1	2	1	2	8	3
1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
2	0	0	0	0	0	3	12	4
2	0	0	0	0	1	0	18	4
2	0	0	0	0	1	1	20	4
2	0	0	0	0	1	2	3	4
2	0	0	0	0	2	0	24	4
2	0	0	0	0	2	1	18	4
2	0	0	0	0	2	2	8	4
2	0	0	0	0	2	3	9	4
2	0	0	0	1	0	0	28	4
2	0	0	0	1	0	1	16	4
2	0	0	0	1	0	2	8	4
2	0	0	0	1	0	3	2	4
2	0	0	0	1	1	0	67	4
2	0	0	0	1	1	1	72	4
2	0	0	0	1	1	2	24	4
2	0	0	0	1	1	3	5	4
2	0	0	0	1	2	0	59	4
2	0	0	0	1	2	1	55	4
2	0	0	0	1	2	2	20	4
2	0	0	0	1	2	3	3	4
2	0	0	0	2	0	0	80	6
2	0	0	0	2	0	1	121	6
2	0	0	0	2	0	2	58	6
2	0	0	0	2	0	3	25	6
2	0	0	0	2	1	0	109	3
2	0	0	0	2	1	1	159	6
2	0	0	0	2	1	2	87	6
2	0	0	0	2	1	3	18	6
2	0	0	0	2	2	0	168	3
2	0	0	0	2	2	1	274	5
2	0	0	0	2	2	2	191	5
2	0	0	0	2	2	3	133	5
2	0	0	1	0	0	0	2	4
2	0	0	1	0	0	1	2	4
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2	0	0	1	1	0	0	8	4
2	0	0	1	1	0	1	8	4
2	0	0	1	1	0	2	1	4
2	0	0	1	1	0	3	1	4
2	0	0	1	1	1	0	41	4

Q	SL	M	SN	D	L	SD	FO	LSP
1	0	1	1	2	1	2	8	3
1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
2	0	0	1	1	1	1	36	4
2	0	0	1	1	1	2	11	4
2	0	0	1	1	1	3	4	4
2	0	0	1	1	2	0	20	4
2	0	0	1	1	2	1	24	4
2	0	0	1	1	2	2	7	4
2	0	0	1	1	2	3	1	4
2	0	0	1	2	0	0	22	6
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2	0	0	1	2	0	3	5	6
2	0	0	1	2	1	0	44	3
2	0	0	1	2	1	1	81	3
2	0	0	1	2	1	2	36	6
2	0	0	1	2	1	3	12	6
2	0	0	1	2	2	0	71	3
2	0	0	1	2	2	1	98	5
2	0	0	1	2	2	2	92	5
2	0	0	1	2	2	3	56	5
2	0	0	2	0	0	0	3	4
2	0	0	2	0	0	1	2	4
2	0	0	2	0	0	2	1	4
2	0	0	2	0	1	0	5	4
2	0	0	2	0	1	1	3	4
2	0	0	2	0	2	0	3	4
2	0	0	2	0	2	1	6	4
2	0	0	2	0	2	2	1	4
2	0	0	2	1	0	0	2	4
2	0	0	2	1	0	1	3	4
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2	0	0	2	1	1	2	6	4
2	0	0	2	1	1	3	2	4
2	0	0	2	1	2	0	10	4
2	0	0	2	1	2	1	8	4
2	0	0	2	1	2	2	8	4
2	0	0	2	1	2	3	5	5
2	0	0	2	2	0	0	27	6
2	0	0	2	2	0	1	31	6
2	0	0	2	2	0	2	18	6
2	0	0	2	2	0	3	11	6
2	0	0	2	2	1	0	55	3

Q	SL	M	SN	D	L	SD	FO	LSP
1	0	1	1	2	1	2	8	3
1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
2	0	0	2	2	1	1	48	3
2	0	0	2	2	1	2	27	6
2	0	0	2	2	1	3	9	5
2	0	0	2	2	2	0	72	3
2	0	0	2	2	2	1	108	5
2	0	0	2	2	2	2	108	5
2	0	0	2	2	2	3	92	5
2	0	1	0	0	0	0	1	2
2	0	1	0	0	0	1	2	4
2	0	1	0	0	0	2	2	4
2	0	1	0	0	1	0	1	4
2	0	1	0	0	2	0	3	4
2	0	1	0	0	2	1	2	4
2	0	1	0	0	2	3	1	4
2	0	1	0	1	0	0	2	4
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2	0	1	0	1	0	3	1	4
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2	0	1	0	1	1	1	9	4
2	0	1	0	1	1	2	4	4
2	0	1	0	1	2	0	12	4
2	0	1	0	1	2	1	12	4
2	0	1	0	1	2	2	3	4
2	0	1	0	1	2	3	2	4
2	0	1	0	2	0	0	7	6
2	0	1	0	2	0	1	12	6
2	0	1	0	2	0	2	5	6
2	0	1	0	2	0	3	1	6
2	0	1	0	2	1	0	11	3
2	0	1	0	2	1	1	27	6
2	0	1	0	2	1	2	13	6
2	0	1	0	2	1	3	1	5
2	0	1	0	2	2	0	21	3
2	0	1	0	2	2	1	37	5
2	0	1	0	2	2	2	24	5
2	0	1	0	2	2	3	23	5
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2	0	1	1	1	1	0	10	4
2	0	1	1	1	1	1	8	4
2	0	1	1	1	1	2	2	4
2	0	1	1	1	2	0	4	4
2	0	1	1	1	2	1	6	4

Q	SL	M	SN	D	L	SD	FO	LSP
1	0	1	1	2	1	2	8	3
1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
2	0	1	1	1	2	2	3	4
2	0	1	1	2	0	0	1	6
2	0	1	1	2	0	1	2	6
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2	0	1	1	2	1	1	9	3
2	0	1	1	2	1	2	9	6
2	0	1	1	2	1	3	1	5
2	0	1	1	2	2	0	14	3
2	0	1	1	2	2	1	18	5
2	0	1	1	2	2	2	9	5
2	0	1	1	2	2	3	10	5
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2	0	1	2	2	1	2	3	5
2	0	1	2	2	2	0	10	3
2	0	1	2	2	2	1	23	5
2	0	1	2	2	2	2	8	5
2	0	1	2	2	2	3	13	5
2	0	2	0	0	0	0	2	4
2	0	2	0	0	0	1	3	4
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2	0	2	0	0	0	3	1	4
2	0	2	0	0	1	1	1	4
2	0	2	0	0	2	0	1	4
2	0	2	0	0	2	1	3	4
2	0	2	0	0	2	2	1	4

Q	SL	M	SN	D	L	SD	FO	LSP
1	0	1	1	2	1	2	8	3
1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
2	0	2	0	0	2	3	2	4
2	0	2	0	1	0	0	2	4
2	0	2	0	1	0	1	3	4
2	0	2	0	1	1	0	11	4
2	0	2	0	1	1	1	5	4
2	0	2	0	1	2	0	4	4
2	0	2	0	1	2	1	3	4
2	0	2	0	1	2	2	3	4
2	0	2	0	1	2	3	1	5
2	0	2	0	2	0	0	11	6
2	0	2	0	2	0	1	12	6
2	0	2	0	2	0	2	8	6
2	0	2	0	2	0	3	8	6
2	0	2	0	2	1	0	13	3
2	0	2	0	2	1	1	16	3
2	0	2	0	2	1	2	8	5
2	0	2	0	2	1	3	8	5
2	0	2	0	2	2	0	40	5
2	0	2	0	2	2	1	45	5
2	0	2	0	2	2	2	39	5
2	0	2	0	2	2	3	54	5
2	0	2	1	0	0	2	1	4
2	0	2	1	0	0	3	1	4
2	0	2	1	0	1	0	1	4
2	0	2	1	0	2	1	3	4
2	0	2	1	1	0	1	2	4
2	0	2	1	1	0	2	1	4
2	0	2	1	1	1	0	8	4
2	0	2	1	1	1	1	5	4
2	0	2	1	1	1	2	1	4
2	0	2	1	1	2	0	5	4
2	0	2	1	1	2	1	6	4
2	0	2	1	1	2	3	2	5
2	0	2	1	2	0	0	3	6
2	0	2	1	2	0	1	3	6
2	0	2	1	2	0	2	1	6
2	0	2	1	2	0	3	1	6
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2	0	2	1	2	1	2	10	5
2	0	2	1	2	1	3	4	5
2	0	2	1	2	2	0	16	5
2	0	2	1	2	2	1	25	5
2	0	2	1	2	2	2	22	5

