Exploring the relationship between metabolic syndrome and sleep amongst adults in the UK

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Abstract

The metabolic syndrome (MetS) is routinely operationalised as a cluster of adverse risk factors for both cardiovascular heart disease and type 2 diabetes. Amongst the risk factors which may contribute to the development (and consequences) of MetS is sleep. The overarching aim of the present thesis is to generate an improved understanding of the available evidence regarding the speculative relationship between sleep and MetS.

After a systematic review and meta-analysis of previous empirical studies exploring the relationship between MetS and sleep, the present study draws on a large-scale, nationally representative survey of UK adults in which directly measured and self-reported MetS symptoms/components and self-reported sleep characteristics have been recorded; and assesses the reliability of self-reported indicators of MetS before re-evaluating the association between MetS and sleep.

The systematic review suggested that, while there is some evidence of an association between MetS and sleep across a range of sleep-related characteristics, this evidence draws on a small number of non-UK cross-sectional studies, some of which involved methods that are prone to error and bias. On the other hand, the self-reported MetS components identified in the UKHLS questionnaires provided substantial agreement with direct measures thereof. The subsequent associations observed between three key components of MetS (elevated waist circumference; high blood pressure; and diabetes – and different combinations thereof) and seven self-reported sleep characteristics were dependent upon: the specific sleep characteristic examined; the choice of referent group used; adjustment for sociodemographic and/or lifestyle covariates; and the use of self-reported or directly measured MetS components. Key differences between these findings and those of previous studies suggest these associations remain speculative and subject to methodological and contextual variation between studies.

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Abbreviations

AHA/NHLBI	American Heart Association/National Heart, Lung, and Blood Institute Scientific statement
BMI	Body Mass Index
BNF	British National Formulary
BP	Blood Pressure
CAPI	Computer Aided Personal Interview
CI	Conference Interval
CPAP	Continues Positive Airway Pressure
CVD	Cardiovascular Disease
DAG	Directed Acyclic Graphs
DM	Diabetes Miletus
EGIR	The European Group for the Study of Insulin Resistance
ESRC	Economic and Social Research Council
ESS	Epworth Sleepiness Scale
EWC	Elevated Waist Circumference
HbA1c	Glycated haemoglobin
HBP	High Blood Pressure
HDL	High Density Lipoprotein
IDF	International Diabetes Federation
ISER	Institute for Social and Economic Research
KQ	Key Question
MESH	Medline Subject Headings
NCPI-ATP III	National Cholesterol Education Program-Adult Treatment Panel III
NHA	Nurse Health Assessment
NHS	National Health Service
NI	Northern Ireland

NICE	National Institute for Clinical Excellence
NPV	Negative Predictive Value
NREM	Non-Rapid Eye Movement
OR	Odds Ratio
OSA	Obstructive Sleep Apnoea
PPV	Positive Predictive Value
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
REM	Rapid Eye Movement
RRR	Relative Risk Ratio
SSS	Stanford Sleepiness Scale
TG	Triglyceride
UKHLS	United Kingdom Household Longitudinal Study
WC	Waist Circumference
WHO	World Health Organization

Chapter 1 Introduction

This chapter sets out to provide the background and rationale underpinning the present thesis' interest in the (theoretical) association between the metabolic syndrome (MetS) and sleep.

1.1 Background

Metabolic syndrome (MetS) is routinely operationalised as a cluster of adverse risk factors for both cardiovascular heart disease and type 2 diabetes. Among these risk factors are abdominal/central obesity, insulin resistance, hypertension, and dyslipidaemia (Dunkley *et al.* 2012); although Reaven's (1988) original hypothesis proposed that insulin resistance as the putative 'single cause' of the subsequent symptoms/components of MetS (i.e. central obesity, high blood pressure, dyslipidaemia and hyperglycaemia/diabetes) in which the 'comorbidity' these signify represent 'more than the sum of their parts' (Reaven 1988).

While the prevalence of MetS among adults in the United States has steadily increased from 32.9% in 2003-2004 to 34.7% in 2011-2012 (Aguilar *et al.* 2015), and although insulin resistance, central obesity and glucose intolerance have all been considered possible causes behind the emergence of MetS, there are a range of other factors occurring at different times within the sequence of events leading up to the cardiovascular and metabolic diseases viewed as the principal clinical consequences of MetS, and there remains substantial uncertainty as to which of these (if any) constitute the single and/or multiple initial cause of MetS (Alberti, Zimmet and Shaw 2006).

Indeed, there is a growing body of evidence (and substantial interest) suggesting that sleep might play a central role in energy metabolism, reflected in part by the observation that both long and short sleep duration appears to have an association with (amongst other things) increased insulin resistance and increased appetite – both of which may contribute to the development to type 2 diabetes, a key symptom/component of MetS (Bartlett *et al.* 2008).

1.2 Sleep

Sleep is commonly defined on the basis of behavioral and physiological phenomena and processes: the behavioral involving a lack of movement, reduced responsiveness to the environment, and decreased cognitive function; the physiological changes evidenced by so-called 'rapid eye movement' (REM) and 'non-REM' (NREM) sleep states which alternate cyclically (Carskadon and Dement 1994). In humans, normal 'entry' into sleep is through NREM – which itself can be subdivided into three stages N1, N2, and N3 (which account for 75-80% of sleep); while REM accounts for only 20-25% of sleep (Chokroverty 2010). To summarizes more of the

detail regarding the specific characteristics of NREM and REM sleep, these characteristics have been summarized in Table 1.1 (below).

Table 1.1 A summary of the behavioral and physiological criteria used to determine wakefulness and sleep (Chokroverty 2010)

Criteria	**Awake**	**Non–rapid eye movement sleep**	**Rapid eye movement sleep**
Posture	Erect, sitting, or recumbent	Recumbent	Recumbent
Mobility	Normal	Slightly reduced or immobile; postural shifts	Moderately reduced or immobile; myoclonic jerks
Response to stimulation	Normal	Mildly to moderately reduced	Moderately reduced to no response
Level of alertness	Alert	Unconscious but reversible	Unconscious but reversible
Eyelids	Open	Closed	Closed
Eye movements	Waking eye movements	Slow rolling eye movements	Rapid eye movements
Electroencephalography	Alpha waves; desynchronized	Synchronized	Theta or saw tooth waves; desynchronized
Electromyography (muscle tone)	Normal	Mildly reduced	Moderately to severely reduced or absent
Electro-oculography	Waking eye movements	Slow rolling eye movements	Rapid eye movements

The clinical assessment of sleep (and sleep-related disorders) requires both detailed history-taking and physical examination. Several subjective tools/instruments have been developed, including the: Epworth Sleepiness Scale (ESS) which assesses daytime sleepiness (Johns 1991); the popular Pittsburgh Sleep Quality Index (PSQI) which assesses sleep quality, ostensibly over the preceding month (Buysse *et al.* 1989); and the Stanford Sleepiness Scale (SSS) which also provides a measure of daytime sleepiness (Hoddes, Zarcone and Dement 1972). In contrast, overnight polysomnography (PSG) is widely considered to be the most important objective 'laboratory test' for the comprehensive assessment of sleep (Chesson Jr *et al.* 1997); which monitors brain function, muscle activity, heart rhythm and eye movement from subjects examined using a 'polysomnograph' while they are asleep. More recently, portable actigraphy (a less expensive and non-invasive technique) has increasingly been used and validated as a reliable alternative for measuring both sleep quality and sleep duration objectively, using accelerometry to record the movement of free-living subjects/study participants (Ferrie *et al.* 2011). The different characteristics of sleep are summarised and defined in Table (1.2).

Table 1.2 Definitions of commonly recognised 'sleep characteristics'

Sleep characteristic	**Definitions**
Sleep duration	Total hours of (usually, nocturnal) sleep attained
Sleep latency	Time taken to fall asleep (often set to < or > 30 minutes or some other time scale)
Sleep disturbance and/or fragmentation	Trouble sleeping due to waking up in the middle of the night or early in the morning
Coughing/snoring while asleep	Coughing or snoring loudly while asleep (often quantified as causing sleep fragmentation or disturbance)
Sleep medication use	Use of medicine(s) - either prescribed or over the counter – specifically to help with sleep
Daytime sleepiness	Difficulty experienced staying awake while conducting a range of daytime activities (including such activities as: driving; eating meals; or engaging in social activities)
Sleep quality	An assessment of the 'overall quality' of sleep

Sleep patterns (particularly the characteristics of these associated with duration, periodicity and depth) are strongly influenced by sex, age and socioeconomic status; with variation in sleep duration and quality occurring at different stages of the life span. In adults 7-8 hours of sleep is widely considered to be that required to 'maintain health' with both 'short' and 'prolonged' sleep durations considered 'unfavourable' (Sharma and Kavuru 2010; Watson *et al.* 2015). Although, recent research has placed more emphasis on insomnia (comprising both protracted sleep latency and fragmented/poorly maintained sleep) and sleep apnoea, the ease with which sleep duration and quality can be assessed using validated (and self-administered) sleep tools/instruments has led to a growing number of studies suggesting that short/prolonged sleep duration and poor sleep quality are both associated with negative health outcomes; and, in particular, that all three sleep characteristics appear to be associated with diabetes, hypertension, cardiovascular disease and obesity (Bixler 2009; Youngstedt and Kripke 2004; Grandner *et al.* 2014).

1.3 Metabolic syndrome

The metabolic syndrome (MetS) which, as we have seen, is rapidly becoming an important medical concern, is now widely operationalized simply as the clustering of multiple metabolic risk factors for both cardiovascular disease (CVD) and type 2 diabetes (Ilanne-Parikka and Tuomilehto 2013; Grundy 2008). These factors include raised blood pressure, raised triglycerides levels, low high-density lipoprotein, hyperglycemia and obesity (particularly 'central obesity'). Along with the specific clinical importance of the metabolic syndrome, there is a concern that MetS is more common among certain racialised social groups (such as those with salient ethnic identities). It has been suggested that each of the individual parameters in the

definition of MetS can often be clustered within such groups and thereby reflects describes the embodiment of disadvantage or biogeographical heritage responsible (Mugo and Sowers 2004). For example, compared to groups with European ancestry, those with African ancestry are often found to have less visceral adipose tissue in some social contexts. They may also be more prevalent to hypertension. In contrast, those with Asian ancestry often appear to have greater adipose tissue in various contexts (Mugo and Sowers 2004; WHO 2011). Despite such differences, it remains unclear whether such differences in the prevalence of MetS-related components are the result of structural, cultural and/or biogeographic selection(Rampal *et al.* 2012).

However, although the risk posed by each of these multiple metabolic risk factors has been recognized for some time, the most recent emphasis has been on their association with the possibility of insulin resistance (Alberti *et al.* 2009) as the 'single' preceding cause (Reaven, 1988). Yet Reaven's (1988) hypothesis is predated by several, much earlier attempts to define MetS including (as suggested by Alberti; 2005) the definition first offered by Kylin in 1923, who recognized the way in which hypertension, hyperglycemia and gout tended to cluster. In 1947, Vague reportedly proposed that central obesity was the single feature most commonly associated with MetS-related 'metabolic disturbances' (Alberti 2005). By 1988 (Isomma et al., 1988), Reaven had labelled MetS "syndrome X", defining this in its more familiar guise as a clustering of glucose intolerance, hypertension, low levels of high density lipoprotein (HDL), and high triglyceride (TG) levels (Isomaa *et al.* 2001). However, although (like 'syndrome x') a number of different names have been proposed to describe the clustering of these metabolic risk factors (including the: 'deadly quartet'; 'plurimetabolic syndrome'; 'insulin resistance syndrome'; and even 'Reaven's syndrome') the 'metabolic syndrome' (MetS) is now considered to be the most appropriate and widely accepted label for this particular suite of cardiovascular risk factors (Alberti, Zimmet and Shaw 2006) – hence the decision to use this term in the present thesis.

Elsewhere, the commonest definitions in use today are those provided by the World Health Organization (WHO): which considers insulin resistance to be the dominant feature of MetS, and diagnosis this as present when it is accompanied by any two of the other risk factors (albeit with 'central obesity' determined using waist to hip ratios [WHR]) (Organization 1999). The European Group for the Study of Insulin Resistance (EGIR) has a similar definition to that proposed by the WHO, except that their obesity criterion relies on waist circumference measurements (WC) rather than WHR (Balkau *et al.* 2002). In contrast, the definition of MetS put forward by the International Diabetes Federation (IDF) interprets WC as a measure of 'abdominal obesity' (as opposed to 'central obesity'), though they also propose assessing this

using WC measures, and view the presence of elevated WC, together with any two of a suite of additional risk factors as sufficient and necessary for diagnosing MetS (International-Diabetes-Federation 2006). More recently, the US National Cholesterol Education Program – Third Adult Treatment Panel (NCEP ATP III) has suggested a simpler definition of MetS based on 'any 3' of a total of 5 possible risk factors (NCEP-ATPIII 2002), although a subsequent update to the NCEP ATP III definition (suggested by the American Heart Association/National Heart, Lung, and Blood Institute Scientific statement (AHA/NHLBI) concludes that elevated WC should be one of the 5 possible risk factors rather than the most important/only required criterion (as proposed, for example, by the IDF) (Grundy 2008; Alberti *et al.* 2009). These disagreements aside, most of the definitions proposed have substantial similarities and are, in many respects, interchangeable (see Table 1.2, below). At the same time, there remains some merit in the NCEP ATP III definition given that it is perhaps both a more appropriate and practical tool for use across clinical and epidemiological contexts; not least because it does not require any dominant feature must be present, only that *any* three of the five features/symptoms/components are evident (Huang 2009).

Table 1.3 A summary of the different definitions and classifications of the metabolic syndrome (MetS) proposed since Reaven's seminal hypothesis was published in 1988.

	WHO 1998	**EGIR 1999**	**IDF 2005**	**NCEP ATP III 2001**	**AHA/NHLBI 2009**
Absolutely required	Insulin resistance (Impaired glucose tolerance, impaired fasting glucose, type 2 diabetes)	Hyperinsulinemia (plasma insulin>75th percentile)	Central obesity (defined as: WC≥94cm in males; ≥80 cm in females)	None	None
Clinical criteria	(Insulin resistance or diabetes plus) Any two of the five characteristics below	(Hyperinsulinemia plus) Any two of the four characteristics below	(Obesity plus) any two of the four characteristics below	Any three of the five characteristics below	Any three of the five characteristics below
Obesity	WHR >0.90 in males, >0.85 in females or BMI>30 kg/m^2	WC≥94cm in males, ≥80 cm in females	Required	WC>40 inches in males>35 inches in females	WC≥102cm (40 inches) in males, ≥88cm (35 inches) in females
TG	≥150 mg/dl or HDL<35mg/dl in male, <39 mg/dl in female	≥177 mg/dl or HDL <39mg/dl	≥150 mg/dl or on treatment for elevated TG	≥150 mg/dl or on treatment for elevated TG	≥150 mg/dl (1.7 mmol/L) or on treatment for elevated TG
HLD			<40 mg/dL in male, <50 mg/dL in female or on treatment for reduced HDL	<40 mg/dL in male, <50 mg/dL in female or on treatment for reduced HDL	<40 mg/dL (1.03 mmol/L) in male, <50 mg/dL (1.3 mmol/L) in female or on treatment for reduced HDL
Blood pressure	≥140/90 mmHg	≥140/90 mmHg or on antihypertensive treatment	>130 mmHg systolic blood pressure, or >85 mmHg diastolic blood pressure, or on antihypertensive treatment	>130 mmHg systolic blood pressure, or >85 mmHg diastolic blood pressure, or on antihypertensive treatment	≥130 mmHg systolic blood pressure, or ≥85 mmHg diastolic blood pressure, or on antihypertensive treatment
Glucose	Required	Required	Fasting glucose≥100mg/dl	Fasting glucose≥100mg/dl or on treatment for elevated glucose	Fasting glucose≥100mg/dl or on treatment for elevated glucose

To a great extent, central obesity rather than generalized obesity has been found to be associated with an increased risk of cardiovascular disease (Janssen, Katzmarzyk and Ross 2004; Zhu *et al.* 2002). This is because increased visceral adipose tissue is associated with metabolic abnormalities, including reduced insulin sensitivity, glucose intolerance, and adverse lipid profiles – all of which are known risk factors for cardiovascular disease and diabetes (Björntorp 1996). Central obesity can be quite simply assessed using waist circumference (WC), which has been suggested to be superior to "waist to hip ratio" (WHR) and "body mass index" (BMI) in predicting metabolic and cardiovascular diseases (simply because BMI is a measurement that does not distinguish between the proportion of weight due to fat or muscle;(WHO 2011). Nevertheless, subjects with lower height are prone to having more abdominal fat compared to taller subjects of the same WC, which may reflect the importance of height as an indicator of health (Park and Kim 2012). Indeed, short stature has been associated with obesity, diabetes, and heart disease primarily because it is a marker of the embodiment of challenging socioeconomic conditions and health hazards in early life (Perelman 2014).

Following closely after obesity (and, particularly, central obesity), insulin resistance is widely considered to be the single most important contributor to MetS, and both obesity and insulin resistance are themselves associated with a range of different contributory sociodemographic characteristics (most notably: age; sex; and poverty). Accordingly, the management of MetS is primarily linked to the management of the modifiable risk factors associated with these three sociodemographic factors (e.g. an atherogenic diet, physical inactivity, and obesity), and has focused (as has so much of health improvement interventions, to-date) on promoting a 'healthy lifestyle' (Grundy 2005). The momentum behind these interventions has been epidemiological evidence suggesting that, in addition to a two-fold increase in the risk of CVD, and a 3.5-5.0 fold risk of developing type 2 diabetes, patients diagnosed with MetS are also subject to an increased risk of: fatty liver; polycystic ovary syndrome; asthma; cholesterol gallstones, and (importantly, given the focus of the present thesis) sleep disturbance (Grundy *et al.* 2004).

1.4 Sleep and MetS

Changes in sleeping patterns have been increasingly recognised in recent years, with most surveys reporting that respondents now sleep only 6.8 hours on average compared to 9 hours a century ago (Sharma and Kavuru 2010). To put this in perspective, more than 30% of US adults aged 30-64 years recently reported having

less than 6 hours of sleep per night (Knutson and Van Cauter 2008). However, what is remarkable about the definitions of 'short' and 'long' sleep duration is that no standardised cut-off point for either have yet been established/agreed. Instead, the majority of studies have defined short sleep as ≤ 5hrs per night, ≤ 6hrs, or < 7hrs, while long sleep duration was defined predominantly as >8hrs or ≥ 9 hrs per night (Cappuccio *et al.* 2010).

This apparent reduction in sleep duration has been accompanied by a number of substantial metabolic and endocrinological changes, namely elevated body mass index (BMI) and obesity, and insulin resistance (Grandner *et al.* 2014; Jennings, Muldoon and Hall 2007). Sleep loss (i.e. sleeping less than required) has also been found to have a strong impact on appetite-regulating hormones (particularly leptin, ghrelin, and orexin), leading to increased appetite and food intake (Markwald *et al.* 2013). Poor sleep quality is strongly associated with reduced levels of leptin (an appetite suppressor hormone), elevated levels of ghrelin (a hormone that increases appetite and controls body weight), and elevated levels of orexin (a hormone that controls hunger and the sleep-wakefulness cycle). At the same time, simply as a consequence of the fatigue and sleepiness associated with shortened, poorer quality sleep, this may in turn cause reduced activity and energy expenditure which further contribute to incipient obesity (Knutson and Van Cauter 2008).

Decreased glucose tolerance and increased insulin resistance has also been found to be associated with sleep loss due, in part, to increased levels of growth hormone and cortisol (hormones involved in glucose regulation), which then lead to an increased risk of diabetes. Sleep loss may likewise trigger elevated blood pressure due to increased activity of the sympathetic nervous system; and to elevated cortisol levels resulting from disturbances to the hypothalamic-pituitary-adrenal axis (which results in a reduction in the clearance rate of free cortisol, and thereby a build-up of circulating cortisol levels; (Bjorvatn *et al.* 2007). Yet another consequence of sleep loss is an increase in both cholesterol and low density lipoprotein (LDL) levels in the blood stream; phenomena that may be explained by increased appetite and food intake (as explained earlier), and/or by increased stress levels and reduced physical activity levels resulting from daytime fatigue (Gangwisch *et al.* 2010).

Overall then, the relation between sleep loss and metabolic dysregulation is both complex and straightforward, involving well-established hormonal pathways, sympathetic stimulation (as discussed above), and inflammation (Sharma and Kavuru 2010). Acute sleep loss has been found to be related to changes in immunological responses, and to an increase in pro-inflammatory cytokines. The presence of

cytokines (small proteins that are important in cell-cell signalling) is itself associated with insulin resistance and diabetes (Knutson and Van Cauter 2008).

1.5 Challenges of self-reported data

With the interest in assessing the relationship between sleep and MetS, only few large scale epidemiological studies have the capacity to collect direct measurements of anthropometric, physiological and objective biological measurements; instead, mostly they rely on self-reported data (Yoong *et al.* 2013; Engstrom *et al.* 2003) which tend to be easier and cheaper to collect. However, like all data, self-reports are not immune from random and systematic sources of errors (Huerta *et al.* 2009; Molenaar *et al.* 2007; Oksanen *et al.* 2010); and because each participant is intimately involved in generating (i.e. accurately remembering and accurately reporting) these forms of data, the risk of systematic bias is heightened. This is because variation in sociodemographic, economic, health and lifestyle characteristics – characteristics that are often central to the aims of large scale population-based epidemiological studies – can determine both the value of self-reported measures, but also the accuracy with which these values are/can be reported. (Goldman *et al.* 2003; Huerta *et al.* 2009; Molenaar *et al.* 2007).

For anthropometric and physiological parameters, ostensibly 'valid' measures of these need to be measured directly so that their values can be compared to the self-reports of these offered by the same participants – an approach that is central to previous validation studies which have compared self-reported data with more objective referent data from a range of alternative sources, including medical records and clinical investigations, as well as direct measurements (Goldman *et al.* 2003; Robinson *et al.* 1997). However, few such studies have access to data from nationally representative samples, and many based these on small samples that only included or excluded ethnic minorities, or populations from a limited geographical area (Goldman *et al.* 2003; Thawornchaisit *et al.* 2013; Vargas *et al.* 1997; Pastorino *et al.* 2014; Leikauf and Federman 2009; Margolis *et al.* 2008).

1.6 Why study the relationship between sleep and Metabolic Syndrome?

One of the key reasons why this study has chosen to focus on the speculative relationship(s) between sleep and MetS in adults is the possibility that such relationships might offer novel insights into the prevention and/or treatment of

associated clinical disease (and their associated risks). However, the underlying theoretical hypothesis (that sleep and MetS are functionally related), remains an area that remains hotly contested, and one that lacks substantial scientific attention. This field would therefore benefit greatly from capitalising on the growing number of large and powerful epidemiological datasets available, and the innovative analytical techniques that have recently been developed to generate aetiological knowledge from these (i.e. knowledge based on causal inference developed from the analysis of observational datasets). Considering the steady increase in obesity and apparent changes to human sleeping patterns; therefore, it is clearly important to expand both the volume and scope of research in this area.

Although there can be little doubt that researchers have gained a firm grasp on a number of important dimensions and characteristics of sleep (most notably those related to sleep duration and quality), and have found MetS to be an important theoretical/prognostic concept for developing our understanding of chronic cardiometabolic disease, there remains considerable uncertainty (and a substantial lack of consensus) regarding: which sleep characteristics (if any) might be (the most) important determinants/causes of MetS; and how best one might operationalise MetS in order to explore its relationship(s) with sleep. Given the growing evidence of strong (cross-sectional and longitudinal) relationships between specific aspects of sleep (particularly, but not exclusively: sleep duration, sleep disturbance/quality, and obstructive sleep apnoea) and specific components of/contributors to MetS (notably, though not exclusively: obesity; glucose intolerance/insulin resistance; hyperlipidaemia; and hypertension), this is an area that warrants additional, and carefully considered, large-scale research – research that requires (and stands to benefit from) thoughtful epidemiological analyses and methodological innovation.

1.7 Study design

In epidemiological research, experimental and observational analytical studies are the two main approaches used to assess whether an exposure (in this instance MetS or sleep) might be associated with a particular outcome (in this instance sleep, or MetS (Eisenmann 2003). However, although experimental studies are said to occupy the highest grade of evidence based on research design (whereas, in fact, systematic reviews and meta-analyses of experimental studies trump these), it is not always true, feasible or efficient to conduct such studies (Rothman 2014), not least when the resources concerned might be better spent elsewhere (such as on areas of enquiry in which the evidence base from cheaper, observational studies is more

persuasive). For these reasons – and not least because it was not considered feasible or ethically defensible to conduct a trial involving interventions that exacerbate MetS or sleep-related problems in order to assess their effects on one another, but also because there are few proven interventions for addressing either MetS (as a whole, rather than separate symptoms/components thereof) or sleep without recourse to pharmacological formulations that may, themselves affect both sleep and MetS – an observational approach was adopted as most pragmatic for the present thesis' evaluation of the relationship between MetS and sleep.

The advantages of observational studies are that: they are relatively inexpensive, quick and easy to conduct; multiple outcomes can often be studied within data collected on a single occasion (hence data collection is only required once); and they are useful for both evaluating and generating hypotheses relevant to the aetiology of disease. However, these kinds of studies do not provide sufficient understanding of the mechanisms underlying any relationship between the exposure(s) and outcome(s) examined to infer causality, simply because they cannot differentiate between cause and association, and cannot identify the direction in which any association might operate. Another important limitation of observational studies is the possible influence of any confounding factors that may create, strengthen and (occasionally) attenuate an apparent relationship between exposure and outcome (Mann 2003).

However, applying a causal path approach (such as using theoretical causal path diagrams in the form of directed acyclic graph, or DAG, to identify potential confounders and likely mediators) can help to minimise some of these limitations associated with observational studies. Such an approach allows data to be analysed in a temporal fashion set against a theoretical chronological sequence, on the basis of which variables (exposure, outcome, and covariates) precede or follow after one another.

1.8 Summary and conclusion

This chapter successfully provided background information on sleep and metabolic syndrome and described the importance of this topic. Following this background, the aim is to generate an improved understanding of the available evidence regarding the speculative relationship between sleep and the metabolic syndrome (MetS). This aim will be operationalised using the following key question

KQ1: “What methodological and empirical insights might be drawn from previous studies examining the relationship between sleep and the metabolic syndrome (MetS) to inform: the focus and conduct of future research; and our understanding of the evidence base regarding ‘unfavourable’ sleep as a possible cause and a possible consequence of MetS?”

Chapter 2 Systematic review of previous studies examining the relationship between sleep and MetS

The present Chapter sets out to explore what might be learnt from the methods used, and findings generated, from previous empirical studies exploring the (possibility of a) relationship between the metabolic syndrome (MetS) and sleep.

2.1 Introduction

Much has been written from both a theoretical and a conceptual basis, regarding the *possible* role that sleep might play in metabolic homeostasis and energy balance, and there is growing evidence from experimental studies that artificially shortened or disturbed sleep has immediate (i.e. acute) effects on glucose metabolism, appetite and satiety (Mullington *et al.* 2009). There is therefore much speculation regarding the potential role that 'unfavourable' or 'less than ideal' sleep might have either in the initiation of MetS (i.e. as the 'cause of the cause', be that insulin resistance as proposed by Reaven in 1988, or some other physiological change) or the facilitation of the impact these postulated physiological changes have on the subsequent development of the symptoms/components of MetS (i.e. central obesity; high blood pressure; dyslipidaemia; and diabetes). This is supported by studies demonstrating a steady decline in the duration and quality of sleep and an increase in the diagnosis of sleep disorders (Knutson *et al.* 2007), both occurring over the same period in which the obesity epidemic has emerged, and the prevalence of type 2 diabetes has been steadily increasing (and occurring at younger and younger ages; (Spiegel *et al.* 2009).

However, most empirical studies exploring the possibility of an association between sleep and MetS have focussed either on clinical conditions with sleep-related effects (such as obstructive sleep apnoea, OSA – a condition that is strongly associated with obesity and hypertension) or on individual symptoms/components of MetS (i.e. obesity, high blood pressure, dyslipidaemia and diabetes). While conditions such as OSA occur while individuals are asleep, it is arguable whether they fairly constitute 'sleep-related characteristics', since they primarily reflect the impact of endogenous physiological and anatomical factors on sleep rather than issues arising out of sleep per se. And while studies examining the relationship between sleep and individual symptoms/components of MetS appear to offer substantial evidence of a link between (short, long and poorer quality) sleep and both obesity and hyperglycaemia/diabetes, few of these studies use the longitudinally collected data required (i.e. from three or more time points) to provide evidence of directionality – i.e. evidence that changes in sleep precede changes in obesity and/or glycaemic control; or vice versa. Moreover, the present thesis was unable to find any reviews of such studies that have critically appraised the potential methodological and analytical flaws involved (not least the possibility of reverse causality, in which the association between obesity/hyperglycaemia and sleep reflects the impact of the former on the latter). The present thesis has also failed to find any studies examining the long-term impact of shortened/disrupted (or improved) sleep on MetS-related

symptoms/components, beyond those examining its immediate, or short-term effects (as described earlier). Yet, even these studies would not provide unequivocal evidence of an association (or relationship) between sleep and MetS (i.e. the specific *combination* of symptoms/components intended to capture something 'greater than the sum of its parts' by way of indicating the possibility of a single preceding cause or trigger, such as the development of insulin resistance earlier in life). There is therefore a pressing need to further examine the relationship between sleep and MetS in order to evaluate what evidence might be available to support the suggestions that the classification of MetS: conveys additional information (i.e. information that information on each of its components, alone, cannot convey); and might have a very particular association (or simply an enhanced, or indeed attenuated, association) with sleep – associations that might help to assess the potential role of sleep in the development of MetS (and thereby each component of MetS), and the subsequent impact of MetS (and each component of MetS) on sleep.

2.2 Aim and objectives

The key aim of this chapter was therefore to re-evaluate the evidence provided by previous studies examining the relationship between MetS and sleep by:

(i) conducting a systematic search to identify any empirical studies examining the association between a formal classification of MetS (as opposed to any one, or other combinations, of its constituent symptoms/components) and sleep-related characteristics;
(ii) identifying any studies conducted in the UK
(iii) identifying any studies using cross-sectional, longitudinal and/experimental designs capable of generating evidence of association, directionality and causality, respectively;
(iv) assessing the likely external validity of any such studies (both in terms of the range of geographical locations in which these have been conducted and the participant recruitment/sampling strategies used);
(v) describing the range of definitions and measurements used to conceptualise and operationalise MetS and different sleep-related characteristics;
(vi) critically appraising the statistical techniques used and the analytical models on which these are applied;

(vii) comparing any effect estimates generated from studies using comparable measures and comparable analytical techniques; and (in as much as this is possible)

(viii) generating combined estimates of any association between different sleep-related characteristics and MetS, using meta-analytical techniques.

In this way, the present Chapter sought to address the following key question as established at the outset of this thesis:

KQ1: "What methodological and empirical insights might be drawn from previous studies examining the relationship between sleep and the metabolic syndrome (MetS) to inform: the focus and conduct of future research; and our understanding of the evidence base regarding 'unfavourable' sleep as a possible cause and a possible consequence of MetS?"

2.3 Methods

2.3.1 Search strategy

A systematic search was performed in Medline with the aim of finding original articles describing studies that had examined the association between sleep and MetS.

2.3.1.1 Search terms

1. Sleep

The search terms selected to capture sleep-related studies included those relevant to both sleep-specific *characteristics* (e.g. duration and latency) and sleep-specific *disorders* (e.g. obstructive sleep apnoea and narcolepsy), and used all available synonyms thereof, namely:

apnoea; central sleep apnoea treatment; central sleep apnoea; dyssomnia; hypersomnia; hypopnoea syndrome; insomnia; nightmare; obstructive sleep apnoea; parasomnias; sleep-related breathing disorders; sleep apnoea; sleep; sleep time; sleep duration; sleep hours; sleep quantity; sleep quality; sleep disorder; sleep disorders; sleep disordered; sleep length; sleep disturbance; sleeplessness; sleepiness; sleep efficiency; sleep latency; sleep problem; sleep disturbance; sleep difficulties; sleep terror; sleep deprivation; time in bed; time spent asleep; time spent sleeping; time sleeping; and time asleep.

These search terms for ‘sleep’ were then combined using the Boolean operator ‘OR’; and were added to those relevant to the ‘metabolic syndrome’ using the operator ‘AND’ (see below).

2. Metabolic syndrome

To identify articles describing studies that specifically addressed the metabolic syndrome (as opposed to the individual components thereof), the search terms used drew on Medical Subject Headings (MeSH) drawn from Medline’s MeSH directory. These MeSH terms included:

> insulin resistance syndrome x; syndrome x, metabolic; syndrome x, insulin resistance; metabolic x syndrome; syndrome, metabolic x; x syndrome, metabolic; dysmetabolic syndrome x; syndrome x, dysmetabolic; reaven syndrome x; syndrome x, reaven; metabolic cardiovascular syndrome; cardiovascular syndrome, metabolic; cardiovascular syndromes, metabolic; syndrome, metabolic cardiovascular

These MeSH terms were then combined with the search terms for ‘sleep’ using the operator ‘AND’.

2.3.2 Filters and limits

Initially, no restrictions (i.e. filters or limits) were applied to the search in order to ensure that all available studies might be included and available for subsequent screening. However, during the application of the review’s exclusion criteria, Medline filters and limits based on human studies and adults 19yrs and older, were used to facilitate the exclusion of studies from the original list of those screened as eligible for consideration.

2.3.3 Inclusion and exclusion criteria

Given that an important aim of the systematic review was to synthesise the findings of any published articles describing primary empirical studies (focussing on articles which set out to assess the relationship between sleep-related characteristics, and/or sleep complications, and a classification of MetS in adults), these design-, topic- and participant-specific criteria constituted the principal ‘inclusion’ criteria relevant to the search undertaken. On this basis, articles identified in the preliminary Medline searches were excluded if they described animal studies (since the aim was to investigate the relationship between Sleep and MetS among human beings), or studies focussing on children or adolescents (since the burden of sleep- and MetS-related problems is likely to be different, and higher, in adults when compared with children; (Crespo *et al.* 2007). Likewise, all studies that assessed the relation between

sleep and only one component of MetS (such as high blood pressure or central obesity alone, rather than a classification of MetS based on at least three of these) were excluded. The rationale for this was the review's aim to assess whether the special cardiometabolic features considered central to the conceptualisation of MetS itself – i.e. as a 'syndrome' identified by the presence of *more than one* [indeed, often three or more] key metabolic and cardiovascular components; see Chapter 1: *Introduction*, for a more detailed summary of the proposed meaning and utility of MetS *per se* as originally conceptualised and subsequently operationalised – displayed any aetiologically insightful associations with sleep-related characteristics. And although the search strategy sought to include not only sleep-related characteristics *and* sleep-related disorders, studies focussing exclusively on one common disorder considered by many to be sleep-*specific* (obstructive sleep apnoea; OSA) were excluded on the grounds that this complex disorder, though defined as a condition occurring only/primarily whilst asleep, is more likely to reflect the impact of respiratory and cardiovascular *on* sleep rather than *as a* function of sleep itself. This is also the reason why, after identifying and critically appraising a small number of experimental (n=9) and longitudinal (n=3) studies captured by the literature search (see Appendix 6.2 and 6.3), it was decided to exclude these from the present Chapter and focus exclusively on studies adopting a cross-sectional design, this was also true for the small number of studies (n=3) adopting a quasi-cohort design, all of which used analyses of change that are likely to have been particularly susceptible to regression to the mean (Tu and Gilthorpe 2007) and none of which actually offer the evidence of directionality they claim (see Appendix 6.2). Likewise, the majority of experimental studies identified in the present Chapter's search focussed exclusively on OSA and used interventions (such as continuous positive airway pressure "CPAP") in participants with OSA to assess its subsequent effect on MetS. Indeed, the few experimental studies that targeted MetS to assess the effect thereof on sleep, all used weight loss alone as the intervention rather than more holistic interventions targeting all of the putative components of MetS simultaneously (i.e. central obesity, high blood pressure, dyslipidaemia *and* diabetes; see Appendix 6.3). As such, there were both pragmatic and substantive scientific reasons for limiting the focus of the present review to only those studies adopting a cross-sectional design. Finally, since the data required for both the synthesis and methodological critique envisaged in the present Chapter required articles describing primary empirical analyses of the association between MetS and sleep that could be carefully (and critically) examined, those published in languages other than English, and those that comprised 'letters', 'comments', 'case reports', 'meeting abstracts', or 'narrative reviews' were also excluded (the latter because these were unlikely to contain sufficient information on such analyses.

2.3.4 Data extraction

Full-text copies of all of the articles meeting the inclusion criteria were close-read for data extraction and critical appraisal purposes. Data were extracted and tabulated using a predesigned collection proforma covering the following information:

Study citation and key characteristics – this included: first (two if only two) author(s) name(s); date of publication; country in which study took place; and sample size at recruitment; and duration;

Participant characteristics – this included: details of the context/study through which recruitment occurred; any explicit inclusion and exclusion criteria; and the sex and age distribution of recruited participants;

The definition and measurement of exposure(s)/intervention(s), outcome(s) and measured covariates – for MetS, this included the classification used and any (self-reported and/or direct) measurement techniques used for each of the constituent MetS components; for sleep-related characteristics, this included the objective and/or subjective tools used (e.g. actigraphy and/or polysomnography; vs. Pittsburgh Sleep Quality Index [PSQI] or the use of 'custom sleep item sets', respectively); and for any available/measured covariates, this included simply a list of these, collated from wherever these were mentioned in the article; and

Analytical modelling – for each analytical model examining the association between MetS itself[1] and sleep-relevant[1] characteristics, this included: the statistical techniques used (e.g. Poisson regression, logistic regression), the format of the exposure and outcome variables (i.e. whether continuous, categorical-binary or categorical-polytomous); the reported inclusion criteria and prevalence of MetS and the specific sleep characteristic examined in any indicator and referent categories; the unadjusted[2] effect estimates of the association between MetS and the specific sleep characteristic examined; a list of the covariates included in any adjustment sets used to generate adjusted effect estimates between MetS and the specific sleep characteristic examined; and the effect estimates for each of these adjusted analytical models.

Note: [1]Where any of the articles examined *either*: components of MetS separately (or combinations of MetS components that did not relate to a formal definition of MetS), *and/or* examined characteristics related to characteristics *relevant* though not considered, for the purposes of this review, *specific* to sleep (such as shift work patterns or OSA), then a note was made that these analyses had been undertaken, but no further details of these were summarised.

[2]Where the article did not report unadjusted associations between MetS and any given sleep characteristic, but where the article *did* report the data required to calculate these, the results of these calculations were included in the tables of extracted effect estimates.

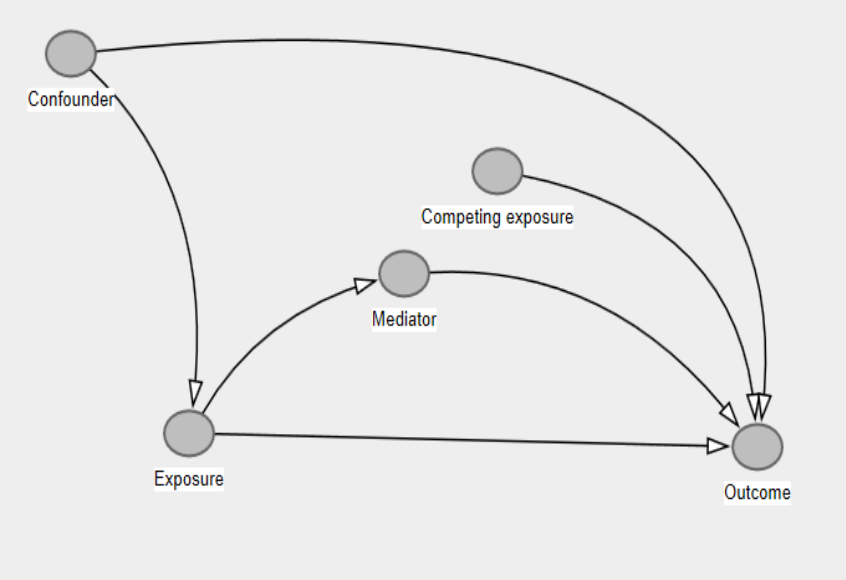
2.3.5 Critical appraisal of analysis

The critical appraisal of the analyses included in each of the studies reviewed was informed by causal path diagrams (in the form of directed acyclic graphs; DAGs). Causal path diagrams were used to conceptualize any likely/plausible relationships between exposure, outcome and all available/measured covariates, from which those variables acting as potential confounders could then be identified (and for which adjustment might then be expected to have been undertaken; (Hernán *et al.* 2002).

Directed acyclic graphs (DAG), are useful graphical tools in observational (and some experimental) epidemiological studies that aim to assess the possibility of a causal link between exposures, outcomes and other measured ('manifest') and unmeasured ('latent') variables – so called 'causal inference' analyses (Fleischer and Roux 2008). Based on *a priori* knowledge about the exposure and outcome of interest, any other variables available to/measured by the study are called covariates. DAGs use arrows (so-called 'arcs') between variables (so-called 'nodes') to denote putative causal effects, and by clarifying which of the variables are causes of *both* the exposure and the outcome, can determine which are necessary to control for in order to adjust for potential confounding (VanderWeele and Robins 2007).

However, from a causal inference perspective, covariates can actually have three different roles within DAGs: they can be: (potential) confounders; (likely) mediators, or competing exposures. As described earlier, a confounder is a variable that is a likely/plausible cause of both the exposure and the outcome, and is not situated on the causal path between exposure and outcome. A mediator is a variable that is a likely/plausible cause of the outcome but for which the exposure is a likely/plausible cause – so that mediators sit on the causal path between exposure and outcome. In contrast, a competing exposure is a variable that is not causally related to the exposure but is a likely/plausible cause of the outcome (or, more specifically, a cause of variance in the outcome). The following diagram (Figure 2.1) illustrates covariates roles in a simple DAG.

Figure 2.1 A stylised directed acyclic graph, demonstrating the distinction between a confounder, a mediator and a competing exposure**.**



In multivariable statistical models, only covariates that fit the formal definition of a confounder *need* to be adjusted for (Pourhoseingholi, Baghestani and Vahedi 2012). Conversely, adjusting for mediators may yield flawed results, while adjusting for competing exposures may not introduce bias but may not always improve precision at the cost of degrees of freedom (Tu and Greenwood 2012)

2.4 Results and Discussion

2.4.1 Search Results

Figure 2.2 summarises the total numbers of articles generated using each of the two sets of search terms (i.e. those for ‘sleep’ and those for ‘metabolic syndrome’), both separately combined (n=507). The results of applying each of the exclusion criteria on these n=507 articles have been summarised in Figure 2.3. Once articles on ‘non-humans’, and those on children and adolescents had been excluded using the relevant Medline filters, only n=238 articles remained. The titles and abstracts (where these were available) of these n=238 papers were carefully examined and a further n=132 articles were excluded on the basis that they were irrelevant, assessed the relation between sleep and only one component of MetS or they were of different language. For each of the remaining n=106 articles, the full-text article was repeatedly close-read to ensure that their content/focus (as classified using only their title and, where available, their abstract) actually met the review’s inclusion criteria; a process that led to the exclusion of a further n=26 articles. The remaining n=80 articles, were filtered by the type of the study, a process that led to identifying n=9 intervention

studies which were all about OSA, n=6 studies about Syndrome Z (the interaction of OSA with MetS), and n=65 observational studies. A final round of assessment, result in further excluding n=44 observational studies that met the review's exclusion criteria. Leaving a total of n=21 articles (containing reports of empirical, cross-sectional studies) that did not meet the review's exclusion criteria (and therefore form the basis of the methodological critique and synthesis of results provided below).

Figure.2.2 Search results for sleep alone, MetS alone and combined

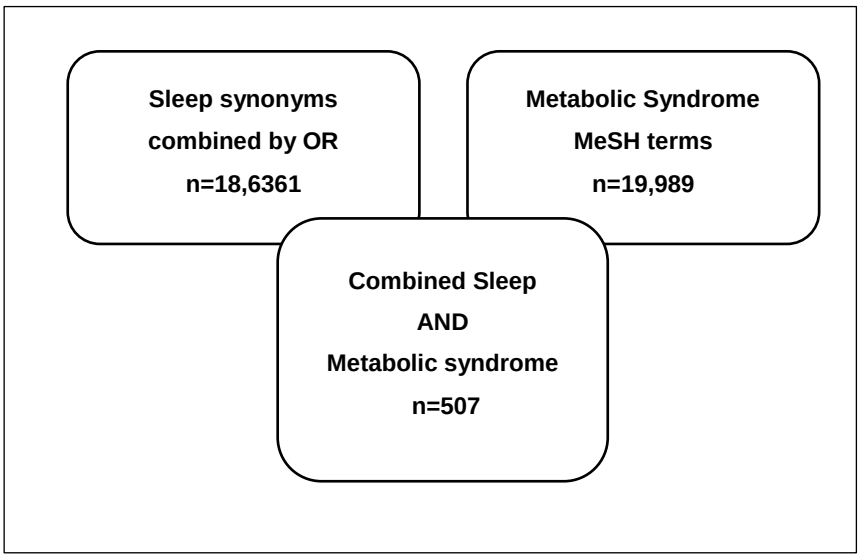
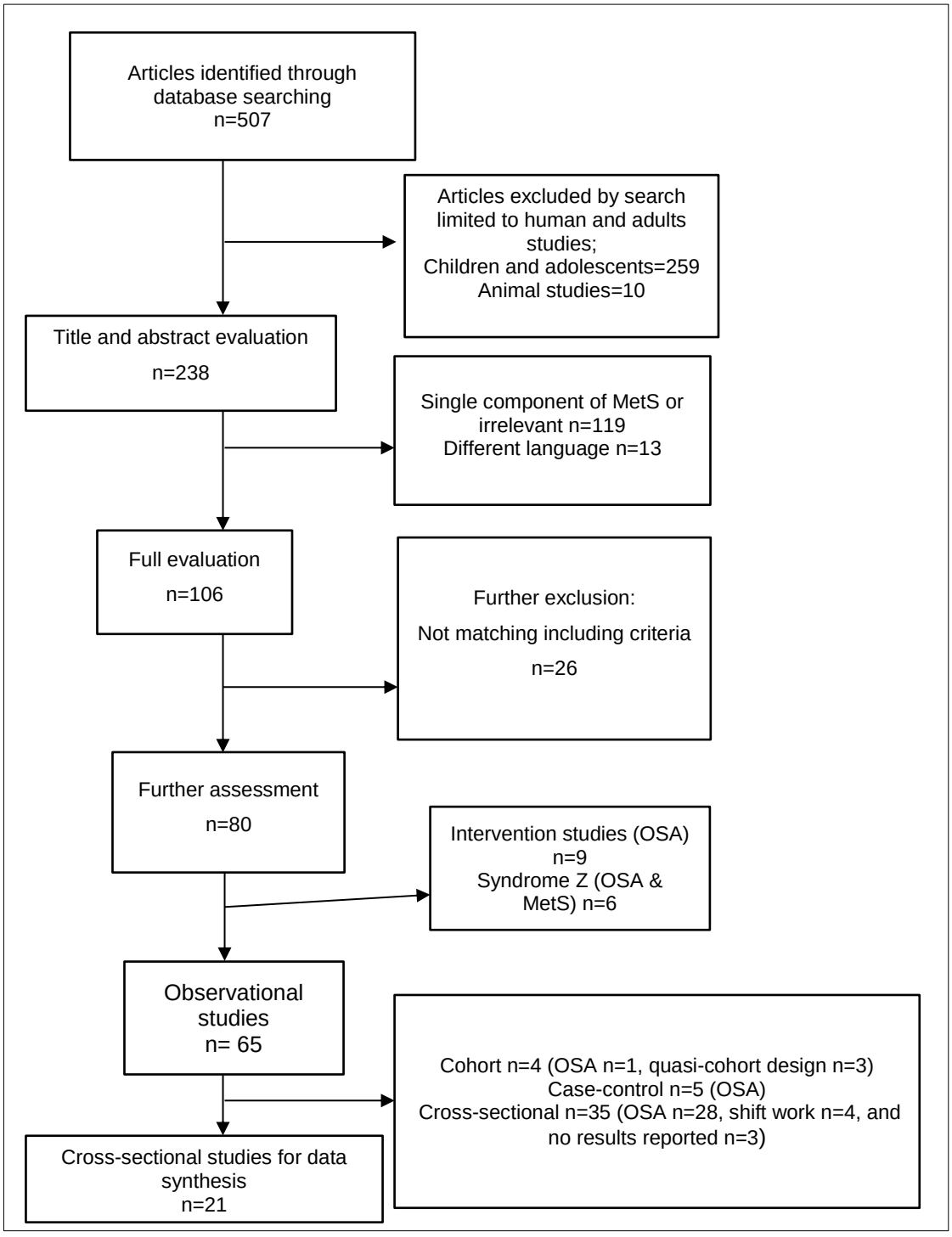


Figure 2.3 Results of applying each of the exclusion criteria.



2.4.2 Studies and participants characteristics

As described in the Methods section of the present Chapter (see above), three separate sets of data were extracted from each of the n=21 articles included in this review, and these have been summarised in: Table 2.1 (key study and participant characteristics); Tables 2.2 and 2.3 (the definition and measurement of exposures and outcomes, and any available covariates); and Table 2.4 (the analytical models each study used to examine the association between MetS and sleep-specific characteristics). While all of these articles described cross-sectional studies that had been conducted between 2006 and 2014, n=2 had been conducted by the same research group (Hall *et al.* 2008; Hall *et al.* 2012), and two pairs of studies appeared to have used the same datasets (Thomas *et al.* 2006) and (Arora *et al.* 2011) using baseline data from the Guangzhou Biobank Cohort Study, as described by (Jiang *et al.* 2006); (Roopa *et al.* 2010) and (Krishnan *et al.* 2012) using data from what appeared to be the same n=358 participants from the Chennai Urban Rural Epidemiology Study). However, on closer inspection it was clear that the studies by Hall et al. (2008; 2012) had been conducted on different datasets (comprising data from the Adult Health and Behaviour Project Registry, and the SWAN Sleep Study, respectively), while those conducted by Thomas et al. (2006) and Arora et al. (2011) focussed on different sleep characteristics (snoring and sleep duration, respectively). This left only the studies by Roopa et al. (2010) and Krishnan et al. (2012), both of which examined similar sleep characteristics and classifications of MetS (though specifying these differently as exposure or outcome), and were flagged as being unlikely to offer evidence independent of one another.

Most of the studies summarised in Table 2.1 had been conducted in Asia (n=11) or North America (n=8), with just two based in Europe (n=2), neither of which had been conducted in the UK. All but n=1 of the studies (Hall *et al.* 2012) included both male and female participants (though only n=1 stratified their analyses by gender), and the original numbers of participants recruited into each of these studies ranged from just n=98 to almost 300 times as many (n=29,333), and while most studies (n=9) were based on fewer than n=1,000 participants, n=7 recruited between n=1,000 and 10,000; and a sizeable proportion (n=5; around a quarter) recruited between n=10,000 and n=30,000 participants. As such this range of sample sizes offers a good basis from which it might be possible to evaluate the possible role of publication bias, provided similar measures and analyses are available for sufficient numbers of small, medium and large-scale studies (see below). In as far as could be determined (from the details provided in each of the articles), most of these studies (n=16) drew on secondary sources of data generated (at least in part) through health care delivery or in the

course of past/ongoing studies, while only n=5 were based on primary studies. The disproportionate number of studies based on secondary data sources presents both strengths and weaknesses to the evidence base these provide regarding the association/relationship between MetS and sleep: these sources often provide data on far larger samples of participants than are feasible to recruited in dedicated primary studies, and when these data include measures collected from previous surveys of the same participants they can offer far more (and more accurate) data on potential confounders; however, a substantial downside to the use of secondary data sources is that the participant sampling frame used, and the choice/measurement of variables (that are then available for inclusion in subsequent, secondary analyses) is not determined by the particular needs of any subsequent/secondary analyses. The latter might, for example, impose participant inclusion and exclusion criteria that might limit the external validity of any secondary analyses (not simply to any specific target population, but also to those populations at different risk from the conditions examined); and in the context of the present review, this might also have influenced the quality and detail provided on particular components of MetS or on the sleep-related characteristics examined. Certainly, there was substantial variation in the sampling frames (and the inclusion/exclusion criteria) used by the n=21 studies summarised in Table 2.1; although for the most part these samples appear to have focussed on otherwise healthy participants rather than those at particular risk of MetS or unfavourable sleep (or an association between the two; as might have been the case had any of the studies only examined overweight or obese participants, or those with a history of sleep disorders). In this respect, the n=21 studies are therefore likely to offer a reasonable basis upon which to examine the association between MetS and sleep in otherwise healthy adult participants.

Table 2.1 key study and participant characteristics mentioned in (and extracted from) n=21 cross-sectional studies containing empirical analyses of the relationship between MetS and sleep; together with any measured sleep characteristics, and any those measured variables relevant to the classification of MetS.

Citation	Sample size	Data source	Period(s) of data collection	Inclusion criteria	Exclusion criteria	Age (limits; range or mean [SD])	Sex distribution
(Mesas *et al.* 2014) Spain	n=10,342	Secondary: Nutrition and Cardiovascular Risk in Spain Study (ENRICA)	2008-2010	As for ENRICA study (≥18yrs); additional inclusion criteria not reported	As for ENRICA study: no specific criteria	≥18yrs	M: n=5,509 F: n=4,833
(Ohkuma *et al.* 2014) Japan	n=4,402	Secondary: Fukuoka Diabetes Registry (FDR)	2008-2010	As for FDR: Diabetic patients; additional inclusion criteria not reported	As for FDR: patients with drug-induced diabetes or undergoing steroid treatment; undergoing renal replacement therapy; with serious diseases other than diabetes (such as advanced malignancies and decompensated liver cirrhosis); unable to visit diabetologists regularly; with type 1 diabetes; who had already eaten breakfast	≥20yrs	M: n=2,494 F: n=1,908
(Saleh and Janssen 2014) USA	n=1,371	Secondary: National Health and Nutrition Examination Survey (NHANES)	2003-2004 and 2005-2006	Non-pregnant adult NHANES participants without chronic disease examined in the 'morning fasting subsample'	NHANES participants: missing one or more components of MetS; who did not have valid accelerometer data for the sedentary time and/or sleep duration measures; with missing one or more of the covariates	20-≥60yrs	M: n=770 F: n=601

(Hung *et al.* 2013) Taiwan	n=3,435	Secondary: database of the Prevention Health Centre of National Cheng Kung University Hospital	2002-2006	Participants who received a health examination	As for the main study: participants who self-reported depression, anxiety, or other psychiatric disorders; with serum creatinine >132.6 mmol/l; who had serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels more than twice the normal upper limit; with a history of cancers, OSA, thyroid diseases, cerebrovascular diseases and chronic pain	47.2yrs (SD: 11.8)	M: n=2,208 F: n=1227
(Chaput *et al.* 2013b) Canada	n=810	Secondary: the Quebec Family Study	Phase 2 (1989-1994) and Phase 3 (1995-2001)	As for the Quebec Family Study: participants displaying a BMI ≥ 32 kg/m^2	As for the Quebec Family study: no specific criteria	18-65yrs	M: n=349 F: n=461
(Lee *et al.* 2013) South Korea	n=301	Primary: Primary care clinic of either Korea University Guro Hospital, Korea University Ansan Hospital or Seoul Veterans Hospital	2007	Accepted to participate	Patients: who had a past/present medical history of heart disease, kidney disease, asthma, lung disease, severe liver disease, other endocrine disease (except diabetes, obesity and dyslipidemia), familial dyslipidemia and history	50.8yrs (SD:13.1)	M: n=187 F: n=114

					of cancer, stroke or other atheromatous vascular disease; Participants who used drugs that could have a potential effect on blood pressure, blood sugar and lipid levels, or body weight (except anti-hypertensive drugs and anti-diabetic drugs); Shift-workers, airline pilots and pregnant or breast-feeding women		
(Stefani *et al.* 2013) South Korea	n=24,511	Secondary: participants from the survey and health examination of the Korea National Health and Nutrition Survey (KNHANS); phases 2–5	Phase 2 (2001); phase 3 (2005); phase 4 (2007–2009); and phase 5 (2010)	As for the KNHNS: civilian noninstitutionalized Individuals >1yr for the Health and nutrition survey; >10yrs for the health behaviour and examination survey	KNHANES participants: younger than 20 years old or older than 79 years old; with missing sleep duration data; who had not fasted for at least 8hrs before blood sampling; who reported a diagnosis of stroke, myocardial infarction, angina, renal failure, liver cirrhosis, and/or any cancers; who were females and reported being pregnant at the time of the survey	20-79yrs	M: n=9,997 F: n=14,514
(Yoo and Franke 2013) USA	n=106	Primary: in conjunction with the annual medical evaluation of the Sworn law	Not reported	Accepted to participate	Participants with incomplete answers	42.3yrs (SD:8.4)	M: not reported F: not reported

		enforcement officers of the Iowa Department of Public Safety					
(Krishnan *et al.* 2012) India	n=358	Secondary: Large cross-sectional study on population from Chennai city	Not reported	Participants with a family history of hypothyroidism	Not reported	20-76yrs	M: n=190 F: n=168
(Kazman *et al.* 2012) USA	n=248	Primary: Community based study targeting African American population	Not reported	Self-identified African American	Participants who were pregnant or taking steroid medications	44yrs (SD:11.5)	M: n=97 F: n=151
(McCanlies *et al.* 2012) USA	n=98	Secondary: The Buffalo Cardio-Metabolic Occupational Police Stress study (BCOPS)	1999	Sworn police officer and willing to participate in the study	As for BCOPS study: had history of mastectomy, removal of lymph nodes, Raynaud's syndrome, diabetes with insulin pump, kidney dialysis, use of blood thinners, high doses of aspirin, any other heart condition or circulatory disorder, history of heart attack, stroke, bypass surgery, carotid artery endarterectomy, transient ischemic attack, or physician-diagnosed CHD	39.61yrs (SD: 7.39)	M: n=59 F: n=39
(Wu *et al.* 2012) Taiwan	n=7,100	Secondary: data from a health examination centre in National Cheng Kung University Hospital in Taiwan	2006-2009	Accepted to participate	Participants: aged <20yrs; with a history of one or more cerebral vascular events, coronary artery disease, and/or thyroid	44.7yrs (SD: 11.8)	M: n=4,298 F: n=2,802

					dysfunction; using sleeping pills, antihypertensive drugs, hypoglycemic and/or lipid lowering agents.		
(Hall *et al.* 2012) USA	n=340	Secondary: Study of Women's Health Across the Nation (SWAN) sleep study	2003-2005	Women (only) in their 'midlife'	As for the SWAN sleep study: using menopausal hormone replacement therapy, chemotherapy, radiation therapy, or oral corticosteroids; on regular night shiftwork; consuming >4 alcoholic drinks/day; who were noncompliance with Core SWAN procedures	46-57yrs	M: n=N/A F: n=340
(Arora *et al.* 2011) China	n=29,333	Secondary: Guangzhou Biobank Cohort Study (GBCS)	2003-2004	50 years and older ambulatory permanent Guangzhou resident	As for GBCS: receiving chemotherapy or radiotherapy for cancer, or dialysis for renal failure	50-96yrs	M: n=8.094 F: n=21,239
(Kobayashi *et al.* 2011) Japan	n=44,452 Analysis sample n=27,792	Primary: patients seen in the annual health checkup program at the Centre for Preventive Medicine at St. Luke's International Hospital	2008	Accepted to participate	Not reported	44.8yrs (SD:12.8)	M: n=22,004 F: n=22,448
(Roopa *et al.* 2010) India	n=358	Secondary: Chennai Urban Rural Epidemiology Study (CURES) phase 3	2003-2004	Accepted to participate	As for CURES study: no specific criteria	20–76yrs	M: n=190 F: n=168

(Hall *et al.* 2008) USA	n=1,214	Secondary: the University of Pittsburgh's Adult Health and Behaviour registry (AHAB)	Not reported	Midlife adults 30-54yrs	As for AHAB: who had clinical history of atherosclerotic cardiovascular disease, chronic kidney, liver disease and/or cancer; with neurologic disorders, schizophrenia, and/or other psychotic ill-nesses; using insulin, glucocorticoids, and/or antiarrhythmic, psychotropic and pregnant women	30-54yrs	M: n=568 F: n=646
(Choi *et al.* 2008) South Korea	n=4,222	Secondary: Korean National Health and Nutrition Survey (KNHNS)	2001	As for the KNHNS: civilian noninstitutionalized Individuals >1yr for the Health and nutrition survey; >10yrs for the health behaviour and examination survey	KNHNS Participants: aged <20yrs; lacking fasting time data or who did not fast for required period of time; without sleep duration data; taking medications to treat the metabolic syndrome	44.1yrs (SD:0.4)	M: n=1,822 F: n=2,400
(Santos, Ebrahim and Barros 2007) Portugal	n=2,164	Primary: Community based study targeting non-institutionalized adults inhabitants of Porto, Portugal	1999-2003	Accepted to participate	Participants who scored less than 24 on the mini-mental state examination scale for the evaluation of cognitive impairment	18-92yrs	M: n=832 F: n=1,332
(Jennings *et al.* 2007) USA	n=210	Secondary: the University of Pittsburgh's Adult Health and Behaviour registry (AHAB)	Not reported	Midlife adults 30-54yrs	As for AHAB: who had clinical history of atherosclerotic cardiovascular disease, chronic kidney, liver	45.8yrs (SD: 6.0)	M: n=120 F: n=90

					disease and/or cancer; with neurologic disorders, schizophrenia, and/or other psychotic ill-nesses; using insulin, glucocorticoids, and/or antiarrhythmic, psychotropic and pregnant women		
(Thomas *et al.* 2006) China	n=10,413 Analysis sample n=8325	Secondary: Guangzhou Biobank Cohort Study (GBCS)	2003-2004	50 years and older ambulatory permanent Guangzhou resident	As for GBCS: receiving chemotherapy or radiotherapy for cancer, or dialysis for renal failure	50-85yrs	M: n=2530 F: n=5,795

2.4.3 Definition and measurement of exposures, outcomes and covariates

All but two of the studies operationalised MetS as the outcome variable, with one (or more) sleep-specific characteristics as the exposure (see Table 2.2); and all operationalised MetS using established classifications: most (n=9) using classifications based on the NCEP ATP III criteria (2002); n=6 based on the AHA/NHLBI criteria (Eckel, Grundy and Zimmet 2005); n=5 on the 'harmonised' criteria (Alberti *et al.* 2009); and n=1 on criteria proposed by the Japan Society for the Study of Obesity [JASSO] criteria (Matsuzawa 2005). All based their classification of MetS on direct measures (rather than self-reports) of MetS components (i.e. central obesity, high blood pressure, dyslipidaemia and diabetes). In contrast, only two of the studies used objective measures of sleep (n=1 using actigraphy; n=1 using polysomnography), and of the remainder just over half (n=10) used established self-reported sleep and/or activity instruments (n=6 using the PSQI. (Buysse *et al.* 1989); n=2 using the modified STOP [Snoring, Tiredness during daytime, Observed apnoea, and high blood Pressure] questionnaire, (Chung *et al.* 2008); and n=1 each the *Stanford* 7-day *Physical Activity* Recall Scale, (Sallis *et al.* 1985), and the International Physical Activity Questionnaire (Hagströmer, Oja and Sjöström 2006); with n=9 using 'custom sleep item sets' (i.e. sleep-related questions developed and/or selected specifically for that study; see Table 2.2).

The diversity of different instruments used, and the large number of studies using custom sleep item sets, may prove a significant challenge to any attempt to synthesise findings from more than a handful of these studies. This is likely to be compounded by the range of different sleep-related characteristics examined. Indeed, although the commonest sleep characteristic examined (sleep duration) was used by n=15 (71.4%) of the studies (for n=11 of which sleep duration was the *only* characteristic examined), only n=5 examined sleep quality (all of whom used the Total PSQI score), only n=4 independent studies examined snoring or 'sleep-related breathing difficulty' (the two Chennai studies using the same instrument; two separate studies using different interpretations of the same instrument; and one study using a custom item), and only n=1 independent study examined: sleep latency; sleep fragmentation; sleep efficiency; sleep medication use; daytime sleepiness (examined by both of the Chennai studies); and two measures derived from polysomnography (Non-REM Beta waves [a measure of wakefulness], and apnoea-hypopnoea index [AHI] events). As such, no single study examined more than n=4 sleep-related characteristics, and most (n=14) only studied one (of which, as reported earlier, most only studied sleep duration). These studies therefore offer evidence of the association

between MetS and sleep that is likely to be strongest for sleep duration (and, possibly, sleep quality) with much sparser information on other sleep characteristics (and most of this from just one study).

Finally, the vast majority of studies provided (at least some) information on a range of available/measured covariates (see table 2.2), for which they offered a varying degree of information on the mean value/prevalence observed both for study participants as a whole and those disaggregated according to MetS and/or sleep-related categories. In all but two instances these data (and data on each component of MetS and each sleep-related characteristic examined) appear to have been collected simultaneously. And while there tended to be more detail provided that was relevant to the time period for which many of the self-reports (and direct measures) of sleep might refer, and any time interval between the measurement of MetS and sleep, there was little consistently reported detail on the when and how each covariate was measured (and rarely sufficient to assess, with any degree of certainty the likely temporal sequence in which each of the social and/or biological characteristics examined by these covariates had occurred). This uncertainty is likely to pose additional challenges to any attempts to generate plausible causal path diagrams from which to identify covariates likely to have acted as confounders, mediators or competing exposures in any relationship between MetS and sleep (as described in some detail, below).

Nonetheless, to assist in this process, all of the ‘available/measured’ covariates (i.e. covariates mentioned in any section of the articles reviewed, indicating that the primary and/or secondary sources of data on which the study was based had provided data on these) were harmonised across studies and categorised into nine conceptual groups, each intended to represent clusters of similarly defined/measured variables capturing characteristics or phenomena considered likely to have been emerged or established/determined at similar time points during the each participant’s lifecourse. These six categories (and the harmonised covariates considered relevant to each) have been summarised in Table 2.3, together with categories labelled ‘Sleep’, ‘Current anthropometric status’ and ‘Current clinical status’ which contain variables relevant to the exposures and outcomes examined by the n=21 different studies (taken from Table 2.2).

Table 2.2 Definition and measurement of exposures/interventions and outcomes, and any available covariates mentioned in (and extracted from) n=21 cross-sectional studies containing empirical analyses of the relationship between MetS and sleep; together with any measured sleep characteristics, and any those measured variables relevant to the classification of MetS.

Citation	Outcome variable specified	Exposure variable specified	Measurement of sleep characteristics (direct measure or self-report)	Classification of MetS used	Measurement of MetS components (direct measure or self-report)	Available covariates	Interval between measurement of covariates, outcome and exposure	Sleep assessment period
Mesas et al. 2014 Spain	MetS	Sleep-related	Sleep latency; sleep fragmentation; sleep medication Custom sleep item set (self-reported)	Harmonized	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; education; occupation; smoking; alcohol; coffee; energy intake; physical activity; diagnosed mental/physical illness; TV time; antihypertensive medication; lipid-lowering medication	No interval	Habitual
Ohkuma et al. 2014 Japan	MetS	Sleep-related	Sleep duration Custom sleep item set (self-reported)	Harmonized	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; early/late onset diabetes; energy intake; smoking; alcohol; exercise; symptomatic mental illness; antidiabetic medication	No interval	Habitual
Saleh and Janssen 2014 USA	MetS	Sleep-related	Sleep duration Actigraphy (directly measured)	Harmonized	Waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; ethnicity; education; socioeconomic status; smoking; alcohol; caffeine; screen time; sedentary time; physical activity	No interval	7 days ahead from collecting data

Hung et al. 2013 Taiwan	Sleep-related	MetS	Sleep quality PSQI (self-reported)	AHA/NHLBI for Asian populations	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; exercise; alcohol; smoking; creatinine levels	No interval	Past month
Chaput et al. 2013 Canada	MetS	Sleep-related	Sleep duration Custom sleep item set (self-reported)	AHA/NHLBI	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; smoking; education; income; coffee; menopausal status; energy intake; alcohol; physical activity	No interval	On average
Lee et al. 2013 South Korea	MetS	Sleep-related	Sleep duration; sleep quality; sleep-related breathing disorder PSQI (self-reported)	NCEP ATPIII (modified using Korean definition of abdominal obesity)	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Sex; age; education; occupation; income; smoking; alcohol; exercise; stress; diagnosed/symptomatic mental illness	No interval	Past month
Stefani et al. 2013 South Korea	MetS	Sleep-related	Sleep duration Custom sleep item set (self-reported)	Harmonized	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; income; occupation; education; smoking; alcohol; physical activity; BMI; energy intake	No interval	On average
Yoo and Franke 2013 USA	MetS	Sleep-related	Sleep duration; sleep quality PSQI (self-reported)	AHA/NHLBI (modified for use with BMI)	Weight; height; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; smoking; physical activity; stress; diagnosed/symptomatic mental illness	No interval	Past month

Krishnan et al. 2012 India	Sleep-related	MetS	Snoring; daytime sleepiness Modified STOP questionnaire (self-reported)	NCEP ATP III (modified using Asia Pacific waist measurement)	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; family history of hyperthyroidism; physical activity; smoking; alcohol	No interval	On average
Kazman et al. 2012 USA	MetS	Sleep-related	Sleep duration; sleep quality; difficulty breathing; snoring PSQI (self-reported)	AHA/NHLBI	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex	No interval	Past month
McCanlies et al. 2012 USA	Mets	Sleep-related	Sleep duration; OSA PSQI; Sleep Apnoea Survey (self-reported)	NCEP ATP III	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; education; smoking; marital status; race/ethnicity; physical activity; occupation	No interval	Past month or past week
Wu et al. 2012 Taiwan	Mets	Sleep-related	Sleep duration Custom sleep item set (self-reported)	NCEP ATP III	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; education; family history of diabetes; family history of hypertension; smoking; alcohol; exercise; BMI	No interval	On average
Hall et al. 2012 USA	MetS	Sleep-related	Sleep duration; sleep efficiency; relative NREM Beta; AHI events PSQI and polysomnography (self-reported and	NCEP ATP III	Waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; race/ethnicity; menopausal status; education; marital status; diagnosed/symptomatic mental illness; symptomatic physical illness; health compliance; current medication; smoking; alcohol; exercise	Exposure (sleep-related) measured 3.6mo after outcome and covariates	Past month for subjective sleep-related 3 nights ahead for objective sleep-related

			directly measured)					
Arora et al. 2011 China	MetS	Sleep-related	Sleep duration Custom sleep item set (self-reported)	Harmonized	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; smoking; alcohol; physical activity; education; diagnosed/symptomatic mental and physical illness; use of hypnotics	No interval	Per day
Kobayashi et al. 2011 Japan	MetS	Sleep-related	Sleep duration Custom sleep item set (self-reported)	JASSO	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; alcohol; smoking; pre-existing physical and mental illness; diagnosed/symptomatic mental and physical illness; current medication; physical activity	No interval	On average
Roopa et al. 2010 India	MetS	Sleep-related	Snoring; daytime sleepiness Modified STOP questionnaire (self-reported)	NCEP ATP III (modified using Asia Pacific waist measurement)	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; physical activity; smoking; alcohol	No interval	On average
Hall et al. 2008 USA	MetS	Sleep-related	Sleep duration Stanford 7-day Physical Activity Recall Scale (self-reported)	AHA/NHLBI	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; race/ethnicity; education; smoking; alcohol; physical activity; blood lipid levels; symptomatic mental illness	No interval	Past week
Choi et al. 2008	MetS	Sleep-related	Sleep duration Custom sleep item set	NCEP ATP III (modified using Asia Pacific waist	Weight; height; waist circumference; blood pressure; and fasting	Age; sex; family history of hypertension; family history of diabetes; residential	No interval	On average

South Korea			(self-reported)	measurement)	haematological analysis (directly measured)	area; education; income; alcohol; smoking; exercise; BMI		
Santos et al. 2007 Portugal	MetS	Sleep-related	Sleep duration Custom sleep item set (self-reported)	NCEP ATP III	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; marital status; education; occupation; physical activity; exercise; smoking; alcohol	No interval	Per day
Jennings et al. 2006 USA	MetS	Sleep-related	Sleep quality PSQI (self-reported)	AHA/NHLBI	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; race/ethnicity; diagnosed/symptomatic mental illness; smoking; alcohol; education; antihypertensive medication	No interval	Past month
Thomas et al. 2006 China	MetS	Sleep-related	Snoring Custom sleep item set (self-reported)	NCEP ATP III (modified using Asia Pacific waist measurement)	Weight; height; waist circumference; blood pressure; and fasting haematological analysis (directly measured)	Age; sex; waist to hip ratio; occupation; education; exercise; smoking; alcohol; blood pressure; blood lipid levels; blood glucose levels	No interval	Past month

Table 2.3 A summary of the 'available covariates' mentioned in (and extracted from) n=21 cross-sectional studies containing empirical analyses of the relationship between MetS and sleep; together with any measured sleep characteristics, and any those measured variables relevant to the classification of MetS.

