The relationship between sleep and glucose control in gestational diabetes

Alia Abdulhamid Alnaji

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Publications and conference presentations

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I dedicate this thesis to Imam Ali (AS) for keeping me going, and I quote him:

"Learn science, as learning it is a virtue, reviewing it is a chant, looking for it is a holy cause and teaching it to those who do not know it is a philanthropy"

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Abstract

This study set out to investigate the association between sleep among pregnant women with gestational diabetes (GDM) and their glucose control. Functional data analysis (FDA) methods were applied to glucose data collected via continuous glucose monitoring (CGM) systems. FDA is an advanced statistical method that respects the complexity of the dense auto-correlated data produced from repeated measurement of glucose over time.

192 pregnant women with GDM at their third trimester were recruited. Over a period of one week participants wore an actigraph (Actiwatch2 Respironics) which is a watch-like device on their non-dominant wrist to objectively measure their sleep, have a professional CGM system (iPro2 Medtronic) attached to them to continuously measure and record their interstitial glucose every 5 minutes, and complete the Pittsburgh Sleep Quality Index (PSQI) questionnaire to self-report their habitual sleep pattern for the previous month. Their demographic data and type of treatment they received were also collected. 152 participants had sufficient data retrieved from them, i.e. the PSQI questionnaire data and at least one night actigraphy-derived sleep data and one 24-hour day of CGM data.

Using FDA methods, sequential glucose values data-points recorded over time with the CGM system were converted into a smooth 24-hour glucose curves with a functional form (as a function of time). The glucose curve was then used as one value, instead of the multiple data-points values it represents. Glucose control was assessed using the smooth glucose curves, as well as, a conventional summary metrics. The associations between participants' actigraphy-derived and self-reported sleep characteristics and glucose control, were evaluated using standard and multilevel regression modelling for the conventional CGM data summary metrics and functional regression modelling for the smooth glucose curves.

The study discovered a positive association between sleep disturbances and glucose control. Sleep disturbances were measured as poor sleep quality, short and long sleep durations compared to an average 6-8 hours sleep duration and difficulties in initiating and maintaining sleep. The timing and the amplitude of these associations were more apparent with FDA regression models than regression models with summary metrics.

This study recommends the use of FDA in research involving the use of CGM systems, and encourages the clinician and the policy makers to consider sleep disturbances as a risk factor in glycaemic dysregulation in GDM.

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List of Abbreviations

AA	Alia Alnaji
AIC	Akaike Information Criterion
ANOVA	Analysis of variances
BG	Blood glucose
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CGM	Continuous glucose monitoring
CI	Confidence Interval
DAG	Directed Acyclic Graph
DE	Del Endersby
df	Degrees of freedom
DIP	Diabetes in pregnancy
DM	Diabetes mellitus
ECG	Electrocardiography
EEG	Electroencephalography
ES	Eleanor Scott
ET	Eberta Tan
FBS	fasting blood sugar
FDA	Functional data analysis
GCV	Generalised Cross Validation
GDM	Gestational diabetes mellitus
HbA1c	Glycosylated haemoglobin
HO	Heather Ong
HOMA2-IR	The Homeostatic Model Assessment - Insulin Resistance
HTN	Hypertension
ICC	Intra-class correlation
IFG	Impaired fasting glucose
IGTT	Intravenous glucose tolerance test
IQR	Interquartile Range
LA	Lina Alrefaai
LGA	Large for gestational age
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NREM	Non-Rapid Eye Movement
OGTT	Oral glucose tolerance test
OR	Odds Ratio

OLS	Ordinary Least Square
OSA	Obstructive Sleep Apnoea
PI	Principle investigator
PIH	Pregnancy induced hypertension
PPBS	Postprandial blood sugar
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RBS	Random blood sugar
REM	Rapid Eye Movement
RLS	Restless Leg Syndrome
RR	Risk Ratio
RRR	Relative Risk Ratio
SD	Standard Deviation
SDB	sleep disordered breathing
SE	Standard Error
SS	sum of the square
SSE	Sum of Squared Errors
SOL	Sleep Onset Latency
T1DM	Type 1 Diabetes
T2DM	Type 2 Diabetes
UK	United Kingdom
USA	United State of America
VPC	Variance partition coefficient
WASO	Wake After Sleep Onset
WHO	World Health Organisation

Chapter 1 Introduction

This thesis has two main elements: Firstly, a translational element involving the evaluation of a clinical question which answer can be translated directly to clinical practice; and secondly, a methodological element involving developing the novel application of advance statistical methods to analyse continuous glucose monitoring (CGM) data. The clinical question under investigation is that are sleep disturbances associated with higher and more variable glucose in pregnant women with gestational diabetes (GDM)? In order to best evaluate this question I developed the application of functional data analysis (FDA) to the CGM data.

The current chapter introduces the background and the rationale of this study. It provides a contextual outline on: sleep and sleep during pregnancy; how to measure sleep using subjective and objective tools; GDM epidemiology, diagnosis and complications; how to measure glycaemic control; CGM technology; traditional methods to analyse CGM data and the advantage of applying FDA to CGM data.

1.1 Sleep and circadian rhythm

Sleep, though recurring every day and lasting about one third of human beings' life, is still a mystery (Frank Marcos, 2006). A very naive definition of sleep is "a rapidly reversible state of immobility and greatly reduced sensory responsiveness" (Siegel, 2008). Sleep is not just a passive, sedentary, low activity, reduced consciousness body state (Kryger, 2005). In fact, while asleep the brain and many organs are highly active undergoing a process of whole body restoration. Whilst asleep distinctive brain activity can be detected using electroencephalogram (EEG). This shows signals demarcating two cyclic recurring sleep modes: 1) rapid eye movement (REM) sleep mode; and 2) non-rapid eye movement (NREM) sleep mode. NREM sleep comprises about 75% of total sleep time and has three stages, stage one is the transition time between being awake and asleep, stage two is the light sleep, while stage three (slow wave sleep) is the deepest and most body restorative sleep stage. On the other hand, REM sleep has only one stage and comprises 25% of total sleep time. During REM sleep the brain is highly active and voluntary muscles are highly flaccid. A complete cycle of these stages last 90 to 100 minutes and a round 4-5 cycles are repeated during a night sleep.

Sleep is one of the vital items to the survival of human beings and all the living creatures. In an animal study, total sleep deprivation led to the death of all rats involved in the study after 11-23 days (Everson et al., 1989), while in human a rare inherited fatal familial insomnia will eventually lead to death within 18 month of onset (Schenkein and Montagna, 2006). Whilst asleep, muscles and damaged body tissues are repaired, the memory is consolidated and assorted different hormones are released. In order for these restorative activities to be fulfilled and for a person to feel rested and refreshed after awakening, human beings need sufficient sleep duration and quality. Disturbed nighttime sleep with inadequate sleep duration and quality has been linked to mood swings, lower attentiveness and feelings of tiredness and weakness the next day (Rogers et al., 2003). Furthermore, chronic sleep disturbances have been linked to the risk of developing various diseases and disorders (Depner et al., 2014; Grandner et al., 2012; Shankar et al., 2010). The mechanism proposed by Hanlon and Van Cauter (2011) is that sleep curtailment induces cellular immune system activation and inflammation. Such inflammatory responses are linked to the risk of developing arthritis, diabetes and cardiovascular disorders (Irwin et al., 2006). It is noticeable that there has been an increase in the prevalence of diabetes in tandem with an increase in the prevalence of chronic sleep curtailment. It has been estimated that average sleep duration has dropped by almost 2 hours in the past 50 years (Knutson et al., 2010). In the United Kingdom and in the United States, a third of the population reports sleeping less than 7 hours per night (National Sleep Foundation, 2005; Barnes et al., 2013). An extended literature review on the association of sleep duration and glucose metabolism is presented in section 1.2.

The two states of sleep and wakefulness run in oscillatory cycles of about 24 hours known as circadian rhythms. These oscillations are entrained by external cues, most importantly the exposure to light and dark, as well as social cues like physical activity and feeding. This means that sleep generally takes place during the night when it is dark, and wakefulness takes place during the day when it is light. The partitioning of sleep and wake is driven by an internal timing system known as the circadian clock. We now know that each cell throughout the human body has an endogenous molecular clock that oscillates over approximately 24 hours (Mohawk et al., 2012; Bargiello and Young, 1984). The oscillations of each of these independent cells are synchronised to each other and the external light/dark cycle through the suprachiasmatic nucleus (SCN) which is located in the brain hypothalamus (Brancaccio et al., 2014). The SCN works like a conductor that unifies and sets the coherence of an orchestra. Circadian rhythms influence nearly all human body systems and behaviours including not only sleep and wakefulness, but also the function of the cardiorespiratory, renal, gastrointestinal, hepatic and immune systems, as well as endocrine hormone release, and core

temperature(Garcia et al., 2001; Cailotto et al., 2005; Warren et al., 1994). Many hormones involved in metabolism, such as insulin, glucagon, corticosterone and leptin, have circadian rhythmicity (La Fleur, 2003). Moreover, circadian rhythms influence metabolism and energy homeostasis in peripheral tissues (Froy, 2010). In animal studies lesions in circadian rhythm regulatory system caused not only sleep/wakefulness irregularities but also, hormone imbalance, obesity, glucose intolerance and diabetes mellitus (Arble et al., 2010; Turek et al., 2005).

In humans, circadian rhythm entrainment to the light/dark cycle is manifested differently in individuals, a feature known as chronotype (Phillips, 2009). Individuals can be characterised into 'morning larks' preferring early bed, sleep and wake-up times, or 'night owls' preferring late bed, sleep and wake-up times (Gale and Martyn, 1998). If an individual's chronotype clashes (out of phase) with work or social requirements then circadian sleep disturbances can occur. For example, if individuals with an early chronotype are made to stay awake late at night for social commitments their underlying circadian rhythms still make them wake-up early next day this leads to sleep deficit. If individuals with a late chronotype who naturally sleep late are made to wake-up early for work commitments, this overrides their natural circadian rhythm and they also get a sleep deficit. Both result in what is referred to as 'social jet lag' and both lead to curtailment of sleep duration, a perception of poor sleep quality and circadian misalignment (Abdullah et al., 2014). However, some studies had found a positive relationship between late chronotype, independent of sleep duration, with glucose intolerance and with higher Glycosylated haemoglobin (HbA1c) , HbA1c is indicator of glycaemic control, in type 2 diabetes (T2DM) patients (Reutrakul et al., 2013) and in participants with prediabetes (Anothaisintawee et al., 2017). Nevertheless, other study found that social jet lag and circadian misalignment but not chronotype were associated with higher HbA1c in in patients with type 1 diabetes (T1DM) (Larcher et al., 2016) and T2DM (Reutrakul et al., 2015) and with insulin resistance in healthy adults (Wong et al., 2015).

1.2 Measuring sleep

Sleep characteristics such as sleep duration, quality and timing can be evaluated both subjectively and objectively. Subjective evaluation consists of tools such as sleep logs/diaries and sleep questionnaires. Sleep logs are the simplest method used to evaluate sleep, though poor compliance with filling them out can bias their results (Herring et al., 2013). An alternative approach involves using questionnaires and there are numerous sleep questionnaires that have been designed for and used in sleep related studies. Among these questionnaires three are most commonly used: 1) the

Pittsburgh Sleep Quality Index (PSQI) questionnaire evaluating reported sleep duration and overall sleep quality (Buysse et al., 1989); 2) the Berlin Sleep Questionnaire evaluating sleep breathing disorders (Netzer et al., 1999); and 3) the Epworth Sleepiness Scale questionnaire evaluating daytime sleepiness and dysfunction resulting from nighttime sleep disturbances (Johns, 1991). However, these are retrospective tools, validated only for certain specific sleep characteristics or disorders, and are highly subjective (Buysse et al., 1989; Johns, 1992; Douglass et al., 1994; Partinen and Gislason, 1995; Netzer et al., 1999).

Polysomnography (PSG) is considered the "gold standard" for objectively measuring sleep (Ancoli-Israel et al., 2003; Kushida et al., 2005). It is usually conducted in a suitably-equipped specialist sleep laboratory where patients/study participants have to spend the night attached to multiple electrodes and related apparatus. PSG measures brain electrical activities, as well as, ocular (eye) muscle and body movement, breathing pattern, pulse rate, blood oxygen level and body temperature. It can demarcate the frequency and duration of sleep stages and it defines sleep onset and sleep offset using multiple inputs including change from waking brain activity to NREM sleep brain activity, ocular movement, drop in body temperature and sedentary body situation.

PSG is widely used for the evaluation of sleep disorders such as sleep disordered breathing (SDB), narcolepsy, parasomnia, sleep related seizure disorder and periodic limb movement sleep disorder. However, polysomnography is not recommended for the diagnosis of circadian rhythm related sleep disorders as it is impractical to apply it continuously for prolonged periods (Kushida et al., 2005). Moreover, polysomnography can be expensive, inconvenient and impractical in studying certain populations (Kushida et al., 2001). In a study asking pregnant women to have overnight polysomnography only 58 agreed out of 430 approached and ten of them withdrew before the start of the procedure (Wilson et al., 2011).

Actigraphy is a rather simpler, non-invasive objective tool to assess sleep characteristics (Ancoli-Israel et al., 2003; Sadeh and Acebo, 2002; Morgenthaler et al., 2007b; Hofstra and de Weerd, 2008; Sadeh, 2011). Actigraphy uses small wearable and portable devices that use accelerometer techniques to estimate sleep/wakefulness by detecting body movement. They assume that the person wearing them is asleep when not moving. Actigraphy, does not need a specialist laboratory. It provides objective information on sleep habits in a patient's/participant's natural sleep environment, and can conveniently estimate sleep/wake patterns continuously for prolonged periods (Kushida et al., 2001). Actigraphy has been used for estimating night time sleep parameters across different age groups, characterizing circadian patterns and sleep disturbances in individuals with insomnia and hypersomnia, and evaluating responses to treatments for circadian rhythm

disorders and insomnia (Littner et al., 2003). However, actigraphy is more valid and accurate in defining sleep characteristics in healthy individuals with no sleep related complaints than in individuals with sleep disturbances (Stone and Ancoli-Israel, 2011). Actigraphy has low specificity in detecting wakefulness while the individual is lying still and thus it has to be used in adjunct to other sleep assessment methods such as sleep logs/diaries (Sadeh, 2011; Tahmasian et al., 2010). Furthermore, the usefulness of actigraphy in defining and monitoring circadian rhythm patterns and sleep characteristics in some populations such as pregnant women has not been fully assessed (Stone and Ancoli-Israel, 2011). More details on the mechanism of action and validation of actigraphy are presented in the methods chapter.

1.3 Role of sleep duration in glucose homeostasis

Sleep is important for health. This section reviews the current evidence for whether sleep is involved in the pathogenesis of type 2 diabetes (T2DM). Evidence for whether sleep in individuals suffering from diabetes has a role in their glucose control is likewise reviewed. Summary tables of the findings of all the studies included in this section is available in Table 1-1 to Table 1-4.

1.3.1 Association between sleep and insulin resistance and glucose intolerance

Insulin resistance impairs insulin mediated cellular glucose uptake in individuals with T2DM. It progresses over many years prior to any clinically manifested glucose dysregulation. Observational and interventional studies have explored the relationship between sleep duration and insulin resistance.

An observational study among non-diabetic overweight-obese participants, compared self-reported sleep duration in insulin-resistant individuals (n= 35) with that seen in insulin-sensitive individuals (n=21). Insulin sensitivity was evaluated using steady-state plasma glucose concentrations during the insulin suppression test. Those with insulin resistance slept 43 minutes less per night (p-value = 0.018). The study also found that 60% of insulin-resistant participants slept less than 7 hours in comparison to only 24% only of insulin-sensitive participants (p-value 0.013) (Liu et al., 2013). In another cross-sectional study among adults over 20 years of age (n=301), PSQI questionnaire was used to evaluate sleep and the extent of Insulin resistance was assessed using fasting insulin concentration and the homeostatic model assessment - insulin resistance (HOMA2-IR) value (Lee et al., 2013). Fasting insulin and HOMA-IR were categorised into high and low groups using their 75th percentile as the cut-off point. Poor sleep quality (PSQI>5) was associated with higher probability of high fasting insulin and high HOMA-

IR (chi2 p-values <0.05), and both short sleep duration < 5.5 hours) and long sleep duration (≥ 8.5 hours) were associated with higher probability of high fasting insulin and high HOMA-IR, compared to average (6.5-7.49 hours) sleep duration, (chi2 p-values >0.05). In the same study poor sleep quality and short and long sleep durations were associated with the metabolic syndrome, (OR 3.83; 95% CI 1.91 to 7.65), (OR 4.89; 95% CI 1.90 to 12.58) and (OR 5.98; 95% CI 1.41 to 25.41), respectively. Whilst observational studies are of interest, there have been a collection of interventional studies looking at the metabolic consequences of both sleep restriction and sleep extension.

Multiple small-sized lab-based crossover studies on healthy young participants have looked at the effect of sleep restriction on glucose tolerance and insulin sensitivity (Nedeltcheva et al., 2009a; Wang et al., 2016b) and insulin sensitivity only (Broussard et al., 2012; Donga et al., 2010; St-Onge et al., 2012). Sleep restriction caused reduction of glucose tolerance in one study (Nedeltcheva et al., 2009a) and a reduction in insulin sensitivity in all the aforementioned studies except one (St-Onge et al., 2012). In this latter study restricting sleep duration was accompanied by controlled feeding conditions. A restricted diet was provided and the participants lost weight in both the habitual and short sleep phases.(St-Onge et al., 2012). It is possible that in the context of negative energy balance, acute short sleep duration does not lead to a state of increased insulin resistance.

Another crossover study of 19 healthy young lean men showed that whilst insulin sensitivity deteriorates after acute sleep restriction it recovers after two days of catch-up sleep (Broussard et al., 2016). Under lab-controlled conditions participants had up to 8.5 hours of sleep per night for 4 consecutive nights and only up to 4.5 hours of sleep for another 4 consecutive nights in a randomised order. After the nights of restricted sleep participants had the opportunity of sleeping 10-12 hours for two nights. Participants had a 23% decrease in insulin sensitivity after 4 days of sleep curtailment compared to normal sleep. However, insulin sensitivity was restored after 2 days of catch-up sleep. Although the study showed that catch-up sleep may reverse the negative impact of short-term sleep deprivation, the long-term impact of repeated sleep deprivation and catch-up sleep cycles on diabetes risk is not known.

These studies were all performed under controlled laboratory environments and explored acute and often severe sleep restriction. In contrast, Robertson et al. (2013) studied participants in their home environment to determine if milder and more chronic sleep restriction, akin to modern daily life voluntary sleep curtailment, has a role to play. Nineteen healthy, young, normal-weight men with habitual sleep durations of 7.0–7.5 hours and no sleep disturbances were randomised to either study arm (1.5 hours reduction in habitual bedtime) or control arm (habitual bedtime) for three weeks. Sleep

restriction led to a decrease in insulin sensitivity at the end of first week. It then recovered to baseline levels at the end of the study period. Whether sleep restriction effects on insulin sensitivity are short lived adaptive responses to an acute stress, or whether they persist longer term requires further investigation.

Given that short sleep duration and sleep restriction are linked to the development of insulin resistance it was timely that one study addressed whether sleep extension has beneficial effects on insulin sensitivity and glucose tolerance. Sixteen young healthy non-obese adults, mostly females, with chronic sleep curtailment had two weeks of habitual (their usual) time in bed followed by 6 weeks of extension time-in-bed in their home environment (Leproult et al., 2015). During the time-in-bed extension phase; participants went to bed an hour earlier and had longer sleep duration during weekdays but sustained the same sleep duration during weekends. The study reported no statistically significant difference between fasting glucose and insulin levels measured at the end of the habitual sleep phase and the extended sleep phase, however the authors did not present any statistics. They reported a "linear relationship", though only showing correlation coefficients, between the relative change in sleep duration and the relative change in fasting glucose (r = +0.65, p-value = 0.017) and insulin levels (r = −0.57, p-value = 0.053). More work is clearly needed to support a potential benefit of sleep extension on glucose tolerance and insulin sensitivity.

1.3.2 Association between sleep and T2DM

Several large cohort studies have investigated the association between sleep duration and the risk of subsequently developing T2DM, studied over varying lengths of follow-up (Yaggi et al., 2006; Gangwisch et al., 2007; Kowall et al., 2016; Holliday et al., 2013; Rafalson et al., 2010; Gutierrez-Repiso et al., 2014; Kita et al., 2012; Tuomilehto et al., 2009; Ferrie et al., 2015; Cespedes et al., 2016). Several large studies in the USA and Germany have shown a U-shaped association between sleep duration and increased risk of T2DM (Gangwisch et al., 2007; Kowall et al., 2016; Yaggi et al., 2006). These studies relied on self-reported sleep duration at baseline and mainly self-reported clinically diagnosed T2DM. Using 7 hours of sleep duration per night as a reference category, those with shorter and longer sleep duration were more likely to develop T2DM over 5-15 years follow-up period, risk estimates ranging between 1.47 to 1.95 for short sleep duration and between 1.40 to 3.12 for long sleep duration. Regression models employed in these studies were adjusted for many potential confounders, mainly; age, physical activity, BMI, alcohol consumption, ethnicity, education, marital status, depression and history of hypertension.

However, not all studies have shown this U-shaped relationship. A large Australian study with more than192,000 adult participants, used information recorded in medical

insurance records and reported a positive association between short <6 hours (but not long) sleep duration and subsequent incidence of T2DM, with 7 hours sleep duration as a reference (Holliday et al., 2013). However, T2DM incidence was determined from hospital admission records. Those who developed T2DM but were not admitted to hospital during the follow-up period could not be identified which might have led to underestimation of the actual diabetes incidence. In addition, the follow-up period was relatively short (mean duration 2.3 years). Moreover, another American cohort study showed that short (but not long) sleep duration, with 6-8 hour sleep duration as a reference, had higher odds of developing impaired fasting glucose (IFG) over six years of follow-up, OR 3.0, 95% CI 1.05-8.59; OR 1.6, 95% CI 0.45-5.42: for short and long sleep duration respectively (Rafalson et al., 2010). Whereas a Finnish study in overweight individuals with impaired glucose tolerance found an increased risk of T2DM only in participants with long sleep duration ≥ 9 hours(HR 2.29, 95% CI 1.38–3.80) (Tuomilehto et al., 2009). However, two recent meta-analyses of nine (Shan et al., 2015) and fourteen (Anothaisintawee et al., 2015) prospective cohort studies have also confirmed the U-shaped relationship (Figure 1-1).

A couple of other studies have investigated the association between short compared to normal sleep duration and the risk of T2DM without examining the U-shaped relationship. The first showed that sleeping ≤7 hours per night was associated with a higher odds of developing T2DM after 6 years follow-up (OR 1.96, 95% CI 1.10-3.50)(Gutierrez-Repiso et al., 2014). The study also found that the odds of becoming obese were significantly higher in subjects who slept ≤7 hours per night (OR 1.99, 95% CI 1.12-3.55). However, the study reported no association between sleep duration and TD2M after 11 years follow-up. This could be related to the attrition in the study population over time and to the mediation effect exhibited by adjusting for weight gain in the regression model. The second study found that sleeping ≤5 hours compared to >7 hours was associated with a higher odds of T2DM after 2 years follow-up (OR 5.37, 95% CI 1.38-20.91)(Kita et al., 2012).
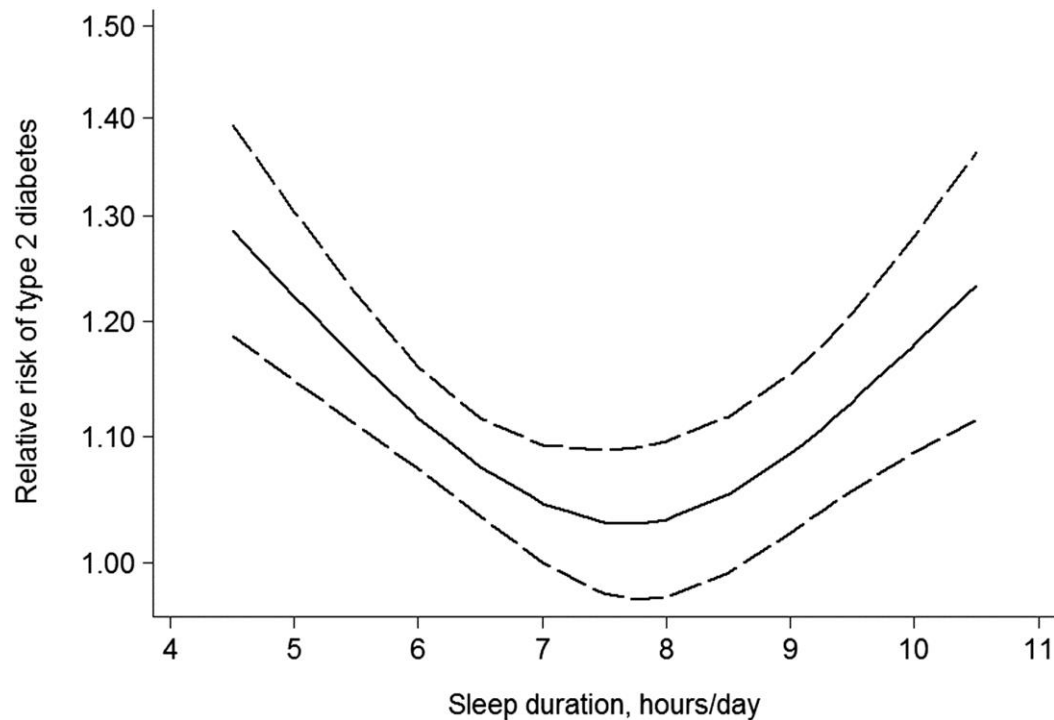
Figure 1-1. U-shaped relationship between sleep duration and risk of T2DM (Shan et al., 2015) ; reused with permission.

Extending the understanding of the relationship between sleep duration and risk of T2DM, the impact of a change in sleep duration over time has also been investigated. In the UK Whitehall II study, the change in sleep duration was calculated for participants without diabetes at the beginning and end of each of four 5-year cycles , while T2DM incidence was observed at the end of the subsequent cycle (Ferrie et al., 2015). Another prospective study (the Nurses' Health Study) examined whether historic changes in women's sleep duration over the preceding 14 years were associated with developing T2DM over the subsequent 12 year follow up (Cespedes et al., 2016). Both studies showed a higher risk of developing T2DM in participants with chronic short sleep duration (≤5.5-6 hours) (Whitehall II study: OR 1.35, 95% CI 1.04- 1.76; Nurses' Health Study: HR 1.10, 95%CI 1.001, 1.21) and in those with an increase of 2 hours or more in their sleep duration over time (Whitehall II study: OR 1.65 , 95% CI 1.15- 2.37; Nurses' Health Study: HR 1.15, 95% CI 1.01- 1.30) compared to those who maintained a 7-8 hour sleep duration. These studies suggest that the adverse metabolic influence of short sleep duration may not be ameliorated by sleeping longer hours later in life.

Although they do not carry the same weight as prospective studies, a couple of large cross-sectional studies (n=130973 and n= 56507, respectively) have shown a U-shaped association between sleep duration and T2DM (Jackson et al., 2013; Buxton and Marcelli, 2010), this association was observed only in White participants but not Black

participants (Jackson et al., 2013) . However, a study among middle-aged and old Chinese people (n= 25184) showed that longer self-reported sleep duration over a 24-hour period (≥ 8 hours compared to 7-7.9 hours) was positively associated with having T2DM, in women but not men (Wu et al., 2015). While, objectively measured sleep duration (using wrist actigraphy) in 2151 multi-ethnic participants showed higher odds of IFG in participants with short sleep duration (≤5 hours), but not those with long sleep duration (≥ 8 hours) compared to participants who slept between 5 and 8 hours. The association was reduced and became non-statistically significant after adjusting for apnoea-hypopnoea index (a measure of sleep hypoxia associated with sleep-disordered breathing) (Bakker et al., 2015). Taken together, these large studies and meta-analyses support that a U-shaped relationship exists between sleep duration and the risk of T2DM.

1.3.3 Association between sleep duration and glycaemic control in patients with diabetes

Given the mounting evidence supporting a relationship between sleep duration and the development of insulin resistance and T2DM, it is relevant to consider whether sleep duration has an impact on glycaemic control in people with established diabetes. Most studies to date are cross-sectional with a sample size ranging from as low as 18 participants to as high as 8543 participants. Most of these studies evaluated glycaemic control using HbA1c except one that used capillary glucose levels (Barone et al., 2015).

Among 4870 Japanese adults, aged ≥20 years with T2DM, shorter and longer self–reported sleep durations, including naps, were positively associated with higher HbA1c levels compared to a sleep duration of 6.5–7.4 hours (Figure 1-2) (Ohkuma et al., 2013). Likewise, a large Korean study which included participants with both T1DM and T2DM reported a U-shaped relationship between self-sleep duration and HbA1c (Kim et al., 2013a). In this later study, being a female or younger than 65 years with short sleep duration was associated with a higher risk of poor glycaemic control. However, only longer self-reported sleep duration (> 9 hours) compared to average (6-9 hours) self-reported sleep duration was associated with poor glycaemic control (higher HbA1c) in T2DM patients in a large Chinese study including 8543 participants aged 40 years or more (Zheng et al., 2015). A smaller Taiwanese study including 46 participants aged 43-83 years with T2DM, found positive association between poor sleep quality (PSQI score ≥ 8 compared to PSQI score ≤ 5) and self-reported sleep efficiency, but not self-reported sleep duration, with poor glycaemic control (higher HbA1c) (Tsai et al., 2012b). While in African Americans with T2DM, perceived sleep debt but not sleep duration was positively associated with poor glycaemic control (Knutson et al., 2006).
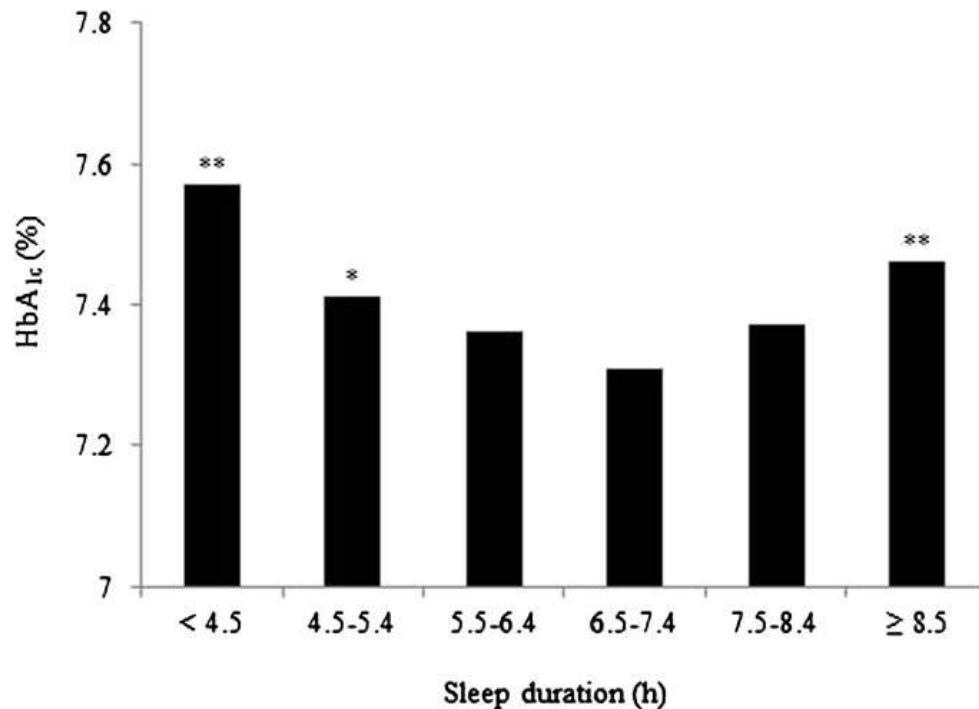
Figure 1-2. Higher HbA1c observed in shorter and longer sleep duration in Japanese T2DM compared to 6.5–7.4 hour sleep duration (*P < 0.05; **P < 0.01) (Ohkuma et al., 2013) ; reused under the Creative Commons Attribution License.

Using wrist actigraphy to objectively measure sleep parameters in 47 T2DM participants, poor sleep quality as estimated by higher moving time during sleep, higher fragmentation index and lower sleep efficiency, (but not sleep duration) was found to correlate slightly with higher HbA1c (Trento et al., 2008). On the other hand, (Borel et al., 2013) observed a higher HbA1c in T1DM participants with actigraphy-measured sleep duration < 6.5 hours compared to those with actigraphy-measured sleep duration > 6.5 hours, (mean HbA1c 8.5% and 7.7% respectively; p-value = 0.001). After adjusting for confounders, they reported a 0.64% increase in mean HbA1c level with shorter sleep duration compared to longer sleep duration, however they did not accompany their estimate with a 95% CI or a p-value. Lastly Barone et al. (2015) assessed sleep parameters in a group of 18 young adults with T1DM using 10 days sleep diaries and one night polysomnography. They assessed glycaemic control by measuring HbA1c after the polysomnography night and by using the overall mean and SD of multiple daily capillary glucose concentrations from a glucometer. Capillary glucose concentrations were recorded for 10 days simultaneous with the sleep diaries. The study showed no correlation between self-reported sleep duration and subjective sleep quality with either mean capillary glucose or SD capillary glucose. However, awakening index and arousal index from the polysomnography were positively correlated with HbA1c. Furthermore, the study reported a positive correlation between self-reported sleep onset latency and

SD glucose. Only correlation coefficients were reported in this study with no adjustment for potential confounders.

In summary, these cross sectional studies propose a potential U-shaped association between both short and long sleep durations and a poor glycaemic control. However, a reverse causality cannot be excluded in these studies. Among individuals with diabetes and hyperglycaemia osmotic symptoms such as nocturia (excessive urination at night), polydipsia (excessive thirst) and restlessness are common (Warren et al., 2003) and may potentially exert detrimental influence on the individuals' sleep duration and quality (Barone and Menna-Barreto, 2011). In addition most studies to date are limited as they have only explored the relationship using subjective self-reported sleep duration. The three small studies that have assessed sleep duration objectively, seem to show weaker relationships to glucose control. An additional limitation is that HbA1c is often chosen as the measure of glucose control, yet it reflects the preceding 3 months of glucose control, and is temporally distant to the assessment of sleep duration, which may weaken any association. Randomised clinical trials with exposure to sleep duration modification (restriction or extending) and/or robust methods of assessing the temporal relation between nighttime sleep and the following daytime glucose control are needed to yield more definitive answers.

Table 1-1 Prospective studies on sleep and the risk of developing T2DM.

Author (year)	Country	Participants	Study design	Exposure	Outcome	Results	Comments
Gangwisch et al. (2007)	USA	8992 adult aged 32-68 years	Prospective cohort	Subjective nighttime sleep duration	T2DM incidence over 8-10 year follow-up period	U-shaped associations	from the NHANES cohort
(Yaggi et al., 2006)	USA	1564 men aged 40-70 years	Prospective cohort study	Subjective nighttime sleep duration	T2DM incidence over 15 year follow-up period	U-shaped associations	from the Massachusetts Male Aging Study
(Kowall et al., 2016)	Germany	4814 adults aged 45-75 years	Prospective cohort study	Subjective nighttime sleep duration	T2DM incidence over 5 year follow-up period	U-shaped associations	from the Heinz Nixdorf Recall study
(Holliday et al., 2013)	Australia	192728 adults aged ≥ 45 selected from medical insurance database	Prospective cohort study	Subjective sleep duration	T2DM incidence over a mean follow up period of 2.3 years	Positive association, only short sleep duration	Diabetes incidents extracted from hospital admission or mortality electronic records, short follow up period
(Rafalson et al., 2010)	USA	363 participants; 91 cases, 272 controls, aged 35-79 years	nested case-control	Subjective sleep duration (weekdays only)	Impaired fasting glucose	Positive association, only short sleep duration	
(Tuomilehto et al., 2009)	Finland	522 participants aged 40–64 years without diabetes	Two Prospective cohorts based	Subjective sleep duration	T2DM incidence over 7 year follow up period	Positive association,	Only in the control arm cohort

		randomly allocated either to a study arm or to a control arm.	on arms of a randomised controlled trial			only long sleep duration	
(Gutierrez-Repiso et al., 2014)	Spain	1145 randomly selected participants aged 16-65 years from the Pizzara study	Prospective cohort	Subjective nighttime sleep duration	T2DM incidence at 6 and 11 years follow up	Positive association only at 6 year follow up	Change in sleep duration over the 11 year follow up
(Kita et al., 2012)	Japan	3570 adults aged 35-55 years	Prospective cohort	Subjective sleep duration and sleep quality	T2DM incidence after 2 year follow up)	Positive spurious association	Statistical issues
(Ferrie et al., 2015)	UK	5613 adults aged 35-55 years from the Whitehall II study	Prospective cohort, four 5-year cycles	Change in nighttime sleep duration in the following cycle	T2DM incidence at the end of subsequent cycle	Positive association, increase ≥ 2 hours	Association could be mediated by weight gain
(Cespedes et al., 2016)	USA	59031 middle aged to old women without diabetes	Prospective cohort study	Change in sleep duration over 14 years	T2DM incidence over 12 year follow up period	Positive association, increase ≥ 2 hours	Association only with increase in sleep duration ≥ 2 h/day, Change in sleep duration from a historic baseline to time of enrolment

NHANES National health and nutrition examination survey

Table 1-2 Cross-sectional studies on sleep and the risk of developing T2DM.

Author, year	Country	Participant	Study design	Exposure	Outcome	Result	Comment
(Jackson et al., 2013)	USA	130943 adults aged 18-85 years from the NHIS (years 2004 to 2011)	Cross sectional	Subjective sleep duration in a 24 hours period	self-reported T2DM status	U-shaped associations	Stronger association in white population
(Buxton and Marcelli, 2010)	USA	56507 adults from the NHIS (years 2004 to 2005)	Cross sectional	Subjective sleep duration in a 24 hours period	self-reported chronic diseases including T2DM	U-shaped associations	multilevel logistic regression
(Wu et al., 2015)	China	25184 adults mean age 63 years from the Dongfeng-Tongji Cohort study	Cross sectional	Subjective sleep duration	Risk of metabolic syndrome including T2DM	No association with nighttime sleep duration	Positive association with daytime napping duration
(Bakker et al., 2015)	USA	2151 participant aged 45-84 years from the Multi-Ethnic Study of Atherosclerosis	Cross sectional	Objective sleep duration	Diabetes	No association	Model adjusted for OSA

NHIS National health interview survey

Table 1-3 Studies on sleep and development of insulin resistance

Author (year)	Country	Participants	Study design	Exposure	Outcome	Results	Comments
Liu et al. (2013)	USA	56 non-diabetic overweight-obese participants	Cross sectional	Subjective sleep duration	Insulin sensitivity	Positive association	Only P-values reported.
Broussard et al. (2012)	USA	7 young healthy participants	Crossover clinical study	Sleep restriction	Insulin sensitivity	Positive association	Small sample size
Nedeltcheva et al. (2009a)	USA	11 young-middle aged healthy participants	Crossover clinical study	Sleep restriction	Insulin sensitivity and glucose tolerance	positive association	Small sample size
Wang et al. (2016b)	USA	15 young healthy non-obese participants	Crossover clinical study	time-in-bed restriction by 1 to 3 hours for 3 nights	Insulin sensitivity and glucose tolerance	Positive association with insulin sensitivity	No association with glucose tolerance
Donga et al. (2010)	The Netherlands	9 healthy participants, mean age 44.6 years	Crossover clinical study	Sleep restriction	Insulin sensitivity	Positive association	Small sample size

St-Onge et al. (2012)	USA	27 healthy young non-obese adults	Crossover clinical study	Time in bed restricted to 4 hours	insulin sensitivity	No association	Participants had controlled diet and lost weight during the study
Robertson et al. (2013)	UK	19 healthy young lean men	Randomised controlled trial	Around 1.5 hours sleep restriction per night for 3 weeks	insulin sensitivity	Positive association only at the end of first week	absence of an overall effect of sleep restriction on insulin sensitivity
Broussard et al. (2016)	USA	19 healthy young lean men	Crossover clinical study	two days of catch-up sleep	Recovery of insulin sensitivity	Positive association	
Leproult et al. (2015)	Belgium	16 healthy young non-obese adults with chronic sleep restriction	Crossover clinical study	Around one hour sleep extension per night for 6 weeks	Fasting glucose and insulin levels	No difference in pre- and post-intervention levels	Moderate correlation between relative change in sleep duration and relative change in fasting glucose and insulin levels

Table 1-4 Studies on sleep and glycaemic control in patients with diabetes

Author (year)	Country	Participants	Study design	Exposure	Outcome	Results	Comments
Ohkuma et al. (2013)	Japan	4870 adults, aged ≥20 years with T2DM	Cross-sectional	Subjective sleep duration including naps	Glycaemic control (HbA1c)	U-shaped associations	
Kim et al. (2013a)	Korea	2134 adults, aged > 20 years with T1DM or T2DM	Cross-sectional	Subjective daily sleep duration	Glycaemic control (HbA1c)	positive associations	J-shaped trend with HbA1c; stronger in females and in the younger age group (<65 years). Association disappear after adjusting for more covariate in the logistic regression model.
Zheng et al. (2015)	China	8543 adults, aged ≥40 years with T2DM or impaired glucose tolerance	Cross-sectional	Subjective nighttime sleep duration	Glycaemic control (HbA1c, FPG, PPG)	Positive association with long sleep duration	Only adjusted means and p-values reported but no estimate of association
(Tsai et al., 2012b)	Taiwan	46 adults, aged 43-83 years with T2DM	Cross-sectional	Subjective sleep duration and quality (PSQI)	Glycaemic control (HbA1c)	Positive association	Participants with diabetic complication or major co-morbidities were excluded. association only with sleep efficiency and PSQI score of 8 or more but not sleep duration

(Knutson et al., 2006)	USA	161 African Americans, mean age 57 years with T2DM	Cross sectional	Subjective sleep duration and sleep quality, modified PSQI, and perceived sleep debt	Glycaemic control (HbA1c)	Positive association	Sleep debt association only in participants without diabetic complication or not using insulin. sleep quality only in participants with diabetic complication or using insulin association
(Trento et al., 2008)	Italy	47 middle aged adults with T2DM and 23 healthy controls	Cross sectional study	Objective sleep parameters; duration and quality using wrist actigraphy	glycaemic control (HbA1c) in T2DM group	Not reported	Weak negative correlation with sleep efficiency and mild positive correlation with moving time while asleep. No estimate measures of association reported
(Borel et al., 2013)	France	79 adults, median age 40 years with T1DM	Cross sectional study	Objective sleep parameters using wrist actigraphy	glycaemic control (HbA1c)	Positive association	
(Barone et al., 2015)	Brazil	18 young adult, aged 20-38 years with T1DM	Cross sectional	Objective sleep measures using wrist actigraphy	Glycaemic control (average glucose from glucometer reading)	No association	Methodological issues

1.4 Sleep during pregnancy and glucose homeostasis

During pregnancy, changes in sleep patterns and sleep duration are commonly reported and are mainly due to the physiological, biochemical and anatomical changes that accompany pregnancy (Balserak and Lee, 2011). These changes are likely to be influenced ,as well , by the concentrations and the circadian rhythms of pregnancy hormones such as oestrogen, progesterone, placental corticotrophin and oxytocin (Pien and Schwab, 2004; Seron-Ferre et al., 1993).

Indeed, sleep is disturbed as early as the first trimester of pregnancy (Facco et al., 2010b; Hedman et al., 2002; Lee et al., 2000), with noticeable sleepiness and a correspondent increase in total sleeping time, although the quality of sleep is deteriorated (higher number of awakenings and less deep sleep), compared to pre-pregnancy sleep quality. As the pregnancy progress, the total amount of sleep begins to decrease, sleep quality declines and the frequency of sleep disturbances increase, reaching a maximum in the third trimester (Hedman et al., 2002; Facco et al., 2010b). Using polysomnography to objectively assess sleep, pregnant women in the third trimester of pregnancy compared to non-pregnant women, had longer wake after sleep onset (WASO) duration, i.e. spent longer awake in the middle of their nighttime sleeping interval, more fragmented sleep, poorer sleep efficiency, more time in light sleep stage, less time in deep sleep stage, and less time in REM sleep stage (Wilson et al., 2011). When assessed subjectively, sleep quality was likewise poorer in pregnant women than non-pregnant women (Ko et al., 2010). The changes in sleep are usually attributed to foetal movements, pregnancy related backache, frequent urination, leg cramps and anxiety (Balserak and Lee, 2011). Despite documentation of changes to the quality and the architecture of sleep during pregnancy, mean sleep duration (both subjective and objectively assessed) in the third trimester of pregnancy was similar to the sleep duration before pregnancy (Lee et al., 2000; Hedman et al., 2002). Hedman et al. (2002) reported mean (SD) of self-reported sleep duration at night of 7.8 (0.9) hours before the pregnancy, 8.2 (0.9) hours in the first trimester, 8.0 (1.0) hours in the second trimester and 7.8 (1.2) hours in the third trimester. Lee et al. (2000) reported mean (SD) of 2-nights polysomnography measured sleep duration of 6.9 (1.0) hours before pregnancy, 7.4 (1.1) hours in first trimester and 6.9 (1.1) hours in the third trimester. Nevertheless, a similar mean does not imply a similar distribution, as pregnant women tend to have higher proportions of both short and long sleep duration compared to non-pregnant women (Alafif et al., 2016).

The detrimental effect of sleep disturbances has now been well demonstrated in the general population, but pregnant women are different, and may not necessarily have the

same responses. There has recently been a surge in literature proposing that sleep disturbances during pregnancy are associated with poor pregnancy outcomes for both mother and infant (Chang et al., 2010), with a higher likelihood of gestational hypertensive disorders, gestational diabetes (GDM), unplanned Caesarean deliveries, intra-uterine growth restriction and still birth (Palagini et al., 2014; O'Brien, 2012; Bourjeily et al., 2010). Sleep disturbances, particularly short sleep duration and sleep disordered breathing, have also been shown to be significantly associated with glucose intolerance in pregnancy (Facco et al., 2010a; Reutrakul et al., 2011) with greater risks among overweight pregnant women (Qiu et al., 2010).

In a cohort of multi-ethnic pregnant women (at 26-28 weeks of gestation) from Singapore (n=686): 43% reported poor sleep quality (PSQI>5) and 11.2% reported short sleep duration (< 6 hours) (Cai et al., 2017). In the same study pregnant women with poor sleep quality and short sleep duration were at higher risk of being diagnosed with GDM (adjusted OR; 95% CI were 1.75; 1.11 to 2.76, and 1.96; 1.05 to 3.66, respectively). In another study from the USA a cohort of pregnant women (n=901) were studied early pregnancy (<14 weeks of gestation) and their sleep was objectively assessed using wrist actigraphy. Only 87% of the participants submitted what the study considered as 'valid' actigraphy records. 27.9% of women had a sleep duration of <7 hours and 2.6% had a sleep duration of >9 hours. Median WASO duration was 42.2 minutes and median mid-sleep point was 03:38 am (Reid et al., 2017). In this cohort short sleep duration (<7 hours) compared to longer sleep duration (≥ 7 hours) and late chronotype (sleep midpoint >05:00 am) compared to earlier chronotype (sleep midpoint ≤ 05:00 am were associated with an increased odds of developing GDM, (OR 2.24; 95% CI 1.11 to 4.53) and (OR 2.58; 95% CI 1.24 to 5.36), respectively. WASO duration was not associated with the odds of developing GDM in this study (Facco et al., 2017).

The association between sleep disturbances and glycaemic control among pregnant women with established pre-pregnancy T1DM or T1DM was not explored. There is only one published study on the association between sleep disturbances and glycaemic control in pregnant women with GDM (Twedt et al., 2015). In this study only 45 pregnant women were enrolled to participate immediately after being diagnosed with GDM. The study excluded women on glucose lowering medications, namely insulin and glyburide. The gestational age of enrolment was very wide ranging between 6 weeks to 33 weeks of gestation, median 28 weeks. Sleep in this study was assessed using actigraphy (Actiwatch Spectrum Respironics device with medium threshold settings). Whereas glycaemic control was assessed using fasting and 1-hour post prandial capillary blood concentrations. Only 37 participants out of the 45 enrolled returned at least one day of sufficient data (i.e. having both sleep and glucose data). They gave rise to 213 nights of actigraphy sleep data with at least one glucose reading the following day. Thus 209

fasting glucose readings, 196 breakfast, 188 lunch, and 204 dinner postprandial readings were available for analysis. The study reported a sleep duration ranging from 1.1 to 12.3 hours with a median of 6.8 hours.

Multiple linear mixed effect regression models, adjusted for maternal age, gestational age at enrolment and pre-pregnancy BMI, were applied in the study to assess the proposed associations. The study found that each one hour increase in sleep duration was associated with lower fasting and 1-hour postprandial capillary blood glucose concentrations, as follows; 2.09 mg/dl (0.12 mmol/l) lower fasting blood glucose concentration (95% CI -3.98 to -0.20 mg/dl), 3.05 mg/dl (0.17 mmol/l) lower post-breakfast blood glucose concentration though not statistically significant (95% CI -6.52 to 0.42 mg/dl), 4.62 mg/dl (0.26 mmol/l) lower post-lunch blood glucose concentration (95% CI -8.75 to -0.50 mg/dl), and 6.07 mg/dl (0.34 mmol/dl) lower post-dinner blood glucose concentration (95% CI -9.40 to -2.73). After categorising sleep duration into groups to assess for a possible U-shaped relation between sleep duration and glucose levels, only short sleep duration (<5 hours) but not long sleep duration (≥9hours) was associated with higher glucose concentration, compared to ≥7 to <9 hours sleep duration. However, the results reported did not show a linear trend of the association especially for post-breakfast and post-dinner associations. After plotting their results for post-breakfast regression model (Figure 1-3), it was very clear that a J-shape/U-shaped association might be present. However, the study had a small sample size of nights with sleep duration of 9 hours or more (only 10 nights out of the total 213 night), which might explain the wide confidence interval and the non-statistically significant results.

Despite the accumulative number of evidence suggesting a substantial relationship between sleep disturbances and; higher risk of developing T2DM and lower glycaemic control in non-pregnant population, and the increase risk of GDM in pregnant women, there is a paucity of research among pregnant women with GDM. Sleep remains largely unrecognised as a potentially modifiable risk factor for diabetes in pregnancy. There is a clear gap in the literature in the association between sleep and glycaemic control in GDM which the current study is trying to bridge.
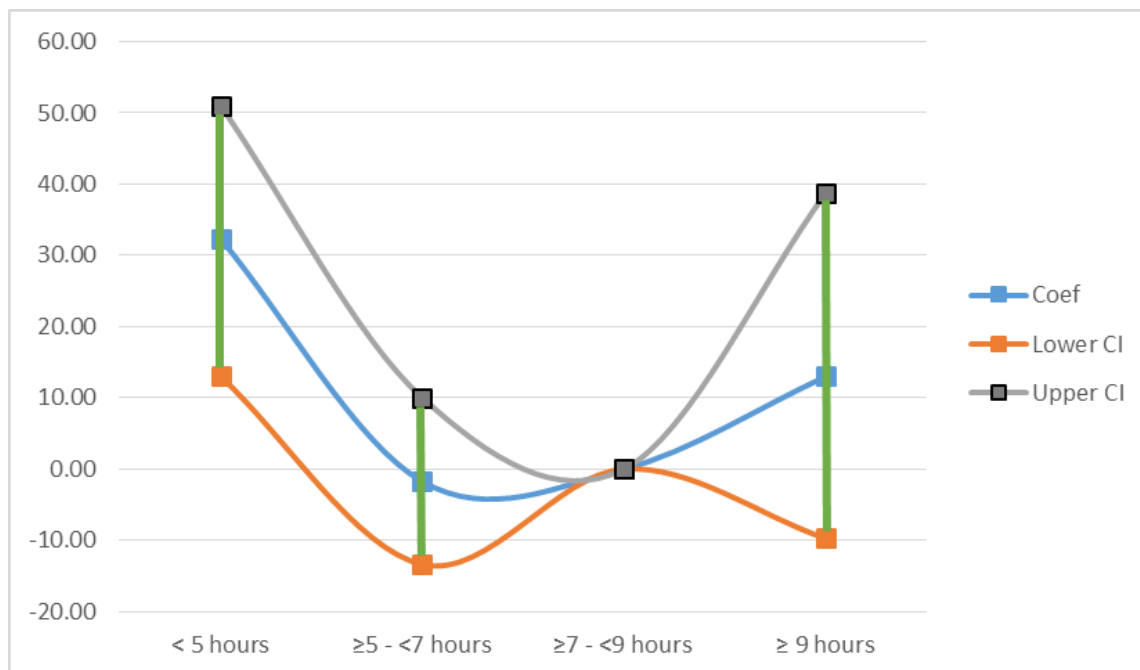
Figure 1-3 Plot of the regression model results (the β coefficient and the Upper and the lower 95% CI limits) of association between sleep duration categories and post-breakfast glucose concentration as reported by Twedt et al. (2015)

1.5 Gestational diabetes (GDM)

1.5.1 Pathophysiology and definition

With the progression of pregnancy and the normal growth of the placenta, a surge in placental and other pregnancy related hormones contributes to insulin resistance of the mother (Kampmann et al., 2015). This leads to less insulin mediated glucose uptake to the mother's muscle/liver/adipose tissues, and allows a higher level of glucose l to circulate in the blood. This allows more glucose to cross the placenta for the 'benefit' of the growing foetus. However to avoid hyperglycaemia, pregnant women usually compensate for the insulin resistance by producing more insulin. A failure in the production of adequate compensatory insulin by the pregnant women will lead to the development of GDM.

GDM was defined previously as any degree of glucose intolerance (hyperglycaemia) with its onset or first recognition during pregnancy (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). This definition includes pregnancy related

hyperglycaemia, as well as, hyperglycaemia caused by pre-gestational diabetes that was first detected during pregnancy. However, a more recent definition by the American Diabetes Association (ADA) excludes patients with overt diabetes from the GDM definition (ADA, 2011; ADA, 2013; ADA, 2014). Likewise, the World Health Organization has classified hyperglycaemia first detected in pregnancy to either GDM or diabetes in pregnancy based on a diagnostic threshold (more details in GDM diagnosis section 1.5.5) (WHO, 2013).

1.5.2 Risk factors

Pregnant women who develop GDM often have a genetic predisposition. Those women with a family history of T2DM are at greater risk, suggesting shared genetic and environmental influences. Pregnant women from Asian, Hispanic, African, Middle-Eastern and Native American ethnic backgrounds have a higher risk of GDM compared to pregnant women from White European ethnic backgrounds. Other established risk factors include: high pre-pregnancy BMI (obese pregnant women have three times the risk of developing GDM compared to lean pregnant women) (Torloni et al., 2009; Chu et al., 2007), and increasing maternal age (7-10 times increase risk in pregnant women aged 25 years or older compared to less than 25 years). For multigravida (women with a previous pregnancy), added risk factors include: GDM in the previous pregnancy, previous macrosomia (giving birth to a big baby weighing more than 4500 g) and previous unexplained stillbirth (Egan et al., 2017).

1.5.3 Prevalence

GDM is highly common worldwide and it is estimated by the International Diabetes Federation (2015) that 1 in 7 births are affected by GDM. However, the prevalence varies across the world affecting from <1% to 28% of all pregnancies (Jiwani et al., 2012) and reaching 39% of pregnancies in obese pregnant women (Egan et al., 2017). This variation in the prevalence is due to variation in the nationally implemented methods and criteria to screen for GDM in different countries and whether the screening is universal for all pregnant women or selective based on high risk criteria. Even in the same country prevalence rates will vary from one region to another depending on the distribution of these risk factors among its population (Kampmann et al., 2015).

1.5.4 Complications

GDM has short and long term sequelae for the pregnant women and their offspring (Egan et al., 2017). Short-term sequelae include a higher risk of macrosomia, and large-for-gestational-age (LGA) infants, polyhydramnios (pathological excessive amniotic fluid surrounding the foetus), caesarean section, neonatal hypoglycaemia, neonatal

hypocalcaemia, neonatal distress syndrome, neonatal intensive care unit admission, and maternal gestational hypertension, (O'Sullivan et al., 2012; Hod et al., 1991; Anand et al., 2017). GDM, even with slight degree of hyperglycaemia, is associated with a 30% higher risk of giving birth to a LGA neonate (O'Sullivan et al., 2012) and around 19.7%- 22.6% of neonates born to mothers with GDM are LGA (Luoto et al., 2011). Glucose circulating in the mother's blood, but not the mother's insulin, can pass the placental barrier freely to the foetal circulation. Thus, a high maternal glucose level results in a high glucose concentration in the foetal circulation. In attempt to control this high influx of glucose, the foetus produces extra insulin. However, insulin is a growth factor and it causes excessive foetal growth, with the extra glucose being stored predominantly as abdominal fat, leading to macrosomia and a LGA neonate. Large foetuses are at higher risk of being delivered by caesarean section and of suffering shoulder dystocia and other birth trauma with vaginal delivery (Hod et al., 1991; Reece et al., 2009; Mitanchez, 2010)

Long-term sequelae for the offspring include: a higher risk of developing obesity, glucose intolerance, T2DM and metabolic syndrome later in life (Yogev and Visser, 2009; Dabelea et al., 2000; Zhu et al., 2016). Whilst maternal dysglycaemia usually returns to a normal level after delivery, the mother is at higher risk of developing GDM in a subsequent pregnancy (England et al., 2015) and at higher risk of developing glucose intolerance and T2DM in the following years, 6.9% at five years and 21.1% at ten years following GDM (Sivaraman et al., 2013).

1.5.5 Diagnosis

Diagnosis of GDM is currently based on the results of an oral glucose tolerance test (OGTT) mostly performed at 24-28 weeks of gestation. However the diagnostic cut-points keep changing and updating based on the emergence of new evidence. Diagnostic criteria varies widely between different health authorities and diabetes associations. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) updated their diagnostic criteria based on the hyperglycaemia and adverse pregnancy outcomes (HAPO) study (Hapo Study Cooperative Research Group, 2008; Metzger et al., 2010). Later on the World Health Organisation (WHO) updated their criteria and followed a similar diagnostic criteria as the IADPSG (WHO, 2013). These criteria recommend testing for hyperglycaemic disorders initially at the first antenatal visit and later on, at 24-28 weeks' gestation if the earlier assessment was normal. High glucose levels are classified as overt diabetes or diabetes in pregnancy (DIP), while lesser values are classified as GDM. GDM can be diagnosed at any time in pregnancy, based on a 75g-load OGTT, if one or more of the following is met: fasting glucose 5.1-6.9 mmol/l (92 -125 mg/dl), 1-hour glucose ≥ 10.0 mmol/l (180 mg/dl) or 2-hour glucose 8.5-11.0 mmol/l (153 -199 mg/dl). On the other hand overt diabetes during pregnancy is

diagnosed at the initial visit if the glycated haemoglobin (HbA1c) level ≥ 6.5% or if at any visit the fasting glucose ≥ 7.0 mmol/l (126 mg/ dl), 2-hour following a 75g-load OGTT glucose ≥ 11.1 mmol/l (200 mg/dl) or random glucose ≥ 11.1 mmol/l (200 mg/ dl) (in the presence of diabetes symptoms and followed by confirmatory fasting glucose or HbA1c).

In the United Kingdom the National Institute for Health and Care Excellence (NICE) guidelines are generally followed, and they published an update to their GDM diagnostic criteria in 2015. They recommend a 75g-load OGTT to test for GDM in women with risk factors at 24–28 weeks of gestation. However an earlier test, arranged immediately after their first antenatal visit, is recommended for women with history of GDM in their previous pregnancy with a repeat test at 24-28 weeks if the earlier was normal (NICE, 2015). Diagnosis of GDM will be confirmed if the fasting glucose level ≥ 5.6 mmol/l or the 2‑hour post glucose load ≥ 7.8 mmol/l. Risk factors determined by NICE to qualify for testing are: BMI > 30kg/m^2, previous macrosomic baby, previous GDM, family history of diabetes in a first-degree relative and an ethnic family background with a high prevalence of diabetes.

On the other hand, the American Diabetes Association (ADA) recommend either a one-step strategy similar to the IADPSG or a two-step strategy screening first by a 50-gram oral glucose challenge test and followed by a 3-hour 100 g glucose load OGTT if the latter was normal (ADA, 2017a).

1.5.6 Management

To avoid complications for both the mother and the offspring an intensive management strategy is followed, even for asymptomatic mothers and those with a mild degree of hyperglycaemia (Metzger et al., 2007). In order to control pregnant women's glucose level, they are advised on lifestyle modification regarding diet modification via individualised advice sessions from dietitians, as well as, performing regular physical exercise. Moreover, they are instructed to daily self-monitor their blood glucose (SMBG) using glucometer devices to test their blood glucose at least four times a day, fasting and one hour after each meal, and to keep their glucose levels within strict defined targets (ADA, 2017b). The latest published glucose level targets during pregnancy are as follows: fasting glucose ≤ 5.3 mmol/l (95 mg/dl) and either one-hour postprandial glucose ≤7.8 mmol/l (140 mg/dl) or two-hour postprandial glucose ≤ 6.7 mmol/l (120 mg/dl) (ADA, 2017b; NICE, 2015). In the case that lifestyle modification was not successful in keeping the blood glucose to target after 1-2 weeks of diagnosis, or if the pregnant woman has a very high fasting glucose level (≥ 7 mmol/l) from the first assessment visit then blood-glucose lowering medication such as metformin and insulin are introduced to the management plan.

1.5.7 Measuring glycaemic control

Whilst glycated haemoglobin (HbA1c), is widely acceptable as a measure of glycaemic control in the non-pregnant population, it is considered less reliable than SMBG as a measure of glycaemic control during pregnancy (Yu et al., 2014b). This has been attributed to the higher turnover and shorter life span of red blood cells during pregnancy and thus less time for the red blood cell haemoglobin molecules to get glycated (Rafat and Ahmad, 2012). This results in lower values of HbA1c during pregnancy which continue to reduce as pregnancy advances (O'Kane et al., 2001). Whilst it has been demonstrated that there is a relationship between average glucose and HbA1c during pregnancy in women with diabetes, the relationship is different to that seen in a non-pregnant population (Law GR et al 2017). Moreover, HbA1c represents the overall mean blood glucose concentration for a preceding period of 8-10 weeks but does not give any information about the variation of glucose concentrations over that period. In a study by Kerssen et al. (2003) pregnant women with T1DM and HbA1c ≤ 7% had around half of their daily blood glucose measured values above the recommended threshold (7.8 mmol/l) .

Daily fasting and 1-hour postprandial SMBG, as stated in the previous section is therefore the recommended tool to clinically evaluate glycaemic control in GDM. Nonetheless, the frequency and timing of SMBG also have some limitations. The postprandial timing assumes that the time from starting food intake until the peak of postprandial glucose concentration is one hour. However, this may not be the case during pregnancy due to pregnancy related delayed gastric emptying. A study aiming to closely assess glucose levels in non-diabetic pregnancy using continuous glucose monitoring found that the time to peak glucose concentration is highly variable with a mean (SD) of 71 (±30) minutes in normal weight women and 88 (±31) minutes in obese women (Yogev et al., 2004). Time to peak glucose concentration in another study involving pregnant women with diabetes (26 GDM on diet, 19 GDM on insulin, and 20 T1DM on insulin) ranged from 75 (±30) minutes to 102 (±47) minutes (Ben-Haroush et al., 2004). Thus it seems likely that the actual postprandial peaks in glucose are being missed by current SMBG, limiting our understanding of the true variation in glucose occurring. Whilst this could be overcome by more frequent SMBG testing, this would necessitate more finger pricks, which are painful, inconvenient and widely disliked. SMBG testing also only takes place during the day when the women are awake and able to perform it. Whilst asleep they are not able to and so overnight glucose levels are not routinely assessed. In a study published by Law et al. (2015) overnight relative hyperglycaemia detected by continuous glucose monitoring (CGM) was associated with a higher risk of having a LGA infant, which supports the fact that SMBG testing is limited

in its usefulness at detecting glucose variations associated with adverse clinical outcomes in pregnancy

To overcome the limitations of SMBG recent advances in technology, now allow closer monitoring of glucose through the use of continuous glucose monitoring systems. Their potential utility in both clinical and research settings is huge (Festin, 2008; Chitayat et al., 2009; Hawkins, 2010; Murphy, 2013).

1.6 Continuous glucose monitoring (CGM) systems

CGM systems measure glucose in the subcutaneous interstitial fluid (ISF) via an electrochemical amperometric sensor (Rebrin and Steil, 2000). They are usually calibrated by SMBG values to predict an estimate of plasma glucose via specific mathematical algorithms (Rebrin et al., 1999; Mastrototaro, 2000). A detailed description of the mechanism of action of CGM is presented in the methods chapter. In brief, most CGM systems record a glucose value every 5 minutes yielding up to 288 of time-ordered successive glucose values per day. This dense time-series data can be presented as a long data list and plotted as glucose curves over time (Figure 1-4). They provide ample information about magnitude, frequency and duration of glucose excursions as well as other diurnal glucose behaviour (Klonoff, 2005; Murphy et al., 2007).However such very dense data as CGM data can also bring challenges for analysis.

Conventionally summary metrics evaluating glycaemic control have been proposed to extract some of the valuable information CGM data potentially provides (Service, 2013; Inchiostro et al., 2013; Rodbard, 2009a; Kovatchev et al., 2006; McDonnell et al., 2005). These summary metrics include: mean , median, standard deviation (SD) and interquartile range (IQR) of glucose concentrations, total area under glucose curve (AUC), AUC above normative range, AUC below normative range, proportion of time spent within, below or above normative range, coefficient of variation of glucose concentrations, mean amplitude of glycaemic excursions (MAGE), mean of daily differences (MODD), J index, M-value, Continuous Overall Net Glycaemic Action (CONGA), the Low Blood Glucose Index (LBGI) and the High Blood Glucose Index (HBGI), the Average Daily Risk Range (ADRR). The information contained within these metrics and the methods for calculating them are described in the following paragraphs (sections 1.6.1 to 1.6.8) with the assistance of six simulated glucose curves; curve A, curve B, curve C, curve D, curve E and curve F (Figure 1-7 to Figure 1-10).
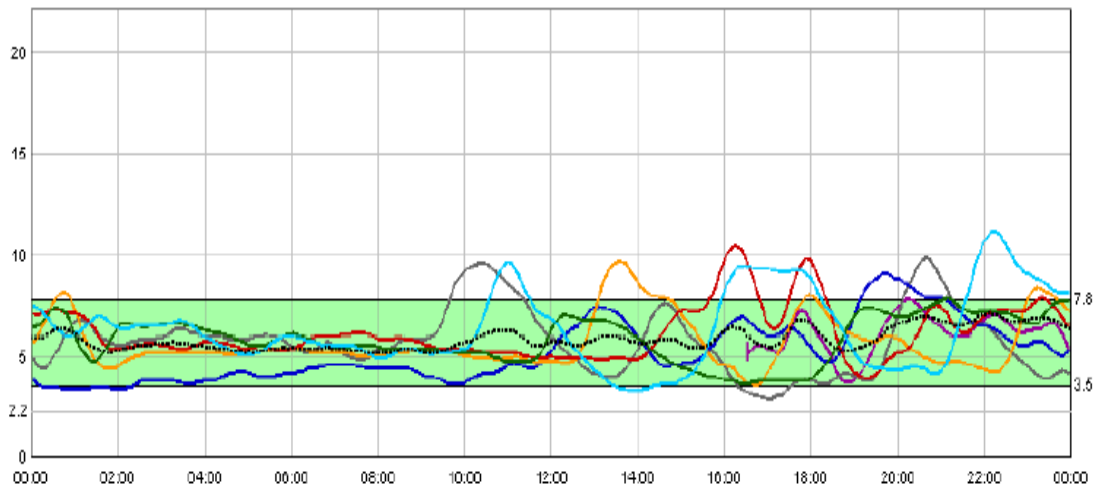
Figure 1-4 CGM system output showing daily glucose curves for one participant

1.6.1 Mean glucose and total AUC

Mean glucose is calculated by dividing the sum of all glucose values across a time period (e.g. 24 hours) by the number of glucose readings obtained during that time period (288 reading in a 24 hour period). Mean is a measure describing the central location in normally distributed data, where half of the data will be above and the other half below the mean (Figure 1-5 Normal distribution curve). However, glucose values have a tendency to be skewed to the right as glucose has a limited lower value of zero and theoretically no upper limit (Figure 1-6). A child from the USA has been recorded to survive a blood glucose level of 147.6 mmol/l (2,656 mg/dl) (GuinnessWorldRecords, 2008). Therefore, a mean glucose will be potentially biased towards higher values. Mean glucose is highly correlated with HbA1c and provides a good estimate of overall glycaemic control (Nathan et al., 2008; Zhou et al., 2013; Law et al., 2017).
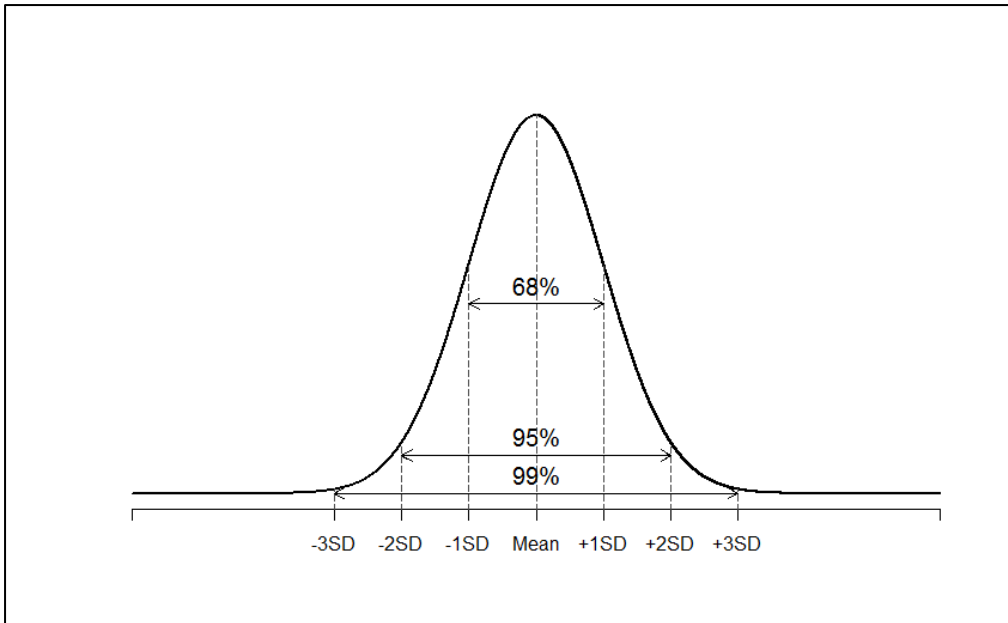
Figure 1-5 Normal distribution curve

It is worth noting that the mean glucose is equivalent to the standardised total AUC. The standardised total AUC equals the sum of the all the trapezoids of 5 minutes width and bounded by a zero lower limit and glucose curve upper limit and then divided by the total duration, e.g. for a 1-hour period there will be twelve 5-minute trapezoids. The height of a trapezoid is equal to the averaged glucose concentration measured over a 5-minute interval and thus the standardised total AUC is calculated by summing the glucose concentrations and dividing them by the number of intervals. This is exactly how a mean glucose is calculated.

However, an overall mean cannot differentiate between glucose curves with different postprandial amplitudes of glucose excursion or diverse variability, neither can it infer the time of day when troublesome glucose concentrations arise. Glucose curve B and glucose curve E for example (Figure 1-7) have the exact same mean glucose (

Table 1-6), though glucose curve E is spending more time within the normative range and has shallower excursions with less proportion of the excursion spreading outside the normative range and thus is more controlled, less variable and more stable than curve B. Therefore, a mean glucose alone cannot fully describe glycaemic control and it needs to be supplemented by other measures of variability.

A median is another measure of central location which is not biased by the skewness of the data. However, a median glucose is less favourable to use than the mean glucose, as it does not estimate the total AUC and there is no study that has examined its correlation to HbA1c.
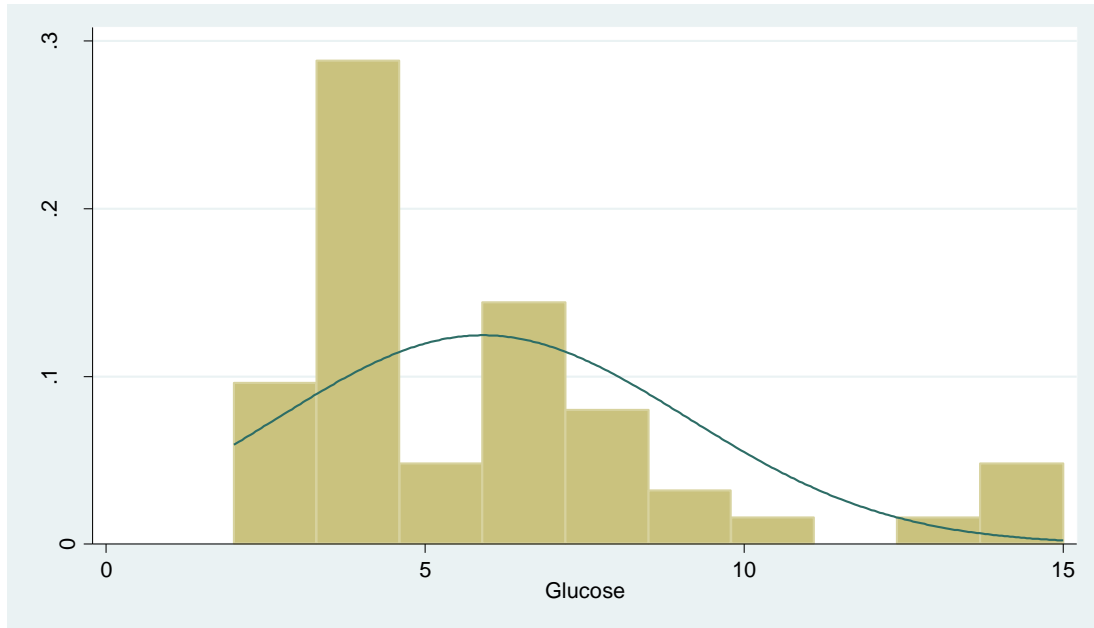
Figure 1-6 Histogram of simulated glucose curve B from Figure 1-10.
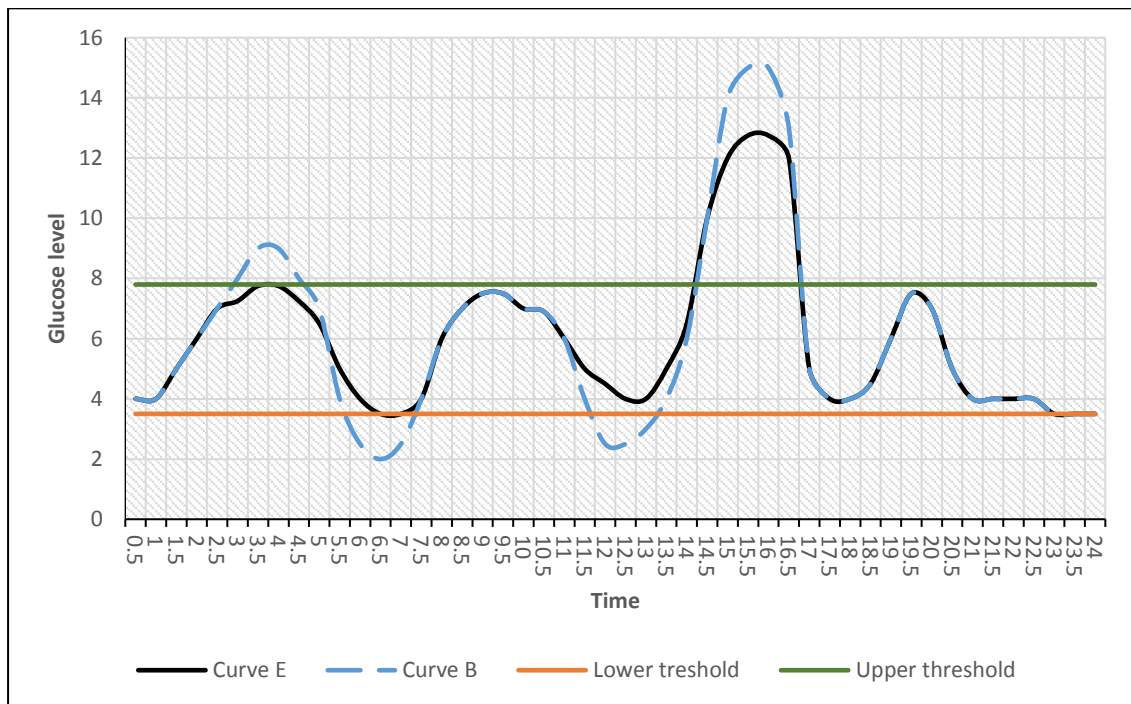
Figure 1-7 Simulated glucose curve B and curve E having the same mean but different variability measures.

1.6.2 Standard deviation (SD) and coefficient of variation (CV)

The SD of glucose, calculates the dispersion of glucose values around its mean. It is a simple method and widely used as a measure of glycaemic variability (DeVries, 2013). The main criticism of using SD is that it is a measure of dispersion in normally distributed data, where the mean ± 2SD will approximately span the middle 95% of the data (Figure 1-5 Normal distribution curve), whereas, as explained previously with the mean glucose (section 1.6.1), glucose data is potentially skewed. However, the SD of glucose was found to be higher in people with diabetes and poor overall glucose control as determined by a higher HbA1c compared to those with diabetes and good overall glucose control, and higher in people with diabetes and good overall glucose control compared to those without diabetes. The SD of mean glucose also correlates highly to other more complicated indices of glucose variability like MAGE, MODD and CONGA (Rodbard, 2012). The SD of glucose can also be standardised and expressed as a percentage of the mean and presented as a coefficient of variation (CV).