Q	SL	M	SN	D	L	SD	FO	LSP
1	0	1	1	2	1	2	8	3
1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
2	0	2	1	2	2	3	18	5
2	0	2	2	0	0	0	1	4
2	0	2	2	0	0	1	1	4
2	0	2	2	0	0	3	2	4
2	0	2	2	0	1	0	1	4
2	0	2	2	0	1	2	1	4
2	0	2	2	0	2	0	2	4
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2	0	2	2	1	2	0	3	4
2	0	2	2	1	2	1	5	4
2	0	2	2	1	2	2	1	5
2	0	2	2	2	0	0	3	6
2	0	2	2	2	0	1	8	6
2	0	2	2	2	0	2	5	6
2	0	2	2	2	0	3	2	6
2	0	2	2	2	1	0	8	3
2	0	2	2	2	1	1	9	3
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2	0	2	2	2	1	3	2	5
2	0	2	2	2	2	0	27	5
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2	1	0	0	0	1	2	5	4
2	1	0	0	0	1	3	2	4
2	1	0	0	0	2	0	3	4
2	1	0	0	0	2	1	6	4
2	1	0	0	0	2	2	5	4
2	1	0	0	0	2	3	1	4
2	1	0	0	1	0	0	10	4
2	1	0	0	1	0	1	16	4
2	1	0	0	1	0	2	1	4
2	1	0	0	1	1	0	42	4

Q	SL	M	SN	D	L	SD	FO	LSP
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1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
2	1	0	0	1	1	1	25	4
2	1	0	0	1	1	2	5	4
2	1	0	0	1	1	3	3	4
2	1	0	0	1	2	0	17	4
2	1	0	0	1	2	1	13	4
2	1	0	0	1	2	2	9	4
2	1	0	0	1	2	3	1	4
2	1	0	0	2	0	0	15	6
2	1	0	0	2	0	1	26	6
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2	1	0	0	2	1	1	57	6
2	1	0	0	2	1	2	16	6
2	1	0	0	2	1	3	6	5
2	1	0	0	2	2	0	46	5
2	1	0	0	2	2	1	63	5
2	1	0	0	2	2	2	38	5
2	1	0	0	2	2	3	36	5
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2	1	0	1	0	1	1	1	4
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2	1	0	1	0	2	0	2	4
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2	1	0	1	0	2	2	1	4
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2	1	0	1	1	0	2	2	4
2	1	0	1	1	1	0	15	4
2	1	0	1	1	1	1	23	4
2	1	0	1	1	1	2	7	4
2	1	0	1	1	2	0	8	4
2	1	0	1	1	2	1	16	4
2	1	0	1	1	2	2	1	4
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2	1	0	1	2	0	3	1	6
2	1	0	1	2	1	0	28	3
2	1	0	1	2	1	1	25	6
2	1	0	1	2	1	2	19	6
2	1	0	1	2	1	3	5	5

Q	SL	M	SN	D	L	SD	FO	LSP
1	0	1	1	2	1	2	8	3
1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
2	1	0	1	2	2	0	34	5
2	1	0	1	2	2	1	38	5
2	1	0	1	2	2	2	40	5
2	1	0	1	2	2	3	17	5
2	1	0	2	0	0	1	1	4
2	1	0	2	0	1	0	1	4
2	1	0	2	0	1	1	2	4
2	1	0	2	0	1	2	1	4
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2	1	0	2	1	0	2	2	4
2	1	0	2	1	1	0	7	4
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2	1	0	2	1	2	1	3	4
2	1	0	2	1	2	2	2	4
2	1	0	2	1	2	3	1	5
2	1	0	2	2	0	0	6	6
2	1	0	2	2	0	1	12	6
2	1	0	2	2	0	2	7	6
2	1	0	2	2	0	3	5	6
2	1	0	2	2	1	0	20	3
2	1	0	2	2	1	1	22	6
2	1	0	2	2	1	2	14	5
2	1	0	2	2	1	3	6	5
2	1	0	2	2	2	0	28	5
2	1	0	2	2	2	1	42	5
2	1	0	2	2	2	2	37	5
2	1	0	2	2	2	3	32	5
2	1	1	0	0	0	0	1	4
2	1	1	0	0	0	1	1	4
2	1	1	0	0	0	2	1	4
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2	1	1	0	1	0	0	2	4
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2	1	1	0	1	1	2	3	4
2	1	1	0	1	2	0	2	4
2	1	1	0	1	2	1	8	4
2	1	1	0	1	2	2	2	4

Q	SL	M	SN	D	L	SD	FO	LSP
1	0	1	1	2	1	2	8	3
1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
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2	1	1	1	1	2	0	5	4
2	1	1	1	1	2	1	1	4
2	1	1	1	1	2	3	1	5
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2	1	1	1	2	1	0	2	3
2	1	1	1	2	1	1	10	6
2	1	1	1	2	1	2	6	5
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2	1	1	2	2	1	0	9	3
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2	1	1	2	2	1	2	4	5
2	1	1	2	2	1	3	1	5

Q	SL	M	SN	D	L	SD	FO	LSP
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1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
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2	1	2	1	2	2	0	12	5
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2	1	2	1	2	2	2	21	5
2	1	2	1	2	2	3	13	5

Q	SL	M	SN	D	L	SD	FO	LSP
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1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
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Q	SL	M	SN	D	L	SD	FO	LSP
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1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
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2	2	1	0	2	2	1	2	5
2	2	1	0	2	2	3	1	5
2	2	1	1	0	0	3	1	4
2	2	1	1	1	1	1	1	4

Q	SL	M	SN	D	L	SD	FO	LSP
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1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
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2	2	1	2	2	1	3	1	5
2	2	1	2	2	2	0	1	5
2	2	1	2	2	2	1	1	5
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2	2	1	2	2	2	3	6	5
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2	2	2	0	0	0	1	2	4
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2	2	2	0	2	2	2	7	5
2	2	2	0	2	2	3	11	5
2	2	2	1	1	1	1	1	4
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2	2	2	1	1	2	0	1	4
2	2	2	1	2	0	0	1	6
2	2	2	1	2	0	2	1	6
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2	2	2	1	2	1	3	1	5
2	2	2	1	2	2	0	5	5
2	2	2	1	2	2	1	2	5
2	2	2	1	2	2	2	5	5
2	2	2	1	2	2	3	11	5
2	2	2	2	0	1	0	1	4
2	2	2	2	1	2	2	1	5
2	2	2	2	2	0	0	2	6
2	2	2	2	2	0	1	1	6
2	2	2	2	2	0	2	1	6
2	2	2	2	2	0	3	2	6
2	2	2	2	2	1	0	4	5
2	2	2	2	2	1	1	2	5

Q	SL	M	SN	D	L	SD	FO	LSP
1	0	1	1	2	1	2	8	3
1	0	1	1	2	1	3	2	3
1	0	1	1	2	2	0	12	3
1	0	1	1	2	2	1	6	3
1	0	1	1	2	2	2	1	3
1	0	1	2	0	0	0	8	1
1	0	1	2	0	0	1	2	1
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2	2	2	2	2	1	3	1	5
2	2	2	2	2	2	0	6	5
2	2	2	2	2	2	1	12	5
2	2	2	2	2	2	2	13	5
2	2	2	2	2	2	3	17	5

8.4 UKHLS pregnant women study

8.4.1 Sleep characteristics

Table 8-19 The seven sleep questions presented in the UKHLS sleep module, and participants' responses before and after re-coding

The Seven sleep questions	Original responses	Responses used in generating sleep clusters	Responses used in running the regression analysis
Q1: How many hours of actual sleep did you usually get at night during the last month? Note: This may be different than the actual number of hours you spent in bed.	*Reported in hours and minutes*	1. Reference (≥ 6 and ≤ 9 hours) *2.* Long sleep (>9 hours) 3. *Short sleep (<6 hours)*	1. Reference (≥ 6 and ≤ 9 hours) *2.* Long sleep (>9 hours) *3. Short sleep (<6 hours)*
Q2: During the past month, how often have you had trouble sleeping because you Cannot get to sleep within 30 minutes?	*1. Not during the past month* 2. *Less than once a week* 3. *Once or twice a week* 4. *Three or more times a week* 5. *More than once most nights*	1. Absent *(1)* 2. *Less than three times a week (2,3)* 3. *Three or more times a week (4&5)*	*1. Absent (1)* 2. *Present (2,3,4&5)*
Q3: During the past month, how often have you had trouble sleeping because you Wake up in the middle of the night or early in the morning?	*1. Not during the past month* 2. *Less than once a week* 3. *Once or twice a week* 4. *Three or more times a week* 5. *More than once most nights*	1. Absent *(1)* 2. *Less than three times a week (2,3)* 3. *Three or more times a week (4&5)*	*1. Absent (1)* 2. *Present (2,3,4&5)*
Q4: During the past month, how often have you had trouble sleeping because you Cough or snore loudly?	*1. Not during the past month* 2. *Less than once a week* 3. *Once or twice a week* 4. *Three or more times a week* 5. *More than once most nights*	1. Absent *(1)* 2. *Less than three times a week (2,3)* 3. *Three or more times a week (4&5)*	*1. Absent (1)* 2. *Present (2,3,4&5)*
Q5: During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	1. *Not during the past month* 2. *Less than once a week* 3. *Once or twice a week* 4. *Three or more times a week*	1. Absent *(1)* 2. *Less than three times a week (2,3)* 3. *Three or more times a week (4)*	*1. Absent (1)* *2. Present (2,3 & 4)*
Q6:During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	1. *Not during the past month* 2. *Less than once a week* 3. *Once or twice a week* 4. *Three or more times a week*	1. Absent *(1)* 2. *Less than three times a week (2,3)* 3. *Three or more times a week (4)*	*1. Absent (1)* 2. *Present (2,3 & 4)*
Q7: During the past month, how would you rate your sleep quality overall?	1. *Very good* 2. *Fairly good* 3. *Very bad* 4. *Fairly bad*	*1. Good (1&2)* 2. *Bad (3&4)*	*1. Good (1&2)* 2. *Bad (3&4)*

8.4.2 Coding of pregnancy variables presented in the UKHLS data set

Table 8-20 Detailed coding of pregnancy variables identified within the UKHLS.