Covariate classification	**Covariates included in adjustment sets**
Family clinical history	Family history of hyperthyroidism; family history of hypertension; family history of diabetes
Sociodemographic	Age; sex; race/ethnicity; marital status
Socioeconomic	Education; occupation; income; residential area;
Clinical history	Pre-existing/diagnosed physical and mental illness; early/late onset diabetes; early/late menopausal onset; height
Current lifestyle	Smoking; alcohol; coffee/caffeine; energy intake; physical activity/exercise; sedentary time; screen/TV time; health compliance
Current clinical status	Blood pressure/hypertension; glucose levels/diabetes; blood lipid levels; symptomatic mental and physical illness; creatinine levels; stress
Current medication	Psychotropic, hypnotic and sleep-affecting drugs; antidiabetic medication; antihypertensive medication; lipid-lowering medication; current medication
Current anthropometric status	Weight; BMI; waist circumference; waist-to-hip ratio
Sleep	Sleep duration; sleep latency; sleep fragmentation; sleep efficiency; sleep medication; snoring; OSA/sleep-related breathing disorder; sleep quality; Non-REM Beta; AHI events; daytime sleepiness; insomnia

2.4.4 Analytical models used and reported effect estimates

The statistical techniques, covariate adjustment sets and effect estimates reported for each of the models used by the n=21 cross-sectional studies included in the present review have been summarised in Table 2.4. As mentioned earlier (see Table 2.2), all but two of these models operationalised sleep-related characteristics as exposures, with MetS as the outcome. One of the studies used only Poisson regression analyses (with MetS categorised as a binary outcome variable), while another used both linear and logistic regression analyses (with the PSQI Total Score operationalised as both a continuous and binary outcome variable). All of the remaining studies used (only) logistic regression analyses, with binary outcome variables based on either the presence/absence of MetS (as defined and classified according to the criteria chosen by each study); or the presence/absence of a specified sleep characteristic (such as snoring or daytime sleepiness). While the referent category used for the latter was usually unambiguous (i.e. the *absence* of or *specified referent* to the category examined), the referent category used for MetS was not clearly described by any of the n=21 studies reviewed. As such, it was not at all clear whether the referent category comprised participants who lacked: *any* of the relevant MetS components; or *only those combinations of MetS components* necessary to achieve the classification of MetS used.

All of the studies contained models that were adjusted for covariates, most reporting a series of models employing just one (n=7), two (n=8) or three (n=3) different adjustment sets, with only n=1 study each employing four, six and seven different adjustment sets, respectively. In contrast, only around half of the studies (n=9) reported effect estimates for unadjusted models, although some of the remainder reported stratified prevalences (of MetS by the specific sleep characteristic examined, or vice versa) from which it was possible to calculate unadjusted effect estimates (see Table 2.4). In the main, the adjustment sets used included different combinations of the various categories of covariates identified amongst the 'available covariates' summarised in Table 2.3 (see earlier) – i.e. family clinical history; sociodemographic characteristics; socioeconomic status; clinical history; current medication; current lifestyle*; current anthropometric status*; presence of MetS-related components ('current clinical status');* and sleep characteristics* (those indicated with an asterisk* representing what are likely to be measures contemporaneous with the cross-sectional measures of sleep and MetS).

On the basis of the models summarised in Table 2.4, there appears strong prima facie evidence that MetS was associated with less favourable sleep across a wide range of sleep-related characteristics, both before and after adjustment for

covariates. This was particularly evident amongst the n=15 studies examining sleep duration (many of which found that both short and long sleep duration was associated with an increased likelihood of MetS), the n=5 that examined sleep quality (many of which reported that MetS was associated with an increased risk of 'poor' sleep quality), and the n=4 independent analyses that examined snoring or 'sleep-related breathing difficulty' (all of which reported an increased risk of snoring associated with MetS). There was also some evidence that MetS was associated with many of the other sleep-related characteristics (each of which were only examined by one of the n=21 studies reviewed), and in particular that: habitual sleep latency, poor sleep efficiency, sleep medication use, Non-REM Beta and AHI events (though not sleep fragmentation and daytime sleepiness) were all associated with an increased risk of MetS. At face value, these findings appear to support the presence of an association between MetS and a wide range of sleep-related characteristics. However, the somewhat equivocal findings (particularly the absence of associations between MetS, short/prolonged sleep duration, poor sleep quality and snoring in some of n=4-15 studies examining these; and the absence of an association between MetS, sleep fragmentation and daytime sleepiness in the two independent studies examining these) suggests that the evidence may be less than secure, or that differences in sampling, measurement and analysis, together with publication bias, may have influenced the evidence these studies provide.

Table 2.4 Analytical models examining the association between MetS and sleep-specific characteristics mentioned in (and extracted from) n=21 cross-sectional studies containing empirical analyses of the relationship between MetS and sleep; together with any measured sleep characteristics, and any those measured variables relevant to the classification of MetS.

Citation	Statistical test(s) used	Outcome/dependent variable; prevalence of indicator; and (referent category)	Exposure/independent variable; prevalence of indicator; and (referent category)	Covariate adjustment sets	Unadjusted and adjusted effect estimates
Mesas et al. 2014 Spain	Logistic regression	MetS (Yes: 22.2%; No[ref]) MetS referent category comprised: Not clear (not identified as MetS)	*1. Sleep latency* (Habitual 14.8%; Not habitual [ref]) *2. Sleep fragmentation* (Habitual 15.9%; Not habitual [ref]) *3. Sleep medication* (Habitual 6.9%; Not habitual [ref])	**M0:** Unadjusted (not reported) **M1:** Sex; age; education; occupation **M2:** M1+smoking; alcohol; coffee **M3:** M2+diagnosed mental/physical illness; diabetes **M4:** M3+sleep duration **M5:** M4+energy intake **M6:** M5+physical activity; TV time **M7:** M6+antihypertensive medication; lipid-lowering medication	*1. Sleep latency* **M0:** Not reported – calculated: **OR:1.55 (95%CI:1.37,1.75)** **M1: OR1.31 (95%CI:1.12,1.53)** **M2: OR:1.28 (95%CI:1.09,1.49)** **M3: OR:1.25 (95%CI:1.06,1.47)** **M4: OR:1.23 (95%CI:1.04,1.46)** **M5: OR:1.23 (95%CI:1.04,1.46)** **M6: OR:1.20 (95%CI:1.01,1.42)** **M7:** OR:1.16 (95%CI:0.97,1.39) *2. Sleep fragmentation* **M0:** Not reported – calculated: **OR:2.76 (95%CI:2.44,3,12)** **M1:** OR:1.15 (95%CI:0.99,1.33) **M2:** OR:1.15 (95%CI:0.99,1.33) **M3:** OR:1.16 (95%CI:0.99,1.36) **M4:** OR:1.14 (95%CI:0.97,1.35) **M5:** OR:1.15 (95%CI:0.97,1.35) **M6:** OR:1.13 (95%CI:0.96,1.33) **M7:** OR:1.09 (95%CI:0.92,1.30) *3. Sleep medication* **M0:** Not reported – calculated: **OR:2.07 (95%CI:1.76,2.43)** **M1: OR:1.27 (95%CI:1.04,1.54)** **M2: OR:1.23 (95%CI:1.01,1.50)** **M3:** OR:1.16 (95%CI:0.93,1.45) **M4:** OR:1.15 (95%CI:0.92,1.44)

					M5: OR:1.15 (95%CI:0.92,1.44) **M6:** OR:1.11 (95%CI:0.88,1.39) **M7:** OR:1.02 (95%CI:0.81,1.29)
Ohkuma et al. 2014 Japan	Logistic regression	MetS (Yes: %Not reported – calculated 54.3%; No[ref]) MetS referent category comprised: Not clear (not identified as MetS) (Separate analyses conducted on: elevated waist circumference; high blood pressure; raised blood triglycerides; and reduced HDL cholesterol)	*1. Sleep duration* (<5.5hrs:14.2%; 5.5-6.4hrs:25.0%; 6.5-7.4hrs [ref]; 7.5-8.4hrs:23.5%; ≥8.5hrs:9.5%)	**M0:** Unadjusted (not reported) **M1:** Age; sex; early/late onset diabetes; energy intake; smoking; alcohol; exercise; symptomatic mental illness; antidiabetic medication	*1.1 Sleep duration <5.5hrs* **M0:** Not reported – calculated: **OR:1.64 (95%CI:1.34,1.99)** **M1: OR:1.71 (95%CI:1.39,2.11)** *1.2 Sleep duration 5.5-6.4hrs* **M0:** Not reported – calculated: OR:1.04 (95%CI:0.88,1.23) **M1:** OR:1.03 (95%CI:0.87,1.22) *1.3 Sleep duration 7.5-8.4hrs* **M0:** Not reported – calculated: OR:1.04 (95%CI:0.88,1.23) **M1:** OR:1.09 (95%CI:0.92,1.29) *1.4 Sleep duration ≥8.5hrs* **M0:** Not reported – calculated: **OR:1.74 (95%CI:1.38,2.20)** **M1: OR:1.48 (95%CI:1.17,1.88)**
Saleh and Janssen	Logistic regression	MetS (Yes: 37.4%; No[ref])	*1. Sleep duration* (quartiles: 3.0-7.2hrs:34.1%;	**M0:** Unadjusted **M1:** Age; ethnicity; screen time	*1.1 Sleep duration <7.2hrs* **M0:** OR:0.86 (95%CI:0.60,1.23)

2014 USA		MetS referent category comprised: Not clear (not identified as MetS) (Separate analyses conducted on: elevated waist circumference; high blood pressure; raised blood triglycerides; elevated plasma glucose; and reduced HDL cholesterol)	7.2-8.6hrs [ref]; 8.6-9.7hrs:35.6%; 9.7-11.8hrs:39.8%)	**M2**: Age; education; physical activity; sedentary time	**M1:** OR:0.90 (95%CI:0.62,1.32) **M2:** OR:0.91 (95%CI:0.62,1.33) *1.2 Sleep duration 8.6-9.7hrs* **M0:** OR:0.93 (95%CI:0.65,1.33) **M1:** OR:0.89 (95%CI:0.61,1.30) **M2:** OR:0.89 (95%CI:0.61,1.29) *1.3 Sleep duration >9.7hrs* **M0:** OR:1.12 (95%CI:0.78,1.60) **M1:** OR:0.97 (95%CI:0.67,1.41) **M2:** OR:0.95 (95%CI:0.66,1.39)
Hung et al. 2013 Taiwan	Linear regression and logistic regression	Sleep quality (PSQI Total Score continuous: per unit; PSQI Total Score categorical: >5 (56.1%); ≤5[ref])	*1.MetS* (Yes: 26.2%; No[ref]) MetS referent category comprised: not identified with MetS (Separate analyses conducted on: central obesity; hyperglycaemia; high blood pressure; and reduced HDL cholesterol)	1. Linear regression: **M0:** Unadjusted (not reported) **M1:** Age; sex; sleep duration **M2:** M1+snoring; alcohol; smoking; exercise; creatinine levels 2. Logistic regression: **M0:** Unadjusted (not reported) **M1:** Age; sex; sleep duration; snoring; alcohol; smoking; exercise; creatinine levels	*1. Sleep quality PSQI Total Score per unit* **M0:** Not reported **M1: β: 0.96 (95%CI:0.76,1.16)** **M2: β: 0.87 (95%CI:0.66,1.07)** *2. Poor sleep quality PSQI score >5* **M0:** Not reported – calculated: **OR:1.51 (95%CI:1.29,1.76)** **M1: OR:1.48 (95%CI:1.25,1.74)**
Chaput et al. 2013 Canada	Logistic regression	MetS (Yes:24.6%; No[ref]) MetS referent category comprised: Not clear (not identified as MetS)	*1. Sleep duration* (≤6hrs:11.1%; 7-8hrs [ref]; ≥9hrs:18.4%)	**M0:** Unadjusted **M1:** age; sex; smoking; education; income; alcohol; coffee; menopausal status **M2:** M2+energy intake; physical activity	*1.1 Sleep duration ≤6hrs* **M0: OR:2.02 (95%CI:1.32,3.23)** **M1: OR:1.80 (95%CI:1.15,2.98)** **M2: OR:1.76 (95%CI:1.08–2.84)** *1.2 Sleep duration ≥9hrs* **M0:** OR:1.46 (95%CI:0.95,2.14) **M1:** OR:1.43 (95%CI:0.91-2.09) **M2:** OR:1.35 (95%CI:0.83-1.99)

Lee et al. 2013 South Korea	Logistic regression	MetS (Yes: 35.2%; No[ref]) MetS referent category comprised: Not clear MetS categorised based on number of risk factors 0, ≥1, ≥2, and ≥3	*1. Sleep duration* (<5.5hrs:16.9%; 5.5-6.49hrs:32.6%; 6.5-7.49hrs[ref]; 7.5-8.49hrs:14.3%; ≥8.5hrs:4.3%) *2. Sleep quality* (PSQI Total Score>5: 41.9%; ≤5[ref]) *3. Sleep-related breathing disorder* (Low risk [ref]; High risk: 34.2%)	**M0:** Unadjusted **M1:** Sex; age; education; occupation; income; smoking; alcohol; exercise; stress; diagnosed/symptomatic mental illness; sleep duration (for PSQI and SRBD); PSQI Total Score (for duration and SRBD); SRDB (for duration and PSQI)	*1.1 Sleep duration <5.5hrs* **M0: OR:6.35 (95%CI:3.01,13.40)** **M1: OR:4.89 (95%CI:1.90,12.58)** *1.2 Sleep duration* 5.5-6.49hrs **M0:** OR:1.40 (95%CI:0.74,2.64) **M1:** OR:1.26 (95%CI:0.59,2.67) *1.3 Sleep duration 7.5-8.49hrs* **M0:** OR:1.09 (95%CI:0.48,2.50) **M1:** OR:1.27 (95%CI:0.50,3.26) *1.4 Sleep duration ≥ 8.5hrs* **M0: OR:5.08 (95%CI:1.51,17.06)** **M1: OR:5.98 (95%CI:1.41,25.41)** *2. Poor sleep quality PSQI Total Score >5* **M0: OR:3.71 (95%CI:2.26,6.10)** **M1: OR:3.83 (95%CI:1.91,7.65)** *3. Sleep-related breathing disorder*: **M0: OR:1.98 (95%CI:1.21,3.24)** **M1: OR:1.92 (95%CI:1.04,3.54)**
Stefani et al. 2013 South Korea	Logistic regression	MetS (Yes: 25%; No[ref]) MetS referent category comprised: Not clear (not identified as MetS)	*1. Sleep duration* (≤5hrs:13.6%; 6hrs:25.7%; 7hrs [ref]; 8hrs:23.4%; ≥9hrs:7.5%)	**M0:** Unadjusted **M1:** age; sex **M2:** M1+ education; occupation; physical activity; smoking; alcohol **M3:** M2+BMI	*1.1 Sleep duration ≤5 hrs* **M0: OR:1.74 (95%CI:1.59,1,91)** **M1:** OR:1.06 (95%CI:0.96,1.17) **M2:** OR:1.04 (95%CI:0.94,1.14) **M3:** OR:1.00 (95%CI:0.90,1.11) *1.2 Sleep duration 6hrs* **M0: OR:1.10 (95%CI:1.01,1.19)** **M1:** OR:1.01 (95%CI:0.93,1.10) **M2:** OR:1.00 (95%CI:0.92,1.09)

					M3: OR:0.95 (95%CI:0.87,1.05) *1.3 Sleep duration 8hrs* **M0:** OR:1.04 (95%CI:0.96,1.13) **M1:** OR:1.02 (95%CI:0.94,1.12) **M2:** OR:1.01 (95%CI:0.92,1.10) **M3:** OR:1.06 (95%CI:0.96,1.17) *1.4 Sleep duration ≥9hrs* **M0: OR:1.32 (95%CI:1.17,1.48)** **M1: OR:1.14 (95%CI:1.00,1.29)** **M2:** OR:1.10 (95%CI:0.97,1.25) **M3: OR:1.31 (95%CI:1.14,1.51)**
Yoo and Franke 2013 USA	Logistic regression	MetS (Yes: 33.0%; No[ref]) MetS referent category comprised: Not clear (not identified as MetS) (Separate analyses conducted on: obesity; hypertension; glucose intolerance; raised blood triglycerides; and reduced HDL cholesterol)	*1. Sleep duration* (≤6hrs:30.2%; >6<8hrs [ref]; ≥8hrs:19.8%)) *2. Sleep quality* ((PSQI Total Score>5: 26.8%; ≤5[ref])	**M0:** Unadjusted (not reported) **M1:** Age; sex; smoking; physical activity **M2:** M1+ diagnosed/symptomatic mental illness	*1.1 Sleep duration ≤6hrs* **M0:** Not reported – calculated: OR:1.40 (95%CI:0.53,3.71) **M1:** OR:1.94 (95%CI:0.65,5.82) **M2:** OR:2.30 (95%CI:0.71,7.50) *1.2 Sleep duration ≥8hrs* **M0:** Not reported – calculated: **OR:4.10 (95%CI:1.41,11.92)** **M1: OR:3.62 (95%CI:1.14,11.52)** **M2: OR:4.89 (95%CI:1.32,18.13)** *2. Poor sleep quality PSQI Total Score >5* **M0:** Not reported – calculated: OR:1.02 (95%CI:0.44,2.37) **M1:** OR:1.56 (95%CI:0.61,4.03) **M2:** OR:2.25 (95%CI:0.70,7.19)

Krishnan et al. 2012 India	Logistic regression	*1. Snoring* (Yes: 40.0%; No[ref]) *2. Daytime sleepiness* (Yes: 59.0%; No[ref])	MetS (Yes: %Not reported; No[ref]) MetS referent category comprised: Not clear (not identified as MetS)	**M0:** Unadjusted **M1:** age **M2:** age; sex **M3:** M2+family history of hyperthyroidism **M4:** M3+physical activity **M5:** M4+smoking **M6:** M5+alcohol	*1. Snoring* **M0: OR:2.56 (95%CI:1.64,4.00)** **M1: OR:2.21 (95%CI:1.38,3.54)** **M2: OR:2.07 (95%CI:1.28,3.36)** **M3: OR:2.03 (95%CI:1.25,3.30)** **M4: OR:2.21 (95%CI:1.28,3.83)** **M5: OR:2.21 (95%CI:1.27,3.83)** **M6: OR:2.19 (95%CI:1.26,3.80)** *2. Daytime sleepiness* **M0:** OR:1.44 (95%CI:0.92,2.26) **M1:** OR:1.31 (95%CI:0.81,2.10) **M2:** OR:1.33 (95%CI:0.83,2.15) **M3:** OR:1.29 (95%CI:0.80,2.09) **M4:** OR:1.27 (95%CI:0.74,2.19) **M5:** OR:1.27 (95%CI:0.74,2.19) **M6:** OR:1.23 (95%CI:0.71.2.12)
Kazman et al. 2012 USA	Logistic regression	MetS (Yes: 39.0%; No[ref]) MetS referent category comprised: Not clear (not identified as MetS)	*1. Sleep duration* (≤6hrs:54.0%; 6-9hrs [ref]; ≥9hrs:8.0%) *2. Sleep quality* (PSQI Total Score>5 (49.0%); ≤5 [ref]) *3. Difficulty breathing* (≥once per week: 19.0%; <once per week [ref]) *4. Snoring* (≥once per week: 26.0%; <once per week [ref])	**M0:** Unadjusted (not reported) **M1:** Age; sex	*1.1 Sleep duration ≤6hrs* **M0:** Stratified prevalences not available to permit calculation **M1:** OR:0.99 (95%CI:0.33,3.00) *1.2 Sleep duration ≥9hrs* **M0:** Stratified prevalences not available to permit calculation **M1:** OR:0.99 (95%CI:0.33,3.00) *2. Poor sleep quality PSQI Total Score >5* **M0:** Stratified prevalences not available to permit calculation **M1:** OR:0.67 (95%CI:0.37,1.21) *3. Difficulty breathing ≥once per week*

					M0: Stratified prevalences not available to permit calculation **M1:** OR:1.15 (95%CI:0.57,2.30) *4. Snoring ≥once per week* **M0:** Stratified prevalences not available to permit calculation **M1: OR:2.57 (95%CI:1.40,4.71)**
McCanlies et al. 2012 USA	Poisson regression	Mets (Yes: 14.0%; No[ref]) MetS referent category comprised: Not clear (not identified as MetS)	*1. Sleep duration* (<6hrs:28.6%; ≥6hrs [ref]) *2. OSA* (Ever: %Not reported; Never[ref])	**M0:** Unadjusted **M1:** Age **M2:** Age; sex **M3:** M2+education; smoking	*1. Sleep duration <6hrs* **M0:** PR:2.50 (95%CI:0.97,6.47) **M1:** PR:2.52 (95%CI:0.98,6.49) **M2:** PR:2.42 (95%CI:0.95,6.12) **M3:** PR:2.29 (95%CI:0.81,6.49) *2. OSA* – Not reported **M0:** Stratified prevalences not available to permit calculation **M1:** Not reported **M2:** Not reported **M3:** Not reported
Wu et al. 2012 Taiwan	Logistic regression	MetS (Yes: %Not reported – calculated for males 17.8%, and females 9.8%; No[ref]) MetS referent category comprised: Not clear MetS are categorised based on number of risk factors 0, 1 or 2, and 3 or more	*1. Sleep duration* (<6hrs:24.6%; 6-8hrs [ref]; >8hrs:3.4%)	**M0:** Unadjusted (not reported) **M1:** Age; education; BMI; smoking; alcohol; exercise	*1.1.1 Sleep duration <6hrs - Males* **M0:** Not reported – calculated: **OR:1.31 (95%CI:1.14,1.50)** **M1: OR:1.28 (95%CI:1.01,1.63)** *1.1.2 Sleep duration <6hrs - Females* **M0:** Not reported – calculated: **OR:1.36 (95%CI:1.04,1.77)** **M1:** OR:1.04 (95%CI:0.72,1.51) *1.2.1 Sleep duration >8hrs - Males* **M0:** Not reported – calculated: OR:1.21 (95%CI:0.87,1.67)

					M1: OR:1.43 (95%CI:0.82,2.48) *1.2.2 Sleep duration >8hrs - Females* **M0:** Not reported – calculated: OR:1.01 (95%CI:0.50,2.04) **M1:** OR:0.90 (95%CI:0.32,2.51)
Hall et al. 2012 USA	Logistic regression	MetS (Yes: 30.9%; No[ref]) MetS referent category comprised: Not clear (not identified as MetS)	*1. Sleep duration* (per additional hr of sleep) *2. Poor sleep efficiency* (per percentage) *3. Relative NREM Beta* (per unit) *4. AHI events* (events per hr) (No raw prevalence reported)	**M0:** Unadjusted (not reported) **M1:** race/ethnicity; menopausal status; education; marital status; health compliance; current medication; smoking; alcohol; exercise. **M2:** M1+BMI	*1. Sleep duration per hr* **M0:** Stratified prevalences not available to permit calculation **M1:** OR:0.89 (95%CI:0.69,1.15) **M2:** OR:0.93 (95%CI:0.71-1.22) *2. Poor sleep efficiency per percent* **M0:** Stratified prevalences not available to permit calculation **M1: OR:1.38 (95%CI:1.05,1.83)** **M2: OR:1.40 (95%CI:1.04,1.89)** *3. Relative NREM Beta per unit* **M0:** Stratified prevalences not available to permit calculation **M1: OR:1.45 (95%CI:1.10,1.91)** **M2: OR:1.45 (95%CI:1.08,1.95)** *4. AHI events per hr* **M0:** Stratified prevalences not available to permit calculation **M1: OR:1.87 (95%CI:1.40,2.51)** **M2: OR:1.73 (95%CI:1.26,2.37)**
Arora et al. 2011 China	Logistic regression	MetS (Yes: 28.0%; No[ref]) MetS referent category	*1. Sleep duration* (<6hrs:13.5%; 6<7hrs:24.4%; 7<8hrs [ref]; 8<9hrs:23.5%; ≥9hrs:8.8%)	**M0:** Unadjusted **M1:** Age; sex **M2:** M1+education; smoking; physical activity; diagnosed mental illness; sleep	*1.1 Sleep duration <6hrs* **M0: OR:1.14 (95%CI:1.05,1.24)** **M1:** OR:0.98 (95%CI:0.90,1.06) **M2:** OR:0.97 (95%CI:0.88,1.06)

		comprised: Not clear (not identified as MetS)		fragmentation; use of hypnotics; daytime sleepiness; alcohol; snoring	*1.2 Sleep duration 6<7hrs* **M0: OR:1.10 (95%CI:1.03,1.18)** **M1:** OR:1.02 (95%CI:0.95,1.09) **M2:** OR:1.00 (95%CI:0.93,1.08) *1.3 Sleep duration 8-9hrs* **M0: OR:1.14 (95%CI:1.06,1.22)** **M1: OR:1.16 (95%CI:1.08,1.25)** **M2: OR:1.16 (95%CI:1.08,1.25)** *1.4 Sleep duration ≥9hrs* **M0: OR:1.18 (95%CI:1.07,1.30)** **M1: OR:1.22 (95%CI:1.11,1.35)** **M2: OR:1.21 (95%CI:1.10,1.34)**
Kobayashi et al. 2011 Japan	Logistic regression	MetS (Yes: 8.7%; No[ref]) MetS referent category comprised: Not clear (not identified as MetS)	*1. Sleep duration* (<6hrs: 26.2%; 6-6.99hrs:40.9%; 7-7.99hrs:24.2%; ≥8hrs[ref])	**M0:** Unadjusted (not reported) **M1:** Age; sex; alcohol; pre-existing physical and mental illness; physical activity	*1.1 Sleep duration <6hrs* **M0:** Not reported – calculated: **OR:0.79 (95%CI:0.68,0.92)** **M1: OR:1.42 (95%CI:1.20,1.68)** *1.2 Sleep duration 6-6.99 hrs* **M0:** Not reported – calculated: **OR:0.71 (95%CI:0.61,0.82)** **M1:** OR:1.12 (95%CI:0.95,1.31) *1.3 Sleep duration 7-7.99hrs* **M0:** Not reported – calculated: **OR:0.79 (95%CI:0.68,0.92)** **M1:** OR:1.02 (95%CI:0.86,1.20)
Roopa et al. 2010 India	Logistic regression	MetS (Yes: 34.6% No[ref]) MetS referent category comprised: Not clear (not	*1. Snoring* (Snores: 40.0%; Does not snore[ref]) *2. Daytime sleepiness*	**M0:** Unadjusted **M1:** Age **M2:** Age; sex **M3:** M2+physical activity **M4:** M3+smoking	*1. Snoring* **M0: OR:2.56 (95%CI:1.64,4.00)** **M1: OR:2.25 (95%CI:1.40,3.59)** **M2: OR:2.11 (95%CI:1.30,3.41)** **M3: OR:2.27 (95%CI:1.31,3.93)**

		identified as MetS)	(Yes:%Not reported; No[ref])	**M5:** M4+alcohol	**M4: OR:2.27 (95%CI:1.31,3.93)** **M5: OR:2.25 (95%CI:1.30,3.91)** *2. Daytime sleepiness* **M0:** Stratified prevalences not available to permit calculation **M1:** Not reported **M2:** Not reported **M3:** Not reported **M4:** Not reported **M5:** Not reported
Hall et al. 2008 USA	Logistic regression	MetS (Yes: 22.3%; No[ref]) MetS referent category comprised: Not clear (not identified as MetS) (Separate analyses conducted on: central obesity; blood glucose levels; hypertension; raised blood triglycerides; and reduced HDL cholesterol)	*1. Sleep duration* (<6hrs:15.4%; 6<7hrs:33.1%; 7-8hrs [ref]; >8hrs:8.2%)	**M0:** Unadjusted (not reported) **M1:** Age; sex; race/ethnicity; education; smoking; physical activity; blood lipid levels; symptomatic mental illness	*1.1 Sleep duration <6hrs* **M0:** Stratified prevalences not available to permit calculation **M1: OR:1.83 (95%CI:1.19,2.80)** *1.2 Sleep duration 6<7hrs* **M0:** Stratified prevalences not available to permit calculation **M1: OR:1.48 (95%CI:1.05,2.10)** *1.3 Sleep duration <6hrs* **M0:** Stratified prevalences not available to permit calculation **M1: OR:1.81 (95%CI:1.04,3.15)**
Choi et al. 2008 South Korea	Logistic regression	MetS (Yes: %Not reported; No[ref]) MetS referent category comprised: Not clear MetS are categorised based on number of risk factors 0, ≥1, ≥2, ≥ 3, ≥4	*1. Sleep duration* (≤5hrs:%Not reported; 6hrs:%Not reported; 7hrs[ref]; 8hrs:%Not reported; ≥9hrs:%Not reported)	**M0:** Unadjusted **M1:** Age; sex; family history of hypertension; family history of diabetes **M2:** M1+residential area; education; income; alcohol; smoking; exercise **M3:** M2+BMI	*1.1 Sleep duration ≤5hrs* **M0: OR:1.74 (95%CI:1.33,2.26)** **M1:** OR:1.23 (95%CI:0.92,1.64) **M2:** OR:1.15 (95%CI:0.85,1.55) **M3:** OR:1.17 (95%CI:0.87,1.59) *1.2 Sleep duration 6hrs* **M0: OR:1.27 (95%CI:1.04,1.56)** **M1:** OR:1.13 (95%CI:0.91,1.40)

		and 5			**M2: OR:1.11 (95%CI:1.01,1.57)** **M3:** OR:1.07 (95%CI:0.85,1.34) *1.3 Sleep duration 8hrs* **M0: OR:1.27 (95%CI:1.01,1.63)** **M1:** OR:1.28 (95%CI:1.00,1.64) **M2: OR:1.26 (95%CI:1.01,1.57)** **M3: OR:1.32 (95%CI:1.01,1.73)** *1.4 Sleep duration ≥9hrs* **M0: OR:1.55 (95%CI:1.15,2.07)** **M1: OR:1.47 (95%CI:1.08,2.00)** **M2: OR:1.46 (95%CI:1.07,1.98)** **M3: OR:1.69 (95%CI:1.17,2.45)**
Santos et al. 2007 Portugal	Logistic regression	MetS (Yes: %Not reported; No[ref]) MetS referent category comprised: Not clear (not identified as MetS)	*1. Sleep duration* (≤6hrs:%Not reported; 7hrs:%Not reported; 8hrs:%Not reported; ≥9hrs[ref])	**M0:** Unadjusted (not reported) **M1:** age; education **M2:** M1+smoking; alcohol	*1.1.1 Sleep duration ≤6hrs - Males* **M0:** Stratified prevalences not available to permit calculation **M1:** OR:0.99 (95%CI:0.51,1.85) **M2:** OR:0.91 (95%CI:0.47,1.76) *1.1.2 Sleep duration ≤6hrs - Females* **M0:** Stratified prevalences not available to permit calculation **M1: OR:0.45 (95%CI:0.27,0.74)** **M2: OR:0.46 (95%CI:0.28,0.75)** *1.2.1 Sleep duration 7hrs - Males* **M0:** Stratified prevalences not available to permit calculation **M1:** OR:0.74 (95%CI:0.45,1.23) **M2:** OR:0.65 (95%CI:0.38,1.11) *1.2.2 Sleep duration 7hrs - Females* **M0:** Stratified prevalences not

					available to permit calculation **M1: OR:0.50 (95%CI:0.33,0.75)** **M2: OR:0.50 (95%CI:0.33,0.76)** *1.3.1 Sleep duration 8hrs - Males* **M0:** Stratified prevalences not available to permit calculation **M1:** OR:0.78 (95%CI:0.48,1.26) **M2:** OR:0.73 (95%CI:0.44,1.21) *1.3.2 Sleep duration 8hrs - Females* **M0:** Stratified prevalences not available to permit calculation **M1: OR:0.60 (95%CI:0.45,0.84)** **M2: OR:0.58 (95%CI:0.41,0.84)**
Jennings et al. 2006 USA	Logistic regression	MetS (Yes: 20.0%; No[ref]) MetS referent category comprised: Not clear (not identified as MetS) (Separate analyses conducted on: obesity; fat percentage; waist circumference; hypertension; blood glucose levels; insulin resistance; raised blood triglycerides; and reduced HDL cholesterol)	*1. Sleep quality* (PSQI Total Score >5: 30.0%; ≤5[ref])	**M0:** Unadjusted (not reported) **M1:** Age; sex **M2:** M1+smoking; alcohol; education	*1. Poor sleep quality PSQI Total Score >5* **M0:** Stratified prevalences not available to permit calculation **M1: OR:1.44 (95%CI:1.01,2.06)** **M2:** Not reported
Thomas et al. 2006	Logistic regression	MetS (Yes: %Not reported – calculated 22.5%; No[ref])	*1. Snoring* (Ever: 51.6%; Never[ref])	**M0:** Unadjusted (not reported) **M1:** Age; sex; waist to hip ratio; occupation; education; exercise;	*1. Snoring* **M0:** Not reported – calculated: **OR:1.18 (95%CI:1.06,1.31)**

China		MetS referent category comprised: Not clear (not identified as MetS) (Separate analyses conducted on: hypertension; dyslipidaemia; central obesity; and diabetes)		smoking; alcohol	**M1: OR:2.16 (95%CI:1.88,2.49)**

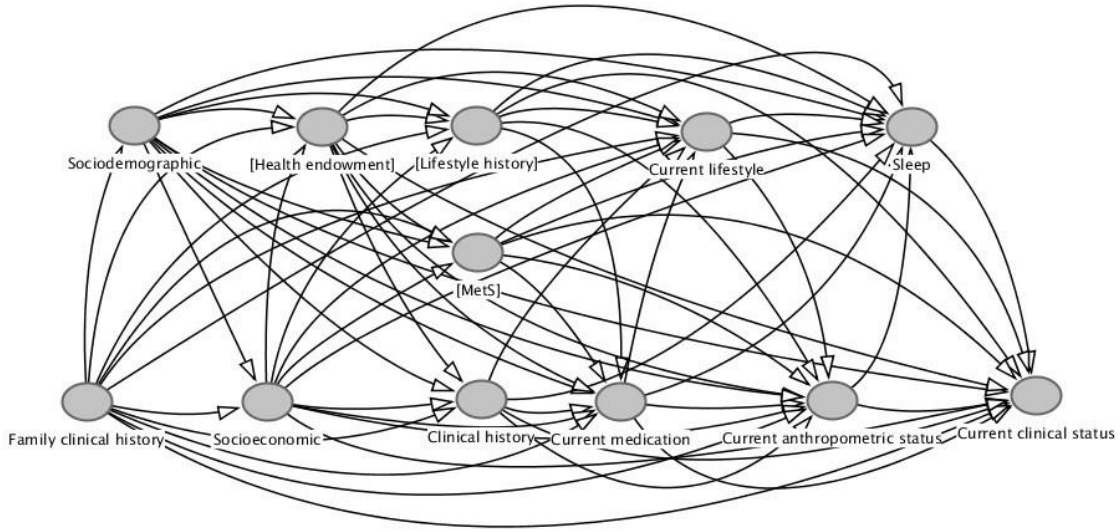
2.4.5 The development of theoretical causal path diagrams to critically appraise the covariate adjustment sets used in multivariable statistical models

To assess these possibilities, and to assist in the critical interpretation of effect estimates generated using models adjusting for very different sets of confounders, the present Chapter first sought to establish whether any of these adjustment sets might have: (i) excluded potential confounders (either because suitable covariates were not available/measured; or because the study in question had failed to adjust for an available/measured confounder); or (ii) adjusted for likely mediators (i.e. covariates falling on the causal path between exposure and outcome – either because these variables were misclassified as potential confounders or because the authors were unaware of the potential bias incurred by adjusting for mediators). This involved, drawing upon the complete list of the covariates that were available to/measured by any of the n=21 studies reviewed (see Table 2.3), and using this list (together with any 'exposure' or 'outcome' variables) to generate a causal path diagram (in the form of a directed acyclic graph; DAG), based on a theoretical evaluation of the likely functional and temporal relationships between each of these variables. This theoretical model was intended to facilitate the identification of covariates acting as potential confounders, likely mediators or competing exposures in any relationship between MetS and sleep. DAGs help in this regard because they specify not only the temporal nature of a speculative causal path between an exposure (occurring at some time in the immediate, recent or distant past) and an outcome (occurring at some time thereafter), on which other variables (i.e. covariates) operate as: 'potential confounders' (i.e. have the potential to act as confounders) if the process, event or phenomenon to which they refer occurred before *both* the exposure and the outcome (in which case the variable concerned is a potential contributory cause of both); or 'likely mediators' (i.e. have the potential to act as mediators) if the event or phenomenon to which they refer occurred *after* the exposure *but before* the outcome (in which case the variable concerned potentially falls on the 'causal path' between exposure and outcome).

In this instance – i.e. when assessing the speculative causal relationships between MetS and sleep-related characteristics, and the relationships between these and any other variables included in the various covariate adjustment sets used by the n=21 cross-sectional studies examined in this review – it was necessary to develop a clear understanding of: what the 'Metabolic Syndrome' (MetS) was understood to mean by each/most of the studies reviewed; and what temporal and aetiological

processes are likely to lie behind its occurrence (and the manner in which it subsequently becomes evident in three or more of symptoms/components considered necessary to classify MetS: central obesity; dyslipidaemia; high blood pressure; and/or diabetes). Notwithstanding substantial disquiet and controversy regarding the validity and utility of MetS as an aetiological and clinical construct/phenomenon (Kahn *et al.* 2005; Kahn 2008; Ahmadi *et al.* 2015; Scuteri *et al.* 2016) – and given that MetS has been *conceptualised* as a marker for insulin resistance initiated at some time in the past (Reaven 1988) while *operationalised* as the specific additive/interactive consequences (i.e. the subsequent symptomatic manifestation) of cardiometabolic comorbidity (e.g. (Scuteri *et al.* 2016) – this theory-driven approach assumed that where researchers explicitly set out to explore the relationship between MetS and sleep they intended to examine the potential role(s) that sleep might play *either* as a potential trigger for (and/or facilitator/cause/enhancer of of) *symptomatic* MetS *or* as a consequence of *subsequent* MetS-related symptoms (central obesity; dyslipidaemia; hypertension; and/or diabetes; or the cardiovascular consequences thereof, such as CHD and stroke). This assumption – together with careful consideration of how the data collection processes and measurement tools used by each of the n=21 cross-sectional studies might have influenced the way in which the data available/collected (on sociodemographic, socioeconomic, lifestyle, anthropometric and clinical factors; as well as on sleep and the symptoms/components of MetS) might reflect related events/phenomena occurring over different time periods *prior to* data collection – is what guided the development of the DAG summarised in Figure 2.4, below.

Figure 2.4 A causal path diagram (in the form of a directed acyclic graph; DAG), summarising the theoretical relationships between the available/measured covariates, exposures and outcomes used by the n=21 cross-sectional studies included in the review. Variables have been grouped into temporally and functionally coherent categories, and three additional categories of unmeasured/unavailable ('latent') variables have been added to facilitate the specification and interpretation of the DAG.



This DAG uses each of the categories of covariates, exposures and outcomes (as classified) in Table 2.3, together with three additional 'latent categories' (indicated in square parentheses; [ ]), which comprise groups of unmeasured variables that are intended to aid both the specification and interpretation of the DAG (particularly by indicating how measures of these variables, had they been available, might have contributed to the causal pathways summarised by the DAG):

'[MetS]' – was intended to signify the speculative physiological event (be that insulin resistance, as originally proposed by Reaven, 1988; or something as yet unknown) postulated by the original MetS hypothesis as the common cause of the subsequent symptoms/components of MetS used by each of the studies examined in the present review to identify/classify MetS;

'[lifestyle history]' – was intended to capture any aspects of earlier behaviours likely to have influenced the later development of both sleep-related factors and MetS-related symptoms/components ; and

'[health endowment]' – was intended to reflect the resilience/vulnerability afforded by an individual's social and biological background, both intergenerationally and during early life (what some have called the 'embodiment' of dis/advantage; (Krieger and Davey Smith 2004; Krieger 2001; Lindau *et al.* 2003), and the subsequent importance of such resilience/vulnerability in the emergence of '[MetS]' (the speculative physiological event, whatever that might turn out to

be), subsequent lifestyle(s) *and* ultimately the symptoms/components of MetS itself.

By attributing three categories of variables ('[lifestyle history]'; 'clinical history'; and '[MetS]') to a common latent cause ('[health endowment]') the DAG acknowledges that each of these might operate as *both* potential causes *and* potential consequences of one another at various times in their development. Thereafter, the positioning of the four remaining categories of covariates within the DAG suggests that all but one of these operate as likely mediators (i.e. on the causal path between '[MetS]' and 'Sleep'), though one category – 'Current clinical status' (a category created to contain contemporaneous measures of potentially labile physiological parameters, such as the cardiometabolic components used by most symptomatic classifications of MetS; i.e. blood glucose and lipid levels, and blood pressure) – was positioned *after* the outcome (sleep) to recognise the likelihood that the sorts of sleep measures collected by the n=21 studies included in the present review were likely to: capture sleep-related events/processes that *had already* occurred (whether the night/day before these were measured, or during the weeks preceding the cross-sectional survey point); and reflect the known susceptibility of cardiometabolic physiological parameters such as these to short term disruption following sleep disturbance (Knutson *et al.* 2007). And while it is debatable whether the temporal sequence of the remaining three categories of variables identified as mediators might operate as indicated within Figure 2.4 – i.e. with 'Current medication' determined by 'Clinical history' (amongst others), and thereafter influencing the more contemporaneously measured 'Current lifestyle' (which, in turn, might be likely to have determined 'Current anthropometric status') – the precise temporal sequence is irrelevant, since any appropriately specified adjustment sets based on this DAG would exclude variables in any of these three categories as likely mediators.

As such, the DAG specified in Figure 2.4 proposes that:

(i) the initiation of MetS (i.e. '[MetS]') should be positioned *before* 'Sleep' (since the events and processes necessary to establish MetS are likely to have occurred at some time prior to the period over which any cross-sectional assessment of sleep occurred; even where the measurement of sleep explicitly requested self-reports over days or weeks preceding measurement);

(ii) several groups of variables are likely to act as confounders (since the processes and events that determined these were likely to have occurred prior to the initiation of '[MetS]');

(iii) several other groups of variables are likely to act as mediators (since it seems plausible that the processes and events that determined these, as measured in the n=21 cross-sectional studies reviewed, would have occurred in the interval between the emergence of MetS symptoms and the measurement of sleep); and

(iv) analyses exploring the relationship between sleep and the *symptoms* of MetS (i.e. some combination of the four or five components of MetS used by most classifications of MetS, namely: central obesity, high blood pressure, dyslipidaemia and diabetes) are likely to be challenging if, as suggested in Figure 2.4, 'Current anthropometric status' (a collection of variables that would contain obesity-related measures) and 'Current medication' were situated *before* 'Sleep', while 'Sleep' was situated before the 'Current clinical status' measures (comprising the non-anthropometric/non-medication-based symptoms/components of MetS, namely: high blood pressure; dyslipidaemia; and diabetes). This temporal arrangement of obesity, medication, sleep and the remaining symptoms of MetS would seem likely provided: (a) obesity emerged/became established some time *before* the cross-sectional measurement of sleep; and (b) more/less favourable sleep had an *acute* impact on the cardiometabolic symptoms of MetS (blood pressure, blood glucose and lipid levels), as recent experimental studies involving shortened/disrupted sleep suggest (Knutson *et al.* 2007).

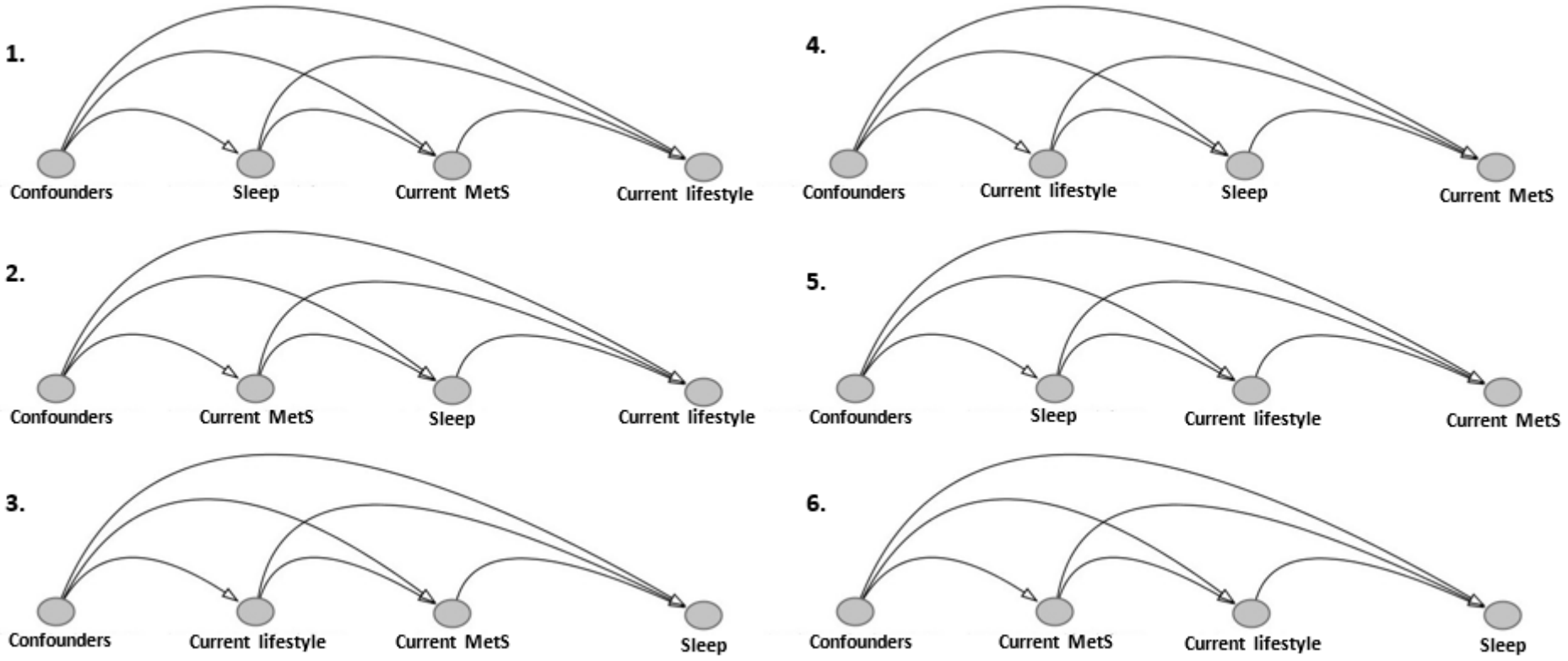
On this basis, given the methods used to measure/classify MetS in the n=21 studies reviewed (none of which had collected variables relevant to insulin resistance prior to the development of the anthropometric and cardiometabolic symptoms/components considered definitive of the subsequent *symptomatic manifestation* of MetS), the DAG summarised in Figure 2.4 suggests that none of the studies reviewed had access to/generated data on all of the variables required to examine the relationship between '[MetS]' and 'Sleep' (whether as a cause or a consequence thereof). This is simply because all of these studies operationalised MetS as the presence of symptomatic 'cardiometabolic comorbidity', and measured this cross-sectionally alongside the assessment of (recent) sleep, and a range of recalled sociodemographic, health and lifestyle factors.

For this reason, however conceptually plausible Figure 2.4 might be, based as it is on Reaven's (1988) original hypothesis (that insulin resistance, or some other physiological phenomenon, is what lies behind the emergence of MetS-related symptoms later in life), this does not offer a model from which it is easy to assess the adjustment sets used by the n=21 studies examined in the present review; first, because it is not clear whether any of these studies sought to assess the association between '[MetS]' and 'Sleep' (although many appear to have intended to do so, using contemporaneous measures of MetS-related symptoms/components as markers for the initiation of/susceptibility to '[MetS]' at some time in the past); and second, because many of these studies classified MetS using variables from more than one of the categories in Figure 2.4, including two categories ('Current medication' and 'Current anthropometric status') considered to precede the contemporaneous measures of sleep and cardiometabolic symptoms/components of MetS (i.e. 'Current clinical status'). It is therefore necessary to offer a simpler theoretical causal framework – one that focuses primarily on the variables that were actually measured by/available to the n=21 studies reviewed (rather than on any implicit/explicit intention these studies may have had to examine '[MetS]'). This, alternative framework simply considers the likely sequence of cause and effect in a manner that reflects the variables collected by/available to the n=21 studies reviewed, and is therefore amenable for use in evaluating the different adjustment sets these studies used in their multivariable statistical analyses.

This simplified approach posits four categories of measured/available variables ('Family clinical history', 'Sociodemographic', 'Socioeconomic' and 'Clinical history') as potential confounders regardless of the causal paths between three others: 'Current lifestyle', 'Sleep' and 'Current MetS' (the latter comprising a new category created in recognition of the fact that all of the n=21 studies used classifications of MetS that relied upon variables contained within the three original categories labelled 'Current medication', 'Current anthropometric status' and 'Current clinical status'; see Table 2.3). Disregarding, for a moment, the *likely* temporal and functional sequence of these three categories of variables ('Current lifestyle', 'Sleep' and 'Current MetS') – i.e. the sequence proposed in Figure 2.3 which places 'Sleep' (as measured) *after* 'Current medication' and 'Current anthropometric status', but *before* 'Current clinical status') – there are only n=6 possible sequences in which these three new categories might be arranged: two with 'Current MetS',

‘Current lifestyle’ and ‘Sleep’ positioned first; two with each of these positioned second; and two with each of these positioned third (see Figure 2.5).

Figure 2.5 Simplified directed acyclic graphs (DAGs) summarising the six theoretical causal paths (1-6) between four categories of variables available to/measured by the n=21 cross-sectional studies reviewed (in which four categories of variables from Table 2.3 [‘Family clinical history’; ‘Sociodemographic’; ‘Socioeconomic’; and ‘Clinical history’] have been incorporated into the single category ‘Confounders’; and three categories of variables from Table 2.3 [‘Current medication’; ‘Current anthropometric status’; and ‘Current clinical status’] have been incorporated into the single category ‘Current MetS’).



2.4.6 The potential impact of unadjusted confounding and mediator adjustment on the association between MetS and sleep

Based on Figure 2.5, it is possible to identify: three possible models for the n=19 studies that considered ‘Sleep’ as the exposure and ‘Current MetS’ as the outcome (DAGs 1, 4 and 5); and three possible models for the n=2 studies that considered ‘Current MetS’ as the exposure and ‘Sleep’ as the outcome (DAGs 2, 3 and 6). All of these models ignore the possibility that some of the variables used to assess specific symptoms/components of MetS might fall on either side of ‘Sleep’ (as suggested in Figure 2.4), and instead assume that the use of such variables/components in the classification of ‘Current MetS’ offers a temporally discrete assessment of MetS status that occurred after (as in DAGs 1, 4 and 5) or before (as in DAGs 2, 3 and 6) ‘Sleep’ as measured. Likewise, while all six possible models recognise the presence of ‘Confounders’, the variables considered relevant as confounders will not only comprise preceding sociodemographic and economic factors (which are known to influence the subsequent patterning of lifestyle, sleep and health), but also the pre-existing health conditions (including the onset of insulin resistance, or whatever physiological phenomenon might be responsible for initiating the onset of, or susceptibility to, the development of *symptomatic* MetS). Since none of the studies reviewed had collected/available data on these specific pre-existing health conditions – and used many of those variables they had measured/available (particularly prescribed antihypertensive or antidiabetic medication) to measure symptoms/components of MetS – the simplification of Figure 2.4 in the DAGs presented in Figure 2.5 implies that perhaps all of the analyses reported by the n=21 studies reviewed are likely to suffer from (substantial) unadjusted confounding.

These points aside, it is nonetheless worth considering which of the DAGs in Figure 2.5 (i.e. in DAGs 1, 4 and 5; or 2, 3 and 6), might place the simplified groups of variables in the correct/most plausible temporal/causal sequence. More specifically, it is necessary to establish whether the variables contained in the category labelled ‘Current lifestyle’ might act as potential confounders or likely mediators in any relationship between ‘Sleep’ and ‘Current MetS’. Given that cross-sectional measures of sleep, and of the anthropometric-, medication- and cardiometabolic symptom-related components of MetS, are likely to reflect, at least in part, the consequences of established/preceding lifestyle characteristics, it might be argued that ‘Current lifestyle’ variables are likely to act as potential confounders. However, if the symptoms (or treatment) of MetS-related components affect (or lead to changes in) lifestyle, then it is plausible that lifestyle might (in part) reflect the impact of MetS symptoms and/or diagnosis thereof.

Certainly, it seems likely that lifestyle (as measured in the studies reviewed) was more fluid and therefore more 'contemporaneous' than MetS; and, as such, would better reflect characteristics emerging *after* the development of MetS. Thus, while 'Current lifestyle' variables might act as *either* confounders *or* mediators in the relationship between 'Current MetS' (as the exposure) and 'Sleep' (as the outcome), the latter (i.e. acting as mediators) seems more likely. Indeed, it seems less likely that cross-sectionally measured sleep characteristics (many of which, as measured in the n=21 studies reviewed, appear to capture recent sleep-related experiences) will have preceded (m)any of the 'Current lifestyle' variables measured by these studies. For these reasons – and notwithstanding the point made earlier (see (iv), above) regarding the use of MetS-related criteria likely to have occurred either side of (cross-sectionally measured) 'Sleep' – the model that appears most plausible in Figure 2.5 is DAG 6, in which: 'MetS' precedes 'Current lifestyle' which, in turn, precedes 'Sleep'. It is therefore surprising that only two of the n=21 studies reviewed actually operationalised MetS as the exposure and 'Sleep' as the outcome (Krishnan *et al.* 2012) and (Hung *et al.* 2013). Nonetheless, DAG 6 in Figure 2.5 remains pertinent (albeit from a *parametric* point of view) for evaluating any adjustment sets used by the remaining n=19 studies (i.e. those that operationalised 'Sleep' as the exposure and 'Current MetS' as the outcome), even if these imply the authors concerned had conceptualised the theoretical (i.e. *non-parametric*) relationships between these (and any covariates they had available/measured) somewhat differently.

On this basis, Table 2.5 summarises an evaluation of any adjustment sets used by models reported by each of the n=21 studies; which contains separate columns for adjustment sets that contained *only* confounders (with a list of any available/measured confounders missing therein), and for adjustments sets that contained *both* confounders and mediators (with any components of sleep or MetS contained therein clearly identified).From Table 2.5 it is clear that all but one (Kazman *et al.* 2012) of the n=21 studies included at least one multivariable analytical model in which the adjustment set(s) used contained variables that were considered to be likely mediators. And while some of these studies also included alternative models containing no likely mediators (n=6 with one such model; n=2 with two; and n=1 with three), only n=2 of these alternative models included all of that study's available/measured covariates considered to be potential confounders. As such, Table 2.5 suggests that all but one of the multivariable analyses presented by the n=21 studies reviewed suffered from either the inclusion of mediators and/or the omission of (available/measured) confounders. While the effect estimates these analyses provide need to be interpreted with caution, what is less clear from Table 2.5, is that few of

these studies had data available/measured on more than a handful of covariates considered likely to act as potential confounders. Indeed, as highlighted earlier, none of the n=21 studies reported data on the wide range of covariates available to/measured by one or more of the other studies. Instead, the available/measured covariates most commonly reported were those relating to current lifestyle (i.e. likely mediators) and current health (i.e. likely exposures/outcomes), with relatively few that were potential confounders (and most of these being sociodemographic or economic factors rather than those pertinent to a familial or personal history of health and lifestyle issues more directly relevant to MetS and sleep).

Assuming that the inclusion of data on each of the covariates summarised in Table 2.3 by at least one of the n=21 studies reviewed indicates that these variables *could* have been available to/measured by many more of these studies, it appears that the principal reason why many (if not all) of the multivariable analyses these studies report are likely to have suffered from unadjusted confounding is because they failed to access/measure (some/many of) the covariates required to address this. In part this may reflect the absence of these variables in the secondary datasets used by the majority of studies reviewed (n=15/21); and in part the practical challenges of accessing/measuring data on covariates acting as potential confounders in studies adopting a cross-sectional design (many of which occurred many months or years prior to the assessment of sleep and MetS). However, it is also likely to reflect a lack of appreciation for the substantial role that unadjusted confounding might play in the effect estimates generated by these (and most other) cross-sectional studies.

Table 2.5 An assessment of the inclusion of available/measured (potential) confounders and likely mediators in each of adjustment sets used by multivariable statistical models reported by the n=21 studies examined in the present review.

Citation	**Available/measured covariates** (from Table 2.2)	**Covariate adjustment sets** (from Table 2.4)	**Adjustment for confounders (not mediators)** (missing potential confounders)[1]	**Adjustment for confounders (and likely mediators)** (included likely mediators)
Mesas et al. 2014 Spain	Age; sex; education; occupation; smoking; alcohol; coffee; energy intake; physical activity; diagnosed mental/physical illness; diabetes; TV time; antihypertensive medication; lipid-lowering medication	**M0:** Unadjusted (not reported) **M1:** Sex; age; education; occupation **M2:** M1+smoking; alcohol; coffee **M3:** M2+diagnosed mental/physical illness; diabetes **M4:** M3+sleep duration **M5:** M4+energy intake **M6:** M5+physical activity; TV time **M7:** M6+antihypertensive medication; lipid-lowering medication	**M1** (diagnosed mental/physical illness)	**M2** (smoking; alcohol; coffee) **M3** (smoking; alcohol; coffee; diabetes*) **M4** (smoking; alcohol; coffee; diabetes;* sleep duration) **M5** (smoking; alcohol; coffee; diabetes;* sleep duration; energy intake) **M6** (smoking; alcohol; coffee; diabetes;* sleep duration; energy intake; physical activity) **M7** (smoking; alcohol; coffee; diabetes;* sleep duration; energy intake; physical activity; antihypertensive medication;* lipid-lowering medication*) *Components of the outcome
Ohkuma et al. 2014 Japan	Age; sex; early/late onset diabetes; energy intake; smoking; alcohol; exercise; symptomatic mental illness; antidiabetic medication	**M0:** Unadjusted (not reported) **M1:** Age; sex; early/late onset diabetes; energy intake; smoking; alcohol; exercise; symptomatic mental illness; antidiabetic medication		**M1** (energy intake; smoking; alcohol; exercise; antidiabetic medication*) *Components of the outcome
Saleh and Janssen 2014 USA	Age; sex; ethnicity; education; socioeconomic status; smoking; alcohol; caffeine; screen time; sedentary time; physical activity	**M0:** Unadjusted **M1:** Age; ethnicity; screen time **M2**: Age; education; physical activity; sedentary time		**M1** (screen time) **M2** (physical activity; sedentary time*) *Component of the exposure
Hung et al. 2013	Age; sex; exercise; alcohol; smoking; creatinine levels	1. Linear regression: **M0:** Unadjusted (not reported) **M1:** Age; sex; sleep duration		**M1** (sleep duration*) **M2** (sleep duration;* snoring;* alcohol; smoking; exercise;

Taiwan		**M2:** M1+snoring; alcohol; smoking; exercise; creatinine levels 2. Logistic regression: **M0:** Unadjusted (not reported) **M1:** Age; sex; sleep duration; snoring; alcohol; smoking; exercise; creatinine levels		creatinine levels**) *Component of the outcome **Component of the exposure
Chaput et al. 2013 Canada	Age; sex; smoking; education; income; coffee; menopausal status; energy intake; alcohol; physical activity	**M0:** Unadjusted **M1:** age; sex; smoking; education; income; alcohol; coffee; menopausal status **M2:** M2+energy intake; physical activity		**M1** (smoking; alcohol; coffee) **M2** (smoking; alcohol; coffee; energy intake; physical activity)
Lee et al. 2013 South Korea	Sex; age; education; occupation; income; smoking; alcohol; exercise; stress; diagnosed/symptomatic mental illness	**M0:** Unadjusted **M1:** Sex; age; education; occupation; income; smoking; alcohol; exercise; stress; diagnosed/symptomatic mental illness; sleep duration (for PSQI and SRBD); PSQI Total Score (for duration and SRBD); SRDB (for duration and PSQI)		**M1** (smoking; alcohol; exercise; stress; sleep duration [for PSQI and SRBD];* PSQI Total Score [for duration and SRBD];* SRDB [for duration and PSQI]*) *Component of the exposure
Stefani et al. 2013 South Korea	Age; sex; income; occupation; education; smoking; alcohol; physical activity; BMI; energy intake	**M0:** Unadjusted **M1:** age; sex **M2:** M1+ education; occupation; physical activity; smoking; alcohol **M3:** M2+BMI	**M1** (income; occupation; education)	**M2** (physical activity; smoking; alcohol) **M3** (physical activity; smoking; alcohol; BMI*) *Component of the outcome
Yoo and Franke 2013 USA	Age; sex; smoking; physical activity; stress; diagnosed/symptomatic mental illness	**M0:** Unadjusted (not reported) **M1:** Age; sex; smoking; physical activity **M2:** M1+ diagnosed/symptomatic mental illness		**M1** (smoking; physical activity) **M2** (smoking; physical activity)

Krishnan et al. 2012 India	Age; sex; family history of hyperthyroidism; physical activity; smoking; alcohol	**M0:** Unadjusted **M1:** age **M2:** age; sex **M3:** M2+family history of hyperthyroidism **M4:** M3+physical activity **M5:** M4+smoking **M6:** M5+alcohol	**M1** (sex; family history of hyperthyroidism) **M2** (family history of hyperthyroidism) **M3** (no missing measured/available confounders)	**M4** (physical activity) **M5** (physical activity; smoking) **M6** (physical activity; smoking; alcohol)
Kazman et al. 2012 USA	Age; sex	**M0:** Unadjusted (not reported) **M1:** Age; sex		
McCanlies et al. 2012 USA	Age; sex; education; smoking; marital status; race/ethnicity; physical activity; occupation	**M0:** Unadjusted **M1:** Age **M2:** Age; sex **M3:** M2+education; smoking	**M1** (sex; education; marital status; race/ethnicity) **M2** (education; marital status; race/ethnicity)	**M3** (smoking)
Wu et al. 2012 Taiwan	Age; sex; education; family history of diabetes; family history of hypertension; smoking; alcohol; exercise; BMI	**M0:** Unadjusted (not reported) **M1:** Age; education; BMI; smoking; alcohol; exercise		**M1** (BMI;* smoking; alcohol; exercise) *Component of the outcome
Hall et al. 2012 USA	Age; race/ethnicity; menopausal status; education; marital status; diagnosed/symptomatic mental illness; symptomatic physical illness; health compliance; current medication;	**M0:** Unadjusted (not reported) **M1:** race/ethnicity; menopausal status; education; marital status; health compliance; current medication; smoking; alcohol; exercise.		**M1** (current medication;* smoking; alcohol; exercise). **M2** (current medication;* smoking; alcohol; exercise; BMI*) *Component of the outcome and/or

	smoking; alcohol; exercise	**M2:** M1+BMI		exposure
Arora et al. 2011 China	Age; sex; smoking; alcohol; physical activity; education; diagnosed/symptomatic mental and physical illness; use of hypnotics	**M0:** Unadjusted **M1:** Age; sex **M2:** M1+education; smoking; physical activity; diagnosed mental illness; sleep fragmentation; use of hypnotics; daytime sleepiness; alcohol; snoring	**M1** (education; diagnosed/symptomatic mental and physical illness; use of hypnotics)	**M2** (smoking; physical activity; sleep fragmentation;* daytime sleepiness;* alcohol; snoring*) *Component of the exposure
Kobayashi et al. 2011 Japan	Age; sex; alcohol; smoking; pre-existing physical and mental illness; diagnosed/symptomatic mental and physical illness; current medication; physical activity	**M0:** Unadjusted (not reported) **M1:** Age; sex; alcohol; diagnosed/symptomatic mental and physical illness; physical activity		**M1** (alcohol; physical activity)
Roopa et al. 2010 India	Age; sex; physical activity; smoking; alcohol	**M0:** Unadjusted **M1:** Age **M2:** Age; sex **M3:** M2+physical activity **M4:** M3+smoking **M5:** M4+alcohol	**M1** (sex) **M2** (no missing measured/available confounders)	**M3** (physical activity) **M4** (physical activity; smoking) **M5** (physical activity; smoking; alcohol)
Hall et al. 2008 USA	Age; sex; race/ethnicity; education; smoking; alcohol; physical activity; blood lipid levels; symptomatic mental illness	**M0:** Unadjusted (not reported) **M1:** Age; sex; race/ethnicity; education; smoking; physical activity; blood lipid levels; symptomatic mental illness		**M1** (smoking; physical activity; blood lipid levels*) *Component of outcome
Choi et al. 2008 South Korea	Age; sex; family history of hypertension; family history of diabetes; residential area; education; income; alcohol; smoking; exercise; BMI	**M0:** Unadjusted **M1:** Age; sex; family history of hypertension; family history of diabetes **M2:** M1+residential area; education; income; alcohol; smoking; exercise **M3:** M2+BMI	**M1** (residential area; education; income)	**M2** (alcohol; smoking; exercise) **M3** (alcohol; smoking; exercise; BMI*) *Component of outcome
Santos et al. 2007 Portugal	Age; marital status; education; occupation; physical activity; exercise; smoking; alcohol	**M0:** Unadjusted (not reported) **M1:** age; education **M2:** M1+smoking; alcohol	**M1** (marital status; occupation)	**M2** (smoking; alcohol)
Jennings et al.	Age; sex; race/ethnicity; diagnosed/symptomatic mental illness;	**M0:** Unadjusted (not reported) **M1:** Age; sex	**M1** (race/ethnicity; diagnosed/symptomatic mental	**M2** (smoking; alcohol)

2006 USA	smoking; alcohol; education; antihypertensive medication	**M2:** M1+smoking; alcohol; education	illness; education)	
Thomas et al. 2006 China	Age; sex; waist to hip ratio; occupation; education; exercise; smoking; alcohol; blood pressure; blood lipid levels; blood glucose levels	**M0:** Unadjusted (not reported) **M1:** Age; sex; waist to hip ratio; occupation; education; exercise; smoking; alcohol		**M1** (waist to hip ratio;* exercise; smoking; alcohol) *Component of outcome

[1] Note: this assessment only considered those covariates that had been measured by/were available to the specific study concerned (see also Tables 2.2 and 2.3).

To assess the possible impact of unadjusted confounding and mediator-adjustment on the effect estimates reported by the n=21 studies examined in the present review, studies using comparable exposures and outcomes were carefully identified (as described below). The intention was then to perform meta-analyses on effect estimates generated both prior to adjustment, and using models that had adjusted for potential confounders alone, or for potential confounders and likely mediators (as summarised in Table 2.5). Fortunately, all of the n=21 studies reviewed used classifications of MetS based on direct measures of MetS symptoms/components, and although a range of different MetS classifications were used, most of these appear broadly comparable (i.e. as measures of the presence of 'Current MetS'; all being based on three or more of: obesity; high blood pressure; dyslipidaemia; and/or diabetes). However, none of the studies presented sufficient detail on the specification of the MetS referent groups they used in their statistical analyses (i.e. whether these groups comprised participants who simply lacked sufficient symptoms/components of MetS to warrant a formal classification of MetS; or those displaying *none* of these symptoms/components) – an issue that may contribute considerable heterogeneity to the findings reported by the n=21 studies reviewed.

Unfortunately, as described earlier (see 3.4.2, above), only three sleep characteristics (duration, quality and snoring/breathing difficulties) were used as exposure or outcome variables by more than one study, and only two of these characteristics (duration and quality) were measured using the same (or comparable) items/instruments in each of the studies examining these. To further complicate comparisons between these studies, one (McCanlies *et al.* 2012) used Poisson regression while the remainder all used logistic regression (albeit one of these also used linear regression; (Hung *et al.* 2013)). Likewise, while all of the studies examining sleep quality used the same instrument (PSQI), the same the cut-off point (good sleep quality ≤5 PSQI Total Score; poor sleep quality >5 PSQI Total Score) and the same referent category (poor sleep quality); those examining sleep duration used a range of different: categories (n=5/14 studies using 5 categories; n=4/14 using either 4 or 3 categories; and n=1 using 'per additional hr of sleep'); cut-off points (one based on quartiles, the others pragmatic yet somewhat arbitrary); and referent categories (n=12 studies using a normative category that ranged from 6-9hrs to 6.5-7.49hrs; n=2 studies using prolonged duration of ≥8hrs or ≥9hrs as the referent; and n=1 using 'per additional hr of sleep' above the average; see Table 2.4). The meta-analyses that follow therefore examine only those studies: using logistic regression analyses; reporting *both* unadjusted effect estimates (or the stratified prevalence data required to calculate these) *and* covariate-adjusted effect estimates in which comparable referent

and indicator categories were available. This involved excluding: (McCanlies *et al.* 2012); which only reported the results of Poisson regression models; (Hall *et al.* 2008; Kazman *et al.* 2012; Santos, Ebrahim and Barros 2007; Jennings *et al.* 2007; Hall *et al.* 2012); none of which reported unadjusted effect estimates or the stratified prevalences required to calculate these; and (Kobayashi *et al.* 2011); since this was the only study remaining that had used prolonged sleep duration as the referent category. This left n=9 studies examining the relationship between sleep duration and MetS, and n=3 studies examining the relationship between (PSQI-defined) sleep quality and MetS (see Table 2.6).