However, the SD of glucose does not reflect the proportion of time spent, or indeed the extent of glucose excursion outside a recommended glucose range in an individual (Figure 1-8).
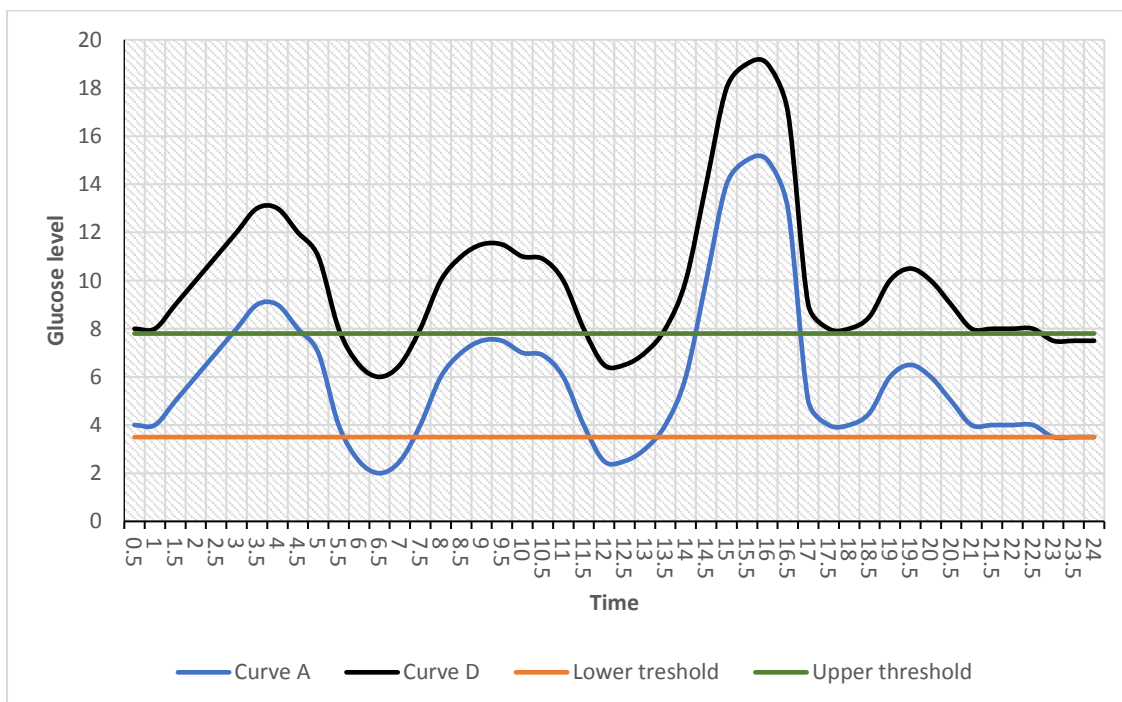
Figure 1-8 Simulated glucose curves A and D have the same SD glucose but have different mean glucose and different proportion of time within the normal range

1.6.3 Time spent within, below or above normative range and AUC above and below normative range

The aim when controlling glucose in people with diabetes is to keep glucose concentration within a tight 'normal' range that is bounded by an upper and lower thresholds while allowing for mild fluctuation around meal times. Binding to and departing across these limits can be quantified by measures like: time spent within, below or above the normative range and AUC-above and AUC-below the normative range.

Time spent within, below or above the normative range can be presented as the actual time duration in hours and minutes in a 24-hour period or as proportion of a rather variable nyctohemeral (day-and-night) duration. Acknowledging that time spent outside the normative range limits differ from the amount of actual glucose concentrations outside the same limits. For example glucose curves F and B (Figure 1-9) have the same amount of time spent outside the normative range limits but clearly different glucose concentrations outside the same limits.

On the other hand, AUC-above and AUC-below the normative range has an emphasis on the amount of glucose concentration outside the normative range without any regards to the time. AUC-above normative range is the area spanning above the upper threshold and bounded by the glucose curve from the top, whereas AUC-below normative range is the area bounded by the lower threshold from the top and glucose curve from the bottom and sides, AUC-above and AUC-below are marked on curve A- Figure 1-10. Both AUC-above and AUC-below normative range are standardised by reporting them as a ratio of the total AUC.
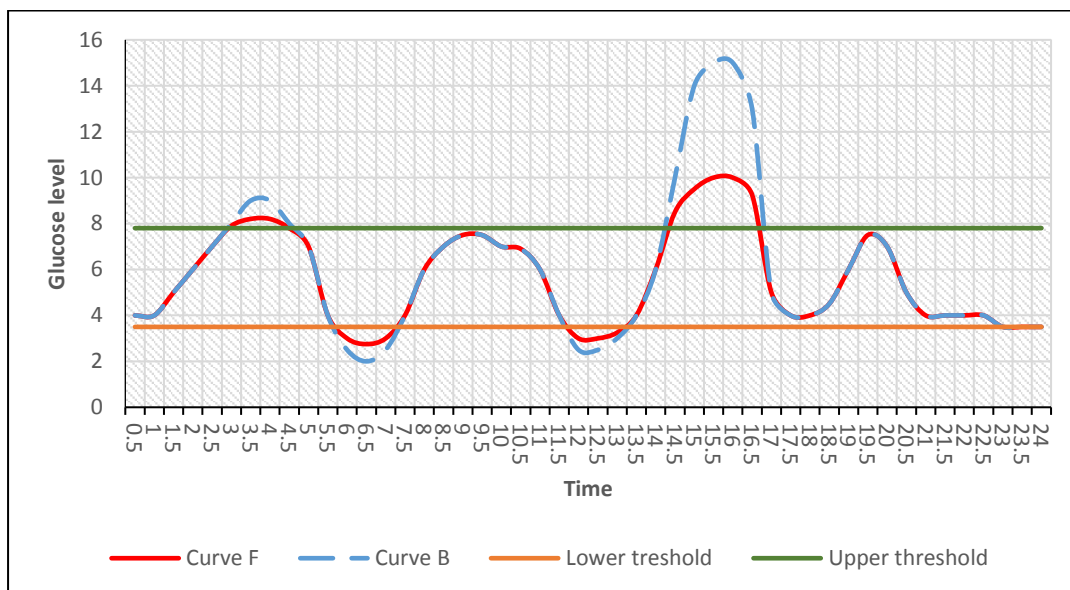
Figure 1-9 Simulated glucose curves F and B have the same duration of time spent above and below the normative range but show different glucose concentrations outside the range
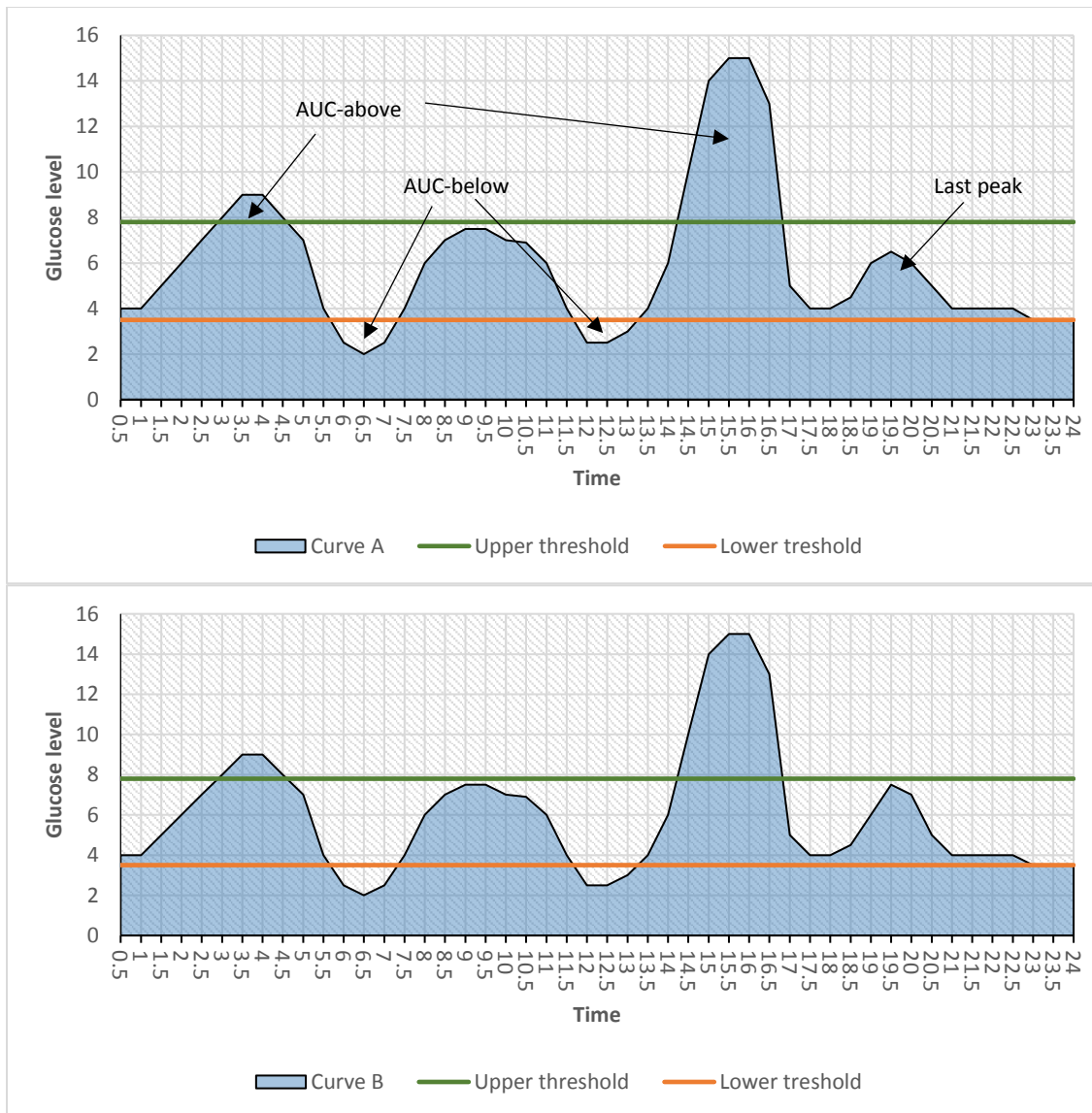
Figure 1-10 Two similar simulated glucose curves; curve A and curve B, except for a higher last peak in curve B

1.6.4 Mean amplitude of glycaemic excursions (MAGE)

The mean amplitude of glycaemic excursions (MAGE) was first described in 1970 as a measure of intra-day glucose variability and stability. With the surge of CGM systems MAGE became widely used in research to describe variability in daily glucose concentrations' (Marling et al., 2011; Inchiostro et al., 2013). The amplitude of glycaemic excursions (glucose peaks) was originally estimated manually by measuring the difference between consecutive nadirs and peaks (or peaks and nadirs) of glucose curves obtained from per hour analysis of venous blood glucose. The mean of all differences that exceeded 1 standard deviation were then calculated (Service et al., 1970). The original manual calculation method is burdensome and as a result many

automated calculation algorithms and software applications have been created to measure MAGE from CGM data (Baghurst, 2011; Czerwoniuk et al., 2011; Marics et al., 2015). However, automated MAGE calculations show poor agreement (Sechterberger et al., 2014). Moreover, the higher than 1SD criteria of including an excursion is arbitrary and may result in a MAGE with a misleading inference. An explanation is offered in the following example: glucose curves A and B are quite similar except for a higher last peak in curve B (Figure 1-10). Calculated manually, MAGE of curve A is (5+5.5+12.5)/3= 7.667 mmol/l as only the first 3 amplitudes of glucose excursions were included and the last one excluded because it is less than 1SD, whereas MAGE of curve B is (5+5.5+12.5+3.5)/4= 6.625 mmol/l as all glucose excursion were higher than 1SD and all of them were included to calculate the mean. A lower MAGE of curve B is misrepresenting the amount of glucose level variability and instability curve B has in compare to curve A.

Table 1-6 displays more summary metrics of curve A and curve B. Therefore, MAGE does not seem to be a good measure of intra-day glucose variability and stability for data derived from CGM systems.

1.6.5 J-index

The J-index combines information from the mean and the SD glucose. It is calculated by squaring the sum of the mean and the SD and then multiplying the result by different factors for glucose measured in mmol/l and mg/dl, Equation 1.1 and Equation 1.2 respectively. In normally distributed data adding 1SD to the mean will encompass around 34% of the data directly above the mean (Figure 1-5). However, what the value of J-index encompasses is not clear, it does not have an established 'normal' range and it has a unit of $mmol^2/l^2$ (mg^2/dl^2) which is not very informative.

$$J-index = 0.324(Mean + SD)^2 \quad \text{glucose measured in mmol/l} \qquad \textbf{Equation 1.1}$$

$$J-index = 0.001(Mean + SD)^2 \quad \text{glucose measured in mg/dl} \qquad \textbf{Equation 1.2}$$

1.6.6 Mean of daily differences (MODD)

MODD is another summary metric from before the era of CGM (Molnar et al., 1972). It was developed by the same group that developed MAGE to measure day to day (inter-day) glucose variations. It is calculated by taking the mean and SD of the differences between pairs of glucose values measured at the same time points (hourly) on two consecutive days. MODD calculation was based on an experiment performed under strict conditions, with similar timing and quantity of meals and activities. However these conditions are not feasible under usual living conditions and thus MODD values will be

distorted by dyssynchrony in the meals and activities timing. An issue that can only be resolved by aligning the curves at peaks and troughs. Therefore MODD cannot be a reliable indicator of inter-day variability for data derived from CGM under normal living conditions.

1.6.7 M-value

The M value was first described to quantify the efficacy of glucose lowering treatment (Schlichtkrull et al., 1965). The estimation basically depends on calculating the ratio of each measured blood glucose to a reference or a preferred blood glucose level of 120 mg/dl (6.7 mmol/l). These ratios are then logarithmically transformed, their absolute value (numeric value without negative/positive sign) cubed and the mean of all the values obtained. A correction factor ($W/20$) is then added to the resulting mean value, where W is the difference between the maximum and minimum blood glucose (BG) values over a 24-hours period (Equation 1.3).

$$M - value = \frac{\sum(|10 * \log\frac{BG}{120}|)^3}{N} + W/20 \qquad \textbf{Equation 1.3}$$

The closer the M-value to zero is the closer the measured BG values to the reference level, however the M-value puts more weight on hypoglycaemic values as displayed in Table 1-5. It was designed in such a way as to provide a treatment safety margin and to avoid hypoglycaemia when comparing the efficacy of different insulin regimens. This is a feature which is totally justifiable when comparing glucose levels following glucose lowering medicines administration. However, it is not a desirable feature when assessing overall glycaemic control.

BG (mg/dl)	M	BG (mg/dl)	M	BG (mg/dl)	M	BG (mg/dl)	M
5	2629.3	85	3.4	165	2.6	245	29.8
10	1256.8	90	2.0	170	3.5	250	32.4
15	736.5	95	1.0	175	4.4	255	35.1
20	471.2	100	0.5	180	5.5	260	37.9
25	316.2	105	0.2	185	6.6	265	40.7
30	218.2	110	0.1	190	7.9	270	43.7
35	153.2	115	0.0	195	9.4	275	46.7
40	108.6	120	0.0	200	10.9	280	49.8
45	77.3	125	0.0	205	12.6	285	53.0
50	55.0	130	0.0	210	14.4	290	56.3
55	38.9	135	0.1	215	16.2	295	59.6
60	27.3	140	0.3	220	18.2	300	63.0
65	18.9	145	0.6	225	20.3	305	66.5
70	12.8	150	0.9	230	22.6	310	70.0
75	8.5	155	1.4	235	24.9	315	73.6
80	5.5	160	2.0	240	27.3	316	74.4

Table 1-5 Calculated M for a range of blood glucose values, $M = (|10 * \log\frac{BG}{120}|)^3$

1.6.8 Continuous Overall Net Glycaemic Action (CONGA)

CONGA was developed specifically to derive variability information from CGM data. It represents the standard deviation of the differences between a glucose concentration value at one time point (k) and a glucose concentration value at the next time point (k + n), for all the glucose concentration data points within a 24-hour period, n could range between 1 and 8 hours. CONGA1 for instance is the SD of all the 1-hour apart differences of all glucose concentrations values measured over a 24-hour period (McDonnell et al., 2005). A closer look at CONGA1 reveals that it represents the SD of the hourly rate of change (speed) of the glucose level over a 24-hour period. Assuming that the rate-of-change is normally distributed and the up-hill rate-of-change (positive speed values) will cancel the down-hill rate-of-change (negative speed values) then the mean rate-of-change will be zero and ±1 CONGA will represent the dispersion of rate-of-change values around the mean and spanning the middle 64% of the rate-of-change values (Figure 1-5) , however the frequency distribution of the rate of change does not always have a normal distribution (Service, 2013).

Figure 1-11 shows that glucose curve C has steeper excursions, i.e. faster rate-of-change, than curve A. Glucose curve C has a higher CONGA1 than glucose curve A (Table 1-6). Thus glucose curve C has more variability according to the CONGA result. It has also a higher SD and M-value than glucose curve A, however, both glucose curves

have the same MAGE value. Further, CONGA has the same trend as SD for all glucose curves presented in Table 1-6.

CONGA could be a good measure of glucose variability. It provides similar information to that which the SD of glucose provides. However, it would be more useful if it assessed the amplitude of rate-of-change and the dynamics of glucose over the time period particularly postprandial (after meals) rather than just assessing the dispersion of the rate-of-change of glucose around its mean.
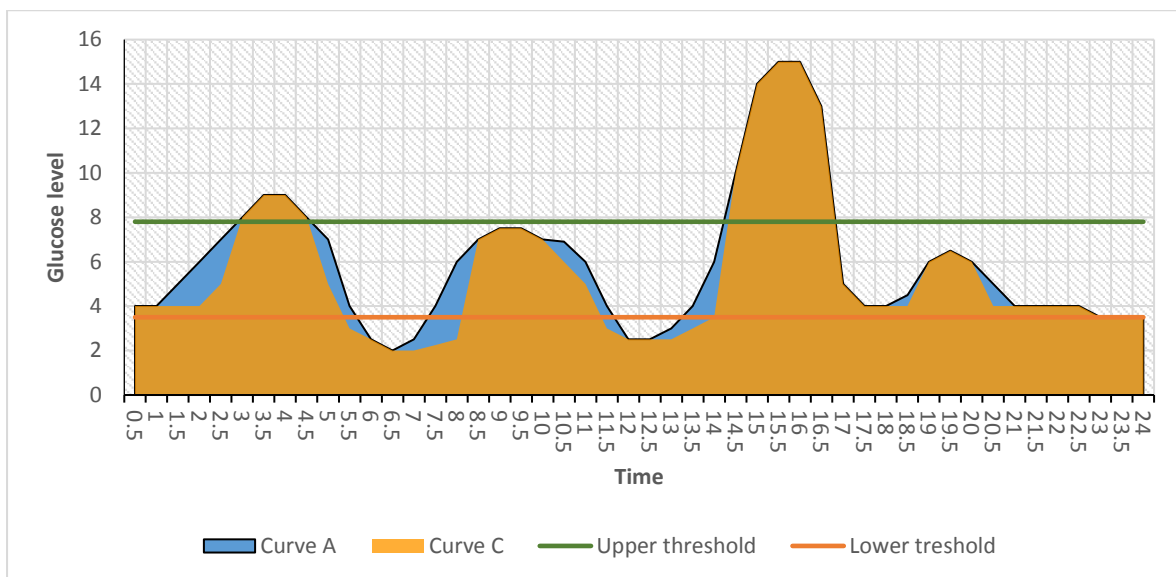
Figure 1-11 Two similar simulated glucose curves; curve A and curve C, except for steeper peaks in curve C

1.6.9 Comments on summary metrics of CGM data

Summarising CGM data into a signal value provides an overall crude estimate of a wealthy data source. Each summary metric evaluates one aspect only, either amplitude or variability, of the whole picture that CGM data provides. Furthermore, summary metrics do not address the extensive temporal information available from CGM namely the diurnal glucose pattern and rate-of-change of glucose.

Moreover, the lack of Gaussian (normal) distribution of CGM data affects the validity of some of the summary metrics. In addition, CGM glucose values are not independent of each other and they constitute a time-series function. Time-series is a collection of observations of a quantity, obtained at successive time points, often with equal intervals between them (Chatfield, 2004). Many of the summary metrics like mean and SD are based on the assumption of independent, identically distributed random variables (IID?) which is not the case in correlated glucose data points from CGM time-series function.

Each time point value is highly correlated to its preceding and subsequent values, mainly within a 60 minute spectrum in CGM data (Rodbard, 2009b). The subsequent observation can be partially predicted by the current and preceding observations. Using summary statistics to describe a time series can be possible only if supplemented with a specific 'autocorrelation function' and a consideration of the time order. However, this specification is only applicable to a stationary time-series with no major trends or cyclic/periodic fluctuations. Calculating usual summary statistics for non-stationary time series as in the case of CGM data "can be seriously misleading" (Chatfield, 2004).

Table 1-6 Summary metrics of six simulated glucose curves, curve A, curve B, curve C and curve G.

Summery metric	Curve A	Curve B	Curve C	Curve D	Curve E	Curve F
Mean (mmol/l)	5.97	6.01	5.51	9.97	6.01	5.62
Median (mmol/l)	5.00	5.00	4.00	9.00	5.00	5.00
SD (mmol/l)	3.17	3.18	3.34	3.17	2.48	2.11
CV	0.53	0.53	0.61	0.32	0.41	0.38
AUC (mmol/l/ minute)	5.97	6.01	5.51	9.97	6.01	5.62
25th percentile (mmol/l)	4.00	4.00	3.50	8.00	4.00	4.00
75th percentile (mmol/l)	7.00	7.13	7.00	11.00	7.06	7.13
IQR (mmol/l)	3.00	3.13	3.50	3.00	3.06	3.13
MAGE (mmol/l)	7.67	6.63	7.67	7.67	5.00	5.00
J index ($mmol^2/l^2$)	27.05	27.36	25.33	55.92	23.37	19.36
Mean+1SD (mmol/l)	9.14	9.19	8.84	13.14	8.49	7.73
Mean-1SD (mmol/l)	2.80	2.83	2.17	6.80	3.52	3.51
Mean+2SD (mmol/l)	12.31	12.37	12.18	16.31	10.98	9.84
Mean-2SD (mmol/l)	-0.37	-0.35	-1.17	3.63	1.04	1.40
M-value	18.74	18.74	27.77	12.55	7.80	10.64
CONGA1 (mmol/l/hour)	3.18	3.23	3.49	3.18	2.50	2.20

1.7 Functional data analysis

FDA is an advanced statistical method that can address both the correlation between adjacent glucose values across the CGM data record, as well as the time dependency the glucose values exhibit (Ramsay and Silverman, 2005). Equally, it has the ability to extract some desirable information from the CGM data, including: the glucose amplitude, variability, diurnal pattern and rate-of-change (Law et al., 2015). Other statistical methods such as missed-effect growth and latent models and other traditional time-series models were adapted to handle complex-structure data similar to those of CGM data. However FDA is considered superior to them as it can manage heterogeneous data and can estimate relationships effect sizes and statistical significance over time (Dass and Shropshire, 2012). FDA methods with application to CGM data are discussed in more details in chapter 2.

1.8 Hypothesis and Aims of this thesis

In summary, numerous observational and some small interventional studies suggest that sleep duration is an important factor in the pathogenesis of insulin resistance and T2DM. In people with diabetes sleep duration and sleep quality is associated with poorer glycose control, although the methodology used to assess this has considerable limitations.

GDM is an extremely common type of diabetes affecting women of childbearing age and has adverse effects in pregnancy and long lasting detrimental effects on the children. Achieving tight glucose control is critical in the management of these pregnancies, to reduce complications. The role of sleep in achieving glucose control in pregnant women with GDM has not been explored.

There are well recognised limitations in the assessment of glucose control by contemporary methods, minimising the accuracy of the information obtained. Continuous glucose monitoring and the application of functional data analysis, offers the opportunity to address this.

My underlying hypothesis is:

Sleep disturbances, such as short or long sleep duration, and lower sleep quality increase the amplitude and variability of blood glucose in pregnant women with gestational diabetes (GDM).

The two aims of my thesis are therefore to:

- Explore the association between sleep and glucose control in pregnant women with gestational diabetes.
- Develop the application of functional data analysis methods to continuous glucose monitoring data to enable a more detailed: 1) evaluation of glucose control and diurnal variation; and 2) analysis of the sleep and glucose relationship.

1.9 Objectives

In order to address these two aims, my thesis has the following key objectives:

1- Evaluate sleep in pregnant women with gestational diabetes subjectively using the PSQI questionnaire and objectively using actigraphy gauging the agreement between the two tools derived sleep characteristics.

2- Assess glycaemic control in pregnant women with gestational diabetes using CGM.

3- Apply FDA methods to daily glucose curves derived from CGM data.

4- Examine the association of subjective and objective sleep characteristics with glucose control using: a) the CGM derived summary indices and b) FDA of daily glucose curves.

5- Explore the causal direction of the relationship between sleep and glucose by also examining the association between glucose levels immediately prior to sleep, with the characteristics of that subsequent night's sleep.

Chapter 2 Functional data analysis (FDA) and its application to CGM data

The present chapter outlines the functional data definition and FDA methods, the steps followed to change CGM data into functional data, and various techniques used to extract descriptive and inferential information from functional data. CGM data collected as a part of this current study was used to demonstrate some of these FDA techniques. However, further specific details on the FDA techniques applied in this study are presented in the Methods chapter, Section 3.9.5, and the results are presented in the Results chapter, Sections 4.3.5.2, 4.6, 4.7 and 4.8.

2.1 Functional data and FDA

FDA is an analytic approach that studies functional data. Functional data are observations generated from measuring/recording consecutive discrete values (data-points) of an underlying smooth process (curve) over a continuous domain such as time, often with multiple curves generated from multiple individuals/records (Ramsay and Silverman, 2005).

Functional data are commonly encountered and are becoming more abundant, especially with the advance in modern data recording and storing technology. The data generated from these technically advanced devices could be of high resolution with frequent recording and low noise or of low resolution with infrequent recording and a noisy signal. Data such as; CGM data, actigraphy data, electrocardiograph (ECG) data, children growth monitoring data, and weather stations' temperature level data, are examples of functional data.

Data-points of functional data are usually measured with some measurement errors (noise) and every data-point is correlated to the data-points surrounding it. These data-points can be represented by a single mathematical function delineating their underlying smooth processes curve and minimising the noise. For example, Figure 2-1 illustrates simulated consecutive discrete data-points of a sigmoid mathematical function with some added random error. FDA aims to represent such data-points with their functional form/object, i.e. the underlying mathematical function. A further descriptive and inferential statistical analysis is then performed on these functional objects as a unit of observation for each participants rather than the multiple correlated discrete data-points.

N.B. the coming paragraphs contain some mathematical notations to enrich the content, however skipping them will not affect the context of the text.

The first step in FDA is a process called smoothing, where these discrete values are fitted with a smooth functional object (curve) defining their underlining signal and removing the surrounding noise. The function can be expressed as:

$$Y_{ij} = X_i(t_j) + e_{ij}$$

Equation 2-1

Where Y_{ij} are observed discrete values for each participant i at sequence j of time t, and $X_i(t_j)$ are the smoothed values (fitted values on the curve) for each participant i at sequence j of time t, and e_{ij} are the noise (error) observed for each participant i at sequence j of time t.

With smoothing the aim is to find the mathematical function of time $X_i(t)$ that is best to fit the observed values and minimise the sum square of error (the vertical distance between observed values and fitted curve). This is usually done by the use of basis expansion (details in Section 2.1.1).

The second step in FDA, is a technique called registration, where all the prominent curvatures (peaks and nadirs) of the fitted smooth curves are aligned (rearranged) to occur around the same time frame. Registration is explained in more detail in Section 2.3.
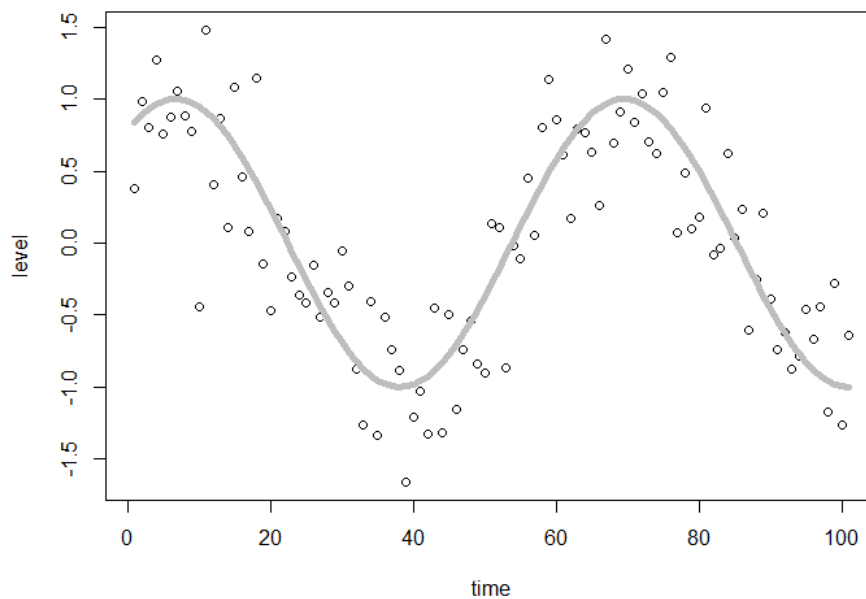
Figure 2-1 Discrete values with some random noise (black hollow circles) of a smooth process represented by a sigmoid mathematical function (grey curve)

2.1.1 Defining functions by basis expansion

Basis expansion is a linear combination of known basis functions (in a similar way to the linear regression model) and is commonly exploited to find the best fitting curve. Hence, for a sufficiently large number (K) of basis functions (ϕ) (pronounced phi) the estimated curve will have the following mathematical notation:

$$X_i(t) = \sum_{k=1}^{K} c_{ik}\ \phi_k(t)$$

<div align="right">

Equation 2-2

</div>

Basis functions can be considered as building blocks that are weighted using coefficients of expansion c_{ik} and summed up to construct a smooth curve. C_{ik} is data driven using ordinary least square (OLS) fitting methods while the type of basis function (ϕ) is determined by the researcher according to the behaviour of the data. Basis function should have features that match those known to belong to the function being estimated. This makes it easier to achieve a satisfactory approximation using a comparatively small number of K basis functions. There are many known and established basis functions, some of them will be discussed next.

2.1.1.1 Polynomial basis functions

The polynomial basis function is one of the oldest, though still widely used, basis. It is a collection of monomials (powers of consecutive positive integers) with the following functional form

$$X_i(t) = P_i(t) = c_{i0} + c_{i1}t^1 + c_{i2}\ t^2 + \ldots\ldots + c_{in}\ t^n$$

<div align="right">

Equation 2-3

</div>

Where the largest exponent n is the degree of the polynomial function $P\ (t)$, time t is the independent variable and c is the regression coefficient. A first degree polynomial is just a linear regression equation, whilst a second degree polynomial is a parabola (U shaped curve) (Figure 2-2). Polynomials are suitable for simple curves. Complex curves with many local features need to be fitted with higher degree polynomials but this usually leads to overfitting (mixing the underlying signal with the surrounding noise). This is mainly due to the high correlation between monomials of high-degree polynomials, making polynomials a global basis functions. Local basis functions are more appropriate for complex curves. Moreover, polynomials usually fit the centre of the data better than the boundaries.
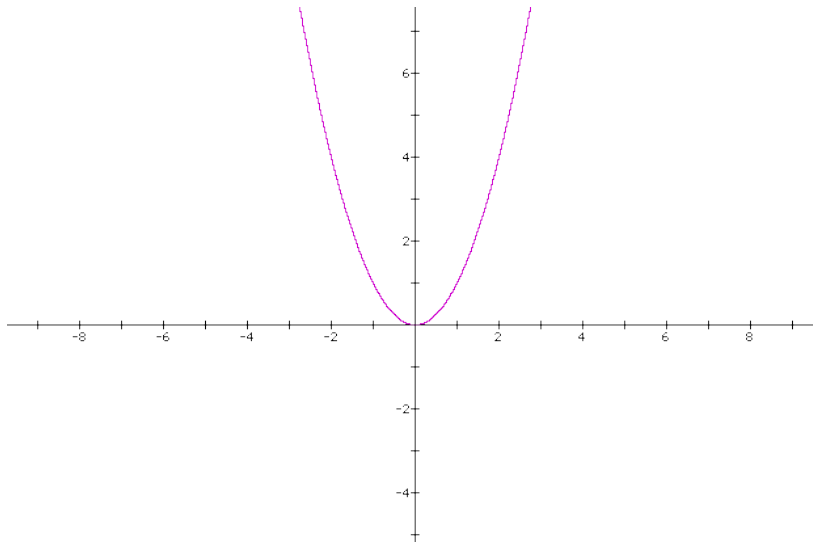
Figure 2-2 A parabola , adapted from (Barron and Kastberg)

2.1.1.2 Fourier basis

The Fourier basis is another old and extensively used basis function. It is a simple basis comprised of a linear combination of a series of sine and cosine waves (**Figure 2-3**) Fourier basis is best used to delineate periodic signals such as ECG signals and weather trend curves with repetition of the signals over a certain period T. It has the following mathematical notation:

$$X_i(t) = c_{i0} + c_{i1} \sin(wt) + c_{i2} \cos(wt) + c_{i3} \sin(2wt) + c_{i4} \cos(2wt) + \ldots\ldots + c_{i(k-1)} \sin((k/2)wt) + c_{i(k)} \cos((k/2)wt)$$

Equation 2-4

Where k is the number of bases excluding the constant term c_{i0} , and the parameter $w = 2\pi/T$.
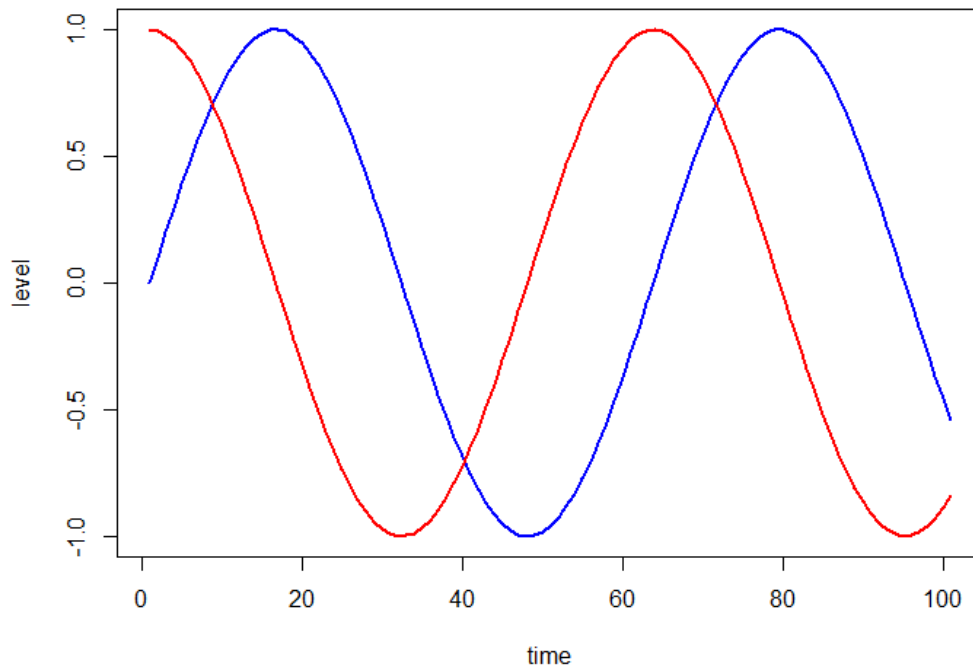
Figure 2-3 Plot of sine wave (blue carve) and cosine wave (red curve)

2.1.1.3 B-spline basis

The B-spline basis is basically piecewise (subintervals over the time axis) polynomials that are linearly summed together to fit a single smooth curve over the whole interval (the time period). The places where these subinterval polynomial pieces connect together are called break points or knots. By forcing adjacent polynomial pieces to be equal (having the same values) at the knots, the resulting curves of spline functions are continuous (i.e. connected without gaps at knots) (**Figure 2-4**).

There are different types of spline bases (De Boor, 1978), however, only B-spline is presented in this thesis. B-spline (short for basis spline) is the most commonly used basis within the FDA framework to fit complex and non-periodic signals. De Boor (1972) and Paul and Marx (1996) can be consulted for detailed statistical properties of B-spline.

B-splines are characterised by their order m which is equal to the spline's polynomial degree $n+1$, number and placement of knots N, and number of bases k. **Figure 2-5** is a plot of 12 cubic B-spline bases (a piecewise polynomial of degree 3 and order 4) with ten knots (eight internal and two external/boundary knots). The plot shows that the polynomial curves overlap and each subinterval (segment between two knots) is covered by a number of polynomials equals to the order of the B-spline m, i.e. four in the case of

cubic B-spline. Moreover, in a B-spline of order m, number of bases k is related to the number of internal knots N, as follows: $k= N+m$, i.e. 12 cubic B-spline bases would have eight internal knots. Thus, after determining the order of B-spline, either estimating the number of bases needed to fit the curve or the minimum number of internal knots needed would be sufficient to calculate the other.

An attractive feature of B-spline is the ease of computing the function derivatives. The first derivative is the velocity - the rate of change of outcome value over time, while the second derivative is acceleration - the rate of change in velocity over time. Derivatives are usually of interest as they can be used to penalise the function roughness (tune down the fluctuation within the curve). More detail about penalisation is found in Section 2.2.
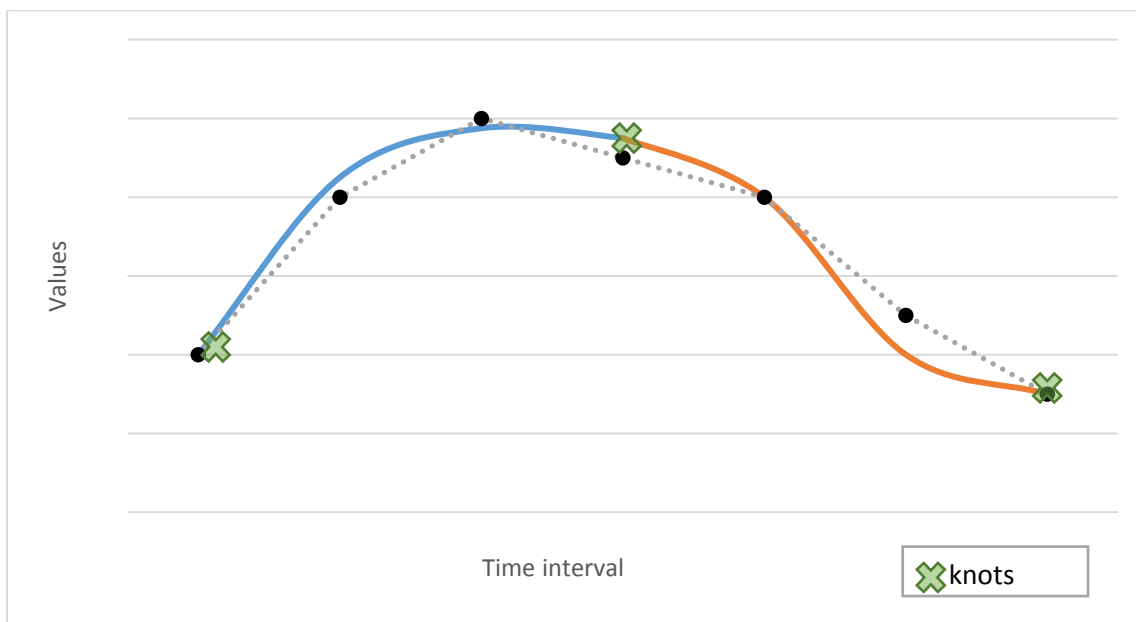
Figure 2-4 Schematic presentation of two piecewise splines (the blue and the orange curves) connected with one middle knot and two peripheral knots, smoothing seven observed discrete data-points (black dots)

Furthermore, derivatives can themselves be explored and examined as data when velocity and acceleration of the measured values are of importance. B-spline's derivatives are continuous (connected at knots without gaps) up to m-2 (i.e. up to the second derivative of a B-spline of order 4 will be continuous).
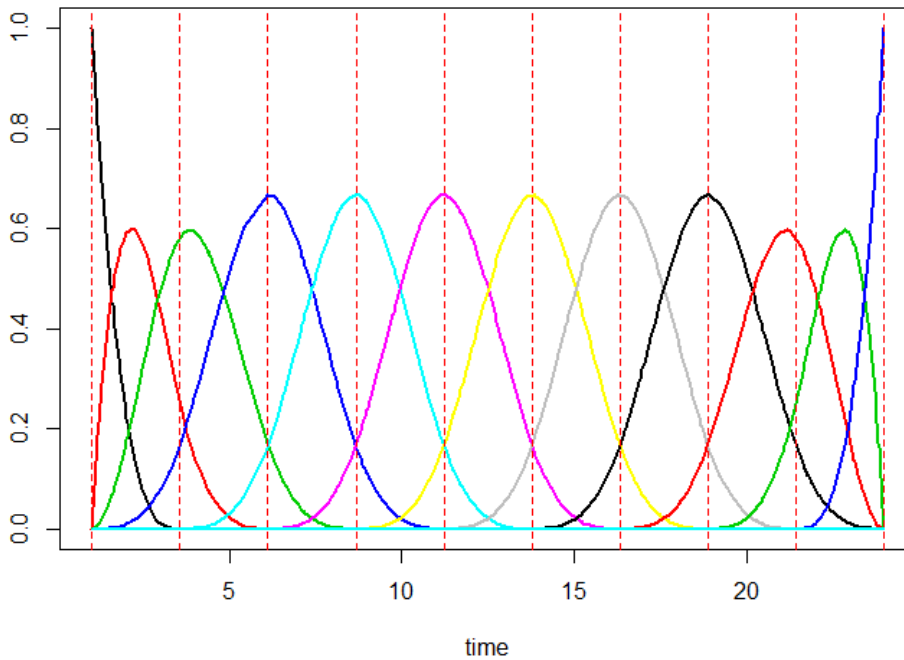
Figure 2-5 Plot of 12 cubic B-spline bases defined over 24 hours interval, with ten equidistance break points and knots (red vertical dashed lines)

Nevertheless, B-splines tend to produce a boundary effect, where the fit of the curve is unstable at the boundary of the interval. Furthermore, choosing the appropriate number of basis functions can be difficult, as a large number of B-spline bases (collection of basis) tend to over-fit the curve to the data-points, while a very low number of bases can miss salient features of the curve. However, different methods of determining the number of bases have evolved and the introduction of the roughness penalties has dealt with the overfitting.

2.2 Basis functions for CGM data

The cubic B-spline basis was chosen to fit a mathematical function (presented as smooth curve) to daily CGM data. Cubic B-splines, as previously mentioned, are the most used bases for non-periodic processes with local features (Ramsay and Silverman, 2005). They are very smooth at their knots and continuous at their first and second derivatives. The cubic B-spline basis was used since higher order polynomials B-splines are rarely needed (Cardot et al., 2003; Prchal and Sarda, 2007). The first step in fitting the cubic B-spline bases to the CGM data is to determine the number and placement of the knots and the number of bases.

2.2.1 Number and placement of knots and number of cubic B-spline bases

Knots were placed at the boundaries of the 24-hour time interval, called external knots, and at equidistant break points of sub-intervals, called internal knots. The number and placement of the internal knots were chosen to best mould the shape of the glucose curve. With cubic B-spline, this can be assisted by some rules of thumb: keeping at least four to five data-points in a sub-interval and having no more than one inflexion (curvature) per sub-interval (Wold, 1974). Moreover, the more parsimonious basis function, i.e. with the smaller number of bases, sufficient enough to represent the features of the fitted curve, is preferred. Using the minimally required number of bases enhances the degree of freedoms available to test subsequent hypotheses and to compute accurate confidence intervals. It also requires less computation and computer memory size and is less likely to mix the noise with the underlying process signal (Ruppert, 2002; Claeskens et al., 2009).

In the extreme case of placing a knot at each point of observation, the estimated curve will merely interpolate (connect) observed data points together and thus the **bias of estimate** will be zero, however, the **variance of estimate** will be very high as noise would be fitted as well. Where, the **bias of estimate** equals the mean of the difference between observed data points and the mean of estimated data points, and the **variance of estimate** equals the mean of the sum of square differences between the estimated points and the mean of estimated points. This conflicts with the reason for why the data points were fitted using basis expansion, i.e. estimating the underlying smooth curve and minimising noise. Thus, some bias should be tolerated to find the best fitting signal, and choosing the number of bases should be based on a trade-off between bias and variance.

This trade-off should minimise the mean sum of squared errors (SSE) and can be estimated using generalised cross validation (GCV) Criterion (Craven and Wahba, 1978; Ruppert, 2002). Here, SSE is the sum of squared differences between the observed data points and the estimated data points (data point on the fitted curve) and GCV is calculated for each curve using **Equation 2-5**. Multiple curves will result in a vector (list) of GCV values, one per curve. The overall mean GCV is used as the criterion for the trade-off for all the curves.

$$GCV = \frac{n * SSE}{(n - df)^2}$$

Equation 2-5

Where n is the number of observed data points and df is the degrees of freedom of the fitted curve. The number of bases that substantially decreases the mean GCV criterion is

chosen. After this minimal number of knots has been reached, a further increase in the number of knots has little effect on the fit (Ruppert, 2002).

2.2.2 Knots placement and number of bases for CGM data

CGM data have 288 data points per 24-hour day measured in 5-minute epochs. That is 12 data-points per hour, six data-points per 30 minutes and only three data-points per 15 minutes. Knots should be placed at more than 15 minutes break points as the 15 minutes subinterval has low number of data points, as per the 'rule of thumb' explained earlier.

Moreover, to determine the best number of bases, GCV criterion was calculated for a wide range of numbers of bases. Figure 2-6 shows a plot of the GCV criterion values across a wide range number of bases (R software codes for generating the GCV criterion and the plot were adapted from Hooker (2008) and are available in R code syntax box 1. The plot demonstrates that there is no substantial decrease in the GCV criterion value (there is less than a 0.05 drop in GCV value per five figures increase in the number of bases) for the number of bases higher than 25 bases, and there is only a trivial decrease in the GCV criterion values for the number of bases higher than 50 bases. Thus, using the GCV criterion to place a knot at an equidistance sub-interval across the 24-hour day indicated the use of 27 to 51 bases. Fitting the CGM data using 51 bases, 47 internal knots would be placed at thirty-minute equidistant break points, while fitting the CGM data using 27 bases, 23 internal knots would be placed at hourly equidistant break points.

To have more insight into the smoothed curve produced by applying these numbers of bases and knots, CGM data were fitted using 51, 27, 15 and seven B-spline basis functions. Figure 2-7 shows five daily glucose curves fitted using these numbers of bases, as follows: plot (A) using 51 cubic B-spline bases with knots every 30 minutes displayed prominent fluctuations and diurnal pattern as well as minor oscillations; plot (B) using 27 cubic B-spline bases with hourly knots displayed prominent fluctuations and diurnal pattern but flattened-out minor oscillations; plot (C) using 15 cubic B-spline bases with knots every two hours flattened both prominent and minor features; while plot (D) using only 7 cubic B-spline bases with knots every four hours severely flattened out the curves.

Therefore, using all the criteria discussed earlier a 27 cubic B-spline bases with hourly knots was chosen to fit the daily glucose curves (from midnight to the following midnight).

R code syntax box 1 GCV criterion

```
# Import CGM data
glucose  <- Alldata [c("idseq", "sensorGlucose" , "glu_time" )]
# Reshape wide
glucose  <- reshape(glucose, timevar="personDateUI", idvar="timeHourMinuteIn5",
direction="wide")
# Glucose matrix
glucose  <- glucose[c(2:length(glucose))]
glucose  <- data.matrix(glucose)
# Define time argument
xx <- seq(1,288,1)-0.5
# Create empty matrix to store GCV values for each daily glucose curve and number of
bases
bgcvs <- matrix(0,652,285)
# Create empty list to store mean GCV values for each number of bases
mean.gcv <- rep(0,285)
# select penalty
curv.Lfd = int2Lfd(2)
# Loop to calculate mean GCV criterion
for(i in 5:285){
# create temporary B-spline basis object
  tempbasisi = create.bspline.basis(c(0,288),nbasis=i)
  # Smooth
  tempglucSmoothi = smooth.basisPar(argvals=xx, y=glucose,fdobj=tempbasisi,curv.Lfd,
lambda = 1)
# extract GCV
  bgcvsi =  tempglucSmoothi$gcv
  mean.gcv[i] = mean(tempglucSmoothi$gcv)
}
# Plot the mean GCV criterions against number of bases
plot(nbasis[5:100],mean.gcv[5:100],type='b', xlab = "Number of basis", ylab = "Mean GCV",
xaxp= c(0,100,20),col="blue")
```
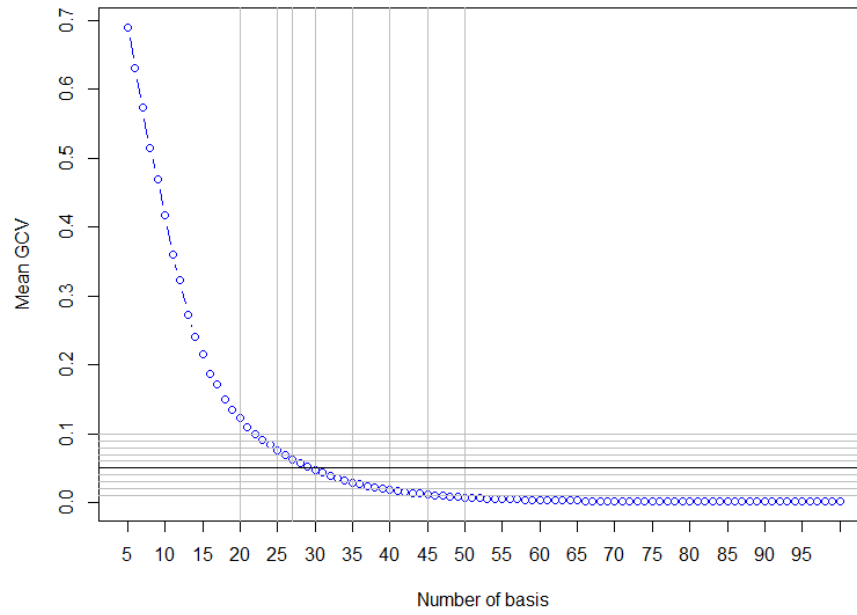
Figure 2-6 Generalised cross validation (GCV) criterion values across a wide range of cubic B-spline basis functions numbers . Fine vertical and horizontal grid lines are only guide lines
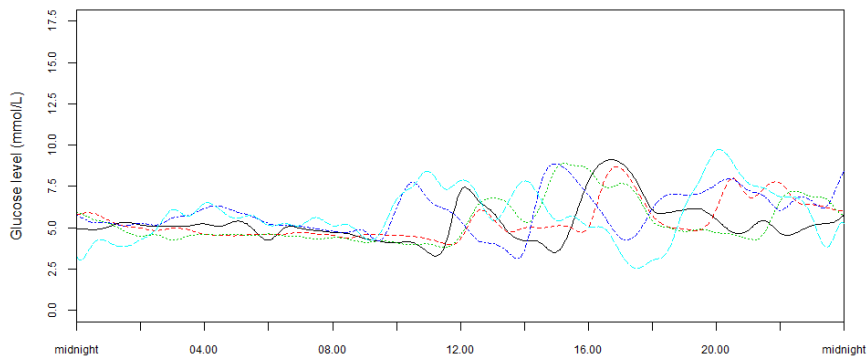
(A) 51 cubic B-spline, knots every 30 minutes
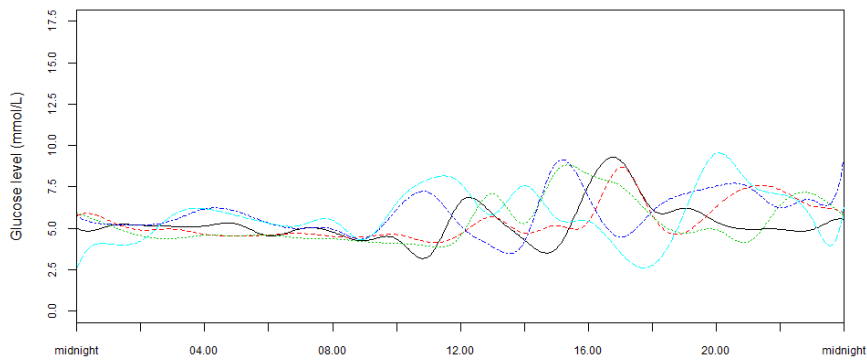
(B) 27 cubic B-spline, knots every one hour
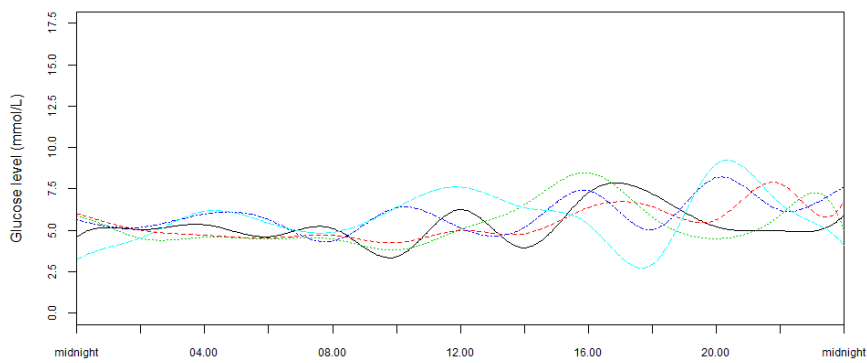
(C) 15 cubic B-spline, knots every two hours
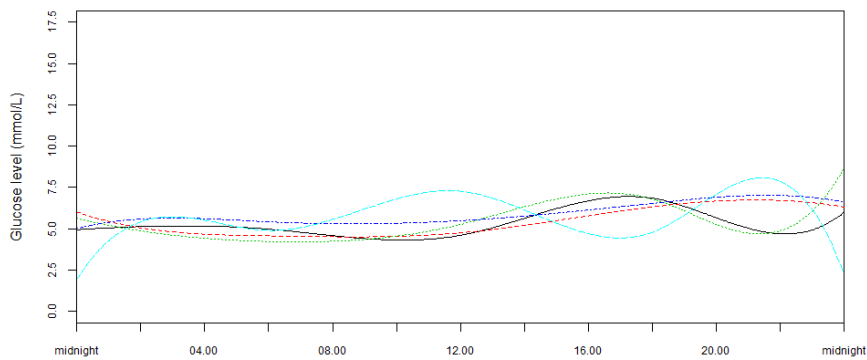
(D) 7 cubic B-spline, knots every four hours

Figure 2-7 Five daily glucose curves smoothed using (A) 51 cubic B-spline, (B) 27 cubic B-spline, (C) 15 cubic B-spline and (D) 7 cubic B-spline

2.2.3 Fitting the smooth curves to CGM data by basis expansion

Fitting the smooth curves to the daily CGM data is done by using the penalised OLS method to linearly combine the cubic B-spline bases. The best fitting curve is the curve that minimised the penalised SSE, whereas the errors are the vertical distance between the fitted curve and the observed CGM data points. The penalty is based on the roughness of the curve (number and depth of the curvatures) and is estimated using the integral of the squared second derivative (acceleration) (Paul and Marx, 1996). Furthermore, a 'smoother parameter' lambda (λ) that measures the rate of exchange between the fit of data, as measured by SSE, and the variability of the data, as measured by the roughness penalty, is also implemented to estimate the curve function (Ramsay et al., 2009). λ is a positive numerical figure (positive number) and a larger λ value will incur more smoothing and less variability to the curve. It is estimated using the GCV criterion in a similar method to estimating the number of bases. $\lambda=4$ was estimated for CGM data used in this thesis.

Figure 2-8 shows the smoothed daily glucose curves of all current study participants' available daily CGM data. Each smoothed curve is used thereafter as the unit of observation in a further functional descriptive and inferential analysis, including: observing the diurnal pattern; calculating the mean curve, the median curve, the standard deviation (SD) curve, interquartile range (IQR) curves and correlation matrix; and running a functional t-test and functional regression analysis.

However, before proceeding with all these statistics, a further essential step is needed. Revisiting the smooth curves plot in Figure 2-8, it looks more like 'tangled spaghetti' with no clear pattern because the prominent features of the curves (i.e. the peaks and the nadirs) do not occur at the same time every day for all the participants, i.e. the curves are not aligned. The timing of the peaks and the nadirs of the glucose curves varies between individuals, as well as between days for the same individual. This depends on: the individuals' glucose circadian rhythms, the timing of food intake, and the timing of physical activity. This variation in the timing of the occurrence of the peaks and nadirs is referred to as 'phase variability', while the variation in the height of the peaks and nadirs is referred to as 'amplitude variability'. The removal/separation of phase variability from amplitude variability by aligning (rearranging) the curves, a procedure referred to as 'registration' in FDA terminology, is paramount. Failing to register the curves leads to a statistically ambiguous results (Marron et al., 2015). This is such that the pointwise mean curve in Figure 2-8, which is clearly a flattened-out curve, does not resemble the expected pattern of the daily glucose curve. This is more obvious in Figure 2-9 where only ten daily curves are displayed with their pointwise mean. Mean glucose curve's peaks are clearly wider and flatter than the plotted glucose curves' peaks. This

misrepresentation of data summary of the unregistered curves applies to other FDA statistical tests as well, and distorts any interpretation extracted from them (Wang et al., 2016a). The registration methods presented in section 2.3.
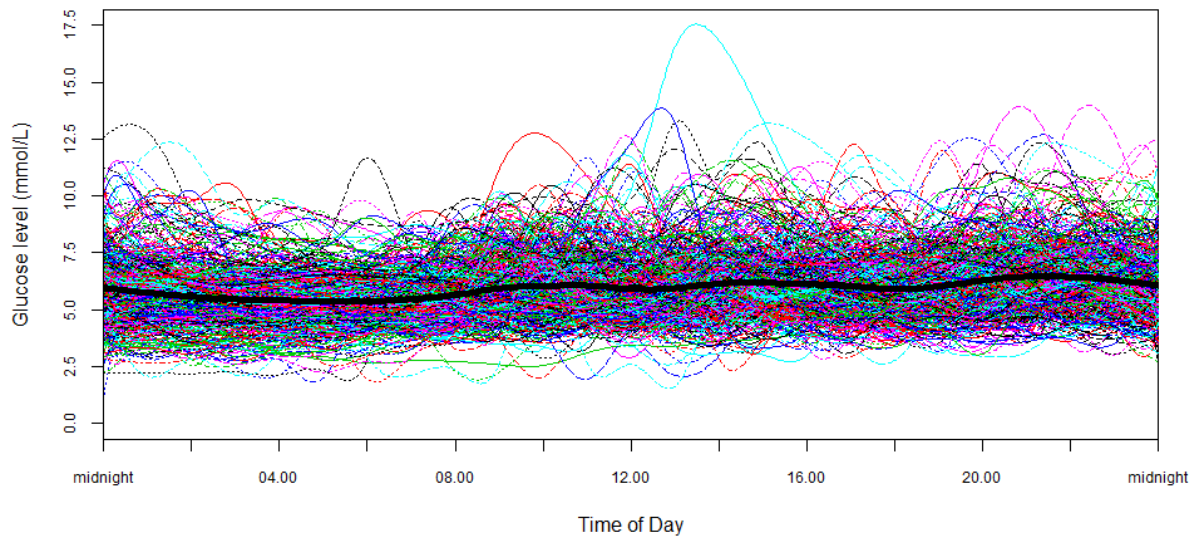
Figure 2-8 Smoothed daily glucose curves, using 27 cubic B-splines, of all available participant data with a superimposed overall pointwise mean curve (bold black curve)
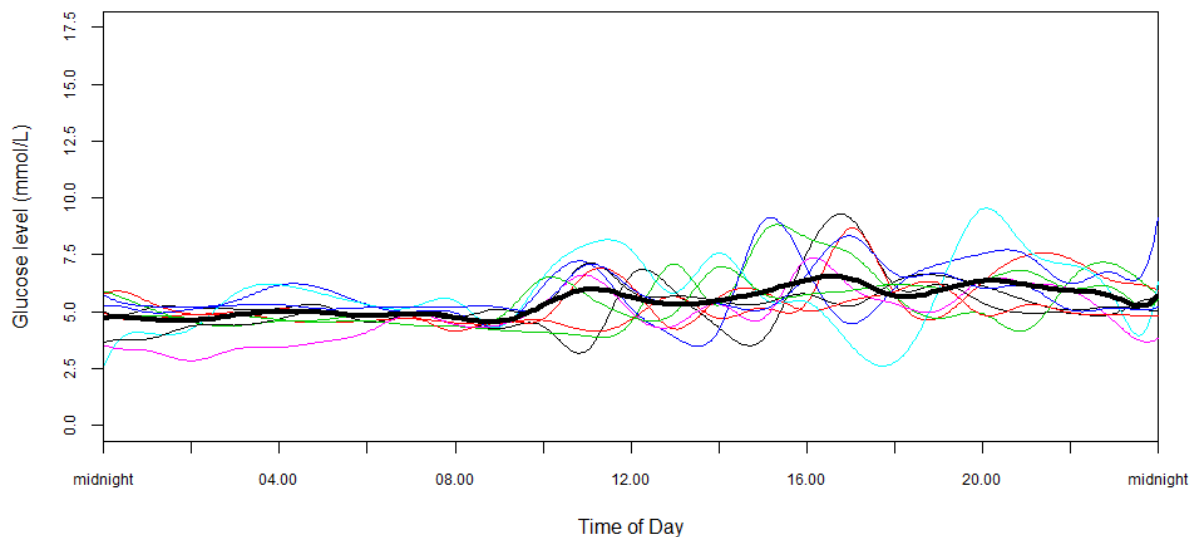
Figure 2-9 Ten daily glucose curves smoothed using 27 cubic B-splines and their pointwise mean curve (bold black curve)

2.3 Registration

Registration is done by rearranging the glucose curves' main features, such as peaks and nadirs, to change them from occurring at variable physical/clock times to occurring at about the same system/argument time using different time-warping statistical-function methods (Ramsay and Li, 1998). These methods depend on either using landmarks or using a continuous criterion.

2.3.1 Registration using landmarks

The landmark registration is the traditional method for time-warping, where the timing of specific features in the curves are aligned to a predefined landmarks or average locations in the time argument (Zhong, 2008; Ramsay and Silverman, 2005). Landmarks have to be clearly identifiable and they usually require manual care in defining and finding them. Moreover, landmarks should be present in all the curves. In glucose curves, these features are usually the peaks associated with a meal intake schedule, i.e. breakfast, lunchtime and dinnertime meals. However, these meals are not universal in all the curves, as some individuals might either miss certain meals or have more frequent meals. Moreover, landmark registration is only aligning features at the predefined landmarks and overlooks aligning other curves' features (Marron et al., 2015). As a result, landmark registration was considered as not suitable for registering glucose curves.

2.3.2 Registration using continuous criterions

The continuous criterion registration method uses the entire curve rather than specified features on the curve and can provide a more widespread curve alignment than the landmark registration method (Zhong, 2008; Ramsay and Silverman, 2005). Continuous registration aligns curves to a reference/target curve (usually the mean of unregistered curves) by transforming or warping the time argument domain of each curve using special methods. The preferred continuous registration method is to use the minimum eigenvalue of cross-product matrix criterion defined by principal components analysis. The minimum eigenvalue method usually works well if the target curve is chosen carefully. Other methods, such as the least squares fitting criterion, are also available, however, it is fundamentally intended to evaluate amplitude rather than phase variability. The least squares criterion uses the time-warping function to minimise not only phase variation, but also amplitude variation, causing a distortion to the shape of the peaks. In contrast to the landmark registration method, the continuous criterions registration method is relatively easier to perform and is fully automated using special commands in the R software 'fda' statistical package.

2.3.3 Registering smoothed daily glucose curves

The continuous criterions registration method was used to register the smoothed daily glucose curves with the mean curve of the unregistered curves as the target curve. Figure 2-10 shows the same ten daily glucose curves in Figure 2-9 after registration, with both the registered and the unregistered mean curves. It is apparent that the registered mean curve has more prominent features and more resemblance to the daily curves. However, although registration brought the curves' prominent features nearer to each other, it did not align them perfectly and further alignments would be favoured. Registration can be improved by iterations, i.e. repeating the registration process several times. At each iteration, the registered curves are re-registered using the mean curve of the previous iteration registered curves. The number of iterations needed depends on the number of curves and the phase variations between them. **Figure 2-11** displays 100 glucose daily curves: unregistered curves in the upper panel, registered curves after five iterations in the middle panel, and the unregistered mean curve together with the improved registered mean curves in the lower panel.
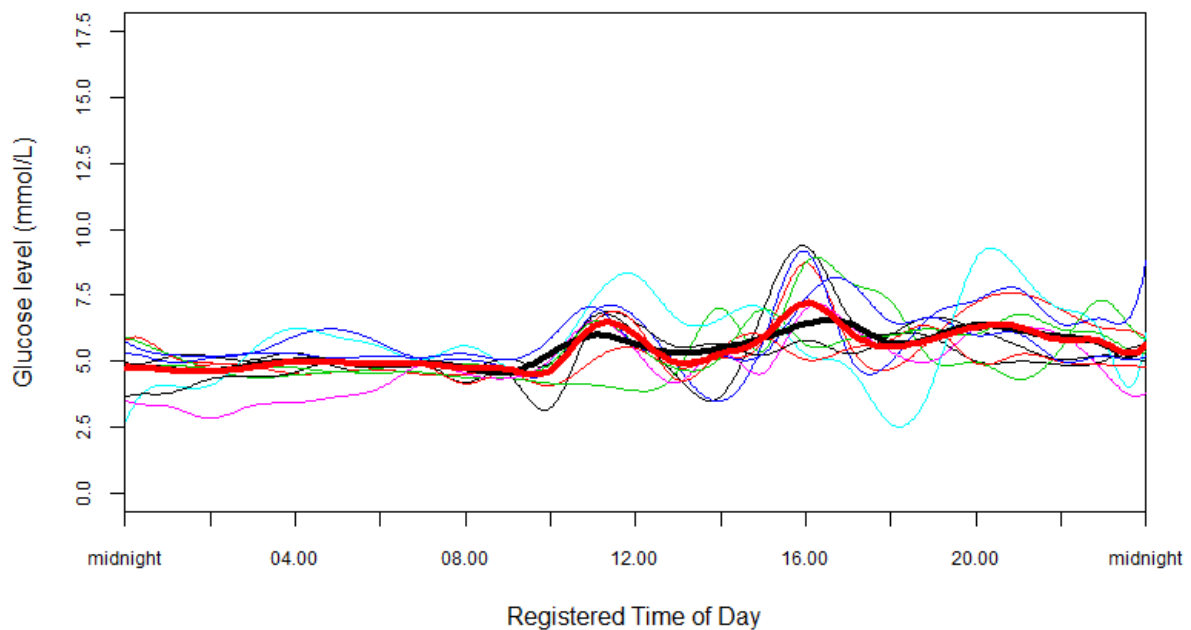
Figure 2-10 Ten registered daily glucose curves smoothed using 27 cubic B-splines with registered mean curve (bold red curve) and unregistered mean curve (bold black curve) superimposed
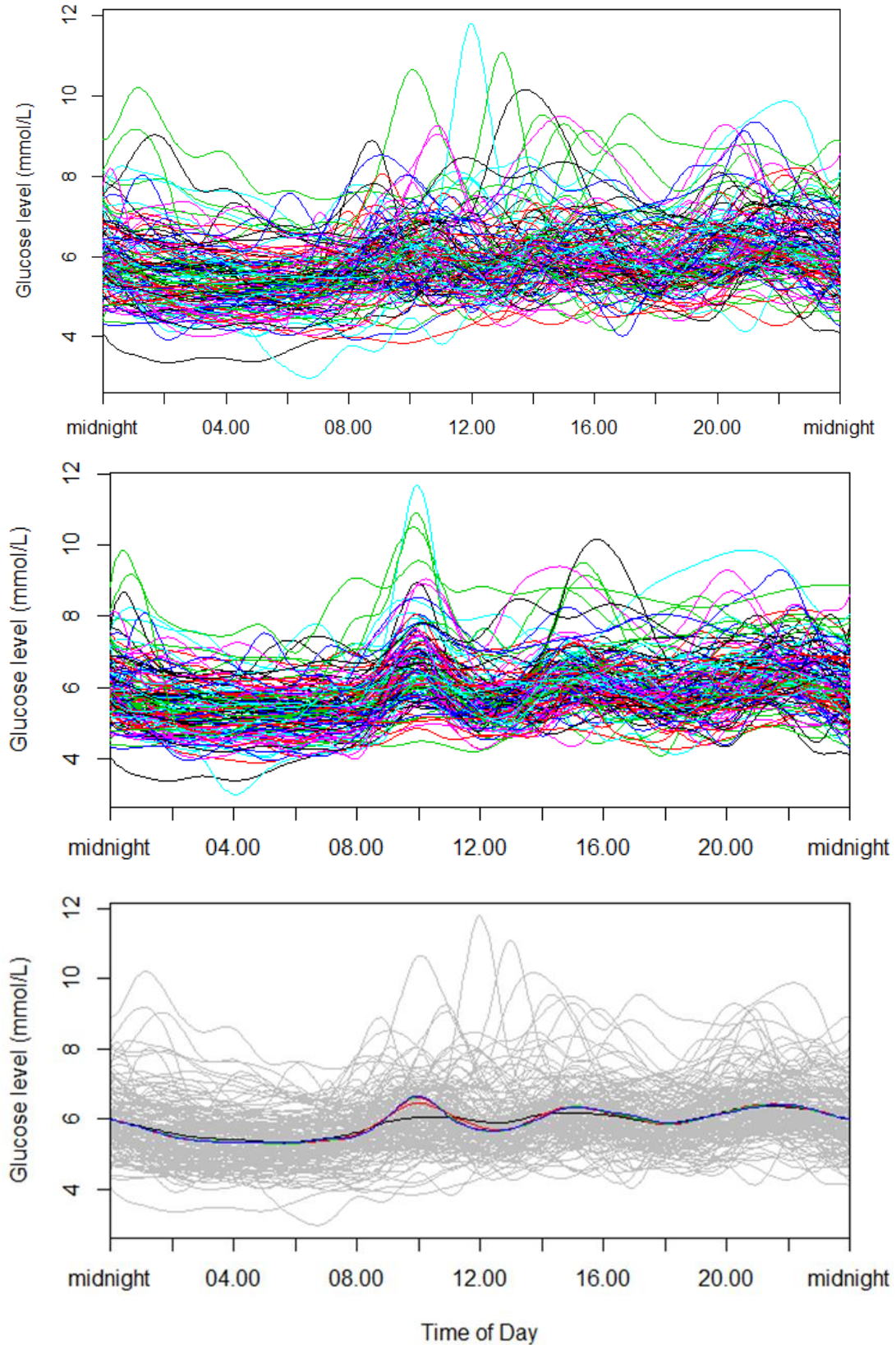
Figure 2-11 Upper panel: unregistered daily glucose curve, middle panel: fifth iteration registered glucose curve, lower panel: mean unregistered curve (black line) and fifth iteration registered mean curves (blue line)

2.4 Functional descriptive statistics

Describing the functions recognises the shape and heterogeneity within the curves, the average behaviour and the variation between curves. This entails calculating; mean, SD, median, IQR curves and covariance and correlation structure. Functional mean and SD curves are the pointwise cross-sectional mean and SD, i.e. they are calculated from all the data-points across all fitted curves at each time point. On the other hand, the functional median and IQR curves, which are less affected by possible outlier curves, are calculated in case the data-points across all the fitted curves are not normally distributed. Median and IQR curves are calculated using the concept of depth (López-Pintado and Romo, 2009), where the curves are ordered from the most centred curve outward prompted by the band depth for functional data, then median (the most cantered curve) and the 25th and the 75th percentiles curves are identified. Further, a functional box plot was also computed using the same band depth method (Sun and Genton, 2011). All descriptive statistics are interpreted in analogy to the standard way in non-functional data.

Moreover, the rate of change of glucose is estimated by calculating the smoothed glucose curve's first derivative, i.e. the curve's velocity. As the rate of change in glucose is not constant, rather it varies across the time of the day, the resulted glucose curve's velocity also varies across time. Thus, a glucose velocity curve (and not just a single numeric figure) is estimated for each glucose curve. The estimated glucose velocity curve is utilised to understand the dynamic characteristics of glucose curves. They also have a mathematical functional form, as do original glucose curves, and thus they can be further incorporated in interstitial analysis, that is they can be compared between groups and the association between them and other variables can be evaluated.

2.5 Functional inferential statistics

2.5.1 Functional t-test

The functional version of the t-test is utilised to test if the difference in daily glucose curves amplitude between two groups is statistically significant, e.g. daily glucose curves of a group of participants with short sleep duration compared to daily glucose curves of a group of participants with average sleep duration. Ramsay et al. suggested a permuatation method for functional t-test (Ramsay et al., 2009; Ramsay and Silverman, 2005). The method entails calculating a point-wise t-statistics score, i.e. using the standard t-statistic formula to calculate the t-statistics value at each time-point of all data-points across all glucose curves in the two groups, and then plotting it in a graph (red solid line in Figure 2-12). A permutation test is then performed to estimate the point-wise

and the maximum 0.05 critical values for the maximum of the t-statistic (dotted and dashed blue lines in Figure 2-12, respectively). A positive test at certain time-points is indicated when the t-statistics line passes over the maximum critical value line.
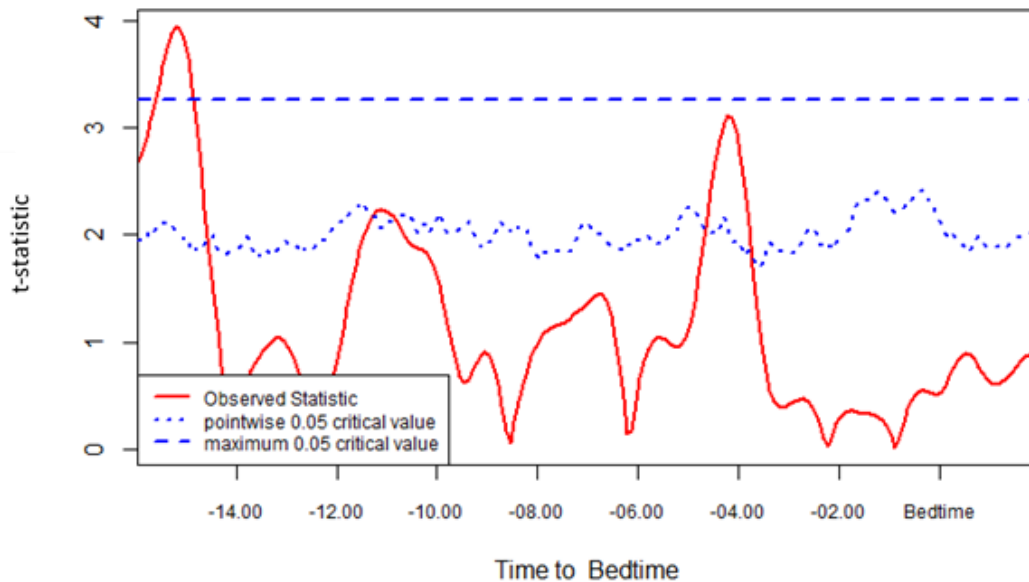
Figure 2-12 Functional permutation t-test graph

2.5.2 Functional regression

The standard regression analysis model allows the evaluation of the relationship between continuous/categorical scaler exposure and outcome variables, where scalar denotes a quantity with magnitude but no direction. These variables, including age, weight, glucose concentrations, sex or a specific diagnosis status, are assessed once at one point in time. On the other hand, the functional regression analysis model allows for the evaluation of the relationship between exposure and outcome variables in the functional space (Ferraty et al., 2012; Dass and Shropshire, 2012; Reiss et al., 2010; Ramsay and Silverman, 2005). Functional regression can be one of the following: 1) scaler-on-function regression modelling scalar outcome and functional exposure; 2) function-on-scalar regression modelling functional outcome and scalar exposure; and 3) function-on-function regression modelling functional outcome and functional exposure. The functional regression coefficient estimate is a function (smooth curve) for scaler-on-function regression and for function-on-scalar regression, and a three-dimensional functional space for function-on-function regression (Figure 2-13). That said, function-on-function regression modelling methodology is still under development (Meyer et al., 2015; Ferraty et al., 2012). Furthermore, a 95% confidence band can also be estimated for the functional coefficient (R code syntax box 2). If the confidence band does not cross

the zero line at certain time-points, then the regression coefficients at these time-points are considered statistically significant (Figure 2-14).
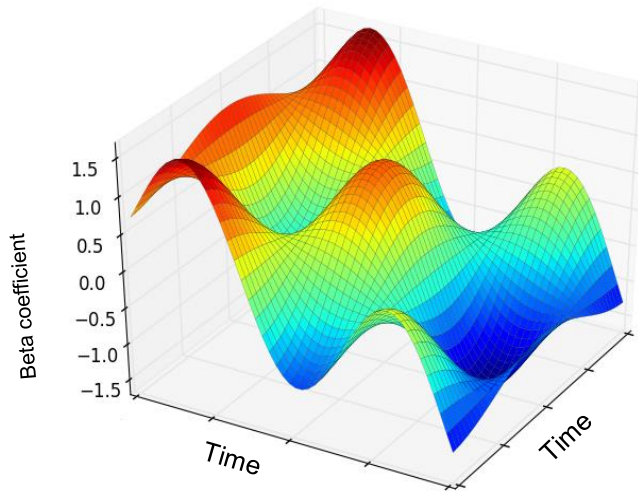
Figure 2-13 Schematic illustration of a three-dimensional functional space coefficients estimate of a function-on-function regression model(image reused from Wikimedia Commons)
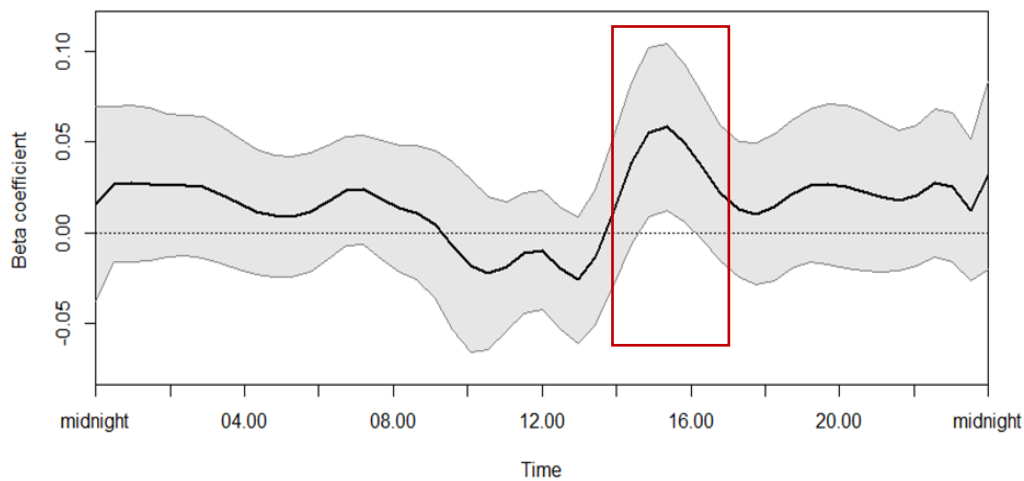
Figure 2-14 Function-on-scalar regression model's coefficient curve (black line) with 95% confidence band (grey-shaded area), showing a time period with statistically significant coefficient (surrounded by a red frame)

R code syntax box 2 Function-on-scalar regression model and 95% confidence band syntax

```
# Run functional regression model

psqi.model <-  fRegress(Reg.glucose ~ psqitot  + age + bmi + ethnicity + parity +
treatment + center+ gest_wk , Data_file)

# Calculate Standard Errors (SE)

# 1) Calculate error matrix

# xx= time argument

errmat.psqi.model <- eval.fd(xx,Reg.glucose) -eval.fd(xx,psqi.model$yhatfdobj$fd)

# 2) Calculate of transposed error matrix

SigmaE.psqiSUNe.model  <- var(t(errmat.psqiSUNe.model))

# 3) Calculate SE

stderr.psqiSUNe.model <- fRegress.stderr (psqi.model,glucose.smooth$y2cMap,
SigmaE.psqiSUNe.model)

# Plot regression coefficient and 95% confidence band

plotbetaChanged (betaestlist= psqi.model$betaestlist$psqitot$fd ,betastderrlist=
stderr.psqiSUNe.model$betastderrlist[[2]])

# Plot regression intercept and 95% confidence band

plotbetaChangedintercept (betaestlist= psqi.model$betaestlist$const ,betastderrlist=
stderr.psqiSUNe.model$betastderrlist[[1]])
```

The function-on-scalar regression modelling strategy was used in this study to evaluate
the association between sleep and glycaemic control. In the generated models, the
outcome variables were either the daily glucose curves or the daily glucose velocity
curves, and the scaler exposures were one sleep characteristic at a time together with
several potential confounders. Scalar-on-function regression models were applied to
evaluate the association between glucose curves and the following night's sleep
variables. As mentioned in the previous paragraph, the resulting functional regression
coefficients are in a functional form (smooth curves). Each value on the coefficient curve
at each time point across the argument time (the 24-hour day) is interpreted similarly to
the standard regression coefficient. Therefore, for a model studying the association
between sleep duration (exposure) and daily glucose curves (outcome), if the value on
the regression coefficient curve is 0.5 at 2.00pm then the interpretation will be that each
hourly increase in sleep duration is associated with a 0.5 mmol/l increase in glucose

concentration at 2.00pm. Thus, the coefficient is time dependent. Moreover, to study a possible U-shaped relation between the scalar exposure and the functional outcome, the exposure can be categorised into groups or a quadratic term of the exposure could be included as a covariate in the regression model in a similar manner to standard regression modelling.