Pregnancy-related variable	Variable in Wave 2	Variable in Wave 5	Original coding	Coding used in the analysis
Caesarean section	**b_pregout1** "outcome of pregnancy"	**e_pregout1** "outcome of pregnancy"	1.Live birth – caesarean 2.Live birth - normal delivery 3.Not live birth	Delivered by caesarean section 0.No (live birth - normal delivery) 1.Yes (live birth - caesarean) Participants responded by "Not live birth" were excluded
Birth weight	**b_bwtoz** "birth weight in ounces"	**e_bwtoz** "birth weight in ounces"	In ounces	Had a macrosomic baby 0.No 1.Yes
	b_bwtk "birth weight in kg"	**e_bwtk** "birth weight in kg"	In grams	Had a low birth baby 0.No 1.Yes
	b_bwtlb "birth weight in pounds"	**e_bwtlb** "birth weight in pounds"	In pounds	
Preterm delivery	**b_bwtxp** "was CHILD'S NAME born within one week of the expected due date?"	**e_bwtxp** "was CHILD'S NAME born within one week of the expected due date?"	0.Yes 1.No	Had preterm delivery 0.No 1.Yes
	b_bwte "was CHILD'S NAME child born early or late"	**e_bwtel** "was CHILD'S NAME child born early or late"	1.Early 2.Late	
	b_bwtwk "How many weeks early/late"	**e_bwtwk** "How many weeks early/late"	Weeks	
Alcohol consumption	**b_pregdrink1** "drank alcohol during pregnancy"	**e_aedrof1** "which of these best describes how often you usually drank alcohol during this pregnancy?"	1.Never drank any alcohol 2.Less than 1-2 pw or occasion, 3.Equal to 3-6 pw or 3-5 per occasion 4.7+ pw/6+ per occasion	Drunk alcohol during pregnancy 0.No 1.Yes
Smoking	**b_pregsmoke1** "smoked during pregnancy"	**e_pregsmoke1** "smoked during pregnancy"	0.Yes 1.No	Smoked during pregnancy 0.No 1.Yes

8.4.3 Coding of confounders presented in the UKHLS dataset

Table 8-21 Detailed coding of covariates identified as confounders within the UKHLS.

Confounder	Variable in Wave 1	Variable in Wave 4	Original coding	Coding used in the analysis
Ethnicity	**a_racel_dv** "ethnic group"	**d_racel_dv** "ethnic group"	1.White (British, Irish, Gypsy or Irish traveller, other) 2.Mixed (White and Black African, White and Black Caribbean, White and Asian, Other mixed) 3.Asian (Indian, Pakistani, Chinese, Other) 4.Black (African, Caribbean, Other Black) 5.Others (Arab, Other)	1.Ethnicity with lower risk of GDM (White) **2.**Ethnicity with higher risk of GDM (Other ethnic groups)
Employment	**a_jbstat** "Please look at this card and tell me what best describes NAME's current employment situation?"	**d_jbstat "**Please look at this card and tell me what best describes NAME's current employment situation?"	1.Unemployed (unemployed, looking after family or home) 2.Self-employed (self-employed, unpaid worker in family business, doing something else) 3.Employed (paid employment (F/T, P/T)) 4.Sick /disabled (on maternity leave, long-term sick or disabled) 5. F/T training or education (on a government training scheme, F/T student)	0.Working at the time of the interview (employed, self-employed) 1.Not working at the time of the interview (Unemployed, Sick /disabled, F/T training or education)
Cohabitation	**a_mlstat_dv** "What is your current legal marital status? Are you…"	**d_mlstat_dv** "What is your current legal marital status? Are you…"	1.Single, never married/in civil partnership 2.Married 3.Civil partner 4.Separated from spouse 5.Divorced	0.Living as couple (married, civil partner) 1.Not living as a couple (single, never married/in civil partnership, divorced, separated from spouse)
Education	**a_hiqual_dv** "Highest educational qualification"	**d_hiqual_dv** "Highest educational qualification"	1.Degree 2.Other higher 3.A level etc. 4.GCSE etc. 5.Other qualification 6.No qualification	1.Degree or higher (degree, other higher) 2.A level and less (A level etc., GCSE etc., other qualification, no qualification)
Medical condition	**a_hconds** "Do you still have…"?	**d_hconds** "Do you still have HCond"?	96. None of these 1. Asthma 2. Arthritis 3. Congestive heart failure 4. Coronary heart disease 5. Angina 6. Heart attack or myocardial infarction 7. Stroke 8. Emphysema 10. Hypothyroidism or an under-active thyroid 11. Chronic bronchitis 12. Any kind of liver condition 13. Cancer or malignancy 14. Diabetes	Does the participant had one of the following chronic medical condition (i.e. cardiovascular, neurological, psychological, metabolic, inflammatory)? 1. No 2. Yes

Confounder	Variable in Wave 1	Variable in Wave 4	Original coding	Coding used in the analysis
			15. Epilepsy 16. High blood pressure 17. Clinical depression 9. Hyperthyroidism or an over-active thyroid	
Parity	**a_lprnt** "Ever had/fathered children"	**d_lnprt** "Ever had/fathered children"	1.Yes 2.No	Parity 0.Nulliparous 1.Multiparous
	a_lnprnt "Number of biological children ever had/fathered"	**d_lnprnt** "Number of biological children ever had/fathered"	Numbers	
	a_nchild_dv "Number of own children in household"	**d_nchild_dv** "Number of own children in household"	Numbers	
Household composition	**a_hhtype_dv** Classification follows closely the household composition classification in the Labour Force Survey	**d_hhtype_dv** Classification follows closely the household composition classification in the Labour Force Survey	0.1 male, aged 65+, no children, 1.1 female, age 60+, no children, 2.1 adult under pensionable age, no children 3.1 adult, 1 child 4.1 adult, 2 or more children 5.Couple both under pensionable age, no children 6.Couple 1 or more over pensionable age, no children 7.Couple with 1 child 8.Couple with 2 children 9.Couple with 3 or more children 10.3 or more adults, no children, incl. at least one couple 11.3 or more adults, 1-2 children, incl. at least one couple 12.3 or more adults, >2 children, incl. at least one couple 13.2 adults, not a couple, both under pensionable age, no children 14.2 adults, not a couple, one or more over pensionable age, no children 15.3 or more adults, no children, excl. any couples 16.2 adults, not a couple, 1 or more children 17.3 or more adults, 1 or more children, excl. any couples	0.Single without children (reference) 1.Single with children 2.Couple with children 3.Couple without children

8.4.4 Missing data

Table 8-22 Distribution of sleep characteristics amongst women with complete and missing data on pregnancy outcomes in the UKHLS (n = 921).

		Participants with missing birth outcomes		Participants with complete birth outcomes	
		n=376	%	n=545	%
Sleep duration	*< 6 hours*	272	72.34	387	71.01
	6 to 9 hours	39	10.37	67	12.29
	> 9 hours	22	5.85	33	6.06
	Missing	43	11.44	58	10.64
Latency	*Absent*	127	33.78	186	34.13
	Present	206	54.79	303	55.6
	Missing	43	11.44	56	10.28
Disturbance	*Absent*	127	33.78	75	13.76
	Present	206	54.79	414	75.96
	Missing	43	11.44	56	10.28
Snoring or	*Absent*	256	68.09	370	67.89
coughing	*Present*	73	19.41	108	19.82
	Missing	47	12.5	67	12.29
Day sleepiness	*Absent*	282	75	410	75.23
	Present	50	13.3	75	13.76
	Missing	44	11.7	60	11.01
Medication	*Absent*	319	84.84	467	85.69
	Present	21	5.59	29	5.32
	Missing	36	9.57	49	8.99
Quality	*Good*	226	60.11	363	66.61
	Bad	115	30.59	134	24.59
	Missing	35	9.31	48	8.81

Table 8-23 Distribution of pregnancy outcomes amongst women with complete and missing data on sleep in the UKHLS (n = 921).

		Participants with missing sleep data		Participants with complete sleep data	
		n=157	**%**	**n=764**	**%**
Macrosomia	*≤ 4000 gm*	71	45.22	355	46.47
	>4000 gm	21	13.38	98	12.83
	Missing	65	41.4	311	40.71
Low birth weight	*Birth weight ≥ 2500 gm*	48	30.57	244	31.94
	Birth weight <2500 gm	44	28.03	209	27.36
	Missing	65	41.4	311	40.71
Preterm labour	*Term*	100	63.69	572	74.87
	Preterm	19	12.1	102	13.35
	Missing	38	24.2	90	11.78
Mode of delivery	*Vaginal*	83	52.87	511	66.88
	Caesarean	35	22.29	157	20.55
	Missing	39	24.84	96	12.57

Table 8-24 Distribution of sociodemographic and health characteristics of women with complete and missing data on sleep or pregnancy outcomes in the UKHLS (n = 921).