Amongst the n=9 studies included in Table 2.6, all of which reported the information on (unadjusted and adjusted) analyses of the relationship MetS and sleep, two reported these separately for male and female study participants (Wu *et al.* 2012), and each of the sex-specific models was therefore treated separately. Of the n=10 separate sets of models: all provided effect estimates unadjusted for any covariates; n=3 adjusted for confounders alone; and n=7 adjusted for both confounders and mediators. Prior to adjustment, most of these models reported that MetS was associated with an increased odds of both the shortest and the longest sleep duration categories specified, although the odds were substantially higher in models reported by two of the smallest studies (Lee *et al.* 2013) and (Yoo and Franke 2013); which examined just n=301 and n=106 participants, respectively), suggesting the possibility of publication bias. In those three studies reporting models that had adjusted (only) for confounders, all displayed consistent attenuation of the effect estimates observed. In contrast, amongst the n=7 studies reporting models that had adjusted for (both) confounders and mediators, in some the effect sizes were attenuated while in others the effect sizes strengthened following adjustment. These findings appear to confirm that the relationship between MetS and sleep duration is susceptible to confounding; and, given that few of the studies included in the present review were able to adjust for more than a handful of available/measured confounders, it is likely that many (if not all) of the adjusted effect estimates they report suffer from unadjusted confounding. Meanwhile, the varied impact of adjusting for covariates considered likely mediators (i.e. those pertinent to ‘Current lifestyle’, as classified in Table 2.3) suggest that these models are affected by “suppression” a phenomenon of increased effect size due the introduction of a third variable to the model (Tu, Gunnell and Gilthorpe 2008).

Unfortunately, none of the n=3 studies providing all of the necessary information on their unadjusted and covariate-adjusted analyses of the relationship between sleep quality and MetS, presented effect estimates adjusted for potential confounders alone, but all included models that had adjusted for *both* confounders and

mediators. The unadjusted models reported by two of these studies found that MetS was associated with a higher odds of poor quality sleep, while the third study found little evidence of any unadjusted association between MetS and sleep quality (see Table 2.6). Following adjustment for potential confounders and likely mediators, the reported odds strengthened for two of these studies and remained essentially unchanged for the third; such that all three studies reported that MetS was associated with a higher adjusted odds of poor sleep quality, again suggesting that covariates considered likely mediators were correctly identified as such in Figure 2.5 (DAGs 5 and 6).

Table 2.6 Studies reporting effect estimates of the association between MetS and/or sleep duration (above) or sleep quality (below) from logistic regression models in which comparable measures and referent categories were used. Odds ratios (with 95% confidence intervals, in parentheses) are presented prior to covariate adjustment, and for any models adjusting for *only* potential confounders or for *both* potential confounders and likely mediators (the model chosen being that adjusting for the largest number of appropriate covariates; see Table 2.5).

Study	**Sex (n)**	**Sleep duration** (referent)	**Unadjusted (M0)** OR (95%CI)	**Adjusted for confounders** (model with most covariates) OR (95%CI)	**Adjusted for confounders and mediators** (model with most covariates) OR (95%CI)
Sleep duration					
Ohkuma et al. 2014 Japan	Males and females (n=4,402)	<5.5hrs 5.5-6.4hrs (6.5-7.4hrs) 7.5-8.4hrs ≥8.5hrs	**1.64 (1.34,1.99)** 1.04 (0.88,1.23) 1.00 1.04 (0.88,1.23) **1.74 (1.38,2.20)**		**1.71 (1.39,2.11)** 1.03 (0.87,1.22) 1.00 1.09 (0.92,1.29) **1.48 (1.17,1.88)**
Saleh and Janssen 2014 USA	Males and females (n=1,371)	3.0-7.2hrs (7.2-8.6hrs) 8.6-9.7hrs 9.7-11.8hrs	0.86 (0.60,1.23) 1.00 0.93 (0.65,1.33) 1.12 (0.78,1.60)		0.91 (0.62,1.33) 1.00 0.89 (0.61,1.29) 0.95 (0.66,1.39)
Chaput et al. 2013 Canada	Males and females (n=810)	≤6hrs (7-8hrs) ≥9hrs	**2.02 (1.32,3.23)** 1.00 1.46 (0.95,2.14)		**1.76 (1.08–2.84)** 1.00 1.35 (0.83-1.99)
Lee et al. 2013 South Korea	Males and females (n=301)	<5.5hrs 5.5-6.49hrs (6.5-7.49hrs) 7.5-8.49hrs ≥8.5hrs	**6.35 (3.01,13.40)** 1.40 (0.74,2.64) 1.00 1.09 (0.48,2.50) **5.08 (1.51,17.06)**		**4.89 (1.90,12.58)** 1.26 (0.59,2.67) 1.00 1.27 (0.50,3.26) **5.98 (1.41,25.41)**
Stefani et al. 2013 South Korea	Males and females (n=24,511)	≤5hrs 6hrs (7hrs) 8hrs ≥9hrs	**1.74 (1.59,1,91)** **1.10 (1.01,1.19)** 1.00 1.04 (0.96,1.13) **1.32 (1.17,1.48)**	1.06 (0.96,1.17) 1.01 (0.93,1.10) 1.00 1.02 (0.94,1.12) **1.14 (1.00,1.29)**	1.00 (0.90,1.11) 0.95 (0.87,1.05) 1.00 1.06 (0.96,1.17) **1.31 (1.14,1.51)**

Yoo and Franke 2013 USA	Males and females (n=106)	≤6hrs (>6<8hrs) ≥8hrs	1.40 (0.53,3.71) 1.00 **4.10 (1.41,11.92)**		2.30 (0.71,7.50) 1.00 **4.89 (1.32,18.13)**
Wu et al. 2012 Taiwan	Males (n=4,298)	<6hrs (6-8hrs) >8hrs	**1.31 (1.14,1.50)** 1.00 1.21 (0.87,1.67)		**1.28 (1.01,1.63)** 1.00 1.43 (0.82,2.48)
	Females (n=2,802)	<6hrs (6-8hrs) >8hrs	**1.36 (1.04,1.77)** 1.00 1.01 (0.50,2.04)		1.04 (0.72,1.51) 1.00 0.90 (0.32,2.51)
Arora et al. 2011 China	Males and females (n=29,333)	<6hrs 6<7hrs (7<8hrs) 8<9hrs ≥9hrs	**1.14 (1.05,1.24)** **1.10 (1.03,1.18)** 1.00 **1.14 (1.06,1.22)** **1.18 (1.07,1.30)**	0.98 (0.90,1.06) 1.02 (0.95,1.09) 1.00 **1.16 (1.08,1.25)** **1.22 (1.11,1.35)**	0.97 (0.88,1.06) 1.00 (0.93,1.08) 1.00 **1.16 (1.08,1.25)** **1.21 (1.10,1.34)**
Choi et al. 2008 South Korea	Males and females (n=4,222)	≤5hrs 6hrs (7hrs) 8hrs ≥9hrs	**1.74 (1.33,2.26)** **1.27 (1.04,1.56)** 1.00 **1.27 (1.01,1.63)** **1.55 (1.15,2.07)**	1.23 (0.92,1.64) 1.13 (0.91,1.40) 1.00 1.28 (1.00,1.64) **1.47 (1.08,2.00)**	1.17 (0.87,1.59) 1.07 (0.85,1.34) 1.00 **1.32 (1.01,1.73)** **1.69 (1.17,2.45)**
Sleep quality					
Hung et al. 2013 Taiwan	Males and females (n=3,435)	Poor (Good)	**1.51 (1.29,1.76)** 1.00		**1.48 (1.25,1.74)**
Lee et al. 2013 South Korea	Males and females (n=301)	Poor (Good)	**3.71 (2.26,6.10)** 1.00		**3.83 (1.91,7.65)**
Yoo and Franke 2013 USA	Males and females (n=106)	Poor (Good)	1.02 (0.44,2.37) 1.00		2.25 (0.70,7.19)

2.4.7 Meta-analyses of unadjusted and (confounder- and/or mediator-)adjusted analyses examining the association between MetS and sleep

The conclusions drawn from the summaries provided in Table 2.6 were largely upheld by the formal meta-analyses summarised in Figure 2.6 and 2.7 for sleep duration and sleep quality, respectively. A total of six separate meta-analyses were possible using odds ratios reported for short and prolonged sleep duration from: unadjusted models (which were reported by all n=9 of the studies included in Table 2.6); confounder (only)-adjusted models (which were reported by only n=3 of the studies); confounder and mediator-adjusted models (which were also reported by all n=9 of the studies).

A comparison of the three meta-analyses conducted on results reported for short sleep duration (see Figure 2.6a) confirmed that the combined estimate generated from unadjusted models suggested that short sleep duration was associated with more than 1.5 times the odds of MetS (OR:1.52; 95%CI:1.26,1.83); and while this was substantially attenuated in models from the n=3 studies that adjusted for confounders alone (OR:1.03; 95%CI: 0.95,1.12), it strengthened again once mediators were included in the adjustment sets used (OR:1.24; 95%CI:1.04,1.47). A similar pattern, though somewhat less pronounced, was observed in the three meta-analyses conducted on results reported for prolonged sleep duration (see Figure 2.6b), in which the combined estimate generated from unadjusted models reported by all n=9 studies suggested that prolonged sleep duration was associated with 1.38 times the odds of MetS (OR:1.38; 95%CI:1.20;1.58), an association that was modestly attenuated following adjustment for confounders alone (OR:1.21; 95%CI:1.11,1.32), but again strengthened close to the unadjusted association (OR:1.34; 95%CI:1.17,1.53) following adjustment for both confounders and mediators.

Although none of the studies examining the association between sleep quality and MetS that were eligible for inclusion in Table 2.6 reported the results of models using adjustment sets containing only confounders, all n=3 of these studies reported the results of unadjusted models *and* models using adjustment sets containing both confounders and mediators (see Figure 2.7). Once again, formal meta-analyses of results from these two sets of models (unadjusted; and both confounder- and mediator-adjusted) confirm that the combined odds generated from unadjusted models (which suggested that poor sleep quality was associated with almost twice the odds of MetS; OR:1.86; 95%CI:0.95,3.363) strengthened substantially (to OR:2.20;

95%CI:1.10,4.37) when based on results from models that adjusted for both confounders and mediators – clear evidence of over-adjustment.

As such, neither set of meta-analyses provide much in the way of reassurance that short or prolonged sleep duration, or poor sleep quality are *actually* associated with MetS. This is likely to be the result of suppression, since the associations observed were clearly attenuated following adjustment for the limited number of confounders available to/measured by the studies examined here; and are therefore likely to be susceptible to further attenuation were it possible to adjust for additional confounders (both latent/unmeasured confounders, and those that were available/measured by the studies reviewed, yet excluded from some of the adjustment set used; see Table 2.5). Likewise, the strengthened combined odds ratios generated following the inclusion of mediators in the covariate adjustment sets used, poses a real challenge to a more circumspect interpretation of the evidence examined by the present Chapter, since these strengthened odds ratios are likely to be interpreted by others (including unwitting journal reviewers and editors) as evidence that the association between sleep duration/quality and MetS is somehow 'independent of' mediators falling on the causal path between sleep and MetS (and also, for those adjustment sets that included these, 'independent of' other sleep characteristics or individual components of MetS; see Table 2.5). Indeed, this may be what lies behind the evidence of publication bias contained in Figures 2.6 and 2.7, in which there is a marked tendency for those studies adding a greater 'percentage weight' to these meta-analyses to have reported odds ratios closer to the null (this is evident from the 'percentage weight' figures presented to the far right of each study-specific OR and 95%CI in each of the meta-analysis plots; figures determined by the sample size, and hence statistical power, of each study). Taken together with the many methodological weaknesses and potential analytical biases identified in the n=21 studies reviewed in the present Chapter, there remains considerable uncertainty as to whether there is any association between sleep and Mets except that generated through confounding, and/or through inappropriate adjustment for mediators. Fresh analyses of well-powered samples, avoiding each of these pitfalls, will be required to address this ongoing uncertainty.

Figure 2.6a Meta-analyses of odds ratios reported for studies examining the association between short sleep duration and MetS using models that were: unadjusted for any covariates (top); adjusted only for confounders (middle); and adjusted for both confounders and mediators (bottom)

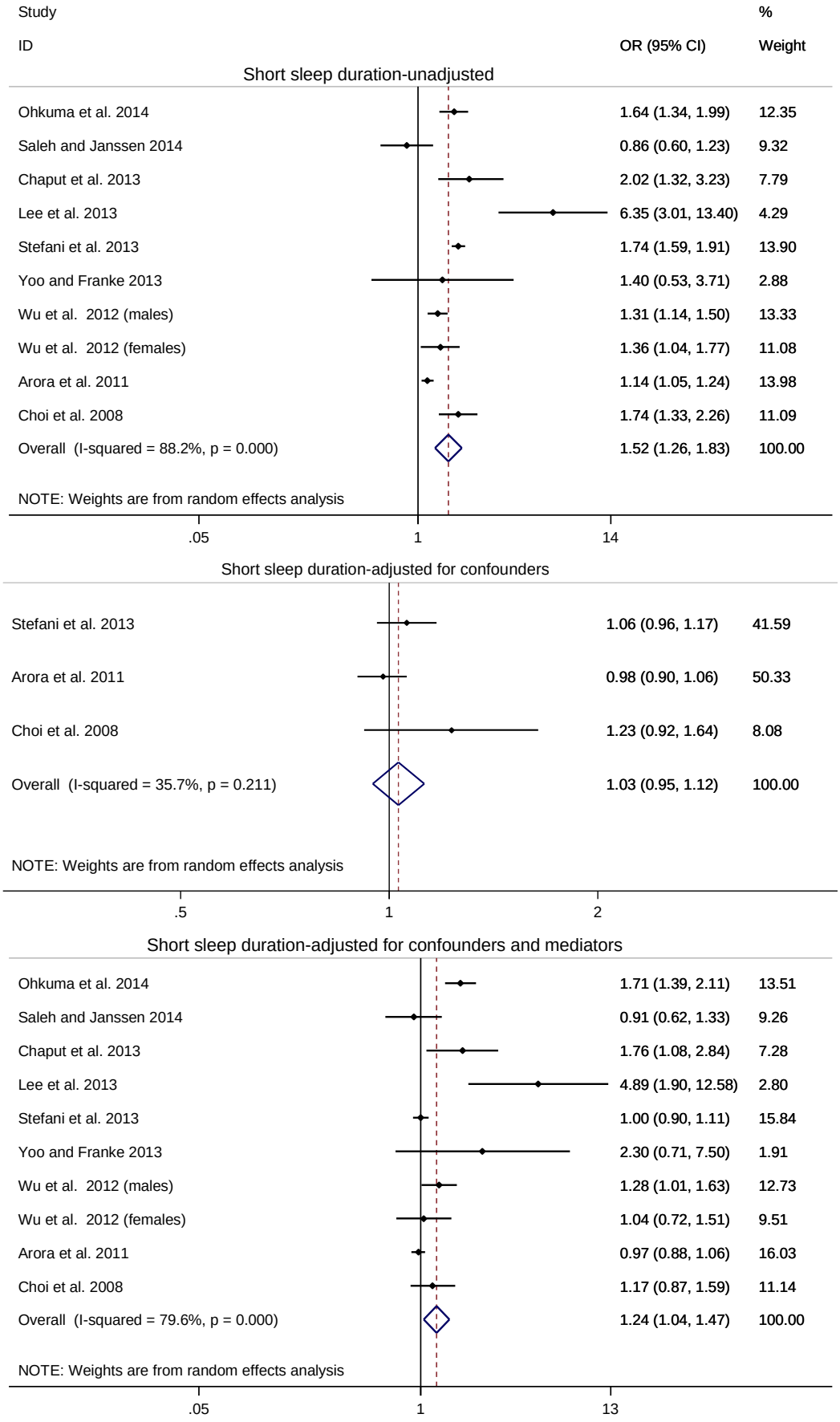


Figure 2.6b. Meta-analyses of odds ratios reported for studies examining the association between long sleep duration and MetS using models that were: unadjusted for any covariates (top); adjusted only for confounders (middle); and adjusted for both confounders and mediators (bottom)

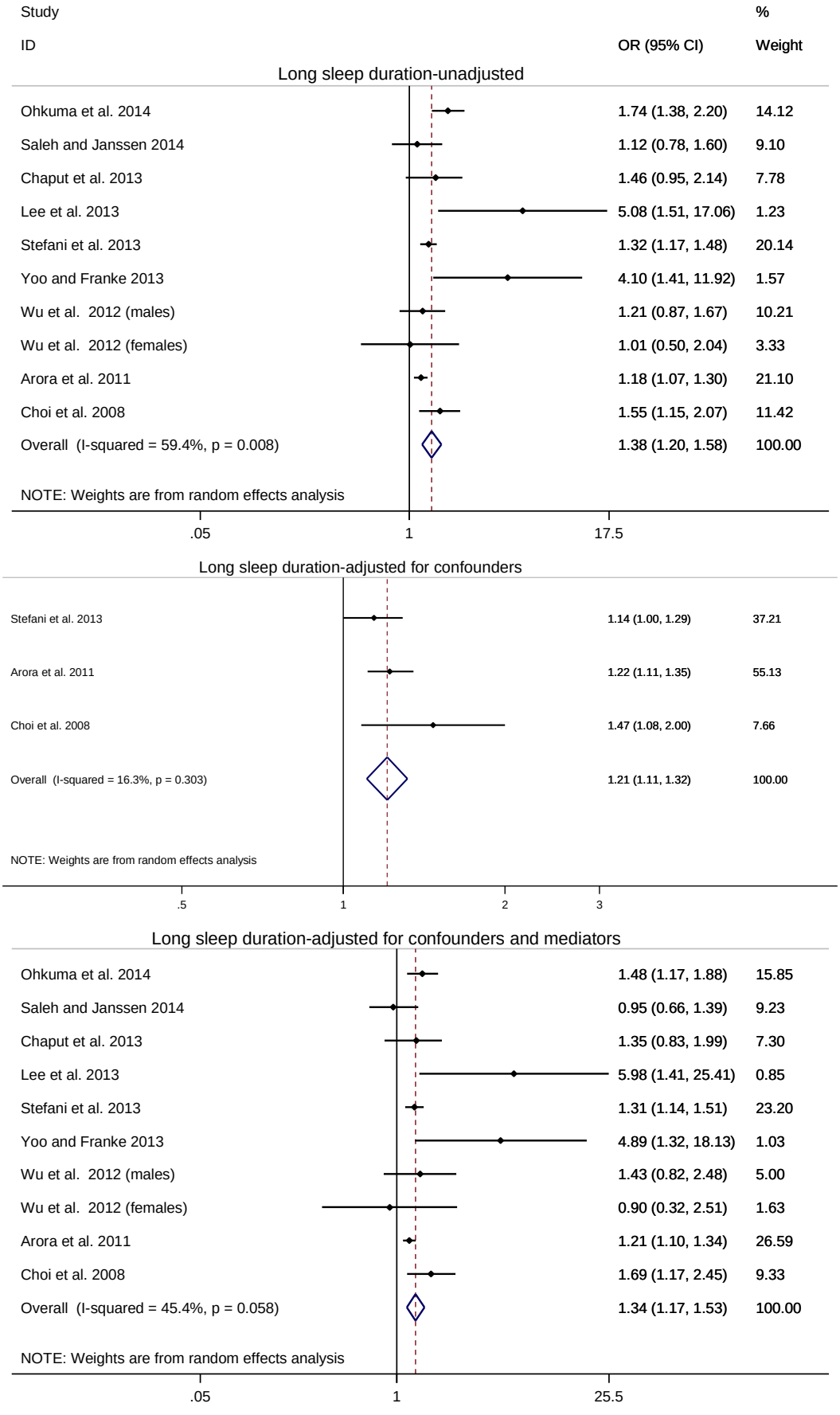
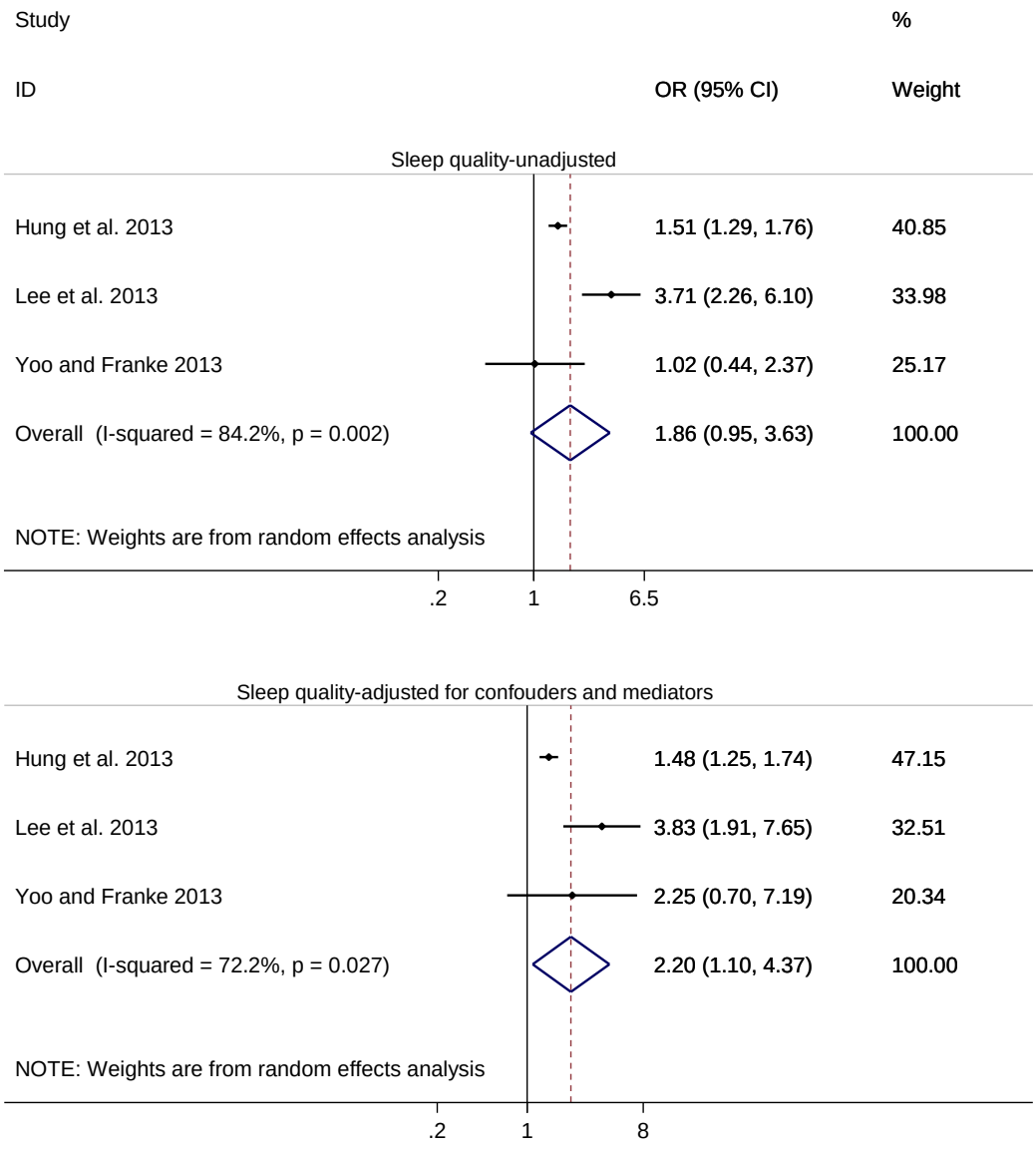


Figure 2.7 Meta-analyses of odds ratios reported for studies examining the association between poor sleep quality and MetS using models that were: unadjusted for any covariates (top); and adjusted for both confounders and mediators (bottom)



2.5 Summary

The literature search conducted for the present review into the association between MetS and sleep, found little evidence generated from experimental studies (beyond those examining the use of CPAP-related, or weight-loss, interventions), and no robust longitudinal analyses of data collected from more than two time points (baseline and follow-up). Instead, the only evidence available on the association between MetS and sleep that had looked beyond the individual symptoms/components of MetS (such as the experimental studies examining weight loss) and beyond clinical sleep disorders (such as obstructive sleep apnoea), comes from cross-sectional studies.

A total of n=21 such studies were identified, conducted between 2006 and 2014, and predominantly in North America and Asia (with only two studies to-date in Europe, neither in the UK). Most of these studies (n=15/21) involved secondary analyses of data from past/ongoing studies, all but one of which included both male and female participants, and around half involving more than n=1,000 participants. For the most part the recruitment of participants involved excluding those with serious pre-existing clinical conditions (including psychiatric diagnoses, cancers, and advanced cardiovascular disease), and few focussed exclusively on patients sampled from clinics providing treatment for these. As such, the samples of participants examined by these studies appear to offer a sound basis for extrapolation to the wider population of (ostensibly healthy) adults in each of the contexts where these studies were based.

Although four different classifications of MetS were used by the studies reviewed, these were all broadly comparable (each requiring the presence of three or more measures of obesity, high blood pressure, dyslipidaemia and diabetes to establish the presence of MetS); and all of the studies based their use of these on direct measures of the four or five measures they used. In contrast, only n=2 of the studies used direct (objective) measures of sleep, the remainder using a wide range of established instruments and custom sleep item sets. There was also little consistency in the specific sleep-related characteristics examined, and although a sizeable number of studies (n=14) involved some measure of sleep duration, only n=6 measured sleep quality and only n=5 assessed snoring/sleep-disordered breathing, with many commonly recognised sleep characteristics (including: sleep latency; sleep fragmentation; sleep efficiency; sleep medication use; daytime sleepiness) examined in analyses on just a single dataset. Moreover, very few of the studies examined more than one or two sleep-related characteristics, which means it is not yet possible to compare whether any association between MetS and sleep depends upon the specific

characteristic of sleep examined, except from the results of individual studies (none of which examined a comprehensive list of sleep-related characteristics), or by comparing across studies that examined different participants, in different contexts, using different methods.

Even where substantial numbers of studies examined the same sleep characteristic (i.e. sleep duration; sleep quality; or snoring/sleep-disordered breathing), a lack of consistency in the instruments used to measure these characteristics, together with variation in the specification and number of response categories used (and in the analytical and reporting practices applied), makes comparisons across these studies challenging. As a result, the present review only found it possible to compare the association between MetS and sleep duration across n=9/14 studies, and between MetS and sleep quality across n=3/6 studies; while inconsistencies in measurement, analysis and reporting meant it was not possible to compare the association between MetS and snoring/sleep-disordered breathing between two or more of the n=5 studies reporting these.

Nonetheless, by comparing the associations between MetS and sleep duration across n=9 broadly comparable studies, and between MetS and sleep quality across n=3 studies with similar approaches to measurement and analysis, it was possible to generate substantial insight into the evidence such cross-sectional studies might offer. Both comparisons suggest that MetS is associated with a higher odds of less favourable sleep duration (i.e. short and prolonged sleep duration), and a higher odds of ‘poor’ sleep quality. However, the strongest associations were observed in studies with comparatively small samples sizes (n<500), which suggests the possibility of publication bias. Moreover, using a theoretical causal path diagram (developed using: a list of the covariates reported by all n=21 studies; and an assessment of how and when data on these variables, and on MetS- and sleep-related variables, were collected) it was possible to compare reported associations between MetS and these two sleep characteristics before and after adjustment for potential confounders (for n=3 of the studies examining sleep duration) and likely mediators (for all n=9 studies examining sleep duration and all n=3 studies examining sleep quality).

These comparisons indicate that most of the unadjusted associations between MetS and sleep duration were substantially attenuated following adjustment for available/measured covariates considered potential confounders; while adjustment for both confounders *and* likely mediators attenuated the associations observed in some studies and strengthened these in others. Similar effects – involving attenuation following adjustment for confounders *alone;* and a mix of attenuated and strengthened associations following adjustment for confounders *and* mediators – were also evident

for many of the other sleep characteristics examined by individual studies. This suggests that many of the associations between MetS and a range of sleep-related characteristics might be susceptible to substantial confounding; and that the inclusion of likely mediators (in addition to potential confounders) in the covariate adjustment sets used, can introduce substantial bias.

While the use of multivariable analyses to generate adjusted estimates of the association between MetS and sleep indicates that most of the studies recognised the potential impact of confounding (and the importance of addressing this through adjustment), none of the studies included in the present review reported data on all of the available/measured covariates mentioned by one or more of the other studies. At the same time, most of the covariate adjustment sets used by the studies reviewed included likely mediators as well as confounders, indicating that few (if any) of the studies recognised the potential for bias associated with inappropriate adjustment for mediators. For these reasons, it seems likely that many (if not all) of the confounder-adjusted estimates (of the association between MetS and sleep) reported by these studies will suffer from unadjusted confounding – simply because the adjustment sets these used omitted covariates acting as confounders (i.e. those covariates that appeared feasible to collect given these were available to/measured by at least some of the other studies). For similar reasons, it seems likely that substantial care is required when interpreting the adjusted estimates reported by many of the cross-sectional studies examining the association between MetS and sleep, to ensure that these do not suffer from bias as a result of the inclusion of likely mediators in their covariate adjustment sets.

2.6 Conclusion

The present review suggests that, while there is some evidence of an association between MetS and sleep across a range of sleep-related characteristics, this evidence draws on a small (n=21) number of cross-sectional studies, some of which involve under-powered samples of participants, and many of which use methods that are prone to error and bias (not least in the analytical techniques they employ). None of these studies were conducted in the UK; and none provide evidence on more than four separate sleep characteristics; while variation in sampling, the variables available/measured, and the measurement and analysis techniques used, make it difficult to provide a comprehensive assessment of the relationship between MetS and sleep across the full range of sleep-related characteristics based on these n=21 studies.

To address these gaps (and flaws) in the evidence available to-date, a suitable dataset was sought that contained appropriate (and sufficient) information to support a de novo analysis using more robust methods. Such a dataset would ideally: have been conducted in the UK (given the absence of any such UK-based studies, to-date); contain data on a range of different sleep characteristics (and, in particular, not simply data on sleep duration and sleep quality); and have sufficient information on MetS-related criteria as well as a broad range of potential confounders to permit suitably adjusted analyses of the potential relationship between MetS and sleep.

2.7 Development of research aim and objectives

2.7.1 Research aim

This thesis sets out to explore, in greater detail, the epidemiological relationship(s) between MetS and sleep at the population level, and to provide clearer evidence of whether variation in MetS might predict changes in sleep patterns (or vice versa). As such, the present study aimed to identify a large-scale, nationally representative survey of UK adults in which suitable data (on sleep, MetS and potential confounders) were available.

2.7.2 Objectives

The overarching aim of the present thesis is to generate an improved understanding of the available evidence regarding the speculative relationship between sleep and the metabolic syndrome (MetS). This aim will be operationalised using three key questions (KQs):

KQ2: “What UK-based datasets are available from which to examine the relationship between sleep and the metabolic syndrome (MetS) to inform: the focus and conduct of future research; and our understanding of the evidence base regarding ‘unfavourable’ sleep as a possible cause and a possible consequence of MetS?”

KQ3: “To what extent might self-reported items relevant to identifying MetS in large datasets offer sufficiently valid measures of MetS symptoms/components to provide a basis upon which to generate a ‘self-reported’ classification of MetS suitable for use in population-based analyses where direct measures of MetS components are not available/feasible?”

and

KQ4: “What methodological and aetiological insights into the association between sleep and MetS might be generated from analyses of such data?”

Each of these three questions have been addressed in successive Chapters of the present thesis, using a range of different methods, including: KQ2 – a search for a suitable dataset containing sufficient/appropriate variables (Chapter 3); KQ3 - the development of self-reported measures of MetS-related symptoms/components, and comparing them to their direct/objective measures; and KQ4 - novel analyses of a contemporary secondary dataset, addressing the flaws identified in the systematic review (Chapter 2), and using the self-reported classification of MetS (Chapter 4).

The analytical Chapters are then followed by the concluding Chapter to the present thesis, which rehearses the key findings from the preceding Chapters, and synthesises what might be learnt by comparing the results of these (and from an assessment their limitations) to generate key recommendations for future research building on the foundation prepared by the present thesis.

Chapter 3 Data sources and analytical methods

The present Chapter identifies a suitable dataset for use in the present study and introduces the methods used in the following (results) Chapter (Chapter 4). It provides further insight into the dataset selected for analysis within the thesis including a description of the study design and sample used; the variables available, and their definitions; data management; and the various statistical methods applied in the analyses that follow.

3.1 Introduction

Given the important statistical advantages (in terms of power) associated with studies examining large scale datasets, the present thesis established at an early stage the need to identify a suitable secondary dataset containing information on MetS and sleep, as well as a suitable range of covariates likely to act as potential confounders. The (secondary) analysis of data from existing datasets – i.e. those that have been collected for different (or, indeed, for generic) research purposes – is a common strategy in epidemiology since it has several advantages over the collection and analysis of primary data. Secondary datasets tend to be available/accessible at much lower cost to the researcher than the collection of primary data; and they often contain high quality data, benefitting (as they often do) from collaborations between multidisciplinary teams of experts across a range of different fields, who are able to advise on the most appropriate validated instruments to use. Many such studies also go through several rounds of developmental 'pilot' phases in which every step of data collection, collation and preparation is scrutinised, practised and evaluated. Nonetheless, such datasets all too often fail to collect all of the necessary data required to address very specific research questions, and researchers using these datasets rarely have any influence over what data have been collected or how. Similarly, researchers analysing secondary data are usually unaware of key details affecting the quality and validity of the data collected, simply because they are rarely involved in the process of designing and administering the measurement tools and surveys used (Cheng and Phillips 2014; Miller and Brewer 2003). It is therefore important, when conducting secondary analyses, to take great care when selecting an existing dataset to ensure that this has sufficient data on relevant variables of interest to address the question(s) in hand.

After a dedicated search for contemporaneous datasets offering large-scale samples with information on MetS, sleep *and* a comprehensive range of potential confounders (see Table 3.1), the present thesis settled on the United Kingdom Household Longitudinal Study (UKHLS).

Table 3.1 Contemporary UK cohort studies that include data on sleep in their secondary datasets.

Name of the study	Sample size and age	Area	Number of sleep characteristics
The United Kingdom Household Longitudinal Study (UKHLS)	50,994 (+10yrs)	Britain	(7)Sleep duration, sleep latency, sleep fragmentation, sleep disturbance due to cough/snore, sleep medication use, daytime sleepiness and sleep quality.
The Hertfordshire Cohort Study	3,000 (+4yrs)	Hertfordshire	(1)Trouble with sleep
National Survey of Health and Development	5,362 (-57yrs)	England, Scotland and Wales	(1)Trouble with sleep
1970 British Cohort Study	17,000 (-33yrs)	England, Scotland and Wales	(2)Sleeping difficulty and Sleep latency
Southampton Women's Survey	12,583 women (+26yrs)	Southampton	(1)Sleep duration
Avon Longitudinal Study of Parents and Children	14,000 pregnant women, the children arising from the pregnancy, and their partners	Avon	(1)Trouble with sleep

The UKHLS displayed many of the key prerequisites of the 'ideal' secondary dataset sought for use in the present thesis: it is based on a nationally representative sample of households recruited throughout the United Kingdom, including samples drawn from England, Scotland, Wales and Northern Ireland; and it has used a longitudinal approach, with regular surveys of each household and each household member (aged ten and above), thus far involving around n=40,000 households. The UKHLS has also succeeded in generating data across a wide spectrum of sleep- and MetS-relevant variables as a result of its multi-topic focus, supported with substantial, sustained funding from consecutive governments (and a number of government departments), as well as from the UK's Economic and Social Research Council (ESRC).

The UKHLS aims include generating – at community, individual and household level – high quality longitudinal data on: social and demographic factors, education, , income, and health; as well as collecting objectively/directly measured health data on a large sub-sample of adult participants (through a dedicated 'Nurse Health Assessment'; NHA). Together, these data are intended to help better understand both short and long-term changes in each of these social characteristics, and to help design/evaluate policy interventions capable of enhancing the wellbeing of the UK population (Knies 2014).

Choosing the UKHLS dataset over other surveys was made on the basis that it offered contemporary data from a large, nationally representative, multi-topic longitudinal survey of UK adults in which components of MetS, sleep characteristics, and a range of potential confounders have been recorded. None of the alternative datasets identified were capable of addressing each of these issues so comprehensively (see Table 3.1)

3.2 The United Kingdom Household Longitudinal Study (UKHLS)

The UKHLS datasets contain anonymised data that are available in the public domain through the UK Data Service, and permitted for use by, amongst others, University-based researchers. However, since any study involving human participants warrants ethical scrutiny, the UKHLS was designed and undertaken in line with the Institute for Social and Economic Research's (ISER) internal Code of Ethics and the Research Ethics Framework of the principal funder (the Economic and Social Research Council; ESRC). This Code and Framework led the UKHLS to obtain formal ethical approval for each successive Wave of the study from the University of Essex Ethics Committee and the National Research Ethics Service. All prospective UKHLS participants were required to provide informed consent; verbal consent being considered adequate for participation in the questionnaire surveys, and for all direct measurements including blood pressure and anthropometric measurements; while written consent was required for any invasive procedures such as the collection of blood samples.

3.2.1 The UKHLS sample design

The UKHLS comprises a number of different sample components. Amongst these, the present thesis drew data primarily from the so-called "general population sample", comprising household members drawn from a representative sample of UK households. To achieve representativeness, the UKHLS general population sample was stratified across addresses selected by postcode in England, Wales and Scotland with households in each strata selected at random. Households from Northern Ireland (NI) drew on a systematically un-clustered random sample of household addresses selected from the NI Land and Property Services Agency's list of domestic addresses. Together these samples generated a total of n=49,915 addresses. However, the study only managed to recruit households at n=30,169 addresses so that the subsequent interviews were conducted on n=50,994 individuals (i.e. on average just over five adults in every three households) during the first Wave ("Wave 1") of the study. , and

these respondents make up the original sample of participants recruited into the UKHLS.

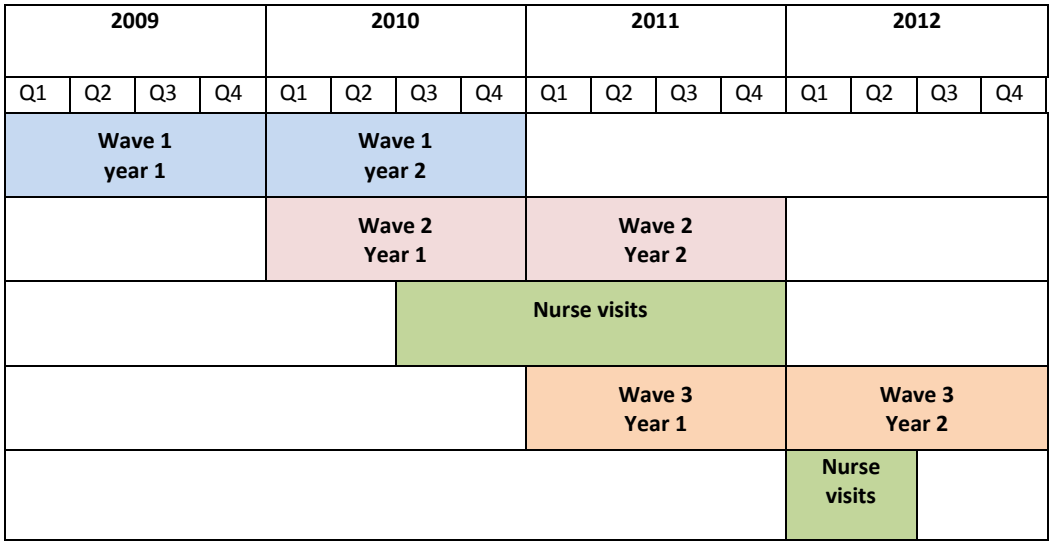
3.2.2 Main survey and Nurse Health Assessment

In 2009 the first UKHLS main survey ('Wave 1') began, with data collection lasting for approximately two years. Subsequent Waves have then taken place at approximately two year intervals, interdigitating with the preceding Wave, such that Wave 1 took place from January 2009 to January 2011, while Wave 2 took place from January 2010 to January 2012 and so on (Knies 2014).

In 2010-2012 the UKHLS augmented the Wave 2 main survey with a home visit-based 'nurse health assessment' (NHA) which involved a detailed examination of a subsample of study participants to provide direct (objective) measures that might be used in the assessment of chronic disease, and for exploring a range of biosocial determinants/components of human health (McFall 2013). These NHA visits took place five months after the completion of the main survey during Wave 2 and extended over 24 months so that these were still underway as the main survey was being completed during Wave 3. In Wave 2 only adult respondents who had completed the main survey, and were not pregnant, and not physically or mentally ill were eligible to participate.

The NHA Wave 2 NHA subsample comprised n=15,646 adults (aged 16yrs and over) each of whom received a home visit from a trained registered research nurse at which the following direct measures were taken: weight, height, percentage body fat, waist circumference, blood pressure, grip strength, and lung function. All of these participants were also eligible to provide a non-fasting blood sample with the exception of those: with clotting or bleeding disorders; taking anticoagulant drugs; who had ever had a fit or convulsion; suffering from hepatitis B or C, or who were HIV positive; and who were not willing to give written consent for this procedure. Of the blood samples collected from this 'sample within the subsample' n=13,258 adults were subsequently subjected to laboratory screening for selected biomarkers, including: cholesterol levels; glycated haemoglobin (HbA1c); high sensitivity C - reactive protein and fibrinogen; haemoglobin and ferritin; and others relevant to liver and kidney function (Benzeval 2014).

Figure 3.1 Wave 1, Wave 2 and Nurse Health Assessment temporal sequence



3.2.3 The UKHLS data collection and processing

Prior to each wave, a small pilot study and 'dress rehearsal' were conducted, which involved a run-through of all proposed data instruments. The collection of data within each selected household comprised an interview involving a range of different types of questionnaires:

1. A household questionnaire (one per household);
2. A face-to-face questionnaire using Computer Aided Personal Interview (CAPI); and
3. A proxy questionnaire for individuals who were not available at the time data were collected and who gave their permission for information to be given by a nominated 'proxy respondent' on their behalf.

Two self-administered questionnaires were also left with households for completion and subsequent return by post:

4. Adult self-completion questionnaire (one per eligible adult aged 16yrs and over); and
5. Young Person self-completion questionnaire (one per eligible youth aged under 16yrs).

The main adult questionnaire delivered face-to-face was organised in 'modules' (such as these containing items on social, educational or health-related issues). Some of these modules (and all of the items they contained) were repeated in every subsequent main adult questionnaire; while others were modified or repeated in their entirety only at intervals of 2-3 subsequent Waves. This pattern of topic-focussed data

collection reflected both the resources available to administer long(er) questionnaires, and constraints related to the burden of data collection placed upon participants (and the importance of retaining participants from one Wave to the next, given the UKHLS' longitudinal design).

Following the fieldwork, data underwent detailed quality control to ensure that answers matched the pre-defined questionnaire item specifications. This was followed by editing, error reporting and coding of any free text information generated by open-ended questions. Data from paper documents (including the Adult and Young Person self-completed questionnaires) were then entered into the dataset, and a range of different codes were applied to the dataset to record different reasons for 'missingness' (i.e. the type, and reason for, any absent valid responses, such as: missing by error or considered implausible; a question not being applicable whether to the respondent concerned or as a result of their answers to previous questions – so-called 'routing'; participant refused to answer; or participants didn't know the answer). Finally, all of the resulting variables were clearly labelled as either 'original' (i.e. the direct responses to items in the relevant questionnaire) or 'derived' (variables that were computed or determined from the direct responses given to one or more of the 'original' variables).

Data from each successive Wave are released in separate files, each containing information on the source (i.e., the household interview, the adult interview, and the youth interview). In each of these files, individual participants are pseudo-anonymised using a unique personal identifier that remains unchanged in any Wave in which they participate, facilitating the linkage of data provided by the same participants in each successive Wave.

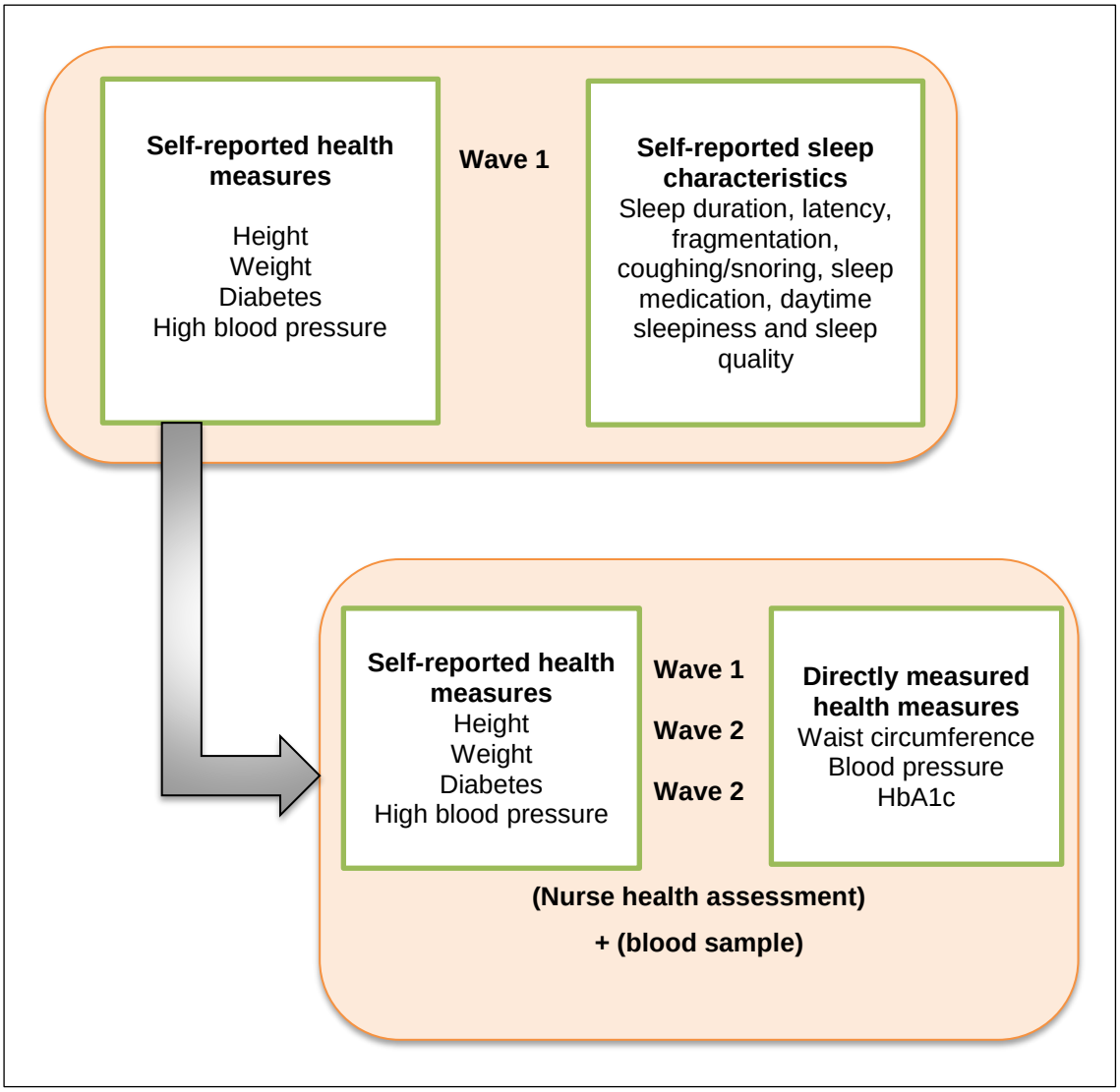
3.3 Study design and samples

To generate datasets relevant to the topic of interest to the present thesis, data from Wave 1, Wave 2 and the Wave 2 NHA were used. Data from these waves were merged into wide format files using the unique participant identifier to link data for the same participant from each of these three (original UKHLS) datasets.

Data from Wave 1 were particularly relevant to exploring the association between MetS and sleep because the questionnaire used in this Wave included data on participants' self-reported weight and height; self-reported clinical diagnoses of high blood pressure and diabetes; and self-reported sleep characteristics. In contrast, data from Wave 2 and Wave 2 NHA did not contain data on self-reported height and weight, nor on self-reported sleep. However, because the questionnaires used and direct

measures recorded in these UKHLS datasets contained self-reported clinical diagnoses of high blood pressure and diabetes (Wave 2) *and* direct measures of height, weight, waist circumference, blood pressure and HbA1c levels (the latter from subsequent laboratory analyses of non-fasting blood samples), together with lists of all prescribed medication (including antihypertensive and antidiabetic medication), these datasets provided the data necessary to assess the level of agreement between self-reported and direct measures of two of the three key components of MetS (high blood pressure and diabetes). Figure 3.2 demonstrates the way in which each of the three UKHLS datasets (Wave 1, Wave 2 and Wave 2 NHA) were used in the present thesis – Wave 1 also providing the self-reported weight and height data used to estimate 'self-reported' waist circumference; an estimate that could then be compared to direct measures of waist circumference recorded during the NHA.

Figure 3.2 The structure of the present study using UKHLS Wave 1, Wave 2, and Wave 2 Nurse Health Assessment datasets



3.4 Study variables and definitions

3.4.1 Sleep characteristics

In Wave 1 of the UKHLS the Adult Self-completion Questionnaire contained seven items which sought information on different sleep-related characteristics. These questions and their response categories mimic those questions contained in the Pittsburgh Sleep Quality Index (PSQI); (Buysse *et al.* 1989) and the Jenkins Sleep Questionnaire (JSQ); (Jenkins *et al.* 1988) – two of the most commonly used validated sleep questionnaires. However, because there is no validated scoring system for the UKHLS sleep questionnaire, each sleep characteristic needed to be considered separately.

The UKHLS sleep-related items asked participants to report their sleep during the month preceding the Wave 1 interview, including self-reports of: sleep duration (actual hours of sleep at night); sleep latency (cannot get to sleep within 30 minutes); sleep fragmentation (trouble sleeping due to waking up in the middle of the night or early in the morning); coughing/snoring (trouble sleeping due to coughing or snoring loudly); sleep medication use (medicine [prescribed or 'over the counter'] to help participants sleep); daytime sleepiness (trouble staying awake while driving, eating meals, or engaging in social activity), and sleep quality (overall sleep quality).

Sleep duration responses were recorded as hours and minutes, whereas all but one of the remaining sleep variables (the exception being sleep quality) were recorded in five categories: "Not during the past month"; "Less than once a week"; "Once or twice a week"; "Three or more times a week"; and "More than once most nights". Sleep quality responses were recorded in four categories as: "very good"; "fairly good"; "fairly bad"; and "very bad".

For use in the present thesis, data on sleep duration were categorised into: short sleep duration (<6 hrs), mid-length sleep duration (≥6-8 hrs) and long sleep duration (>8hrs). This categorisation of sleep duration was made on the basis of the U-shaped association between sleep duration and adverse health consequences (Ohkuma *et al.* 2014); and because previous studies have found that MetS may be associated with both short sleep duration (≤6hrs) and long sleep duration (≥9hrs; as compared to 7-8 hrs; (Chaput *et al.* 2013b).

All of the sleep variables (latency, fragmentation, loud coughing/soring, medication, daytime sleepiness and sleep quality) were dichotomised based upon the presence or absence of the sleep-related condition – which for all of the sleep characteristics except sleep quality, resulted in dichotomisation close to the median

value with: 0=“Not during the past month” and 1= “At some time during the past month” (comprising: “Less than once a week”, “Once or twice a week”, “Three or more times a week”, or “More than once most nights”). While the sleep quality variable was dichotomised to: 0=“very good”; and 1= “fairly good”, “fairly bad”, or “very bad”.

3.4.2 The classification of ‘Metabolic Syndrome’ (MetS)

Although, as described in the introductory Chapter to the present thesis (see: Chapter 1: *Introduction*), a wide range of definitions and classifications of MetS have been proposed, most of these generally agree that the syndrome should be recognised as present if three or more of five key components are present, namely: obesity (particularly central obesity); insulin resistance or symptoms of poor glucose regulation; high blood pressure; and dyslipidaemia (comprising elevated TG and/or low HDL levels). While some definitions place greater emphasis on (central) obesity or insulin resistance as pre-requisites for MetS (i.e. requiring one or other to be present together with two or more of the remainder), other definitions define MetS simply as the presence of any 3 of the 5 possible components.

Of the various definitions for MetS, the NCPI-ATP III (Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III) 2001) is considered to be one of the most useful, simply because it is known to be the easiest to apply in both epidemiological and clinical settings. Importantly, it does not base its definition on any preconceived concept regarding the cause of MetS (i.e. whether this be central obesity or insulin resistance), and as a result does not require any particular component of MetS to be present; instead being defined simply as the presence of any three components of MetS (Eckel, Grundy and Zimmet 2005; Huang 2009). It is for this reason that the NCPI-ATP III was chosen as the formal classification of MetS examined in the present thesis.

Within its classificatory framework, the NCPI-ATP III defines each component of MetS as follows:

1. Elevated waist circumference ≥ 102 cm for men and ≥ 88 cm for women
2. Poor glucose regulation involving either fasting glucose ≥ 110 mg/dl, and/or antidiabetic medication
3. High blood pressure involving either systolic ≥ 130 and/or diastolic ≥ 85 mm Hg, and/or antihypertensive medication
4. Dyslipidaemia involving raised blood triglycerides ≥ 150 mg/dl and/or relevant medication

5. Dyslipidaemia involving reduced HDL-C < 40 mg/dl in males and < 50 mg/dl in females and/or relevant medication

Unfortunately, because the UKHLS provided no data on dyslipidaemia (whether by self-report or from fasting blood samples), the data available for use in the present thesis required the use of a modification of the NCPI-ATP III classification, in which MetS was simply defined as the presence of three risk factors: elevated waist circumference , high blood pressure and diabetes. Furthermore, since the present thesis was interested in exploring the potential utility of self-reported MetS components (and assessing the validity of these by comparing them to direct measures thereof), a further modification applied in the present thesis involved the use of cut-offs for all three components (elevated waist circumference, high blood pressure and diabetes) based on those proposed by the UK NHS (through the UK's National Institute for Clinical Excellence; NICE – the body charged with establishing clinical guidelines and standards for use within the NHS, and therefore the thresholds of each of these components that would lead to formal clinical diagnoses as reported by UKHLS participants who had received any such diagnosis).

For this reason, the present thesis defined each component of MetS as follow:

Table 3.2 Definition of MetS using data available within current UKHLS datasets

Risk factor	**Defining level**
Waist circumference	
Men	≥ 102cm
Women	≥ 88cm
Blood pressure	≥140/90 mmHg and/or prescribed antihypertensive medication
Diabetes	HbA1c ≥ 48 mmol/mol and/or prescribed antidiabetic medication

Based on these cut-offs of these three components of MetS, two separate variables could be generated from UKHLS data generated by questionnaire (i.e. Wave 1 and Wave 2) or from direct measures (i.e. recorded in the Wave 2 NHA): self-reported MetS and directly measured MetS.

3.4.3 Directly measured MetS components and classification

3.4.3.1 Directly measured waist circumference

All NHA participants were eligible to receive direct measurements of their waist circumference unless they were pregnant, in a wheelchair, or had a colostomy/ileostomy (McFall 2013). Waist circumference was measured twice at the midpoint between the lower rib and the top of the hips using a tape measure with an insertion buckle at one end. Measurements were recorded to the nearest millimetre. An elevated waist circumference variable was generated and defined as: WC ≥ 102cm for males, WC ≥ 88cm for females.

3.4.3.2 Directly measured high blood pressure

Blood pressure measurements were made using a validated portable blood pressure monitor (Omron HEM 907). The NHA research nurse took three measurements from the right arm with participants sitting in a comfortable position with their feet on a flat floor, and having been able to relax for 5 minutes before the first reading was taken. The research nurse recorded whether participants had eaten, drunk alcohol, smoked or been physically active during 30 minutes preceding these measurements (McFall 2013).

The nurses were also tasked with checking and recording any prescribed antihypertensive medications used by each participant – a classification based on prescriptions for any drugs prescribed for the treatment of hypertension.

In line with NICE hypertension guidelines (NICE 2011a), the lower reading of the last two systolic and diastolic measurements for each participant was used to classify high blood pressure if these reached or exceeded a BP of ≥140/90 mmHg (i.e. the level recommended for the diagnosis of stage 1 hypertension); and this, together with any prescribed antihypertensive medication formed the basis for classifying high blood pressure amongst UKHLS participants in the present thesis

3.4.3.3 Directly measured indicators of diabetes

Among the biomarkers that were subsequently analysed within the non-fasting blood samples collected during the NHA was glycated haemoglobin (HbA1c). This offers a measure of the proportion of haemoglobin that are bound to glucose, and as such can be used as a marker for undiagnosed or poorly managed diabetes during the 8-12 weeks preceding the blood sample.

As for antihypertensive medication, the NHA research nurse recorded whether each participant had been prescribed antidiabetic medication – a classification based on prescriptions for insulin, metformin, or any other drugs prescribed for the treatment of diabetes.

In line with NICE guidelines (NICE 2011b) for the diagnosis of diabetes using HbA1c, a cut-off point of HbA1c ≥ 48 mmol/mol was used to classify the presence of diabetes; and this, together with any prescribed antidiabetic medication formed the basis for classifying diabetes amongst UKHLS participants in the present thesis.

3.4.3.4 Directly measured MetS classification

As described earlier, directly measured MetS was classified as the presence of all three directly measured risk factors: elevated waist circumference; high blood pressure; and diabetes.

3.4.4 Self-reported MetS components and classification

3.4.4.1 Self-reported waist circumference

As mentioned previously, survey participants were not asked to report their waist circumference for the Wave 1 or Wave 2 questionnaires. Instead, participants were only asked to report their body weight and height with the following question in Wave 1 alone: “I would like to ask you about your height and weight, how tall are you without shoes? And what is your current weight without clothes?”. Height could be reported in either feet and inches or metres and centimetres, the former being converted to metric units in a unified, derived variable. Similarly weight could be reported in either stones and pounds or kilograms, and reports given in imperial units were again metricised and used to generate a unified derived variable in kilogrammes.

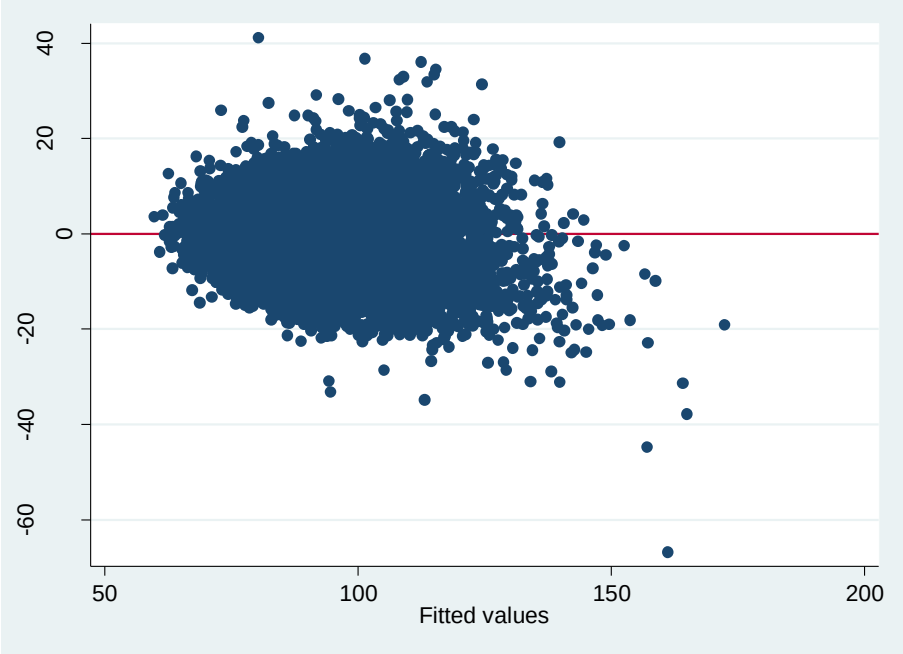
Using these self-reported data on weight and height, the present study sought to estimate ‘self-reported’ measures of waist circumference. This involved using NHA-derived direct measures of waist circumference, weight and height to generate linear regression models (stratified for age and sex) that fitted waist circumference as a function of body mass index (BMI: weight in kg ÷ [height in metres]^2). This approach had previously been used and validated by (Bozeman *et al.* 2012), who recommended its use in the absence of direct waist circumference measurements.

As mentioned earlier (see also Figure 3.2, above), direct measurements were available in the Wave 2 NHA dataset, which recruited n=15,646 participants. However, after excluding missing observations for: waist circumference; weight and height (hence BMI); sex; age; and data from participants on whom there were problems with waist circumference measurement, the sample available for analysis comprised n=14,669 participants. On these data the following equation was used to summarise the relationship between waist circumference BMI and age, as:

$$\text{Estimated waist circumference} = a + b_1\,\text{BMI} + b_2\,\text{Age} + e$$

To assess the fit of this model, residuals were plotted against the fitted values (see Figure 3.3) and this revealed a well-fitted model, since the residuals showed no pattern and were randomly scattered around the horizontal line.

Figure 3.3 Residual plot to assess the goodness fit of estimated waist circumference.



Six additional models were also developed (three for males, one each for those aged <40yrs, 40-<60yrs and ≥60yrs; and three for females, one each for those aged <40yrs, 40-<60yrs and ≥60yrs). The results obtained for each of these models have been presented in Table 3.3

Table 3.3 Coefficients (intercepts/constants and slopes) generated from regressions of (directly measured) waist circumference on (directly measured) BMI and age for n=14,669 participants in the UKHLS NHA, conducted separately for male and female UKHLS participants.

	Males		Females	
	Coefficient	**95% CI**	**Coefficient**	**95% CI**
	Age <40yrs			
Constant	23.1	21.6, 24.5	26.7	25.3, 28.1
BMI	2.40	2.34, 2.45	1.99	1.95, 2.03
age	0.204	0.169, 0.239	0.160	0.125, 0.196
	Age 40-<60yrs			
Constant	26.4	24.1, 28.7	26.5	24.4, 28.6
BMI	2.35	2.30, 2.40	2.06	2.02, 2.09
age	0.144	0.106, 0.183	0.109	0.071, 0.147
	Age ≥60yrs			
Constant	29.1	26.2, 31.9	31.4	28.4, 34.3
BMI	2.41	2.36, 2.46	2.05	2.00, 2.10
age	0.0765	0.044, 0.109	0.0430	0.008, 0.079

To estimate 'self-reports' of waist circumference, self-reported data on weight and height from Wave 1 of the UKHLS were first used to generated self-reported BMI, and then waist circumference, using the age- and sex- specific coefficients summarised in Table 3.3. Finally, these estimated 'self-reports' of waist circumference were used to generate a derived variable denoting 'elevated (self-reported) waist circumference'

defined as WC ≥ 102cm for males and WC ≥ 88cm for females (based on the cut-off values proposed by NICE).

To assess the level of error involved in the estimation of waist circumference, the same equations were applied to predict an estimated (direct measure of) waist circumference using the direct measures of BMI collected in Wave 2 NHA (i.e. the data that had been used to generate the coefficients summarised in Table 3.3). These estimates of (directly measured) waist circumference were then compared to the original direct measures of waist circumference, after classifying both the estimates and the original measurements as 'elevated' or 'not elevated' using the same NICE-proposed cut-offs (i.e. WC ≥ 102cm for males, WC ≥ 88cm for females).

A comparison of these two classifications of elevated waist circumference (one estimated, the other 'original') found that the estimated values had: a sensitivity of 82.5%; a specificity of 89.0%; a positive predictive value of 85.6%; a negative predictive value of 86.5%; overall agreement of 86.10%; and a Cohen's kappa value of 0.72. These comparisons suggest that (notwithstanding that these were derived from the *same* direct measures of BMI and age) the estimated 'direct measures' of elevated waist circumference offered good evidence of validity for directly measured 'elevated waist circumference' – evidence that the estimation approach used was broadly robust (though not, necessarily, that this would be similarly robust for estimates based on self-reported BMI; as will be discussed later in the present thesis).

3.4.4.2 Self-reported high blood pressure

Items generating data on self-reported clinical diagnoses of high blood pressure were available in both the Wave 1 and Wave 2 questionnaire. In Wave 1 (through the CAPI) participants were asked "Has a doctor or other health professional ever told you that you have any of the conditions listed on this card?" for which the sixteenth condition listed was "High blood pressure". A subsequent question then asked: "Do you still have high blood pressure?". In Wave 2 participants were asked "Since [the date on which the Wave 1 main adult questionnaire was completed] has a doctor or other health professional newly diagnosed you as having any of the following conditions?" (one of which was, again, 'high blood pressure'). A subsequent question then asked "do you still have [newly diagnosed health condition]".

Subsequently, for the analyses conducted using Wave 2 data, self-reports of clinical diagnoses of high blood pressure was identified as 'still' at Wave 1 *or* 'still' at Wave 2, while for the analyses conducted using Wave 1 data, self-reported measure of high blood was identified as 'still' at Wave 1 alone.

3.4.4.3 Self-reported diabetes

Items generating self-reported clinical diagnosis of diabetes were also available in both the Wave 1 and Wave 2 questionnaires. In the Wave 1 questionnaires participants were asked “Has a doctor or other health professional ever told you that you have any of the conditions listed on this card?” for which the fourteenth condition listed was “Diabetes”. A subsequent questions then asked: “Do you still have diabetes?” and “What age were you when you were first told you had diabetes?”. In Wave 2 participants were asked “Since [the date on which the Wave 1 main adult questionnaire was completed] has a doctor or other health professional newly diagnosed you as having any of the following conditions?” (for which, again, one of the conditions listed was ‘diabetes’). A subsequent question then asked “do you still have [newly diagnosed health condition]”.

Subsequently, for the analyses conducted using Wave 2 data, self-reported diabetes was identified as ‘still’ at Wave 1 (and diagnosed at ≥ 20yrs to ensure that this variable was more likely to capture Type 2 [i.e. late onset] diabetes rather than Type 1 [i.e. early onset] diabetes) or ‘still’ at Wave 2 alone. On the other hand, for the analyses conducted using Wave 1 data, self-reported diabetes was identified as ‘still’ at Wave 1 alone (and a diagnosis made at age ≥20yrs).

3.4.4.4 Self-reported MetS classification

Self-reported MetS classification was identified as the presence of all three self-reported risk factors together: elevated estimated ‘self-reported’ waist circumference (WC ≥ 102cm for males, WC ≥ 88cm for females); self-reported clinical diagnosis of high blood pressure; and self-reported clinical diagnosis of diabetes.

3.4.5 Covariates

Based on the narrative review that had been undertaken during the initiation of the present thesis (Appendix 6.1) and on the systematic review conducted in the previous Chapter (Chapter 2: *A Systematic review of previous studies examining the relationship between sleep and MetS*), a subset of relevant covariates were selected for consideration as potential confounders, possible mediators and/or competing exposures. However, because the secondary data source chosen for the present thesis’ analyses restricted the specific variables that had been measured/were available to those collected by the UKHLS, the covariates chosen were in large part determined by what the UKHLS datasets could provide. In another words, while there was no alteration or modification to the overarching research questions posed by the present thesis, the analyses conducted needed to be adaptable to the availability of

variables within the UKHLS datasets (and these were therefore somewhat constrained by what variables had already been collected, and in what form these variables had been measured).

Among the variables considered to be likely to be associated with both sleep and MetS (and which had been measured/were available within the UKHLS dataset) were a range of sociodemographic, health, lifestyle and behavioural characteristics collected by the questionnaires used in either Wave 1 and/or Wave 2. These were:

- Sex (male; female)
- Age (>30 years old; 30-39 years; 40-49 years; 50-59 years; 60 years or older) – derived from 'age group' variable: 13 categories
- Marital/cohabitation status (single; cohabiting; separated and divorced; widowed) – 'derived from legal marital status' variable: 10 categories
- Educational attainment, presented as the current highest qualification achieved (higher degree; other degree; A-level; GCSE; other qualification; no qualifications).
- Occupation (management and professional; intermediate; small employers and own account; lower supervisory and technical; semi-routine; routine and never worked long time; unemployed; retired; student) – derived from 'current job defined' based on the five category version of the National Statistics Socio-economic Classification (NS-SEC; (Chandola and Jenkinson 2000) .
- Parenthood (not responsible for any child; responsible for one or more child) – derived from 'number of children aged under 18 responsible for': 8 categories.
- Household structure (empty nesters; dwelling-sharing childless adults; partnered with child; partnered with children; large family majority with overcrowding; single parent household; extended family, majority with overcrowding) – after (Fowler *et al.* 2014).
- Physical health (a continuous scale with a range of 0 "low functioning" to 100 "high functioning" based on the SF-12; (Gandek *et al.* 1998).
- Mental health (a continuous scale with a range of 0 "low functioning" to 100 "high functioning" based on the SF-12; (Gandek *et al.* 1998).
- Number of servings of fruit/vegetables per day (1; 2; 3; 4; 5; 6; and more than 6). Derived from 'number of servings of fruit/vegetables per day': 17 categories.

- Sport activity (0; 1-2; 3-4; 5-6; ≥7) – derived from ‘sport activity ranking scale’ from 0 to 10, with 0 being 'doing no sport at all' and 10 being 'very active'.
- Smoking (never smoked; quit smoking; smokes less than 10 cigarettes per day; smokes 10-20 cigarette per day; smoke more than 20 cigarette per day) – derived from ‘usual number of cigarettes smoked per day’, ‘ever smoked cigarettes’ and ‘current smoking’ variables.
- Alcohol consumption (almost every day; five or six days a week; three or four days a week; once or twice a week; once or twice a month; once every couple of months; once or twice a year; not at all in the last 12 months) – derived from ‘alcohol drinking frequency during the last 12 months’: 9 categories.
- Time difference in days between Wave 2 NHA interview and Wave 2 main survey; calculated by subtracting Wave 2 NHA date from Wave 2 main survey interview date.
- Time difference in days between Wave 2 NHA and Wave 1 main survey; calculated by subtracting Wave 2 nurse health interview date from Wave 1 main survey interview date.
- Some activities that were believed to affect the NHA blood pressure measurements including: eating, smoking, drinking alcohol, and doing vigorous exercise in the 30 minutes preceding blood pressure measurement (not mentioned, mentioned)
- Units used to self-report weight (stones, kilograms)
- Units used to self-report height (feet and inches, meters and centimetres)
- Participant-based assessment of the accuracy of self-reported weight (fairly sure, estimate)
- Participant-reported time when last weighed (a scale ranging from ‘last week’ to ‘more than five years ago’).

3.5 Data transformation

For analytical reasons such as improving results interpretation; easier comparison and/or discussion, some variables required transformation as recoded; or derived new variables. Examples of how some of the variables were transformed in this fashion are listed below:

1. Merging categories

   Some categorical variables were recoded into fewer categories by combining some categories. An example of this is the marital/cohabitation status variable where the original responses were reduced to fewer categories by combining some categories (Table 3.4).

Table 3.4 An example for recoded categorical variable into fewer categories by combinding some categories.

Original variable		Re-categorised variable	
De facto marital status	Frequency	Cohabiting status	Frequency
Refusal	3	Missing	16
Don't know	13		
Single and never married/in civil partner	11,917	Single	11,917
Married	25,726	Cohabit	31,485
In a registered same-sex civil partners	90	Separated or Divorced	4,291
Separated but legally married	1,148	Widowed	2,988
Divorced	3,132		
Widowed	2,984		
Separated from civil partner	11		
A former civil partner	1		
A surviving civil partner	4		
Living as couple	5,668		
Total	50,697	Total	50,697

2. Replace values with different values from another variable

   This method was applied to reduce invalid responses primarily when one of the categories within a given variable indicated that this was ‘inapplicable’ (either because the question had been asked in previous wave of the UKHLS; or because the answer had already been provided by another, preceding question). The true values for these ‘inapplicable’ observations were traced and replaced using either the earlier variable from the same UKHLS Wave or a similar variable collected at a preceding Wave (in the present thesis this was only feasible for

some ‘inapplicable’ data in the NHA and/or Wave 2 datasets, for which preceding datasets were available).