2.5.2.1 Assessing regression models' goodness of fit

For assessing the models' fit, the squared multiple correlation function R^2 and the adjusted R^2 are calculated. R^2 assesses the variation in the outcome that could be explained by the model

$$R^2 = \frac{SStotal - SSresiduals}{SStotal}$$

Equation 2-6

Where $SStotal$ is the sum of the square difference between the observed outcome variable data-points and their overall mean and it represents the total variation in the model

$$SStotal = \sum (observed\ glucose\ values(t) - mean\ glucose(t))^2$$

Equation 2-7

Whereas $SSresiduals$ is the sum of the square difference between the observed outcome variable data-points and the model's fitted data-points and it represents the unexplained variation

$$SSresiduals = \sum (observed\ glucose\ values(t) - fitted\ glucose\ values(t))^2$$

Equation 2-8

However, the R^2 value can be inflated by adding more covariates to the regression model and thus cannot be used to compare models with different numbers of covariates. On the contrary, adjusted R^2 only increases if the added covariate improves the model more than what would be expected by chance. The adjustment is based on the number of covariates (p), the sample size (n), and the unexplained part of variation in the model $(1 - R^2)$.

$$R^2_{adj} = R^2 - \left(\frac{p}{n - p - 1}\right)(1 - R^2)$$

Equation 2-9

2.6 Approaching multiple days of CGM recording

CGM data are usually collected from the participants/patients for multiple days ranging from one to six 24-hour days (mid-night to the following midnight). Smoothing these daily CGM data will result in one to six daily smooth glucose curves per participant/patient. A participant's daily glucose curves are correlated and are not independent of each other. Using these daily glucose curves would make it necessary to consider their correlations by applying a multilevel mixed-effect functional methods (Scheipl et al., 2014; Spitzner et al., 2003; Morris et al., 2006; Crainiceanu et al., 2009). However, these methods are computationally complicated (Crainiceanu et al., 2009).

The approach that I developed in this thesis was to calculate the registered mean glucose curves for all the participants, using the following steps: 1) each participant's daily glucose curves were aligned separately with two registration iterations, each participant needed to have at least two 24-hour glucose curves; 2) the pointwise mean curve was calculated for each participant's registered glucose curves; 3) all participants' specific mean glucose curves were aggregated and registered, five registration iteration was needed at this step; 4) lastly, the registered mean glucose curves were used for descriptive and inferential functional analyses and they will be referred to in the rest of this thesis as the 'average-glucose curves'. These steps were programmed to operate using a 'registration loop'. The registration loop is an R software syntax for repeating function commands codes written by me (details of which are in R code syntax box 3).

R code syntax box 3 Registration loop

```
# Import CGM data

glucoseAllid <- Alldata [c("idseq", "days","sensorGlucose" , "glu_time" )]

# Create empty matrix to store the mean glucose curves of the participants'
unregistered mean glucose curves, with number of rows equal to number of
daily CGM readings (288 readings) per day, and number of columns equal to the
number of participants

emptymatrix <- matrix( nrow = 288, ncol = 146)  # matrix for 146 participants

# Create 2 empty matrices to store the mean glucose curves of the participants'
mean glucose curves after first and second registrations' iterations, with
number of rows equal to number of daily CGM readings (288 readings) per day,
and number of columns equal to the number of participants

Registeredmatrix1 <- matrix( nrow = 288, ncol = 146)

Registeredmatrix2 <- matrix( nrow = 288, ncol = 146)

# Define the time argument, that is 288 time-points across the 24-hour day

xx2= seq(100/12,2400,100/12)-(100/24)

length(xx2)  # 288 time-points

# Create the B-spline basis function

basisobj27 = create.bspline.basis(c(0,2400),nbasis=27)    # B-spline

fdParobj = fdPar(fdobj=basisobj27, Lfdobj=2, lambda=4)   # applying penalties

# The registration loop

for (i in 1:146) {

#read data

        glucosei <-  glucoseAllid[which(glucoseAllid$idseq==i),c(
        "days","sensorGlucose" , "glu_time" )]

# reshape

        wide_glucosei <- reshape(glucosei,timevar ="days" , idvar = "glu_time",
        direction = "wide")

        glucoseDailyi <- wide_glucosei[c(2:length(wide_glucosei))]

        glucoseDailymatrixi <- data.matrix(glucoseDailyi)
```

```
#smooth

        glucose.smoothi   <- smooth.basis(argvals=xx2, y=glucoseDailymatrixi,
        fdParobj)

        glucose.fdi <- glucose.smoothi$fd

# calculate the mean

        mean.fdi <- mean.fd(glucose.fdi)

        emptymatrix[,i]= eval.fd(xx2, mean.fdi)

# register first iteration

        reg.fdi <- register.fd( mean.fdi,glucose.fdi)

        registeredi <- fd(coef= reg.fdi$regfd$coefs, basisobj = reg.fdi$regfd$basis,
        fdnames = reg.fdi$regfd$fdnames)

# calculate first iteration's mean glucose curves and store them

        mean.regi <- mean.fd(registeredi)

        Registeredmatrix[,i]= eval.fd(xx2, mean.regi)

# register second iteration

        reg2.fdi <- register.fd( mean.regi,glucose.fdi)

        registered2i <- fd(coef= reg2.fdi$regfd$coefs, basisobj = reg2.fdi$regfd$basis,
        fdnames = reg2.fdi$regfd$fdnames)

# calculate second iteration's mean glucose curves and store them

        mean.reg2i <- mean.fd(registered2i)

        Registeredmatrix2[,i]= eval.fd(xx2, mean.reg2i)

}

# Register all the second iteration's mean glucose curves

registeredmatrix.fd <- smooth.basis(argvals=xx2, y=Registeredmatrix2, fdParobj)

reg.mean.curves <- register.fd(mean.fd(registeredmatrix.fd$fd),registeredmatrix.fd$fd )
```

2.7 Summary

Glucose values measured continuously using CGM systems have an underlying smooth process with a highly correlated adjacent discrete data point's measure over time. FDA deals with the complexity of CGM data by transforming its data-points to a mathematical function of time presented as a smooth curve over a time argument axis of a 24-hour duration. The transformation can be performed using a penalised B-spline basis function expansion, with 27 basis functions and knots placed hourly. Daily glucose curves' prominent features, i.e. peaks and nadirs, vary by amplitude and phase. Amplitude variation is an indicator of glucose concentration and glycaemic control, while phase variation is an indicator of glucose circadian rhythm and timing of meals and physical activities. Daily glucose curves are aligned so their prominent features occur at around the same time using a continuous registration method. Registration preserves the amplitude variation and removes the phase variation. This is indispensable to identify glycaemic control differences between individuals.

The shape and the dynamic behaviour (rate of change) of the daily glucose curves can be explored by calculating: the mean curve, the SD curve, the median curve, the IQR curves, the correlation structure, and the glucose velocity curves. Furthermore, functional regression models enable the study of the associations, together with the time-dependency of these associations, between different variables (sleep variables in this study) and the daily glucose curves and the daily glucose velocity curves, while adjusting for potential confounders.

Chapter 3 Methods

This chapter explains the methods employed in the current study including: study design and sample size calculation. Further, it includes a detailed description of the tools and devices used for measuring sleep and glycaemic control, with their mechanism of action, validity and practical consideration while applying them. Moreover, it explicitly presents the recruitment protocol and the statistical analysis methods applied to find the best answers for the study objectives.

3.1 Study design, setting and study participants

This was a cross sectional study that was part of larger longitudinal cohort project (Leeds and York GDM cohort) studying sleep, glucose variability and pregnancy outcomes in pregnant women with gestational diabetes.

Participants were pregnant women diagnosed with gestational diabetes (GDM) during their current pregnancy according to NICE guidelines. They were mainly recruited from the Diabetes in Pregnancy (DIP) clinics at Leeds Teaching Hospitals NHS Trust. The DIP clinic at York Teaching Hospitals NHS Trust joined and served as a second recruitment centre for a few months only. According to Leeds clinics' unpublished audit figures, they manage an average of 500 pregnant women with GDM every year.

3.1.1 Inclusion and exclusion criteria

All pregnant women aged 18-45 years attending the recruitment centres with a current diagnosis of gestational diabetes, at approximately 32 weeks of gestation were eligible to be included in the study. Exclusion criteria included those with multiple pregnancy, severe co-existent medical or psychiatric conditions and non-English speaking.

3.2 Sample size estimation

A total of 148 participants were needed to be recruited for this study to answer the objective 'evaluating the association between sleep duration and glucose control'. The sample size estimation was based on 80% power and a 0.05 significance level, to detect a clinically relevant difference in mean glucose level of up to 0.6 mmol/l, with a SD of 1.1, and accommodated for 20% missing data. This estimated sample size also provided 80% power to detect a 0.25 correlation coefficient away from the null. Details of the methods used for the sample size estimation are as follows:

3.2.1 Sample size estimation for two independent groups t-test

In order to estimate the sample size for a two independent sample means hypothesis test, the following assumptions were made: 1) the ratio of the exposure (short sleep duration) in a pregnant population. A ratio of exposed: non-exposed of 1:2 was specified as around a third of pregnant women are known to have short sleep duration (Signal et al., 2014; Facco et al., 2010b); 2) The CGM-derived mean and SD glucose level in pregnant women with gestational diabetes (with and without short sleep duration). At the time of estimating the sample size there were no published studies on sleep duration and CGM derived glucose levels in pregnant women with GDM. However, studies using CGM in GDM pregnancies had reported a mean (SD) glucose level of 5.4 mmol/l (1.1) (Dalfrà et al., 2011) , with a mean glucose of 5.5 moll/l (0.6) for participants on diet treatment only and 6.6 moll/l (0.7) for participants on diet and insulin treatment (Chen et al., 2003). Thus the reported maximum SD of 1.1 was used to estimate this study sample size. 3) The clinically worthwhile difference (effect size) in mean glucose level. A 0.5% difference in HbA1c was associated with a higher risk of complications in gestational diabetes (Evers et al., 2002). This is equivalent to an estimated average glucose difference of 0.8 mmol/l, using ADA published equation for estimating average glucose (eAG) from HbA1c values[*] ($eAG_{mg/dl}$ = 28.7 X HbA1c – 46.7 ; $eAG_{mmol/l}$ = $eAG_{mg/dl}$ /18) (Nathan et al., 2008). This estimation equation was generated from non-pregnant population. However, association between eAG and HbA1c during pregnancy has been shown to be different (Law et al., 2017). Thus to be conservative a smaller effect size value of 0.6 mmol/l was selected.

The Stata statistical package was used to estimate the sample size needed to detect a range of effect sizes in mean glucose level between pregnant women with GDM and either short or normal sleep duration, with assumed equal variance of (1.1 mmol/l) , with 80% and 90% power and 0.05 significant level (Table 3-1).

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[*] available from: http://professional.diabetes.org/diapro/glucose_calc

Table 3-1 Estimated required sample size for two independent groups t-test with 2:1 ratio of exposure, SD(1.1), a range of effect size, with 80% and 90% power and 0.05 significant level

Effect size (mmol/l)	Estimated sample size with 80% power	Estimated sample size with 90% power
0.1	4278	5724
0.2	1071	1434
0.3	477	639
0.4	270	360
0.5	174	231
0.6	123	162
0.7	90	120
0.8	69	93

3.2.2 Sample size estimation for multiple linear regression and for functional regression

VanVoorhis and Morgan (2007) presented in their article various sample size calculation's 'rules of thumb' for multiple linear regression analysis such as: 1- minimal size of 50 and add 8 more participants for each covariate, 2- minimal sample size of 104 plus number of covariates, and 3- a sample size of 10-30 participants for each covariate. Using these 'rules of thumb' for a regression model with 6 covariates, estimated required sample sizes were: 90= (50+8*6), 110= (104+6), and 60 to180= (6*10 to 6*30) participants, respectively. A more sophisticated method involving the use of coefficient of determination ($R^{2)}$ or correlation coefficient (r) were suggested by Algina and Olejnik (2003). Figure 3-1 shows a graph produced by Stata statistical package of the sample size estimation for 80% and 90% power with 0.05 significant level for a range of correlation coefficients. As there is no a *priori* information on the correlation between sleep duration (or other sleep parameters) and glycaemic indices, I chose to power the study to be able to detect 0.25 correlation coefficient away from the null. Further, no published sample size estimation methods for FDA hypothesis testing was found.
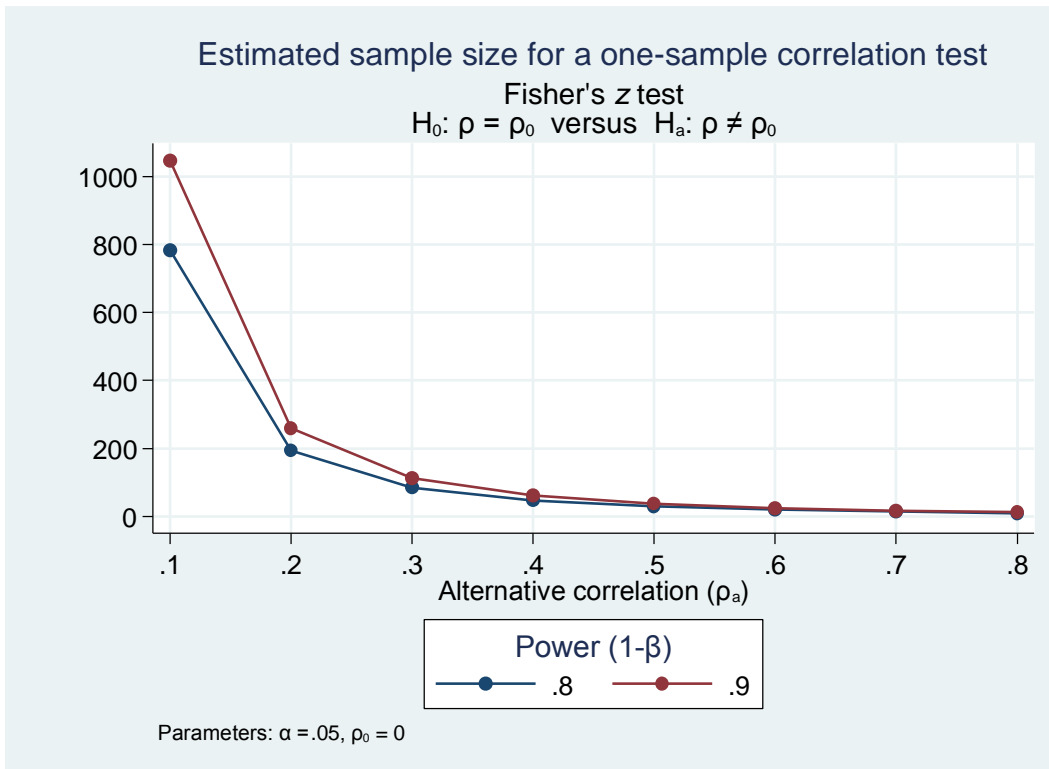
Figure 3-1 Graph showing estimated sample size for different correlation coefficient

3.3 Measuring sleep

Sleep was evaluated subjectively using The Pittsburgh Sleep Quality Index (PSQI) questionnaire and measured objectively using wrist actigraph. Details of these methods are presented in the following sections.

3.3.1 The Pittsburgh Sleep Quality Index (PSQI)

3.3.1.1 The PSQI instrument

The PSQI is a score derived from a self-administered questionnaire measuring sleep quality over the previous month (Buysse et al., 1989). The questionnaire consists of nineteen items that yield scores on seven components, and an extra five items not included in the scoring, to be filled only if a bed partner is present. The seven component scores are: 1) habitual sleep duration score (actual time spent asleep at night); 2) sleep latency score (frequency and duration in minutes between bedtime and sleep onset time); 3) subjective sleep quality score (a subjective feeling of sleep satisfaction); 4) habitual sleep efficiency score (proportion of duration slept at night to total duration of time-in-bed); 5) sleep disturbance score (causes and frequency of sleep disturbances);

6) daytime dysfunction score (trouble staying awake during the day and while engaging in social activity; and 7) use of sleep medication score. The other non-scored items are related to snoring and breathing-related sleep disorders. Each component is scored with a Likert scale from 0 to 3, a score of ''0'' indicates no difficulty, while a score of "3" indicates severe difficulty. All component scores are summed to yield a global/total score ranging from 0 to 21. Higher total scores indicate a poorer sleep quality, with participants scoring 5 or less considered to have a good sleep quality. A copy of PSQI questionnaire and PSQI administration instructions and scoring in Appendix A and Appendix B, respectively.

Whilst a subjective tool, the PSQI potentially offers a more holistic approach to assessing the complex architecture of sleep than objective measures like polysomnography and actigraphy. It addresses both the quantitative and the qualitative aspects of an individual's personal sleep experience while acknowledging the relative importance that different parts of these aspects vary between individuals.

3.3.1.2 PSQI reliability and validity

The PSQI instrument has been found to have good internal consistency (good correlation between its components) as measured by Cronbach's $\alpha \geq 0.70$ (Cronbach, 1951) and it has been found to have between a fair to good test-retest reliability (results are consistent over time) in multiple populations, including pregnant women in the first trimester (Carpenter and Andrykowski, 1998; Backhaus et al., 2002; Beck et al., 2004; Jomeen and Martin, 2007; Skouteris et al., 2009; Mollayeva et al., 2016; Qiu et al., 2016). Moreover, it is a highly valid instrument, a total PSQI score >5 has a sensitivity of 89-98.7 and specificity of 84.4-86.5 relative to clinical and polysomnography evaluation (Buysse et al., 1989; Backhaus et al., 2002). However, different populations may require higher cut-off scores (Mollayeva et al., 2016; Dietch et al., 2016). Although there have been no validation studies using a score of 5 as a cut-off score during pregnancy, it is still widely used in research (Okun et al., 2011).

3.3.1.3 PSQI extent of use

The PSQI is widely used in medical literature with 7227 medical documents citing the original article as of 22/05/2017 (Scopus). The original questionnaire is written in English and it has been translated into 56 additional languages. The questionnaire is available free of charge from Department of Psychiatry, University of Pittsburgh web page (http://www.psychiatry.pitt.edu/node/8240). The web page also provides a Microsoft Access database file for free download and automatically scoring and generating all components and total scores.

3.3.1.4 Practical procedure

The PSQI questionnaires were administered on paper-form to the participants at recruitment for them to complete. The data was uploaded from the retrieved questionnaire to the Microsoft Access database file and all the component scores and the PSQI total score were automatically generated. All participants' data were then exported from the database file and saved as a comma separated values (CSV) files.

PSQI-derived sleep variables (characteristics) that were exploited in further analyses in this research were: 1) the PSQI total score, 2) reported sleep duration, 3) sleep onset latency (SOL) duration, 4) sleep efficiency (SE), 5) subjective rating of sleep quality, and 6) mid-sleep time. Mid-sleep time was calculated as the mid time between reported bedtime and getting-up time.

3.3.2 Wrist actigraphs

Wrist actigraphs were first introduced to measure sleep and circadian rhythms in the seventies, evolved quickly and became widely used in clinical settings and in research (Morgenthaler et al., 2007a). They are light weight, comfortable to wear, non-invasive, wrist-worn watch/bracelet like devices that can be used to measure sleep for multiple nights in the individuals' residence and under usual living conditions. This is in contrast to polysomnography which is usually laboratory based and involves attaching many leads and wires to individuals doing the sleep study (Ancoli-Israel et al., 2003). Actigraphs are basically motion sensors that detect activity by means of a build-in accelerometers. They provide continuous data of mobility/immobility periods which are used as an objective estimator of wake/sleep periods as absence of movement is a sign of being asleep (Martin and Hakim, 2011).

3.3.2.1 Mechanism of actigraphs

Wrist actigraphs use either solid-state piezoelectric or micro electrochemical system (MEMS) accelerometers (Patrick et al., 1996; Andrejašic, 2008) to measure acceleration forces caused by movement, of various intensities and at several axis and directions. This is done by transferring mechanical energy from acceleration into electrical current. The amplitude and the frequency of the electrical current's waves is proportional to that of acceleration force. MEMS accelerometers factor in acceleration forces exhibited on the body by gravity while piezoelectric accelerometers do not.

The measurements occur almost continuously, around 10 times per second or more depending on the resolution of the device. Electrical current from very low acceleration (like those related to breathing or to vibrations transferred through the mattress from the movement of a bed partner) and from very high acceleration (beyond the physiological

abilities of human motion, like those related to being in a transportation vehicle) are filtered out. The bandpass filter width varies between different actigraphs brands and depends on the accelerometer technology used (Ancoli-Israel et al., 2003). Electrical current in 'Hz' unit is then converted to acceleration in 'g' unit. Gravity unit 'g' is equal to the rate of acceleration of a free falling body to Earth caused by gravity, and that is 9.80616 meter/second^2 at sea level at 45° latitude and mean sea level. Acceleration forces are digitalised into activity counts and averaged over a predefined epoch (time-slot) of 1,2,5,15,30,60 seconds or even 5 and 10 minutes and stored in the device memory. The methods used to transfer electrical current to acceleration, then into activity counts are not standardised between different accelerometers types and vendors (Tryon, 2011). This should be taken in consideration before trying to compare readings from different actigraphs.

3.3.2.2 Placement of actigraphs

Another factor that influences the activity count is the site of placement of the actigraphy device. Where all body parts move during walking or running this is not the case during sitting or lying down sleeping, reading a book or streaming the net with a smart phone. Placing the actigraph on the wrist rather than other sites like the trunk or the ankle is preferred to measure motion delineating wake/sleep phases (Ancoli-Israel et al., 2015). Wearing the actigraph on the wrist of the non-dominant hand is the most common practice and is reported in the majority of validation studies. However, Sadeh et al. (1994) reported similar validation results from actigraphs placed simultaneously on the wrists of both dominant and non-dominant hands.

3.3.2.3 From activity counts to sleep/wake

Epoch-by-epoch activities' count data stored in the actigraphs is uploaded to compatible computer software where it is processed using a sleep-scoring algorithm (Ancoli-Israel et al., 2003). Several automated scoring algorithms are available. One of the oldest algorithms, though still used, is the Cole et al. (1992) algorithm. It is basically a logistic regression prediction model. The algorithm coefficients were derived from a model using polysomnography sleep/wake scores as the outcome and activity counts of a specific epoch together with four adjacent epochs before and 2 epochs after it as the exposure. Whilst, the Sadeh et al. (1994) scoring algorithm is based on a probability-of-sleep (PS) formula derived from discriminant data analysis. A specific epoch is scored sleep (immobile) if PS ≥ zero, and wake (mobile) otherwise. Other algorithms were much simpler, each epoch is scored sleep/wake depending on a designated weighted activity count threshold; low threshold (20 counts per epoch), medium threshold (40 counts per epoch) and high threshold (80 counts per epoch).

Some actigraphy software has several built-in algorithms and allows researchers to select the most appropriate one for their research (Ancoli-Israel et al., 2015). Nevertheless, most of these algorithms were developed and validated using various actigraphy devices from different manufacturers and there is no consensus nor recommendation on which is the best algorithm (Sadeh and Acebo, 2002). New algorithms are also being continuously developed (Tilmanne et al., 2009; Nakazaki et al., 2014). They are still using modalities of multiple linear and logistic regression modelling with adjacent epochs as the exposure variables, however they are not considering the autocorrelation structure between adjacent epochs' activity counts and how the resulting multicollinearity can bias the multiple regression model coefficients (Gilthorpe, 2011a). Our research team is developing a new algorithm utilising the advance in statistical methods and a better understanding of autocorrelation of activity behaviour over time (on going-work). Methods of functional data analysis have been applied to raw actigraphy data, to model and characterise physical activity, but not yet to identify sleep and wake phases (Morris et al., 2006).

After scoring each epoch throughout the recording period as 'sleep' or 'wake' the software package algorithm marks the time-in-bed Interval for each night-day. The time-in-bed interval, also referred to as 'rest Interval', is defined as the time window between bedtime and getting-up from bed time. The major/main sleep interval is located within the major rest interval and the algorithm delineates it by marking; sleep onset time, sleep end time and any awakening intervals between sleep-onset and sleep-end. Most software packages' accuracy in automatically marking major rest Intervals is poor. Thus, major rest intervals need to be manually adjusted for each night-day of every actigraphy recording. Failing to do so results in distorted and untrue actigraphy derived sleep variables (Chow et al., 2016; Ancoli-Israel et al., 2015). Manual adjustment is done by the help of: 1) sleep diaries, 2) markers from event marker button, if integrated within the actigraphs and activated, 3) sharp changes in light level, if a light sensor is integrated within the actigraph, indicating light turned on/off at the time of waking-up/getting to sleep, as well as, 4) sharp changes in activity count from/to sedentary level that usually accompanies sleep/wake activity pattern.

3.3.2.4 Accuracy of Actigraphy

Actigraphs have been extensively validated against polysomnography. However, as stated before, different actigraphs have different technical specifications and use different algorithms. Nevertheless, many researchers have meticulously reviewed published articles on the accuracy and validation of actigraphs (Van de Water et al., 2011; Stone and Ancoli-Israel, 2011; Sadeh, 2011; Martin and Hakim, 2011; Acebo and LeBourgeois, 2006; Ancoli-Israel et al., 2003; Sadeh and Acebo, 2002). Epoch-by-epoch

comparison against polysomnography, showed that actigraphs have high sensitivity with ~85%-90% ability to correctly score an epoch as 'sleep', and poor specificity with only ~30%-60% ability to correctly score an epoch as 'wake'. Overall concordance accuracy (actigraph ability to correctly score an epoch as either 'sleep' or 'wake') was high (~80%) for healthy individuals with normal sleep but low in individuals with disturbed sleep especially in individuals with insomnia (difficulty initiating or maintaining sleep). Insomnia patients can lie in bed 'motionless' while awake. Actigraphs are just a motion sensors and cannot differentiate between motionless wake status versus sleep status.

Further, actigraphs tend to underestimate sleep onset latency (SOL) duration and wake after sleep onset (WASO) duration, and overestimate actual sleep duration and sleep efficiency (SE). However, adjunct use of a sleep diary log can significantly improve these estimates (Kushida et al., 2001).

3.3.2.5 Actigraphy practical procedure followed in this research

3.3.2.5.1 Actigraphy device used

Actiwatch 2 actigraphs from Philips© Respironics were used (Figure 3-2). They have tri-axis solid state piezoelectric accelerometers, with high resolution at a sampling rate of 32 Hz (~ 30 measurements per second), bandwidth filter of 0.35-7.5 Hz, with detected acceleration range of 0.5-2 g peak value and they can store results in up to a minimum of 15 seconds epochs. Further, they are lightweight (16 grams with band), have a sleek design and small size (measurement of 43mm x 23mm x 10 mm) with a lithium rechargeable battery, making them more comfortable to wear and least disturbing. They are waterproof at a depth of one metre for 30 minutes, so participants do not have to take them off during water related activity. They incorporate a one Mbit non-volatile memory that can store activity and light data up to 7.5 days for 15 seconds epochs and up to 30 days for 1-minute epochs. Integrated within the Actiwatch 2 actigraphs are photopic illuminance light sensors and event marker buttons, but not a heat sensor to detect off wrist status (Philips). Data records from the actigraphs were downloaded to Actiware® computer software (version 6.02), via a docking station and a USB cable, where they were stored and scored.

3.3.2.5.2 Configuring the Actiwatches

Actiwatch 2 actigraphs need to be configured before handing them in to participants for recording. Configuration involves connecting the Actiwatch to Actiware software where: previous data is retrieved and Actiwatch memory is cleaned. This is followed by programming the Actiwatch to record a new participant's activity with: an anonymous unique identification number and non-traceable information, a pre-set epoch length (15 seconds epoch length was chosen to get the highest resolution possible), and a pre-

programmed recording start date and time. This is done in advance to recruitment and the Actiwatch is placed in 'rest mode' until the pre-programmed date/time. The only method to check if the Actiwatches are configured is to connect them to Actiware and check their configuration status. Thus each Actiwatch was labelled with their configuration status using a small sticky note wrapped around its band. Further, the device serial number was also documented in a data collection sheet together with the participant's identification number and date of recording to avoid mixing-up records.

Figure 3-2 Actiwatch 2 actigraph (Source: http://www.actigraphy.respironics.com)

3.3.2.5.3 Cleaning the Actiwatches

In between use, Actiwatches were washed and meticulously cleaned according to the manufacturer's instructions using a wet cloth and a non-alcoholic detergent or if heavily soiled under running water then dried with a soft tissue and left to completely air-dry.

3.3.2.5.4 Placement of the Actiwatches and duration of recording

They were attached securely by a member of research team to the participants' non-dominant wrist. They were not fitted to be so tight as to be uncomfortable to wear, nor so loosely as to move freely around the wrist. Activity was recorded for seven days from the date of recruitment, coinciding with CGM recording.

3.3.2.5.5 Safety consideration and adverse events

Actiwatches are non-invasive and considered to be low risk medical devices. Furthermore, they are unlikely to cause any allergic reaction at the site of skin contact as Actiwatches' cases and bands are made of a high grade polymers and the buckles are made of titanium. However, participants were instructed to contact the research team if

they experienced any adverse reaction and to immediately remove the Actiwatch if the reaction was intense.

3.3.2.5.6 Participants instructions

Participants were instructed to keep wearing the actigraph for the whole duration of data collection without removing it. In case they developed any adverse events (as stated previously) or if they decided to stop participating in the study then they were asked to remove it, keep it in a safe place and hand it in on their next appointment. However if they just wanted to take it off temporarily they were asked to record the time period it was not worn in the sleep diary log sheet (Appendix C). They also needed to record in their sleep logs: bed-time (the time they tuck-in and settled in bed ready to sleep), sleep-onset time (the time they thought they fell asleep), sleep-end time (the time they woke-up from sleep) and the get-up from bed time (the time they finally got-up from their bed).

At the start of the study, a few participants were also instructed to press the event marker button at the side of Actiwatch to mark their bed-time and get-up time. This instruction was not emphasised later on as participants found it confusing especially as there was no indication, like a clicking- sound or light-flash, if it did work or not. Participants kept repeatedly pressing it on some occasions and totally forgetting about it on others.

3.3.2.5.7 Actigraphy data records; retrieving, editing and cleaning

Activity data records from the Actiwatches were retrieved using the Actiware software. For each record, the Actiware: 1) automatically scores the activity epochs using a specific algorithm, 2) generates rest and sleep Intervals, 3) instantly calculates various sleep variables, and 4) produces an actogram (visual display of daily plotted activity data) (Figure 3-3). The actogram illustrates, in addition to activity data, light data from the light sensor, markers from events marker button in case it was pressed and the rest and the sleep intervals.

To improve the accuracy of the actigraphy-derived sleep variables (as previously explained in section 3.3.2.4), the demarcation of the major rest intervals, i.e. bed times and getting-up from bed times, were manually edited. Using the intervals manipulation facility in the Actiware and with the help of the actogram (Figure 3-4), major rest intervals were edited in according to the methods mentioned in section 3.3.2.3 except for event marker method. The editing was made by the consensus of two researchers; Alia Alnaji (AA) and Eleanor Scott (ES) for the first 20 participants and by AA only for the remaining.

Moreover, each record's actogram was manually inspected and 'cleaned' to exclude partial night's sleep intervals (caused by interrupted activity recoding due to participant taking-off the Actiwatch in the mid of sleep interval or due to device-related issues), as

well as, excluding periods of activity recorded before the participant started wearing the device, after finally taking it off, and during temporary off-wrist periods. Furthermore, records with noisy readings, manifest as continuous nights-days vibration-like activity (apparent during rest intervals and off-wrist intervals) are mostly a result from faulty devices and thus were also excluded (Figure 3-5). After all editing, Actiware re-calculated sleep variables for each night-day of the record and produced an aggregate of all nights-days. These results together with the actogram were printed out in a clinician's report and given to the participants (an example of the clinician's report is available in the Appendix D).
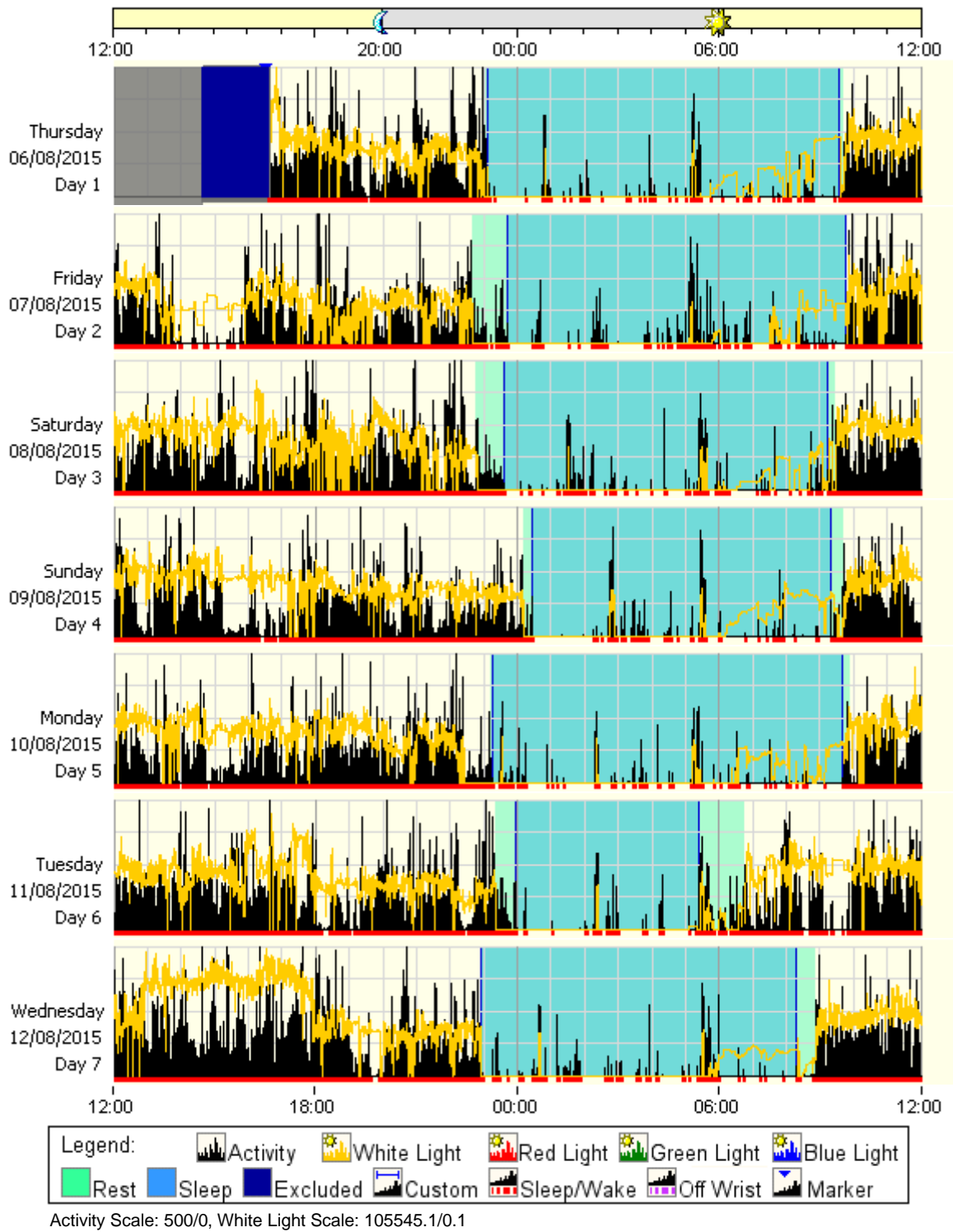
Figure 3-3 An actogram
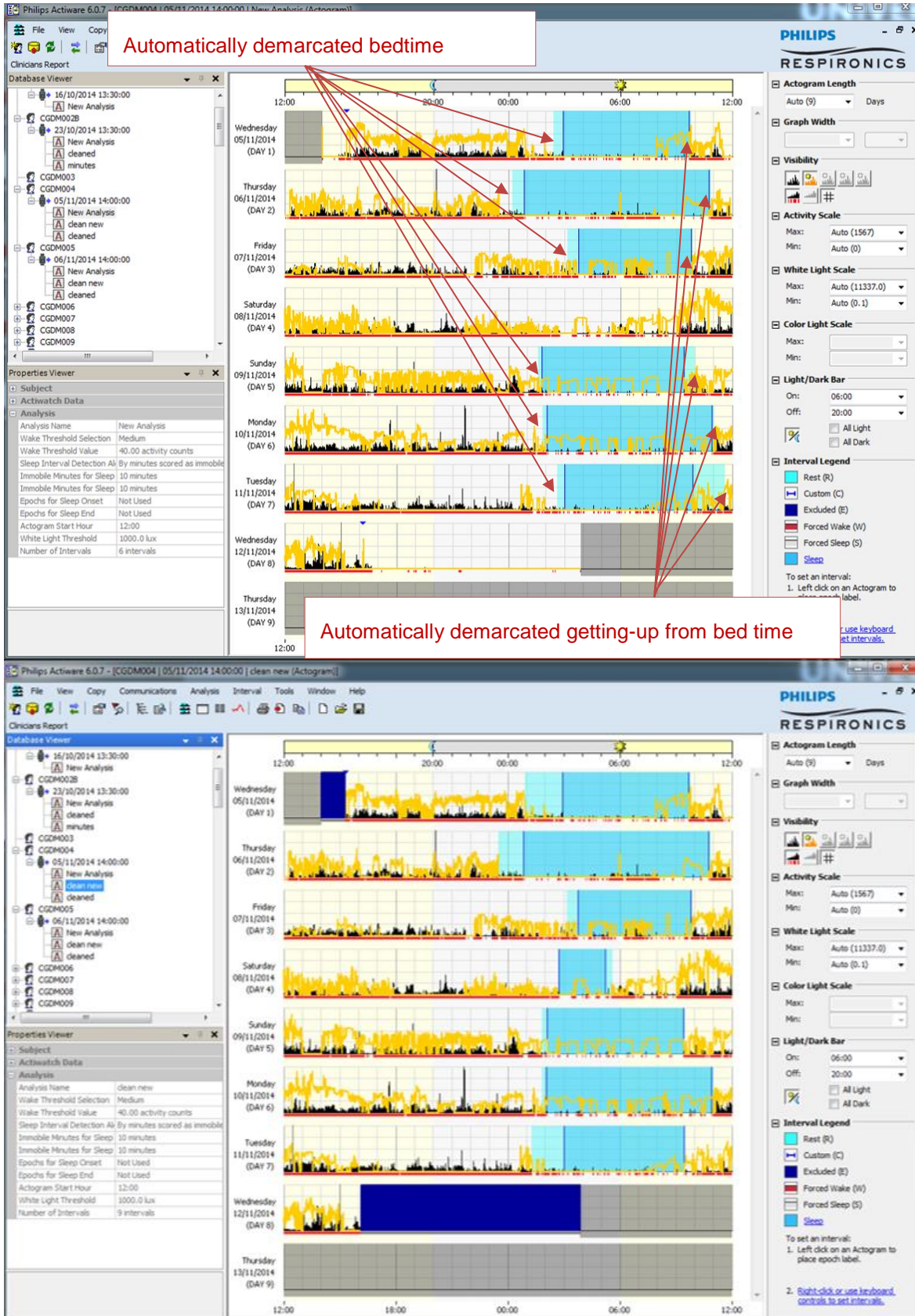
Figure 3-4 Actiware software interface showing a participant's actogram before editing (upper panel) and after editing (lower panel)
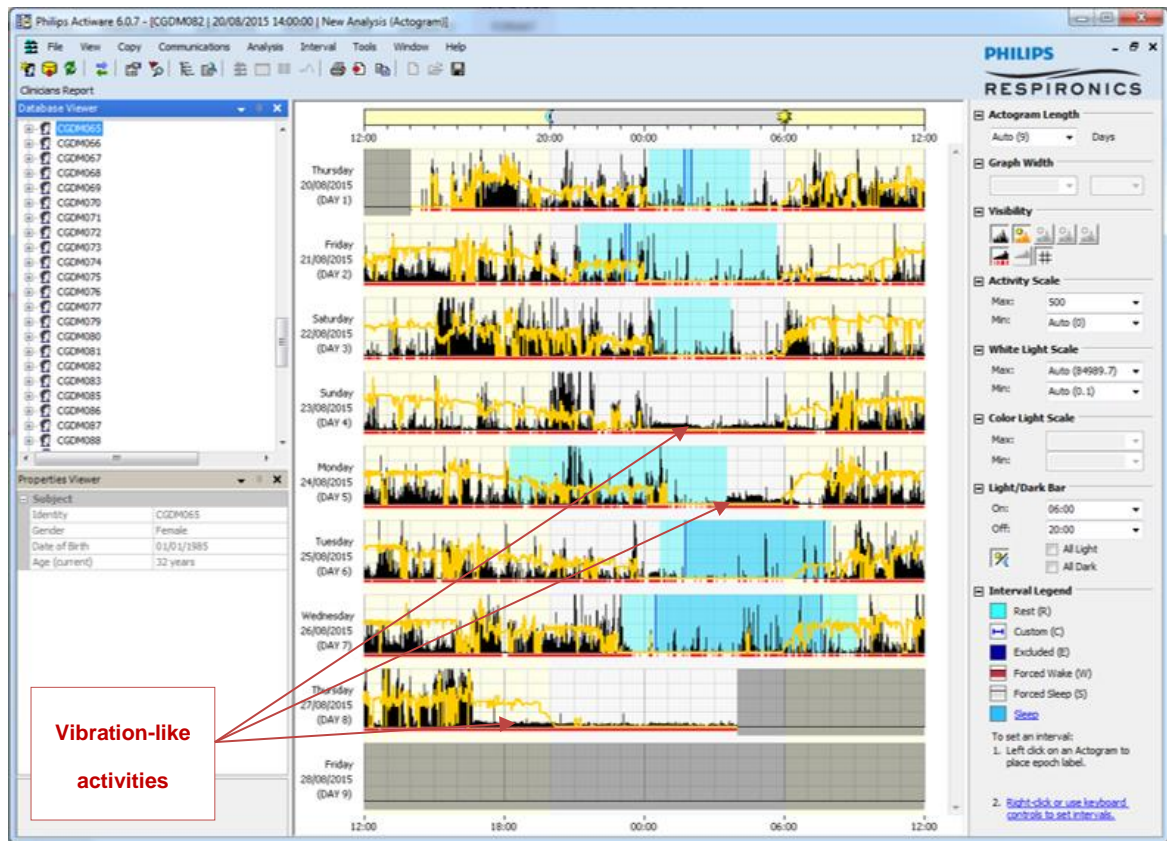
Figure 3-5 Actiware software interface showing a participant's actogram with a vibration-like activities

3.3.2.5.8 Actiware algorithms and settings

Epochs scoring method

Actiware scores all epochs in each recoding as either 'sleep' or 'wake' based on their weighted activity counts. The weighted activity count in a 15-second epoch is calculated based on activity counts of the epoch in question and those immediately surrounding it, as follows: weighted activity count = epoch activity count + 0.2 (sum of activity counts of adjacent epochs, 4 epochs each side) + 0.04 (sum of activity counts of next adjacent epochs, 4 epochs each side). If the weighted activity exceeds the pre-defined threshold the epoch is scored as 'wake', otherwise it is scored as 'sleep'.

Sleep interval detection methods

After the rest interval is demarcated, sleep interval is automatically defined using either the immobile minutes method or the sleep epochs method, as follows:

1- Using the immobile minutes method:

Detecting sleep onset: Beginning with the first epoch of the rest interval, the algorithm identifies the first group of epochs of a selected duration for which all epochs but one are

scored as immobile (i.e. having zero activity count). Sleep onset is then set to the first epoch of the period satisfying these requirements.

Detecting sleep end: Beginning with the last epoch of the rest interval, the algorithm identifies the last group of epochs of a selected length for which all epochs but one are scored as immobile. Sleep end is then set to the last epoch of the period satisfying these requirements.

2- Using sleep epochs method:

Detecting sleep onset: Beginning with the first epoch of a rest interval, the algorithm identifies the first group of epochs scored as sleep that is at least of a pre-specified number of epochs in length. Sleep onset is then set to the first epoch of the period satisfying these requirements.

Detecting sleep end: Beginning with the last epoch of a rest interval, the algorithm identifies the last group of epochs scored as sleep that is at least of a pre-specified number of epochs in length. Sleep end is then set to the last epoch of the period satisfying these requirements.

Planned Actiware algorithm setting

Medium activity threshold (40 counts per epoch) was chosen to score epochs as 'sleep' or 'wake'. This threshold setting have been found to balance between sensitivity and specificity (Meltzer et al., 2012; Paquet et al., 2007) and to estimate sleep variables, when used in adjunct with sleep diary log, that do not significantly differ from those obtained using polysomnography (Kushida et al., 2001). In addition, 10 minute immobility method was chosen for detecting sleep onset and sleep end, as it is recommended by the manufacturer. Moreover, these settings was commonly used in research during pregnancy (Coo Calcagni et al., 2012; Bei et al., 2012; Tsai et al., 2013; Herring et al., 2014; Twedt et al., 2015; Tsai et al., 2016b; Reid et al., 2017; Facco et al., 2017) and thus using it helps to compare this study results to others.

3.3.2.5.9 Actigraphy-derived sleep variables

Actiware produces many actigraphy-derived sleep variable summaries (See appendix E for the whole list). The following (daily and overall averaged aggregates) were used: **1) sleep duration**; this is actual time spent asleep, during rest interval, between falling asleep (sleep onset) and final awakening (sleep end). **2) Sleep onset latency (SOL) duration**; this is the length of time from bedtime to sleep onset, SOL is an indicator of initial sleep insomnia (i.e. difficulty in falling asleep at the beginning of night). **3) Wake after sleep onset (WASO)**; this is the duration of time spent awake after falling asleep, measured in minute, WASO is an indicator of maintaining sleep insomnia (i.e. difficulty in

maintaining sleep). **4) Sleep efficiency (SE)**; this is the proportion of sleep duration out of time-in-bed duration, SE is an indicator of sleep quality and disturbance. As well as, **5) Mid-sleep time**; this is the midpoint between bedtime and getting-up time was calculated, Mid-sleep is an indicator of chronotype.

3.4 Measuring glucose control

Participants' glucose control was assessed using a CGM system for 6 days. In contrary to SMBG meters, CGM systems offer close monitoring of glucose concentrations and allow exploration of the glucose pattern and rate of change during the day and overnight.

3.4.1 Mechanism of CGM systems

CGM systems are minimally invasive amperometric biosensors. Glucose concentrations are measured through electrochemical detection. A glucose oxidase enzyme-coated electrode sensor placed subcutaneously reacts with glucose titration in the interstitial fluid of subcutaneous tissue and produces electrical signals proportional to the glucose titration (Ocvirk et al., 2017). CGM systems measure an interstitial glucose concentration between 2.2 and 22.2 mmol/l (40 and 400 mg/dl) (Kiechle, 2001). Measurements are almost continuous and an average value of these electrical signals are received and stored in a recorder connected to the sensor. However, sensors measure interstitial glucose concentrations which are different from blood glucose concentrations, thus the CGM systems use built-in algorithms to estimate blood glucose concentrations from the interstitial glucose concentrations, in a process called calibration (Rossetti et al., 2010). Capillary blood glucose levels estimated by SMBG glucometer are usually used for calibration. The number of calibrating SMBG readings needed for calibration depends on the type and the specification of the CGM system. Most available CGM systems need 1-3 *in-vivo* SMBG readings for calibration except for a new generation FreeStyle Libre Abbott CGM system which is *in-vitro* factory pre-calibrated (Abbott).

CGM systems can be either: 1) real-time CGM systems where calibration is performed in real-time and glucose concentration results are displayed on a monitor directly available for the patients/participants and/or practitioners/researchers; or 2) professional/masked CGM systems where calibration is performed retrospectively after removing the sensor and uploading the recorder information to a computer software interface. As calibration occurs retrospectively in the masked CGM systems, the results are masked from both the patients and the practitioners till then. Nevertheless, the retrospective calibration enables the CGM system's algorithm to utilise the SMBG values that both precede and follow in time a certain sensor interstitial glucose value. This optimises the algorithm's function and allows masked CGM to be more accurate than real-time CGM, which can

only use the preceding SMBG calibration values. More details about accuracy of CGM systems in the next section.

3.4.2 Accuracy of CGM systems

The accuracy of a CGM system depends on the sensor used, the precision of SMBG glucometer measurements used for calibration and the algorithm incorporated to predict blood glucose concentrations from the sensor's interstitial glucose readings. Furthermore, medications like paracetamol and vitamin C supplements, as well as tissue oedema may affect CGM system accuracy (Signal et al., 2013; Kiechle, 2001). Multiple methods have been used to evaluate the accuracy of CGM systems (Bailey et al., 2016). The following three methods are commonly reported.

3.4.2.1 Mean absolute relative difference (MARD)

CGM accuracy is usually measured using MARD. This is the mean of all the absolute relative difference (ARD) between calibrated CGM values and reference glucose values, estimated at the same time points (Equation 3-1 and Equation 3-2). The reference glucose values are usually plasma glucose concentrations or capillary glucose concentrations (other than those used in calibration) (Kirchsteiger et al., 2015). The MARD is an error metric and a lower value is favoured. A CGM glucose value of 7.2 mmol/l and a reference glucose value of 6 mmol/l represents an absolute relative difference (ARD) of 20% (Equation 3-1). As the equation uses the absolute value of the difference (i.e. the difference is never negative) ARD cannot represent the direction of the bias. Thus a sensor value of 4.8 mmol/l and a reference reading of 6 mmol/l represents an ARD of 20% as well. Moreover, it is a relative value, i.e. the difference is weighted to the reference glucose concentration, therefore it is biased to the smaller hypoglycaemic values. For example, a difference of 0.5 mmol/l from a reference glucose of low value such as 3.5 mmol/l will yield an ARD of 14.3%, whereas a 0.5 mmol/l difference from a reference glucose of high value such as 10.5 mmol/l will yield an ARD of 4.8%. This has a clinical use as the amount of error around hypoglycaemia is usually more critical. The median absolute relative difference (MedARD) is also commonly used.

$$ARD\left(t_k\right) = \frac{\left|\,CGM\left(t_k\right) - reference\left(t_k\right)\,\right|}{reference\left(t_k\right)} * 100$$

Equation 3-1

$$MARD = \frac{1}{N}\sum_{k=1}^{N} ARD\left(t_k\right)$$

Equation 3-2

Whereas (t_k) is time point t for glucose reading event k , k = 1, 2, 3,....N

3.4.2.2 Bland-Altman difference plot

Accuracy can also be evaluated using a Bland-Altman difference plot. The mean of all the CGM and the reference glucose values estimated at the same time points are plotted against their differences (Figure 3-6). A mean of all the differences away from zero suggests a systematic bias (error). The closer the difference to the zero and the less dispersion of the data points the better the agreement between the CGM and the reference glucose values. Upper and lower limits of agreement are calculated then by adding and subtracting 1.96 SD of the differences between the sensor and the reference glucose values and represent dispersion of variations around the mean. If there is a Gaussian distribution, 95% of data points are located between these limits. Moreover, the Bland-Altman plot can also scrutinise for proportional bias, i.e. if the disagreement (error) increases or decreases with higher values of glucose.
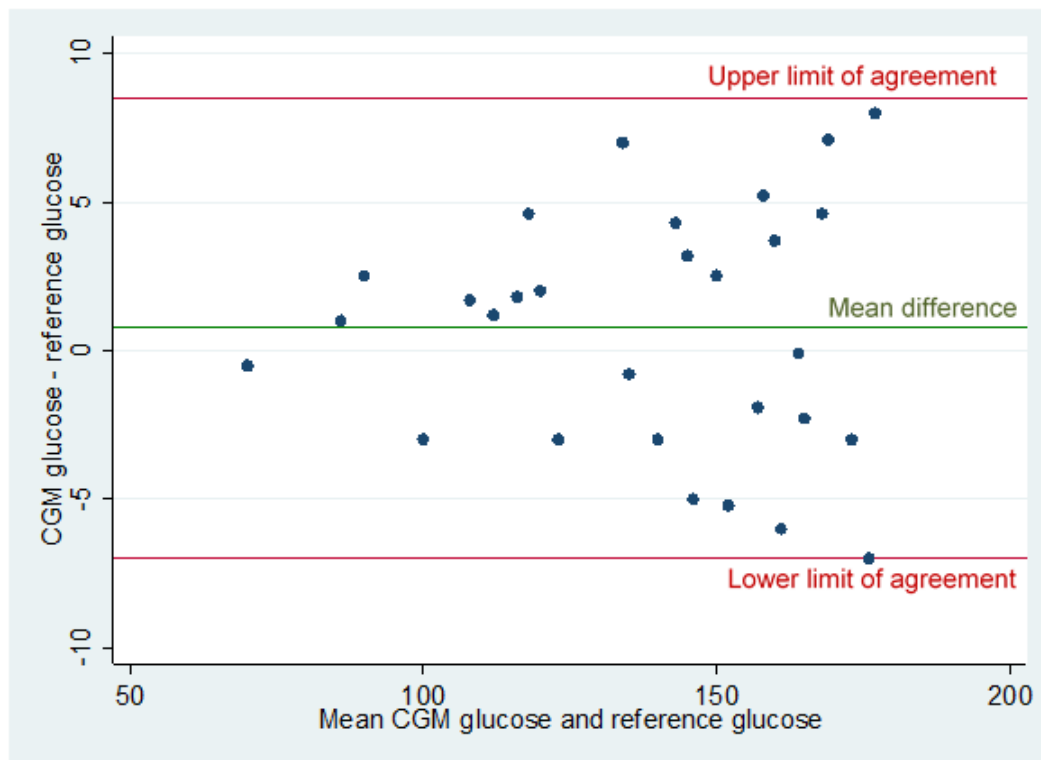
Figure 3-6 Bland-Altman plot of simulated CGM and reference glucose values

3.4.2.3 Error grid analysis (EGA)

Error grid analysis (EGA) for assessing the clinical accuracy of CGM was developed to assess the effect of CGM results on treatment decisions. It was adapted from the original Clarke Error Grid Analysis which was used to evaluate clinical safety and accuracy of SMBG from glucometers (Clarke, 2005; Clarke et al., 1987). It compares self-measured glucose values, e.g. on CGM, to laboratory measured glucose values. The grid is divided into zones A to E with severity of error increasing as the data points lie away from zone A (Figure 3-7). Parkes modified Clarke's zones slightly and constructed different error grids for T1DM and T2DM patients (Parkes et al., 2000). A surveillence error grid was recently added to the list with colour-coded risk level zones (Figure 3-8) (Klonoff et al., 2014; Kovatchev et al., 2014b).
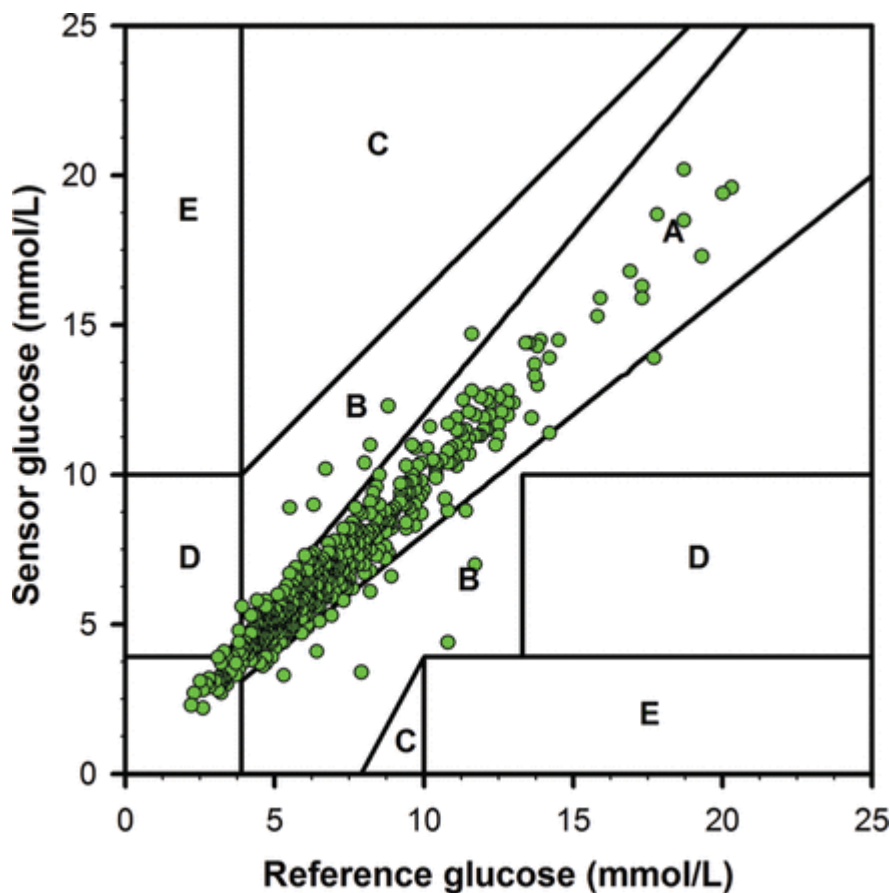
Figure 3-7 Original Clarke Error Grid Analysis (Beardsall et al., 2013), reused with permission.
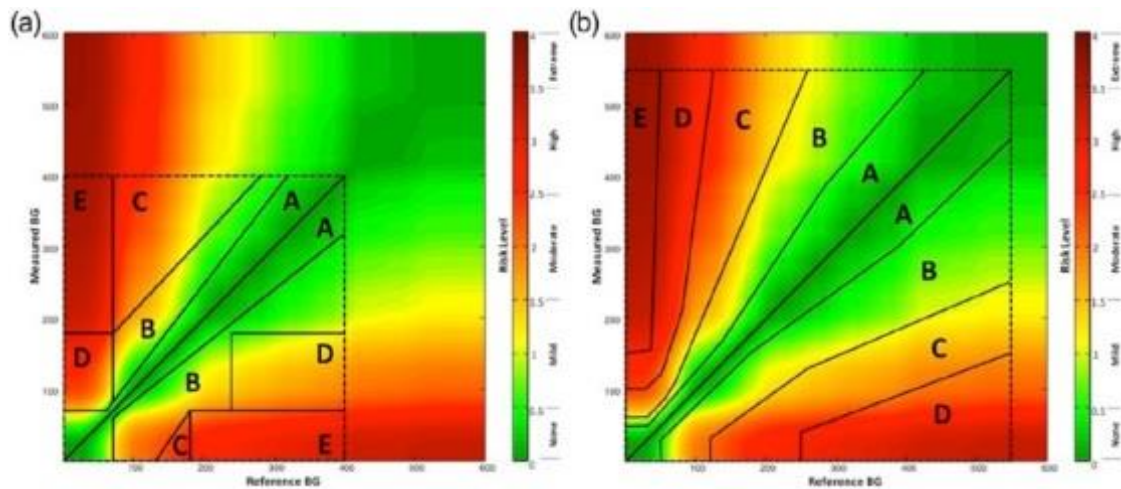
Figure 3-8 Surveillance error grid with superimposed (a) Clarke's error grid and (b) Parkes's error grid(Klonoff et al., 2014) ; reused under the Creative Commons Attribution License.

3.4.2.4 Evaluation of CGM systems accuracy

The American Association of Clinical Endocrinologists Consensus Panel on Continuous Glucose Monitoring stated in 2010 that most available CGM systems have a MARD of 10% to 20% and only 60% to 80% of glucose readings fall into zone A of the Clarke error grid (Blevins et al., 2010). In addition there is usually a time lag of 5-10 minutes between SMBG and sensor glucose especially during a period of rapid glucose rate change. In contrary to SMBG glucometers, there is no established consensus or criteria on what is the minimum acceptable limit for CGM system inaccuracy. Furthermore, they are only approved for supplementary use with SMBG (Bailey et al., 2016). In a simulation study an estimate of at least 10% MARD was needed for non-adjunct (standalone) use of CGM for safe insulin dosing and avoiding hypoglycaemic episodes (Kovatchev et al., 2014a).

In the last 16 years there has been a huge development and improvement of CGM sensors and algorithms (Facchinetti, 2016). In a study published in 2008; three commonly available CGM systems were tested simultaneously on 14 adults with T1DM. These were; Guardian (Medtronic), FreeStyle Navigator (Abbott) and Dexcom STS (a first-generation device). They were all real-time CGM systems and their results were compared to venous blood glucose. Respectively, they had a MARD of 15.2%, 15.3% and 21% during euglycaemia and a MARD of 16.2%,10.3% and 21.5% during hypoglycaemia (Kovatchev et al., 2008). In the same study Clarke error grid analysis showed that 98.9%,98.6%, 98.3% of data points were in zones A+B during euglycaemia, respectively, while during hypoglycaemia 84% and 97% of the points were in zones A+B for Guardian and Navigator, whilst no sufficient data for Dexcom. In a more recent study (Damiano et al., 2013) the previous 3 CGM systems were tested again for accuracy. Six

adults with T1DM and no endogenous insulin secretion participated and the sensors were tested simultaneously. The 48-h MARD for the Guardian, the Navigator and the Dexcom Seven Plus were 20.2 ± 6.8%, 11.8 ± 3.8%, 16.5 ± 6.7%, respectively. Clarke error grid analyses results were as follows: the Guardian achieved 63.7% of points in zone A, 33.2% in zone B, 0.3% in zone C, and 2.1% in zone D; the Navigator achieved 80.6% of points in zone A, 18.3% in zone B, 0% in zone C, and 1.0% in zone D; and the Dexcom achieved 76.2% of points in zone A, 22.7% in zone B, 0.9% in zone C, and 0.1% in zone D.

3.4.3 CGM system used in this study

Medtronic professional iPro2 CGM system was used in this study. IPro2 system is approved by the FDA (United State Food and Drug Administration) (FDA, 2016). It consists of a disposable sensor, the Enlite© sensor, and a reusable attachable recorder device. IPro2 is a "masked" CGM system where neither the participants nor the researcher team can see the CGM results until it is downloaded into a computer software interface. A masked CGM was preferred in the current study to avoid any potential change in behaviour produced by real-time awareness of glucose concentration (Feig et al., 2017).

3.4.4 Accuracy of Medtronic CGM systems

The Medtronic MiniMed (2006) published accuracy performance results for its Guardian RT system were a MARD of 19.7 ±18.4% , 62% of the readings were within 20% of reference plasma blood glucose and 61.7% of points in zone A, 34.4% in zone B, 0.2% in zone C, 3.5 % in zone D and 0.2% in E zone in Clarke error grid analyses. However these results were for Guardian CGM with the Sof-Sensor® which was in use before the Enlite® sensor. Using the new Enlite sensor and an improved algorithm (Paradigm® Veo™) a Medtronic sponsored clinical study published a much improved accuracy with a MARD of 13.6%, a bias of 2.1 mg/dl, and 72.7% and 83.7% of the readings were within 15% and 20% of the reference venous blood glucose (Bailey et al., 2014; Keenan et al., 2012). Lower accuracy performance for Enlite sensors than those published by the manufacturer were reported by Freckmann et al. (2013) and Matuleviciene et al. (2014) with a MARD of 16.4% and 17.9%, respectively. However, Freckmann et al. did not use the Paradigm algorithm and they used cappilary blood glucose values as a reference. Whereas Matuleviciene et al. used a self-monitoring glucometer device and not a standard laboratory test to measure venous blood glucose level. This could have affected the validity of the reference glucose as the most accurate SMBG devices have a MARD of 5% (Freckmann et al., 2015a; Freckmann et al., 2015b). Calhoun et al. (2013) reviewed the accuracy of the Medtronic's Enlite sensors using MiniMed Paradigm® Veo

calibration algorithm and the Sof-Sensors using Guardian® REAL-Time CGM calibration algorithm. The review evaluated nocturnal CGM data (10 PM- 6 AM) from 8 different studies. These studies used different blood glucose references varying from laboratory standard venous blood to capillary blood by glucometers, involved participants in paediatrics and/or adult age ranges, and some of these studies were not published. The review found that Enlite sensors tend to underestimate blood glucose over the entire reference glucose range (-15 mg/dl median bias), while Sof-sensors overestimate in the lower range and underestimate in the upper range of the reference glucose (-1 mg/dl median bias), with more variability (represented by wider interquartile range (IQR)) in the bias proportional to higher glucose level for both sensors (Figure 3-9). Enlite and Sof-sensor had MedARD of 15% and 12%, respectively. 66% of Enlite and 73% of Sof-sensor glucose values were within 15 mg/dl difference from the reference glucose values for reference glucose values ≤75 mg/dl, and within 20% difference from the reference glucose values for reference glucose values >75 mg/dl. Furthermore, Taleb et al. (2016) using Enlite sensors with the new algorithm and laboratory standard plasma glucose level as a reference, have reported a similar accuracy performance as Medtronic's published results with a mean bias of -0.18 mmol/l and a MARD of 12.38% during rest. However, they reported a mean bias of -0.15 mmol/l and a higher MARD of 19.90% during exercise.
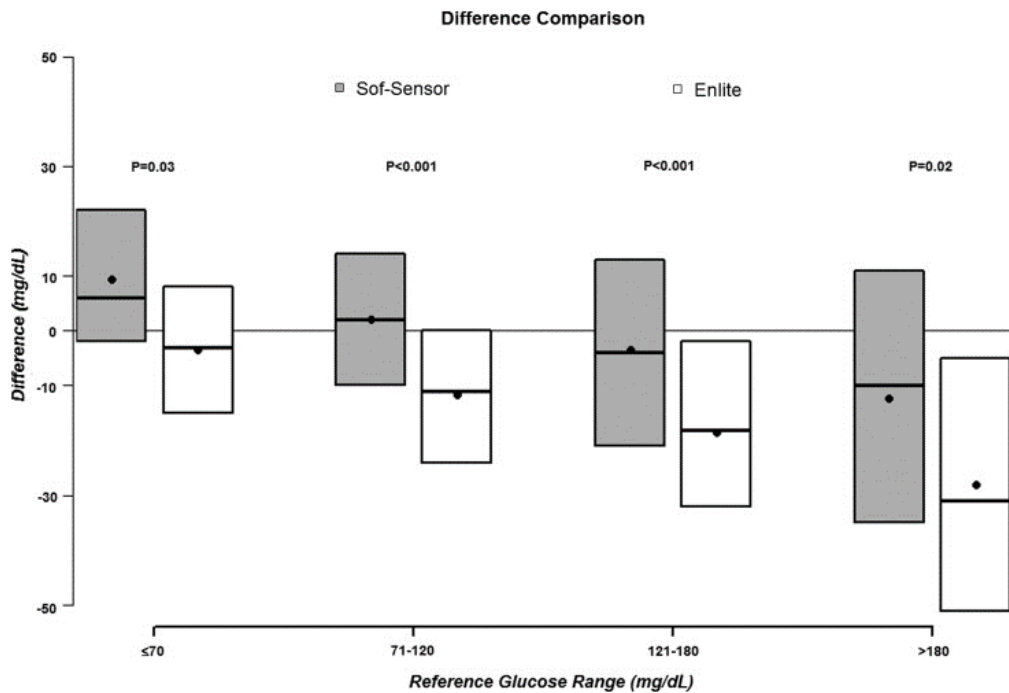
Figure 3-9 Box plot of Sof-Sensor and Enlite sensor bias over ranges of reference glucose level (Calhoun et al., 2013) Black dots denote the mean bias, and boxes denote the median (IQR). Reused with permission.

3.4.5 Accuracy of Medtronic professional iPro CGM system

A high accuracy performance was published by Medtronic's website and Medtronic's sponsored clinical studies for professional iPro2 CGM with Sof-sensors and capillary blood readings as the reference (Medtronic Diabetes, 2012; Welsh et al., 2012). They reported a MARD of 9.9% in adults and 10.1% in children, and 99.0% of adult and 98.4% of paediatric values were within zones A and B of the Clarke error grid. However, the IPro2 user guide manual published slightly different results (Medtronic MiniMed, 2016b). It presented the result of a study in which Enlite sensors were inserted to the abdomen and the buttocks of 64 adult participants with T1DM. IPro2 retrospective algorithm was used to calibrate the sensors' values incorporating a minimum of 4 SMBG values. To assess the accuracy of the IPro2 results, the CGM derived glucose values were compared to, apparently, the same SMBG values that were used for calibration. 11.6% and 10.4% MARDs were reported for abdominal insertion site and buttock insertion site, retrospectively. With an overall 97.7% of the readings were in Clarke Error grid zones A and B, and 87.1% of the CGM readings were within 20% of the reference readings. Another accuracy result from a clinical study performed by Medtronic was published online on the ClinicalTrials.gov website under ClinicalTrials.gov Identifier NCT01112696, last verified in July 2012. Accuracy was defined as proportion of sensor derived glucose within 20% agreement with paired laboratory standard venous blood glucose (YSI) and

within 20 mg/dl if YSI <80 mg/dl, with higher proportion suggests better accuracy. In this study 98 T1DM and T2DM patients participated and completed 6 days of CGM recording giving a total of 5857 paired sensor and YSI readings. 79.45 % of the CGM readings met the accuracy criteria. However it was not specified at the clinical trials website which algorithm was used to calibrate the CGM readings.

To gain a better insight on accuracy of professional iPro2 CGM with Enlite sensor, I performed a systematic review of studies looking at the accuracy of iPro2 including only those performed by independent researchers (not employed by or under influence of Medtronic).

3.4.6 Systematic review of studies on accuracy of iPro2

3.4.6.1 Search strategy

Embase and Ovid MEDLINE(R) databases; (year 2000 to date; search last updated on 24/4/2017) were explored using explicit search terms. Full details presented in Table 3-2. The search returned 29 journal articles after excluding reviews and conference abstracts.

Table 3-2 Search terms

#	Search terms	results
1	CGM	4008
2	CGMS	1716
3	continuous glucose monitor*	7511
4	1 or 2 or 3	8673
5	Medtronic	28732
6	4 and 5	1134
7	ipro2	125
8	Ipro	188
9	professional	422853
10	retrospective	1379156
11	7 or 8 or 9 or 10	1792636
12	6 and 11	257
13	accur*	1305189
14	valid*	1178583
15	performance	1538002
16	MARD	419
17	ARD	2078
18	13 or 14 or 15 or 16 or 17	3509970
19	12 and 18	80
20	remove duplicates from 19	60
21	Limit 20 to journal articles (exclude reviews and conference abstract)	29

3.4.6.2 Search results

All the articles were fully scrutinised and only 6 were included (Thomas et al., 2017; Munekage et al., 2016; Schaupp et al., 2015; Akintola et al., 2015; Signal et al., 2013; Dungan et al., 2013). Other articles were excluded for multiple reasons: not presenting accuracy results for iPro2 (Fokkert et al., 2017; Thomas et al., 2016), using subcutaneous Medtronic Sentrino® CGM system which is designed to display real-time glucose levels ICU patients (Wollersheim et al., 2016; Punke et al., 2015), did not evaluate device accuracy (Crenier, 2014; Chen et al., 2015; Del Rio et al., 2014), review and not primary article (Zisser et al., 2015), used Dexcom CGM system (Argento et al., 2014), special case of one 5 years old child with acute lymphoblastic leukaemia with 9.4% MARD reported between CGM values and SMBG calibration values (Visavachaipan et al., 2013), investigating real-time prediction model of serum glucose concentration (Pappada et al., 2013), examining accuracy of the Combo-Set sensor prototype (insulin pump and sof-sensor combination) using real-time algorithm (O'Neal et al., 2013), used a prototype of iPro CGM to test accuracy of CGM during Hypo- and Hyperbaric Conditions and sponsored by Medtronic (Adolfsson et al., 2012), sensors were attached to vinous blood circuit (tubes) of an extracorporeal (outside the body) life support system and not inserted to subcutaneous tissue (Steil et al., 2011), testing Paradigm Veo algorithm (Keenan et al., 2010), used a microdialysis type of CGM systems (Nielsen et al., 2009), or used Medtronic real-time CGM (Mastrototaro et al., 2008; Maia and Araujo, 2006; Maia and Araujo, 2005c; Maia and Araújo, 2007; Maia and Araujo, 2005b; Araujo and Maia, 2005; Maia and Araujo, 2005a).

3.4.6.3 Review results

Only two articles studied participants with T2DM while the four others studied either healthy participants or severely ill hospitalised participants with no diabetes. None studied pregnant women with diabetes. Although not funded by or working for Medtronic, some of the authors disclosed some connection to Medtronic.

Munekage et al. (2016) reported a poor accuracy performance of iPro in critically ill patients with a very high MARD of 44%, wide Bland-Altman plot limits of agreement and high bias between CGM and blood glucose. However, they inserted iPro CGM in the upper arm and used arterial blood glucose for calibration. Akintola et al. (2015) using venous blood glucose for calibration reported a MARD of 17.6% in healthy adults for only a 24-hour period of CGM recording. The four other studies used cabillary SMBG as a reference and reported a very good accuracy performance similar to those published by Medtronic. Thomas et al. (2017) reported MedARD ranging between 11.2% -13.2% in 10 healthy athletes using the abdominal insertion site. Evaluating iPro accuracy in 84 non-critically ill hospitalised adults with T2DM, Schaupp et al. (2015) reported 9.6% MARD,

6.5% MedARD, zero mmol/l median bias, and 98.7% of the values within A+B error grid zones. Though they used the same 4 capillary blood glucose for calibration and for accuracy assessment. Another study involving hospitalised patients with T2DM with and without congestive heart failure (CHF), reported MARD of 11% in CHF and 8% in non-CHF, and 98.5% of CHF and 98.7% of non-CHF CGM glucose values were within A+B error grid zones (Dungan et al., 2013). Lastly, Signal et al. (2013) evaluated the accuracy of iPro devices inserted on the abdomen and on the thigh. They recruited 10 critically ill adults in the ICU and inserted two iPro devices concurrently, one device at each insertion site. They reported a MARD of 11.8% for the abdomen and 12.4% for the thigh. A summary of the included articles' results are presented in Table 3-3.

