



MONASH University

Sleep during pregnancy: a novel opportunity to change the health of two generations

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Thesis abstract

Obesity continues to be a global concern of pandemic proportions. Excessive gestational weight gain (GWG) increases the risk of women becoming overweight or obese. Despite current strategies, 50% of women gain above the guidelines for GWG. This increases the risk of conditions such as gestational diabetes mellitus (GDM), pre-eclampsia and birth complications. Long term, excessive GWG also increases the risk of overweight and obesity, diabetes and cardiovascular disease for both mother and infant.

In the non-pregnant population, short sleep and disturbed sleep are associated with various chronic diseases such as obesity, type 2 diabetes mellitus and cardiovascular disease. Sleep disturbance in pregnancy is common, regardless of whether sleep disturbance was present pre-conception. Despite strong relationships shown in the non-pregnant population, the relationship between sleep during pregnancy and outcomes such as GWG, glucose tolerance and dietary intake is unknown. The overall aim of this thesis was to investigate the impact of sleep during pregnancy on GWG, glucose tolerance and maternal diet.

Part A of this thesis systematically reviewed available literature for interventions designed to reduce GWG. The aim was to evaluate the efficacy of intervention to reduce the risk of GDM and infant birth anthropometrics. The resultant literature had two behavioural intervention targets; diet and/or physical activity. This confirmed that modifying sleeping behaviour was a novel intervention target. Furthermore, dietary interventions were the most effective at reducing the risk of GDM and infant birthweight. Interventions in women who were overweight or obese preconception were not effective at reducing the risk of GDM.

Part B of this thesis accessed data from the Australian Longitudinal Study on Women's Health to investigate relationships between sleeping behaviour during pregnancy, dietary intake, antenatal and postnatal outcomes. Through latent class analysis and linear regression,

analyses revealed that sleep quality was associated with higher carbohydrate intake, lower monounsaturated fat intake, increased risk of emotional distress during labour, and postpartum anxiety after controlling for potential confounders.

Part C of this thesis reports on results from a randomised controlled trial conducted to determine the feasibility of improving sleep behaviours to improve sleep quality and quantity. This was completed through extending time in bed, reducing light exposure and education regarding sleep hygiene principles. The intervention provided was considered not to be a feasible. Participants reported a reluctance to reduce TV and streaming services and extending time spent in bed. These reported barriers are important to inform future research.

This thesis presents evidence that sleeping behaviour is a novel and worthy target for interventions designed to reduce GWG and the risk of GDM. Sleep quality may protect against adverse outcomes such as poorer dietary quality and improve mental health postpartum. However, it is currently unclear how to support women to improve sleep quality in pregnancy. Future interventions targeting sleep need to involve women in the planning of interventions, commence early in pregnancy and take into consideration women's reluctance to reduce evening screen time.

Declaration

This thesis is an original work of my research and contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature:

Print Name:

Date:

Academic Achievements During Candidature

Published manuscripts included in this thesis

Bennett C, Walker R, Blumfield M, Gwini S, Ma J, Wang F, Wan Y, Dickinson H, Truby H. Interventions designed to reduce excessive gestational weight gain can reduce the incidence of gestational diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials. *Diabetes Research and Clinical Practice*, 141 (2018): 69-79.
<https://doi.org/10.1016/j.diabres.2018.04.010> – Available in [Chapter 2](#) and [Appendix 1](#)

Bennett C, Walker R, Blumfield M, Gwini S, Ma J, Wang F, Wan Y, Truby H. Attenuation of maternal weight gain impacts infant birthweight: systematic review and meta-analysis. *Journal of developmental origins of health and disease* (2018): 1-9.
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Bennett C, Cain S, Blumfield M. Monounsaturated fat intake is associated with improved sleep quality in pregnancy. *Midwifery*. Accepted July 2019.
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Manuscripts published or submitted during candidature not included in this thesis

Truby H, Bennett C, Martins C. A review of the short- and long-term impact of weight loss on appetite in youth: what do we know and where to from here? *Proceedings of Nutrition* (Submitted 29th of September 2019).

Walker R, Bennett C, Kumar A, Adamski M, Blumfield M, Truby H. Evaluating Online Continuing Professional Development Regarding Weight Management for Pregnancy Using the New World Kirkpatrick Model. *Journal of Continuing Education in the Health Professions*. 2019. 36(3): 210-217

Walker R, Kumar A, Bennett C, Blumfield M, Truby H. Maternal gestational weight gain during pregnancy: prioritising the conversation. *Journal of Primary Health*, 24(1), 4-8.

Walker R, Bennett C, Blumfield M, Gwini S, Ma J, Wang F, Wan Y, Truby H. Attenuating Pregnancy Weight Gain—What Works and Why: A Systematic Review and Meta-Analysis. *Nutrients*. 2018. 10(7): 944.

Walker R, Kumar A, Bennett C, Blumfield M, Truby H. Evaluating health professional's change in practice when weighing women during pregnancy: outcomes from a low-intensity intervention. *Nurse Education in Practice* (Submitted May 11th 2019).

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Mo L, Mansfield D, Joham A, Cain S, Bennett C, Blumfield M, Teede H, Moran L. Sleep disturbances in women with and without polycystic ovarian syndrome in an Australian national cohort. *Clinical Endocrinology*: <https://doi.org/10.1111/cen.13922>

List of conference presentations

Bennett C, Cain S, Blumfield M. Dietary monounsaturated fat intake may be protective for sleep during pregnancy. Developmental Origins of Health and Disease Conference (DOHaD) World Congress, Melbourne, October, 2019 (Poster)

Bennett C, Cain S, Blumfield M. Sleeping behaviour during pregnancy increases the risk of adverse birth and postpartum outcome. Developmental Origins of Health and Disease (DOHaD) World Congress, Melbourne, October, 2019 (Poster)

Bennett C, Walker R, Blumfield M, Gwini S, Ma J, Wang F, Wan Y, Dickinson H, Truby T. Interventions designed to reduce gestational weight gain can reduce the incidence of GDM: systematic review and meta-analysis. 10th Asia Pacific Conference on Clinical Nutrition, Adelaide Nov 2017 (Oral)

Bennett C, Walker R, Blumfield M, Gwini S, Ma J, Wang F, Wan Y, Dickinson H, Truby T. 'Interventions designed to reduce gestational weight gain can reduce the incidence of gestational diabetes: a systematic review and meta-analysis. Australian Diabetes in Pregnancy Society conference, Canberra October 2017 (Poster)

Bennett C, Cain S, Blumfield M. Is there a relationship between dietary intake and sleep in pregnancy? Nutrition Society, Summer Conference, Leeds UK, July 2018 (Poster with 3-minute oral)

Bennett C, Cain S, Blumfield M. Dietary monounsaturated fat intake may be protective for sleep during pregnancy. Developmental Origins of Health and Disease World Congress, Melbourne, October 2019 (Poster)

Bennett C, Cain S, Blumfield M. Sleeping behaviour during pregnancy increases the risk of adverse birth and postpartum outcomes. Developmental Origins of Health and Disease World Congress, Melbourne, October 2019 (Poster)

Scholarships, awards and funding

2019 – NHMRC CRE PCOS Seed grant funding (\$10,000)

2019 – Developmental Origins of Health and Disease (DOHAD) Society Student Travel Award

2019 – 1st place in the Department of Nutrition, Dietetics and Food 3 Minute Thesis Senior Category

2018 – Nestle Nutrition Institute Young Researcher of the Year – Australia and New Zealand

2018 – Monash University Student Travel Grant

2017 – Monash University Platform Access Grant for microbiome analysis - collaboration with Dr. Ricardo Costa (PI) and Dr. Nicole Kellow

2017 – Nutrition Society of Australia (NSA) Travel Grant

2017 – Australasian Diabetes in Pregnancy Society (ADIPS) Travel Grant

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Monash university teaching contributions and commitments

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PHY3102 – Nutrition, Body Weight and Metabolism – Demonstrator: 2016, 2017, 2018

M6002 – Extending Empathy – Co-convenor: 2016, 2017, 2018, 2019

NUT1001 – Personal and Professional Perspectives in Nutrition – Tutor: 2019

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes *three* original papers published in peer reviewed journals and *one* submitted publication under review. The core theme of the thesis is to investigate the impact of sleep during pregnancy on dietary and physiological outcomes. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Department of Nutrition, Dietetics and Food under the supervision of Prof. Helen Truby, Dr. Michelle Blumfield and Assoc. Prof. Sean Cain.

In the case of (*Chapters 2,3,5 and 6*) my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status	Nature and extent of candidate's contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
2	Interventions designed to reduce excessive gestational weight gain can reduce the incidence of gestational diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials	Published - <i>Diabetes research and clinical practice</i>	70%: Concept, literature review, statistical analysis and manuscript preparation	Dr. Ruth Walker data collection and draft feedback 10%, Dr. Michelle Blumfield concept and draft feedback 5%, Dr. Stella-May Gwini statistical review 5%, Ms. Jianhua Ma, Mr. Fenglei, Wang Ms. Yi Wan and Dr. Hayley Dickinson data collection 5% Prof. Helen Truby concept and draft feedback 5%	Dr. Ruth Walker (yes) No others
3	Attenuation of maternal weight gain impacts infant birthweight: systematic review and meta-analysis	Published - <i>Journal of Developmental Origins of Health and Disease</i>	70%: Concept, literature review, statistical analysis and manuscript preparation	Dr. Ruth Walker data collection and draft feedback 10%, Dr. Michelle Blumfield	Dr. Ruth Walker (yes) No others

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5	Monounsaturated fat intake is associated with improved sleep quality in pregnancy	Published – Midwifery	70%: Concept, statistical analysis and manuscript preparation	Assoc Prof. Sean Cain concept and draft feedback 10%, Dr. Michelle Blumfield LCA statistical analysis and draft feedback 20%	N/A
6	Poor sleep quality during pregnancy increases the risk of adverse birth and postpartum outcomes	Submitted – Obstetrics and Gynecology	70%: Concept, statistical analysis and manuscript preparation	Assoc Prof. Sean Cain concept and draft feedback 10%, Dr. Michelle Blumfield LCA statistical analysis and draft feedback 20%	N/A

I have / have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature:

Date:

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature:

Date:

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Chapter 7

N/A

Abbreviations

ALSWH – Australian Longitudinal Study of Women’s Health

APGAR – Appearance, pulse, grimace, activity and respiration

BMI – Body mass index

CRP – C- reactive protein

EEG - Electroencephalogram

GDM – Gestational diabetes mellitus

GUSTO - Growing up in Singapore Towards healthy Outcomes

GWG – Gestational weight gain

KTA – Knowledge to action

LBW – Low birth weight

LCA – Latent class analysis

LGA – Large for gestational age

IADPSG - International Association of the Diabetes in Pregnancy Study Groups

IGUR – Intrauterine growth restriction

IOM – Institute of Medicine

IL-6 – Interleukin 6

NREM – Non-rapid eye movement

OSA – Obstructive sleep apnoea

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta- Analyses

PSG - Polysomnography

REM – Rapid eye movement

SGA – Small for gestational age

SDB – Sleep disordered breathing

SOL – Sleep onset latency

SWS – Slow wave sleep

T2DM – Type 2 Diabetes Mellitus

TIB – Time in bed

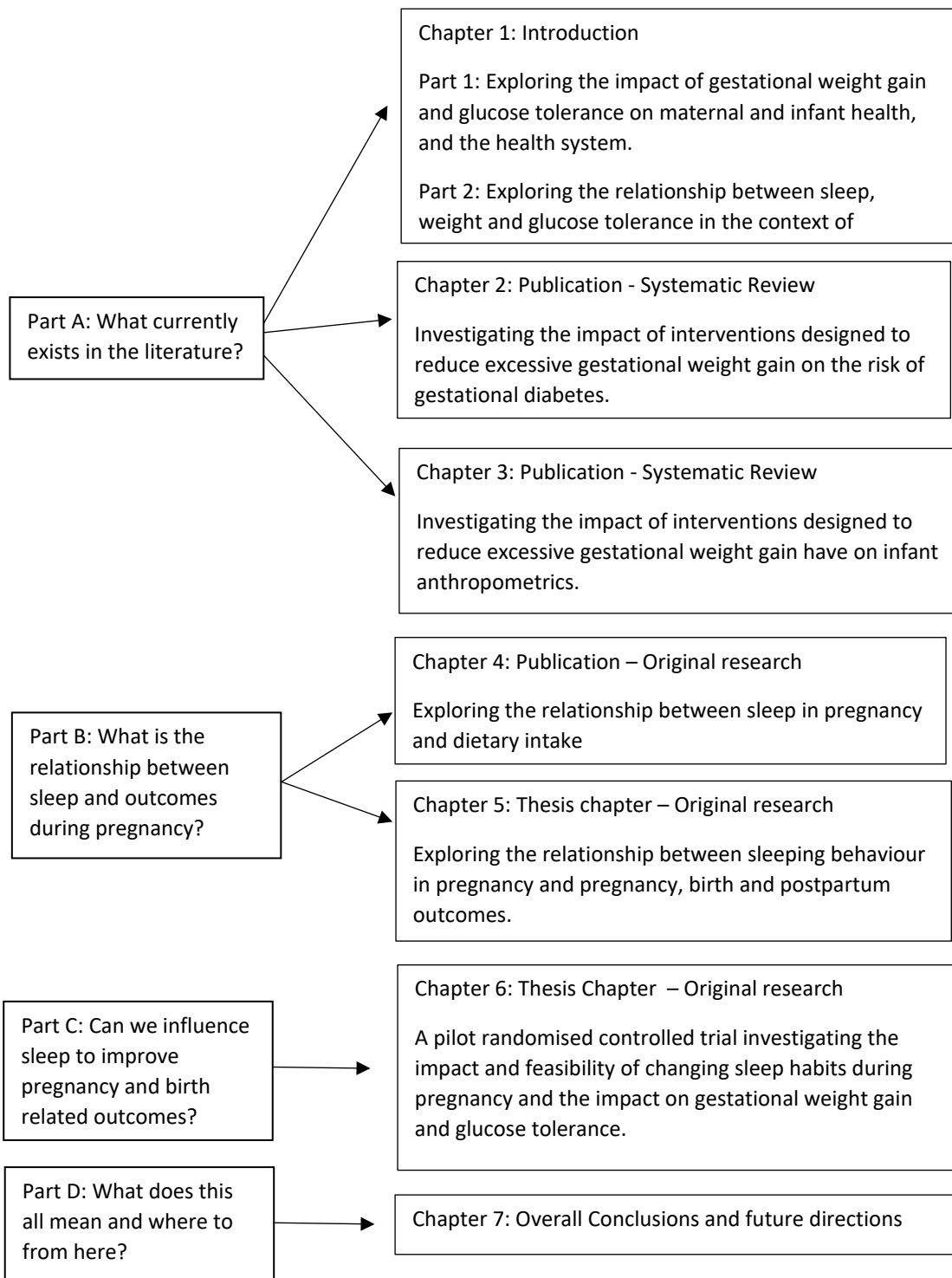
TNF- α – Tumour necrosis factor- alpha

TST – Total sleep time

WHO – World Health Organisation

WASO – Wake after sleep onset

Thesis Outline



Due to this thesis including published works, references are located at the end of each chapter.

Part A - What currently exists in the literature?

CHAPTER 1 - Introduction

Part 1: Obesity and weight gain background and in the context of pregnancy

1.1 The big picture problem

1.1.1 A 'wicked problem'

Overweight and obesity, defined as a Body Mass Index (BMI) $>25\text{kg/m}^2$, has long been acknowledged as a global public health concern of pandemic proportions (1). Current international estimates (2016) suggest that 52% of the adult population and 24-27% of children are overweight or obese (2). In Australia, the rates of overweight and obesity are higher than the international average, impacting 63.4% of the adult population and 27.4% of children aged 5-17 (3). Obesity increases the risk of many non-communicable metabolic diseases including type-2 diabetes mellitus (T2DM), cardiovascular disease, stroke, osteoarthritis, cancer (including endometrial, breast, colon, kidney, gallbladder and liver), anxiety, depression and all-cause mortality (4). The increased risk of these diseases is attributable to many interrelated mechanisms caused by increased adipocyte deposition, which alters inflammatory signalling pathways and endocrine signalling (5). Excessive adipose tissue deposited centrally around the torso, referred to as visceral fat, is one of the highest predictors for metabolic syndrome (6). Visceral fat is metabolically active and increases the inflammatory cytokine response (7). Furthermore, visceral fat has an inverse relationship with adiponectin and leptin sensitivity, which adversely influence insulin resistance (7). Internationally, obesity and associated diseases account for a loss of 3-10 disease-free years, which negatively impact productivity and quality of life (8). A conservative estimate suggests the direct cost of obesity in Australia is \$8.6 billion per year (9). However, an older more extensive review reported that in 2005 the indirect costs of

obesity could be up to \$56.6 billion, increasing as prevalence increases (10). Despite numerous international and local strategies and policies aimed to reduce the prevalence of obesity (2, 11), there has been minimal success (1), with prevalence almost tripling since 1975 (2). Clearly, novel and cost-effective methods of intervening and preventing obesity are desperately needed.

1.1.2 Risk factors for obesity

Obesity is a multifaceted condition with complex aetiology (12). The cause of obesity can be summarised as an imbalance between energy consumption and expenditure, leading to a positive energy balance and consequential weight gain (12). However, the factors that lead to this imbalance include social, environmental, behavioural, genetic and medical factors. Broadly, these factors can be categorised as modifiable or non-modifiable. For obvious reasons, modifiable risk factors are often leveraged for intervention strategies. Modifiable risk factors of obesity include dietary intake (13), physical activity (13), sedentary activity (13) and sleep (14). Many large public health interventions have targeted diet (15, 16), physical activity (17, 18) and more recently sedentary activity (16). However, despite recent research showing strong associations between sleep, body weight (14) and diabetes risk (19), sleep is yet to be leveraged as an intervention strategy. Well recognised non-modifiable risk factors include age, gender and ethnicity and genetic profile. While these risk factors cannot be influenced by interventions, they can be used to target modifiable behavioural strategies to certain population groups, to equip them with skills to reduce their susceptibility of obesity and associated chronic disease (20). Well-recognised groups identified as having an increased risk of obesity include pre-natal women, pregnant women, children, adolescents, menopausal women, groups with particular genetic heritage

(including Southeast Asian and Pacific Islanders (21)) and those from low socio-economic backgrounds (20).

1.1.3 Diabetes and obesity

T2DM is one of the most common metabolic complications or comorbidities of obesity in Australia (22). Compared to a healthy BMI (18.5-24.9 kg/m²), a BMI of 25-30kg/m² (overweight) increases the risk of T2DM by 50% (23). This risk continues to increase as BMI increases, with a BMI ≥40 kg/m² associated with a 410% increased risk of T2DM (23). Three mechanisms link obesity with the progression of T2DM. First, excess energy consumption promotes deposition of triglycerides in adipocytes. Under conditions of normal insulin sensitivity, the secretion of insulin inhibits lipolysis which reduces the amount of fatty acids released into circulation (24). As the adipocytes grow in size, they become less sensitive to the insulin signals and therefore release more fatty acids into circulation (24). The fatty acids can be deposited into non-adipose organs, which ultimately cause lipotoxicity which interferes with insulin signalling and beta-cell dysfunction, contributing to hyperglycaemia (24). Secondly, due to adipocyte expansion without adequate vascularisation, this can cause hypoxia increasing inflammatory signalling and apoptosis (25). Adipocyte apoptosis increases the inflammatory response which triggers intracellular signalling pathways (JNK, PKR or IKK) which also inhibit insulin action (26). Finally, animal and *in vitro* models show decreased insulin sensitivity drives β-cell proliferation to compensate for hyperglycaemia (26). However, the hyperproliferation and additional stress on the β-cell can lead to apoptosis (26). Furthermore, adipocyte deposition in the pancreatic β-cell (ectopic storage) can contribute to altered gene expression, insulin secretion and increased apoptosis (27). Both factors leading to apoptosis of the β-cell increases the chances of needing insulin

therapy in T2DM. Therefore, strategies that prevent obesity and therefore chronic inflammation become secondary prevention strategies for T2DM.

1.1.4 Prevention and treatment of obesity

To curb the obesity pandemic both prevention and treatment have a role to play. However, the reach and method are significantly different between the two. Figure 1.1 summarises the approaches most common in developed nations. Obesity prevention strategies are categorised into three levels; universal, targeted and indicated (20). Universal prevention aims to reduce the incidence of obesity. This pertains to public health strategies that prevent obesity occurring in the first instance. Targeted prevention aims to reduce the prevalence in high-risk groups or individuals. Indicated prevention aims to prevent those who are already overweight progressing to obesity and preventing the development of other chronic diseases in those with increased weight status. While targeted and indicated strategies have an important role in tackling obesity, universal prevention has a dual function, whereby prevention of obesity in-turn reduces the burden of the disease long-term. These strategies are particularly important when considering obesity, as treatment is possible but weight regain after initial weight loss is common, even after weight loss attempts including surgery (28).

The levels of obesity treatment have been succinctly summarised by the United Kingdom's National Health Service tier classification system (29). The first level includes universal interventions, covering healthy eating and physical activity via public health messages aimed at healthy adults. Level two interventions become more targeted towards individuals and include community lifestyle, diet and pharmacotherapy interventions. Level three interventions require specialist obesity services delivered in tertiary care. Finally, the top-level includes individual surgical interventions such as bariatric surgery, aimed specifically at

those with comorbidities associated with high levels of body fat. As treatments move up the tiers, the delivery cost per capita increases.

Many systematic reviews have aimed to evaluate the efficacy of obesity treatments (30-33). Weight loss > 5% total body weight is considered adequate to improve metabolic outcomes (34). However, reviews that have evaluated behavioural interventions conclude that some weight loss can be sustained at the 12-month follow-up, but success is limited to 0.1-4.9% of total body weight (30-32). The limited success of interventions long term is complex, but may involve factors such as reduced motivation long-term (35), metabolic adaptive responses (36) and reduced support after concluding the intervention. These findings confirm that obesity is complicated. Further, a systematic review of the efficacy of obesity treatment studies reported that studies in this area are fraught with issues including high attrition rates, lack of blinding and lack of follow up beyond 12-months (32). Medical interventions including bariatric surgery have higher success rates (33), but are more expensive, less accessible and have an increased risk of medical and nutritional complications (37). These challenges highlight the importance of and need for more effective prevention strategies.

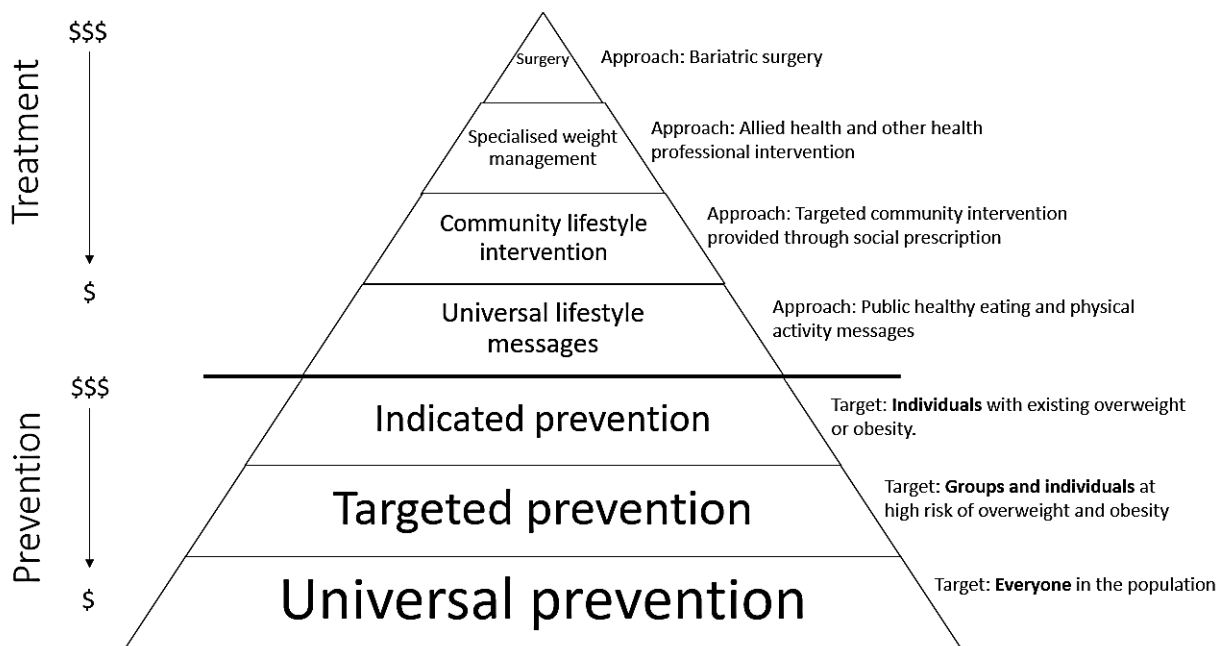


Figure 1.1 Prevention and treatment of obesity (adapted from (20) and (29))

1.1.5 Risk of obesity in women of childbearing age

Women of childbearing age (18-40 years) are a vulnerable population for weight gain and obesity (38). Even without overweight and obesity in this life-stage, early adulthood weight gain influences the weight trajectory, increasing the risk of obesity in later life (39). Women of childbearing age are not immune to behavioural factors that lead to positive energy balance and also have an increased risk factor or pregnancy weight gain and postpartum weight retention (38). An Australian longitudinal cohort study of women aged 18-23 studied over 7 years showed that women who had children gained 2-3kg more compared to their nulliparae counterparts (40). The reasons for this disparity are numerous, but a major contributor is gestational weight gain (GWG), particularly if the weight gain is above the recommended guidelines. Weight gain above the recommended guidelines leads to increased risk of post-partum weight retention and therefore a higher BMI long term (41).

Therefore, preventing excessive weight gain in pregnancy can mitigate the increased risk of obesity and other non-communicable diseases for women who enter motherhood.

1.2 Weight gain during pregnancy

GWG is an important indicator of the health and progression of a pregnancy (42). This section takes a historical overview of GWG and how recommendations have altered over time.

1.2.1 History of guidelines

As the understanding of obstetrics and gynaecology has evolved, so have the GWG guidelines. Since the late 19th century it has been recognised that excessive weight gain during pregnancy was undesirable (43). However, at this time this observation was based upon the rationale that excessive GWG was associated with larger infants and therefore more difficult labour (44). As caesarean section was a relatively new procedure to the medical community at the time, the risks associated were exceptionally high, making this procedure a last resort. Throughout the 19th century, to minimise the risk of a caesarean section, women at risk of macrosomia were encouraged to limit their weight gain through 'dieting' and calorie restriction (43). It wasn't until 1941 that it was recognised that sub-optimal GWG was associated with nutritional deficiencies in both the mother and child (43). Therefore, 20-25lbs (9.1-11.3kg) of gradual weight gain was recommended (45).

1.2.2 Current gestational weight gain guidelines

Currently, there is no global consensus on how much weight a woman should gain during pregnancy (46). However, the best evidence and guidance available is from the American Institute of Medicine (IOM) (47). These guidelines were revised in 2009 after a review of the available literature. The IOM recommendations are now adopted internationally by many

countries, including Australia (46, 48, 49). The revised guidelines include stratification of GWG by preconception BMI; indicating the higher the BMI, the less GWG is recommended (47) (see Table 1.1). The guidelines recognise that a woman’s preconception BMI is a significant contributor to complications during pregnancy. Entering pregnancy at a higher BMI has been shown to increase the risk of excessive GWG, gestational diabetes mellitus (GDM), pre-eclampsia, large for gestational age (LGA) babies and need for a caesarean section delivery (50). Therefore, the IOM guidelines were reformulated to take this into account.

Table 1.1: The Institute of Medicine (IOM) Gestational Weight Gain Guidelines per pre-conception BMI category (47)

Pre-conception BMI category	Total weight gain expected (kg)	Weekly weight gain expected (kg)
Underweight (<18.5kg/m ²)	12.5-18	0.44-0.58
Healthy weight (18.5-24.9 kg/m ²)	11.5-16	0.35-0.50
Overweight (25.0-29.9 kg/m ²)	7-11.5	0.23-0.33
Obese (>30.0kg/m ²)	5-9	0.17-0.27

1.2.3 Gestational weight gain in the current context

Unfortunately, these guidelines may not reflect the challenges of the current obesogenic environment. The obesogenic environment refers to the socio-ecological environment that promotes energy intake and decreases opportunities for energy expenditure (51). Over the last decade, supermarket opening hours have extended, availability of processed foods has increased, food delivery services have increased, overall physical activity has decreased and

screen time has increased, which all promote and sustain the obesogenic environment (1). Since the IOM guidelines were published in 2009, Australia and other countries such as America continue to see an increase in the incidence of overweight and obesity. Between 1998-2002 it was estimated that around 34% of women were entering pregnancy with overweight or obesity (52). Recent statistics suggest that 48% of women in Australia are overweight or obese during pregnancy (53). Furthermore, 40-70% of women gain in excess of the guidelines (54, 55). The significant increase in women entering pregnancy with overweight or obesity and lack of guideline adherence may require the current guidelines to be reviewed with a view to a contemporary perspective of the population's challenges within the current socio-ecological context. Novel and evidence-based interventions are needed to address the changing risk factors related to the current socio-ecological environment, to reduce or reverse the risk of negative metabolic phenotypes related to pregnancy weight gain which can persist into later life (56).

1.2.4 Gestational weight gain components

Weight gain during pregnancy is comprised of many components including; foetal-placental unit, water, minerals, protein, breast tissue, blood volume and adipose tissue (47). The composition of weight gained during pregnancy is relatively standard across pre-conception BMI categories, apart from the accrual of fat mass (57). Women with a preconception BMI $\geq 26.0 \text{ kg/m}^2$ have on average 4kg more fat mass deposition, compared to than those with a pre-conception BMI of 19.8-26.0 kg/m^2 (57). Furthermore, those who gain above the IOM recommendations are more likely to have fat retention post-partum (57).

Until recently, a significant literature gap existed regarding pregnancy energy expenditure in women with obesity. This literature gap has influenced the reliability of recommendations

regarding energy intake in pregnancy. A recent study conducted by Most *et al.* (2019) used objective measures of energy expenditure and their results challenge the current recommendations for energy intake during pregnancy. Results suggest that women with obesity pre-conception women do not require any additional energy intake during gestation as the IOM GWG guidelines can be met through pre-pregnancy energy intake (58). It was reported that 125 ± 52 kcal/d less than energy expenditure (net deficit) is sufficient to promote weight gain in fat free mass components (breast tissue, placental-foetal components etc) by utilising existing adipose tissue for additional energy required for growth (58). Confirming postulations from the American College of Obstetricians and Gynecologists, that obese women may need fewer calories than the IOM had previously recommended (59).

1.2.5 Getting gestational weight gain right

However, simply reducing GWG is not an appropriate solution. Both weight gain above and below the guidelines have been associated with an increased risk of adverse maternal and infant outcomes (60).

1.2.5.1 Inadequate gestational weight gain

Weight gain below the guidelines is often associated with undernutrition and can also be an indicator of poor foetal growth. Women who gain less weight than the IOM guidelines (as per preconception BMI) are more likely to have longer hospital stays and their offspring are more likely to be small for gestational age (SGA), need special care nursery (SCN) or neonatal intensive care unit admission (NICU) (61). The Dutch famine provided a unique opportunity to observe the impacts of severe nutrition restriction on pregnancy outcomes. From data collected during the famine and upon follow-up that women exposed to the

Dutch famine during pregnancy had infants with lower birthweights compared to infants conceived and born pre-famine (62). These data also showed that the timing of nutritional insult *in utero* influences health outcomes for the offspring (63). Babies whose mothers were exposed to famine in early gestation (first trimester) were larger and heavier at birth (63). Later in life, the exposed infants had an almost threefold increase in coronary heart disease and more deleterious lipid profile and higher rates of obesity, than those not exposed to the famine (63). Mid-gestation (second trimester) exposure was associated with obstructive airway disease and microalbuminuria, independent of birthweight (63). While late gestation (third trimester) exposure was associated with impaired glucose tolerance later in adult life (63). Overall, infants exposed to malnutrition during the Dutch famine *in utero* had a higher risk of coronary heart disease (64), obesity (64) and diabetes (65), later in life. These findings provided important landmark findings that supported the importance of nutrition and adequate weight gain during pregnancy (66). Furthermore, these findings underpinned the developmental origins of health and disease (DOHaD) hypothesis developed by Barker *et al.*, with the Hertfordshire cohort, linking birthweight (regardless of nutritional insult) to cardiovascular disease (67).

1.2.5.2 Excessive gestational weight gain

In developed countries, guidelines need to consider GWG in an obesogenic environmental context. Whereby, food is readily available, physical activity is low, screen time is high and therefore weight gain is a normal physiological response to the environment (68). Exceeding the IOM GWG guidelines increases the risk of pregnancy complications such as GDM (69), pre-eclampsia (70) and emergency caesarean section (61, 69). Children born to mothers who gain excessive weight during the pregnancy are more likely to be born large for gestational age (LGA), more likely to acquire infection (61) and have an increased length of

hospital stay (61). The DOHaD theory suggests that children born to mothers that gain excessive weight during pregnancy are also at higher risk of obesity (71, 72), higher blood pressure (73) and type 2 diabetes mellitus (74), later in life. Therefore, optimising weight gain during pregnancy is an opportunity to influence the health of both mother and child. Interventions that reduce excessive GWG have the potential to impact the obesity trajectory of two generations (71, 75). However, despite current strategies and interventions, up to 70% of women still gain above the recommended guidelines for GWG (55). Therefore, more research needs to be conducted into the aetiology of weight gain and novel strategies to optimise GWG and glucose tolerance during pregnancy.

1.2.6 Gestational diabetes mellitus

As with obesity and diabetes, excessive GWG increases the risk of GDM (76). GDM is a strong and independent risk factor for pregnancy complications such as pre-eclampsia, birth weight >90 percentile, caesarean section delivery, preterm birth, birth trauma and neonatal intensive care admission (77). It is important to note that even during a non-complicated pregnancy, insulin sensitivity decreases as pregnancy progresses (78). Decreased insulin sensitivity in pregnancy is attributable to altered lipid metabolism, increasing as pregnancy progresses (78). The increased free fatty acids in circulation coupled with the increase of placental human growth hormone and adipokines (TNF- α) reduces peripheral insulin sensitivity (78). While a healthy pregnancy exhibits some insulin resistance, GDM is above normal limits. The definition of GDM is 'hyperglycaemia first detected in pregnancy' (79). Current international guidelines for the diagnosis of GDM recommend a positive diagnosis of GDM if one or more of the following criteria is met: i) fasting plasma glucose between 5.1-6.9mmol/L, or the following after a 75g oral glucose tolerance test ii) 1- hour plasma glucose \geq 10mmol/L and iii) 2-hour plasma glucose = 8.5-11.0mmol/L (80). These criteria

were developed by the International Association of the Diabetes in Pregnancy Study Groups (IADPSG) on the basis of pregnancy complication risks such as gestational age >90th percentile, cord-C peptide >90th percentile and neonatal body fat > 90th percentile as per the Hypoglycaemia and Adverse Pregnancy Outcomes (HAPO) study results (80) and endorsed by the World Health Organisation (WHO) (79).

It should also be acknowledged that even without overt GDM, maternal hyperglycaemia has the potential to cause short- and long-term health complications. The HAPO study reported even maternal hyperglycaemia below the IADPSG criteria for GDM increases the risk impaired fasting glucose, overweight and obesity in the offspring in adolescence, even after controlling for potential confounders (81, 82). Furthermore, a Canadian study of 259,164 pregnant women published in *Lancet Diabetes Endocrinology* in 2019 reported for each 1 mmol/l increase in glucose at 24–28 weeks gestation, there was a 13% risk increase of maternal cardiovascular disease, even after adjusting for confounders (age, ethnicity, income, urban and rural living) (83). This relationship persisted when women with GDM were removed (83). Therefore, this highlights the need to support women across the glycaemic spectrum, to improve the health of mother and infant long term.

1.2.7 Teachable moment theory

A 'teachable moment' is a term to describe a time where the opportunity to intervene intersects with a health event that often has an emotional response, increases the perception of risk or causes a redefinition of self-concept (84). Due to the intersection of these factors, teachable moments can be leveraged with low- dose interventions, to produce meaningful health behaviours changes (84). Given this definition, it is not surprising that pregnancy is often referred to as a 'teachable moment' for long-term weight

management and obesity prevention (85). The teachable moment theory has been expanded to also include the capability, opportunity, motivation and behaviour framework. Therefore, in the context of pregnancy, the mother must have the opportunity and capability to positively influence her motivation to change behaviour (86). The pregnancy and postpartum period should, therefore, be viewed as a series of teachable moments, to disrupt unhealthful behaviours and replace them with healthy habits (86).

1.2.8 What has been already been achieved to support weight management during pregnancy?

Weight management in pregnancy has been a hotly researched topic with the resultant literature, subjected to many systematic reviews (42, 87-89). The most recent and comprehensive review reported 89 randomised controlled trials that aimed to reduce excessive GWG (90). The interventions in these trials many fall into one of four categories; diet, physical activity, lifestyle (diet and physical activity) and eHealth. Meta-analyses suggested that diet focused interventions were the most successful with a weighted mean difference of 3.3kg between intervention and control groups (90). Further, physical activity alone and physical activity + diet interventions produced a weighted mean difference of around 1kg (90). Despite the plethora of research conducted in this area, the majority of pregnant women in Australia will still gain excessive weight (55) and consequently, the prevalence of GDM is growing (91). Novel and evidenced-based methods are needed to better support women to experience healthy weight gain during pregnancy, reduce the risk of GDM and consequently reduce the risk of negative metabolic phenotypes persisting into later life for both mother and infant (56).

Part 2: Sleep a pillar of health

1.3 Sleep in the non-pregnant population

1.3.1 What is sleep?

Sleep is defined as a period of rest characterised by closed eyes, reduced respiratory rate, lowered responsiveness to external stimuli and decreased electromyographic activity (92). It is a vital component of human health. Sleep has two broad categories that occur in ~45-minute periods and alternate between each other forming a 90-minute cycle, rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep (93). REM, by definition, is characterised by rapid movement of the eye as well as an increased respiratory rate, blood pressure, heart rate, brain temperature and brain blood flow (93). On an electroencephalogram (EEG) REM sleep looks similar to wakefulness with low amplitude, high-frequency waves. Alternatively, NREM sleep is characterised by gradual slowing of EEG frequency but increasing amplitude of EEG waves, also referred to as slow wave sleep (SWS). As the amplitude increases, the depth of sleep increases and can be characterised into three categories NREM1 (N1), NREM2 (N2) and NREM3 (N3) (93). During NREM heart rate reduces and body temperature decreases. During the latter half of the night, there is less NREM sleep and a higher proportion of REM (93).

1.3.2 Why do we sleep?

In the past, there have been many theories suggested as to why we sleep. The first major theory is referred to as the 'null function' theory (94). Whereby, the function of sleep is to preserve energy, an adaptive evolutionary mechanism, which decreases energy expenditure during times that are low risk for predators and will not impact on the ability to search for food or mate (95). However, recent evidence challenges this theory. Contemporary research

suggests that sleep is a restorative process that initiates many different functions such as energy conservation, memory consolidation, physiological and psychological development, modulation of immune responses and brain waste removal (92).

1.3.3 Investigating the relationship between sleep and chronic disease risk

Short sleep duration and poor sleep quality are strong risk factors for obesity (14, 96), central adiposity (97) and diabetes (98). However, studies linking chronic disease risk to short sleep duration or poor-quality sleep have been observational and therefore cannot conclude causality (14, 19, 99). Meta-analyses of observational studies have provided consistent results to strengthen the theory that sleep restriction may be an underlying cause or significant factor in the development of chronic conditions such as obesity (14, 100), diabetes (19) and cardiovascular disease (99).

The mechanisms that support the relationship between short sleep duration and the emergence of chronic diseases such as obesity and T2DM are not yet fully elucidated. Possible mechanisms which partially explain these relationships can be classified into biological and environmental factors. Biologically, the first mechanism that was explored was a decrease in satiety hormones and an increase in hunger hormones, during sleep restricted conditions (101). Laboratory studies show that decreased sleep increases the activity of orexigenic neurons which produce hormones such as ghrelin (hunger hormone) and a decrease of hormones such as leptin (satiety hormone), leading to increased food intake (102, 103). However, this potential mechanism has received some criticism as results have been hard to replicate in the free-living setting (104). It has been suggested that in obesogenic environments such as Australia, America and the United Kingdom, an increase in food intake could be driven more by hedonic responses than endocrine responses (104).

A second potential biological mechanism which links disturbed sleep and chronic disease is reduced glucose tolerance. During periods of sleep deprivation, glucose responsiveness has been shown to be 30% lower, compared to the rested state (105). This finding was contextualised by increased heart rate during sleep deprivation, higher cortisol levels and a decrease in thyrotropin (105). This mechanism is believed to be explained by an increase in HPA-axis activity during short sleep (105). Whereby, short sleep increases cortisol levels, which in-turn decreases beta-cell responsiveness and results in glucose insensitivity (105). Furthermore, during periods of sleep deprivation the brain has decreased glucose utilisation, regardless of insulin responsiveness (105), increasing total glucose available in circulation. In the context of HPA-axis upregulation, this may compound and further exacerbate glucose insensitivity, increasing the risk of T2DM and obesity.