One example of this is the ‘occupation’ variable, where ‘inapplicable’ data among the Five Class NS-SEC responses were replaced with another categories from other variables, as summarised in Table 3.5 (below)

Table 3.5 An example for recoded categorical variable by replacing values with different values from another categorical variable

Wave 1 Current job: Five Class NS-SEC		Wave 1 current economic activity	New employment variable	
Category	Frequency		Category	Frequency
Missing	220		Missing	592
Inapplicable	22,517	Unemployed or family care or unpaid family business or doing something else	Management & professional	11,072
			Intermediate	3,697
			Small employers & own account	2,694
Management and professional	11,270	Retired	Lower supervisory & technical	2,073
Intermediate	3,838	Full time student or government training scheme	Semi-routine, routine & never worked or long term unemployed	9,196
Small employers and own account	2,774		Unemployed	7,399
Lower supervisory and technical	2,123	Long-time sick or disabled	Retired	10,108
Semi-routine, routine and never worked long time	7,955		Student	3,866
Total	50,697			50,697

3. <u>Categorising continuous variables</u>

Some continuous variables needed to be categorised to ensure these were more meaningful (i.e. easier to apply and interpret), or to facilitate comparison between ostensibly distinct groups. For example, as we have already seen, sleep duration was categorised into three categories from a continuous variable (sleep duration in hours and minutes) in order to identify and compare participants reporting short sleep, mid-length sleep and long sleep duration (see

Table 3.6, below)

Table 3.6 An example for recoded continuous variable to categorical variable

Wave 1 sleep duration as continuous hours of sleep	Wave 1 recoded sleep duration into categories	Freq.
Sleep duration in hours as a continuous scale	Missing	12,556
	<6 hrs	4,659
	≥6-8 hrs	28,538
	> 8 hrs	4,944
	Total	50,697

4. Dichotomizing categorical variables

This method was applied to generate binary variables from categorical variables with more than two categories (so-called polytomous categorical variables). An example of this involved generating a binary variable for 'number of children adult is responsible for', where 0 reflected a participant who was responsible for no children, and 1 where the adult was responsible for one or more children (see Table 3.7, below).

Table 3.7 An example for recoded categorical variable to dichotomous variable

Wave 2 number of children aged under18 an adult responsible for		New binary variable	
Number of children	Freq.	Number of children	Frequency
Proxy	3,882	Proxy	3,882
0	40,622	0 (no child)	40,622
1	4,449		
2	3,856	1 (one or more)	10,093
3	1,320		
4	348		
5	88		
6	20		
7	8		
8	2		
9	2		
Total	54,597		54,597

5. Recoding continuous variables to a string

In UKHLS datasets dates were coded with separate variables for the interview day, the month of interview and the year of interview. It was therefore necessary to transform these into a single (string) variable in order to calculate the

'difference in time interval' for NHA, Wave 1 and Wave 2 data collection events. The procedure used in this instance is summarised in Table 3.8 (below)

Table 3.8 An example for recoded date continuous variables to a string variable

Health assessment or Wave 2 or Wave 3 interview date	New string variable
Date interview with respondent was started as date of day	A string of the date as "DMY" D: Day M: Month Y: Year
Date interview with respondent was started as month	
Date interview with respondent was started as year	

3.6 Identifying study samples

Each Wave of the UKHLS used self-administered and/or interviewer-administered questionnaires to collect a range of self-reported variables (sociodemographic, socioeconomic and health) from study participants and their households. In addition, the second Wave of the study used a questionnaire containing additional items on contemporaneous diet and lifestyle factors, and was followed by a dedicated "Nurse Health Assessment" (NHA) during which direct anthropometric, and physiological measurements and blood analyses (together with a list of all prescribed and over-the-counter medication taken) were recorded for a subsample of n=13,258 UKHLS participants. Given that the aims of the present study included comparing self-reports and direct measures of each component of MetS, and all three components combined (the formal classification of MetS adopted in the present study); and examining both objective (directly measured) and subjective (self-reported) assessments of the three key components of MetS (central obesity, diabetes and hypertension), the samples of UKHLS participants examined in the present thesis comprised those with data on self-reported sleep and either:

Sample 1: *both* self-reported and directly measured data on each MetS component (for which data should have been available for most of those participants included in the UKHLS NHA); or

Sample 2: *only* self-reported data on MetS components (for which data should have been available for all UKHLS participants).

The first of these samples (for which data on both sources of each component of MetS were potentially available) was constrained by the smaller number of UKHLS

participants selected for inclusion in the NHA; while the second of these samples (for which only data on self-reported components of MetS were required) potentially included all participants in Wave 1 of the UKHLS.

Since data from both self-reported and directly measured components of MetS were required for the analyses conducted in the present thesis, and since the self-reported sleep data necessary for inclusion in these analyses were available only for participants included at Wave 1 of the UKHLS (see section 3.3), both of the samples examined drew on participants providing data in either ***both*** Wave 2 and its associated NHA (i.e. the smaller first sample) or Wave 1 alone (i.e. the larger second sample). As such, the two samples examined can be summarised as follows:

Sample 1: Only those adult participants who were eligible for inclusion in the Wave 2 NHA who had complete data on: all seven self-reported sleep characteristics (recorded in Wave 1); self-reported MetS components (waist circumference estimated from self-reported weight and height in Wave 1; and self-reported clinical diagnoses of diabetes and hypertension recorded in Wave 2); directly measured MetS components (recorded during the NHA); and relevant self-reported covariates (sociodemographic and lifestyle from data recorded in Wave 2).

Sample 2: Only those adult participants providing data in Wave 1 who had complete data on: all seven self-reported sleep characteristics; self-reported MetS components; and relevant self-reported covariates (excluding data on lifestyle which were only recorded in the Wave 2 questionnaires).

Figures 3.4 and 3.5 summarise how each of the two sample was generated from the data available from Wave 1, Wave 2 and the NHA of the UKHLS. The identification of suitable samples for analyses involved removing any adult participants who lacked complete data on sleep characteristics, self-reported and directly measured MetS components (and MetS itself), or on the sociodemographic, economic, health and lifestyle variables. Table 3.9 summarises the distribution of all self-reported sleep characteristics, self-reported and directly measured components of MetS (and MetS itself, classified as a combination of all three) and all potential confounders including diet and lifestyle variables among Sample 1. Table 3.10 summarises the distribution of all self-reported sleep characteristics, self-reported MetS, directly measured components of MetS (and MetS itself, classified as a combination of all three) and all potential confounders among Sample 2.

Figure 3.4 A summary of the steps taken to generate Sample 1 using UKHLS participants who had completed data on sleep characteristics, directly measured MetS components, self-reported measures of MetS and relevant covariates.

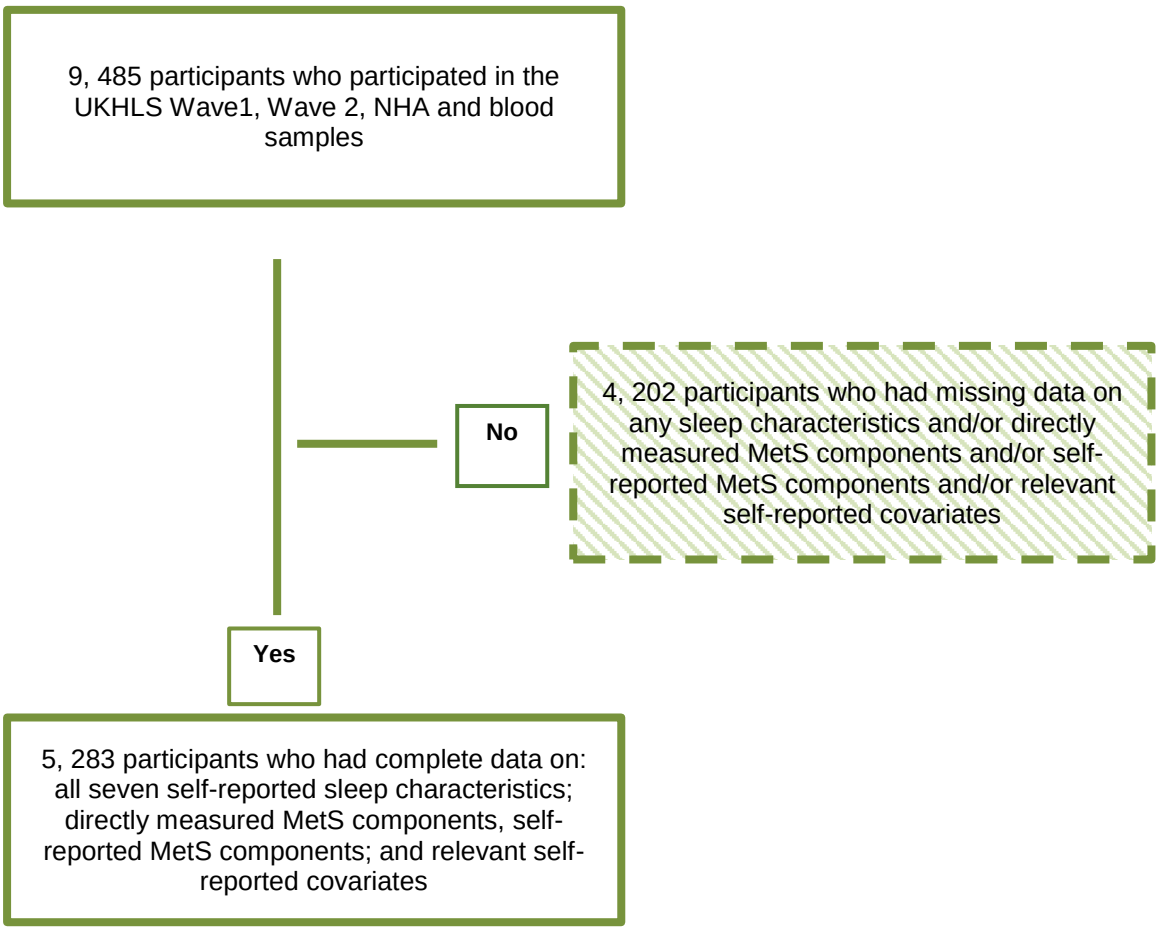


Figure 3.5 A summary of the steps taken to generate Sample 2 using UKHLS participants who had completed data on self-reported measures of MetS and sleep

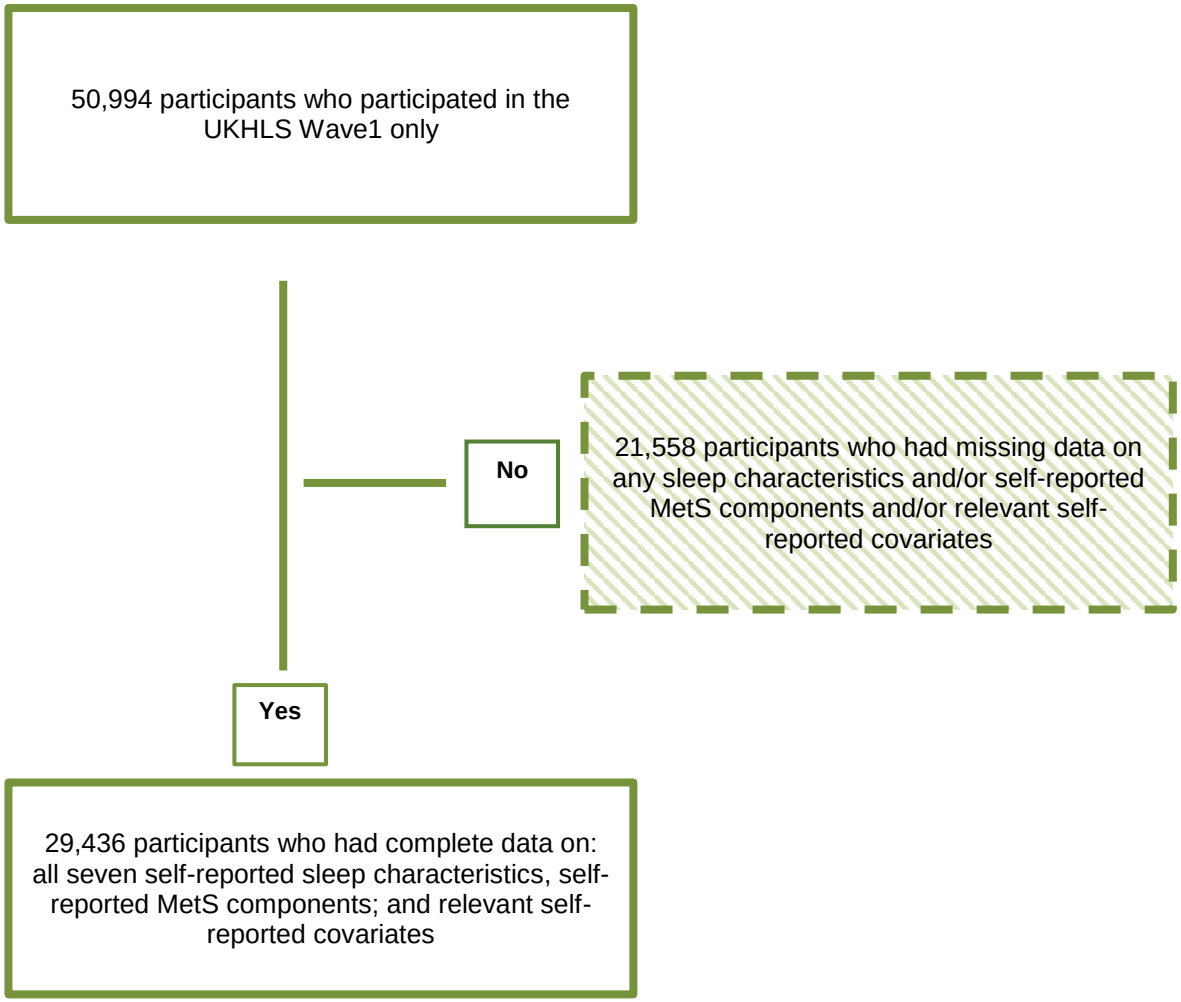


Table 3.9 Variation in the distribution of: sociodemographic and lifestyle characteristics; self-reported and directly measured MetS components (and combinations thereof); and self-reported sleep characteristics, for all adult (≥16yrs) participated in Wave 1, Wave 2 and NHA of the UKHLS (n=9,485) and complete data on all self-reported *and* directly measured variables (Sample 1; n=5,283). All variables have been categorised with the distribution across categories summarised as frequencies (n) with percentages in parentheses (%).

		UKHLS Wave 1 participants n=9,485	**Sample 1 n=5,283**
Sociodemographic characteristics			
Covariates		n (%)	n (%)
Sex	Missing	0 (0.0)	0 (0.0)
	Male	4,171 (44.0)	2,387 (45.2)
	Female	5,314 (56.0)	2,896 (54.8)
Age	Missing	0 (0.0)	0 (0.0)
	Below 30 years old	943 (9.9)	543 (10.3)
	30-39 years old	1,310 (13.8)	794 (15.0)
	40-49 years old	1,921 (20.2)	1,154 (21.8)
	50-59 years old	1,838 (19.4)	1,107 (20.9)
	60years or older	3,473 (36.6)	1,685 (32.0)
Marital/cohabitation status	Missing	0 (0.0)	0 (0.0)
	Single	1,282 (13.5)	689 (13.0)
	Cohabited	6,502 (68.5)	3,841 (72.7)
	Separated and Divorced	997 (10.5)	507 (9.6)
	Widowed	704 (7.4)	246 (4.7)
Educational attainment	Missing	9 (0.1)	0 (0.0)
	Degree	2,123 (22.4)	1,332 (25.2)
	Other higher degree	1,290 (13.6)	777 (14.7)
	A-level	1,709 (18.0)	1,001 (19.0)
	GCSE	1,845 (19.4)	1,080 (20.4)
	Other qualification	1,104 (11.6)	538 (10.2)
	No qualification	1,405 (14.8)	555 (10.5)
Employment status	Missing	77 (0.8)	0 (0.0)
	Management and professional	2,205 (23.2)	1,485 (28.1)
	Intermediate	719 (7.6)	460 (8.7)
	Small employers and own account	514 (5.4)	284 (5.4)

	Lower supervisory and technical	398 (4.2)	252 (4.8)
	Semi-routine, routine and never worked long-term	1,608 (16.9)	850 (16.1)
	Unemployed	915 (9.6)	510 (9.6)
	Retired	2,815 (29.7)	1,284 (24.3)
	Student	234 (2.5)	158 (3.0)
Household structure[1]	Missing	4 (0.0)	0 (0.0)
	Empty nesters	5,680 (59.9)	3,139 (59.5)
	Dwelling sharing childless adults	1,137 (12.0)	550 (10.4)
	Partnered with child	1,241 (13.1)	779 (14.8)
	Partnered with children	593 (6.2)	355 (6.7)
	Large family, majority with overcrowding	347 (3.7)	208 (3.9)
	Single parent household	310 (3.3)	164 (3.1)
	Extended family, majority with overcrowding	173 (1.8)	84 (1.6)
Daily number of servings of fruit and vegetables consumed	Missing	70 (0.7)	0 (0.0)
	1	732 (7.7)	383 (7.2)
	2	2,013 (21.2)	1,079 (20.4)
	3	2,407 (25.4)	1,370 (25.9)
	4	1,823 (19.2)	1,054 (20.0)
	5	1,631 (17.2)	939 (17.8)
	6 and more	809 (8.5)	458 (8.7)
Sport activity ranking	Missing	4 (0.0)	0 (0.0)
	no sport at all	2,460 (25.9)	1,145 (21.7)
	1-2	1,724 (18.2)	979 (18.5)
	3-4	1,836 (19.4)	1,076 (20.4)
	5-6	1,820 (19.2)	1,069 (20.2)
	7-very active	1,641 (17.3)	1,014 (19.2)
Smoking status	Missing	7 (0.1)	0 (0.0)
	Never smoke	3,771 (39.8)	2,134 (40.4)
	Quit smoking	3,854 (40.6)	2,216 (41.9)
	Smoke less than 10 cig/day	556 (5.9)	305 (5.8)
	Smoke 10-20 cig/day	1,136 (12.0)	559 (10.6)
	Smoke more than 20 cig/day	161 (1.7)	69 (1.3)
Alcohol consumption during the last 12	Missing	985 (10.4)	0 (0.0)

months	almost every day	811 (8.5)	502 (9.5)
	five or six days a week	530 (5.6)	348 (6.6)
	three or four days a week	1,356 (14.3)	892 (16.9)
	once or twice a week	2,418 (25.5)	1,550 (29.3)
	once or twice a month	1,260 (13.3)	777 (14.7)
	once every couple of months	745 (7.8)	475 (9.0)
	once or twice a year	740 (7.8)	402 (7.6)
	not at all in the last 12 months	640 (6.7)	337 (6.4)
Self-reported sleep characteristics			
Sleep duration	Missing	1,303 (13.7)	0 (0.0)
("…hours of actual sleep did you usually get	<6 hrs	1,010 (10.6)	582 (11.0)
at night during the last month?")	6-8 hrs	6,318 (66.6)	4,159 (78.7)
	>8 hrs	854 (9.0)	542 (10.3)
Sleep latency	Missing	1,640 (17.3)	0 (0.0)
("…trouble sleeping because you cannot	Not during the past month	3,156 (33.3)	2,210 (41.8)
get to sleep within 30 minutes?")	During the past month	4,689 (49.4)	3,073 (58.2)
Sleep fragmentation	Missing	1,394 (14.7)	0 (0.0)
("…trouble sleeping because you wake up	Not during the past month	1,472 (15.5)	1,049 (19.9)
in the middle of the night or early in the	During the past month	6,619 (69.8)	4,234 (80.2)
morning?")			
Coughing/snoring loudly	Missing	2,324 (24.5)	0 (0.0)
("…trouble sleeping because you cough or	Not during the past month	4,367 (46.0)	3,291 (62.3)
snore loudly?")	During the past month	2,794 (29.5)	1,992 (37.7)
Sleep medication	Missing	1,054 (11.1)	0 (0.0)
("…taken medicine [prescribed or over-the-	Not during the past month	7,029 (74.1)	4,475 (84.7)
counter] to help you sleep?")	Presence of the event	1,402 (14.8)	808 (15.3)
Daytime sleepiness	Missing	1,067 (11.3)	0 (0.0)
("…had trouble staying awake while driving,	Not during the past month	7,184 (75.7)	4,531 (85.8)
eating meals, or engaging in social	During the past month	1,234 (13.0)	752 (14.2)
activity?")			
Sleep quality	Missing	986 (10.4)	0 (0.0)
("During the past month how would you rate	Good quality	2,050 (21.6)	1,332 (25.2)
your sleep quality overall?")	Poor quality	6,449 (68.0)	3,951 (74.8)
Metabolic Syndrome (MetS)			
Self-reported MetS components	Missing	516 (5.4)	0 (0.0)

	Elevated waist circumference (EWC)	1,826 (19.2)	1,101 (20.8)
	High blood pressure (HBP)	672 (7.1)	350 (6.6)
	Diabetes (DM)	128 (1.3)	57 (1.1)
	EWC and HBP	645 (6.8)	322 (6.1)
	EWC and DM	172 (1.8)	73 (1.4)
	HBP and DM	90 (0.9)	34 (0.6)
	EWC and HBP and DM	181 (1.9)	93 (1.8)
	None	5,255 (55.4)	3,253 (61.6)
Directly measured MetS components	Missing	1,076 (10.9)	0 (0.0)
	Elevated waist circumference (EWC)	2,347 (23.7)	1,453 (27.5)
	High blood pressure (HBP)	704 (7.1)	386 (7.3)
	Diabetes (DM)	61 (0.6)	23 (0.4)
	EWC and HBP	1,064 (10.7)	606 (11.5)
	EWC and DM	163 (1.7)	93 (1.8)
	HBP and DM	84 (0.8)	39 (0.7)
	EWC and HBP and DM	269 (2.7)	132 (2.5)
	None	4,137 (41.8)	2,551 (48.3)

Table 3.10 Variation in the distribution of: sociodemographic; self-reported measured MetS components (and combinations thereof); and self-reported sleep characteristics, for all adult (≥16yrs) participated in Wave 1 (n=50,994) and complete data on all self-reported measured variables (Sample 2; n=29,436). All variables have been categorised with the distribution across categories summarised as frequencies (n) with percentages in parentheses (%).

		UKHLS Wave 1 participants n=50,994	**Sample 2 n=29,436**
Sociodemographic characteristics			
Covariates		n (%)	n (%)
Sex	Missing	0	0 (0.0)
	Male	23,208 (45.5)	13,673 (46.5)
	Female	27,786 (54.5)	15,763 (53.5)
Age	Missing	0 (0.0)	0 (0.0)
	Below 30 years old	11,543 (22.6)	7,085 (24.1)
	30-39 years old	9,317 (18.3)	5,784 (19.6)
	40-49 years old	9,707 (19.0)	5,855 (20.0)
	50-59 years old	7,683 (15.1)	4,430 (15.0)
	60years or older	12,744 (25.0)	6,282 (21.3)
Marital/cohabitation status	Missing	17 (0.1)	0 (0.0)
	Single	12,009 (23.5)	6,972 (23.7)
	Cohabited	31,642 (62.0)	18,849 (64.0)
	Separated and Divorced	4,319 (8.5)	2,373 (8.1)
	Widowed	3,007 (5.9)	1,242 (4.2)
Educational attainment	Missing	92 (0.2)	0 (0.0)
	Degree	10,954 (21.5)	7,428 (25.2)
	Other higher degree	5,537 (10.9)	3,559 (12.1)
	A-level	9,591 (18.8)	6,011 (20.4)
	GCSE	10,526 (20.6)	6,201 (21.1)
	Other qualification	5,225 (10.2)	2,677 (9.1)
	No qualification	9,069 (17.8)	3,560 (12.1)
Employment status	Missing	593 (1.2)	0 (0.0)
	Management and professional	11,121 (21.8)	7,731 (26.3)
	Intermediate	3,713 (7.3)	2,451 (8.3)
	Small employers and own account	2,709 (5.3)	1,588 (5.4)

	Lower supervisory and technical	2,080 (4.1)	1,345 (4.6)
	Semi-routine, routine and never worked long-term	9,257 (18.1)	5,050 (17.2)
	Unemployed	7,448 (14.6)	3,875 (13.2)
	Retired	10,171 (20.0)	4,994 (17.0)
	Student	3,902 (7.6)	2,402 (8.2)
Household structure[1]	Missing	65 (0.1)	0 (0.0)
	Empty nesters	24,710 (48.5)	14,302 (48.6)
	Dwelling sharing childless adults	8,240 (16.2)	4,530 (15.4)
	Partnered with child	7,465 (14.6)	4,745 (16.1)
	Partnered with children	3,175 (6.2)	1,998 (6.8)
	Large family, majority with overcrowding	3,369 (6.6)	1,709 (5.8)
	Single parent household	2,181 (4.3)	1,262 (4.3)
	Extended family, majority with overcrowding	1,789 (3.5)	890 (3.0)
Self-reported sleep characteristics			
Sleep duration ("…hours of actual sleep did you usually get at night during the last month?")	Missing	12,620 (24.8)	0 (0.0)
	<6 hrs	4,716 (9.2)	3,223 (11.0)
	6-8 hrs	28,684 (56.2)	22,344 (75.9)
	>8 hrs	4,974 (9.8)	3,869 (13.1)
Sleep latency ("…trouble sleeping because you cannot get to sleep within 30 minutes?")	Missing	13,893 (27.2)	0 (0.0)
	Not during the past month	15,228 (29.9)	12,489 (42.4)
	During the past month	21,873 (42.9)	16,947 (57.6)
Sleep fragmentation ("…trouble sleeping because you wake up in the middle of the night or early in the morning?")	Missing	13,230 (25.9)	0 (0.0)
	Not during the past month	8,538 (16.8)	7,272 (24.7)
	During the past month	29,226 (57.3)	22,164 (75.3)
Coughing/snoring loudly ("…trouble sleeping because you cough or snore loudly?")	Missing	16,997 (33.3)	0 (0.0)
	Not during the past month	21,378 (41.9)	18,823 (64.0)
	During the past month	12,619 (24.8)	10,613 (36.0)
Sleep medication ("…taken medicine [prescribed or over-the-counter] to help you sleep?")	Missing	11,215 (22.0)	0 (0.0)
	Not during the past month	32,827 (64.4)	24,777 (84.2)
	Presence of the event	6,952 (13.6)	4,659 (15.8)
Daytime sleepiness ("…had trouble staying awake while driving,	Missing	11,269 (22.1)	0 (0.0)
	Not during the past month	33,469 (65.6)	24,808 (84.3)

eating meals, or engaging in social activity?")	During the past month	6,256 (12.3)	4,628 (15.7)
Sleep quality	Missing	10,773 (21.1)	0 (0.0)
("During the past month how would you rate	Good quality	9,954 (19.5)	7,566 (25.7)
your sleep quality overall?")	Poor quality	30,267 (59.4)	21,870 (74.3)
Metabolic Syndrome (MetS)			
Self-reported MetS components	Missing	6,763 (13.3)	0 (0.0)
	Elevated waist circumference (EWC)	8,489 (16.7)	5,611 (19.1)
	High blood pressure (HBP)	2,672 (5.2)	1,514 (5.1)
	Diabetes (DM)	574 (1.1)	325 (1.1)
	EWC and HBP	2,510 (4.9)	1,415 (4.8)
	EWC and DM	704 (1.4)	370 (1.3)
	HBP and DM	423 (0.8)	217 (0.7)
	EWC and HBP and DM	726 (1.4)	393 (1.3)
	None	28,133 (55.2)	19,591 (66.5)

3.7 Implications of missing data

Missing data can be a substantial problem in epidemiological studies involving human participants. Despite researchers' best efforts, missing data arise due to respondents refusing or forgetting/being unable to answer questions, or due to participants withdrawing/dropping out of the study. It may also occur where researchers forget to include questions/items at relevant points within the data collection tools, or simply due to errors in data collection, collation and/or transcription (Raghunathan 2004; Brick and Kalton 1996).

Missing data are important because analysing datasets with missing observations can lead to a number of problems, ranging from reduced statistical power (and hence increased random error), to unrepresentative and biased estimates (Sterne *et al.* 2009; Brick and Kalton 1996). The variety and extent of the impact depends on a combination of the proportion of the sample affected, and the reason(s) why the data are missing. Missing data are typically categorised as being either missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR); (Kim and Curry 1977). Data are MCAR when there is no systematic reason for the missingness such that the group with complete data are an unbiased subsample of the total dataset. For MCAR data, the only concern is therefore the loss of statistical power. Data are MAR when it is more likely to be missing in certain groups (e.g. men from more deprived socioeconomic circumstances) or for certain reasons which have been observed. MAR data may produce biased estimates unless the uneven pattern of missingness can be accounted for. Data are MNAR when it is more likely to be missing in certain groups or for certain reasons which have not been observed. MNAR data may produce biased estimates, for which there are currently no clear or effective solutions (Pigott 2001; Rubin 1976; Kim and Curry 1977).

The nature of the missingness, i.e. whether the data are MCAR, MAR or MNAR, determines the most appropriate method of handling and analysing the data. Unfortunately, it can be difficult to distinguish between these types, and MNAR can never be formally excluded (since it depends on data which, by definition, have not been collected; (Pigott 2001). Several methods are available for handling missing data. By far the most common approach is list wise deletion, also known as complete case analysis, yet epidemiologists are increasingly using a more sophisticated approach known as multiple imputation (MI).

3.7.1 Complete case analysis

A complete case analysis involves the exclusion of all participants where data are missing for any of the variables under examination (Saunders *et al.* 2006). The advantage of this method is its simplicity, since no further data manipulation is required before analysis. For that reason, most statistical packages, including Stata (the statistical software used in the present thesis) will conduct a complete case analysis for most procedures (such as logistic regression) by default, and without warning (Pigott 2001).

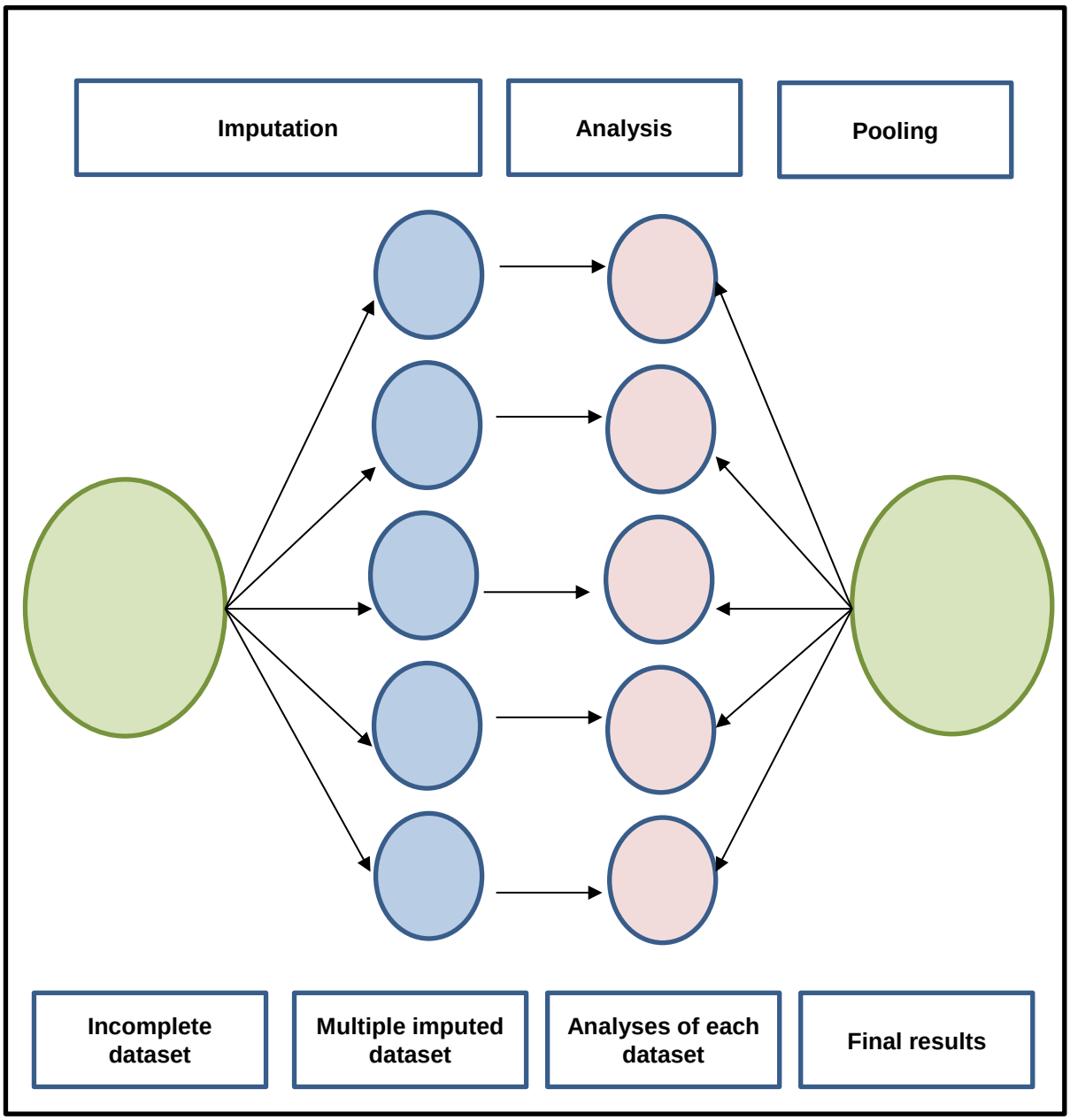
Complete-case analyses are appropriate where only a few cases are missing and the sample size is sufficiently large, since there is likely to be a limited impact on the statistical power, and the remaining sample (i.e. after the exclusion the small proportion of participants with missing data) is likely to still be broadly representative of the population (Schafer and Graham 2002; Saunders *et al.* 2006; Kim and Curry 1977). Conversely, when there are large amounts of missing data, complete-case analyses are prone to inferential bias (since the sample may not be representative of the population) and to increased random error (Pigott 2001).

To resolve bias resulting from data that are MAR a more sophisticated approach is required, such as inverse-probability weighting or multiple imputation, the latter of which can also increase the statistical power.

3.7.2 Multiple imputation

Multiple imputation (MI) is a computational technique for analysing data with missing values, which aims to minimise bias and maximise precision. Like traditional, or 'single imputation', missing values for individual variables are predicted from other observed variables. These predicted (imputed) values are used to replace missing values and create a new imputed dataset. Direct analysis of these singly imputed data would produce less biased estimates than the incomplete data, but with greatly inflated precision; since there is no accounting for the uncertainty of the prediction. To account for this, multiple imputation repeats the process several times, with each imputed dataset taking different values from the distribution of predicted values, such that as a group they reflect the uncertainty of the estimate. Each imputed dataset is then analysed individually (although this process is typically automated) and the results pooled to incorporate the uncertainty between datasets (Wayman 2003; Sterne *et al.* 2009) (Figure 3.6).

Figure 3.6 Diagrammatic representation of multiple imputation. Figure adapted from *Missing Data and Multiple Imputation in Clinical Epidemiology Research* (Pedersen *et al.* 2017)



Multiple Imputation for Multivariate Data

Multivariate missing data can occur when there are missing values in more than one variable in the dataset. In this scenario, the predictors required for the imputation themselves have missing values; predicting these may in turn be dependent on other variables with missing values. This is further complicated by the range of potential variable types, e.g. continuous, binary, nominal and ordinal (Van Buuren and Oudshoorn 1999; Van Buuren *et al.* 2006). In general, two approaches are employed to address the challenge of imputing multivariate missing data, these are joint modelling (JM) MI and fully conditional specification (FCS) MI - also known as MI by chained equations (MICE) (Kropko *et al.* 2014; Van Buuren 2007).

In JM MI, a single predictive model is applied for all multivariate missing data. This typically includes a set of correlated complete predictor variables as well as the incomplete variables to be imputed; in this case the same model is applied for both imputation and analysis afterwards. One benefit of this approach is it is not too computationally demanding. However, this method has some drawbacks, especially in the presence of a mix of variable types (e.g. binary, categorical or continuous), where the results are prone to bias (Van Buuren 2007; Kropko *et al.* 2014).

FCS on the other hand permits each variable to be predicted by its own model. The immediate benefit is that this allows the correct parameterisation of variables taking different forms, e.g. linear variables with linear regression, binary with logistic regression, nominal with multinomial logit regression, and ordinal with ordered logit regression (Van Buuren *et al.* 2006; Van Buuren 2007; Kropko *et al.* 2014). Computationally, however, this approach is particularly demanding - since it involves iteratively repeating each model (hence 'chained') with ever improving estimates until the values stabilise.

MI model specification

As with all predictive models, specification of the multiple imputation model is important to avoid inaccurately imputed values and biased results. This can be achieved through applying different principles.

- To maximise the chances that the data are MAR nor MNAR, the imputation model should draw on as much observed information as possible. However, including more than 15 to 25 variables can create problems with multicollinearity (Van Buuren, Boshuizen and Knook 1999).
- The imputation model should include all the variables that will be included in the analysis model, including the outcome variable (Moons *et al.* 2006).

- All variables that help with predicting missing values - including those that are not essential for the analysis (so-called 'auxiliary variables') should be included in the imputation model. (Hsu *et al.* 2006).
- As with the analytical model, any relevant and necessary interaction terms and non-linear transformations should be included in the imputation model (White, Royston and Wood 2011).
- Since the distribution of imputed estimates tend to be normally distributed, non-normal continuous variables should be transformed to an approximate normal distribution before the imputation. Prior to conducting the analyses, these imputed values can be easily transformed back to their original scale (White, Royston and Wood 2011).

Unfortunately, the substantial number of UKHLS participants with missing data in Wave 1, 2 and the NHA, and the large number of variables under examination, made it impractical to perform multiple imputation with any of the data in the present thesis. It was hoped that a sensitivity analysis could at least be performed to compare the observed data to those generated using multiple imputation. MICE was therefore attempted on the models described in Chapter 4, but Stata IC 14.2 was unable to even store the required number of estimates for chaining to be performed. Even when selecting a reduced variable set, the computational demand was so high as to make the approach entirely impractical in the context of the UKHLS given current computing power. While the computational demand could have been reduced using a simpler multivariate imputation method, such as JM, the mix of variable types (binary, ordinal, and nominal) makes this equally unhelpful. It was therefore decided that all analyses would rely on a complete-case analysis. To evaluate the risk of bias, and the plausibility of the MCAR assumption, the present thesis focussed carefully on examining the differences between the included and excluded cases (as described in detail within the ‘results’ chapter, Chapter 4). Only modest signs of predictable missingness were generally identified, suggesting that any resultant bias should be small. No method can of course discount the possibility of MNAR, and the inability to perform a confirmatory MI analysis means that the specific effects estimates (and the generalisability of these to the UKHLS population, and to other populations) should be viewed with caution.

3.8 Statistical methods and data analysis

3.8.1 Analysis approach

As introduced earlier (see Chapter 1: *Introduction*), the analytical designs adopted in the present thesis were informed by causal path diagrams in the form of DAGs (see also Chapter 2 section 2.3.5).

3.8.2 Statistical software

All analyses were performed using Stata software. However, in order to deal with the large dataset, and to allow merging data from more than one Wave of the UKHLS, Stata/SE was used in preference to Stata/IC (the latter only capable of managing moderate-sized datasets). For this reason, a single-user Stata/SE (version 13; StataCrop 2013) was purchased and installed on the University desktop C-drive (StataCrop 2013).

3.8.3 Descriptive analyses

In order to summarise the distribution of variables amongst each of the (incomplete- and complete-data) samples of UKHLS participants examined in the present thesis, descriptive analyses were extensively used. In these analyses, continuous variables were summarised by calculating the mean and standard deviation (SD); while categorical variables were summarised as frequencies with percentages in parentheses (%)

3.8.4 Accuracy analysis

Before relying on 'self-reported' data as plausible measures of each of the three MetS components (and for classifying MetS based thereon), the present thesis considered it important – and (given the availability of directly measured data from a substantial subsample of participants in the Wave 2 NHA) meaningful – to evaluate the extent to which these (self-reported) data might accurately reflect (and/or deviate from) the results obtained from direct measures thereof. For this reason, a range of different measures of accuracy were chosen for use in the analysis summarised in Chapter 4 (Part I) (*How reliable are self-reported indicators of elevated waist circumference, diabetes and high blood pressure and classifications of MetS based thereon?*) to assess whether the two sources of MetS data (self-reports vs. directly measured) agree to a sufficient degree to warrant further use in the analyses summarised in the same Chapter. The measures of agreement used were: sensitivity; specificity; positive and negative predictive values (PPV and NPV); total agreement; and Cohen's kappa statistic.

3.8.4.1 Sensitivity, Specificity, PPV and NPV

Sensitivity is defined as the ability of a measurement to correctly identify true positives. In the present thesis it represents the proportion of those participants who tested positive for each component/classification of directly measured MetS that was correctly identified by self-reported measures thereof. Specificity is defined as the ability of a measurement to correctly identify true negatives. In the present thesis, this is the proportion of those participants who tested negative for each component/classification of directly measured MetS that was correctly identified by self-reported measures thereof (Peacock and Peacock 2011; Lalkhen and McCluskey 2008).

PPV is the proportion of those who actually have the condition (i.e. who are 'positive' according to direct measures) among those whose self-reports are 'positive' (where 'positive' means the presence of a component/classification of MetS). Likewise, NPV is the proportion of those who actually do not have the condition (i.e. who are 'negative' according to direct measures) among those whose self-reports are 'negative' (where 'negative' means the absence of a component/classification of MetS; (Peacock and Peacock 2011; Lalkhen and McCluskey 2008).

In general, a measure with high sensitivity will correctly identify individuals with the condition, and a test with high specificity will correctly identify individuals who do not have the condition. However, in practice, measures are unlikely to have both high sensitivity and high specificity (Peacock and Peacock 2011). Alternatively, a good test can have high sensitivity and low specificity or low sensitivity and high specificity, in this case all false positives ('negative' according to direct measures but 'positive' according to self-reports) will be identified as free of the condition (Lalkhen and McCluskey 2008).

3.8.4.2 Overall agreement and kappa statistics

The overall agreement is calculated as the proportion of cases for which different measures agree (in respect of *both* 'present' or 'absent' conditions) – the different measures in this instance being those based on self-reports of MetS components and a classification of MetS itself based on these; and those based on direct measures of MetS components and a classification of MetS itself based on these. However, the notion of 'overall agreement' tends to be misleading since it ignores the possibility of agreement simply by chance. It is therefore recommended that overall agreement and Cohen's kappa are used together (Peacock and Peacock 2011), since Cohen's kappa is an agreement-related parameter that assesses the extent of agreement between different measures that takes into account the likelihood of agreement simply by

chance (Peacock and Peacock 2011; Campbell, Machin and Walters 2010; Viera and Garrett 2005). Interpreting different values of Cohen's kappa tends to be based on somewhat arbitrary criteria, such as that suggested by (Viera and Garrett 2005); for instance Kappa <0 is considered to indicate poor agreement which is less than chance agreement, 0.01-0.20 slight agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 substantial agreement; and 0.81-0.99 almost perfect agreement.

3.8.5 Regression analysis

Regression involves fitting a model comprising a dependent variable (the 'outcome') and the independent variable ('exposure'), with the form of regression used (be this linear or logistic) dependent on the form in which the exposure and outcome variables are available/measured (Chap 2003).

In the present study logistic regression analysis was applied in Chapter 4. Logistic regression models are applied when the dependent variable is categorical (and more usually, dichotomous) such as diseased Yes/No. It is used when the aim of the analyses is to assess whether an event or condition occurred or not. Logistic regression uses logarithmic transformation to allow a linear relationship to be predicted (using the maximum likelihood statistic). The regression coefficients produced can then be presented in the form of odds ratios (ORs) – the ratio of the odds that an event/condition occurred to the odds that it did not (Chap 2003) . The OR can vary from 0 to infinity, with a value of 1.00 being the null value (i.e. those 'exposed' having no different odds of the outcome to those who were not 'exposed'). An OR of <1 can be interpreted as those with the 'exposure' being associated with a lower odds of having the outcome; while an OR>1 can be interpreted as those with the 'exposure' being associated with a higher odds of having the outcome.

In the subsequent analysis/results chapter (i.e. Chapter 4), univariable logistic regression models were initially applied to generate unadjusted ORs with their respective 95% confidence intervals (CI). These were then followed by models including covariate adjustment sets (of variables considered potential confounders) to generate (confounder-) adjusted ORs, again with their respective 95%Cis (Chap 2003).

When the dependent (outcome) variable was polytomous (i.e. had more than two categories with no natural order amongst them), multinomial logistic regression was used. Multinomial logistic regression is an extension of logistic regression that breaks the regression into a series of binary regressions and compares each group to a base group comprising the referent category for the dependant variable (Dobson and Barnett 2008). Estimates generated using multinomial logistic regression can be

expressed as relative risk ratios (RRR) with their 95% (CI), where each category can be interpreted in a similar way to the OR with reference to the base category.

3.9 Summary and conclusion

The present Chapter successfully identified both a suitable dataset for assessing the relationship between sleep and MetS in a contemporary UK-based population (the UKHLS), and one that also offered suitable items for generating 'self-reported' measures of each of the MetS components (elevated waist circumference [estimated from self-reported height and weight), diabetes and high blood pressure) and a classification of MetS based thereon. This Chapter also successfully identified suitable items within the UKHLS datasets that offered 'direct' measures of each of the MetS components (elevated waist circumference, diabetes and high blood pressure) and a classification of MetS based thereon. Finally, this Chapter successfully identified two different samples with data on: self-reported sleep characteristics and either self-reported and directly measured MetS (Sample 1); or only self-reported measures of MetS (Sample 2) suitable for analysis in the subsequent chapter (Chapter 4). The source, forma, manipulation and analysis of these data are also described in some detail, as is consideration of the potential impact of high rates of missingness for data pertaining to both Sample 1 and 2,

Looking ahead to the next chapter (Chapter 4), this contains empirical analyses that aim to address many of the shortcomings identified in Chapter 2: (*A Systematic review of previous studies examining the relationship between sleep and MetS*), by analysing the association between MetS and no fewer than seven different sleep-related characteristics, using self-reported and directly measured data from a single, large contemporary study – the UK Household Longitudinal Study (UKHLS); analyses in which covariate adjustment was carefully specified with reference to a DAG. As such, Chapter 4 provides the first study to examine the association between MetS and sleep in the UK. It is also the first such study to use causal path diagrams (in the form of directed acyclic graphs; DAGs) to identify which of the variables available within the UKHLS might be necessary to include as potential confounders in any covariate adjustment sets. However, before proceeding to these analyses, Chapter 4 (Part I) examines the potential utility of developing and using self-reported data to generate valid measures of MetS components (and a classification of MetS itself, based thereon) – data that are likely to extend the scope and statistical power of future studies examining the association between MetS and sleep to those datasets (like the UKHLS) where there are large(r) samples of participants with (self-reported) data on the symptoms/components of MetS. As such, Chapter 4 will establish whether the

limited evidence generated by the n=21 studies examined in the review (Chapter 2), might be extended to include the wealth of data available within existing cross-sectional datasets containing relevant self-reported data on sleep and on variables offering valid indicators of MetS-related symptoms/components.

Chapter 4 Results

The present Chapter draws on the analysis of previous cross-sectional studies exploring the association between MetS and sleep (Chapter 2: *A systematic review of cross-sectional studies examining the association between MetS and sleep*) in which none of these studies were found to have been conducted in the UK or to have used self-reports of any MetS components (nor classifications of MetS based on self-reported MetS components). To this end, one of the aims of Chapter 3 (*Data Sources and Analytical Methods*) was to identify any suitable items in the UKHLS datasets which might offer a suitable basis for generating 'self-reported' measures of each of the MetS components (elevated waist circumference, diabetes and high blood pressure) for which direct measures were known to have been collected during the UKHLS Nurse Health Assessment (NHA). Chapter 3 identified two items in the main questionnaire used in Wave 1 (the UKHLS Wave in which self-reported sleep data were collected for the first time) capable of identifying participants who recalled/reported that they had been told "by a doctor or other health professional" that they had "high blood pressure" and/or "diabetes". However, no comparable items on elevated waist circumference or dyslipidaemia were found, although items requesting self-reports of height and weight were available in the Wave 1 questionnaire (the only Wave to-date in which these items have been included), and by using these together with direct measures of height, weight and waist circumference, Chapter 3 generated suitable equations (stratified by age and sex) with which to estimate waist circumference from self-reports of height and weight, and therefore generate estimates of 'self-reported' waist circumference.

In the present Chapter, Part 1 takes the development and evaluation of these self-reports and direct measures of the three key components of MetS (and a classification of MetS itself based on the presence of all three) one step further, by comparing these different measures to assess the potential validity and utility of self-reported MetS. As such, under Part 2, the present Chapter draws on (and seeks to address) each of the methodological limitations of the previous studies examined in Chapter 2; and on the development (and evaluation) of self-reported indicators of three key MetS components. The findings generated from each of these preceding Chapters are then brought to bear on data collected from the UK Household Longitudinal Study (UKHLS), to generate a more comprehensive understanding of the evidence provided by previous cross-sectional analyses of the relationship between MetS and sleep.

Part I

4.1 How reliable are self-reported indicators of elevated waist circumference, diabetes and high blood pressure and classifications of MetS based thereon?

4.1.1 Aim and objectives

The key aim of this Part of the present Chapter was to evaluate the potential utility of self-reported indicators as measures of three key components of MetS (elevated waist circumference, high blood pressure and diabetes; and a classification of MetS based on a combination of all three of these components) by:

using analyses of sensitivity, specificity, positive predictive value, negative predictive value, overall agreement and Cohen's kappa (κ) to evaluate the validity of self-reported MetS components (and a classification of MetS based on a combination of all three components) as compared to direct measures thereof;

As such, Part I of the present Chapter sought to address the following key question as established at the outset of this thesis:

KQ3: "To what extent might self-reported items relevant to identifying MetS in large datasets offer sufficiently valid measures of MetS symptoms/components to provide a basis upon which to generate a 'self-reported' classification of MetS suitable for use in population-based analyses where direct measures of MetS components are not available/feasible?"

4.1.2 Methods

The present Chapter (Part I) drew on Sample 1 (see Chapter 3) of the UKHLS comprising participants who had data on *both* self-reported *and* directly measured MetS components; and data on all relevant sociodemographic, economic, health, lifestyle and sleep parameters – data that had been collected primarily by questionnaire, or during the Nurse Health Assessment, in Wave 2; while relying on self-reports of sleep and self-reports of height and weight (which, as described in Chapter 3:, were necessary to generate estimates of self-reported waist circumference) from items that had only been included in UKHLS questionnaires at Wave 1.

4.1.2.1 Self-reported indicators of MetS components the classification of MetS (itself) based thereon

Four different self-reported indicators were identified within the UKHLS questionnaires for which Part I of the present Chapter was able to assess their agreement with direct measurements thereof:

1. 'Elevated waist circumference' (EWC) based on estimates of reported waist circumference (WC) generated from self-reports of height and weight (as described in Chapter 3), with cut-offs for *elevated* WC based on those proposed by the NCPI-ATP III MetS definition: WC ≥ 102cm for males; WC ≥ 88cm for females.
2. Self-reports of clinically diagnosed high blood pressure, generated by items available in both Wave 1 and Wave 2 UKHLS questionnaires ("Has a doctor or other health professional ever told you that you have… high blood pressure" and "Do you still have high blood pressure?").
3. Self-reports of clinically diagnosed diabetes, generated by the same bank of questions as that for high blood pressure (see 2, above).
4. A classification of 'self-reported MetS' based on a combination of all three (self-reported) components of MetS (i.e. 1-3, above).

More detail on why these indicators were considered a suitable basis for generating self-reported measures of these three key MetS components is provided in Chapter 3 (section 3.4.4)

4.1.2.2 Directly measured MetS components and the classification of MetS (itself) based thereon

Four different sets of direct measurements were identified from those collected during the UKHLS NHA as suitable for use as 'direct measures' of the same three components of MetS, and the combination of all three. These measurements form the basis upon which the present Chapter examined the potential validity of self-reports described earlier (see 4.3.2, above):

1. 'Elevated waist circumference' (EWC) based on direct measurements of waist circumference (WC) undertaken as part of the suite of anthropometric measurements collected during the NHA, with cut-offs for elevated WC again based on those proposed by the NCPI-ATP III MetS definition: WC ≥ 102cm for males, WC ≥ 88cm for females.
2. 'High blood pressure' (HBP) based on direct measurements of systolic and diastolic blood pressure, classified as 'high' BP according to the diagnostic cut-

offs (BP ≥140/90 mmHg) recommended by the UK's National Institute of Clinical Excellence (NICE; and thereby the same criteria as those underpinning the clinical diagnosis of high blood pressure in the UK NHS, on which valid self-reports of a clinical diagnosis of HBP would have been based) *and/or* the inclusion of antihypertensive medication in the records of all prescribed medication made during the NHA.

3. Diabetes based on the analysis of non-fasting blood samples (collected during the NHA) for HbA1c, again using the cut-off recommended by the UK's NICE (HbA1c ≥ 48 mmol/mol) as sufficient for the diagnosis of diabetes (and therefore one of the criteria underpinning the clinical diagnosis of diabetes in the UK NHS, on which valid self-reports of diabetes diagnosis would have been based), *and/or* the inclusion of antidiabetic medication in the records of all prescribed medication made during the NHA.
4. MetS classification based on a combination of all three directly measured components of MetS (as described in 1-3, above).

Once again, more details on the direct measurements involved in collecting data on each of these components of MetS is provided in Chapter 3 (section 3.4.3)

4.1.3 Statistical analysis plan

Preliminary descriptive analyses were performed to describe the distribution of self-reported and directly measured MetS components (and MetS itself) amongst Sample 1 (as described earlier) and to compare these distributions with those observed amongst UKHLS participants examined in Wave 1, Wave 2 and/or the NHA (i.e. all participants recruited by the UKHLS up to and including the NHA). These descriptive analyses were summarised as frequencies with percentages in parentheses (%), or as mean values with standard deviations in parentheses (SD).

Further details of the descriptive analytical techniques chosen for use in the present Chapter have been provided in Chapter 3 (section 3.8.3).

To assess the extent to which self-reported measures of the three key MetS components (and the classification of MetS itself based on a combination of these) differ from those directly measured, a range of different tests (many designed for use in diagnostic tests) were applied. These comprised tests of sensitivity, specificity, positive and negative predictive values (PPV and NPV), total agreement and tests using the Cohen's kappa statistics. More details of these analyses have been described earlier in Chapter 3 (section 3.8.4).

4.1.4 Results

4.1.4.1 The distribution of self-reported and directly measured MetS components amongst Sample 1

Table 4.1 summarises the distribution of self-reported and directly measured MetS components (and MetS itself, classified as a combination of all three) of UKHLS participants in the NHA who also participated in the Wave 1 and Wave 2 main surveys (n=9,485), and those participants with complete data on self-reported and direct measures (n=5,283).

Considering first the missingness rate among the main sample, it can be seen that this was low (1.2%-1.7%) for self-reports and direct measures that were only collected from participants selected for inclusion in the NHA, while it was slightly higher (8.3%) for direct measures that required blood analysis. These levels of missingness result in a substantial fall in the numbers of participants with complete data on all variables available for analysis (a reduction in the sample available of 55.7%).

Table 4.1 The distribution of self-reported and directly measured MetS components (and MetS itself) amongst participated in Wave 1, Wave 2 and NHA of the UKHLS (n=9,485) and the complete dataset (n=5,283)

		UKHLS NHA participants n=9,485	Complete Sample 1 n=5,283
Components of MetS			
Elevated waist circumference			
SR- WC	Missing	0 (0.0)	0 (0.0)
	Not elevated WC	6,647 (70.1)	3,694 (69.9)
	Elevated WC	2,838 (29.9)	1,589 (30.1)
Directly measured WC	Missing	115 (1.2)	0 (0.0)
	Not elevated WC	5,084 (53.6)	2,999 (56.8)
	Elevated WC	4,286 (45.2)	2,284 (43.2)
High blood pressure			
SR-BP	Missing	157 (1.6)	0 (0.0)
	Not HBP	7,679 (81.0)	4,484 (84.9)
	HBP	1,649 (17.4)	799 (15.1)
Directly measured BP	Missing	152 (1.6)	0 (0.0)
	Not HBP	6,981 (73.6)	4,120 (78.0)
	HBP	2,352 (24.8)	1,163 (22.0)
Diabetes			
SR-diabetes	Missing	124 (1.3)	0 (0.0)
	Not diabetic	8,761 (92.4)	5,026 (95.1)
	Diabetic	600 (6.3)	257 (4.9)
Directly measured Hba1c	Missing	800 (8.4)	0 (0.0)
	Not diabetic	8,086 (85.3)	4,996 (94.6)
	Diabetic	599 (6.3)	287 (5.4)
MetS classification			
SR-MetS	Missing	159 (1.7)	0 (0.0)
	Not MetS	9,145 (96.4)	5,190 (97.2)
	MetS	181 (1.9)	93 (1.8)
Directly measured MetS	Missing	1,030 (10.9)	0 (0.0)
	Not MetS	8,186 (86.3)	5,151 (97.5)
	MetS	269 (2.8)	132 (2.5)

4.1.4.2 Analyses of agreement between self-reported and directly measured MetS (and classifications of MetS based thereon)

The sensitivity and specificity, positive predictive values (PPVs), negative predictive values (NPVs), agreement and Cohen's kappa statistics were calculated to determine the extent that self-reported measures of MetS, and its individual components, were in agreement the directly observed measures. These are summarised in Table 4.2. Sensitivities ranged from 46.2% to 75.3% and while specificities ranged from 96.8% to 99.4%. The self-reported indicator of diabetes was more likely to identify direct diagnoses of diabetes (i.e. based on HbA1c and prescribed medication) than any of the other self-reported MetS component measures (or MetS itself). Of those who reported that a clinician had told them they had diabetes, 75.3% were identified as having diabetes from their HbA1c levels and/or medication records. This was followed by elevated waist circumference; among those whose self-reported height and weight indicated they had elevated waist circumference, 61.6% were so classified from direct measurement. In contrast, self-reported high blood pressure (HBP) displayed lower sensitivity for directly measured HBP; only 57.4% who reported a clinical diagnosis had a correspondingly high blood pressure measurement and/or were using antihypertensive medication. Similarly for the presence of MetS, classification using self-reported information displayed only 46.2% sensitivity compared with classification based on direct measures.

In general, much higher levels of specificity were observed between self-reported and directly measured MetS components (and the classification of MetS involving a combination of all three). This suggests that self-reported measures were more capable of identifying participants who were free of MetS and each of its components, although this conclusion is prone to the effects of prevalence on the measurement of both sensitivity and specificity (Brenner and Gefeller 1997). To provide an example, 99.2% of participants considered free of diabetes (based on direct measurements of HbA1c and medication), and 99.4% considered free of MetS (based on direct measurements) were correctly identified using self-reported measures.

Meanwhile the positive predictive values (PPVs) calculated for these analyses (which, in this instance, indicates the proportion of participants *with* self-reported MetS components [or the classification of MetS based on these] that actually display this component/classification based on directly measured MetS components) found that only 65.6% classified as having (self-reported) MetS were classified as such based on directly measured MetS components. However the PPVs were calculated for each of the three separate MetS components were higher than this level. And, as for the

higher levels of specificity described earlier, the negative predictive values (NPVs) calculated were substantially higher than the PPVs (ranging from 76.2%-98.6%; see Table 4.2), with NPVs as high as 98.6% for self-reported vs. directly measured diabetes and MetS itself.

Finally, the analyses and calculations summarised in Table 4.2 also indicate that the overall agreement (the proportion of cases for which self-reported and directly measured data agree, regardless of the presence or absence of MetS components or MetS itself) was reasonable, ranging from 79.92% to 98.05% with the highest level of overall agreement achieved for the classification of MetS itself. Nonetheless, the Cohen's kappa statistics generated to evaluate levels of agreement between self-reported and directly measured MetS components (and the classification of MetS itself based on these) suggested that the level of agreement ranged from 0.53 'moderate' to 0.78 'substantial', with the highest values of Cohen's kappa for diabetes, followed by high blood pressure, MetS and then elevated waist circumference.

Table 4.2 A summary of the sensitivity, specificity, PPV, NPV, overall agreement and Cohen's kappa statistic (κ) calculated for comparisons between MetS components (and the classification of MetS itself based on a combination of all three) derived from self-reported indicators or by direct measurement.

	Sensitivity % (95%CI)	**Specificity % (95%CI)**	**PPV % (95%CI)**	**NPV % (95%CI)**	**Overall agreement %**	**Kappa κ**
SR-Measures						
SR-EWC	61.6 (59.5,63.6)	93.9 (93.0,94.7)	88.5 (86.8,90.0)	76.2 (74.8,77.6)	79.92	0.57
SR-HBP	57.4 (54.5,60.3)	96.8 (96.2, 97.3)	83.6 (80.9, 86.1)	89.0 (88.0,89.9)	88.15	0.61
SR-DM	75.3 (69.8, 80.1)	99.2 (98.9, 99.4)	84.0 (79.0, 88.3)	98.6 (98.2, 98.9)	97.88	0.78
SR-MetS	46.2 (37.5, 55.1)	99.4 (99.1, 99.6)	65.6 (55.0, 75.1)	98.6 (98.3, 98.9)	98.05	0.53

SR-EWC: elevated waist circumference estimated from self-reports of height and weight (as described in Chapter 3: *Data Sources and Analytical Methods*); SR-HBP: self-reported clinical diagnoses of high blood pressure; SR-DM: self-reported clinical diagnoses of diabetes mellitus; and SR-MetS: the metabolic syndrome classification based on the presence of SR-EWC, SRHBP *and* SR-DM combined

4.1.5 Discussion

Limitations

The findings presented in Part I of the present Chapter are prone to three substantive limitations, namely: the absence of data on waist circumference generated directly by self-report (rather than by estimation); the substantial time period(s) between the measurement of the self-reported and direct measures of MetS components (and classification of MetS itself based thereon) examined; and the inherent risk of 'false positives' and 'false negatives' in both self-reports and direct measures of MetS components (and the classification of MetS based on these). In the absence of an item (or items) on waist circumference in any of the UKHLS questionnaires providing data for the present Chapter, self-reported waist circumference had to be estimated from the only two self-reported anthropometric characteristics available: height and weight, items on which were only included in the Wave 1 questionnaire. As described in Chapter 3 the approach adopted to estimate 'self-reports' of waist circumference (from self-reports of height and weight) used equations based on the relationship between *direct measures* of height, weight *and* waist circumference (collected from participants in the NHA) and then applied these equations to self-reports of height and weight for all participants providing data on these in responses to the Wave 1 questionnaire. This approach to estimation is fraught with potentially erroneous assumptions, the most important of which are that: (i) the relationship between height, weight and waist circumference is similar regardless of whether these are self-reported or directly measured; (ii) the relationship between height, weight and waist circumference can be used to predict waist circumference with a sufficient degree of accuracy (using height and weight alone) to permit the accurate classification of individuals displaying elevated waist circumference (i.e. displaying this key component of MetS); and (iii) there is no systematic variation in the relationship between these three variables amongst individuals with different heights and/or weights, or those with different sociodemographic or economic characteristics. In the absence of self-reported data on waist circumference it is not possible to assess whether the first of these issues (see (i), above) poses a substantive concern, but it is an issue that warrants serious consideration given contemporary social preference for tallness and slimness, which result in the differential over-reporting of height and the under-reporting of weight in most high-income settings (Yoong *et al.* 2013; Dekkers *et al.* 2008). As for the second (i.e. (ii), above), a comparison of elevated waist circumference based either on direct measures of waist circumference or on estimates of directly measured waist circumference (the latter using direct measures of height and weight to estimate 'measured' waist circumference using the equation describing

the relationship between direct measures of height, weight *and* waist circumference) found overall agreement of 86.10% (see Chapter 3). This suggests that a similar level of precision is likely to be possible when using self-reported height and weight to estimate 'self-reported' waist circumference. Indeed, given the three potential weaknesses of this approach *and* the fact that the self-reports of height and weight used to estimate self-reported waist circumference were collected (in Wave 1 of the UKHLS) around 18 months *before* the direct measurements of waist circumference were taken (during the UKHLS NHA, shortly after Wave 2), it is frankly surprising that estimated 'self-reports' of elevated waist circumference achieved such high levels of sensitivity (61.6%), specificity (93.9%), PPV (88.5%), NPV (76.2%) and overall agreement (79.9%; see Table 4.2, above). And since there is a some evidence to suggest that many people (particularly those who are overweight and/or have large waist circumferences) may find it very difficult to measure their waist circumference – or even to find the midpoint between the lower border of the ribs and the upper border of the pelvis where most auxologists recommend the measurement be taken (Cullum *et al.* 2004; Dekkers *et al.* 2008) – it may even be that estimates of waist circumference generated using self-reports of height and weight are no worse than self-reported waist circumference.

Meanwhile, an additional consequence of the lack of items generating self-reports of waist circumference in any of the UKHLS questionnaires – and the inclusion of items requesting self-reports of height and weight only in the questionnaire used in Wave 1 (items have not, to-date, re-appeared in any of the questionnaires used in subsequent Waves) – is that the data used to estimate 'self-reported' waist circumference were collected around 18 months before the direct measures of waist circumference were recorded at the NHA. This compares to an interval of only around 5 months between the self-reports of (clinical diagnoses of) high blood pressure and diabetes collected during Wave 2, and the direct measures of these two components of MetS during the NHA. Neither of these intervals are ideal for analyses assessing the potential validity of two different measures of the same characteristics, not least when all three components of MetS examined in the present Chapter are susceptible to change over time (not least as a result of an increasing tendency for weight gain, rising blood pressure and an increased risk diabetes with age). In fact, an important marker of quality applied to the critical appraisal of studies comparing two diagnostic tests is that there should be no interval between the applications of each (Bossuyt *et al.* 2015). In both instances the time interval between the collection of self-reports and direct measures, be that 5 or 18 months, will have introduced the possibility that (some) participants experience a change in one (or more) of the MetS components examined,

and will have reduced the apparent validity of all three self-reported measures. Unfortunately, there is little that can be done to address this issue in the present thesis given its reliance on data from the UKHLS, chosen specifically because it offered a contemporary survey of both self-reports *and* direct measures of MetS components (as well as data on a comprehensive list of n=7 sleep characteristics) for a large sample of adults designed to be representative of the UK population. Nonetheless, this inherent weakness in the likely comparability of self-reported and direct measures of MetS components is nonetheless reassuring if, as seems likely, this weakness is in part responsible for what might otherwise appear relatively modest levels of sensitivity, specificity, PPV, NPV and overall agreement observed.

Setting aside such reassurances, the additional possibility that self-reports of elevated waist circumference, high blood pressure and/or diabetes were more (or less) susceptible to 'false positives' and/or 'false negatives' than direct measures thereof, might appear to pose a serious limitation of the present Chapter's findings. 'False positives' would occur where, for example, erroneous self-reports or direct measurements for individuals who did *not* display elevated waist circumference, high blood pressure and/or diabetes led these individuals to be classified as having (one or more) of these components of MetS. Likewise, 'false negatives' would occur when erroneous data led individuals who had (one or more of) these MetS components to be classified as free of these. Estimates of waist circumference based on self-reports of height and weight would be particularly prone to 'false negatives' given the tendency for under-reporting body weight (Dekkers *et al.* 2008). Likewise, the high prevalence of undiagnosed blood pressure and diabetes – together with substantial variation in 'health literacy' amongst individuals with different sociodemographic characteristics, economic circumstances and lifestyles (Halladay *et al.* 2016) – would also tend to make self-reports of these MetS components susceptible to 'false negatives', particularly amongst individuals with modest 'health literacy'. At the same time, direct measures of waist circumference, high blood pressure and diabetes can also be susceptible to 'false negatives' and 'false positives', and under the measurement protocols used by the UKHLS NHA (which did not require participants to be fasted, rested or abstain from smoking prior to measurement) it seems likely that more 'false positives' than 'false negatives' are likely to have occurred simply because eating, activity and smoking (along with the likely stress of measurement/examination), are likely to have led to a rise in blood pressure, blood glucose levels and even, perhaps, waist circumference. As such, the higher risk of 'false positives' amongst direct measures of the three MetS components examined in the present Chapter (and of 'false negatives' amongst self-reports of these components, as discussed above),

would have contributed to the somewhat different prevalences of self-reported vs. directly measured MetS components summarised in Table 4.1; and would also have attenuated all of the measures used to compare these two different measures of MetS components summarised in Table 4.2. However, whilst this differential susceptibility to 'false negatives'/'false positives' might undermine the validity of both self-reports *and* direct measures of MetS components at the *individual* level, the self-reports developed for use in the present thesis (and compared to direct measures thereof in the present Chapter) might still prove useful for the analysis of the potential causes and consequences of these MetS components (and a classification of MetS based thereon) at the *population* level – such as the analyses exploring their relationship(s) with self-reported sleep as described in the next Part of this Chapter: (*Re-evaluating the association between self-reported sleep and MetS*). For each separate component of MetS, this might well be the case provided the risk of 'false negative/positive' values was unaffected by those factors being investigated as potential causes or consequences (in this instance, sleep), or by other variables that, in turn, influence or are influenced by these (i.e., here, variables acting as confounders in the relationship between MetS and sleep). However, for this to be true for the classification of 'MetS itself' (based as this is, in the present thesis, on a combination of all three MetS components), any differential risk of 'false negatives' vs. 'false positives' amongst the constituent components of MetS might not only undermine the precision of a MetS classification based thereon, and introduce further bias to population-based analyses of its relationship with speculative causes and/or consequences. Unfortunately, given the data available within the UKHLS, it is not possible to assess the *differential* impact of what seems likely to be a higher risk of 'false negatives' amongst self-reported components of MetS and a higher risk of 'false positives' amongst direct measures of these components. Instead, the best the present Chapter can provide is some (limited) reassurance that self-reports of all three MetS components (and the classification of MetS itself based on these) appear to offer reasonable-to-good levels of sensitivity, specificity, PPV, NPV and overall agreement for direct measures thereof.

Methodological considerations

Notwithstanding these three key limitations, and the limited degree to which Part I of the present Chapter was able to avoid, address or even ameliorate these, this Chapter (Part I) was nonetheless designed to avoid a number of flaws evident in many previous studies examining the validity of self-reported MetS components (and related anatomical or physiological characteristics). For example, many such studies have only studied male or female participants (e.g. (Margolis *et al.* 2008; Engstrom *et al.* 2003; Colditz *et al.* 1986); others focussed exclusively on specific populations

(including minority ethnic groups, specific age groups or those living in particular geographical contexts: (Leikauf and Federman 2009; Kriegsman *et al.* 1996; de Menezes, Oliveira and de Sousa Fischer 2014; Martin *et al.* 2000). In contrast, the data used in Part I of the present Chapter was only limited to participants recruited by the UKHLS (in a sample designed to be broadly representative of the UK's sociodemographically diverse populations). And while the items used to collect self-reports of high blood pressure and diabetes in the UKHLS questionnaires specifically asked whether these had "ever" been diagnosed by a "doctor or other health professional", many other studies used items that did not include these important features (de Menezes, Oliveira and de Sousa Fischer 2014; Vargas *et al.* 1997; Okura *et al.* 2004; Molenaar *et al.* 2007; Bowlin *et al.* 1996; Huerta *et al.* 2009). Finally, the availability of data generated using measurements undertaken by the UKHLS itself (rather than secondary data sourced from medical records or clinician-derived data), is likely to have offered much more reliable (and accurate) information on the three MetS components than that used by/available to many of the previous studies examining the validity of self-reports vs. medical/clinical records (Oksanen *et al.* 2010; Martin *et al.* 2000; Robinson *et al.* 1997; Okura *et al.* 2004) (Kehoe *et al.* 1994; Kriegsman *et al.* 1996).