3.4.6.4 Review conclusion

The iPro professional CGM system with Enlite sensors, has a good accuracy performance. More accuracy studies are needed specifically in individuals with diabetes and in pregnant women with DIP.

Table 3-3 Summary of studies on accuracy of professional Medtronic CGM system

Author (year)	population	Duration	Insertion site	Calibration	Reference blood glucose	Accuracy results
1) Thomas et al. (2017)	10 adult athletes, none with diabetes	4-6 days	Abdomen	3-4 Capillary blood by glucometer	Capillary blood by glucometer	MedARD 11.2% - 13.2%
2 Munekage et al. (2016)	15 critically ill surgical patients intensive care unit (ICU) , none with diabetes	3592 comparative samples (starting at operation theatre till discharge from ICU)	Upper arm	arterial blood glucose	Venous blood by intravenous continuous glucose monitor	MARD 44 % Bland-Altman plot 9 5% agreement limit -67 to + 57 mg/dl Mean bias -5.2 mg/dl
3) Akintola et al. (2015)	34 healthy adults	24-hour	Abdomen	4 Capillary blood glucose by glucometer	Venous blood by laboratory method	MARD 17.6% -2.21 to + 2.41 mmol/l 95% agreement limits Mean bias 0.1 mmol/l

4) Schaupp et al. (2015)	84 hospitalised adults with T2DM	501 patient-days	Not specified	4 Capillary blood glucose by glucometer	The same 4 Capillary blood by glucometer used for calibration	MARD 9.6%, MedARD 6.5% 98.7% in A+B zones of error grid Median bias 0 mmol/l
5) Signal et al. (2013) (letter with primary research results)	10 critically ill adults in the ICU	Not specified	Two devices; abdomen and thigh)	4 capillary blood glucose by glucometer	Frequent capillary blood glucose by glucometer	MARD; abdomen site 11.8% and thigh site 12.4%
6 Dungan et al. (2013)	T2DM hospitalised adults; 43 with congestive heart failure (CHF) and 32 with no CHF Patients were either having uncontrolled hyperglycaemia or using significant amount of insulin	43 hours in CHF and 32 hours in non-CHF	abdomen	4 capillary blood glucose by glucometer	Hourly capillary blood glucose by glucometer	(11%) in CHF and (8%) in non-CHF 98.5% of CHF and 98.7% of non-CHF in A+B zones of error grid

3.4.7 The iPro2 CGM system practical procedures followed in this research

The sensor was inserted transcutaneously using an automated insertion device (serter) and an introducer hollow-needle incorporated with the sensor (Figure 3-10). The needle is automatically retracted after the insertion while the sensor electrode remains in the subcutaneous tissue (Figure 3-11). The recorder (memory device) is then attached and the whole CGM system secured in place with medical adhesive films or over-tapes. Practical steps as recommended in the Medtronic's user guide were strictly followed (Medtronic MiniMed, 2016b). All clinical research staff received training on the use of iPro2 professional CGM system from the Medtronic company representatives and the online step-by-step training manual and videos (Medtronic MiniMed, 2016a) . The iPro2 devices' serial numbers were recorded in the participants' data collection sheets together with participants' identification numbers and dates of recording before connecting them to the sensors in order to avoid mixing-up participants records.

3.4.7.1 Insertion sites

The best location for sensor insertion are areas with sufficient subcutaneous fat including: abdominal area including the front, sides, and back of the body, and upper buttock area. Areas to avoid include areas with tight fitting clothes, areas with hard skin or scars, body areas which move a lot during physical activity, areas around the waist or two inches around the belly button. In the current study either left or right upper buttock areas were used as they were considered more convenient for pregnant women (Figure 3-12). Accuracy of Enlite® glucose sensor's buttock area insertion site was not found to be significantly different compared to an abdominal insertion site (Bailey et al., 2014).

Figure 3-10 iPro2 professional CGM system and serter (Source:
https://www.medtronic-diabetes.co.uk)
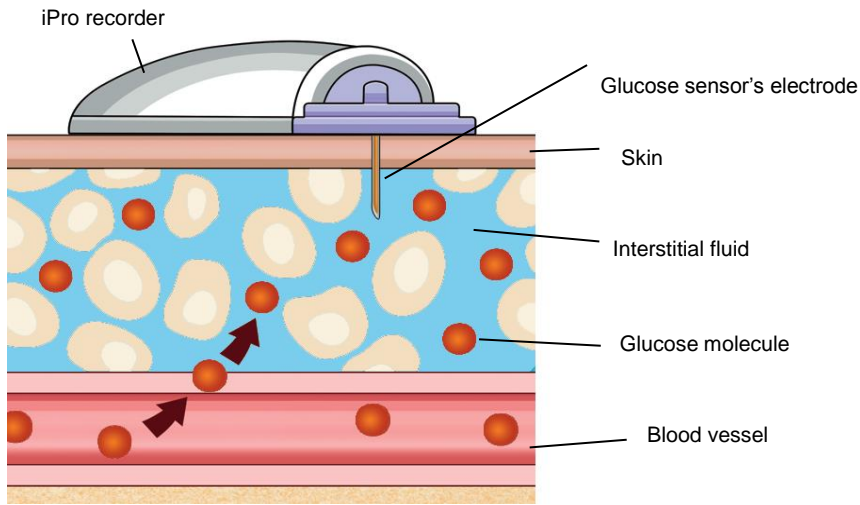
Figure 3-11 Diagrammatic picture of iPro2 professional CGM system in situ

(Source: https://www.medtronic-diabetes.co.uk)
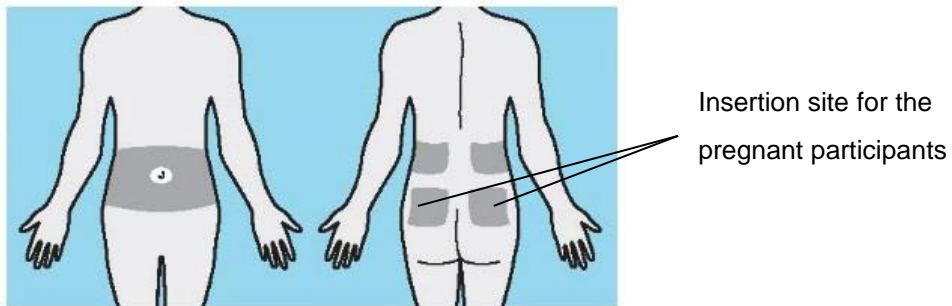
Figure 3-12 iPro2 CGM insertion sites (Source: https://www.medtronic-diabetes.co.uk)

3.4.7.2 Infection control procedures

The skin at the site of insertion was inspected for any signs of infection and then prepared by alcohol swab and left to air-dry before insertion. Universal infection control precautions procedure were used during handling the sensor to avoid potential blood and body fluid contact. This included washing hands with water and detergents or using alcohol rub, wearing gloves and preparing sterile gauze to use in case of bleeding from the insertion site. Used sensors were disposed in sharps containers, memory parts were cleaned from tape adhesive residues using a medical adhesive remover (Zoff © Adhesive Remover Wipes[1] was used) and thoroughly cleaned and disinfected according to the manufacturer instructions before being reused.

3.4.7.3 Safety and adverse events following CGM

CGM systems are usually well tolerated (Jadviscokova et al., 2007; Yu et al., 2014a; Kosiborod et al., 2014). In the current study there were no reports of insertion site infection or major adverse events. Only 3 participants removed the CGM system after experiencing itching related to the adhesive tape.

3.4.7.4 Duration of recording

Patients wore the CGM system for one week from recruitment day. They returned on day seven for device removal. The iPro2 CGM system is waterproof and no limitations were required for water related activities. They were instructed to continue wearing the device for the whole period unless they experienced any adverse events or they decided that they no longer wished to participate in the study. In this case or in case the CGM system fell out, they were advised to keep it in a plastic bag and return it to the clinic.

3.4.7.5 Calibration

In the iPro2 CGM system an average interstitial glucose value is stored every five minutes, providing up to 288 interstitial glucose measurements per day. It is not pre-calibrated and thus it needs an *in-vivo* calibration using glucose values from SMBG glucometers. In this study participants used various types of glucometers as provided by the DIP clinic. Participants were instructed to record at least 4 SMBG reading per day as per standard DIP clinical care. They were provided by a log sheet to record the values and the timings of their SMBG readings (Appendix F).

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[1] Available from smith&nephew http://www.smith-nephew.com/uk/products/wound_management/product-search/zoff/

3.4.8 CGM data

Data from the CGM system's recorders were downloaded to the computer using the Carelink interface which is the manufacturer's online software (Medtronic CareLink). SMBG readings were input manually to Carelink. The software built-in algorithm used the SMBG readings to calibrate the interstitial glucose values and produced estimated blood glucose values. The algorithm needed at least one SMBG reading every 12 hours to operate. Calibration readings further apart and missing calibration readings resulted in a failure of the algorithm and no estimation of blood glucose level generated. Missing calibration readings was caused when participants either did not record their SMBG values on the log sheet or they forgot to document the timing of the recorded SMBG measurements.

Carelink produces different summary reports (example available in Appendix G) and stores all the downloaded sensors values, time-points of recording (in 5-minute epochs) and the calibrated glucose values in a dense long CSV table format. 288 estimated blood glucose values are expected in a 24 hours period. Each participant's raw glucose data were exported as CSV files from Carelink and read into Stata statistical package where all participants' data were merged and then were saved as Stata file.

3.4.8.1 CGM data cleaning

Data from day zero (day of recruitment/sensor insertion) were excluded from any analysis as this data is considered less accurate. This is due to a temporary shift in the subcutaneous interstitial fluid equilibrium caused by insertion wound and associated trauma (Heller and Feldman, 2008). Summary report metrics from Carelink were not used in the analysis, instead daily and overall CGM summary metrics for each participant were computed in Stata. Daily metrics were calculated either for a 24-hour day (from midnight to next midnight) or for a variable-length day (from wakeup time to next wakeup time) depending on the specific objective being addressed by the study and analysis techniques employed. Partial 24-hour or variable-length days with missing data caused by either device failure or missing calibration readings, were excluded. Missing glucose data especially around glycaemic excursions (peaks and nadir) may bias the summary metrics by either overestimating or underestimating their values (Fonda et al., 2013). Further, FDA of CGM data requires a complete dataset of equal time periods without missing values. Imputation of missing CGM data was not used in this study as it needed information that was not collected, namely: 1) caloric, carbohydrate and other nutrient intake, and 2) energy expenditure (Hernandez and Barbour, 2013).

3.4.9 Planned CGM data summary metrics

Acknowledging their limitations, some of the CGM summary metrics were calculated and used to compare the current research results to other researchers' results. These summary metrics were: mean glucose; SD glucose; proportion of time within, above and below target; and ratio of AUC-above and AUC-below targets. The normative target range was set to be between 3.5 mmol/l lower threshold and 7.8 mmol/l upper threshold. NICE recommends a blood sugar below 5.3 mmol/l fasting and 7.8 mmol/l one hour after meal for pregnant women with diabetes (NICE, 2015). Though, they do not recommend a lower limit except for those on glucose lowering medications (namely insulin and glibinclamide) to maintain their capillary blood glucose level above 4 mmol/l in order to lower the risk of iatrogenic (clinically induced) severe hypoglycaemia. The American Diabetes Association Workgroup on Hypoglycaemia (2005) defined hypoglycaemia as all episodes of an abnormally low plasma glucose concentration that expose the individuals to potential harm, whereas severe hypoglycaemia is hypoglycaemia that requires the assistance of another person and impedes self-management. However, the hypoglycaemic threshold is debated and in-general a glucose level ≤ 3.9 mmol/l (70 mg/dl) is set as a conservative lower limit to alert individuals with diabetes for a higher probability of severe hypoglycaemia (Seaquist et al., 2013; Cryer, 2009). In contrary to hyperglycaemia, hypoglycaemia during pregnancy in humans does not appear to have detrimental effects on the offspring, albeit it is still detrimental for the mothers' wellbeing (Ringholm et al., 2012; Rosenn et al., 1995; Frier and Fisher, 2007). A lower limit of 3.5 mmol/l was set as a hypoglycaemic threshold in this study to allow comparisons with others (Stewart et al., 2016; Feig et al., 2016).

3.5 Study protocol

The current section set out the original study protocol, the reasons it was modified, the methods used to improve recruitment into the study and the final study protocol.

3.5.1 Original study protocol

Women diagnosed with GDM, at 26-28 weeks of gestation, were referred to attend the DIP clinic within a week, and followed-up every 1-2 weeks thereafter. At their first DIP visit, they were approached by the research team and given general information about the study. Those who showed interest were provided with detailed written information about the study and offered the opportunity to ask questions and find out more about the research study. If they were still keen to participate, they were asked to sign a written consent and were given a unique identifier code. They were asked to complete the PSQI sleep questionnaire and wear the actigraph and a member of the research team set the

CGM system for them. Baseline characteristics including: age, measured weight and height at first antenatal visit, measured weight at recruitment visit, gestation in weeks at recruitment visit, medications including glucose lowering medications, comorbidities, reported ethnic backgrounds and OGTT results were collected from participants' files using a data collection sheet (Appendix H). Participants were asked to complete a sleep diary and a glucometer readings log sheet (Appendix C and Appendix F). They were also provided with an iPro2 user instructions sheet and research team contact information. They were asked to return to clinic after 1 week for all paperwork and devices to be retrieved. They were instructed to remove the devices and put them in a plastic bag and return them during their next visit if they experienced any complications or if they decided to withdraw from the study for any reason.

They were followed up during their regular DIP clinic visit at 32-34 gestation weeks and asked to repeat the same procedure again. All participants continued to receive GDM standard management by the DIP clinic's multidisciplinary clinical team as recommended by NICE (NICE, 2008; NICE, 2015). A flow chart of this study protocol summary presented in Figure 3-13.

First contact
- First DIP clinic visit. At 26-28 weeks of gestation.
- Study information, recruitment and informed consent.
- PSQI sleep questionnaire
- CGM and glucometer log
- Actigraphy and sleep log

Second contact
- Follow up after 1 week
- Retreiving devices and questionnaire

Third contact
- DIP clinic visit at 32-34 weeks of gestation
- PSQI sleep questionnaire
- CGM and glucometer log
- Actigraphy and sleep log

Fourth contact
- Follow up after 1 week
- Retreiving devices and questionnaire

Figure 3-13 Flow chart of the original study protocol

3.5.2 The need to change the original study protocol and how this decision was reached

Four months into the study cohort recruitment (October 2013-January 2014) only one participant had been recruited in the study. This was a very poor uptake considering the abundance of study-eligible pregnant women with gestational diabetes attending the DIP clinic every month (30 potential participants on average every month). Studies that looked into reasons for declining participation in clinical studies found that it was mostly related to issues with study protocol (Brintnall-Karabelas et al., 2011; Williams et al., 2007; Thoma et al., 2010). Thus a decision was made to revisit the study protocol and find out how to improve the recruitment rate. Several steps were taken as follows:

3.5.2.1 Appreciating the research environment

The DIP clinic is very busy and the first DIP clinic visit is particularly stressful and relatively long. It is the visit the pregnant women make directly after being diagnosed with gestational diabetes. It was observed how this diagnosis came as a shock for many of the pregnant ladies who blamed themselves for not being careful enough to avoid having such a condition. Others were afraid of having to take injections as they had heard from friends or read on the internet, and they were also concerned about possible complications to themselves and their babies. The consultation visit is a lengthy one as the pregnant women have to see all the multidisciplinary clinical team: midwife and obstetrician to check on mother's and foetus's general health, diabetologist for diabetes and glycaemic control information and plan, dietitian for diet consultation including instructions on recording dietary intake for the coming week, and nurse assistant for instructions on the use of capillary blood glucose meter (glucometer). Adding information about research and recruitment to the study at this same visit was overwhelming and unpractical.

3.5.2.2 Taking feedback from potential participants

During attempts to recruit potential participants, most of the reasons for declining were mainly something like: "Do I have to do this as well? If not I'm not bothered!" or "Sorry I can't I'm too busy". Others however were afraid of potential complications of using the CGM system and a few could not wear the Actiwatch due to some restrictions at their work place.

3.5.2.3 Involving DIP clinic's clinical staff

The principle investigator (PI) and AA had a group discussion with the DIP medical team as involving people with direct contact with the study population would potentially improve the understanding of the research environment. The DIP medical team had

raised their concerns about the practicality and the timing of recruitment and how it may interfere with the patients' care. Harm could be introduced by adding emotional or psychological distress or interfering with their comprehension of important information and instructions they are receiving from the medical team for managing their GDM complicated pregnancy (Babbie, 2014).

Involving medical staff led to being awarded a highly commended certificate from the BMJ awards for Diabetes team of the year to Leeds Diabetes in Pregnancy team for EMBARC (EMBedding an Active Research Culture) in the Diabetes in Pregnancy clinic project. An award that recognised an innovative project that has measurably improved care in diabetes (Appendix I).

3.5.2.4 Incentives for participating

Small to moderately sized monetary incentives of $1-$15 have been found to significantly increase recruitment rate in trials and response rate in surveys compared to no incentives (Ulrich et al., 2005; Edwards et al., 2005; Martinson et al., 2000). The original study protocol did not include any incentives.

3.5.3 Restructured final study protocol

The following steps were taken based on the reassessment of the original study protocol, discussions with clinical staff and patients, and recommendations to improve recruitment rate found in the literature (Bower et al., 2014; Thoma et al., 2010):

- Change recruitment time to around 32 weeks of gestation, giving patients time to understand their GDM condition and be more experienced with using the glucometer and food choices.
- Simplify study protocol with collecting data only once.
- Distributing research culture among staff and patients. Study flyers (Appendix J) were given to the clinical staff and distributed in the waiting area.
- Adding incentives: £10 pound voucher and full CGM and Actigraphy reports.

A flow chart of the final study protocol is presented in Figure 3-14.
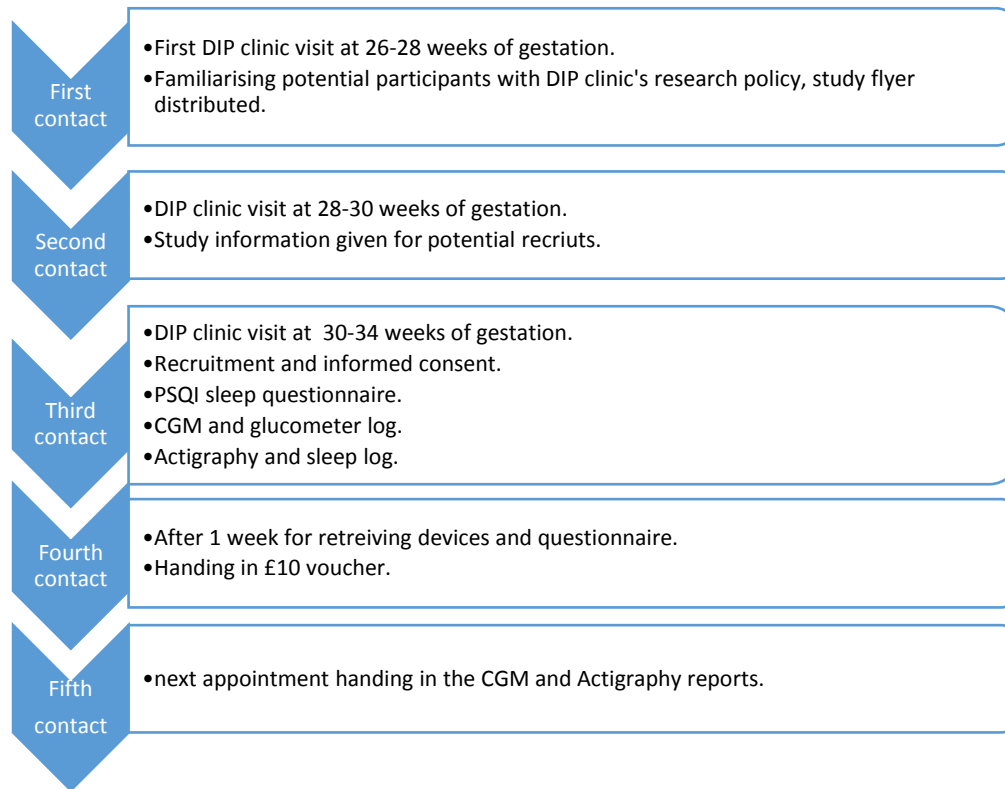
Figure 3-14 Flow chart of the final recruitment protocol

3.6 Ethical considerations

The research was performed under the NHS and Leeds Teaching Hospitals Trust (LTHT) research governance standards and GMC codes of conduct for research. NHS Local Research Ethics Committee approval was obtained prior to the start of the research for the original protocol and then for the amendment; REC reference 13/H/0268 on 19/09/2013 and 17/11/2014 respectively. NHS site specific approval at Leeds Teaching Hospitals Trust was granted on 14/11/ 2013, LTHT R&D number; ED13/10839 (122874/WY). All research team members had completed an introduction to good clinical practice (GCP) online e-learning course and had research passports with letter of access to conduct research from Leeds Teaching Hospitals NHS Trust. Ethics documents are available in Appendix K to Appendix Q.

Participants were provided with full written study information sheets and the study was explained by the research team prior to their enrolment. Written informed consent was obtained from all the participants before commencing the study. Participants had the right to withdraw from the study at any time-point thereafter. Participation did not affect the standard clinical care provided by clinical staff.

3.7 Database management

The study database was built using data collected from different tools. Demographic, anthropometrics and other participant's characteristics were collected via data collection sheets, entered into Microsoft Excel spreadsheet then exported to Stata software and stored as Stata data file. Raw CGM data were exported as separate long CSV files for each participant, then they were all appended using Stata software and stored in a very long Stata data file. PSQI scoring and reported sleep variables datasheets were exported from the PSQI Microsoft Access database file to Stata software and stored as Stata data file. Actigraphy-derived daily sleep characteristics for all the participants were exported from the Actiware software as one large Microsoft Excel spreadsheet to Stata software and stored as Stata data file.

All these Stata data files were merged to form one large database linked using the following two identifiers: 1) the participants' unique study number and 2) the date of recorded data. The date of getting-up from sleep as recorded by actigraphy was linked to the date of CGM recording, as such the night sleep (the exposure variable) will chronologically precede the CGM recording day (the outcome variable), and thus allowing temporality in the relation between sleep and glucose control. This arrangement of data was used throughout the analysis except for when examining the impact of glucose level around bed time on the immediately following night sleep. In that latter situation CGM data were arranged to chronologically precede the immediately following night sleep.

Multiple sub-databases were created to ease manipulation and analysis of variables when exploring a specific study objective.

3.8 Data security

All the study's sheets, forms, configured devices and electronic databases including/relating to: data collection sheets, PSQI questionnaires, glucometer logs, sleep diaries, CGM systems and records, actigraphy configuration and records and the merged databases were totally anonymised using unique allocated study identifier number (ID) with no link to participants' confidential information. They were all stored in University of Leeds secure offices and servers except for CGM data which was uploaded and stored via Medtronic CareLink online secure software data management webpage. Databases were regularly updated and backed up. A linkage list of the participants study ID with their confidential information including: name, NHS number and date of birth were retained with the research nurse. A paper-form of the list was kept in a locked drawer inside a secure office within LTHT and YTHT premises and an electronic Excel-

spreadsheet list was encrypted and saved in a secure LTHT and YTHT servers. The linkage list was needed in order to follow the participants' pregnancy outcome.

3.9 Statistical methods

3.9.1 Descriptive analysis

A detailed description of the full dataset and the complete dataset (participants' records with no missing variables) is presented in the results chapter. Continuous variables such as; age, BMI, gestational age at recruitment, OGTT results (fasting and 2-hours post prandial), PSQI total score, sleep duration, sleep efficiency, SOL duration, WASO, bedtime, getting-up time, glucose readings from CGM, proportion of time within/above/below glucose target, ratio of glucose AUC below/ above threshold to the total glucose AUC were presented as mean and SD if normally distributed or as median and Interquartile range (IQR) if not normally distributed.

Categorical variables or grouped continuous variables were summarised as frequencies and proportions. These data such as: PSQI total score where a score of 5 or less is considered to be good sleep quality and a score of more than 5 is considered to be poor sleep quality; Parity status (number of living children) was grouped into nulliparous (0 living children) and parous (one or more living children); type of medication used to manage GDM (no medication diet only, Metformin 500 mg twice daily, Metformin 1g twice daily, Insulin with/without Metformin), and ethnicity.

Ethnicity was self-reported by participants and obtained from their health file. Ethnicity data was comprised of a long list of multiple ethnicity groups, as per the health files information form. In order to use this data in the analysis, the ethnicity groups were recoded initially into four broad categories; White, Black, Asian and Others, as shown in Table 3-4. However, in further analyses, Asian, Black and Others ethnicity groups were recoded into one broader category of Non-white ethnicity.

Table 3-4 Original health file self-reported ethnicity groups and the recoded broad ethnicity categories

Original health file ethnicity category	Recoded broad ethnicity category
• White British • White Irish • White others	White
• Indian • Pakistani • Bangladeshi • Other Asian backgrounds • Mixed White and Asian	Asian
• Black African • Black Caribbean • Other Black backgrounds • Mixed White and Black	Black
• Chinese • Arab • Any other ethnic group • Not stated	Others

3.9.2 Agreement between reported and actigraphy measured sleep characteristics

The Bland-Altman difference plot method was used to evaluate the agreement between reported and actigraphy sleep characteristics (Bland and Altman, 1986; Giavarina, 2015). These were: sleep duration, sleep efficiency, SOL duration, bedtime, and getting-up from bed time. The method involves, separately per sleep variable, calculating the differences and the averages of each participants sleep variable's values reported by PSQI and measured by actigraphy, calculating the mean and SD of the differences, followed by drawing a scatter plot of the differences (y- axis) against the averages (x-axis), drawing horizontal line crossing the y-axis at the mean of the differences, and 2 more horizontal lines crossing the y-axis at the mean±1.96 SD of the differences. The mean±1.96 SD lines demarcate the upper and lower limits of agreement where 95% of the data points lie in between. The narrower the distance between the upper and lower limits of agreement and the less dispersion of the data points the better the agreement between the reported and actigraphy measured sleep variable. A mean of the difference

of actigraphy minus reported sleep variable larger or smaller than zero is suggestive of a systematic bias (error) where actigraphy, respectively, overestimate or underestimate reported sleep variable. In addition the Bland-Altman plot can detect trends in the relationship, i.e. proportional bias, between the differences and the averages, like in instance if large differences were observed with smaller values of the sleep variable and only slight differences observed with large values of the sleep variable, or vice versa. Proportional bias can be checked by a linear regression model of the differences on the averages. A statistically significant slope (β coefficient) of the model best fitted line is indicative of proportional bias (Ludbrook, 2010).

3.9.3 Standard regression analysis

The associations between different reported and overall actigraphy-measured sleep characteristics (the exposures) with overall CGM derived glycaemic characteristics (the outcomes) were tested using standard multivariable regression analysis models. Regression analysis estimates the associations between exposures and outcomes by identifying a 'best fitting' line connecting their data points. The 'best fitting' line is identified using ordinary least square (OLS) method. Regression line of a simple model, having only one exposure (x), has the equation in the form:

$$Y_i = \alpha + \beta\, x_i +\, e_i \quad , \quad e_i \sim N(0, \sigma^2)$$

Equation 3-3

Where Y_i is the fitted outcome for the ith participant. α is the line intercept and represent the expected outcome if the $x_i = 0$. β is the slope of regression line, or the regression coefficient, of exposure x_i . The regression coefficient represents the expected amount of change in the outcome for each unit increase in the exposure. e_i is the residual error, residuals are assumed to be normally distributed, with zero mean and variance σ^2 and homogeneously distributed across values of exposure.

Each standard regression model is one from a series of models having one sleep characteristic as the exposure and one glycaemic characteristics as the outcome, at a time. All models were adjusted for potential confounders, details of the confounders and the methods used to identify them are given in section 3.9.6.

Reported sleep characteristics were variables obtained from PSQI questionnaire, i.e. PSQI total score, reported sleep duration, reported sleep efficiency, reported SOL duration, mid-sleep time, subjective rating of sleep quality. Overall actigraphy-measured sleep characteristics were the calculated mean of all available night's actigraphy sleep data. Overall actigraphy-measured sleep characteristics used were: sleep duration, sleep efficiency, SOL duration, mid-sleep time and WASO. Overall CGM derived glycaemic characteristics were the calculated mean of all daily valid CGM data record's

summary measures. The valid CGM data record was the CGM record with no-missing data over a 24-hour day that is 288 CGM glucose readings from midnight to next midnight. Overall summary measures used were: average glucose, SD glucose, proportion of time within/above/below glucose target and ratio of glucose AUC below/ above threshold to the total glucose AUC. Figure 3-15 displays a schematic mapping of exposures and outcomes variables and their potential relationship.
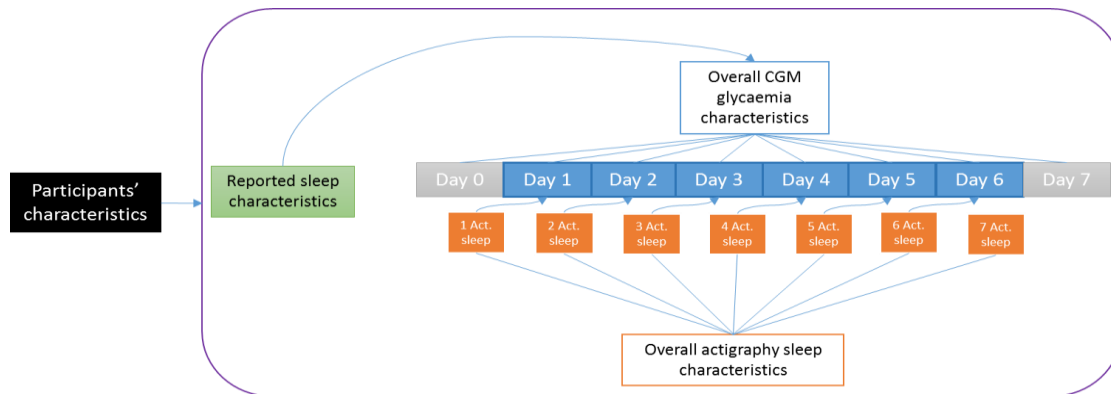
Figure 3-15 Schematic mapping of exposures and outcomes variables and potential relationship

Linear regression modelling was applied for continuous variables outcomes. However variables such as; proportion of time within/above/below glucose target and ratio of glucose AUC below/ above threshold to the total glucose AUC, although numeric they are proportions and ratios and thus limited by a lower value of zero (0%) and upper value of 1 (100%). Furthermore, these variables were strongly skewed as their values were aggregated either at 100% or just below it for some of the variables, or at 0% and just above it for the other variables. This resulted in some issues when applying the linear regression modelling strategy. That is the models' post-estimation diagnostic showed models' residuals which were non-normally distributed and non- homoscedastic (non-constant variance across the values of the exposure). These issues affect the validity of the regression models. A possible solution to deal with these issues was to apply logarithmic transformation to the skewed data, however, it was not effective. Another solution was to calculate robust standard errors (SE) , however it is very conservative and leads to a very wide 95% CI which would lead to a higher probability of type II error (i.e. incorrectly accepting a null hypothesis of no association) and would also result in a prediction of outcome values outside their (0% to 100%) natural range. A third solution was to cut these proportion and ratio variables into binary outcome (two groups): 0; lower and 1; higher, based on their median values and then apply logistic regression modelling methods (Scott Long, 1997). A more statistically advanced solution was to apply a

fractional heteroskedastic probit regression model with zero/one inflated beta with robust standard errors (Bayes and Valdivieso, 2016). Fractional outcome regression models could be fitted in Stata software version14, however, model specifications and interpretation of model's coefficients are not straightforward. Therefore the third solution, categorising these outcomes into binary variables, was chosen and applied. Nevertheless, this option had its caveats as categorising variables could introduce measurement errors.

The grouping of data was as follows: proportion of duration within recommended range groups; lower ≤ 93% and higher > 93%, proportion of duration above recommended range groups; lower ≤ 4.4% and higher >4.4%, proportion of duration below recommended range groups; lower =0.0% and higher > 0.0%, ratio of AUC above recommended range; lower ≤ 0.43% and higher > 0.43%, ratio of AUC above recommended range; lower = 0.0% and higher > 0.0%. Logistic regression models odds ratios (OR) and 95% CI are presented in the result chapter,

To examine potential U/J shaped relationships between sleep duration and glycaemic characteristics two methods were used. The first method was by applying polynomial regression: simply adding a quadratic term (squared sleep duration) in addition to the linear term (sleep duration) in the regression model. The second method was by categorising sleep duration into 3 categories: average, short and long. The literature categorising a 'normal/average' sleep duration is extremely varied, with ranges between '7-8', '7-9', '6-8' and '6-9' were all proposed. Thus the decision was made to use data driven cut points using the interquartile range where 50% of participants' sleep duration data lie. Thus 6-8 hours was defined as the average sleep duration, less than 6 hours was defined as short sleep duration and more than 8 hours as long sleep duration.

To determine the best fitting model, the likelihood ratio test was implied if the models were nested (large model has all the terms (variables) a smaller model has plus some extra terms) as in the case when comparing the fit of linear term only sleep duration regression model and linear and quadratic term sleep duration regression model. Akaike information criteria (AIC) and Bayesian information criteria (BIC) were used to determine best fitting model in case of non-nested models like in the case when comparing linear tem sleep duration model and sleep categories regression model. The best fitting models are presented in the results chapter.

SOL duration was categorised according to the established cut point of initial insomnia (difficulty in falling asleep at the start of sleep period) as: normal; SOL duration <30 minute, and High; SOL duration ≥ 30 minutes (Lichstein et al., 2011).

3.9.4 Multilevel mixed effect regression analysis

Multilevel data analysis involves analysing data with a hierarchical structure, for example like in the case where individuals are nested within a clinic, clinics nested within a city, cities nested within a health authority and so forth. Each level in this hierarchy is influenced by the level they are nested in, i.e. individuals are influenced by the clinic they receive medical advice from, moreover, clinics in the same city are influenced by common practices, and cities follow strategies imposed by their local authority. Likewise, clinic performance is influenced by the characteristics of individuals seeking help there and cities strategies might change based on performance of the clinics operating within its jurisdiction.

In the current research, although it was not sampled in a clustered hierarchical manner but rather a longitudinal fashion, the multiple days of measurements of CGM glucose and actigraphy are considered to be nested within participants. Sleep and CGM glucose might differ between days within the same participant, however they are potentially more correlated to each other than to sleep and CGM glucose from days belonging to other participants. This correlation violates the assumption of independent variables necessary for the validity of a standard regression model. Moreover, modelling the association between daily sleep and CGM data and ignoring their dependence and clustering within participants would lead to spurious association and type I error in statistical hypothesis testing as it would potentially result in narrower 95% CI and a smaller p-value. One method to overcome this dilemma is to summarise the multiple days' data into one overall measurement per participant, usually by calculating their mean, and then applying standard regression models as in the previous section 3.9.3. This method can answer the question of how the overall sleep characteristic is related to an overall glycaemic characteristic, however it cannot give an answer of how night sleep is directly related to the following day/night's glycaemic characteristics. Moreover, this method cannot identify the variability in the relationship between days within the same participant and the variability in the relationship between various participants. On the other hand, another, more appropriate method is multilevel modelling as it can answer the direct relationship question and avoid the cumbersome clustering issue by incorporating the hierarchal structure in the model. Moreover, it can identify between days within participant variability and between various participants variability. Multilevel modelling is also referred to as mixed effect regression as it consists of two parts: a fixed part similar to the standard regression and a random part where the between and within participants variation is specified (Snijders and Bosker, 2012; Hox, 2010).

Random intercept multilevel models were applied. It allows for variation in the model's intercept between participants, i.e. random effect, however all participants would have the same regression line slope, i.e. fixed effect.

The multilevel model specification for outcome Y_{ij} on ith day of jth participant is as follows:

$$Y_{ij} = \alpha + \beta\, x_{ij} + \zeta_j + e_{ij} \quad , \quad \zeta_j \sim N(0, \psi)\; e_i \sim N(0, \theta)$$

Equation 3-4

Where α is the overall model intercept and represent the expected outcome if the $x_{ij} = 0$. In a random intercept model the intercept is allowed to vary a cross participants, the amount of variation, random effect, is specified by the error term ζ_j (pronounced zeta). ζ_j is specific for each participant and assumed to have a normal distribution with 0 mean and variance ψ (pronounced psi), ψ represents the between participant variability. β is the slope of all participants' regression lines. It is interpreted in a similar way to the standard regression model coefficient, also referred to as the fixed effect of the multilevel model. e_{ij} is the residual error for the ith day of the jth participant, residuals are assumed to be normally distributed, with zero mean and variance θ (pronounced theta), represents the within participants variability. The sum of the two error terms ζ_j and e_{ij} represent model's total residual error (Rabe-Hesketh and Skrondal, 2012).

Further, correlation between days within participants, also referred to as intra-class correlation (ICC), was calculated from the model as follow:

$$ICC = \frac{\psi\ (between\ participant\ variance)}{\psi(between\ participants\ variance) + \theta(within\ participants\ variance)}$$

Equation 3-5

Reported sleep characteristics were only evaluated once for each participants, however, actigraphy measured sleep characteristics and CGM glucose were evaluated for multiple days (Figure 3-15). Valid CGM day definition used for multilevel models differs from the definition in section 3.9.3. It was defined as the day/night period, with no missing CGM glucose data, that directly followed a night sleep. Day/night period is the day period following a night sleep, starting from the time participant getting-up from bed, plus the following night sleep period up to the time of next getting-up from bed (see Figure 3-16 for schematic illustration). Daily getting-up from bed time was extracted from actigraphy data. Available actigraphy night sleep daily data were used.

Proportion and ratio variables outcomes were grouped in a similar categories as explained in section 3.9.3 and multilevel logistic regression models were applied.

For each multilevel model the model fit was compared to model fit of standard regression analysis of daily data without acknowledging the hierarchy, using likelihood ratio test.
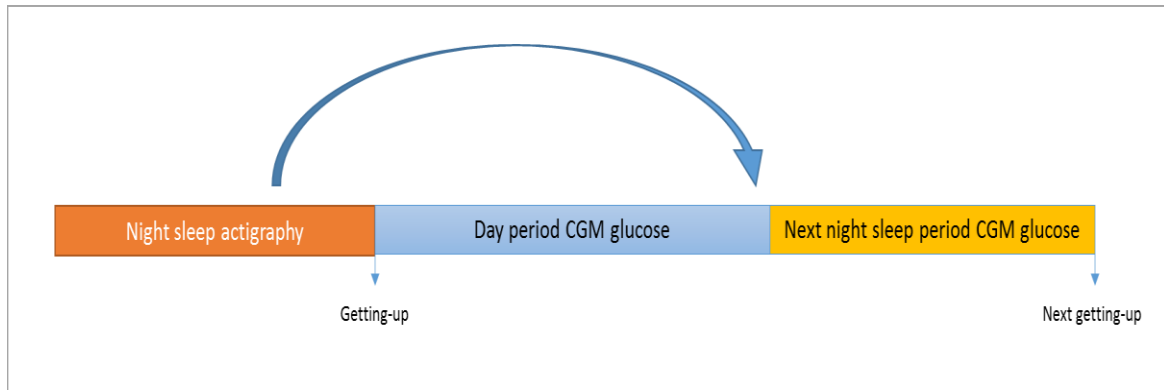
Figure 3-16 Schematic illustration of the relationship between actigraphy measured night sleep and demarcation of the following day/night period CGM glucose

3.9.5 Functional data analysis and functional regression models

All participants' 24-hour daily CGM data records were fitted with smooth curves using a 27 penalised cubic B-spline basis expansion with knots placed at 1-hour equidistance intervals as explained previously in Chapter 2. The resulting smooth daily glucose curves were registered using the registration loop and all participants average-glucose curves were estimated and registered.

The following descriptive statistics for all participants' average-glucose curves were calculated: the point-wise mean and SD curves, median and IQR curves using functional boxplot, correlation matrix, and glucose velocity curves.

Several function-on-scalar regression models were produced to examine the associations between reported sleep characteristics from PSQI questionnaire and the overall actigraphy-measured sleep characteristics (the exposures) and the average-glucose curves (the outcome). In addition, another set of function-on-scalar regression models were produced to examine the association between reported sleep characteristics from PSQI questionnaire and the overall actigraphy-measured sleep characteristics (the exposures) and the glucose velocity curves, in order to examine how much variation in rate-of-change of glucose concentration can be explained by sleep

characteristics. 95% confidence bands were calculated for all the coefficient curves from all the aforementioned regression models.

Further, to examine the reverse association, that is the association of glucose concentrations around bedtime with the daily actigraphy-derived sleep characteristics of the directly following sleep, the following steps were followed: 1) All available CGM data records were rearranged differently. Instead of a 24-hour day duration, they were rearranged into a16-hour interval duration spanning from 14 hours before bedtime to 2 hours after bedtime. The daily bedtimes were extracted from the actigraphy records. This rearrangement of CGM data was performed using time-series syntax commands in Stata software. Figure 3-17 presents a schematic display of this CGM data rearrangement; 2) These 16-hour CGM data intervals were fitted into smoothed curves using the same 27 penalised cubic B-splines basis expansions.

Scalar-on-function regression models were produced to examine the associations between the 16-hour interval glucose curves (the exposures) and the following sleep actigraphy-measures: sleep efficiency, WASO and SOL durations. To examine the association between the 16-hour interval glucose curves and the actigraphy-measured sleep duration, the curves were categorised into three groups: curves that were followed by short sleep duration (< 6 hours), curves that were followed by long sleep duration (>8 hours) and curves that were followed by average sleep duration (6-8 hours). Mean glucose curves were estimated and compared for all the three groups. Permutation functional t-tests were calculated to evaluate the presence of a statistically significant differences in glucose concentration between the groups. That is the difference between the mean glucose curves of the glucose curves that were followed by short and average actigraphy-measured sleep durations, and is the difference between mean glucose curves of the glucose curves that were followed by long and average actigraphy-measured sleep durations.

All the functional regression models were adjusted for the same set of confounders used in the standard regression models. These confounders are identified in section 3.9.6 .
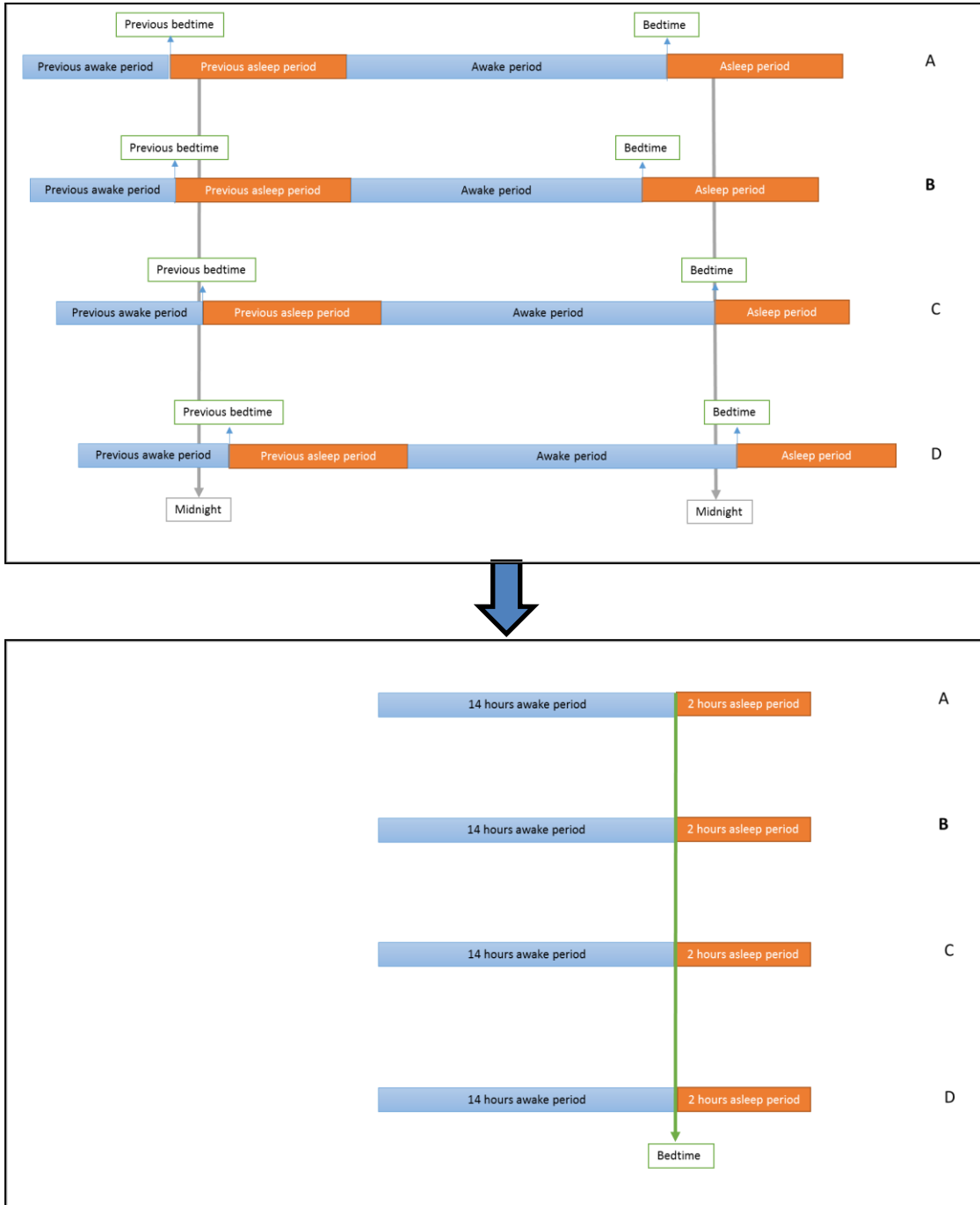
Figure 3-17 Schematic demonstration of the rearrangement of CGM records (A, B, C and D) to study the association between glucose concentration around bedtime and the characteristics of the following sleep (N.B lengths of the horizontal bars are not proportionate to scale)

3.9.6 Adjusting regression models for potential confounders

The Directed Acyclic Graph (DAG) causal diagram method (Greenland et al., 1999; Gilthorpe, 2011b; Pearl, 2016) was used to identify the minimal adjustment set, i.e. the minimum set of confounders, for estimating the adjusted total effect of sleep variables on glycaemic variables. DAGs are basically visualising, through diagrams, unidirectional assumed causal relationships between a set of variables. A variable that is causally associated with the outcome and the exposure but not on the causal pathway from the exposure to the outcome is identified as a 'confounder' (Greenland et al., 1999). On the other hand, a variable that lies on the pathway between the exposure and the outcome is identified as a 'mediator'. Moreover, a variable that is hypothesised to be causally linked to the outcome but not the exposure is identified as a 'competing exposure'. A regression analysis model should be adjusted for confounders, to avoid confounders' bias. The model can include competing exposures, to narrow the confidence limit of the model estimates, but should avoid including mediators in the model, to avoid introducing extra bias (Gilthorpe, 2011b).

The DAG presented in Figure 3-18 was plotted using Dagitty program tool (available from http://www.dagitty.net/development/dags.html#). In this DAG the green shaded oval shape with black arrow head is the 'exposure', the blue shaded oval shape with black bar is the 'main outcome', other blue shaded oval shapes are 'mediator' variables that are lying in the middle of the causal path, red shaded oval shapes are the 'confounder' variables. The identified confounders are: age, booking BMI, ethnicity, type of treatment and parity status. In a multilevel model where weekend and weekdays can be identified from the daily data, weekend/weekday status was also added to the confounder set (Figure 3-19).

3.10 Statistical software

The software Stata (StataCorp, 2014) was used to merge and store data files into a large database. It was also used for data manipulation, producing CGM summary metrics, descriptive analysis, multivariable regression and multilevel regression analyses. The software R (2010) with package 'fda' was used for functional data analysis.
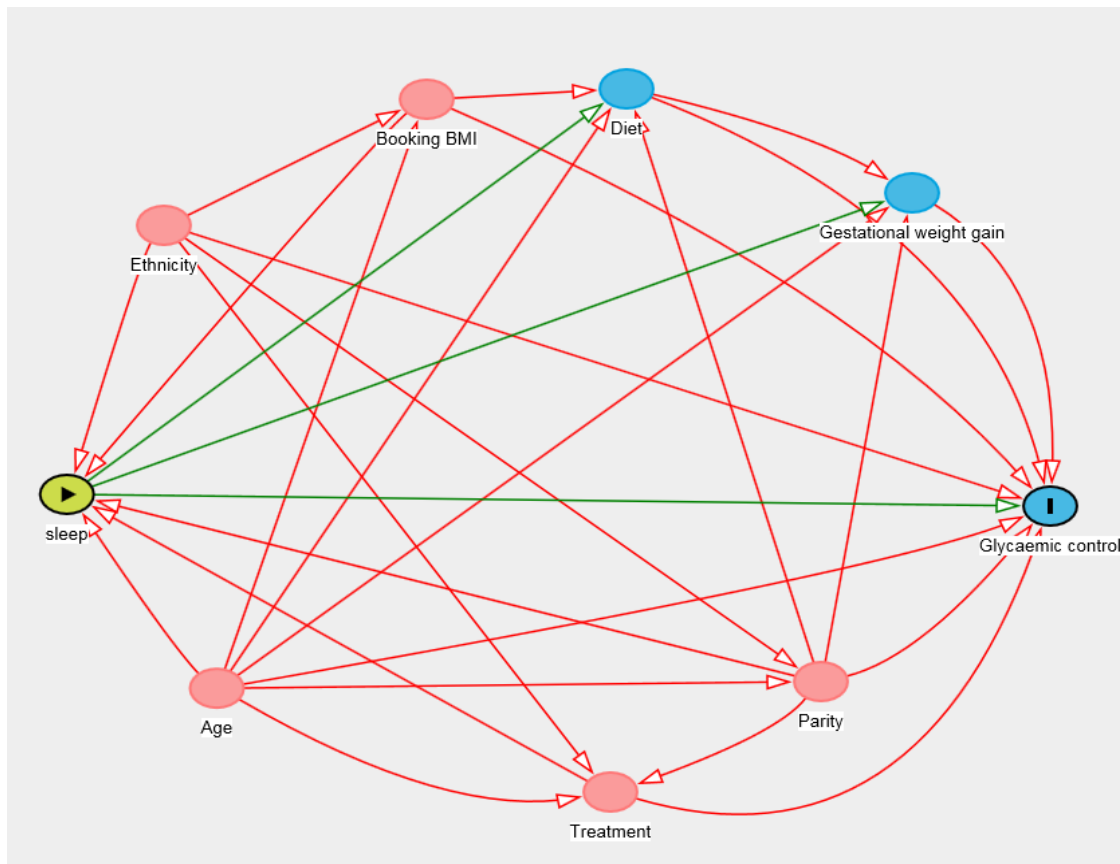
Figure 3-18 DAG of causal relationship between sleep variables (main exposure) and glycaemic control variables (main outcome) and other covariates
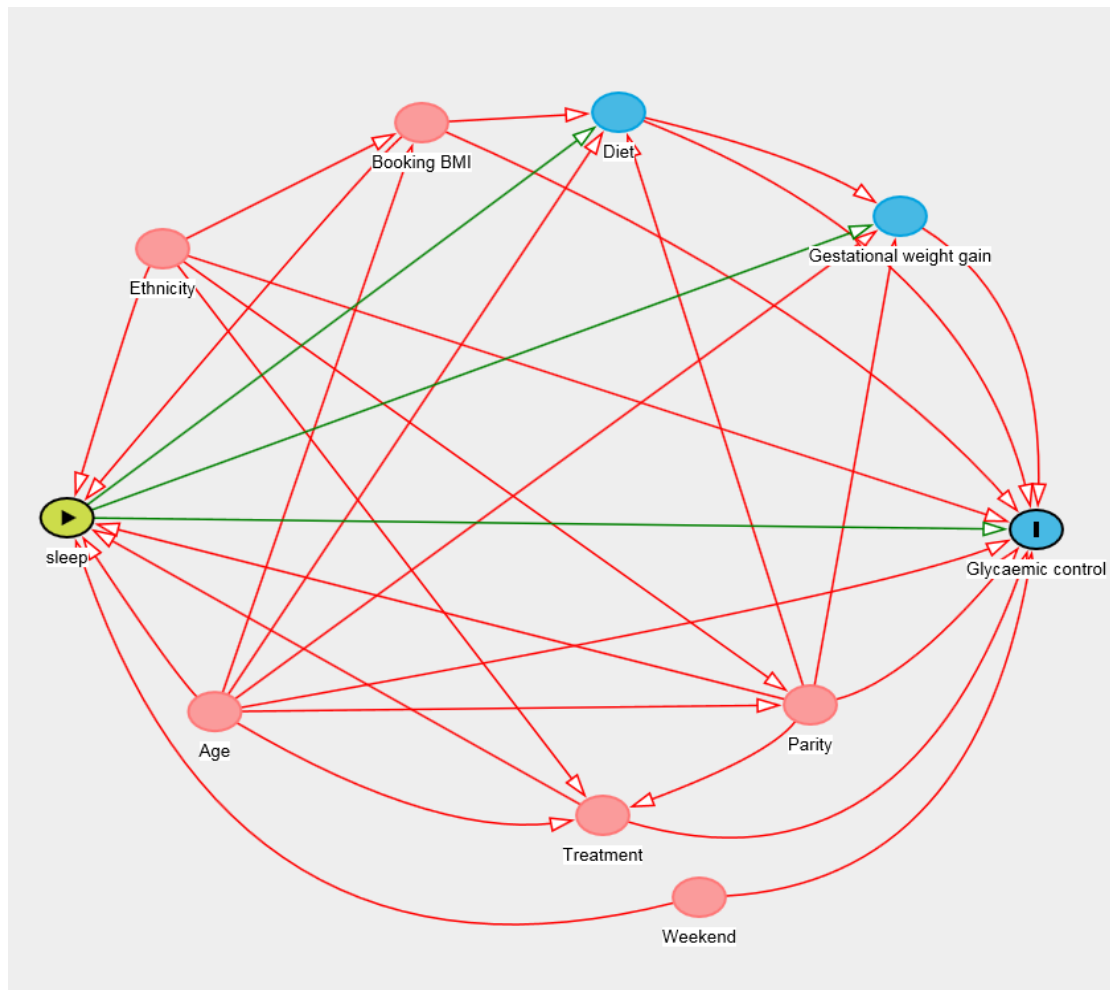
Figure 3-19 DAG of causal relationship between sleep variables (main exposure) and glycaemic control variables (main outcome) and other covariates including weekend/weekday variable

Chapter 4 Results

4.1 Participants recruited

4.1.1 Original recruitment policy; recruitment around 28 weeks of gestation

The recruitment of participants was started in LTHT-DIP clinic by Dr Eberta Tan (ET) in the period from November 2013 to January 2014 inclusive. Although there were approximately 35 eligible pregnant women with GDM per month, only one consented and participated in the study. This participant had 6 days of CGM recording, completed the PSQI questionnaire, but returned no actigraphy recording as she decided not to wear the Actiwatch.

Recruitment attempts were started by myself (AA) in the period from September-November 2014 inclusive. AA was able to recruit seven participants. All of them completed the PSQI questionnaire, two participants took-off the Actiwatches at home, and only three consented for CGM to be inserted.

4.1.2 Final recruitment policy; recruitment around 32 weeks of gestation

Recruitment at 32weeks of gestation started on the last week of November 2014 and continued until the end of April 2017. Recruitment was carried out by AA, DE and LA. In Leeds, clinics were held on Wednesday and Thursday afternoons. Usually only one member of the research team was able to recruit during the clinic. Due to limited equipment, the maximum number of subjects that could be recruited per month was between 14-16 participants. Each participant required 30-40 minutes for consenting, setup and instructions. Out of 910 eligible potential recruits, 170 participants were recruited over 26 calendar months from LTHT-DIP.

York (YTHT-DIP) joined the research from October 2015 to June 2016. Fourteen participants were recruited from this centre during this period. Recruitment was carried out by HO.

4.2 Final dataset

In total 192 participants were recruited into the study (8 participants from LTHT-DIP with original recruitment policy, 170 participants from LTHT-DIP with final recruitment policy, and 14 participants from YTHT-DIP with final recruitment policy). However only 152 participants had full data records available from PSQI questionnaire, actigraphy and CGM (Figure 4-1). Ten participants did not fill their PSQI questionnaire at all, and one filled it partially. 26 participants had no actigraphy data due to: taking the Actiwatch off at home (n=5); a fault in the Actiwatch (n=16); and the Actiwatch was not configured correctly to start recording at time of recruitment (n= 5). 169 participants had at least one full day of CGM data. Missing CGM data was mainly due to participants not recording their glucometer reading at all, or not recording the time of the glucometer reading (n=14). The glucometer reading together with the time it was measured are necessary for calibrating the CGM interstitial glucose values. Other causes included: the participants did not consent to have CGM iPro (n=4); the participants removed the CGM at home (n=3); the CGM fell off from one participant; and no data were retrieved from one participant's CGM.

4.3 Description of participants

4.3.1 Demographic and basic characteristics

The mean (SD) age of participants was 32.8 (5.3) years. They were predominantly from white ethnicity background (60.9%) and obese with a BMI mean (SD) of 30.1 (6.5) Kg/m^2. 34.9% of the participants were nulliparous (had no children previously). Mean (SD) gestational age at the time of recruitment was 31.5 (1.1) weeks. Around half of the participants were on diet management only for their GDM at the time of recruitment. Participant OGTT results were: fasting glucose mean (SD) 4.8 (0.8) mmol/l and 2-hour glucose mean (SD) 8.9 (1.2) mmol/l. Those participants with no missing data records (n=152) had similar demographics and basic characteristics to those for all participants (Table 4-1).
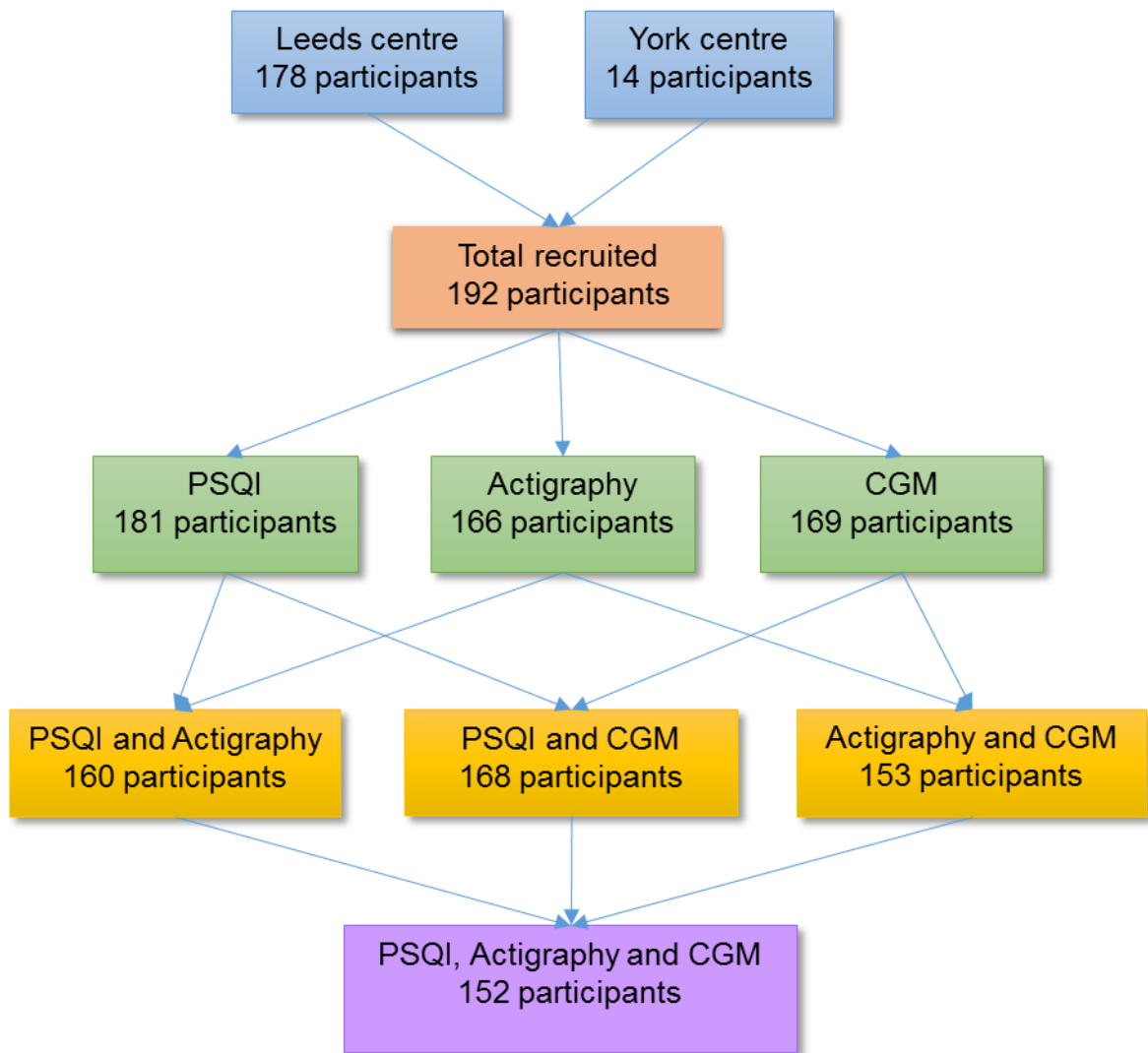
Figure 4-1 Flowchart of participants recruitment and attrition with number of participants with available data from PSQI questionnaire, Actigraphy and CGM

Table 4-1 Demographic and basic characteristics of all recruited participants and participants with complete records

Participants; n	All participants; 192	Complete records;152
Age (years); mean (SD)	32.8 (5.3)	32.7 (5.1)
BMI (kg/m2); mean (SD)	30.1 (6.5)	30.6 (6.4)
OGTT results; mean (SD)		
Fasting glucose (mmol/l)	4.8 (0.8)	4.9 (0.8)
2 hours glucose (mmol/l)	8.9 (1.2)	8.8 (1.2)
Week of gestation; mean (SD)	31.5 (1.1)	31.3 (1.2)
Treatment; n (%)		
Diet	95 (49.5 %)	71 (46.7%)
Diet with metformin 500 mg	44 (22.9 %)	35 (23.0%)
Diet with metformin 1 g	31 (16.1 %)	26 (17.1%)
Diet with metformin and insulin	22 (11.5 %)	20 (13.2%)
Parity		
Nulliparous; n (%)	67 (34.9%)	52 (34.2%)
Parous; n (%)	125 (65.0%)	100 (65.8%)
Ethnicity; n (%)		
White	117 (60.9 %)	95 (62.5%)
Asian	41 (21.4 %)	30 (19.7%)
Black	21 (10.9 %)	19 (12.5%)
Others	13 (6.8 %)	8 (5.3%)
Recruitment centre		
Leeds	178 (92.7 %)	140 (92.1%)
York	14 (7.3 %)	12 (7.9%)

4.3.2 Self-reported sleep characteristics

The participants sleep characteristics, recorded using PSQI questionnaire are presented in Table 4-2. 67.4% of the participants self-reported poor sleep quality with a mean PSQI score >5, a median PSQI score of 7, and the middle 50% of participants' PSQI score ranging between 5 and 10. Self-reported sleep duration was slightly skewed to the shorter sleep duration with median (IQR) 7(6, 8) hours. Self-reported sleep efficiency was also skewed to the left (skewed to the smaller value) with median (IQR) 81.4% (71.0 %, 91.1%). Sleep onset latency of 30 minutes or more was self-reported by 46% of the participants, with SOL median (IQR) 25 (15, 40) minutes. Participants reported, on average, going to bed to sleep at 10:35 PM and getting up from bed at 07:30 AM. 47% of the participants reported a fairly bad or very bad subjective sleep quality, only 12.7% reported sleepiness and trouble staying awake during daytime once or more a week, and 12.7% stated that keeping up enthusiasm to get things done was a very big problem.

The most common cause for disturbed sleep (reported to occur three or more times a week) were: bathroom visits (80.7%) and wake up in the middle of night or early morning (71.9%), followed by having pain (31.0%), cannot get sleep within 30 minutes (27.1%) and feeling too hot (23.2%) (Table 4-3).

4.3.3 Actigraphy measured sleep characteristics

Actigraphy data was available for 166 participants. Each participant had 1-6 nights of actigraphy data and actigraphy-derived sleep characteristics. These sleep characteristics are as follows: sleep duration; sleep efficiency; sleep onset latency (SOL) duration; wake after sleep onset (WASO) duration; bedtime; get-up from bed time; sleep onset time and wake-up time. Overall actigraphy-derived sleep characteristics per participant were estimated by calculating the mean of the daily sleep characteristics.

Table 4-4 displays a summary of all participants overall actigraphy-derived sleep characteristics. Median (IQR) of the overall sleep duration was 7.4 (6.7 to 8.0) hours. Overall sleep efficiency had a median of 83.7% and IQR from 76.1% to 87.4%. Median (IQR) of the overall SOL was 20.4 (12.2, 35.0) minutes with 31% of the participants having SOL duration of 30 minutes or more. The mean actigraphy detected bedtime was at 11:11 PM and the mean getting-up from bed time was at 08:10 AM.

Table 4-2 Self-reported sleep characteristics

Total responses; n	181
PSQI total score; median(IQR)	7 (5,10)
Poor sleep (PSQI score > 5); n (%)	122 (67.4 %)
Self-reported sleep duration (hours)	
Mean (SD)	6.9 (1.5)
Median (IQR)	7 (6,8)
Sleep efficiency (%); median (IQR)	81.4 (71.0, 91.1)
SOL duration (minutes); median(IQR)	25 (25)
Bedtime (HH:MM); mean (SD)	22:35 (01:19)
Get-up time (HH:MM); mean (SD)	07:30 (01:25)
Subjective sleep quality; n (%)	
Very good	14(7.7%)
Fairly good	89 (49.1%)
Fairly bad	62 (34.3%)
Very bad	16 (8.8%)
Trouble staying awake during daytime; n (%)	
Not during the past month	125 (69.1 %)
Less than once a week	33 (18.2 %)
Once or twice a week	14 (7.7 %)
Three or more times a week	9 (5.0 %)
Keep up enthusiasm to get things done; n (%)	
No problem at all	36 (19.9 %)
Only a very slight problem	78 (43.1 %)
Somewhat of a problem	44 (24.3 %)
A very big problem	23 (12.7 %)

N.B. (HH:MM) is a 24-hour clock format

Table 4-3 Self-reported causes of trouble sleeping among 181 participants as stated in the PSQI questionnaire

Cause	0	1	2	3
Cannot get to sleep within 30 minutes	27.6 %	21.0 %	24.3 %	27.1 %
Wake up in the middle of night or early morning	6.6 %	5.0 %	16.6 %	71.9 %
Bathroom visits	6.1 %	2.2 %	11.1 %	80.7 %
Cannot breath comfortably	58.5 %	15.5 %	14.4 %	11.6 %
Cough or snore loudly	58.6 %	19.3 %	8.3 %	13.8 %
Feel too cold	74.0 %	13.8 %	11.1 %	1.1 %
Feel too hot	28.2 %	23.8 %	24.8%	23.2%
Had bad dreams	54.1 %	27.6 %	13.3 %	5.0%
Have pain	28.1 %	18.8 %	22.1 %	31.0 %

(0; not during the past month, 1; less than once a week, 2; once or twice a week, 3; three or more times a week)

Table 4-4 Overall actigraphy-measured sleep characteristics

Available data; n	166
Sleep duration (hours);	
Mean (SD)	7.3 (1.2)
Median (IQR)	7.4 (6.7, 8.0)
Sleep efficiency (%); median (IQR)	83.7 (76.1, 87.4)
SOL duration (minutes); median(IQR)	20.4 (12.2, 35.0)
WASO (minutes); median(IQR)	46.1 (31.5)
Bedtime (HH:MM); mean (SD)	23:11 (01:27)
Get-up time (HH:MM); mean (SD)	08:10 (01:19)
Sleep-onset time (HH:MM); mean (SD)	23:39 (01:34)
Wake-up time (HH:MM); mean (SD)	07:50 (01:20)
Snooze duration (minutes); median (IQR)	17.3 (15.9)

N.B. (HH:MM) is a 24-hour clock format

4.3.4 Agreement between self-reported and actigraphy-measured sleep characteristics

160 participants had self-reported and actigraphy-measured sleep characteristics data available. Agreements between the self-reported and the overall actigraphy-measured sleep duration, sleep efficiency, SOL duration, bedtime and getting-up time were tested using the Bland-Altman method. Table 4-5 summarises the results and is detailed in the sections below (0 and 4.3.4.2). Whilst actigraphy is compared to self-reported sleep characteristics throughout, this does not imply that either is considered the 'gold standard' reference.