The third potential biological mechanism associated with short sleep is neurological dietary disinhibition. Poor quality sleep and short sleep have been associated with decreased dietary inhibition (106, 107). Functional MRI studies show that during sleep deprivation, appetitive evaluation centres of the brain (anterior cingulate cortex, lateral orbital frontal cortex and anterior insula cortex) had reduced activity when presented with desirable food (108). Meanwhile, there is an increase in amygdala activity and no difference in typical reward centres such as the ventral striatum (108). Therefore, in the context of short sleep, there may be an improper evaluation of the 'healthiness' of foods. Behaviourally, this translates to an increased desirability of energy dense foods (108). Excess consumption of these foods increases the risk of weight gain (108). One study which restricted sleep for a 24- hour period and utilised fMRI food desire task resulted in the equivalent to a 2520kJ increase in energy intake per day (108). Therefore, altered food evaluation, leads to an increased desirability of energy dense foods, increasing the likelihood of weight gain.

However, the risk of dietary disinhibition and weight gain is not a one-size-fit-all approach. Those with higher dietary disinhibition traits are more vulnerable to overeating and weight gain under short sleep conditions (107). This knowledge provides a window of opportunity for the use of dietary inhibition as a screening tool, to reduce the risk of vulnerable individuals.

The final potential mechanism that has been hypothesised is that short sleep increases the opportunity and timing of food intake. Environmentally, if wake time is extended, the opportunity to eat expands, increasing the risk of positive energy balance when living in an obesogenic environment (101). Biologically, extended wake time may further increase the likelihood of eating foods later at night. Laboratory studies have shown that carbohydrate loads after 8 pm have a higher glucose and insulin response (109), possibly related to pancreatic β cell circadian rhythm oscillation and decreased cell sensitivity to insulin (110). However, further investigation is required to confirm these mechanisms to explain the relationships observed between short sleep and increased chronic disease.

1.3.4 Sleep as a possible tool to support behavioural lifestyle interventions

Weight loss trials indicate that sleep time is a critical factor for intervention success (111, 112). It has been shown that sleeping more than 7 hours per night can increase the likelihood of weight loss success in a weight loss intervention by 33% (111). A two-week cross over study an energy restricted diet under both an 8.5-hour time in bed and 5.5-hour time in bed protocol (112). Interestingly, the 8.5-hour protocol resulted in a higher loss of fat mass (1.4kg vs 0.6kg) than the 5.5-hour protocol (112). Moreover, the short sleep protocol increased the amount of lean mass lost (1.5kg in 8.5-hour protocol vs 2.4kg in 5.5-hour protocol), which demonstrated that short sleep may hinder the efforts of dietary

restriction due to fat mass being preserved at the expense of lean muscle mass (112).

Furthermore, studies in shift workers have shown that women may be more vulnerable to changes in weight associated with sleep and circadian misalignment (113). This is due to women having higher ghrelin response and lower leptin and energy expenditure during periods of circadian misalignment (113). Suggesting that for women, it may be particularly important to ensure adequate sleep quality and appropriate sleep timing, to support other behavioural interventions.

1.4 Sleep during pregnancy

In pregnancy, sleep disturbance (short sleep or reduced sleep quality) is common, regardless of whether sleep disturbance is experienced prior to pregnancy (114). It is reported that up to 97% of women experience sleep disturbance during pregnancy at varying severities and gestations (115). The rate of sleep disturbance increases throughout pregnancy but can present as early as the first trimester (116, 117). While the general structure of sleep is the same in pregnancy (REM, non-REM and arousal/wakefulness) the key changes in pregnancy are related to the time spent in each phase (118). The two major factors that alter sleep during pregnancy are related to physical discomfort/changes and endocrine changes (116, 118). Physical factors such as foetal movement, physical discomfort, urinary frequency, leg cramps, gastric reflux and difficulty finding a comfortable sleeping position all increase period of wake after sleep onset (WASO) (116, 118). The endocrine changes relate to progesterone, prolactin, oestrogen and cortisol. Progesterone secreted by the placenta increases in concentration as the pregnancy progresses. Firstly, progesterone, when delivered intravenously can cause drowsiness and has been shown to increase NREM sleep, shorten sleep onset latency (SOL) and decrease waking after sleep onset (WASO) (119).

Prolactin has a similar effect on non-REM sleep during pregnancy (118). Similarly, oestrogen secretion increases over the course of pregnancy. Previously it was suggested that oestrogen reduced the time spent in REM sleep (119). However, this has recently been challenged by studies investigating hormone replacement therapy, suggesting oestrogen may in fact increase time spent in REM sleep and decrease latency period before transitioning to REM (119, 120). Furthermore, cortisol, which is often associated with stress but also increases during pregnancy, has been shown to decrease sleep quality (121). These factors combined with physical changes contribute to the increase in sleep disturbance during pregnancy.

Due to the factors already mentioned, the rate and type of sleep disturbance experienced alters as a woman progresses through the trimesters of pregnancy. In the first trimester, women often take more naps due to increased daytime sleepiness which is associated in an increased in total sleep time (TST) over a 24-hour period (116, 118, 119). Subjectively women also report increased sleep latency, defined as the time it takes to fall asleep (118). Objectively, there are decreases in NREM stages 3 and 4 sleep (118). Clinically, there is also a proportion of the pregnant population (~13%) that experience sleep deficiency or insomnia during the first trimester (122). In the second trimester, sleep disturbance tends to mildly improve and TST normalises (118). This is potentially due to acclimation to hormones related to pregnancy (119). Consequently, women may experience more energy and less day time drowsiness (119). As a result, fewer women meet insomnia diagnostic criteria in the second trimester compared to the first (123). However, there is a further decrease in REM and NREM stage 3 and 4 sleep (118). In the final trimester, there is a significant increase in sleep disturbances experienced. Women report waking three-five times per night due to needing to urinate, physical discomfort, leg cramps, gastric reflux or

spontaneous awakening (118). This leads to the shortest sleep duration of all trimesters (123). Objectively measured sleep reports increased time spent in NREM stage 1 sleep but decreased time in REM and NREM stages 3 and 4 (118). So, sleep disturbance can occur in any trimester but evidence shows that the majority of sleep disturbance occurs in the first and final trimester of pregnancy and can have interindividual variation.

1.4.1 Methods of assessing sleep during pregnancy

There are many ways sleep can be measured, but methods fall into one of two categories; objective or subjective. Objective methodologies include polysomnography (PSG) or actigraphy. PSG is considered the gold standard methodology for measuring sleep and diagnosing clinical sleep conditions such as OSA (124) and insomnia (125). PSG involves participants wearing surface electrodes overnight. These electrodes are placed on specific areas of the head and face to obtain data regarding the electrical waves produced by the brain (electroencephalography (EEG)), eye movements, heart rate, respiratory rate and muscle activity (126). When these data are collated, they can be used to determine which phase of REM or NREM sleep the participant experienced. These data require a trained technician to interpret and score which can be time consuming.

The second method, to obtain objective sleep data, is actigraphy. Actigraphy is often collected using a watch-like device that is worn on the wrist (126), but actigraphy devices can also be worn on the hip (127), upper arm (128) or ankle (129). Wrist-worn actigraphy provides the best accuracy when measuring sleep (127-129). The device detects movement via an accelerometer, which can be used to determine the difference between wakefulness, rest and sleep (126). Depending on the device used, some also capture light exposure data, which can assist with interpretation of the data generated (126). Actigraphy provides a

cheaper and less intrusive alternative to PSG, meaning it can be used in larger samples of free-living subjects. Compared to PSG, actigraphy shows good validity, but actigraphy does not provide the specificity and range of data that PSG provides including sleep staging and spectral analysis (126).

Subjective methods of measuring sleep come in two main forms; diaries or questionnaires (130). Subjective methodologies by their nature, rely heavily on the participant's ability to assess and recall their own sleep. Diaries are the main prospective form of subjective data collection available (131). They form part of a 'gold standard methodology', allowing researchers and clinicians to triangulate and confirm data collected through devices such as PSG and actigraphy (130). In those with sleep disturbance, subjective methodologies of measuring sleep often overestimate sleeping difficulties due to sleep misperception (misperceiving light sleep for wakefulness) (132). Given that sleep disturbance is common in pregnancy, it has been suggested that subjective sleep methods, in particular diaries may be unreliable (133). Compared to PSG, women in the first trimester significantly underestimate TST (~51 minutes) (133). As pregnancy progresses through to the third trimester, women tend to slightly overestimate TST (~8 mins) (133). Regardless of trimester, the majority of pregnant women overestimate sleep onset latency, often confusing the first 10 minutes of sleep in NREM as wakefulness (133).

Questionnaires are the most common form of collecting sleep data (117, 131).

Questionnaires have low participant burden and are a cost-effective method of assessing sleep in pregnancy. However, many of the questionnaires currently used in pregnancy have not been validated for use in pregnant populations. For example, a common questionnaire the Pittsburgh Sleep Quality Index (PSQI), which provides information on seven domains

including sleep quality, quantity, sleep latency, sleep efficiency, sleep disturbance, medication use and daytime functioning over the last month (134). The PSQI has not been validated in pregnancy. Validation in the non-pregnant population shows good validity in a clinical sample of individuals with insomnia, using PSG as the criterion (135), but not in a non-clinical sample using actigraphy (136) or PSG (134) as the criterion. Another commonly used questionnaire is the Insomnia Severity Index (137). This questionnaire aims to capture the severity of symptoms such as difficulty falling asleep, staying asleep or waking up too early in the last two weeks. While this questionnaire is widely used in the literature, it also has not been validated in pregnancy. Non-pregnant validation shows good internal consistency but poor validity when compared to PSG (137). Unlike the other questionnaires, the Berlin Questionnaire has had validation testing in a pregnant sample. The Berlin Questionnaire aims to identify the risk of OSA. This questionnaire has shown poor consistency in pregnancy when compared to PSG (138). However, the questions relating to snoring highly correlated with oxygen desaturation in pregnancy (138). It is unclear whether this questionnaire can then be used to predict complications associated with OSA in pregnancy (138).

While these methods have substantial limitations, subjective methodology in the assessment of sleep is considered a starting point due to the prohibitively expensive equipment needed for objective sleep measurement (130). Therefore, subjective self-reported methods form the majority of sleep data collected in large epidemiological studies (117, 131). Despite these methods having poor validity when compared to objective methods, it has been suggested that subjective and objective sleep measure different variables (132). Subjective sleep is measuring the perception of sleep and objective sleep measured the physical state of sleep, which are not always the same (132). Therefore, the

results from validity studies such as those presented in this thesis need to be interpreted with caution and in the context of our current knowledge.

Another commonly used in the subjective sleep measure are clinical interviews. This method is less commonly used in sleep pregnancy literature (139). This method requires a psychologist or trained interviewer to conduct an interview with a participant regarding their sleeping behaviour. It is often used in the context of insomnia or other sleep conditions (140). This is commonly conducted on an unstructured basis (140). However, structured formats are available such as the Duke Structured Interview for Sleep Disorders (141). Studies validating this method against the gold standard are lacking (140, 142).

Regardless of the methodology, each method has its own strengths and limitations. When considering a method for a study it is important to consider the following: i) the specificity of data needed to answer the research question, ii) the cost of personnel and equipment required, iii) time-frame of data that needs to be captured (ie. one night or a month) and iv) sample size required (130).

1.4.2 The relationship between sleep during pregnancy and adverse pregnancy outcomes

While sleep disturbance is common during pregnancy, its severity can vary significantly (143). Sleep disturbance has been associated with many different adverse pregnancy outcomes including but not limited to hypertension/pre-eclampsia (144), GDM (131), pre-term birth (145, 146) and depression (antenatal and postnatal) (123, 147). The mechanisms are depicted in figure 2.1. Three overarching postulated mechanisms may explain the relationship between sleep and adverse pregnancy outcomes; inflammation, melatonin secretion and circadian misalignment.

Inflammation is considered a major biological mechanism that explains the relationships observed between sleep and many adverse health outcomes. Decreased sleep quality, sleep quantity, sleep disordered breathing (SDB) and disruption of sleep continuity are all associated with increased concentrations of pro-inflammatory cytokines such as Interleukin-6 (IL-6), C-reactive protein (CRP) and tumour necrosis factor-alpha (TNF- α) (130, 148). SDB is a clinical diagnosis encompasses many disorders related to decreases in oxygen saturation and increased microarousals whilst sleeping (149). The relationship between clinical and sub-clinical sleep disturbance and inflammation appears to be bi-directional, whereby increased inflammatory cytokines increase due to disturbed sleep but also contribute to disturbed sleep (148). Increased sympathetic nervous system activity observed during disturbed sleep and clinical conditions such as SDB also consequently increase the inflammatory response (148). The increased inflammatory response related to increased sleep disturbance has been postulated as the mechanism behind the relationship between sleep disturbance and GDM (150), preterm birth (130) and potentially pregnancy hypertension (130). Increased oxidative stress and increases in sympathetic nerve activity also contribute to inflammation. Increases in oxidative stress are primarily observed in clinical conditions such as SDB (151). The oxygen desaturation caused by SDB increases oxidative stress as there is an increase in free-radicals due to a decrease in antioxidant levels. The consequence of this pathway leads to increases in pro-inflammatory cytokines (151). Furthermore, increased sympathetic nervous system activity is seen in both SDB and sleep disturbance. Increase sympathetic nervous activity increases vasoconstriction and endothelial damage (151). The increased vasoconstriction can lead to pregnancy hypertension and the increased endothelial damage also increases inflammation (151).

While these factors can be clearly linked in clinical conditions, it is less clear whether sub-clinical sleep disturbance has similar responses and outcomes.

A novel pathway that has recently been suggested as a possible factor influencing the relationship between sleep and adverse pregnancy outcomes is melatonin. Melatonin is a hormone produced by the pineal gland (152). The release of melatonin is primarily controlled by the suprachiasmatic nucleus (SCN) in the hypothalamus. Melatonin promotes sleep (152). The release of melatonin decreases when exposed to light. Melatonin has two mechanisms whereby it may support a healthy pregnancy. First, melatonin easily crosses the placental barrier and consequently enters foetal blood circulation. Once in circulation melatonin helps to program the circadian rhythms of the foetus. More importantly, melatonin also functions as an endocrine and immunomodulator, increasing antioxidant species and therefore decreasing reactive oxygen species damage (152). For this reason, melatonin as a pharmaceutical supplement has been postulated as a treatment for intrauterine growth restriction (IUGR) (153). However, environmental methods of increasing endogenous melatonin have not yet been studied. Secondly, animal studies show that exogenous melatonin delivery decreases insulin resistance, potentially through reprogramming pancreatic β -cells (154). Observational evidence in humans supports this theory (155). A cross-sectional study of women in the Nurses' Health Study II showed that higher nocturnal melatonin was inversely related to insulin levels and insulin resistance (155). When considering the impact of this mechanism one must consider it in the modern context where the rapid proliferation of devices such as smartphones, computers and other electronic devices have significantly increased our exposure to close bright light over recent years.

The last mechanism that may explain the relationship between adverse outcomes and sleep is circadian misalignment. This is particularly relevant when considering the risk of women engaged in shift work, but to a lesser extent woman exposed to travel which may induce 'jet-lag'. Women working shift work while pregnant are at increased risk of adverse outcomes such as preterm delivery, low birth weight (LBW), SGA and miscarriage (156, 157). Shift work and travel cause chronobiological desynchrony (158). Chronobiological desynchrony is a term that describes when waking patterns are out of synchrony to the diurnal (awake during the night and asleep during the day) pattern. This influences many endocrine and metabolic factors including but not limited to melatonin secretion. So, while the impacts of shift-work may be also moderated by inflammatory pathways related to melatonin, women who work shift work are also at higher risk of glucose intolerance (159). In experimental studies of non-pregnant shift workers, it has been shown that glucose tolerance is significantly lower during the night, compared to during the day despite similar insulin profiles (109). This is a particular concern as the food available to night shift workers tends to be of poorer quality (160) and higher in refined carbohydrates, therefore increasing the risk of hyperglycaemia (109) and potential adverse pregnancy outcomes.

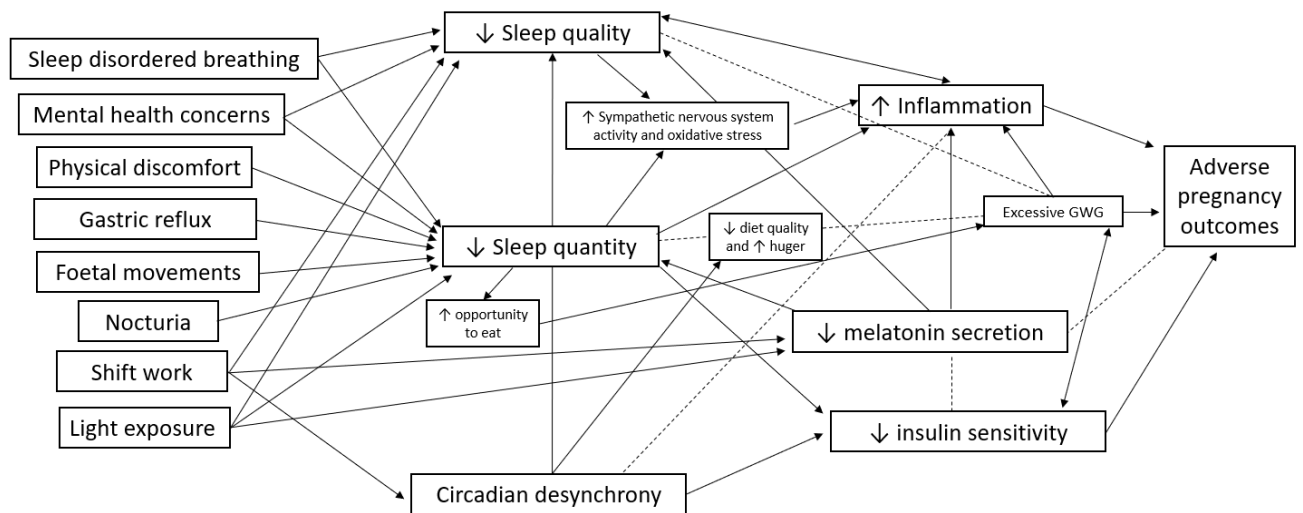


Figure 2.1: Possible pathways linking sleep and adverse pregnancy outcomes. Note solid lines represent where strong evidence is available and dashed lines represent where evidence is emerging.

1.5 The research gap

Given the increasing prevalence of overweight and obesity in the pregnant population, increasing rates of excessive GWG and increasing prevalence of GDM, novel and cost-effective methods of reducing the risk of complications and long-term metabolic programming resulting from GDM or excessive GWG are needed. In terms of translation, sleep provides a relatively accessible lifestyle behaviour that could be utilised to reduce the risk of pregnancy complications and the risk of long-term health implications. Currently, there are no practical evidence-based sleep recommendations available to pregnant women (161). A recent review of evidence-based advice available to pregnant women on the internet identified a lack of resources, lack of consensus between resources and inclusion of misinformation in the resources (161). Unlike other lifestyle factors reviewed (diet and physical activity) there was a clear lack of guidance regarding sleep. Only two websites were

identified to provide guidance on sleep (155). The advice to improve sleep quality was generic (sleep hygiene) and not necessarily related to pregnancy specific sleep concerns (161). Sleep duration was not mentioned. Therefore, particularly in Australia, there is a clear need for support and resources to encourage women to have healthy sleep habits.

Further, whether sub-clinical sleep disturbance impacts metabolic outcomes such as weight gain and glucose tolerance, as seen in the non-pregnant population, remains unclear. To date, only one recently published article has investigated the relationship between sleep and weight gain during pregnancy, using observational data (162). Results suggest that pregnant women who experienced poor quality short sleep (<6.6 hours) and were overweight or obese pre-conception, were more likely to experience excessive GWG (162). However, there were significant limitations associated with this study. The most prominent limitation in this study was that sleep duration was only assessed for 3-days during late pregnancy using wrist actigraphy, as opposed to the standard 7-day protocol. Furthermore, the sample only included n=10 obese women from the San Francisco area, which may reduce the generalisability of these findings. These data are also observational so causality cannot be inferred. These factors were both identified by the authors as a limitation and the manuscript calls for further investigation into this topic.

In contrast, the relationship between sleep quality and glucose tolerance in pregnancy has been examined by many studies, particularly in adults with clinical conditions such as SDB (163-165). In non-clinical populations, observational studies have reported an association between short sleep duration and GDM diagnosis (166, 167). However, the relationship between GWG, sub-clinical glucose intolerance and sleep (both quality and quantity) in pregnant non-clinical populations is currently unknown. There is also a lack of data from populations with similar ethnic profiles to Australia.

1.6 Aims of this thesis

The overall aim of this thesis is to investigate the impact of sleep quality and quantity in pregnancy on maternal dietary and physiological outcomes. This will be addressed through the following sub-aims:

1. To systematically evaluate the effectiveness of current interventions designed to reduce excessive gestational weight gain and their impact on secondary outcomes such as GDM and infant anthropometric outcomes at birth (Part A).
2. To investigate the existing relationship between sleep and dietary intake in pregnancy and pregnancy outcomes in an Australian cohort (Part B).
3. To design and test the feasibility of using sleep duration as intervention to influence sleep behaviour in an attempt to reduce weight and improve glucose tolerance during pregnancy (Part C).

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CHAPTER 2

Interventions designed to reduce excessive gestational weight gain can reduce the incidence of gestational diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials

The following study has been published and is reproduced with permission from Elsevier and can be found in [Appendix 1](#): Bennett CJ, Walker RE, Blumfield ML, Gwini SM, Ma J, Wang F, Wan Y, Dickinson H, Truby H. Interventions designed to reduce excessive gestational weight gain can reduce the incidence of gestational diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials. *Diabetes research and clinical practice*. 2018 Jul 1;141:69-79. DOI: <https://doi.org/10.1016/j.diabres.2018.04.010>

2.1 Introduction

The prevalence of GDM is increasing globally (1) and currently affects between 9-16% of all pregnancies (2). GDM is a failure to maintain glucose homeostasis with resultant metabolic and inflammatory stress to mother and foetus (2). Immediate implications of GDM for obstetric care include macrosomia, the need for emergency caesarean section and risk of prematurity (3). In the longer term, epigenetic programming of the foetus to be more susceptible to metabolic diseases will have a major impact on the health system (4). In women diagnosed GDM, glucose tolerance often returns to normal after birth, but their risk of developing T2DM later in life is increased 7-12-fold (5).

During pregnancy, excessive GWG can independently increase the risk of developing GDM by 53% (6). Compared to women with a healthy BMI, women who are overweight or obese at

conception are two and four times more likely to develop GDM, respectively (7). Furthermore, genetic heritage influences the risk of GDM. Women with backgrounds from Eastern Asia, India, Bangladesh, Pakistan, and Mexico are two to seven times more likely to develop GDM compared to Caucasians, even after adjusting for maternal age, education and pre-pregnancy weight (8).

The IOM has published recommendations for GWG based on pre-pregnancy BMI (9) but no global consensus exists (10). Strategies that can reduce excessive GWG and possibly the risk of GDM risk have particular relevance in developing nations such as China which have increasing rates of overweight and obesity contributing to the double burden of disease (11). Migratory patterns, combined with the ethnic and cultural diversity of populations, mean that clinicians will see women with varying degrees of risk for developing GDM and the 'one size fits all' model to screening women for glucose intolerance may need refining. Understanding more about what interventions and advice are successful, and in what populations, is important for clinical decision making.

Previous reviews have largely been conducted in literature published in English, with studies published in Spanish, Portuguese or Chinese databases being excluded. This reduces the ethnic diversity of the populations examined and impacts on the generalisability of results. The population of China accounts for 20% of the world's population, this presents a substantial gap in the literature. While maternal weight gain may influence subsequent maternal insulin resistance, surprisingly it is unknown if interventions designed to reduce excessive GWG can also reduce the incidence of GDM (12). Given these two inter-related issues, the aim of this review was to (i) comprehensively evaluate the global impact of

interventions designed to prevent excessive GWG on the incidence of GDM, and (ii) to examine whether the effects differ by maternal BMI or ethnicity.

2.2 Methods

2.2.1 Protocol and registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews (PRISMA) statement. The systematic review was registered with PROSPERO (CRD: 42016035907) and this paper reports specifically on the pre-specified secondary outcomes of the protocol. The primary aims of the protocol have previously been reported (13).

2.2.2 Data Sources and searches

The search strategy was conducted using two parallel methods. Two native English speakers (RW and CB) independently conducted the search in the following databases: Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL, Scopus, and LILACS. The MEDLINE search strategy that was adapted for all databases, is outlined in Appendix 1. Two native Mandarin speakers (JM and FW) independently conducted the search in CNKI, WangFang, and VIP databases.

2.2.3 Study selection

The search was conducted in April 2016. Duplicates were removed via an electronic automated title and author search. Following the removal of duplicates, all title and abstracts were independently screened by two reviewers and assessed for eligibility using the inclusion/exclusion criteria (Table 2.1). All conflicts were resolved by an independent third reviewer. Full texts were reviewed via the same process. All systematic reviews located in the search were subjected to manual hand searching of reference lists for possible included trials.

If no full text could be retrieved or further information was required, corresponding authors were contacted via email.

2.2.4 Eligibility criteria

A summary of the inclusion and exclusion criteria is presented in Table 2.1. To limit bias, there was no limit on the age of women, the length of intervention, the content of the intervention, publication language or date.

Table 2.1: Summary of inclusion exclusion criteria

Inclusion	Exclusion
- Randomized controlled trials	- Studies in animals
- Conducted in humans	- Studies conducted in women with existing GDM prior to commencement of intervention
- Primary or secondary aim to reduce/prevent excessive GWG	- Studies that aimed to encourage GWG
- Reported on incidence of GDM in both the intervention and control groups, separately	- Studies in duplication populations (multiple studies reporting on the same population, only the largest sample was included)
- All languages and countries were included	

2.2.5 Data extraction and Quality Assessment

Data extraction was completed by JM, FW and YW for studies published in Chinese databases, and by RW and CB for studies published in English and languages other than Mandarin or Cantonese using a data extraction template that was adapted from the Cochrane data extraction template for Randomised Controlled Trials (14). Studies published in Mandarin or Cantonese were extracted in the native language and translated for analysis. All data were independently extracted and reviewed by at least two reviewers. In the case of missing data, authors were contacted via email.

The incidence of GDM was recorded as number of participants with GDM or the number of participants assessed for GDM in the study (if specified) or else all women in the study. If studies only reported a proportion, the number of participants with GDM was calculated from the total number of participants.

Assessment of methodological quality was completed using the Cochrane Risk of Bias for Randomised Controlled Trials (14). The overall risk of bias was determined on the following seven domains: random allocation sequence, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias. Bias was then allocated to 'high', 'unclear' or 'low' for each of the domains. If domains were all 'low' the study was considered at low risk of bias overall. If studies had one or more 'unclear' domains but no 'high' domains, the study was considered at unclear risk of bias overall. If a study had one or more domains that were 'high' the overall study was considered at high risk of bias. All manuscripts were independently assessed by two reviewers for risk of bias. If reviewers disagreed on any domain of the bias tool, resolutions were made between two primary reviewers (RW, CB or JM and FW). If no resolution could be made, a blinded reviewer would make a third decision, with the binding decision formed by the domain with the majority of reviewer's decisions. This is in accordance with the Cochrane Handbook (14). No study was excluded based on the risk of bias.

2.2.6 Data synthesis and Analysis

The main outcome measure of this review was the incidence of GDM. Secondary outcomes of this review were the impact of maternal pre-pregnancy BMI and country where the study was conducted. Ethnicity was very poorly and inconsistently reported. Where it was reported, proportions or number of women were not separated into intervention and control groups,

making it impossible to conduct a meta-analysis to explore this factor. Therefore, the region in which the study was conducted was used as a surrogate measure of ethnicity.

Included studies were pooled into three categories for meta-analysis and one for qualitative synthesis, defined by the intervention type: diet alone, physical activity alone, lifestyle (diet and physical activity) and 'other' (self-weighing, continuous care, IOM guideline education and prescribed metformin for women without GDM).

Meta-analyses were conducted to compare GDM incidence in control and intervention groups. Comparison of GDM incidence was reported as relative risk (RR) with 95% confidence intervals. Cochrane Handbook thresholds for interpretation were used (14). Meta-analyses were conducted separately for each of the three intervention categories and sub-analysis was done by BMI and geographical region. BMI categories were collapsed into the following categories to reduce the risk of having subcategories with only one study: healthy weight, overweight and obese, or all BMI's included (where authors did not specify a BMI range). Geographical region was classified according to the country the study was conducted in. The countries were categorized into regions as defined by the United Nations (UN) geographical subregions (15). The UN regions as used in these analyses are based on continental geographical regions, homogeneity of population demographics and population size, to enable more accurate comparisons (15). To assess bias in meta-analyses the following steps were taken; i) random effects meta-analyses were conducted and heterogeneity was assessed using the I^2 statistic; ii) funnel plots were used to analyze if small sample numbers influenced the results of the meta-analyses; iii) sensitivity analyses were used to assess the bias of one study on the overall result of the meta-analyses. Studies were excluded from meta-analysis if- they could not be classified into one of the three interventions types (16-20)

or if they had no true control (21-23). One study had three arms (two interventions and one control), hence only the most intensive arm was included in the meta-analysis to avoid representation from duplicate control participants (24). Statistical analyses were conducted using Stata/SE 13.1. P-values <0.05 were considered statistically significant.

2.3 Results

The flow diagram of included studies is outlined in Figure 2.1. Initially, 20,517 manuscripts were identified from the search. A total of 45 studies (n=15,293 participants) satisfied the inclusion criteria and were included in the systematic review. Included studies were published between 2002 and 2016. The studies included women between 9-28 weeks' gestation, with singleton, non-complicated pregnancies. Interventions lasted an average of 25 weeks (range 9-34 weeks). Twenty-six studies exclusively included or stratified for women with a pre-pregnancy BMI in the overweight or obese category (BMI $\geq 25\text{kg/m}^2$). In total there were 15 countries and regions represented, Australia and New Zealand (n=8), Asia (n=8), Western Europe (n=2), Southern Europe (n=7), Northern Europe (n=9), North America (n=10) and one multicentre trial conducted across Europe.

Of the included studies, 11 studies (n=3388 participants) were dietary interventions (Table 2.2), 9 were physical activity interventions (n=2981 participants) (Table 2.3), 20 studies were lifestyle interventions (n=7274 participants) (Table 2.4) and 5 studies were classified as 'other' (n=1550 participants) (Table 2.5). Of the 45 included studies, only five studies stratified results by BMI (25-29) and only one study investigated two different interventions (physical activity alone and lifestyle) (30).

Thirty-seven studies were meta-analysed (24-60). Reasons for exclusion from meta-analyses included (i) studies in the 'other' category as the interventions were too heterogeneous to compare (n=5), and (ii) no true control (n=3) (21-23).

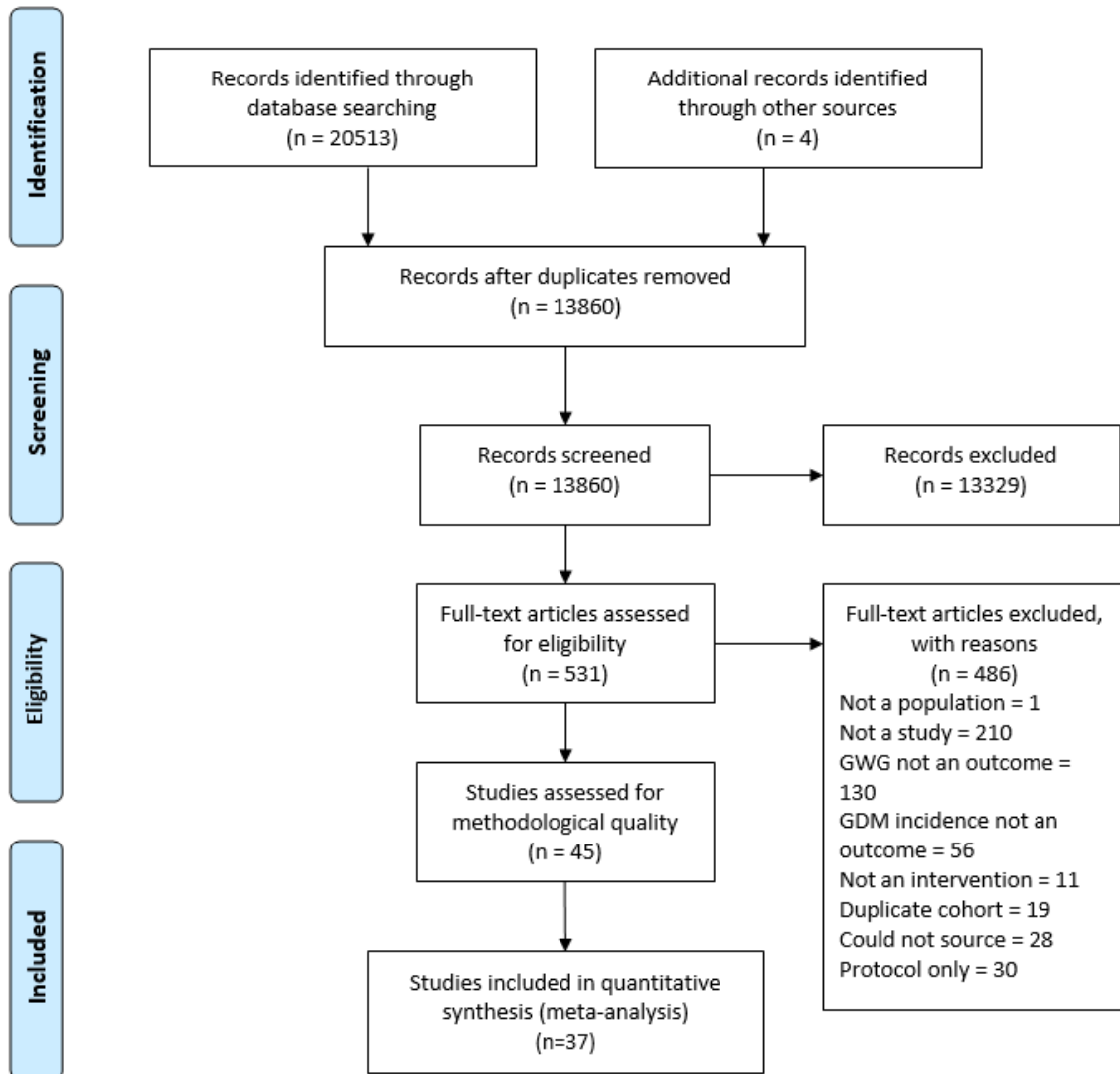


Figure 2.1: PRISMA flow diagram of included studies

2.3.1 Incidence of GDM

Diet alone interventions significantly reduced the risk of developing GDM by 44% (RR: 0.56, 95% CI: 0.36, 0.87, $p=0.009$, I^2 53.0%, $p=0.03$) (Figure 2.2), while physical activity alone interventions reduced the risk by 38% (RR: 0.62, 95% CI: 0.50, 0.78, $p<0.001$, I^2 0.0%, $p=0.909$)

(Figure 2.3). Lifestyle interventions that included both dietary and physical activity components did not significantly increase or decrease the risk of developing GDM (RR: 0.90, 95% CI: 0.77, 1.05, $p=0.187$, I^2 33.0%, $p=0.072$) (Figure 2.4).

2.3.2 Body Mass Index (BMI)

Of the 37 studies included in the meta-analyses, 16 studies included women from all BMIs or did not specify BMI inclusion criteria. In the studies that included all BMIs or did not specify inclusion criteria, diet alone interventions and physical activity alone interventions significantly reduced the risk of developing GDM by 44% (RR: 0.56, 95% CI: 0.32, 0.96, $p=0.035$, $I^2=62.4\%$, $p=0.014$) (Figure 2.2) and 35% (RR: 0.65, 95% CI: 0.50, 0.85, $p=0.001$, I^2 0.0% $p=0.909$) (Figure 2.3), respectively. In the lifestyle interventions meta-analysis there was no significant difference between interventions and control groups in the reduction of GDM (RR: 0.73, 95% CI: 0.43, 1.22, $p=0.231$, I^2 57.2% $p=0.072$) (Figure 2.4). Twenty-two studies specifically included or stratified women who were overweight and obese, however, no intervention category significantly reduced the risk of developing GDM. Four studies included only women of a healthy BMI. No diet alone interventions included only women of a healthy BMI and there was no significant difference between intervention and control in the incidence of GDM.

2.3.3 Geographical region

There were four regions represented: Australia and New Zealand ($n=3$), Asia ($n=8$), Europe (Southern $n=8$, Western $n=1$, and Northern $n=8$) and America ($n=11$). No intervention category resulted in a reduction of the risk of GDM in Australia and New Zealand, America or Northern Europe. As only one study was conducted in Western Europe, no further conclusions can be drawn from this. However, physical activity studies conducted in

Southern Europe (n=7) reduced the risk of developing GDM by 37%, with little to no heterogeneity (RR: 0.63, 95% CI: 0.50, 0.80), $p < 0.001$, $I^2 = 0.0\%$ $p = 0.712$) (Figure 2.5). Diet alone (n=4) and lifestyle Interventions (n=4) conducted in Asia resulted in a reduction in GDM risk of 62% (RR: 0.38, 95% CI: 0.24, 0.59, $p < 0.001$ $I^2 = 0.2\%$ $p = 0.390$) (Figure 2.6) and 32% (RR: 0.68, 95% CI: 0.54, 0.86, $p = 0.001$, $I^2 = 0.0\%$ $p = 0.583$) (Figure 2.7) with little to no heterogeneity, respectively.