The potential utility of self-reported MetS components

Since the principal aim of Part I of the present Chapter was to assess the extent to which it might be possible to rely upon self-reports of three key components of MetS (elevated waist circumference, high blood pressure and diabetes; and thereafter on a classification of MetS based thereon) to examine their association with seven self-reported sleep characteristics (analyses that are summarised in Part 2 of this Chapter), it is reasonable to conclude that Part I of this Chapter largely succeeded in achieving this aim. Notwithstanding a number of inherent limitations in the availability and measurement of self-reported indicators of MetS-relevant components (as detailed extensively above), comparisons between self-reports and direct measures of three key MetS components (and a classification of MetS itself based thereon) suggest that MetS still had considerable potential utility, not least as a result of their high specificity (ranging from 93.4%-99.4%) and high negative predictive values (NPVs; ranging from 76.2%-98.6%; see Table 4.2). Indeed, although self-reports of the three MetS components (and the classification of MetS itself based thereon) had lower sensitivity (ranging from just 46.2% to 75.3%) and lower positive predictive values (PPVs; ranging from 65.6% to 88.5%), they still displayed moderate-to-strong overall agreement with direct measures (overall agreement between the two ranging from 79.9% to 98.0%) and associated values of Cohen's kappa (a coefficient generally

considered to offer a better assessment of agreement since it takes into account the possibility of agreement simply by chance;(Landis and Koch 1977) that ranged from 0.50 (considered 'moderate' and 'fair-to-good' evidence of agreement by Landis and Koch, 1977; and Fleiss 1981, respectively) to 0.79 (considered 'substantial' by Landis and Koch, 1977; and as 'excellent' by Fleiss, 1981)

Clearly, self-reports of some MetS components offer more valid measures of directly measurements than others: self-reports of diabetes offering greater levels of agreement with direct measures than did self-reports of high blood pressure; and self-reports of high blood offering more valid measures of (directly measured) high blood pressure than the estimated 'self-reports' of elevated waist circumference did for direct measurements thereof. This is likely to reflect the fact that conditions with clearer symptoms (including those more proactively targeted by public health screening programmes – such as hypertension), and those requiring regular/continuous monitoring and follow-up (with changes to lifestyle, medication and daily routines – such as diabetes) are more likely to be better remembered and better reported (Leikauf and Federman 2009; Goldman *et al.* 2003). Indeed, Goldman et al. (Goldman *et al.* 2003) found that self-reported hypertension (49.4%) displayed lower sensitivity than self-reported diabetes (85.2%); likewise El Fakiri et al. (El Fakiri, Bruijnzeels and Hoes 2007) reported moderate levels of agreement between self-reports and direct measures of hypertension (Cohen's kappa=0.63) and substantial agreement between self-reports and direct measures of diabetes (Cohen's kappa=0.84). Far fewer studies have attempted to validate self-reports of waist circumference, all of which found substantial underestimation by both males and females (Spencer, Roddam and Key 2004; Rimm *et al.* 1990; Hall and Young 1988; Han and Lean 1998). One of these studies (Han and Lean 1998), sought to validate self-reports of elevated waist circumference (defined as: >1020mm in men; and >880mm in women) and found that these had a sensitivity of 35.3% and 44.9% and a specificity of 98.5% and 90.7% for males and females, respectively – levels that are broadly comparable with what the present Chapter found using estimated 'self-reports' of elevated waist circumference.

And, while self-reports of all three MetS components (and the use of these to classify MetS itself) may offer better measures of their *absence* than their *presence* (as indicated by their higher specificity and NPVs than their sensitivity and PPVs) – and while the differential validity of each component appears to reduce the validity of 'self-reported' MetS itself (i.e. MetS based on self-reports of MetS components) – these self-reports still attain remarkable levels of agreement with the direct measures they were intended to replace (not least since these direct measures were recorded 5-18 months *after* the self-reports collected in Waves 1 and 2 of the UKHLS). As such it

seems likely that self-reported measures of MetS may have substantial utility, not least for population-based epidemiological studies (where often only the collection of data using self- or interviewer-administered surveys is feasible).

Clearly, there is still much to learn about the validity of self-reported MetS components (and classifications of MetS itself based thereon), and how these might be strengthened by innovations in questionnaire content, delivery and design. Although these are beyond the scope of the present thesis, the priorities for further research in this area (including the development of more reliable/valid items for inclusion in survey questionnaires) will be discussed in further detail in the final Discussion Chapter of this thesis. In the meantime it is worth evaluating the potential utility of self-reported MetS components (and the classification of MetS itself based on these) by comparing the findings these generate with those generated using directly measured MetS components in analyses exploring the association between MetS and sleep in the next Part of this Chapter (Part 2).

4.1.6 Summary and conclusion

The analyses conducted in Part I of the present Chapter confirm that self-reports of all three of the MetS components examined (i.e. those for which suitable items were identified in the UKHLS questionnaires to generate, or estimate, self-reported measures of these: elevated waist circumference; high blood pressure; and diabetes) had a lower prevalence amongst UKHLS participants than that observed from direct measures thereof. And since the classification of MetS adopted in the present thesis (comprising the presence of all three of these MetS components) was generated from data on each constituent component of MetS, it is not surprising that the prevalence of self-reported MetS was also lower than that observed when using MetS classified using direct measures of each MetS component.

These differences in prevalence (together with the substantive time intervals between the collection of self-reports and direct measures of MetS in the UKHLS; and the need to use self-reported height and weight to estimate 'self-reports' of waist circumference, because items to generate the latter were not included in UKHLS questionnaires) contributed to lower levels of sensitivity, specificity, positive predictive value, negative predictive value, overall agreement and Cohen's kappa than might otherwise have been achieved for these self-reports of MetS components (and the classification of MetS itself based thereon). Indeed, given the limitations of the data available within the UKHLS, it is surprising (and somewhat reassuring) that agreement between these two sources of data remained substantial (particularly when assessed

using Cohen’s kappa to address the risk of chance agreement between MetS components categorised simply as binary variables: present vs. absent).

Part II

4.2 Re-evaluating the association between self-reported sleep and MetS

The empirical evidence providing the principal motivation for the present thesis comprised a range of observational studies reporting ostensibly clear associations between less favourable sleep and poor health (Kaur, Sharma and Singh 2015) – studies in which *inter alia* self-reports of (both long and short) sleep duration and poor sleep quality were associated with a variety of health-related problems. In particular, such studies have found that short (≤6hrs) and prolonged (≥9hrs) sleep duration are both associated with an increased risk of insulin resistance, hyperglycaemia, obesity, dyslipidaemia and/or cardiovascular disease (Lee *et al.* 2013; Barone and Menna-Barreto 2011; Mesas *et al.* 2014). Meanwhile, self-reports of poor sleep quality have been found to be associated with both insulin resistance and obesity, even after adjustment for sleep duration (Kazman *et al.* 2012; Hung *et al.* 2013).

Given that many of these cardiometabolic factors are characteristic of the so-called 'Metabolic Syndrome' (MetS) – a cluster of risk factors for coronary heart disease that comprise: (central) obesity, hyperglycaemia, hypertension, elevated levels of triglycerides and lower levels of high-density lipoprotein cholesterol (Alberti *et al.* 2009) – there has been growing interest in the possibility that unfavourable sleep might represent an important cause of MetS (as suggested by associations between sleep duration, sleep quality and various classifications of MetS) (Xi *et al.* 2014; Ohkuma *et al.* 2014; Lee *et al.* 2013; Hung *et al.* 2013; Arora *et al.* 2011) However, there is growing evidence that unfavourable sleep could be both a cause and a consequence of MetS, since a number of studies have reported an increased prevalence of sleep disorders amongst individuals with poor glycaemic control (Hung *et al.* 2013; Barone and Menna-Barreto 2011).

The findings of these studies are certainly intriguing, yet it is clear from Chapter 2 that the bulk of the evidence they provide stems from observational analyses of cross-sectional datasets, while the few experimental studies focussed primarily on obstructive sleep apnoea (or, occasionally, obesity) and therefore offer limited insight into other (non-clinical) sleep characteristics. Although a small number of studies were identified that claimed to adopt longitudinal designs, none of these had data collected at more than two time points and all adopted analytical strategies that were particularly

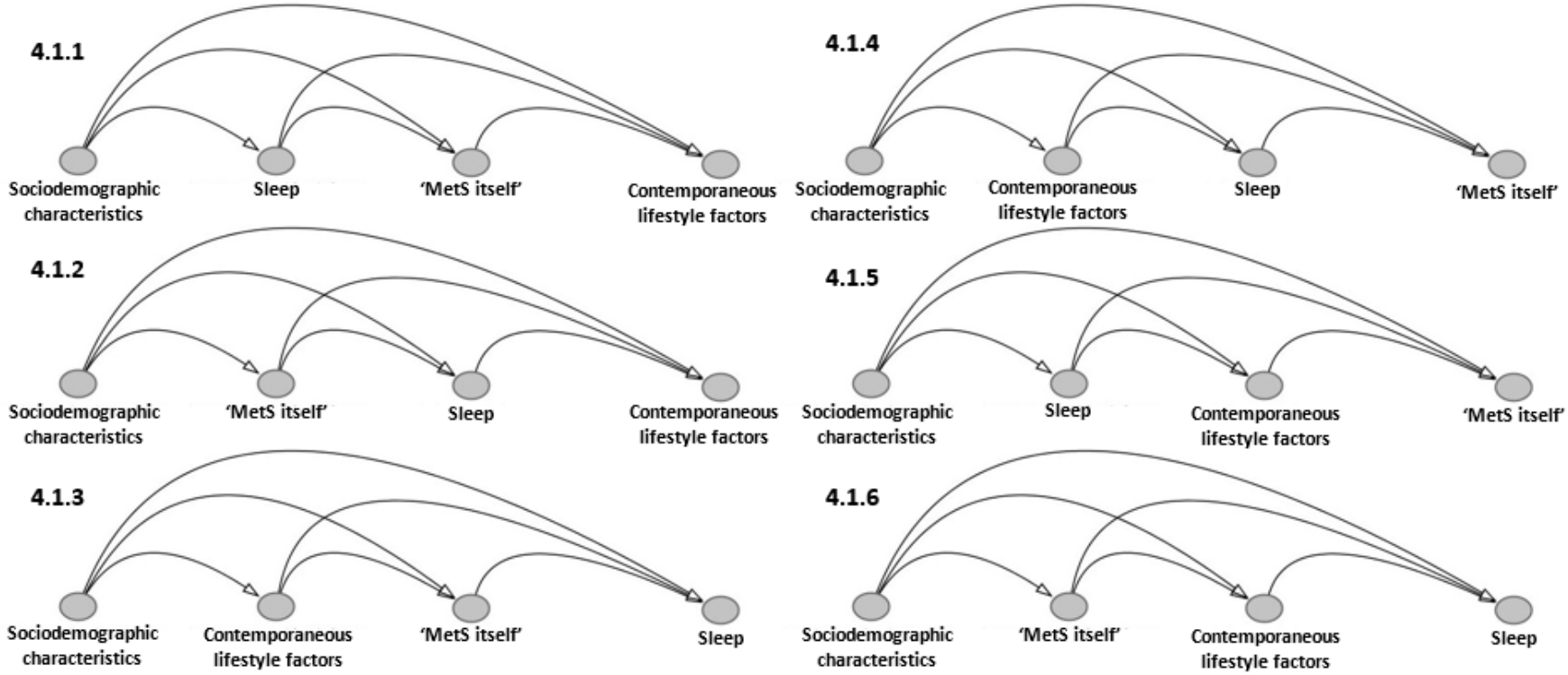
susceptible to bias from regression to the mean. What evidence there is thus relies on cross-sectional data that are ill-equipped to provide evidence of directionality and causality (i.e. whether less favourable sleep might precede MetS, whether MetS might precede less favourable sleep, or both). At the same time, none of these cross-sectional studies have examined more than a few characteristics of sleep (most focussing on sleep duration (Ohkuma *et al.* 2014; Chaput *et al.* 2013b; Stefani *et al.* 2013; Wu *et al.* 2012; Arora *et al.* 2011), with fewer examining sleep latency, sleep fragmentation/maintenance or snoring (Mesas *et al.* 2014; Lee *et al.* 2013; Chedraui *et al.* 2013)). Indeed, even those studies that measured sleep using multi-item quasi-psychometric instruments (such as the Pittsburgh Sleep Quality Index), examined each of the separate sleep characteristics measured by the different items these instruments contain (Hung *et al.* 2013; Jennings *et al.* 2007) – a substantial oversight given the important insights such analyses might have offered.

Additional flaws in the design, sampling and analysis of previous cross-sectional studies include the small, clinic-based samples employed - which are susceptible to inadequate statistical power, and are likely to have limited external validity (Chaput *et al.* 2013b; Yoo and Franke 2013; McCanlies *et al.* 2012; Roopa *et al.* 2010) - and a lack of consensus on the referent group used. Some studies used referent groups comprised of participants that lacked *any* components of MetS or *any* unfavourable sleep characteristics while others used referent groups that only lacked the specific component(s) of MetS or unfavourable sleep that were being examined. These differences are likely to result in very different effect estimates of the association between MetS and sleep. Many studies also fail to report the rationale for the inclusion (or exclusion) of specific covariates within the adjustment sets used in their multivariable statistical analyses. Many of these analyses will therefore be at risk of under-adjustment confounding (by failing to measure *and* adjust for potential confounders) and/or inappropriate adjustment for mediators (covariates falling on the causal path between MetS and sleep).

These analytical concerns were mapped out in some detail in Chapter 2, where a series of six possible causal path diagrams were presented (in the form of directed acyclic graphs; DAGs) using a list of all the covariates measured by the cross-sectional studies reviewed (see Figure 2.4, on page 59). It is worth reproducing a simplification of this figure in the present Chapter (see Figure 4.1, overleaf) to revisit why the present thesis proposes that only one of these DAGs can reflect the temporal sequence of MetS, sleep and other covariates when collected by previous cross-sectional studies. Without repeating the arguments, it is nonetheless instructive to remind that the most plausible model - based on what is known about the time taken

for these characteristics to develop, and when/how these were measured - is Model 4.1.6, in which: sociodemographic factors precede the initiation/development of MetS which, then, precedes contemporaneous lifestyle factors which, finally, precede self-reported sleep. This is therefore the model adopted for the current analyses, which assume (for cross-sectional analyses of the relationship between MetS and sleep) that: sociodemographic factors are the only potential confounders that require adjustment; and that contemporaneous lifestyle factors are likely to act as mediators in any relationship between MetS and sleep and should not therefore be included in the adjustment set for any multivariable analyses thereof).

Figure 4.1 Simplified directed acyclic graphs (DAGs) summarising the six theoretical causal paths (4.1.1-4.1.6) between cross-sectionally measured data on: contemporaneous lifestyle factors, sleep and MetS. Adapted from Figure 2.5 in Chapter 2 (*A systematic review of cross-sectional studies examining the association between MetS and sleep*).



4.2.1 Aim and objectives

The key aim of Part II of this chapter was to re-evaluate the association between MetS and self-reported sleep by examining any variation in this association related to:

(ix) the use of different referent groups (specifically: individuals without all three of the key components of MetS available within the UKHLS; and individuals without the specific key component[s] used for each classification of MetS examined in (ii), above);

(x) the use of objective (direct measurements) and subjective (self-reports) of each of the three components of MetS examined; and

(xi) the inclusion of lifestyle variables in the adjustment sets used to control for potential confounding when evaluating the (confounder adjusted) association between sleep and MetS.

(xii) different characteristics of self-reported sleep (specifically: sleep duration, latency, disturbance, coughing/snoring, medication, quality and daytime sleepiness);
different classifications of MetS (based on one, two or all of three key components available within the UKHLS: central obesity; hypertension; and diabetes);

A final aim of Part II of the present Chapter was to:

(xiii) apply the use of self-reported MetS components (and combinations of MetS components) to a large, population based sample designed to be representative of the UK population and thereby demonstrate: not only their potential utility for analysing the association between different components/combinations of MetS and sleep in large-scale epidemiological surveys; but also what evidence these surveys might offer regarding the association between MetS and sleep (not least in the UK, where there have been no such studies to-date).

As such, Part II of the present Chapter sought to address the following key questions as established at the outset of this thesis:

KQ4: “What methodological and aetiological insights into the association between sleep and MetS might be generated from analyses of large dataset?”

4.2.2 Methods

4.2.2.1 Study design and sample

The data on which this Chapter's (Part II) analyses were based originate from the UKHLS Sample 1 and Sample 2 (see Chapter 3). As such, the two samples examined were identified as follows:

Sample 1: Only those adult participants who were eligible for inclusion in the Wave 2 NHA who had complete data on: all seven self-reported sleep characteristics (recorded in Wave 1); self-reported MetS components (central obesity from data recorded in Wave 1; diabetes and hypertension recorded in Wave 2); directly measured MetS components (recorded during the NHA); and relevant self-reported covariates (sociodemographic and lifestyle from data recorded in Wave 2).

Sample 2: Only adult participants providing data in Wave 1 who had complete data on: all seven self-reported sleep characteristics; self-reported MetS components; and relevant self-reported covariates (excluding data on lifestyle which were only recorded in the Wave 2 questionnaires).

4.2.2.2 Self-reported sleep characteristics

Wave 1 of the UKHLS included seven items relevant to sleep in its 'Adult Self-completion Questionnaire'. These generated data on seven sleep characteristics during the month preceding the survey: sleep duration ("hours of actual sleep"); sleep latency ("cannot get to sleep within 30 minutes"); sleep quality ("sleep quality overall"); sleep fragmentation ("wake up in the middle of the night or early in the morning"); coughing/snoring ("cough or snore loudly"); sleep medication use ("medicine [prescribed or 'over the counter'] to help you sleep"); and daytime sleepiness ("trouble staying awake while driving, eating meals, or engaging in social activity").

Data on sleep duration were categorised into <6 hrs, ≥6-8, and >8hrs, and sleep quality was dichotomised as ("Very good" vs. "Fairly good" "Fairly bad" and "Very bad"). The remaining sleep variables (the items for which all used frequency-related response options) were dichotomised to binary variables with "Not during the past month" and "At some time during the past month" (comprising: "Less than once a week", "Once or twice a week", "Three or more times a week" and "More than once most nights") as the two resulting categories. More detail on the measurement and categorisation of these sleep variables is provided in Chapter 3 (section 3.4.1).

4.2.2.3 Metabolic syndrome components and classification

Since one aim of the present Chapter (Part II) was to examine the association between sleep and different components/combinations of MetS (based on one, two or all of three of the key components available within the UKHLS), it was necessary to establish suitable definitions for each of these components and for the classification of 'MetS itself' based on combinations of these. Based on the review of MetS classifications used by previous studies examining the association between sleep and MetS (see Chapter 2), the empirical analyses conducted in this thesis focussed on a formal classification of MetS (and the definitions of each component of MetS used therein) as defined by the NCPI-ATP III (see also Chapter 3). However, because the UKHLS did not provide data on two of the components of MetS relevant to dyslipidaemia (triglycerides and HDL cholesterol) that are included in the definition of MetS proposed by the NCPII-ATP III, the analyses in this thesis have focussed on just three components: elevated waist circumference (as a marker for central obesity); high blood pressure; and diabetes. The NCPI-ATP III definition defines each of these components as follows:

Central obesity: waist circumference ≥ 102 cm for men and ≥ 88 cm for women;

Diabetes: fasting serum glucose ≥ 100 mg/dL, and/or the use of antidiabetic medication; and

High blood pressure: systolic blood pressure ≥ 130 mm Hg, or diastolic blood pressure ≥ 85 mm Hg , and/or the use of antihypertensive medication (Huang 2009).

For Sample 1 (for whom data were available on both directly measured and self-reported MetS components), data from the NHA alone were used to identify participants with central obesity, high blood pressure and prescribed medication for blood pressure (see also Chapter 3). The assessment of diabetes relied upon HbA1c measurements and prescribed antidiabetic medication rather than on fasting serum glucose levels, since fasting blood samples were not collected during the UKHLS NHA). Equivalent self-reported measures of each of these MetS components (for use in analyses involving both Sample 1 and Sample 2) were generated from: self-reports of height and weight (collected in Wave 1, and used to estimate waist circumference, as described in Chapter 3); and self-reported clinical diagnoses of "high blood pressure" and "diabetes" (described in greater detail in Chapter 3).

The analyses that follow compare the association between sleep and the presence of: each MetS component alone; each pair of MetS components; and all three components together – the latter comprising the classification of 'MetS itself' examined in the present Chapter (based on the NCPII-ATP III definition). As such,

'directly measured MetS (itself)' was defined as the presence of: central obesity (directly measured WC ≥ 102cm for males, WC ≥ 88cm for females); high blood pressure (BP ≥140/90 mmHg and/or on prescribed medication for blood pressure); and diabetes (HbA1c ≥ 48 mmol/mol and/or prescribed antidiabetic medication). In contrast, 'self-reported MetS' was defined as: the presence of central obesity (estimated WC ≥ 102cm for males, WC ≥ 88cm for females – where WC was estimated from self-reports of height and weight); and self-reports of clinically diagnosed high blood pressure and of clinically diagnosed diabetes.

More details on the definition of directly measured and self-reported MetS components, and on the classification of 'MetS itself' used (based on the NCPI-ATP III definition) is described in Chapter 3 (see section 3.4.2)

4.2.2.4 Covariates

Following the theoretical DAGs that were generated from previous cross-sectional studies of the association between MetS and sleep (see Chapter 2), the Wave 1 and Wave 2 UKHLS questionnaires were carefully examined to identify items capable of providing relevant data for analysis.

These comprised a range of sociodemographic variables (age; sex; marital status/cohabition; educational attainment, employment status; and household composition), and a number of contemporaneous lifestyle variables (habitual fruit and vegetable consumption [as a marker for diet]; smoking status; alcohol consumption; and participation in sport). Further detail on the questionnaire items used to generate each of these variables can be found in Chapter 3.

4.2.3 Statistical analysis

1. Descriptive analyses

Descriptive analyses were undertaken to summarise the distribution of the exposure and outcome variables, and each of the available covariates, for both: the original UKHLS and NHA samples; and the two analytical samples with complete data for all relevant variables (i.e. Samples 1 and 2). Summaries of each variable were presented as frequencies (n) with percentages (%) in parentheses.

2. Unadjusted and adjusted analyses of the association between sleep and MetS

A series of (unadjusted and adjusted) logistic regression models were used to establish whether any variation in the association between (different characteristics of) sleep and (different combinations of) MetS components was related to: the use of

different referent groups; the use of directly measured vs. self-reported components of MetS; and the inclusion of contemporaneous lifestyle variables in any adjustment sets used.

Sample 1:

Two sets of models were used to examine UKHLS participants in the first sample (Sample 1 – for which data were available on both directly measured and self-reported components of MetS, *and* data on contemporaneous lifestyle variables); one set using directly measured components of MetS, and the other using self-reported components of MetS. Both sets examined the association between different MetS component combinations (i.e. one, two or all three) and each of the available sleep characteristics, using both referent groups (those who did not display *any* components of MetS and those who did not display *the particular* MetS component or combination being examined). These were evaluated without adjustment for other covariates, adjusted for sociodemographic factors alone, and adjusted for both sociodemographic and contemporaneous lifestyle factors.

Sample 2:

A single set of models was then used to examine UKHLS participants in the second sample (Sample 2 – which included a larger proportion of UKLHS participants, but lacked data on directly measured components of MetS, and data on contemporaneous lifestyle variables). As before, these models examined the association between different MetS component combinations (i.e. one, two or all three) and each sleep characteristic, using both referent groups (those who did not display *any* components of MetS and those who did not display *the particular* component or combination being examined). These were evaluated before and after adjustment for sociodemographic factors, but not for both sociodemographic and contemporaneous lifestyle factors, since no data were available on the latter. These three sets of logistic regression models (n=16 models in all) have been summarised in Table 4.3. (See also Appendix; Tables 6.9 - 6.25)

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Table 4.3 Summary of the statistical models used to examine whether any variation in the relationship between (different characteristics of) sleep and (different combinations of) MetS components was associated with: the use of different referent groups; the use of directly measured vs. self-reported components of MetS; and the inclusion of contemporaneous lifestyle variables in any adjustment sets used.

Figure	Sample	Measurement of MetS components	Referent group used	Adjustment for sociodemographic variables	Adjustment for lifestyle variables
4.2	Sample 1 (n=5,283)	Directly measured	Participants do not display ***any*** components of MetS	No	No
4.3	Sample 1 (n=5,283)	Directly measured	Participants do not display ***any*** components of MetS	Yes	No
4.4	Sample 1 (n=5,283)	Directly measured	Participants do not display ***any*** components of MetS	Yes	Yes
4.5	Sample 1 (n=5,283)	Directly measured	Participants do not display ***the particular*** combination of MetS components being examined	No	No
4.6	Sample 1 (n=5,283)	Directly measured	Participants do not display ***the particular*** combination of MetS components being examined	Yes	No
4.7	Sample 1 (n=5,283)	Directly measured	Participants do not display ***the particular*** combination of MetS components being examined	Yes	Yes
4.8	Sample 1 (n=5,283)	Self-reported	Participants do not display ***any*** components of MetS	No	No
4.9	Sample 1 (n=5,283)	Self-reported	Participants do not display ***any*** components of MetS	Yes	No
4.10	Sample 1 (n=5,283)	Self-reported	Participants do not display ***any*** components of MetS	Yes	Yes
4.11	Sample 1 (n=5,283)	Self-reported	Participants do not display ***the particular*** combination of MetS components being examined	No	No
4.12	Sample 1 (n=5,283)	Self-reported	Participants do not display ***the particular*** combination of MetS components being examined	Yes	No
4.13	Sample 1 (n=5,283)	Self-reported	Participants do not display ***the particular*** combination of MetS components being examined	Yes	Yes
4.14	Sample 2 (n=29,436)	Self-reported	Participants do not display ***any*** components of MetS	No	Not available
4.15	Sample 2 (n=29,436)	Self-reported	Participants do not display ***any*** components of MetS	Yes	Not available
4.16	Sample 2 (n=29,436)	Self-reported	Participants do not display ***the particular*** combination of MetS components being examined	No	Not available
4.17	Sample 2 (n=29,436)	Self-reported	Participants do not display ***the particular*** combination of MetS components being examined	Yes	Not available

4.2.4 Sample 1 Results

4.2.4.1 Descriptive analyses

Table 4.4 summarises the distribution of sociodemographic and lifestyle variables, self-reported and directly measured MetS components, and seven self-reported sleep characteristics UKHLS participants who had participated in all Waves up until the NHA (i.e. the main sample; n=9,485); and those participants with complete data on all self-reported and directly measured variables; and all self-reported variables (i.e. Sample 1; n=5,283).

Considering first the missingness among the main sample, it can be seen that the rate of missingness was negligible (0.0%-0.8%) for most of the sociodemographic and health variables collected in the Wave 2 questionnaire, except for alcohol consumption (10.4%), and the self-reported sleep characteristics (10.4%-24.5%) collected only in Wave 1 using the adult self-completion questionnaire. Looking at the missingness rate among the self-reported and directly measured components of MetS, it can be seen that it was low (5.4%) for self-reports, but moderate (10.4%) for direct measures that were collected from participants selected for inclusion in the NHA and who had provided blood sample.

These levels of missingness result in a moderate fall in the numbers of participants with complete data on all variables available for analysis in Sample 1 (a fall of n=9,485 to n=5,283 participants). The exclusion of such a substantial number of participants from the analytical sample (Sample 1) is likely to constrain the external validity of these analyses (i.e. the generalisability of the results that might be affected by biased sub-sample selection and small sample sizes) if the reduction in sample size was accompanied by changes in the distribution of key variables. To assess this possibility it is worth comparing the distribution of these variables in the main sample with that observed in Sample 1. By examining the distribution of all variables, it is clear that both samples had a very similar distribution. In particular, around 55% of participants in both samples were female, aged 60yrs or more (~30%). Participants in both samples were also less likely to be single (~13%) and more likely to be married/cohabiting (~73%); and were less likely to have no educational qualifications (~11%) and more likely to be in ‘management or professional’ employment (~28%).

Table 4.4 Variation in the distribution of: sociodemographic and lifestyle characteristics; self-reported and directly measured MetS components (and combinations thereof); and self-reported sleep characteristics, for all adult (≥16yrs) participated in Wave 1, Wave 2 and NHA of the UKHLS (n=9,485) and complete data on all self-reported *and* directly measured variables (Sample 1; n=5,283). All variables have been categorised with the distribution across categories summarised as frequencies (n) with percentages in parentheses (%).

		UKHLS Wave 1, Wave 2 and NHA participants n=9,485	**Sample 1 n=5,283**
Sociodemographic characteristics			
Covariates		n (%)	n (%)
Sex	Missing	0 (0.0)	0 (0.0)
	Male	4,171 (44.0)	2,387 (45.2)
	Female	5,314 (56.0)	2,896 (54.8)
Age	Missing	0 (0.0)	0 (0.0)
	Below 30 years old	943 (9.9)	543 (10.3)
	30-39 years old	1,310 (13.8)	794 (15.0)
	40-49 years old	1,921 (20.2)	1,154 (21.8)
	50-59 years old	1,838 (19.4)	1,107 (20.9)
	60years or older	3,473 (36.6)	1,685 (32.0)
Marital/cohabitation status	Missing	0 (0.0)	0 (0.0)
	Single	1,282 (13.5)	689 (13.0)
	Cohabited	6,502 (68.5)	3,841 (72.7)
	Separated and Divorced	997 (10.5)	507 (9.6)
	Widowed	704 (7.4)	246 (4.7)
Educational attainment	Missing	9 (0.1)	0 (0.0)
	Degree	2,123 (22.4)	1,332 (25.2)
	Other higher degree	1,290 (13.6)	777 (14.7)
	A-level	1,709 (18.0)	1,001 (19.0)
	GCSE	1,845 (19.4)	1,080 (20.4)
	Other qualification	1,104 (11.6)	538 (10.2)
	No qualification	1,405 (14.8)	555 (10.5)
Employment status	Missing	77 (0.8)	0 (0.0)
	Management and professional	2,205 (23.2)	1,485 (28.1)

	Intermediate	719 (7.6)	460 (8.7)
	Small employers and own account	514 (5.4)	284 (5.4)
	Lower supervisory and technical	398 (4.2)	252 (4.8)
	Semi-routine, routine and never worked long-term	1,608 (16.9)	850 (16.1)
	Unemployed	915 (9.6)	510 (9.6)
	Retired	2,815 (29.7)	1,284 (24.3)
	Student	234 (2.5)	158 (3.0)
Household structure[1]	Missing	4 (0.0)	0 (0.0)
	Empty nesters	5,680 (59.9)	3,139 (59.5)
	Dwelling sharing childless adults	1,137 (12.0)	550 (10.4)
	Partnered with child	1,241 (13.1)	779 (14.8)
	Partnered with children	593 (6.2)	355 (6.7)
	Large family, majority with overcrowding	347 (3.7)	208 (3.9)
	Single parent household	310 (3.3)	164 (3.1)
	Extended family, majority with overcrowding	173 (1.8)	84 (1.6)
Daily number of servings of fruit and vegetables consumed	Missing	70 (0.7)	0 (0.0)
	1	732 (7.7)	383 (7.2)
	2	2,013 (21.2)	1,079 (20.4)
	3	2,407 (25.4)	1,370 (25.9)
	4	1,823 (19.2)	1,054 (20.0)
	5	1,631 (17.2)	939 (17.8)
	6 and more	809 (8.5)	458 (8.7)
Sport activity ranking	Missing	4 (0.0)	0 (0.0)
	no sport at all	2,460 (25.9)	1,145 (21.7)
	1-2	1,724 (18.2)	979 (18.5)
	3-4	1,836 (19.4)	1,076 (20.4)
	5-6	1,820 (19.2)	1,069 (20.2)
	7-very active	1,641 (17.3)	1,014 (19.2)
Smoking status	Missing	7 (0.1)	0 (0.0)
	Never smoke	3,771 (39.8)	2,134 (40.4)
	Quit smoking	3,854 (40.6)	2,216 (41.9)
	Smoke less than 10 cig/day	556 (5.9)	305 (5.8)
	Smoke 10-20 cig/day	1,136 (12.0)	559 (10.6)

	Smoke more than 20 cig/day	161 (1.7)	69 (1.3)
Alcohol consumption during the last 12 months	Missing	985 (10.4)	0 (0.0)
	almost every day	811 (8.5)	502 (9.5)
	five or six days a week	530 (5.6)	348 (6.6)
	three or four days a week	1,356 (14.3)	892 (16.9)
	once or twice a week	2,418 (25.5)	1,550 (29.3)
	once or twice a month	1,260 (13.3)	777 (14.7)
	once every couple of months	745 (7.8)	475 (9.0)
	once or twice a year	740 (7.8)	402 (7.6)
	not at all in the last 12 months	640 (6.7)	337 (6.4)
Self-reported sleep characteristics			
Sleep duration ("…hours of actual sleep did you usually get at night during the last month?")	Missing	1,303 (13.7)	0 (0.0)
	<6 hrs	1,010 (10.6)	582 (11.0)
	6-8 hrs	6,318 (66.6)	4,159 (78.7)
	>8 hrs	854 (9.0)	542 (10.3)
Sleep latency ("…trouble sleeping because you cannot get to sleep within 30 minutes?")	Missing	1,640 (17.3)	0 (0.0)
	Not during the past month	3,156 (33.3)	2,210 (41.8)
	During the past month	4,689 (49.4)	3,073 (58.2)
Sleep fragmentation ("…trouble sleeping because you wake up in the middle of the night or early in the morning?")	Missing	1,394 (14.7)	0 (0.0)
	Not during the past month	1,472 (15.5)	1,049 (19.9)
	During the past month	6,619 (69.8)	4,234 (80.2)
Coughing/snoring loudly ("…trouble sleeping because you cough or snore loudly?")	Missing	2,324 (24.5)	0 (0.0)
	Not during the past month	4,367 (46.0)	3,291 (62.3)
	During the past month	2,794 (29.5)	1,992 (37.7)
Sleep medication ("…taken medicine [prescribed or over-the-counter] to help you sleep?")	Missing	1,054 (11.1)	0 (0.0)
	Not during the past month	7,029 (74.1)	4,475 (84.7)
	Presence of the event	1,402 (14.8)	808 (15.3)
Daytime sleepiness ("…had trouble staying awake while driving, eating meals, or engaging in social activity?")	Missing	1,067 (11.3)	0 (0.0)
	Not during the past month	7,184 (75.7)	4,531 (85.8)
	During the past month	1,234 (13.0)	752 (14.2)
Sleep quality ("During the past month how would you rate your sleep quality overall?")	Missing	986 (10.4)	0 (0.0)
	Good quality	2,050 (21.6)	1,332 (25.2)
	Poor quality	6,449 (68.0)	3,951 (74.8)

Metabolic Syndrome (MetS)			
Self-reported MetS components	Missing	516 (5.4)	0 (0.0)
	Elevated waist circumference (EWC)	1,826 (19.2)	1,101 (20.8)
	High blood pressure (HBP)	672 (7.1)	350 (6.6)
	Diabetes (DM)	128 (1.3)	57 (1.1)
	EWC and HBP	645 (6.8)	322 (6.1)
	EWC and DM	172 (1.8)	73 (1.4)
	HBP and DM	90 (0.9)	34 (0.6)
	EWC and HBP and DM	181 (1.9)	93 (1.8)
	None	5,255 (55.4)	3,253 (61.6)
Directly measured MetS components	Missing	1,076 (10.9)	0 (0.0)
	Elevated waist circumference (EWC)	2,347 (23.7)	1,453 (27.5)
	High blood pressure (HBP)	704 (7.1)	386 (7.3)
	Diabetes (DM)	61 (0.6)	23 (0.4)
	EWC and HBP	1,064 (10.7)	606 (11.5)
	EWC and DM	163 (1.7)	93 (1.8)
	HBP and DM	84 (0.8)	39 (0.7)
	EWC and HBP and DM	269 (2.7)	132 (2.5)
	None	4,137 (41.8)	2,551 (48.3)

[1]Household structure as classified by (Fowler *et al.* 2014)

4.2.4.2 Potential analytical determinants of variation in the association between sleep and MetS

Figures 4.2-4-13 summarise the results of logistic regression analyses examining the relationship between each MetS component, combination of MetS components, and the seven self-reported sleep characteristics available from participants in the UKHLS NHA (see also Table 4.3 for a full list of these). Figures 4.2-4.7 use directly measured MetS components, while Figures 4.8-4.13 use self-reported data as measures of each MetS component. The first three of each set of Figures (i.e. Figures 4.2-4.4 and 4.8-4.10) use those participants who did not display *any* of the three MetS components as the referent group; while the second three of each set of Figures (i.e. Figures 4.5-4.7 and 4.11-4.13) use those participants who did not display *the particular* component (or combination of components) being examined as the referent. Finally, in each set of three Figures, the models summarised in the first (i.e. Figures 4.2, 4.5, 4.8 and 4.11) are unadjusted for any potential confounders, while the second (i.e. Figures 4.3, 4.6, 4.9 and 4.12) and third (i.e. Figures 4.4, 4.7, 4.10 and 4.13) summarise models adjusted for sociodemographic (age, sex, marital/cohabitation status, educational attainment and household composition) and contemporaneous lifestyle (diet, smoking status, alcohol consumption and sport participation) factors, respectively.

To address each of the key questions posed by the present Chapter (Part II) it is necessary to read within and across these 12 Figures in order to assess whether any variation in the relationship between (different characteristics of) sleep and (different combinations of) MetS components was associated with: the use of different referent groups; the use of directly measured vs. self-reported components of MetS; and the inclusion of sociodemographic and contemporaneous lifestyle variables in any adjustment sets used. To facilitate this process, it is worth considering, first, the likely impact of the three methodological issues on the analysis of MetS itself (which, in the present study, was defined as a combination of all three available components of MetS; i.e. elevated waist circumference *and* high blood pressure *and* diabetes): (i) the use of different referent groups; (ii) the use of directly measured vs. self-reported components of MetS; and (iii) the adjustment for potential (sociodemographic) confounders and possible (lifestyle) mediators

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Figure 4.2 Logistic regression analyses of the relationship between different directly measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, before adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

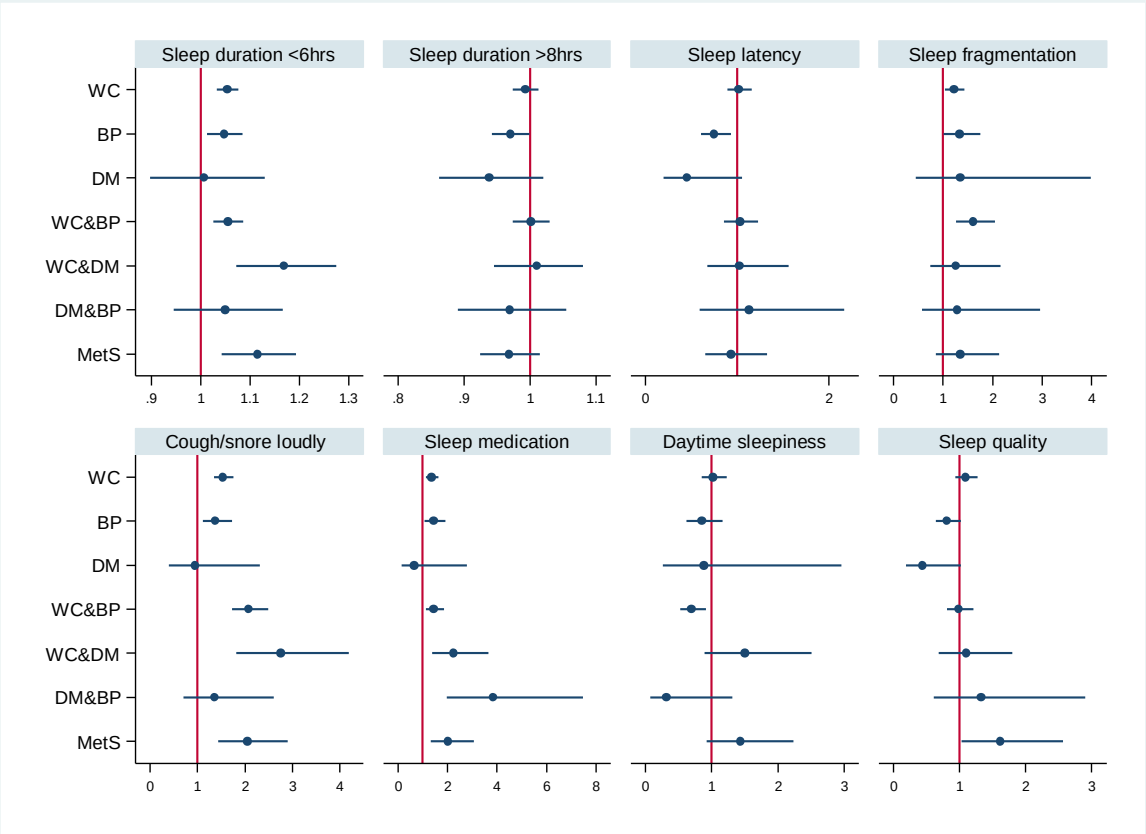


Figure 4.3 Logistic regression analyses of the relationship between different directly measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

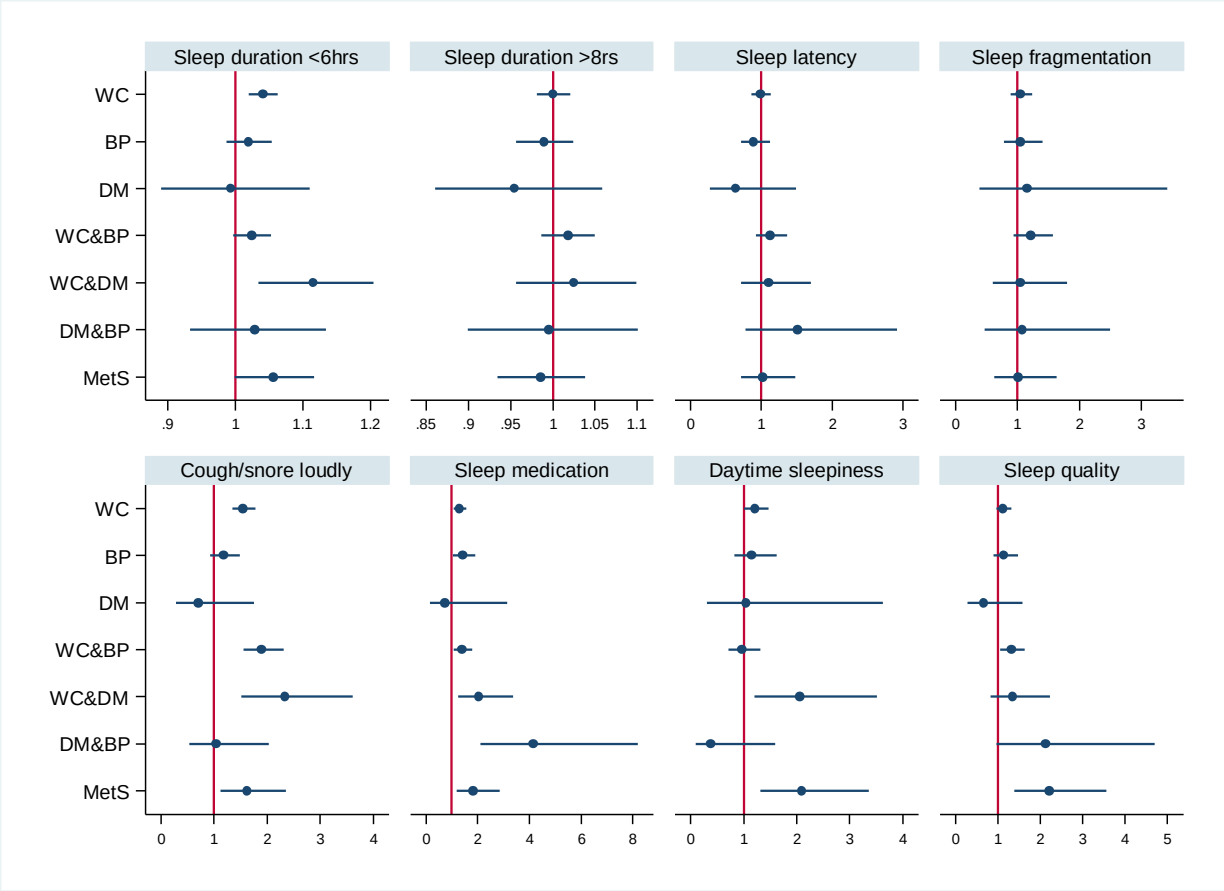


Figure 4.4 Logistic regression analyses of the relationship between different directly measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

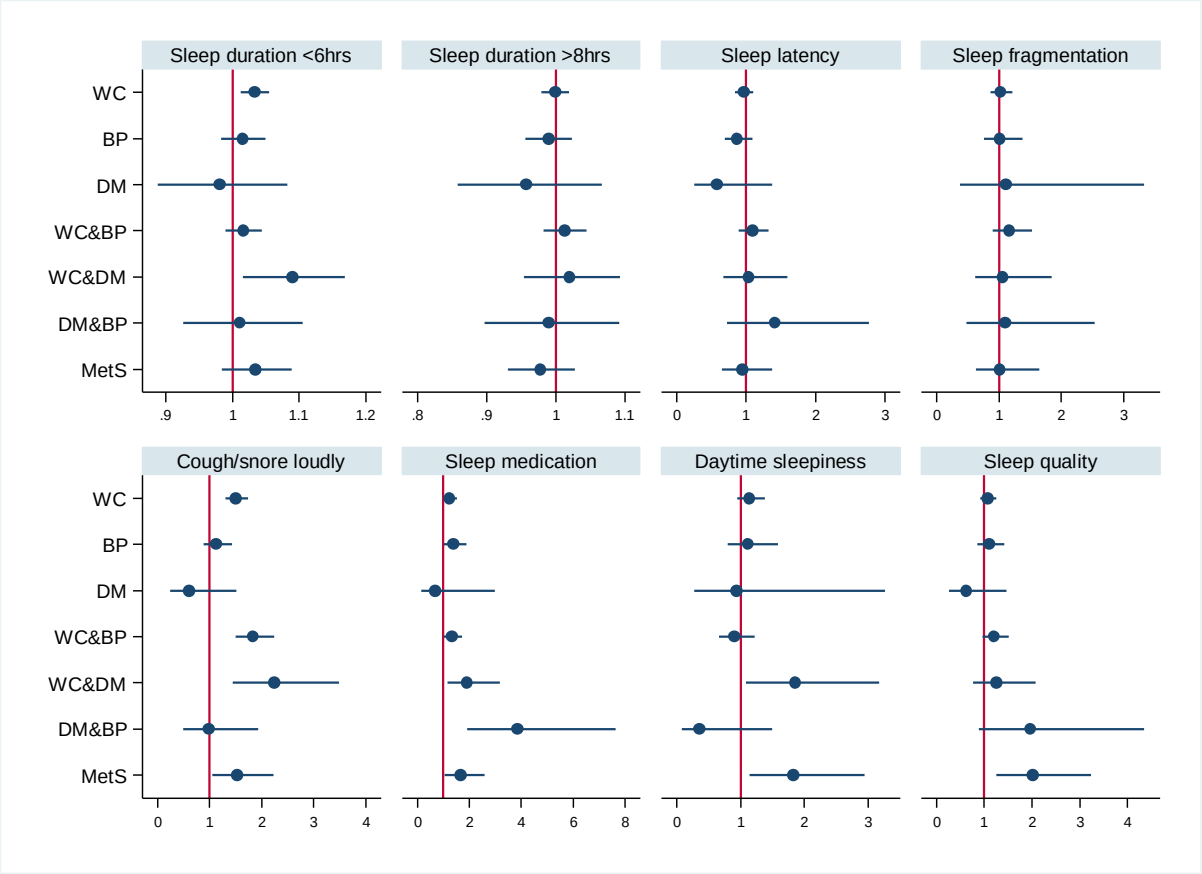


Figure 4.5 Logistic regression analyses of the relationship between different directly measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, before adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

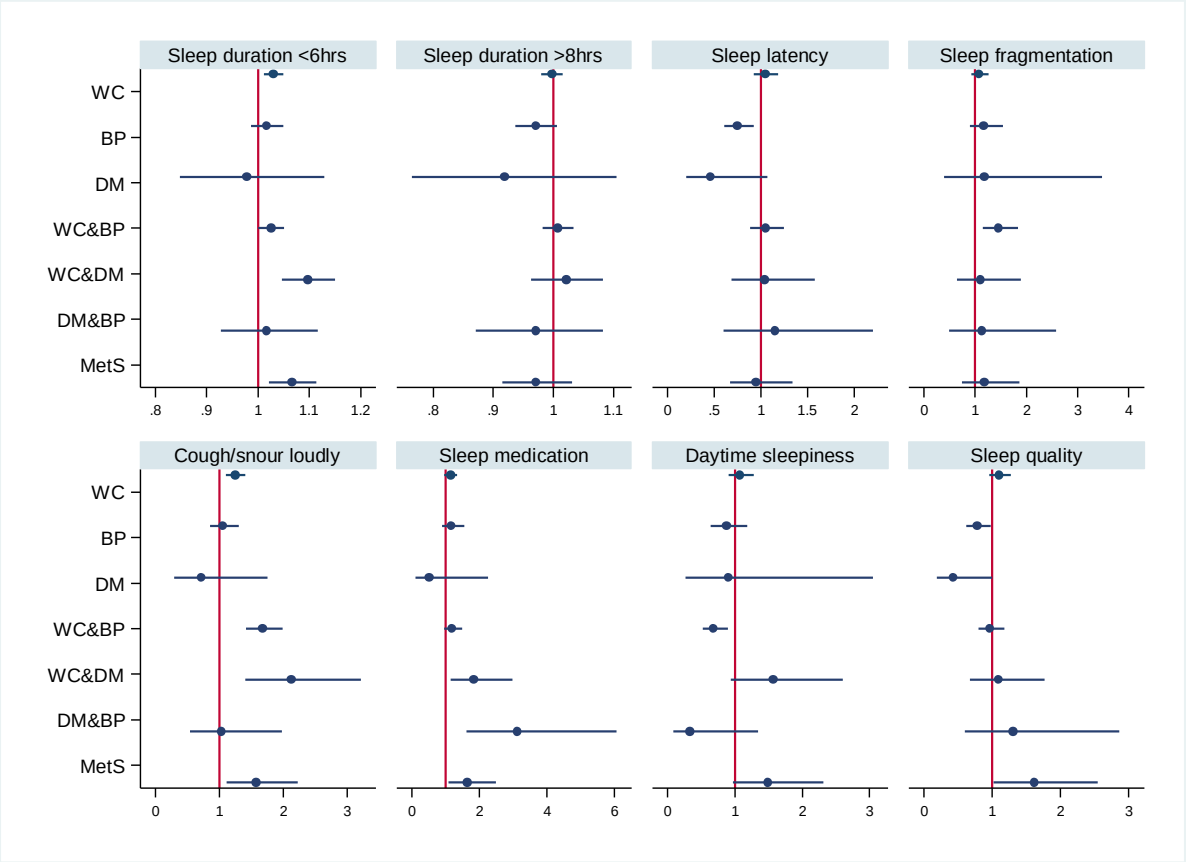


Figure 4.6 Logistic regression analyses of the relationship between different directly measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

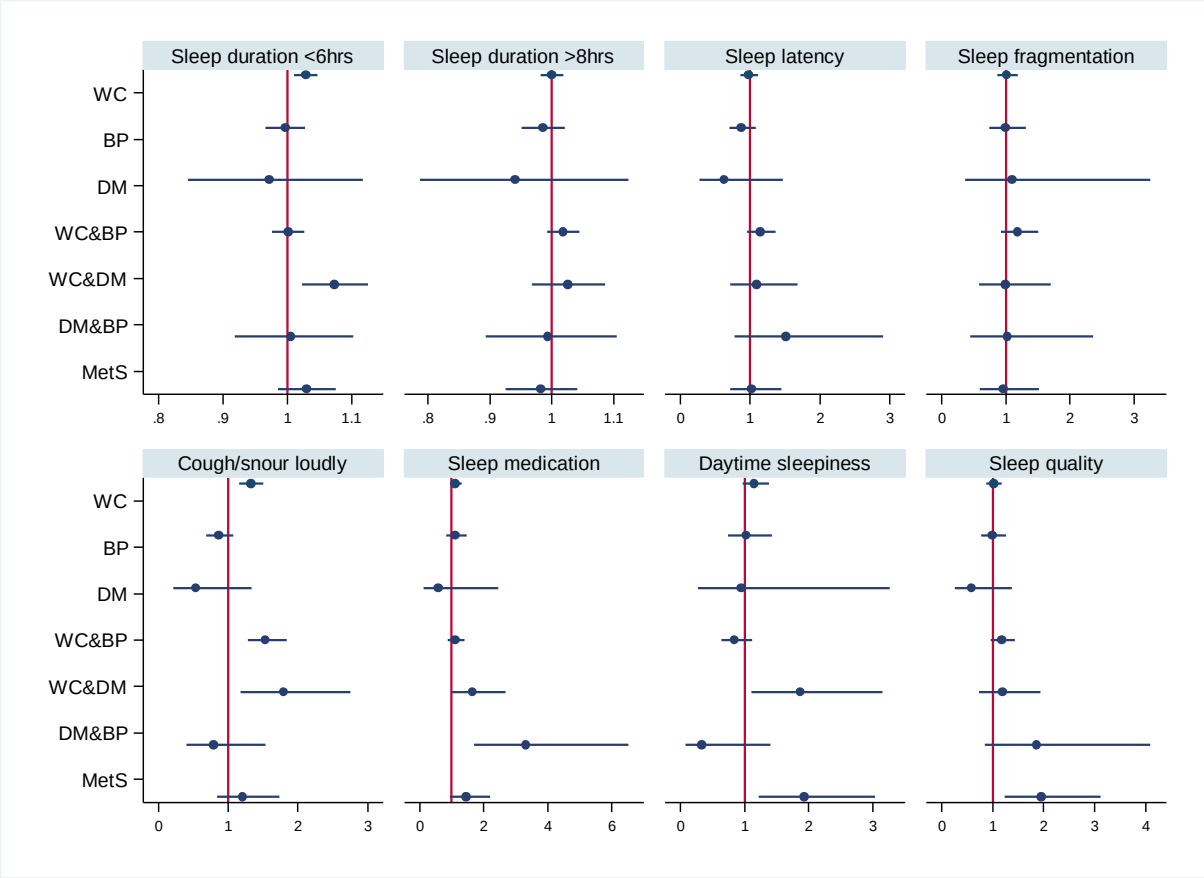


Figure 4.7 Logistic regression analyses of the relationship between different directly measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

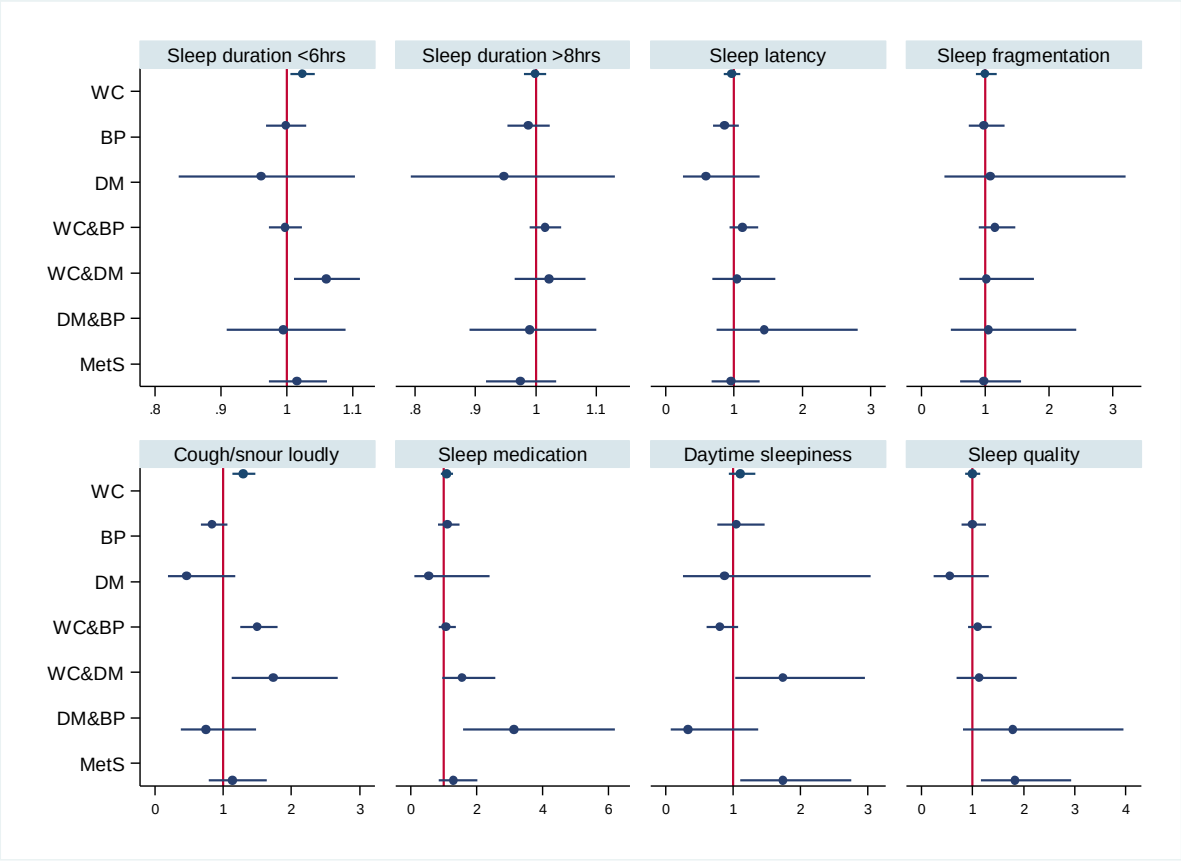


Figure 4.8 Logistic regression analyses of the relationship between different self-reported components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, before adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses**.**

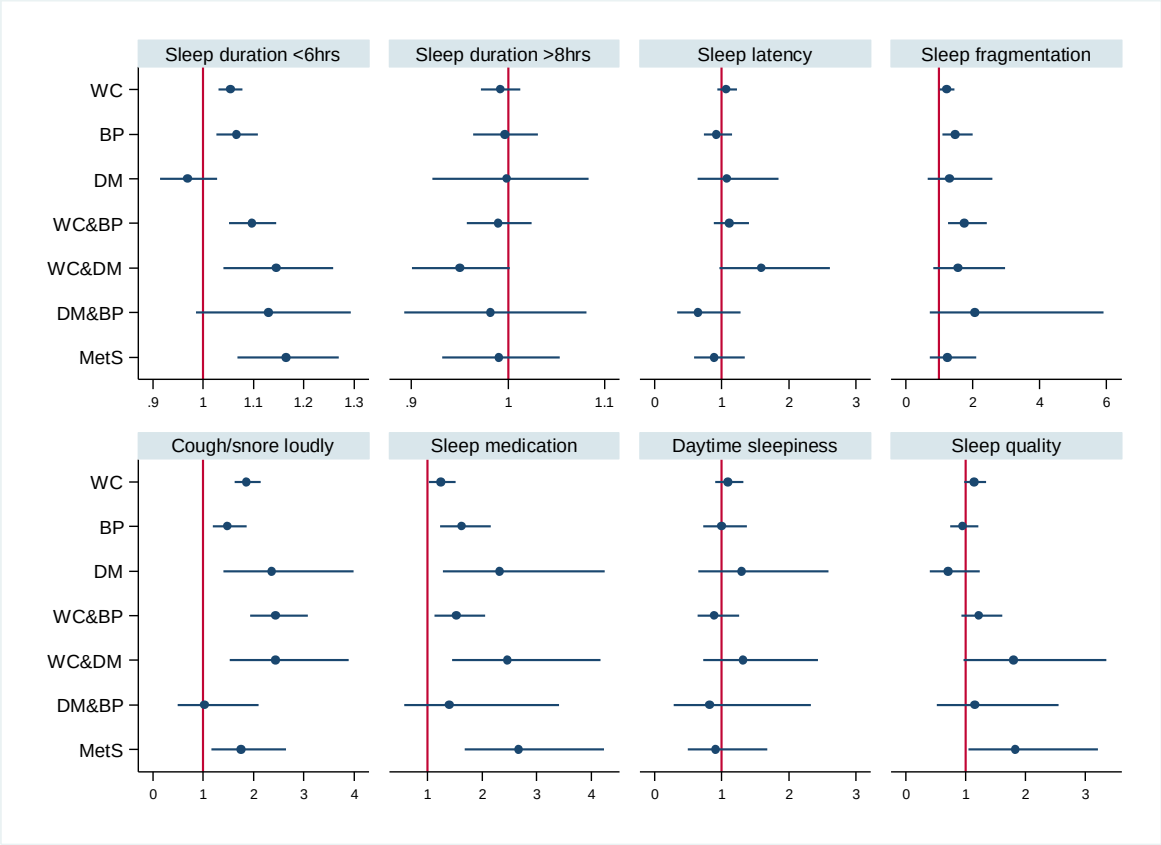


Figure 4.9 Logistic regression analyses of the relationship between different self-reported components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses**.**

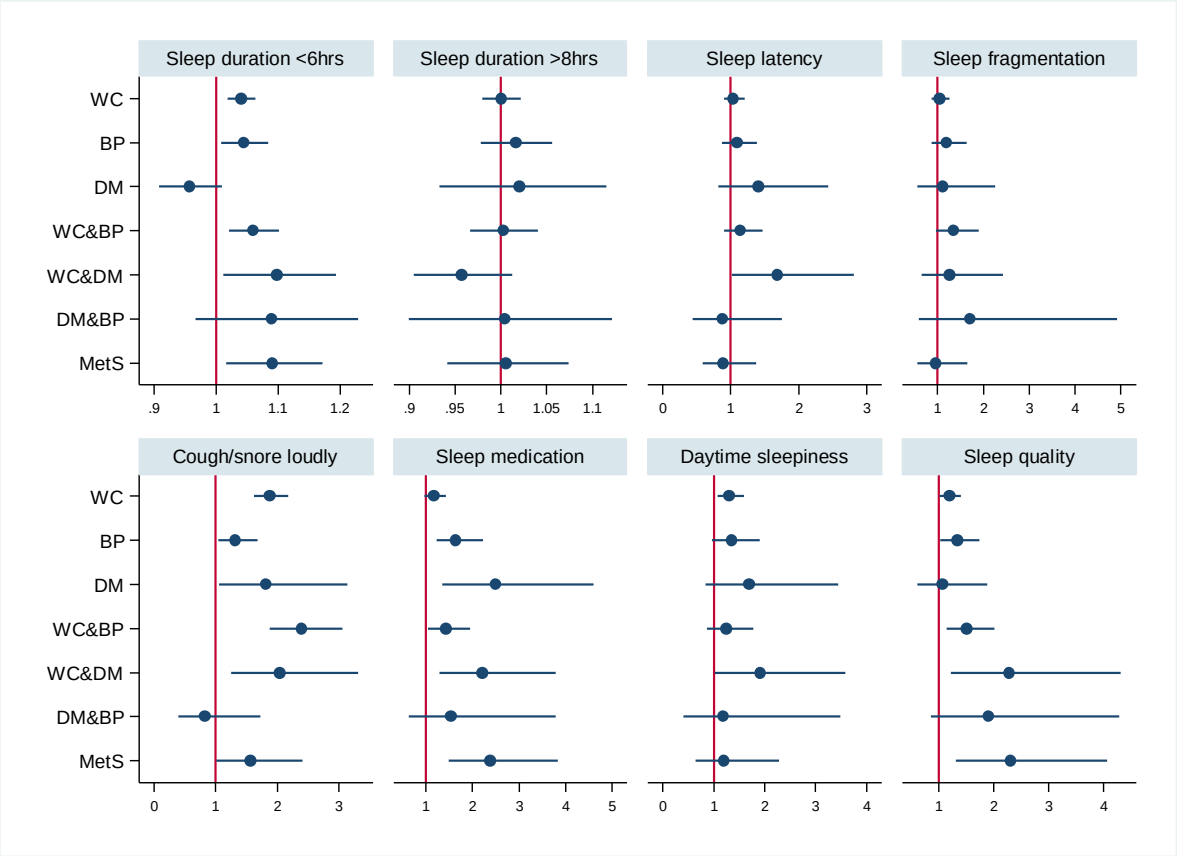


Figure 4.10 Logistic regression analyses of the relationship between different self-reported components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses**.**

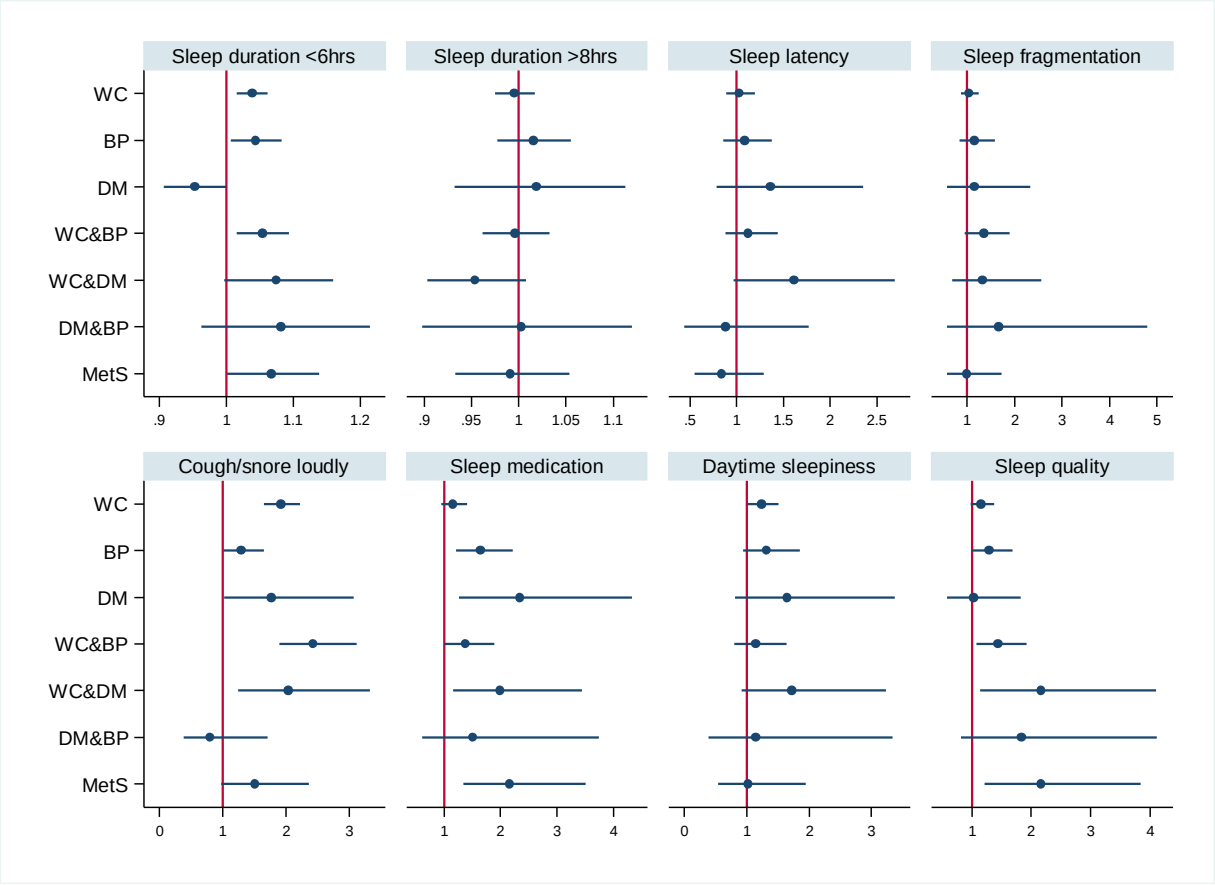


Figure 4.11 Logistic regression analyses of the relationship between different self-reported components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, before adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses**.**

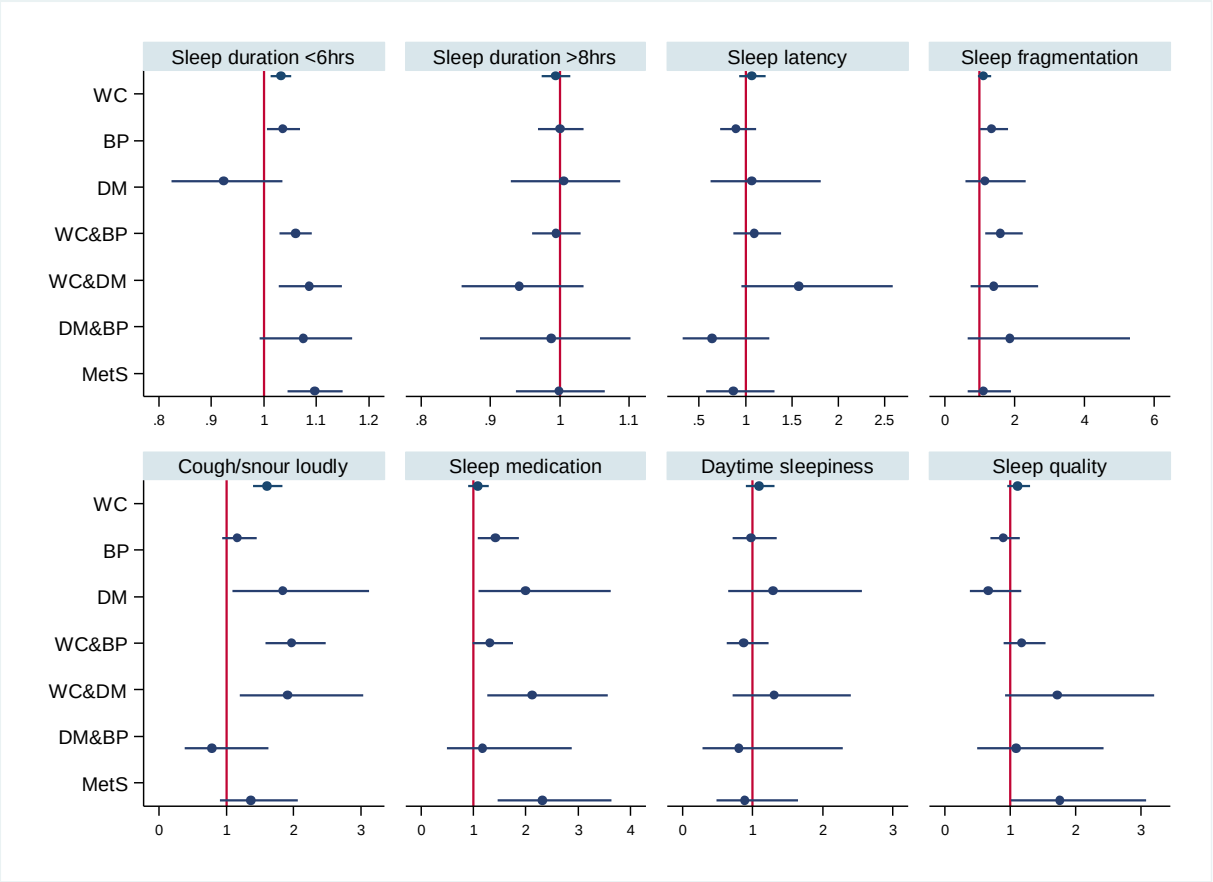


Figure 4.12 Logistic regression analyses of the relationship between different self-reported components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses**.**

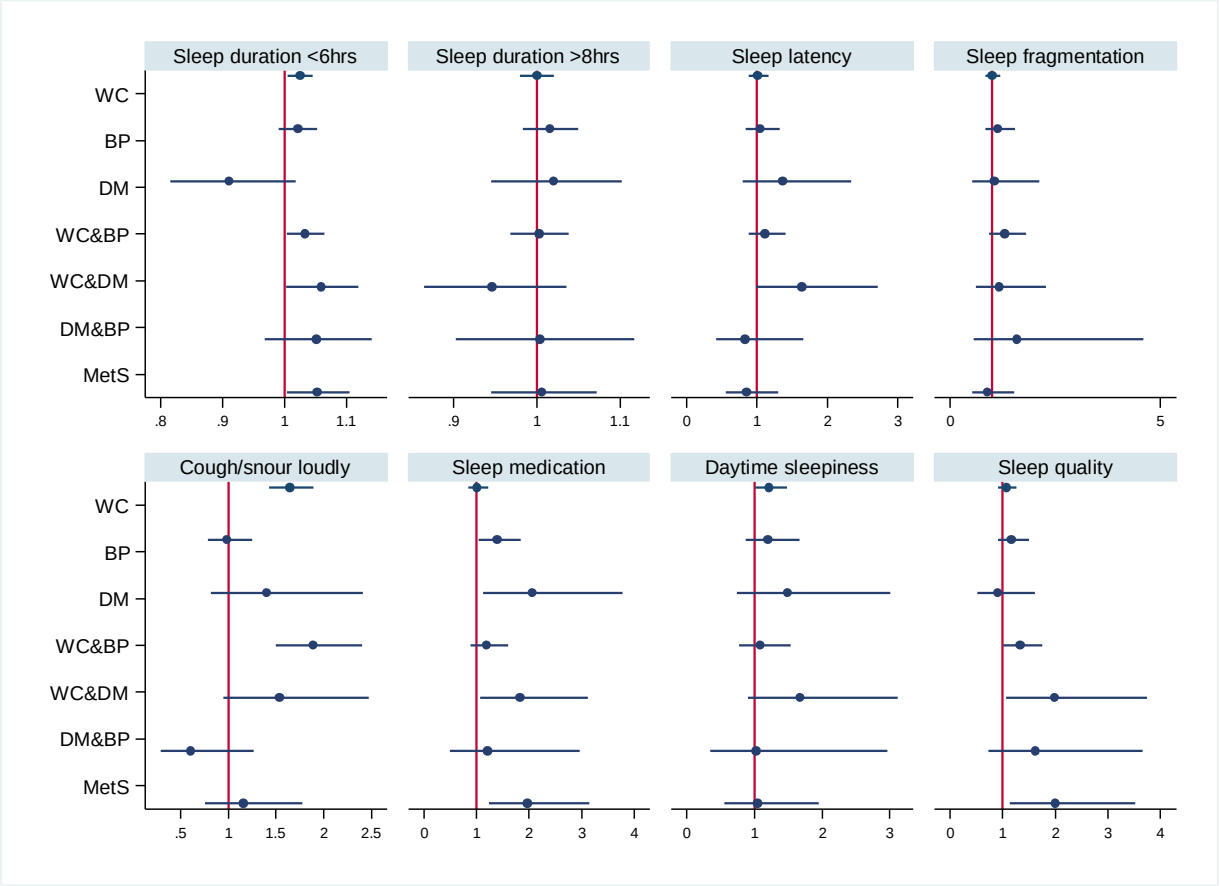
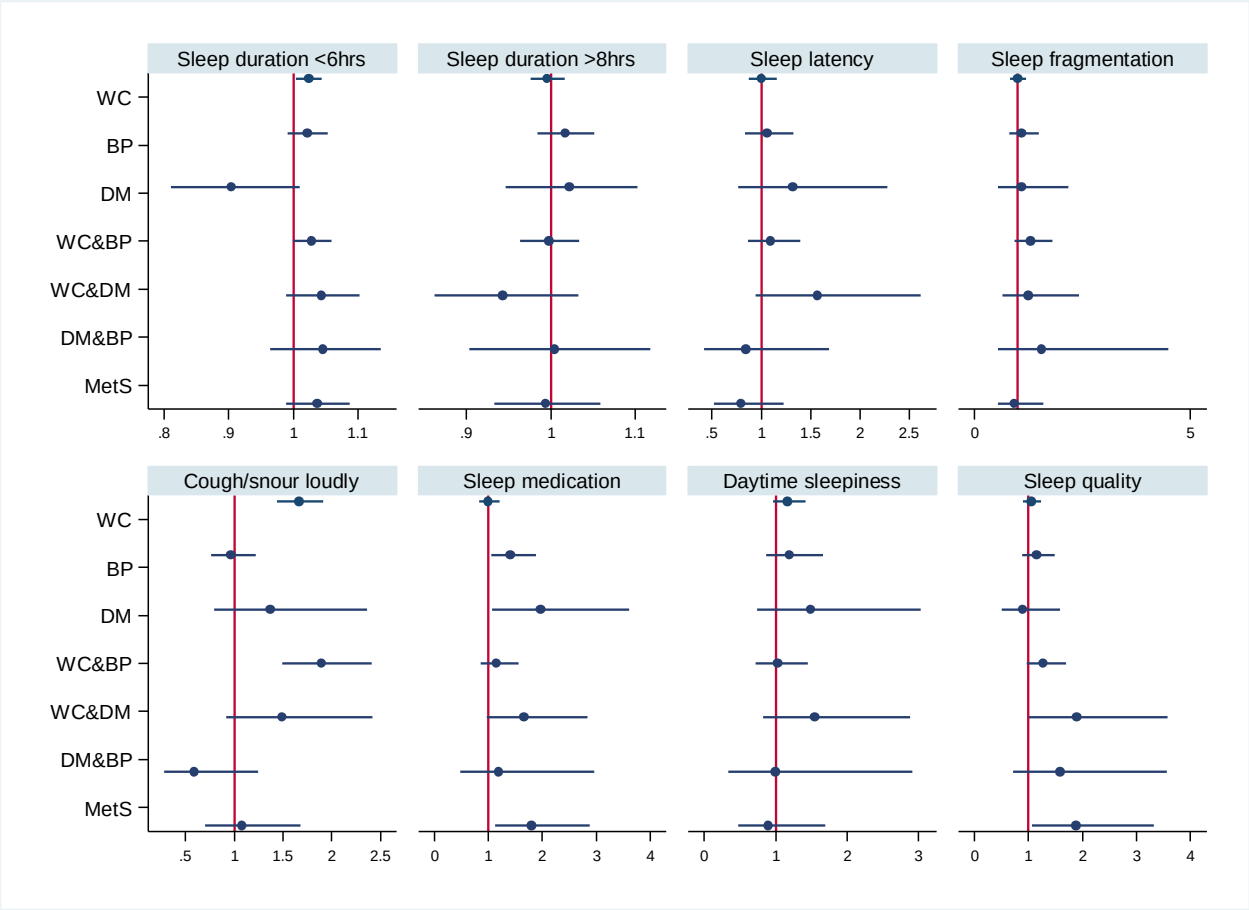


Figure 4.13 Logistic regression analyses of the relationship between different self-reported components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses**.**



4.2.4.3 Methodological factors influencing analyses of the association between MetS and sleep

4.2.4.3.1 The impact of different referent groups on the associations between MetS and sleep

Assuming that directly measured components of MetS offer the most accurate basis upon which to classify MetS (as a combination of elevated waist circumference, high blood pressure and diabetes), and based solely on comparisons between the unadjusted models summarised in Figures 4.2 (using participants that did not display *any* of the three MetS components as the referent) and 4.5 (using, as the referent for MetS itself, participants displaying fewer than all three of the MetS components), it is clear that both Figures reveal very similar relationships between MetS and the seven self-reported sleep characteristics. MetS was associated with a higher risk of short sleep duration (≤6hrs), loud coughing/snoring, sleep medication use and poor sleep quality in both sets of analyses.