Table 4-5 Bland-Altman method agreement result between actigraphy and PSQI sleep parameters (n=160)

Sleep characteristic	Mean difference (Actigraphy- PSQI)	Limits of agreement	Evaluation of agreement
Sleep duration (hours; minutes)	00;27	-02;50 to 03;41	Poor
Sleep efficiency (%)	2.9	-30.0 to 35.9	Poor
SOL (minutes)	- 3.4	-67.2 to 60.4	Poor
Bedtime (hours; minutes)	00;38	-01;10 to 02;26	Poor
Getting-up time (hours; minutes)	00;42	-01;30 to 02;54	Poor

4.3.4.1 Agreement between self-reported and overall actigraphy-measured sleep duration

A systematic bias was detected between actigraphy-derived sleep duration and self-reported sleep duration with a mean difference of 27 minutes. Poor agreement was observed with limit of agreements ranging from -02;50 hours; minutes to 03;41 hours; minutes (Figure 4-2). Moreover, a proportional bias was also observed between the two tools as the differences in sleep durations assessed by them tended to increase for shorter sleep durations and increase for longer sleep durations. Akin actigraphy overestimated sleep duration compared to self-reported at lower values of sleep duration, where self-reported overestimated sleep duration at higher values of sleep duration. Figure 4-3. depicts the linear association between the average self-reported and actigraphy-measured sleep durations and their differences. The regression

coefficient of this line is -0.45 hour (95% CI -0.68 to -0.22, p-value <0.001) indicate that for each 1 hour increase in the average sleep duration there is a statistically significant 27 minutes less difference between actigraphy and self-reported sleep durations. For example, a participant with actigraphy-measured sleep duration of 7.00 hours would report 6.55 hours sleep duration, whilst a participant with actigraphy-measured sleep duration of 6.00 hours would report 5.10 hours of sleep, and a participant with actigraphy-measured sleep duration of 9.00 hours would report 8.55 hours of sleep.
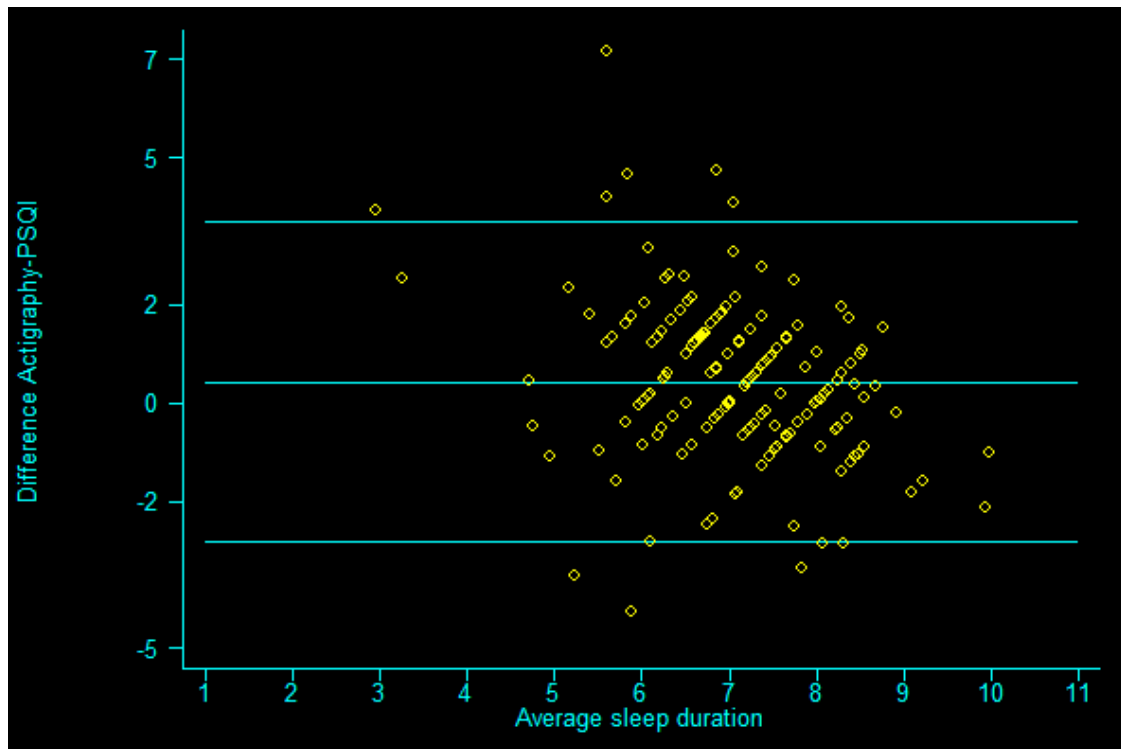
Figure 4-2 Bland-Altman plot of agreement between self-reported and actigraphy-measured sleep durations
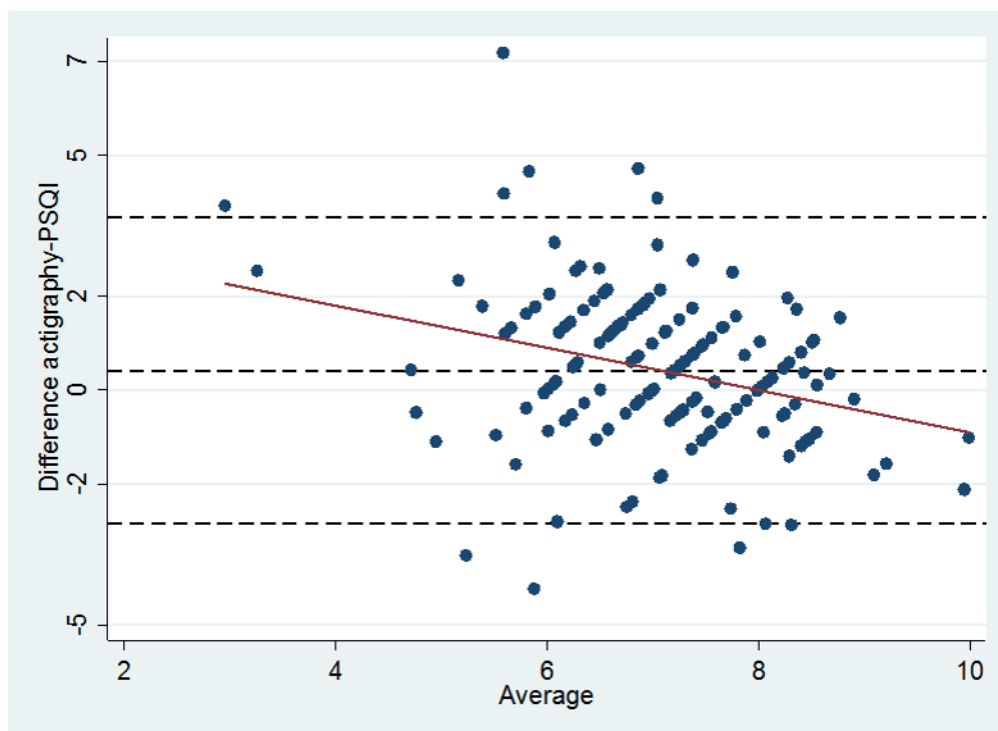
Figure 4-3 Sleep duration bland-Altman plot with best fitted regression line between the average self-reported and actigraphy-measured sleep durations and their differences

4.3.4.2 Agreement between self-reported and actigraphy measured-sleep efficiency

Actigraphy estimated a higher sleep efficiency compared to self-reported sleep efficiency by 2.9% on average. Poor agreement was observed with a limit of agreement ranging from as low as -30.0% to +35.9%. Proportional bias between the average sleep efficiencies and their differences was also observed with actigraphy overestimating sleep efficiency at lower values of sleep efficiency and underestimating sleep efficiency at higher values (Figure 4-4). Simple linear regression modelling between the averages and the differences of actigraphy-measured and self-reported sleep efficiencies revealed a decrease of 8.9% in the difference for each 10.0% increase in the average (95% CI -1.10% to -0.67%, p-value <0.001) (Figure 4-5). For clarification, a participant with actigraphy-measured sleep efficiency of 83.00% would report 80.1% sleep efficiency, whilst a participant with actigraphy-measured sleep efficiency of 73.00% would report 61.20% sleep efficiency, and a participant with actigraphy-measured sleep efficiency of 93.00% would report 99.00% sleep efficiency.
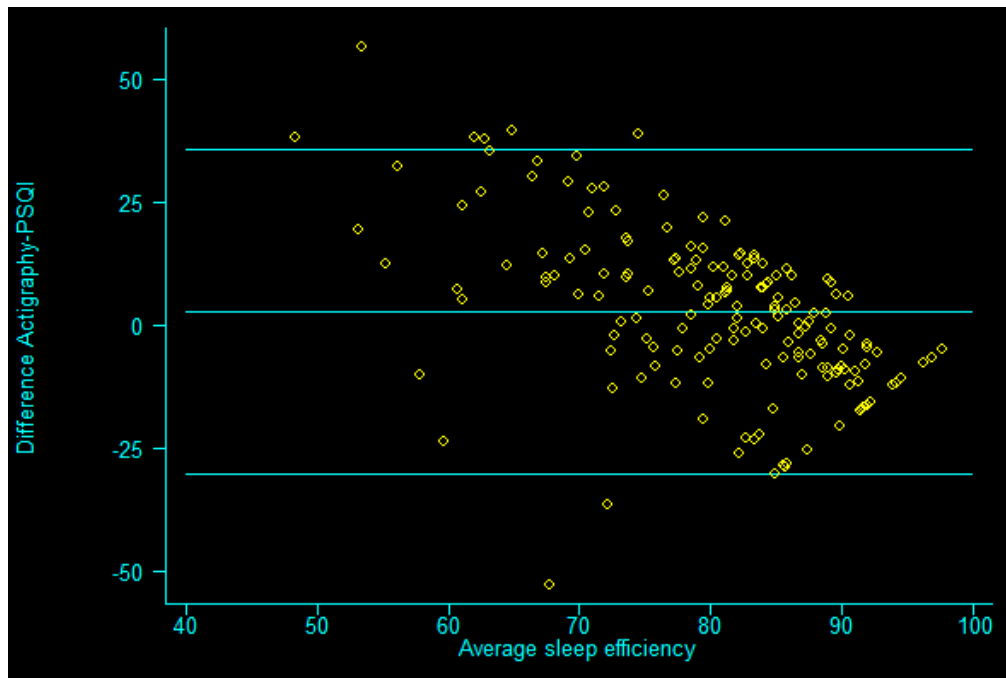
Figure 4-4 Bland-Altman plot of agreement between self-reported and actigraphy-measured sleep efficiency
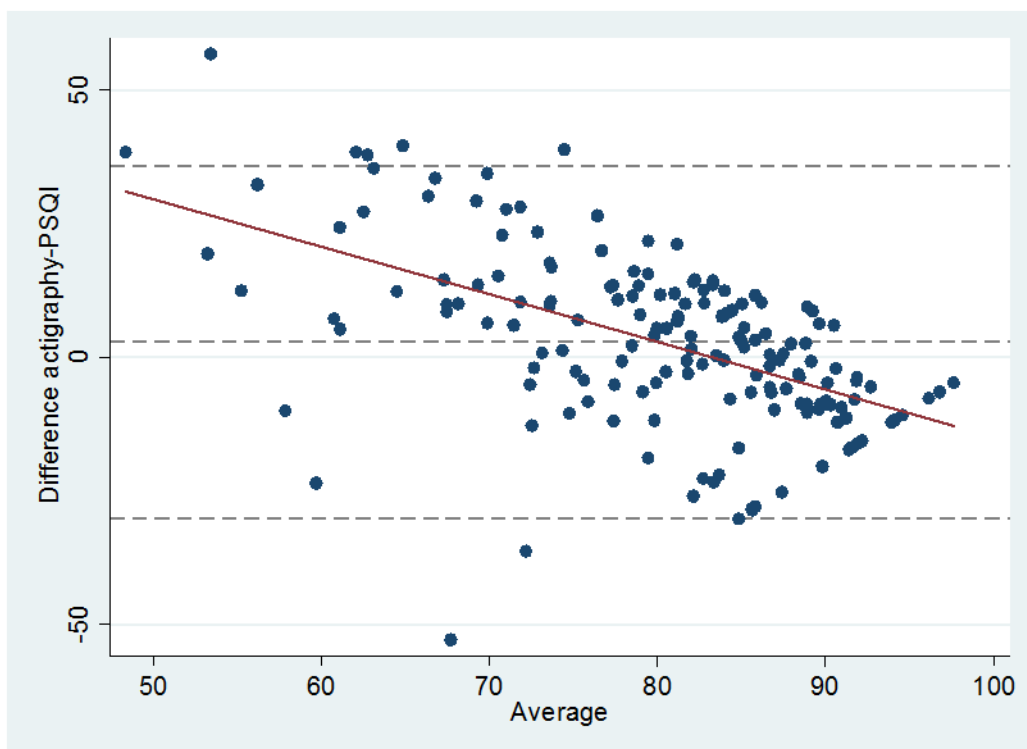
Figure 4-5 Sleep efficiency bland-Altman plot with best fitting regression line between the average self-reported and actigraphy-measured sleep efficiencies and their differences

4.3.4.3 Agreement between self-reported and overall actigraphy-measured bedtime

Actigraphy estimated a later bedtime of 37 minutes on average compared to self-reported bedtime. Poor agreement was observed with a wide limit of agreement ranging from 01:10 (hours: minutes) earlier to 02:26 (hours: minutes) later bedtime (Figure 4-6).
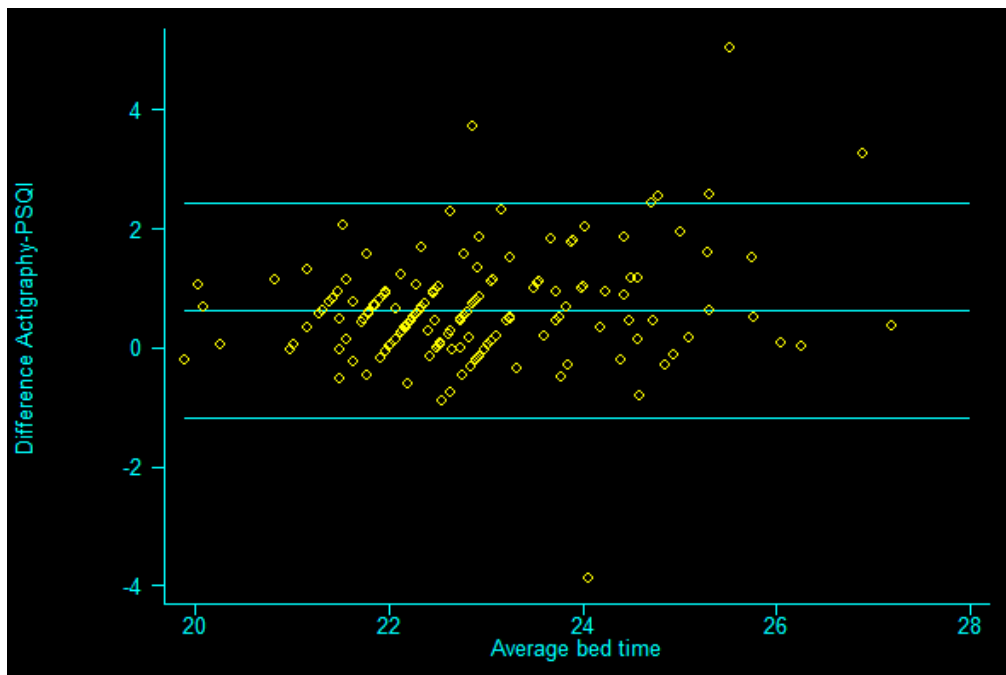
Figure 4-6 Bland-Altman plot of agreement between self-reported and actigraphy-measured bedtime

4.3.4.4 Agreement between self-reported and overall actigraphy-measured getting-up time

Actigraphy estimated a later getting-up from bedtime of 42 minutes on average compared to self-reported bedtime. The limit of agreement was wide ranging from 01:30 (hours: minutes) earlier to 02:54 (hours: minutes) later getting-up time (Figure 4-7).
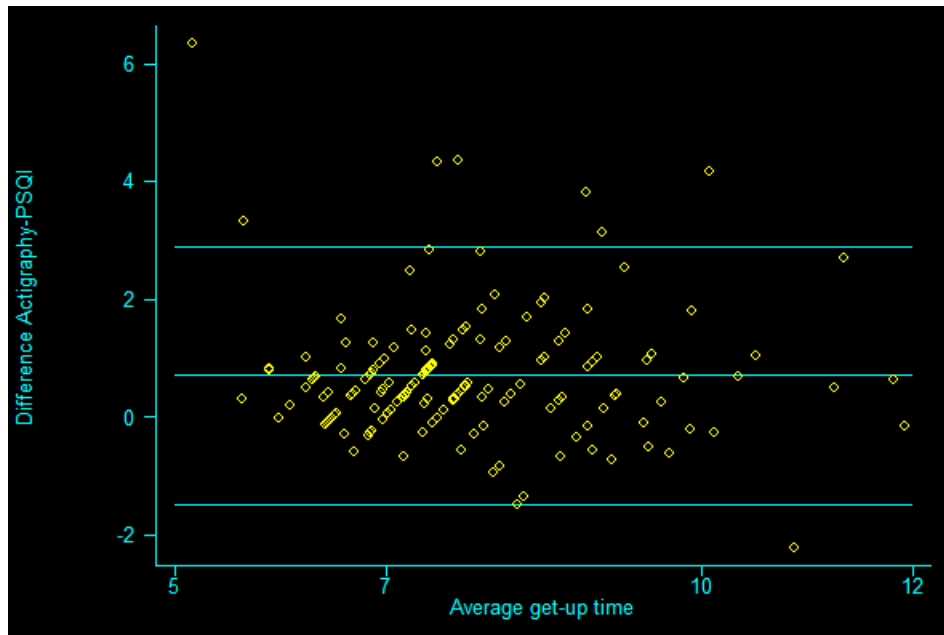
Figure 4-7 Bland-Altman plot of agreement between self-reported and actigraphy-measured getting-up time

4.3.4.5 Agreement between self-reported and actigraphy-measured SOL duration

Poor agreement was also detected between self-reported and actigraphy measured SOL duration. The mean difference was -3.39 minutes, limit of agreement -67.17 minutes to 60.40 minutes (Figure 4-8).
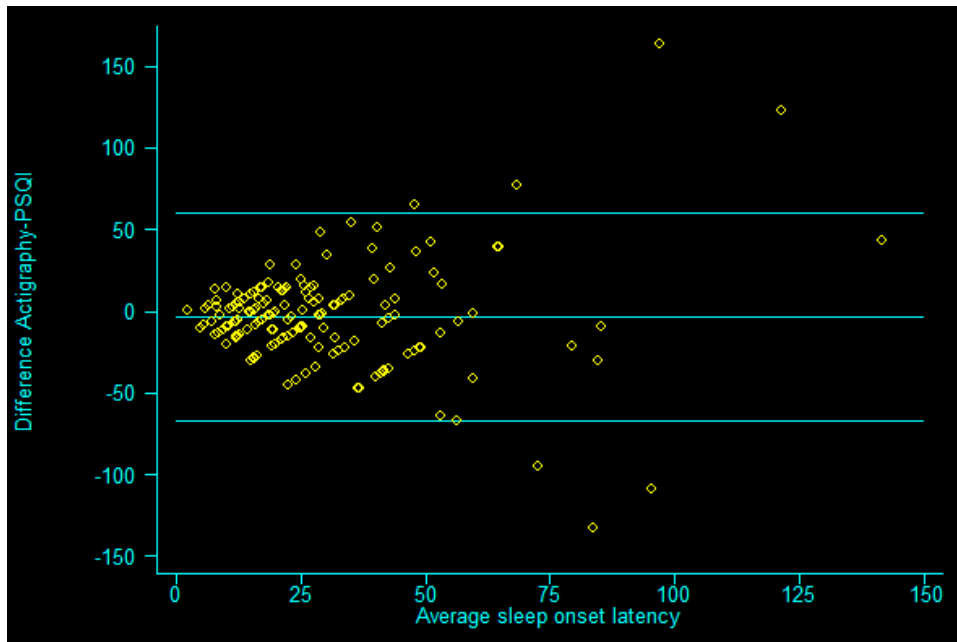
Figure 4-8 Bland-Altman plot of agreement between self-reported and actigraphy-measured sleep onset latency duration

4.3.5 Glycaemic characteristics

169 participants had at least one full day of CGM data. Glycaemic characteristics were defined using CGM summary statistics and using CGM registered daily average-glucose curves.

4.3.5.1 CGM summary statistics

The overall mean (SD) of daily glucose-average was 5.88 (0.66) mmol/l, while the overall mean (SD) of daily glucose-SD was 1.09 (0.35) mmol/l . The mean IQR was from 5.13 mmol/l to 6.53 mmol/l. 50% of participants had a glucose level within target for 93%-100% of the time (i.e. 22:23 (hours: minutes) to 24:00 (hours: minutes) per 24-hour day). Furthermore, 50% of the participants spent more than 64 minutes with a glucose level above recommended target. 50% of the participants spent 4 minutes or less with a glucose level in the hypoglycaemic zone and 25% of the participants spent more than 31 minutes in the hypoglycaemic zone. The ratio of the hyperglycaemic glucose concentration (i.e. glucose-AUC above the target) to the total daily glucose concentration ranged between 0% and 11.12%, however it did not exceed 0.44% in half of the participants and did not exceed 1.13% in a three quarter of the participants. On the other hand, the ratio of the hypoglycaemic glucose concentration (i.e. glucose-AUC below the target) to the total daily glucose concentration ranged between 0% and 6.22%, though did not exceed 0.004% in fifty percent of participants (Table 4-6).

Table 4-6 CGM derived overall summary glycaemic characteristics of 169 participants

Mean-glucose (mmol/l); Mean(SD)	5.88 (0.66)
SD-glucose (mmol/l); Mean(SD)	1.09 (0.35)
Median-glucose (mmol/l); Mean(SD)	5.74 (0.66)
25th percentile-glucose (mmol/l); Mean(SD)	5.13 (0.60)
75th percentile-glucose (mmol/l); Mean(SD)	6.53 (0.80)
Minimum-glucose (mmol/l); Mean(SD)	3.43 (0.79)
Maximum-glucose (mmol/l); Mean(SD)	9.74 (1.64)
Proportion-time glucose-in target (%); Median(IQR); (range)	93.26 (87.04,97.22); (32.64, 100)
Proportion-time glucose-above target (%); Median (IQR); (range)	4.51 (2.08, 10.42); (0.00, 67.36)
Proportion-time glucose-below target (%); Median (IQR); (range)	0.28 (0.00, 2.20); (0.00, 32.55)
Minutes glucose-in target; Median(IQR); (range)	1342 (1253, 1399); (470, 1440)
Minutes glucose-above target; Median (IQR); (range)	64 (27,138); (0, 970)
Minutes glucose-below target; Median (IQR); (range)	4 (0, 31); (0, 468)
Ratio glucose-AUC above recommended target (%); Median (IQR); (range)	0.44 (0.12, 1.13); (0.00, 11.12)
Ratio glucose-AUC below recommended range(%); Median (IQR); (range)	0.004 (0.00, 0.14); (0.00, 6.22)

4.3.5.2 CGM registered daily average-glucose curves

Mean and SD

The mean and SD curves of the participants' diurnal glucose concentrations are presented in Figure 4-9. The mean curve shows some prominent features in the diurnal glucose pattern: flattened glucose level overnight (from 02:00 am to 07:15 am), pre-breakfast (dawn) ridge (from 07:15 am to 7:45 am), breakfast meal peak (from 07:45 am to 12:30 pm), lunch meal peak (from 12:30 pm to 06:00 pm) and dinner meal peak (from 06:00 pm to 02:00 am).

The mean (SD) at some of these prominent time-points were as follows: mid-way overnight (04:00 am) 5.39 (0.79) mmol/l; fasting (08:00 am) 5.46 (0.76) mmol/l; breakfast peak (10:00 am) 6.77 (1.08) mmol/l; nadir between breakfast and lunch peaks(12:30 pm) 5.42 (0.70) mmol/l; lunch peak (03:00 pm) 6.66 (1.04); nadir between lunch and dinner peaks (06:00 pm) 5.86 (0.84) mmol/l; and dinner's peak's (10:00) 6.48 (0.85) mmol/l. Figure 4-9 shows that at the meals' peak glucose, around 22% of participants' glucose levels were higher than the upper recommended glucose target of 7.8 mmol/l.
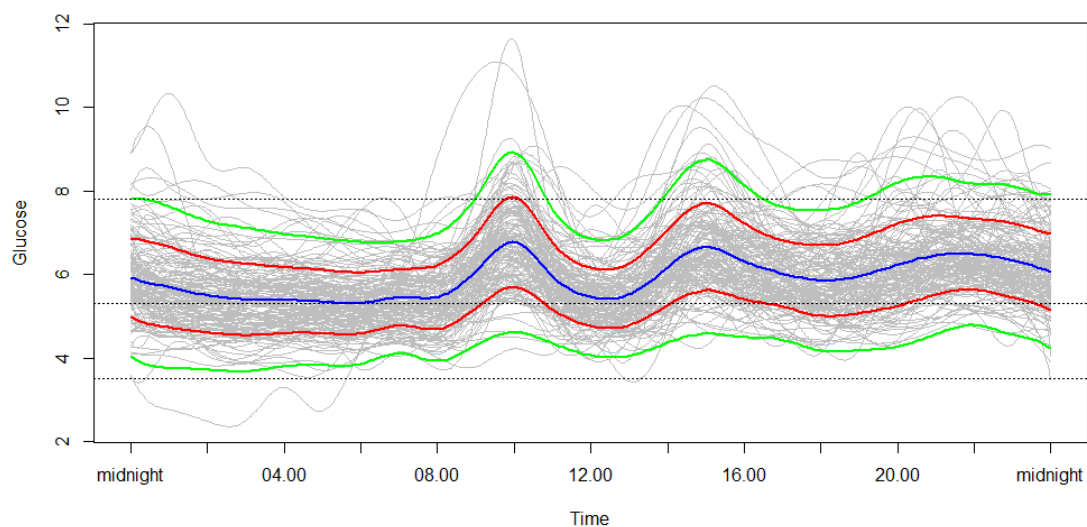
Figure 4-9 Registered average-curve curves; overall point-wise mean curve (red), ±1SD curve (red), and ± 2SD (green curve). Dashed lines demarcate recommended ranges; 3.5 mmol/l hypoglycaemic threshold, 5.3 mmol/l recommended fasting level and 7.8 mmol/l hyperglycaemic threshold

Median and IQR

A functional box plot of the glucose curves (Figure 4-10) also demonstrates that only 75% of the curves rested within the recommended range (between 3.5 to 7.8 mmol/l) while the upper quarter of participants' glucose curves stretched above that range. The functional box plot also shows that the median glucose curves at 08:00 am were just above the fasting recommended target of 5.3 mmol/l and half the participants' curves were above that fasting target.
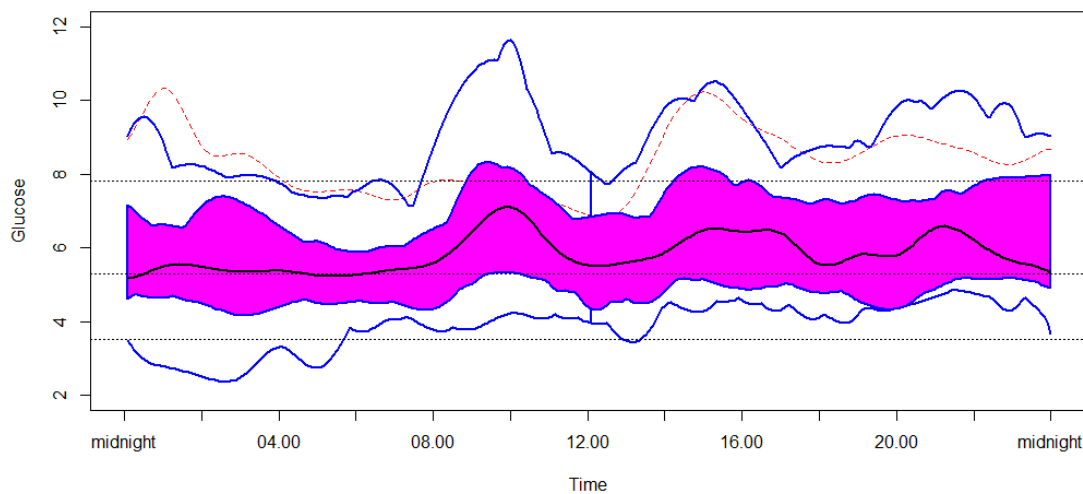
Figure 4-10 Functional boxplot of registered average-curves. Middle curve is the median, pink-shaded area is the interquartile range, inner blue curves are the 25th and the 75th percentile curves, outer blue curves are the lowest and upper range, dashed red curve is an outlier and black dotted lines demarcate recommended ranges

Correlation matrix

The glucose values across all participants, as well as within participants, were highly correlated at the period between midnight up to before breakfast with correlation coefficients above 0.6. These correlations are displayed as the 'hot' yellow and red shades on the correlation plots (Figure 4-11). During daytime, correlations were much lower and were the least around breakfast and the lunch peaks, displayed as the cold blue shades on the correlation plots (Figure 4-11). High correlation coefficients is noticed within around 30 minutes of the diagonal line in the correlation plot between 08:00 to 24:00 HH:MM, indicating high auto-correlation (within-participants correlations) between glucose values within 30 minutes.
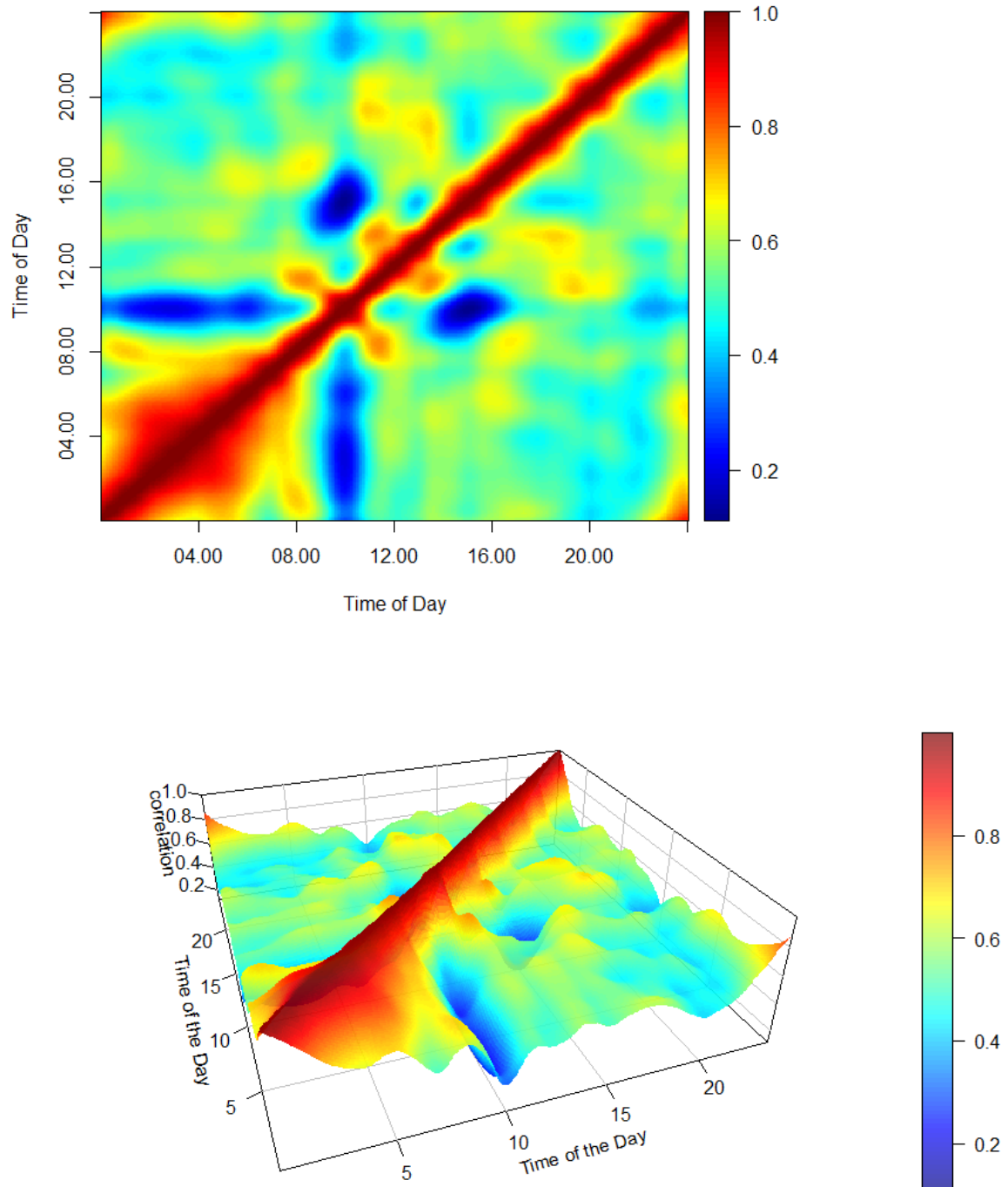
Figure 4-11 2D and 3D filled contoure plot of glucose correlation matrix

Glucose curves velocity

The rate of change of glucose values, as estimated by the glucose velocity curves, for all participants' average-glucose curves and the mean glucose velocity curve ±SD curves are presented in Figure 4-12 and Figure 4-13, respectively. Positive sections of the velocity curves (above the horizontal zero line) represent the speed of uphill side of a glucose peak, while negative sections of the velocity curves (below horizontal zero line) represent the speed of the downhill side of a glucose peak (Figure 4-14). The mean glucose velocity at main meals was as follows: breakfast meal ranged between 0.8 mmol/l/hour for the uphill side of the glucose peak and -0.8 mmol/l/hour downhill side of the glucose peak, lunch meal ranged between 0.7 mmol/l/hour for the uphill side of the glucose peak and 0.5 mmol/l/hour for the downhill side of the glucose peak, and dinner meal ranged between 0.3 mmol/l/hour for the uphill side of the glucose peak and 0.2 mmol/l/hour for the downhill side of the glucose peak.
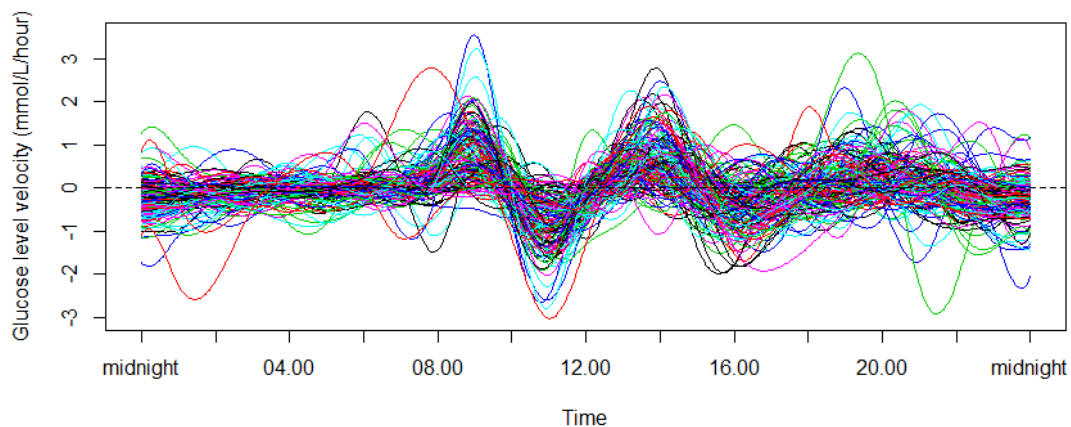
Figure 4-12 Velocity curves of the 146 participants' average-glucose curves
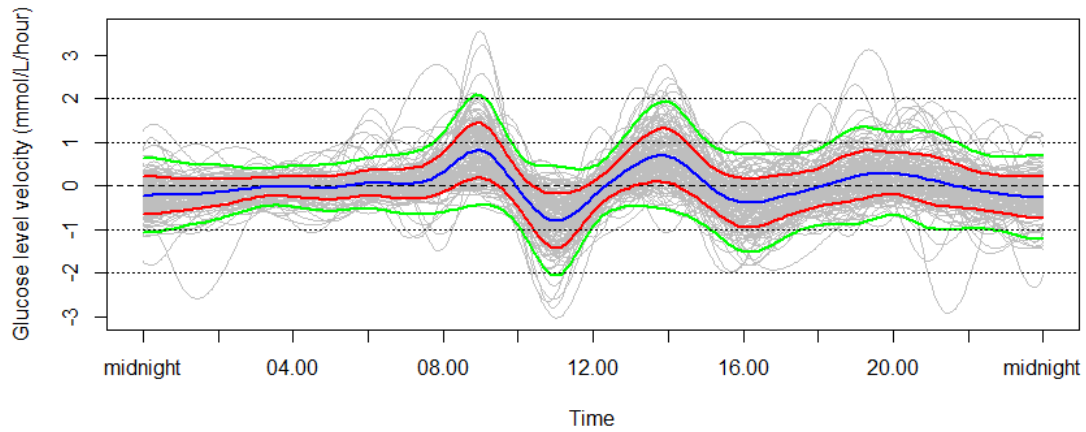
Figure 4-13 Glucose velocity mean curve (Blue), ±1SD curves (red) and ±2SD curves (green)
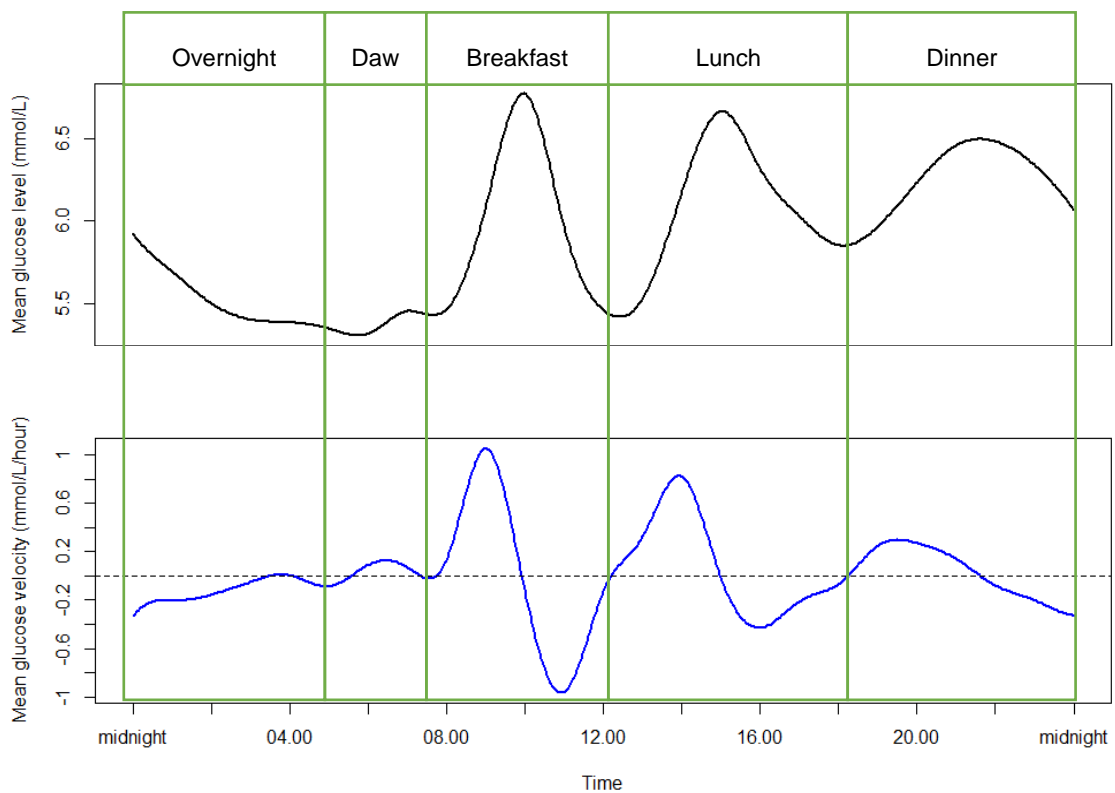
Figure 4-14 Mean glucose curve (upper panel) and mean glucose velocity curve (lower panel) Green bars separate prominent mean glucose level curve's features and correspondent inflections in the velocity curve, namely; overnight level, dawn ridge, breakfast peak, lunch peak and dinner peak.

4.4 Standard regression models results of the associations between self-reported and overall actigraphy measured sleep characteristics and overall glycaemic characteristics

4.4.1 Self-reported sleep characteristics and overall glycaemic characteristics

This section present the results of multiple linear (Table 4-7) and multiple logistic (Table 4-8) regression models of the association between self-reported sleep characteristics (the predictors); PSQI total score, sleep duration, sleep efficiency, SOL duration, mid-sleep time and subjective sleep quality rating, and overall summary glycaemic characteristics (the outcomes).

PSQI total score

Each unit increase in the PSQI total score was associated with a 0.027 mmol/l increase in the overall average glucose (Figure 4-15). The association was not statistically significant, but model diagnostics showed that participants 170 and 148 were extreme outliers and exerted very high residuals (Figure 4-16). Running the adjusted linear model after removing the data for these two participants improved the association coefficient and gave a statistically significant result (β 0.030; 95% CI 0.005 to 0.056; p-value 0.019). Furthermore, the PSQI total score was positively associated with the overall glucose SD (β 0.026; 95% CI 0.011 to 0.039; p-value <0.001) (Figure 4-17)

Participants with a higher PSQI score had a lower odds of spending more than 93% of the day within glucose targets (OR 0.90; 95% CI 0.82 to 0.99; p-value 0.037) (Figure 4-18), and a higher odds of spending more time in the hyperglycaemic zone (OR 1.15; 95% CI 1.04 to 1.27; p-value 0.008). Moreover, a higher PSQI score was associated with a higher odds of having a higher ratio of glucose concentration in the hyperglycaemic zone (OR 1.16; 95% CI 1.05 to 1.28; p-value 0.003)

Self-reported sleep duration

A J-shaped relationship was observed between the self-reported sleep duration and the average glucose (Figure 4-19). In reference to 6-8 hours self-reported sleep duration, sleeping less than 6 hours was associated with a 0.21 mmol/l increase in average glucose (95% CI -0.167 to 0.379), while sleeping more than 8 hours was associated with a 0.410 mmol/l increase in the average glucose (95% CI 0.129 to 0.691). On the other hand, a linear relationship was observed between self-reported sleep duration and SD glucose with 0.041 mmol/l lower SD glucose for each hour slept (95% CI -0.076 to -0.005).

No association was observed between self-reported sleep duration and duration of time that glucose spent within or above the recommended range. However, each hour longer spent asleep lowered the odds of spending time in the hypoglycaemic zone (OR 0.74; 95% CI 0.58 to 0.94; p-value 0.014). Shorter sleep duration compared to 6-8 hours of sleep duration were associated with higher odds of having a higher ratio of glucose concentration in hyperglycaemic zone, however the association was not statistically significant after adjusting for confounders (OR 2.54 ; 95% CI 0.96 to 6.68). On the other hand, each hour increase in the sleep duration was associated with a statistically significant lower odds of having a higher ratio of glucose concentration in the hypoglycaemic zone (OR 0.76; 95% CI 0.60 to 0.96).

Self-reported sleep efficiency

Self-reported sleep efficiency was not associated with average glucose or SD glucose. No statistically significant associations were observed with other summary glycaemic characteristics except for a lower odds of spending time in the hypoglycaemic zone with each 10% increase in self-reported sleep efficiency (OR 0.78; 95% CI 0.63 to 0.98).

Self-reported SOL duration

Self-reported sleep onset latency of 30 minutes or more was associated with a higher average glucose (β 0.221; 95% CI 0.022 to 0.421; p-value 0.030) and a higher SD glucose (β 0.129; 95% CI 0.021 to 0.237; p-value 0.020). It was also associated with half the odds of spending time within the glucose target range (OR 0.48; 95% CI 0.24 to 0.96) and double the odds of spending time in the hyperglycaemic zone (OR 2.01; 95% CI 1.004 to 4.04). Furthermore, it was also associated with a higher odds of having a higher ratio of glucose concentration in the hyperglycaemic zone (OR 2.51; 95% CI 1.27 to 4.96).

Mid-sleep time

Later self-reported chronotype (higher mid-sleep time) was not associated with any of the overall summary glycaemic characteristics.

Subjective sleep quality rating

A deterioration in the participant's subjective sleep quality rating had a linear association with average glucose, with a 0.145 mmol/l higher average glucose for each deterioration in rating of subjective sleep quality. However no associations were found with SD glucose or other summary glycaemic characteristics.
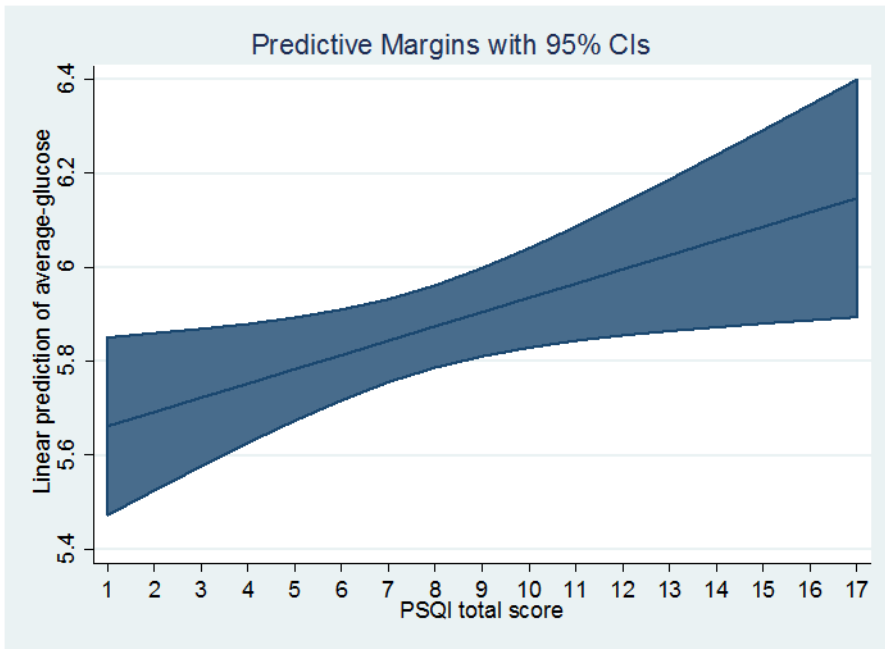
Figure 4-15 Predictive margins and 95% CI of the association between PSQI total score and overall average glucose
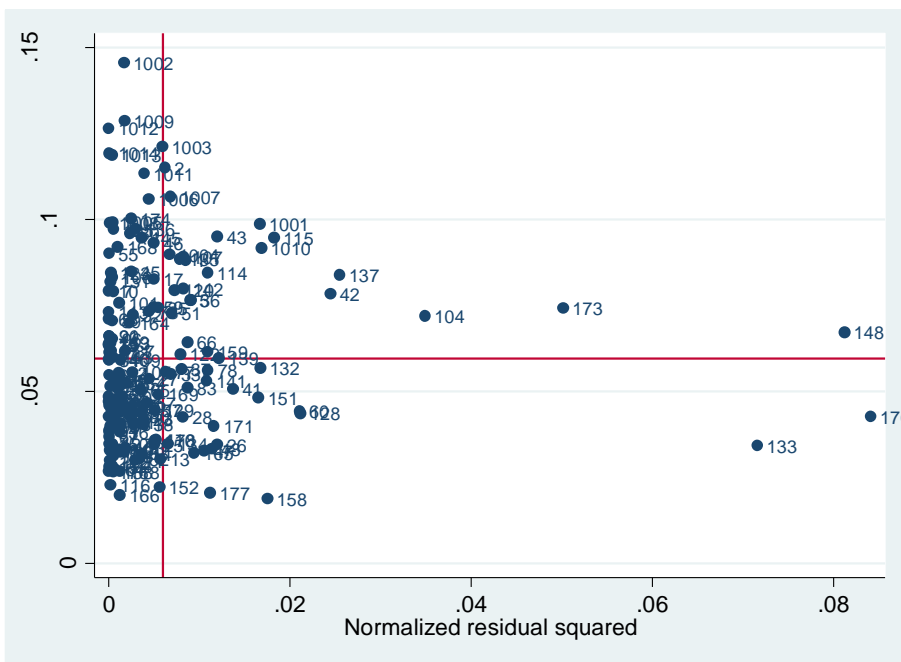
Figure 4-16 Leverage versus normalised residual squared of PSQI total score and average glucose multiple linear regression model. The lines on the chart show the average values of leverage and the residuals squared. Points above the horizontal line have higher-than-average leverage; points to the right of the vertical line have larger-than-average residuals
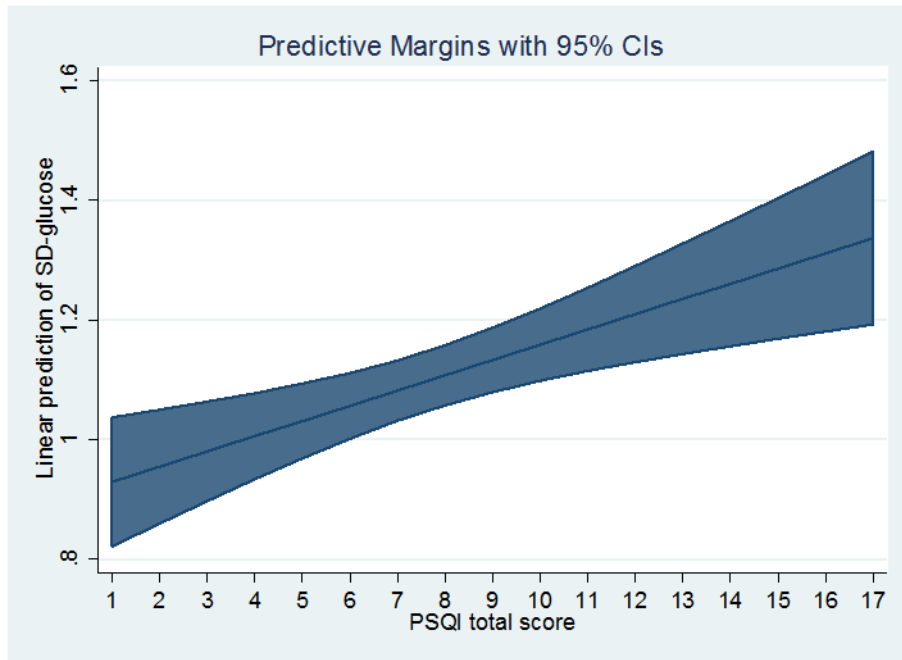
Figure 4-17 Predictive margins and 95% CI of the association between PSQI total score and overall SD glucose
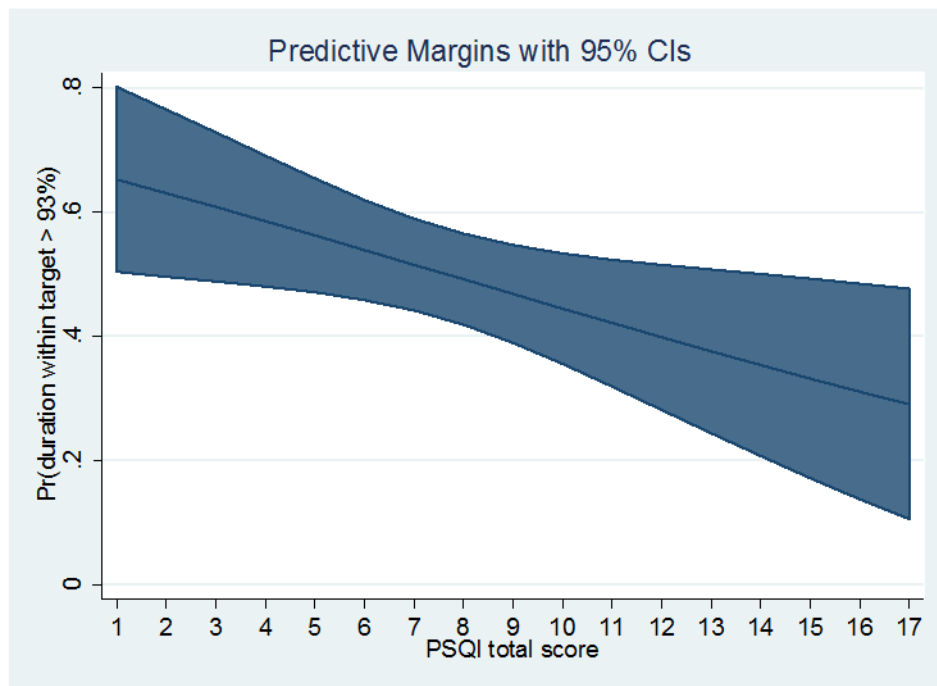
Figure 4-18 Predictive margins and 95% CI of the association between PSQI total score and the probability of spending more time (>93%) within glucose target

Figure 4-19 Predictive margins and 95% CI of the association between self-reported sleep duration and overall average glucose

Table 4-7 Linear regression models results of the association between self-reported sleep characteristics and overall average and SD glucose

Glycaemic characteristics	n=168	Unadjusted models			Adjusted models*		
	Self-reported sleep characteristics	β	95% CI	p-value	β	95% CI	p-value
Average glucose (mmol/l)	PSQI total score**	**0.034**	**0.007 to 0.061**	**0.014**	**0.027**	**-0.001 to 0.054**	**0.056**
	PSQI sleep duration (hours)						
	Short sleep vs. 6-8 hours	**0.208**	**-0.065 to 0.481**	**0.012**	**0.106**	**-0.167 to 0.378**	**0.017**
	Long sleep vs. 6-8 hours	**0.414**	**0.127 to 0.700**		**0.410**	**0.129 to 0.690**	
	PSQI sleep efficiency (10%)	-0.014	-0.081 to 0.052	0.670	-0.002	-0.063 to 0.067	0.949
	PSQI SOL duration ≥30 minutes	**0.276**	**0.077 to 0.474**	**0.007**	**0.221**	**0.022 to 0.421**	**0.030**
	PSQI mid-sleep time (hour)	-0.066	-0.151 to 0.019	0.127	-0.061	-0.154 to 0.031	0.192
	PSQI subjective sleep quality (score)	**0.142**	**0.011 to 0.273**	**0.034**	**0.145**	**0.018 to 0.272**	**0.026**
SD glucose (mmol/l)	PSQI total score	**0.028**	**0.014 to 0.042**	**<0.001**	**0.026**	**0.011 to 0.039**	**<0.001**
	PSQI sleep duration (hours)	**-0.048**	**-0.083 to -0.013**	**0.007**	**-0.041**	**-0.076 to -0.005**	**0.026**
	PSQI sleep efficiency (10%)	**-0.042**	**-0.076 to -0.001**	**0.018**	-0.003	-0.007 to 0.0002	0.063
	PSQI SOL duration ≥30 minutes	**0.148**	**0.042 to 0.254**	**0.006**	**0.129**	**0.021 to 0.237**	**0.020**
	PSQI mid-sleep time (hour)	-0.039	-0.084 to 0.007	0.095	-0.042	-0.092 to 0.008	0.104
	PSQI subjective sleep quality (score)	0.07	-0.01 to 0.14	0.067	0.06	-0.01 to 0.13	0.102

* Models were adjusted for; age, BMI at booking visit, ethnicity, treatment type, gestational age and recruitment centre

** Model post estimation diagnostics showed some outliers, adjusted model results after excluding outliers presented in the text

Table 4-8 Logistic regression models results of the association between self-reported sleep characteristics and overall duration within/above/ below recommended glucose range and ratio of AUC higher/ lower than the recommended glucose range

Glycaemic characteristics	n=168	Unadjusted models			Adjusted models*		
	Self-reported sleep characteristics	OR	95% CI	p-value	OR	95% CI	p-value
Higher duration (>93%) within recommended range	**PSQI total score**	**0.88**	**0.80 to 0.96**	**0.003**	**0.89**	**0.81 to 0.99**	**0.028**
	PSQI sleep duration (hours)						
	Short sleep vs. 6-8 hours	0.54	0.23 to 1.28	0.320	0.84	0.320 to 2.212	0.743
	Long sleep vs. 6-8 hours	0.92	0.38 to 2.21		1.154	0.430 to 3.94	
	PSQI sleep efficiency (10%)	1.15	0.94 to 1.41	0.181	1.07	0.85 to 1.33	0.580
	PSQI SOL ≥30 minutes	**0.43**	**0.23 to 0.81**	**0.008**	**0.48**	**0.24 to 0.96**	**0.038**
	PSQI mid-sleep time (hour)	1.21	0.93 to 1.57	0.163	1.27	0.92 to 1.77	0.150
	PSQI subjective sleep quality	0.75	0.50 to 1.12	0.154	0.82	0.53 to 1.28	0.383
Higher duration (>4.0%) above recommended range	PSQI total score	**1.16**	**1.06 to 1.27**	**0.001**	**1.15**	**1.04 to 1.27**	**0.008**
	PSQI sleep duration						
	Short sleep vs. 6-8 hours	2.59	1.07 to 6.24	0.067	1.98	0.74 to 5.27	0.248
	Long sleep vs. 6-8 hours	1.81	0.74 to 4.41		1.68	0.62 to 4.57	
	PSQI sleep efficiency (10%)	0.86	0.70 to 1.05	0.140	0.89	0.72 to 1.12	0.346
	PSQI SOL ≥30 minutes	**2.29**	**1.23 to 4.26**	**0.009**	**2.01**	**1.00 to 4.04**	**0.049**
	PSQI mid-sleep time	0.83	0.64 to 1.08	0.172	0.82	0.59 to 1.13	0.226
	PSQI subjective sleep quality	1.39	0.93 to 2.01	0.110	1.39	0.87 to 2.18	0.133
	PSQI total score	1.06	0.97 to 1.14	0.185	1.09	0.99 to 1.19	0.062
	PSQI sleep duration (hours)	**0.79**	**0.64 to 0.98**	**0.035**	**0.74**	**0.58 to 0.94**	**0.014**

Higher duration (>0.0%) below recommended range	**PSQI sleep efficiency (10%)**	0.83	0.67 to 1.02	0.081	**0.78**	**0.62 to 0.98**	**0.033**
	PSQI SOL ≥30 minutes	0.97	0.52 to 1.78	0.911	1.14	0.58 to 2.24	0.698
	PSQI mid-sleep time	0.85	0.65 to 1.11	0.243	0.81	0.59 to 1.11	0.184
	PSQI subjective sleep quality	1.09	0.73 to 1.63	0.669	1.18	0.76 to 1.81	0.462
Higher ratio (>0.43%) of AUC above recommended range	**PSQI total score**	**1.17**	**1.07 to 1.28**	**0.001**	**1.16**	**1.05 to 1.28**	**0.003**
	PSQI sleep duration						
	Short sleep vs. 6-8 hours	**3.07**	**1.24 to 7.58**	**0.034**	2.53	0.96 to 6.68	0.131
	Long sleep vs. 6-8 hours	1.81	0. 74 to 4.41		1.66	0.63 to 4.35	
	PSQI sleep efficiency (10%)	0.81	0.66 to 1.01	0.057	0.85	0.68 to 1.06	0.153
	PSQI SOL ≥30 minutes	**2.68**	**1.43 to 5.03**	**0.002**	**2.51**	**1.27 to 4.96**	**0.008**
	PSQI mid-sleep time	0.88	0.68 to 1.14	0.323	0.90	0.66to 1.24	0.527
	PSQI subjective sleep quality	1.43	0.95 to 2.14	0.087	1.39	0.90 to 2.16	0.142
Higher ratio (>0.0%) of AUC below recommended range	PSQI total score	1.04	0.96 to 1.13	0.324	1.07	0.97 to 1.18	0.154
	PSQI sleep duration (hours)	**0.81**	**0.65 to 0.99**	**0.048**	**0.76**	**0.60 to 0.96**	**0.023**
	PSQI sleep efficiency (10%)	0.89	0.72 to 1.08	0.242	0.83	0.66 to 1.03	0.097
	PSQI SOL ≥30 minutes	0.86	0.47 to 1.58	0.628	1.04	0.53 to 2.06	0.910
	PSQI mid-sleep time	0.86	0.66 to 1.11	0.248	0.85	0.61 to 1.16	0.286
	PSQI subjective sleep quality	1.08	0.73 to 1.61	0.695	1.17	0.76 to 1.82	0.479

*Models were adjusted for; age, BMI at booking visit, ethnicity, treatment type, gestational age and recruitment centre

4.4.2 Overall actigraphy measured sleep characteristics and overall glycaemic characteristics

This section presents the results of multiple linear and multiple logistic regression models of the association between overall actigraphy measured sleep characteristics (the predictors): sleep duration, sleep efficiency, SOL duration, mid-sleep time and WASO duration, and overall summary glycaemic characteristics (the outcomes).

A negative linear relationship was detected between the actigraphy measured sleep duration and the SD glucose (β -0.060; 95% CI -0.110 to -0.010; p-value 0.019). Furthermore, a higher actigraphy sleep efficiency was associated with a lower SD glucose (β -0.113; 95% CI -0.177 to -0.050; p-value 0.001), and an actigraphy SOL duration ≥ 30 minutes was associated with a higher SD glucose (β 0.178; 95% CI 0.058 to 0.298; p-value 0.004). On the other hand, no association, neither linear nor U-shaped, between the actigraphy measured sleep duration and the overall average glucose was detected using multiple linear regression. Moreover, none of the actigraphy measured sleep characteristics was associated with the overall average glucose.

Furthermore, an actigraphy SOL duration ≥ 30 minutes was associated with a lower odds of spending time within the recommended glucose targets (OR 0.43; 95% CI 0.19 to 0.96). Each 10 minute increase in WASO duration was associated with a16% higher odds of having a glucose concentration above the recommended targets (Figure 4-20). Other associations were not statistically significant. The actigraphy mid-sleep time was not associated with the summary glycaemic measures.
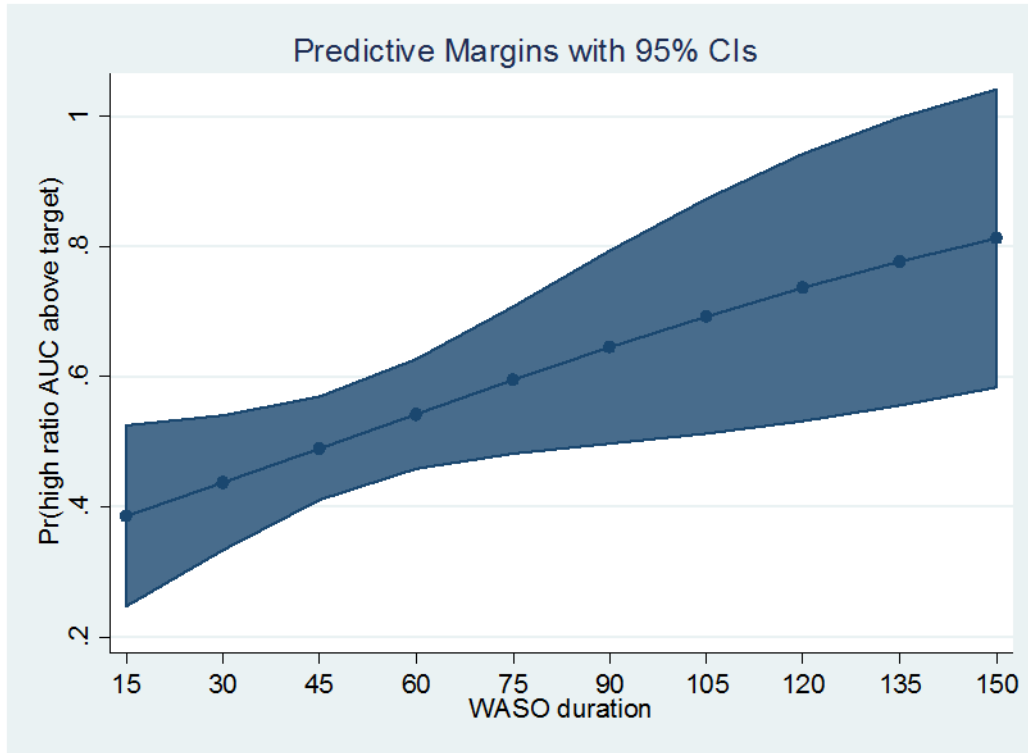
Figure 4-20 Predictive margins and 95% CI of the association between WASO duration and the probability of having higher concentration of glucose above recommended target

Table 4-9 Linear regression models results of the association between actigraphy measured sleep characteristics and overall average and SD glucose

Glycaemic characteristics	n=153	Unadjusted models			Adjusted models*		
	Actigraphy sleep characteristics	β	95% CI	p-value	β	95% CI	p-value
Overall average glucose (mmol/l)	Actigraphy sleep duration (hours)	0.027	-0.068 to 0.122	0.576	0.039	-0.055 to 0.132	0.415
	Actigraphy sleep efficiency (10%)	-0.099	-0.217 to 0.019	0.101	-0.075	-0.196 to 0.046	0.208
	Actigraphy SOL ≥30 minutes	0.104	-0.126 to 0.333	0.372	0.123	-0.103 to 0.348	0.285
	Actigraphy mid-sleep time (hours)	0.055	-0.028 to 0.137	0.193	0.040	-0.050 to 0.131	0.381
	Actigraphy WASO (10 minutes)	**0.056**	**0.014 to 0.097**	**0.009**	**0.048**	**0.005 to 0.091**	**0.028**
Overall SD glucose (mmol/l)	**Actigraphy sleep duration (hours)**	**-0.053**	**-0.102 to -0.003**	**0.036**	**-0.060**	**-0.110 to -0.010**	**0.019**
	Actigraphy sleep efficiency (10%)	**-0.101**	**-0.169 to -0.048**	**0.001**	**-0.113**	**-0.177 to -0.050**	**0.001**
	Actigraphy SOL ≥30 minutes	**0.167**	**0.049 to 0.285**	**0.006**	**0.178**	**0.058 to 0.298**	**0.004**
	Actigraphy mid-sleep time (hours)	0.041	-0.002 to 0.088	0.061	0.044	-0.004to 0.092	0.070
	Actigraphy WASO (10 minutes)	0.024	0.001 to 0.046	0.037	0.021	-0.002 to 0.045	0.075

* Models were adjusted for; age, BMI at booking visit, ethnicity, treatment type, gestational age and recruitment centre

Table 4-10 Logistic regression models results of the association between actigraphy measured sleep characteristics and overall duration within/above/ below recommended glucose range and ratio of AUC higher/ lower than the recommended glucose range

Glycaemic characteristics	n=153	Unadjusted models			Adjusted models*		
	Actigraphy sleep characteristics	OR	95% CI	p-value	OR	95% CI	p-value
Higher duration (>93%) within recommended range	Actigraphy sleep duration (hours)	1.06	0.80 to 1.41	0.670	1.06	0.77 to 1.47	0.713
	Actigraphy sleep efficiency (10%)	1.45	0.99 to 2.12	0.056	1.42	0.93 to 2.17	0.108
	Actigraphy SOL ≥30 minutes	**0.48**	**0.24 to 0.96**	**0.038**	**0.43**	**0.19 to 0.96**	**0.038**
	Actigraphy mid-sleep time (hours)	0.82	0.64 to 1.06	0.126	0.82	0.59 to 1.14	0.239
	Actigraphy WASO (10 minutes)	0.90	0.79 to 1.03	0.133	0.92	0.79 to 1.07	0.318
Higher duration (>4.0%) above recommended range	Actigraphy sleep duration (hours)	1.06	0.80 to 1.40	0.700	1.09	0.79 to 1.51	0.595
	Actigraphy sleep efficiency (10%)	0.73	0.50 to 1.06	0.095	0.77	0.51 to 1.18	0.239
	Actigraphy SOL ≥30 minutes	1.49	0.75 to 2.97	0.248	1.52	0.69 to 3.34	0.293
	Actigraphy mid-sleep time (hours)	1.23	0.95 to 1.59	0.110	1.17	0.85 to 1.61	0.340
	Actigraphy WASO (10 minutes)	**1.16**	**1.02 to 1.34**	**0.024**	1.15	0.98 to 1.35	0.096
Higher duration (0.28%) below recommended range	Actigraphy sleep duration (hours)	1.03	0.78 to 1.37	0.814	1.00	0.74 to 1.36	0.975
	Actigraphy sleep efficiency (10%)	1.01	0.71 to 1.44	0.954	0.92	0.61 to 1.37	0.686
	Actigraphy SOL ≥30 minutes	1.03	0.52 to 2.04	0.928	1.01	0.48 to 2.12	0.975
	Actigraphy mid-sleep time (hours)	0.91	0.71 to 1.17	0.466	0.91	0.68 to 1.23	0.540
	Actigraphy WASO (10 minutes)	0.95	0.84 to 1.08	0.425	0.98	0.85 to 1.13	0.784
Higher ratio (>0.43%) of AUC above recommended range	Actigraphy sleep duration (hours)	1.05	0.79 to 1.39	0.79	1.05	0.77 to 1.43	0.757
	Actigraphy sleep efficiency (10%)	0.76	0.53 to 1.10	0.152	0.78	0.52 to 1.17	0.222
	Actigraphy SOL ≥30 minutes	1.44	0.73 to 2.85	0.296	1.57	0.75 to 3.34	0.232
	Actigraphy mid-sleep time (hours)	1.17	0.91 to 1.51	0.211	1.18	0.87 to 1.61	0.285
	Actigraphy WASO (10 minutes)	**1.17**	**1.02 to 1.34**	**0.026**	**1.16**	**1.00 to 1.36**	**0.049**

Higher ratio (>0.00%) of AUC below recommended range	Actigraphy sleep duration (hours)	0.91	0.69 to 1.21	0.531	0.89	0.65 to 1.21	0.445
	Actigraphy sleep efficiency (10%)	0.98	0.69 to 1.40	0.928	0.85	0.56 to 1.28	0.443
	Actigraphy SOL ≥30 minutes	0.96	0.49 to 1.89	0.906	0.92	0.43 to 1.97	0.837
	Actigraphy mid-sleep time (hours)	0.91	0.71 to 1.16	0.452	0.96	0.71 to 1.30	0.787
	Actigraphy WASO (10 minutes)	0.92	0.81 to 1.05	0.231	0.97	0.84 to 1.12	0.646

* Models were adjusted for; age, BMI at booking visit, ethnicity, treatment type, gestational age and recruitment centre

4.5 Multilevel regression models results for the association between self-reported and daily actigraphy measured sleep characteristics and daily glycaemic characteristics

4.5.1 Multilevel regression models results for the association between self-reported sleep characteristics and daily glycaemic characteristics

This section presents the results of multilevel mixed effect linear (Table 4-11) and mixed effect logistic (Table 4-12) regression models of the association between self-reported sleep characteristics (the predictors); PSQI total score, sleep duration, sleep efficiency, SOL duration, mid-sleep time and subjective sleep quality rating, and daily summary glycaemic characteristics (the outcomes). Models were adjusted for weekend/weekday in addition to the set used in the overall study. Only complete dataset used in these analyses as CGM data intervals (days) were defined using daily actigraphy bedtime and getting-up time. The dataset consisted of 149 participants with 795 days, 1-6 days per participant. Multilevel mixed effect regression models for the analysis of this data had an improved fit over ordinary, only fixed term, regression models (log likelihood p-value <0.001). The variance partition coefficient (VPC) ranged between 50% and 60% for the linear models and the intra-class correlation coefficient (ICC) ranged between 36% and 40% for the logistic models.

PSQI total score

A higher PSQI total score was associated with: a higher SD glucose (β 0.022; 95% CI 0.009 to 0.036; p-value 0.001); a lower odds of spending more than 93% of the daily time within the recommended glucose target (OR 0.89, 95% CI 0.81 to 0.97, p-value 0.010); a higher odds of spending more than 4% of the daily time above the recommended glucose target (OR 1.15; 95% CI 1.05 to 1.26; p-value 0.003); and a higher odds of having a higher ratio of glucose concentration (>0.43%) in the hyperglycaemic zone (OR 1.18; 95% CI 1.08 to 1.30; p-value <0.001). Moreover, a higher PSQI was associated with a higher, but statistically non-significant, average glucose (β 0.018; 95% CI -0.011 to 0.047; p-value 0.230). However, the model post estimation caterpillar residuals plot revealed participant 170 to be a potential outlier (Figure 4-21). Running the model while excluding participant 170 improved the model coefficients (β 0.029; 95% CI 0.002 to 0.057; p-value 0.037).

Self-reported sleep duration

Compared to sleeping 6-8 hours, sleeping more than 8 hours was associated with 0.483 mmol/l higher average glucose (95% CI 0.161 to 0.744). Sleeping less than 6 hours was

associated with, a non-statistically significant, 0.151 increase in average glucose (Figure 4-22). Each hour increase in the sleep duration was associated with a 0.045 mmol/l decrease in the SD glucose (95% CI -0.064 to -0.002). Furthermore, both long and short sleep duration, compared to 6-8 hours, had lower odds of spending more than 93% of the time within glucose recommended targets, higher odds of spending more time above the recommended targets and higher odds of having higher concentration of glucose in hyperglycaemic zones. However none of these associations were statistically significant. Lastly, the longer the sleep duration the less likely the participants were to develop hypoglycaemia.

Self-reported SOL duration

Self-reported sleep onset latency duration of 30 minutes or more was associated with: a 0.301 mmol/l (95% CI 0.028 to 0.442) increase in daily average glucose; a 0.121 mmol/l (95% CI 0.007 to 0.199) increase in the daily SD glucose; a 62% (95% CI 0.20 to 0.73) lower odds of spending time within the glucose target range; more than twice the odds (95% CI 1.20 to 4.31) of spending more time in the hyperglycaemic zone; and three times the odds (95% CI 1.59 to 5.91) of having a higher ratio of glucose concentration above the recommended range.

No statistically significant associations were observed between self-reported sleep efficiency, self-reported mid-sleep time and subjective sleep quality rating, with daily summary glycaemic measures.
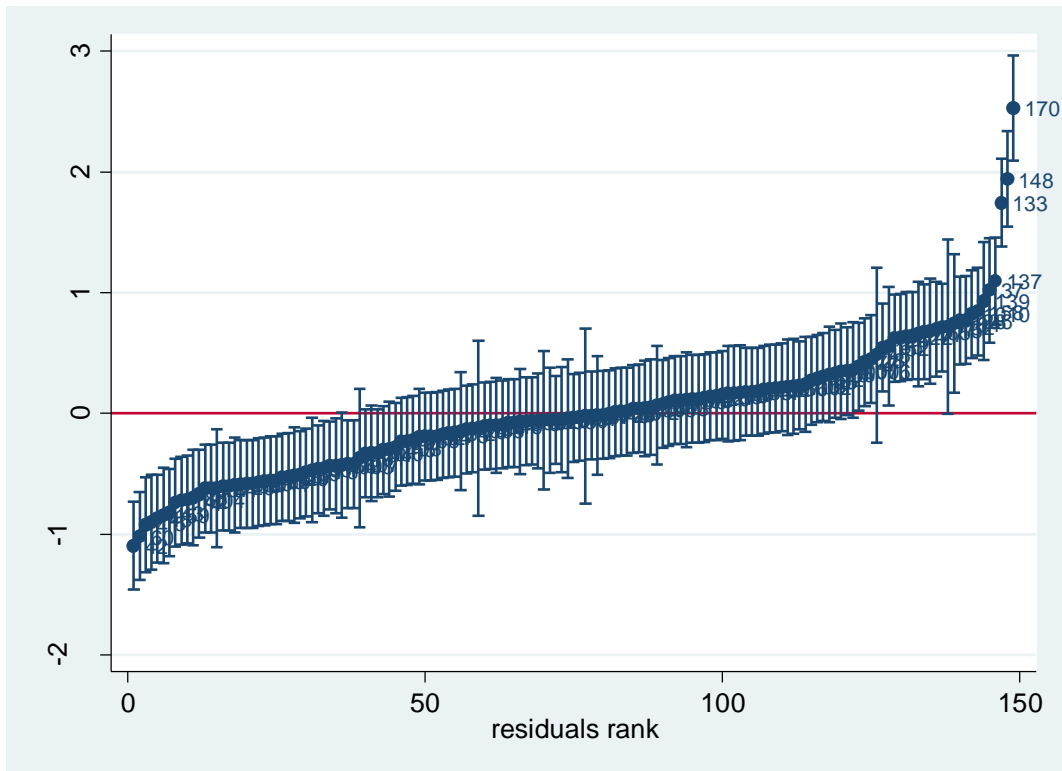
Figure 4-21 Caterpillar plot of PSQI and average glucose model's residuals with very high residuals for participant number 170
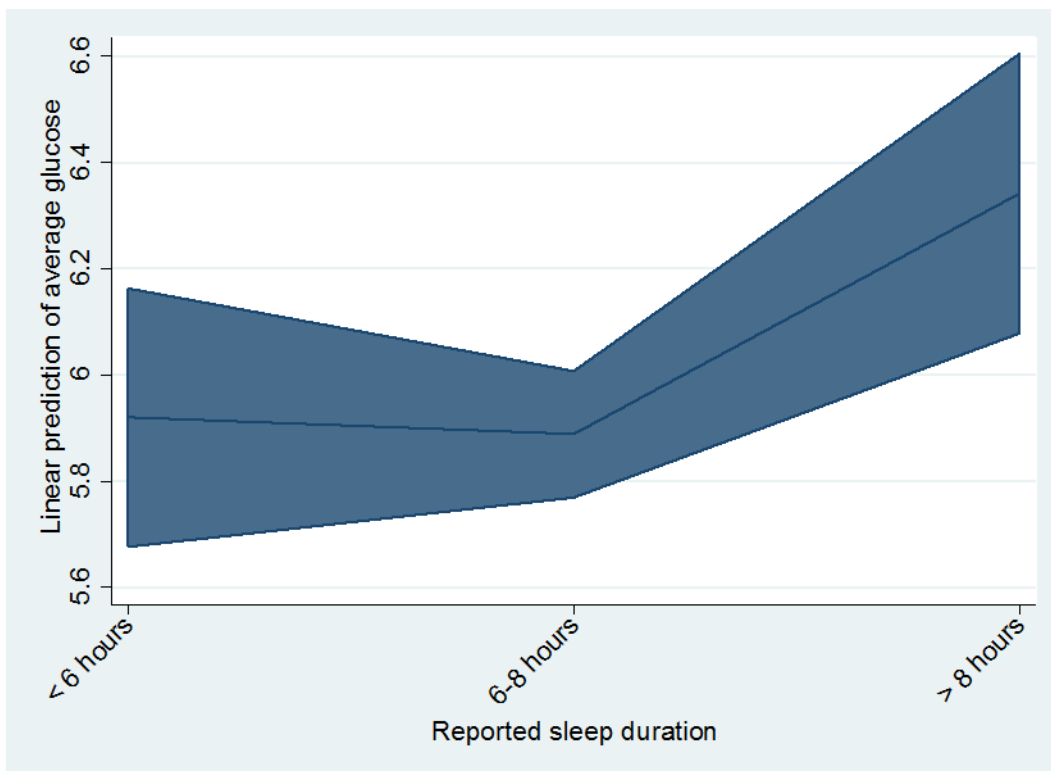
Figure 4-22 Predictive margins and 95% CI of the association between self-reported sleep duration and daily average glucose
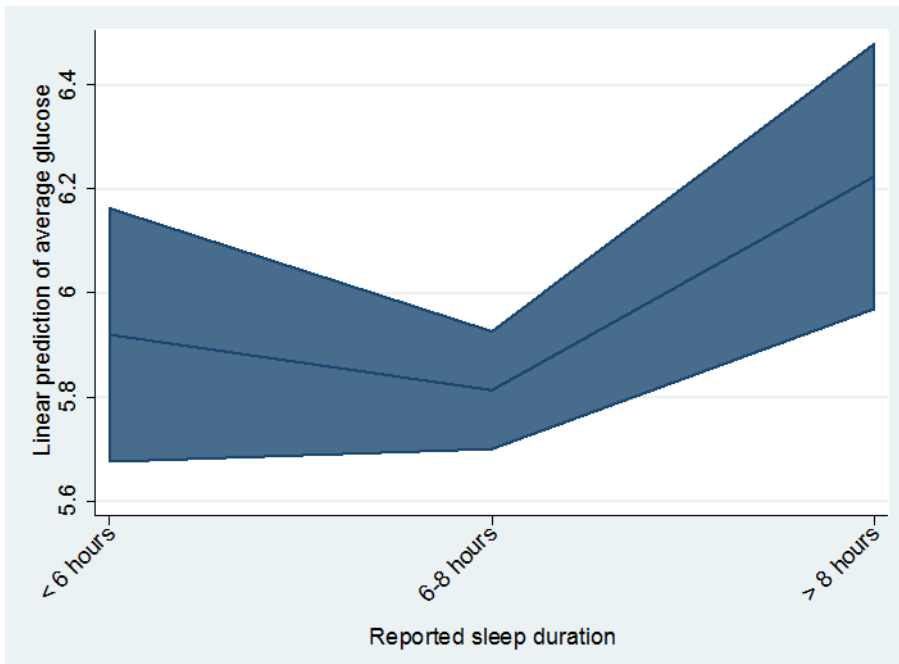
Table 4-11 Multilevel linear regression models results of the association between self-reported sleep characteristics and daily average and SD glucose

. participants=149	Unadjusted models fixed effects			Adjusted models* fixed effects			Adjusted models random effect		
Main exposure	β	95% CI	p-value	β	95% CI	p-value	SD between participants (95% CI)	SD within participants (95% CI)	VPC** (95% CI)
Daily average glucose (mmol/l) models									
PSQI total score	0.027	-0.00 to 0.057	0.070	0.018	-0.011 to 0.047	0.230	0.58 (0.51 to 0.66)	0.47 (0.45 to 0.51)	0.60 (0.53 to 0.66)
PSQI sleep duration***									
Short sleep	**0.151**	**-0.131 to 0.433**	**0.005**	**0.031**	**-0.244 to 0.306**	**0.009**	0.56 (0.49 to 0.64)	0.48 (0.45 to 0.51)	0.60 (0.51 to 0.65)
Long sleep	**0.483**	**0.21 to 0.85**		**0.453**	**0.161 to 0.744**				
PSQI sleep efficiency (10%)	-0.001	-0.072 to 0.070	0.979	0.015	-0.053 to 0.083	0.664	0.59 (0.51 to 0.67)	0.48 (0.45 to 0.51)	0.60 (0.53 to 0.67)
PSQI SOL ≥30 minutes	**0.301**	**0.089 to 0.513**	**0.005**	**0.235**	**0.028 to 0.442**	**0.026**	0.57 (0.50 to 0.65)	0.48 (0.45 to 0.51)	0.59 (0.51 to 0.65)
PSQI mid-sleep time (hours)	-0.047	-0.143 to 0.049	0.337	-0.056	-0.156 to 0.045	0.278	0.58 (0.51 to 0.66)	0.48 (0.45 to 0.51)	0.60 (0.53 to 0.66)
PSQI subjective sleep quality score	0.093	-0.048 to 0.234	0.198	0.103	-0.033 to 0.239	0.136	0.58 (0.51 to 0.66)	0.48 (0.45 to 0.51)	0.60 (052 to 0.66)
Daily SD glucose (mmol/l) models									
PSQI total score	**0.026**	**0.013 to 0.040**	**<0.001**	**0.022**	**0.009 to 0.036**	**0.001**	0.25 (0.22 to 0.29)	0.25 (0.24 to 0.26)	0.50 (0.43 to 0.58)
PSQI sleep duration (hours)	**-0.045**	**-0.077 to -0.013**	**0.006**	**-.033**	**-0.064 to -0.002**	**0.038**	0.25 (0.22 to 0.29)	0.25 (0.24 to 0.26)	0.50 (0.43 to 0.58)
PSQI sleep efficiency (10%)	-0.034	-0.066 to -0.002	0.040	-0.024	-0.056 to 0.007	0.126	0.26 (0.23 to 0.30)	0.25 (0.24 to 0.26)	0.52 (0.44 to 0.59)
PSQI SOL ≥30 minutes	**0.121**	**0.021 to 0.221**	**0.017**	**0.103**	**0.007 to 0.199**	**0.035**	0.26 (0.22 to 0.29)	0.25 (0.24 to 0.26)	0.51 (0.44 to 0.59)
PSQI mid-sleep time (hours)	-0.028	-0.072 to 0.0170	0.225	-0.021	-0.067 to 0.025	0.365	0.26 (0.23 to 0.30)	0.25 (0.24 to 0.26)	0.52 (0.44 to 0.59)
PSQI subjective sleep quality score	0.051	-0.014 to 0.116	0.127	0.044	-0.019 to 0.107	0.172	0.26 (0.23 to 0.30)	0.25 (0.24 to 0.26)	0.52 (0.44 to 0.59)

* Models were adjusted for; age, BMI at booking visit, ethnicity, treatment type, gestational age, weekend and recruitment centre. ** Variance partition coefficient.*** compared to 6-8 hours of sleep.