		Missing sleep or medical data		Complete sleep and medical data	
		n=468	%	n=453	%
Age	*≤ 19 years*	14	2.99	13	2.87
	20-29 years	129	27.56	102	22.52
	30-39 years	129	27.56	106	23.4
	≥ 40 years	28	5.98	9	1.99
	Missing	168	35.9	223	49.23
Parity	*Nulliparous*	261	55.77	312	68.87
	Multiparous	207	44.23	141	31.13
	Missing	0	0	0	0
Ethnicity	*Lower risk of GDM*	342	73.08	351	77.48
	Higher risk of GDM	124	26.5	99	21.85
	Missing	2	0.43	3	0.66
Cohabitation	*Not cohabited*	66	14.1	108	23.84
	Cohabited	402	85.9	344	75.94
	Missing	0	0	1	0.22
Smoking	*Not current smoker*	309	66.03	379	83.66
	current smoker	48	10.26	74	16.34
	Missing	111	23.72	0	0
Alcohol	*No alcohol consumption*	287	61.32	345	76.16
	Alcohol consumption	71	15.17	108	23.84
	Missing	110	23.5	0	0
Employment	*Currently working*	25	5.34	32	7.06
	Currently not working	270	57.69	278	61.37
	Missing	173	36.97	143	31.57
Education	*Degree and higher*	234	50	219	48.34
	A level and Lower	196	41.88	196	43.27
	Missing	38	8.12	38	8.39

8.5 Association between sleep variables and pregnancy outcomes in participants at risk of GD

8.5.1 Ethical approval letter for the Scott/Ciantar study.

NHS
Health Research Authority
NRES Committee Yorkshire & The Humber – Bradford

Yorkshire & Humber REC Office
Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

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06 June 2012

Dr Etienne Ciantar
Academic SpR in Obstetrics & Gynaecology
Leeds Teaching Hospitals NHS Trust
Academic Unit of Obstetrics & Gynaecology
D Floor, Clarendon Wing
Leeds General Infirmary
LS1 3EX

Dear Dr Ciantar

Study title: **A pilot study to assess the duration and quality of sleep in pregnant women with diabetes and how this relates to pregnancy outcomes and glycaemic control.**
REC reference: **12/YH/0156**

Thank you for your letter of 31 May 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of

the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		05 March 2012
Covering Letter		14 May 2012
Covering Letter		31 May 2012
Letter from Sponsor		22 February 2012
Other: CV - Dr. Etienne Ciantar		05 March 2012
Participant Consent Form	2	14 May 2012
Participant Information Sheet: Pre-gestational diabetes	3	31 May 2012
Participant Information Sheet: Gestational diabetes	3	31 May 2012
Protocol	1	05 March 2012
Questionnaire: Berlin Questionnaire		
Questionnaire: Pittsburgh Sleep Quality Index	1	
REC application	3.1	21 February 2012
Referees or other scientific critique report	1	14 December 2011
Response to Request for Further Information		14 May 2012
Response to Request for Further Information		31 May 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

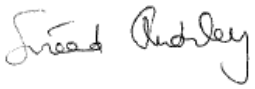
You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/YH/0156	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely



pp Dr Ian Woollands
Chair

Email: sinead.audsley@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Dr Derek Norfolk, Leeds Teaching Hospitals Trust*
Ms Anne Gowing, Leeds Teaching Hospitals NHS Trust

8.5.2 Data extraction method

8.5.2.1 Identifying the study's variables

The existing published literature was searched, and clinicians were consulted to identify potential key variables that might play a role in the association between sleep and pregnancy outcomes. The potential variables were then assessed for their availability in the medical records used at Leeds Teaching Hospitals NHS Trust.

In this stage, a simple hypothetical directed acyclic graph (DAG) was drawn to anticipate the key variables to extract (Figure 6-2). The variables were arranged according to their temporal sequences (i.e., when the 'event' or 'process' these variables represented had occurred in the pregnancy). Their suggested relationships were symbolised using unidirectional arrows. From the hypothetical DAG (Figure 6-2), the priority variables were assigned to be the pre-pregnancy events and individual features (e.g., pre-pregnancy weight, previous pregnancies history and SES), possible confounders from the early pregnancy events (e.g., multiple pregnancies) and outcomes of interest (e.g., maternal and neonatal complications). Late pregnancy events were considered proxies for sleep and were not set as priority variables (e.g., GHTN, PE and foetal distress).

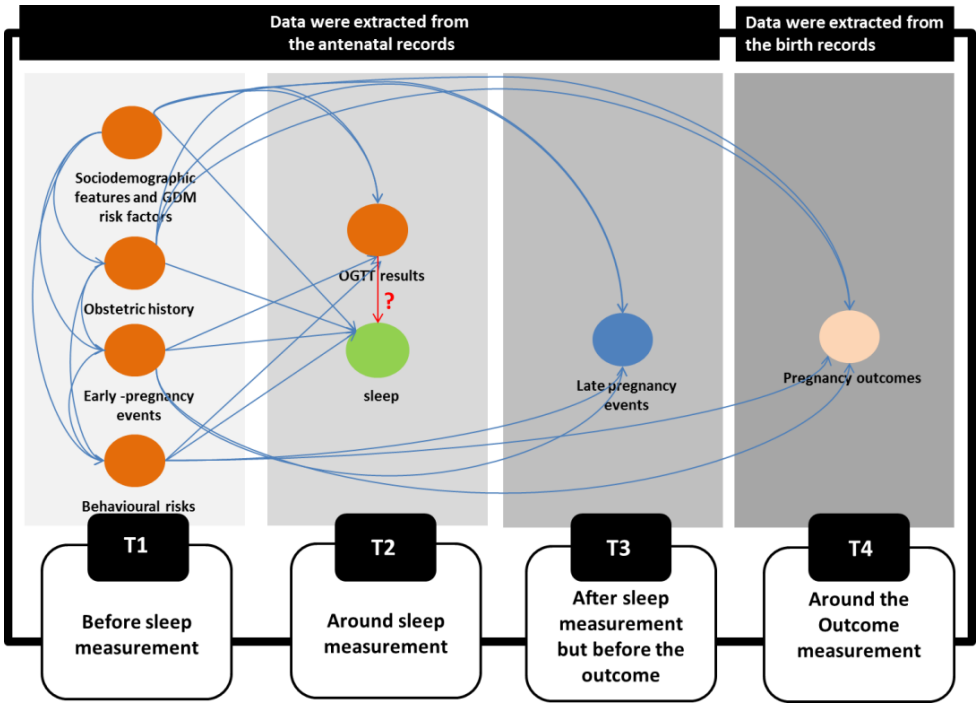


Figure 8-6 Hypothetical directed acyclic graph showing the temporal relationship amongst variables likely to have been available for participants the Scott/Ciantar study

If a variable was not available in the records, its proxy was gathered instead. For example, a postcode was used instead of socioeconomic status, and the booking weight at the first antenatal visit was used instead of the pre-pregnancy weight. Each medical file consisted of the following records:

Antenatal records: personal information, health information, family history, obstetric history, anthropometric data, midwife and physician notes, laboratory records and ultrasound records

Birth records: personal information, current pregnancy complications, admission details, birth details, new-born records and discharge summary

Diabetic antenatal clinic records: physician notes

Each variable was given a reference number and then plotted against the record's name and the page number in that record to create a guide for the extractors.

When all the variables of interest were identified, a detailed DAG was generated. The available variables were then arranged according to their temporal sequence. A DAG was drawn using the available variables to identify those that might be confounders, mediators or competing exposures in each possible (and available) specified outcome.

8.5.2.2 Collecting data from the clinical records

Before the data were collected, the following criteria were established:

I. Only variables required for adjustment in any analyses between sleep and each pregnancy outcome were extracted from the medical records (an approach that was intended to increase the efficiency of data extraction).
II. The data for each extracted variable were examined for quality (i.e., precision, consistency, accuracy and missingness), and only variables of acceptable quality were considered for inclusion in the analysis.
III. Data were collected at the end of the pregnancy period first from the hard copy of the record. If missingness was encountered, the missing data were searched for in the online records available in the library. The medical records were inspected carefully, and the extracted data were transferred to an Excel sheet as follows:

First, the information was reported on the Excel sheet exactly as it was written in the records (e.g., neonatal complications at birth were written on the Excel sheet as they were in the records before deriving the NICU admission and prematurity variables from the details). Subsequently, coding took place after revising the gathered data.

The objectively measured variables (e.g., weight) were reported on the Excel sheet as they were recorded by health professionals in the medical records in numbers and units. The units were converted into a single unified unit when the quality of the variable was determined.

If a variable (e.g., maternal age) was reported in different locations in the records (e.g., in the personal information sheet, in the first antenatal visit sheet and in the labour information sheet), all these data were gathered and reported separately in several columns in Excel to examine their consistency and to compensate for missingness in one location.

In recording medical diagnoses, objective measurements were used to confirm the diagnosis instead of subjective measurements (e.g., depending on US to diagnose large for gestational age foetus (LGA) and not fundal height).