Both sets of analyses also revealed that MetS was consistently associated with an elevated risk of sleep fragmentation and daytime sleepiness, and with a lower risk of prolonged sleep (≥8hrs). However, a comparison of these two sets of models indicates that the inclusion of participants who might have had one or two (though not all three) components of MetS in Figure 4.5 substantially attenuated the associations observed in Figure 4.2 (where the referent group included only healthy participants – i.e. participants who did not display *any* components of MetS).

For example, using a healthy referent group, the unadjusted association between MetS and short sleep duration was stronger (RRR:2.60; 95%CI:1.64,4.13; Figure 4.2) than when using a referent group that included participants displaying one or two MetS components (RRR:1.88; 95%CI:1.20,2.94; Figure 4.5); likewise, the odds of loud coughing/snoring (OR:2.04; 95%CI:1.44,2.90), using sleep medication (OR:2.01; 95%CI:1.32,3.08), and poor quality sleep (OR:1.62; 95%CI:1.03,2.57), were all higher when assessed using a healthy referent group than when the referent group included some participants displaying one or two components of MetS (coughing/snoring OR:1.57; 95%CI:1.11,2.22; sleep medication OR:1.65; 95%CI:1.09,2.50; poor sleep quality OR:1.61; 95%CI:1.02,2.54).

Indeed, looking further afield than MetS itself to individual components of MetS (and different pairs of these), and including those analyses using self-reported MetS, a consistent pattern of effect attenuation is evident when comparing models using participants that do not display *any* components of MetS vs. those in which the

referent group includes some participants displaying one, two and/or (for those models examining just one or two components) all three components of MetS (i.e. MetS itself as classified in the present Chapter). These comparisons indicate that the referent group used influences the strength of any association between MetS and sleep; a finding that may not be surprising given the increased risk of less favourable sleep observed for many of the three components (and combinations of components) of MetS, as will be examined in greater detail later.

4.2.4.3.2 The impact of using directly measured vs. self-reported MetS on the association between MetS and sleep

Given the attenuation of effect size observed when using referent groups containing *some* vs. *no* participants displaying (one or more) MetS components, the comparisons that follow focus on models using healthy referent groups (i.e. referent groups comprising participants who displayed no components of MetS; Figures 4.2 and 4.8). These offer a comparison of unadjusted models examining the association between MetS and sleep where MetS was based on either: directly measured components (i.e. using measurements of waist circumference, blood pressure, HbA1c and diabetic medication undertaken during the UKHLS NHA; Figure 4.2); or self-reported indicators thereof (i.e. using self-reported height and weight to estimate waist circumference, and self-reported clinical diagnoses of high blood pressure and diabetes; Figure 4.8). In this instance there was a tendency for the associations between MetS and sleep to be stronger where MetS was based on self-reported indicators of each MetS component (i.e. Figure 4.8) than where the MetS had been directly measured (i.e. Figure 4.2).

In particular, the unadjusted associations between directly measured MetS and short sleep duration (<6hrs; RRR:2.60; 95%CI:1.64,4.14), sleep medication (OR:2.01; 95%CI:1.32,3.08), and poor sleep quality (OR:1.62; 95%CI:1.03,2.57) were all lower than those observed between self-reported MetS and sleep (short duration RRR:3.41; 95%CI:2.06,5.63; medication OR:2.67; 95%CI:1.69,4.21; poor quality OR:1.84; 95%CI:1.05,3.22). However, this was not the case for loud coughing/snoring (directly measured MetS OR:2.04; 95%CI:1.44,2.90; self-reported MetS OR:1.75; 95%CI:1.16,2.65) and closer examination of the remaining sleep characteristics (prolonged sleep >8hrs; latency; fragmentation and daytime sleepiness – none of which had strong associations with MetS indicates that some (latency and fragmentation) had very similar effect estimates with both directly measured and self-reported MetS, while others displayed either an attenuation of risk when using self-reported MetS (daytime sleepiness) or an attenuated risk when using directly measured MetS (prolonged sleep).

Looking elsewhere in Figures 4.2 and 4.8 across associations between separate (and different combinations of) MetS components, a similar pattern is evident: some effect estimates appear unaffected, some were attenuated and some were strengthened when using directly measured vs. self-reported indicators of MetS components. These findings mirror the conclusions drawn in Part I of the present Chapter, suggesting that self-reported indicators of MetS components (and classifications of MetS itself, based thereon) are broadly comparable to those provided by direct measurements thereof. The potential value of self-reported indicators of MetS components will be assessed in greater detail later (see 4.2.6.2, below), where these have been used to explore the association between MetS and sleep amongst a much larger number of UKHLS participants than those included in the NHA.

4.2.4.3.3 The impact of adjusting for potential (sociodemographic) confounders and possible (lifestyle) mediators on the association between MetS and sleep

Assuming that models using directly measured components of MetS and referent groups containing (only) healthy participants are likely to offer the most accurate assessment of any relationship(s) between MetS components (and combinations of MetS components) and sleep, the final methodological issue examined in Part II of this Chapter of the thesis (the impact of adjustment for sociodemographic and contemporaneous lifestyle factors) will once again focus on analyses of MetS itself (i.e. elevated waist circumference *and* diabetes *and* high blood pressure) as summarised in Figures 4.2-4.4. Figure 4.2 includes the results of models examining the unadjusted association between MetS and sleep, while in Figures 4.3 and 4.4 these models have been adjusted for a range of sociodemographic factors or for both sociodemographic and contemporaneous lifestyle factors, respectively.

In all three Figures MetS was associated with a increased risk of short sleep duration (<6hrs), loud coughing/snoring, sleep medication use, and poor sleep quality. However, the effect estimates of the first three sleep characteristics were all attenuated following adjustment for sociodemographic and lifestyle factors (unadjusted: short duration RRR:2.60; 95%CI:1.64,4.13; coughing/snoring OR:2.04; 95%CI:1.44;2.90; medication OR:2.01; 95%CI:1.32,3.08; sociodemographic adjusted: short duration RRR:1.72; 95%CI:1.05,2.80; coughing/snoring OR:1.62; 95%CI:1.12,2.35; medication OR:1.83; 95%CI:1.18,2.85; sociodemographic and lifestyle adjusted: short duration OR:1.41; 95%CI:0.86,2.31; coughing/snoring OR:1.52; 95%CI:1.04,2.22; medication OR:1.65; 95%CI:1.05,2.58).

Indeed the association between MetS and short sleep duration was no longer statistically significant after adjustment for both sociodemographic and lifestyle factors. In contrast, the odds of poor quality sleep (OR:1.62; 95%CI:1.03,2.57) strengthened following adjustment for sociodemographic factors (OR:2.21; 1.38,3.55) and were then only partially attenuated following (additional) adjustment for contemporaneous lifestyle factors (OR:2.01; 95%CI:1.25,3.23). Likewise, MetS was only modestly associated with an increased odds of daytime sleepiness before adjustment (OR:1.43; 95%CI:0.92,2.23) but this association strengthened following adjustment for sociodemographic factors (OR:2.01; 95%CI:1.31,3.36) only to become somewhat attenuated following additional adjustment for contemporaneous lifestyle factors (OR:1.83; 95%CI:1.13,2.94).

Broadly similar patterns were evident in the trends observed between MetS and the three remaining sleep characteristics (prolonged sleep duration, >8hrs; sleep latency; and sleep fragmentation), for each of which the associations observed were attenuated following adjustment for sociodemographic factors, but either strengthened slightly (prolonged duration and latency) or remained largely unaffected (fragmentation) following adjustment for contemporaneous lifestyle factors. These patterns were also evident in the associations observed for different MetS components (and different combinations of MetS components) in Figures 4.2, 4.3 and 4.4 – and for models using self-reported indicators of MetS components in Figures 4.8, 4.9 and 4.10 – suggesting that, in most instances, adjustment for potential confounders (i.e. sociodemographic factors) ***and*** possible mediators (i.e. contemporaneous lifestyle factors) attenuated the association between MetS components and sleep. However, for two sleep characteristics (sleep quality and daytime sleepiness) their unadjusted associations with MetS were strengthened following adjustment for sociodemographic factors, and were only then somewhat attenuated following subsequent (additional) adjustment for lifestyle factors.

These findings indicate that sociodemographic and lifestyle factors play a different role in the relationship between MetS and different characteristics of sleep. For some (notably: short duration, loud coughing and medication), where adjustment resulted in the attenuation of effect estimates, it is likely that sociodemographic and contemporaneous lifestyle factors act as confounders in the association between MetS and sleep. For others (notably: poor quality and daytime sleepiness), the role of sociodemographic and contemporaneous lifestyle factors is less clear, and it may be that (at least some of these) factors may play a more important role as competing exposures which are unaffected by MetS yet influence the likelihood or accuracy of

reporting poor sleep quality and/or daytime sleepiness. This is an issue that will be discussed in more detail later in this Chapter.

4.2.4.4 Variation in the association between MetS and sleep amongst different components (and combinations of MetS components) and different sleep characteristics

Having established that the use of referent groups comprising participants displaying some vs. no components of MetS influenced the strength of the associations between MetS and sleep – and that these associations were also influenced both by the use of directly measured vs. self-reported indicators of MetS components, and by adjustment for sociodemographic and contemporaneous lifestyle factors (see above) – all that remains is to assess whether these associations depend upon the specific MetS components used (or combinations of these), and/or on the specific self-reported sleep characteristics examined. Assuming that models using healthy referent groups, directly measured components of MetS, and analyses adjusted for potential confounders (i.e. sociodemographic factors) and/or possible mediators (i.e. contemporaneous lifestyle factors) offer the most valid insights into the associations between different components of MetS (and combinations thereof) and different sleep characteristics, what follows focusses primarily on Figures 4.3 and 4.4, with Figures 4.6 and 4.7 offering an indication of how different MetS components (and different combinations of these) fare when used to explore the association between MetS and sleep when the referent group includes some participants displaying other components (or combinations of components) of MetS.

4.2.4.4.1 Does the association between MetS and sleep depend upon the specific MetS components (or combination of MetS components) used?

Both sets of models summarised in Figures 4.3 and 4.4 display a similar pattern of associations between different MetS components (and combinations of MetS components) and the seven different self-reported sleep characteristics. As discussed previously, in both Figures MetS itself (i.e. the presence of elevated waist circumference *and* high blood pressure *and* diabetes) was associated with a higher odds of: loud coughing/snoring; sleep medication; poor sleep quality; and daytime sleepiness; while in Figure 4.3 MetS itself was also associated with a higher risk of short sleep duration (<6hrs). None of the other MetS components (or combinations of MetS components) displayed significant associations with as many different sleep characteristics, though elevated waist circumference alone was associated with four sleep characteristics (short duration, coughing/snoring, medication and daytime

sleepiness) in Figure 4.3 and with all but one of these (not daytime sleepiness) in Figure 4.4.

Indeed, a larger number of sleep characteristics displayed significant associations with elevated waist circumference alone, or in combination with diabetes (4 sleep characteristics in Figure 4.3, and 3 sleep characteristics in Figure 4.4) or high blood pressure (3 sleep characteristics in Figure 4.3, and 2 sleep characteristics in Figure 4.4) than that observed for high blood pressure alone (just 1 sleep characteristic in both Figure 4.3 and 4.4), diabetes alone (none in either Table) or both combined (just 1 sleep characteristic in both Figure 4.3 and 4.4). This appears to suggest that elevated waist circumference alone was the single most important component of MetS in terms of its association with sleep; and since MetS itself (i.e. elevated waist circumference *and* high blood pressure *and* diabetes) was only associated with one additional sleep characteristic (sleep quality) than elevated waist circumference alone in either Figure 4.3 or 4.4, it appears as if the contribution of diabetes and high blood pressure to these associations is relatively minor.

However, it is important to emphasise that there was substantial variation in the number of participants displaying only one component of MetS (or only one combination of two or three MetS components) – only n=23/5,283 (0.4%) participants displaying diabetes alone, and only n=39/5,283 (0.7%) participants displaying diabetes and high blood pressure alone, for example. While many more were associated with the 1,453/5,283 (27.5%) participants displaying elevated waist circumference alone, and the 132/5,283 (2.5%) participants with MetS itself (i.e. all three components of MetS).

A very different picture emerges from the models summarised in Figures 4.6 and 4.7, in which the referent groups used comprise all participants with any combination of MetS components *other than* that being examined. In contrast to the models in Figures 4.3 and 4.4, in which the effect estimates indicate the risk of less favourable sleep amongst participants displaying a given (combination of) MetS component(s) as compared to those participants displaying none, the models in Figures 4.6 and 4.7 offer a clearer indication of whether participants displaying a given (combination) of MetS component(s) have a different risk of less favourable sleep than all other participants in the sample examined (which, in this instance, comprise those who took part in the UKHLS NHA). In this instance, a combination of elevated waist circumference and diabetes displayed strong associations with the highest number of sleep characteristics (4: short duration, coughing/snoring, medication and daytime sleepiness) while MetS itself was only associated with 2 (daytime sleepiness and sleep quality), the same number of characteristics as that achieved by elevated waist

circumference alone (though, in this instance, the sleep characteristics concerned were short duration and coughing/snoring).

Indeed, high blood pressure alone and diabetes alone were not associated with any of the 7 sleep variables; and combinations of elevated waist circumference and high blood pressure, and of high blood pressure and diabetes, were only associated with a higher risk of one sleep characteristic each (coughing/snoring and medication, respectively). The interpretation of these very different patterns amongst each component, and combination of components, of MetS is that each poses a different (and somewhat) distinct risks to different characteristics of sleep over and above those posed by other MetS components (and combinations thereof) and this may be explained by latent confounding of one risk factor to another. The potential aetiological and clinical utility of these findings will be considered in greater detail in the Discussion section of the present Chapter (see 4.2.6 below).

4.2.4.4.2 Does the association between MetS and sleep depend upon the specific sleep characteristics examined?

As mentioned in the preceding section, there was not only substantial variation in the associations observed between different components of MetS (and combinations thereof) and self-reported sleep characteristics, but there was also substantial variation in the sleep characteristics most frequently associated with one or more (combination of) MetS components. From Figures 4.3 and 4.4 it is clear that sleep medication was more often associated with different (combinations of) MetS components than any other sleep characteristic. The next characteristic most commonly associated with MetS was coughing/snoring, followed by short duration and daytime sleepiness, and sleep quality. Indeed, three sleep characteristics (prolonged duration, >8hrs; latency and fragmentation) displayed no significant associations with any (combinations of) MetS characteristics.

Far fewer of the components/combinations of MetS were associated with self-reported sleep characteristics when the referent group used contained some participants displaying one or more components of MetS (see Figures 4.6 and 4.7). Most striking amongst these was the fall in the number of associations between components/combinations of MetS and the use of sleep medication (which fell from n=6/7 in Figures 4.3 and 4.4, to just n=2/7 in Figure 4.6 and n=1/7 in Figure 4.7). The components/combinations of MetS most affected by this decline in associations with sleep were elevated waist circumference alone and those combinations of MetS components that included this MetS component (i.e. elevated waist circumference and: high blood pressure; and both high blood pressure and diabetes – MetS itself).

These findings further confirm the important role that elevated waist circumference is likely to play in the associations observed between different components/combinations of MetS and sleep, since the inclusion of (some) participants with elevated waist circumference in the referent group used in these analyses (i.e. the models summarised in Figures 4.6 and 4.7) will have diluted any difference in sleep between these participants and those with the particular MetS component/combination being studied. These findings also confirm the likely importance of sleep medication (whether prescribed or over-the-counter, as specified in the UKHLS questionnaire) as a marker of poor sleep associated with a wide range of MetS components/combinations, since when participants with these were included in the referent group the association between the component/combination being examined and self-reported sleep medication use was substantially attenuated.

4.2.5 Sample 2 Results

4.2.5.1 Descriptive analysis

Table 4.5 summarises the distribution of sociodemographic and lifestyle variables, self-reported and directly measured MetS components, and seven self-reported sleep characteristics of UKHLS participants in Wave 1 (n=50,994), and those of these participants with complete data on all self-reported variables from Wave 1 alone (i.e. Sample 2; n=29,436). Looking first at those variables exhibiting the highest rates of missingness amongst Wave 1 participants, it is clear that: rates of missingness were low (≤1.2%) for the sociodemographic variables generated by items in the main adult questionnaire used in Wave 1; were higher (at 13.3%) for self-reported MetS components; and were much more pronounced (at 21.1%-33.3%) for self-reported sleep characteristics collected using the adult self-completion questionnaire in Wave 1.

These levels of missingness result in a substantial fall in the numbers of participants with complete data on all variables available for analysis in Sample 2 (n=29,436, 57.7% of the n=50,994 participants in Wave 1). The exclusion of such a large number of participants from the analytical sample (i.e. Sample 2) is likely to constrain the external validity of these analyses if the reduction in sample size was accompanied by changes in the distribution of key variables. To assess this possibility it is worth comparing the distribution of these variables in Sample 2 with that observed in the complete sample of participants in Wave 1. By examining the distribution of sociodemographic variables (which had only modest rates of missingness), it is clear that participants in Sample 2 were similar to participants in Wave 1 overall. In particular, a greater proportion of Sample 2 participants were female (~54%), aged <30yrs (~24%). Participants were also less likely to be single (~24%) and more likely to be married/cohabiting (~64%); and were less likely to have no educational qualifications (~12%) and more likely to be in ‘management or professional’ employment (~26%). These results suggest that the analyses based on Sample 2 are likely to be broadly representative of the UKHLS sample as a whole, not least given that the sampling frame used was, itself, designed to be representative of the UK population as a whole.

Table 4.5 Variation in the distribution of: sociodemographic; self-reported MetS components (and combinations thereof); and self-reported sleep characteristics, for all adult (≥16yrs) participated in Wave 1 (n=50,994) and complete data on all self-reported measured variables (Sample 2; n=29,436). All variables have been categorised with the distribution across categories summarised as frequencies (n) with percentages in parentheses (%).

		UKHLS Wave 1 participants n=50,994	**Sample 2 n=29,436**
Sociodemographic characteristics			
Covariates		n (%)	n (%)
Sex	Missing	0	0 (0.0)
	Male	23,208 (45.5)	13,673 (46.5)
	Female	27,786 (54.5)	15,763 (53.5)
Age	Missing	0 (0.0)	0 (0.0)
	Below 30 years old	11,543 (22.6)	7,085 (24.1)
	30-39 years old	9,317 (18.3)	5,784 (19.6)
	40-49 years old	9,707 (19.0)	5,855 (20.0)
	50-59 years old	7,683 (15.1)	4,430 (15.0)
	60years or older	12,744 (25.0)	6,282 (21.3)
Marital/cohabitation status	Missing	17 (0.1)	0 (0.0)
	Single	12,009 (23.5)	6,972 (23.7)
	Cohabited	31,642 (62.0)	18,849 (64.0)
	Separated and Divorced	4,319 (8.5)	2,373 (8.1)
	Widowed	3,007 (5.9)	1,242 (4.2)
Educational attainment	Missing	92 (0.2)	0 (0.0)
	Degree	10,954 (21.5)	7,428 (25.2)
	Other higher degree	5,537 (10.9)	3,559 (12.1)
	A-level	9,591 (18.8)	6,011 (20.4)
	GCSE	10,526 (20.6)	6,201 (21.1)
	Other qualification	5,225 (10.2)	2,677 (9.1)
	No qualification	9,069 (17.8)	3,560 (12.1)
Employment status	Missing	593 (1.2)	0 (0.0)
	Management and professional	11,121 (21.8)	7,731 (26.3)
	Intermediate	3,713 (7.3)	2,451 (8.3)
	Small employers and own account	2,709 (5.3)	1,588 (5.4)

	Lower supervisory and technical	2,080 (4.1)	1,345 (4.6)
	Semi-routine, routine and never worked long-term	9,257 (18.1)	5,050 (17.2)
	Unemployed	7,448 (14.6)	3,875 (13.2)
	Retired	10,171 (20.0)	4,994 (17.0)
	Student	3,902 (7.6)	2,402 (8.2)
Household structure[1]	Missing	65 (0.1)	0 (0.0)
	Empty nesters	24,710 (48.5)	14,302 (48.6)
	Dwelling sharing childless adults	8,240 (16.2)	4,530 (15.4)
	Partnered with child	7,465 (14.6)	4,745 (16.1)
	Partnered with children	3,175 (6.2)	1,998 (6.8)
	Large family, majority with overcrowding	3,369 (6.6)	1,709 (5.8)
	Single parent household	2,181 (4.3)	1,262 (4.3)
	Extended family, majority with overcrowding	1,789 (3.5)	890 (3.0)
Self-reported sleep characteristics			
Sleep duration ("…hours of actual sleep did you usually get at night during the last month?")	Missing	12,620 (24.8)	0 (0.0)
	<6 hrs	4,716 (9.2)	3,223 (11.0)
	6-8 hrs	28,684 (56.2)	22,344 (75.9)
	>8 hrs	4,974 (9.8)	3,869 (13.1)
Sleep latency ("…trouble sleeping because you cannot get to sleep within 30 minutes?")	Missing	13,893 (27.2)	0 (0.0)
	Not during the past month	15,228 (29.9)	12,489 (42.4)
	During the past month	21,873 (42.9)	16,947 (57.6)
Sleep fragmentation ("…trouble sleeping because you wake up in the middle of the night or early in the morning?")	Missing	13,230 (25.9)	0 (0.0)
	Not during the past month	8,538 (16.8)	7,272 (24.7)
	During the past month	29,226 (57.3)	22,164 (75.3)
Coughing/snoring loudly ("…trouble sleeping because you cough or snore loudly?")	Missing	16,997 (33.3)	0 (0.0)
	Not during the past month	21,378 (41.9)	18,823 (64.0)
	During the past month	12,619 (24.8)	10,613 (36.0)
Sleep medication ("…taken medicine [prescribed or over-the-counter] to help you sleep?")	Missing	11,215 (22.0)	0 (0.0)
	Not during the past month	32,827 (64.4)	24,777 (84.2)
	Presence of the event	6,952 (13.6)	4,659 (15.8)
Daytime sleepiness ("…had trouble staying awake while driving,	Missing	11,269 (22.1)	0 (0.0)
	Not during the past month	33,469 (65.6)	24,808 (84.3)

eating meals, or engaging in social activity?")	During the past month	6,256 (12.3)	4,628 (15.7)
Sleep quality	Missing	10,773 (21.1)	0 (0.0)
("During the past month how would you rate your sleep quality overall?")	Good quality	9,954 (19.5)	7,566 (25.7)
	Poor quality	30,267 (59.4)	21,870 (74.3)
Metabolic Syndrome (MetS)			
Self-reported MetS components	Missing	6,763 (13.3)	0 (0.0)
	Elevated waist circumference (EWC)	8,489 (16.7)	5,611 (19.1)
	High blood pressure (HBP)	2,672 (5.2)	1,514 (5.1)
	Diabetes (DM)	574 (1.1)	325 (1.1)
	EWC and HBP	2,510 (4.9)	1,415 (4.8)
	EWC and DM	704 (1.4)	370 (1.3)
	HBP and DM	423 (0.8)	217 (0.7)
	EWC and HBP and DM	726 (1.4)	393 (1.3)
	None	28,133 (55.2)	19,591 (66.5)

4.2.5.2 Population-based assessment of the association between (self-reported) MetS and (self-reported) sleep characteristics amongst a representative sample of adults from the UK

Having established that self-reported indicators could provide reasonably valid measures of the three key components of MetS examined in the present thesis (see Part I of the present Chapter); and having demonstrated in Part II of the present Chapter that these self-reported measures of MetS displayed very similar relationships with self-reported sleep to those observed for directly measured MetS components, the final aim of Part II of the present Chapter was to assess the potential utility of self-reported MetS components in larger, population-based studies of any associations between MetS and sleep. To demonstrate this potential, the present Part repeated the analyses of self-reported MetS and self-reported sleep conducted on the n=5,283 participants in the UKHLS NHA (for whom data on both self-reported and directly measured components of MetS were available) on the far larger number of UKHLS participants (n=29,436) providing only data on self-reported MetS in Wave 1 (Figures 4.14, 4.15, 4.16 and 4.17). Once again, these models generated very similar findings to those observed in the smaller (NHA) sample (of n=5,283), MetS itself being associated with elevated risks of no fewer than n=6/7 self-reported sleep characteristics (including sleep fragmentation), even after adjustment for sociodemographic confounding (Figure 4.15): short duration (RRR:2.32; 95%CI:1.80,2.99); fragmentation (OR:1.44; 95%CI:1.09,1.92); loud coughing/snoring (OR: 2.53; 95%CI:2.05,3.12); medication (OR:2.25; 95%CI:1.79-2.84); daytime sleepiness (OR:1.59; 95%CI:1.21,2.11); quality (OR:1.53;95%CI:1.20,1.94). In part, the larger number of self-reported sleep characteristics associated with MetS here simply reflects the greater statistical power of the larger number of participants involved (i.e. those included in Sample 2; n=29,436); in part, these reflect the absence of lifestyle factors in the adjustment sets used in these analyses (since items on lifestyle factors were not included in the UKHLS questionnaires used in Wave 1). As such, the effect estimates presented in Figure 4.15 are also likely to reflect the impact of unadjusted confounding (for lifestyle factors and any other latent confounders), and are unlikely to be as strong as they appear. Nonetheless, since the sociodemographic characteristics of participants in Sample 2 were very similar to those in Wave 1 as a whole (see Table 4.5), and since the latter were selected with the intention of generating a representative sample of the UK population, the results summarised in Table 4.15 offer the first comprehensive assessment of the association between MetS and sleep in the UK population. This assessment indicates that a variety of MetS components, and combinations thereof, display strong associations with a number of

self-reported sleep characteristics, and suggest that MetS is associated with an elevated risk of less favourable sleep outcomes.

Figure 4.14 Logistic regression analyses of the relationship between different self-reported measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=29,436 participants included in Wave 1 of the UKHLS, before adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses**.**

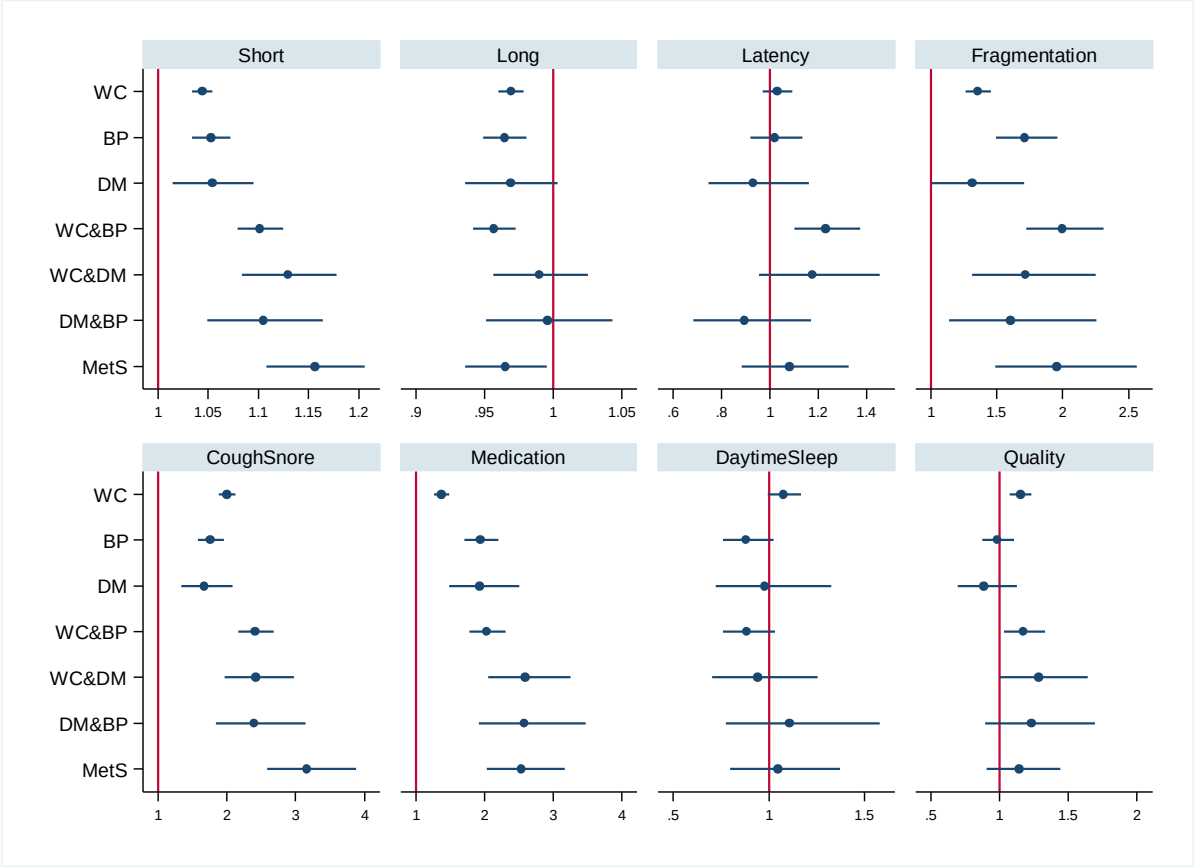


Figure 4.15 Logistic regression analyses of the relationship between different self-reported measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=29,436 participants included in Wave 1 of the UKHLS, after adjustment for sociodemographic variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses**.**

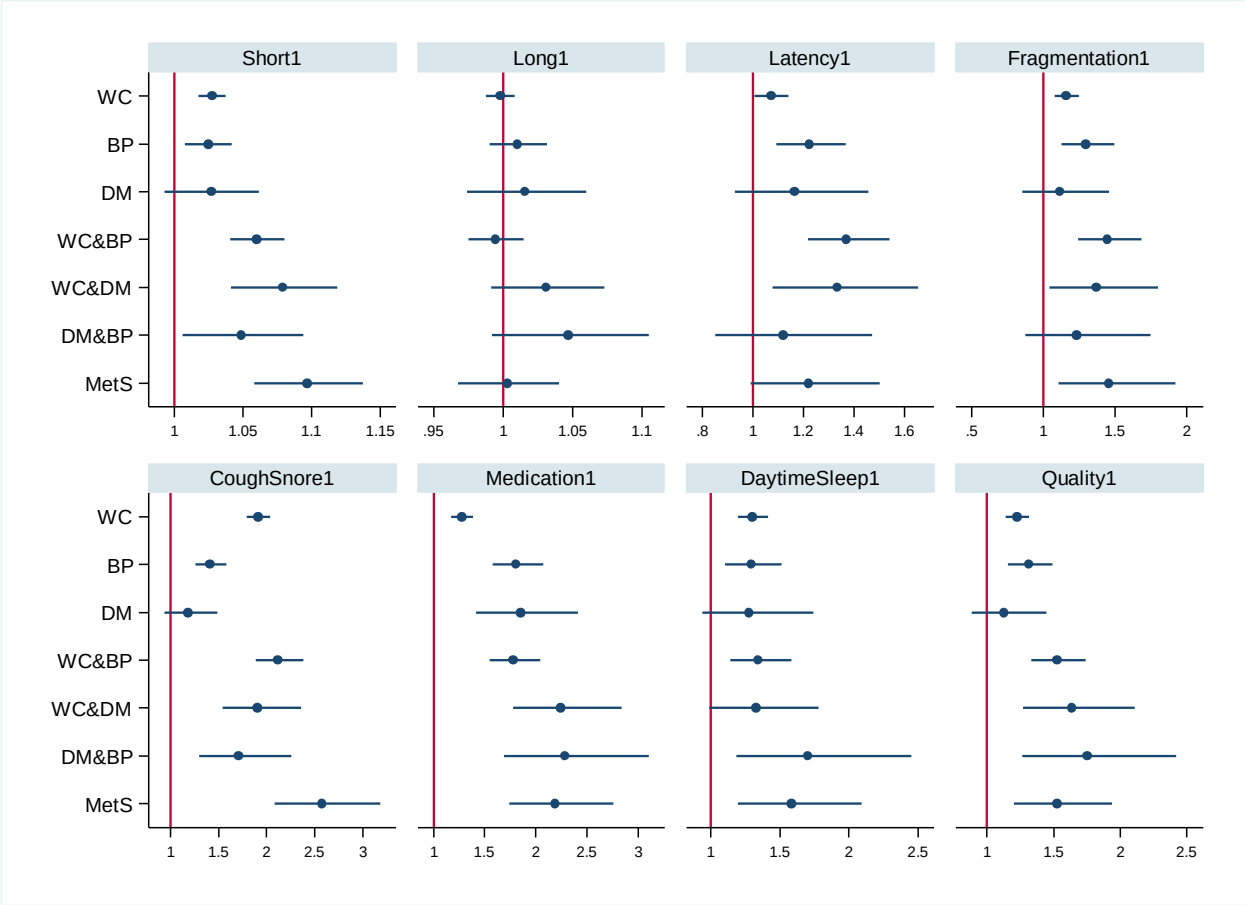


Figure 4.16 Logistic regression analyses of the relationship between different self-reported measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=29,436 participants included in Wave 1 of the UKHLS, before adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses**.**

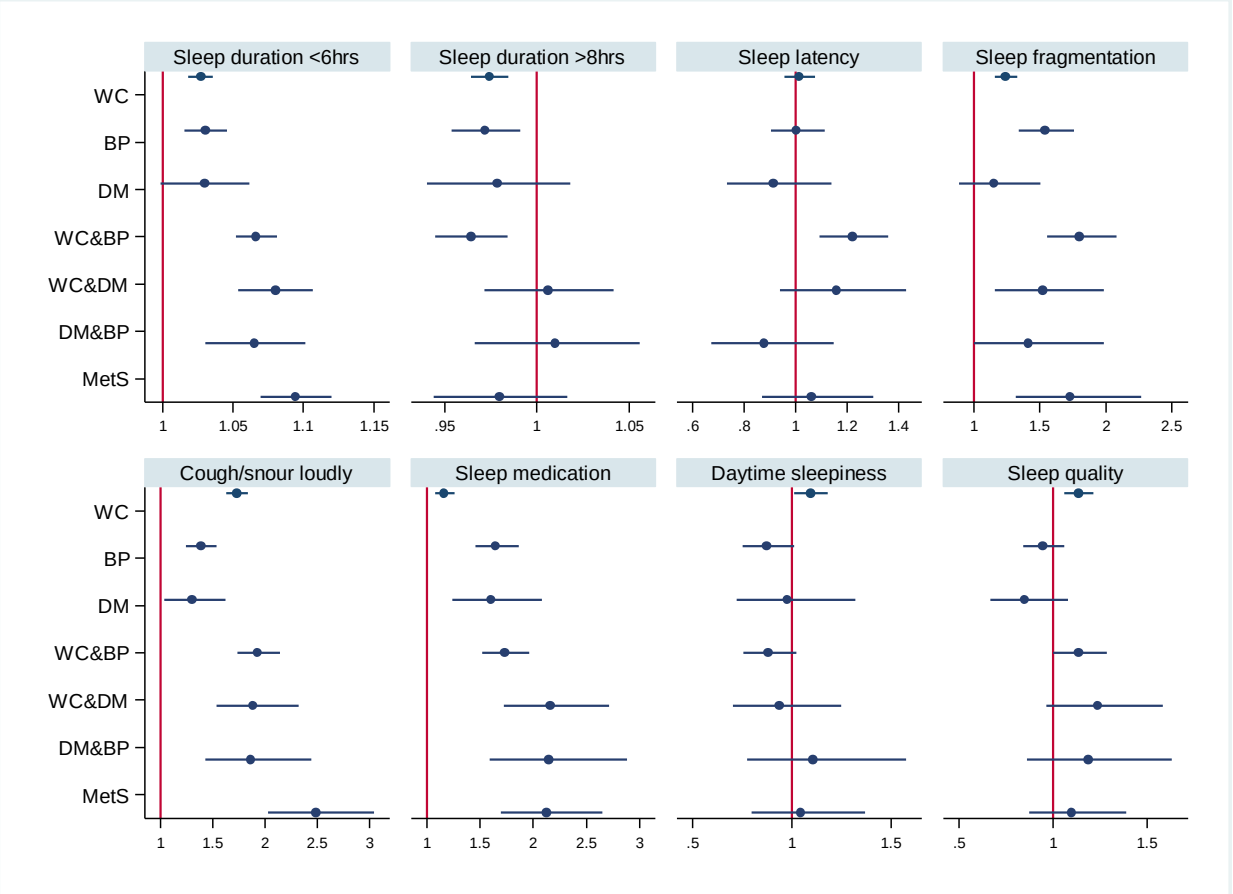
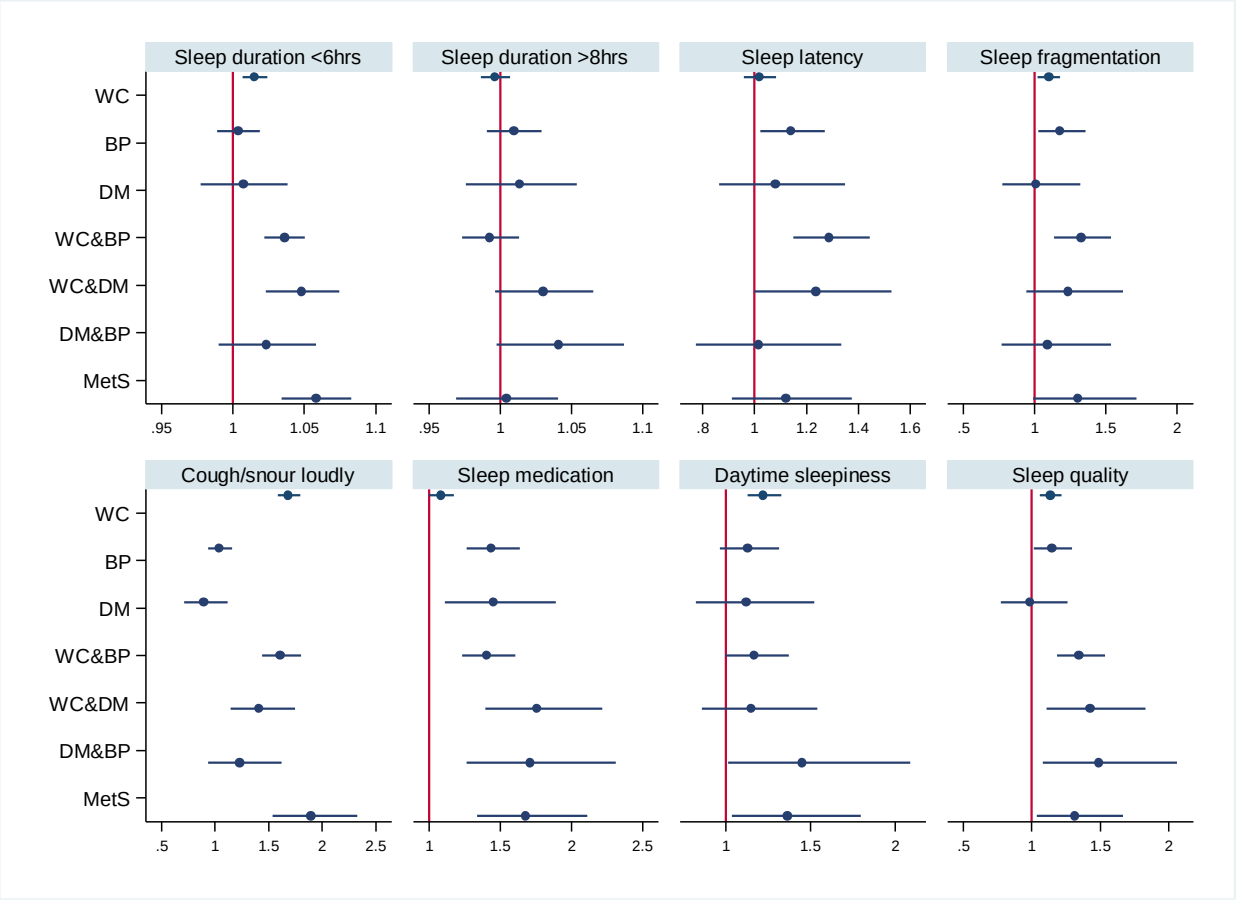


Figure 4.17 Logistic regression analyses of the relationship between different self-reported measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=29,436 participants included in Wave 1 of the UKHLS, after adjustment for sociodemographic lifestyle variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). Results are given as relative risk ratios for sleep duration (RRRs; for multinomial logistic analyses) or odds ratios for sleep latency, sleep fragmentation, cough/snore loudly, sleep medication, daytime sleepiness and sleep quality (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses**.**



4.2.6 Discussion

Limitations

The data presented in Part II of this Chapter are limited in a number of key respects, including the absence of data on dyslipidaemia; the specific cut-off values used for each component of MetS; the absence of data on self-reported waist circumference; the different sociodemographic characteristics of participants in Sample 1 and Wave 1; the limited numbers of participants with complete data (together with the fact that it proved impracticable to perform multiple imputation; see Chapter 3); and the limited prevalence of some components of MetS (and for some MetS component combinations).

The collection of non-fasting blood samples during the NHA meant that these could not provide reliable measures of blood lipid values. Since the assessment of dyslipidaemia remains challenging (and highly contested; see, for example (Ridker 2014)) without such samples – not least in non-clinical populations with access to over-the-counter lipid lowering medicine and supplements (Danavi, Memon and Phan 2015; Qato *et al.* 2016) –robust data on dyslipidaemia were not available for UKHLS participants in the NHA. At the same time, the development of reliable self-assessment tools for collecting self-reported data on dyslipidaemia remains elusive (Tolonen *et al.* 2014), and none of the items included in any of the Wave 1 and Wave 2 UKHLS questionnaires generated data on plausible (let alone valid) self-reported indicators of blood lipid levels. For these reasons the present thesis was unable to include this important component of MetS (whether directly measured or self-reported) in its analysis of the association between MetS and sleep in the UKHLS. However, it was able to include all three of the other key components of MetS considered relevant to the classification of MetS itself (i.e. elevated waist circumference, high blood pressure and diabetes). Since most of the classifications of MetS itself used in previous studies exploring the association between MetS and sleep require the presence of at least three separate MetS components, the classification of MetS itself adopted in the present thesis (and used in the analyses presented in Part II of the present Chapter), would have identified a substantial proportion of those UKHLS participants with MetS as recognised by most of these classifications – i.e. UKHLS participants exhibiting a combination of elevated waist circumference ***and*** high blood pressure ***and*** diabetes.

Nonetheless, since the classification of MetS itself used in Part II of the present Chapter may have excluded a number of UKHLS participants with dyslipidaemia together with any two of the other three MetS components, these participants would have been included in the referent group for those analyses (i.e. those summarised in: Figures 4.5, 4.6 and 4.7; Figures 4.11, 4.12 and 4.13; and Figures 4.16 and 4.17, where the referent group included participants who did not display ***the particular*** component (or combination of components) of MetS being examined. This would also have been the case for those analyses using referent groups comprising ostensibly healthy participants who did not

display *any* of the three MetS components available (i.e. those analyses summarised in Figures 4.2, 4.3 and 4.4; Figures 4.8, 4.9 and 4.10; and Figures 4.14 and 4.15), simply because some of these ('healthy') participants may have actually displayed dyslipidaemia. However, unless the distribution of dyslipidaemia varied substantially across those groups of participants displaying three, two, one or none of the three other MetS components, the lack of data on dyslipidaemia should not have had a substantial impact on the direction or strength of associations observed between different MetS components (or different combinations of MetS components) and sleep. Unfortunately limited contemporary data are available on the distribution of these four MetS components (elevated waist circumference, high blood pressure, diabetes *and* dyslipidaemia) for samples or populations representative of the UK population. For this reason the impact of a lack of data on dyslipidaemia on the findings of Part II of the present Chapter's analyses remains unclear.

While the absence of data on dyslipidaemia may limit the specificity of any associations observed between other components/combinations of MetS and sleep, and may limit any comparison with previous studies in which data on dyslipidaemia were available (and were included in the analysis of any association between MetS and sleep), a further challenge to the comparability of the analyses conducted in Part II of the present Chapter with those from previous studies is the somewhat different cut-off points used to classify 'high' blood pressure and a 'diagnosis' of diabetes. These differences stem from the present thesis' interest in developing, evaluating and analysing self-reported indicators of MetS components to facilitate their use in larger population based samples than might otherwise be possible given the constraints of collecting direct measurements of MetS components from large numbers of participants. Indeed, these constraints are clearly evident from the decision to select only a small proportion of UKHLS participants for inclusion in the NHA, on whom direct measurements of MetS components (and other physiological and anthropometric characteristics) were then collected – a decision determined in part by the costs involved, and in part by participation-related concerns (McFall 2013).

For the purposes of the present thesis, which aimed to develop valid self-reported measures of MetS, it was necessary to examine the items available within the UKHLS questionnaires that might plausibly measure each component of MetS. As mentioned earlier, no suitable items were found on which a plausible self-report of dyslipidaemia might be based, and since the NHA itself did not provide suitable blood samples to generate direct measures of this component of MetS, a decision was taken to exclude consideration of dyslipidaemia as a component of MetS in the present thesis. However, the adult main UKHLS questionnaires did contain self-reported clinical diagnoses of both "high blood pressure" and "diabetes", and to establish relevant, directly measured referents for these two (self-reports of) clinical diagnoses, it was necessary to determine the clinical definitions

that were likely to have been used by the clinicians responsible (i.e. by the clinicians who had first told participants that they had “high blood pressure” and/or “diabetes”). Since these definitions are currently provided by the UK’s National Institute for Clinical Excellence (NICE 2011a; NICE 2011b), the most valid comparisons available between a “self-reported clinical diagnosis” of both “high blood pressure” and “diabetes” were those relevant to the specific definitions of these that would have been used by the clinicians concerned (see also Chapter 3 – in which the rationale for the choice of cut-offs used is presented in more detail). These definitions differ somewhat to those recommended by the NCPI-ATP III (Huang 2009). In particular, the definition of “high blood pressure” recommended by the NCPI-ATP III is >130 mmHg systolic or >85 mmHg diastolic, while NICE recommend that a Stage 1 formal diagnosis of “high blood pressure” is when blood pressure ≥140/90 mmHg. Likewise, the NCPI-ATP III recommend that “diabetes” be determined by fasting glucose ≥100 mg/dl, while NICE recognise three diagnostic tests of diabetes – fasting blood glucose levels ≥ 7.0 mmol/l, blood glucose levels ≥ 11.1 mmol/l following a standard oral glucose tolerance test, and/or HbA1c levels ≥ 48 mmol/mol – and since the UKHLS NHA only provided data on HbA1c the present thesis had to rely on these data alone in order to determine the presence of diabetes. Elsewhere, since antihypertensive and diabetic medication are also recognised as valid measures of “high blood pressure” and “diabetes” by the NCPI-ATP III, the detailed records of these collected from UKHLS participants during the NHA allowed this information to be applied in an identical fashion to that recognised by the NCPI-ATP III. It is therefore only in the modest differences in cut-off values for blood pressure and in the use of HbA1c values rather than that recommended by the NCPI-ATP III. While these differences are likely to have resulted in slightly more UKHLS participants identified as displaying these two components of MetS, and might thereby have altered both the magnitude and/or precision of any association(s) between these and sleep observed, it is unlikely that these differences would have been sufficient to substantially accentuate or attenuate the associations observed.

As for the assessment of elevated waist circumference, the cut-offs used for these were precisely as defined by the NCPI-ATP III, and the only differences in the classification of directly measured data on this component of MetS stem from the different measurement protocols used by the NHA and those recommended by the NCPI-ATP III. There were, however, no items requesting self-reports of waist circumference in any of the UKHLS questionnaires. Indeed, the only anthropometric variables for which self-reports were collected were height and weight. It was therefore necessary to assess the possibility of generating a reliable estimate of waist circumference based on self-reports of height and weight alone. The approach used to generate these estimates has been described in some detail in Chapter 3, and comparisons of these with the direct measurements of waist circumference collected during the NHA have been described in substantial detail in Part I of the present Chapter – comparisons suggesting that self-reported estimates of ‘elevated

waist circumference' derived from self-reported height and weight displayed comparable levels of sensitivity, specificity and predictive value to those observed for self-reports of high blood pressure and diabetes. Thus, despite the present thesis' reliance on *estimates* of self-reported waist circumference, these are unlikely to have introduced any greater lack of precision to the specification of this component of MetS than that associated with the use of self-reported high blood pressure or diabetes. Therefore, notwithstanding the limited validity of self-reported MetS components *per se* (as assessed in Part I of the present Chapter), the approaches used to generate these in the present study resulted in self-reported measures of all three components that were broadly similar in terms of their validity and potential utility, based as they were on the limited data available from self-reported indicators in the UKHLS – items that are to a large extent comparable to those used by many other questionnaire-based population surveys, both in the UK and further afield.

Finally, despite the potential benefits of using self-reported measures of MetS components for examining the prevalence of these (and any associations thereof with sociodemographic, lifestyle and other factors – including sleep, as in the present thesis) in far larger samples than might be possible using direct measurements alone, the power of any such analyses is inevitably determined not only by the total number of participants but by the prevalence of the key characteristics examined (in this instance both MetS and more/less favourable sleep). This is an issue in the present thesis, even though it deliberately chose the UKHLS as its data source on the basis that this offered not only the largest contemporary survey of sleep in the UK (using a sampling frame that aimed to be broadly representative of the UK population), but also provided directly measured data on three components of MetS from a sizeable subsample of participants (i.e. those selected for inclusion in its NHA). Indeed, even though the number of UKHLS participants with complete data on self-reported *and* directly measured MetS (Sample 1) and on self-reported variables from Wave 1 (Sample 2) were far higher than those achieved by most previous studies of the association between MetS and sleep, the low prevalence of some MetS components (and some combinations of these) mean that the analyses thereof may have been inadequately powered. For example, in the smaller of the two analytical samples (Sample 1, n=5,283) fewer than 3% of participants displayed MetS itself (i.e. the combination of all three MetS components: elevated waist circumference; *and* high blood pressure; *and* diabetes), fewer than 1.5% displayed diabetes alone (i.e. with neither of the other two components of MetS), and fewer than 1.0% displayed both high blood pressure and diabetes alone (i.e. with neither of these alone, or in combination with elevated waist circumference). Even in the larger of the two analytical samples (Sample 2, n=29,436) there were only n=393 participants with MetS itself, n=325 with diabetes alone, and only n=217 with both high blood pressure and diabetes alone. These modest sample sizes are likely to explain why none of the effect estimates generated for the associations between MetS itself and three of the self-reported sleep characteristics (prolonged duration, >8hrs; latency, and

fragmentation) achieved strong associations except (for sleep fragmentation) in Sample 2, despite some evidence of strong trends for an decreased risk of prolonged sleep duration and an increased risk of sleep fragmentation amongst participants displaying MetS itself. The very different prevalence of each component of MetS (and each combination of these) is also likely to explain why some (particularly diabetes alone, and high blood pressure and diabetes alone) had so few associations with any sleep characteristics; and why others (particularly elevated waist circumference alone, by far the most prevalent component of MetS; see Tables 4.4 and 4.5) more commonly displayed associations with almost as many self-reported sleep characteristics as MetS itself. As with all epidemiological analyses, the impact of differences in statistical power on the patterns of 'significant' results in the present study emphasises the importance of focusing on effect size estimates rather than on any (statistical) confidence in these. This possibility warrants further investigation using larger samples of participants displaying these specific components of MetS (and/or combinations of these). Nevertheless, given that in both Sample 1 and 2 the prevalence of MetS itself (i.e. the combination of all three MetS components: elevated waist circumference; ***and*** high blood pressure; ***and*** diabetes) was only consistently higher than that observed for three other components/combinations of MetS (diabetes alone; high blood pressure and diabetes; and elevated waist circumference and diabetes), the fact that MetS itself displayed a larger number of strong associations with different self-reported sleep characteristics than any of the remaining (more prevalent) components/combinations of MetS (elevated waist circumference alone; high blood pressure alone; and elevated waist circumference and high blood pressure) provides good evidence to suggest that MetS itself has association(s) with self-reported sleep across a broader range of sleep characteristics than that observed for any of the other three components/combinations of MetS. As such, Part II of the present Chapter's analyses provide stronger evidence than might seem likely (given the modest prevalence of MetS) that self-reported sleep appears most sensitive to the combination of all three components of MetS rather than any other combination thereof.

Generalizability

Since the distribution of sociodemographic characteristics amongst participants in Sample 2 ***was*** very similar to that amongst those in Wave 1, the findings generated on data from Sample 2 are likely to be broadly generalizable to both the UKHLS and the wider UK population. Nevertheless, because these data did not include the lifestyle variables available to participants in Sample 1, and since the impact of adjusting for these variables in multivariable analyses of Sample 2 suggests that (contrary to the theoretical causal path diagram chosen to guide these analyses) these operated as confounders rather than mediators, it is likely that the effect estimates generated by the fully adjusted models used for Sample 2 (in which there was no adjustment for lifestyle factors) suffer from unadjusted confounding. However, given the efforts made to address possible confounding effects in

the analysis of data from Sample 1, and given the very similar results observed amongst both samples (Sample 1 and 2), the results from Sample 2 might still be broadly generalizable.

Methodological considerations

Notwithstanding these limitations, the comprehensive analyses conducted in Part II of the present Chapter successfully addressed two of the potential flaws identified in the thesis' review of previous studies exploring the association between MetS and sleep (see Chapter 2):

(i) the use of referent groups containing unhealthy vs. healthy participants; and

(ii) the use of potentially inadequate and/or inappropriate adjustment sets:

(i) A comparison of models analysing the association between MetS and sleep using different referent groups – those containing participants who did not display ***any*** of the three available components of MetS and those using referent groups containing some participants displaying components of MetS (and combinations of these) other than ***the particular*** component(s) being examined – found very similar associations for MetS itself (i.e. the classification based on elevated waist circumference ***and*** high blood pressure ***and*** diabetes), although these were somewhat attenuated when the referent group included some participants displaying other combinations of MetS components. This may not be surprising given that some of these combinations of MetS components (particularly those that included elevated waist circumference) also had strong associations with a number of self-reported sleep characteristics (regardless of the referent group used) – meaning that the inclusion of these participants in the referent group used to evaluate the association between MetS itself and sleep will have included (within the referent) participants with other combinations of MetS components that were, themselves, associated with unfavourable outcomes across a number of sleep characteristics. Another possibility is the contribution each MetS component might have made to another; obesity, for example, is known to contribute to both diabetes and hypertension (Han and Lean 2016).

(ii) Meanwhile, the differential impact of adjustment for sociodemographic and contemporaneous lifestyle factors on the association between MetS itself and sleep demonstrates some of the challenges facing the identification of potential confounders and likely/possible mediators in analyses applying a causal path approach to cross-sectionally collected observational data. Setting aside the limited capacity for such data to generate persuasive evidence of causality, this thesis has argued consistently that even cross-sectionally collected data should be amenable to temporal interpretation and analytical modelling using causal path diagrams wherever the information available on the timing and methods of data collection permit an assessment of 'where' each of the measured variables might be temporally arranged within the causal path diagram (Pearl 2000; Glass *et al.* 2013;

Rottman and Hastie 2014). It was on this basis that six separate directed acyclic graphs (DAGs) were presented in Chapter 2, and the plausibility of each discussed in relation to the datasets and statistical models used by each of the studies reviewed therein. It was also the basis on which the analyses undertaken for the present Chapter (Part II), using cross-sectional data from the UKHLS, assumed that: sociodemographic factors were likely to act as potential confounders in the association between MetS and sleep; while contemporaneous lifestyle factors were likely to operate as possible mediators (variables falling on the causal path between the exposure and the outcome).

These assumptions were based on a theoretical understanding of the likely inter-relationships between the four groups of variables available for inclusion in the present Chapter's (Part II) analyses (i.e. sociodemographic factors, MetS components, contemporaneous lifestyle factors and self-reported sleep characteristics). Indeed, although it is likely that the last three of these groups of variables might, at different stages of the lifecourse, act as both cause and effect of one another, the simultaneous cross-sectional collection of these variables in the UKHLS means that, as measured therein, these variables are most likely to be arranged in a specific sequence: 'sociodemographic factors' preceding 'MetS components' preceding 'contemporaneous lifestyle factors' preceding 'sleep characteristics'. On a similar basis the present thesis was critical of many of the previous cross-sectional studies reviewed in Chapter 2, particularly when: these assumed that contemporaneous (or relatively recent) measures of sleep were possible causes of MetS components likely to have developed at some stage in the more distant past; and contemporaneous lifestyle factors were included in the adjustment sets of the multivariable analyses these studies undertook. Yet, in the absence of sleep, lifestyle and MetS component data collected throughout the lifecourse, all of these analyses (including those conducted in Part II of the present Chapter) overlook the potential role of these, preceding yet latent variables operating as confounders in any analysis of cross-sectionally measured MetS, sleep and lifestyle. With only cross-sectional measures of these three variables it is also hard to model the longer-term and shorter-term impacts of each group of variables given, for example, that there is substantial evidence that the development of central obesity (a key component of MetS) is accompanied by (subsequent) changes in self-reported sleep (Ford *et al.* 2014), while acute changes in sleep duration (particularly experimental restriction of sleep duration) (Gonnissen *et al.* 2013) can cause immediate changes to glucose metabolism, appetite and satiety (and thereby, perhaps, short-term changes in body weight).

Within the context of cross-sectionally collected data with little, if any, data collected throughout the lifecourse, the path diagrams used to support the modelling of likely causal relationships are severely limited by the absence of earlier measurements. As such, the DAGs used in the present thesis are not only speculative, but also severely limited in their

capacity to support the analysis of cross-sectionally measured data *where* previous measures of the exposure, outcome and other covariates are unavailable. Thus, while the present Chapter proposed, on ostensibly sound theoretical and functional grounds, that: sociodemographic factors are likely to precede the development of all three MetS components; these components are likely to precede self-reported sleep, and that contemporaneous lifestyle measures are likely to fall between MetS and sleep (thereby operating as likely mediators), the results of analyses examining the association between MetS components and sleep before and after adjusting for (first) sociodemographic and (then, also) lifestyle factors, do not entirely support these assumptions.

Certainly, for most of the self-reported sleep characteristics with strong unadjusted relationships with MetS (i.e. short duration, loud coughing/snoring and medication), adjustment for sociodemographic factors led to the attenuation of the effect estimates observed, as might be expected were these factors to be operating as confounders. However, adjustment for sociodemographic factors strengthened the association between MetS and two other sleep characteristics (quality and daytime sleepiness), neither of which had had strong associations with MetS prior to adjustment. While, for the (subsequent, additional) adjustment for contemporaneous lifestyle factors, all of which were originally thought to be likely/possible mediators in the association between MetS and sleep, their inclusion in the adjustment sets used in the present Chapter's analyses led to a consistent attenuation of the effect estimates between MetS and self-reported sleep. It is possible that this attenuation in the magnitude of some effect sizes and the strengthening observed in others, is an indication of suppression effects (Tu, Gunnell and Gilthorpe 2008). Such phenomena have been defined by Genger (Conger 1974) as:

> ''a variable which increases the predictive validity of another variable (or set of variables) by its inclusion in a regression equation,''

The potential utility of self-reported MetS components

Having somewhat resolved (or at least clarified) these two important methodological concerns, the present Chapter (Part II) made substantial progress assessing the analytical utility of MetS components generated from self-reported indicators (rather than from direct measurements of these). The broad comparability of self-reported and directly observed MetS components was established previously in Part I of the present Chapter, which contained analyses demonstrating a reasonable level of sensitivity, specificity and predictive value.

Following on from these analyses, the analyses conducted in Part II of the present Chapter confirm that, to a large extent, the associations observed between directly measured MetS itself (i.e. the classification based on elevated waist circumference *and* high

blood pressure *and* diabetes) and self-reported sleep characteristics were very similar to those observed when self-reported MetS was used. In both sets of analyses, MetS itself was associated with an increased risk of the same four sleep characteristics (short duration, <6hrs; loud coughing/snoring; medication; and quality), and these effect estimates (and those for daytime sleepiness) responded similarly to adjustment for sociodemographic and lifestyle factors. While these analyses suggest that both sources of MetS data offer similar utility when exploring its association with self-reported sleep, the modest attenuation of effect estimates generated by models using self-reported, as opposed to directly measured, MetS indicates the impact of the finite level of agreement observed between these two sources of MetS data in Part I. This may have an impact on the precision of estimates generated by smaller samples of participants (where any association between MetS and sleep may be dwarfed by the additional variance attributable to incomplete the limited validity of self-reported MetS). However, since self-reported MetS components are likely to be of principal benefit to large-scale population-based studies where the costs of directly measuring large numbers of participants is likely to be prohibitive, the consistency observed in the results of models using directly-measured and self-reported MetS in the present study suggest that self-reported MetS may offer substantial scope for future population-based studies.

This potential was demonstrated in the present study by repeating the analyses of self-reported MetS and self-reported sleep conducted on the n=5,283 participants in the UKHLS NHA (for whom data on both self-reported and directly measured components of MetS were available) on the far larger number of UKHLS participants (n=29,436) providing only data on self-reported MetS in Wave 1. Given the very similar findings generated by these models to those generated by analyses of the smaller number of (older, and potentially unhealthier) participants selected for inclusion in the UKHLS NHA, these offer the first population-based assessment of the association between MetS and sleep using self-reported indicators as measures of MetS components. They confirm that, even when using self-reported MetS components, these components are associated with an increased risk of short sleep, loud coughing/snoring, sleep medication use and (again, after adjustment for sociodemographic factors) sleep quality and daytime sleepiness.

These analyses also found that MetS itself was associated with a higher risk of sleep fragmentation (waking up “in the middle of the night or early in the morning”) – suggesting the absence of this association among participants in Sample 1 (which was limited to those included in the UKHLS NHA) might reflect some of the differences in the distribution of sociodemographic factors amongst participants included Wave 1 and the NHA (see Table 4.4). Unfortunately, the absence of items on contemporaneous lifestyle factors in the UKHLS Wave 1 questionnaires meant that it was not possible to assess the impact of including these in the adjustment sets used in analyses of the larger sample

(Sample 2); but it was possible to run these analyses using both of the referent groups examined in analyses of the smaller (NHA) sample, and this again confirmed a very similar pattern of associations between MetS and self-reported sleep to that found in the earlier analyses. For these reasons, one can have substantial confidence that self-reported indicators of MetS components offer a sound basis for assessing the relationship between MetS and self-reported sleep in larger population-based samples (such as Wave 1 of the UKHLS) and that the analyses presented in the present Chapter (Part II) confirm that self-reported MetS is associated with an increased risk of a number of self-reported sleep characteristics amongst UKHLS participants representative of the UK population.

The differential association between different components (and combinations of components) of MetS and different self-reported sleep characteristics

Although both sets of analyses involving UKHLS participants (whether from the NHA or Wave 1) suggest that MetS itself (i.e. the classification based on elevated waist circumference ***and*** high blood pressure ***and*** diabetes) is associated with an increased risk of up to five self-reported sleep characteristics (short duration, loud coughing/snoring, medication, quality and daytime sleepiness), it is also clear from these analyses that elevated waist circumference was the single most important component of MetS in terms of its association with sleep. This is because elevated waist circumference alone was consistently associated with more self-reported sleep characteristics than either of the other two MetS components (high blood pressure and diabetes), and that the pairs of MetS components containing elevated waist circumference (i.e. elevated waist circumference ***and*** high blood pressure; or elevated waist circumference ***and*** diabetes) tended to be associated with more self-reported sleep characteristics than the other MetS components alone or combined. Indeed, the only additional self-reported sleep characteristic associated with MetS itself that was not associated with elevated waist circumference alone was sleep quality, suggesting that self-reported sleep quality is particularly sensitive to the combination of MetS components included in the classification of MetS itself.