Table 4-12 Logistic regression models results of the association between self-reported sleep characteristics and overall duration within/above/ below recommended glucose range and ratio of AUC higher/ lower than the recommended glucose range

participants=149	Unadjusted models fixed effects			Adjusted models* fixed effects			Adjusted models random effects	
Main exposure	OR	95% CI	p-value	OR	95% CI	p-value	Variance component (95% CI)	ICC** (95% CI)
Higher duration (>93%) within recommended range models								
PSQI total score	**0.84**	**0.77 to 0.94**	**0.001**	**0.89**	**0.81 to 0.97**	**0.010**	2.15 (1.30 to 3.56)	0.40 (0.28 to 0.52)
PSQI sleep duration								
Short sleep vs. 6-8 hours	0.30	0.12 to 0.75	0.014	0.47	0.20 to 1.11	0.114	2.01 (1.34 to 3.64)	0.40 (0.29 to 0.53)
Long sleep vs. 6-8 hours	0.39	0.14 to 1.05		0.50	0.20 to 1.24			
PSQI sleep efficiency (10%)	1.15	0.91 to 1.45	0.236	1.05	0.86 to 1.31	0.596	2.32 (1.41 to 3.79)	0.41 (0.30 to 0.54)
PSQI SOL ≥30 minutes	**0.31**	**0.15 to 0.62**	**0.001**	**0.38**	**0.20 to 0.73**	**0.003**	2.12 (1.28 to 3.51)	0.39 (0.28 to 0.52)
PSQI mid-sleep time (hours)	1.14	0.84 to 1.53	0.398	1.20	0.88 to 1.61	0.238	2.08 (1.28 to 3.39)	0.39 (0.28 to 0.51)
PSQI subjective sleep quality score	0.71	0.46 to 1.10	0.131	0.73	0.49 to 1.10	0.135	2.01 (1.23 to 3.29)	0.38 (0.27 to 0.50)
Higher duration (>4.0%) above recommended range models								
PSQI total score	**1.18**	**1.07 to 1.30**	**0.001**	**1.15**	**1.05 to 1.26**	**0.003**	2.07 (1.27 to 3.38)	0.39 (0.28 to 0.51)
PSQI sleep duration								
Short sleep vs. 6-8 hours	2.18	0.87 to 5.48	0.131	1.53	0.64 to 3.64	0.355	2.20 (1.36 to 3.55)	0.40 (0.29 to 0.52)
Long sleep vs. 6-8 hours	2.09	0.76 to 5.70		1.78	0.71 to 4.46			
PSQI sleep efficiency (10%)	0.87	0.69 to 1.09	0.213	0.92	0.74 to 1.13	0.401	2.22 (1.31 to 3.46)	0.39 (0.29 to 0.51)
PSQI SOL ≥30 minutes	**2.67**	**1.34 to 5.34**	**0.005**	**2.27**	**1.20 to 4.31**	**0.012**	2.23 (1.38 to 3.61)	0.40 (0.29 to 0.52)
PSQI mid-sleep time (hours)	0.90	0.66 to 1.23	0.519	0.95	0.67 to 1.30	0.778	2.29 (1.42 to 3.70)	0.40 (0.30 to 0.53)
PSQI subjective sleep quality score	1.42	0.90 to 2.24	0.128	1.46	0.95 to 2.22	0.083	2.20 (1.38 to 3.56)	0.40 (0.29 to 0.52)
Higher duration (>0.0%) below recommended range models								
PSQI total score	1.01	0.92 to 1.12	0.778	1.00	0.90 to 1.11	0.906	1.98 (1.00 to 3.95)	0.37 (0.23 to 0.55)
PSQI sleep duration								
Short sleep vs. 6-8 hours	1.78	0.72 to 4.40	**0.035**	1.70	0.69 to 4.21	**0.021**	1.60 (0.76 to 3.37)	0.32 (0.19 to 0.51)
Long sleep vs. 6-8 hours	**0.26**	**0.07 to 0.95**		**0.22**	**0.06 to 0.80**			
PSQI sleep efficiency (10%)	0.94	0.74 to 1.20	0.629	0.96	0.75 to 1.21	0.707	1.98 (1.00 to 3.94)	0.38 (0.23 to 0.55)
PSQI SOL ≥30 minutes	0.65	0.31 to 1.38	0.261	0.64	0.31 to 1.34	0.242	1.89 (0.96 to 3.85)	0.37 (0.23 to 0.54)
PSQI mid-sleep time (hours)	0.79	0.56 to 1.11	0.173	0.77	0.54 to 1.11	0.161	1.84 (0.90 to 3.71)	0.36 (0.21 to 0.53)

PSQI subjective sleep quality score	1.01	0.62 to 1.65	0.959	0.93	0.56 to 1.53	0.777	1.98 (1.00 to 3.94)	0.38 (0.23 to 0.54)
Higher ratio (>0.43%) of AUC above recommended range models								
PSQI total score	**1.15**	**1.06 to 1.25**	**0.001**	**1.18**	**1.08 to 1.30**	**<0.001**	2.13 (1.27 to 3.58)	0.39 (0.27 to 0.52)
PSQI sleep duration								
Short sleep vs. 6-8 hours	2.78	1.05 to 7.40	0.069	1.94	0.79 to 4.80	0.248	2.38 (1.44 to 3.93)	0.42 (0.30 to 0.54)
Long sleep vs. 6-8 hours	2.14	0.76 to 6.07		1.70	0.66 to 4.34			
PSQI sleep efficiency (10%)	0.78	0.61 to 0.99	0.046	0.83	0.66 to 1.03	0.092	2.38 (1.44 to 3.93)	0.42 (0.30 to 0.54)
PSQI SOL ≥30 minutes	**3.43**	**1.66 to 7.11**	**0.001**	**3.06**	**1.59 to 5.91**	**0.001**	2.16 (1.30 to 3.61)	0.40 (0.28 to 0.52
PSQI mid-sleep time (hours)	0.87	0.63 to 1.22	0.434	0.93	0.68 to 1.29	0.688	2.44 (1.48 to 4.03)	0.42 (0.30 to 0.54)
PSQI subjective sleep quality score	1.32	0.88 to 1.98	0.179	1.41	0.95 to 2.08	0.086	2.38 (1.44 to 3.93)	0.42 (0.31 to 0.55)
Higher ratio (>0.0%) of AUC below recommended range models								
PSQI total score	1.01	0.92 to 1.12	0.778	1.00	0.90 to 1.11	0.906	1.98 (0.99 to 3.95)	0.37 (0.23 to 0.54)
PSQI sleep duration								
Short sleep vs. 6-8 hours	1.78	0.72 to 4.40	**0.035**	1.70	0.68 to 4.21	**0.021**	1.60 (0.76 to 3.38)	0.33 (0.19 to 0.51)
Long sleep vs. 6-8 hours	**0.26**	**0.07 to 0.94**		**0.22**	**0.06 to 0.80**			
PSQI sleep efficiency (10%)	0.94	0.74 to 1.20	0.629	0.96	0.75 to 1.21	0.707	1.97 (0.99 to 3.93)	0.37 (0.23 to 0.54)
PSQI SOL ≥30 minutes	0.65	0.31 to 1.38	0.261	0.64	0.31 to 1.41	0.242	1.89 (0.94 to 3.81)	0.37 (0.23 to 0.54)
PSQI mid-sleep time (hours)	0.79	0.56 to 1.11	0.173	0.77	0.54 to 1.11	0.161	1.84 (0.90 to 3.71)	0.36 (0.21 to 0.53)
PSQI subjective sleep quality score	1.01	0.62 to 1.65	0.959	0.93	0.56 to 1.53	0.787	1.98 (0.99 to 3.94)	0.37 (0.23 to 0.54)

* Models were adjusted for; age, BMI at booking visit, ethnicity, treatment type, gestational age, weekend and recruitment centre.

** Residual intraclass correlation.

4.5.2 Multilevel regression models results for the association between daily actigraphy measured sleep characteristics and daily glycaemic characteristics

This section presents the multilevel mixed effects models results; linear models (Table 4-13) and logistic models (Table 4-14), of the association between actigraphy measured sleep indices during each night to the following days glycaemic characteristics (from getting up from bed to getting up the next day). The data consists of 795 nights and 795 days for 149 participants with 1-6 nights/days per participant. Likelihood-ratio tests comparing the multilevel models to ordinary linear and logistic regression models were highly significant (p-value < 0.001). VPC for linear models ranged between 52% and 60%, and residuals ICC for logistic models ranged between 37% and 42%.

Short actigraphy measured sleep duration, compared to 6-8 hours of sleep, was associated with a higher average glucose the following day (β 0.119; 95% CI 0.004 to 0.234) and a higher SD glucose the following day(β 0.064; 95% CI 0.004 to 0.124). However the Wald test p-values of the joint statistical significant of sleep categories (short, 6-8 hours, and long) as a whole was not conclusive, 0.089 and 0.091 respectively. Furthermore, short sleep duration had a higher odds of hyperglycaemia and lower odds of being within the target range. None of these associations were statistically significant.

Sleep onset latency of 30 minutes or more was associated with a 0.127 mmol/l higher average glucose the following day (95% CI 0.037 to 0.216; p-value 0.006). It was also associated with a slightly higher SD glucose and lower odds of being in the glucose target range and a higher odds of hyperglycaemia. None of these associations were statistically significant.

Each 10% increase in sleep efficiency was associated with an 18% lower odds of having a high ratio of glucose above the recommended target (95% CI 0.67 to 1.00; p-value 0.049). Furthermore, later chronotype had: a lower odds of hypoglycaemia; a lower odds of spending time below the recommended glucose target (OR 0.72; 95% CI 0.55 to 0.95; p-value 0.014) and a lower odds of a high ratio of glucose concentration below the recommended target (OR 0.72; 95% CI 0.55 to 0.94; p-value 0.014).

Table 4-13 Multilevel linear regression models results of the association between actigraphy measured sleep characteristics and daily average and SD glucose

n=795, cluster=149	Unadjusted models fixed effects			Adjusted models* fixed effects			Adjusted models random effect		
Main exposure	β	95% CI	p-value	β	95% CI	p-value	SD between cluster (95% CI)	SD within cluster (95% CI)	VPC** (95% CI)
Daily average glucose (mmol/l)									
Actigraphy sleep duration									
Short sleep vs. 6-8 hours	**0.129**	**0.013 to 0.244**	0.070	**0.119**	**0.004 to 0.234**	0.089	0.58 (0.51 to 0.66)	0.48 (0.45 to 0.51)	0.60 (0.53 to 0.66)
Long sleep vs. 6-8 hours	0.060	-0.035 to 0.148		0.059	-0.032 to 0.151				
Actigraphy sleep efficiency (10%)	-0.016	-0.054 to 0.022	0.403	-0.014	-0.052 to 0.024	0.471	0.58 (0.51 to 0.67)	0.48 (0.45 to 0.51)	0.60 (0.53 to 0.66)
Actigraphy SOL ≥30 minutes	**0.127**	**0.038 to 0.217**	**0.005**	**0.127**	**0.037 to 0.216**	**0.006**	0.58 (0.51 to 0.66)	0.48 (0.45 to 0.50)	0.60 (0.53 to 0.66)
Actigraphy WASO (10 minutes)	-0.006	-0.020 to 0.007	0.378	-0.006	-0.021 to 0.007	0.342	0.59 (0.51 to 0.67)	0.48 (0.45 to 0.51)	0.60 (0.53 to 0.66)
Actigraphy mid-sleep time (hours)	0.031	-0.010 to 0.072	0.142	0.030	-0.015 to 0.075	0.198	0.58 (0.51 to 0.67)	0.48 (0.45 to 0.51)	0.59 (0.52 to 0.66)
Daily SD glucose (mmol/l)									
Actigraphy sleep duration									
Short sleep vs. 6-8 hours	**0.061**	**0.001 to 0.121**	**0.045**	**0.064**	**0.004 to 0.124**	0.091	0.26 (0.23 to 0.30)	0.25 (0.24 to 0.26)	0.52 (0.44 to 0.60)
Long sleep vs. 6-8 hours	0.028	-0.020 to 0.075		0.026	-0.021 to 0.074				
Actigraphy sleep efficiency (10%)	0.001	-0.018 to 0.021	0.918	0.000	-0.018 to 0.020	0.952	0.26 (0.23 to 0.30)	0.25 (0.24 to 0.26)	0.53 (0.44 to 0.60)
Actigraphy SOL ≥30 minutes	0.032	-0.015 to 0.078	0.185	0.032	-0.014 to 0.079	0.173	0.26 (0.23 to 0.30)	0.25 (0.24 to 0.26)	0.52 (0.44 to 0.60)
Actigraphy WASO (10 minutes)	0.000	-0.007 to 0.007	0.988	-0.000	-0.007 to 0.007	0.986	0.26 (0.23 to 0.30)	0.25 (0.24 to 0.26)	0.52 (0.44 to 0.60)
Actigraphy mid-sleep time (hours)	0.006	-0.015 to 0.027	0.593	0.004	-0.019 to 0.027	0.774	0.26 (0.23 to 0.30)	0.25 (0.24 to 0.26)	0.52 (0.44 to 0.60)

* Models were adjusted for; age, BMI at booking visit, ethnicity, treatment type, gestational age, recruitment centre and weekend.
** Variance partition coefficient.

Table 4-14 Multilevel logistic regression models results of the association between actigraphy measured sleep characteristics and daily duration within/above/ below recommended glucose range and ratio of AUC higher/ lower than the recommended glucose range

n=795, cluster=149	Unadjusted models fixed effects			Adjusted models* fixed effects			Adjusted models random effect	
Main exposure	OR	95% CI	p-value	OR	95% CI	p-value	variance component (95% CI)	ICC** (95% CI)
Higher duration (>93%) within recommended range models								
Actigraphy sleep duration								
Short sleep vs. 6-8 hours	0.84	0.48 to 1.48	0.831	0.91	0.511 to 1.59	0.923	2.04 (1.25 to 3.32)	0.38 (0.27 to 0.50)
Long sleep vs. 6-8 hours	0.94	0.60 to 1.48		0.94	0.59 to 1.46			
Actigraphy sleep efficiency (10%)	1.17	0.97 to 1.42	0.109	1.14	0.95 to 1.37	0.168	2.00 (1.22 to 3.27)	0.38 (0.27 to 0.50)
Actigraphy SOL ≥30 minutes	0.66	0.42 to 1.03	0.067	0.66	0.42 to 1.03	0.067	2.01 (1.23 to 3.29)	0.38 (0.28 to 0.50)
Actigraphy mid-sleep time (hours)	0.89	0.74 to 1.06	0.178	0.91	0.75 to 1.10	0.326	2.00 (1.22 to 3.27)	0.38 (0.28 to 0.51)
Actigraphy WASO (10 minutes)	0.96	0.90 to 1.03	0.262	0.97	0.90 to 1.04	0.390	2.01 (1.23 to 3.30)	0.39 (0.28 to 0.50)
Higher duration (>4.0%) above recommended range models								
Actigraphy sleep duration								
Short sleep vs. 6-8 hours	1.32	0.74 to 2.37	0.185	1.23	0.69 to 2.17	0.723	2.23 (1.38 to 3.62)	0.40 (0.30 to 0.52)
Long sleep vs. 6-8 hours	1.11	0.70 to 1.76		1.14	0.72 to 1.79			
Actigraphy sleep efficiency (10%)	0.86	0.70 to 1.04	0.119	0.86	0.71 to 1.04	0.135	2.20 (1.35 to 3.55)	0.40 (0.29 to 0.52)
Actigraphy SOL ≥30 minutes	1.39	0.89 to 2.19	0.151	1.39	0.89 to 2.19	0.154	2.21 (1.37 to 3.57)	0.40 (0.29 to 0.52)
Actigraphy mid-sleep time (hours)	1.12	0.94 to 1.35	0.210	1.17	0.96 to 1.42	0.112	2.18 (1.34 to 3.53)	0.40 (0.29 to 0.52)
Actigraphy WASO (10 minutes)	1.04	0.97 to 1.11	0.318	1.03	0.96 to 1.11	0.357	2.20 (1.36to 3.57)	0.40 (0.29 to 0.52)
Higher duration (>0.0%) below recommended range models								
Actigraphy sleep duration							1.95 (0.97 to 3.90)	0.37 (0.23 to 0.54)

Short sleep vs 6-8 hours	0.73	0.34 to 1.55	0.414	0.76	0.35 to 1.62	0.593		
Long sleep vs. 6-8 hours	0.80	0.44 to 1.49		0.75	0.41 to 1.39			
Actigraphy sleep efficiency (10%)	1.13	0.87 to 1.45	0.358	1.10	0.86 to 1.42	0.446	1.97 (0.99 to 3.93)	0.38 (0.23 to 0.54)
Actigraphy SOL ≥30 minutes	1.00	0.54 to 1.84	0.999	1.04	0.56 to 1.92	0.896	1.99 (0.99 to 3.97)	0.38 (0.23 to 0.55)
Actigraphy mid-sleep time (hours)	**0.83**	**0.66 to 1.04**	**0.108**	**0.72**	**0.55 to 0.95**	**0.014**	2.18 (1.09 to 4.36)	0.40 (0.25 to 0.57)
Actigraphy WASO (10 minutes)	0.97	0.89 to 1.07	0.551	0.98	0.90 to 1.08	0.710	1.97 (0.99 to 3.92)	0.37 (0.23 to 0.54)
Higher ratio (>0.43%) of AUC above recommended range models								
Actigraphy sleep duration								
Short sleep vs. 6-8 hours	1.69	0.92 to 3.10	0.192	1.59	0.88 to 2.90	0.249	2.46 (1.49 to 4.06)	0.43 (0.31 to 0.55)
Long sleep vs. 6-8 hours	1.29	0.80 to 2.07		1.28	0.80 to 2.05			
Actigraphy sleep efficiency (10%)	0.83	0.67 to 1.02	0.078	**0.82**	**0.67 to 1.00**	**0.049**	2.30 (1.38 to 3.81)	0.41 (0.30 to 0.54)
Actigraphy SOL ≥30 minutes	1.13	0.71 to 1.79	0.615	1.16	0.73 to 1.83	0.531	2.40 (1.45 to 3.97)	0.42 (0.32 to 0.55)
Actigraphy mid-sleep time (hours)	1.05	0.87 to 1.27	0.629	1.10	0.90 to 1.35	0.325	2.37 (1.44 to 3.93)	0.42 (0.30 to 0.54)
Actigraphy WASO (10 minutes)	1.05	0.97 to 1.13	0.189	1.05	0.98 to 1.13	0.149	2.36 (1.43 to 3.90)	0.42 (0.30 to 0.54)
Higher ratio (>0.0%) of AUC below recommended range models								
Actigraphy sleep duration								
Short sleep vs. 6-8 hours	0.72	0.34 to 1.55	0.634	0.76	0.35 to 1.62	0.593	1.95 (0.97 to 3.90)	0.37 (0.23 to 0.54)
Long sleep vs. 6-8 hours	0.80	0.43 to 1.49		0.77	0.41 to 1.39			
Actigraphy sleep efficiency (10%)	1.13	0.87 to 1.45	0.358	1.10	0.86 to 1.41	0.446	1.97 (0.99 to 3.93)	0.38 (0.23 to 0.54)
Actigraphy SOL ≥30 minutes	1.00	0.54 to 1.84	0.999	1.04	0.56 to 1.92	0.896	1.98 (0.99 to 3.97)	0.38 (0.23 to 0.55)
Actigraphy mid-sleep time (hours)	0.83	0.66 to 1.04	0.108	**0.72**	**0.55 to 0.94**	**0.014**	2.18 (1.09 to 4.36)	0.40 (0.25 to 0.57
Actigraphy WASO (10 minutes)	0.97	0.89 to 1.07	0.551	0.98	0.90 to 1.08	0.710	1.97 (0.99 to 3.91)	0.37 (0.23 to 0.54)

* Models were adjusted for; age, BMI at booking visit, ethnicity, treatment type, gestational age, weekend and recruitment centre.

** Residual intraclass correlation.

4.6 Function-on-scalar regression models results for the association between self-reported and overall actigraphy measured sleep characteristics and average-glucose curves

This section presents the results from the functional regression models where self-reported sleep characteristics from the PSQI questionnaire and the actigraphy-measured sleep characteristics were used to explain variation in the CGM glucose curves. The outcome in these models was the registered average-glucose curves. All models were adjusted for the same set of confounders used in the ordinary regression models.146 participants with at least two days of complete CGM recoding were included in this analysis.

4.6.1 Functional regression models results for the association between self-reported sleep characteristics and the average-glucose curves

4.6.1.1 PSQI total score model

Each single score increase in the PSQI total score was associated with a 0.06 mmol/l increase in the glucose level (95% CI 0.01 to 0.10) at the lunch peak (Figure 4-23). Higher than zero regression beta coefficient was also observed at other times of the day although the association was only statistically significant at the lunch peak time.
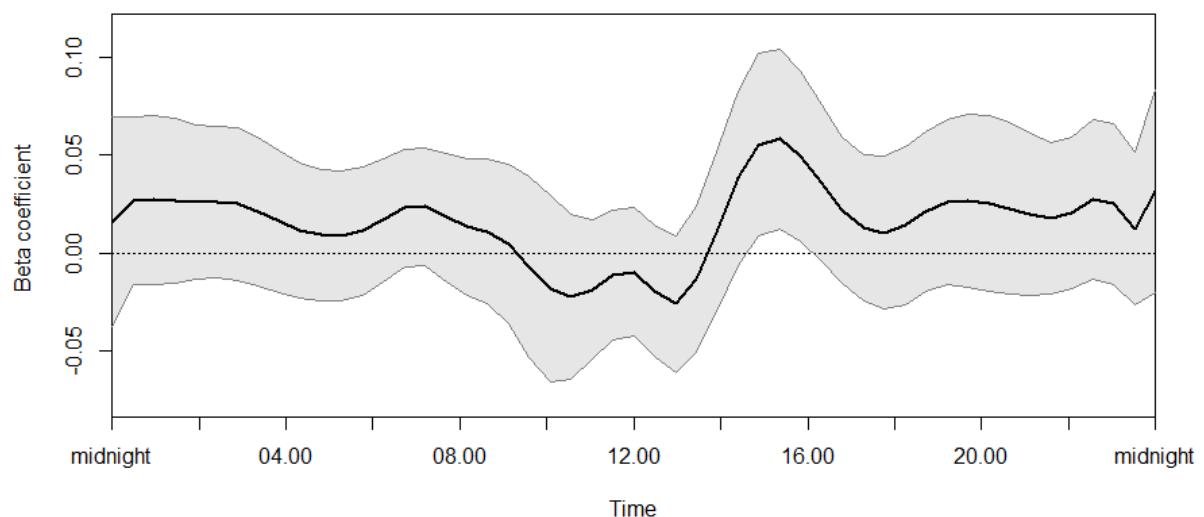
Figure 4-23 Functional regression model coefficient curve; PSQI total score and glucose curves

4.6.1.2 Self-reported sleep duration models

Different relationships between self-reported sleep duration and the glucose level at different times of the day were observed. The functional regression model with self-reported sleep duration linear term only (Figure 4-24) revealed a linear positive relationship between the self-reported sleep duration and the glucose level overnight (at 05:00 am; β 0.08 mmol/l increase in glucose level for each hour slept; 95% CI 0.01 to 0.15) and at the nadir between breakfast and lunch peaks (at 12:30 pm; β 0.12 mmol/l increase in glucose level for each hour slept; 95% CI 0.05 to 0.20).
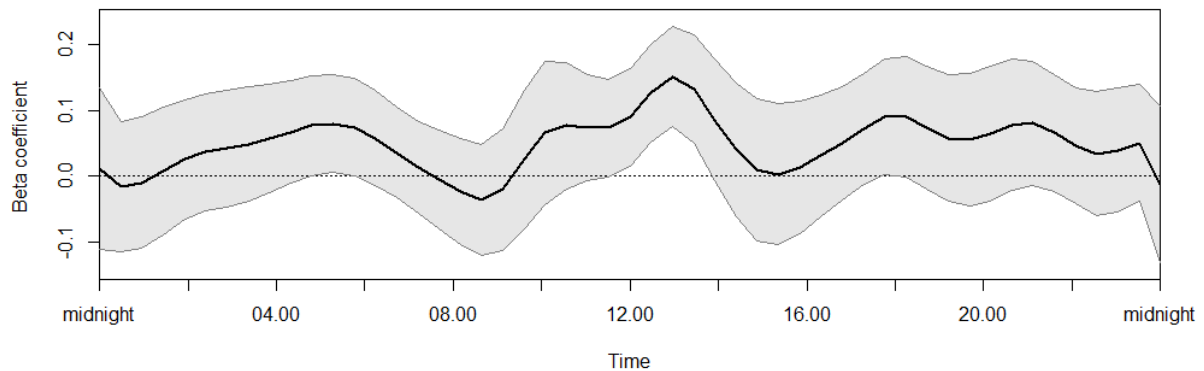
Figure 4-24 Functional regression model coefficient curve of linear term only self-reported sleep duration and glucose curves

On the other hand, the functional regression model with combined linear and quadratic (squared self-reported sleep) terms of self-reported sleep duration revealed a U-shaped relationship at other parts of the day (Figure 4-26); immediately after midnight (at 12:30 am; linear term (β -0.61; 95% CI -1.10 to -0.21); quadratic term (β 0.05; 95% CI 0.02 to 0.08)), at breakfast peak (at 08:30 am; linear term (β -0.55; 95% CI -0.92 to -0.20); quadratic term (β 0.04; 95% CI 0.02 to 0.08)), and at the nadir between lunch and dinner peaks (at 06:00 pm; linear term (β -0.48; 95% CI -0.88to -0.09); quadratic term (β 0.04; 95% CI 0.01 to 0.07)). Figure 4-26 displays this U-shaped relationship at 08:30 am. Self-reported sleep duration of around 5-8 hours predicted the lowest glucose level.
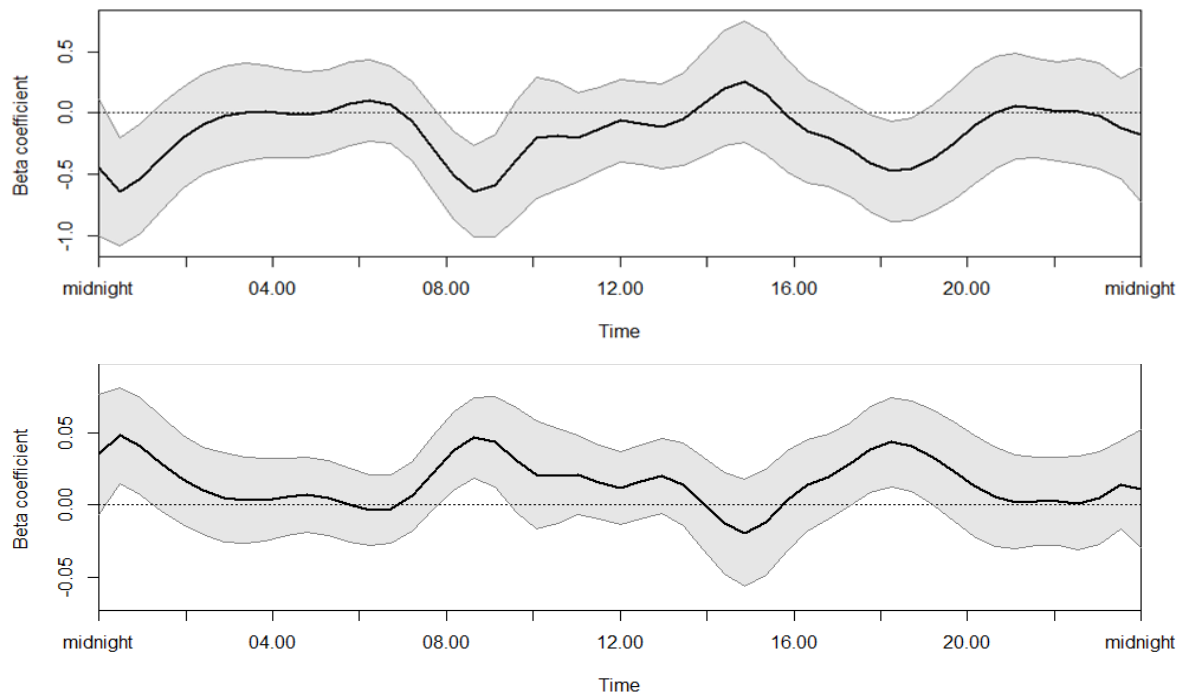
Figure 4-25 Functional regression model coefficient curves of the association between self-reported sleep duration combined linear term (upper panel) and quadratic term (lower panel), and glucose curves
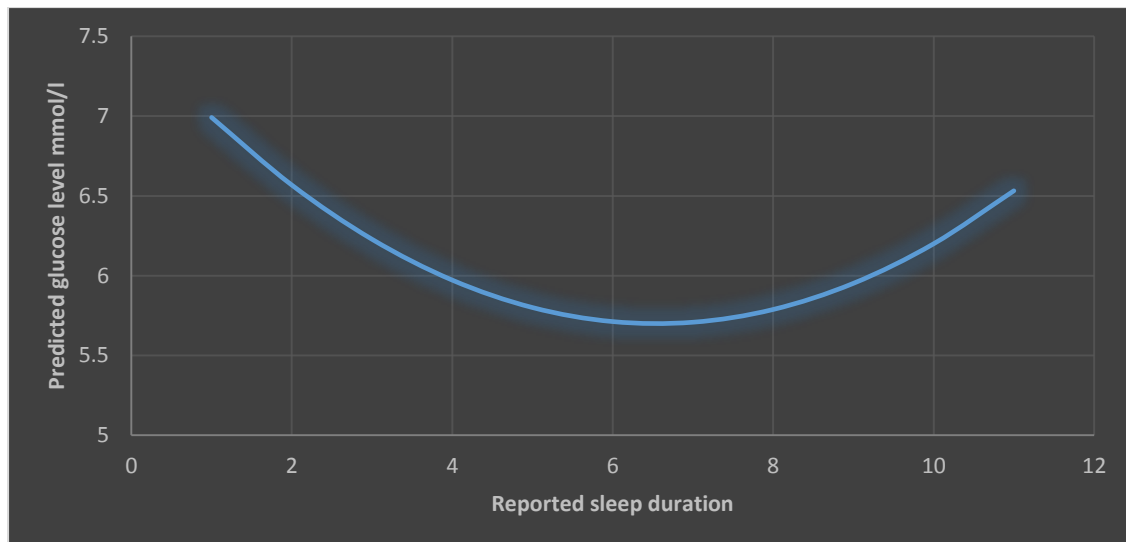
Figure 4-26 U-shaped relationship of predicted glucose level at 08:30 am and self-reported sleep duration (For participant with mean age, mean BMI, white ethnicity, 31 weeks of gestation, nulliparous, on diet management only and recruited from Leeds centre)

4.6.1.3 Self-reported SOL duration model

A Self-reported SOL duration of 30 minutes or more compared to shorter SOL duration was associated with having higher glucose levels overnight (at 02:00 am; β 0.37; 95% CI 0.10 to 0.64), at the lunch peak (at 03:00 pm; β 0.45; 95% CI 0.12 to 0.77) and at the dinner peak (at 08:00 pm; β 0.50; 95% CI 0.20 to 0.80) (Figure 4-27).
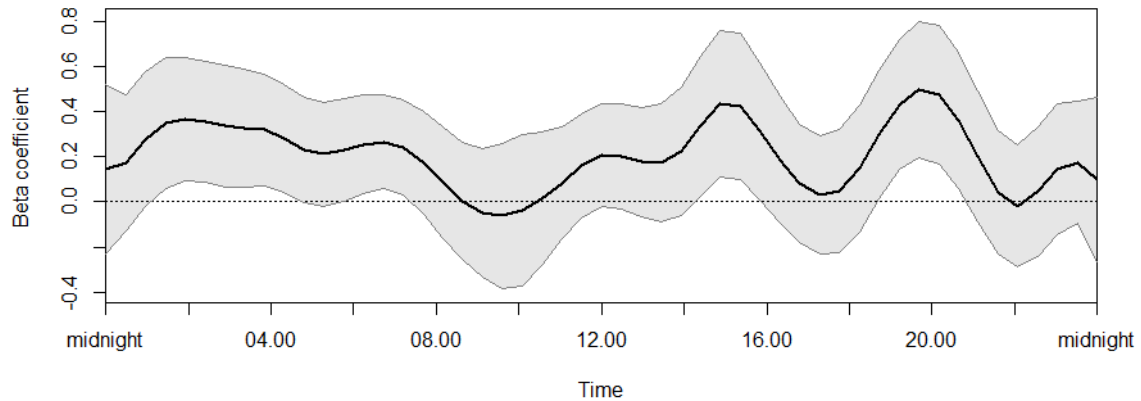
Figure 4-27 Functional regression model coefficient curve; self-reported SOL duration of 30 minutes or more and glucose curves

4.6.1.4 Self-reported sleep efficiency model

Each 10% increase in self-reported sleep efficiency was associated with a 0.1 mmol/l increase in glucose level at 12:30 pm (95% CI 0.04 to 0.12).
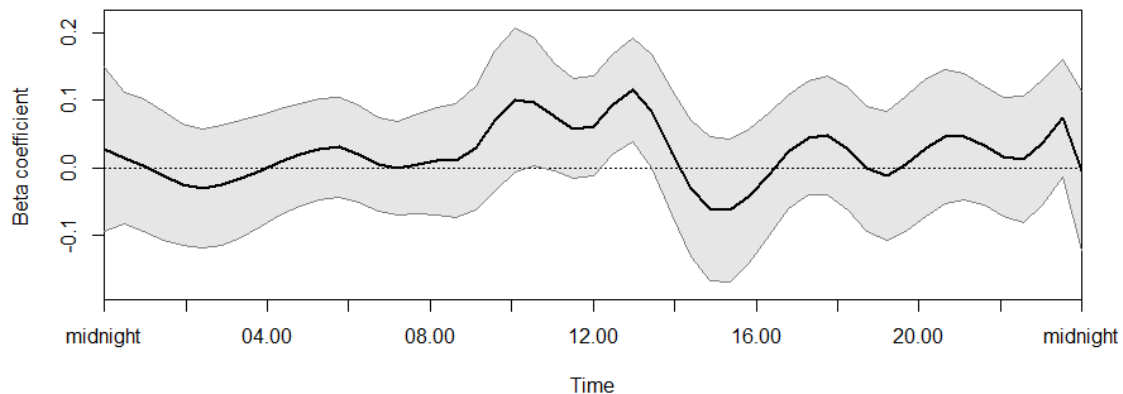
Figure 4-28 Functional regression model coefficient curve; self-reported sleep efficiency (10%) and glucose curves

4.6.1.5 Self-reported mid-sleep time model

Each one hour later mid-sleep time was associated with a 0.19 mmol/l higher glucose level overnight, but lower glucose at the breakfast and dinner peaks, 0.16mmol/l and 0.21 mmol/l respectively (Figure 4-29).
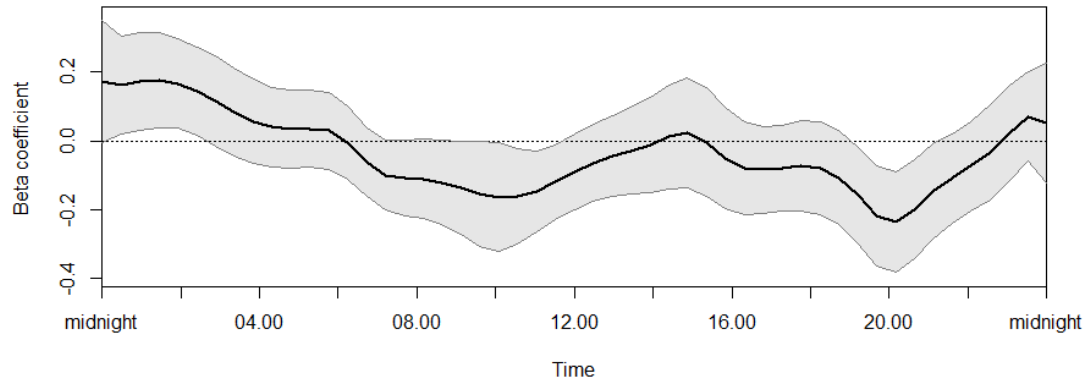
Figure 4-29 Functional regression model coefficient curve; Mid-sleep time (hours) and glucose curves

4.6.1.6 Subjective sleep quality rating model

Each deterioration in the subjective sleep quality rating was associated with a 0.22 mmol/l increase in the glucose level at the lunch peak (Figure 4-30).
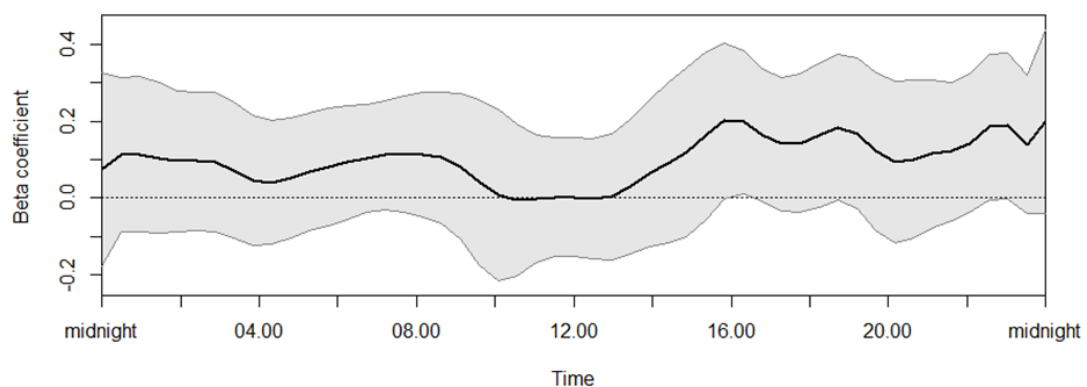
Figure 4-30 Functional regression model coefficient curve; Subjective sleep quality rating and glucose curves Subjective sleep quality rating

4.6.2 Functional regression models results for the association between actigraphy measured sleep characteristics and the average-glucose curves

4.6.2.1 Actigraphy measured sleep duration models

The functional regression model with actigraphy measured sleep duration (linear term only) revealed a negative association between the sleep duration and the glucose level just after midnight, as each hour slept longer was associated with a 0.11 mmol/l lower glucose level (95% CI -0.03 to -0.28) (Figure 4-31). In other parts of the day, the coefficient curve was above zero indicating a positive linear association, however the confidence range passed the zero no association line.
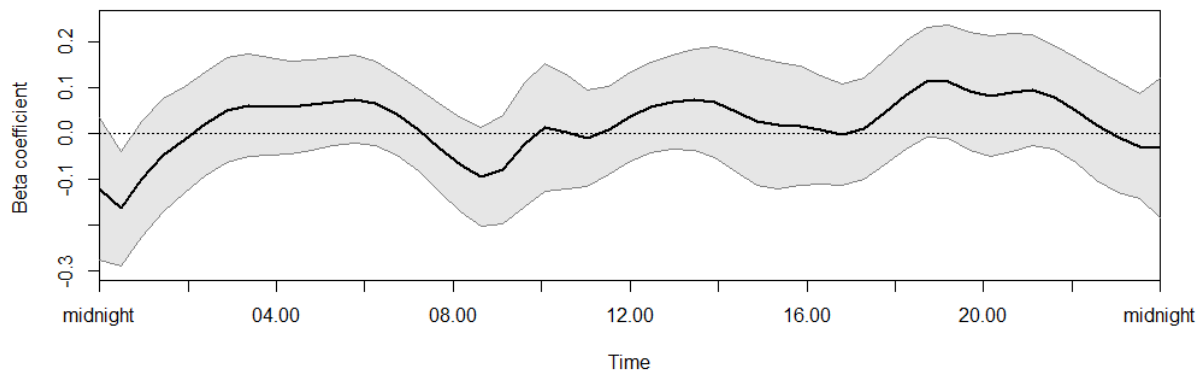
Figure 4-31 Functional regression model coefficient curve of actigraphy measured sleep duration, linear term only, and glucose curves

On the other hand, the regression model with combined linear and quadratic terms of actigraphy measured sleep duration revealed a J-shaped association with the glucose curves observed at the nadir between the breakfast and lunch peaks (at 12:15 pm; linear term (β -1.10; 95% CI -0.35 to -1.85); quadratic term (β 0.085, 95% CI 0.035 to 0.135)) (Figure 4-32). This J-shaped relationship is displayed in Figure 4-33.
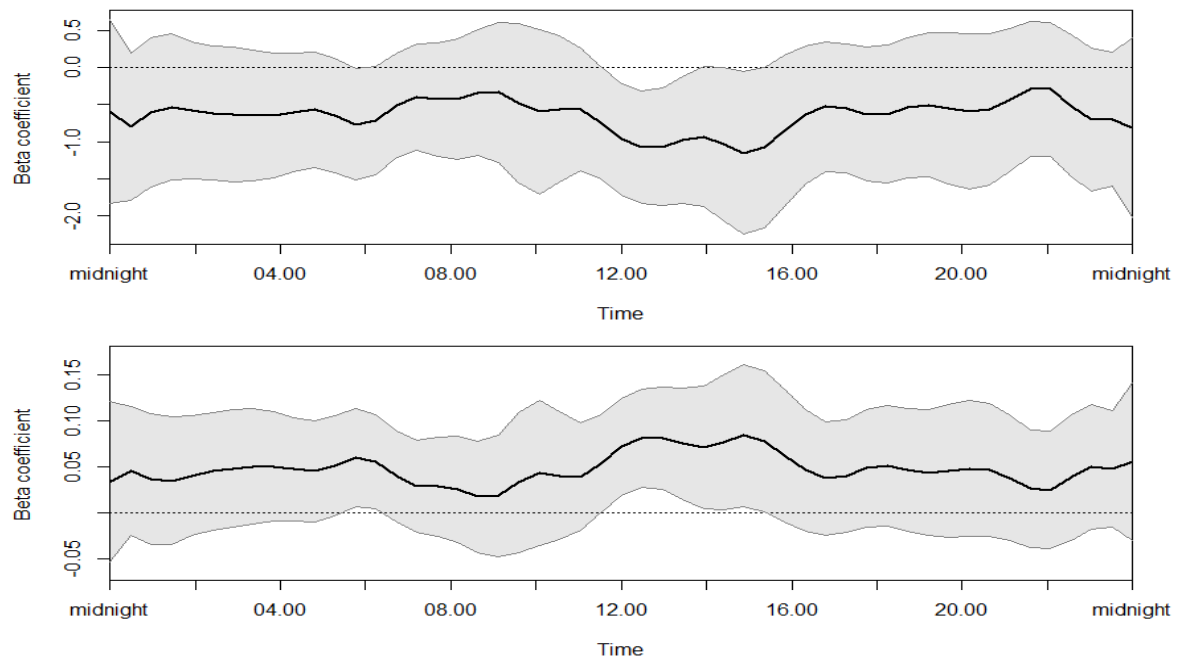
Figure 4-32 Functional regression model coefficient curves of association between actigraphy measured sleep duration combined linear term (upper panel) and quadratic term (lower panel), and glucose curves
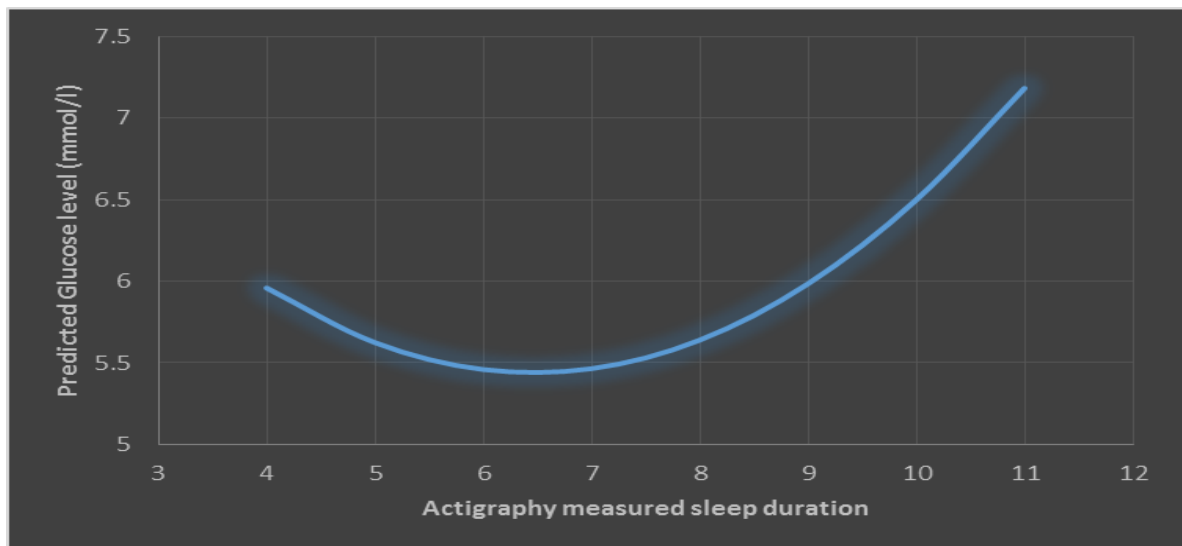
Figure 4-33 J-shaped relationship of predicted glucose level at 12:30 pm and actigraphy measured sleep duration (For participant with mean age, mean BMI, white ethnicity, 31 weeks of gestation, nulliparous, on diet management only and recruited from Leeds centre)

4.6.2.2 Actigraphy measured SOL duration model

An actigraphy measured SOL duration of 30 minutes or more was not associated with higher glucose levels compared to a shorter SOL duration.
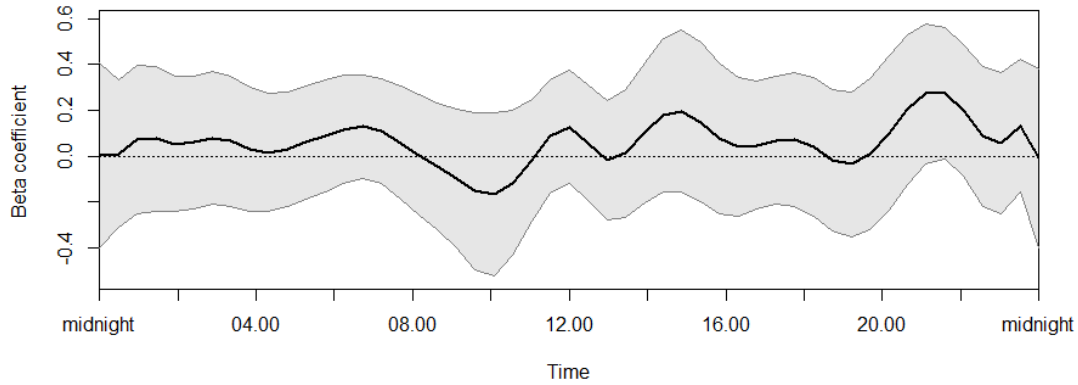
Figure 4-34 Functional regression model coefficient curve; actigraphy measured SOL duration of 30 minutes or more and glucose curves

4.6.2.3 Actigraphy measured sleep efficiency model

Higher sleep efficiency was associated with having lower glucose levels in many parts of the day (Figure 4-35). However this association was statistically significant, for each 10 % increase in the efficiency, at the time period between midnight and 04:00 am (at 12:30 am; β -0.25, 95% CI -0.08 to -0.41), after the pre-breakfast ridge (at 07:45 am; β -0.15, 95% CI -0.02 to -0.26), and after the lunch peak (at 03:30 pm; β -0.20, 95% CI -0.02 to -0.38).
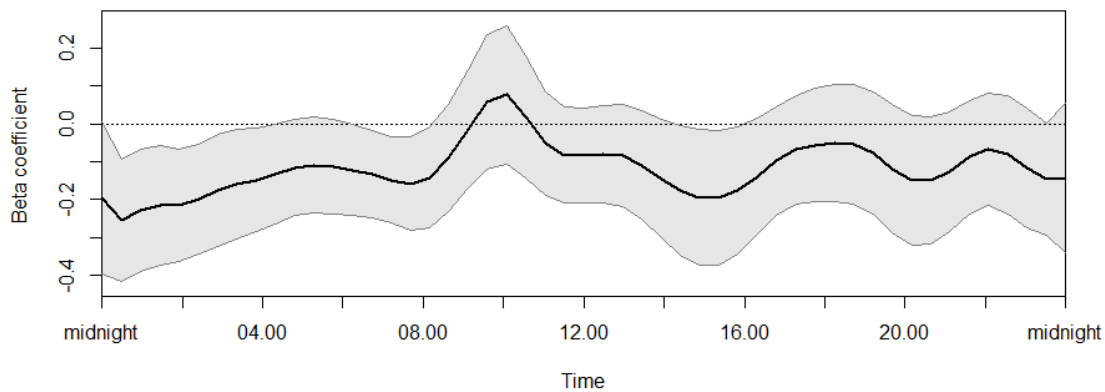
Figure 4-35 Functional regression model coefficient curve; actigraphy measured sleep efficiency (10%) and glucose curves

4.6.2.4 Actigraphy mid-sleep time model

The functional regression coefficient curve of the association between the mid-sleep time and the glucose curve showed a negative association after midnight and a positive association at the dinner peak (Figure 4-36). Each hour later mid-sleep time was associated with a 0.09 mmol/l lower glucose level at 12:30am (95% CI -0.05 to -0.14) and a 0.05 mmol/l higher glucose level at 08:00 pm (95% CI 0.00 to 0.09).
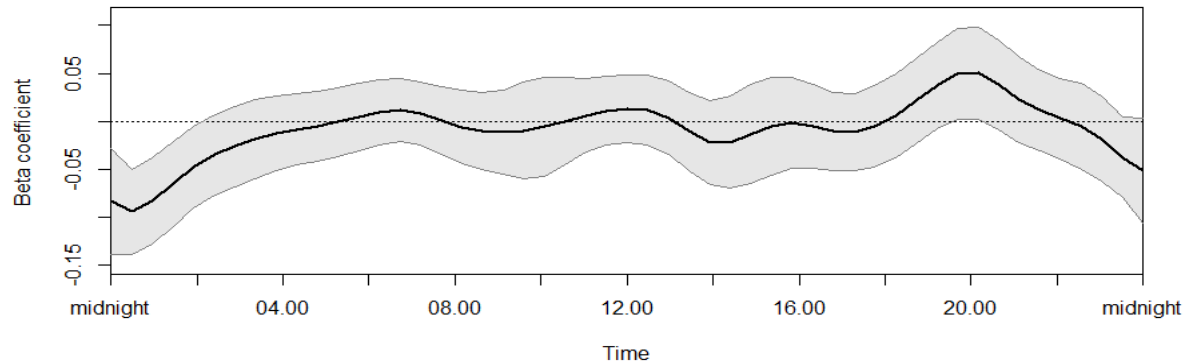
Figure 4-36 Functional regression model coefficient curve; actigraphy measured sleep mid-sleep time (hours) and glucose curves

4.6.2.5 WASO model

Each 10 minutes longer WASO duration was associated with a 0.05 mmol/l (95% CI 0.02 to 0.12) higher glucose level in most parts of the day except at the breakfast peak and around mid-night (Figure 4-37).
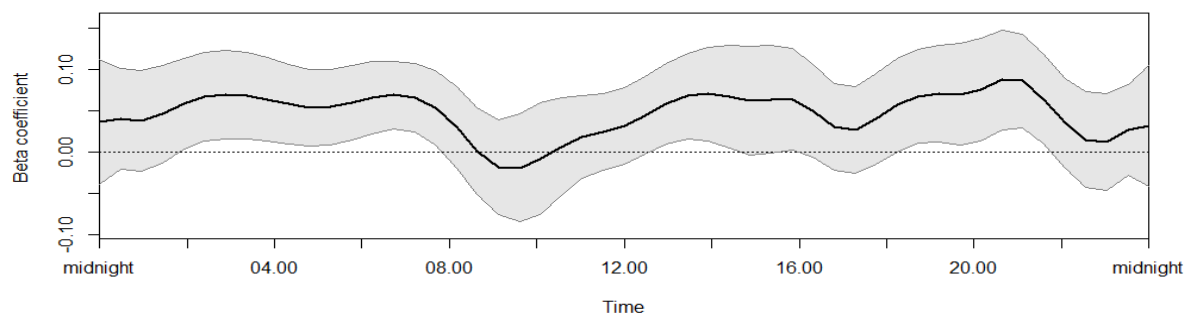
Figure 4-37 Functional regression model coefficient curve; actigraphy measured WASO (10 minutes) and glucose curves

4.7 Function-on-scalar regression models results for the association between self-reported and actigraphy measured sleep characteristics and the glucose velocity curves

This section presents results from the functional regression models where self-reported sleep characteristics from PSQI questionnaire and actigraphy measured sleep characteristics were used to explain variation in the CGM glucose velocity curves. The outcome in these models was the velocity curve of the registered average-glucose curve. All models were adjusted for the same set of confounders used in the ordinary regression models.146 participants with at least two days of complete CGM recordings were included in this analysis. As velocity curves have positive upturns and negative downturns, interpreting the regression coefficient is not as simple as interpreting the regression coefficient in section 0. A positive coefficient indicates an increase in value of positive speed (meaning a faster ascending side of the glucose peak) however it indicates a smaller value of the negative speed (meaning a slower descending side of the glucose peak) (Table 4-15). On the other hand, a negative coefficient indicates less positive speed value (meaning a slower ascent) and a more negative speed value (meaning a faster descent). Coefficient curves will be presented together with the intercept curve of the functional regression model to facilitate interpretation. The intercept curves represent the model's adjusted mean velocity curve for participants of mean age, mean BMI, mean gestational age, nulliparous, white ethnicity, on diet management only and recruited from the Leeds centre

		Regression's coefficient sign	
		Positive	Negative
Glucose velocity sign	Positive	Faster ascend	Slower ascend
	Negative	Slower descend	Faster descend

Table 4-15 Key table of how to interpret the regression coefficients of glucose velocity functional regression models

4.7.1 Function-on-scalar regression models results for the association between self-reported sleep characteristics and the glucose velocity curves

4.7.1.1 PSQI total score and velocity curves

A higher PSQI total score (indicating poorer sleep quality) associated with a faster ascent and descent of the glucose peak at lunch time (Figure 4-38); each unit increase in PSQI total score is associated with a 0.041 mmol/l/hour (95% CI 0.022 to 0.061) and a 0.025 mmol/l/hour (95% CI 0.005 to 0.045) increase in the speed of the ascent and descent of the glucose peak at lunch time, respectively. A higher PSQI total score was also associated with a slower ascent of the breakfast peak.
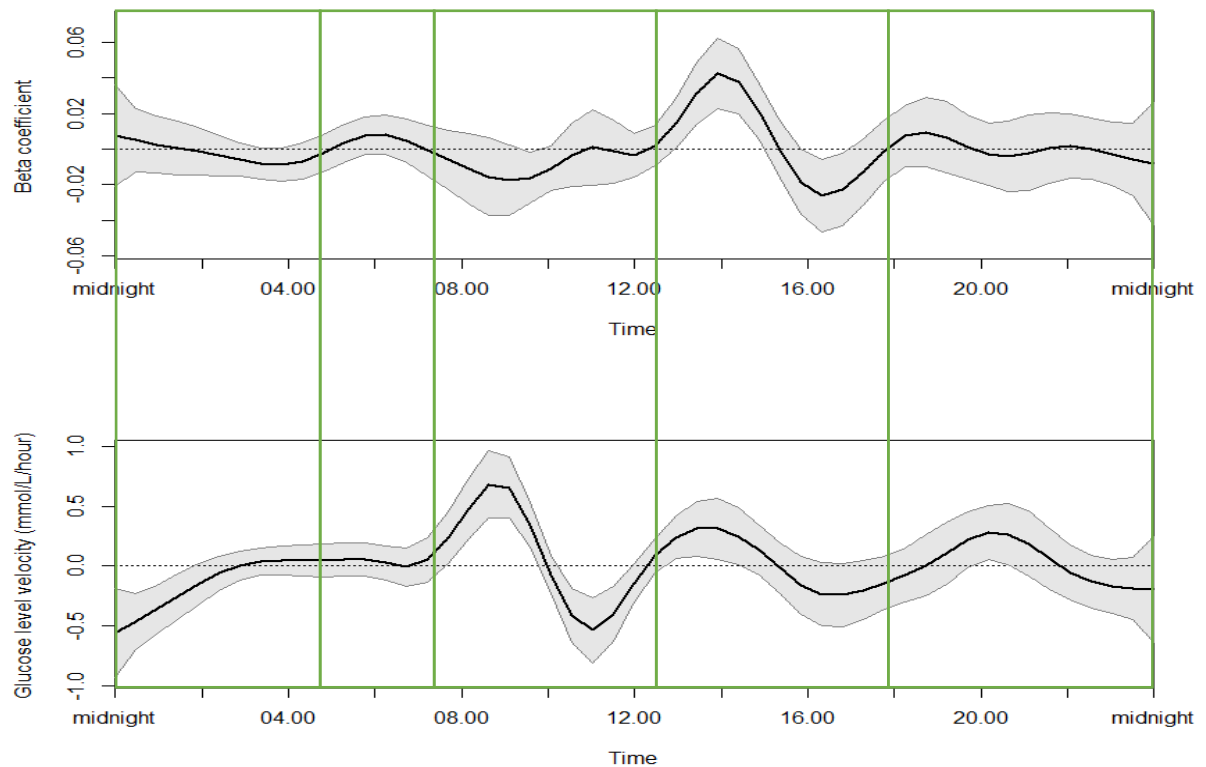
Figure 4-38 Functional regression model's coefficient (upper panel) and intercept (lower panel) curves of the association between PSQI total score and glucose velocity curves

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4.7.1.2 Self-reported sleep duration and velocity curves

Each hour increase in self-reported sleep duration is associated with a slower dawn ridge (β -0.04; 95% CI -0.05 to -0.01), faster ascent but slower descent of the breakfast peak (β -0.04; 95% CI -0.05 to -0.01) and (β 0.04; 95% CI 0.01 to 0.07) respectively, and a slower ascent of lunch peak (β -0.07; 95% CI -0.13 to -0.03).
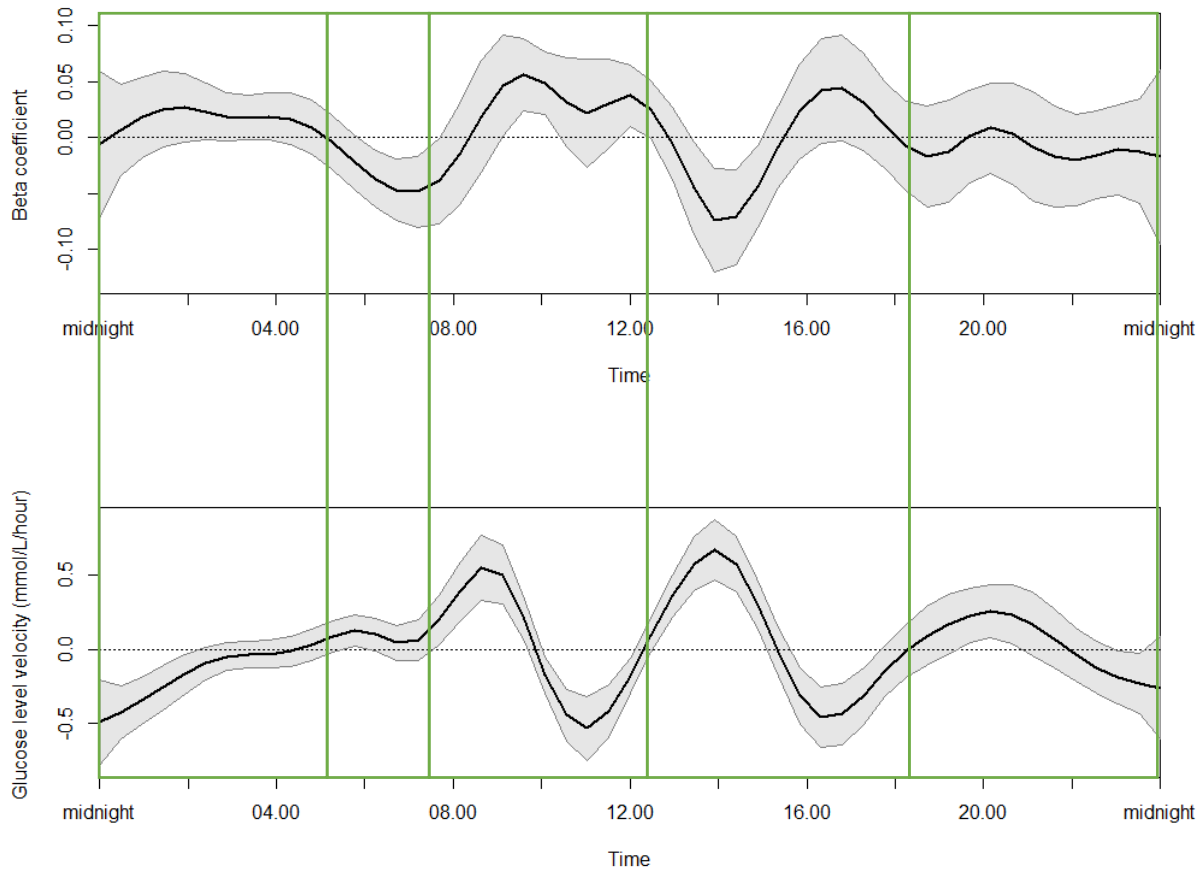
Figure 4-39 Functional regression model's coefficient (upper panel) and intercept (lower panel) curves of the association between self-reported sleep duration (hours) and glucose velocity curves

4.7.1.3 Self-reported sleep efficiency (10%)

Higher self-reported sleep efficiency was associated with: increased velocity of the glucose curve overnight indicating a slower descent, increased velocity of the ascending side of the breakfast peak (at 09:30 am; β 0.05, 95% CI 0.01 to 0.09), while no association with the velocity of the descending side of the peak. Higher sleep efficiency was also associated with a slower ascent and descent of the lunch peak (at 02:00 pm; β -0.09, 95% CI -0.01 to -0.12) and (at 04:15 pm; β 0.06, 95% CI 0.02 to 0.10), respectively. Furthermore, a slower descent of the glucose level overnight (at 04:00 am; β 0.03, 95% CI 0.01 to 0.0.05) for each 10% increase in self-reported sleep efficiency was also visible (Figure 4-40).
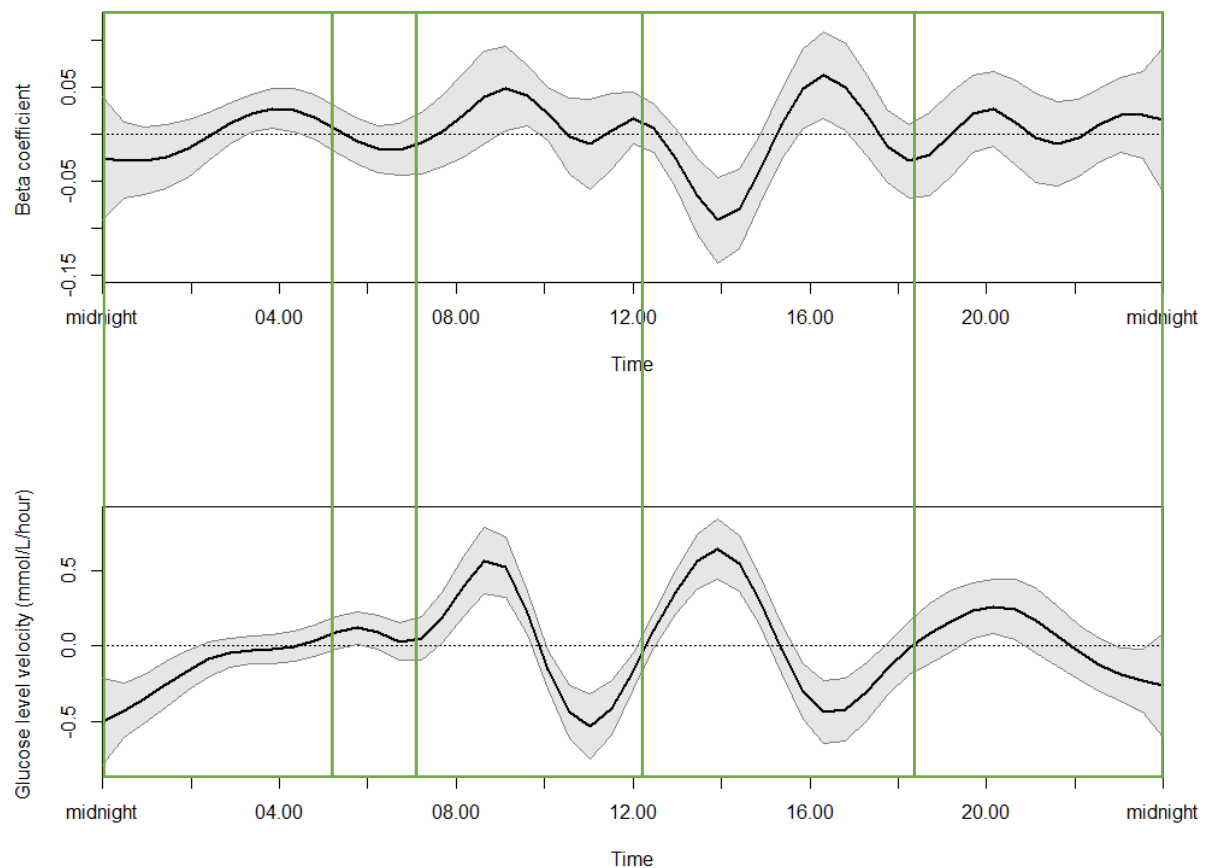
Figure 4-40 Functional regression model's coefficient (upper panel) and intercept (lower panel) curves of the association between self-reported sleep efficiency (10%) and glucose velocity curves

4.7.1.4 Self-reported SOL

Self-reported SOL of 30 minutes or more was associated with a slower ascent of the breakfast peak (at 08:15 am; β -0.17, 95% CI -0.04 to -0.24), a faster descent of the lunch peak (at 04:15 pm; β -0.21, 95% CI -0.11 to -0.31), but a slower ascent and descent of the dinner peak, (at 09:00 pm; β -0.27, 95% CI -0.12 to -0.40) and (at 12:15 am; β 0.18, 95% CI 0.05 to 0.30), respectively (Figure 4-41).
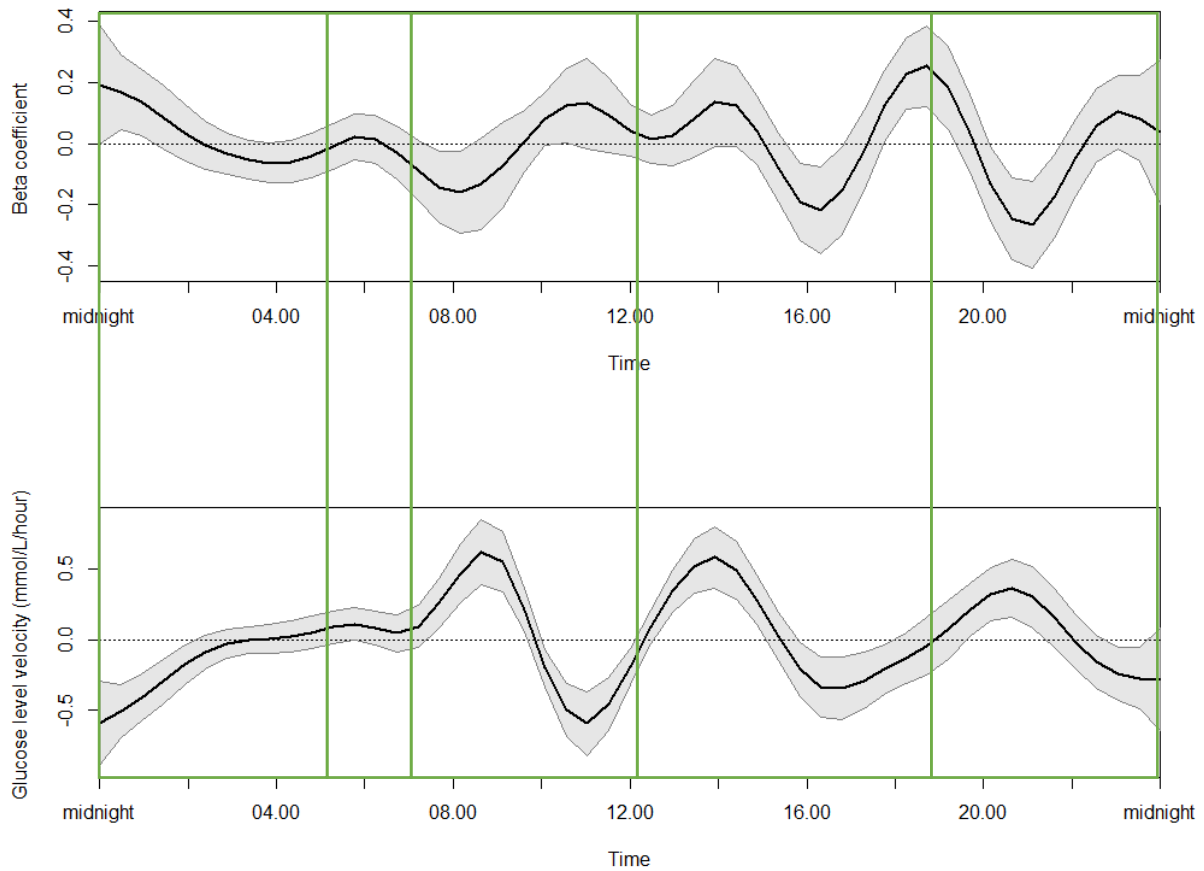
Figure 4-41 Functional regression model's coefficient (upper panel) and intercept (lower panel) curves of the association between self-reported SOL (> 30 minutes) and glucose velocity curves

4.7.1.5 Self-reported mid-sleep time

A later self-reported mid-sleep time was associated with a faster descent in glucose level overnight (at 03:00 am; β -0.05, 95% CI -0.03 to -0.09), a slower ascent at dawn (at 06:00 am; β -0.03, 95% CI -0.04 to -0.10) and a slower descent of the dinner peak (at 11:00 pm; β 0.10, 95% CI 0.04 to 0.14) (Figure 4-42). Furthermore, a later self-reported mid-sleep time was associated with a slower descent of the glucose level at the nadir between the breakfast and lunch peaks (at 12:15pm), but a faster descent of the glucose levels at the nadir between the lunch and dinner (at 07:30pm).
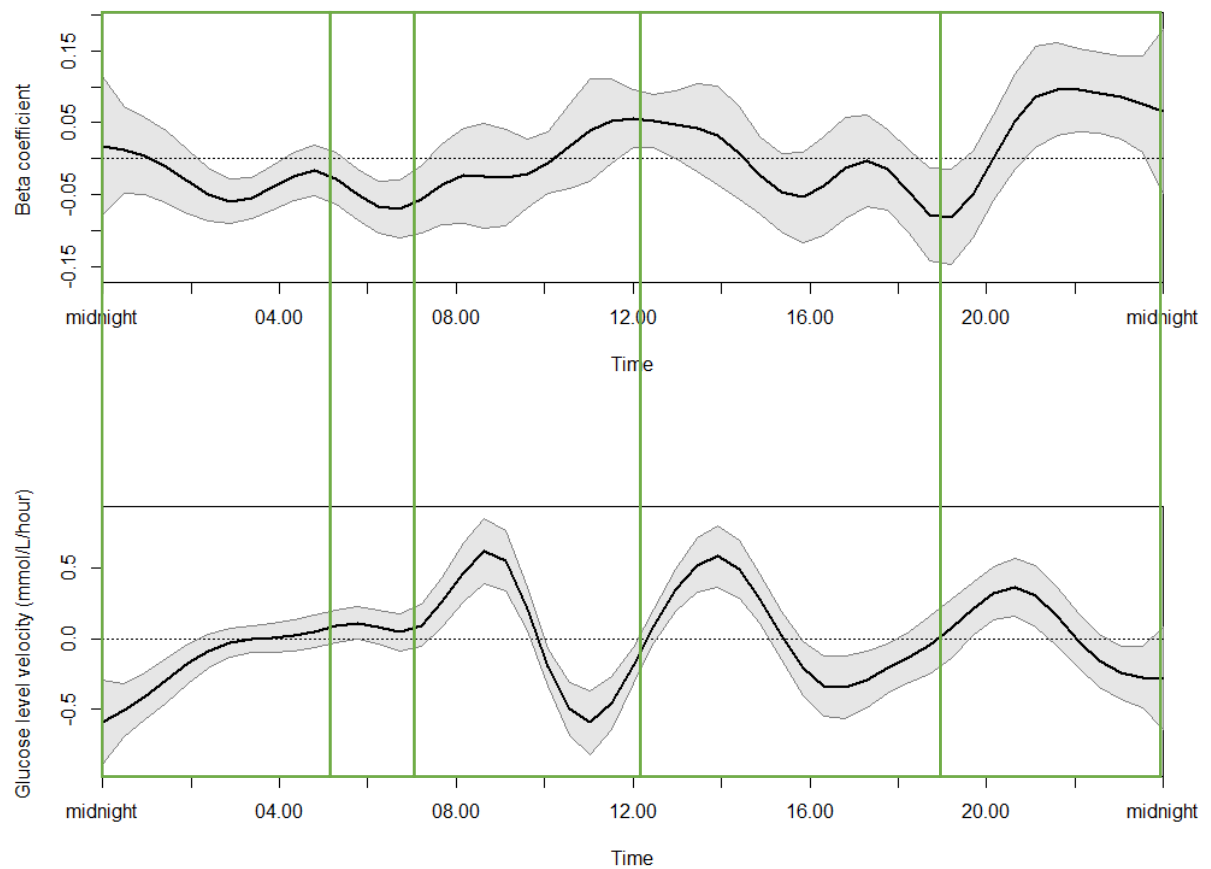
Figure 4-42 Functional regression model's coefficient (upper panel) and intercept (lower panel) curves of the association between self-reported mid-sleep time (hours) and glucose velocity curves

4.7.1.6 Self-reported subjective sleep quality rating

Subjective rating of sleep quality was not associated with the glucose level the following day (Figure 4-43).
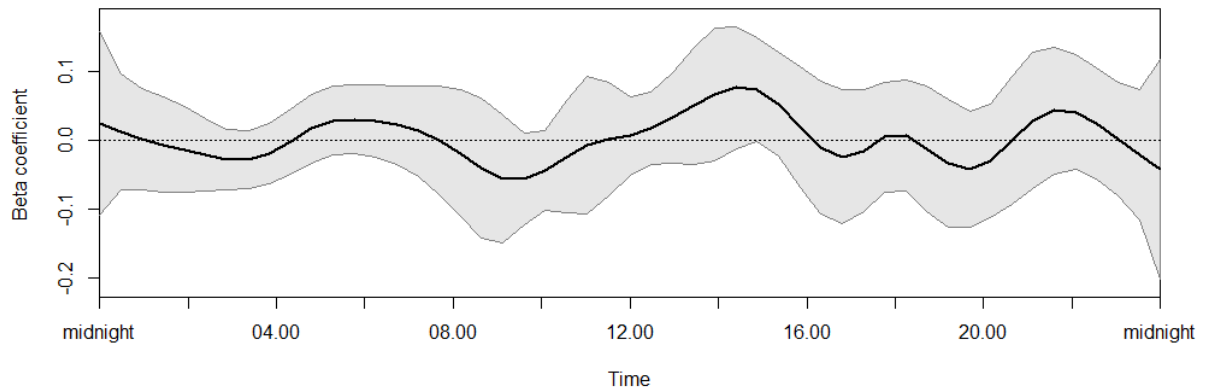
Figure 4-43 Functional regression model's coefficient curve of the association between self-reported subjective sleep quality rating and glucose velocity curves

4.7.2 Function-on-scalar regression models results for the association between actigraphy measured sleep characteristics and the glucose velocity curves

4.7.2.1 Actigraphy measured sleep duration

The actigraphy sleep duration predictor and glucose curves velocity outcome linear functional regression model showed that longer sleep duration was associated with a lower rate of change of glucose level before the breakfast meal (at 07:30 am; β -0.08, 95% CI -0.12 to -0.04), as well as a slower downhill descent of lunch and dinner peaks, (at 06:00 pm; β 0.07, 95% CI 0.01 to 0.12) and (at 01:00 am; β 0.10, 95% CI 0.05 to 0.14), respectively (Figure 4-44).
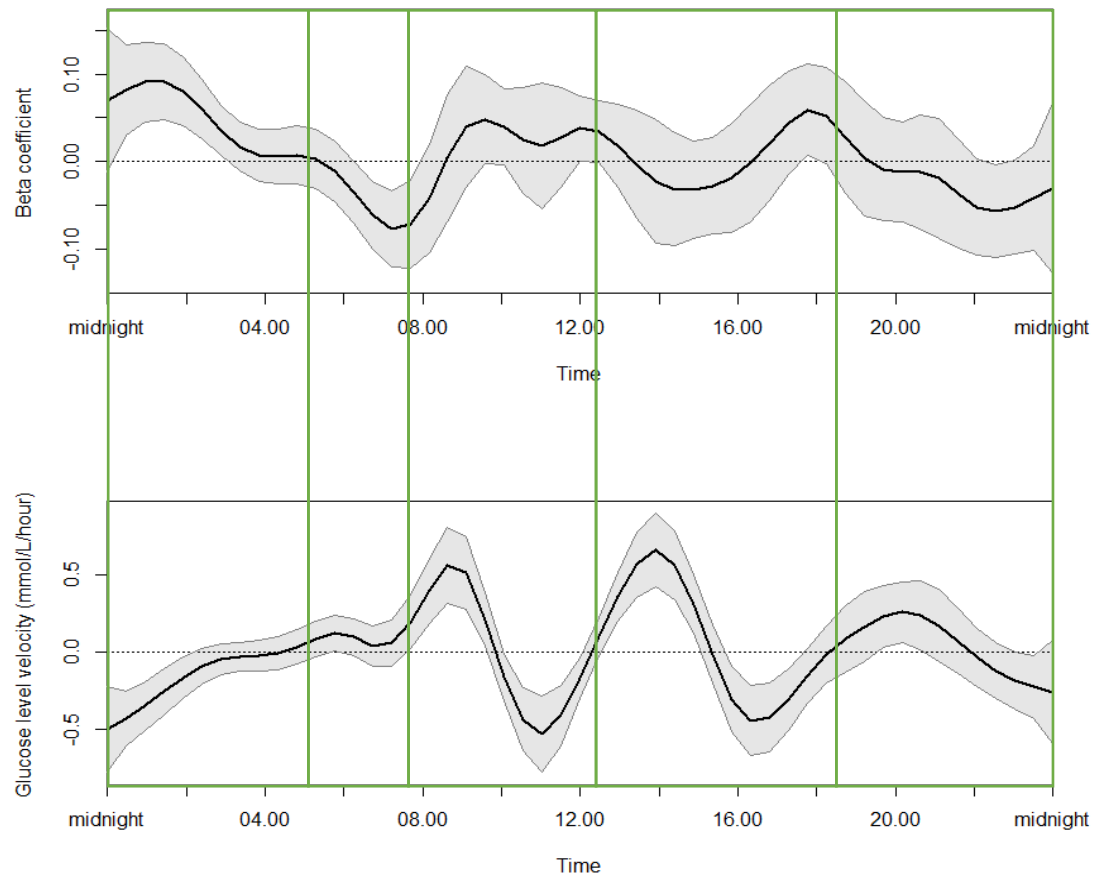
Figure 4-44 Functional regression model's coefficient (upper panel) and intercept (lower panel) curves of the association between actigraphy measured sleep duration (hours) and glucose velocity curves