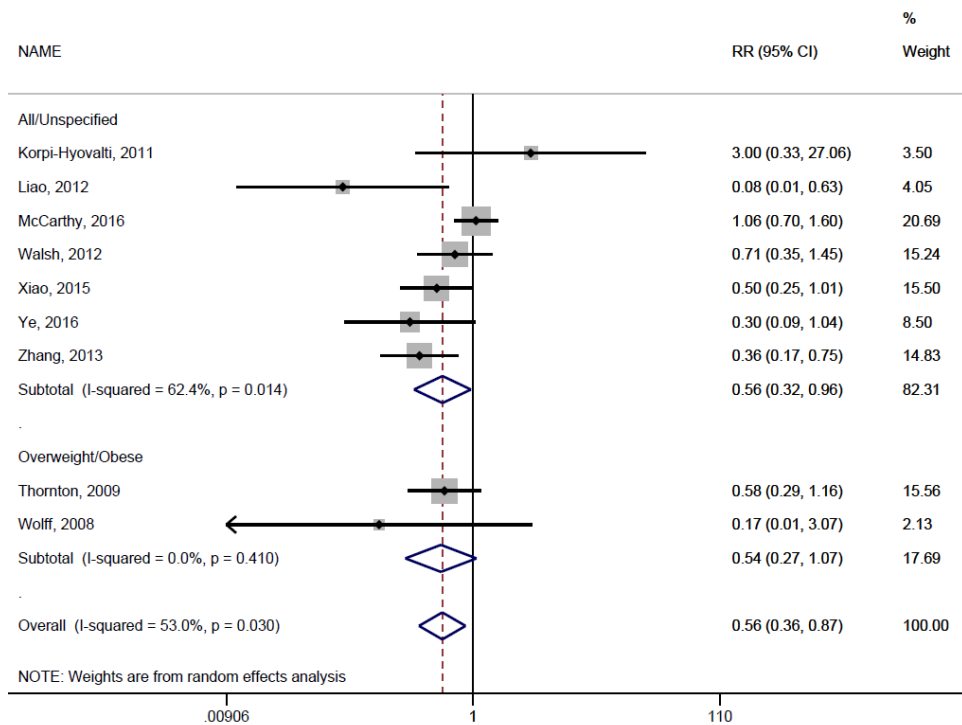


Figure 2.2: Incidence of GDM in diet alone interventions designed to reduce excessive GWG- stratified by BMI

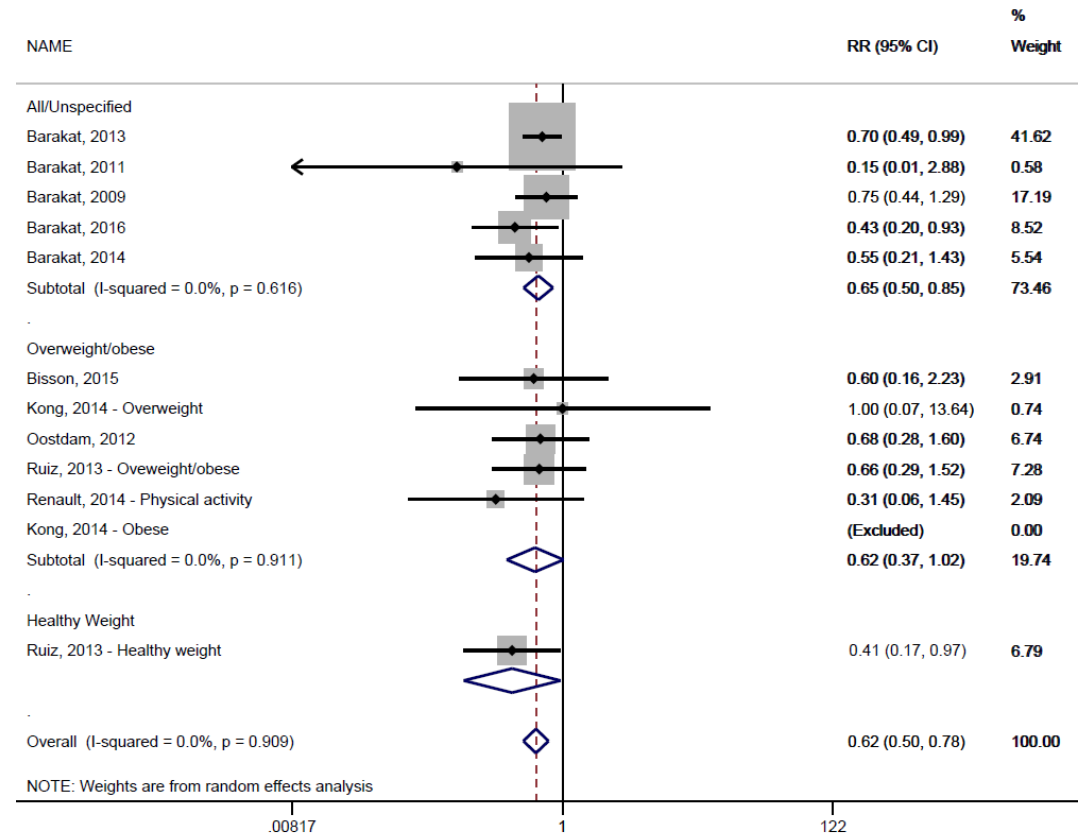


Figure 2.3: Prevalence of GDM in physical activity alone interventions designed to reduce excessive GWG – stratified by BMI

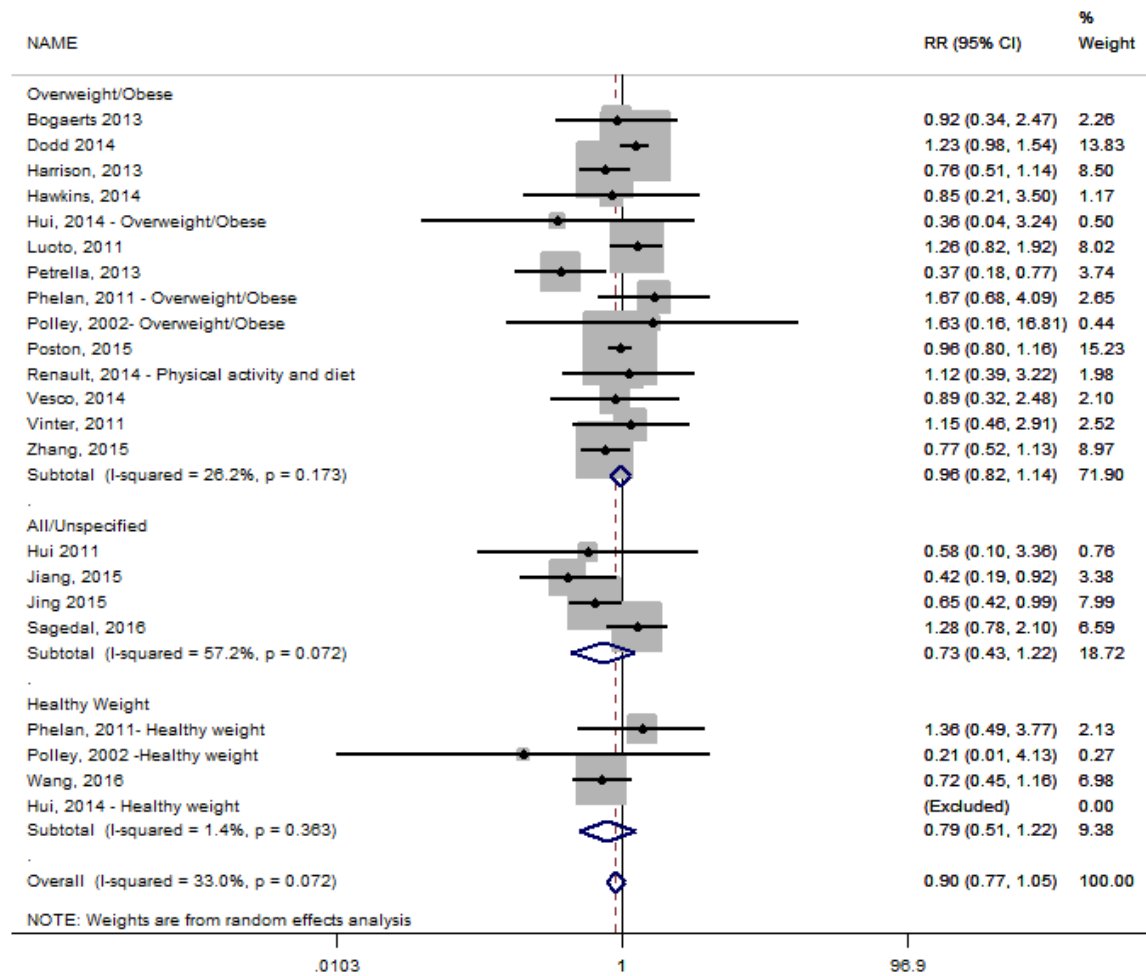


Figure 2.4 Incidence of GDM in diet alone interventions designed to reduce excessive GWG- stratified by BMI

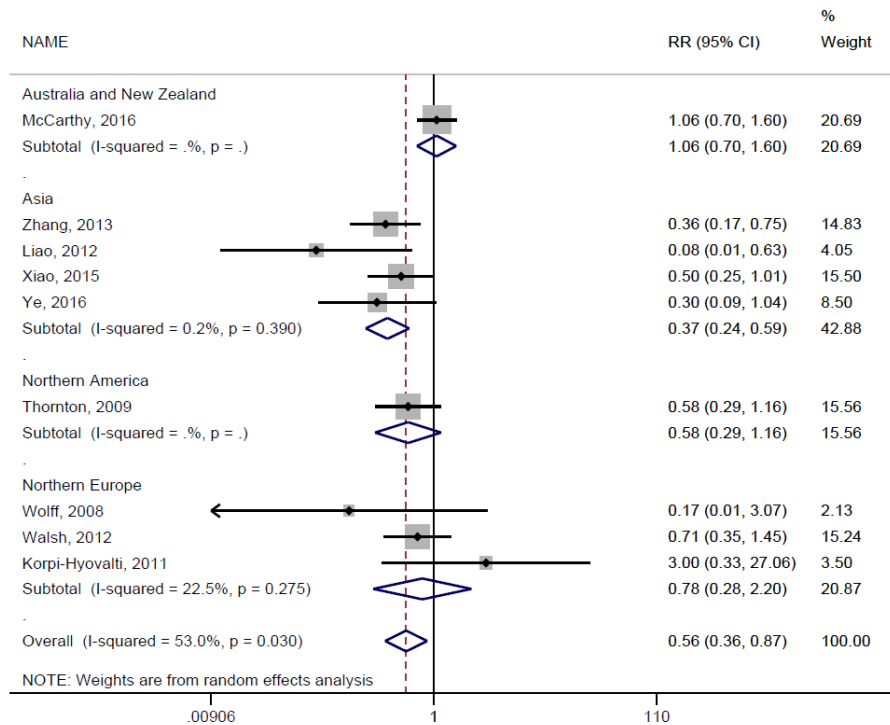


Figure 2.5: Incidence of GDM in diet alone interventions designed to reduce excessive GWG – stratified by region

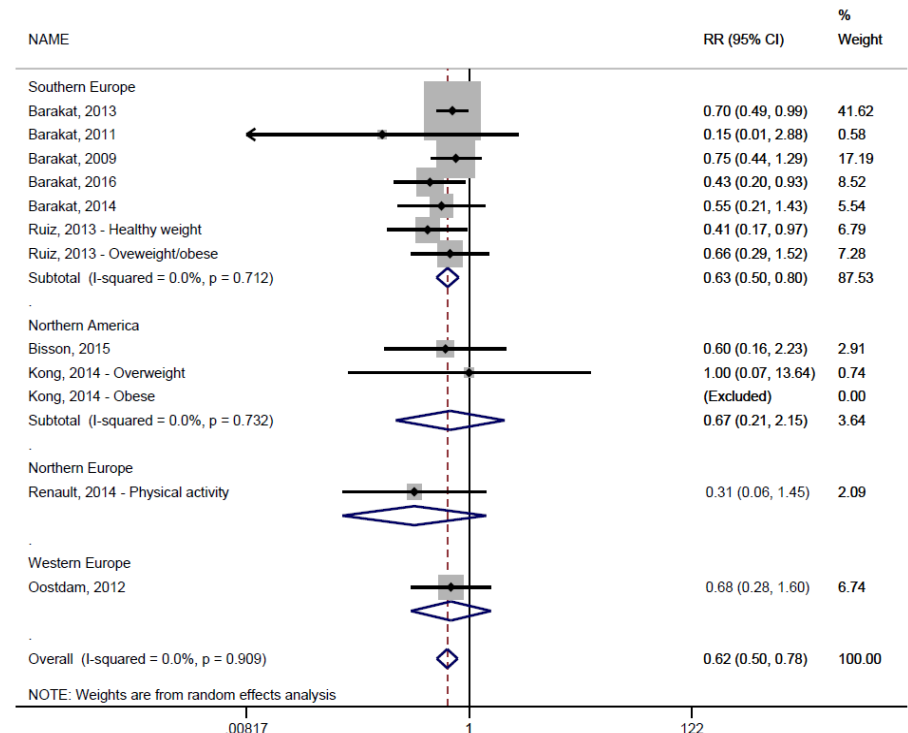


Figure 2.6 Incidence of GDM in diet alone interventions designed to reduce excessive GWG – stratified by region

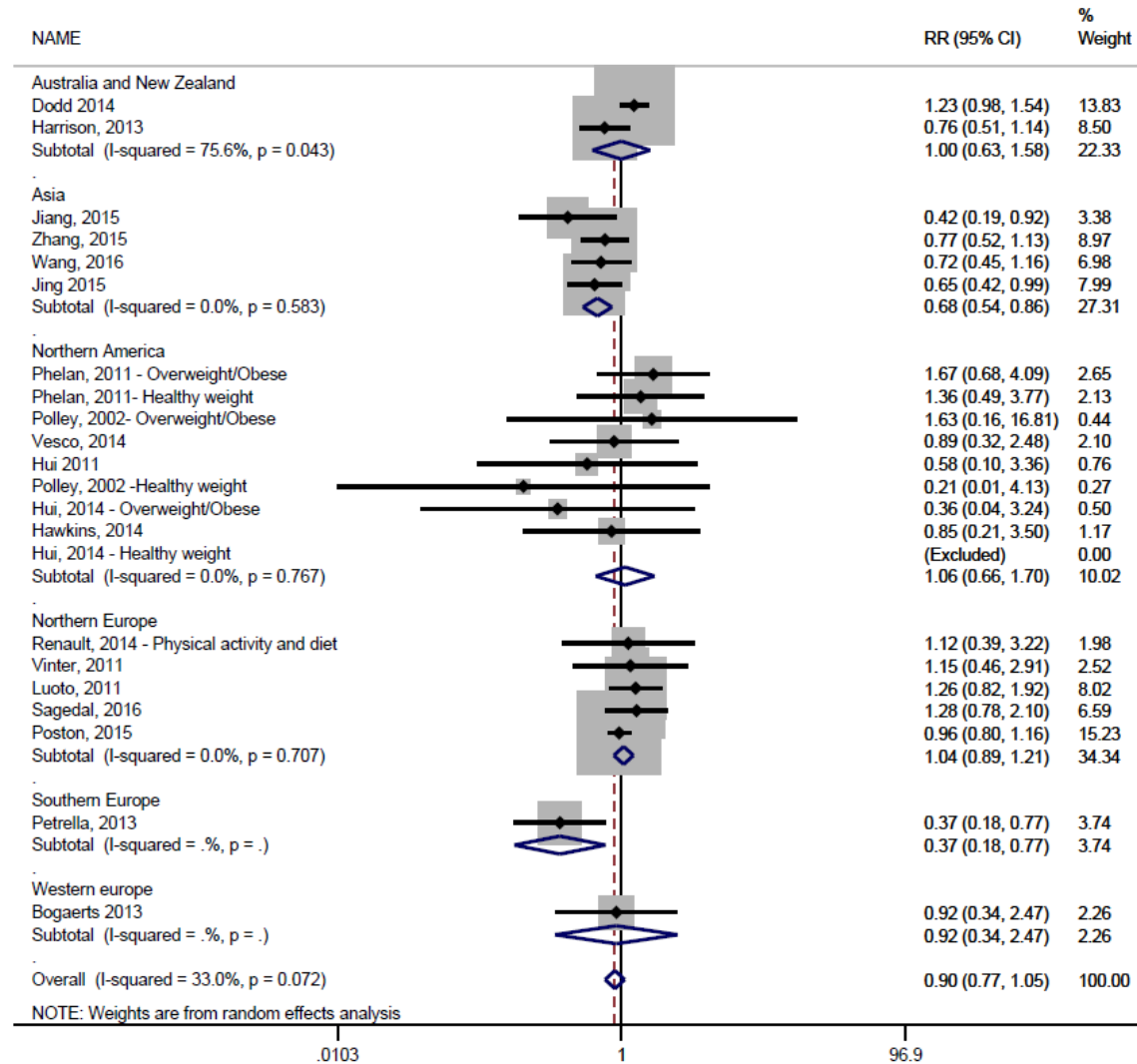


Figure 2.7: Prevalence of GDM in lifestyle interventions designed to reduce excessive GWG – stratified by region

2.3.4 Studies not included in meta-analysis

Studies not included in the meta-analysis include two dietary interventions (21, 22), one lifestyle intervention (23) and five studies classified as 'other' (16-20). The dietary studies (low glycemic index compared to healthy eating (22) and low glycemic index compared to high fiber diet (21)) and lifestyle intervention (healthy eating, physical activity and healthy eating with physical activity) did not have true controls and therefore could not be included in the relevant meta-analysis. The characteristics and results of the 'other' studies too heterogeneous to be compared via meta-analysis are presented in Table 2.5. These studies did not significantly differ from the other included studies in terms of inclusion criteria. They were all conducted in singleton pregnancies, three conducted in all/unspecified BMIs (16, 18, 22) and four were conducted in women who were overweight/obese (17, 19, 20, 23). The interventions included in the 'other' category included a drug trial of metformin against placebo in women without GDM (20), weight tracking intervention (16, 18), a holistic multidisciplinary intervention (including psychologists, food technologists, weight tracking and continuity of care providers) (19) and a technology-based behavioural intervention based on social cognitive theory (17).

2.3.5 Risk of bias

Of the 45 studies included, 12 received a high overall risk of bias, 32 received an unclear risk of overall bias and only one was considered a low risk of overall bias (Supplementary figures 1-4, available on request). Of the diet alone studies, four studies from Asia received a high risk of overall bias due to one or a combination of the following: inadequate reporting of random sequence allocation and/or blinding protocol. The other seven diet alone studies were considered an unclear risk of bias due to ambiguous reporting of blinding protocol or

inability to check reported outcomes with planned outcomes due to studies not having a published protocol. Of the physical activity only studies, three from Southern Europe received a high overall risk of bias, due to not having a published protocol. The other six studies received an unclear overall risk of bias due to ambiguous reporting of a combination of the following; allocation concealment procedure, blinding protocol, or study protocol not published. Of note, six were from the same research group (29, 31-34, 60). Of the lifestyle studies, five received a high overall risk of bias due to blinding protocol and incomplete outcome data. Three of these studies were from Asia, one from across Europe and one from North America. Fourteen studies received an unclear overall risk of bias due to ambiguous reporting on one or a combination of the following: randomisation protocol, blinding procedure, incomplete outcome data or not having a published study protocol. One lifestyle study from Northern Europe received a low overall risk of bias. Of studies in the 'other' category, all were considered to have an unclear risk of overall bias due to ambiguous reporting for a combination of the following: random sequence allocation, blinding procedure, incomplete outcome data or not having a published study protocol (49). Visual, subjective assessment of funnel plots suggest a low to medium level of publication bias (Supplementary Figures 5-7, available on request).

2.3.5 Sensitivity analysis and publication bias

Sensitivity analysis removes studies from the meta-analysis individually and reports the change of the RR. Sensitivity analyses found that in all intervention categories the RR was influenced by each study. The physical activity sensitivity analysis resulted in a CI range within the reported CI range for the overall category. However, the diet and lifestyle categories resulted in CI's beyond the range reported for the overall group. When analyses were re-run

without studies that were influencing the result, the RR did not significantly change (Supplementary Figures 8-10, available on request).

2.4 Discussion

This review found that single behavior interventions, such as diet or physical activity, designed to reduce excessive GWG were more effective than standard antenatal care in reducing the incidence of GDM. However, interventions were less effective in women with a high pre-pregnancy BMI. Interventions designed to reduce excessive GWG also reduced the incidence of GDM in Asia and Southern Europe. However, in regions such as America, Australia and other parts of Europe there was no reduction in the incidence of GDM.

It has been argued that interventions during pregnancy only have a very modest impact on weight, with average weight reductions of 2kg that are not physiologically significant, especially in women overweight or obese at conception (61). Our analysis suggests that the additive benefit of managing GWG results in a risk reduction in GDM, and this is arguably a major benefit of weight management during pregnancy. Emerging and compelling evidence from epigenetic studies would indicate that a reduction in GDM will impact positively on the health trajectory of the baby and potentially of the next generation (62). Animal models studying imprinting genes show permanent disruption of metabolism caused by sub-optimal maternal diets (63). This serves to demonstrate the importance of early life nutrition being a window of opportunity to profoundly influence health trajectories including the risk of developing diabetes (64).

Findings from our meta-analyses show that interventions that require change in a single behavior only, that is diet or physical activity alone, were effective in reducing the risk of GDM. However, when combined as a 'lifestyle' change, they are no longer effective to reduce

the risk of GDM. Sustainable behavior change needs to be conducted in small and manageable stages (65). Developing self-efficacy, according to Social Cognitive Theory (SCT), is important as it supports individuals to progress to achieve behavior change (66). Interventions that are effective must support the development of individual self-efficacy in their target group (65). If many different behaviors are targeted simultaneously, this may induce the opposite response. This is highlighted by studies reporting that women who were overweight or obese preconception required more support to maintain lifestyle changes than those who were of a healthy weight (18, 25, 28). Suggesting that women without healthy dietary and exercise habits preconception may require more support to self-efficacy. Therefore, changing habits of both physical activity and diet simultaneously may simply be too difficult when contextualized by an overlay of physical and psychological adaptations required by simply being pregnant (48).

The impact of maternal BMI on intervention outcome and risk of developing GDM found that those entering pregnancy with a high BMI were unlikely to benefit from the intervention in terms of reducing their risk of GDM. Women with obesity enter pregnancy with a pre-existing degree of glucose intolerance and insulin insensitivity (53), already placing them at increased risk of developing GDM. Furthermore, the recommended weight gain during pregnancy for a woman who is overweight or obese preconception is much more restricted than those of healthy weight (9), compounding their risk of developing GDM. Some experts suggest that women who are already obese should be encouraged not gain any additional weight during pregnancy (49). Our analysis lends support to earlier, more targeted and specific interventions, tailored to population sub-groups whose risk of GDM is raised. In addition, more needs to be done to prevent GDM in these high-risk women, before conception. Outcomes from bariatric surgery for eligible women with obesity may be an option to support

the metabolic health of their offspring (64). With obstetricians and health professionals being highly trusted sources of advice, they are well positioned to support not only the health of their patients but of future generations.

Physiologically in the broader population, dietary interventions are proposed to work and to reduce the risk of GDM by simply limiting the amount of weight gained via modifying energy intake. Physical activity interventions potentially have two modes of action and will differ depending on what the intervention components (i) an increase in physical movement will increase in energy expenditure but this needs to be a substantial and sustained rise to impact on weight loss and (ii) resistance style training can increase the amount of GLUT-4 transporters peripherally and improve (67) insulin sensitivity but not necessarily impact on activity energy expenditure. The role of maternal behaviors, in particular reducing dietary fat and regular activity are profoundly important in epigenetic programming of metabolic disease risk in offspring (68).

This review includes all countries without language or date limits, increasing the generalisability of these findings to a worldwide audience. Unfortunately, it was uncommon for the included studies to report sufficient demographic details for their population to enable highly sensitive separate meta-analyses for ethnicity to be conducted. This is a limitation of these studies and must be addressed in future studies to unravel cause and effect in different populations. Importantly, our findings allow some initial exploration of why some regions such as Asia and Southern Europe are able to be more effective in reducing the risk of GDM than others such as Australia, New Zealand or North America. This may be partly explained by the cultural suitability of interventions. The theory of cultural influence has previously been mentioned in the systematic review by Flynn et al (69). Both North American and the

Australia/New Zealand regions have diverse ethnic groups represented in the population. In Australia and the United States, it is estimated that about one-quarter of the population are first- or second-generation migrants (70, 71). The largest migratory growth comes from China and India (70, 71). Culture has been linked to behavior change through preferred learning style, especially when considering learning through a collectivism or individualism paradigm (72). For example, a recent systematic review considering the role of culturally appropriate care in the non-pregnant diabetic population suggests that the Chinese culture influences the way patients like to receive care (73) and that interventions may be more effective if the information is didactically communicated (73, 74). This didactic style was present in the included studies located in China. This highlights the differences in learning and communication styles that may influence intervention efficacy. It is unclear whether, or to what extent culture may be influencing efficacy. Future research is required to consider culture and ethnicity. It is strongly urged that all research conducted in ethnically diverse populations (e.g. Australia, Canada, UK, and the USA) report sufficient data surrounding the ethnicity of their sample. Interventions that aim to reduce the risk of GDM, need to be tailored specifically for diverse populations or different interventions developed and delivered to population subgroups.

All but one study received an overall 'unclear' or 'high' risk of bias due to lack of clarity of reporting methods and outcomes. This suggesting that the methodological reporting in studies designed to reduce excessive GWG needs to improve. Of the studies that received a high risk of bias, 7 were conducted in Asia, 3 were conducted in Southern Europe, one from North America and one from Northern Europe. Studies that were published in a language other than English were more likely to receive an overall high risk of bias because two or more domains were inadequately described. This may be due to journals particularly in areas such

as China having different reporting standards to those in English journals (75). All other studies that received a 'high' rating only had one domain inadequately described. It must be noted that the physical activity studies conducted in Southern Europe were conducted by the same research group and therefore may pose some unconfirmed publication bias. For future studies, especially those published in languages other than English, it is suggested that researchers use the Cochrane Risk of Bias tool (14) along with Consort guidelines (76) to improve methodological reporting internationally.

2.4.1 Strengths and limitations

A limitation of this review was the high level of heterogeneity found in some meta-analyses. This was possibly due to genetic, ethnic and cultural differences in the populations represented. Therefore, random effects models were used in analyses to control for heterogeneity. Future meta-analyses will be strengthened by increasing the quality of reporting interventions, international consensus of diagnostic criteria for GDM and characteristics of participants, such as ethnicity in each group. For transparency, in this review available data has been reported in characteristics and results tables. Regional analyses indicate there are differences by country that are possibly due to the cultural appropriateness of the interventions themselves. Despite countries such as Australia, UK, and the USA being comprised of different ethnicities, this is the first review to consider geographical location as a factor that may contribute to the efficacy of an intervention to reduce GWG. However, it is also possible that the effect observed from the intervention is due to individual intervention design and not due to cultural or geographic variation. To improve the ability to synthesize literature from interventions studies, more attention needs to be given to reporting ethnicity in all groups and descriptions of intervention style and underpinning theoretical base should

also be reported. Results are strengthened by the diverse range of international regions and population size represented.

2.5 Conclusion

Worldwide interventions designed to reduce excessive GWG that target single behaviors (i.e. a change in diet or change in physical activity NOT both combined) were found to reduce the incidence of GDM. While this is true for women across a range of BMI's, interventions were less effective in women with a high pre-pregnancy BMI. When analyses were stratified by region, Asia and Southern Europe were the only regions where interventions reported a significant reduction in the risk of developing GDM, compared to other regions (Australia/NZ, Northern America, and Northern Europe). These regional differences indicate that other factors possibly physiological and/or behavioral responses to intervention type must be taken into consideration when planning GDM prevention strategies, certainly, the one size fits all approach is not supported.

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Table 2.2: Characteristics of dietary intervention studies					
First author	Setting and date	Population	Intervention	Prevalence of GDM and GDM Criteria (% (n))	Quality
Korpi-Hyovalti ⁴²	Finland	Singleton pregnancy, 8-12 weeks gestation, risk of GDM. Excluded: GDM.	10 individual dietary counselling sessions throughout pregnancy. Recommended energy 50-55% CHO, 15-20% protein, 30% fat Duration: 28-32 weeks	Int: 11% (3/27) Con: 4% (1/27) <i>Criteria: NR</i>	Random: Low AC: Unclear Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear
Liao ⁴³	Wuzhou, China Mar 2010 – Mar 2012	Singleton pregnancy.	3 face-to-face individualised dietary counselling sessions. Duration: 16 – 24 weeks	Int: 1% (1/100) Con: 12% (12/100) <i>Criteria: NR</i>	Random: High AC: High Blinding: High Data: Unclear SR: Unclear Other: High Overall: High
McCarthy ⁴⁵	Melbourne, Australia Apr 2011 – Dec 2011	Singleton pregnancy, <20 weeks gestation, >18 years old, overweight or obese. Excluded: Diabetes.	A counselling session with simple dietary advice based on the Australian Guide to Healthy Eating. Self-weighing encouraged. Duration: 25 weeks	Int: 19 % (35/184) Con: 28% (37/187) <i>Criteria: Australasian Diabetes in Pregnancy Society (ADIPS)</i>	Random: Low AC: Low Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear

Markovic ²¹	Camperdown, Australia Jan 2011 - Oct 2012	Singleton pregnancy, 12-20 weeks gestation, high risk of GDM Excluded: Pre-existing diabetes, special dietary requirements.	5 individual dietary consultations with a dietitian. Recommended energy 40-45% CHO, 15-25% protein, 25-30% fat. Low-GI: Target GI ≤50 HF: Target GI 60 Duration: 20-26 weeks	LGI: 13.9% (10/72) -ITT HF: 13.4% (9/67) - ITT <i>Criteria:</i> <i>Criteria:</i> <i>Australasian Diabetes in Pregnancy Society (ADIPS)</i>	Random: Low AC: Low Blinding: Low Data: Low SR: Unclear Other: Low
Moses ²²	Australia Feb 2010 – Sep 2012	Singleton pregnancy, < 20 weeks gestation, ≥18 years old. Excluded: Diabetes, special dietary requirements, medical conditions that may compromise metabolic status, medications known to affect body weight.	Healthy eating: Advice based on the Australian Guide to Healthy Eating Low-GI: Advice based on low-GI diet. 4 counselling sessions for both groups (3 face-to-face and a phone call) Duration: 18 weeks	Low-GI: 7.6% (23/296) Healthy eating: 7.6% (21/280) <i>Criteria:</i> <i>Australasian Diabetes in Pregnancy Society (ADIPS)</i>	Random: Unclear AC: Unclear Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear
Thornton ⁵⁰	New York, USA Jun 1998- May 2005	Singleton pregnancy, 12-28 weeks gestation, obese. Excluded: diabetes, HTN, chronic renal disease.	Energy restricted diets to 24kcal/kg/day. Recommended energy 40% CHO, 30% protein, 30% fat. Duration: 12-28 weeks	Int: 16.4% (11/116) Con: 9.4% (19/116) <i>Criteria: NR</i>	Random: Low AC: Low Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear

Walsh ⁵³	Dublin, Ireland Jan 2007- Jan 2011	Singleton pregnancy, <18 weeks gestation, >18 years old, previously delivered an infant >4kg. Excluded: Previous GDM, drug use.	A group education session regarding general healthy eating and low-GI foods. Duration: 24 weeks	Int: 3% (12/350) Con: 5% (18/371) <i>Criteria: American Diabetes Association Criteria</i>	Random: Low AC: Low Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear
Wolff ⁵⁵	Copenhagen Denmark	Singleton pregnancy, <15 weeks gestation, >18 years old, obese. Excluded: >45 years old, medical complications that affect foetal growth.	10 x 1-hour consultations with a dietitian based on Danish dietary recommendations. Recommended energy 55% CHO, 15-20% protein, 30% fat. Duration: 25 weeks	Int: 0% (0/23) Con: 10% (3/27) <i>Criteria: NR</i>	Random: Low AC: Unclear Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear
Xiao ⁵⁶	Peking, China Aug 2014 – Dec 2014	Singleton pregnancy, < 12 weeks gestation, 18 – 34 years old, primiparous. Excluded: family history of diabetes.	Women given health education and advice regarding the IOM recommendations for GWG. They were monitored every 4 weeks. Women who did not reach, or who exceeded weight gain targets were monitored more regularly. Duration: 28 weeks	Int: 4% (11/286) Con: 8% (18/299) <i>Criteria: NR</i>	Random: High AC: High Blinding: High Data: Unclear SR: Unclear Other: Unclear Overall: High

Ye ⁵⁷	Guangzhou, China May 2012 – May 2013	Not reported	5 x counselling sessions regarding health coaching and individualised dietary advice based on the Chinese Society of Nutrition Pregnancy Guidelines. Duration: 28 weeks	Int: 5% (3/60) Con: 16% (10/60) <i>Criteria: NR</i>	Random: Low AC: Low Blinding: High Data: Unclear SR: Unclear Other: Low Overall: High
Zhang ⁵⁸	Ningbo, China Jan 2011 – Dec 2011	Singleton pregnancy, < 12 weeks gestation, mild physical activity.	Individualised dietary assessment based on nutrition management software. Duration: 28 weeks	Int: 4% (9/236) Con: 11% (25/236) <i>Criteria: NR</i>	Random: High AC: High Blinding: High Data: Unclear SR: Unclear Other: High Overall: High

Abbreviations: Int= Intervention, Con= Control, ITT= Intention To Treat Analysis, NR= Not reported, CHO= carbohydrate. Superscript numbers indicate associated reference.

Table 2.3: Characteristics of physical activity studies included

First author	Setting	Population	Intervention	Prevalence of GDM and GDM Criteria (% (n))	Quality
Barakat 2013 ²⁹	Madrid, Spain Sep 2007 – Jan 2011	Singleton pregnancy, sedentary, no contraindications to exercise.	Group exercise classes, 50-55 mins, 3/week. Sessions consisted of aerobic, muscle strength and flexibility activities. Duration: 28 weeks	Int: 19.5% (41/210) Con: 14.7% (32/218) <i>Criteria: WHO</i>	Random: Unclear AC: Unclear Blinding: Unclear Data: Low SR: High Other: Unclear Overall: High
Barakat 2009 ³¹	Madrid, Spain Jan 2000 - Mar 2002	Singleton pregnancy, sedentary, no risk of pre-term delivery, no contraindications to exercise.	Group exercise classes, 35-40 mins, 3/week. Sessions were individually controlled and consisted of light-moderate PA. Duration: 26 weeks	Int: 23.6% (17/72) Con: 31.4% (22/70) <i>Criteria: 75g OGTT - 2 hours point >7.8mmol/L</i>	Random: Unclear AC: Unclear Blinding: Unclear Data: Unclear SR: High Other: Unclear Overall: High

Barakat 2016 ⁶⁰	Madrid, Spain Dec 2011 Jan 2015	Singleton pregnancy. Excluded: diabetes or GDM at baseline, risk of preterm delivery.	Group exercise classes, 50-55 mins, 3/week. Each session consisted of a warm-up, core session of moderate resistance exercise, and a cool-down. Duration: 30 weeks	Int: 2.4% (9/382) Con: 5.5% (21/383) <i>Criteria: NR</i>	Random: Low AC: Unclear Blinding: Unclear Data: Low SR: Unclear Other: Unclear Overall: Unclear
Barakat 2011 ³³	Madrid, Spain	Singleton pregnancy Excluded: Contraindications such as CVD, risk of premature labour, diabetes.	Group exercise classes, 35-45 mins, 3/week, 2 x land-based and 1 aquatic. Each session consisted of a warm-up, core session of light resistance activities, and cool-down. Duration: 30 weeks	Int: 0% (0/40) Con: 7% (3/43) <i>Criteria: 100g OGTT >95mg/dl at baseline, >180mg/dl at 1 hour, >155mg/dl at 2 hours, >140mg/dl at 3 hours</i>	Random: Unclear AC: Unclear Blinding: Unclear Data: Low SR: Unclear Other: Unclear Overall: Unclear
Barakat 2014 ³⁴	Madrid, Spain	Singleton pregnancy. Excluded: Contraindications to exercise.	Group exercise classes, 55-60 mins, 3/week. Sessions consisted of a warm-up, core session of toning and resistance activities, and cool-down. Duration: 30 weeks	Int: 4.3% (6/138) Con: 7.9% (12/152) <i>Criteria: NR</i>	Random: Low AC: Unclear Blinding: Unclear Data: Low SR: High Other: Unclear Overall: High

Bisson ³⁵	Quebec, Canada Oct 2011 - Nov 2013	Singleton pregnancy, > 18 years, Obese. Excluded: Contraindications to exercise, a high level of pre-gestational exercise.	A 12-week, supervised exercise Program at a hospital-based centre Participants were individually supervised once/week and invited to 2 more sessions/week. On non-training days women were encouraged to be as active as possible. Duration: 12 weeks	Int: 13% (3/24) Con: 21% (5/24) <i>Criteria: NR</i>	Random: Low AC: Low Blinding: Unclear Data: Low SR: Low Other: Low Overall: Unclear
Kong ²⁶	Iowa, United States	Singleton pregnancy, 18-45 years, overweight or obese, < 3 x 30 mins of leisure activity in the 6 months before enrolment. Excluded: History of chronic disease such as CVD, thyroid disease, prior GDM, smoking.	An unsupervised walking program, consisting of a safety training session for using a treadmill and US PA guidelines. Women were given a treadmill for intervention and encouraged to walk in any setting. Duration: 22 weeks	<i>Overweight</i> Int: 11.1% (1/9) Con: 11.1% (1/9) <i>Obese</i> Int: 0% (0/9) Con: 0% (0/10) <i>Criteria: NR</i>	Random: Low AC: Low Blinding: Low Data: Low SR: Unclear Other: Low Overall: Unclear
Oostdam ⁴⁶	Amsterdam Netherlands Jan 2007 Jan 2011	Singleton pregnancy, overweight or obese with previous GDM, macrosomia or first-grade relative with T2DM. Excluded: > 20 weeks gestation, < 18 years, GDM, HTN, alcohol or drug use, other health complications.	2 x 60-minute PA sessions with aerobic and strength exercises supervised by a physiotherapist at participating hospital. Duration: 25 weeks. Women also followed up 12 weeks post-partum.	Int: 14.6% (7/49) Con: 21.6% (11/52) <i>Criteria: NR</i>	Random: Low AC: Low Blinding: Unclear Data: Unclear SR: Low Other: Low

Ruiz ²⁹	Madrid, Spain Sep 2007 Jan - 2011	Singleton pregnancy, sedentary, not at risk of pre-term delivery. Excluded: Contraindication to exercise	Group exercise classes, 55-60 mins, 3/week. Session consisted of a warm-up, core session of moderate intensity aerobic and resistance exercises, and cool-down. Duration: 30 weeks	<i>Healthy weight</i> Int: 2.1% (7/335) Con: 5.1% (18/352) <i>Overweight/obese</i> Int: 6.2% (9/146) Con: 9.3% (12/129) <i>Criteria: NR</i>	Random: Low AC: Unclear Blinding: Unclear Data: Low SR: Low Other: Low Overall: Unclear
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Abbreviations: Int= Intervention, Con= Control, NR= Not reported, WHO= World Health Organisation. Superscript numbers indicate associated reference.