The participants' medical records were handled securely within the Trust's premises. The extracted data were stored on a secure (password-protected) hard drive at the university, which only authorised personnel were able to access. No personal identification data (names, complete address and complete NHS number) were recorded, as each participant was given a unique study identification number.

8.5.2.3 Data cleaning and coding

The data were carefully gathered from medical records and then transcribed on an Excel sheet without modifying or paraphrasing sentences or words. These data were then revised for recoding according to the following criteria:

Continuous variables that acted as confounders and required adjustment in the regression models (e.g., maternal BMI and age) were kept continuous whereas the continuous variables that were chosen as outcomes (i.e., weeks of gestation, birth weight, Apgar score and estimated blood loss) were transformed into binaries to estimate the odds ratio.

Categorical variables were recoded as binary variables to reduce the number of categories, which allowed us to increase the number of adjusted confounders without losing the stability of the regression models.

Variables with open details (e.g., neonatal transferred details or labour ward admission details) were used in one of two ways:

To examine the consistency of other variables, such as the labour ward admission details, including a summary of current pregnancy complications, which was used to examine the consistency of development of LGA or current GDM.

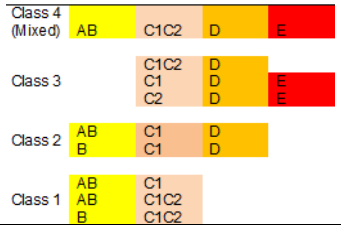
Generating new variables according to yes or no responses. For example, transferred neonatal details and discharge summaries were both used to generate an NICU admission variable that had a yes or no response.

(Table 8-25) presents a detailed summary of the extraction and coding of each variable.

Table 8-25 Details of data extracted from the medical records for use as analytical variables in the Scott/Ciantar study.

Variable name	Medical records	Section	Question	Original coding	New coding
Birth weight	Birth records	New-born details	"Birth weight "	Grams	Low birth weight 0.No 1.Yes Macrosomia 0.No 1.Yes
Preterm	Birth records	1. New-born details 2. Admission to the delivery ward details	"Weeks of gestation"	Weeks	Preterm 0.No 1.Yes
Caesarean delivery	Birth record	1. Caesarean delivery details 2. Discharge summary	Mode of delivery	• Normal vaginal delivery • Forceps assessed vaginal delivery • Emergency caesarean delivery • Elective caesarean delivery	Caesarean delivery 1. No 2. Yes
Estimated blood loss	Birth records	Delivery details	"Estimated blood loss"	Continuous variable	Blood loss >500 ml 0.No 1.Yes
3rd degree tear or more	Birth records	Delivery details	"Degree of tear"	• First • Second • Third • Fourth	0.Absent (first, second) 1.Present (third, fourth)
Apgar scores	Birth records	New-born details	"0 minutes Apgar's score" and "5 minutes Apgar's score"	Scale from 0 to 10	Low Apgar score <7 0.No 1.Yes
NICU admission	Birth records	1. New-born details 2. Discharge summary	"Transfer, details"	Open ended response	Admitted to NICU 0.No 1.Yes
Previous GDM	Antenatal records	Health problems	"Have you ever had any of the following -diabetes"	Yes or no responses plus details	Previous history of GDM 0.No 1.Yes
		Obstetric history	"Previous pregnancies details" -"any problems during pregnancy"	Yes or no responses plus details	
		Midwife notes	It was mentioned as risk factors of GDM and causes of OGTT referral	Open ended response	
	Diabetic antenatal clinic records	Physician notes in the first visit	It was mentioned as risk factors of GDM	Open ended response	

Variable name	Medical records	Section	Question	Original coding	New coding
Family history of DM	Antenatal records	Family history details	"Does anyone in your family have any of the following- Diabetes	Yes or no responses plus details	Family history of DM 0.No 1.Yes
		Midwife notes	It was mentioned as risk factors of GDM and causes of OGTT referral	Open ended response	
	Diabetic antenatal clinic records	Physician notes in the first antenatal visit	It was mentioned as risk factors of GDM	Open ended response	
History of previous macrosomia	Antenatal records	Obstetric details	"Previous pregnancies details"- birth weight	1.Yes 2.No	Previous history of macrosomia 0.No 1.Yes
		Midwife notes	It was mentioned as risk factors of GDM and causes of OGTT referral	Open responses	
	Diabetic antenatal clinic records	Physician notes in the first visit	It was mentioned as risk factors of GDM		
Obstetric history	Antenatal records	Obstetric history details	"Previous pregnancies details"- "any problems: during pregnancy, labour and birth and after birth"	Yes or no response plus details	0. Non-significant obstetric history 1.Significant obstetric history (Miscarriages before 12 weeks, Miscarriages after 12 weeks, Still births, Caesarean sections, Birthweight under 2.5 kg, and Gestation under 37 weeks)
			Obstetric summary; 1.Miscarriages before 12 weeks 2.Miscarriages after 12 weeks 3.Still births 4.Caesarean sections 5.Birthweight under 2.5 kg 6.Gestation under 37 weeks	1.Yes 2.No	
Gender of the new-born	Birth records	New-born details	"gender of the new-born"	1. Male 2. Female	0.No 1.Yes
OGTT test results	Antenatal records	For women with or without GDM, it was reported from the lab investigation results	Two readings; fating and 2 hours post prandial	Mmol/l	Continuous variable
		For women with GDM, it was reported from the physician notes in the first diabetic antenatal clinic	Two readings were recorded; fating and 2 hours post prandial		

Variable name	Medical records	Section	Question	Original coding	New coding
Socio-economic status (SES)	Antenatal records	Personal information	Derived from the post code using the six social grades identified by the UK Office for National Statistics (ONS) available at: http://www.ons.gov.uk/ons/index.html		1.Higher SES (classes 1 and 2) 2.Lower SES (classes 3 and 4)
Parity	Antenatal records	Obstetric history details	"Previous pregnancies details" 1.Type of birth 2.Number of birth Under the section of important information -"para" "obstetric summary" which included the number of; 1.Live births 2.Miscarriages before 12 weeks 3.Miscarriages after 12 weeks 4.Still births 5.Total pregnancies	Yes or no plus details Was reported as numbers of pregnancies + number of parities+ number of miscarriages 1.Yes 2.No	Parity 0.Nulliparous (0 parity) 1.Multiparous (≥ 1)
Ethnicity	Antenatal records	Personal information	"How would you describe yourself"	1.Bangladeshi 2.Black African 3.Black Caribbean 4.Chinese 5.Indian 6.Pakistani 7.White	0.Ethnicity without risk of GDM (white) 1. Ethnicity with risk of GDM (Bangladeshi, Black African, Black Caribbean, Chinese, Indian, Pakistani)
Cohabitation	Antenatal records	Personal information	"Are you…." "Do you have a husband or partner?"	1.Married 2.Separated 3.Widowed 4.Divorced 1.Yes 2.No	Cohabited 1. No 2. Yes

Variable name	Medical records	Section	Question	Original coding	New coding
Medical condition	Antenatal records	Health information	"Have you ever had any of the following…."	• Anaesthetic problem • Asthma or chest problems • Blood transfusion • Diabetes • Epilepsy • Fertility problems • Vaginal infections • Heart problems • High blood pressure • Kidney or urinary problems • Liver disease or hepatitis • Mental health problems • Operations • Physiological difficulties • Thrombosis	Health condition 0.No 1.Yes
Smoking	Antenatal records	Health details	Have you ever smoked "When did you stop smoking" "Number of cigarettes smoked a day"	1.Yes 2.No Date Number	Current smoker 0.No 1.Yes
Alcohol	Antenatal records	Health details	"Do you drink alcohol" "How many units of alcohol do you drink each week?"	1.Yes 2.No Number	Drinking alcohol during current pregnancy
BMI in the first antenatal visit	Antenatal records	Anthropometry details	"Important information-BMI "	Kilogram /meter^2	• Underweight <18.5 • Normal <25 & ≥ 18.5 • Overweight <30 &≥ 25 • Obese ≥ 30
Maternal age	Antenatal records Birth records	Personal information Midwife notes Diabetic antenatal clinic Admission details	Age	Years	Years

8.5.3 Quality of variables extracted from the medical records

Table 8-26 Quality of the variables extracted from the medical records of participants who were included in the Scott/Ciantar study, according to their accuracy, consistency and precision.