4.7.2.2 Actigraphy measured SOL duration

Thirty minutes or more actigraphy measured SOL duration, compare to less than 30 minutes, was associated with a 0.14 mmol/l/hour (95% CI 0.05 to 0.28) faster ascent of the glucose level at the dinner peak (Figure 4-45).
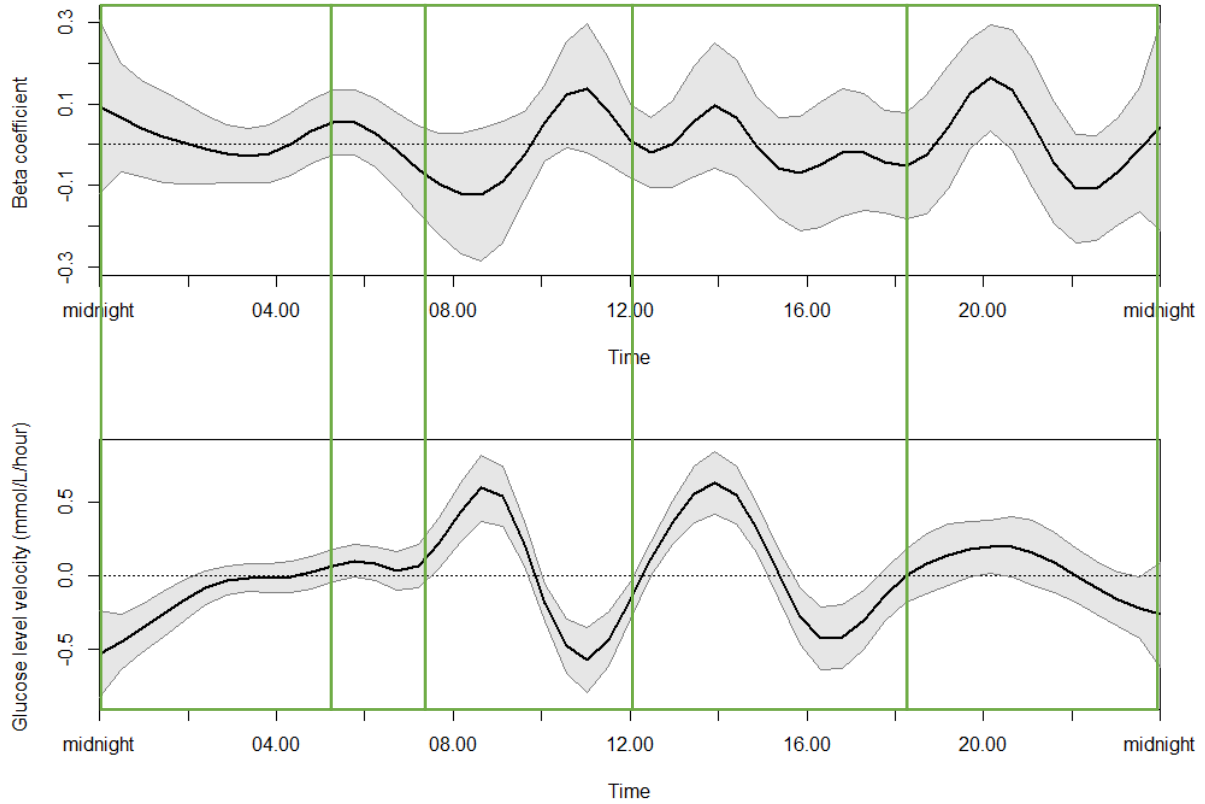
Figure 4-45 Functional regression model's coefficient (upper panel) and intercept (lower panel) curves of the association between actigraphy measured SOL duration, thirty minutes or more compared to less than thirty minutes, and glucose velocity curves

4.7.2.3 Actigraphy measured sleep efficiency (10%)

Each 10% increase in actigraphy measured sleep efficiency was associated with a 0.12 mmol/l (95% CI 0.04 to 0.19) increase in the ascending speed of the breakfast peak. Furthermore, better (higher) sleep efficiency was associated with a slower descent of the glucose level overnight (Figure 4-46).
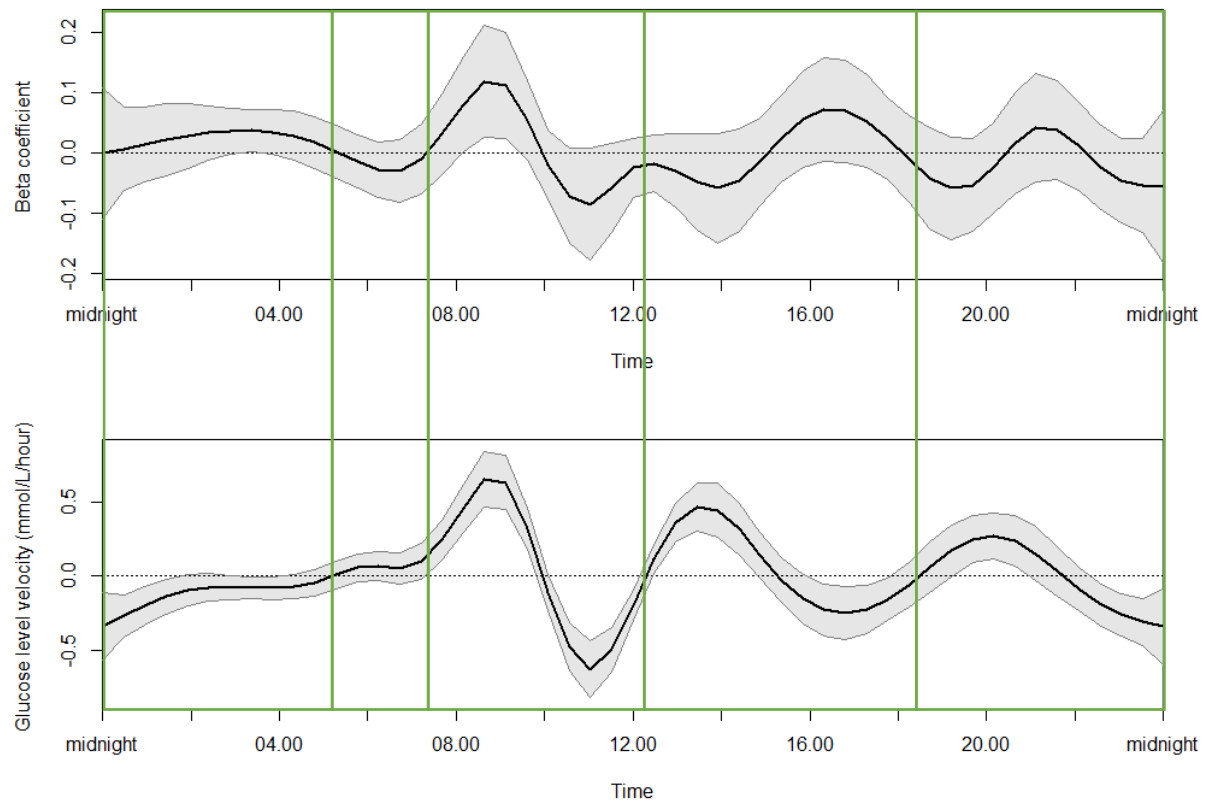
Figure 4-46 Functional regression model's coefficient (upper panel) and intercept (lower panel) curves of the association between actigraphy measured sleep efficiency (10%) and glucose velocity curves

4.7.2.4 Actigraphy mid-sleep time

Later mid-sleep time (hours) was associated with a 0.02 mmol/l/hour (95% CI 0.04 to 0.01) slower rate of change of the glucose level at the nadir between the breakfast and lunch peaks but a 0.04 mmol/l/hour (95% CI 0.02 to 0.05) faster rate of change at the nadir between the lunch and dinner peaks (Figure 4-47). Moreover, it was associated with a 0.03 (95% CI 0.02 to 0.04) slower descent of the glucose level overnight.
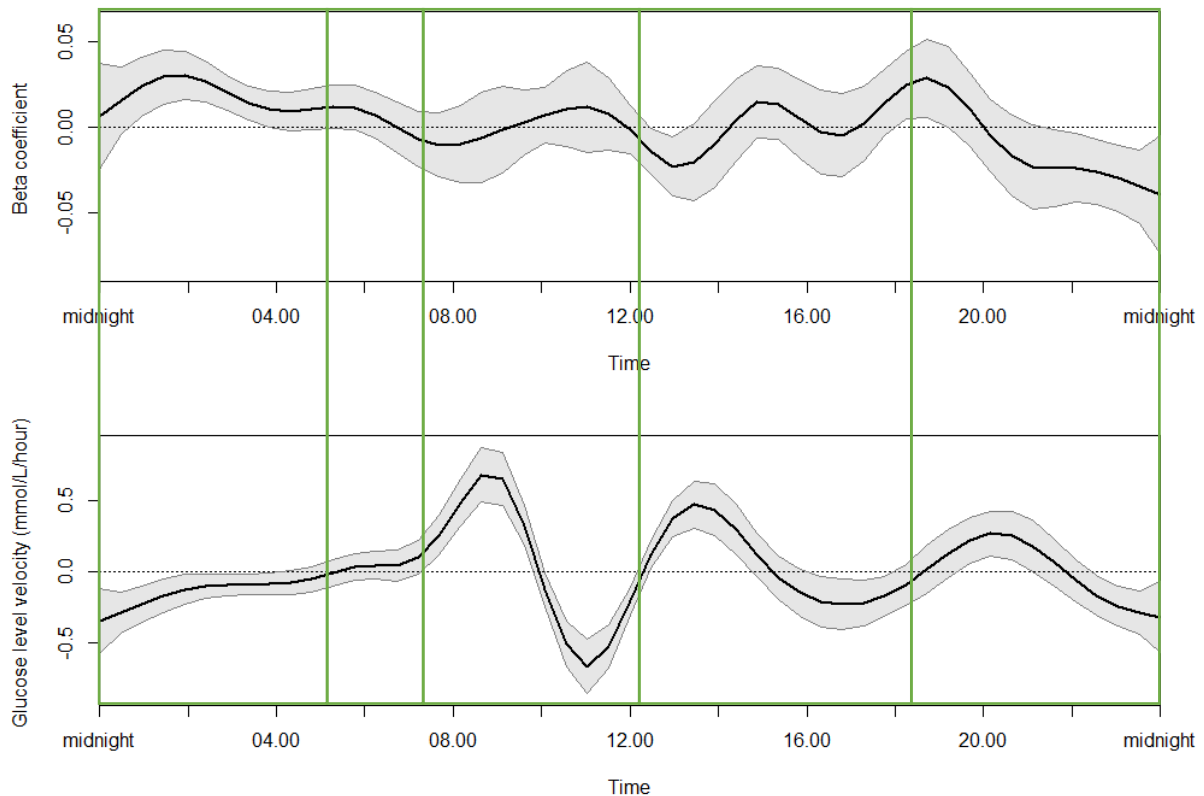
Figure 4-47 Functional regression model's coefficient (upper panel) and intercept (lower panel) curves of the association between actigraphy measured sleep duration (hours) and glucose velocity curves

4.7.2.5 WASO

Higher WASO duration (per 10 minutes) was associated with a slower ascent of the breakfast glucose peak (at 08:00 am; β -0.04; 95% CI -0.08 to -0.03) and a faster descent of the dinner glucose peak (at 10:00 pm; β -0.03; 95% CI -0.06 to -0.02) (Figure 4-48).
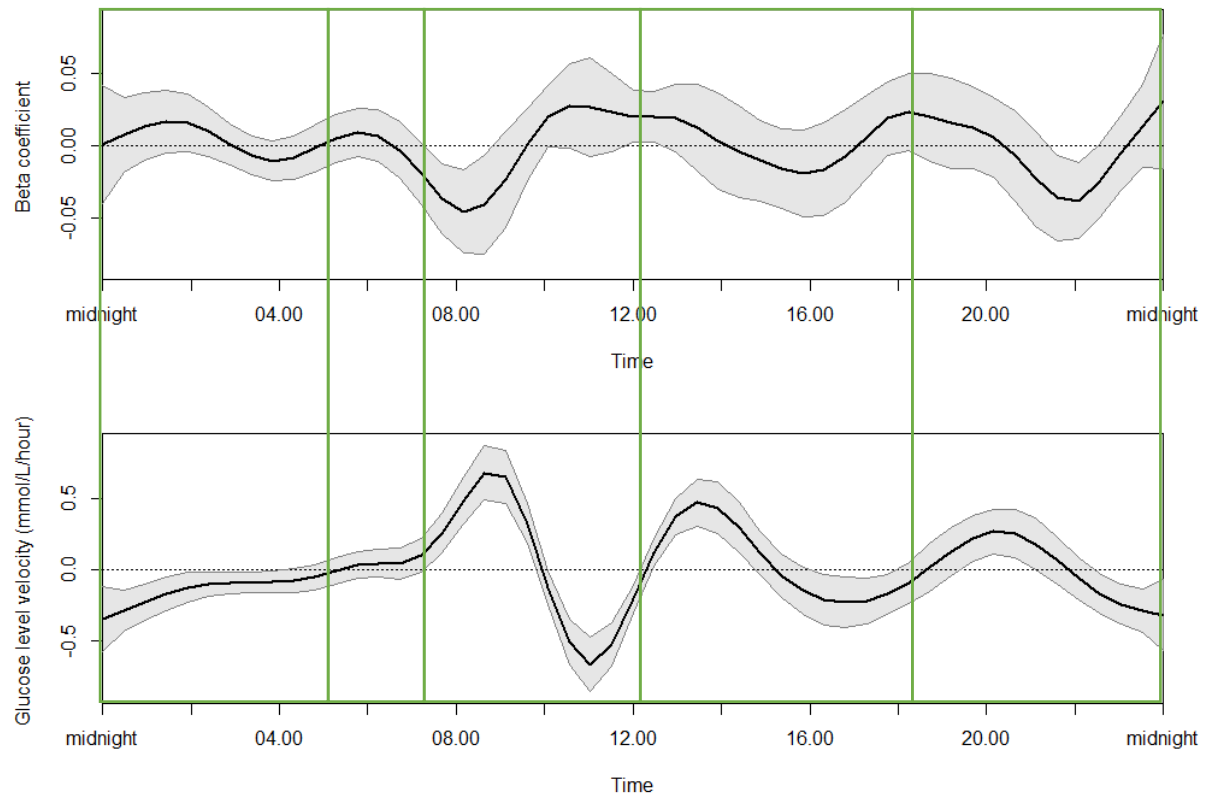
Figure 4-48 Functional regression model's coefficient (upper panel) and intercept (lower panel) curves of the association between actigraphy measured WASO (10 minutes) and glucose velocity curves

4.8 Association between glucose level before and around bedtime and actigraphy measured sleep characteristics

4.8.1 Actigraphy measured sleep duration

All available daily glucose curves were aligned to bedtime to examine if the glucose level around bedtime, 2 hours before bedtime and the first 2 hours in bed, had any association with the subsequent actigraphy measured sleep duration. The dataset consisted of 792 glucose curves from 146 participants with 2-6 glucose curves per participant. Figure 4-49 displays the mean glucose curves of the daily glucose curves that preceded long (>8hours), short (<6 hours) and average (6-8hours) actigraphy measured sleep duration. The mean glucose curve of the daily glucose curves that preceded the long sleep duration had about 0.25 mmol/l on average higher glucose levels around bedtime compared to the mean glucose curve of the daily glucose curves that preceded average sleep duration. On the contrary, glucose levels, around bedtime, of the mean glucose curve of the daily glucose curves that preceded short sleep duration were almost identical to the glucose levels of the mean glucose curve of the daily glucose curves that that preceded the average sleep duration. However, a permutation t-test of the differences were not statistically significant. Figure 4-50 depict that around bedtime the observed t statistics (red curve) did not exceed the statistically significant maximum 0.05 critical value (barred blue line). Values prior to 2-hours before bedtime glucose curves were not registered to meal peaks, and as such a difference in the glucose levels earlier in the day could not be explored.
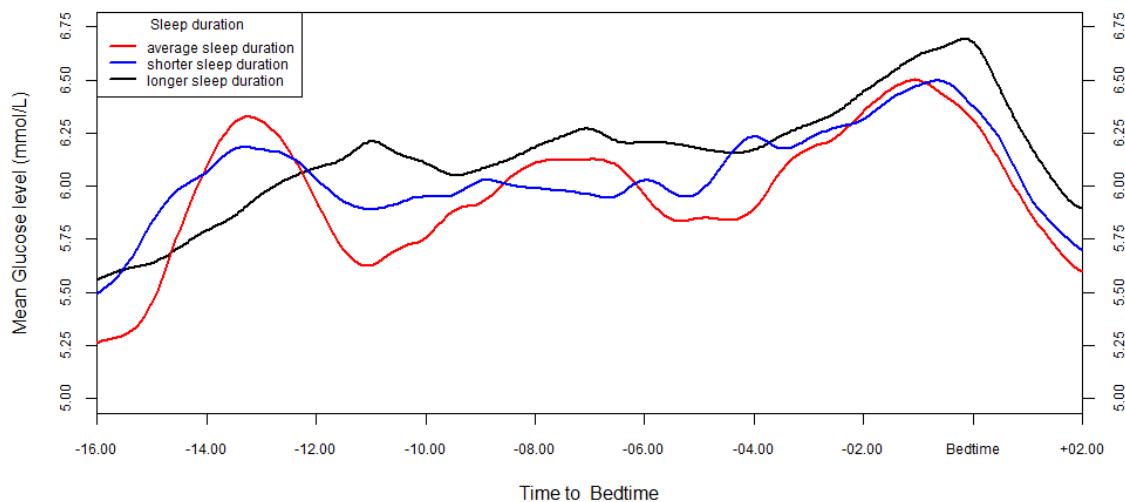
Figure 4-49 Mean glucose curves of daily glucose curves that preceded long, short and average actigraphy measured sleep duration Higher glucose levels around bedtime was followed by longer actigraphy measured sleep duration
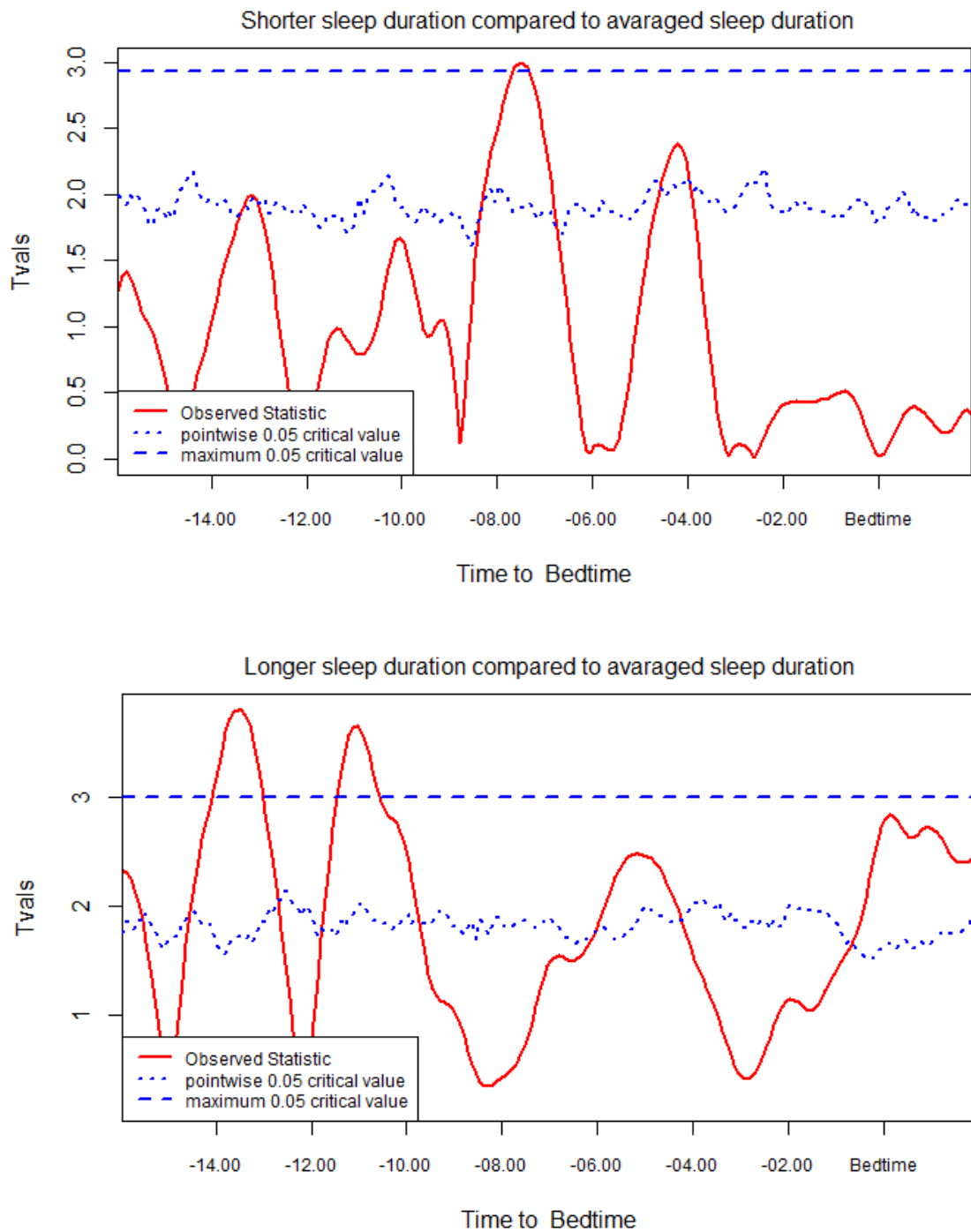
Figure 4-50 Permutation t-test for the difference between: mean glucose curves of daily glucose curves that preceded short and average actigraphy measured sleep duration (upper panel), and mean glucose curves of daily glucose curves that preceded long and average actigraphy measured sleep duration (lower panel)

4.8.2 Other actigraphy measured sleep characteristics

Scalar-on-function regression models, where glucose curves are the predictor of the regression models, of the associations between the glucose curves level around bedtime and actigraphy measured sleep efficiency, WASO or SOL durations showed no associations (Figure 4-51).
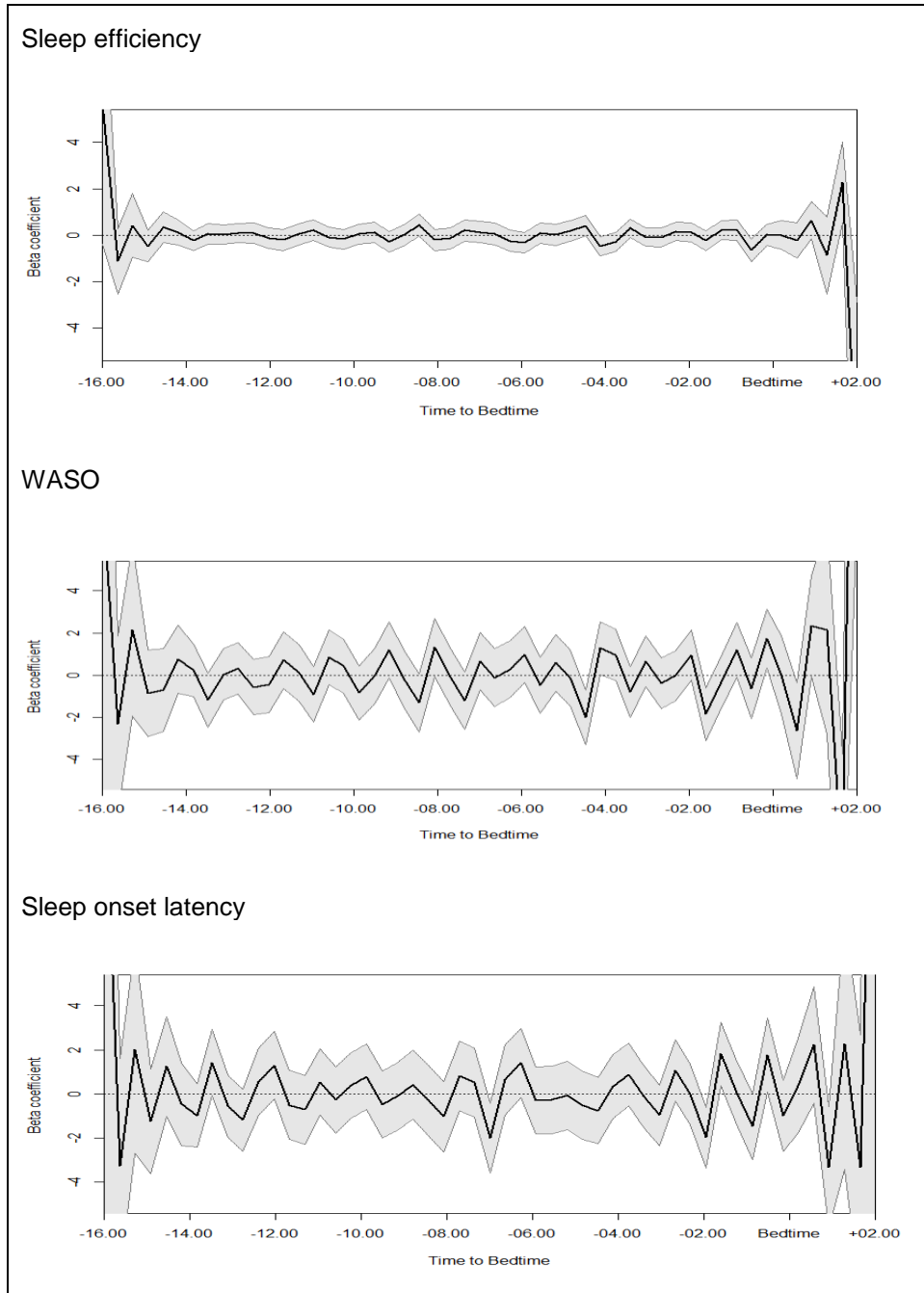
Figure 4-51 Functional on scalar regression models' coefficients curves of the associations between glucose curves levels around bedtime and actigraphy measured sleep efficiency, WASO duration and SOL duration

Chapter 5 Discussion

The research presented in this thesis is the first to examine the association between sleep and glucose control in GDM, with complete data records for 152 participants, assessing sleep characteristics using both subjective (PSQI) and objective (actigraphy) tools, using CGM to closely observe glucose control and applying FDA to analyse the CGM data. The key novel findings are that among pregnant women with GDM: 1) Poor sleep quality measured using PSQI total score was positively associated with higher glucose amplitude, more variability and faster rate-of-change; 2) Self-reported and actigraphy-derived sleep durations had a U-shaped association with glucose concentrations (though not sustained in all the statistical methods) and a positive association with glucose rate-of-change; and 3) Applying FDA methods to CGM data was practical and advantageous in extracting valuable detail and information .

These main findings support the underlying stated hypothesis of this thesis, that:

> 'Sleep disturbances, such as short or long sleep duration, and lower sleep quality, increase the amplitude and variability of blood glucose in pregnant women with gestational diabetes (GDM).'

This current chapter summarises the research findings and compares them to other published studies, discusses the statistical methods used, sets out the study limitations, and expands on the study's clinical implications and future perspectives.

5.1 Summary of the study findings

This section outlines the main findings and discusses them in reference to other studies'. The order of discussing these findings is in the same order as the objectives enumerated in chapter one. For clarity the objectives were to:

6- Evaluate sleep in pregnant women with gestational diabetes subjectively using the PSQI questionnaire and objectively using actigraphy gauging the agreement between the two tools derived sleep characteristics.

7- Assess glycaemic control in pregnant women with gestational diabetes using CGM.

8- Apply FDA methods to daily glucose curves derived from CGM data.

9- Examine the association of subjective and objective sleep characteristics with glucose control using: a) the CGM derived summary indices and b) FDA of daily glucose curves.

10- Explore the causal direction of the relationship between sleep and glucose by also examining the association between glucose levels immediately prior to sleep, with the characteristics of that subsequent night's sleep.

5.2 Assessing sleep

5.2.1 Actigraphy versus self-reported sleep

This study assessed sleep in pregnant women with GDM by using the PSQI questionnaire (a subjective tool) and actigraphy (an objective tool) to measure various sleep characteristics. Although they are both supposedly measuring sleep, their comparative values with regards to sleep duration, SOL duration, sleep efficiency, bedtime, and getting-up from bed time had poor agreement between them. These results are broadly consistent with previous research on agreement between: PSQI and actigraphy (the SenseWear Pro Armband) sleep characteristics in women (Segura-Jimenez et al., 2015); self-reported sleep duration and actigraphy (The Basic Mini Motionlogger Actigraph) in adolescents (Guedes et al., 2016); and PSQI and actigraphy (Actiwatch-16) in young adults (Lauderdale et al., 2008). Concurring with my results, Lauderdale et al. (2008) reported both systematic and proportional biases between self-reported and actigraphy sleep duration in young adults. Studies during pregnancy have also revealed discordance between self-reported and actigraphy-measured sleep characteristics. Herring et al. (2013) found poor agreement between self-reported sleep duration from PSQI questionnaire and actigraphy-measured sleep duration (Actiwatch-64) among pregnant women at 18 to 25 weeks of gestation. They reported a limit of agreement ranging from around -4 hours to +4 hours and a systematic bias of 25 minutes. However, in contrast to the results of this study it was the self-reported sleep duration that overestimated the actigraphy-derived sleep duration. Furthermore, among pregnant women in their third trimester Tsai et al. (2012a) reported an average 22 minutes longer self-reported sleep duration than actigraphy-derived sleep duration (using Actiwatch2 device). Bei et al. (2010) did not observe systematic bias but they reported no correlation between the two measures of sleep among pregnant women in their third trimester.

The discrepancy between sleep characteristics assessed by either tool is expected. Each one of these tools is capturing different facets of sleep architecture and the validity of both tools are jeopardised by several limitations. Self-reported sleep characteristics are totally subjective and they suffer from recall bias. This bias could be a differential one (i.e. varies between individuals) as individuals with certain conditions or sleep disorders may recall their sleep experience (like sleep duration, SOL and frequency of disturbed night sleep) more vividly than individuals with a relatively better sleep experience.

Furthermore, individuals may round their sleep duration to the nearest 15 minutes (reporting 6.5, 6.45, 7.00 and so forth) and SOL to the nearest minutes (reporting 10, 15, 20 and so forth). Individuals may also report a typical 'stand out' night rather than an average of more usual nights (Girschik et al., 2012). Nevertheless, during pregnancy the PSQI's psychometric properties (i.e. reliability and validity of the PSQI tool) showed good internal consistency (i.e. the PSQI component scores are closely related as a group) as evaluated by Cronbach's alpha reliability statistic >0.7, test-retest reliability (evaluated by intra class correlation coefficient) and construct validity (assessed by confirmatory factor analysis) (Skouteris et al., 2009; Jomeen and Martin, 2007; Qiu et al., 2016). The construct validity was improved further after excluding the use of sleep medication score (Jomeen and Martin, 2007).

Actigraphy measures inactivity as an indicator of sleep, Whilst inactivity is a symptom of sleep some individuals with insomnia can keep still in bed while awake for prolonged period of time (de Souza et al., 2003; Stone and Ancoli-Israel, 2011). Actigraphy's ability to identify immobile wake status is frail and this impacts on its accuracy in assessing sleep in individuals with insomnia. On the other hand, pregnant women often experience restlessness while asleep as they feel uncomfortable staying in one position. The impact of pregnancy mobility while in bed on the accuracy of actigraphy in assessing sleep is unknown. Actigraphy was found to underestimate total sleep time duration in a population of restless individuals with severe obstructive sleep apnoea, usually having frequent apnoea-related movement while asleep (Kim et al., 2013b). Validation studies on actigraphy against polysomnography during pregnancy are lacking and warrant future investigation.

Polysomnography is still considered the 'gold standard' for measuring sleep and would have been the tool of choice to validate the actigraphy, as it can delineate sleep stages and the amount of time spent in deep sleep and it uses different techniques to define sleepiness and wakefulness. However, polysomnography is expensive, usually laboratory-based, and measures sleep for a limited period of time within an artificial environment. Moreover, it requires an expert technician to administer and attach its electrodes to the participants and then to read its output. It was not practical to use it in this study, which aimed to assess women in their usual home environment for a week at a time. It is also worth noting that neither polysomnography nor actigraphy can capture the individuals' perception and satisfaction with the sleep experiences they had, which the PSQI does. This study's results and the results of the aforementioned studies among pregnant women do not imply any preference for self-reported or actigraphy sleep measurements tools, rather they support assessing sleep in pregnant women by using both tools.

5.2.2 Sleep characteristics

The median self-reported and actigraphy-measured sleep duration in this study were 7 hours and 7.4 hours, respectively. 25% of the participants reported sleeping less than 6 hours of sleep per night, 25% reported sleeping more than 8 hours, and only 5% reported a sleep duration more than 9 hours. The median WASO duration was 46.1 minutes and the other self-reported and actigraphy-derived sleep characteristics were as follows: median sleep efficiency 81.4% and 83.7%; median SOL duration 25 minutes and 20.4 minutes; mean bedtime 22:35 HH:MM and 23.11 HH:MM, and mean get-up from bed time 07:30 HH:MM and 08:10 HH:MM, respectively. These results are in line with previously published results among pregnant women (Tsai et al., 2016c; Lee, 1998; Facco et al., 2010b; Twedt et al., 2015; Reid et al., 2017).

Twedt et al. (2015) used actigraphy (Actiwatch Spectrum, Phillips Respironics) to objectively assess sleep in 37 pregnant women with gestational diabetes. Data were also analysed using the Actiware software and the algorithm set to medium threshold, similar to my study, and revealed a median sleep duration of 6.8 hours. Out of the 213 recorded nights; 46.3% of the nights showed sleep durations >5 and ≤7 hours, 37.8% of them showed sleep durations >7and ≤9 hours, 11% showed sleep durations < 5 hours and 4.8% showed sleep durations > 9 hours sleep duration. However the proportions of participants with overall short or long sleep duration were not reported. Objective sleep duration in pregnant women without diabetes has also been assessed. Data were collected from a large US cohort (n=782) using actigraphy (Actiwatch Spectrum, Phillips Respironics) before the 23rd week of gestation and analysed using the same medium threshold (Reid et al., 2017). 86.8% had valid actigraphy records (of those invalid records; 40% were due to watch failure and 60% were due to participants noncompliance). They reported the following actigraphy-derived sleep characteristics: median sleep duration 7.4 hours, median sleep efficiency 85.2%, median WASO 42.2 minutes, and median sleep-midpoint 03:38 am. 27.9% of the pregnant women in this study had a sleep duration of <7 hours and 2.9% had a sleep duration of > 9 hours.

Whilst among 2427 pregnant women responding to an internet-based PSQI questionnaire in the USA, across all months of pregnancy the mean self-reported sleep duration was 6.75 hours and 37.9% reported sleeping 6 hours or less. Those respondents in their 7th month of pregnancy had a mean self-reported sleep duration of 6.63 hours and 40.1% of them reported sleeping 6 hours or less (Mindell et al., 2015). Another cohort at 30 weeks of gestation had a mean self-reported sleep duration of 7.0 hours and 39.9% of them had short sleep duration (<7 hours) (Facco et al., 2010b)

Furthermore, studies of self-reported sleep duration and quality in the general population have also presented similar figures. A British cohort of 224 non-pregnant women aged

49-54 years reported a mean sleep duration of almost 7 hours, and a median sleep efficiency of 85% (IQR 75% to 91%) (Leng et al., 2014). Among 103 993 adults aged 37–63 years with no diabetes or cardiovascular diseases recruited from 2007 to 2010 into the UK Biobank cohort, 21.3% reported <7 hours sleep and 5.3% reported > 8 hours of sleep (Cassidy et al., 2016). Analysis of sleep data collected at wave 1 (2009-2011) of the UK Household Longitudinal Study Surveys (n=16427) revealed a mean sleep duration of 7.4 hours in adult participants aged 16-63 years. 56% of participants reported sleeping between seven and less than nine hours per night. 35% slept less than seven hours per night and 10% slept nine hours or more. Moreover, 22% of the participants rated their sleep quality as bad (Barnes et al., 2013). Among women aged between 16-60 years participating in the survey (n=9215), 78.6 % slept 6-8 hours, 9.8% slept <6 hours and 11.6% slept >9 hours. Around 10% of women participants aged between 16-44 years reported sleeping less than 6 hours and 25% of them rated their sleep quality as bad (Meadows and Arber, 2011).

Comparing sleep duration in aged-matched pregnant and non-pregnant women using the UK Household Longitudinal Study Surveys, Alafif et al. (2016) demonstrated that pregnant women had higher risk of reporting both short sleep <7hours (RRR 1.22) and long sleep >9 (RRR 1.45) compared to non-pregnant women. Pregnant women were also more likely to report bad sleep quality (RRR 1.6) and to report more difficulty staying awake during the day (RRR 1.28) compared to non-pregnant women.

In summary, sleep duration and sleep quality in pregnant women with GDM obtained in this study seem to be very similar to that obtained from other studies involving pregnant women with and without GDM. Pregnant women are more likely to have shorter and longer sleep durations, and poorer sleep quality than non-pregnant women. However, to my knowledge there is no published study comparing sleep in pregnant women with established GDM and pregnant women without diabetes.

5.2.3 Sleep quality as assessed by PSQI total score

More than 67% of the study participants had poor sleep quality as indicated by a PSQI total score of more than five, and they had a median PSQI total score of seven. Similar results were reported in a recent systematic review and meta-analysis of sleep quality as assessed by PSQI during pregnancy (Sedov et al., 2017). They reviewed 24 articles from 12 different countries and included pregnant women in different trimesters of pregnancy. They concluded that the PSQI total score is high during pregnancy with an average value of 6.1 and ranged from a mean of only 3.96 among at 14 weeks gestation to as high as 8.55 among women at weeks gestation. The mean PSQI total score was 8.1 for all studies that included women in their third trimester. The percentage of women with poor sleep (PSQI>5) ranged between 20.8 % and 76.3%.

Among the studies included in this review Mindell et al. (2015) reported 75.1% of women having poor sleeper and a mean PSQI score of 8.55 in a multi-ethnic American pregnant women at seven months gestation. Blair et al. (2015) reported a mean PSQI score of 6.9 at 19-30 weeks gestation with no statistically significant difference between African American and European American pregnant women. In another study among multi-ethnic American pregnant women at around 22nd weeks of gestation Qiu et al. (2016) reported a mean PSQI total score of 5.23 and 37% of participant had poor sleep quality. At 30-32 weeks of gestation, Okun et al. (2011) reported a higher mean PSQI score of 7.79 for American pregnant women who had eventually delivered their new-borns prematurely, and a PSQI score of 5.26 for pregnant women who had eventually delivered their new-borns at term. Whilst Facco et al. (2010b) surveyed a cohort of 189 pregnant American women at early pregnancy (mean gestation 13.8 weeks) and later in pregnancy (mean gestation 30.0 weeks). They reported mean PSQI total scores of 5.4 and 6.3, and 39.0% and 53.5% reported poor sleep quality (PSQI>5), respectively. The only published article from the UK (to my knowledge) was among pregnant women in early pregnancy (around 14 weeks of gestation). They reported a PSQI total score of 6.21 among depressed women and 3.23 among non-depressed women (classification of depression was based on the Edinburgh Postnatal Depression Scale) and 26% of the women had a PSQI>5 (Jomeen and Martin, 2007).

The results of this thesis and the findings from these multiple previous research studies suggests that poor sleep quality is very common during pregnancy and worsens with the advance of pregnancy. Identifying pregnant women with poor sleep quality might require the use of a higher cut-off point than the 5 PSQI threshold used in the general population. A cut-off point of around 6-7 might be more appropriate for instance during the third trimester, when so many women experience sleep disturbance, however this will require further investigation.

5.3 Assessing glucose control

5.3.1 CGM derived summary metrics

The overall mean-glucose and SD-glucose mean (SD) in this study were 5.88 (0.66) mmol/l and 1.09 (0.35) mmol/l, respectively. Half of the participants in this study experienced glucose concentrations above the 7.8 mmol/l upper recommended threshold for more than 60 minutes per day and a quarter of the participants spent more than 2 hours and thirty minutes per day above this threshold. To understand the meaning of these values, some references are needed. However, as mentioned in the introduction chapter, there are no established references or normative thresholds for CGM derived summary metrics in women with GDM. There are several published studies on CGM

summary metrics from healthy individuals and one from pregnant women without diabetes. In a study collecting 4 days of masked CGM data from 22 normal weight and 16 obese pregnant women without diabetes around 28 weeks gestation from the USA, the overall mean-glucose mean (SEM) was 5.22 (0.16) mmol/l for normal weight participants and 5.72 (0.16) mmol/l for obese participants (Harmon et al., 2011). A study based in the UK, obtained 3 days of masked CGM data from 78 healthy multi-ethnic individuals without diabetes, and found an overall mean-glucose and SD-glucose mean (SD) of 5.1 (0.5) and 1.5 (0.7), respectively (Hill et al., 2011). In 434 healthy Chinese using Medtronic CGM system (masked/real-time specification is not available) the mean-glucose was 5.77 (0.57) mmol/l and the SD-glucose was 0.79 (0.32) (Zhou et al., 2009). Whereas in 29 healthy Japanese using the MiniMed Medtronic real-time CGM system, the mean-glucose and the SD-glucose were 6.4 (0.8) and 1.2(0.4) (Nomura et al., 2011) and in 32 healthy Americans using Abbott FreeStyle Navigator real-time CGM system, the mean-glucose and the SD-glucose were 5.67 (0.39) and 1.00 (0.22), respectively (Mazze et al., 2008). In summary, the results obtained in my study, of treated GDM, showed mean-glucose results that were slightly higher than those reported in healthy individuals (except for the result from the Japanese study). Whilst the SD-glucose was either similar, smaller or higher than that reported in healthy individuals.

Half of the participants in my study experienced glucose concentrations above the 7.8 mmol/l upper recommended threshold for more than 60 minutes per day and a quarter of the participants spent more than 2 hours and thirty minutes per day above this threshold. These results are higher than those reported in healthy individuals. Among healthy individuals Borg et al. (2010) found that glucose concentrations did not exceed the 7.8 mmol/l threshold in only 7% of the participants. Half the participants spent more than 26 minutes per day above this limit and a quarter of the participants experienced glucose levels above this limit for at least 75 minutes per day. Another study reported glucose concentrations within the range of healthy participants 70 mg/dl to 125 mg/dl (3.89 mmol/l to 6.94 mmol/l) for 91% only of the total duration of CGM (Derosa et al., 2009). This may suggest room for improving the treatment of women with GDM, to achieve more 'normal' time within glucose targets than were achieved in my current study.

5.3.2 FDA of CGM data

By fitting the CGM data into daily glucose curves, FDA has revealed the diurnal glucose pattern and the rate-of-change of glucose across the day, and it has enabled the calculation of the mean and SD of glucose concentrations across the 24-hour day. FDA has shown that the mean fasting/ pre-breakfast glucose concentrations for around half of the participants exceeded the 5.3 mmol/l recommended upper threshold, and that the

mean postprandial glucose concentrations for around a quarter of the participants exceeded the 7.8 mmol/l recommended upper threshold.

These glucose curves have also shed some light on the behaviour of glucose in pregnant women with GDM. The time to postprandial peak was around two hours in this study. Longer than one hour time to peak was reported during pregnancy with and without diabetes, mean (SD) 82 (18) minutes and 74 (23) minutes, respectively (Buhling et al., 2005). In my study the breakfast peak had a higher amplitude and a faster rate-of-change than the lunch and dinner peaks. The breakfast peak has previously been reported to be higher than the lunch and dinner peaks in healthy individuals, albeit consuming the same standardised meals (Freckmann et al., 2007). This could be related to the circadian rhythms of insulin; the high and fast up-hill side of the breakfast's peak could be explained by the lower concentrations of circulating insulin in the morning compared to later times in the day, and the fast down-hill side of the breakfast's peak could be explained by the higher post-meal insulin response observed in the morning compared to later times in the day (Sensi and Capani, 1976; Van Cauter et al., 1992; Boden et al., 1996).

5.4 Sleep and glucose control

This section summarises the main findings pertaining to the association of; PSQI total score sleep quality, reported and actigraphy-measured sleep durations, reported and actigraphy-measured SOL duration, reported and actigraphy-measured mid-sleep time, WASO duration, and glucose control as assessed by summary metrics and smooth glucose curves.

5.4.1 PSQI total score sleep quality and glucose control

I found that a higher PSQI total score implying poorer sleep quality was associated with a higher amplitude and more variability of glucose concentrations. This was revealed from the adjusted standard regression models as well as the multilevel regression models incorporating within participants' variation in the modelling strategy. Each one score increase in PSQI total score was related to: 0.027 mmol/l increase in mean-glucose, 0.026 mmol/l increase in SD-glucose (denoting higher variability), 11% lower odds of having glucose concentrations within the recommended range, and 15% higher odds of having glucose concentrations above the upper threshold limit.

Further FDA regression models on the association between PSQI total score and smooth glucose curves and glucose velocity curves has yielded stronger associations giving more details about the relationship. The FDA models revealed that at lunch time, each one score increase in PSQI total score was associated with a 0.06 mmol/l increase

in glucose concentration and a 0.025 mmol/l/hour increase in the rate-of-change of glucose concentrations.

5.4.2 Self-reported and actigraphy-derived sleep durations and glucose control

The relationship between sleep duration as measured by actigraphy and as self-reported in the PSQI questionnaire with mean-glucose were not identical. Whereas, compared to 6-8 hours sleep duration, the short actigraphy-derived sleep duration but not the long was associated with higher mean-glucose, it was the long self-reported sleep but not the short which was associated with higher mean-glucose (Figure 5-1). On the other hand, their relationship to SD-glucose were more similar, as both short actigraphy-derived and self-reported sleep durations, but not long sleep duration were associated with higher SD-glucose (Figure 5-2). There were no associations between sleep duration, neither actigraphy-derived nor self-reported, with glucose concentrations being within or above the recommended glucose concentration range.
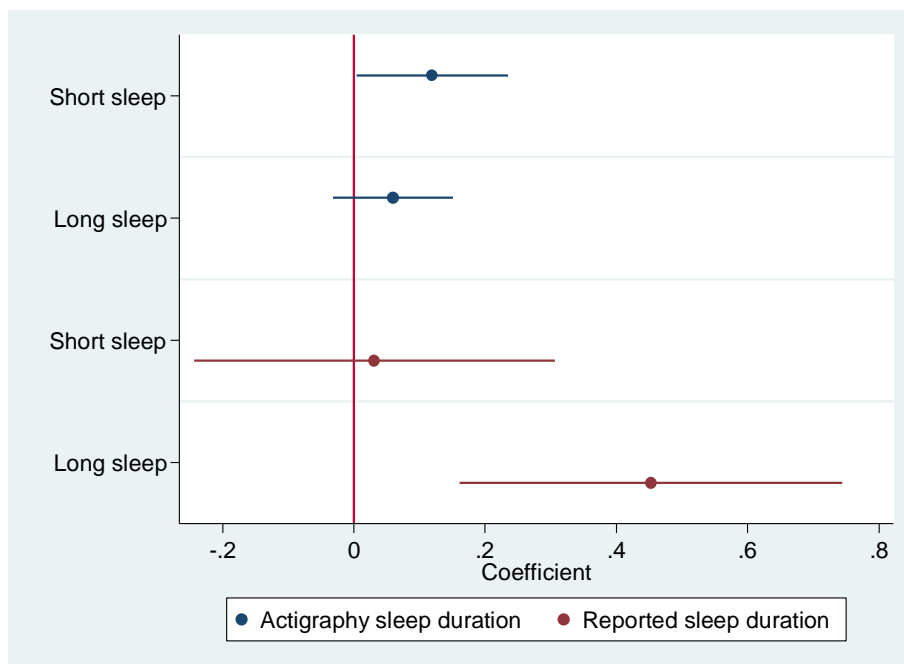
Figure 5-1 Coefficients plot of the results of multilevel regression models of self-reported and actigraphy-derived sleep durations with mean-glucose (the dot represent the coefficient and the line depict the 95% CI, short and long sleep compared to 6-8 hours sleep duration)
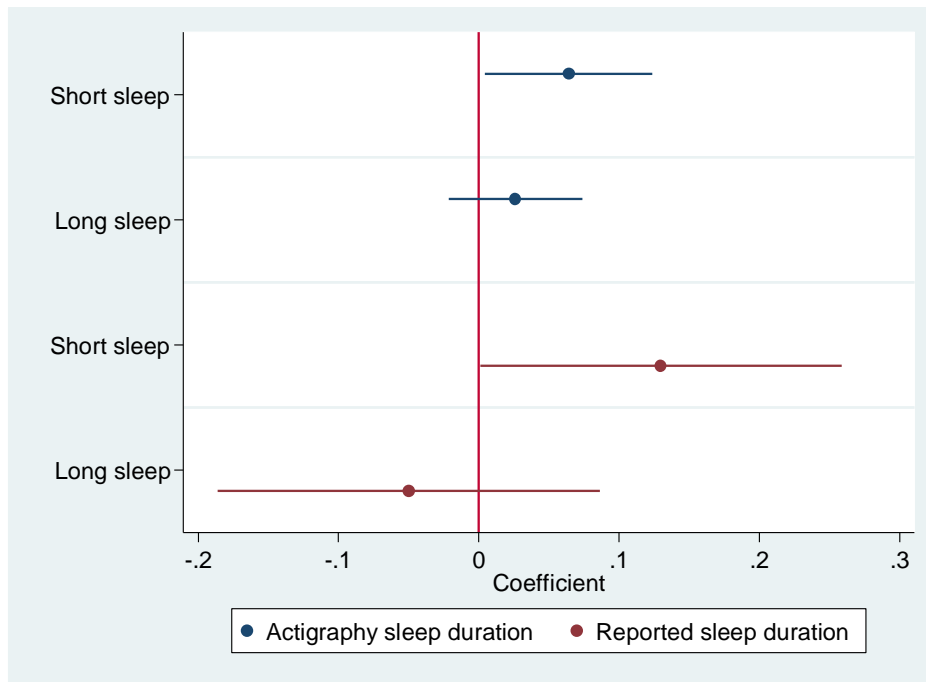
Figure 5-2 Coefficients plot of the results of multilevel regression models of self-reported and actigraphy-derived sleep durations with SD-glucose (the dot represent the coefficient and the line depict the 95% CI, short and long sleep compared to 6-8 hours sleep duration)

Using FDA, self-reported sleep duration showed a complex relationship with smooth glucose curves and glucose velocity curves. Each one hour increase in self-reported sleep duration was associated with a 0.08 mmol/l increase in glucose concentration at dawn time (04:00 to 08.00 am) and a 0.12 mmol/l increase in glucose concentration at the time between the breakfast and the lunch meals. Whereas there was a U-shaped association between self-reported sleep duration and glucose concentrations just after midnight, at breakfast, and at the time between lunch and dinner.

On the other hand, actigraphy-derived sleep duration had a negative association with glucose concentration after midnight (i.e. the shorter the actigraphy-derived sleep duration the higher the glucose concentration) and a J-shaped association (higher association estimated for longer sleep duration than for shorter sleep duration) with glucose concentrations at lunch.

Moreover, longer self-reported sleep duration was associated with: a slower rise of glucose at the dawn ridge, associated with glucose concentrations that were already higher than those with shorter sleep duration; a faster ascent but slower descent of the breakfast peak which could be related to insulin depletion overnight and higher insulin resistance; and a slower ascent of lunch peak associated with glucose concentrations that were already high before lunch.

5.4.3 Self-reported and actigraphy-derived SOL duration and glucose control

A self-report of taking thirty minutes or longer to fall asleep at night after going to bed (indicative of initial insomnia), was associated with glucose dysregulation as revealed by assorted methods used in this study. SOL≥ 30 minutes was associated with a 0.235 mmol/l increase in mean glucose, a 0.103 mmol/l increase in SD-glucose, a 62% lower odds of having glucose concentrations within the target range, and more than twofold the odds of having glucose concentrations above the upper threshold limit. FDA revealed that SOL≥ 30 minutes was associated with higher glucose concentrations between midnight and breakfast, at lunch time and at dinner time. The maximum association was at dinner time were it was associated with a 0.50 mmol/l increase in glucose concentration. SOL≥ 30 minutes was also associated with a slower ascent and descent of breakfast peak and faster descent of lunch peak.

Actigraphy-derived SOL duration was associated with CGM summary metrics: mean-glucose (not statistically significant), SD-glucose, proportion time within target >93%, proportion time above target >4%. However, most of these associations did not remain significant in the multilevel regression models except for a positive association with mean-glucose. Actigraphy-derived SOL duration did not show a significant association with glucose curves.

5.4.4 Other self-reported and actigraphy-derived sleep characteristics and glucose control

Other self-reported and actigraphy-derived sleep characteristics including sleep efficiency, mid-sleep time, subjective sleep quality and WASO duration were not associated with higher glucose amplitude or variability using the CGM summary metrics. Unexpectedly, the functional regression coefficient curve of self-reported sleep efficiency and glucose curves depicted a positive association, with each 10% increase in sleep efficiency associated with a 0.10 mmol/l increase in glucose concentrations around noon. Later reported mid-sleep time was associated with higher glucose concentrations after midnight but lower glucose concentrations at breakfast and dinner times. Though not statistically significant, a poorer subjective rating of sleep quality was associated with higher glucose concentrations in the period from lunch peak till midnight. Actigraphy-derived longer WASO duration (an indicative of sleep disturbance and maintenance insomnia or simply biphasic sleep) was associated with higher glucose concentrations. For each 10 minutes increase in WASO duration there was around 0.05 mmol/l increase in glucose concentrations after midnight till breakfast time, at lunch peak and at dinner peak. That is a 1 hour WASO duration would result in a 0.3 mmol/l increase in glucose concentrations at these time intervals.

5.4.5 Reverse causality

Using FDA this study did not find any association between higher glucose concentrations at the time of going to sleep and the following sleep duration, efficiency, WASO duration or SOL duration. Nights that were followed by a longer sleep duration had a 0.25 mmol/l glucose higher at bedtime and at 2 hours after bedtime than nights that were followed by 6-8 hours of sleep, however the differences were not statistically significant.

5.4.6 This study findings compared to findings from other studies

Among pregnant women with established GDM

Twedt et al. (2015) reported a negative linear association between actigraphy-derived sleep duration and fasting and one-hour postprandial capillary blood glucose, however a curvilinear relation more than a linear one was more likely to explain their results. After categorising sleep duration into groups, they elicited a U-shaped trend, albeit the association was only statistically significant for the very short sleep duration group (< 5hours) compared to the (≥7 to <9 hours) reference sleep duration group. The study suffered low power issues with a sample size of only 37 participants and just 10 nights of the 213 nights they recorded were in the long sleep duration group (> 9 hours). In the present study only short actigraph-derived sleep duration (<6 hours) was associated with higher mean-glucose and SD-glucose (compared to 6-8 hours sleep duration), while a U-shaped relationship was revealed at the time interval between breakfast and lunch using FDA. In contrast to the present study, Twedt et al. (2015) had also reported a negative association between chronotype and fasting blood glucose. Unlike the present study, they did not find any association between WASO duration and fasting or postprandial blood glucose concentrations.

The findings from my study on the relationship between sleep and glucose control, is also supported by other observational studies that looked at the risk of developing GDM in pregnant women with <7 hours compared to ≥ 7 hours self-reported sleep duration (Facco et al., 2010a; Reutrakul et al., 2011) and with ≤4 hours compared to ≥ 9 hours self-reported sleep duration(Qiu et al., 2010).

Individuals with T2DM or T1DM

Previous studies of individuals with T2DM or T1DM, were mainly cross-sectional observational studies, used various tools to assess sleep (polysomnography, actigraphy or questionnaire) and they evaluated glycaemic control chiefly via a single HbA1c reading or a fasting blood glucose level (Lee et al., 2017; Reutrakul et al., 2016). In an extensive systematic review and meta-analysis among adult participants with T2DM, Lee et al. (2017) included fifteen observational studies evaluating the association between subjective (mainly using PSQI questionnaire) sleep duration and quality with glycaemic

control. They found a U-shaped association between sleep duration and HbA1c and fasting blood glucose, as well as, higher HbA1c with poorer sleep quality. However, different studies used different sleep duration categories, and different PSQI-poor quality sleep cut-off points. In one study using actigraphy only, sleep efficiency weakly negatively correlated with HbA1c (r = −0.29; p-value = 0.047) with no measure estimate of the association reported by the authors (Trento et al., 2008). On the other hand, a systematic review and meta-analysis among adult participants with T1DM, Reutrakul et al. (2016) found that: in questionnaire based studies those with longer sleep duration and good sleep quality (as specified by the questionnaire used in the study) had lower HbA1c, while in polysomnography and actigraphy based studies there were no associations between HbA1c and stages of sleep, sleep efficiency (>85%) or sleep duration.

Healthy individuals

In a laboratory-based study, 14 healthy young men were monitored at baseline (2 days) and during 5 days/nights of restricted sleep duration (5 hours in bed). The experimental period was tightly controlled with standardised meals and only light physical activity allowed within the lab premises. At day 1 of the baseline and after five nights of restricted sleep, glucose concentrations together with other hormones were assayed using blood sampled from an indwelling intravenous catheter at fasting and then every 2 hours. Glucose was also monitored using a CGM system (The Medtronic Guardian® REAL-Time) with 2 hourly capillary blood calibration. Participants had higher glucose concentrations after five nights of restricted sleep (5 hours in bed) compared to baseline values (Reynolds et al., 2012). Mean glucose concentrations was higher by 0.6 mmol/l after 5 nights of sleep restriction compared to baseline, mean (SD) were 5.5 (0.1) mmol/l and 4.9 (0.1), respectively. Glucose concentrations were higher at breakfast than at lunch and dinner similar to the results of the study presented in this thesis. They showed an exaggerated post prandial glucose response after sleep restriction, particularly after breakfast Figure 5-3 and Figure 5-4 depict the study results. The study also found higher insulin secretion in the first half of the day and higher cortisol and adrenocorticotropic hormone (ACTH) in the second half of the day, after five days of restricted sleep compared to baseline (Figure 5-3).
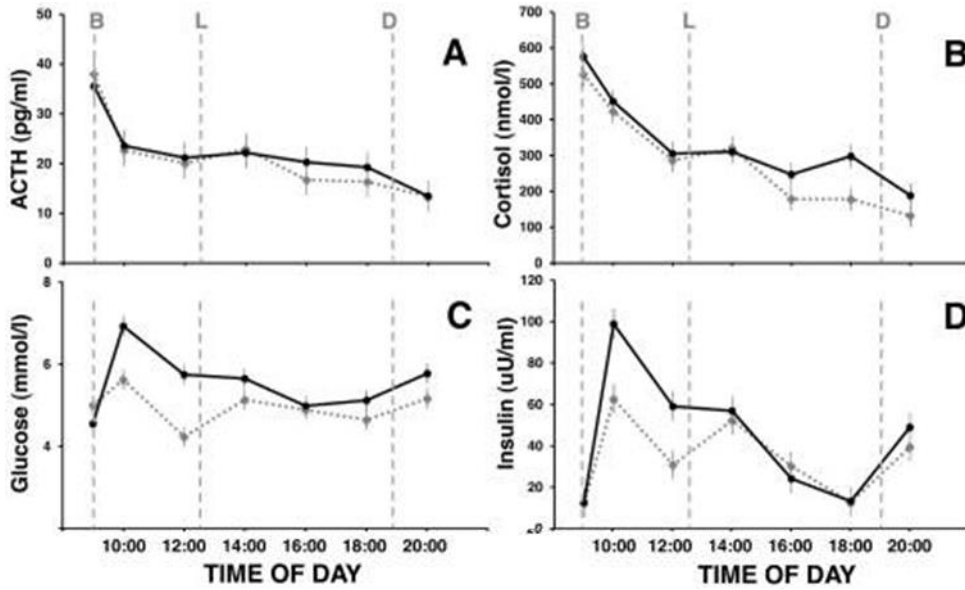
Figure 5-3 Glucose and hormonal assays results from 2 hours apart intravenous blood samplings on baseline day 1 (grey dotted line) and after five nights of sleep restriction (black solid line) (Reynolds et al., 2012) ; reused under the Creative Commons Attribution License.
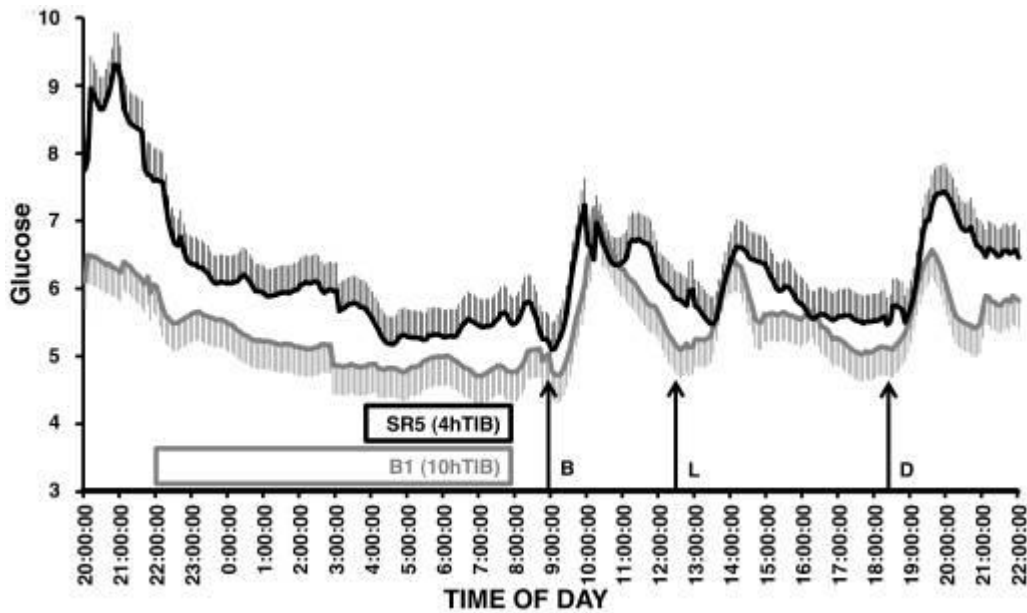
Figure 5-4 Glucose curves from CGM system on baseline day 1 (B1 grey curve) and after five nights of sleep restriction (SR5 black curve); adapted from (Reynolds et al., 2012) ; reused under the Creative Commons Attribution License.

In another experimental study involving 11 young men, glycaemic response to a high carbohydrate breakfast meal was much higher after six nights of induced partial sleep deprivation (4 hours in bed only) compared to the glycaemic response of the same content breakfast meal after six nights of recovery sleep (12 hours in bed), albeit similar insulin concentrations measured in both situations. In the same study, glycaemic responses and insulin concentrations after lunch and dinner did not differ. However, an intravenous glucose tolerance test (IGTT) done after five nights of sleep deprivation showed a pattern similar to that seen in individuals with impaired glucose tolerance, The IGTT normalised after 6 nights of recovery sleep. (Spiegel et al., 1999). In another study with a lesser degree of sleep restriction, 15 young healthy adults were evaluated after 3 nights of sleep deprivation (restricted time in bed by 1-3 hours less than their usual) and after 3 nights of their usual sleep duration. Glucose concentrations after the OGTT test were similar after the nights of sleep deprivation to those after usual sleep duration, however the fasting insulin concentration and insulin excreted during the OGTT after the sleep deprivation nights were much higher than those after the regular sleep duration nights (Wang et al., 2016b). Taken together, these experimental sleep restriction studies and a few others (Donga et al., 2010) are very suggestive of an insulin resistant state induced by sleep deprivation with possible underlying hormonal imbalance (more details in next section).

5.4.7 Clinical relevance

This study has shown a statistically significant association between PSQI total score as estimated poor sleep quality and glucose concentration with 0.06 mmol/l increase in glucose concentration for each score increase in PSQI total score. Although the association was statistically significant, a worsening/improvement of 10 scores in the PSQI total score is required to produce a clinically significant results of 0.6 mmol/l in glucose concentration (as discussed previously in Methods chapter, section 3.2). With PSQI total scores ranging from "0" (best sleep quality) to "21" (worst sleep quality) and a median PSQI score observed in this study of "7", a difference of 10 scores in PSQI total score is potentially attainable. Furthermore, as depicted in Figure 4-26, compared to sleeping 6-8 hours, sleeping just 2- 4 hours per night was associated with 0.8-0.3 mmol/l higher glucose concentration, whilst sleeping 10 hours per night was associated with 0.5 mmol/l higher glucose concentration. These associations are both statistically and clinically significant. Nevertheless, further research and a clinical trial aiming to improve sleep quality and duration is needed to ascertain if these associations are causal.

5.5 Proposed pathophysiological mechanisms

There are many postulated pathophysiological mechanisms of the relationship between sleep disturbance and glucose metabolism, mainly through the stimulation of insulin resistance and the effect of sleep on hormonal balance. In experimental studies among healthy young individuals sleep disturbances were linked to alteration in the secretion of important hormones involved in the metabolism of glucose - cortisol, growth hormone, glucagon, the appetite regulating hormones (leptin and ghrelin) and thyroid hormone.

Sleep disturbances, such as sleep deprivation and poor sleep quality, are perceived by the body as stressors that trigger the activation of the hypothalamic-pituitary-adrenal axis, as well as, inhibit the recovery the hypothalamic-pituitary-adrenal axis activation caused by other stressors leading to higher circulating levels of stress hormones (Leproult et al., 1997; Palagini et al., 2014).

Stress hormones, like cortisol, activate the production of glucose through glycogenolysis (degradation of stored glycogen) and gluconeogenesis (synthesis of new glucose molecules mainly in the liver). They also trigger the release of hunger hormones (such as ghrelin) and the suppression of satiety hormones (such as leptin) leading to more food intake. Stress hormones suppress the production of insulin as well. All these hormonal mechanisms lead to a surge in the circulating blood glucose. Under a normal sleep/wake pattern cortisol exhibits a circadian rhythm characterised by a rise of cortisol concentration in the second half of sleep till it reaches a peak at dawn and in the early morning, then the cortisol concentration declines again to reach its lowest levels at the first two hours of sleep (Davidson et al., 1991). Studies investigating the relationship between sleep deprivation and cortisol secretion have not found a statistically significant difference between the mean 24-hour cortisol levels following a sleep deprived night compared to a non-sleep deprived night. They did find a statistically significant higher, around 37% to 45% , nocturnal cortisol level following a sleep deprivation night (Davidson et al., 1991; Leproult et al., 1997; Redwine et al., 2000; Spiegel et al., 1999; Reynolds et al., 2012). Furthermore, better sleep quality as indicated by a higher proportion of slow wave sleep (deepest sleep) was negatively correlated with cortisol levels measured the next day. Whilst, a poorer sleep quality and disturbed sleep as indicated by a higher proportion of stage 1 NREM sleep (lightest sleep) and WASO were positively correlated with cortisol levels measured the next day (Vgontzas et al., 1999). Moreover, poor sleep quality (PSQI>5) was also associated with higher levels of inflammatory markers (interleukin-8) among African American pregnant women (Blair et al., 2015)

Growth hormone (GH) is another important hormone that is released mainly during sleep, especially during slow wave sleep in the first half of the night's sleep (Van Cauter and Plat, 1996). GH is a hormone that is responsible for the regeneration of body cells and tissues and plays a role in the restorative action of sleep. It also plays a major role in glucose metabolism (Gunawardane et al., 2015). GH counteracts the effects of insulin on glucose metabolism, suppresses muscle uptake of glucose, stimulates gluconeogenesis and thus raises blood glucose levels. The absent or reduced levels of GH seen in those with insomnia, sleep deprivation and those with a low proportion of deep sleep (Redwine et al., 2000; Lieb et al.) causes a marked insulin hypersensitivity and hypoglycaemia overnight and this could explain the positive linear association between sleep duration and glucose concentration at the second half of the night observed in section 1.6.1.2 of the current study. Hypoglycaemia triggers a counter regulatory response by the body to return to the euglycaemic state. These counter regulatory responses include the inhibition of insulin secretion and the stimulation of glucagon and cortisol secretion. Fasting glucagon concentration was significantly higher (p=0.003) following restricted sleep than ad libitum sleep (Wang et al., 2016b). These hormones cause endogenous production of glucose leading to higher levels of circulating blood glucose and resulting in the dawn phenomenon in the early morning. They also causes the fast and the exaggerated response to the breakfast meal (Sprague and Arbeláez, 2011). Moreover, chronic GH deficiency is counterbalanced by insulin resistance (Gunawardane et al., 2015). In addition, following a depletion of growth hormone after a sleep deprived night, a recovery night will be accompanied by higher than baseline production of GH during sleep (Redwine et al., 2000). Individuals with intact pancreatic beta-cell function counteract higher levels of GH by hyperinsulinemia, however if long term, it may cause insulin resistance in the liver, adipose tissue and skeletal muscle (Moller et al., 1991). Placental growth hormones which have a major role in glucose metabolism during pregnancy (Frankenne et al., 1988) may add to the complexity of the hormonal turbulence that accompanies sleep disturbance. To the best of my knowledge there is no study examining the relationship between sleep disturbances and placental growth hormone.

Sleep disturbance, mainly sleep curtailment has also been linked to an increased appetite and craving for carbohydrate rich snacks (Shlisky et al., 2012). In a clinical trial involving 12 healthy men, plasma leptin and ghrelin concentrations and subjective ratings of hunger and appetite were monitored after 2 days of restricted sleep duration and after 2 days of extended sleep duration. Leptin was 8% lower, ghrelin was 28% higher and participants rated higher hunger and appetite especially for high carbohydrate contents foods after sleep curtailment compared to sleep extension (Spiegel et al., 2004). In another study nine healthy men were subjected to; one night of 7 hours sleep

duration, one night of 4.5 hours restricted sleep duration and one night of total sleep deprivation, separated by 2-week washing periods. Mean (SD) plasma ghrelin concentration had a negative relationship with sleep duration as follows: 0.85 (0.06) ng/ml after total sleep deprivation, 0.77 (0.04) ng/ml after sleep restriction, and 0.72 (0.04) ng/ml after 7 hours sleep duration. Moreover, Hunger ratings indicated stronger feelings of hunger in relation to the extent of sleep deprivation. However, mean plasma leptin levels were not affected by sleep duration (Schmid et al., 2008). A further clinical study among twelve healthy young men also reported increased energy consumption and higher pre-breakfast and pre-diner perceived hunger after one night of 4 hours restricted sleep duration compared to energy consumption and perceived hunger after one night of 8 hours sleep duration (Brondel et al., 2010). On the other hand, Nedeltcheva et al. (2009b) did not find any difference in leptin and ghrelin levels after 5.5 hours in bed restricted sleep duration compared to 8.5 hours in bed sleep duration, albeit they reported increased consumption of calories from high carbohydrate contents snacks after the restricted sleep duration night. Another study did not find any association between sleep curtailment and perceived hunger, appetite hormones level or total energy intake (St-Onge, 2013).

Lastly, the effect of sleep on thyroid and thyroid stimulating hormones (TSH). In normal conditions TSH levels surge in the night (around 4-5 hours before usual sleep time) and lower after sleep onset (Allan and Czeisler, 1994). However, with total sleep deprivation, TSH levels stay elevated and increase further overnight (Knutson et al., 2007; Allan and Czeisler, 1994). Elevated TSH stimulates the secretion of excess thyroid hormone in the circulation. Thyroid hormone leads to a higher circulating blood glucose via multiple mechanisms including suppression of insulin secretion, enhancing renal excretion of insulin, alteration of glucose metabolism and glycogenolysis (Potenza et al., 2009). Nevertheless, after two days of total sleep deprivation the amplitude of the TSH surge diminishes due to the exerted negative-feedback by higher thyroid hormone levels (Van Cauter et al., 1994). In the Spiegel et al. (1999) sleep curtailment study, described in details in section 5.4.6, thyroid hormone concentrations were higher after six nights of partial sleep deprivation compared to its level after six nights of sleep recovery, mean (SD) 9·1 (0·3) ng/dl and 8·5 (0·3) ng/dl, respectively, $p < 0·01$. Furthermore, Baumgartner et al. (1993) studied the effect of partial sleep deprivation on TSH among 10 healthy young women under strict laboratory conditions. After spending 3 hours asleep (from 10:30 pm to 01:30 am) the women were woken and they stayed awake till the next sleep time. TSH was markedly elevated following the sleep interruption and remained so during the course of the following day. TSH decreased again in the next sleep period. Though these changes in thyroid and TSH recovered fast after recovery sleep, multiple

episodes of sleep curtailment and sleep recovery may lead to the development of insulin resistance (Spiegel et al., 2005).

In summary, the hormonal turmoil caused by sleep curtailment and poor sleep quality are all likely to contribute to the hyperglycaemic state and insulin resistance (Figure 5-6). Nonetheless, while there are many postulated mechanistic pathways between short sleep duration and glycaemic dysregulation, the link between long sleep duration and such glycaemic dysregulation is still obscure.

Excess sleep and spending a prolonged time in bed are associated with many disadvantageous health impacts and even with higher mortality (Patel et al., 2006), as too much of a good thing is not necessarily good! Sleep can be looked upon similarly to food, where food intake is necessary for wellbeing, yet both starvation and overeating are detrimental for health. Indeed, long sleep was associated with a higher mortality risk in older adults than short sleep (Youngstedt and Jean-Louis, 2011). Postulated mechanisms of oversleeping include a lack of motive (nothing to do after waking-up), depression, daytime lethargy, lower physical activity and sedentary life style (Grandner and Drummond, 2007). Furthermore, longer sleep may not be accompanied by a good proportion of deep refreshing slow wave sleep (Youngstedt and Kripke, 2004). Individuals with sleep-disordered sleeping may compensate for low sleep quality by oversleeping. Long sleep has been linked to impairment in health status, daily activities and work productivity even in a group of individuals without underlying diseases such as sleep-disordered breathing and depression (Dean et al., 2010). In experimental studies, extending sleep duration for young adults with habitual sleep duration of 7-8 hours resulted in an impairment of mood and lower cognitive abilities (Taub and Berger, 1973; Reynold et al., 2014). In another sleep extension randomised clinical study, increasing the habitual sleep duration by more than 2 hours per day for one week was associated with a 2-fold increase in the levels of inflammatory markers (Interleukin-6) (Figure 5-5) and even increased the level of daytime sleepiness compared to the habitual sleep baseline week (Reynold et al., 2014). However, in this particular study although the allocation of the study participants to the study groups was randomised it is clear in Figure 5-5 that the control group had higher baseline Interleukin-6 concentrations. A possible inflammatory process linked to long sleep duration may be implicated in the impairment of glucose regulation possibly through pancreatic beta cell destruction and insulin resistance (Kristiansen and Mandrup-Poulsen, 2005).