These findings indicate that the choice of MetS components, and the combinations of these, are likely to influence the associations observed with self-reported sleep. At the same time, these findings also indicate that: some self-reported sleep characteristics are more sensitive to individual MetS components (and to specific combinations thereof); and there are (at least) two self-reported sleep characteristics (prolonged sleep duration and sleep latency) that may not be associated with MetS, while a third (sleep fragmentation) that may only be associated with MetS in population-based analyses. As such, the meaning of these (present and absent) relationships between different components/combinations of MetS and different self-reported characteristics remains unclear. While it is possible that the relationship between MetS and sleep is MetS-component- ***and*** sleep characteristic-specific, it may also be that: these relationships are primarily driven by obesity (which in turn affects,

to differing degrees, both blood pressure and glucose metabolism); and/or some self-reported sleep characteristics are more reliable measures of MetS-relevant sleep phenomena than others. These uncertainties require additional research beyond the scope of this thesis, not least because they are not amenable to investigation using analyses of observational data alone. Yet, they do to some extent explain the somewhat inconsistent findings reported by the studies reviewed in Chapter 2, which used a range of different MetS components and classifications, and focussed on a range of different sleep characteristics. The analyses presented in the present study make substantial progress towards explaining these inconsistencies and, by examining a comprehensive list of no fewer than seven self-reported sleep characteristics, reveal the extent of variation in their associations with MetS. In the process, the present Chapter has made a novel contribution to this area of study by helping to narrow down the scope of our uncertainty, and creating a firm basis upon which priorities for future research can be identified. These will be considered in greater detail in the final Discussion Chapter of this thesis.

4.2.7 Summary and conclusion

The analyses conducted in the present Chapter reveal that the associations observed between three key components of MetS (elevated waist circumference; high blood pressure; and diabetes – and different combinations of these three components) and seven different self-reported sleep characteristics are dependent upon: the choice of referent population used; adjustment for sociodemographic *and* lifestyle covariates; and the use of self-reported or directly measured data on each MetS component.

When compared to healthy participants (i.e. those displaying none of the three MetS components), and following adjustment for sociodemographic and lifestyle factors, participants displaying all three MetS components had an elevated risk of: short sleep duration (<6hrs); trouble sleeping due to loud coughing and snoring; using medication to help them sleep; experiencing difficulty staying awake during the day; and reporting the quality of their sleep as less than ‘very good’.

Elevated waist circumference (as a marker of central obesity) appeared to make the most important contribution to the associations observed between MetS and sleep; while short sleep duration, loud coughing/snoring and the use of sleep medication were the three sleep characteristics most strongly associated with MetS.

These findings were somewhat attenuated, but otherwise largely unaffected, when MetS components were based on self-reported indicators as opposed to direct measurement of each MetS component; suggesting that self-reported MetS might have substantial utility in large-scale population-based surveys where it is not feasible to collect direct measurements of each component of MetS.

To demonstrate the potential utility of self-reported MetS components in such contexts, data on these were generated for a larger sample of survey participants, and their associations with self-reported sleep characteristics were found to be very similar to those observed in a smaller sample of the same participants for whom data on directly measured MetS components had been collected.

Since this, larger sample of participants displayed a similar distribution of sociodemographic characteristics to those recruited to provide a representative sample of the UK population, it is likely that the associations between MetS and sleep observed in the analysis of this larger sample are broadly generalizable to the UK population as a whole.

Chapter 5 Discussion

5.1 Summary of findings

At the outset of the present thesis – which set as its overarching aim an improved understanding of the available evidence regarding the speculative relationship between sleep and the metabolic syndrome (MetS) – three key questions (KQs) were posed:

KQ1: "What methodological and empirical insights might be drawn from previous studies examining the relationship between sleep and the metabolic syndrome (MetS) to inform: the focus and conduct of future research; and our understanding of the evidence base regarding 'unfavourable' sleep as a possible cause and a possible consequence of MetS?"

KQ2: "What UK-based datasets are available from which to examine the relationship between sleep and the metabolic syndrome (MetS) to inform: the focus and conduct of future research; and our understanding of the evidence base regarding 'unfavourable' sleep as a possible cause and a possible consequence of MetS?"

KQ3: "To what extent might self-reported items relevant to identifying MetS in large datasets offer sufficiently valid measures of MetS symptoms/components to provide a basis upon which to generate a 'self-reported' classification of MetS suitable for use in population-based analyses where direct measures of MetS components are not available/feasible?"

and

KQ4: "What methodological and aetiological insights into the association between sleep and MetS might be generated from analyses of such data?"

Each of these four questions have been addressed in successive Chapters of the present thesis, using a range of different methods, including: KQ1 - a systematic review of published empirical studies (Chapter 2); KQ2 - exploring and identifying a UK based dataset that contains suitable data; KQ3 - the development of three self-reported measures of MetS-related symptoms/components, and comparing them to their direct/objective measures (Chapter 4, Part I); and KQ4 - novel analyses of a contemporary secondary dataset provided by the UK Household Longitudinal Study (UKHLS), addressing the flaws identified in the preceding systematic review (Chapter 2), and using the self-reported classification of MetS presented in (Chapter 4, Part II).

The aims of the final Chapter of this thesis (i.e. the present Chapter) are to: summarise and synthesise the main findings from each of the preceding analytical Chapters; identify the limitations of these, and of the thesis as a whole; and make recommendations for further methodological and empirical research that lead on from, and build upon, the contribution made to research on the relationship between sleep and MetS by the present thesis. As such, the present study addressed the requirement for originality

by adopting a large-scale, mixed-methods epidemiological approach, using: a critical review of previous empirical studies; and observational analyses of large population datasets – the latter informed by cutting edge advances in the development of techniques to support the analysis of causal inference, developing, validating and applying a novel approach to the classification of MetS using self-reported information on clinical diagnoses of obesity, hypertension and diabetes (as markers for three key clinical components of MetS that would be difficult to obtain from direct measurements on the large population samples that are ideal for use in epidemiological analyses). Although the present thesis was unable to perform a confirmatory MI, and instead had to rely on complete-case based analyses, the present study nonetheless broke fresh ground by exploring in greater detail the epidemiological evidence for any association between MetS (both directly measured and self-reported) and seven different sleep characteristics amongst a representative sample of UK adults (the first such study to be conducted in the UK, and only the third such study outside of Asia and North America).

5.1.1 The systematic review of previous empirical studies exploring the relationship between sleep and MetS

The original contribution made by the present thesis draw and build upon the review, critical appraisal and detailed synthesis of previous studies exploring the association between sleep and MetS, as summarised in Chapter 2. This was the first review of its kind to attempt such a detailed critical assessment of the evidence to-date. However, while Chapter 2 adopted a deliberately broad search strategy – one that intended to capture evidence of association, directionality and effect from cross-sectional, longitudinal and experimental studies, respectively – the only studies it found that met its explicit inclusion criteria (which set a clear focus on: empirical studies exploring sleep-related characteristics rather than clinical conditions occurring during/associated with sleep [particularly OSA]; and studies using robust analytical designs) were those using a cross-sectional design.

Since cross-sectional study designs can only provide evidence of association (and not of ‘directionality’ or ‘effect’) (Miller and Brewer 2003), the principal limitation of the synthesis of evidence presented in Chapter 2 stems from its reliance on previous studies adopting a cross-sectional design. Nonetheless, since this is the design used by the majority of speculative studies exploring the plausibility of existing (or novel) hypotheses – including, in this instance, the possibility that ‘unfavourable’ sleep might trigger, promote or facilitate the development of MetS – and since such studies are routinely used to generate and replicate hypotheses, and thereby establish the merits of conducting more resource-intensive studies (i.e. those adopting longitudinal and experimental designs), there is still substantial value in critically appraising the methods used, and synthesising the findings reported by, empirical cross-sectional studies. Indeed, detailed examination of n=21 studies examining the association between sleep and MetS, each using ostensibly ‘cross-sectional’

data (i.e. data collected cross-sectionally though, from a causal perspective, including variables relevant to events and phenomena emerging at different times across the lifecourse), identified a number of methodological flaws and sufficient variation in measurement and analytical approach to pose substantive challenges to the synthesis of their findings.

Around half of the studies involved fewer than n=1,000 participants, and while none examined more than four sleep-related characteristics, most of the ten discrete characteristics examined by one or more of these studies had only been examined by a single study (the exceptions being: sleep duration, examined by n=14/21 studies; sleep quality by n=6/21; and snoring/sleep-related breathing difficulties by n=5/21). Few of the studies reported a comprehensive list of potential confounders amongst their measured/available covariates, and none included all of the covariates that were measured by/available to any of the other studies. This meant that none of the studies were able to adjust for all of the potential confounders that appeared to be available to/measureable by other studies, so that even the adjusted effect estimates presented by those studies reporting a good number (and range) of available/measured confounders are likely to have suffered from unadjusted confounding (Fewell, Smith and Sterne 2007). At the same time, almost all of the studies included likely mediators (identified using theoretical causal path diagrams, in the form of DAGs) in many of their covariate adjustment sets, so that the effect estimates these models provided are likely to have been subject to bias as a result of the so-called ‘ reversal paradox’ (Tu, Gunnell and Gilthorpe 2008).

Evidence to support these analytical concerns was generated using meta-analyses of odds ratios reported by any two or more studies using sufficiently comparable measures of the same sleep characteristics to permit direct comparison – in this instance: n=9 studies examining the association between short and prolonged sleep duration and MetS; and n=3 studies examining the association between poor sleep quality (as measured using the Pittsburgh Sleep Quality Index) and MetS. In three separate sets of meta-analyses, MetS was found to be associated with a higher combined odds of short/prolonged sleep duration and a higher combined odds of poor sleep quality. Although these combined estimates were substantially attenuated following adjustment for only those covariates considered likely to act as potential, the inclusion of covariates considered to act as likely mediators in the covariate adjustment sets used (together with components of sleep and/or MetS, in some of the adjustment sets used) tended to strengthen the combined odds obtained. In this way, the critical appraisal of these studies’ methods, and the synthesis of these studies’ findings, (as presented in Chapter 2 of the present thesis) cast considerable doubt on the evidence provided by the cross-sectional studies it reviewed. While, at face value, these studies seem to suggest that a variety of ‘unfavourable’ sleep characteristics *are*, at the very least, *associated with* an increased odds of MetS, the fact that none of these studies made much

effort to address the very real possibility of confounding, and that the strongest effect estimates reported were for studies with very small numbers of participants (and those using covariate adjustment sets containing likely mediators and components of the exposure and/or outcome) means that little confidence can be placed on the findings they report, however plausible and attractive their findings might seem.

Nonetheless, Chapter 2's critical appraisal of these studies' methodological and analytical techniques did succeed in identifying a number of important issues that warranted serious consideration in the subsequent analyses envisaged for inclusion in the present thesis, particularly:

- the value of examining large samples of participants to achieve sufficient statistical power (not least for potentially rare events, such as MetS symptoms/components occurring in isolation or in unusual combinations) to minimise the risk of type 1 statistical errors;
- the need to carefully specify the composition of the referent groups used (particularly regarding their inclusion of: only those participants exhibiting *none* of the symptoms/components of MetS; or participants exhibiting ≤3 of the symptoms/components considered necessary to warrant a classification of MetS);
- the benefit of using theoretically driven causal path diagrams to inform the identification of (a comprehensive list of) potential confounders and likely mediators, and thereby ensure that analyses of any association between MetS and each of the available/measured sleep characteristics could be optimally adjusted for a sufficiently broad range of potential confounders (thereby minimising the risk of unadjusted confounding, while avoiding the bias caused by adjustment for likely mediators); and
- the value of comparing the association between MetS and a range of different sleep characteristics using data from the same source/participants (to facilitate an assessment of the relative importance of these characteristics as potential causes, consequences, or simply correlates, of MetS).

5.1.2 The development and validation of 'self-reported' MetS based on self-reported indicators of key MetS symptoms/components

The first of these issues was addressed in subsequent Chapters of the present thesis by selecting a large ongoing study (the UK Household Longitudinal Study; UKHLS) that had collected substantial data on a range of sleep characteristics and potential confounders, as well as direct measures of three key symptoms/components of MetS (waist circumference, blood pressure, markers of blood glucose levels, and prescribed medication for hypertension and diabetes). However, although these direct measures of MetS

symptoms/components were available on a sizeable subsample of UKHLS participants (n>5,000), the present thesis sought to extend its analyses to the much larger number of UKHLS participants providing data on self-reported sleep characteristics and potential confounders, by exploring the possibility of using self-reported anthropometric data and clinical diagnoses of high blood pressure and diabetes as the basis for developing a valid 'self-report' of MetS (i.e. a classification of MetS based on self-reported indicators of these three components of MetS).

To this end, Chapter 4 (Part I) presented the first attempt to develop a 'self-report' of MetS based on self-reported indicators available within the UKHLS dataset, and validate these by comparing them to the direct measures of MetS components collected from participants in the study's Nurse Health Assessment (NHA). Despite the substantial interval between the collection of self-reported and directly measured data (which ranged from 5-18months between the surveys in which these data were generated); and despite the necessity of estimating 'self-reported' waist circumference using self-reports of weight and height (which were the only two anthropometric variables included in the survey questionnaires used by the UKHLS), 'self-reported' MetS displayed a remarkably good level of agreement with 'directly measured' MetS.

5.1.3 Cross-sectional analyses of the association between MetS and seven self-reported sleep characteristics using data from the UKHLS

The final analytical Chapter 4 (Part II) in the present thesis drew heavily on the findings of the two preceding Chapters to generate what aimed to be the most comprehensive and robust analyses to-date of cross-sectional data on self-reported sleep characteristics and both self-reports and direct measures of MetS. Incidentally, these were also the first such analyses undertaken on data from the UK, and since the UKHLS aimed to recruit participants providing a representative sample of UK adults, the results of these analyses are likely to be broadly generalizable to the adult population of the UK as a whole. Importantly, all of these analyses involved substantial numbers of participants (in excess of n=5,000 participants); and all were repeated using two precisely specified referent groups (the first comprising participants displaying *none* of the three MetS symptoms/components examined; the second comprising all 'MetS-free' participants, some of whom will have displayed one or two, though not all three, MetS symptoms/components). Great care was taken to identify as many covariates acting as potential confounders for inclusion in the covariate adjustment sets used in these analyses. Similar care was taken to identify covariates acting as likely mediators in the association between MetS and sleep, and while mediators were excluded from the adjustment sets used to assess the impact of confounding on the unadjusted associations observed, mediators were included in the adjustment sets used by a third set of models to confirm whether their inclusion might

strengthen the associations observed and thereby offer some reassurance that these covariates had been correctly specified as likely mediators.

In the event, the inclusion of lifestyle factors (i.e. the covariates considered likely to act as mediators in any association between MetS and sleep) in the covariate adjustment sets used by the multivariable models presented in Chapter 4 (Part II) did not tend to strengthen the associations observed; and instead the inclusion of covariates considered potential confounders *or* likely mediators was found to attenuate associations between MetS and some sleep characteristics, while strengthening those of others. These findings in part reflect the degree of guesswork (in other words, 'imprecision') involved when specifying the temporal positioning of cross-sectionally collected variables in theoretical causal path diagrams, and the use of these diagrams to identify which covariates are likely to act as confounders, and which as mediators. And while such an approach, at the very least, offers greater clarity to others regarding the rationale for including some covariates and excluding others from the adjustment sets used, this approach remains fraught with problems when cross-sectionally measured covariates are able to act as: both contemporaneous measures of the factor concerned; or proxies for past measures of these (or, indeed, other past/present events, characteristics or phenomena). The use of different adjustment sets in the multivariable models used in Chapter 4 (Part II) therefore throw some doubt on the covariates specified as mediators in Chapter 2, and on the reassurance the meta-analyses presented therein provide that these 'mediators' had been correctly specified (i.e. reassurance based on the observation that adjustment for these 'mediators' tended to strengthen the association between MetS and sleep).

Nonetheless, the multivariable models presented in Chapter 4 (Part II) do confirm that a range of different self-reported sleep characteristics display strong associations between MetS and sleep in which MetS is consistently associated with 'less favourable' sleep. Somewhat unsurprisingly, these associations were strongest when the referent group used comprised participants displaying *none* of the three MetS symptoms/components examined (i.e. neither elevated waist circumference; nor high blood pressure; nor diabetes) than when the referent group contained some participants displaying two or less of these symptoms/components (i.e. fewer than the three specified by the classification of MetS used). Since the latter is the approach assumed to have been used by the n=21 cross-sectional studies reviewed in Chapter 2 (none of which provided unequivocal descriptions of the MetS symptoms/components displayed by participants in their 'MetS-free' referent groups), it is worth comparing the findings reported by these earlier studies to those provided by the adjusted models used in Chapter 4 (Part II) to re-evaluate the association between MetS (based on direct measures of MetS symptoms/components) and each of the seven self-reported sleep characteristics included in the UKHLS dataset.

In Chapter 2, the previous studies reviewed suggested there was evidence that MetS was associated with an increased risk of: short/prolonged sleep duration and MetS (based on the findings presented in n=9 separate studies); poor sleep quality (in n=6 studies); snoring/sleep-disordered breathing (in n=5 studies); and habitual sleep latency, poor sleep efficiency, sleep medication use, Non-REM Beta and AHI events (each from the findings presented in just n=1 study). These are very different to the limited number of sleep-related characteristics found to be associated with MetS based on directly measured symptoms/components summarised in: Figure 4.6 (following adjustment for covariates considered potential confounders); and Figure 4.7 (following adjustment for covariates considered potential confounders or likely mediators) – in both of which the referent group contained some participants displaying up to two (though not all three) symptoms/components of MetS. In these Figures, MetS was only associated with two sleep-related characteristics (poor quality sleep, and a higher frequency of daytime sleepiness), and there was little substantive evidence of an association with any of the other five characteristics examined (sleep duration, latency, fragmentation, medication and coughing/snoring loudly). Short sleep duration, loud coughing/snoring and/or the use of sleep medication *were* also associated with MetS (i.e. in addition to the associations observed for daytime sleepiness and poor sleep quality in Figures 4.6 and 4.7) in analyses using participants displaying *none* of the three MetS symptoms/components as the referent (following adjustment for confounders and mediators; see Figures 4.3 and 4.4).

This better reflects the range of sleep characteristics reportedly associated with MetS amongst the n=21 studies reviewed in Chapter 2. Indeed, the two previous studies (albeit, both using the same source of data) that had examined the association between daytime sleepiness and MetS in Chapter 2 (Roopa *et al.* 2010; Krishnan *et al.* 2012), and the single study examining the association between sleep fragmentation and MetS (Mesas *et al.* 2014), also reported no such associations – as did none of the analyses in Figures 4.3, 4.4, 4.6 or 4.7 of Chapter 4 (Part II). Nonetheless, the single study included in Chapter 2 that had examined the association between sleep latency and MetS (Mesas *et al.* 2014) *did* report a strong association between the two, while none of the analyses in Figures 4.3, 4.4, 4.6 or 4.7 did so.

These disparities in the findings presented in Chapters 2 and 4 (Part II) may simply reflect the different methodological approaches used to measure and analyse both MetS and sleep in the previous studies reviewed (in Chapter 2) and in the subsequent *de novo* analyses conducted (for Chapter 4 Part II). It is therefore tempting to conclude (given the larger number of sleep characteristics showing a strong association with MetS when the referent group included only those participants who displayed *none* of the symptoms/components of MetS; see Figures 4.3 and 4.4) that the poorly specified/described referent groups used by the studies reviewed in Chapter 2 had *actually*

used referent groups comprising only ‘healthy’ participants (i.e. those displaying *none* of the symptoms/components of MetS examined). Yet, to a large extent the review assumed (on the basis of the limited descriptions these studies provided) that their referent groups had *actually* included some participants displaying one or two (though not three or more) of these symptoms/components. It certainly seems more likely that this was the case (if only on the basis of what could be construed from the limited information contained in each of the articles concerned), and that the larger number of sleep characteristics found to be associated with MetS in the review of the previous studies conducted in Chapter 2 simply reflects the tendency for publication bias; not least because, for most of these characteristics, these had only been examined by a single study.

This comparison of the results obtained from the review of previous studies exploring the association between MetS and sleep (in Chapter 2), and those generated from *de novo* analyses of seven sleep characteristics and direct measures of MetS based on data from the UKHLS (in Chapter 4 Part II), is nonetheless compromised by three further (and potentially key) differences between the datasets used: the first regarding the time interval between the measurement of sleep and the measurement of MetS; the second being the absence of dyslipidaemia from the classification of MetS applied to data from the UKHLS; and the third being the differential exclusion of unhealthy participants from the UKHLS Nurse Health Assessment (in which only a subsample of UKHLS participants took part) and from the samples examined by those studies reviewed in Chapter 2.

While the vast majority of studies reviewed in Chapter 2 used/collected data on sleep and symptoms/components of MetS at the same point in time (see Table 2.2), the self-reported sleep data used in Chapter 4 Part II’s analyses examining their association with directly measured components of MetS had been collected around 18 months *before* the Nurse Health Assessment (when direct measurements of waist circumference, blood pressure, HbA1c levels and prescribed medication data were collected). This is a substantial amount of time, and any changes in sleep patterns or behaviours in the intervening period might substantially weaken any genuine association between these and directly measured MetS.

At the same time, all of the studies reviewed in Chapter 2 had access to or directly measured lipid levels in fasting blood samples, and included criteria based on these levels a fourth (and occasionally a fifth) symptom/component in the classifications of MetS they used. In contrast, the UKHLS NHA did not collect the fasting blood samples required for the measurement of dyslipidaemia and for this reason the classification of MetS used in Chapters 4 (Part I) and (Part II) of the present study had to rely on only three symptoms/components of MetS (elevated waist circumference, high blood pressure and diabetes) rather than the four or five different components more commonly used (i.e. by the four different classificatory schemes used by the n=21 studies reviewed in Chapter 2).

Although this will have reduced the number of UKHLS participants who were classified as having/displaying MetS (since this would have excluded participants with two of the three measured symptoms/components dyslipidaemia who *also* displayed unmeasured dyslipidaemia) it would also have meant that participants displaying dyslipidaemia would have been included in the referent groups used in Figures 4.3-4.5 (who were intended to be free of *any* components of MetS). This may be a substantial limitation of the *de novo* analyses presented in Chapters 4 (Part I) and (Part II) of the present thesis, although the emphasis many classifications of MetS place on the three symptoms/components used to classify MetS in these Chapters' analyses of UKHLS data (and particularly the importance of central obesity; see Table 1.3), means that the classification of MetS used in these Chapters is likely to be broadly comparable with those used by the previous studies reviewed in Chapter 2 (although further research is warranted to confirm this).

Finally, while it is certainly plausible that the differential exclusion of unhealthy UKHLS participants from that study's NHA may mean that any associations between the sleep- and MetS-related characteristics of these participants were (far) less pronounced than those examined in the studies reviewed in Chapter 2, the latter also routinely excluded participants with severe, chronic and/or acute health conditions (see Table 2.1) or drew on secondary datasets from studies that had done so when recruiting/sampling their study participants. As such, it is possible that the associations observed between MetS and sleep in this subsample of UKHLS participants (Sample 1) was very different to those occurring across the UKHLS as a whole, or amongst the samples of participants examined by most (if not all) of the studies reviewed in Chapter 2. Nevertheless, this does seem the least likely reason for the very different patterns of association between MetS and sleep observed in the studies and analyses described in Chapters 2 and 4 (Part II).

5.1.3.1 Towards consensus on evidence of associations between sleep and MetS generated by the studies reviewed in Chapter 2 and the analyses presented in Chapter 4 (Part II)

In part to address the first and third of the three potential limitations identified above, and in part to test the utility of 'self-reported MetS' in analyses examining the relationship between sleep and MetS, Chapter 4 (Part II) repeated the analyses conducted on 'directly measured MetS' using the classification of 'self-reported MetS' developed and validated in Chapter 4 (Part I). These analyses benefitted from the use of sociodemographic-, sleep- and MetS-related variables that had been recorded during the same wave of the UKHLS (i.e. using the Wave 1 interviewer- and self-administered questionnaires), for which there was no interval between the collection of sleep- and MetS-related data. These analyses also benefitted from the much larger number of UKHLS participants with complete data on self-reported variables ('Sample 2': n=29,436) than those with direct measures of MetS symptoms/components collected during the NHA ('Sample 1': n=5,283; see Table 4.4). And

although these analyses relied upon a classification of MetS based on self-reported indicators of elevated waist circumference (estimated from self-reports of height and weight), high blood pressure (derived from self-reported clinical diagnoses of hypertension) and diabetes (also derived from self-reported clinical diagnoses), this classification demonstrated substantial agreement with the directly measured symptoms/components of MetS (and the classification of MetS itself based thereon) in the detailed validation analyses conducted in Chapter 4 (Part I).

Using the analyses of these data, then, as the basis for comparing the findings of previous studies (as summarised in Chapter 2) with those generated from analyses of (self-reported) data from the UKHLS it is clear that these found very similar patterns of association to those identified in analyses focussing only on participants with direct measures of MetS (i.e. those involved in the UKHLS NHA; compare Figures 4.3 and 4.15 [for those analyses using 'MetS-free' participants as referent], Figures 4.6 and 4.17 [for those analyses using participants with ≤two MetS symptoms/components as referent]). None of these analyses (all of which were adjusted for covariates considered potential confounders, though not for lifestyle factors considered likely mediators, since these were not available for the larger sample of participants from Wave 1 alone) found evidence of an association between MetS and prolonged sleep duration or extended sleep latency, though they did find that MetS was associated with an increased odds of: short sleep duration; loud coughing/snoring; sleep medication use; poor quality sleep; daytime sleepiness; and (in some, but not all models) sleep fragmentation. These therefore remain somewhat at odds with the associations reported by the studies reviewed in Chapter 2: none of which reported an association between MetS and sleep fragmentation or daytime sleepiness (though evidence on these were provided only by analyses using just one dataset each); while all n=3/3 of the comparable analyses identified in Chapter 2 (see Table 2.6) found that MetS was associated with a higher odds of prolonged sleep duration (Stefani *et al.* 2013; Arora *et al.* 2011; Choi *et al.* 2008).

On the basis of these comparisons it is therefore difficult to provide an unequivocal assessment of the likely associations between different sleep characteristics and MetS, save to say that the best available evidence from cross-sectional studies using broadly comparable measurement and analytical techniques is that MetS is associated with a higher risk of 'unfavourable sleep' across a range of different sleep characteristics, and that the strength of these associations varies amongst: studies using direct measures and self-reports of MetS; those conducted in different settings; and those using different covariate adjustment sets to reduce the likelihood of unadjusted confounding. It remains to be seen whether these associations simply reflect a correlation between sleep and cardiometabolic health characteristics resulting from unadjusted confounding (i.e. from unadjusted or latent confounding); or whether these associations reflect a causal relationship between all (or

even just some) of these sleep characteristics and MetS (and, if so, whether any sleep characteristics prove to be causes or consequences of MetS, or both).

5.2 Recommendations for future research

Against the backdrop of the somewhat equivocal findings generated (from a review of existing studies exploring the association between MetS and sleep, and *de novo* analyses of this association using both directly measured and self-reported variables to classify MetS), the present thesis nonetheless sets a firm baseline upon which future research into this potentially important association might be based. Of particular importance, moving forwards, will be studies that address all of the principal flaws (and methodological challenges) identified in the review of previous studies summarised in Chapter 2 of the present thesis (many of which proved difficult to address in the *de novo* analyses undertaken in Chapter 4 Part II), namely:

- studies examining sufficient numbers of participants (including sufficient numbers displaying both 'unfavourable' sleep and/or MetS) to minimise the risk of type 1 error;
- studies with access to data on a (much broader) range of potential confounders, including: a family and/or personal history of sleep- and MetS-related disorders and risks; more detailed data on lifestyle factors and living circumstances relevant to the development of 'unfavourable' sleep characteristics and the physiological triggers/modifiers of MetS-related symptoms and components;
- studies capable of accurately distinguishing between (preceding) confounders and (interceding) mediators in any relationship between sleep and MetS (so that the adjustment sets used can include the former and exclude the latter); and
- studies that more clearly describe, define and justify the inclusion and exclusion criteria used during both the recruitment of study participants and the specification of the referent groups used in subsequent analyses.

While there would also be substantial benefit in establishing a limited number of instruments, techniques and classifications for the standardisation of measurements on sleep characteristics and MetS, the proliferation of instruments (and MetS classifications) available suggests this seems unlikely to occur. Instead it would be worth encouraging all future studies to use a limited number of such measures *in addition* to any others they are keen to explore (perhaps as a prerequisite to publication in the small number of journals where the majority of these studies have been published to-date; see (Chapter 2); or at the very least to present analyses that use/include standard cut-off points for some of the sleep characteristics used (most notably, for sleep duration) – an approach that benefitted the synthesis of findings from those studies using the Pittsburgh Sleep Quality Index (PSQI), all

of which used the same ‘PSQI Total Score’ cut-off point to distinguish between ‘good’ and ‘poor’ sleep quality – thereby enabling direct comparisons to be made between the results of all of these studies.

While addressing these methodological and analytical flaws, and some of the challenges facing comparisons and syntheses of findings generated by studies using very different techniques, the list of recommendations provided above will not alone move our understanding of the possible direction and mechanisms involved in any association between MetS and sleep. To make progress in these areas, future studies will be required to:

- establish either standard and/or reference cut-off points for each of the sleep characteristics examined, in order to enhance the clinical utility of the thesis’ findings;
- use data collected at three or more time points to conduct longitudinal analyses capable of demonstrating whether changes in sleep lead to changes in MetS and vice versa;
- use interventions capable of improving specific sleep characteristics (beyond those addressing the clinical conditions that can affect sleep, such as obstructive sleep apnoea) in randomised control trials to establish their impact on MetS (particularly over a longer time period than that used by studies demonstrating that artificially shortened or artificially disturbed sleep causes short-term effects on cardiometabolic factors, appetite/satiety and related behaviours);
- use interventions capable of addressing MetS itself (rather than just one or two symptoms/components thereof) in randomised control trials to establish their impact on a range of sleep-related characteristics; and
- examining the plausibility of biochemical and physiological mechanisms in any relationship between sleep and MetS, using in vitro and in vivo studies as appropriate (with particular attention paid to the potential for therapeutic interventions aimed at attenuating or eliminating these processes or key steps therein).

Finally, one of the greatest challenges faced by this study was the impracticability of applying multiple imputation. Therefore, additional work is required to undertake multiple imputation on the UKHLS data to address the issue of extensive (and potentially non-random) missingness in the datasets analysed – a necessary (yet potentially very time-consuming) step that should precede any substantive interpretation and application of the analyses conducted on complete case data as currently reported in this thesis.

These, then, are what lies ahead for research into the association between sleep and MetS. With no pun intended (given that the name chosen for the team of students and

staff who have been researching this issue: the Temporal Influences on Metabolic Events' Research Group; 'TIME'), time will tell whether there is more to the associations between sleep and MetS reported by previous studies, and in the *de novo* analyses conducted for the present thesis, than meets the eye

References

AGRAWAL, S., S. K. SHARMA, V. SREENIVAS and R. LAKSHMY. 2011. Prevalence of metabolic syndrome in a north Indian hospital-based population with obstructive sleep apnoea. *Indian J Med Res,* **134**(5), pp.639-44.

AGUILAR, M., T. BHUKET, S. TORRES, B. LIU and R. J. WONG. 2015. Prevalence of the metabolic syndrome in the united states, 2003-2012. *JAMA,* **313**(19), pp.1973-1974.

AHMADI, A., J. LEIPSIC, G. FEUCHTNER, H. GRANSAR, D. KALRA, R. HEO, S. ACHENBACH, D. ANDREINI, M. AL-MALLAH and D. S. BERMAN. 2015. Is metabolic syndrome predictive of prevalence, extent, and risk of coronary artery disease beyond its components? Results from the multinational coronary CT angiography evaluation for clinical outcome: an international multicenter registry (CONFIRM). *PloS one,* **10**(3), pe0118998.

ALBERTI, G. 2005. Introduction to the metabolic syndrome. *European Heart Journal Supplements,* **7**(suppl D), pp.D3-D5.

ALBERTI, K., R. H. ECKEL, S. M. GRUNDY, P. Z. ZIMMET, J. I. CLEEMAN, K. A. DONATO, J.-C. FRUCHART, W. P. T. JAMES, C. M. LORIA and S. C. SMITH. 2009. Harmonizing the metabolic syndrome a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. *Circulation,* **120**(16), pp.1640-1645.

ALBERTI, K., P. ZIMMET and J. SHAW. 2006. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabetic Medicine,* **23**(5), pp.469-480.

ARORA, T., C. Q. JIANG, G. N. THOMAS, K. B. LAM, W. S. ZHANG, K. K. CHENG, T. H. LAM and S. TAHERI. 2011. Self-reported long total sleep duration is associated with metabolic syndrome: the Guangzhou Biobank Cohort Study. *Diabetes Care,* **34**(10), pp.2317-9.

BALKAU, B., M.-A. CHARLES, T. DRIVSHOLM, K. BORCH-JOHNSEN, N. WAREHAM, J. S. YUDKIN, R. MORRIS, I. ZAVARONI, R. VAN DAM and E. FESKINS. 2002. Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. *Diabetes & metabolism,* **28**(5), pp.364-376.

BARONE, M. T. and L. MENNA-BARRETO. 2011. Diabetes and sleep: a complex cause-and-effect relationship. *Diabetes research and clinical practice,* **91**(2), pp.129-137.

BARTLETT, D., N. MARSHALL, A. WILLIAMS and R. GRUNSTEIN. 2008. Sleep health New South Wales: chronic sleep restriction and daytime sleepiness. *Internal medicine journal,* **38**(1), pp.24-31.

BENZEVAL, M., DAVILLAS, APOSTOLOS, KUMARI, MEENA, LYNN, PETER. 2014. Understanding Society:UK Household Longitudinal Study: Biomarker User Guide and Glossary. *Colchester: University of Essex*.

BIXLER, E. 2009. Sleep and society: an epidemiological perspective. *Sleep Medicine,* **10**, pp.S3-S6.

BJÖRNTORP, P. 1996. The regulation of adipose tissue distribution in humans. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity,* **20**(4), pp.291-302.

BJORVATN, B., I. SAGEN, N. ØYANE, S. WAAGE, A. FETVEIT, S. PALLESEN and R. URSIN. 2007. The association between sleep duration, body mass index and metabolic measures in the Hordaland Health Study. *Journal of sleep research,* **16**(1), pp.66-76.

BLOOM, H. G., I. AHMED, C. A. ALESSI, S. ANCOLI-ISRAEL, D. J. BUYSSE, M. H. KRYGER, B. A. PHILLIPS, M. J. THORPY, M. V. VITIELLO and P. C. ZEE. 2009. Evidence-based recommendations for the assessment and management of sleep disorders in older persons. *Journal of the American Geriatrics Society,* **57**(5), pp.761-789.

BOSSUYT, P. M., J. B. REITSMA, D. E. BRUNS, C. A. GATSONIS, P. P. GLASZIOU, L. IRWIG, J. G. LIJMER, D. MOHER, D. RENNIE and H. C. DE VET. 2015. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *Radiology,* **277**(3), pp.826-832.

BOWLIN, S. J., B. D. MORRILL, A. N. NAFZIGER, C. LEWIS and T. A. PEARSON. 1996. Reliability and changes in validity of self-reported cardiovascular disease risk factors using dual response: the behavioral risk factor survey. *Journal of clinical epidemiology,* **49**(5), pp.511-517.

BOZEMAN, S. R., D. C. HOAGLIN, T. M. BURTON, C. L. PASHOS, R. H. BEN-JOSEPH and C. S. HOLLENBEAK. 2012. Predicting waist circumference from body mass index. *BMC medical research methodology,* **12**(1), p1.

BRENNER, H. and O. GEFELLER. 1997. Variation of sensitivity, specificity, likelihood ratios and predictive values with disease prevalence. *Statistics in medicine,* **16**(9), pp.981-991.

BRICK, J. M. and G. KALTON. 1996. Handling missing data in survey research. *Statistical methods in medical research,* **5**(3), pp.215-238.

BUYSSE, D. J., C. F. REYNOLDS, T. H. MONK, S. R. BERMAN and D. J. KUPFER. 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research,* **28**(2), pp.193-213.

CAMPBELL, M. J., D. MACHIN and S. J. WALTERS. 2010. *Medical statistics: a textbook for the health sciences.* John Wiley & Sons.

CAPPUCCIO, F. P., L. D'ELIA, P. STRAZZULLO and M. A. MILLER. 2010. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep,* **33**(5), p585.

CARSKADON, M. A. and W. C. DEMENT. 1994. Normal human sleep: an overview. *Principles and practice of sleep medicine,* **4**, pp.13-23.

CHANDOLA, T. and C. JENKINSON. 2000. The new UK National Statistics Socio-Economic Classification (NS-SEC); investigating social class differences in self-reported health status. *Journal of Public Health,* **22**(2), pp.182-190.

CHAP, T. L. 2003. Introductory biostatistics. *A John Wiley & Sons Publication*.

CHAPUT, J.-P., J. MCNEIL, J.-P. DESPRES, C. BOUCHARD and A. TREMBLAY. 2013a. Short sleep duration as a risk factor for the development of the metabolic syndrome in adults. *Preventive Medicine: An International Journal Devoted to Practice and Theory,* **57**(6), pp.872-877.

CHAPUT, J. P., J. MCNEIL, J. P. DESPRES, C. BOUCHARD and A. TREMBLAY. 2013b. Seven to eight hours of sleep a night is associated with a lower prevalence of the metabolic syndrome and reduced overall cardiometabolic risk in adults. *PLoS One,* **8**(9), pe72832.

CHEDRAUI, P., G. SAN MIGUEL, D. VILLACRESES, A. DOMINGUEZ, W. JARAMILLO, G. S. ESCOBAR, F. R. PEREZ-LOPEZ, A. R. GENAZZANI and T. SIMONCINI. 2013. Assessment of insomnia and related risk factors in postmenopausal women screened for the metabolic syndrome. *Maturitas,* **74**(2), pp.154-9.

CHENG, H. G. and M. R. PHILLIPS. 2014. Secondary analysis of existing data: opportunities and implementation. *Shanghai Arch Psychiatry,* **26**(6), pp.371-375.

CHESSON JR, A. L., R. A. FERBER, J. M. FRY, M. GRIGG-DAMBERGER, K. M. HARTSE, T. D. HURWITZ, S. JOHNSON, G. A. KADER, M. LITTNER and G. ROSEN. 1997. The indications for polysomnography and related procedures. *Sleep,* **20**(6), pp.423-487.

CHOI, J. K., M. Y. KIM, J. K. KIM, J. K. PARK, S. S. OH, S. B. KOH and A. EOM. 2011. Association between short sleep duration and high incidence of metabolic syndrome in midlife women. *Tohoku J Exp Med,* **225**(3), pp.187-93.

CHOI, K., J. LEE, H. PARK, S. BAIK, D. CHOI and S. KIM. 2008. Relationship between sleep duration and the metabolic syndrome: Korean National Health and Nutrition Survey 2001. *International Journal of Obesity,* **32**(7), pp.1091-1097.

CHOKROVERTY, S. 2010. Overview of sleep & sleep disorders.

CHUNG, F., B. YEGNESWARAN, P. LIAO, S. A. CHUNG, S. VAIRAVANATHAN, S. ISLAM, A. KHAJEHDEHI and C. M. SHAPIRO. 2008. STOP QuestionnaireA Tool to Screen Patients for Obstructive Sleep Apnea. *The Journal of the American Society of Anesthesiologists,* **108**(5), pp.812-821.

COLDITZ, G. A., P. MARTIN, M. J. STAMPFER, W. C. WILLETT, L. SAMPSON, B. ROSNER, C. H. HENNEKENS and F. E. SPEIZER. 1986. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *American journal of epidemiology,* **123**(5), pp.894-900.

CONGER, A. J. 1974. A Revised Definition for Suppressor Variables: a Guide To Their Identification and Interpretation. *Educational and Psychological Measurement,* **34**(1), pp.35-46.

COUGHLIN, S., L. MAWDSLEY, J. MUGARZA, J. WILDING and P. CALVERLEY. 2007a. Cardiovascular and metabolic effects of CPAP in obese males with OSA. *European Respiratory Journal,* **29**(4), pp.720-727.

COUGHLIN, S. R., L. MAWDSLEY, J. A. MUGARZA, J. P. WILDING and P. M. CALVERLEY. 2007b. Cardiovascular and metabolic effects of CPAP in obese males with OSA. *Eur Respir J,* **29**(4), pp.720-7.

CRESPO, P. S., J. A. P. PERERA, F. A. LODEIRO and L. A.-E. AZUARA. 2007. Metabolic syndrome in childhood. *Public health nutrition,* **10**(10A), pp.1121-1125.

CULLUM, A., A. MCCARTHY, D. GUNNELL, G. D. SMITH, J. STERNE and Y. BEN-SHLOMO. 2004. Dietary restraint and the mis-reporting of anthropometric measures by middle-aged adults. *International journal of obesity,* **28**(3), pp.426-433.

DANAVI, J. V., S. B. MEMON and B. A. P. PHAN. 2015. Statin alternatives: a review of over-the-counter lipid-lowering supplements. *Alternative and Complementary Therapies,* **21**(5), pp.198-209.

DASKALOPOULOU, S., D. MIKHAILIDIS and M. ELISAF. 2004. Prevention and treatment of the metabolic syndrome. *Angiology,* **55**(6), pp.589-612.

DAY, C. 2007. Metabolic syndrome, or What you will: definitions and epidemiology. *Diabetes and vascular disease research,* **4**(1), pp.32-38.

DE MENEZES, T. N., E. C. T. OLIVEIRA and M. A. T. DE SOUSA FISCHER. 2014. Validity and Concordance Between Self-Reported and Clinical Diagnosis of Hypertension Among Elderly Residents in Northeastern Brazil. *American journal of hypertension,* **27**(2), pp.215-221.

DEKKERS, J. C., M. F. VAN WIER, I. J. HENDRIKSEN, J. W. TWISK and W. VAN MECHELEN. 2008. Accuracy of self-reported body weight, height and waist circumference in a Dutch overweight working population. *BMC medical research methodology,* **8**(1), p69.

DOBSON, A. J. and A. BARNETT. 2008. *An introduction to generalized linear models.* CRC press.

DORKOVA, Z., D. PETRASOVA, A. MOLCANYIOVA, M. POPOVNAKOVA and R. TKACOVA. 2008. Effects of continuous positive airway pressure on cardiovascular risk profile in patients with severe obstructive sleep apnea and metabolic syndrome. *Chest,* **134**(4), pp.686-92.

DUNKLEY, A., K. CHARLES, L. GRAY, J. CAMOSSO-STEFINOVIC, M. DAVIES and K. KHUNTI. 2012. Effectiveness of interventions for reducing diabetes and

cardiovascular disease risk in people with metabolic syndrome: systematic review and mixed treatment comparison meta-analysis. *Diabetes, Obesity and Metabolism,* **14**(7), pp.616-625.

ECKEL, R. H., S. M. GRUNDY and P. Z. ZIMMET. 2005. The metabolic syndrome. *The Lancet,* **365**(9468), pp.1415-1428.

EISENMANN, J. C. 2003. Secular trends in variables associated with the metabolic syndrome of North American children and adolescents: a review and synthesis. *Am J Hum Biol,* **15**(6), pp.786-94.

EL FAKIRI, F., M. A. BRUIJNZEELS and A. W. HOES. 2007. No evidence for marked ethnic differences in accuracy of self-reported diabetes, hypertension, and hypercholesterolemia. *Journal of clinical epidemiology,* **60**(12), pp.1271-1279.

ENGSTROM, J. L., S. A. PATERSON, A. DOHERTY, M. TRABULSI and K. L. SPEER. 2003. Accuracy of self-reported height and weight in women: an integrative review of the literature. *Journal of Midwifery & Women's Health,* **48**(5), pp.338-345.

Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). 2001. *JAMA,* **285**(19), pp.2486-97.

FERRIE, J. E., M. KUMARI, P. SALO, A. SINGH-MANOUX and M. KIVIMÄKI. 2011. Sleep epidemiology—a rapidly growing field. *International journal of epidemiology,* **40**(6), pp.1431-1437.

FEWELL, Z., G. D. SMITH and J. A. STERNE. 2007. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. *American Journal of Epidemiology,* **166**(6), pp.646-655.

FLEISCHER, N. and A. D. ROUX. 2008. Using directed acyclic graphs to guide analyses of neighbourhood health effects: an introduction. *Journal of epidemiology and community health,* **62**(9), pp.842-846.

FORD, E. S., C. LI, A. G. WHEATON, D. P. CHAPMAN, G. S. PERRY and J. B. CROFT. 2014. Sleep duration and body mass index and waist circumference among US adults. *Obesity,* **22**(2), pp.598-607.

FOWLER, H., G. T. ELLISON, E. M. SCOTT and G. R. LAW. 2014. The importance of household composition in epidemiological analyses of sleep: Evidence from the Understanding Society longitudinal panel survey. *Open Journal of Epidemiology,* **2014**.

GANDEK, B., J. E. WARE, N. K. AARONSON, G. APOLONE, J. B. BJORNER, J. E. BRAZIER, M. BULLINGER, S. KAASA, A. LEPLEGE and L. PRIETO. 1998. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. *Journal of clinical epidemiology,* **51**(11), pp.1171-1178.

GANGWISCH, J. E., D. MALASPINA, L. A. BABISS, M. G. OPLER, K. POSNER, S. SHEN, J. B. TURNER, G. K. ZAMMIT and H. N. GINSBERG. 2010. Short sleep duration as a risk factor for hypercholesterolemia: analyses of the National Longitudinal Study of Adolescent Health. *Sleep,* **33**(7), p956.

GLASS, T. A., S. N. GOODMAN, M. A. HERNÁN and J. M. SAMET. 2013. Causal inference in public health. *Annual review of public health,* **34**, pp.61-75.

GOLDMAN, N., I.-F. LIN, M. WEINSTEIN and Y.-H. LIN. 2003. Evaluating the quality of self-reports of hypertension and diabetes. *Journal of clinical epidemiology,* **56**(2), pp.148-154.

GONNISSEN, H. K., R. HURSEL, F. RUTTERS, E. A. MARTENS and M. S. WESTERTERP-PLANTENGA. 2013. Effects of sleep fragmentation on appetite and related hormone concentrations over 24 h in healthy men. *British Journal of Nutrition,* **109**(04), pp.748-756.

GRANDI, A. M., E. LAURITA, C. MARCHESI, A. M. MARESCA, F. SOLBIATI, A. BERNASCONI, M. MAROGNA, C. SALINA, E. NICOLINI and L. GUASTI.

2012a. OSA, metabolic syndrome and CPAP: Effect on cardiac remodeling in subjects with abdominal obesity. *Respiratory medicine,* **106**(1), pp.145-152.

GRANDI, A. M., E. LAURITA, C. MARCHESI, A. M. MARESCA, F. SOLBIATI, A. BERNASCONI, M. MAROGNA, C. SALINA, E. NICOLINI, L. GUASTI, F. COLOMBO and A. VENCO. 2012b. OSA, metabolic syndrome and CPAP: effect on cardiac remodeling in subjects with abdominal obesity. *Respir Med,* **106**(1), pp.145-52.

GRANDNER, M. A., S. CHAKRAVORTY, M. L. PERLIS, L. OLIVER and I. GURUBHAGAVATULA. 2014. Habitual sleep duration associated with self-reported and objectively determined cardiometabolic risk factors. *Sleep Medicine,* **15**(1), pp.42-50.

GRUNDY, S. M. 2005. Metabolic syndrome scientific statement by the american heart association and the national heart, lung, and blood institute. *Arteriosclerosis, thrombosis, and vascular biology,* **25**(11), pp.2243-2244.

GRUNDY, S. M. 2008. Metabolic syndrome pandemic. *Arteriosclerosis, thrombosis, and vascular biology,* **28**(4), pp.629-636.

GRUNDY, S. M., H. B. BREWER, J. I. CLEEMAN, S. C. SMITH and C. LENFANT. 2004. Definition of metabolic syndrome report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on scientific issues related to definition. *Circulation,* **109**(3), pp.433-438.

GRUNDY, S. M., J. I. CLEEMAN, S. R. DANIELS, K. A. DONATO, R. H. ECKEL, B. A. FRANKLIN, D. J. GORDON, R. M. KRAUSS, P. J. SAVAGE and S. C. SMITH. 2005. Diagnosis and management of the metabolic syndrome an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation,* **112**(17), pp.2735-2752.

HAGSTRÖMER, M., P. OJA and M. SJÖSTRÖM. 2006. The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. *Public health nutrition,* **9**(06), pp.755-762.

HALL, M. H., M. F. MULDOON, J. R. JENNINGS, D. J. BUYSSE, J. D. FLORY and S. B. MANUCK. 2008. Self-reported sleep duration is associated with the metabolic syndrome in midlife adults. *Sleep,* **31**(5), pp.635-43.

HALL, M. H., M. L. OKUN, M. SOWERS, K. A. MATTHEWS, H. M. KRAVITZ, K. HARDIN, D. J. BUYSSE, J. T. BROMBERGER, J. F. OWENS, I. KARPOV and M. H. SANDERS. 2012. Sleep is associated with the metabolic syndrome in a multi-ethnic cohort of midlife women: the SWAN Sleep Study. *Sleep,* **35**(6), pp.783-90.

HALL, T. and T. YOUNG. 1988. A validation study of body fat distribution as determined by self-measurement of waist and hip circumference. *International journal of Obesity,* **13**(6), pp.801-807.

HALL, W., L. T. CLARK, N. K. WENGER, J. WRIGHT JR, S. K. KUMANYIKA, K. WATSON, E. W. HORTON, J. M. FLACK, K. FERDINAND and J. GAVIN 3RD. 2002. The metabolic syndrome in African Americans: a review. *Ethnicity & disease,* **13**(4), pp.414-428.

HALLADAY, J. R., K. E. DONAHUE, C. W. CENÉ, Q. LI, D. M. CUMMINGS, A. L. HINDERLITER, C. L. MILLER, B. A. GARCIA, E. LITTLE and M. RACHIDE. 2016. The association of health literacy and blood pressure reduction in a cohort of patients with hypertension: The heart healthy lenoir trial. *Patient Education and Counseling*.

HAN, T. and M. LEAN. 1998. Self-reported waist circumference compared with the 'Waist Watcher'tape-measure to identify individuals at increased health risk through intra-abdominal fat accumulation. *British Journal of Nutrition,* **80**(01), pp.81-88.

HAN, T. S. and M. E. LEAN. 2016. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. *JRSM cardiovascular disease,* **5**, p2048004016633371.

HERNÁN, M. A., S. HERNÁNDEZ-DÍAZ, M. M. WERLER and A. A. MITCHELL. 2002. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *American journal of epidemiology,* **155**(2), pp.176-184.

HODDES, E., V. ZARCONE and W. DEMENT. 1972. Development and use of Stanford Sleepiness scale (SSS). *In: Psychophysiology*: CAMBRIDGE UNIV PRESS 40 WEST 20TH STREET, NEW YORK, NY 10011-4211, pp.150-&.

HOSSAIN, J. L. 2002. The prevalence, cost implications, and management of sleep disorders: an overview. *Sleep and Breathing,* **6**(2), pp.85-102.

HSU, C. H., J. M. TAYLOR, S. MURRAY and D. COMMENGES. 2006. Survival analysis using auxiliary variables via non-parametric multiple imputation. *Statistics in medicine,* **25**(20), pp.3503-3517.

HUANG, P. L. 2009. A comprehensive definition for metabolic syndrome. *Disease Models and Mechanisms,* **2**(5-6), pp.231-237.

HUERTA, J. M., M. J. TORMO, J. M. EGEA-CAPARRÓS, J. B. ORTOLÁ-DEVESA and C. NAVARRO. 2009. Accuracy of self-reported diabetes, hypertension, and hyperlipidemia in the adult Spanish population. DINO study findings. *Revista Española de Cardiología (English Edition),* **62**(2), pp.143-152.

HUNG, H. C., Y. C. YANG, H. Y. OU, J. S. WU, F. H. LU and C. J. CHANG. 2013. The association between self-reported sleep quality and metabolic syndrome. *PLoS One,* **8**(1), pe54304.

IGUCHI, A., H. YAMAKAGE, M. TOCHIYA, K. MURANAKA, Y. SASAKI, S. KONO, A. SHIMATSU and N. SATOH-ASAHARA. 2013. Effects of weight reduction therapy on obstructive sleep apnea syndrome and arterial stiffness in patients with obesity and metabolic syndrome. *J Atheroscler Thromb,* **20**(11), pp.807-20.

ILANNE-PARIKKA, P. and J. TUOMILEHTO. 2013. Lifestyle Intervention: Prevention of Complications to the Metabolic Syndrome. *The Metabolic Syndrome.* Springer, pp.63-85.

INTERNATIONAL-DIABETES-FEDERATION. 2006. The IDF consensus worldwide definition of the metabolic syndrome. [online]. Available from: https://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf.

ISOMAA, B., P. ALMGREN, T. TUOMI, B. FORSÉN, K. LAHTI, M. NISSÉN, M.-R. TASKINEN and L. GROOP. 2001. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes care,* **24**(4), pp.683-689.

JANSSEN, I., P. T. KATZMARZYK and R. ROSS. 2004. Waist circumference and not body mass index explains obesity-related health risk. *The American journal of clinical nutrition,* **79**(3), pp.379-384.

JENKINS, C. D., B.-A. STANTON, S. J. NIEMCRYK and R. M. ROSE. 1988. A scale for the estimation of sleep problems in clinical research. *Journal of clinical epidemiology,* **41**(4), pp.313-321.

JENNINGS, J., M. MULDOON and M. HALL. 2007. Self-reported sleep qual-ity is associated with the metabolic syndrome. *Sleep,* **30**(2), pp.219-223.

JENNINGS, J. R., M. F. MULDOON, M. HALL, D. J. BUYSSE and S. B. MANUCK. 2007. Self-reported sleep quality is associated with the metabolic syndrome. *Sleep,* **30**(2), pp.219-23.

JIANG, C., G. N. THOMAS, T. H. LAM, C. M. SCHOOLING, W. ZHANG, X. LAO, P. ADAB, B. LIU, G. M. LEUNG and K. K. CHENG. 2006. Cohort profile: the Guangzhou Biobank Cohort Study, a Guangzhou–Hong Kong–Birmingham collaboration. *International journal of epidemiology,* **35**(4), pp.844-852.

JOHNS, M. W. 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *sleep,* **14**(6), pp.540-545.

KAHN, R. 2008. Metabolic syndrome--what is the clinical usefulness? *The Lancet,* **371**(9628), pp.1892-1893.

KAHN, R., J. BUSE, E. FERRANNINI and M. STERN. 2005. The metabolic syndrome: time for a critical appraisal. *Diabetes care,* **28**(9), pp.2289-2304.

KAUR, G., V. SHARMA and A. SINGH. 2015. Association of sleep quality with general health: an Indian college students study. *International Journal of Medical Science and Public Health,* **4**(12), pp.1767-1771.

KAZMAN, J. B., P. A. ABRAHAM, S. A. ZENO, M. POTH and P. A. DEUSTER. 2012. Self-reported sleep impairment and the metabolic syndrome among African Americans. *Ethn Dis,* **22**(4), pp.410-5.

KEHOE, R., S.-Y. WU, M. C. LESKE and L. T. CHYLACK. 1994. Comparing self-reported and physician-reported medical history. *American Journal of Epidemiology,* **139**(8), pp.813-818.

KIM, J.-O. and J. CURRY. 1977. The treatment of missing data in multivariate analysis. *Sociological Methods & Research,* **6**(2), pp.215-240.

KNIES, G. E. 2014. Understanding Society –UK Household Longitudinal Study: Wave 1-4, 2009-2013, User Manual. *Colchester: University of Essex*.

KNUTSON, K. L., K. SPIEGEL, P. PENEV and E. VAN CAUTER. 2007. The metabolic consequences of sleep deprivation. *Sleep medicine reviews,* **11**(3), pp.163-178.

KNUTSON, K. L. and E. VAN CAUTER. 2008. Associations between sleep loss and increased risk of obesity and diabetes. *Annals of the New York Academy of Sciences,* **1129**(1), pp.287-304.

KOBAYASHI, D., O. TAKAHASHI, G. A. DESHPANDE, T. SHIMBO and T. FUKUI. 2011. Relation between metabolic syndrome and sleep duration in Japan: a large scale cross-sectional study. *Intern Med,* **50**(2), pp.103-7.

KRIEGER, N. 2001. Theories for social epidemiology in the 21st century: an ecosocial perspective. *International journal of epidemiology,* **30**(4), pp.668-677.

KRIEGER, N. and G. DAVEY SMITH. 2004. "Bodies count," and body counts: social epidemiology and embodying inequality. *Epidemiol Rev,* **26**, pp.92-103.

KRIEGSMAN, D. M., B. W. PENNINX, J. T. M. VAN EIJK, A. J. P. BOEKE and D. J. DEEG. 1996. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly: a study on the accuracy of patients' self-reports and on determinants of inaccuracy. *Journal of clinical epidemiology,* **49**(12), pp.1407-1417.

KRISHNAN, P. V., A. S. VADIVU, A. ALAPPATT and M. KAMESWARAN. 2012. Prevalence of sleep abnormalities and their association among hypothyroid patients in an Indian population. *Sleep Med,* **13**(10), pp.1232-7.

KROPKO, J., B. GOODRICH, A. GELMAN and J. HILL. 2014. Multiple imputation for continuous and categorical data: Comparing joint multivariate normal and conditional approaches. *Political Analysis,* **22**(4), pp.497-519.

LALKHEN, A. G. and A. MCCLUSKEY. 2008. Clinical tests: sensitivity and specificity. *Continuing Education in Anaesthesia, Critical Care & Pain,* **8**(6), pp.221-223.

LANDIS, J. R. and G. G. KOCH. 1977. The measurement of observer agreement for categorical data. *Biometrics,* **33**(1), pp.159-74.

LEE, J., Y. S. CHOI, Y. J. JEONG, J. LEE, J. H. KIM, S. H. KIM, S. H. JOE and T. H. JEON. 2013. Poor-quality sleep is associated with metabolic syndrome in Korean adults. *Tohoku J Exp Med,* **231**(4), pp.281-91.

LEIKAUF, J. and A. D. FEDERMAN. 2009. Comparisons of Self-Reported and Chart-Identified Chronic Diseases in Inner-City Seniors. *Journal of the American Geriatrics Society,* **57**(7), pp.1219-1225.

LINDAU, S. T., E. O. LAUMANN, W. LEVINSON and L. J. WAITE. 2003. Synthesis of scientific disciplines in pursuit of health: The interactive biopsychosocial model. *Perspectives in biology and medicine,* **46**(3 Suppl), pS74.

LOPEZ-CANDALES, A. 2001. Metabolic syndrome X: a comprehensive review of the pathophysiology and recommended therapy. *Journal of medicine,* **32**(5-6), p283.

MANBER, R. and R. ARMITAGE. 1999. Sex, steroids, and sleep: a review. *Sleep,* **22**(5), pp.540-55.

MANN, C. 2003. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emergency Medicine Journal,* **20**(1), pp.54-60.

MARGOLIS, K. L., L. QI, R. BRZYSKI, D. E. BONDS, B. V. HOWARD, S. KEMPAINEN, S. LIU, J. G. ROBINSON, M. M. SAFFORD and L. T. TINKER. 2008. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. *Clinical Trials,* **5**(3), pp.240-247.

MARKWALD, R. R., E. L. MELANSON, M. R. SMITH, J. HIGGINS, L. PERREAULT, R. H. ECKEL and K. P. WRIGHT. 2013. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. *Proceedings of the National Academy of Sciences,* **110**(14), pp.5695-5700.

MARTIN, L. M., M. LEFF, N. CALONGE, C. GARRETT and D. E. NELSON. 2000. Validation of self-reported chronic conditions and health services in a managed care population. *American journal of preventive medicine,* **18**(3), pp.215-218.

MATSUZAWA, Y. 2005. Metabolic syndrome-definition and diagnostic criteria in Japan. *Journal of atherosclerosis and thrombosis,* **12**(6), pp.301-301.

MCCANLIES, E. C., J. E. SLAVEN, L. M. SMITH, M. E. ANDREW, L. E. CHARLES, C. M. BURCHFIEL and J. M. VIOLANTI. 2012. Metabolic syndrome and sleep duration in police officers. *Work,* **43**(2), pp.133-9.

MCFALL, S. L., PETERSEN, JAKOB, KAMINSKA, OLENA, LYNN, PETER. 2013. Understanding Society –UK Household Longitudinal Study: Wave 2 Nurse Health Assessment, 2010-2012, Guide to Nurse Health Assessment. *Colchester: University of Essex.*

MESAS, A. E., P. GUALLAR-CASTILLON, E. LOPEZ-GARCIA, L. M. LEON-MUNOZ, A. GRACIANI, J. R. BANEGAS and F. RODRIGUEZ-ARTALEJO. 2014. Sleep quality and the metabolic syndrome: the role of sleep duration and lifestyle. *Diabetes Metab Res Rev,* **30**(3), pp.222-31.

MILLER, R. L. and J. D. BREWER. 2003. *The AZ of social research: a dictionary of key social science research concepts.* Sage.

MOLENAAR, E. A., E. J. VAN AMEIJDEN, D. E. GROBBEE and M. E. NUMANS. 2007. Comparison of routine care self-reported and biometrical data on hypertension and diabetes: results of the Utrecht Health Project. *The European Journal of Public Health,* **17**(2), pp.199-205.

MOONS, K. G., R. A. DONDERS, T. STIJNEN and F. E. HARRELL. 2006. Using the outcome for imputation of missing predictor values was preferred. *Journal of clinical epidemiology,* **59**(10), pp.1092-1101.

MOTA, P. C. 2011. Relationship between metabolic syndrome & obstructive sleep apnoea in a hospital-based urban population. *Indian J Med Res,* **134**(5), pp.594-6.

MOTA, P. C., M. DRUMMOND, J. C. WINCK, A. C. SANTOS, J. ALMEIDA and J. A. MARQUES. 2011. APAP impact on metabolic syndrome in obstructive sleep apnea patients. *Sleep Breath,* **15**(4), pp.665-72.

MUGO, M. and J. R. SOWERS. 2004. Metabolic syndrome: implications of race and ethnicity. *Ethnicity and Disease,* **14**, pp.S2-26.

MULLINGTON, J. M., M. HAACK, M. TOTH, J. M. SERRADOR and H. K. MEIER-EWERT. 2009. Cardiovascular, Inflammatory, and Metabolic Consequences of Sleep Deprivation. *Progress in Cardiovascular Diseases,* **51**(4), pp.294-302.

NCEP-ATPIII. 2002. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation,* **106**(25), pp.3143-421.

NICE, N. I. F. H. A. C. E. 2011a. *Hypertension in adults: diagnosis and management.* NICE guideline CG127.

NICE, N. I. F. H. A. C. E. 2011b. *Type 2 diabetes prevention: population and community-level interventions.* NICE guideline PH35.

OHKUMA, T., H. FUJII, M. IWASE, S. OGATA-KAIZU, H. IDE, Y. KIKUCHI, Y. IDEWAKI, T. JODAI, Y. HIRAKAWA, U. NAKAMURA and T. KITAZONO. 2014. U-shaped association of sleep duration with metabolic syndrome and insulin resistance in patients with type 2 diabetes: the Fukuoka Diabetes Registry. *Metabolism,* **63**(4), pp.484-91.

OKSANEN, T., M. KIVIMÄKI, J. PENTTI, M. VIRTANEN, T. KLAUKKA and J. VAHTERA. 2010. Self-report as an indicator of incident disease. *Annals of epidemiology,* **20**(7), pp.547-554.

OKTAY, B., E. AKBAL, H. FIRAT, S. ARDIC and M. KIZILGUN. 2009. CPAP treatment in the coexistence of obstructive sleep apnea syndrome and metabolic syndrome, results of one year follow up. *Acta Clin Belg,* **64**(4), pp.329-34.

OKURA, Y., L. H. URBAN, D. W. MAHONEY, S. J. JACOBSEN and R. J. RODEHEFFER. 2004. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *Journal of clinical epidemiology,* **57**(10), pp.1096-1103.

ORGANIZATION, W. H. 1999. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. *Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation.* pp.59-59.

OYAMA, J., H. YAMAMOTO, T. MAEDA, A. ITO, K. NODE and N. MAKINO. 2012. Continuous positive airway pressure therapy improves vascular dysfunction and decreases oxidative stress in patients with the metabolic syndrome and obstructive sleep apnea syndrome. *Clin Cardiol,* **35**(4), pp.231-6.

PARK, Y. S. and J. S. KIM. 2012. Association between waist-to-height ratio and metabolic risk factors in Korean adults with normal body mass index and waist circumference. *The Tohoku journal of experimental medicine,* **228**(1), pp.1-8.

PASTORINO, S., M. RICHARDS, R. HARDY, J. ABINGTON, A. WILLS, D. KUH and M. PIERCE. 2014. Validation of self-reported diagnosis of diabetes in the 1946 British birth cohort. *Primary care diabetes*.

PEACOCK, J. and P. PEACOCK. 2011. *Oxford handbook of medical statistics.* Oxford University Press.

PEARL, J. 2000. *Causality: Models, Reasoning, and Inference.* Cambridge: Cambridge University Press.

PEDERSEN, A. B., E. M. MIKKELSEN, D. CRONIN-FENTON, N. R. KRISTENSEN, T. M. PHAM, L. PEDERSEN and I. PETERSEN. 2017. Missing data and multiple imputation in clinical epidemiological research. *Clinical Epidemiology,* **9**, p157.

PERELMAN, J. 2014. Are chronic diseases related to height? Results from the Portuguese National Health Interview Survey. *Economics & Human Biology,* **15**, pp.56-66.

PIGOTT, T. D. 2001. A review of methods for missing data. *Educational research and evaluation,* **7**(4), pp.353-383.

POURHOSEINGHOLI, M. A., A. R. BAGHESTANI and M. VAHEDI. 2012. How to control confounding effects by statistical analysis. *Gastroenterology and Hepatology from bed to bench,* **5**(2), p79.

QATO, D. M., J. WILDER, L. P. SCHUMM, V. GILLET and G. C. ALEXANDER. 2016. Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. *JAMA internal medicine,* **176**(4), pp.473-482.

RAGHUNATHAN, T. E. 2004. What do we do with missing data? Some options for analysis of incomplete data. *Annu. Rev. Public Health,* **25**, pp.99-117.

RAMPAL, S., S. MAHADEVA, E. GUALLAR, A. BULGIBA, R. MOHAMED, R. RAHMAT, M. T. ARIF and L. RAMPAL. 2012. Ethnic differences in the prevalence of metabolic syndrome: results from a multi-ethnic population-based survey in Malaysia. *PloS one,* **7**(9), pe46365.

REAVEN, G. M. 1988. Role of insulin resistance in human disease. *Diabetes,* **37**(12), pp.1595-1607.

RIDKER, P. M. 2014. LDL cholesterol: controversies and future therapeutic directions. *The Lancet,* **384**(9943), pp.607-617.

RIMM, E. B., M. J. STAMPFER, G. A. COLDITZ, C. G. CHUTE, L. B. LITIN and W. C. WILLETT. 1990. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology,* **1**(6), pp.466-473.

ROBINSON, J. R., T. K. YOUNG, L. L. ROOS and D. E. GELSKEY. 1997. Estimating the burden of disease: comparing administrative data and self-reports. *Medical care*, pp.932-947.

ROOPA, M., M. DEEPA, K. INDULEKHA and V. MOHAN. 2010. Prevalence of sleep abnormalities and their association with metabolic syndrome among Asian Indians: Chennai Urban Rural Epidemiology Study (CURES-67). *J Diabetes Sci Technol,* **4**(6), pp.1524-31.

ROTHMAN, K. J. 2014. Six Persistent Research Misconceptions. *Journal of General Internal Medicine,* **29**(7), pp.1060-1064.

ROTTMAN, B. M. and R. HASTIE. 2014. Reasoning about causal relationships: Inferences on causal networks. *Psychological bulletin,* **140**(1), p109.

RUBIN, D. B. 1976. Inference and missing data. *Biometrika,* **63**(3), pp.581-592.

SALEH, D. and I. JANSSEN. 2014. Interrelationships among sedentary time, sleep duration, and the metabolic syndrome in adults. *BMC Public Health,* **14**(1), p1.

SALLIS, J. F., W. L. HASKELL, P. D. WOOD, S. P. FORTMANN, T. ROGERS, S. N. BLAIR and R. S. PAFFENBARGER. 1985. Physical activity assessment methodology in the Five-City Project. *American journal of epidemiology,* **121**(1), pp.91-106.

SANTOS, A. C., S. EBRAHIM and H. BARROS. 2007. Alcohol intake, smoking, sleeping hours, physical activity and the metabolic syndrome. *Prev Med,* **44**(4), pp.328-34.

SAUNDERS, J. A., N. MORROW-HOWELL, E. SPITZNAGEL, P. DORÉ, E. K. PROCTOR and R. PESCARINO. 2006. Imputing missing data: A comparison of methods for social work researchers. *Social work research,* **30**(1), pp.19-31.

SCHAFER, J. L. and J. W. GRAHAM. 2002. Missing data: our view of the state of the art. *Psychological methods,* **7**(2), p147.

SCHENCK, C. H., M. W. MAHOWALD and R. L. SACK. 2003. Assessment and management of insomnia. *JAMA: the journal of the American Medical Association,* **289**(19), pp.2475-2479.

SCUTERI, A., O. H. FRANCO, H. VÖLZKE, M.-H. SHIN, S.-S. KWEON, E. RIETZSCHEL, L. RYLIŠKYTĖ, I. STRAZHESKO, C.-H. CHEN and E. G. LAKATTA. 2016. The relationship between the metabolic syndrome and arterial wall thickness: A mosaic still to be interpreted. *Atherosclerosis,* **255**, pp.11-16.

SHARMA, S. and M. KAVURU. 2010. Sleep and metabolism: an overview. *International journal of endocrinology,* **2010**.

SHARMA, S. K., S. AGRAWAL, D. DAMODARAN, V. SREENIVAS, T. KADHIRAVAN, R. LAKSHMY, P. JAGIA and A. KUMAR. 2011. CPAP for the metabolic syndrome in patients with obstructive sleep apnea. *N Engl J Med,* **365**(24), pp.2277-86.

SMITH JR, S. C. 2007. Multiple risk factors for cardiovascular disease and diabetes mellitus. *The American journal of medicine,* **120**(3), pp.S3-S11.

SOPKOVA, Z., Z. DORKOVA and R. TKACOVA. 2009. Predictors of compliance with continuous positive airway pressure treatment in patients with obstructive sleep apnea and metabolic syndrome. *Wien Klin Wochenschr,* **121**(11-12), pp.398-404.

SPENCER, E. A., A. W. RODDAM and T. J. KEY. 2004. Accuracy of self-reported waist and hip measurements in 4492 EPIC–Oxford participants. *Public health nutrition,* **7**(06), pp.723-727.

SPIEGEL, K., E. TASALI, R. LEPROULT and E. VAN CAUTER. 2009. Effects of poor and short sleep on glucose metabolism and obesity risk. *Nat Rev Endocrinol,* **5**(5), pp.253-261.

STATACROP. 2013. Stata Statistical Software: Release 13. *College Station, TX: StataCorp LP*.

STEFANI, K. M., H. C. KIM, J. KIM, K. OH and I. SUH. 2013. The influence of sex and age on the relationship between sleep duration and metabolic syndrome in Korean adults. *Diabetes Res Clin Pract,* **102**(3), pp.250-9.

STERNE, J. A., I. R. WHITE, J. B. CARLIN, M. SPRATT, P. ROYSTON, M. G. KENWARD, A. M. WOOD and J. R. CARPENTER. 2009. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj,* **338**, pb2393.

THAWORNCHAISIT, P., F. DE LOOZE, C. M. REID, S.-A. SEUBSMAN, A. SLEIGH and T. C. S. TEAM. 2013. Validity of self-reported hypertension: findings from the Thai cohort study compared to physician telephone interview. *Global journal of health science,* **6**(2), p1.