Variables	Recording method	Accuracy	Consistency	Precision
Age	Recorded by the midwife during the first antenatal visit.	Age in the first visit antenatal was chosen to be included in the analysis, as it preceded all events of interest. There was a slight difference between it and the age when the questionnaire was collected, and medical data were gathered (few months).	It was consistent compared to the date of birth.	Because it was reported in years, the level of precision was less than if it had been reported in months.
Postcode and derived SES	Recorded by the midwife during the first antenatal visit.	It was accurate because it was crucial information, and it was updated for each visit. SES information was estimated using the postcode based on the six social grades invented by the UK Office for National Statistics (ONS): http://www.ons.gov.uk/ons/index.html	It was consistent compared with the patient identification information presented in the identification slip.	The derived level of SES was not precise, as it projected a rough estimation based on the postcode only and not on all the indicators of SES (e.g., education, job and income). Estimation using postcode gives an idea about the neighbourhood rather than a particular household.
Ethnic group	Reported by the participants	Participants occasionally were mistaken about their ethnicity with other measurements. As a result, rather than choosing one of the available categories, they wrote their understanding of ethnicity, which in some cases was their religion (e.g., Sikh) or nationality (e.g., British, Iranian and Chinese) In the case of religion, ethnicity was coded as missing, and in the case of nationality, ethnicity was coded as appropriate.	No other records to compare	The categories were both broad and limited, and they depended on the participants' statement of their ethnic origin. The number of categories was further reduced during the analysis, and the focus was directed to categorising ethnicity based on the associated risk of developing GDM and not on the precise ethnic groups.
Marital status	Reported by the participants	Having both limited and broad categories might have affected the accuracy of the variables. For instance, some participants did not choose a response from the available choices but described their status as engaged or widow, for example.	Consistent with the partnership variable	The martial status might change over the course of pregnancy, which might affect the precision if it was not updated in the medical notes. However, because the interest was not the legal status but the presence of a

Variables	Recording method	Accuracy	Consistency	Precision
		In a later stage, this variable was merged with the partnership variable to compensate for missingness in both variables. It was termed cohabiting and categorised as a binary.		partner, the variable was used to generate a new variable, which was the presence of a partnership.
Partnership	Reported by the participants	Reported as either yes or no without further details. However, in a later stage, this variable was merged with the marital status variable to compensate for missingness in both variables.	Consistent with the marital status	
History of smoking	Reported by the participants	Few participants reported the date that they had quit smoking as the date of their first antenatal visit. If the patient reported the date she stopped smoking as the date of the first antenatal visit or within the last week, the participant was considered a current smoker. In the beginning, four groups were defined (i.e., current smoker, ex-smoker, passive smoker and never smoked), but because of the small number of participants in each group, it was further reduced to either current smoker or not a current smoker, which caused a further loss of information and deceased the level of accuracy	The history of smoking was derived from three questions in the records. 1.Have you ever smoked: (yes, no)? 2.Date stopped smoking: _/_/_ 3.Number of cigarettes per day: ___ 4.Does your partner smoke? Using word “ever” in the question made it difficult to understand the current smoking status of a participant especially if not all the three questions were answered by her. E.g., a participant might respond by choosing yes for the first question then leaving the rest empty, which made it unclear if she still smoked or had stopped.	Measurement of smoking only once in early pregnancy and the use of yes and no responses might not be a precise reflection of the smoking status because it might change during pregnancy, as well as the number of cigarettes and the amount of inhaled smoke.
Alcohol	Reported by the participants	Participants might not be accurate about reporting their consumption status and the amount of alcohol they consumed. In addition, some participants did not respond to the question, which might be linked to their unwillingness to divulge the consumption of alcohol. The variable was reduced later in the analysis to yes or no. This reduction caused the loss of much information.	Compared with the unit per week variable	Measurement of alcohol consumption only once in early pregnancy and the use of yes and no responses might not be a precise reflection of the drinking status, which might change during pregnancy, as well as the number of consumed units.

Variables	Recording method	Accuracy	Consistency	Precision
Family history of DM	Reported by the participants	Reported by participants as yes or no	Compared with the risk factor of gestational diabetes recorded in notes by the midwife and physician, which were consistent	Precision depended on the reliability of the participant.
DM in first degree relative	Reported by the participants	If a participant mentioned that her mother, father, sister or brother had a history of diabetes, the response was considered yes. However, many participants neglected to indicate who had a history of DM.	Compared with the risk factors of gestational diabetes in the notes by the midwife and physician, which were consistent	Precision depended on the reliability of the participant.
History of previous GDM	Reported by the participants	The accuracy depended on the accuracy of the participants.	Compared with the following variables: history of DM, risk factor of GDM and previous pregnancy complications, which were consistent	Precision depended on the reliability of the participant.
BMI	Measured by the midwife during the first antenatal visit	Calculated by the midwife and reported rounder up to different decimal numbers	Compared with the risk factors of GDM in the notes by the midwife and physician; the height and weight	The precision depended on the precision of the measured weight, which was determined by different scales in different settings and different health professionals. These different situations might have affected the level of precision.
Parity	Recorded by the midwife during the first antenatal visit	Reported based on a given history, so the accurately depended on the participant. Parity indicated birth and did not reflect in full what happened with previous pregnancies such as miscarriages after 12 weeks and before 20 weeks, which might limit the accuracy of this variable in influencing the association between sleep and pregnancy outcomes. In addition, it did not till details of multiple pregnancies	Compared with the number of previous pregnancies, the number of still or live births and the number of miscarriages, inconsistent reporting was found, especially in the number of previous pregnancies and parity. Perhaps the inconsistency was linked to the understanding of a midwife of how to report the variable, which should be reported in the following format: P = number of pregnancies + number of deliveries after 20 + terminated pregnancy before 20 weeks	Precision depended on the reliability of the participant

Variables	Recording method	Accuracy	Consistency	Precision
Previous obstetric complications	Recorded by the midwife during the first antenatal visit.	Derived from details of previous pregnancies and the numbers of still births, live births, miscarriages, caesarean deliveries, neonatal deaths and low birth weights Reported based on the history given by the participant, so its accuracy depended on the participant. In addition, as midwives did not provide information, we had trace them to other locations in the records, which might have affected the accuracy of the variable, especially in relation to events occurring before or after 12 weeks of gestation. Previous obstetric complications was categorised as the presence or absence of complications, which led to the loss of information.	Variables used to generate this variable were examined against each other. Inconsistency was found between the reported numbers, the details of previous pregnancies and the reported parity. Large amounts of missingness were also found in the number of previous obstetric events.	Precision depended on the reliability of the participant
OGTT results	Reported as lab test results on the lab paper slip or in the first visit to the diabetic antenatal clinic.	Reported in mmol/l as fasting and 2 hours postprandial. The numbers were approximated to the second decimal point.		Many factors might affect the precision of the readings, e.g. fasting of the participants, accurate 2 hours period between the two readings and GA Repeating the reading might not give similar result if repeated in different circumstances.
Gestational age when delivery occurred	Recorded by the midwife based on the early ultrasound	Reported in weeks and days. However, because it was reported based on an early ultrasound, there is still some chance of error of one week or two. Subsequently, the variable was divided into term and preterm (< 37 weeks)	Compared with the birth plan in the diabetic antenatal care notes for women with GDM and with the notes of the midwife for the last antenatal visit for women without GDM. It also was compared with early ultrasound records and neonatal birth details, which were consistent.	Depended on the Ultrasound machine and the technician as different sitting might lead into a different result However, the result was compared with last menstrual period and fundal height and sometimes 4 weeks different was noticed

Variables	Recording method	Accuracy	Consistency	Precision
Mode of delivery	Recorded by the midwife after birth	It was sometimes not reported as an emergency or an elective caesarean delivery, especially in the online records. Because of the lack of consistency and accuracy in reporting the instrumental delivery and the reasons for caesarean, the variable was categorised as a caesarean delivery or a vaginal delivery without further details.	Compared with previous obstetric history for emergency caesarean and elective caesarean, as well as the number of previous caesareans, which were consistent. Also compared with neonatal complications and US records for breach presentation, which were consistent.	
Estimated blood loss	Recorded by the midwife after birth	It depended on the midwife's estimation, so it was not an accurate measurement.	It was examined against discharge summary details, and it was consistent.	The precision was low since it was depended on the estimation and different midwives
Birth weight	Recorded by the midwife after birth	Birth weight was measured by the midwife immediately after birth using a neonatal scale. Hence, the accuracy of the variable depended on the accuracy of the scale. The birth weight was reported in grams. However, the analysis generated two variables. Macrosomia (birth weight > 4,000 g) and LBW (birth weight < 2,500 g). As a result some information was lost.	Compared with the following variables: estimated foetal weight in the last ultrasound; neonatal complication; the indication of NICU admission; prematurity records; and presence of twin pregnancy A good level of consistency was found.	The weight was taken by different scale in different setting by different health professionals which might affected precision
Gender	Recorded by the midwife after birth			
NICU admission	Recorded in the transfer records by the midwife	The reasons for NICU admission were varied (e.g., prematurity and genetic anomalies); dividing the responses into yes or no led to the loss of valuable information.	Compared with the following variables: neonatal complication: prematurity, gestational age, multiple pregnancies, mode of delivery and foetal growth. The variables were consistent.	

8.5.4 Missing data

8.5.4.1 Mechanisms of missingness of missing data

Of the 193 participants who were successfully recruited at the beginning of the study, the files of 15 participants were lost at the end of the study, and their medical data were not gathered (Figure 8-7). The reasons for the loss of the medical records are the following:

I. Medical files were lost in another department
II. Medical files were transformed into online records and could not be accessed.
III. Participants delivered outside Leeds, and their medical files were transferred to another NHS trust.

Only 127 of the remaining 178 participants with accessible medical records had complete medical records of the outcomes of interest (i.e., delivery mode, blood loss, preterm delivery, birth weight, NICU admission and Apgar score) and the covariates (i.e.**,** age, race, alcohol, smoking, BMI, age, SES, parity, sex of the neonate, health condition, partner and OGTT results; Figure 8-8). In dividing the number of accessible medical records by the number complete medical records, we found the completion rate of the medical records to be 71.34%.