Taken together these effects manifested by a longer sleep duration may lead to lower uptake of glucose by body tissue and less utilization of glucose due to lower demand, ultimately resulting in a higher circulating blood glucose (Figure 5-6).
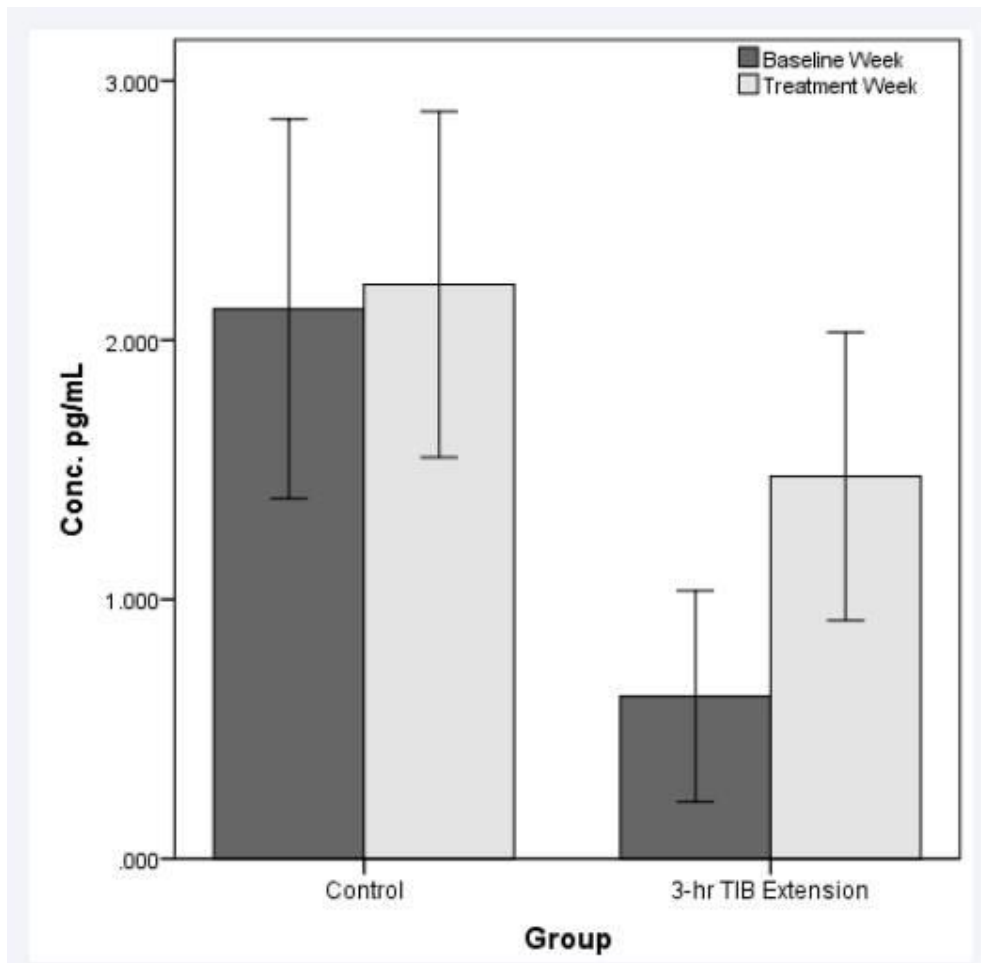
Figure 5-5 Interleukin-6 mean (SE bars) levels at the end of baseline weeks and experiment week for the control and time-in-bed (TIB) extension groups (Reynold et al., 2014); reused under the Creative Commons Attribution License.
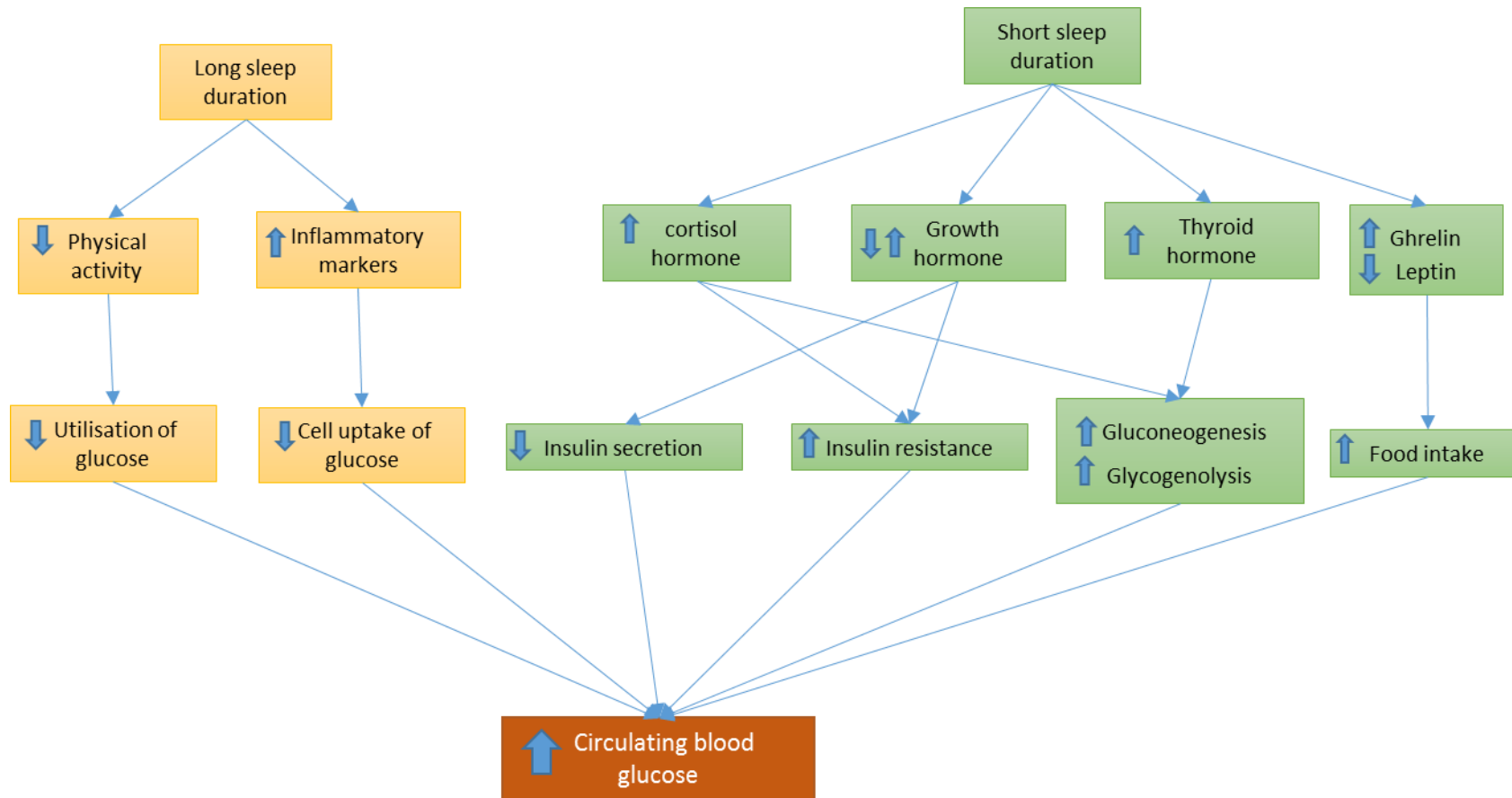
Figure 5-6 Schematic diagrams depicting the pathophysiological mechanism of the causal pathway between sleep duration and glycaemia

5.6 Study limitations

Epidemiological studies, as in my present study, can show strength of associations but they cannot prove causality. Furthermore, they are subjected to multiple issues that can distort the validity of the observed associations. Confounding bias, volunteer bias, measurement bias, recall bias, loss to follow-up, and reverse causation are some of these issues (Stuckless and Parfrey, 2009). As such, the findings of this study are inherently susceptible to a number of substantive biases. My results therefore need to be interpreted in the context of several limitations.

5.6.1 Confounding bias

The results of this study might be susceptible to confounding bias due to insufficient adjustments in the regression models for some potential confounder variables, namely diet, physical activity and sleep-disordered breathing (Skelly et al., 2012).

Diet and physical activity

Dietary intake data was not collected as a part of this study. The Actiwatches measured activity counts, however they were not supplemented by heart rate data and thus energy expenditure could not be estimated from them. Furthermore, heart rate was also required to confirm if the accelerations detected by the Actiwatches during the day were caused by the participants' body movement due to them being active or rather the accelerations were an artefact from simply being in an accelerating transportation vehicle. Nevertheless, the putative causal links between sleep, diet, physical activity and glucose control are fraught with complexity (Dolezal et al., 2017; Frank et al., 2017). It can be argued that diet and physical activity are not acting as confounders rather they are mediators in the causal path between sleep and glucose control (Figure 5-7). Sleep impact on glucose control could be interceded by its effect on the dietary amounts and choices and on the perceived exhaustions and enthusiasm to perform physical activity (VanHelder and Radomski, 1989; Hogenkamp et al., 2013). In the case of being mediators, adjusting for diet and physical activity in the regression model is not recommended (Richiardi et al., 2013; Gilthorpe, 2011b; Schisterman et al., 2009). Thus confounding bias is unlikely to have affected this study as a result of not adjusting for diet and physical activity. However, residual confounding bias from other unknown/unmeasured confounders could still affect the results of this study (Fewell et al., 2007; Jager et al., 2008).

Sleep-disordered breathing

There is a ream of articles on the association between snoring, sleep apnoea and other sleep-disordered breathing with the risk of developing diabetes and other metabolic syndrome diseases in general population (Seetho and Wilding, 2014; Shaw et al., 2008; Punjabi et al., 2004; Sabanayagam et al., 2012) and with the risk of GDM in pregnant women (Luque-Fernandez et al., 2013; Qiu et al., 2017; Ge et al., 2016; Bisson et al., 2014; Bourjeily et al., 2010). However, the results have been inconsistent and moderated by obesity. Sleep-disordered breathing is a potential confounder in the association between sleep and glucose control, as it can be associated with glucose control through hypoxia, as well as causing sleep disturbances (short sleep duration, poor sleep quality and sleepiness during the day) (Figure 5-8). I was not able to adjust for sleep-disordered breathing and this could potentially expose the study findings to confounding bias.
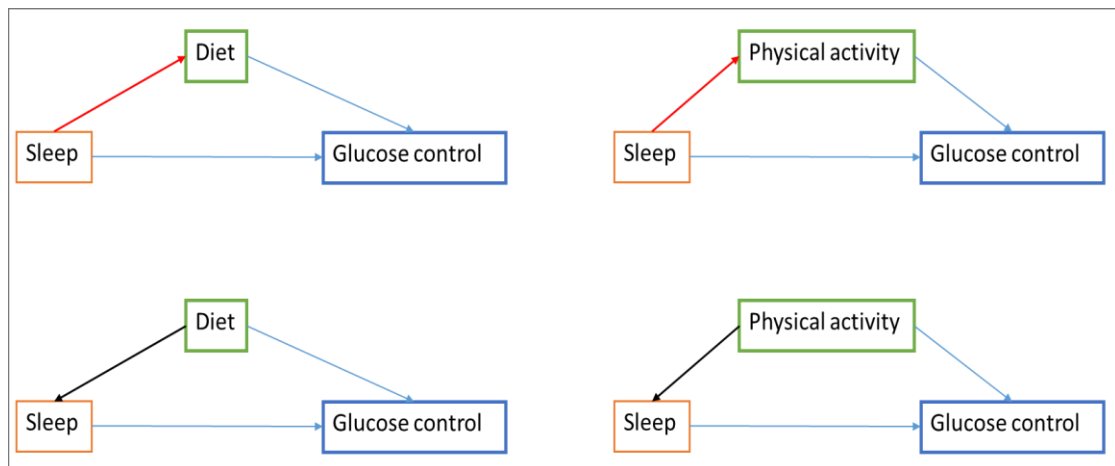
Figure 5-7 Causal diagrams of the association between sleep and glucose control showing diet and physical activity as; a mediators (right and left upper panel) and a confounders (right and left lower panel)
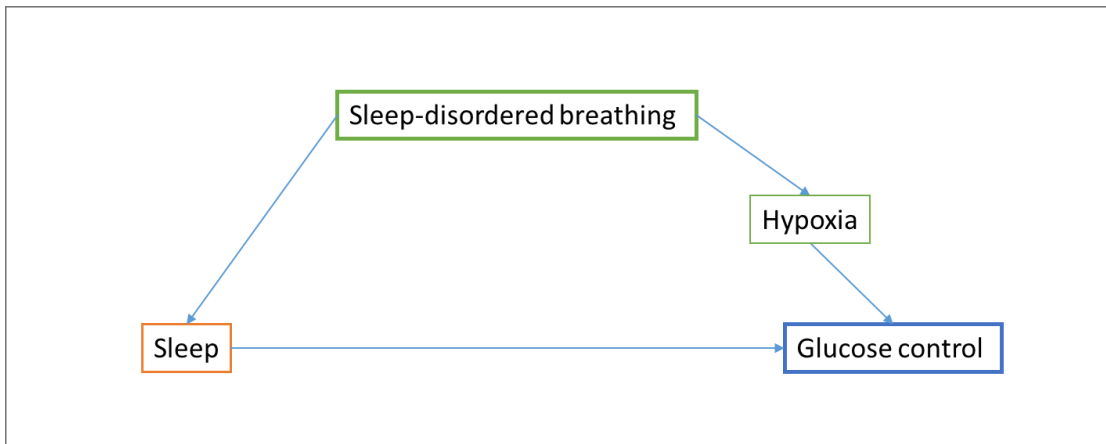
Figure 5-8 Causal diagrams of the association between sleep and glucose control showing sleep-disordered breathing as a confounder

5.6.2 Monophasic versus biphasic sleep

Sleep in newborns and in the early years of a human beings life is described as polyphasic (i.e. having multiple sleep/wake cycles within the 24-hour day) (Crabtree and Williams, 2009). This sleep pattern changes rapidly to become one of a more solid sleep interval during the night, with wakefulness during the day (i.e. monophasic sleep). However, biphasic sleep (i.e. having a core sleep interval during the night and a nap/multiple naps or a short sleep interval during the day) is common in some cultures and can take different forms. One form is represented by the midday siesta seen in some European and Latino cultures (Nieto, 2015), midday napping in China (Brunt and Steger, 2004) and midday Qailulah in some Islamic cultures (Tumiran et al., 2015; BaHammam, 2011). This form is common in countries where the temperatures are usually high at noon. To avoid direct sun heat and avoid dehydration, residents of hot climates have adapted to take midday rest and nap around noontime and then resume work in the afternoon, however this practice is less common among residents of cold climates (Bursztyn, 2013). Another form of biphasic sleep is when the individual wakes up in the morning after sleeping for several hours during the night to do some rituals or duties for a couple of hours or less and then resumes sleeping for a couple more hours (Matuzaki et al., 2014). For instance a woman may wakeup in the morning to prepare breakfast for her children, walk them to school and then return home to enjoy a few more hours of sleep. A third form of biphasic sleep is when individuals doze and take naps as a form of rectification for a short night sleep.

Some researchers endorse napping of 10- 30 minutes in the midday, but not later in the day, as a healthy sleep behaviour (Tumiran et al., 2015; Milner and Cote, 2009; Dhand and Sohal, 2006). However, other research has linked napping, especially when

combined with short sleep duration, to the development of T2DM (Leng et al., 2016), however this association was not evident in another study (Kowall et al., 2016). A systematic review and meta-analysis of studies investigating the association between napping and the risk of cardiovascular disease and T2DM concluded that long naps of more than 40 minutes per day, but not shorter naps, were associated with a higher risk of T2DM, and naps longer than 60 minutes were associated with a higher risk of cardiovascular diseases (Yamada et al., 2016; Yamada et al., 2015).

Napping frequency and duration could modify the main sleep duration (Rawal et al., 2017). However, my study has only assessed the core/main night sleep interval and did not investigate napping or midday sleep intervals. This may have subjected the study results to a misclassification bias.

5.6.3 Non-random sampling, volunteer bias and generalisability of the study results

The study population were consecutive recruits from pregnant women with GDM attending the DIP clinic. Although the consecutive sampling method is a non-probability sampling method, it was the most practical and suitable sampling method for this study and it was unlikely to have caused any systematic bias (Henry, 1990). However, volunteers may not share the same characteristics as non-responders, such as their age, ethnicity, the level of glucose control or the extent of sleep disturbance. This volunteer bias may endanger the validity of the study findings (Salkind, 2010). So, a high non-response (decline) rate may have biased the results of this study, as the responders might not be representative of the sampled (source) population (i.e. population of pregnant women with GDM attending Leeds and York DIP clinics) (Stuckless and Parfrey, 2009). This may affect the internal validity of the study results, i.e. the degree to which the study findings yield a correct inference about the association between the exposure and the outcome in the source population (Rothman and Greenland, 2005; Gail and Benichou, 2000). Likewise, it can affect the external validity of the study results, i.e. the generalisability of the study inference to the target population (i.e. pregnant women with GDM in general) (Gail and Benichou, 2000).

However, it is unlikely that validity of this study has been substantially affected. The mean age distribution of the study participants was around 32 years old and it ranged between 18-45 years. This is the same age distribution expected for women of child bearing age. Comparing the ethnicity distribution of the study participants to the ethnicity distribution of the England and Wales 2011 general population published census results showed some differences (Office for National Statistics, 2012). White ethnicity accounted for the majority in the census (86.0% of the population), however they only compromised 60.9% of this study's participants. The proportion of other ethnic groups were much

higher in this study compared to the census results, as follows: Asian 21.4% vs. 7.5%, Black 10.9% vs. 3.3%, and other ethnic groups 6.8% vs.1.0%. However, this could reflect the difference in the prevalence of GDM among various ethnic groups, as well as the selective risk factor based screening for GDM advised by NICE and followed in Leeds and York NHS Trusts. Adjusting for the participants' characteristics, in a similar manner to adjusting for confounders, can also control some of the potential bias and improve the validity of the study findings (Rothman et al., 2008). However, the inference from this study cannot be extrapolated to T1DM and T2DM. The association between sleep and glucose control in T1DM and T2DM needs investigating.

5.6.4 Limited resources

The iPro CGM systems and the Actiwatches were relatively expensive. The price of the Medtronic iPro system was £1377, the price of the Enlite sensor was £53 for each sensor, £275 for a pack of five sensors, £525 for a pack of ten sensors. The Actiwatch was £613 each (£740 including VAT). With the limited funds I had, only a limited number of these devices were available at a time. Adding to this I had some degree of Actiwatch failure which led to the loss of 5% of actigraphy records in this study. This was similar to the proportion reported by other research among pregnant women (Reid et al., 2017). The limited number of these two systems, meant that I could not recruit more women in the time frame I had.

With the surge of cheap and widely commercially available generic accelerometers wrist-bands gadget and smart phones applications, it is tempting to use them instead of the expensive professional actigraphs. However, they are usually of low resolution, more prone to measuring artefact, have no clear specifications and have been found to have low sleep measuring accuracy (Ancoli-Israel et al., 2015; Meltzer et al., 2015; Evenson et al., 2015; Toon et al., 2016). Moreover, smart phone applications consume a phones battery and may require connecting them to an electrical source during the night and placing them under the pillow or mattress while asleep. This could expose the individual to a burning risk from the phone battery overheating and exploding.

5.6.5 Measurement errors

Glucose measurements

Though CGM systems have the advantage of close monitoring of glucose levels in a continuous fashion enabling the recognition of glucose daily patterns and enhancing the detection of hyperglycaemic and hypoglycaemic episodes over an extended period of days, it is not without a caveat. In addition to the expensive cost and the relatively low uptake by the potential participants, measurements errors could affect the accuracy of the results. At a time of rapid blood glucose rate-of-change interstitial glucose may

experience a time lag of 5 to 15 minutes behind the blood glucose (Boyne et al., 2003; Rossetti et al., 2010). The lag happens as glucose takes time to diffuse from the capillaries to the interstitial compartment. At times of rapid glucose change there is a discrepancy of interstitial and blood glucose concentrations. Nonetheless, in the latest advanced CGM systems' algorithms lags are considered and slightly controlled for using some statistical filters (Pleus et al., 2015; Schmelzeisen-Redeker et al., 2015; Hayter et al., 2009). Rapid rate-of-change and the associated lag also affect the accuracy of the CGM readings (Kumareswaran et al., 2013; Scuffi et al., 2012). Furthermore, the accuracy of the CGM system depends on the accuracy of the glucometer used to measure the capillary blood glucose. In the current study various glucometers from different manufacturers were used by the participants, as per supply by the DIP clinics. Accuracy of these glucometers may vary leading to lower accuracy of CGM calibrations (Rossetti et al., 2010). However, any measurement bias resulting from glucometer inaccuracy is less likely to be differential and any measurement bias would be towards the null.

Sleep measurements

As discussed earlier both PSQI and actigraphy sleep assessments have not been validated against polysomnography during pregnancy. Measurement error and misclassification of sleep characteristics could result from these two measurement tools inaccuracy. Furthermore, actigraphy objectively measures movement and lack of movement as crude estimates of being awake or asleep. However, it requires manual and subjective manipulation to determine bedtime and getting out of bed time, which renders it not totally objective. It also erroneously identifies being unsettled and frequent change of sleeping position while asleep, which is common during late trimester pregnancy, as being awake.

Measurement errors due to categorisation of variables

Measurement errors could have been introduced by categorising continuous variables into groups in the current study (Tu and Greenwood, 2012; Royston et al., 2006). Sleep duration was categorised into three groups to explore the postulated U-shaped relationship in some of the regression models, SOL duration was categorised in two groups to mimic the clinical diagnosis of initial insomnia, other proportion and ratio variables were categorised to enhance the validity of the regression models. To be consistent in the approach applied for categorisation, cut-points used were either: a clinical reference value such as in the case of SOL duration; the 25th and the 75th percentiles for categories of three groups such in the case of sleep duration; and the median for categories of two groups such in proportion of time within target range variable.

5.7 Discussion of the FDA methods

Application of FDA methods to the CGM data enabled appreciation of the temporal sequences and the correlations between glucose data-points. It enabled the display of the CGM data as visual, easily comprehensible, and logically explicable glucose curves. Descriptive data extracted by the FDA methods (including the mean, the SD, the median and the interquartile range of glucose curves) had more physiological meaning and known reference values compared to overall summary metrics such as mean-glucose and SD-glucose. Using the smoothing methods enabled the presentation of the daily glucose curves as one unit instead of multiple adjacent points. It also provided a novel insight on the relationship between glucose curves at different times of the day with multiple covariates. The timing and the amplitude of the association were easily interpretable in a similar manner to the interpretation of standard regression models.

In this study I developed a registration loop to align and then extract a single daily curve for each participant to elude the need to use multilevel mixed effect FDA due to its computational complexity. Further work is needed to improve and simplify the application of the multilevel mixed effect FDA to CGM data needs.

Registration aligned the glucose curves and separated the amplitude variation from phase variation, however it was not perfect. Some curves' peaks and troughs were located far from most of the other curves' peaks and could not be aligned even after multiple iterations. This residual phase variation may disrupt the findings of this study. Further registration needs sufficient computer memory space and takes a relatively long time for each iteration. The time and the computer memory capacity required for registration increases with denser data and larger number of records. Adequate computer memory capacity is also required for extracting the regression model coefficients' standard errors in order to construct the 95% confidence band.

Whilst registration was essential in this research to identify the variation in glucose curves' amplitudes and how much of the variation could be explained by various sleep characteristics, other research may be more concerned with the variation in timing of glucose curves' peaks and nadirs, i.e. phase variation. In the later condition registration would not be advisable. Moreover, CGM data from GDM patients may be expected to be more homogeneous and less variable than CGM data from pregnant women with T1DM and T2DM, especially those on insulin treatment. FDA methods have been applied to data from these populations but without using full registration (Law et al., 2015).

Other statistical methods that have been used to analyse longitudinal data such as multilevel growth models can technically be applied to CGM data, however they lack

some of the beautiful features of FDA methods such as registration. To my knowledge there are no published studies applying these methods to CGM data.

FDA tools are relatively new and they are developing with fast momentum. However, they have not been widely adopted among researchers and statisticians at the same speed functional data are produced by the advance in devices and technologies. Furthermore, FDA tools are available only in some much specialised, R and MATLAB, statistical software, which need professional training and good experience in such software.

5.8   Planned publications

1- Relationship of sleep to glucose control in gestational diabetes: a study using continuous glucose monitoring and functional data analysis; in preparation for Diabetes Care

2- Analysis of continuous glucose monitoring data; from summary metrics to functional data analysis In preparation for Diabetes Technology & Therapeutics

3- CGM-FDA R software package; the study CGM-FDA code syntax formulated into a package to be deposited in The Comprehensive R Archive Network - R Project (CRAN R-project).

4- Poor agreement between subjective and objective sleep measures among pregnant women with gestational diabetes; in preparation for Sleep.

5.9 Future research

1- Extending the findings from my research, I am planning to investigate the direct association of sleep characteristics measured during the last trimester of GDM pregnancy to pregnancy outcome.

2- Analysis of the relationship between CGM summary metrics and glucose smooth curves with infant birthweight is ongoing with cooperation with other members of the research team.

3- Another rather technical research study is to do with actigraphy data. Manual editing of bedtime and getting-up from bed time is time consuming and tedious. Building an algorithm to automatically integrate the bedtimes and getting-up times from the sleep diary together with other indicators such as activity levels and light levels would improve the feasibility and potentially the results of the actigraphy.

4- Validating the application of the FDA smoothing methods and the registration-loop developed in this thesis to secondary CGM data from T1DM and T2DM patients.

5.10 Implications and future recommendations

This study has shown the clear advantage of analysing CGM data using FDA methods. Future studies involving the use of CGM should ensure the use of FDA analysis methods as described in this thesis. The R software codes syntax written as part of this study and a planned CGM-FDA R software package will facilitate the use of these methods by many researchers.

This study has also demonstrated the repercussions of sleep disturbances on glucose control. Therefore this study calls upon both clinicians and policy makers to attend more closely to sleep disturbance as a potentially modifiable risk factor for glucose dysregulation in pregnant women with GDM. Intervention strategies for sleep improvement and enhancement were find to be feasible and effective during pregnancy (Lee et al., 2016; Tsai et al., 2016a).

A randomised clinical trial studying the effect of sleep enhancement (using several methods such as sleep hygiene techniques instructions and cognitive therapy) on improving glycaemic control would strengthen the evidence extracted from this study. Sleep hygiene techniques include avoiding caffeine at night, practicing mindfulness and yoga, performing mild physical exercise, having more exposure to natural light during the day and avoiding blue light and electronic gadgets during nighttime and especially before going to bed.

Further investigation of the role of sleep disturbances on glycaemic control in pregnant women with T1DM and T2DM warrant investigation. Evidence to date from T1DM and T2DM people in the general population has been based on cross-sectional single value glycaemic evaluations. Studies using CGM systems have the potential to shed more light on the potential associations.

Despite the extensive work done in this research to the application of FDA methods to CGM data, there is abundant room for further progress. Particularly in regards to multilevel functional regression modelling.

Lastly, future research should be undertaken to validate PSQI questionnaire and actigraphy-derived sleep characteristics against polysomnography at different trimesters during pregnancy. Emphasis should be put on developing and validating actigraphy-algorithms during pregnancy.

5.11 Conclusion

Gestational Diabetes (GDM) is extremely prevalent and is associated with a higher risk of complications to the mothers and the newborns. Sleep disturbances have been associated with lower glycaemic control among non-pregnant population with T1DM and T2DM. There is a paucity of such studies among pregnant women with diabetes with only one small sample size study among pregnant women with GDM. This gap in literature leads to the main study aim which was to evaluate the association between sleep of pregnant women with GDM and their glycaemic control.

Over the course of two years and ten months, this study was able to recruit 192 pregnant women with GDM at their third trimester from a main recruitment centre (the diabetes in pregnancy clinics at Leeds hospital trust) and a secondary recruitment centre (the diabetes in pregnancy clinics at York hospital trust). Recruitment was challenging particularly at the beginning, however with some modulation in the study protocol the take-up by potential participants had improved remarkably.

To cover multiple facets of sleep structure of the pregnant women, sleep was assessed subjectively using the Pittsburgh Sleep Quality Index (PSQI) self-reported questionnaire and objectively using actigraphy device (Actiwatch2 Respironics). To assess the glycaemic control, close monitoring of glucose concentrations was accomplished using masked CGM system (iPro2 Medtronic). 152 participants had sufficient data retrieved from them, i.e. the PSQI questionnaire data and at least one night actigraphy-derived sleep data and one 24-hour day CGM data.

Data from CGM systems are dense and highly auto-correlated, summarising these extensive data into one-value summary metrics, which is the usual approach, risk the loss of the inherent information within them. Functional data analysis (FDA) is an advance statistical method that can accommodate dense auto-correlated data and it was first used to analyse CGM data in 2015. This study has further developed and improved the application of FDA methods to CGM data.

Though they had poor agreement between their values, both self-reported and actigraphy-derived sleep characteristics of pregnant women with GDM reflected the degree of sleep disturbances. This was particularly in form of poor sleep quality and higher proportion of both shorter and longer sleep durations than average (6-8 hours).

FDA methods presented consecutive discrete CGM data-points as smooth glucose curves with a functional form, i.e. function of time. Penalised B-spline basis expansion was used to achieve this functional form. Phase variation, i.e. the variation of the timing of glucose curves peaks and nadirs, was separated from amplitude variation, i.e. the variation of the height of glucose curves peaks and nadirs, by aligning the curves using

continuous registration method. Registered smooth glucose curved revealed the physiological diurnal glucose pattern of the participants, and the identification the average and the variability of this diurnal pattern was feasible by calculating the mean, the SD, the median and the IQR curves.

Standard regression models using various CGM summary metrics as the outcome, and functional regression models using the registered smooth curves as the outcome was applied to study the associations of different sleep characteristics on the glycaemic control. These models demonstrated a positive association between sleep disturbances, mainly poor sleep quality, short and long sleep duration, sleep onset latency and wake after sleep onset duration, with higher glycaemic amplitude, variability and rate-of-change. With FDA showing the time of the day where these associations are mainly located.

To conclude, the analyses presented in this thesis, confirm that sleep disturbances are associated with suboptimal glucose control in women with GDM.

Appendices

Appendix A   PSQI questionnaire

Subject's Initials_____ID#_____Date_____Time_____ AM / PM

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

    BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

    NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

    GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

    HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

    Not during the   Less than   Once or twice   Three or more
    past month_____   once a week_____ a week_____   times a week_____

b) Wake up in the middle of the night or early morning

    Not during the   Less than   Once or twice   Three or more
    past month_____   once a week_____ a week_____   times a week_____

c) Have to get up to use the bathroom

    Not during the   Less than   Once or twice   Three or more
    past month_____   once a week_____ a week_____   times a week_____

d) Cannot breathe comfortably

Not during the   Less than   Once or twice   Three or more
past month_____ once a week_____ a week_____ times a week_____

e) Cough or snore loudly

Not during the   Less than   Once or twice   Three or more
past month_____ once a week_____ a week_____ times a week_____

f) Feel too cold

Not during the   Less than   Once or twice   Three or more
past month_____ once a week_____ a week_____ times a week_____

g) Feel too hot

Not during the   Less than   Once or twice   Three or more
past month_____ once a week_____ a week_____ times a week_____

h) Had bad dreams

Not during the   Less than   Once or twice   Three or more
past month_____ once a week_____ a week_____ times a week_____

i) Have pain

Not during the   Less than   Once or twice   Three or more
past month_____ once a week_____ a week_____ times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the   Less than   Once or twice   Three or more
past month_____ once a week_____ a week_____ times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good   _____

Fairly good   _____

Fairly bad   _____

Very bad   _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the   Less than   Once or twice   Three or more
past month_____   once a week_____   a week_____   times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the   Less than   Once or twice   Three or more
past month_____   once a week_____   a week_____   times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all   _____

Only a very slight problem   _____

Somewhat of a problem   _____

A very big problem   _____

10. Do you have a bed partner or room mate?

No bed partner or room mate   _____

Partner/room mate in other room   _____

Partner in same room, but not same bed   _____

Partner in same bed   _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the   Less than   Once or twice   Three or more
past month_____   once a week_____   a week_____   times a week_____

b) Long pauses between breaths while asleep

Not during the   Less than   Once or twice   Three or more
past month_____   once a week_____   a week_____   times a week_____

c) Legs twitching or jerking while you sleep

Not during the   Less than   Once or twice   Three or more
past month_____   once a week_____   a week_____   times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the   Less than   Once or twice   Three or more
past month_____   once a week_____   a week_____   times a week_____

e) Other restlessness while you sleep; please describe_____

_____

Not during the   Less than   Once or twice   Three or more
past month_____   once a week_____   a week_____   times a week_____

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Psychiatry Research, 28:193-213, 1989.

Appendix B   PSQI Form Administration Instructions and Scoring

Form Administration Instructions

The range of values for questions 5 through 10 are all 0 to 3.

Questions 1 through 9 are not allowed to be missing except as noted below. If these questions are missing then any scores calculated using missing questions are also missing. Thus it is important to make sure that all questions 1 through 9 have been answered.

In the event that a range is given for an answer (for example, '30 to 60' is written as the answer to Q2, minutes to fall asleep), split the difference and enter 45.

Reference

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research* 28:193-213, 1989.

Scores – reportable in publications

On May 20, 2005, on the instruction of Dr. Daniel J. Buysse, the scoring of the PSQI was changed to set the score for Q5J to 0 if either the comment or the value was missing. This may reduce the DISTB score by 1 point and the PSQI Total Score by 1 point.

PSQIDURAT   **DURATION OF SLEEP**
IF Q4 $\geq$ 7, THEN set value to 0
IF Q4 < 7 and $\geq$ 6, THEN set value to 1
IF Q4 < 6 and $\geq$ 5, THEN set value to 2
IF Q4 < 5, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDISTB   **SLEEP DISTURBANCE**
IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) = 0, THEN set value to 0

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) $\geq$ 1 and $\leq$ 9, THEN set value to 1

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 9 and $\leq$ 18, THEN set value to 2

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 18, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQILATEN   **SLEEP LATENCY**
First, recode Q2 into Q2new thusly:
IF Q2 $\geq$ 0 and $\leq$ 15, THEN set value of Q2new to 0
IF Q2 > 15 and $\leq$ 30, THEN set value of Q2new to 1

IF Q2 > 30 and $\leq$ 60, THEN set value of Q2new to 2
IF Q2 > 60, THEN set value of Q2new to 3
Next
IF Q5a + Q2new = 0, THEN set value to 0
IF Q5a + Q2new $\geq$ 1 and $\leq$ 2, THEN set value to 1
IF Q5a + Q2new $\geq$ 3 and $\leq$ 4, THEN set value to 2
IF Q5a + Q2new $\geq$ 5 and $\leq$ 6, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDAYDYS   **DAY DYSFUNCTION DUE TO SLEEPINESS**
IF Q8 + Q9 = 0, THEN set value to 0
IF Q8 + Q9 $\geq$ 1 and $\leq$ 2, THEN set value to 1
IF Q8 + Q9 $\geq$ 3 and $\leq$ 4, THEN set value to 2
IF Q8 + Q9 $\geq$ 5 and $\leq$ 6, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIHSE   **SLEEP EFFICIENCY**
Diffsec = Difference in seconds between day and time of day Q1 and day

Q3

Diffhour = Absolute value of diffsec / 3600
newtib =IF diffhour > 24, then newtib = diffhour – 24
        IF diffhour $\leq$ 24, THEN newtib = diffhour
(NOTE, THE ABOVE JUST CALCULATES THE HOURS BETWEEN
GNT (Q1) AND GMT (Q3))
tmphse = (Q4 / newtib) * 100

IF tmphse $\geq$ 85, THEN set value to 0
IF tmphse < 85 and $\geq$ 75, THEN set value to 1
IF tmphse < 75 and $\geq$ 65, THEN set value to 2
IF tmphse < 65, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQISLPQUAL   **OVERALL SLEEP QUALITY**
Q6
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIMEDS   **NEED MEDS TO SLEEP**
Q7
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQI   **TOTAL**
DURAT + DISTB + LATEN + DAYDYS + HSE + SLPQUAL + MEDS
Minimum Score = 0 (better); Maximum Score = 21 (worse)
Interpretation: TOTAL $\leq$ 5 associated with good sleep quality
                TOTAL > 5 associated with poor sleep quality

Appendix C   Sleep diary

Daily Sleep Diary

Complete the diary each morning ("Day 1" will be your first morning). Don't worry too much about giving exact answers, an estimate will do.

I.D. _____   Date _____

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Enter the Weekday (Mon, Tues, Wed, etc.)	Thursday / Friday	Friday / Saturday	Saturday / Sunday	Sunday / Monday	Monday / Tuesday	Tuesday / Wednesday	Wednesday / Thursday
At what time did you go to bed last night?							
After settling down, how long did it take you to fall asleep?							
After falling asleep, about how many times did you wake up in the night?							
After falling asleep, for how long were you awake during the night in total?							
At what time did you finally wake up?							
At what time did you get up?							
How would you rate the quality of your sleep last night? 1 2 3 4 5 V. Poor V. Good							
Times you took off the actiwatch:							

Appendix D   Actigraphy clinicians' report

Subject ID: CGDM081
DOB: **Age:**   **Gender:** Female
Recording Period: from 19/08/2015 15:14:00 to 27/08/2015 05:08:45

Indications for Use:

Summary Statistics:

	Bed Time	Get Up Time	Time in Bed (hours)	Total Sleep Time (hours)	Onset Latency (minutes)	Sleep Efficiency (percent)	WASO (minutes)	#Awak.
Min	21:59:30	06:24:30	7:54:30	6:06:45	3.25	67.98	47.75	67
Max	23:57:00	08:32:15	9:40:45	6:49:15	57.00	79.14	92.50	84
Avg	22:44:38	07:30:36	8:45:57	6:30:36	22.86	74.45	67.61	73.86

Interpretation:

| 1 **Subject ID:** | CGDM081 |
| **DOB:** | |
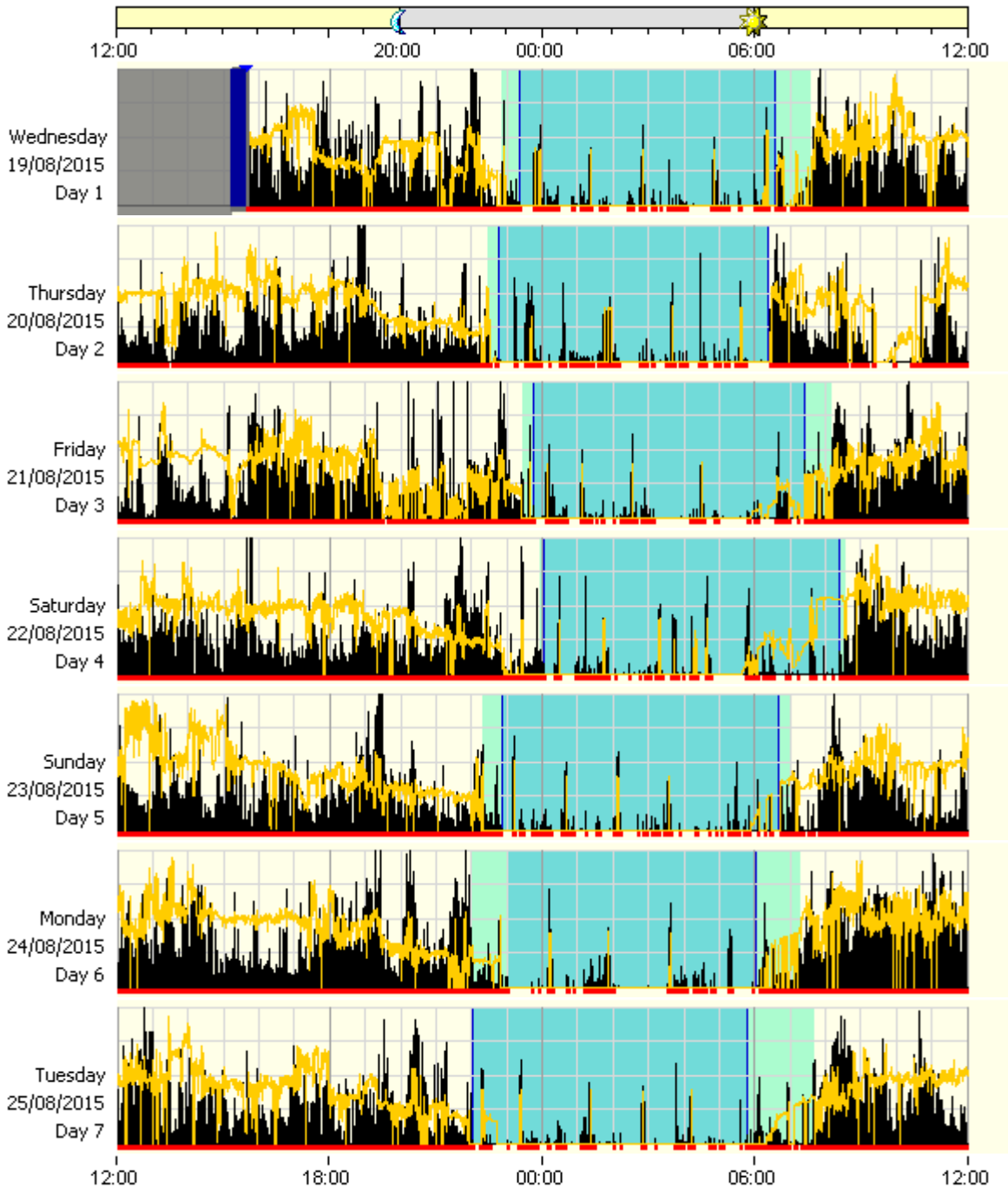
Actogram:

1	**Subject ID:**	CGDM081
	DOB:	

Actogram:

Activity Scale: 500/0, White Light Scale: 84989.7/0.1
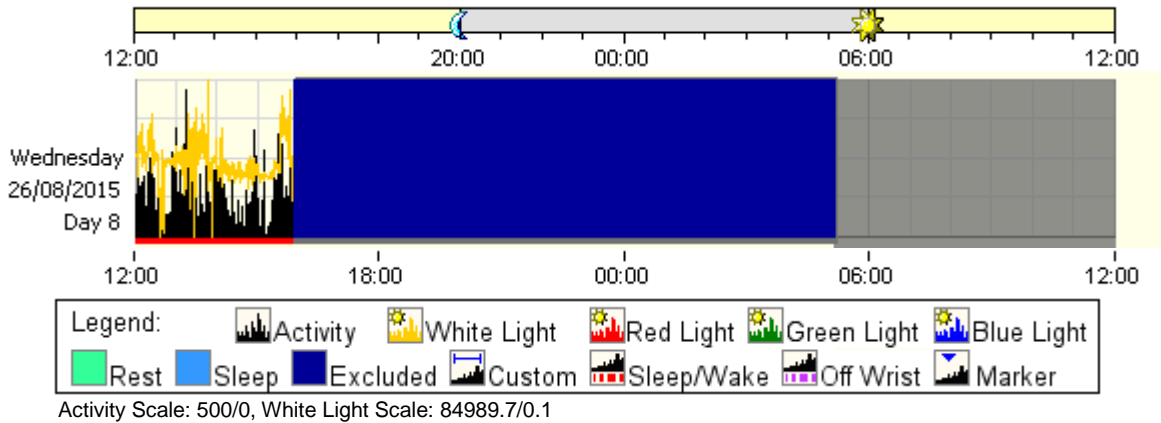
Daily Statistics:

Date	Bed Time	Get Up Time	Time in Bed (hours)	Total Sleep Time (hours)	Onset Latency (minutes)	Sleep Efficiency (percent)	WASO (minutes)	#Awak.
Wednesday 19/08/2015	22:53:15	07:33:00	8:39:45	6:06:45	28.75	70.56	67.25	78
Thursday 20/08/2015	22:30:00	06:24:30	7:54:30	6:15:15	17.75	79.08	81.25	81
Friday 21/08/2015	23:28:00	08:07:45	8:39:45	6:31:30	16.00	75.32	68.75	67
Saturday 22/08/2015	23:57:00	08:32:15	8:35:15	6:47:45	6.50	79.14	92.50	73
Sunday 23/08/2015	22:21:15	07:01:00	8:39:45	6:49:15	30.75	78.74	58.50	84
Monday 24/08/2015	22:03:30	07:15:30	9:12:00	6:15:15	57.00	67.98	47.75	67
Tuesday 25/08/2015	21:59:30	07:40:15	9:40:45	6:48:30	3.25	70.34	57.25	67
Wednesday 26/08/2015	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN

Each day represented above is from 12:00:00 to 12:00:00 on the next day.

Summary Statistics:

	Bed Time	Get Up Time	Time in Bed (hours)	Total Sleep Time (hours)	Onset Latency (minutes)	Sleep Efficiency (percent)	WASO (minutes)	#Awak.
Min	21:59:30	06:24:30	7:54:30	6:06:45	3.25	67.98	47.75	67
Max	23:57:00	08:32:15	9:40:45	6:49:15	57.00	79.14	92.50	84
Avg	22:44:38	07:30:36	8:45:57	6:30:36	22.86	74.45	67.61	73.86

Appendix E   Actiware derived sleep intervals and summary statistics

Interval Definitions

Rest intervals- These are periods of time when the subject activity is low and the subject is likely to be at rest. When set, they are indicated on the Actogram by aqua shading. Typically this will be used to indicate the in-bed period. Actiware will automatically apply the sleep interval detection algorithm once a rest interval is defined.

The first data point in the rest interval is used for the bed time and the last data point as the get-up time.

Sleep Intervals- These are periods of time when the subject is likely to be asleep. These intervals are created automatically by the software once a rest interval is defined. They represent the periods of time between sleep onset and sleep end and are indicated by blue shading.

Active Intervals- These are periods of time when the subject activity indicates that they are alert and moving. Active Intervals are created automatically when rest intervals are set and include all periods not included in a rest or excluded interval. No shading is used to indicate these intervals.

Excluded Intervals- These are periods of time that are excluded from all analytical calculations. These intervals are intended to indicate when subjects remove the Actiwatch or for periods of invalid data. These are generally set manually and are indicated by dark blue shading.

Interval Information

Start Date - The date for the first epoch of any given interval.

Start Day - The day of the week for the first epoch of any interval.

Start Time - The time for the first epoch at the start of any given interval.

Duration - The time elapsed between the start time and the end time of any given interval, in minutes.

End Date - The date for the last epoch of any given interval.

End Day - The day of the week for the last epoch of any given interval.

End Time - The time for the last epoch at the end of any given interval.

Activity Statistics

Total AC - The sum of all valid physical activity counts for all epochs for the given interval.

Avg AC/min - The average of all valid physical activity counts for all epochs for the given interval divided by the epoch length in minutes.

Avg AC/epoch - The average of all valid physical activity counts for all epochs for the given interval.

Std AC - The standard deviation of all valid physical activity counts for all epochs for the given interval.

Max AC - The largest valid physical activity value recorded during the given interval.

Total Invalid Time (activity) - The epoch length in minutes multiplied by the total number of epochs for a given interval for which the physical activity count value is invalid. This may occur under multiple circumstances including excluded intervals, device error, communication error, data corruption, time the logger is in the docking station, or time between data collection sessions.

%Invalid AC - The total invalid time (activity) divided by interval duration multiplied by 100.

Sleep/Wake Statistics

Note: In order for an epoch to be score-able as sleep or wake, it must have a valid physical activity count, and in addition there must be a sufficient number of epochs before and after the epoch being scored that also have valid physical activity counts.

Sleep Time - The total number of epochs for the given interval scored as sleep by Actiware (or manually set as sleep by you) multiplied by the epoch length in minutes.

% Sleep - The percentage of epochs in an interval that are scored as sleep. Scored total sleep time divided by (interval duration minus total invalid time (sleep/wake)) multiplied by 100.

 # Sleep Bouts - The total number of continuous blocks of epochs where each epoch is scored as sleep for the given interval.

Avg Sleep Bout - The scored total sleep time divided by the number of sleep bouts for the given interval.

Onset Latency - The time required for sleep to start after initiating the intent to sleep. The time between the start of a given rest interval and the sleep interval start time, in minutes, and is controlled by the sleep interval detection algorithm.

Snooze Time - The time required to become active after sleep end. The time between the end of a given sleep interval and the end of the rest interval, and is controlled by the sleep interval detection algorithm.

Sleep Efficiency - The percentage of time spent in bed sleeping. Scored total sleep time divided by (interval duration minus total invalid time (sleep/wake)) of the given rest interval multiplied by 100.

WASO (Wake After Sleep Onset) - This is the total number of epochs between the start time and the end time of the given sleep interval scored as wake by Actiware software (or manually set as wake by you using Actiware software) multiplied by the epoch length in minutes.

Note: WASO is identical to scored total wake time when the given interval is a sleep interval.

Wake Time - The total number of epochs between the start time and the end time of the given interval scored as wake by Actiware software (or manually set as wake by you) multiplied by the epoch length in minutes.

% Wake - The percentage of epochs in an interval that are scored as wake. Scored total wake time divided by (interval duration minus total invalid time (sleep/wake)) multiplied by 100.

 # Wake Bouts - The total number of continuous blocks of epochs where each epoch is scored as wake for the given interval.

Avg Wake Bout - The scored total wake time divided by the number of wake bouts for the given interval.

Invalid Time SW - The total number of epochs for the given interval for which the sleep/wake scoring algorithm did not have enough data to determine a sleep or wake score multiplied by the epoch length in minutes.

Note: The insufficient data condition can be caused by invalid or manually excluded epochs.

%Invalid SW - The percentage of epochs for a given interval for which the sleep/wake scores are invalid. Total invalid time (sleep/wake) divided by interval duration multiplied by 100.

Mobility Statistics

Note: In order to be score-able as IMMOBILE or MOBILE, an epoch must have a valid physical activity count.

Immobile Time - The total number of epochs for the given interval scored as IMMOBILE by Actiware software multiplied by the epoch length in minutes.

% Immobile - The percentage of epochs in the given interval scored as immobile. Scored total immobile time divided by (interval duration minus total invalid time (activity)) multiplied by 100.

 # Immobile Bouts - The total number of continuous blocks of epochs where each epoch is scored as immobile for the given interval.

Avg Imm Bout - The scored total immobile time divided by the number of immobile bouts for the given interval.

#1min Imm Bouts - The number of immobile bouts that are one minute in length for the given interval.

%1min Imm Bouts - The percentage of immobile bouts that are one minute in length for the given interval.

Mobile Time - The total number of epochs for the given interval scored as MOBILE by Actiware software multiplied by the epoch length in minutes.

% Mobile - The percentage of epochs in the given interval scored as mobile. Mobile time divided by (interval duration minus total invalid time (activity)) multiplied by 100.

 # Mobile Bouts - The total number of continuous blocks of epochs where each epoch is scored as mobile for the given interval.

Avg Mob Bout - The scored total mobile time divided by the number of mobile bouts for the given interval.

Fragmentation Index - This is an index value that includes mobility and short sleep bouts. The sum of percent mobile and percent one minute immobile bouts divided by the number of immobile bouts for the given interval.

Light Statistics

Illuminance is used for white or photopic light measurements and is expressed in lux. Coloured (RGB or red-green-blue) light is measured in irradiance or flux. Irradiance has units of uW/cm^2 (microwatts per square centimetre). Flux has units of photons/cm^2/s (photons per square centimetre per second).

Note: Irradiance/flux (red-green-blue light) statistics apply to the Actiwatch Spectrum, Spectrum PRO and Spectrum Plus.

Total Exposure - The sum of all valid light data in minutes.

Avg Light - The average light value for the given interval.

Std Light - The standard deviation of the light values for the given interval.

Max Light - The largest light value for the given interval.

TALT - The total accumulation of time, in minutes, during which the Actiwatch was exposed to an intensity of illumination above the given illuminance or irradiance/flux threshold.

Invalid Time L - The total number of epochs for the given interval for which the light value is invalid. This may occur under multiple circumstances including excluded intervals, device error, communication error, data corruption, time the logger is in the docking station, or time between data collection sessions.

% Invalid Time L - Total invalid time (illuminance or irradiance/flux) divided by interval duration multiplied by 100.

Advanced - Press this button to adjust the **Enhanced Sleep Statistics** setting described in the Sleep/Wake Statistics section of this help topic.

Note: For all above standard deviation statistics, standard deviation is computed with (n – 1) rather than (n) in the denominator of the variance.

Appendix F   Glucose Log

The Leeds Teaching Hospitals NHS
NHS Trust

Title of Project: Does variation in circadian glucose profiles predict macrosomia in gestational diabetes?
Name of Principal Investigator: Dr Eleanor Scott, Consultant in Diabetes and Endocrinology

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BLOOD GLUCOSE LOG SHEET

For the next 7 days, please record your <u>blood glucose meter readings</u> and the <u>time</u> they were taken in the log sheet below:

	Time of the day	Time	Blood glucose reading
Today Day 0	now	:	
Day: Wednesday	1 hours from now	:	
Thursday	1 hour after lunch	:	
Date: / /	1 hour after dinner	:	
Day 1	Before breakfast	:	
Day: Thursday	1 hour after breakfast	:	
Friday	1 hour after lunch	:	
Date: / /	1 hour after dinner	:	
Day 2	Before breakfast	:	
Day: Friday	1 hour after breakfast	:	
Saturday	1 hour after lunch	:	
Date: / /	1 hour after dinner	:	
Day 3	Before breakfast	:	
Day: Saturday	1 hour after breakfast	:	
Sunday	1 hour after lunch	:	
Date: / /	1 hour after dinner	:	
Day 4	Before breakfast	:	
Day: Sunday	1 hour after breakfast	:	
Monday	1 hour after lunch	:	
Date: / /	1 hour after dinner	:	
Day 5	Before breakfast	:	
Day: Monday	1 hour after breakfast	:	
Tuesday	1 hour after lunch	:	
Date: / /	1 hour after dinner	:	
Day 6	Before breakfast	:	
Day: Tuesday	1 hour after breakfast	:	
Wednesday	1 hour after lunch	:	
Date: / /	1 hour after dinner	:	
Day 7	Before breakfast	:	
Day: Wednesday	1 hour after breakfast	:	
Thursday	1 hour after lunch	:	
Date: / /	1 hour after dinner	:	

Please return the device with this completed log sheet on

Date _____ at Place _____

Appendix G   Medtronic Carelink CGM summary report

Medtronic

Daily Overlay for CGDM046
06-May - 12-May-2015
(7 days)

Medtronic iPro2 Recorder   #3055439

Sensor Data (mmol/L)

Wed 06-May   Thu 07-May   Fri 08-May   Sat 09-May   Sun 10-May   Mon 11-May   Tue 12-May   Average
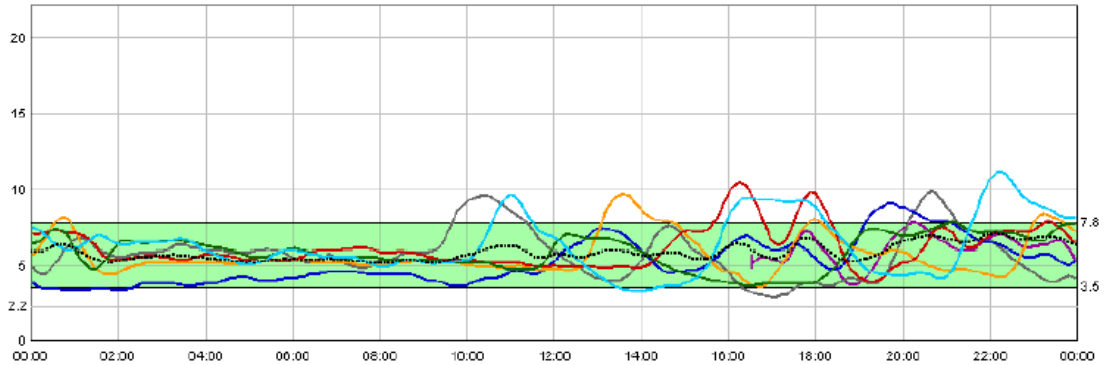
	Wed 06-May	Thu 07-May	Fri 08-May	Sat 09-May	Sun 10-May	Mon 11-May	Tue 12-May	Average / Total
# Sensor Values	90	288	288	288	288	288	288	1,818
Highest	7.8	9.9	9.0	9.7	10.4	7.8	11.2	11.2
Lowest	3.7	2.9	3.3	3.6	3.9	3.7	3.3	2.9
Average	6.1	5.7	5.2	5.7	6.2	5.8	6.4	5.8
Standard Dev.	1.0	1.6	1.5	1.3	1.3	1.1	1.9	1.5
MAD %	4.1	5.6	12.4	3.0	4.2	2.2	9.7	6.2
Correlation	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
# Valid Calibrations	2	4	4	3	3	3	3	22
Designation	X							

X: Use Clinical Judgment   S: No Sensor Data   C: No Calibration BG's

Excursion Summary (mmol/L/day)

	Wed 06-May	Thu 07-May	Fri 08-May	Sat 09-May	Sun 10-May	Mon 11-May	Tue 12-May	Average / Total
# Excursions	0	3	2	4	3	1	4	17
# High Excursions	0	2	1	4	3	1	3	14
# Low Excursions	0	1	1	0	0	0	1	3
AUC Above Limit	0.00	0.14	0.05	0.08	0.12	0.00	0.33	0.11
AUC Below Limit	0.00	0.02	0.01	0.00	0.00	0.00	0.01	0.01

Duration Distribution (hh:mm)

Above 7.8	0:00	0%	2:50	12%	1:55	8%	2:50	12%	2:10	9%	0:05	0%	5:40	24%	15:30	10%
Within (3.5 - 7.8)	7:30	100%	20:00	83%	20:00	83%	21:10	88%	21:50	91%	23:55	100%	17:30	73%	131:55	87%
Below 3.5	0:00	0%	1:10	5%	2:05	9%	0:00	0%	0:00	0%	0:00	0%	0:50	3%	4:05	3%

Appendix H   Data collection sheet

The Leeds Teaching Hospitals **NHS**

NHS Trust

DATA COLLECTION FORM

Title of Project: Does variation in circadian glucose profiles predict macrosomia in gestational diabetes?

Name of Principal Investigator: Dr Eleanor Scott, Consultant in Diabetes and Endocrinology

SCREENING VISIT

Researcher's name: ....

Date: ....   Gestation: .... Weeks

Please tick boxes done

☐   1) Satisfies inclusion criteria and no exclusion criteria present

(Inclusion criteria: Gestational Diabetes Mellitus based on positive 75g OGTT at ~26 weeks gestation)
(Exclusion criteria: Multiple pregnancy, significant medical or psychiatric condition, non-English speaking)

☐   2) Patient's information sheet handed.

STUDY VISIT

Researcher's name: ....

Date: ....   Gestation: .... weeks

Please tick boxes done

☐   1)   Consent form explained and signed

☐   2)   Patient Coding Form completed

☐   3)   Actiwatch serial number recorded ....

☐   4)   Actiwatch fitted

☐   5)   iPro serial number recorded ....

☐   6)   CGMS sensor inserted

☐   7)   iPro connected & flashing

☐   8)   CGMS blood glucose log sheet & instructions given.

☐ 9) Berlin Pittsburgh Sleep Quality Index questionnaires completed

☐ 10) Current weight taken ………………………. kg

☐ 11) Return visit arranged with patient. Please provide details:

Place……………………………………………………………………………………..

Date and time………………………………………………………………………

☐ 12) Letter to GP prepared

☐ 13) Data from handheld notes obtained:

- Age at booking: …………………………years

- Weight at booking: …………………….kg   Height at booking: …………………….m

- Para: ……………………………….

- EDD: ……………………………….

- OGTT: Date: ……………………………………………

     OGTT 0 min glucose: …………………………………mmol/L

     OGTT 120 min glucose: …………………………………mmol/L

- Current medication for GDM:

☐ Metformin, dosage: ☐ Insulin, type & dosage:

…………………………………………   …………………………………………

☐ Others, specify medication & dosage: ☐ No medication currently

…………………………………………

- Other medications currently taking: ……………………………………………………………………………………..

☐ 14) HbA1c: Date ……………………   Result ……………………

          Date ……………………   Result ……………………

Patient Identification Number: CGDM _____

RETURN VISIT

Researcher's name: ……………………………………………………   Date: ……………………………………………

Please tick boxes done

☐ 1) CGMS removed.

☐ 2) Actiwatch removed.

☐ 3) Glucose monitoring log sheet and sleep diary retrieved.

Data upload

Researcher's name: ……………………………………………………   Date: ……………………………………………

Please tick boxes done

☐ 1) CGMS data uploaded

☐ 2) Actiwatch data uploaded

Comments:

Appendix I   Highly commended certificate from the BMJ awards 2016
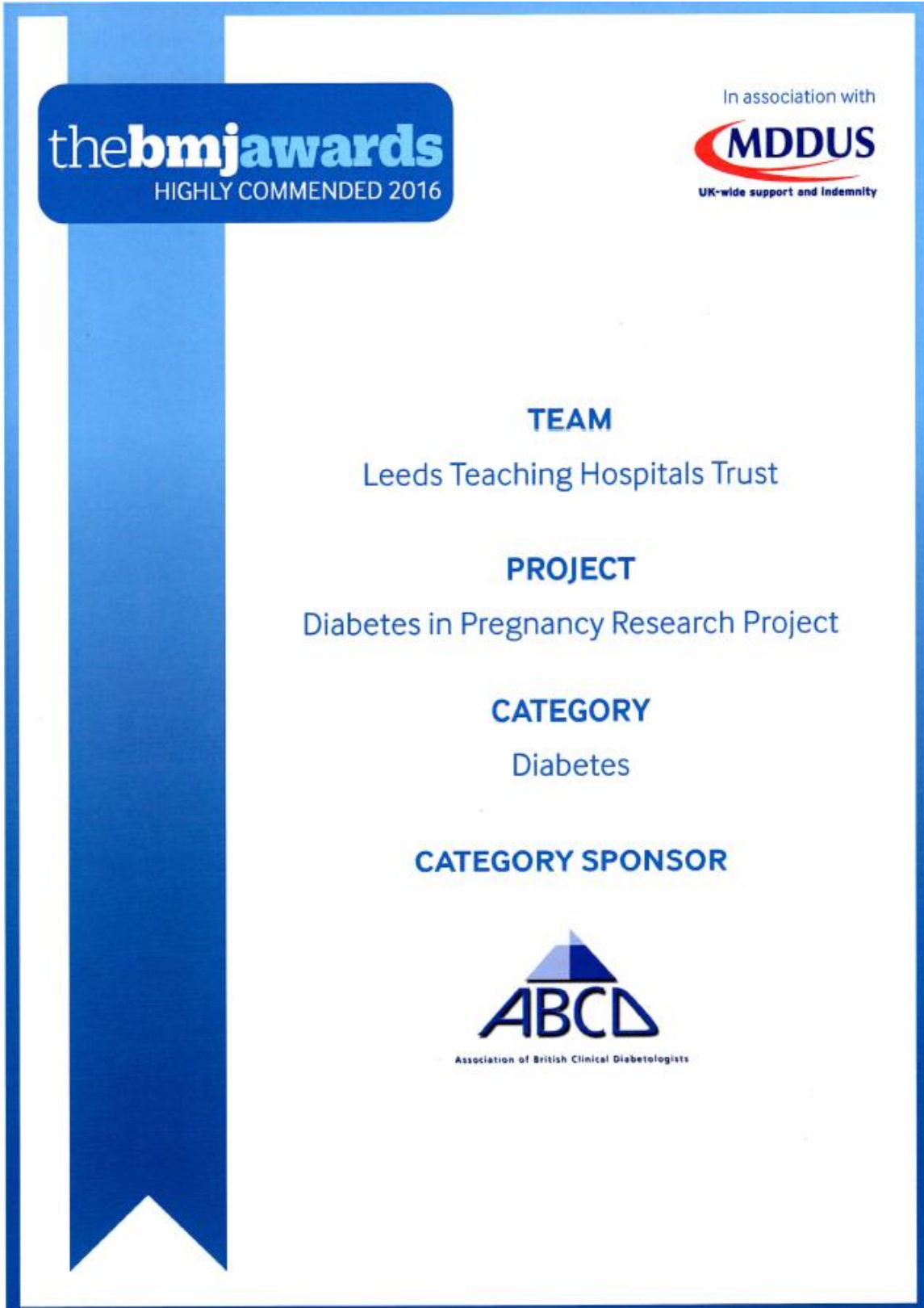
Appendix J   Study flyer

RESEARCH STUDY OPPORTUNITY

Does Variation in Circadian Glucose Profiles Predict Macrosomia in Gestational Diabetes?

How does the timing and quantity of blood sugar increase the chances of a lady with gestational diabetes giving birth to a very

large baby?

Contact: DIPResearch@outlook.com

What is Gestational Diabetes?

Gestational diabetes is a condition in which there is too much glucose in the pregnant woman's blood, especially during the third trimester of pregnancy. If untreated this condition can have harmful effects on the Mother and the unborn baby, both in the short and long term. One of the most common effects is for the baby to grow too large, causing problems for the mother and the baby. This is the focus of our study.

What are we investigating?

When a woman has diabetes, the amount of glucose in her blood varies over time and these glucose levels can become very high. If a woman is pregnant, then her baby will experience these high blood sugar levels. This study is investigating the link between variation in the amount of glucose circulating in the blood throughout the day, and the likelihood of a woman giving birth to a large, macrosomic baby.

What is Macrosomia?

A macrosomic baby is one that is excessively large for its gestational age.

Why is this Research Important?

Macrosomia can have complications for both the Mother and the baby. Maternal complications of giving birth to a macrosomic baby include difficulties in vaginal birth, such as tearing of tissue in the genital area, and bleeding after delivery. Macrosomic babies can be born with a higher than normal blood sugar level, and they are more likely to be obese in childhood.

Version 1: 30/9/2014

How YOU can contribute to this valuable research!

If you are a pregnant woman with Gestational Diabetes, between 18-45 years, with no pre-existing medical conditions then you may be a suitable

1. We will ask you to fill in two short questionnaires about your sleeping habits and one about you eating habits.

2. We will ask you to wear an 'Actiwatch' for one week. This is simply worn like a watch and it records motion and light. This will provide information about your sleeping and waking patterns.

3. Finally we will provide you with a small Continuous Glucose Monitoring Device called the iPro™CGM. This is designed to provide a more complete picture of your glucose levels. It is a small and discreet device that measures glucose levels all day, every day—revealing hyperglycaemia (very high blood sugar levels), hypoglycaemia (very low blood sugar levels), in details that may otherwise be missed with finger pricks testing alone. It will be put on in the clinic and removed after one week. The majority of people do not feel it being attached - it is pain free.

A £10 'Love To Shop' voucher will be given to participants as a small 'Thank You' for completing the study. Your iPro™CGM and Actiwatch reports can be given to you if you would like to understand more about your own blood sugar levels and sleep

If you are interested in participating in this study please let a member of your Diabetes in Pregnancy Team know!

Appendix K   Favourable ethical opinion of the study

NHS
Health Research Authority

NRES Committee Yorkshire & The Humber - Leeds Bradford

North East REC Centre
Room 002
TEDCO Business Centre
Viking Industrial Park
Rolling Mill Road
Jarrow
NE32 3DT

Telephone: 0191 4283545

19 September 2013

Dr Eleanor M Scott
Senior Lecturer in Medicine, Consultant in Diabetes and Endocrinology
University of Leeds and Leeds Teaching Hospitals NHS Trust
Division of Cardiovascular and Diabetes Research, LIGHT Laboratories,
Clarendon Way
University of Leeds
Leeds
LS2 9JT

Dear Dr Scott

Study title:	Does variation in circadian glucose profiles predict macrosomia in gestational diabetes?
REC reference:	13/YH/0268
IRAS project ID:	122874

Thank you for your e-mail correspondence of 18th September 2013.   I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 29 August 2013

Documents received

The documents received were as follows:

Document	Version	Date
Covering Letter	e-mail correspondence	18 September 2013
Other: E-mail correspondence re: indemnity certificate		
Participant Information Sheet	2	18 September 2013

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	Version	Date

A Research Ethics Committee established by the Health Research Authority

Covering Letter	e-mail correspondence	18 September 2013
Evidence of insurance or indemnity		21 September 2012
GP/Consultant Information Sheets	Version 1	09 July 2013
Investigator CV	Dr Eleanor Scott	09 July 2013
Other: CV	Alia Abdulhamid Alnaji	
Other: CV	Eberta Tan	
Other: Peer Review x 2		12 July 2013
Other: E-mail correspondence re: indemnity certificate		
Participant Consent Form	Version 1	09 July 2013
Participant Information Sheet	2	18 September 2013
Protocol	Version 1	09 July 2013
Questionnaire: Berlin Questionnaire		
Questionnaire: Pittsburgh Sleep Quality Index		
REC application	Version 3.5	23 July 2013

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

13/YH/0268	Please quote this number on all correspondence

Yours sincerely

Hayley Jeffries
Committee Co-ordinator

E-mail: nrescommittee.yorkandhumber-leedsbradford@nhs.net

Copy to: Claire Skinner, University of Leeds

Dr Derek Norfolk, Research and Development, Leeds TH NHS Trust

Appendix L Favourable ethical opinion of the amendment

NHS

Health Research Authority

NRES Committee Yorkshire & The Humber - Bradford Leeds

Room 002
TEDCO Business Centre
Viking Industrial Park
Rolling Mill Road
Jarrow
NE32 3DT

Tel: 0191 428 3384

17 November 2014

Dr Eleanor M Scott
Senior Lecturer in Medicine, Consultant in Diabetes and Endocrinology
University of Leeds and Leeds Teaching Hospitals NHS Trust
Division of Cardiovascular and Diabetes Research, LIGHT Laboratories,
Clarendon Way
University of Leeds
Leeds
LS2 9JT

Dear Dr Scott

Study title:	Does variation in circadian glucose profiles predict macrosomia in gestational diabetes?
REC reference:	13/YH/0268
Amendment number:	Substantial Amendment 1, 30/09/14
	(Protocol changes to increase recruitment)
Amendment date:	20 October 2014
IRAS project ID:	122874

The above amendment was reviewed at the meeting of the Sub-Committee held on 13 November 2014 by correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a **favourable** ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Copies of advertisement materials for research participants	1	30 September 2014
Notice of Substantial Amendment (non-CTIMP)	Substantial Amendment 1, 30/09/14	20 October 2014
Participant consent form	3	30 September 2014
Participant information sheet (PIS)	3	30 September 2014
Research protocol or project proposal	2	30 September 2014

A Research Ethics Committee established by the Health Research Authority

NRES Committee Yorkshire & The Humber - Bradford Leeds

Attendance at Sub-Committee of the REC meeting on 13 November 2014 by correspondence

Committee Members:

Name	Profession	Present
Dr Janet Holt (Chair)	Senior Lecturer	Yes
Ms Rebecca Forster	Research Fellow	Yes

Also in attendance:

Name	Position (or reason for attending)
Miss Sarah Prothero	REC Assistant

Appendix M   Letter of access for research

The Leeds Teaching Hospitals **NHS**

NHS Trust

RECRUITMENT SERVICE

Ground Floor, Trust Headquarters, St James's Hospital, Beckett Street, Leeds, LS9 7TF

Private and Confidential	Enquiries to:	Jennie Ikin
Alia Alnaji	Direct Line:	(0113) 20 65980
23 Lilac Court	Our Ref:	**LOA/NON NHS**
Killingbeck	Date:	20th May 2014
Leeds		
LS14 6GQ		

Dear Alia

Letter of access for research - Project Title - Does variation in circadian glucose profiles predict macrosomia in gestational diabetes?

This letter confirms your right of access to conduct research through The Leeds Teaching Hospitals NHS Trust for the purpose and on the terms and conditions set out below. This right of access commences on **26th May 2014** and ends on **25th May 2017** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at The Leeds Teaching Hospitals NHS Trust has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to The Leeds Teaching Hospitals NHS Trust premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through The Leeds Teaching Hospitals NHS Trust, you will remain accountable to your employer **The University of Leeds** but you are required to follow the reasonable instructions of **Dr Eleanor Scott** in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with The Leeds Teaching Hospitals NHS Trust policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with The Leeds Teaching Hospitals NHS Trust in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on The Leeds Teaching Hospitals NHS Trust premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.
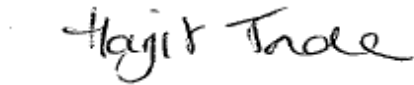
We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Where required by law, your HEI employer will initiate your Independent Safeguarding Authority (ISA) registration, and thereafter, will continue to monitor your ISA registration status via the on-line ISA service. Should you cease to be ISA-registered, this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity. You MUST stop undertaking any regulated activity.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

The Leeds Teaching Hospitals NHS Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

Harjit Tanda
Head of HR.

cc: R&D office at Leeds Teaching Hospitals NHS Trust
        HR department of the substantive employer (and provider of honorary clinical contract, where applicable)

Appendix N   Good Clinical Practice e-learning course Certificate of Completion

NHS
National Institute for
Health Research

Clinical Research Network

Certificate of Completion

Alia Alnaji

has completed

**Introduction to Good Clinical Practice (GCP)
e-learning course**

A practical guide to ethical and scientific quality
standards in clinical research

on 07/01/2014

Modules completed

Introduction to Research in the NHS
Good Clinical Practice and Standards in Research
Study Set-up and Responsibilities
The Process of Informed Consent
Data Collection and Documentation
Safety Reporting
Summary

**National Institute for
Health Research
Clinical Research Network**

http://learning.nihr.ac.uk/learning/SCORMPackages/a322a3c2-87ee-4802-a03f-acc6b   07/01/2014

Appendix O   Site approval

The Leeds Teaching Hospitals **NHS**

NHS Trust

Michael Wood

14/11/2013

Research & Development

Leeds Teaching Hospitals NHS Trust
34 Hyde Terrace
Leeds
LS2 9LN

Dr Eleanor M Scott
Senior Lecturer
Division of Cardiovascular and Diabetes Research
LIGHT Laboratories
Clarendon Way
Leeds
LS2 9JT

Tel: 0113 392 2878
Fax: 0113 392 6397

r&d@leedsth.nhs.uk
www.leedsth.nhs.uk

Dear Dr Eleanor M Scott

Re: NHS Permission at LTHT for: Does variation in circadian glucose profiles predict macrosomia in gestational diabetes?
LTHT R&D Number: ED13/10839 (122874/WY)
REC: 13/YH/0268

I confirm that *NHS Permission for research* has been granted for this project at The Leeds Teaching Hospitals NHS Trust (LTHT). NHS Permission is granted based on the information provided in the documents listed below. All amendments (including changes to the research team) must be submitted in accordance with guidance in IRAS. Any change to the status of the project must be notified to the R&D Department.

Permission is granted on the understanding that the study is conducted in accordance with the *Research Governance Framework for Health and Social Care*, ICH GCP (if applicable) and NHS Trust policies and procedures available at http://www.leedsth.nhs.uk/academic/research-development/

This permission is granted only on the understanding that you comply with the requirements of the *Framework* as listed in the attached sheet "Conditions of Approval".

If you have any queries about this approval please do not hesitate to contact the R&D Department on telephone 0113 392 2878.

Indemnity Arrangements

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority 'Clinical Negligence Scheme for NHS Trusts' for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers

Chairman Mike Collier CBE Chief Executive Maggie Boyle

The Leeds Teaching Hospitals incorporating:
Chapel Allerton Hospital   Leeds Dental Institute   Seacroft Hospital
St James's University Hospital   The General Infirmary at Leeds   Wharfedale Hospital

use the
NHS Number
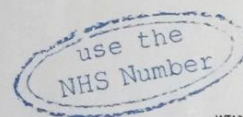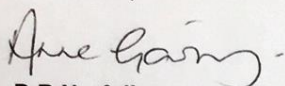
WTA280

with an employment contract (substantive or honorary) with the Trust. The Trust only accepts liability for research activity that has been managerially approved by the R&D Department.

The Trust therefore accepts liability for the above research project and extends indemnity for negligent harm to cover you as investigator and the researchers listed on the Site Specific Information form. Should there be any changes to the research team please ensure that you inform the R&D Department and that s/he obtains an appropriate contract, or letter of access, with the Trust if required.

Yours sincerely

PP **Dr D R Norfolk**
Associate Director of R&D

Approved documents
The documents reviewed and approved are listed as follows

Document	Version	Date of document
NHS R&D Form	3.5	23/07/2013
SSI Form	3.5	21/09/2013
Directorate Approval		29/10/2013
REC Letter confirming favourable opinion		29/08/2013
Protocol	1.0	09/07/2013
Patient information sheet	2.0	18/09/2013
Consent form	1.0	09/07/2013
GP/Consultant information sheets	1.0	09/07/2013
Questionnaire: Berlin		
Questionnaire: Pittsburgh Sleep Quality Index		
Evidence of Insurance		21/09/2012

Appendix P   Official Medtronic's patient instructions for iPro®2 use

Patient Instructions — iPro2

Simple tips, instructions and guidelines for iPro2 use

Blood glucose (BG) testing

- On the **first day:**
  - Take your first BG meter reading at least 1 hour after you leave the physician's office.
  - Take a second BG meter reading at least 3 hours after you leave the physician's office.
  - Collect at least one more meter reading before going to bed.
- Collect at least 4 BG meter readings each day, such as before breakfast, lunch, dinner, and bedtime.
- Do not change any settings on your meter during the study, even if a daylight savings time change occurs.
- Use the same blood glucose meter for all BG meter readings.
- Do not let anyone else use your meter during the study.
- Do not use control solution during the study.

Log sheet entries

- Write down your BG meter readings, food or drink and number of carbohydrates, physical activity and duration, medications and dosages, and other events (such as feeling hypoglycemic, stress, or illness).
- Keep the log sheet with you at all times so you can write down the information immediately after each event. Record the time and date within 5 minutes of each BG meter reading.

Care and wearing

- Live your life with your normal behaviors. If you normally exercise, then exercise.
- Keep tape over the sensor and iPro2 to prevent accidental removal or sensor movement. If the sensor comes out even a small amount, it may stop working. If new tape is needed, just put it over the existing tape. If the sensor comes out, place the sensor and iPro2 into a plastic resealable bag and notify your physician's office.
- Check the site 4 times a day to ensure that the sensor and iPro2 are firmly connected, the sensor is still fully inserted, and there is no bleeding or irritation.
  - If the sensor is partly pulled out, attempt to gently push it back into place.
  - Remove the sensor if you have redness, pain, tenderness, or swelling at the site, and notify your physician's office.
- You may shower and swim while wearing the iPro2 and sensor. The iPro2 is watertight at a depth of up to 2.4 meters (8 feet) for 30 minutes. There is no time limit if you are swimming on the surface of a pool or showering.
- Insulin should be injected at least 7.5 centimeters (3 inches) away from the sensor insertion site, and insulin pump infusion should be at least 5 centimeters (2 inches) from the sensor insertion site.
- The iPro2 must be removed (but the sensor can be left in) prior to an x-ray, CT scan or MRI. Simply reconnect the iPro2 afterward.

6025476-0U1_c

Medtronic

Appendix Q   Permission letter to use PSQI in the current research

Alia Alnaji

From:	Gasiorowski, Mary <GasiorowskiMJ@upmc.edu>
Sent:	09 January 2015 18:57
To:	Alia Alnaji
Subject:	RE: PSQI Request
Follow Up Flag:	Flag for follow up
Flag Status:	Flagged

Sent on behalf of Dr. Buysse

Dear Alia,

You have my permission to use the PSQI for your research study. You can find the instrument, scoring instructions, the original article, links to available translations, and other useful information at www.sleep.pitt.edu under the Instruments tab. Please ensure that the PSQI is accurately reproduced in any on-line version (including copyright information). We request that you to cite the 1989 paper in any publications that result.

Note that Question 10 is not used in scoring the PSQI. This question is for informational purposes only, and may be omitted during data collection per requirements of the particular study.

This copyright in this form is owned by the University of Pittsburgh and may be reprinted without charge only for non-commercial research and educational purposes. You may not make changes or modifications of this form without prior written permission from the University of Pittsburgh. If you would like to use this instrument for commercial purposes or for commercially sponsored research, please contact the Office of Technology Management at the University of Pittsburgh at 412-648-2206 for licensing information.

Good luck with your research.

Sincerely,

Daniel J. Buysse, M.D.
Professor of Psychiatry and Clinical and Translational Science
University of Pittsburgh School of Medicine
E-1123 WPIC
3811 O'Hara St.
Pittsburgh, PA 15213
T: (412) 246-6413
F: (412) 246-5300
buyssedj@upmc.edu

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