Table 3: Characteristics of lifestyle interventions included

First author	Setting and date	Population	Intervention	Prevalence of GDM and Criteria (% (n))	Quality
Bogaerts ²⁴	Flanders Belgium Mar 2008 – Apr 2011	Singleton pregnancy, < 15 weeks gestation, obese, literate in Dutch. Excluded: Type 1 diabetes, primary need for nutrition advice.	Brochure: A purpose-deigned brochure regarding diet, PA and limiting excessive GWG. LS: 4 x 1.5-2 hour group sessions regarding energy intake. Recommended energy 50-55% CHO, 9-11% protein, 30-35% fat Motivational interviewing, food diaries and label reading used (in addition to brochure). Duration: 25 weeks	Brochure: 21.1% (7/58) LS: 11.8% (9/78) Con: 11.1% (7/63) <i>Criteria: Australasian Diabetes in Pregnancy Society (ADIPS)</i>	Random: Low AC: Low Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear

Dodd ³⁶	Adelaide, Australia Jun 2008 – Dec 2011	Singleton pregnancy, 10 – 20 weeks gestation, overweight or obese Excluded: Pre-existing diabetes	3 x face-to face meetings and 3 phone calls consisting of dietary and LS advice Women were provided with meal plans, recipes and snack ideas. Duration: 22 weeks	Overall: Int: 14% (148/1080) Con: 11% (120/1073) <i>Criteria:</i> South Australian: Positive 75g OGTT and fasting \geq 5.5mmol/L or 2 hour \geq 7.8 mmol/L	Random: Low AC: Low Blinding: Low Data: Unclear SR: Low Other: Low Overall: Unclear
Harrison ³⁷	Melbourne, Australia	Singleton pregnancy, 12 – 15 weeks gestation, overweight or obese, high risk of GDM. Excluded: Diabetes, pre-existing medical conditions, BMI > 45	Four individual behaviour change sessions based on social cognitive theory. Recommendations made for diet, PA, goal setting and self-monitoring. Duration: 14 weeks	Int: 31% (27/87) Con: 44.9% (35/78) <i>Criteria:</i> <i>International Association for Diabetes and Pregnancy Study Groups (IADPSG)</i>	Random: Low AC: Low Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear

Hawkins ³⁸	Massachusetts, United States Apr 2010 – Aug 2011	Singleton pregnancy, < 18 weeks gestation, 18 – 40 years old, overweight or obese, < 30 minutes PA/week. Excluded: Type 2 diabetes, heart or renal disease, contraindications to moderate PA.	6 x face-to-face counselling sessions with 5 phone calls regarding diet and PA. Duration: 20-26 weeks	Int: 10% (3/30) Con: 12.2% (4/34) <i>Criteria: NR</i>	Random: Unclear AC: Unclear Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear
Hui ²⁵	Manitoba, Canada Jul 2004 – Feb 2010	Singleton pregnancy, < 26 weeks gestation. Excluded: diabetes, contraindications to PA	LS advice regarding PA and diet. Group PA sessions at local gym 3-5 times/week. 2 x dietary and GWG counselling sessions provided at enrolment and 2 months after enrolment. Duration: 10-16 weeks	Int: 2.0% (2/102) Con: 3.4% (3/88) <i>Criteria: Canadian Diabetes Association 2008 Guideline</i>	Random: Low AC: Low Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear

Hui ³⁹	Manitoba, Canada May 2009 – Dec 2011	Singleton pregnancy, < 20 weeks gestation. Excluded: diabetes, contraindications to PA	LS advice regarding PA and diet. Group PA sessions 3-5 times/week. 2 x dietary and GWG counselling sessions provided at enrolment and 2 months after Enrolment. Duration: 27 weeks	Healthy weight Int: 0% (0/27) Con: 0% (0/30) Overweight/ Obese Int: 10% (3/29) Con: 4% (1/27) <i>Criteria:</i> <i>Canadian Diabetes Association 2008 Guideline</i>	Random: Low AC: Low Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear
Jiang ⁴⁰	Wuhan, China Mar 2013 – Oct 2013	Not reported	Nutrition education and counselling regarding PA. Duration: 27 weeks	Int: 8% (8/100) Con: 19% (19/100) <i>Criteria: NR</i>	Random: Low AC: High Blinding: High Data: Unclear SR: Unclear Other: Unclear Overall: High
Jing ⁴¹	Chengdu, China Sep 2012 – Sep 2013	Singleton pregnancy, > 18 years Excluded: diabetes, pregnancy complications.	1 x 20-minute health education session regarding GWG and GDM. Manuals were given regarding diet PA. Participants could contact a trained graduate to ask questions and receive feedback at 16-20 weeks and 20-24 weeks. Duration: 12 weeks	Int: 22.6% (26/115) Con: 34.9% (37/106) <i>Criteria: NR</i>	Random: Low AC: Unclear Blinding: Unclear Data: Low SR: Unclear Other: Unclear Overall: Unclear

Luoto ⁴⁴	Piranmaa, Finland Oct 2007 – Dec 2008	Singleton pregnancy, at least one risk factor for GDM. Excluded: Abnormal baseline OGTT, pre-pregnancy diabetes, contraindications to PA, substance abuse, psychiatric illness	LS advice regarding PA and diet in regular antenatal visits. PA counselling focused on increasing leisure time. Diet counselling based on the Finnish dietary recommendations. Duration: 29 weeks	Int: 20.5% (44/216) Con: 16.3% (29/179) <i>Criteria: American Diabetes Association 2010</i>	Random: Low AC: Unclear Blinding: Unclear Data: Unclear SR: Low Other: Low Overall: Unclear
Petrella ⁴⁷	Modena, Italy Apr – Oct 2011	Singleton pregnancy, > 18 years old, overweight or obese. Excluded: chronic diseases, previous GDM, smokers, bariatric surgery, regular PA, supplements known to affect body weight	A one-hour counselling session regarding an energy restricted diet: 1500kcal/day + 200 kcal/day for obese or 300kcal/day overweight. Women were also encouraged to exercise 30 minutes, 3 days/week. Duration: 27 weeks	Int: 23.3% (7/33) Con: 57.1% (16/28) <i>Criteria: American Diabetes Association 2010</i>	Random: Low AC: Low Blinding: Unclear Data: Unclear SR: Unclear Other: Low Overall: Unclear
Phelan ²⁷	Rhode Island United States 2006 - 2008	Singleton pregnancy, 10-16 weeks gestation, > 18 years old, BMI 19.8 - 40kg/m ² , non-smoker. Excluded: major health or psychiatric disease, weight-loss during pregnancy, history of ≥3 Miscarriages.	1 x session regarding GWG, PA and energy intake (20kcal/kg/day). Emphasis placed on self-monitoring. Food diaries, scales and pedometer provided and women received supportive phone calls throughout pregnancy. Duration: 27 weeks	Healthy weight Int: 8.8% (8/90) Con: 6.5% (6/92) Overweight/ Obese Int: 13.6% (11/81) Con: 8.1% (7/86) <i>Criteria: NR</i>	Random: Low AC: Low Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear

Polley ²⁸	Pittsburgh, USA	Singleton pregnancy, < 20 weeks gestation, >18 years of age. Excluded: underweight, high risk pregnancy.	Lifestyle advice offered at regular clinic visits regarding GWG, PA and diet. Between each visit women were mailed newsletters and contacted by phone. Women with excessive GWG were provided with extra counselling. Duration: 24 weeks	Healthy weight Int: 0% (0/30) Con: 6.6% (2/31) Overweight Int: 7.4% (2/27) Con: 4.5% (1/22) <i>Criteria: NR</i>	Random: Unclear AC: Unclear Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear
Poston ⁴⁸	United Kingdom	Singleton pregnancy, 15 – 18 weeks gestation, > 16years, obese Excluded: Underlying disorders or prescribed metformin	Women received advice on self-monitoring, problem solving, barriers to behaviour change, and enlisting social support. Women set SMART goals regarding PA and diet, received a PA DVD and were encouraged to choose low GI CHO and reduce saturated fat. Duration: 9 weeks	Int: 25% (160/629) Con: 26% (172/651) <i>Criteria: International Association for Diabetes and Pregnancy Study Groups (IADPSG)</i>	Random: Low AC: Unclear Blinding: Unclear Data: Unclear SR: Low Other: Unclear Overall: Unclear

Renault ³⁰	Copenhagen, Denmark Mar 2009 – Mar 2012	Singleton pregnancy, > 18 years, < 16 weeks gestation, obese. Excluded: diabetes, serious diseases limiting PA, bariatric surgery, alcohol or drug abuse.	PA + D: PA and diet intervention. Women advised to increase PA to 11,000 steps/day. They also had contact with a dietitian every 2 weeks (alternating between outpatients and phone calls). PA: PA intervention. Women advised to increase PA to 11,000 steps per day. Duration: 26 weeks	PA + D: 3.8% (6/130) PA: 1.6% (2/125) Con: 5.2% (7/134) <i>Criteria: NR</i>	Random: Unclear AC: Unclear Blinding: Unclear Data: Low SR: Low Other: Unclear Overall: Unclear
Sagedal ⁴⁹	Norway Sep 2009 - Feb 2013	Singleton pregnancy, ≤20 weeks gestation, pre- pregnancy BMI ≥19 kg/m ² , literate in Norwegian or English Excluded: diabetes, contraindication to PA, substance abuse.	2 x phone consultations (baseline and 4 – 6 weeks later). Dietary advice included portion sizes, regular meals, snacking, increasing intake of water, fruits, and vegetables. Women also provided access to a gym, cooking class, and LS booklet. Duration: 24 weeks	Int: 11.8% (32/296) Con: 9.1% (25/295) <i>Criteria: WHO</i>	Random: Low AC: Low Blinding: Low Data: Low SR: Low Other: Low Overall: Low

Simmons ²³	Barcelona, Cambridge, Vienna, Leuven, Copenhagen, Poznan, Padova, Galway, Amsterdam, Jan 2012 – Aug 2013	Singleton pregnancy, <20 weeks gestation, ≥18 years, pre-pregnancy BMI ≥29kg/m ² . Excluded: pre-existing diabetes, inability to walk ≥100m, requiring a complex diet, chronic medical condition, psychiatric illness	5 x face-to-face sessions and 4 x optional phone sessions with either PA, HE or a combination of both. Duration: 25 weeks	HE: 28% (10/36) PA: 31% (11/35) HE + PA: 42% (15/42) <i>Criteria: WHO</i>	Random: Low AC: Low Blinding: Low Data: High SR: Unclear Other: Unclear Overall: High
Vesco ⁵¹	Oregon and Washington, United States Oct 2009 - July 2011	Singleton pregnancy, > 18 years, obese. Excluded: diabetes, medical conditions requiring nutrition care.	2 x individual counselling sessions at randomisation and weekly group sessions to assist women to maintain their weight within 3% of their baseline weight. Dietary advice was based on DASH diet. Women also advised to participate in 30 mins of moderate PA/day Duration: 19-32 weeks	Int: 11% (6/56) Con: 12% (7/58) <i>Criteria: NR</i>	Random: Low AC: High Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: High
Vinter ⁵²	Odense, Denmark Oct 2007 – Oct 2010	Singleton pregnancy, 10-14 weeks gestation, 18-40 years, obese Excluded: chronic medical disorders, previous obstetric complications.	4 x dietary counselling sessions to limit GWG to 5kg. Energy based on BMI and 30-60 minutes PA/day encouraged. Women provided with pedometer, gym membership, and 1 x training session per week Duration: 20 weeks	Int: 6.0% (9/150) Con: 5.2% (8/152) <i>Criteria: 2 hour OGTT ≥9mmol/L</i>	Random: Low AC: Low Blinding: Unclear Data: Low SR: Low Other: Low Overall: Unclear

Wang ⁵⁴	Peking, China Sep 2012 - Jan 2013	Singleton pregnancy, at least one risk factor for GDM. Excluded: diabetes.	3 x LS counselling sessions regarding diet, PA and GWG. Reinforcement of LS advice given accordingly. Duration: 22 weeks	Int: 17.2% (23/134) Con: 23.9% (33/138) <i>Criteria: International Association for Diabetes and Pregnancy Study Groups (IADPSG)</i>	Random: Unclear AC: Unclear Blinding: Unclear Data: Low SR: High Other: High Overall: High
Zhang ⁵⁸	Peking, China Apr 2011 – Apr 2012	Singleton Pregnancy, 6 – 12 weeks gestation, > 18 years, BMI > 28kg/m ² , primiparous. Excluded: Metabolic disease, disability, mental illness, liver, lung or heart disease.	Counselling regarding LS every 2-4 weeks. Recommendations included balanced diet, low-GI, and walking 30 mins/day. Women also received a one and a half hour nutrition education lecture. Duration: 28-34 weeks	Int: 29.8% (42/141) Con: 38.8% (28/72) <i>Criteria: NR</i>	Random: Low AC: Low Blinding: High Data: Unclear SR: Unclear Other: Unclear Overall: High

Abbreviations: Int= Intervention, Con= Control, NR= Not reported, WHO= World Health Organisation, OGTT= Oral Glucose Tolerance Test. Superscript numbers indicate associated reference.

Table 2.5: Characteristics of other interventions included

First author	Setting and date	Population	Intervention	Prevalence of GDM and GDM Criteria (% (n))	Quality
Brownfoot ¹⁶	Melbourne, Australia Jan 2010 – Nov 2012	Singleton pregnancy, < 21 weeks gestation, antenatal care through hospital clinic. Excluded: <18 years, >45 years, medical comorbidities, substance abuse, inability to speak English.	Women were weighed at each antenatal visit. All clinic rooms had the IOM guidelines displayed and clinicians were encouraged to discuss appropriate GWG with patients. Duration: 22 weeks	Int: 5.4% (21/386) Con: 5.3% (21/396) <i>p=0.93</i> <i>Criteria: NR</i>	Random: Unclear AC: Low Blinding: Unclear Data: Low SR: Low Other: Low Overall: Unclear
Herring ¹⁷	Philadelphia, United States 2013 – 2014	Singleton pregnancy, < 20 weeks gestation, > 18 years old, BMI 25-45kg/m ² in first trimester, African American Medicaid recipient, cell phone with text messaging, Facebook account Excluded: Requiring specialised nutrition care, tobacco use	Promotion of behaviour change goals regarding energy intake, PA and self-weighing. Skills training and support were delivered using self-monitoring texts with personalised feedback, a closed Facebook group, and health coach calls throughout pregnancy. Duration: 28 weeks	Int: 4% (1/27) Con: 4% (1/29) <i>p=1.00</i> <i>Criteria: Local hospital criteria</i>	Random: Low AC: Low Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear
Jeffries ¹⁸	Melbourne, Australia Jul 2007 – May 2008	Singleton pregnancy, 18-45 years old. Excluded: pre-existing diabetes, non-English speaking	Education regarding GWG guidelines. Women's weights were recorded at 16, 20, 24, 28, 30, 32 and 34 weeks. Duration: 25 weeks	Int: 10.5% (13/124) Con: 9.0% (10/111) <i>p=0.83</i> <i>Criteria: Local hospital criteria</i>	Random: Low AC: Low Blinding: Unclear Data: Low SR: Unclear Other: Low Overall: Unclear

Quinlivan ¹⁹	Melbourne, Australia	Singleton pregnancy, overweight or obese Excluded: foetal abnormalities, wanted to relinquish infant after birth, unable to attend clinic, non-English speaking	An intervention with four key aspects: a) Continuity of care, b) Assessing weight gain at each antenatal visit, c) Dietary intervention by a food technologist at each antenatal visit, d) Psychological assessment and intervention if indicated Duration: 30 weeks	Int: 6% (4/63) Con: 29% (17/61) <i>p</i> =0.043 <i>Criteria: WHO</i>	Random: Low AC: Low Blinding: Unclear Data: Unclear SR: Unclear Other: Unclear Overall: Unclear
Syngelaki ²⁰	London, United Kingdom Oct 2010 – Jun 2013	Singleton pregnancy, 12-18 weeks gestation, BMI >35kg/m ² Excluded: <18 years old, major foetal defect detected, history of GDM, kidney, heart or liver failure, hyperemesis gravidarum, prescribed metformin before screening, sensitivity to metformin.	Metformin was initiated at an initial dose of 1g per day and increased 0.5g per week to a maximum dose of 3g per day in week five. Both control and intention groups received advice regarding healthy eating and low GI foods, and were encouraged to exercise 30 minutes per day Duration: 25 weeks	Int: 12.4% (25/202) Con: 11.3% (22/195) <i>p</i> =0.74 <i>Criteria: NR</i>	Random: Low AC: Low Blinding: Low Data: Unclear SR: Unclear Other: Unclear Overall: Unclear

Abbreviations: Int= Intervention, Con= Control, NR= Not reported, WHO= World Health Organisation. Superscript numbers indicate associated reference.

CHAPTER 3

What impact do these interventions have on the foetus growth and therefore birth anthropometrics?

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[3](#). The reference pertaining to this publication is: Bennett CJ, Walker RE, Blumfield ML, Ma J, Wang F, Wan Y, Gwini SM, Truby H. Attenuation of maternal weight gain impacts infant birthweight: systematic review and meta-analysis. *Journal of developmental origins of health and disease*. 2019 Aug;10(4):387-405.

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3.1 Introduction

GWG can be an indicative factor of both maternal and infant complications during pregnancy (1, 2). The IOM stipulates guidelines in which weight gain during pregnancy can be classified as adequate, inadequate or excessive (3). In an attempt to reduce pregnancy complications, the IOM reviewed the GWG the guidelines in 2009 to include stratification by pre-conception BMI (3). The higher the pre-conception BMI, the less weight a woman is recommended to gain during pregnancy. While inadequate GWG is still a problem in many developing nations, excessive GWG is experienced by almost half the pregnant population in developed nations (1, 4). Excessive GWG increases the risk of pregnancy complications such as GDM, pre-eclampsia and caesarean section delivery (3). In the long term, women who gain excessive weight during pregnancy are also at higher risk of postnatal weight retention and therefore obesity and related diseases later in life (5).

Gestational weight gain has a significant impact on the developing foetus in utero. Excessive GWG is associated with an increased risk of large for gestational age (LGA) infants (>90%

percentile) and macrosomia (birthweight >4000g) (6). However, the complications of excessive GWG are not limited to the size of the infant at birth. In the short term, children born to mothers who gained excessive GWG are more likely to acquire infection (7), have lower five-minute activity, pulse, grimace, appearance and respiration (APGAR) scores (7), suffer from meconium aspiration syndrome (7), hypoglycaemia (7) and are more likely to have increased length of hospital stay at birth (7, 8). In the long term, children who are born to mothers that experienced excessive weight gain during pregnancy are also more likely to have higher BMI z-scores as children (9) and suffer from obesity, diabetes and high blood pressure later in life (10). In contrast, inadequate GWG impairs foetal growth, increasing the risk of SGA infants, lower lean body mass, fat mass and head circumference (11). In the long term, children of mothers who gain inadequate weight during pregnancy may be at higher risk of obesity (12), cardiovascular disease (13), breast cancer (12) and glucose intolerance (12) in later life. This suggests that interventions designed to reduce gestational weight gain may have a significant influence on both the mother and the health of the next generation (14).

Many reviews have considered the effect of diet, physical activity and lifestyle interventions on GWG (15-17). Of the reviews that have considered infant outcomes, two have shown no difference in any measures reported (15, 16) and one reported a significant reduction in birthweight in physical activity interventions (17). It remains unclear whether these interventions also impact infant anthropometry and thus impact offspring health in the longer term (18). Due to the severity of consequences related to undesirable foetal growth for both mother and baby, there is an urgent need to address this gap in the literature (18). Previous reviews in this area have been significantly limited in the translation of results due to two reasons; i) a small samples of studies included (≤ 4 studies) and/or ii) exclusion of

papers published in languages other than English, reducing global translatability and possibly inducing bias to the overall effect reported (19-21). Therefore, the aim of this systematic review was to evaluate differences in infant anthropometric outcomes (birthweight, birth length, macrosomia, LGA, SGA and LBW) in studies designed to reduce excessive gestational weight gain.

3.2 Methods

3.3.1 Protocol and registration

This systematic review was conducted according to the PRISMA guidelines and the protocol has been registered with PROSPERO (CRD: 42016035907). This manuscript reports on the secondary outcomes of this protocol. The primary outcomes have been reported elsewhere (22).

3.2.2 Eligibility criteria

The details of the inclusion exclusion criteria have been previously outlined (22). Briefly, studies were eligible if they were randomised controlled trials, conducted in humans with a primary or secondary aim to reduce excessive GWG. Studies that aimed to encourage GWG were excluded. This review also required studies to report on birthweight, birth length, SGA (<10th centile), LGA (>90th centile), LBW (<2500g) or macrosomia (>4000g). To limit bias, there was no limit on the age of women, the length of intervention, the content of the intervention, publication language or date.

3.2.3 Search strategy and selection process

A systematic search was conducted using the following electronic databases: Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL, Scopus, LILACS and Clinical Trials.gov was also searched at the same time. The search strategy and keywords used are outlined in Appendix

2. Two native Mandarin speakers (JM and FW) also independently conducted the systematic search in: China National Knowledge Infrastructure (CNKI), WangFang and VIP databases. The search was conducted in April 2016. Duplicates were removed via an electronic automated title and author search. Following the removal of duplicates, all title and abstracts were independently screened by two reviewers. Any conflicts were resolved by an independent third reviewer (HT). Full texts were retrieved and reviewed via the same process. Corresponding authors were contacted if full texts were unable to be retrieved or further information was required. Systematic reviews identified through the search process were subject to a manual hand searching of reference lists for possible included trials. Multiple publications from the same dataset were reviewed and the publication with the largest sample size was included.

3.2.4 Data extraction and Quality Assessment

Data extraction was completed by JM, FW and YW for studies published in Chinese languages (Mandarin or Cantonese), and by RW and CB for studies published languages other than Chinese languages. Data were extracted using a template adapted from the 'Cochrane data extraction template for Randomised Controlled Trials' (23). All data were independently extracted and reviewed by at least two reviewers (CB and RW for studies published in languages other than Mandarin or Cantonese and JM, FW and YW for studies published in Mandarin or Cantonese).

Assessment of the methodological quality of studies was completed using the Cochrane Risk of Bias for Randomised Controlled Trials (24). The overall risk of bias was determined via the following domains: random allocation sequence, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias. Bias was then allocated to 'high', 'unclear' or 'low' for each of the

domains. If domains were all 'low' the study was considered low risk of bias overall. If studies had one or more 'unclear' domains but no 'high' domains, the study was considered an unclear risk of bias overall. If a study had one or more domains that were 'high' the overall study was considered a high risk of bias. All manuscripts were independently assessed by two reviewers for risk of bias. If reviewers disagreed on any domain of the bias tool, resolutions were made between two primary reviewers (RW, CB or JM and FW). If no resolution could be made, a blinded reviewer would make a third decision, with the binding decision formed by the domain with the majority of reviewer's decisions. This was in accordance with the Cochrane Handbook (25).

3.2.5 Statistical analysis

The main outcome measures were birthweight, birth length, macrosomia, LBW, SGA and LGA. Studies were pooled into intervention categories for analysis. Eight categories emerged from the resultant literature: Diet alone, physical activity (PA) alone, lifestyle (diet and PA), other, GDM diet, GDM lifestyle, GDM metformin and GDM 'other'. Studies categorised as 'other' did not have interventions that satisfied the other categories listed. Where studies reported results of subgroups but not overall results (such as by maternal BMI category), the groups were combined using the Cochrane formula for combining groups (25). For studies with more than one arm, only the most intensive arm was chosen for the meta-analysis as not to duplicate representation from control groups (26-31). However, an exception to this rule was a study conducted by Ainuddin et al compared metformin alone, metformin and insulin and insulin alone (30). For this study, only the metformin and insulin alone arms were included in the meta-analysis to ensure appropriate comparison to other studies included. Further, comparator groups were defined as standard care following antenatal care guidelines as appropriate. Studies that reported standard error of the mean (SEM) were

converted to standard deviation (SD) (32-38). Studies were excluded from the meta-analysis for the following reasons: (i) No true control (n=6) (33-35, 39-41), (ii) inadequate statistical reporting (42, 43), (iii) studies did not have standard criteria for LGA (26, 44), SGA (26) or macrosomia (45) (iv) studies that were too heterogeneous to compare (Other and GDM Other category) (36, 46-49) and (v) data were reported as mean \pm SEM but when converted to SD data were biologically implausible (32).

Actual mean difference meta-analyses were conducted on birthweight and birth length to enable ease of interpretation (50). Risk ratio meta-analyses were conducted for dichotomous data which includes the prevalence of LGA, SGA, macrosomia and LBW. Random effects meta-analyses were conducted in all instances. The I^2 statistic was used as an assessment of heterogeneity, with an I^2 statistic of >50% regarded as substantial heterogeneity (25). Funnel plots were used to visually analyse if large studies were influencing the results of the meta-analyses. Sensitivity analyses were conducted removing one study at a time, to assess the bias of one study. Meta-regression used 'high' risk of bias as a covariate to explain heterogeneity and explore the relationship with effect size of studies with a 'high' risk of bias. Statistical analyses were conducted using Stata/SE 13.1. P-values <0.05 were considered statistically significant.

3.3 Results

Of the 20,578 records screened, 77 studies were included in this review (Figure 3.1). Information regarding the intervention and demographic information are available in Supplementary Tables 2-6 (Available upon request). Briefly, all interventions included singleton pregnancies with mean maternal age ranging from 24-36 years, baseline BMI ranging from 20.2-38.6 and percentage of preterm births ranging from 0.8-19%. Further, the

included studies represent results from 19, 806 infants from 20 countries including: America, Australia, New Zealand, Brazil, Canada, China, Denmark, Finland, Iran, Ireland, Italy, Germany, Spain, United Kingdom, Pakistan, Norway, Belgium, Turkey, Sweden and The Netherlands.

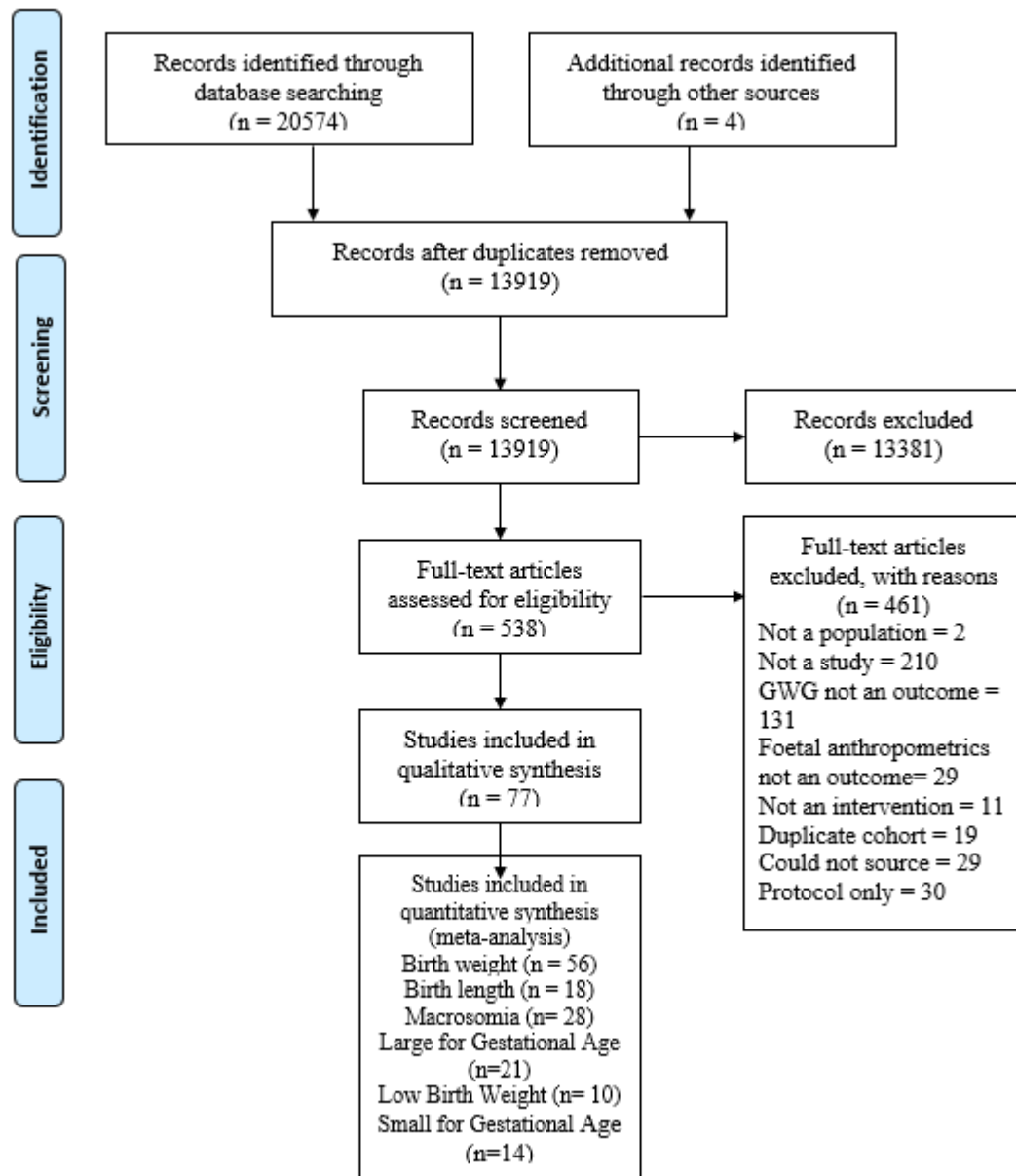


Figure 3.1: PRISMA diagram of included studies

Interventions were categorised into the following groups; Diet (n=14)(29, 35, 37, 39, 40, 45, 51-58), PA (n=18)(32, 33, 44, 59-74), lifestyle (diet and PA) (n=21) (26-28, 31, 43, 74-89), diet

alone for women with GDM (n=6)(33, 34, 38, 42, 90-92), metformin compared to standard care of insulin for women with GDM (n=5)(30, 93-96), metformin compared to glyburide for women with GDM (n=1)(41), lifestyle for women with GDM (n=5)(67, 97-101), PA for women with GDM (n=1)(102), 'other' in women without GDM (n=5)(36, 46-49) and 'other' for women with GDM (n=1)(103). Study characteristics and methodological quality have been reported previously (22). For individual results reported in this review, see tables 3.1-5.

3.3.1 Overall

Regardless of intervention type, studies designed to reduce excessive GWG reduced offspring birthweight by 71g (WMD: -70.67 95% CI: -101.90, -39.43, $p<0.001$, $I^2=67.2\%$) (n=56 studies, Figure 3.2) and reduced the risk of macrosomia by 16% (RR: 0.84 95% CI 0.73 - 0.98, $p=0.026$, $I^2=46.9\%$) (n=28 studies, Figure 3.3). Studies that reported LGA incidence (n=20 studies, Figure 3.4) reduced the prevalence of LGA by 19% (RR: 0.81, 95% CI: 0.68-0.96, $p=0.015$, $I^2=45.4\%$). No intervention type significantly influenced the birth length (Figure 3.5), risk of LBW (Figure 3.6) or SGA (Figure 3.7).

3.4.2 Interventions in women without GDM

Diet interventions reduced infant birthweight by 99g (WMD: -98.8 95% CI: -178.85 to -18.76, $p=0.016$, $I^2=79.3\%$). Lifestyle and PA interventions did not result in a difference in birthweight (Figure 3.2). Physical activity interventions reduced the risk of macrosomia by 59% (RR: 0.41, 95% CI: 0.25 – 0.68, $p<0.001$, $I^2=16.3\%$, Figure 3.3). No significant differences in risk of macrosomia were found for any other intervention type. The risk of LGA was reduced 65% by diet interventions (RR: 0.35, 95% CI: 0.17-0.72, $p=0.004$, $I^2=6.6\%$, Figure

3.5). No other intervention type had significant results for birthweight, birth length, macrosomia, LBW, SGA and LGA.

3.3.3 Interventions in women with GDM

Diet and lifestyle interventions in women with GDM decreased infant birthweight by 211g and 296g, respectively (WMD: -210.74, 95% CI: -374.77 to -46.71, $p=0.012$, $I^2=58.87\%$ and WMD: -295.93 95% CI: -501.76 to -91.10, $p=0.005$, $I^2=73.6\%$, respectively). Furthermore, interventions that used metformin did not significantly reduce or increase birth weight compared to insulin (Figure 3.2). No other intervention type had significant results for birthweight, birth length, macrosomia, LBW, SGA and LGA.

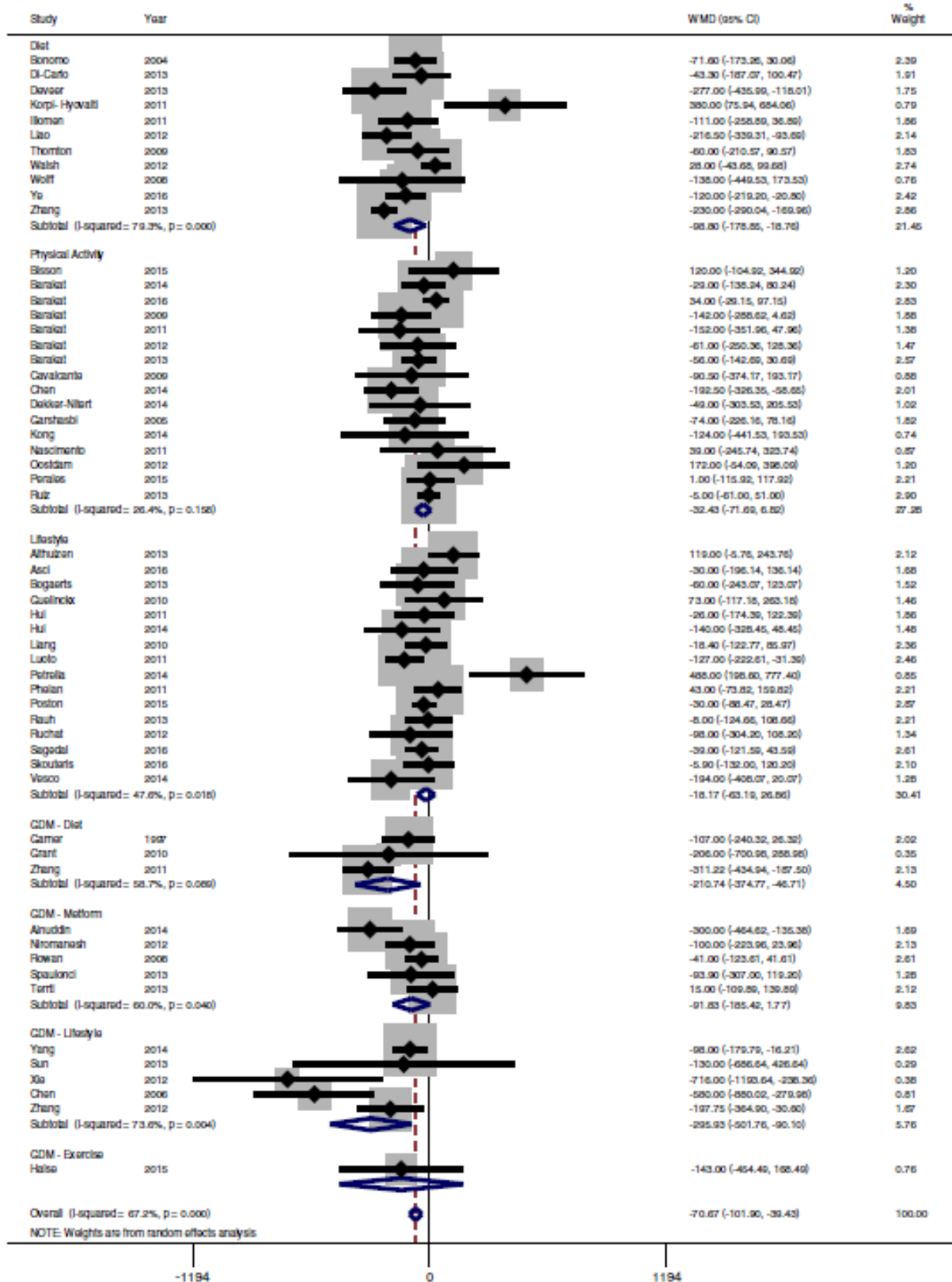


Figure 3.2 Infant birthweight weighted mean difference meta-analysis of randomized controlled trials designed to reduce excessive gestational weight gain

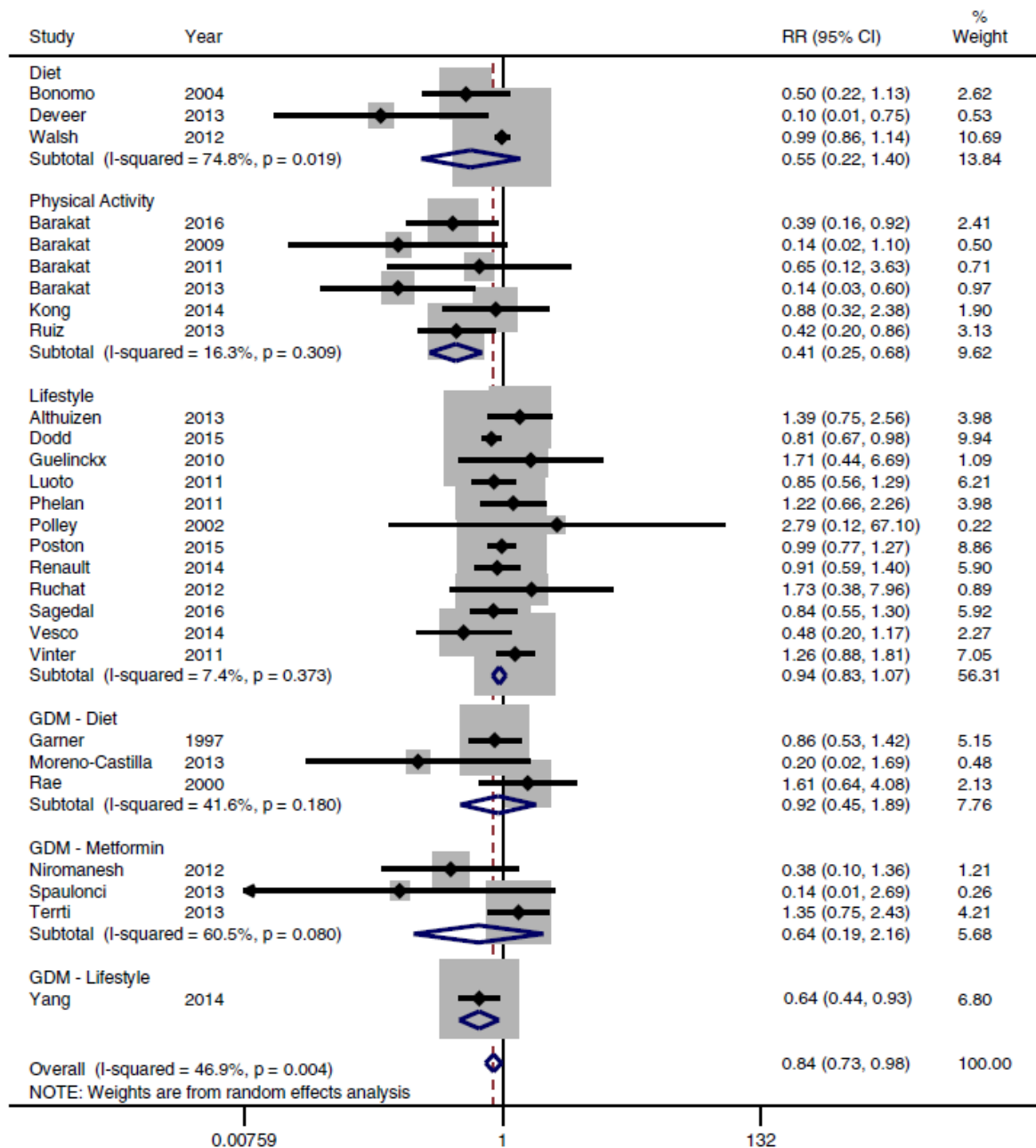


Figure 3.3 Macrosomia relative risk meta-analysis of randomized controlled trials designed to reduce excessive gestational weight gain

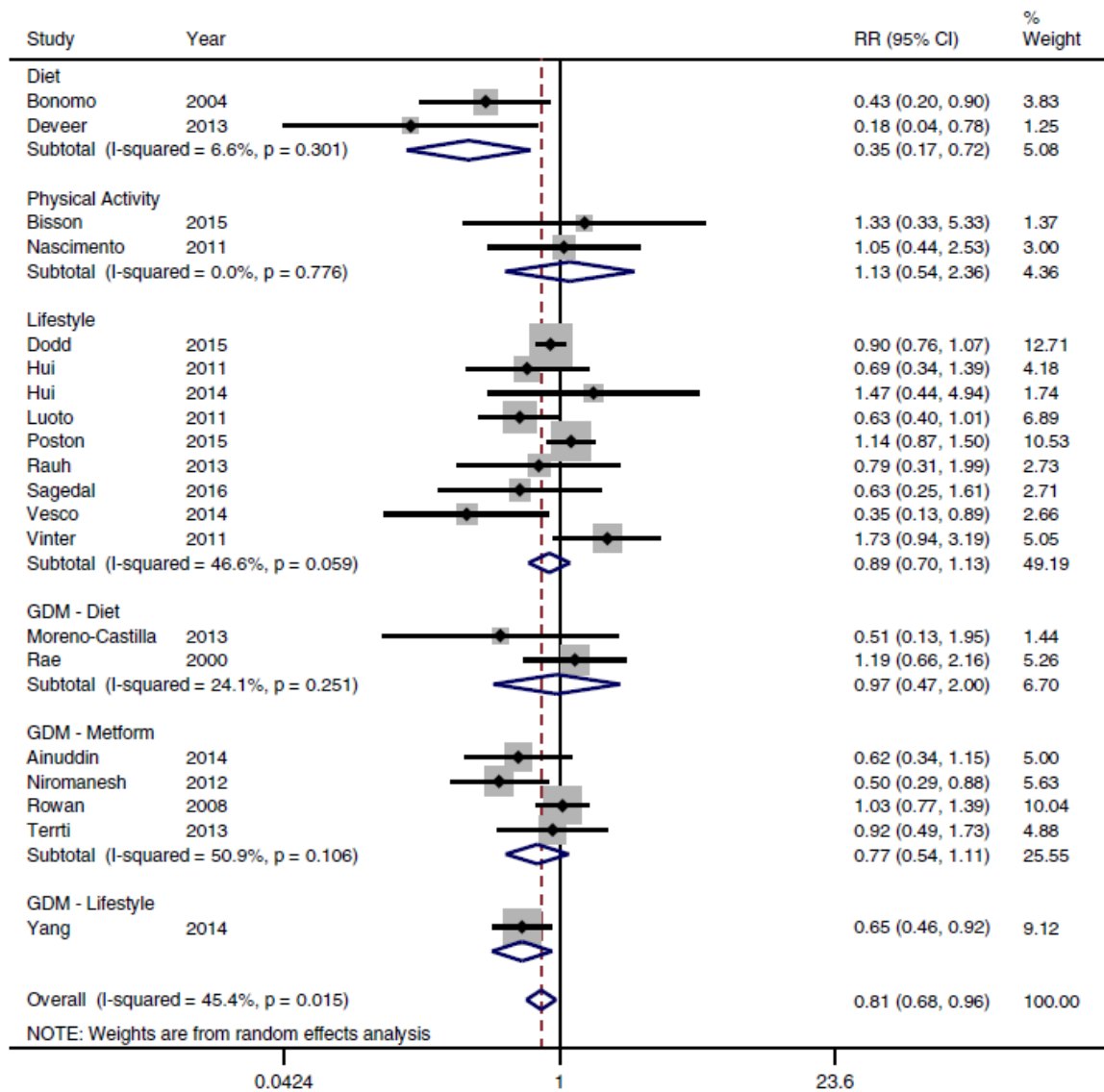


Figure 3.4 Large for gestational age relative risk meta-analysis of randomized controlled trials designed to reduce excessive gestational weight gain

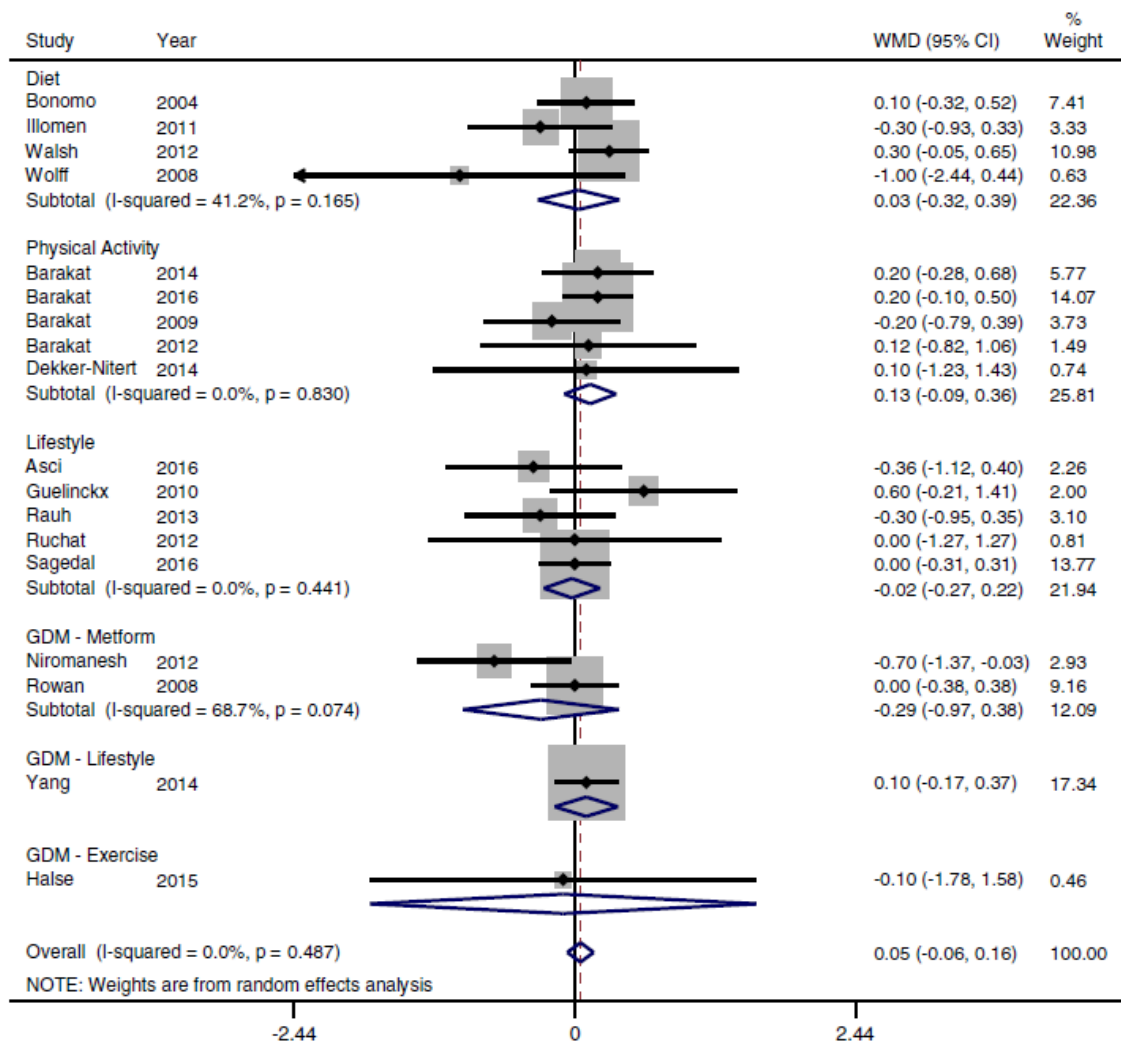


Figure 3.5 Infant birth length weighted mean difference meta-analysis of randomized controlled trials designed to reduce excessive gestational weight gain