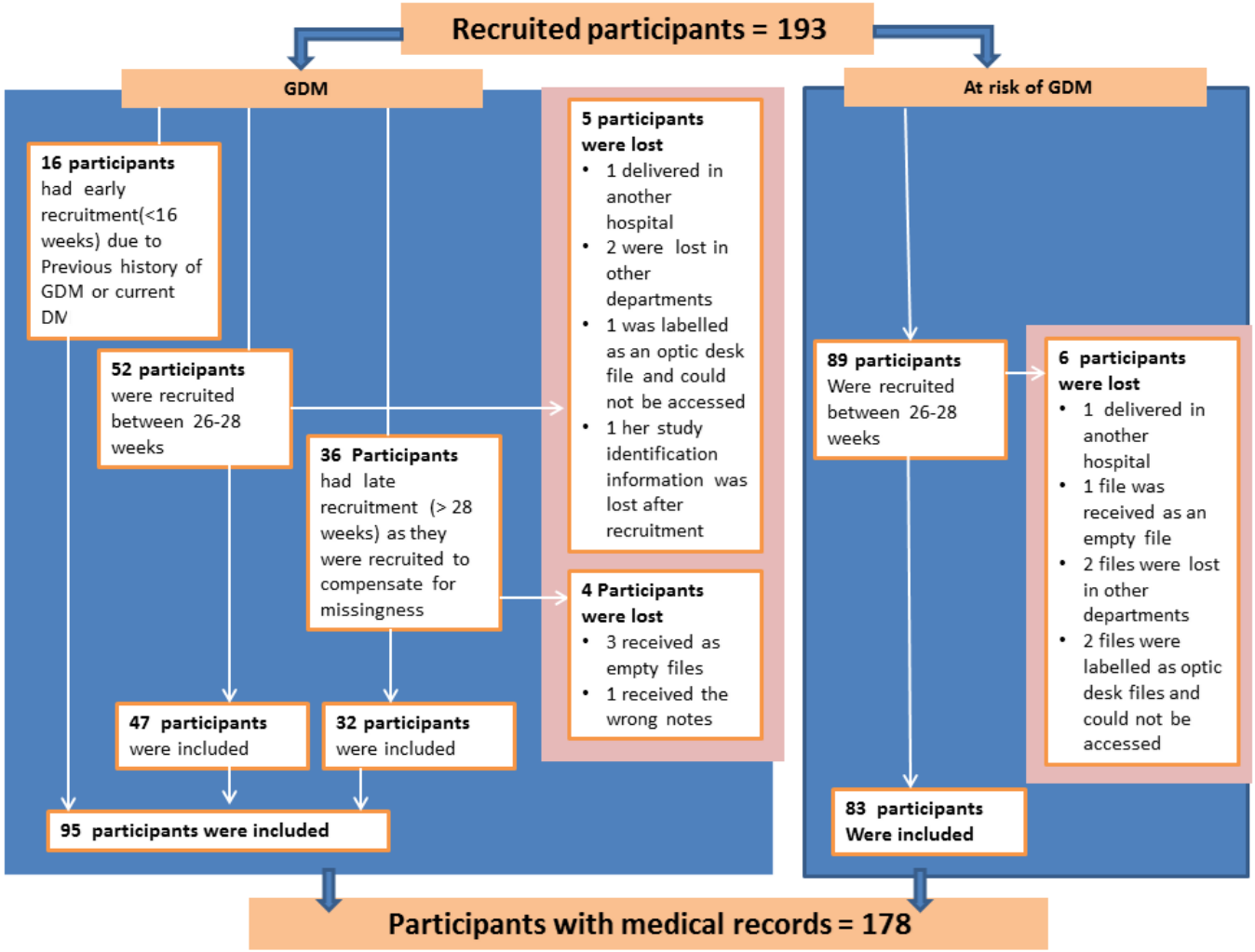


Figure 8-7 Flow chart summarising the numbers and mechanisms of missingness of the lost medical records for Scott/Ciantar study participants whose medical records could not be located.

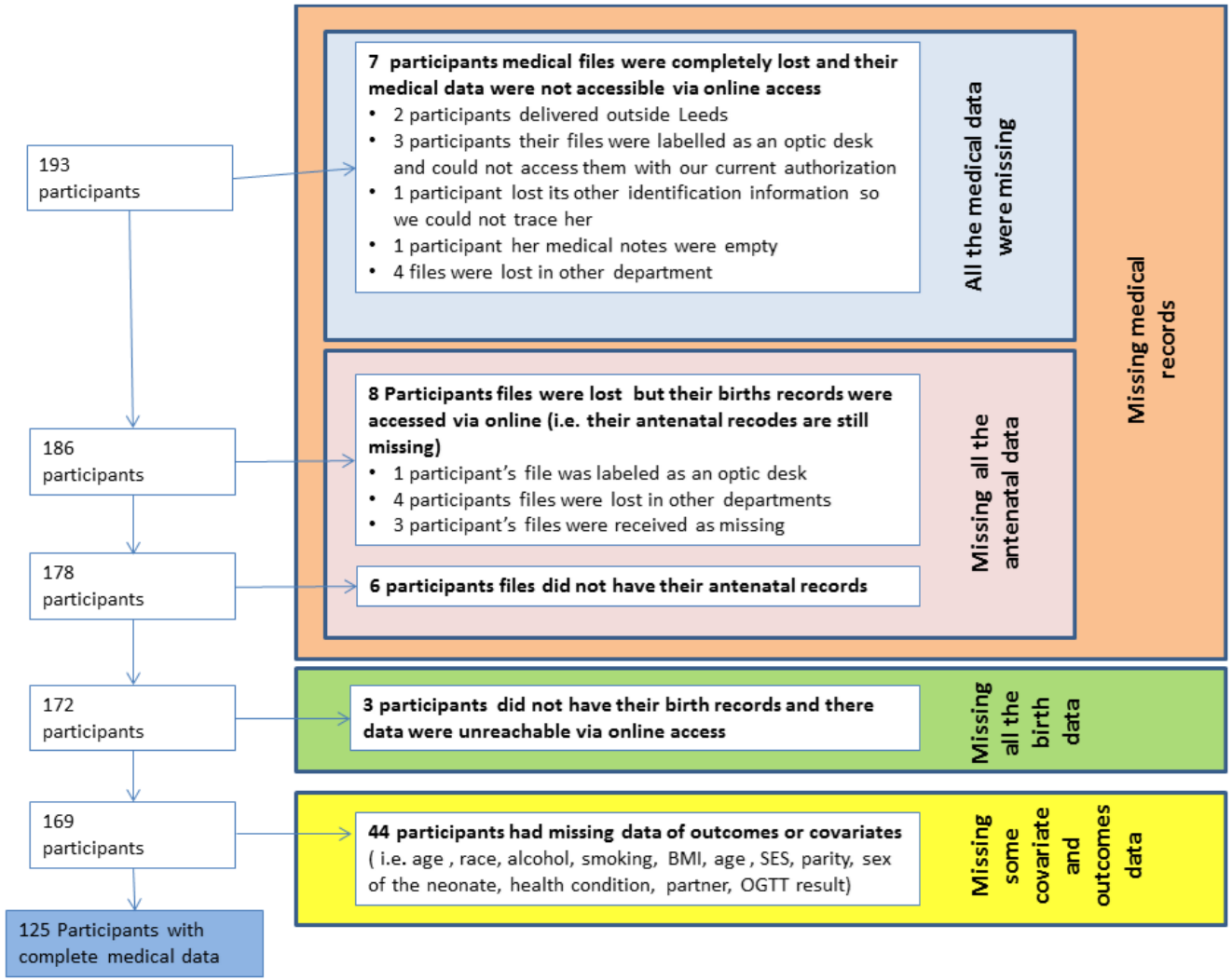


Figure 8-8 Flow chart summarising the numbers and mechanisms of missingness of missing clinical medical data amongst Scott/Ciantar study participants.

Of the 193 participants who were recruited in the study, nine participants did not return their sleep questionnaires. However, two participants without questionnaires were excluded because they did not fit the inclusion criteria (Figure 8-9). Nineteen of the 180 women who returned their questionnaires did not respond to some questions (Figure 8-9).

The completion rate of the sleep questionnaire was 162 (the number of participants who responded to all questions), which was divided by 180 (the number of participants who returned their questionnaire) and then multiplied by 100 = 85.56%.