THOMAS, G. N., C. Q. JIANG, X. Q. LAO, S. M. MCGHEE, W. S. ZHANG, C. M. SCHOOLING, P. ADAB, T. H. LAM and K. K. CHENG. 2006. Snoring and vascular risk factors and disease in a low-risk Chinese population: the Guangzhou Biobank Cohort Study. *Sleep,* **29**(7), pp.896-900.

TIMAR, O., F. SESTIER and E. LEVY. 2000. Metabolic syndrome X: a review. *The Canadian journal of cardiology,* **16**(6), pp.779-789.

TOLONEN, H., P. KOPONEN, J. S. MINDELL, S. MÄNNISTÖ, S. GIAMPAOLI, C. M. DIAS, T. TUOVINEN, A. GÖBWALD and K. KUULASMAA. 2014. Under-estimation of obesity, hypertension and high cholesterol by self-reported data: comparison of self-reported information and objective measures from health examination surveys. *The European Journal of Public Health,* **24**(6), pp.941-948.

TROXEL, W. M., D. J. BUYSSE, K. A. MATTHEWS, K. E. KIP, P. J. STROLLO, M. HALL, O. DRUMHELLER and S. E. REIS. 2010. Sleep symptoms predict the development of the metabolic syndrome. *Sleep,* **33**(12), pp.1633-40.

TU, Y.-K. and D. C. GREENWOOD. 2012. *Modern methods for epidemiology.* Springer Science & Business Media.

TU, Y.-K., D. GUNNELL and M. S. GILTHORPE. 2008. Simpson's Paradox, Lord's Paradox, and Suppression Effects are the same phenomenon – the reversal paradox. *Emerging Themes in Epidemiology,* **5**(1), p2.

TU, Y. K. and M. S. GILTHORPE. 2007. Revisiting the relation between change and initial value: a review and evaluation. *Statistics in medicine,* **26**(2), pp.443-457.

VAN BUUREN, S. 2007. Multiple imputation of discrete and continuous data by fully conditional specification. *Statistical methods in medical research,* **16**(3), pp.219-242.

VAN BUUREN, S., H. C. BOSHUIZEN and D. L. KNOOK. 1999. Multiple imputation of missing blood pressure covariates in survival analysis. *Statistics in medicine,* **18**(6), pp.681-694.

VAN BUUREN, S., J. P. BRAND, C. GROOTHUIS-OUDSHOORN and D. B. RUBIN. 2006. Fully conditional specification in multivariate imputation. *Journal of statistical computation and simulation,* **76**(12), pp.1049-1064.

VAN BUUREN, S. and K. OUDSHOORN. 1999. *Flexible mutlivariate imputation by MICE.* Leiden: TNO.

VANDERWEELE, T. J. and J. M. ROBINS. 2007. Directed acyclic graphs, sufficient causes, and the properties of conditioning on a common effect. *American journal of epidemiology,* **166**(9), pp.1096-1104.

VARGAS, C. M., V. L. BURT, R. F. GILLUM and E. R. PAMUK. 1997. Validity of self-reported hypertension in the National Health and Nutrition Examination Survey III, 1988–1991. *Preventive medicine,* **26**(5), pp.678-685.

VGONTZAS, M., AN and M. KALES, A. 1999. Sleep and its disorders. *Annual Review of Medicine,* **50**(1), pp.387-400.

VIERA, A. J. and J. M. GARRETT. 2005. Understanding interobserver agreement: the kappa statistic. *Fam Med,* **37**(5), pp.360-363.

WATSON, N. F., M. S. BADR, G. BELENKY, D. L. BLIWISE, O. M. BUXTON, D. BUYSSE, D. F. DINGES, J. GANGWISCH, M. A. GRANDNER, C. KUSHIDA, R. K. MALHOTRA, J. L. MARTIN, S. R. PATEL, S. F. QUAN and E. TASALI. 2015. Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society on the Recommended Amount of Sleep for a Healthy Adult: Methodology and Discussion. *Sleep,* **38**(8), pp.1161-83.

WAYMAN, J. C. 2003. Multiple imputation for missing data: What is it and how can I use it. *In: Annual Meeting of the American Educational Research Association, Chicago, IL*, pp.2-16.

WHITE, I. R., P. ROYSTON and A. M. WOOD. 2011. Multiple imputation using chained equations: issues and guidance for practice. *Statistics in medicine,* **30**(4), pp.377-399.

WHO. 2011. Waist circumference and waist-hip ratio: Report of a WHO expert consultation, Geneva, 8-11 December 2008.

WOLKOVE, N., O. ELKHOLY, M. BALTZAN and M. PALAYEW. 2007. Sleep and aging: 2. Management of sleep disorders in older people. *Canadian Medical Association Journal,* **176**(10), pp.1449-1454.

WU, M. C., Y. C. YANG, J. S. WU, R. H. WANG, F. H. LU and C. J. CHANG. 2012. Short sleep duration associated with a higher prevalence of metabolic syndrome in an apparently healthy population. *Prev Med,* **55**(4), pp.305-9.

XI, B., D. HE, M. ZHANG, J. XUE and D. ZHOU. 2014. Short sleep duration predicts risk of metabolic syndrome: A systematic review and meta-analysis. *Sleep Medicine Reviews,* **18**(4), pp.293-297.

YOO, H. and W. D. FRANKE. 2013. Sleep habits, mental health, and the metabolic syndrome in law enforcement officers. *J Occup Environ Med,* **55**(1), pp.99-103.

YOONG, S. L., M. L. CAREY, C. D'ESTE and R. W. SANSON-FISHER. 2013. Agreement between self-reported and measured weight and height collected in general practice patients: a prospective study. *BMC medical research methodology,* **13**(1), p38.

YOUNGSTEDT, S. D. and D. F. KRIPKE. 2004. Long sleep and mortality: rationale for sleep restriction. *Sleep Medicine Reviews,* **8**(3), pp.159-174.

ZHU, S., Z. WANG, S. HESHKA, M. HEO, M. S. FAITH and S. B. HEYMSFIELD. 2002. Waist circumference and obesity-associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds. *The American journal of clinical nutrition,* **76**(4), pp.743-743.

Chapter 6 Appendix

6.1 Identifying suitable/necessary covariates

To identify the suitable/necessary covariates to include in this analyses, a search for narrative reviews of both MetS and sleep were undertaken to provide a basis on which established/theoretical determinants and consequences of each might be identified. The results of the searches (for narrative reviews and information for determinants/consequences of sleep and MetS contained therein) are summarised in tables 7.1 and 7.2 respectively. For both topics, 'saturation' was achieved and confirmed once 11 narrative reviews had been close-read. (See figure 7.1 and 7.2)

Table 6.1 Results from the narrative reviews search identifying the suitable/necessary sleep covariates.

Covariates	(Carskadon and Dement 1994)	(Manber and Armitage 1999)	(Bixler 2009)	(Vgontzas and Kales 1999)	(Bloom *et al.* 2009)	(Hossain 2002)	(Chokroverty 2010)	(Ferrie *et al.* 2011)	(Sharma and Kavuru 2010)	(Wolkove *et al.* 2007)	(Schenck, Mahowald and Sack 2002)
Age	✓		✓	✓	✓	✓	✓	✓		✓	✓
Gender		✓		✓		✓	✓	✓	✓		
Ethnicity									✓		
Socioeconomic factors*		✓	✓			✓	✓	✓	✓		✓
Genetic determinants	✓			✓					✓		
Length of prior waking	✓			✓	✓	✓				✓	
Circadian rhythms	✓			✓		✓		✓	✓	✓	✓
Day time sleep				✓	✓	✓	✓			✓	
Drug ingestion	✓	✓		✓	✓	✓	✓			✓	✓
Alcohol	✓		✓	✓	✓	✓	✓	✓		✓	✓
Smoking			✓	✓	✓	✓		✓		✓	
Physical activity			✓	✓	✓					✓	✓
Obesity			✓	✓				✓			
Travel across multiple time zones		✓							✓		✓
Depression			✓			✓	✓	✓		✓	✓
Chronic health conditions	✓		✓	✓	✓		✓			✓	
Emotional stress			✓	✓	✓	✓	✓				✓
Environment**				✓	✓			✓	✓	✓	✓
Sleep apnea syndromes	✓			✓	✓	✓	✓	✓		✓	
Insomnia	✓		✓	✓	✓	✓	✓	✓		✓	✓
Restless Legs Syndrome					✓					✓	

*socioeconomic factors: income, education, poverty, ethnicity, and (nature, time, and duration of work)
**environment: noise, light, bed partners with sleep disorders, TVs, computers, and work in the bedroom, sleeping Surface

Table 6.2 Results from the narrative reviews search identifying the suitable/necessary MetS covariates.

Covariates	(Timar, Sestier and Levy 2000)	(Grundy *et al.* 2005)	(Lopez-Candales 2001)	(Hall *et al.* 2002)	(Eckel, Grundy and Zimmet 2005)	(Grundy *et al.* 2005)	(Alberti *et al.* 2009)	(Grundy *et al.* 2004)	(Day 2007)	(Smith Jr 2007)	(Daskalopoulou, Mikhailidis and Elisaf 2004)
Gender	✓			✓	✓		✓	✓	✓		
Physical inactivity	✓	✓		✓		✓				✓	
Obesity	✓	✓		✓	✓	✓	✓	✓		✓	✓
Genetic	✓	✓	✓			✓		✓			✓
Adipose tissue disorders		✓								✓	
Ethnicity		✓			✓	✓			✓		
Aging		✓			✓	✓	✓	✓	✓		✓
Endocrine disorders		✓	✓			✓		✓			
Lifestyle (diet,PA,smoking)			✓	✓	✓		✓	✓		✓	✓

Figure 6.1 Saturation of sleep search for suitable/necessary covariates

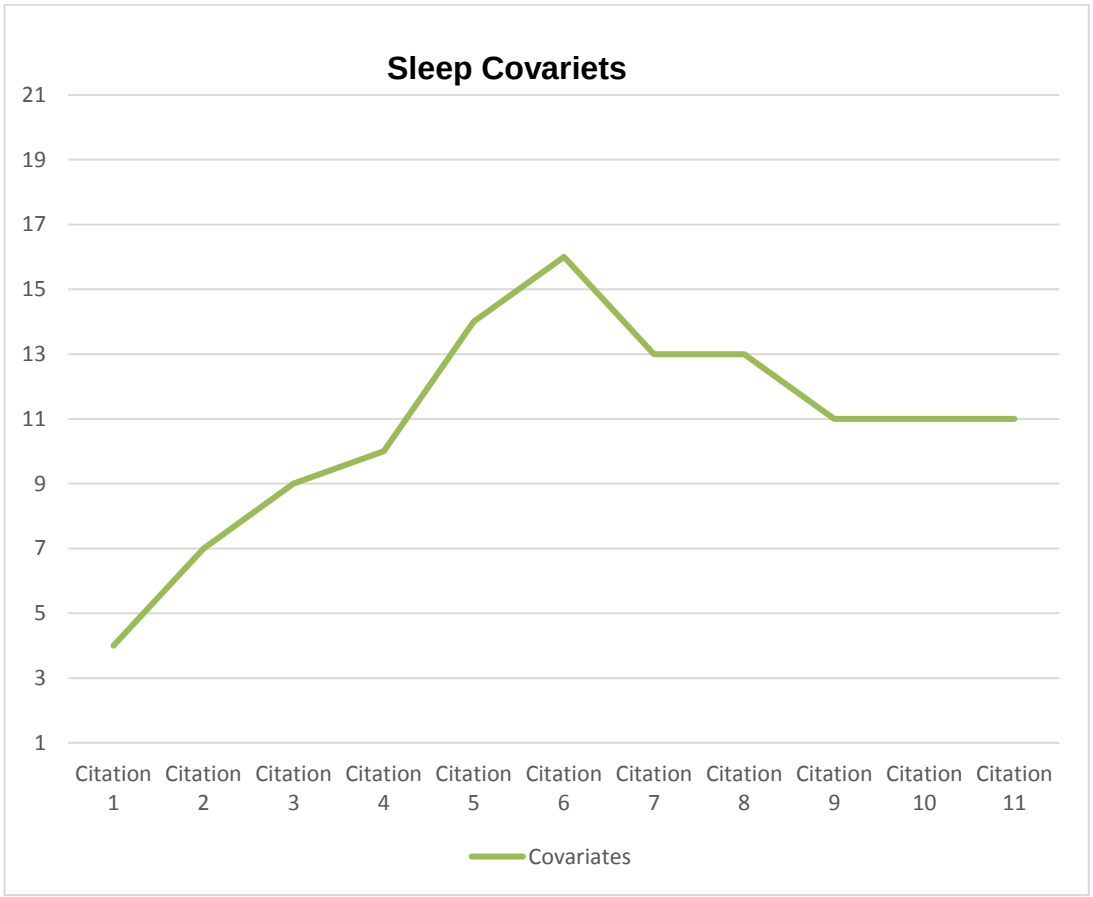
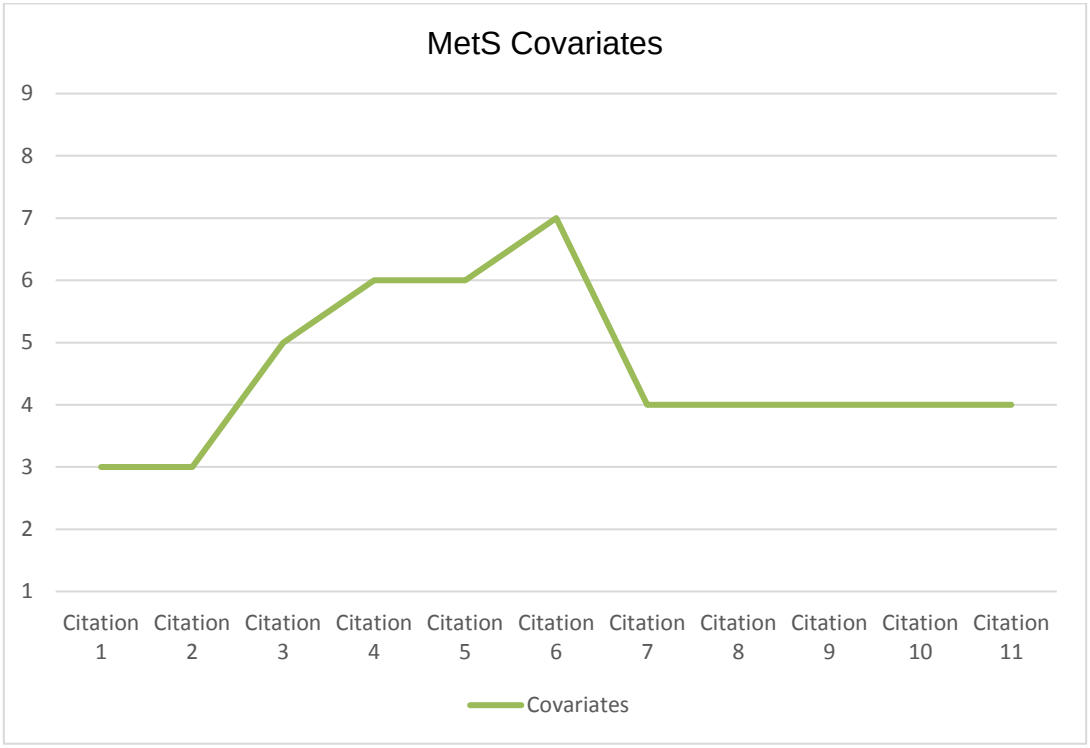


Figure 6.2 Saturation of MetS search for suitable/necessary covariates



6.2 Intervention studies

6.2.1 Study and population characteristics

Among the 9 articles that met inclusion criteria, majority of studies were conducted in European countries (n=6) while the rest (n=3) were conducted in Asian countries among them two in Japan and one in India. Seven studies were cohort studies (prospective observational studies), and only two studies were randomised control trails (RCT). Sample size ranged between studies from 20 to 86, while the average age ranged between 45 to 56 years old. Most of the studies recruited both male and female while only three studies recruited males only. All studies but two mentioned withdrawal rate that ranged from 4% to 47%. Only RCT's reported power calculation for their sample size but none of the other studies.

There was a diversity among population characteristics, n=6 studies mentioned that participants were recruited mainly from sleep clinics, while the remaining 3 studies recruited their participants one from outpatient clinic, one from respiratory outpatient clinic and one did not mention site of recruitment. With regards to inclusion criteria, three studies included patients with OSA and MetS, another four included only patients with OSA and one study included obese patients with MetS. The following Table 7.3, summarises above information.

Table 6.3 Study and population characteristics of intervention studies

Citation	Study design	Sample size	Population	Age	Sex
Sharma et al. 2011 India	RCT	4/90 Total=86	Pt with moderate or greater severity OSA and excessive daytime somnolence from sleep laboratory	45±8	77 M 9 F
Coughlin et al. 2007 UK	RCT	7/42 Total=35	Pt with OSA attending Sleep Disordered Breathing Clinic	49±8	100% M
Iguchi et al. 2013 Japan	Longitudinal	27/60 Total=33	Obese patients who had MS at out-patient clinic	51	11 M 22 F
Oyama et al. 2011 Japan	Single-arm prospective	21/53 Total=32	Pt with MS and OSA	54±9	19 M 13 F
Grandi et al. 2011 Italy	Longitudinal	15/56 Total=41	Pt with OSA, obesity and non-diabetic at the respiratory out-patients clinic	56±11	100% M
Mota et al. 2010 Portugal	Prospective observational study	74	Pt referred to Sleep-Disordered Breathing Clinic, with newly diagnosed moderate/severe OSA	50±8	100% M
Oktay et al. 2009 Turkey	Single-arm prospective	18/38 Total=20	Pt diagnosed with both OSA and MS attended at sleep disorders centre	54±1	13 M 7 F
Sopkova et al. 2009 Slovakia	Prospective observational study	51	Pt with OSA and MS attending at the sleep unit at a tertiary referral teaching hospital.	54±10	42 M 8 F
Oktay et al. 2009 Turkey	Single-arm prospective	34/66 Total=32	Pt with severe OSA and MS who's attending the sleep unit at the tertiary referral teaching hospital	54±10	27 M 5 F

6.2.2 MetS and sleep measures

Different MetS definitions were used among studies, however the most frequently used criteria was the criteria proposed by the US National Cholesterol Education Program-Adult Treatment Panel III (NCPI-ATP III) that was used by six of the reviewed studies. Two studies followed the International Diabetes Federation (IDF) definition and one study followed the Japanese criteria. All of the nine interventional studies identified sleep disorder as OSA and it was assessed as apnoea-hyponea index score using polysomnography except for the study conducted by Mota et al. (Mota 2011) that was assessed as manual respiratory disturbance index. Similarly the Epworth Sleepiness Scale was used among most of the studies to assess daytime sleepiness.

Out of the nine studies the majority (n=6) assessed the effectiveness of continues positive airway pressure (CPAP) treatment, while two studies assessed weight therapy (one assessed weight therapy and one weight therapy and CPAP) and finally only one study assessed the outcome of autoadjusting positive airway pressure (APAP) treatment. With regards to duration of intervention, there was variation among the period of intervention. It varied from 3 months to one year. Moreover, the degree of

assessment ranged from baseline, one week, one month, and up to 18 months. The following Table 7.4, summarises above information.

Table 6.4 MetS and sleep measures of intervention studies

Citation	Sleep classification		MetS definition	Method of intervention	Degree of assessment
	Criteria	Method of assessment			
(Sharma *et al.* 2011)	OSA Daytime sleep	AHI ESS	NCEP ATP-III	CPAP for 3m followed by sham for 3m or vice versa with 1m washout in between	Baseline, 3 month, 6 month
(Coughlin *et al.* 2007b)	OSA Daytime sleep	AHI ESS	NCEP ATP-III	CPAP/sham for 6 weeks	Baseline and 6 weeks
(Iguchi *et al.* 2013)	OSA	AHI ODI	NCEP ATP-III (WC modification for Japan)	Weight reduction therapy for 3 months	Baseline and 3 months
(Oyama *et al.* 2012)	OSA Daytime sleep	AHI ESS	Japanese criteria	CPAP for 3 months	Baseline and after 3months
(Grandi *et al.* 2012b)	OSA Daytime sleep	AHI ESS	NCEP ATP-III	Weight management& CPAP for 18 moth	Baseline, 6 month, 18 month
(Mota *et al.* 2011)	OSA Daytime sleep	RDI ESS	NCEP ATPIII	APAP for 6 months	Baseline, 1 week, 1 month, 3 months, 6 months
(Oktay *et al.* 2009)	OSA Sleep disorder	AHI standard questionnaire	NCEP ATPIII	CPAP for 1 year	Baseline and 1 year
(Sopkova, Dorkova and Tkacova 2009)	OSA Sleep quality	AHI ESS	IDF	CPAP for 8 weeks	Baseline and 8 weeks
(Dorkova *et al.* 2008)	OSA Daytime sleepiness	AHI ESS	IDF	CPAP for 8 weeks	Baseline and 8 weeks

6.2.3 Analysis strategy and results from intervention studies

a. Results from randomized controlled trials

Both RCT's conducted by Sharma et al. (Agrawal *et al.* 2011) and Coughlin et al. (Coughlin *et al.* 2007a) used placebo/sham CPAP therapy for control group and cross over the intervention and placebo group after 3 months and 6 weeks respectively. The primary outcome of both studies was to assess reduction in metabolic abnormalities. Sharma et al. (Agrawal *et al.* 2011) reported that CPAP treatment had significantly reduced systolic blood pressure, diastolic blood pressure, serum total cholesterol, non-high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides,

and glycated hemoglobin. They also reported that the frequency of the metabolic syndrome was reduced in 13% of intervention group. On the other hand, Coughlin et al. (Coughlin *et al.* 2007a) reported reduction in mean systolic and diastolic blood pressure in intervention group but no changes were observed in glucose, lipid, insulin resistance and metabolic syndrome.

b. Results from other studies

There was an inconsistency among the primary defined outcome, which varies between the effect of intervention on OSA and respiratory changes among patients with metabolic syndrome, or evaluating the improvement in MetS and its components after intervention. In general it was agreed among all reviewed studies that there was a significant association between metabolic syndrome and sleeping disorder (AHI). One example of that, Iguci et al. (Iguchi *et al.* 2013) reported that the log AHI was found to be associated with the number of MetS risk factors (log AHI, $p<0.01$; age and gender adjusted). Weight management therapy among both studies that followed this method (Iguchi *et al.* 2013; Grandi *et al.* 2012a) significantly decreased BMI, WC, and BP ($p<0.05$). However, while Iguchi et al. (Iguchi *et al.* 2013) found significant effect of weight management on AHI, Grandi et al. (Grandi *et al.* 2012a) referred the change in all respiratory parameters to the CPAP treatment alone rather than weight management.

CPAP or APAP treatment significantly improve MetS by decreasing its prevalence among the studied populations a finding that was mentioned by some studies (Mota 2011; Oktay *et al.* 2009; Dorkova *et al.* 2008). Moreover, CPAP and APAP significantly improves BMI, WC, BP and lipids a result that was agreed by (Oyama *et al.* 2012; Mota 2011; Oktay *et al.* 2009; Dorkova *et al.* 2008). On the other hand Oyama et al. and Oktay et al. found no significant association between the use of CPAP and blood glucose (Oyama *et al.* 2012; Oktay *et al.* 2009). With regards to the effect of CPAP on AHI and ESS there was an inequality among results. While Oyama et al. showed significant improve of AHI and ESS, Oktay et al. and Dorkova et al. found no significant changes (Oyama *et al.* 2012; Oktay *et al.* 2009; Dorkova *et al.* 2008). Finally compliance with CPAP treatment considered as the most important factor for positive outcomes (Dorkova *et al.* 2008; Sopkova, Dorkova and Tkacova 2009). The following Table 7.5, summarises above information.

Table 6.5 Analysis strategy and results from intervention studies

Citation	Predefined outcome	Results
Sharma et al. 2011 India	Reduction in the frequency of MetS	CPAP treatment significantly decreases all MetS parameters. The frequency of the MetS was reduced after CPAP therapy, a reversal found in 13% of pt undergoing CPAP therapy vs.1% of pt undergoing sham CPAP
Coughlin et al. 2007 UK	The difference between data at the end of each treatment period, rather than the change from individual baseline values	Mean waking systolic and diastolic blood pressure fell by 6.7 and 4.9 mmHg, respectively, compared with sham CPAP. No change was observed in glucose, lipids, insulin resistance or the proportion of patients with metabolic syndrome.
Iguchi et al. 2013 Japan	Effect of weight reduction therapy on OSA and arterial stiffness	Log AHI sig associated with the number of MetS risk factors (adj age&sex). Sign effect of weight change on BP, BMI,WC, AHI
Oyama et al. 2011 Japan	Change in vascular function and Biochemical markers	CPAP markedly improved AHI. WC, body weight, BMI, and arterial blood pressure were decreased significantly after treatment with CPAP
Grandi et al. 2011 Italy	changes of respiratory, BP, metabolic and LV parameters from basal to second evaluation	Sig effect of weight therapy on BMI, WC, BP, TG, FG. CPAP sig effect on all respiratory parameters and only BMI and WC
Mota et al. 2010 Portugal	therapy effectiveness with evaluation of the clinical symptoms and APAP compliance	APAP sig decreased prevalence of MetS from 63.5% to 47.3%, sig reduce BP (p=0.018) and TG (p=0.001). No sig change in Wt or BMI
Oktay et al. 2009 Turkey	Improvement in MetS & its components	Prevalence of MetS decreased by 45%.Sig differences after CPAP in WC (p=0.002), HDL (p=0.001) and BMI (p=0.01)
Sopkova et al. 2009 Slovakia	Improvement in MetS & its components	Obesity was present in all (100%), arterial hypertension in (94%); fasting plasma glucose levels were increased in (55%) patients and serum triglycerides in (71%); serum HDL cholesterol was reduced in (59%) patients.
Dorkova et al. 2008 Slovakia	Assessed adherence, glucose and lipid profile, systemic inflammation, oxidative stress, and global CVD	CPAP for > 4 h/night sig reduced systolic BP and diastolic BP ($p = 0.001$ and $p = 0.006$, respectively), total cholesterol ($p = 0.002$), and reductions in the global CVD risk (from 18.8 ± 9.8 to $13.9 \pm 9.7\%$, $p = 0.001$). No sig changes with CPAP < 4 h/night.

6.2.4 Discussion of intervention studies

In this part of the review the focus was on experimental studies that implemented an intervention treatment to improve the association between metabolic syndrome and sleep disorders namely obstructive sleep apnea.

While randomized control trials are well known for being a better experimental study design, most of the studies involved in this review were longitudinal in nature

and mainly single arm design. The two RCT studies (Sharma *et al.* 2011; Coughlin *et al.* 2007b) included in this review can be considered of good quality as they both mentioned sample size and power calculation, randomly allocated their participants to either intervention or control group, used double blinded method, used placebo, cross over the intervention and control group after a wash period, clearly define inclusion and exclusion criteria, and specify reason for withdrawal and dropout. Finally, the baseline characteristics of both RCT participants may differ in intervention and control group, but this was a cross-over design thus these differences had not affected the outcome of the studies.

On the other hand, most of the retrieved intervention studies have been limited in a number of ways. Most of them were single arm prospective studies thus the absence of any control group could affect the study outcome. Moreover, none of these prospective studies describe sample size and power calculation. And some of them didn't mention reason for withdrawal and dropout (Mota *et al.* 2011; Sopkova, Dorkova and Tkacova 2009). Nevertheless, short-term follow up were almost presented among all studies that were conducted on relatively small sample size. Withdrawal is another potential concern among these studies that may affect internal validity.

Most of these studies have suffered from inconsistent assessment criteria for both MetS and sleep, however the majority of studies referred to the NCPI-ATP III definition, but different classification of AHI were used to define OSA. Nevertheless, another inconsistency is intervention method, one study evaluated the effect of APAP, and one study evaluated the effect of weight reduction therapy alone, while the rest studied the effect of CPAP on different outcomes.

Notwithstanding these limitations, the present review was able to conclude that MetS was significantly correlated with OSA and that CPAP improved not only AHI but also some parameters of MetS such as BMI and blood pressure. On the other hand, weight reduction therapy even for short period of time improved metabolic dysfunction and severity of OSA. CPAP compliance was considered as important factor in achieving these outcomes. Finally, Large sample size, randomized studies with long follow up period that not only study the outcome of CPAP but also used multiple intervention along with CPAP with proper compliance are the need of current time. Moreover, the importance of screening programs for OSA is important for the early detection of cardio metabolic risk. In addition weight management programs are important to improve both metabolic and sleep disorders.

6.3 Cohort studies

Out of total 31 observational studies, 3 were cohort studies

6.3.1 Study and population characteristics

Basic characteristics from cohort studies are summarised in Table 7.6.

Table 6.6 Study and population characteristics of cohort studies

Citation	Sample size	Population	Age	Sex	Follow-up period
Chaput et al. Canada 2013 (Chaput *et al.* 2013a)	293	Quebec Family Study Free of MetS at baseline	18-65	M 136 F 164	6 years
Choi et al. South Korea 2011 (Choi *et al.* 2011)	1107	Korean Genomic Rural cohort	40-70	M 386 F 721	2-4 years
Troxel et al. USA 2010 (Troxel *et al.* 2010)	812	Community-based prospective study. Free of MetS at baseline	45-74	67% F	3 years

6.3.2 MetS and sleep measures

All selected studies looked for the changes in MetS at follow-up period as a result of changes in sleep parameters. Two studies considered sleep duration as the exposure variable but one considered the exposure as sleep disturbance related to insomnia and sleep disordered breathing. All sleep parameter were measured subjectively through self-administered questionnaires, two studies defined MetS based on the NCEP-ATP III definition and one refereed to the American Heart Association definition. The following Table 7.7 summarises these information.

Table 6.7 MetS and sleep measures of observational cohort studies

Citation	Exposure (independent)	Outcome (dependant)	Sleep assessment method	MS definition
Chaput et al. Canada 2013 (Chaput *et al.* 2013a)	Sleep duration (re=7-8hrs)	MetS	Self-administered questionnaire	American Heart Association/National Heart, Lung, and Blood Institute's criteria
Choi et al. South Korea 2011 (Choi *et al.* 2011)	Sleep duration (ref=6-7.9hrs)	MetS	Self-administered questionnaire	NCEP-ATP III
Troxel et al. USA 2010 (Troxel *et al.* 2010)	Sleep disturbance related to insomnia and SDB	MetS	Self-administered questionnaire	NCEP-ATP III

6.3.3 Analysis strategy and results

Among studies that looked for the association between MetS and sleep duration, after adjusting for potential confounders they reported significant association between short sleep duration and MetS. Chaput et al. (Chaput *et al.* 2013a) compare short sleep duration in referent to 7-8 hours' sleep per night, while Choi et al. (Choi *et al.* 2011) compared short sleepers to 6-7.9 hours per night. However, Choi et al. found no significant association between males' short sleeper and MetS. On the other hand, Troxel et al. (Troxel *et al.* 2010) after considering potential confounders, found that disturbance in sleep significantly predicts MetS after follow-up (Table 7.8).

Table 6.8 Analysis strategy and results from observational cohort studies

Citation	Covariates	Adjusted covariates	Results
Chaput et al. Canada 2013 (Chaput *et al.* 2013a)	Age, sex, total annual family income, smoking, alcohol, coffee intake, daily caloric intake, and cardiorespiratory fitness.	1st M: age & sex 2nd M: Age, sex, smoking, total annual family income, alcohol, coffee intake, daily caloric intake, and cardiorespiratory fitness.	Short sleep duration ≤ 6hrs significantly increase MetS RR 1st M: RR: 2.01 (1.30-3.05) 2nd M: RR: 1.74 (1.05-2.72)
Choi et al. South Korea 2011 (Choi *et al.* 2011)	Age, BMI, Smoking, Alcohol, Physical activity, Menopause status	1st M unadjusted 2nd M: age, BMI, menopause (F) 3rd M: age, BMI, Smoking, Alcohol, PA, and Menopause (F) *analysis was stratified by sex	Short sleep duration < 6hrs significantly associated with HR of MetS in F only. 1st M (HR: 1.83 CI 1.10-3.05) 2nd M (HR: 1.89 CI 1.12-3.18) 3rd M (HR: 1.80 CI 1.06-3.05)
Troxel et al. USA 2010 (Troxel *et al.* 2010)	Age, sex, race, marital status, smoking, alcohol, PA, depression, AHI	1st M: Age, sex, race, marital status, study randomisation, smoking, alcohol, PA, depression 2nd M: 1 + AHI	Difficulty falling asleep, unrefreshing sleep, and loud snoring significantly predicted MetS. Adjusted OR=1.81 (1.08-3.05), 1.71 (1.06-2.74), 2.30 (1.35-3.93) respectively. AHI were as well associated significantly with MetS adjusted OR=1.23 (1.02-1.74)

6.4 Results from the unadjusted and adjusted analyses of the association between sleep and MetS presented in Tables

The three sets of logistic regression models (n=16 models in all) have been summarised in Table 5.1.

Table 6-9 Summary of the statistical models used to examine whether any variation in the relationship between (different characteristics of) sleep and (different combinations of) MetS components was associated with: the use of different referent groups; the use of directly measured vs. self-reported components of MetS; and the inclusion of contemporaneous lifestyle variables in any adjustment sets used.

Table	Sample	Measurement of MetS components	Referent group used	Adjustment for sociodemographic variables	Adjustment for lifestyle variables
6.10	Sample 1 (n=5,283)	Directly measured	Participants do not display ***any*** components of MetS	No	No
6.11	Sample 1 (n=5,283)	Directly measured	Participants do not display ***any*** components of MetS	Yes	No
6.12	Sample 1 (n=5,283)	Directly measured	Participants do not display ***any*** components of MetS	Yes	Yes
6.13	Sample 1 (n=5,283)	Directly measured	Participants do not display ***the particular*** combination of MetS components being examined	No	No
6.14	Sample 1 (n=5,283)	Directly measured	Participants do not display ***the particular*** combination of MetS components being examined	Yes	No
6.15	Sample 1 (n=5,283)	Directly measured	Participants do not display ***the particular*** combination of MetS components being examined	Yes	Yes
6.16	Sample 1 (n=5,283)	Self-reported	Participants do not display ***any*** components of MetS	No	No
6.17	Sample 1 (n=5,283)	Self-reported	Participants do not display ***any*** components of MetS	Yes	No
6.18	Sample 1 (n=5,283)	Self-reported	Participants do not display ***any*** components of MetS	Yes	Yes
6.19	Sample 1 (n=5,283)	Self-reported	Participants do not display ***the particular*** combination of MetS components being examined	No	No
6.20	Sample 1 (n=5,283)	Self-reported	Participants do not display ***the particular*** combination of MetS components being examined	Yes	No
6.21	Sample 1 (n=5,283)	Self-reported	Participants do not display ***the particular*** combination of MetS components being examined	Yes	Yes
6.22	Sample 2 (n=29,436)	Self-reported	Participants do not display ***any*** components of MetS	No	Not available
6.23	Sample 2 (n=29,436)	Self-reported	Participants do not display ***any*** components of MetS	Yes	Not available
6.24	Sample 2 (n=29,436)	Self-reported	Participants do not display ***the particular*** combination of MetS components being examined	No	Not available
6.25	Sample 2 (n=29,436)	Self-reported	Participants do not display ***the particular*** combination of MetS components being examined	Yes	Not available

Table 6-10 Logistic regression analyses of the relationship between different directly measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, before adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 1 (n=5,283)	**Sleep characteristics** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *any* components of Mets)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.75 (1.42,2.16)	0.99 (0.80,1.22)	1.01 (0.89,1.16)	1.21 (1.03,1.43)	1.54 (1.35,1.76)	1.36 (1.14,1.63)	1.02 (0.85,1.22)	1.09 (0.94,1.27)
	High BP	1.61 (1.15,2.25)	0.73 (0.49,1.09)	0.75 (0.61,0.93)	1.33 (1.01,1.75)	1.38 (1.10,1.72)	1.44 (1.08,1.92)	0.85 (0.62,1.17)	0.81 (0.64,1.02)
	DM	1.01 (0.23,4.35)	0.38 (0.05,2.82)	0.45 (0.20,1.05)	1.35 (0.46,4.00)	0.95 (0.39,2.31)	0.65 (0.15,2.79)	0.87 (0.26,2.96)	0.44 (0.19,1.02)
Two	**Elevated WC and high BP**	1.78 (1.35,2.35)	1.08 (0.81,1.44)	1.03 (0.86,1.23)	1.61 (1.26,2.04)	2.07 (1.73,2.48)	1.45 (1.14,1.84)	0.69 (0.52,0.91)	0.99 (0.81,1.21)
	Elevated WC and DM	3.70 (2.23,6.16)	1.38 (0.72,2.66)	1.02 (0.67,1.56)	1.27 (0.74,2.16)	2.75 (1.81,4.18)	2.25 (1.38,3.65)	1.50 (0.89,2.51)	1.10 (0.68,1.80)
	High BP and DM	1.63 (0.63,4.24)	0.73 (0.22,2.40)	1.30 (0.59,2.16)	1.30 (0.57,2.95)	1.35 (0.71,2.60)	3.83 (1.97,7.45)	0.31 (0.75,1.31)	1.33 (0.61,2.90)
Three	**MetS**	2.60 (1.64,4.13)	0.78 (0.40,1.51)	0.93 (0.65,1.32)	1.34 (0.85,2.13)	2.04 (1.44,2.90)	2.01 (1.32,3.08)	1.43 (0.92,2.23)	1.62 (1.03,2.57)

Table 6-11 Logistic regression analyses of the relationship between different directly measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 1 (n=5,283)	**Sleep characteristics** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *any* components of Mets)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad Quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.54 (1.24,1.92)	1.06 (0.85,1.33)	0.98 (0.86,1.13)	1.04 (0.88,1.24)	1.54 (1.34,1.78)	1.29 (1.07,1.56)	1.21 (1.01,1.46)	1.12 (0.96,1.30)
	High BP	1.24 (0.87,1.77)	0.90 (0.59,1.38)	0.89 (0.71,1.12)	1.04 (0.77,1.40)	1.17 (0.92,1.49)	1.41 (1.03,1.91)	1.15 (0.82,1.62)	1.15 (0.89,1.48)
	DM	0.87 (0.20,3.82)	0.50 (0.06,3.77)	0.63 (0.27,1.49)	1.15 (0.38,3.42)	0.70 (0.28,1.75)	0.73 (0.17,3.15)	1.05 (0.30,3.63)	0.67 (0.29,1.85)
Two	**Elevated WC and high BP**	1.35 (0.99,1.82)	1.25 (0.91,1.71)	1.12 (0.92,1.36)	1.21 (0.93,1.57)	1.90 (1.56,2.31)	1.38 (1.06,1.78)	0.97 (0.72,1.31)	1.31 (1.05,1.63)
	Elevated WC and DM	2.77 (1.63,4.72)	1.52 (0.77,2.99)	1.10 (0.71,1.69)	1.04 (0.60,1.79)	2.34 (1.52,3.61)	2.04 (1.24,3.35)	2.06 (1.21,3.51)	1.35 (0.82,2.23)
	High BP and DM	1.36 (0.51,3.65)	0.97 (0.29,3.28)	1.50 (0.77,2.92)	1.08 (0.47,2.49)	1.04 (0.53,2.04)	4.14 (2.09,8.20)	0.37 (0.09,1.59)	2.12 (0.96,4.69)
Three	**MetS**	1.72 (1.05,2.80)	0.90 (0.45,1.78)	1.02 (0.71,1.47)	1.01 (0.63,1.63)	1.62 (1.12,2.35)	1.83 (1.18,2.85)	2.01 (1.31,3.36)	2.21 (1.38,3.55)

Table 6-12 Logistic regression analyses of the relationship between different directly measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 1 (n=5,283)	**Sleep characteristics** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *any* components of Mets)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad Quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.43 (1.15,1.78)	1.03 (0.82,1.30)	0.96 (0.84,1.10)	1.03 (0.87,1.22)	1.50 (1.30,1.73)	1.25 (1.04,1.52)	1.14 (0.94,1.38)	1.06 (0.91,1.25)
	High BP	1.18 (0.82,1.70)	0.89 (0.58,1.37)	0.87 (0.69,1.09)	1.02 (0.76,1.38)	1.12 (0.88,1.42)	1.37 (1.01,1.87)	1.12 (0.79,1.58)	1.10 (0.85,1.42)
	DM	0.72 (0.16,3.22)	0.51 (0.07,3.91)	0.58 (0.24,1.37)	1.11 (0.37,3.33)	0.60 (0.23,1.51)	0.68 (0.16,2.98)	0.93 (0.27,3.26)	0.62 (0.26,1.46)
Two	**Elevated WC and high BP**	1.23 (0.91,1.67)	1.17 (0.85,1.62)	1.09 (0.89,1.32)	1.17 (0.90,1.52)	1.83 (1.50,2.24)	1.33 (1.02,1.73)	0.90 (0.66,1.21)	1.21 (0.97,1.51)
	Elevated WC and DM	2.32 (1.35,3.97)	1.40 (0.71,2.77)	1.03 (0.67,1.60)	1.06 (0.61,1.84)	2.24 (1.44,3.49)	1.92 (1.16,3.18)	1.85 (1.08,3.18)	1.26 (0.76,2.08)
	High BP and DM	1.13 (0.42,3.08)	0.90 (0.26,3.04)	1.42 (0.73,2.77)	1.10 (0.48,2.54)	0.97 (0.49,1.93)	3.84 (1.93,7.64)	0.35 (0.08,1.49)	1.96 (0.88,4.35)
Three	**MetS**	1.41 (0.86,2.31)	0.78 (0.39,1.57)	0.95 (0.65,1.37)	1.02 (0.63,1.65)	1.52 (1.04,2.22)	1.65 (1.05,2.58)	1.83 (1.13,2.94)	2.01 (1.25,3.23)

Table 6-13 Logistic regression analyses of the relationship between different directly measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, before adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 1 (n=5,283)	**Sleep characteristics** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *the particular* MetS component[s] being examined)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad Quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.36 (1.13,1.63)	1.01 (0.82,1.23)	1.05 (0.93,1.18)	1.08 (0.93,1.26)	1.25 (1.10,1.41)	1.14 (0.97,1.35)	1.07 (0.90,1.27)	1.10 (0.96,1.27)
	High BP	1.15 (0.84,1.58)	0.73 (0.50,1.08)	0.75 (0.61,0.92)	1.17 (0.89,1.54)	1.05 (0.85,1.30)	1.18 (0.89,1.55)	0.87 (0.64,1.18)	0.78 (0.62,0.98)
	DM	0.71 (0.16,3.06)	0.38 (0.05,2.85)	0.46 (0.20,1.07)	1.18 (0.40,3.47)	0.72 (0.30,1.76)	0.53 (0.12,2.25)	0.90 (0.27,3.05)	0.44 (0.19,0.99)
Two	**Elevated WC and high BP**	1.30 (1.01,1.68)	1.12 (0.85,1.47)	1.05 (0.88,1.25)	1.46 (1.15,1.84)	1.68 (1.41,1.99)	1.20 (0.96,1.50)	0.68 (0.52,0.89)	0.97 (0.80,1.18)
	Elevated WC and DM	2.68 (1.63,4.41)	1.41 (0.74,2.71)	1.04 (0.69,1.58)	1.11 (0.65,1.88)	2.12 (1.40,3.21)	1.84 (1.14,2.97)	1.56 (0.94,2.60)	1.09 (0.67,1.76)
	High BP and DM	1.15 (0.45,2.98)	0.75 (0.22,2.43)	1.15 (0.60,2.20)	1.13 (0.50,2.57)	1.03 (0.54,1.97)	3.14 (1.62,6.06)	0.32 (0.08,1.35)	1.30 (0.60,2.85)
Three	**MetS**	1.88 (1.20,2.94)	0.79 (0.41,1.52)	0.94 (0.67,1.34)	1.18 (0.75,1.86)	1.57 (1.11,2.22)	1.65 (1.09,2.50)	1.49 (0.97,2.31)	1.61 (1.02,2.54)

Table 6-14 Logistic regression analyses of the relationship between different directly measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 1 (n=5,283)	**Sleep characteristics** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *the particular* MetS component[s] being examined)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad Quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.34 (1.11,1.63)	1.03 (0.84,1.27)	0.97 (0.85,1.11)	1.01 (0.86,1.19)	1.32 (1.16,1.50)	1.11 (0.94,1.32)	1.15 (0.97,1.37)	1.02 (0.88,1.18)
	High BP	0.94 (0.67,1.31)	0.84 (0.56,1.26)	0.87 (0.70,1.08)	0.99 (0.74,1.31)	0.86 (0.68,1.07)	1.11 (0.83,1.48)	1.03 (0.74,1.43)	0.99 (0.78,1.26)
	DM	0.67 (0.15,2.96)	0.47 (0.06,3.58)	0.63 (0.27,1.47)	1.09 (0.37,3.25)	0.53 (0.21,1.33)	0.57 (0.13,2.46)	0.95 (0.28,3.27)	0.59 (0.25,1.37)
Two	**Elevated WC and high BP**	1.04 (0.79,1.36)	1.23 (0.92,1.66)	1.14 (0.95,1.36)	1.18 (0.93,1.51)	1.53 (1.28,1.83)	1.10 (0.87,1.39)	0.85 (0.64,1.12)	1.18 (0.96,1.44)
	Elevated WC and DM	2.20 (1.31,3.68)	1.46 (0.75,2.84)	1.09 (0.71,1.68)	0.99 (0.58,1.70)	1.80 (1.17,2.75)	1.64 (1.01,2.67)	1.87 (1.11,3.16)	1.19 (0.73,1.94)
	High BP and DM	1.06 (0.40,2.81)	0.93 (0.28,3.11)	1.50 (0.78,2.91)	1.03 (0.45,2.36)	0.79 (0.40,1.53)	3.33 (1.70,6.53)	0.33 (0.08,1.40)	1.86 (0.85,4.10)
Three	**MetS**	1.33 (0.83,2.12)	0.84 (0.43,1.65)	1.01 (0.71,1.45)	0.95 (0.60,1.52)	1.21 (0.84,1.73)	1.44 (0.94,2.21)	1.93 (1.22,3.04)	1.96 (1.23,3.11)

Table 6-15 Logistic regression analyses of the relationship between different directly measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 1 (n=5,283)	**Sleep characteristics** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *the particular* MetS component[s] being examined)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad Quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.29 (1.06,1.57)	1.02 (0.82,1.25)	0.96 (0.85,1.09)	1.00 (0.85,1.17)	1.29 (1.13,1.47)	1.09 (0.92,1.30)	1.11 (0.93,1.32)	0.99 (0.86,1.15)
	High BP	0.96 (0.69,1.35)	0.86 (0.57,1.29)	0.86 (0.69,1.07)	0.98 (0.73,1.30)	0.84 (0.67,1.06)	1.12 (0.84,1.49)	1.05 (0.76,1.46)	0.99 (0.78,1.26)
	DM	0.59 (0.13,2.65)	0.50 (0.07,3.82)	0.58 (0.25,1.38)	1.07 (0.36,3.20)	0.47 (0.18,1.18)	0.55 (0.13,2.39)	0.87 (0.25,3.03)	0.56 (0.24,1.32)
Two	**Elevated WC and high BP**	0.99 (0.76,1.30)	1.19 (0.88,1.60)	1.12 (0.94,1.35)	1.15 (0.90,1.47)	1.50 (1.25,1.80)	1.08 (0.85,1.37)	0.80 (0.60,1.07)	1.11 (0.91,1.37)
	Elevated WC and DM	1.93 (1.14,3.25)	1.38 (0.71,2.70)	1.05 (0.68,1.61)	1.02 (0.60,1.76)	1.74 (1.13,2.68)	1.57 (0.96,2.56)	1.74 (1.03,2.95)	1.14 (0.69,1.86)
	High BP and DM	0.93 (0.34,2.49)	0.88 (0.26,2.96)	1.45 (0.74,2.82)	1.05 (0.46,2.42)	0.75 (0.38,1.48)	3.14 (1.59,6.20)	0.32 (0.08,1.36)	1.79 (0.81,3.95)
Three	**MetS**	1.14 (0.71,1.83)	0.75 (0.38,1.48)	0.96 (0.67,1.37)	0.97 (0.61,1.55)	1.14 (0.79,1.64)	1.31 (0.85,2.02)	1.74 (1.10,2.75)	1.84 (1.16,2.93)

Table 6-16 Logistic regression analyses of the relationship between different self-reported components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, before adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 1 (n=5,283)	**Sleep characteristics** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *any* components of Mets)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad Quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.72 (1.39,2.13)	0.98 (0.78,1.23)	1.07 (0.93,1.23)	1.21 (1.02,1.44)	1.86 (1.62,2.14)	1.25 (1.03,1.51)	1.09 (0.90,1.32)	1.14 (0.98,1.22)
	High BP	1.91 (1.38,2.63)	1.05 (0.73,1.51)	0.92 (0.74,1.15)	1.48 (1.10,2.00)	1.49 (1.19,1.86)	1.63 (1.23,2.16)	0.99 (0.72,1.37)	0.95 (0.74,1.22)
	DM	0.60 (0.18,1.94)	0.95 (0.40,2.25)	1.08 (0.63,1.84)	1.30 (0.65,2.58)	2.36 (1.40,4.00)	2.33 (1.28,4.24)	1.30 (0.65,2.59)	0.71 (0.41,1.23)
Two	**Elevated WC and high BP**	2.34 (1.71,3.21)	1.01 (0.68,1.49)	1.11 (0.88,1.40)	1.74 (1.26,2.42)	2.44 (1.94,3.07)	1.53 (1.13,2.05)	0.89 (0.63,1.26)	1.23 (0.93,1.62)
	Elevated WC and DM	2.90 (1.64,5.14)	0.58 (0.21,1.60)	1.59 (0.96,2.62)	1.56 (0.81,2.97)	2.44 (1.53,3.89)	2.46 (1.46,4.16)	1.32 (0.72,2.43)	1.80 (0.96,3.36)
	High BP and DM	2.80 (1.0,6.57)	0.95 (0.28,3.18)	0.65 (0.33,1.28)	2.07 (0.73,5.90)	1.02 (0.49,2.09)	1.40 (0.58,3.40)	0.81 (0.29,2.33)	1.15 (0.52,2.55)
Three	**MetS**	3.41 (2.06,5.63)	1.11 (0.54,2.25)	0.89 (0.59,1.34)	1.23 (0.72,2.10)	1.75 (1.16,2.65)	2.67 (1.69,4.21)	0.91 (0.49,1.67)	1.84 (1.05,3.22)

Table 6-17 Logistic regression analyses of the relationship between different self-reported components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 1 (n=5,283)	**Sleep characteristics** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *any* components of Mets)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad Quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.53 (1.23,1.91)	1.06 (0.83,1.35)	1.04 (0.90,1.20)	1.05 (0.87,1.25)	1.88 (1.62,2.17)	1.17 (0.96,1.42)	1.30 (1.07,1.59)	1.19 (1.01,1.40)
	High BP	1.64 (1.16,2.31)	1.26 (0.86,1.87)	1.09 (0.86,1.38)	1.19 (0.87,1.63)	1.32 (1.04,1.68)	1.65 (1.22,2.22)	1.35 (0.96,1.90)	1.33 (1.03,1.73)
	DM	0.50 (0.15,1.63)	1.17 (0.49,2.80)	1.41 (0.82,2.43)	1.12 (0.56,2.26)	1.82 (1.05,3.13)	2.49 (1.35,4.59)	1.69 (0.83,3.44)	1.07 (0.60,1.88)
Two	**Elevated WC and high BP**	1.82 (1.30,2.54)	1.12 (0.74,1.69)	1.15 (0.90,1.46)	1.35 (0.96,1.90)	2.39 (1.87,3.05)	1.43 (1.05,1.95)	1.24 (0.86,1.77)	1.51 (1.14,2.00)
	Elevated WC and DM	2.24 (1.24,4.06)	0.60 (0.21,1.70)	1.69 (1.01,2.82)	1.25 (0.65,2.42)	2.03 (1.25,3.30)	2.21 (1.29,3.78)	1.91 (1.02,3.58)	2.29 (1.21,4.32)
	High BP and DM	2.26 (0.93,5.48)	1.18 (0.35,4.04)	0.87 (0.44,1.75)	1.71 (0.59,4.91)	0.82 (0.39,1.72)	1.53 (0.62,3.78)	1.19 (0.41,3.49)	1.91 (0.85,4.29)
Three	**MetS**	2.28 (1.35,3.87)	1.20 (0.58,2.49)	0.89 (0.58,1.37)	0.96 (0.55,1.65)	1.56 (1.01,2.41)	2.38 (1.48,3.83)	1.20 (0.64,2.28)	2.30 (1.31,4.07)

Table 6-18 Logistic regression analyses of the relationship between different self-reported components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 1 (n=5,283)	**Sleep characteristics** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *any* components of Mets)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad Quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.50 (1.20,1.88)	0.99 (0.78,1.27)	1.03 (0.89,1.19)	1.04 (0.86,1.24)	1.91 (1.65,2.22)	1.15 (0.94,1.41)	1.23 (1.01,1.51)	1.16 (0.98,1.37)
	High BP	1.62 (1.14,2.29)	1.25 (0.84,1.84)	1.08 (0.85,1.37)	1.15 (0.84,1.58)	1.29 (1.01,1.65)	1.64 (1.21,2.21)	1.31 (0.94,1.84)	1.29 (0.99,1.68)
	DM	0.44 (0.13,1.46)	1.14 (0.47,2.74)	1.36 (0.79,2.35)	1.15 (0.57,2.32)	1.77 (1.02,3.07)	2.34 (1.27,4.33)	1.65 (0.81,3.37)	1.03 (0.58,1.82)
Two	**Elevated WC and high BP**	1.71 (1.22,2.40)	1.03 (0.68,1.56)	1.12 (0.88,1.44)	1.34 (0.95,1.89)	2.43 (1.90,3.12)	1.38 (1.01,1.89)	1.14 (0.80,1.64)	1.44 (1.08,1.92)
	Elevated WC and DM	1.90 (1.04,3.48)	0.55 (0.19,1.56)	1.61 (0.96,2.69)	1.32 (0.68,2.56)	2.03 (1.24,3.32)	1.99 (1.15,3.43)	1.71 (0.91,3.23)	2.17 (1.15,4.10)
	High BP and DM	2.14 (0.87,5.27)	1.15 (0.33,3.95)	0.88 (0.44,1.77)	1.66 (0.58,4.80)	0.80 (0.38,1.70)	1.51 (0.61,3.74)	1.13 (0.39,3.34)	1.83 (0.81,4.12)
Three	**MetS**	1.90 (1.11,3.25)	0.99 (0.47,2.07)	0.84 (0.54,1.29)	0.99 (0.57,1.72)	1.51 (0.97,2.36)	2.16 (1.34,3.50)	1.02 (0.54,1.94)	2.16 (1.22,3.84)

Table 6-19 Logistic regression analyses of the relationship between different self-reported components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, before adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 1 (n=5,283)	**Sleep characteristics** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *the particular* MetS component[s] being examined)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad Quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.38 (1.13,1.69)	0.98 (0.78,1.23)	1.07 (0.93,1.22)	1.11 (0.94,1.32)	1.60 (1.40,1.83)	1.08 (0.90,1.29)	1.09 (0.90,1.31)	1.11 (0.95,1.30)
	High BP	1.46 (1.07,1.99)	1.06 (0.74,1.52)	0.90 (0.72,1.12)	1.35 (1.01,1.82)	1.17 (0.93,1.45)	1.42 (1.08,1.87)	0.98 (0.72,1.34)	0.90 (0.70,1.15)
	DM	0.44 (0.14,1.43)	0.96 (0.41,2.25)	1.06 (0.62,1.81)	1.17 (0.85,2.31)	1.85 (1.09,3.12)	2.00 (1.10,3.62)	1.28 (0.65,2.55)	0.67 (0.38,1.17)
Two	**Elevated WC and high BP**	1.82 (1.34,2.47)	1.02 (0.69,1.50)	1.10 (0.87,1.38)	1.60 (1.16,2.22)	1.98 (1.58,2.48)	1.32 (0.99,1.76)	0.87 (0.62,1.22)	1.18 (0.90,1.55)
	Elevated WC and DM	2.19 (1.24,3.86)	0.57 (0.21,1.60)	1.57 (0.96,2.58)	1.40 (0.73,2.67)	1.91 (1.20,3.04)	2.12 (1.26,3.56)	1.31 (0.72,2.40)	1.72 (0.92,3.21)
	High BP and DM	2.10 (0.90,4.89)	0.95 (0.29,3.19)	0.64 (0.32,1.25)	1.86 (0.65,5.30)	0.79 (0.38,1.62)	1.19 (0.49,2.88)	0.80 (0.28,2.28)	1.01 (0.49,2.43)
Three	**MetS**	2.60 (1.58,4.25)	1.11 (0.55,2.26)	0.87 (0.58,1.31)	1.11 (0.65,1.88)	1.37 (0.91,2.07)	2.31 (1.47,3.64)	0.89 (0.48,1.64)	1.77 (1.01,3.08)

Table 6-20 Logistic regression analyses of the relationship between different self-reported components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 1 (n=5,283)	**Sleep characteristics** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *the particular* MetS component[s] being examined)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad Quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.30 (1.06,1.60)	1.03 (0.82,1.30)	1.01 (0.88,1.16)	1.00 (0.84,1.19)	1.64 (1.43,1.89)	1.01 (0.84,1.22)	1.22 (1.01,1.48)	1.08 (0.92,1.26)
	High BP	1.27 (0.92,1.77)	1.23 (0.84,1.80)	1.05 (0.83,1.32)	1.13 (0.83,1.54)	0.99 (0.78,1.25)	1.39 (1.04,1.85)	1.20 (0.86,1.66)	1.17 (0.90,1.50)
	DM	0.37 (0.11,1.23)	1.11 (0.47,2.65)	1.36 (0.79,2.34)	1.06 (0.53,2.12)	1.40 (0.82,2.41)	2.06 (1.12,3.77)	1.49 (0.73,3.00)	0.92 (0.52,1.61)
Two	**Elevated WC and high BP**	1.42 (1.04,1.96)	1.07 (0.72,1.60)	1.11 (0.88,1.41)	1.30 (0.93,1.81)	1.89 (1.50,2.40)	1.19 (0.88,1.60)	1.09 (0.77,1.54)	1.33 (1.01,1.76)
	Elevated WC and DM	1.72 (0.96,3.09)	0.57 (0.20,1.60)	1.64 (0.99,2.72)	1.18 (0.61,2.27)	1.53 (0.95,2.47)	1.83 (1.08,3.11)	1.67 (0.90,3.11)	1.99 (1.06,3.74)
	High BP and DM	1.71 (0.71,4.11)	1.12 (0.33,3.79)	0.83 (0.42,1.65)	1.60 (0.56,4.58)	0.61 (0.29,1.27)	1.21 (0.49,2.96)	1.02 (0.35,2.96)	1.63 (0.73,3.65)
Three	**MetS**	1.75 (1.04,2.93)	1.15 (0.56,2.36)	0.85 (0.56,1.30)	0.89 (0.51,1.53)	1.16 (0.75,1.77)	1.97 (1.24,3.14)	1.04 (0.55,1.95)	2.00 (1.14,3.52)

Table 6-21 Logistic regression analyses of the relationship between different self-reported components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=5,283 participants included in the UKHLS NHA, after adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 1 (n=5,283)	**Sleep characteristics** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *the particular* MetS component[s] being examined)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad Quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.28 (1.04,1.58)	0.98 (0.78,1.24)	1.00 (0.87,1.15)	0.99 (0.83,1.18)	1.66 (1.44,1.91)	1.00 (0.83,1.21)	1.17 (0.96,1.42)	1.05 (0.90,1.24)
	High BP	1.30 (0.93,1.80)	1.26 (0.86,1.84)	1.05 (0.84,1.32)	1.09 (0.80,1.49)	0.97 (0.76,1.22)	1.41 (1.06,1.87)	1.20 (0.86,1.67)	1.15 (0.89,1.48)
	DM	0.34 (0.10,1.13)	1.12 (0.47,2.67)	1.32 (0.77,2.27)	1.09 (0.54,2.18)	1.37 (0.79,2.36)	1.96 (1.06,3.60)	1.49 (0.74,3.03)	0.90 (0.51,1.58)
Two	**Elevated WC and high BP**	1.36 (0.98,1.87)	1.01 (0.68,1.52)	1.09 (0.86,1.39)	1.29 (0.93,1.81)	1.90 (1.49,2.41)	1.15 (0.85,1.55)	1.02 (0.72,1.45)	1.28 (0.97,1.69)
	Elevated WC and DM	1.48 (0.82,2.67)	0.54 (0.19,1.52)	1.57 (0.94,2.61)	1.25 (0.65,2.41)	1.49 (0.92,2.42)	1.65 (0.97,2.83)	1.54 (0.83,2.88)	1.89 (1.01,3.57)
	High BP and DM	1.64 (0.67,4.03)	1.12 (0.33,3.84)	0.84 (0.42,1.69)	1.56 (0.54,4.48)	0.56 (0.28,1.24)	1.20 (0.48,2.96)	1.00 (0.34,2.92)	1.59 (0.71,3.56)
Three	**MetS**	1.47 (0.87,2.48)	0 .98 (0.47,2.03)	0.80 (0.52,1.22)	0.92 (0.54,1.59)	1.08 (0.70,1.68)	1.79 (1.12,2.87)	0.90 (0.48,1.69)	1.88 (1.07,3.32)

Table 6-22 Logistic regression analyses of the relationship between different self-reported measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=29,436 participants included in Wave 1 of the UKHLS, before adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 2 (n=29,436)	**Sleep parameter** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *any* components of Mets)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.50 (1.37,1.65)	0.79 (0.72,0.87)	1.03 (0.97,1.09)	1.36 (1.26,1.46)	2.00 (1.88,2.13)	1.37 (1.26,1.48)	1.08 (0.99,1.16)	1.15 (1.07,1.23)
	High BP	1.63 (1.18,2.24)	0.80 (0.56,1.14)	0.93 (0.74,1.14)	1.31 (1.01,1.71)	1.67 (1.34,2.13)	1.93 (1.49,2.51)	0.98 (0.72,1.32)	0.88 (0.69,1.12)
	DM	1.61 (1.38,1.88)	0.76 (0.64,0.90)	1.02 (0.92,1.14)	1.71 (1.50,1.96)	1.76 (1.58,1.95)	1.94 (1.71,2.20)	0.88 (0.76,1.02)	0.98 (0.87,1.10)
Two	**Elevated WC and high BP**	2.24 (1.93,2.58)	0.74 (0.62,0.89)	1.23 (1.10,1.37)	1.99 (1.72,2.30)	2.41 (2.16,2.68)	2.03 (1.78,2.31)	0.88 (0.76,1.03)	1.17 (1.03,1.33)
	Elevated WC and DM	2.76 (2.13,3.58)	1.09 (0.80,1.48)	1.18 (0.95,1.45)	1.72 (1.31,2.25)	2.42 (1.97,2.97)	2.59 (2.03,3.17)	0.94 (0.71,1.26)	1.28 (0.99,1.64)
	High BP and DM	2.42 (1.70,3.43)	1.11 (0.75,1.65)	0.89 (0.68,1.17)	1.60 (1.14,2.25)	2.40 (1.84,3.14)	2.58 (1.91,3.47)	1.10 (0.77,1.58)	1.23 (0.89,1.69)
Three	**MetS**	3.06 (2.40,3.90)	0.87 (0.63,1.22)	1.08 (0.88,1.32)	1.96 (1.49,2.56)	3.17 (2.59,3.88)	2.54 (2.03,3.17)	1.04 (0.80,1.37)	1.14 (0.90,1.44)

Table 6-23 Logistic regression analyses of the relationship between different self-reported measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=29,436 participants included in Wave 1 of the UKHLS, after adjustment for sociodemographic variables. The referent group comprised participants who did not display *any* of the three components of MetS examined (elevated waist circumference, diabetes and high blood pressure). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 2 (n=29,436)	**Sleep parameter** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *any* components of Mets)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.32 (1.20,1.46)	1.01 (0.92,1.12)	1.07 (1.00,1.14)	1.15 (1.07,1.24)	1.88 (1.77,2.01)	1.28 (1.18,1.39)	1.29 (1.19,1.41)	1.22 (1.13,1.31)
	High BP	1.35 (1.14,1.59)	1.06 (0.89,1.28)	1.21 (1.08,1.35)	1.30 (1.13,1.50)	1.39 (1.24,1.56)	1.85 (1.62,2.12)	1.29 (1.10,1.52)	1.30 (1.15,1.47)
	DM	1.38 (0.99,1.91)	1.14 (0.79,1.63)	1.15 (0.92,1.44)	1.13 (0.86,1.47)	1.17 (0.93,1.47)	1.88 (1.44 ,2.46)	1.28 (0.92,1.71)	1.12 (0.88,1.44)
Two	**Elevated WC and high BP**	1.77 (1.51,2.07)	0.98 (0.81,1.19)	1.37 (1.22,1.54)	1.44 (1.24,1.68)	2.08 (1.85,2.34)	1.82 (1.59,2.09)	1.35 (1.14,1.59)	1.52 (1.33,1.73)
	Elevated WC and DM	2.14 (1.64,2.80)	1.42 (1.03,1.95)	1.33 (1.08,1.65)	1.37 (1.04,1.79)	1.88 (1.52,2.33)	2.28 (1.80,2.89)	1.33 (0.99,1.79)	1.64 (1.27,2.11)
	High BP and DM	1.79 (1.25,2.57)	1.44 (0.96,2.16)	1.11 (0.84,1.46)	1.25 (0.88,1.77)	1.71 (1.30,2.25)	2.38 (1.75,3.23)	1.72 (1.19,2.48)	1.74 (1.26,2.40)
Three	**MetS**	2.32 (1.80,2.99)	1.12 (0.80,1.57)	1.22 (0.99,1.51)	1.44 (1.09,1.92)	2.53 (2.05,3.12)	2.25 (1.79,2.84)	1.59 (1.21,2.11)	1.53 (1.20,1.94)

Table 6-24 Logistic regression analyses of the relationship between different self-reported measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=29,436 participants included in Wave 1 of the UKHLS, before adjustment for sociodemographic and contemporaneous lifestyle variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 2 (n=29,436)	**Sleep parameter** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *the particular* MetS component[s] being examined)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.27 (1.17,1.39)	0.82 (0.75,0.90)	1.01 (0.96,1.07)	1.24 (1.16,1.33)	1.73 (1.62,1.83)	1.16 (1.08,1.26)	1.09 (1.01,1.18)	1.13 (1.06,1.21)
	High BP	1.31 (1.13,1.53)	0. 81 (0.68,0.95)	1.00 (0.90,1.11)	1.53 (1.34,1.75)	1.38 (1.25,1.53)	1.65 (1.45,1.86)	0.87 (0.75,1.01)	0.94 (0.84,1.06)
	DM	1.32 (0.96,1.81)	0.85 (0.60,1.21)	0.91 (0.73,1.14)	1.15 (0.89,1.50)	1.30 (1.04,1.62)	1.60 (1.24,2.08)	0.97 (0.72,1.32)	0.85 (0.67,1.08)
Two	**Elevated WC and high BP**	1.87 (1.62,2.15)	0.78 (0.65,0.94)	1.22 (1.09,1.36)	1.80 (1.55,2.08)	1.93 (1.73,2.14)	1.73 (1.53,1.96)	0.88 (0.75,1.02)	1.13 (1.01,1.29)
	Elevated WC and DM	2.25 (1.74,2.92)	1.17 (0.86,1.59)	1.16 (0.94,1.43)	1.52 (1.16,1.98)	1.89 (1.54,2.32)	2.16 (1.72,2.71)	0.93 (0.70,1.25)	1.24 (0.96,1.58)
	High BP and DM	1.96 (1.38,2.77)	1.19 (0.80,1.76)	0.88 (0.67,1.15)	1.41 (1.01,1.98)	1.87 (1.43,2.44)	2.14 (1.59,2.88)	1.10 (0.77,1.57)	1.19 (0.86,1.63)
Three	**MetS**	2.50 (1.97,3.19)	0.93 (0.67,1.30)	1.06 (0.87,1.30)	1.73 (1.32,2.27)	2.48 (2.03,3.04)	2.12 (1.70,2.65)	1.04 (0.80,1.37)	1.10 (0.87,1.39)

Table 6-25 Logistic regression analyses of the relationship between different self-reported measured components (and combinations of components) of MetS and seven self-reported sleep characteristics, amongst n=29,436 participants included in Wave 1 of the UKHLS, after adjustment for sociodemographic lifestyle variables. The referent group comprised participants who do not display *the particular* component (or combination of components) of MetS being examined (but may have displayed none, one or all of the others). All results are given as relative risk ratios (RRRs; for multinomial logistic analyses) or odds ratios (ORs; for binary logistic regression analyses), with 95% confidence intervals (95%CI) in parentheses.

Sample 2 (n=29,436)	**Sleep parameter** referent	**Sleep duration** 6-8hrs		**Sleep latency** not during the past month	**Sleep fragmentation** not during the past month	**Cough/snore loudly** not during the past month	**Sleep medication** not during the past month	**Daytime sleepiness** not during the past month	**Sleep quality** good quality
No. of MetS components (referent: do not display *the particular* MetS component[s] being examined)		<6hrs	>8hrs	During the past month	During the past month	During the past month	During the past month	During the past month	Bad quality
		RRR (95%CI)	**RRR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
One	**Elevated WC**	1.17 (1.07,1.28)	0.99 (0.90,1.09)	1.02 (0.96,1.08)	1.10 (1.02,1.18)	1.68 (1.58,1.79)	1.09 (1.01,1.18)	1.22 (1.13,1.33)	1.14 (1.06,1.22)
	High BP	1.05 (0.90,1.23)	1.10 (0.92,1.31)	1.14 (1.02,1.27)	1.18 (1.03,1.35)	1.04 (0.93,1.16)	1.44 (1.26,1.64)	1.13 (0.97,1.13)	1.15 (1.02,1.30)
	DM	1.10 (0.79,1.52)	1.15 (0.80,1.65)	1.08 (0.86,1.35)	1.01 (0.77,1.32)	0.89 (0.71,1.12)	1.45 (1.11,1.89)	1.12 (0.82,1.52)	0.99 (0.77,1.26)
Two	**Elevated WC and high BP**	1.45 (1.25,1.68)	0.98 (0.81,1.18)	1.29 (1.15,1.44)	1.32 (1.14,1.54)	1.61 (1.44,1.80)	1.41 (1.23,1.60)	1.17 (0.99,1.137)	1.34 (1.18,1.53)
	Elevated WC and DM	1.73 (1.33,2.25)	1.41 (1.03,1.93)	1.23 (0.99,1.53)	1.23 (0.94,1.62)	1.41 (1.14,1.74)	1.76 (1.39,2.21)	1.15 (0.86,1.54)	1.42 (1.11,1.83)
	High BP and DM	1.35 (0.95,1.94)	1.51 (1.01,2.26)	1.01 (0.77,1.33)	1.09 (0.77,1.54)	1.23 (0.93,1.62)	1.71 (1.26,2.31)	1.45 (1.01,2.09)	1.49 (1.08,2.06)
Three	**MetS**	1.85 (1.44,2.37)	1.12 (0.80,1.57)	1.12 (0.91,1.37)	1.30 (0.99,1.72)	1.89 (1.54,2.33)	1.68 (1.34,2.11)	1.36 (1.04,1.80)	1.31 (1.04,1.66)