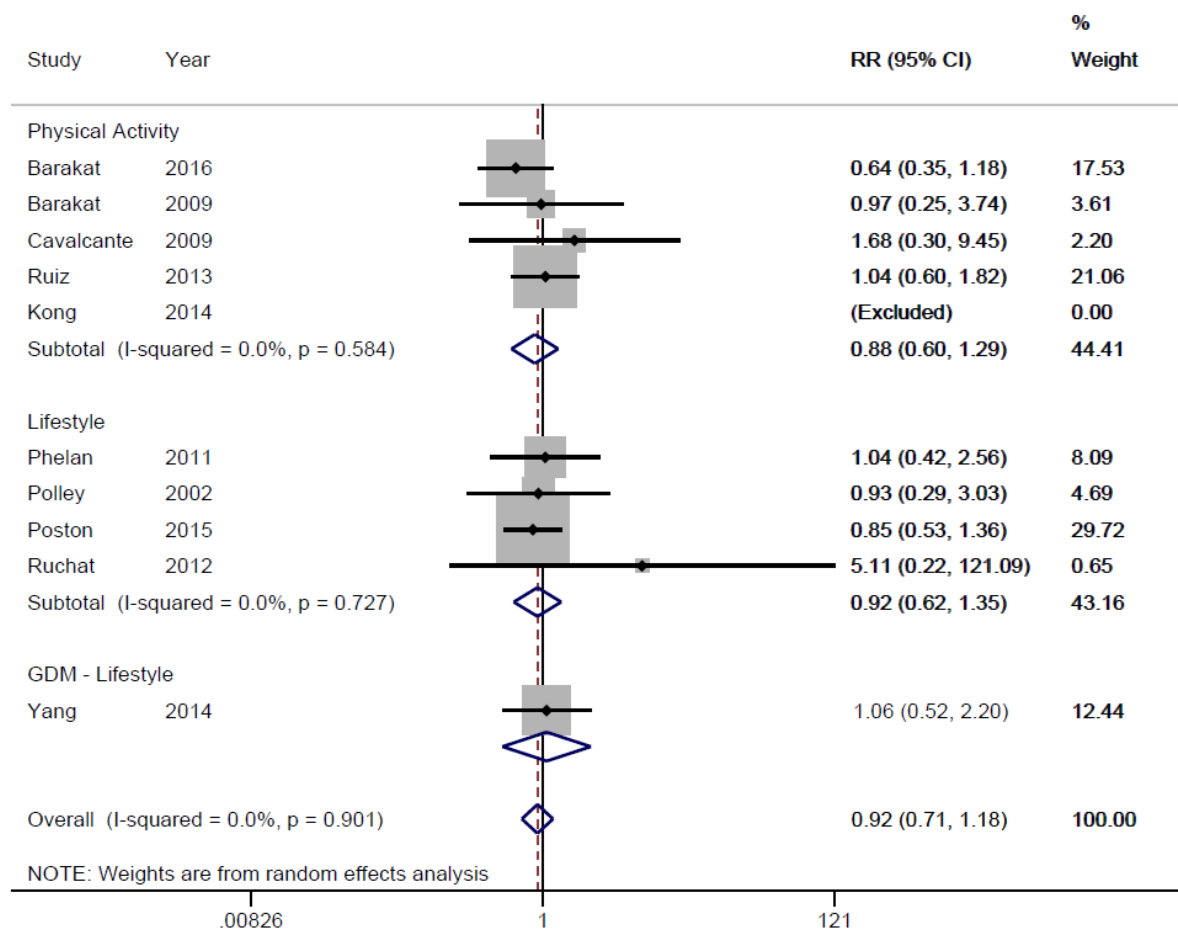


Figure 3.6 Low birth weight risk ratio meta-analysis of randomized controlled trials designed to reduce excessive gestational weight gain

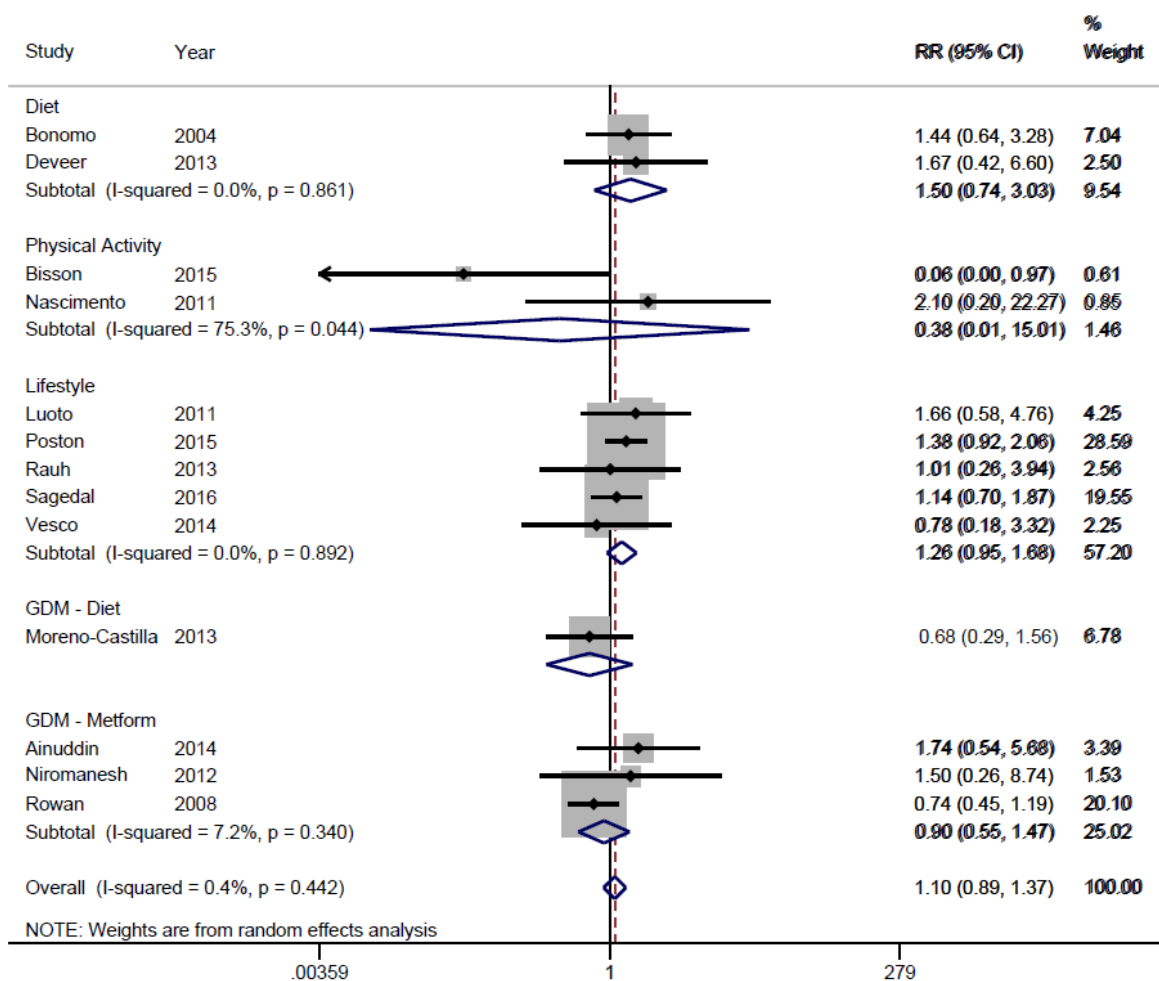


Figure 3.7 Small for gestational age risk ratio meta-analysis of randomized controlled trials designed to reduce excessive gestational weight gain

3.3.4 Risk of bias

Overall risk of bias ratings are available in Tables 1-5. Twenty-one studies received an overall ‘high risk’ of bias. Of the studies that received a ‘high risk’ of bias half did not clearly state the blinding protocol of participants or personnel. Furthermore, almost half did not adequately explain the randomisation procedure (n=9) or method of allocation concealment (n=8). Fifty-five studies received an overall ‘unclear risk’ of bias. Of the studies that received an overall ‘unclear risk’, n=44 did not state the blinding of personnel and n=43 did not state the blinding of participants. Regardless of the overall risk of bias, n=52 studies received an

'unclear' for selective outcome reporting due to an inability to check reported outcomes with planned outcomes due to studies not having a published protocol. Visual, subjective assessment of funnel plots suggest a low to medium level of publication bias (Available on request).

3.3.5 Sensitivity analyses

When single studies were removed to examine sensitivity of estimates, the WMD and RR did not alter considerably, indicating that no single study introduced a high degree of bias.

3.3.6 Meta-regression quality assessment

'High risk' of bias used a covariate had a significant negative effect on the birthweight analysis ($b = -106.82$, 95% CI: -171.71 , -41.94 , $p = 0.002$). No other meta-analysis effect size was significantly impacted by risk of bias.

3.4 Discussion

This review found that interventions designed to prevent excessive GWG during pregnancy had a significant impact on infant anthropometric outcomes including birthweight, macrosomia and LGA. In women without GDM, diet interventions were effective in reducing birthweight, while physical activity interventions reduced the risk of macrosomia. In women with GDM, both diet and 'lifestyle' interventions reduced offspring birthweight.

Results indicate that interventions delivered to the mother during the antenatal period can reduce birthweight and the risk of macrosomia and LGA. Previous research has suggested that a reduction of only 1-2kg during pregnancy is not enough to reduce adverse pregnancy outcomes, especially in the overweight and obese population, and hence interventions are not worthwhile (104). However, this theory is not supported by the findings of this systematic review. The primary outcomes of this review showed that interventions designed

to reduce GWG, were modestly successful, but only reduced GWG by 1-2kg on average (22), which is consistent with previous systematic reviews (16, 17, 21). In juxtaposition, the infant anthropometric results of this review are contrary to some previous reviews, which suggest that there was no significant difference between infant birth weight and risk of macrosomia, when intervention and control groups were compared (15, 17). The current review builds on the previous review as it has a more diverse sample and is tightly controlled for bias. Furthermore, results suggest that regardless of the IOM classifications of excessive GWG, interventions can reduce the risk of adverse infant anthropometric outcomes associated with excessive GWG.

Maternal diet has been shown to influence infant body composition (105). Multiple methods of dietary interventions that lead to macronutrient distribution manipulation were included in this review. The success of diet interventions observed in this review are supported by findings from animal and human studies which suggested that manipulating the macronutrient distribution to provide a low protein diet could increase fat deposition (106), predominantly centrally deposited (107), which in turn can also affect an infant's body composition (105, 108). More specifically, maternal low protein and low protein: carbohydrate ratio diets are associated with abdominal fat deposition (105). Further, maternal high polyunsaturated fat diets are associated with healthful upper thigh fat deposition (105). Therefore, the results of this review support existing literature and suggest offspring of women who are at high risk of excessive GWG may benefit from maternal dietary counselling in pregnancy.

The influence of interventions on infant anthropometric outcomes in women with GDM was the most profound. Women with GDM are three times as likely to have a high birthweight

infant compared to normoglycaemic mothers, due to increased insulin resistance in the mother (109). The modified Penderson's Hypothesis purports that the size of the infant is not directly fuel mediated, but indirectly through foetal hyperinsulinemia response which increases fat deposition (110). This hypothesis suggests that maternal glycaemic control is imperative to the health of the foetus and therefore the decreased risk of macrosomia and LGA may be partially explained by improved glycaemic control in the intervention groups compared to controls. The results of this study highlight the importance of maternal glycaemic and GWG control in GDM for the health of both mother and child, supporting currently primary care guidelines. Furthermore, interventions that reduce infant birthweight and risk of macrosomia and LGA, without increasing adverse outcomes such as SGA and LBW may have long term positive outcomes for the infants. Infants born macrosomic are more likely need a caesarean section delivery, suffer from birth trauma and have an increased risk of severe neonatal morbidity (111).

The birthweight meta-analyses had two significant outliers (54, 74). Both of these outliers had larger infants in the intervention group compared to the control group. One of the studies had 7kg higher mean baseline maternal weight than the intervention and there was no significant difference in GWG between the control and the intervention (54). These factors may have contributed to the increased birthweight in the intervention group. The other study had 30% of the infants in the control group born pre-term, whereas no infant in the intervention was born pre-term (74). This does not seem to be accounted for in the statistical analysis of infant birthweight. These factors need to be considered when interpreting the results of the birthweight meta-analysis as the result may be slightly attenuated due to these studies.

3.4.1 Strengths and limitations

A strength and novel aspect of this systematic review was the international sample of studies included. This is the first systematic review considering the infant anthropometrics of studies designed to prevent GWG that has included studies from China, largely inaccessible to those outside of China. The Chinese population contribute almost 20% of the world's population (112). Furthermore, globalisation is increasing and therefore, healthcare settings and recommendations need to be applicable to a wider variety of ethnicities. A limitation of this review was the inclusion of only a small number of studies that addressed the outcomes SGA and LBW. For future studies considering the role of intervention in preventing or reducing GWG, it is recommended to report infant outcomes such as SGA and LBW. Further, the majority of studies defined macrosomia to be >4000g. However, it has been suggested that a cut off of >4500g may be more indicative of complications in some ethnic groups (113). Therefore, future studies should endeavour to use appropriate cut offs for the ethnic population represented (114). Another limitation of this review is that n=28 studies included in this review were considered to be 'high' risk of bias. To ensure these studies were not significantly influencing results a meta-regression was conducted with 'high-risk' as a covariate. This showed that birthweight, but no other outcome was significantly influenced. Therefore, the weighted mean difference of birthweight should be interpreted with caution. However, this highlights that research in this area need to improve reporting clarity and transparency. Not including studies with a high risk of bias would have significantly reduced the translatability of results to a global sample, as studies published in languages other an English had a higher prevalence of high risk of bias. Further, the meta-analyses show high statistical heterogeneity. However, steps were taken to account or examine the effects of this issue e.g. use of random effects model and conducting sensitivity

analyses. It is recognised by the authors of this review that to blind participants in a diet, exercise or lifestyle intervention is extremely difficult. However, future studies in this area should clearly report the blinding procedure of both participants and personnel. As with any systematic review, the results of this review contain the available evidence and therefore is limited by the selection bias of the studies included.

3.5 Conclusion

Interventions designed to reduce excessive GWG produce a small reduction in infant birthweight and risk of macrosomia and LGA, without influencing birth length or risk of adverse outcomes such as LBW and SGA. Regardless of the intervention type (diet, physical activity or lifestyle (diet + physical activity)), these interventions have the potential to significantly reduce the life-long consequences of high birthweight in offspring born to women at high risk of excessive GWG and GDM. Interventions designed to reduce excessive GWG are confirmed to be an important strategy available to improve the health of the next generation.

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Table 3.1: Infant anthropometric outcomes in studies with a dietary intervention								
First author	Setting and Date	Birthweight (g) (Mean (SD) unless otherwise specified)	Birth length (cm) (Mean (SD) unless otherwise specified)	Macrosomia (%) (>4000g)	Large for gestational age (%) (>90 th percentile)	Small for gestational age (%) (<10 th percentile)	Low birth weight (%) (<2500g)	Overall risk of bias
Bonomo ⁵¹	Milan, Italy 1997 –2002	3365 (436), 3436.6 (462) <i>p</i> =NS	50.2 (1.7), 50.1 (2.0) <i>p</i> =NS	5.3, 10.7, <i>p</i> =NS	6, 14 <i>p</i> =0.046	8.7, 6.0 <i>p</i> =NS	-	Unclear
Deveer ⁵²	Turkey Published 2013	3310 (342.4), 3587 (460.2) <i>p</i> =0.001	-	2, 20 <i>p</i> =0.004	4, 22 <i>p</i> =0.007	10, 6 <i>p</i> =0.461	-	High
Di Carlo ⁵³	Naples, Italy Jun 2010 – Jun 2011	BW: 3078.2 (372.3), 3121.5 (430) <i>p</i> =0.6	-	-	-	-	-	Unclear
Ilmonen ²⁹	Finland Apr 2002- Nov 2005	Diet+ probiotic 3489 (431), Diet+ placebo 3602 (439), Control 3600 (515) <i>p</i> =0.209	Diet+ probiotic 50.7(1.8), Diet+ placebo 51.3(1.7), Control 51.0(2.2) <i>p</i> =0.197	-	-	-	-	Unclear
Korpi-Hyovalti ⁵⁴	Finland Published 2012	BW: 3871 (567), 3491 (573) <i>p</i> =0.047	-	-	-	-	-	Unclear
Liao ⁵⁵	Wuzhou, China Mar 2010 – Mar 2012	BW: 3100.1 (304.74), 3216.6 (547.52) <i>p</i> =0.037	-	-	-	-	-	High

Markovic ³⁹	Camperdown, Australia Jan 2011 - Oct 2012	Low GI: 3450 (410) High fibre: 3430 (510) <i>p</i> =0.845	-	Low GI: 9.7, High fibre: 14.9, <i>p</i> =0.349	Low GI: 5.6, High fibre: 6.0 <i>p</i> =0.916	Low GI: 5.6, High fibre: 7.5 <i>p</i> =0.648	-	Unclear
Moses ³⁵	Australia Feb 2010 – Sep 2012	Healthy eating: 3443(485), Low GI: 3465(430) <i>p</i> =0.57	Healthy eating: 50.3(3.3), Low GI: 50.3 (1.7) <i>p</i> =0.96	Healthy eating: 13.9, Low GI: 10.5, <i>p</i> =0.25	-	-	-	Unclear
Rhodes ⁴⁰	Boston, USA Jan 2007 – Jun 2009	Low- GI: 3507 (412), Low-fat: 3133 (671) <i>p</i> =0.03	-	Low- GI: 8, Low-fat: 5 <i>p</i> =1.0	Low GI: 8, Low-fat 14 <i>p</i> =0.65	-	-	Unclear
Thornton ⁴⁵	New York, USA Jun 1998- May 2005	3526 (608.4), 3586 (560.8) <i>p</i> =0.4	-	(>4500g): 7.8, 3.4 <i>p</i> =0.153	-	-	-	Unclear
Walsh ⁵⁷	Dublin, Ireland Jan 2007- Jan 2011	4034 (510), 4006 (497) <i>p</i> =0.449	52.9 (2.7), 52.6 (2.1) <i>p</i> =0.189	51, 51 <i>p</i> =0.88	-	-	-	Unclear
Wolff ⁵⁸	Copenhagen, Denmark Published 2008	3575 (617), 3895 (485) <i>p</i> =NR	52(3), 53(2) <i>p</i> = NR	-	-	-	-	Unclear
Ye ⁵⁶	Guangzhou, China May 2012 – May 2013	3390 (240), 3510 (310) <i>p</i> =0.019	-	-	-	-	-	High
Zhang ³⁷	Ningbo, China Jan 2011 – Dec 2011	3326 (292), 3556 (369) <i>p</i> <0.05	-	-	-	-	-	High

Results presented: Intervention, control. Abbreviations: NR= Not reported, NS= Not significant, GI= Glycaemic index. ‘-’ = data not available. Superscript numbers indicate associated reference.

Table 3.2: Infant anthropometric outcomes in studies with a physical activity intervention								
First author	Setting and Date	Birthweight (g) (Mean (SD) unless otherwise specified)	Birth length (cm) (Mean (SD) unless otherwise specified)	Macrosom ia (%) (>4000g)	Large for gestational age (%) (>90 th percentile)	Small for gestation al age (%) (<10 th percentil e)	Low birth weight (%) (<2500g)	Risk of bias
Barakat 2013 ⁶²	Madrid, Spain Sep 2007 – Jan 2011	3201 (446), 3257 (496) $p=0.208$	-	1, 10 $p=0.002$	-	-	-	High
Barakat 2011 ⁶³	Madrid, Spain	3250 (493), 3402 (328) $p>0.05$	-	5, 10 $p>0.05$	-	-	-	Unclear
Barakat 2012 ⁵⁹	Madrid, Spain	3404 (465), 3465 (411) $p>0.05$	50.07 (2.4), 49.95 (1.9) $p>0.05$	-	-	-	-	Unclear
Barakat 2009 ⁶⁰	Madrid, Spain Jan 2000 - Mar 2002	3165 (411), 3307 (477) $p>0.1$	49.5 (1.8), 49.7 (1.8) $p>0.1$	1.4, 10 $p>0.1$	-	-	-	High
Barakat 2016 ⁶¹	Madrid, Spain Dec 2011- Jan 2015	3252 (438), 3218 (453) $p=0.29$	50.0 (2.2), 49.8 (2.1) $p=0.11$	1.8, 4.7 $p=0.03$	-	-	4.2, 6.5 $p=0.15$	Unclear
Barakat 2014 ⁶⁴	Madrid, Spain	3203 (461), 3232 (488) $p=0.56$	49.5 (2.07), 49.7 (2.06) $p=0.98$	-	-	-	-	High
Bisson ⁶⁵	Quebec, Canada Oct 2011 - Nov 2013	3575 (425), 3455 (368) $p=NR$	-	-	17, 13 $p=NR$	0, 8 $p=NR$	-	Unclear
Cavalcante ⁶⁶	Sao Paulo, Brazil Mar 2002 - Nov 2004	3222.2 (562.7), 3312.7 (656.1) $p=0.54$	-	-	-	-	10, 5 $p=0.54$	High

Chen ⁶⁷	Chendou, China	3172.1 (312.59), 3364.6 (368.07) <i>p</i> =NR	-	-	-	-	-	-	High
Clapp 2000 ³²	Ohio, United States	3660 (800), 3430 (900) <i>p</i> =0.05*	51.8 (1.4), 50.6 (1.5) <i>p</i> =0.05	-	-	-	-	-	Unclear
Clapp 2002 ³³	Ohio, United States	Lo-Hi** [†] : 3340 (357), Mod-Mod [†] : 3440 (392), Hi-Lo ‡: 3900 (350) <i>p</i> <0.0001	Lo-Hi: 51.1(1.5), Mod-Mod [†] : 51.2(1.5), Hi-Lo ‡: 52.6 (1.0) <i>p</i> =NR	-	-	-	-	-	Unclear
Dekker-Nikert ⁶⁸	Brisbane, Australia	3548(459), 3597(304) <i>p</i> =NR	50.6 (2.2), 50.5 (1.8) <i>p</i> =NR	-	-	-	-	-	High
Garshasbi ⁶⁹	Tehran, Iran Apr 2003- Jan 2004	3426(675), 3500(431) <i>p</i> =0.82	-	-	-	-	-	-	High
Kong ⁷⁰	Iowa, United States	<i>Overweight</i> : 3760 (440), 3590 (460), <i>p</i> =NR <i>Obese</i> : 3540(510), 3940 (480), <i>p</i> =NR	-	<i>Overweight</i> : 33, 11 <i>p</i> =NR <i>Obese</i> : 22, 50 <i>p</i> =NR	-	-	<i>Overweight</i> : 0, 0 <i>p</i> =NR <i>Obese</i> : 0, 0 <i>p</i> =NR	-	Unclear
Nascimento ⁷¹	Sao Paulo, Brazil Aug 2008 - Mar 2010	3267.4 (700.4), 3228.4(591.3) <i>p</i> =0.790	-	-	24.2, 24.2 <i>p</i> =1.0	6.1, 3.0 <i>p</i> =1.0	-	-	Unclear
Oostdam ⁴⁴	Amsterdam, Netherlands Jan 2007- Jan 2011	3524 (591), 3352(591) <i>p</i> =0.14	-	-	12.8, 1 <i>p</i> =NR [§]	-	-	-	Unclear
Perales ⁷²	Madrid, Spain	3347(307.04), 3346(307.04)	-	-	-	-	-	-	Unclear

	Oct 2009 - Jan 2013	$p=0.99$						
Ruiz ⁷³	Madrid, Spain Sep 2007 - Jan 2011	3234(453), 3239(433) $p=NR$	-	2.1, 5.0 $p=NR$	-	-	5.0, 4.8 $p=NR$	Unclear

Results presented: intervention, control. Abbreviations: NR= not reported; NS= not significant. Symbols: ‘-’= data not available; *Reported as mean \pm SEM; **Lo-Hi: 20 minutes 5 days a week through week 20, gradually increasing to 60 minutes 5 days a week by week 24 and maintaining that regimen until delivery; †Mod-Mod: 40 minutes 5 days a week from week 8 until delivery; ‡Hi-Lo: 60 minutes 5 days a week through week 20, gradually decreasing to 20 minutes 5 days a week by week 24 and maintaining that regimen until delivery; §reported >97th percentile. Superscript numbers indicate associated reference.

Table 3.3: Infant anthropometric outcomes in studies with a lifestyle intervention

First author	Setting and Date	Birthweight (g) (Mean (SD) unless otherwise specified)	Birth length (cm) (Mean (SD) unless otherwise specified)	Macrosomia (%) (>4000g)	Large for gestational age (%) (>90 th percentile)	Small for gestational age (%) (<10 th percentile)	Low birth weight (%) (<2500g)	Overall risk of bias
Althuizen ⁷⁵	Netherlands Feb 2005 – May 2006	3550 (466), 3431 (456) $p=NR$	-	19, 14 $p=NR$	-	-	-	High
Asci ⁷⁶	Istanbul, Turkey Jun 2011 – Jul 2012	3268 (380), 3298 (423) $p=0.76$	50.04 (1.78), 50.40 (1.90) $p=0.29$	-	-	-	-	Unclear
Bogaerts ³¹	Flanders, Belgium Mar 2008 – Apr 2011	Brochure: 3386(682), Lifestyle: 3444 (503), Control: 3504(583) $p=0.54$	-	-	-	-	-	Unclear
Dodd ⁷⁷	Adelaide, Australia Jun 2008 – Dec 2011	-	-	15, 19 $p=0.04$	19, 21 $p=0.24$	-	-	Unclear
Guelinckx ²⁷	Leuven, Belgium Mar 2006 – Jan 2008	Passive: 3585(398), Active: 3492(468), Control:	Passive 51.0(2.1), Active: 50.6(2.0), Control: 50.0(1.8)	Passive: 13.5 Active: 11.9 Control: 7.0 $p=0.312$	-	-	-	Unclear

		3419(425) <i>p</i> =0.106	<i>p</i> =0.182					
Hawkins ⁷⁸	Massachusetts, United States Apr 2010 – Aug 2011	3338.8(640.7), 3429.8(532.6) <i>p</i> = 0.64	-	-	-	-	-	Unclear
Hui 2012 ⁷⁹	Manitoba, Canada Jul 2004 – Feb 2010	3490(509), 3516 (530) <i>p</i> =0.73	-	-	11.8, 17.0 <i>p</i> =0.41	-	-	Unclear
Hui 2014 ⁸⁰	Manitoba, Canada May 2009 – Dec 2011	Healthy weight 3356 (474), 3633 (555) <i>p</i> =0.047 Overweight/ Obese 3665 (506), 3650 (481) <i>p</i> =0.26	-	-	Healthy weight 7, 11 <i>p</i> =0.902 Overweight/ Obese 15, 3 <i>p</i> = 0.13	-	-	Unclear
Liang ⁸¹	Bingzhou, China Jul 2005 – Nov 2008	3313.1(385.7), 3331.5 (393.7) <i>p</i> >0.05	-	-	-	-	-	High
Luoto ⁸²	Pirkanmaa, Finland Oct 2007 – Dec 2008	3313.1 (385.7), 3331.5 (393.7) <i>p</i> =0.035	-	17.2, 20.8 <i>p</i> =0.31	12.1, 19.7 <i>p</i> =0.043	4.7, 2.9 <i>p</i> =0.53	-	Unclear
Petrella ⁷⁴	Modena, Italy April – Oct 2011	3498 (342), 3010 (715) <i>p</i> =0.001	-	-	-	-	-	Unclear

Phelan ⁸³	Rhode Island, United States 2006 - 2008	Healthy weight 3367(459), 3271(467) <i>p</i> =NR Overweight/ Obese 3430(650), 3442(629) <i>p</i> =NR	-	Healthy weight 7, 3 <i>p</i> =NR Overweight/ Obese 17, 16 <i>p</i> =NR	-	-	Healthy weight 4, 3 <i>p</i> =NR Overweight/ Obese 6, 5 <i>p</i> =NR	Unclear
Polley ⁴³	Pittsburgh, USA	Health weight 3133, 3226.4 <i>p</i> =NR Overweight 3282.8, 3349.0 <i>p</i> =NR	-	Health weight 3, 0 <i>p</i> =NR Overweight 0, 0 <i>p</i> =NR	-	-	Health weight 13, 10 <i>p</i> =NR Overweight 4, 9 <i>p</i> =NR	Unclear
Poston ⁸⁴	United Kingdom	3420(580), 3450(580) <i>p</i> =0.37	-	14, 14 <i>p</i> =0.93	13, 11 <i>p</i> =0.35	7, 5 <i>p</i> =0.12	4, 5 <i>p</i> =0.93	Unclear
Rauh ⁸⁵	Munich, Germany Feb 2010 – Aug 2011	3406 (406), 3414 (445) <i>p</i> =0.890	51.4(2.4), 51.7(2.4) <i>p</i> =0.351	-	6.4, 8.9 <i>p</i> =0.495	3.8, 3.8 <i>p</i> =0.985	-	Unclear
Ruchat ²⁸	Ontario, Canada	Low*: 3559 (391), 3550(378) <i>p</i> =NR Mod†: 3452(453), Control‡: 3550(378) <i>p</i> =NR	Low*: 51.0 (2.0), Mod†: 51.1 (2.7), Control‡: 51.1 (2.5) <i>p</i> =NR	Low*: 9, Mod†: 12, Control ‡: 7 <i>p</i> =NR	-	-	Low*: 0, Mod†:4, Control‡: 0 <i>p</i> =NR	Unclear
Renault ²⁶	Copenhagen, Denmark Mar 2009 – Mar 2012	Median (IQR) PA+ D: 3605 (1945-5450),	-	PA+D: 22%, PA: 30%, Cont: 25% <i>p</i> =NS	PA+D: 6.9%, PA: 6.4%, Cont: 6.7% <i>p</i> =NS [#]	PA+D: 5.4%, PA: 3.2%, Cont: 1.5%	-	Unclear

		PA: 3695 (805-4910), Control: 3641(1223-5280)					$p=NS^{\S}$	
Sagedal ⁸⁶	Norway Sep 2009 - Feb 2013	3411(485), 3450(538) $p=0.361$	50.0 (2.1), 49.9 (2.7) $p=0.867$	11.8, 14.0 $p=0.451$	2.4, 3.7 $p=0.351$	10.5, 9.2 $p=0.679$	-	Low
Skouteris ⁸⁷	Melbourne, Australia Aug 2011 – Aug 2013	3517.56 (507.89), 3523.46 (531.35) $p =NR$	-	-	-	-	-	Unclear
Vesco ⁸⁸	Oregon and Washington, United States Oct 2009 - July 2011	3484 (583), 3678 (583) $p =NR$	-	11, 22 $p=NR$	9, 26 $p=NR$	5, 7 $p=NR$	-	High
Vinter ⁸⁹	Denmark, Oct 2007- 2010	Median (IQR) 3742 (3464- 4070), 3593 (3335-3930) $p=0.039$	-	32, 25.3 $p=0.07$	15.4, 11.7 $p=0.340$	-	-	Unclear

Results presented: intervention, control. Abbreviations: IQR= Interquartile range, NR= not reported, NS= Not significant, PA= Physical activity, D = Diet Symbols: *Low = low intensity physical activity + diet intervention; †Mod = moderate intensity physical activity +diet intervention; ‡Control= Dietary advice; ‘-’= data not available; #= 124% of relative birthweight and [§] = 76% or less of relative birthweight. Superscript numbers indicate associated reference.

Table 3.4: Infant anthropometric outcomes in studies in women with gestational diabetes mellitus

First author	Setting and Date	Birthweight (g)	Birth length (cm)	Macrosomia (%) (>4000g)	Large for gestational age (%) (>90 th percentile)	Small for gestational age (%) (<10 th percentile)	Low birth weight (%) (<2500g)	Overall risk of bias
Diet								
Garner ⁹⁰	Ottawa, Canada Sep 1991 – May 1994	3437 (575), 3544 (601) <i>p</i> =0.118	-	16.1, 18.7 <i>p</i> =0.666	-	-	-	Unclear
Grant ³⁸	Toronto, Canada Apr 2006 - Jan 2007	3124 (526), 3330 (984) <i>p</i> =NS	-	-	-	-	-	Unclear
Louie ³⁴	Camperdown, Australia	LGI: 3300 (686), HF: 3300 (671) <i>p</i> =0.619	LGI: 49.7(2.1), HF: 49.7 (2.0) <i>p</i> =0.995	LGI: 2.1 HF:6.7 <i>p</i> =0.286	LGI: 12.8 HF: 4.4 <i>p</i> =0.157	LGI: 10.6 HF: 8.9 <i>p</i> =0.787	-	Unclear
Moreno-Castilla ⁹¹	Catalonia, Spain Nov 2008 – Jul 2011	-	-	1.4, 6.7 <i>p</i> =0.21	4.1, 8 <i>p</i> =0.49	10.8, 16.0 <i>p</i> =0.47	-	Unclear
Rae ⁴²	Perth, Australia Feb 1992 – Jun 1995	3461 (NR), 3267 (731) <i>p</i> =0.105	-	16.7, 10.7 <i>p</i> =NR	28.8, 24.6 <i>p</i> =NR	-	-	Unclear
Zhang ⁹² 2011	Shandong, China Feb 2009 – Jul 2009	3279.5 (447.9), 3590.7(457.8) <i>p</i> <0.05	-	-	-	-	-	High
Metformin								

Ainuddin ³⁰	Karachi, Pakistan Dec 2008 – Dec 2010	M: 3400(400), M + I: 3300(500), I: 3700(500) , <i>M and M+I: p = 0.546,</i> <i>M + I and I: p=0.001</i> <i>M and I: p=0.002</i>	-	-	M: 23.3, M+I 28.1, I 37.3 M and M+ I <i>p=0.632</i> M and I <i>p=0.115</i> I and M+I <i>p=0.359</i>	M: 11.6, M+I: 15.6, I: 6.6 M and M+ I <i>p=0.432</i> M and I <i>p=0.273</i> I and M+I <i>p=0.138</i>	-	High	
Niromanesh ⁹³	Tehran, Iran Dec 2010 – Jan 2012	3300 (400), 3400 (400) <i>p=0.005</i>	50.4 (2.0), 51.1 (2.3) <i>p=0.033</i>	3.8, 10.0 <i>p=0.118</i>	17.5, 35.0 <i>p=0.12</i>	3.8, 2.5 <i>p=1</i>	-	Unclear	
Rowan ⁹⁴	Australia and New Zealand Oct 2002 – Nov 2006	3372 (572), 3413 (569) <i>p=0.33</i>	50.3 (2.8), 50.3 (2.4) <i>p=0.91</i>	-	19.3,18.6 <i>p=0.83</i>	7.2, 9.7 <i>p=0.21</i>	-	Unclear	
Silva ⁴¹	Brazil Jul 2008 – Oct 2009	G: 3463 (535.6) M: 3360 (509.5) <i>p=0.36</i>	-	G:15 M: 6.2 <i>p=0.24</i>	G: 22.5, M: 9.4 <i>p=0.14</i>	-	-	Unclear	
Spaulonci ⁹⁵	Sao Paulo, Brazil Nov 2007 – Jan 2010	3143.7 (446.6), 3237.6 (586.8) <i>p=0.390</i>	-	0, 6.5 <i>p=0.242</i>	-	-	-	Unclear	
Tertti ⁹⁶	Turku, Finland Jun 2006 – Dec 2010	3604 (488), 3589 (448) <i>p=NR</i>	-	20, 15 <i>p=0.38</i>	14.5, 15.9 <i>p=0.8</i>	-	-	Unclear	
Lifestyle									
Chen ¹⁰¹	Foshan, China Oct 2001 – Oct 2005	3210 (750), 3790 (690) <i>p<0.05</i>	-	-	-	-	-	High	

Sun ⁹⁷	Guangzhou, China May 2012 – Dec 2012	3220 (1320), 3350 (2160) <i>p</i> <0.05	-	-	-	-	-	High
Xie ⁹⁸	Wuzhou, China Oct 2006 – Oct 2010	3074 (770), 37920 (690) <i>p</i> =NR	-	-	-	-	-	High
Yang ⁹⁹	Tianjin, China Dec 2010 – Oct 2012	3371 (530), 3469 (570) <i>p</i> =0.021	50.1 (1.8), 50.2 (1.9) <i>p</i> =0.248	11.2, 17.5 <i>p</i> =0.019	-	-	4.1, 3.9 <i>p</i> =0.865	Unclear
Zhang ²⁰¹² ¹⁰⁰	Shenzhen, China Jul 2009 – Jan 2011	3403.3 (326.5), 3601.1 (409.9) <i>p</i> <0.05	-	-	-	-	-	High
Physical Activity								
Halse ¹⁰²	Perth, Australia	3176 (526), 3319 (478) <i>p</i> >0.05	49.8 (2.5), 49.9 (2.9) <i>p</i> >0.05	-	-	-	-	Unclear
Other								
Jie ¹⁰³	Guangdong, China Sep 2012 – Sep 2014	-	-	8, 27 <i>p</i> =0.000	-	-	-	High

Results presented: Intervention, control. M = Metformin, I= Insulin, G= Glyburide, LGI= Low Glycaemic Index, HF= High Fibre, NS= Not significant, NR= Not reported. Symbols: ‘-’= data not available. Superscript numbers indicate associated reference.

Table 3.5: Infant anthropometric outcomes in studies with an intervention categorised as ‘other’

First author	Setting and Date	Birthweight (g) (Mean (SD) unless otherwise specified)	Birth length (cm) (Mean (SD) unless otherwise specified)	Macrosomia (%) (>4000g)	Large for gestational age (%) (>90 th percentile)	Small for gestational age (%) (<10 th percentile)	Low birth weight (%) (<2500g)	Overall risk of bias
Brownfoot ⁴⁷	Melbourne, Australia Jan 2010 – Nov 2012	3404.7 (561.3), 3364.9 (623.8) <i>p</i> =0.36	-	-	7.3, 7.1 <i>p</i> =0.97	9.2, 12.6 <i>p</i> =0.16	-	Unclear
Herring ⁴⁹	Philadelphia, United States 2013 – 2014	3147, 3361 <i>p</i> =NR	-	-	8, 7 <i>p</i> =1.0	4, 0 <i>p</i> =0.48	-	Unclear
Jeffries ⁴⁸	Melbourne, Australia Jul 2007 – May 2008	3416 (452.4), 3421(504.7) <i>p</i> =0.95	-	-	6.5, 9.9 <i>p</i> =0.47	7.3, 10.8 <i>p</i> =0.37	-	Unclear
Quinlivan ³⁶	Melbourne, Australia	3500 (556), 3400 (781) <i>p</i> =0.162	-	-	-	-	-	Unclear
Syngelaki ⁴⁶	London, United Kingdom Oct 2010 – Jun 2013	-	-	-	16.8, 15.4 <i>p</i> =0.79	-	-	Unclear

Results presented: Intervention, control. Abbreviations: NS = Not Significant, NR = Not reported. ‘-’= data not available. Superscript numbers indicate associated reference.

Part B: What is the relationship between sleep and outcomes during pregnancy?

CHAPTER 4

Monounsaturated fat intake is associated with improved sleep quality in pregnancy

The following study has been published and is reproduced with permission from Elsevier and is available in [Appendix 4](#): Bennett C.J., Cain S.W. and Blumfield M.L. Monounsaturated fat intake is associated with improved sleep quality in pregnancy. *Midwifery*. 2019; 78: 64-70. DOI: <https://doi.org/10.1016/j.midw.2019.07.019>

Preamble

Given that no study in the systematic reviews presented in this thesis (Chapters 2 and 3) considered the role of sleep as an intervention strategy (1), this provides strong rationale that investigation into whether sleep during pregnancy may influence outcomes such as weight gain and glucose tolerance. The following three chapters investigate the relationship between sleep, diet, pregnancy, birth and postpartum outcomes from an firstly from an observational approach and then from an exploratory feasibility interventional approach.

4.1 Introduction

Maternal dietary intake is important to support a healthy pregnancy (2). It is well established that broad malnutrition in pregnancy increases the risk of pregnancy complications including intrauterine growth restriction (3), SGA and preterm birth (4).