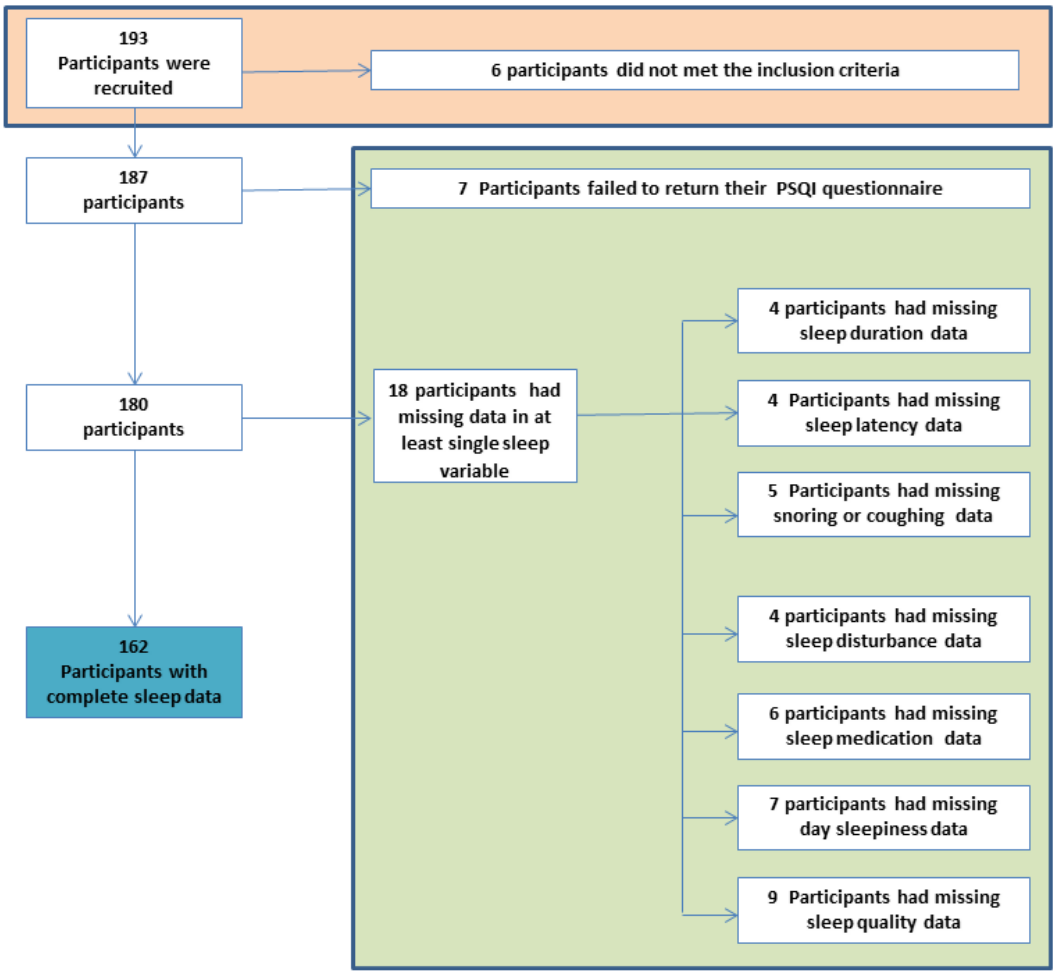


Figure 8-9 Flow chart summarising the numbers, and mechanisms, of missing sleep data for the Scott/Ciantar study participants.

The number of participants who completed the sleep questionnaire and who had complete medical data was 108: completion rate = (108/187) x 100 = 57.4 %. (Figure 8-10).

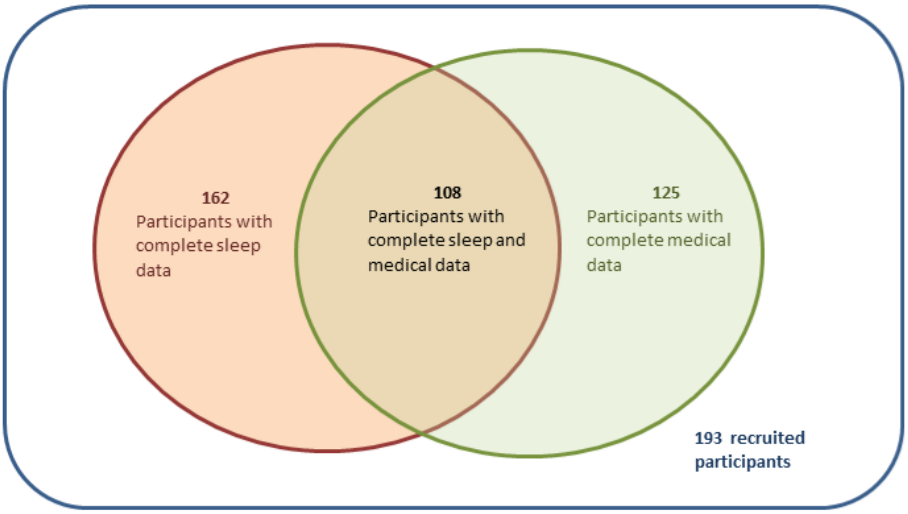


Figure 8-10 Summary of the number of participants in the Scott/Ciantar study with complete medical and sleep data.

8.5.4.2 Number and characteristics of missing data

Table 8-27 Socio-demographic features of participants with missing sleep data compared to those of participants with complete sleep data in the Scott/Ciantar study (N = 187)

		Missing sleep data		Complete sleep data	
		n=25	%	n=162	%
Age	*≤ 19 years*	1	4	4	2.47
	20-29 years	10	40	58	35.8
	30-39 years	12	48	91	56.17
	≥ 40 years	2	8	9	5.55
	Missing	0	0	0	0
Parity	*Nulliparous*	8	32	67	41.36
	Multiparous	15	60	84	51.85
	Missing	2	8	11	6.79
SES	*Higher class*	6	24	62	38.27
	Lower class	17	68	96	59.26
	Missing	2	8	4	2.47
Ethnicity	*Lower risk of GDM*	6	24	32	19.75
	Higher risk of GDM	16	64	113	69.75
	Missing	3	12	17	10.49
Cohabitation	*Not cohabited*	3	12	11	6.79
	Cohabited	19	76	138	85.19
	Missing	3	12	13	8.02
Smoking	*Not current smoker*	18	72	116	71.6
	Current smoker	4	16	16	9.88
	Missing	3	12	30	18.52
Alcohol	*No alcohol consumption*	17	68	116	71.6
	Alcohol consumption	4	16	21	12.96
	Missing	4	16	25	15.43
BMI	*Underweight*	0	0	0	0
	Normal weight	6	24	37	22.84
	Overweight	6	24	46	28.4
	obese	10	40	65	40.12
	Missing	3	12	14	8.64

Table 8-28 Frequency distribution of birth outcomes amongst participants with missing sleep data compared to those of participants with complete sleep data in the Scott/Ciantar Scott/Ciantarstudy (N = 187)

		Missing sleep data		Complete sleep data	
		n=25	%	n=162	%
EBL	*≥ 500 ml*	15	60	105	64.81
	<500 ml	10	40	57	35.19
	Missing	0	0	0	0
Low birth weight	*Birth weight ≥ 2500 gm*	25	100	142	87.65
	Birth weight <2500 gm	0	0	7	4.32
	Missing	0	0	13	8.02
Apgar at birth	*≥ 7*	23	92	147	90.74
	<7	2	8	15	9.26
	Missing	0	0	0	0
Preterm labour	*Term*	24	96	146	90.12
	Preterm	0	0	8	4.94
	Missing	1	4	8	4.94
Mode of delivery	*Vaginal*	16	64	103	63.58
	Caesarean	8	32	49	30.25
	Missing	1	4	10	6.17
NICU admission	*No admission*	24	96	136	83.95
	Admission	1	4	9	5.56
	Missing	0	0	17	10.49

The frequency distribution of sleep characteristics in the participants with missing data was similar to the distribution of characteristics in those with complete data (Table 8-29).

The sleep duration of participants with missing data was mainly within the reference range (75%, n= 45). Latency (70.97%, n= 44) and disturbance (93.55%, n = 58) tended to be present, whereas the usage of medication (3.23%, n=2) and snoring (25.8%, n=116) were almost absent. Quality was reported as good to fairly good (54.84%, n= 34) and day sleepiness (59.68%, n= 37) was absent in approximately half of these participants.

Table 8-29 Frequency distribution of sleep characteristics amongst participants in the Scott/Ciantar study who had complete and missing medical data (N = 187)

		Participants with missing medical data		Participants with complete medical data	
		n=62	%	N=125	%
Sleep duration	*Short sleep (<6)*	10	16.13	23	18.4
	Reference range (6-9)	45	72.58	74	59.2
	Long sleep (>9)	4	6.45	20	16
	Missing	3	4.84	8	6.4
Latency	*Absent*	15	24.19	36	28.8
	Present	44	70.97	81	64.8
	Missing	3	4.84	8	6.4
Disturbance	*Absent*	1	1.61	12	9.6
	Present	58	93.55	105	84
	Missing	3	4.84	8	6.4
Snoring or coughing	*Absent*	42	67.74	75	60
	Present	16	25.81	42	33.6
	Missing	4	6.45	8	6.4
Day sleepiness	*Absent*	37	59.68	78	62.4
	Present	20	32.26	38	30.4
	Missing	5	8.06	9	7.2
Medication	*Absent*	55	88.71	114	91.2

		Participants with missing medical data		Participants with complete medical data	
		n=62	**%**	**N=125**	**%**
	Present	2	3.23	3	2.4
	Missing	5	8.06	8	6.4
Quality	*Good*	34	54.84	72	57.6
	Bad	25	40.32	40	32
	Missing	3	4.84	13	10.4

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