Whereas, overnutrition during pregnancy, as **indicated by** excessive gestational weight gain and obesity, increases the risk of pre-eclampsia, caesarean section, gestational diabetes and stillbirth (4, 5). A maternal diet during pregnancy, characterised by low protein and high carbohydrate intake, can lead to babies being born with greater abdominal adiposity (6) and

increased blood pressure during early childhood (7). The quality of each macronutrient can also make a difference. Low glycaemic index diets in pregnancy have been shown to reduce the risk of large for gestational age infants (8). High polyunsaturated fat and low saturated fat intakes during pregnancy are associated with babies with higher levels of protective mid-thigh adiposity (6). While optimal infant body composition remains unclear, birthweight has a J-shaped relationship with diabetes and cardiovascular disease (9), u-shaped relationship with obesity in boys and a simple positive relationship in girls (10). This suggests that macronutrient intake during pregnancy and consequently foetal growth may influence offspring risk of chronic disease in later life (11). Supporting optimal macronutrient intake during pregnancy is a public health priority as supports a healthy pregnancy but also has positive intergenerational effects (12).

In non-pregnant adults, short sleep length and poor quality sleep are associated with an increase in carbohydrate (13) and fat (14) consumption. Mechanisms for the relationship, as shown in laboratory studies, suggest that decreased sleep time causes an increase in activity of the orexigenic neurons which produce hormones such as ghrelin and a decrease of satiety hormones such as leptin (15), decreasing dietary inhibition (16). While the relationship between sleep and dietary intake has been studied in women of childbearing age (14, 17-19), there is limited research in pregnancy.

Sleep duration and sleep quality are both altered during pregnancy, due to many physiological and hormonal changes (20). Majority of pregnant women will experience some form of sleep disturbance, regardless of whether they experienced such symptoms pre-conception (21, 22). Both reduced and disturbed sleep during pregnancy have been associated with an increased risk of gestational diabetes (23, 24), longer labour (25), birth

complications (26) and poor mental health in the antenatal and post-natal period (27). However, the relationship between sleep and macronutrient intake in pregnancy is less clear. Two preliminary studies that explored this relationship have produced mixed results in samples not generalisable to the Australian population (28, 29). Chang et al. investigated the relationship between sleep and fat intake in a group of overweight or obese pregnant women of largely African American descent and low socioeconomic status (28). Results showed sleep disturbance was positively related to fat intake, but only in the second trimester. However, this study only looked at dietary fat intake without consideration for the other macronutrients. Alternatively, results from a recent pregnancy cohort study conducted in Singapore – Growing up in Singapore Towards healthy Outcomes (GUSTO) found that sleep quality was positively associated with diet quality at 26-28 weeks gestation (n=497) (29). However, in this study only dietary patterns were reported, thus making it difficult to determine actual macronutrient intakes. Due to these methodological and demographic differences, additional research is required to fully elucidate whether a relationship exists between macronutrient intake and sleeping behaviour during pregnancy. Given the strong relationships that have been found between sleep and macronutrient intake in non-pregnant populations, coupled with the importance of maternal macronutrient intake during pregnancy, the aim of this study was to investigate the relationships between sleeping behaviour and macronutrient intake in pregnant women. This study tested the *a priori* hypothesis that pregnant women with sleep disturbance will have unfavourable macronutrient distribution compared to those without sleep disturbance.

4.2 Methods

4.2.1 Sample

This study uses cross-sectional data collected as part of the Australian Longitudinal Study on Women's Health (ALSWH). The ALSWH is an Australian population-based survey that recruited women from three age groups in 1996; 18-23 years (1973-78 cohort; n=14,247), 45-50 years (1946-51 cohort; n=13,715) and 70-75 years (1921-26 cohort; n=12,432) (30, 31). Women were recruited from the national health care system database (Medicare), with oversampling of women from rural and remote areas to allow comparisons across areas (30). Since 1996, the ALSWH have issued seven surveys to the 1973-1978 cohort. The present study retrieved data from pregnant women in the 1973-1978 cohort survey 5 conducted in 2009 (n=605, mean age: 33.5 ± 1.4). For this analysis, inclusion criteria included being pregnant at the time of survey 5. Women were excluded if they satisfied the following criteria: i) sleep data available were biologically implausible (<3 hours and >12 hours; n=114) and ii) energy intake was biologically implausible (<4500kJ and >20,000kJ; n=54)(32). Therefore, a total of 437 pregnant women were included in the analysis. This survey was selected as it included women of childbearing age and the most comprehensive sleep and dietary information of a large Australian population-based cohort. Ethical approval for the study was obtained from the Human Research Ethics Committee for the University of Newcastle and the University of Queensland's Medical Research Ethics Committee. Further details of the ALSWH have been published elsewhere (30, 31, 33).

4.2.3 Data collection

The Dietary Questionnaire for Epidemiological Studies version 2 (DQESv2) was used to collect dietary data (34) in the 1973-1978, cohort survey 5. The DQESv2 is a 74-item food

frequency questionnaire, that reports on the previous 12 months of intake and has been validated against a weighed food records in a cohort of young Australian women (35). The DQESv2 collects frequency of consumption through the following options: never, <1 per month, 1-3 times per month, once per week, twice per week, 3-4 times per week, 5-6 times per week, once per day, twice per day, ≥ 3 times per day. Serving size is estimated through standard serves (ex. '1 slice of bread') but also through pictorial representation of vegetables and meat dishes. Nutrient composition was then calculated using Australian nutrient composition data from NUTTAB95 (36). Glycaemic index and glycaemic load were derived using international tables (37).

Sleep data were obtained via self-report. Sleep duration was reported on both a work day and non-work day with the question, "How much time did you spend sleeping on each of these days?". Respondents could self-report the number of hours and minutes for each type of day. Additional sleeping behaviours were examined with the questions: (1) How often during the last week did you feel "My sleep was restless" on a frequency scale: rarely or none of the time (<1 day), some or little of the time (1-2 days), occasionally or moderate amount of the time (3-4 days), or most or all of the time (5-7 days); (2) In the past month, "Have you had difficulty falling asleep?", yes or no; (3) In the last 12 months have you had any of the following, "Severe tiredness" or "Difficulty sleeping" on a frequency scale: never, rarely, sometimes or often. Self-reported sleep questions such as those listed above have been shown to have good internal consistency (38) and reliability (39).

The ALSWH survey also included a range of demographic characteristics (e.g. age, education, income, marital status, area of residence), health behaviours (e.g. smoking status, physical activity) and psychosocial measures (e.g. self-rated health status using items from the Short-

Form 36 Health Survey and depression symptoms using the Centre for Epidemiological Studies 10 item questionnaire (30,31). Pre-pregnancy body mass index (BMI) was calculated using self-reported pre-pregnancy height and weight ($BMI = \text{weight (kg)} / \text{height (m)}^2$) and classified using the World Health Organisation categories (40).

4.2.3 Statistical analysis

Main outcome measures included energy intake (kJ), percentage energy (%E) of carbohydrate, %E protein, %E total fat, %E saturated fat, %E monounsaturated fat, %E polyunsaturated fat, %E fibre, %E sugars, protein to carbohydrate ratio (kJ:kJ ratio), glycaemic index and glycaemic load. Total carbohydrate was defined as fructose, glucose, sucrose, lactose, maltose, galactose, maltotriose, starch, glycogen, oligosaccharides, maltodextrin and dextrins), excluding sugar alcohols (41). Sugars were defined as fructose, glucose, sucrose, maltose, lactose and galactose (41).

Sleeping behaviour pattern was the predictor variable. Latent class analysis (LCA) was chosen to derive mutually exclusive groups within the sleep behaviour data. All sleep variables listed above were imputed in the LCA and modelled to fit 2-4 classes. The Lo-Mendell-Rubin likelihood ratio test was used to determine the number of classes and women were classified into mutually exclusive classes according to their highest predicted probability of class membership (42). Multiple imputation methods were used to estimate values of missing sleep data for (i) restless sleep in the last week (n=3); (ii) difficulty falling asleep in the past month (n=1); severe tiredness in the last 12 months (n=6); and (iv) difficulty sleeping in the last 12 months (n=4). Ten iterations were used to produce 10 imputed datasets for regression analyses, where parameter estimates were summarised.

Variables used in the analyses were tested for normality. Comparisons were performed using the Kruskal-Wallis test for continuous data and the chi-square statistic for categorical data. Data were log transformed for regression analysis. The relationships between sleeping behaviour patterns and dietary intake in pregnant women were analysed in a series of linear regression models: (1) examining the associations of sleeping behaviour patterns and diet alone (crude model); (2) adjusted for area of residence, depression symptoms, difficulty managing on income, education level and parity; (3) further adjusted for continuous pre-pregnancy body mass index. Covariates were selected for linear regression if they were statistically correlated to the outcome variable or have clinical relevance for inclusion. Other potential confounders (marital status, trimester and self-rated health) were excluded from analyses because they produced a change-in-estimate of <10% and thus did not meaningfully influence the estimates (43). Latent Class 1 was denoted as the reference category for LCA models. Statistical analyses were performed using Intercooled Stata 14.0 (Stata) and Mplus version 7.3 to fit the latent class models. *P* values <0.05 were considered statistically significant.

4.3 Results

The LCA identified three sleeping behaviour patterns (Table 5.1). Latent Class 1 (LC1) was categorised by sleeping on average 7.6 hours (457 ± 41 minutes) on a weekday and 8.2 hours (488 ± 44 minutes) on a non-weekday, with little to no adverse sleep associated symptoms. Latent Class 2 (LC2) was categorised by sleeping 8.3 hours (499 ± 46 minutes) on a weekday and 8.4 hours (530 ± 49 minutes) on a non-weekday. A large proportion LC2 participant's experienced adverse sleep associated symptoms such as severe tiredness (64.8%), difficulty sleeping (40.4%), restless sleep (50.2%) and difficulty falling asleep

(41.3%). Latent Class 3 (LC3) was categorised by sleeping on average 6.5 hours (390 ± 40 minutes) on a weekday and 6.9 hours (415 ± 46 minutes) on a non-weekday. The majority LC3 participants experienced sleep associated symptoms such as severe tiredness (60.8%), difficulty sleeping (53.0%), restless sleep (75.8%) and difficulty falling asleep (55.2%).

Demographic and characteristics of the sample are presented in Table 4.1. Women in LC2 and LC3 were more likely to report lower self-rated health and higher depressive symptoms compared to women in LC1 (LC2 4.1% and LC3 4.1% vs LC1 0%, $p=0.03$; LC2 18.8% and LC3 27.8% vs LC1 4.2%, $p<0.001$). Women in LC3 were more likely to report difficulty managing on income compared to LC1 and LC2 (LC3 28.3% vs LC1 43.3% and LC2 30.4%, $p=0.033$).

Women in LC3 had a higher prevalence of living in rural areas compared to LC1 (LC3 9.3% vs LC1 1.2%, $p=0.023$). Pregnant women excluded from the analysis due to exclusion criteria were not statistically different on any reported demographic variables to women included in final analysis.

4.3.1 Crude analysis

Dietary intake by latent sleep class are presented in Table 4.2. Compared with LC1, women in LC2 reported lower percentage energy of monounsaturated fat (LC2 13.4%E vs LC1 12.7%E, $p=0.03$), lower percentage energy from starch (LC2 19.8%E vs LC1 21.4%E, $p=0.012$) and lower glycaemic load (LC2 86.2 vs LC1 94.8, $p=0.019$). Whereas LC2 reported higher percentage energy from fibre, compared with LC3 (LC2 5.1%E vs LC3 4.5%E, $p=0.017$). There were no significant differences in energy or macronutrient intake between LC1 and LC3 (Table 5.2).

4.3.2 Multivariate analysis

Dietary unstandardized coefficients per sleep class are presented in Table 4.3. In models adjusted for education, difficulty managing on income, parity, area of residence and depression (Model 2), LC2 was negatively associated with total fat ($b = -0.032$, 95% CI: $-0.063, -0.002$, $p=0.04$) and monounsaturated fat ($b = -0.05$, 95%CI: $-0.085, -0.16$, $p=0.005$), and positively associated with carbohydrate ($b = 0.033$, 95%CI: $0.007, 0.059$, $p=0.031$) intakes. After further adjustment for BMI (Model 3), LC2 remained negatively associated with total fat ($b = -0.032$, 95%CI: $-0.063, -0.002$, $p=0.039$) and monounsaturated fat ($b = -0.05$, 95%CI: $-0.085, -0.015$, $p=0.005$), and positively associated with carbohydrate ($b = 0.031$, 95%CI: $0.005, 0.057$, $p=0.020$) intake. There were no significant associations between LC1 and LC3.

4.4 Discussion

This study considered the relationship between sleep behaviour and dietary intake in a large sample of pregnant women from Australia. Results demonstrate that sleeping behaviour is associated with dietary intake in pregnancy, but only in those who reported average sleep duration (approximately 8 hours per night). These results did not support the *a priori* hypothesis. Women in LC1 who reported average sleep with no adverse sleep symptoms consumed a higher percentage energy from monounsaturated fat and a lower percentage energy from carbohydrates, compared to women with a higher proportion of sleeping difficulties such as severe tiredness, difficulty sleeping and restless sleep (LC2). Short sleep (LC3) was not associated with any differences in dietary intake, compare to LC1.

Our findings are supported by recent evidence from the GUSTO cohort (29). Specifically, pregnant women living in Singapore ($n=497$), with 'poor' sleep (characterised by PQSI > 5)

were associated with a lower adherence to the vegetable-fruit-rice pattern but a higher adherence to the seafood-noodle pattern and higher energy from discretionary foods, while 'short' sleep (≤ 6 hours) had no association with dietary patterns or eating behaviours (29). Similarities were also found in the dietary intakes of the reference group within each cohort. In the GUTSO cohort, pregnant women who reported good quality sleep of average length (8.0 hours \pm 1.2) had a diet with qualities comparable to the Mediterranean diet (high in monounsaturated fat and low in refined carbohydrates) (29), which is similar to the dietary intakes reported by LC1 in this study. Given there are many cultural and ethnic differences (for example culturally acceptable foods, diet patterns (44) and genetic differences influencing pregnancy complications such as GDM (45)) between this study and the GUTSO cohort, this study builds upon the findings of GUSTO and aids extrapolation to populations similar to Australia. Further research is needed to identify the extent cultural orientation and ethnic differences impact the relationship between sleep and diet. Further, understanding macronutrient intake provides additional depth to our understanding of the relationship and possible intervention leverage. Therefore, this study builds upon previous research but provides further depth and cultural diversity to strengthen extrapolation to other western populations such as America and the UK.

Sleep duration was not associated with macronutrient intakes of pregnant women in this sample, despite research in non-pregnant populations reporting a strong relationship between short sleep and increased carbohydrate (13) and fat intake (14, 46, 47). Although it remains unclear why pregnant populations display different relationships to sleep and dietary intake compared to non-pregnant populations, we have hypothesised two potential mediators. Firstly, changes in maternal physiology during pregnancy naturally alter sleep

duration and sleeping quality (48), which can impact both mood (49), hypothalamic–pituitary–adrenal axis (50), inflammatory and immune responses (50). Considering the majority of pregnant women experience sleep disturbance (51), there may be compensatory mechanisms that protect against significant dietary change. This hypothesis is based upon the rationale that in the non-pregnant population marked dietary changes occur with short and poor quality sleep (52), however in pregnancy this does not appear to be the case. Future studies are required to confirm this hypothesis. Secondly, pregnant women who experienced shorter sleep in this study (LC3) were more likely to report depressive symptoms and difficulty managing on income, compared to other women (LC1 and LC2). In Australia, pregnant women who present with risk factors for depression or anxiety receive additional antenatal care as recommended by the Australian antenatal care guidelines (53). Researchers were unable to control for the health information provided in these sessions and therefore, any additional antenatal care received may have impacted on the dietary intakes of these women. Further research to confirm the mechanisms driving these findings is required before recommendations can be made to guide clinical practice (54).

Poor sleep quality during pregnancy was associated with poorer physical health and greater depressive symptoms. Pregnant women in LC2 were more likely to report poorer mental and physical health, compared to LC1. Similar relationships were seen between pregnant women in the LC2 and LC3 groups. Results are supported by previous research conducted in both pregnant (50, 55-57) and non-pregnant populations (58) which demonstrates a strong relationship between sleep difficulties and poor mental health. Antenatal depression during pregnancy increases the risk of outcomes such as preterm birth (49), low birth weight (49), developmental delay in the offspring (59) and postpartum depression (60, 61). This relationship has been shown to be bi-directional and complex (49). Improving both sleeping

quality and quantity during pregnancy may be an important strategy to reduce the risk of birth complications and mental health in the perinatal and postpartum periods (62). Further, poorer diet quality has been associated with poorer mental health in both the pregnant (63) and non-pregnant populations (64). Therefore, educating women on healthy sleep hygiene practices along with healthy eating advice may help support mental health in the antenatal period and therefore support better nutrition and antenatal outcomes.

Nausea and vomiting are common in pregnancy, particularly in the first trimester. The nausea experienced is caused by the sudden increase in human chorionic gonadotropin (65). It has been shown that women who experience nausea and vomiting have been reported to have higher energy and carbohydrate intake (66). Nausea and vomiting in the first trimester have been associated with sleep disturbances (48). However, whether or sleep and nausea are linked or simply coincide together is unclear as both can be caused by pregnancy related endocrine changes. In this sample we were unable to obtain data on nausea and vomiting specifically related to pregnancy. Nausea and vomiting may be a potential mediator of the relationship observed in this study and requires further study to confirm this relationship.

Limitations of this study relate to its cross-sectional nature and self-reported data collected. However, the large sample size is a strength. Despite the subjective nature of this study, rigorous analyses have been conducted with biologically plausible cut points applied for both sleep and dietary intake data (32). The food frequency questionnaire administered was designed to capture the previous 12-months intake (34). However, research shows that food frequency questionnaires more accurately reflect current dietary intake due to recall bias (67). Self-reported sleep data may overestimate sleep duration and also be prone to bias (68). However, objective measures of sleep are unsuitable for use in large population-based

cohorts like the ALSWH and similar results have been found between objective and subjective measured sleep have been reported in pregnancy (69). Furthermore, this study was conducted in 2009, meaning at the time of publication this data was 10 years old. Key factors that may impact the generalisability of these results include the proliferation of smartphones, in the prevalence of overweight and obesity and changes in dietary patterns. However, it is important to note that both sleep (29) and dietary data (70) reported by pregnant women in this study are similar to those reported by other more contemporary population-based pregnancy cohorts.

4.5 Conclusion

In conclusion, this study provides evidence that sleeping behaviour has a significant relationship with dietary intake in pregnancy, but only in those who reported average sleep duration (approximately 8 hours per night). Pregnant women who reported good quality sleep and average duration (LC1) consumed higher percentage energy from monounsaturated fat and lower percentage energy from carbohydrates, compared to women who reported a similar sleep duration but increased sleeping difficulties during pregnancy (LC2). Results suggest that higher monounsaturated fat intakes, at the expense of carbohydrate intakes, may be protective against poorer sleep quality in pregnancy. However, more research is needed to confirm the relationship. Due to the long-lasting implications of maternal macronutrient intake during pregnancy for both mother and baby, this should be a research priority. In the meantime, health professionals are urged to discuss healthy eating and sleep hygiene practices with women in antenatal care to support pregnancy outcomes.

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Table 4.1: Characteristics of pregnant women in the Australian Longitudinal Study on Women's Health, by latent sleep class

	n for item ¹	LC1 (n=167) ²	LC2 (n=173) ³	LC3 (n=97) ⁴	p-value ⁵
Sleeping behaviour					
Workday sleep duration (hours) (Mean ± SD)	437	7.6 ± 0.7 ^{a,b}	8.3 ± 0.7 ^{a,c}	6.5 ± 0.7 ^{b,c}	<0.001
Non-workday sleep duration (Mean ± SD)	437	8.1 ± 0.7 ^{a,b}	8.8 ± 0.8 ^{a,c}	6.9 ± 0.7 ^{b,c}	<0.001
Severe tiredness (%)	437	23.9 ^{a,b}	64.8 ^{a,c}	60.8 ^{b,c}	<0.001
Difficulty sleeping (%)	437	0.0 ^{a,b}	40.4 ^{a,c}	53.0 ^{b,c}	<0.001
Restless sleep (%)	437	14.7 ^{a,b}	50.2 ^{a,c}	75.8 ^{b,c}	<0.001
Difficulty falling asleep (%)	437	7.4 ^{a,b}	41.3 ^{a,c}	55.2 ^{b,c}	<0.001
Demographics					
		Median (IQR)	Median (IQR)	Median (IQR)	
Age (years)	437	33.3 (32.2 – 34.7)	33.3 (32.4-34.6)	33.5 (32.3 – 34.6)	0.994
Height (cm)	434	166 (163-171)	167 (163-172)	165 (162-168)	0.077
Weight (kg)	434	64 (57-74)	65 (59-72)	66.5 (58-78.5)	0.416
BMI (kg/m ²) ⁶	432	23.1 (20.8-26.5)	23.5 (20.8-26.4)	24.1 (21.7-28.2)	0.079
Parity	437	2 (1,3) ^a	2 (1,2) ^{a,b}	2 (2,3) ^b	<0.001
		% (n)	% (n)	% (n)	
Trimester	437				
First		22.2 (37)	22.5 (39)	13.4 (13)	0.192
Second		44.3 (74)	41.0 (71)	40.2 (39)	
Third trimester		33.5 (56)	36.4 (63)	46.4 (45)	
Fair/poor rated self-health	437	0 (0) ^{a,b}	4.1 (7) ^a	4.1 (4) ^b	0.030
Depressive symptoms (CESD ≥10) ⁷	434	4.2 (7) ^{a,b}	18.8 (32) ^a	27.8 (27) ^b	<0.001
Difficulty managing on income	434	28.3 (47) ^a	30.4 (52) ^b	43.3 (42) ^{a,b}	0.033
Post-school education ⁸	422	90.8 (148)	86.0 (141)	84.2 (80)	0.235
Current smoker	436	2.4 (4)	1.74 (3)	5.2 (5)	0.244
Married or Defacto	436	97.6 (163)	98.8 (170)	99.0 (96)	0.584
Area of residence	425				0.023
Urban		67.1 (108)	62.5 (105)	56.3 (54)	
Rural		31.7 (51)	33.9 (57)	34.4 (33)	
Remote		1.2 (2) ^a	3.6 (6)	9.4 (9) ^a	
BMI Class ⁹	432				0.230
Underweight		3.2 (6)	4.1 (7)	2.1 (2)	
Healthy weight		63.3 (105)	59.4 (101)	57.3 (55)	
Overweight		24.1 (40)	23.5 (40)	19.8 (19)	
Obese		9.0 (15)	12.9 (22)	20.8 (20)	

SD: Standard Deviation, IQR: Interquartile Range. ¹ Questions were not compulsory and therefore n for item has been indicated, ²Latent Class One: ~ 7.8 hours sleep/day, with little to no adverse sleep associated symptoms, ³Latent Class Two: ~ 8.3 hours sleep/day with sleep difficulties and severe tiredness, ⁴ Latent Class Three: ~6.6 hours sleep/day with sleep difficulties and severe tiredness, ⁵ P-value determined by chi-X² for categorical data and Kruskal-Wallis for continuous data, ⁶ BMI = Body Mass Index (pre-pregnancy), ⁷ Depression as classified by the Centre for Epidemiological Disease (CESD) Scale ≥10, ⁸ Higher education was defined as year 12 or equivalent such as technical education, ⁹ Classified by World Health Organisation categories. Differences between groups are denoted by superscript letters.

Table 4.2: Dietary analysis of pregnant women in the Australian Longitudinal Study on Women's Health, by latent sleep class (n=437)

	LC1 (n=167) ¹	LC2 (n=173) ²	LC3 (n=97) ³	p-value ⁴
	Median (IQR)	Median (IQR)	Median (IQR)	
Energy (kJ)	6694 (5707-8108)	7563 (5953-8780)	7262 (6137-8457)	0.054
Fat (% E)	38.0 (34.8-39.7)	36.8 (34.1-39.7)	37.7 (35.2-41.4)	0.133
Saturated (% E)	15.9 (13.9-17.9)	15.7 (13.7-17.5)	16.1 (13.7-18.2)	0.472
Monounsaturated Fat (% E)	13.4 (12.1-14.3) ^a	12.7 (11.6-13.8) ^a	13.3 (11.9-14.3)	0.026
Polyunsaturated Fat (% E)	4.9 (4.0-6.3)	4.8 (3.9-5.9)	4.8 (4.0-6.2)	0.686
Protein (% E)	16.6 (17.5-21.4)	19.7 (18.1-21.1)	19.3 (17.5-20.8)	0.550
CHO (% E)	43.0 (39.9-46.1)	43.8 (41.1-46.1)	43.3 (39.4-46.7)	0.431
Sugar (% E)	20.2 (16.6-23.4)	20.4 (17.4-23.4)	20.3 (16.8-23.0)	0.781
Fibre (% E)	4.9 (4.2-5.7)	5.1 (4.4-5.8) ^a	4.5 (4.0-5.5) ^a	0.017
Starch (%E)	22.4 (19.9 – 25.1) ^a	23.0 (21.1-25.4) ^a	22.7 (20.8-24.9)	0.012
Protein to carbohydrate ratio (kJ:kJ)	0.45 (0.39-0.52)	0.46 (0.40-0.50)	0.44 (0.33 – 0.45)	0.886
Glycaemic index	49.9 (47.9-52.7)	50.2 (48.1-52.4)	51.2 (48.6-53.8)	0.066
Glycaemic load	86.2 (73.6-107.5) ^a	94.8 (76.7-117.0) ^a	95.6 (78.6-115.9)	0.019

%E: Percentage energy, kJ: Kilojoule, IQR: Interquartile Range. ¹Latent Class One: ~ 7.8 hours sleep/day, with little to no adverse sleep associated symptoms, ²Latent Class Two: ~ 8.3 hours sleep/day with sleep difficulties and severe tiredness, ³ Latent Class Three: ~6.6 hours sleep/day with sleep difficulties and severe tiredness, ⁴ p-value derived from kruskall-wallis. Differences between groups are denoted by superscript letters. Median; 25th and 75th percentiles in parentheses (all such values).

Table 4.3: Multivariate linear regression analysis of energy and macronutrient intake by latent class

	Model 1			Model 2			Model 3			
	b	95% CI	p-value	b	95% CI	p-value	b	95% CI	p-value	
Energy (kJ)	LC1	----		---			---			
	LC2	0.063	0.009, 0.116	0.022	0.024	-0.038, 0.086	0.441	0.022	-0.040, 0.084	0.480
	LC3	0.050	-0.012, 0.112	0.114	0.003	-0.070, 0.075	0.945	-0.001	-0.075, 0.073	0.979
Fat (%E)	LC1	----		----			----			
	LC2	-0.020	-0.046, 0.006	0.130	-0.032	-0.063, -0.002	0.040	-0.032	-0.063, -0.002	0.039
	LC3	0.005	-0.026, 0.036	0.763	-0.014	-0.049, 0.022	0.454	-0.015	-0.051, 0.021	0.405
Saturated Fat (%E)	LC1	----		---			---			
	LC2	-0.015	-0.055, 0.027	0.487	-0.029	-0.075, 0.018	0.227	-0.030	-0.076, 0.018	0.228
	LC3	0.007	-0.042, 0.057	0.780	0.000	-0.058, 0.059	0.990	-0.003	-0.063, 0.056	0.918
Polyunsaturated Fat (%E)	LC1	----		---			---			
	LC2	-0.023	-0.088, 0.042	0.480	-0.026	-0.100, 0.048	0.492	-0.029	-0.104, 0.047	0.453
	LC3	0.008	-0.067, 0.083	0.831	-0.049	-0.137, 0.039	0.274	-0.048	-0.137, 0.041	0.287
Monounsaturated Fat (%E)	LC1	----		---			----			
	LC2	-0.034	-0.064, -0.004	0.028	-0.050	-0.085, -0.016	0.005	-0.050	-0.085, -0.015	0.005
	LC3	-0.002	-0.038, 0.033	0.909	-0.022	-0.062, 0.018	0.279	-0.023	-0.063, 0.017	0.262
Protein (%E)	LC1	----		---			---			
	LC2	0.005	-0.024, 0.034	0.744	-0.005	-0.039, 0.029	0.770	-0.000	-0.034, 0.034	0.986
	LC3	-0.014	-0.050, 0.021	0.429	-0.006	-0.049, 0.037	0.789	-0.003	-0.045, 0.040	0.900
Carbohydrates (%E)	LC1	----		---			---			
	LC2	0.019	-0.004, 0.042	0.109	0.033	0.007, 0.059	0.013	0.031	0.005, 0.057	0.020
	LC3	0.005	-0.024, 0.035	0.724	0.019	-0.015, 0.053	0.282	0.018	-0.016, 0.053	0.291
Sugars (%E)	LC1	----		---			---			
	LC2	0.021	-0.025, 0.071	0.400	0.035	-0.021, 0.091	0.215	0.032	-0.024, 0.088	0.266

	LC3	0.010	-0.051, 0.072	0.746	0.051	-0.018, 0.120	0.146	0.050	-0.020, 0.120	0.163
Fibre (%E)	LC1	---			---			---		
	LC2	0.039	-0.007, 0.084	0.094	0.049	-0.002, 0.101	0.060	0.050	-0.002, 0.102	0.060
	LC3	-0.034	-0.093, 0.025	0.257	-0.009	-0.079, 0.061	0.809	-0.006	-0.077, 0.064	0.858
Starch (%E)	LC1	---			---			---		
	LC2	0.021	-0.017, 0.058	0.285	0.036	-0.009, 0.081	0.114	0.035	-0.010, 0.081	0.129
	LC3	0.006	-0.039, 0.051	0.791	-0.005	-0.060, 0.050	0.865	-0.003	-0.059, 0.052	0.906
Glycaemic index	LC1	---			---			---		
	LC2	0.001	-0.014, 0.015	0.945	0.002	-0.014, 0.018	0.819	0.001	-0.015, 0.017	0.899
	LC3	0.018	-0.000, 0.037	0.053	0.005	-0.016, 0.026	0.649	0.006	-0.016, 0.027	0.606
Glycaemic load	LC1	---			---			---		
	LC2	0.082	0.022, 0.141	0.007	0.059	-0.011, 0.129	0.096	0.054	-0.016, 0.124	0.127
	LC3	0.073	0.004, 0.143	0.040	0.026	-0.058, 0.110	0.542	0.023	-0.062, 0.108	0.595
Protein to carbohydrate ratio %E:%E	LC1	---			---			---		
	LC2	-0.014	-0.057, 0.03	0.536	-0.038	-0.088, 0.012	0.134	-0.031	-0.080, 0.019	0.225
	LC3	-0.020	-0.076, 0.037	0.492	-0.024	-0.091, 0.042	0.469	-0.021	-0.087, 0.045	0.528

Model 1: Crude regression, Model 2: area of residence, depression symptoms, difficulty managing on income, education level and parity, Model 3: model 2 plus pre-pregnancy BMI. Bold text indicates significant result.

4.7 References

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CHAPTER 5

Poor sleep quality during pregnancy increases the risk of adverse birth and postpartum outcomes

5.1 Introduction

Sleep is a vital factor for the maintenance of health. In the non-pregnant population, sleep disruption (short sleep and/or poor quality sleep) has been associated with diabetes (1), cardiovascular disease (2) and obesity (3). However, during pregnancy sleep becomes increasingly difficult due to many hormonal and physical factors (4). The majority of women experience sleep disturbance during pregnancy, with the prevalence increasing as pregnancy progresses (4).

Sleep disturbances during pregnancy can occur early in the first trimester, while the type of sleep disturbance a woman experiences often changes over the progression of the pregnancy. During the first trimester sleep duration increases, sleep onset latency increases and there is a decrease in sleep efficiency (5). In the second trimester, there a decrease in non-rapid eye movement sleep (6) and subjective sleep quality (7) and an increase in number and time of nighttime awakening (4). By the third trimester, subjective sleep quality is at its lowest (8) due to increased night-time awakenings, a decrease in total sleep duration and an increased prevalence of clinical sleep disorders such as obstructive sleep apnoea (9). Overall, there is a higher proportion of subjective sleep quality in pregnant women compared to non-pregnant women (4). While the majority of pregnant women experience sleep disturbance of some kind, the degree of severity may influence clinical outcomes (10).

Previous research investigating the impact of sleep duration and sleep quality in pregnancy on antenatal outcomes lacks consensus (11). A recent systematic review was conducted on both objective and subjective measures of sleep, including prospective patient data from women 12.4-29.5 weeks gestation (12). The results suggested that short sleep (<6.25 hrs) in pregnancy was associated with a 184% increased likelihood of developing GDM (12). However, the results of this review were not supported by another meta-analysis of prospective data from women between 10-28 weeks gestation which suggested that long sleep duration (>9 hours) but not short sleep duration in early to mid-pregnancy was associated with GDM (13). This meta-analysis used prospective data from women between 10 weeks to 28 weeks gestation. While these reviews include similar studies, the difference in findings may relate to when the sleep data was collected as sleep disturbance in the second trimester have been associated with a higher risk of GDM than sleep disturbances in the first trimester (14), or different criteria for short sleep (<6.25 hours vs <9 hours) (12,13). Furthermore, in some studies, both sleep quality and quantity have been associated with caesarean section delivery (15-17), whereas in others only sleep quality was associated with caesarean section delivery (18). Moreover, a scoping systematic review and meta-analysis investigating sleep quality, quantity and outcomes such as birthweight, risk of SGA, LBW and pre-term birth found that conclusions are difficult to ascertain as literature is scant, with variations in the definitions of sleep duration (11). This literature gap has been regarded as a research priority (11) and thus further research to determine the relationship between both sleep length and sleep quality on health outcomes for mother and child is required (11). Therefore, the aim of this study was to investigate the impact of sleeping behaviour patterns during gestation on pregnancy, birth and postpartum outcomes. This study tested an *a priori* hypothesis that women with poorer sleep behaviours (poorer sleep quality and

shorter sleep duration) would have higher prevalence of pregnancy complications such as GDM, need a c-section delivery and have poorer postpartum mental health.

5.2 Methods

5.2.1 Participants

The Australian Longitudinal Study on Women's Health (ALSWH) is a nation-wide cohort study that has been conducted every 3-4 years since 1996. The ALSWH obtains data on women's mental and physical aspects of health from three cohorts, defined by birth year: 1973–78 (aged 18–23 at baseline), 1946–51 (aged 45–50 at baseline), and 1921–26 (aged 70–75 at baseline). In 2012 a new cohort was added born 1989-95 (18-23). Women were recruited from the national medical database (Medicare), with oversampling from rural and remote locations to allow comparison (19). Further description of the ALSWH has been described elsewhere (20).

This study was a secondary data analysis that used demographic and sleep data from survey 5 of the ALSWH 1973-78 cohort aged 31-36 in 2009 (n=8199, including all pregnant and non-pregnant women) and self-reported pregnancy, birth and postpartum outcome data (pertaining to the pregnancy recorded at survey 5) reported as 'child data' from survey 6 (n=605). These surveys were used because they provided the most comprehensive and contemporary data set of a representative Australian sample of pregnant women that includes sleep data. Women were excluded from this study if their sleep data were missing (n=94) or biologically implausible (<3 hours and >12 hours; n=17). A total of 491 pregnant women were included in the analyses.

5.2.2 Ethics

The Australian Longitudinal Study on Women's Health (ALSWH) obtained Ethics approval from the Human Research Ethics Committees at the University of Newcastle and the University of Queensland Human Research Ethics Committees.

5.2.3 Data collection

Outcome measures included pregnancy, birth and post-partum outcomes. The following pregnancy outcomes were collected: antenatal anxiety, antenatal depression, gestational diabetes and gestational hypertension. The following birth outcomes were collected: birthweight (g), birth length (cm), LBW (<2500g), high birth weight (HBW; >4000g), elective caesarean section, emergency caesarean section, induction, long labour (>36 hours), gas use during delivery, epidural, episiotomy, premature birth (<36 weeks gestation), vaginal tear, use of forceps and emotional distress during delivery. The following postnatal outcomes were collected: Intensive Care Unit (NICU)/ Special Care Nursery (SCN) admission, time breast fed (months), postnatal anxiety and postnatal depression.

Sleeping behaviour was used as the predictor variable. Sleeping behaviour data were collected via self-reported questions in survey 5. Sleep duration was reported as hours and minutes on both a workday and non-workday. Sleep quality data were obtained using the following questions: (1) How often during the last week did you feel "My sleep was restless" on a frequency scale: rarely or none of the time (<1 day), some or little of the time (1-2 days), occasionally or moderate amount of the time (3-4 days), or most or all of the time (5-7 days); (2) In the past month, "Have you had difficulty falling asleep?", yes or no; (3) In the last 12 months have you had any of the following, "Severe tiredness" or "Difficulty sleeping" on a frequency scale: never, rarely, sometimes or often. Similar agreement has been found

between sleep duration and sleep quality variables collected from pregnant women via self-reported and objective measures (21).

Survey 5 also included a range of demographic characteristics (e.g., age, education, income, marital status, area of residence), health behaviours (e.g., smoking status, physical activity) and psychosocial measures (e.g., self-rated health status and depression symptoms). BMI was calculated using self-reported pre-pregnancy height and weight ($BMI = \text{weight (kg)} / \text{height (m)}^2$) and classified using the World Health Organisation categories (22).

5.2.4 Statistical analysis

Main outcome measures included the following dichotomous variables: antenatal anxiety, antenatal depression, gestational diabetes, gestational hypertension, premature birth, elective caesarean section, emergency caesarean section, induction, long labour (>36 hours), gas use during delivery, epidural, episiotomy, vaginal tear, use of forceps, emotional distress during delivery, LBW (<2500g), HBW (>4000g), Neonatal Intensive Care Unit (NICU)/ Special Care Nursery (SCN) admission, postnatal anxiety and postnatal depression. The following continuous variables were also included: birthweight (kg), birth length (cm) and months breastfed. The predictor variable was sleeping behaviour pattern. The method used to generate the sleeping behaviour pattern variable has been described elsewhere (23, 24). Briefly, latent class analysis (LCA) was chosen to derive sleeping behaviour patterns because of its ability to classify pregnant women into mutually exclusive groups. Sleep variables entered into the analysis include: sleep duration on a weekday (mins), sleep duration on a weekend (mins) and sleep quality data including – frequency scales of ‘my sleep was restless’, ‘severe tiredness’ or ‘difficulty sleeping’ and dichotomous ‘Have you had difficulty falling asleep?’. Women were categorised into the LCA groups according to their highest

predicated probability of class membership. Multiple imputation methods were used to estimate the values of missing sleep data.

Continuous variables used in the analyses were tested for normality. Comparisons were performed using an ANOVA or Kruskal-Wallis test for continuous data and chi-square statistic or Fisher's exact test for categorical data. The relationships between sleeping behaviour pattern and pregnancy, birth and postpartum outcomes in pregnant women were analysed in a series of logistic and linear regression models: (i) examining the associations between sleeping behaviour pattern and each pregnancy, birth and postpartum outcome (crude model) and (ii) adjusted for BMI, self-rated health, difficulty managing on income, depression and trimester. Except for the multivariate regression model for antenatal depression, depression was not included as a covariate. Covariates were selected for regression models if they were statistically correlated with the predictor variable (sleeping behaviour pattern). Latent Class 1 (LC1) was denoted as the reference category for LCA models. Statistical analyses were performed using Intercooled Stata 14.0 (Stata) and Mplus version 7.3 to fit the latent class models. *P* values <0.05 were considered statistically significant.

5.3 Results

Participant characteristics and sleeping behaviours are presented in Table 5.1. Latent Class 1 (LC1) was characterised by women who had an average sleep length (mean 7.7 hrs/day) with little to no adverse sleep associated symptoms. Latent Class 2 (LC2) was characterised by an average sleep length (mean 8.4 hrs/day) and sometimes or often experiencing adverse sleep associated symptoms (severe tiredness, difficulty sleeping, restless sleep or difficulty falling asleep). Latent Class 3 (LC3) was characterised by a short sleep length (mean

6.6 hrs/day) and sometimes or often experiencing adverse sleep symptoms (severe tiredness, difficulty sleeping, restless sleep or difficulty falling asleep).

Pregnant women in LC1 and LC2 reported a lower mean BMI, compared to those in LC3 (23.0 kg/m² (LC1) and 23.5kg/m² (LC2) vs 24.3 kg/m² (LC3), p=0.026). Women in LC1 also reported lower rates of depression (5.3% (LC1) vs 19.7% (LC2) and 25.0% (LC3), p<0.001) and fair/poor rated self-rated health (0.6% (LC1) vs 4.2% (LC2) and 4.5% (LC3), p=0.030), compared to those in LC2 and LC3.

Pregnancy, birth and postpartum outcomes are presented by sleeping behaviour class in Table 5.2. Pregnant women in LC2 reported greater emotional distress during labour (16.8% (LC2) vs 6.4% (LC1) and 8.0% (LC3); p=0.003) and post-natal anxiety (11.0% (LC2) vs 2.7% (LC1)/(LC3); p=0.001) compared to pregnant women in both LC1 and LC3. While, pregnant women in LC2 also experienced a greater number of NICU admissions compared to those in LC3 (13.6% (LC2) vs 5.4% (LC3), p=0.040).

5.3.1 Crude analysis

Table 5.3 highlights the regression analyses for pregnancy, birth and postpartum outcomes according to sleeping behaviour pattern. In univariate regression analyses (Model 1), LC2 was associated with a 3 times greater likelihood of emotional distress during labour (OR: 2.970, 95% CI: 1.479 – 5.965, p=0.002), 1.6 times more likely to have an epidural (OR: 1.597, 96% CI: 1.031 – 2.473, p=0.036), 4.6 times more likely to suffer from postnatal depression (OR: 4.548, 95% CI: 1.677 – 12.331, p=0.003) and having a baby 0.8cm shorter in length (b= -0.779, 95% CI -0.776 to -0.007, p=0.048) compared with those in the reference group (LC1). Interestingly, women with short sleep (LC3) were 54% less likely to require forceps during

labour (OR: 0.464 (0.226 - 0.955, $p=0.037$), compared to women with average sleep length and no adverse sleep symptoms (LC1).

5.3.2 Multivariate analysis

In models adjusted for BMI, self-rated health, difficulty managing on income, depression and trimester (Model 2), LC2 was associated with a 3.3 times greater likelihood of emotional distress during delivery (OR: 3.271, 95% CI: 1.589 – 6.736, $p<0.001$), 2.2 times higher odds for an emergency C-section (OR: 2.176 , 95% CI: 1.000-4.739, $p=0.050$), 1.9 times more likely to have an epidural (OR: 1.907, 95% CI: 1.197 – 3.037, $p=0.007$), 4.2 times more likely to suffer from postnatal anxiety (OR: 4.216, 95% CI: 1.518 – 11.709, $p=0.006$) and having a baby that is 0.8cm shorter in length ($b= -0.816$, 95% CI: -1.626 to -0.005, $p=0.048$), compared to LC1. No relationships between sleeping behaviour and pregnancy, birth or postpartum outcomes were found between LC3 and LC1.

5.4 Discussion

This study investigated the relationship between sleeping behaviour pattern during gestation and pregnancy, birth and post-partum outcomes. The results indicate that the LC2 sleeping behaviour pattern during pregnancy, characterised by approximately 8.4 hours of poor-quality sleep, is associated with an increased risk of adverse birth and post-partum outcomes. These findings did not support the *a priori* hypothesis. Compared to pregnant women who reported 7.7 hours of good quality sleep (LC1), women in LC2 reported an increased likelihood of emotional distress during labour, emergency caesarean section, epidural use and post-natal anxiety. In addition, women in LC1 had slightly longer babies, but this was not clinically significant. Interestingly, the short (6.6 hrs/day) poor quality

sleeping pattern (LC3) was not associated with any adverse pregnancy, birth or postpartum outcomes, compared to LC1.

In this study sleep duration during pregnancy does not appear to influence pregnancy outcomes and therefore did not support the hypothesis. The short (<6.6 hours) sleeping pattern in this study (LC3) was not associated with any pregnancy, birth or postpartum outcomes. These findings support previous epidemiological research that shows that sleep length during pregnancy is not associated with adverse pregnancy outcomes including birthweight (25, 26), small for gestational age (26), low birth weight infants (26), preterm birth (27) and GDM (13). However, other studies have found associations between short sleep and gestational diabetes mellitus (12), long labour (15, 16) and preterm birth (11). Possible reasons for inconsistent results in the literature may include (i) ethnicity of participants, and (ii) definition of short sleep. Firstly, particularly when considering GDM, ethnicity is known to impact pregnancy and birth-related outcomes by possible genetic mechanisms, social-cultural factors and interaction with healthcare including patient-provider bias (28). Asian, Hispanic and African American ethnicities have been reported as significant risk factors for GDM (29). The meta-analysis that concluded that short sleep is associated with GDM (<6-7 hours) had approximately 91% of participants (three out of eight subjective sleep studies) from vastly different ethnic profiles to that of the Australian population (12). Two studies exclusively included participants of Asian ethnicity (30, 31) and the other included study contained approximately 50% Hispanic or African American pregnant women (14). Future studies are required to confirm whether ethnicity influences the relationship between sleep and pregnancy outcomes. Secondly, there are a broad range of classifications of short sleep from ≤ 4 hours (32) to < 9 hours (13). These definitions are

used to create categorical sleep variables, which makes it difficult to compare results across studies and may contribute to the lack of consensus, as evidenced by the difference in conclusions between the two major systematic reviews of sleep and GDM (12, 13).

Furthermore, the difference between results may be due to the studies ability to control for confounding factors. In the case of pre-term birth, Okun et al found that pre-term birth was associated with short sleep, however, after adjustment for confounding factors such as depression, marital status, age and employment, the relationship was no longer significant (27). Furthermore, the trimester of sleep disturbance has also been shown to be an important factor that may influence the risk of adverse outcomes (14, 18). Future studies are needed to identify the point at which short sleep produces clinically significant outcomes and allows controls for potential confounding factors to allow comparison and aid the development of intervention studies.

This study confirms the strong relationship between subjective sleep in pregnancy and maternal mental health outcomes (33-36). After controlling for confounding factors, pregnant women who experienced poor quality sleep (LC2) had a 320% increased odds of developing post-partum anxiety. These findings support previous studies that reported sleep quality, but not quantity, is associated with mental health outcomes in late pregnancy (37) and post-partum (38). Clinically diagnosed postnatal anxiety is estimated to impact 17% of new mothers (39). However, this statistic may severely underestimate the proportion of women who experience anxiety following childbirth as up to 50% of new mothers report anxiety-related symptoms (40). Epidemiological research suggests that postnatal anxiety is associated with an increased risk of reduced breastfeeding duration (39), increased healthcare use (39) and can adversely impact infant bonding (41). It has been suggested that

this association is attributable to the restorative benefits of sleep (42). Women who have self-perceived 'adequate' sleep during pregnancy may have experienced more restorative mechanisms of sleep and were less vulnerable to changes post-partum (42). As discussed in Chapter 4, in Australia those identified as having antenatal mental health concerns have care provided through a 'high risk' stream, whereby they receive additional care (43). This may explain the lack of relationships observed between sleeping behaviour and pregnancy, birth and postpartum outcomes in LC1 and LC3. Considering the impact that poor mental health can have on the mother, child, and public health system, further research in this area is urgently needed during pregnancy and postpartum.

Sleeping behaviour characterised by poor sleep quality but average sleep length (LC2) was associated with an increased odds of emergency caesarean section, emotional distress during delivery and epidural administration. Previous research supports the association between poor sleep quality and emergency caesarean section (44) and caesarean section (not otherwise specified) (15, 16, 18). These results may be inter-related as i) epidurals are commonly used as anaesthesia during caesarean (45); and ii) fear of childbirth, which may cause emotional distress during labour, has been shown to increase the risk of an emergency caesarean section (46). Further, supporting this theory, fear of childbirth has also been associated with sleep disturbance (47). The biological mechanisms related to our findings are poorly understood due to limited research in the area (48), but could be explained by two possible mechanisms: i) the upregulation of cytokine markers; and/or ii) sympathetic nervous system activation (10). Sleep disturbance in pregnant and non-pregnant adults has been linked to an increase in pro-inflammatory cytokines (48). The literature investigating the link between sleep disturbance and pregnancy complications via

the pro-inflammatory pathway is currently limited (48). However, inflammatory cytokines such as IL-6 have been associated with poor quality sleep (49). Inflammatory cytokines such as IL-6 but also IL-1 and TNF-alpha have been linked to pregnancy complications such as preterm birth (50), premature labour (50), pre-eclampsia (51) and intrauterine growth restriction (52). Furthermore, in non-pregnant adults, lab-induced pro-inflammatory cytokines such as IL-6 have also been shown to decrease mood within 3 hours (53). It is possible the relationships between sleeping behaviour and emotional distress, emergency caesarean section and postpartum anxiety, found in this study, are also influenced by this mechanism. Disturbed sleep may also upregulate the sympathetic nervous system, which then produces more pro-inflammatory cytokines and contributes to a positive feedback loop (48). For example, pro-inflammatory cytokines can influence the concentration of hormones such as norepinephrine, dopamine, serotonin and cortisol, which are high in women with postpartum mental health concerns (34). However, whether cytokines and an upregulated sympathetic nervous system play a role in the relationship between sleep disturbance and mental health outcomes during pregnancy remains unknown. The effect of variations in sleeping behaviour on cytokine activity requires further investigation.

Weight status prior to conception is widely understood as a risk factor for pregnancy and birth complications (54). As explored in Chapter 2 in this thesis, women with overweight and obesity prior to conception have higher risk of GDM (54) and do not respond as well to interventions to reduce the risk of GDM (55). In this study, the relationship between BMI and antenatal outcomes was not observed. While there was a significantly higher BMI in LC3 compared to LC1 and LC2, the median BMI was still within the healthy weight range and the 75th percentile for LC3 was slightly higher than those in LC1 and LC2 but all were within the

overweight category. Therefore, the relationship between BMI and adverse antenatal outcomes may not have been observed due to the relatively moderate BMI in this sample.

Limitations of this study include the use of self-reported data. Previous studies have shown that self-reported pregnancy, birth, and post-partum outcomes from the ALSWH are a reliable and cost-effective method of collecting such data (56). In pregnancy, subjective and objective measures of sleep have been found to have similar agreement (21). Sleeping behaviour data are further strengthened by the use of plausible cut points (<3 hours and >12 hours) to reduce bias, with similar cut points being used previously in population-based studies (32, 57). Comparably, the average sleep length reported in this cohort (6.6-8.4 hrs/day) was similar to that reported by other population-based pregnancy cohorts (4, 27, 58). However, results must be interpreted with caution as this sample reported higher education levels than the national average for women of a similar age (88% vs 67%) (59). This may have been influenced by the older average age, compared to average age of first pregnancy in Australia (33.5 vs 30.5 years) (30). The education level may have also influenced the lower rates of smoking (2.9% vs 9.9%) and lower prevalence of overweight and obesity (36.1 vs 45%) found in this sample, compared to the national average of pregnant women in Australia (60). The birthweights reported were relatively similar (3.5 vs 3.3kg), but the rates of caesarean section (25% vs 34%) and prevalence of GDM (4% vs 12%) were lower than the national averages (60). Lastly, due to the observational nature of this study causality cannot be conferred.

5.5 Conclusion

This study provides evidence that sleeping behaviour during pregnancy has an important relationship with pregnancy and birth-related health outcomes. Sleeping behaviour during

pregnancy, characterised by approximately 8.4 hours of poor-quality sleep, was associated with an increased odds of emotional distress during labour, need for an emergency caesarean section, epidural use and post-natal anxiety, compared to women with optimal sleep quality. Future research is required to understand the mechanisms behind these results in order to inform opportunities for intervention. Results suggest that sleep quality during pregnancy could be an important consideration in screening and maternal health interventions to reduce potential complications during pregnancy or postpartum. Improved sleeping behaviour during pregnancy may help reduce the risk of many adverse pregnancy and birth-related health outcomes.

5.6 Acknowledgements

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Table 5.1: Characteristics and sleeping behaviour by latent sleep class

Outcome	n	LC1 ¹ (n=188)	LC2 ² (n=191)	LC3 ³ (n=112)	P-value
Demographics					
Age (years)*	491	33.6 (1.5)	33.5 (1.4)	33.5 (1.4)	0.743 ⁴
Height (cm)**	487	166 (162-170)	166 (162-171)	165 (162-168)	0.168 ⁵
Weight (kg)**	487	63.5 (57-74)	64.5 (58-72)	68 (58-78)	0.174 ⁵
BMI (kg/m ²)**	484	23.0 (20.8-26.4) ^a	23.5 (20.7-26.3) ^b	24.3 (21.8-28.3) ^{a,b}	0.026 ⁵
Parity**	491	2 (1-3) ^a	2 (1-2) ^{a,b}	2 (1.5-3) ^b	<0.001 ⁵
		% (n)	% (n)	% (n)	
Trimester					0.260 ⁴
First		23.4 (44)	22.5 (43)	14.3 (16)	
Second		42.6 (80)	42.9 (82)	42.0 (47)	
Third		34.0 (64)	34.6 (66)	43.8 (49)	
Self-reported poor or fair health	491	0.6 (1) ^{a,b}	4.2 (8) ^a	4.5 (5) ^b	0.030 ⁷
Depression ⁸	486	5.3 (10) ^{a,b}	19.7 (37) ^a	25.0 (28) ^b	<0.001 ⁶
Post school education	474	90.6 (165)	85.7 (156)	85.5 (94)	0.270 ⁶
Married or defacto relationship	489	97.9 (183)	99.0 (188)	99.1 (111)	0.623 ⁷
Difficulty managing on income	488	27.3 (51)	29.6 (56)	40.2 (45)	0.056 ⁶
Metropolitan area of residence	477	68.0 (123)	63.8 (118)	53.6 (60)	0.056 ⁶
Current smoker	490	3.2 (6)	1.6 (3)	4.5 (5)	0.288 ⁷
Sleep outcomes					
Sleep duration on a work day*	491	7.6 (0.7) ^{a,b}	8.3 (0.8) ^{a,c}	6.5 (0.7) ^{b,c}	<0.001 ⁴
Sleep duration on a non-work day*	491	8.1 (0.7) ^{a,b}	8.8 (0.8) ^{a,c}	6.9 (0.8) ^{b,c}	<0.001 ⁴
Severe tiredness (sometime or often)	485	21.8 (41) ^{a,b}	67.5 (129) ^a	58.9 (68) ^b	<0.001 ⁶
Difficulty sleeping (sometimes or often)	487	0 (0) ^{a,b}	40.3 (77) ^{a,c}	52.6 (59) ^{b,c}	<0.001 ⁷
My sleep was restless (sometimes or often)	488	12.2 (23) ^{a,b}	52.4 (99) ^{a,c}	75.9 (85) ^{b,c}	<0.001 ⁶
Difficulty falling asleep (sometime or often)	490	4.8 (9) ^{a,b}	44.5 (85) ^a	54.5 (61) ^b	<0.001 ⁶

Note: ¹Latent Class One: ~ 7.7 hours sleep/day, with little to no adverse sleep associated symptoms, ²Latent Class Two: ~ 8.4 hours sleep/day with sleep difficulties and severe tiredness, ³ Latent Class Three: ~6.6 hours sleep/day with sleep difficulties and severe tiredness, P-value determined by ⁴ANOVA or ⁵Kruskal-Wallis for continuous data and ⁶χ² or ⁷Fisher's exact for categorical data and ⁸Depression as classified by the Centre for Epidemiological Disease (CESD) Scale ≥10. Categorical data presented as % (n), continuous data presented as *=mean (SD) or ** = median (interquartile range).

Table 5.2: Pregnancy, birth and postpartum outcomes by sleep class

	n	LC1 ¹ (n=188)	LC2 ² (n=191)	LC3 ³ (n=112)	P-value
		% (n)	% (n)	% (n)	
Pregnancy outcomes					
Antenatal depression	488	1.1 (2)	3.7 (7)	0.9 (1)	0.221 ⁴
Antenatal anxiety	489	2.7 (5)	4.7 (9)	0.9 (1)	0.166 ⁴
Gestational Diabetes	490	6.4 (12)	3.2 (6)	1.8 (2)	0.130 ⁴
Gestational Hypertension	491	3.7 (7)	6.3 (12)	7.1 (8)	0.377 ⁵
Birth Outcomes					
		% (n)	% (n)	% (n)	
Elective C-section	490	17.1 (32)	15.7 (30)	14.3 (16)	0.807 ⁵
Emergency C-Section	490	6.4 (12)	11.5 (22)	8.0 (9)	0.205 ⁵
Emotional distress during labour	490	6.4 (12) ^a	16.8 (32) ^{a,b}	8.0 (9) ^b	0.003 ⁵
Epidural	491	26.6 (50)	36.7 (70)	25.9 (29)	0.053 ⁵
Episiotomy	489	12.2 (23)	16.4 (31)	7.1 (8)	0.064 ⁵
Gas use during labour	488	25.5 (48)	31.2 (59)	20.7 (23)	0.127 ⁵
LBW ⁸	491	3.2 (6)	2.1 (4)	1.8 (2)	0.753 ⁴
Long Labour ⁹	490	4.3 (8)	5.8 (11)	2.7 (3)	0.466 ⁴
Induction	491	19.2 (36)	24.1 (46)	21.4 (24)	0.505 ⁵
HBW ¹⁰	491	11.2 (21)	11.5 (22)	11.6 (13)	0.991 ⁵
Premature-birth ¹¹	490	3.7 (7)	3.7 (7)	1.8 (2)	0.616 ⁴
Vaginal tear	490	17.0 (32)	23.2 (44)	14.3 (16)	0.119 ⁵
Use of forceps	490	19.2 (36)	20.4 (39)	9.9 (11)	0.052 ⁵
		Mean (SD)	Mean (SD)	Mean (SD)	
Weight (kg)	368	3.52 (0.55)	3.48 (0.50)	3.52 (0.52)	0.767 ⁶
Length (cm)	302	51.4 (2.29)	50.64 (3.12)	50.8 (3.45)	<0.125 ⁶
Postpartum Outcomes					
		% (n)	% (n)	% (n)	
NICU ¹² or SCN ¹³ admission	491	8.0 (15)	13.6 (26) ^a	5.4 (6) ^a	0.040 ⁵
Postnatal depression	490	4.3 (8)	9.4 (18)	7.1 (8)	0.143 ⁵
Postnatal anxiety	489	2.7 (5) ^a	11.1 (21) ^{a,b}	2.7 (3) ^b	0.001 ⁵
		Med (IQR)	Med (IQR)	Med (IQR)	
Months breastfed		10 (5-13)	10 (4-14)	9 (4-12)	0.446 ⁷

Note: ¹Latent Class One: ~ 7.7 hours sleep/day, with little to no adverse sleep associated symptoms, ²Latent Class Two: ~ 8.4 hours sleep/day with sleep difficulties and severe tiredness, ³ Latent Class Three: ~6.6 hours sleep/day with sleep difficulties and severe tiredness, P-value determined by ⁴Fisher's exact or ⁵X² for categorical data and ⁶ANOVA or ⁷Kruskal-Wallis for continuous data, ⁸LBW= Low birthweight (<2500g), ⁹Long labour = labour longer than 36 hours, ¹⁰HBW= High birthweight (>4000g), ¹¹Premature birth = <36 weeks gestation ¹²Neonatal Intensive Care Unit, ¹³Special Care Nursery. Bold text indicates significant result.

Table 5.3: Regression analyses for pregnancy, birth and postpartum outcomes according to sleeping behaviour pattern (n=491)

		Model 1		Model 2	
		Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Pregnancy outcomes					
Antenatal anxiety	LC2	1.810 (0.595 - 5.505)	0.296	1.725 (0.547 - 5.444)	0.352
	LC3	0.328 (0.038 - 2.843)	0.312	0.306 (0.034 - 2.780)	0.293
Antenatal depression*	LC2	3.558 (0.729 - 17.354)	0.117	3.267 (0.657 - 16.252)	0.148
	LC3	0.833 (0.075 - 9.297)	0.882	0.683 (0.057 - 8.231)	0.764
Gestational diabetes	LC2	0.478 (0.176 - 1.302)	0.149	0.383 (0.127 - 1.171)	0.093
	LC3	0.267 (0.059 - 1.214)	0.087	0.221 (0.045 - 1.079)	0.062
Gestational hypertension	LC2	1.733 (0.667 - 4.504)	0.259	1.692 (0.616 - 4.645)	0.307
	LC3	1.969 (0.701 - 5.642)	0.196	1.710 (0.572 - 5.115)	0.337
Birth outcomes					
Elective C-section	LC2	0.903 (0.524 - 1.556)	0.712	0.786 (0.441 - 1.400)	0.413
	LC3	0.807 (0.421 - 1.549)	0.520	0.583 (0.287 - 1.184)	0.136
Emergency C-Section	LC2	1.898 (0.911 - 3.957)	0.087	2.176 (1.000 - 4.739)	0.050
	LC3	1.274 (0.519 - 3.128)	0.597	1.470 (0.540 - 3.442)	0.512
Emotional distress during delivery	LC2	2.970 (1.479 - 5.965)	0.002	3.271 (1.589 - 6.736)	<0.001
	LC3	1.281 (0.522 - 3.145)	0.605	1.363 (0.570 - 3.794)	0.425
Epidural	LC2	1.597 (1.031 - 2.473)	0.036	1.907 (1.197 - 3.037)	0.007
	LC3	0.964 (0.566 - 1.642)	0.894	1.132 (0.640 - 2.003)	0.669
Episiotomy	LC2	1.407 (0.787 - 2.519)	0.250	1.619 (0.888 - 2.950)	0.116
	LC3	0.552 (0.238 - 1.280)	0.166	0.700 (0.294 - 1.665)	0.420
Gas use during labour	LC2	1.324 (0.844 - 2.075)	0.221	1.414 (0.885 - 2.258)	0.147
	LC3	0.762 (0.449 - 1.340)	0.346	0.932 (0.518 - 1.675)	0.814
HBW	LC2	1.035 (0.549 - 1.954)	0.915	1.069 (0.552 - 2.073)	0.843
	LC3	1.044 (0.501 - 2.178)	0.908	1.047 (0.484 - 2.267)	0.907
Induction of labour	LC2	1.339 (0.819 - 2.190)	0.244	1.345 (0.805 - 2.247)	0.257
	LC3	1.152 (0.645 - 2.055)	0.633	1.347 (0.735 - 2.469)	0.336
Long labour	LC2	1.383 (0.543 - 3.518)	0.469	1.541 (0.586 - 4.050)	0.380
	LC3	0.619 (0.161 - 2.384)	0.486	0.616 (0.153 - 2.477)	0.495
LBW	LC2	0.649 (0.181 - 2.337)	0.508	0.640 (0.170 - 2.470)	0.509
	LC3	0.551 (0.109 - 2.780)	0.471	0.517 (0.095 - 2.816)	0.446
Premature-birth	LC2	0.989 (0.340 - 3.877)	0.984	0.657 (0.302 - 4.028)	0.940
	LC3	0.470 (0.096 - 2.304)	0.352	0.421 (0.078 - 2.292)	0.317
Use of forceps	LC2	1.083 (0.653 - 1.796)	0.756	1.026 (0.977 - 2.145)	0.375
	LC3	0.464 (0.226 - 0.955)	0.037	0.499 (0.232 - 1.077)	0.076
Vaginal tear	LC2	1.469 (0.884 - 2.442)	0.138	1.506 (0.890 - 2.549)	0.127
	LC3	0.813 (0.432 - 1.559)	0.532	0.977 (0.498 - 1.912)	0.945
		Unadjusted b (95% CI)		Adjusted b (95% CI)	
Birth length (cm)	LC2	-0.776 (-1.545, -0.007)	0.048	-0.816 (-1.626, -0.005)	0.048
	LC3	-0.610 (-1.486 - 0.267)	0.172	-0.850 (-1.777 - 0.077)	0.072
Birthweight (kg)	LC2	-0.041 (-0.165 - 0.083)	0.513	-0.036 (-0.165 - 0.093)	0.585
	LC3	-0.001 (-0.141 - 0.139)	0.988	-0.028 (-0.176 - 0.120)	0.712
Postpartum outcomes					
NICU or SCN admission	LC2	1.817 (0.930 - 3.553)	0.081	1.886 (0.936 - 3.800)	0.076
	LC3	0.653 (0.246 - 1.734)	0.392	0.731 (0.267 - 1.999)	0.542
Postnatal anxiety	LC2	4.548 (1.677 - 12.331)	0.003	4.216 (1.518 - 11.708)	0.006

	LC3	1.016 (0.238 - 4.338)	0.982	0.946 (0.212 – 4.211)	0.942
Postnatal depression	LC2	2.328 (0.987 - 5.494)	0.054	2.142 (0.882 – 5.201)	0.093
	LC3	1.721 (0.628 - 4.722)	0.292	1.665 (0.580 – 4.782)	0.344
		Unadjusted b (95% CI)		Adjusted b (95% CI)	
Months breastfed	LC2	-0.399 (-1.976 – 1.177)	0.619	-0.330 (-1.935 – 1.274)	0.686
	LC3	-0.933 (-2.777 – 0.911)	0.320	-0.785 (-2.684 – 1.113)	0.417

Notes: Model 1: Univariate analysis, Model 2: Multivariate analysis controlling for BMI, self-rated health, difficulty managing on income, depression and trimester. *Antenatal depression not controlled for depression.

Abbreviations: LC1 = Latent Class One: ~ 7.7 hours sleep/day, with little to no adverse sleep associated symptoms LC2 = Latent Class Two: ~ 8.4 hours sleep/day with sleep difficulties and severe tiredness, LC3 = Latent Class Three: ~6.6 hours sleep/day with sleep difficulties and severe tiredness, Long labour = labour longer than 36 hours, LBW= Low birthweight (<2500g), HBW= High birthweight (>4000g), NICU = Neonatal Intensive Care Unit, SCN = Special Care Nursery. Bold text indicates significant result. Reference = LC1.

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Part C: Can we influence sleep to improve pregnancy and birth related outcomes?

CHAPTER 6

A pilot study to investigate the feasibility of increasing sleep opportunity on influencing gestational weight gain and glucose tolerance: Sleeping Mums Study

This thesis chapter is presented in the format of a manuscript as it is planned to submit this to a peer reviewed journal in the future.

6.1 Introduction

It is widely accepted that optimising gestational weight gain (GWG) an important and potentially modifiable factor that can impact on the short and long term health for both mother and baby (1, 2). A recent systematic review highlighted that interventions designed to reduce excessive gestational weight gain have two main behavioural targets, diet and/or physical activity (3). However, these interventions have only been able to reduce the amount of weight gained during pregnancy by 1-2kg, which is unlikely to influence clinical outcomes associated with GWG (3). This is further highlighted by the meta-analysis presented in Chapter 2, which reports that for women who are overweight or obese preconception, diet, physical activity and lifestyle strategies were ineffective at reducing the risk of GDM (4). Therefore, given the increasing rates of increased BMI preconception, excessive GWG and GDM, novel strategies are needed.

Short sleep and poor sleep quality have been shown to have strong relationships with increased body weight (5) and decreased glucose tolerance (6) in the non-pregnant population. As previously discussed, during pregnancy, sleep disturbances are common, regardless of whether women experienced any sleep disturbance prior to pregnancy (7).

Observational studies that have examined the relationship between sleep duration and glucose tolerance have produced conflicting results. Some studies have shown that decreased sleep time is associated with impaired glucose tolerance (8-11), while others including Chapter 5 of this thesis have found no relationship (12). Many studies have simply categorised sleep as short (<6.25 hours) or long duration. However, one study has observational study has attempted to find at what point sleep duration becomes clinically significant in terms of GDM risk. Interestingly, this study indicated that sleeping longer than 10 hours per night may actually increase the risk of GDM (10). Additionally, sleeping approximately nine hours per night during pregnancy is reported to provide the lowest risk for outcomes such as GDM (10).

Time in bed (TIB) is defined as the time a person physically spends in bed, often associated with low light conditions and limited stimuli but not necessarily sleep. Using data from the non-pregnant population it has been shown increasing time in bed has been reported to increase sleep time (13) and insulin sensitivity in adults (14). Multiple factors including light exposure and circadian misalignment of central and peripheral clocks may influence these outcomes (15). Previous studies have called for interventions to test the manipulation of sleep behaviour on pregnancy outcomes with objective outcomes (9, 11, 16). Observational studies have further suggested that interventions that increase maternal sleep time may have a substantial positive impact on glucose tolerance and therefore the long term health of mother and baby (9). In Australia, the average person aged between 25-44 years reports sleeping seven hours per night (17). Furthermore, up to 66% of adults report one or more sleeping difficulties (including difficulty falling asleep, waking up during the night, daytime tiredness or mood disturbances related to sleep (17). In pregnancy data from the ALSWH as

analysed in this thesis (Chapters 4 and 5), suggest that women in pregnancy are sleeping between 6.5-8.3 hours per night, with a high proportion experiencing common sleep disturbances. Therefore, it is likely women in pregnancy were not reaching the nine hours postulated to be the lowest risk of GDM (10). However, prospective intervention studies with objective measures of sleep are required to confirm causality (18) and inform evidence-based practice guidelines (11).

While sleep quantity has been postulated as a potential moderator of adverse pregnancy outcomes, sleep quality has more recently been postulated an important factor (19). This is supported by the observational studies using the ALWSH data presented in this thesis (Chapters 4 and 5) which suggest that sleep quality may increase the risk of adverse pregnancy, birth, postpartum and maternal pregnancy dietary intake (20). Furthermore, a recent meta-analysis suggested that objective but not subjective sleep quality is associated with an increased risk of GDM (19). Again, intervention studies are clearly needed to confirm causality (19).

A recent report suggests around 50% of Australians aged 25-44 years either watch television and/or are on the internet within an hour of going to bed (17). Melatonin is an important regulator of sleep-wake cycles and sleep quality (21). Light at night suppresses melatonin secretion (22). However, the wavelength of the light is potentially more disrupting than the brightness. The wavelength most disruptive to melatonin secretion is short wavelength (446-483nm) blue light (23), which is the form emitted by devices such as smartphones and computers. Exposure to blue light has a dose-like response to melatonin secretion, the more exposure to blue light the less melatonin is produced (22). This suggests that limiting light exposure at night may decrease the likelihood of sleep disturbance and

increase sleep quality and consequently, decrease weight gain and improve glucose tolerance in a pregnant woman. Research that explores the benefits of improving sleep quality and quantity in pregnancy is required to confirm causality of the relationships between sleep, weight gain and glucose tolerance (18, 19). Therefore, the aim of this study was to investigate the feasibility and acceptability of a sleep intervention designed to improve sleep opportunity and improve sleep quality through decreasing nocturnal light exposure during pregnancy in prima gravida women. The hypothesis being, a sleep intervention may be an effective method of improving lifestyle behaviour in pregnancy. Further, by ameliorating adverse sleep associated behaviours this may improve outcomes such as GWG and glucose tolerance.

6.2 Methods

6.2.1 Participants and setting

This feasibility study had a parallel randomised controlled design and was conducted in Melbourne, Australia from 2016-2019. Participants were recruited through Monash Health low-risk antenatal outpatient clinics. Ethical approval was granted through Monash Health Human Ethics Research Committee (HREC no. 16368A) and Monash University Human Ethics Research Committee (HREC no. 1163).

6.2.2 Eligibility criteria

Women were eligible to participate if they satisfied the following criteria: 18-45 years of age, ≤ 15 weeks gestation, primigravida and with a singleton non-complicated pregnancy.

Women were excluded on the basis of the following criteria: night shift work in the last three years (to reduce the risk of chronobiological misalignment), travel beyond three hours-time difference to Melbourne in the last three months or plans to travel across more

than three time zones during study period (again to reduce the risk of chronobiological misalignment), high risk of sleep conditions such as insomnia and obstructive sleep apnoea (as defined by the Insomnia Sleep Index (24, 25) and the Berlin Questionnaire (26), respectively), pre-conception diagnosed sleep disorders, pre-conception diagnosed mental health conditions, regular use of pharmacotherapies related to sleep, weight stability or metabolism (including sleeping tablets, opiates, steroids, hormone replacements, glycaemic control or sedatives), pre-existing metabolic health conditions (including but not limited to diabetes, thyroid disease and high cholesterol) and if they smoked.

Design: Study visits were matched with women’s standard antenatal care appointments (V1: 10-15 weeks, V2: 20-22 weeks, V3: 24-26 weeks, V4: 28-32 weeks). Study design is depicted in Figure 1. Following participant recruitment and screening participants provided informed consent. Participants were randomised using a computer-generated sequence compiled by a bio-statistician. Participants and personnel were not blinded in this study due to the nature of the intervention.

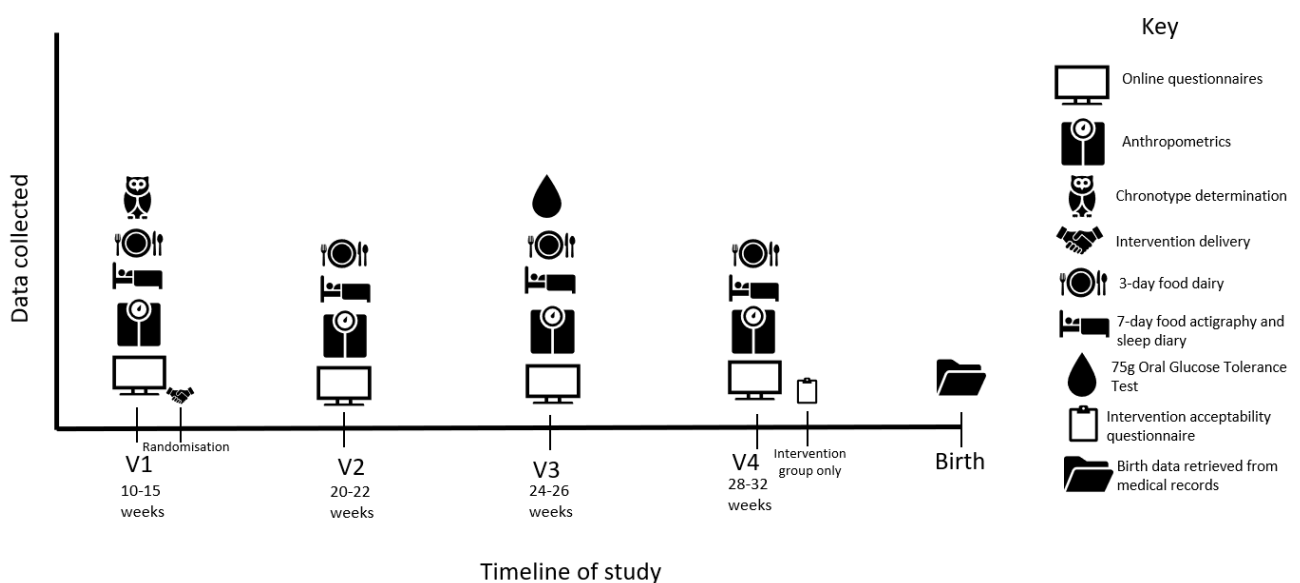


Figure 6.1: Study design and data collected at each visit

6.2.3 Intervention

The intervention involved a single education session delivered by a researcher, which was supported by a take home handout. It was underpinned by the Capability, Opportunity, Motivation – Behaviour change framework (COM-B) (27). The COM-B suggests education can change behaviour by increasing psychological capability and motivation through reflection (27). The intervention was delivered at a separate meeting to the four study visits. This design was used to enable uncontaminated baseline data collection and maximal intervention time. The education session informed participants of the scientific basis underpinning the link between sleep and weight gain and diabetes in the non-pregnant population. The intervention had an adaptation to improve acceptability as compliance to the intervention was low, hence the initial intervention will be referred to as Part A and the adapted intervention as Part B. Part A intervention (n=5) required participants to spend 10 hours' time in bed, on five nights per week for a minimum of 12 weeks, with limited blue, white and yellow light exposure during this time. The light restriction was discussed to include limiting exposure to TV, computer, handheld backlit devices and bright room light. During the meeting the participants current bedtime and sleeping behaviour was discussed, the researcher then discussed with the participant how to adapt to comply with the intervention. The handout was developed to educate participants on how to optimise their sleep hygiene to improve sleep quality (encouraging a regular sleep schedule, comfortable environment, relaxation before bed and reducing light exposure) and sleeping position (on side rather than on back). This handout was adapted from the Sleep Health Foundation '10 top tips for a good night's sleep' (28), 'Common Sleep Mistakes' (29), 'Sleep During Pregnancy' (30) and the National Sleep Foundation 'relaxation exercise' (31). Tips particularly pertinent to pregnancy related sleep disturbance were chosen for inclusion on

the handout. Participants were provided with a red-light torch (45.8 lux, measured in darkness at 12 inches and a direct angle) which they are instructed to use as the primary light source during the 10-hour restriction, including for trips to the bathroom, if necessary. After feasibility data were collected in regards to Part A (n=5) and results from the ALSWH chapters 4 and 5 were available, the intervention was adapted (TIB restriction was removed) and delivered as intervention Part B (n=5). Therefore, the Part B intervention focused on improving sleep quality.

Women in the control group were provided with standard antenatal care as per clinical guidelines in the hospital, with no specific advice given for sleeping behaviour. Both groups received a brochure containing the 'Australian Guide to Healthy Eating in Pregnancy' at baseline (32).

6.2.4 Outcome measures

Feasibility was assessed using Bowen *et al.* key areas framework for feasibility studies (33). The framework includes areas such as acceptability, implementation, practicality, adaptation and limited-efficacy testing. Demand, integration and expansion were not assessed as part of this study as it was outside of the scope of a novel pilot study.

Acceptability: Acceptability was assessed through an online questionnaire at the completion of the study for both Part A (n=5) and Part B (n=5) intervention participants. The questionnaire included questions about how many nights on average they believed they were able to comply to the intervention. Participants in the intervention group were asked to explore barriers and enablers to complying to the intervention through questions such as 'During the time you were part of the study, what stopped you from spending 10 hours in

bed without exposure to direct light?'. The answers to these questions complimented the objective sleep data collected.

Implementation: Implementation was assessed through the successful delivery of the intervention to the participants randomised to the intervention group.

Practicality: Practicality was obtained through identifying any protocol deviations due to limited resources. Any protocol deviations were recorded by the researchers at the time of protocol deviation.

Adaptation: Acceptability information was reviewed after Part A due to low compliance with the intervention. This was used to inform an intervention adaptation for Part B in an attempt to improve feasibility.

Limited efficacy testing: Limited-efficacy testing was conducted using the following sleep, physiological and dietary intake parameters:

Sleep parameters: Participants wore wrist actigraphy devices (Actiwatch Pro, Phillips Respironics) for 7 consecutive days and nights after each study visit. Participants were informed to wear the device at all times except for when exposed to water (showering, swimming etc) or participating in contact sport. A 7-day sleep diary was concurrently completed. The sleep diary noted bedtime, wake time, time to fall asleep and any reason for taking the watch off. The sleep diary was used in conjunction with actigraphy data to improve the validity of sleep data collected. The actigraphy data were analysed using Phillips Actiware 6.0.9 (Phillips-Respironics, Mini Mitter, Bend, OR). Actiwatches were configured for 30 second epochs. The default Actiware sleep scoring was utilised unless there was more than 10-minute deviation between actigraphy and sleep diary data. If there was more than a 10-minute deviation between actigraphy and sleep diary an informed decision was made

utilising the activity, light exposure and details reported in the sleep diary. Measures of sleep extracted from the data included nocturnal TIB, TST, SOL, WASO, sleep efficiency and time in bed before rise (time between waking and getting out of bed).

Physiological parameters:

Gestational weight gain: Preconception weight was self-reported at baseline. Weight was measured fasted, on a hard-flat surface, wearing light clothing on the same set of scales to the nearest 0.01kg at V1, V2, V3 and V4.

Body composition: Skinfold thickness was determined via Harpenden Callipers to the nearest 0.2mm. Skinfolds, arm circumference and height were measured according to the International Standards for Anthropometric (ISAK) standards by a level-1 trained anthropometrist (CB). As per ISAK protocol measurements were taken at a 90° angle. Two measurements of the skinfold were taken and averaged. Unless the difference between the two measurements were >7.5%, then a third measurement was performed and the median of the three measurements were used. Arm circumference was measured as the mid-point between the acromiale and radiale. The measurement was taken with a metal tape measure, at eye-level when the arm was relaxed by the participants side. Height was measured on a portable SECA stadiometer using stretch stature after the participant had been positioned using the Frankfort Plane. Body composition was determined via the LIMIT equation (using tricep, subscapular and bicep skinfolds, arm circumference and height) validated in a population of Australian pregnant women and suitable for those who are overweight or obese (34).

Glucose tolerance and birth outcomes: Glucose tolerance was assessed via a 75g 2-hour oral glucose tolerance test (OGTT) was conducted as standard antenatal care at 24-26 weeks gestation.

Birth outcomes included gestational age at delivery (weeks), delivery method (vaginal, planned caesarean section or emergency caesarean section) and birth weight (g). These data were extracted from medical records.

Dietary intake:

Dietary intake was assessed at all four visits via a three-day diet diary. The diet diary was completed for two-week days and one weekend day. Following the completion of the diet diary, a research dietitian reviewed the diary for completion and confirmed any ambiguous information. The food diaries were analysed using Foodworks 9 AusFoods2017 and AusNut2017 databases (Xyris Software Pty Ltd, Qld, Australia, 2017).

Covariate measures include demographics, mental health and chronotype data.

Demographic and chronotype data were collected at baseline via an online platform (Qualtrics XM, Provo, UT). The demographics questionnaire was adapted from the Australian Longitudinal Study of Women's Health (ALSWH), young cohort (born 1973-1975) (35). Chronotype was defined at baseline using the 'Owl and Lark' questionnaire (36).

Mental health status was captured through Edinburgh postnatal depression questionnaire, delivered online at all four visits (V1,V2,V3, V4) (37).

6.2.5 Statistical analysis

BMI was calculated as kg/m² and categories were as per the WHO BMI guidelines. Weight gain was calculated by two methods: measured weight gain and total gestational weight gain. Measured weight gain was calculated as the difference between baseline and V4 (28-

32 weeks gestation). Total weight gain was calculated as the difference between self-reported pre-pregnancy weight and weight at V4. Body fat percentage change was calculated as the difference between V4 body fat percentage and baseline body fat percentage. To assess differences between control and intervention, categorical statistics were analysed via chi-squared or Fishers exact if the expected cell count was <5. Continuous data were tested for normality. Mann-Whitney U test was performed on non-parametric continuous data to compare the difference between intervention and control or Phase A and B interventions. A repeated measures ANCOVA was planned for weight gain and body fat percentage, but due to data violating assumptions of normality, sphericity and equal variance, the test was not completed. Statistical analysis was guided by the Monash Biostatistics Platform. Statistical significance was set at $p < 0.05$.

6.3 Results

A total of 158 women were invited to participate in the study. Of these, 69 were screened and 21 were eligible and agreed to participate in the study, please see Figure 7.2 for more information. Demographic and characteristic information of women included in the analysis are available in Table 7.1. The sample had a median age of 30.0 (IQR: 28.5 – 31.5), pre-pregnancy BMI 22.2kg/m² (IQR: 20.5-24.4) and 100% of participants were living with their partner. The median gestational age of participants at baseline was 15.0 weeks (IQR: 14.0 - 15.0). Participants randomised to the intervention had a higher proportion of Caucasian ethnicity (80% vs 27%, $p=0.009$). On average women were followed up for 16.2 weeks, with no statistically significant difference between control and intervention groups in follow up ($P=0.809$).

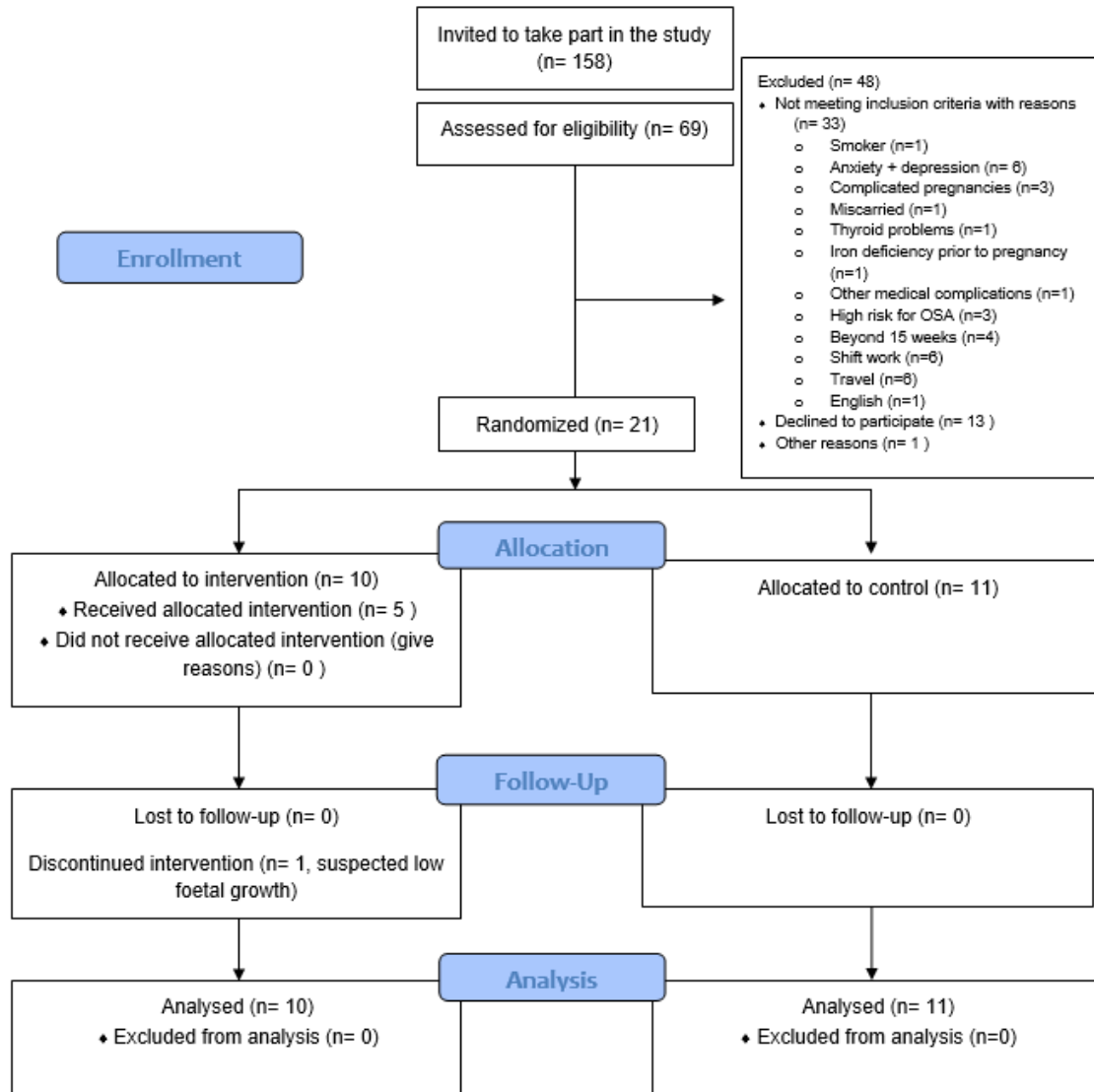


Figure 6.2: CONSORT flow diagram of included participants

Acceptability:

Part A: Participants in Part A intervention (n=5) reported that tiredness and darkness of evenings in winter helped them comply with the 10-hour in bed regime. Reported reasons that hindered compliance to the 10-hour regime were work commitments (60%), family commitments (40%) and TV/streaming services (40%). The non-compliance to the 10-hour in bed regime was confirmed by the actigraphy data as there was no difference in time in bed (mins), total sleep time (% or mins), sleep efficiency, wake after sleep onset (% or mins),

sleep onset latency (mins) or time to rise at V1, V2, V3 and V4 between intervention and control groups, data not shown. Due to this insight the intervention was adapted to Part B.

Part B: Participants in Part B (n=5) also reported the same enablers, reporting tiredness and darkness of evenings in winter helped improve their compliance to the intervention.

However, barriers for noncompliance to the light restriction were TV/streaming services (60%), not being able to sleep (40%), personal commitments like early morning exercise (20%) and social media (20%).

Implementation: A total of n=21 participants were randomised. All 10 participants randomised to the intervention received the intervention 1 week after the baseline data collection.

Practicality: There were no protocol deviations.

Adaptation: Due to acceptability data collected in Part A, Part B was adapted to remove the TIB restriction. However, all other parts of the intervention remained the same with the aim to develop an intervention that improves sleeping behaviour in pregnancy. There were no significant differences between Part A and Part B, at any visit in sleep parameters TIB (mins), TST (% or mins), sleep efficiency, WASO (% or mins), SOL (mins) or time to rise, as measured by actigraphy ($p > 0.05$ at all visits, data not shown).

Table 6.1: Demographic characteristics of intervention and control groups

Characteristics	Intervention (n=10)	Control (n=11)	P-value
	Median (25-75 th percentile)	Median (25-75 th percentile)	
Age (years)	29.5 (29-31)	30.0 (27.5-31)	0.654
Gestational age (weeks)	15.0 (14.0-15.0)	14.0 (14.0-15.0)	0.349
Pre-conception weight* (kg)	63.5 (56.0-67.0)	62.0 (55.5-72.5)	0.654
Pre-conception BMI* (kg/m ²)	21.7 (20.4 – 23.7)	23.9 (21.1 – 28.2)	0.197
First measured weight (kg)	67.9 (59.3-70.0)	65.6 (56.0-74.9)	0.973
Baseline body fat (%)	26.8 (23.1-28.9)	28.5 (26.5 – 33.0)	0.085
	% (n=)	% (n=)	
Living with partner	100% (10)	100 (11)	N/A
BMI			
Healthy weight	80 (8)	55 (6)	0.361 ^(F)
Overweight or obese	20 (2)	46 (5)	
Ethnicity			0.009 ^(F)
Caucasian	80 (8)	27.3 (3)	
Asian	10 (1) ^a	73 (8) ^a	
Pacific islander	10 (1)	0 (0)	
Education			0.635 ^(F)
Certificate/diploma	20 (2)	36 (4)	
University degree	80 (8)	64 (7)	
Household Income (AUD)			0.625 ^(F)
\$52,000-77,999	10 (1)	18 (2)	
\$78,000-103,999	10 (1)	9 (1)	
\$104,000 – 129,999	10 (1)	18 (2)	
\$130,000 -159,999	30 (3)	0 (0)	
>\$156,000	20 (2)	18 (2)	
Prefer not to specify	20 (2)	36 (4)	
Self-rated health			0.291 ^(F)
Excellent	40 (4)	9 (1)	
Very good	50 (5)	55 (6)	
Good	10 (1)	27 (3)	
Fair	0 (0)	9 (1)	
Neutral Chronotype	100 (10)	82 (9)	0.476 ^(F)
Low risk of depression [#]	80 (8)	91 (10)	0.586 ^(F)

Notes: ^a Denotes significant difference, *Self-reported, [#]As defined by the Edinburgh Post Natal Depression Scale, ^(F)Fishers exact test

Limited efficacy testing:

Sleep parameters: Overall the sample had a median 9.0 hours TIB (8.1-9.7), 7.2 hours (7.0-8.3) TST, 49.7 mins (41.3-60.7) WASO and 12.4 mins (9.5-15.1) SOL at baseline. Between each visit (ie. V1 and V2, V2 and V3 and V3 and V4) there were no significant differences in TIB (mins), TST (% or mins), sleep efficiency (%), WASO (% or mins), SOL (mins) or time to rise (mins), measured by actigraphy ($p>0.05$). The mean days of data collection via Actiwatch was 7.4.

Results of sleep parameters by randomisation groups are available in Table 7.2. The intervention group were spending more TIB than the control group (9.7 vs 8.2 hours, $p=0.019$ at baseline). There were no differences in any other sleep parameter at baseline. At V2 the intervention group continued to have longer time in bed than the control (9.5 vs 8.5 hours, $p=0.021$). There were no other differences between intervention and control group in other sleep parameters at any time point.

Table 6.2: Sleep Characteristics by intervention and control groups

Sleep characteristic	Median (25-75 th percentile)	Median (25-75 th percentile)	p-value*
Baseline	Intervention (n=9)	Control (n=9)	
TIB (hours)	9.7 (8.8-9.8)	8.2 (8.1-9.1)	0.019
TST (hours)	8.3 (7.2-8.6)	7.0 (6.3-7.8)	0.063
Sleep efficiency (%)	85.4 (83.0-87.7)	85.7 (83.0-88.4)	1.000
WASO (mins)	53.8 (45.2-60.7)	46.8 (37.6-56.5)	0.546
Wake time (%)	9.5 (8.0-11.8)	9.4 (7.4-11.4)	1.000
SOL (mins)	12.4 (10.7-16.8)	12.4 (7.3-14.3)	0.436
TIB before rise (mins)	13.0 (8.6-18.3)	11.7 (10.3-17.4)	0.863
Visit 2	Intervention (n=8)	Control (n=10)	
TIB (hours)	9.5 (8.8-9.8)	8.5 (8.2-9.0)	0.021
TST (hours)	8.0 (7.0-8.4)	7.0 (6.7-7.5)	0.068
Sleep efficiency (%)	85.9 (82.2-88.5)	83.9 (82.6-85.3)	0.237
WASO (mins)	45.4 (42.8-51.2)	43.4 (39.9-54.1)	0.573
Wake time (%)	8.3 (7.8-10.5)	9.8 (8.7-10.9)	0.515
SOL (mins)	13.9 (10.1-24.0)	16.2 (13.4-22.2)	0.897
TIB before rise (mins)	12.1 (6.3-16.5)	16.0 (13.1-19.8)	0.101
Visit 3	Intervention (n=7)	Control (n=10)	
TIB (hours)	8.6 (7.9-8.8)	8.4 (7.8-9.5)	0.962
TST (hours)	6.9 (6.6-7.4)	7.0 (6.6-7.3)	0.813
Sleep efficiency (%)	85.8 (82.2-89.1)	82.8 (79.4-87.5)	0.475
WASO (mins)	43.9 (32.9-55.3)	54.5 (29.2-64.1)	0.813
Wake time (%)	7.6 (7.2-11.5)	11.2 (6.5-12.6)	0.962
SOL (mins)	13.7 (10.1-16.9)	18.9 (13.5-27.9)	0.230
TIB before rise (mins)	7.2 (6.5-14.7)	19.5 (13.1-21.9)	0.070
Visit 4	Intervention (n=9)	Control (n=10)	
TIB (hours)	9.1 (8.5-9.9)	8.6 (8.3-8.9)	0.278
TST (hours)	7.2 (6.7-8.0)	7.2 (6.1-7.4)	0.604
Sleep efficiency (%)	85.7 (82.3- 88.7)	82.5 (79.6-86.3)	0.211
WASO (mins)	45.0 (32.4-50.3)	46.5 (39.4-57.9)	0.604
Wake time (%)	9.0 (7.8-9.7)	9.4 (7.9-13.2)	0.447
SOL (mins)	10.2 (8.8-18.7)	15.6 (10.4-19.5)	0.243
TIB before rise (mins)	11.6 (8.4-14.3)	14.6 (9.8-18.1)	0.549

Notes: *p-value obtained through Mann-Whitney U Test as data were non-parametric. Deviation in sample size is due to invalid actigraphy studies and n=1 withdrawal at before visit 4. Bold text signifies significant result.

Abbreviations: TIB = Time in bed, TST = total sleep time, WASO = wake after sleep onset, SOL = sleep onset latency.

Physiological parameters:

Physiological parameters (anthropometric, glucose tolerance and birth outcomes) are available in Table 7.3. The intervention group had higher total GWG (14.6 vs 8.9kg, $p<0.001$) and measured GWG (10.0 vs 8.0kg, ($p=0.007$), compared to the control group. However, there were no statistically significant difference in percentage body fat change, OGTT results, gestational age at delivery, GDM diagnosis or delivery mode.

Table 6.3: Physiological parameter measures by intervention and control groups

	Intervention (n=10)	Control (n=11)	p-value
	Median (25-75 th percentile)	Median (25-75 th percentile)	
Total measured weight gain (kg)	10.0 (9.1-11.3)	8.0 (6.7-8.6)	0.007
Total weight gain (kg)*	14.6 (13.6-15.0)	8.9 (7.0-10.7)	<0.001
Total body fat change (%)	4.5 (4.1-5.2)	2.9 (1.6-4.0)	0.056
OGTT Fasting (mmol/l)	4.4 (4.2-4.4)	4.6 (4.4-4.9)	0.095
OGTT 1 hour (mmol/l)	6.5 (5.8-7.3)	7.8 (6.7-9.1)	0.067
OGTT 2 hour (mmol/l)	6.0 (4.4-6.6)	6.1 (5.1 -7.6)	0.295
Birth weight (g)	3313 (3140-3400)	2900 (2785-3393)	0.251
Gestational age at delivery (weeks)	39.7 (39.0-40.1)	39.6 (38.9 – 40.0)	0.468
	n (%)	n (%)	
GDM diagnosis (ADIPS)	1 (10)	3 (27)	0.586
Emergency C-Section	2 (20)	2 (18)	1.000

P-value obtained through Mann-Whitney U Test for continuous data or Fishers exact for categorical data.

Dietary intake:

Dietary intake of intervention and control groups are presented in Table 7.4. The intervention group consumed significantly more fibre at baseline, compared to control (35g vs 24g, p=0.043). There were no other significant differences in macronutrient intake at any time point.

Table 7.4: Macronutrient intake by randomisation status			
Outcome	Intervention (n=10)	Control (n=11)	P-value
Nutritional intake			
Energy (kJ/day)	Intervention (Med (IQR))	Control (Med (IQR))	
V1	8300 (7203 – 10384)	8427 (7566 – 10047)	0.756
V2	9778 (8011 -9983)	8294 (7622 - 8936)	0.132
V3	9749 (8643 – 10240)	8314 (7509 – 9384)	0.314
V4	9562 (8901 – 10229)	9510 (8510 – 10605)	0.941
Protein %E			
V1	16.8 (15.1 – 19.5)	17.5 (15.4 – 20.6)	0.654
V2	15.6 (13.2 – 17.9)	17.5 (14.8 – 20.4)	0.114
V3	16.7 (13.9 – 20.8)	16.5 (15.1 – 19.6)	1.000
V4	15.8 (15.2 – 18.6)	16.9 (13.5 – 18.2)	0.824
Fat %E			
V1	35.4 (31.8 – 39.5)	33.4 (28.5 -38.4)	0.387
V2	36.6 (33.4-37.8)	32.2 (29.4 – 35.0)	0.085
V3	35.7 (32.3 – 38.5)	32.7 (27.3 – 35.3)	0.387
V4	34.0 (32.5 – 36.1)	35.4 (31.9 – 37.9)	0.766
Saturated Fat %E			
V1	11.2 (10.1 – 12.4)	11.6 (9.6 – 13.3)	0.973
V2	12.8 (12.3 – 16.5)	12.6 (10.2 – 14.3)	0.349
V3	12.7 (10.7 – 15.6)	10.1 (8.7 – 12.4)	0.114
V4	13.9 (13.9 – 14.6)	12.9 (9.7 – 13.9)	0.112
Monounsaturated fat %E			
V1	16.0 (14.3 – 18.5)	15.5 (12.2 – 16.7)	0.426
V2	14.2 (13.7 – 16.6)	13.1 (11.6 – 14.0)	0.085
V3	15.3 (13.8 – 16.2)	14.8 (11.6 – 15.7)	0.705

V4	13.7 (12.3 – 14.2)	14.1 (12.6 – 17.2)	0.603
Polyunsaturated fat %E			
V1	6.6 (5.5 – 7.7)	5.7 (4.5 – 6.0)	0.223
V2	5.6 (4.9 – 6.8)	5.6 (4.7-6.6)	1.000
V3	6.3 (6.0 – 6.5)	6.3 (5.0-7.4)	0.654
V4	5.2 (5.8 – 5.9)	5.8 (4.8 – 7.6)	0.503
Carbohydrates %E			
V1	41.5 (37.0 -43.5)	41.9 (38.2 – 51.8)	0.512
V2	45.2 (41.2 – 46.4)	47.4 (42.2 – 49.8)	0.512
V3	42.4 (40.1 – 47.4)	47.4 (44.4 – 51.8)	0.349
V4	47.5 (39.1 – 48.8)	43.8 (42.2 - 49.3)	0.941
Starch %E			
V1	23.3 (19.8 – 24.7)	28.1 (22.5-34.5)	0.251
V2	24.7 (22.4 – 29.0)	30.5 (25.6 – 33.9)	0.223
V3	25.2 (22.8 – 28.4)	30.1 (26.7 – 34.3)	0.114
V4	27.0 (23.9 – 27.4)	26.6 (24.8 – 32.4)	0.824
Sugar %E			
V1	19.3 (18.0 – 22.7)	16.5 (14.9 – 21.8)	0.512
V2	18.8 (16.0-21.6)	16.9 (134.0 – 19.5)	0.314
V3	17.6 (16.7 – 20.1)	17.4 (16.1 – 18.3)	0.557
V4	17.4 (15.4 – 23.3)	17.8 (15.9 – 20.3)	0.824
Fibre (g)			
V1	35.1 (30.9-37.0)	24.0 (19.6 – 27.0)	0.043
V2	29.8 (27.8 – 36.7)	24.5 (20.3 – 28.7)	0.085
V3	31.9 (28.0-34.7)	25.0 (20.7 – 33.9)	0.251
V4	27.8 (24.9 – 29.4)	27.6 (24.5-29.1)	0.941
P-value obtained through Mann-Whitney U Test. *Based on self-reported pre-pregnancy weight.			

6.4 Discussion

This study was designed to explore whether a focus on sleeping behaviour had potential to become a lifestyle intervention during pregnancy. The intervention delivery and data collection protocol were considered to be practical. However, the intervention was not considered acceptable by participants, citing issues such as personal and work commitments, along with a reluctance to reduce nocturnal light exposure from streaming services and TV as the major barriers, even after the intervention was adapted to reduce time in bed.

Acceptability analysis showed that women struggled to comply with the intervention due to barriers beyond their individual responsibilities. Behaviour change theory suggests that motivation, capability and opportunity need to align before behaviour change will occur (27). The barriers to intervention compliance included personal and work commitments, which suggested that despite the intervention engaging motivation and capability, opportunity was not supported as part of this intervention, reducing behaviour change potential (27). Behaviour change maintenance is supported by five key elements: motive, self-regulation, resources, habit and both environmental and social influences (38). According to this theory, the barriers reported suggest women may have lacked the opportunity supported by their environmental and social influences, which may have impacted successful behaviour change (27, 38). The participants role in society (personally and professionally) significantly influenced their ability to sustain this behaviour. A previous study exploring barriers to changing lifestyle in pregnancy suggests that partner, family, midwife and/or peer support were important factors for successful behaviour change (39). These results provide important insights into supporting pregnant women to improve their

sleeping behaviour. Involving healthcare staff, partners and peers in future interventions may help ameliorate the barriers and gap in opportunity reported in this study.

The efficacy of the intervention on sleep parameters cannot be assessed as the intervention was not powered to detect such differences. In previous studies increased TIB has increased TST (13, 14). However, in these studies participants had habitual short sleep, other risk factors such as obesity and studies were conducted in the non-pregnant population.

Furthermore, interventions such as the one presented in this study focusing on sleep quality through sleep hygiene principles have reported improvements in self-reported sleep parameters such as SOL and quality (40). Despite the low power, women in both the intervention and control groups in this study were low risk of sleep disturbance and may have already self-selected healthy sleep habits. Despite the majority of pregnant women experiencing sleep disturbance of some kind, the breadth and severity of symptoms varies (41). An intervention such as the one trialled in this study may need to target those with clinically disrupted sleep. However, it must be noted that this intervention would not be suitable for those with or at risk of insomnia as bedtime restriction is clinically indicated (42). Furthermore, a recent intervention using sleep enhancement strategies in non-clinical sample of women in pregnancy focusing on relaxation, lifestyle and environmental factors resulted in increased TST and decreased WASO in the post-partum period (43). Therefore, potentially the data collection period for this intervention was too short to collect long-term implications. This study highlights the need for future research to elucidate guidelines or cut points for adequate sleep in pregnancy, which would allow identification of those outside the 'normal' ranges and consider post-partum sleep implications.

While there was no difference in risk of depression in the women enrolled in this study, poor mental health is a significant barrier to adequate sleep in pregnancy (44). This was highlighted by Chapters 4 and 5 of this thesis, where the prevalence of depressive symptoms had a stepwise relationship with sleep latent classes. Mental health has a bidirectional relationship with sleep quality and quantity (44, 45). However, observational evidence suggests that poor sleep quality in early pregnancy may predict risk of depression in later pregnancy (46, 47). Further, sleep quality in late pregnancy has been identified by multiple studies as a risk factor for post-partum depression (48, 49). Future research investigating the impact of a sleep focused psychological intervention (cognitive behavioural therapy) on aspects of mental health is currently being conducted, but results not yet available (50). It is recommended for future research investigating the role of sleep as a lifestyle intervention in pregnancy either consider mental health in the intervention design or monitor mental health throughout the intervention to allow post-hoc analysis.

The most cited barrier by participants to reduce nocturnal light exposure was the inability to restrict streaming services and TV screen time. This was an important finding that must be considered in future intervention design. Depending on the device these services were consumed, the light may change the damaging effect on melatonin production. Melatonin is a hormone primarily produced by the pineal gland which facilitates sleep in humans (51). However, to a lesser extent it is also produced by the ovaries and placenta (52). Melatonin production is primarily controlled by the circadian rhythm. However, the pineal melatonin circadian rhythm can be disrupted by light exposure (51). Even exposure to light from regular room lighting before going to bed has been shown to affect melatonin secretion, affecting sleep length and quality (53). In pregnancy, nocturnal serum melatonin steadily increases throughout the gestational period (54) and readily crosses the placental barrier

(52). It is hypothesised that melatonin may influence foetal maturation and pre-eclampsia risk (52). It is currently unclear whether light disruption to melatonin may influence this proposed action. Evidence from pregnant shift workers who are often exposed to light during the night are known to have disrupted melatonin secretion (55, 56) and have higher rates of pregnancy complications such as LBW and SGA (57). Therefore, future research is needed to: i) explore the mechanism between melatonin and pregnancy outcomes and ii) consider strategies to improve the acceptability of a light restriction. Possibilities may include testing smart phone applications that reduce blue light exposure or adjusted room lighting.

This study has many strengths, but also some limitations. A strength of this study was the ability to recruit and retain women at a public hospital engaging in standard antenatal care. However, this form of recruitment was slow and labour-intensive. Internet recruitment has been suggested as a possible solution to improve the feasibility of recruitment (58). It must also be noted that compared to Australian women of a similar age, this sample had an increased proportion of higher education (64 and 80% vs 40%) (59), which may reduce the generalisability of these results. A strength of this study was the use of objective sleep data because it provides reliable sleep information as compared with the gold-standard polysomnography (60). However, the data collection method used to collect the objective sleep data resulted in 13.3% (n=11 records) of actigraphy data being invalid due to hardware failure. Despite this amount of invalid data, TIB, TST, WASO and SOL were all comparable to previous actigraphy studies in pregnancy (61, 62). Another limitation of this exploratory study was the lack of stakeholder engagement into the intervention design itself. This may have contributed to the low compliance to the intervention. It has been shown that involving end-users in intervention design can improve the acceptability, sustainability and

quality of the intervention. This may have contributed to the low compliance to the intervention. It has been shown that involving potential end-users in intervention design can improve the acceptability, sustainability and quality of the intervention (63). It is recommended that future interventions considering sleep as a lifestyle factor in pregnancy utilise the co-design framework to improve acceptability (64).

6.5 Conclusion

This intervention was designed to increase sleep opportunity and increase sleep quality through reduced nocturnal light exposure; however, the intervention was not found to be acceptable. Reported barriers to compliance included reluctance to reduce nocturnal TV and streaming services and personal and work commitments. This study provides important insights to change the sleeping behaviour of pregnant women, including needing social support (family and work) and reliance of blue light emitting devices at night. Future studies should endeavour to elucidate what the optimal sleeping behaviour in pregnancy is to reduce pregnancy complications and how best to support women to obtain such sleeping behaviour.

6.6 Future directions

The learnings from this exploratory feasibility study suggest that future studies should aim to determine whether sleep quality and/or quantity can be manipulated to reduce the risk of excessive GWG and GDM. It is not recommended that data from this study is used for a power calculation as the intervention had low compliance and therefore the effect size does not represent the efficacy of the intervention. Pilot studies are imperative to test the feasibility of interventions and therefore are encouraged to have less focus on hypothesis testing and efficacy testing (65). This was the first study investigating the role of sleep in

GWG and glucose tolerance. Therefore, further preliminary work needs to be conducted before a larger powered trial could occur. It is recommended that the target for this intervention to be sleep quality rather than quantity, given the results of this study and the findings from both Chapters 4 and 5. It is recommended that any future studies use following key learnings from this study which are as follows:

1. Australian women are willing to engage in a study involving sleep as a novel lifestyle factor during pregnancy.
2. Women need to be consulted on how best to support them to improve their sleep quality and quantity.
3. Other options to improve melatonin secretion may include removing barriers to accessing devices, such as testing blue light filters on smartphones.
4. Involving bed partners may help provide the support necessary to change sleep habits during pregnancy.
5. Advice provided on-line and accessed by women can be misleading and needs to be addressed in any sleep intervention (66).
6. Objective measures of sleep need to be incorporated into clinical trials to ensure that both quantity and quality of sleep can be measured.

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**Part D: What does this all mean and where to from here?
Discussion and recommendations for research and practice**

CHAPTER 7

Discussion and Future directions

7.1 Preamble

The work presented in this thesis was informed by the growing literature base which suggests that short sleep and poor sleep quality increases the risk of chronic diseases such as obesity, T2DM and cardiovascular disease (1-3). This, coupled with our knowledge of the prevalence of sleep disturbance in pregnancy (4), the question was asked:

‘What impact does sleep quality and quantity in pregnancy have on dietary and physiological outcomes?’

To answer this question three parts were defined:

Part A: What interventions are currently being used to reduce excessive gestational weight and do they have any impact on risk of GDM or infant birthweight?

Part B: Is there a relationship between sleep in pregnancy and outcomes such as dietary intake and pregnancy outcomes?

Part C: If a relationship is found, can we design an intervention that is feasible that aims to manipulate sleeping behaviour to improve pregnancy outcomes?

7.2 Summary of main findings

7.2.1 Part A: What interventions are currently being used to reduce excessive gestational weight and do they have any impact on risk of GDM or infant birthweight?

Impact on GDM (Chapter 2):

Diet and PA interventions reduced the risk of GDM. Lifestyle interventions and BMI did not significantly influence GDM risk. However, the efficacy of the interventions differed by pre-pregnancy BMI and country of origin. Therefore, this study does not support a blanket approach to GDM reduction. It highlighted that intervention needs to occur earlier for women who are overweight and obese preconception, as no intervention was effective in reducing the risk of GDM in this population. Furthermore, factors such as cultural acceptability of the intervention need to be considered.

Impact on infant anthropometrics (Chapter 3):

Overall, interventions designed to reduce excessive GWG also reduced infant birthweight, risk of macrosomia and LGA. Interventions did not significantly impact negative outcomes such as LBW and SGA. When analysed by intervention category (diet, physical activity and lifestyle), dietary interventions were the most effective. Diet interventions reduced birthweight in women without GDM and 211g in women with GDM. Therefore, interventions designed to reduce maternal weight during pregnancy can reduce infant birthweight without increasing the risk of negative outcomes such as SGA or LBW.

7.2.1.2 Discussion and future directions

Overall this work suggests that interventions designed to reduce excessive GWG have positive impacts on glucose tolerance and infant birthweight. Potentially these results are interrelated as poor glucose tolerance during pregnancy is a risk factor for larger birthweight infants. However, whether this is the mechanism behind the results of chapters 2 and 3 is beyond the scope of these reviews. Results indicate that dietary interventions were the most effective at reducing the risk of GDM and increased birthweight.

Furthermore, lifestyle interventions whereby two lifestyle behaviours are changed at once were less effective than single behaviour strategies in women without GDM.

Results showed that the efficacy of the intervention varies by country of study. Therefore, cultural and/or genetic factors may influence the efficacy of interventions designed to influence these outcomes. Currently, there is no global consensus on the best way to collect data on ancestry/ethnicity for use in biomedical and clinical studies. Developing standardised terminology has been highlighted by the US National Institute on Minority Health and Health Disparities as a research priority (5). Cultural learning orientation may also be an important factor to consider when delivering interventions to diverse cultural populations (6). This finding has been highlighted by a recent paper investigating the ethnic differences in the dietary management of GDM. The findings from this paper suggest that Chinese migrant women consider Australian dietary management of GDM to be void of cultural sensitivity (7). While this paper highlights issues with treatment and not prevention, it supports the findings of this thesis that interventions need to be culturally appropriate. As migration to countries such as Australia continues to increase (8), factors such as these may provide further insights as to why some interventions are successful in some samples but not in others.

The results of the GDM systematic review further highlighted that for women who were overweight or obese pre-conception, interventions delivered in pregnancy were not effective in reducing the risk of GDM. However, women with GDM who received the intervention with a dietary component had smaller babies than those who did not receive the intervention. This highlights that women with overweight and obesity may have different GDM aetiology to those that enter pregnancy overweight or obese. While

excessive energy intake and subsequent weight gain may contribute to GDM risk, it is likely that women that enter pregnancy with obesity may also have underlying glucose intolerance, beta-cell dysfunction and inflammation which significantly increases the risk of GDM independent of weight gain (9). This theory has been explored through observational data considering mothers with GDM (10). The offspring from mothers who were overweight or obese and had GDM had increased odds of being born macrosomic, LGA and having a BMI Z-score within the overweight range during childhood when controlling for GWG, compared to mothers with GDM within the healthy weight range (10). Highlighting the need to support women preconception and in early pregnancy to reduce the risk of adverse intrauterine metabolic programming (10) and maternal metabolic phenotypes later in life (11).

The studies presented in this thesis suggest that for women who are overweight or obese early intervention is necessary to reduce the risk of adverse pregnancy complications and most importantly the intervention is required to have a dietary component. However, this would require systematic change. Currently, dietitians are only involved in antenatal care after GDM diagnosis is made. To bridge this gap, dietitians or other upskilled health professionals would be involved to provide dietary advice in a prevention paradigm, to reduce burden and costs associated with developing GDM.

7.2.2 Part B: Is there a relationship between sleep in pregnancy and outcomes such as dietary intake and pregnancy outcomes?

7.2.2.1 Summary of results

Two questions were asked of the data from a representative sample of Australian pregnant women:

1. Is there a relationship between sleeping behaviour in pregnancy and dietary intake?
(Chapter 4)
2. Is there a relationship between sleeping behaviour in pregnancy and pregnancy, birth and postpartum outcomes? (Chapter 5)

The results from Chapters 4 and 5 indicate that there is a relationship between sleep quality and dietary intake and pregnancy, birth and postpartum outcomes. After adjusting for potential confounders, women with sleeping behaviour classified by average sleep length (~8 hours) and sometimes or often experiencing adverse sleep-associated symptoms (severe tiredness, difficulty sleeping and restless sleep) were associated with a lower percentage energy (%E) total fat and %E monounsaturated fat and higher intake of %E carbohydrate, compared to women with average sleep length and no adverse sleep-associated symptoms. In terms of pregnancy, birth and postpartum outcomes, models adjusted for potential confounders showed that women with sleeping behaviour categorised by average sleep length and adverse sleep-associated symptoms were associated with a greater likelihood of emotional distress during delivery, emergency C-section, epidural and postnatal anxiety. Unexpectedly, no relationships were found between women with short sleep (~6.6 hours) and diet, pregnancy, birth or postpartum outcomes, compared to women with average sleep length and no adverse sleep associated symptoms.

7.2.2.2 Discussion and future directions

Results indicate that sleeping behaviour is a likely target for future interventions that aim to optimise pregnancy outcomes. However, these findings alone cannot confirm the directionality of the relationship or the optimal sleeping behaviour during pregnancy, due to the observational nature of the data collected. However, the results suggest that sleep may

be a useful target to optimise pregnancy outcomes and therefore screening women in pregnancy for poor quality sleep may help identify women at higher risk of post-partum complications.

Interestingly, no associations were found between short sleep and dietary intake, pregnancy, birth or postpartum outcomes in both studies. This may be explained by: i) sample size; ii) sleep misperception; iii) short sleep not short enough and iv) inter-individual sleep requirement variation. Firstly, the sleeping behaviour group categorised by short sleep length (LC3) had the lowest proportion of participants. This may have impacted the strength of the regression analysis. However, the analyses followed the prudent rule of having at least 10 participants per covariate included in the regression model (12). More recent reports have suggested sample sizes as low as 2 participants per co-variate provide adequate strength to regression analysis to reduce type-1 error (13). Second, it is possible that the 'short sleep' group (LC3) may have underestimated how much they were actually sleeping. Sleep misperception is a common trait of those with short sleep (14). In a clinical sample of those with insomnia despite objective measures such as EEG detecting sleep onset, those with insomnia perceived this sleep as wakefulness (14). Third, and related to the second reason is that sleep length may not have been short enough to have physiological impact. A recent systematic review reported <6.25 hours sleep each night was associated with an increased risk of GDM (15). Therefore, coupled with possible sleep misperception, the sample in this analysis may not have had sleep short enough to negatively influence physiological mechanisms. Fourth, there may be interindividual variations in sleep requirements. Just as we recognise individuals require different energy intake, it is recognised that individuals may require different quantities of sleep (16).

Therefore, a hypothesis as to why this sample did not show any association between short

sleep and adverse pregnancy, birth and postpartum outcomes may relate to the inter-individual variation in required sleep for adequate functioning. Therefore, the unexpected results found in these studies may be partially explained by one or a combination of these factors.

7.2.3 Part C: If there is a relationship can we design a feasible and acceptable intervention to manipulate sleeping behaviour to improve pregnancy outcomes (Chapter 6)

7.2.3.1 Summary of results

Results from Chapters 2 and 3 confirmed that no intervention involved a sleep component as a method of reducing excessive GWG. Results from Chapters 4 and 5 suggested that poor sleep quality was associated with increased carbohydrate, decreased fat and monounsaturated fat, and outcomes such as likelihood of emotional distress during delivery, epidural use, need for an emergency caesarean section and postpartum anxiety. Considering these results, a feasibility study was conducted to investigate if manipulating sleeping behaviour in pregnancy was feasible.

Acceptability data collected from participants post-intervention suggested that this was not an acceptable method of manipulating sleep in pregnancy. The major barriers to acceptability included: time commitments (personal/work) and TV/streaming services. Therefore, an adaptation was conducted (Part B intervention) in an attempt to improve acceptability, removing the time in bed restriction and only including the light restriction. This was also not found to be feasible as due to similar reasons including TV/streaming services and participants reporting not being able to sleep. There were no differences in any

parameters of sleep quality or quantity between Part A and B intervention or control and intervention at any time point.

7.2.3.2 Discussion and future directions

This intervention trialled a novel method of engaging women in a lifestyle intervention using sleep as the main vehicle. While this intervention was not considered feasible it does show that women were willing to engage in a sleep intervention during pregnancy. It also provides important guidance for future studies planning to utilise sleep as a lifestyle intervention in pregnancy.

This study used a light restriction intervention. Since the completion of the study, further study has provided insight, suggesting a light intervention may be appropriate for individuals who are highly sensitive to light. A recent study conducted by Phillips *et al.* showed that there are significant variations in light sensitivity at night (17). At 30 lux (dim indoor light at night or light emitted by electronic devices) can cause 50% melatonin suppression (17). Furthermore, some participants had the same response to a 10-lux light source (17). Indicating that while most people are sensitive to light at night, some individuals may be highly sensitive and may therefore provide an optimal target for an intervention such as that trialled in the Sleeping Mums Study (Chapter 6). However, at present there is no simple test to determine intraindividual differences to melatonin suppression as the study by Philips *et al* was the first to systematically investigate this theory (17). A Dim Light Melatonin Onset saliva test would be required in conjunction with systematically testing response to levels of light exposure (17). In the future it would be ideal in the clinical setting to have a screening tool to identify those who are highly sensitive to melatonin.

Optimal sleeping behaviour in pregnancy is still unknown. In the non-pregnant population, the sleep guidelines published by The National Sleep Foundation were updated in 2015 to include age specific recommendations for optimal sleep duration (18). While many studies show inverse associations between short sleep duration, poor sleep quality and adverse outcomes such as GDM and pre-term birth, it is still unclear at what point sleeping behaviour becomes a risk factor for adverse outcomes (15, 19-21). For example, it is clear that when considered as a categorical variable short sleep is associated with increased risk of GDM (15). However, the definition of short sleep ranges from ≤ 4 hours to < 9 hours (15, 21). The authors of a recent systematic review suggested a cut off of 6.25 hours, based on data from the non-pregnant population (15). However, this does not consider that the majority of the pregnant population will experience sleep disturbance (22). It is recommended that future studies distinguish at what point sleep duration starts to increase the risk of adverse antenatal and post-natal outcomes. Ideally, this would be a powered randomised controlled trial to test the hypothesis that a lifestyle intervention including sleep duration and sleep quality advice positively impacts on health outcomes such as GDM.

7.3 Overall strengths and limitations

Chapters 2,3,4,5,6 and have individual study strength and limitations identified in the discussion section of each chapter. Chapters 2,3 and 4 have been peer reviewed, strengthening the manuscript with objective input from peers, reviewers and editorial staff.

A strength of this research is that it builds upon previous research investigating the role of sleep in pregnancy and outcomes and provides an Australian perspective. Chapter 4 is one of three studies globally to which has investigated the impact of sleep duration and quality in pregnancy on dietary intake (23-25). It was the only study to report macronutrient

intakes, providing important insights into the relationship between sleep and dietary intake during pregnancy. Furthermore, Chapters 4 and 5 support previous research, confirming that sleep quality is associated with postpartum mental health (26-29). However, previous research heavily features women from with Asian ethnicity or from low socio-economic status on supplemental nutrition programs. Therefore, Chapters 4 and 5 improve generalisability of findings, improving the potential of translation. Chapter 6 provides the first randomised controlled trial to focus on sleep in pregnancy as a mode of influencing lifestyle behaviours. This provides the first step in understanding the causal relationship between sleep and factors such as GWG, GDM, pregnancy outcomes and maternal diet. Limitations include the education level of participants within all three samples included in this thesis (Chapters 4,5 and 6). All samples reported significantly higher proportions of women with post-school education, compared to the national average (30). This is a common limitation of research in pregnancy and clinical trials more broadly (31). It is internationally recognised that maternal education above schooling level (12 years) is a protective factor for pregnancy outcomes such as SGA babies (32), pre-term birth (32) and maternal mortality (33). Lower levels of maternal education, coupled with increasing gestation and income have been shown to be significant risk factors for poor quality of sleep (22). Therefore, the participants included in this thesis are unlikely to represent women at highest risk of sleep disturbance and/or pregnancy complications. However, this research provides for the first time an insight to the relationship between maternal sleep and pregnancy complications. Sleep provides a cost effective and accessible resource for all women, particularly those of low education or SES. Consequently, it would be advantageous for future research to consider the feasibility of engaging a more vulnerable populations, such as those of a lower education level in sleep in pregnancy interventions.

7.4 Future directions

7.4.1 Rationale

This thesis addressed an important innovation in our need to support change in modifiable behaviours during pregnancy. Chapter 2 showed that earlier intervention is required to reduce the risk of developing GDM if a woman enters pregnancy overweight or obese. This poses a significant issue as screening for GDM in Australia occurs at 24-26 weeks, at which point it may be too late to intervene (34). Considering a large proportion of the obstetric population gain excess weight (35, 36) and the prevalence of GDM is still increasing (37), new and novel approaches are needed. This thesis has showed that sleep is related to dietary intake, maternal mental health and need for an emergency caesarean section (Chapters 4 and 5). However, Chapter 6 identified some enablers and barriers to changing sleep behaviour in pregnancy. Given the learnings from this thesis, a proposed plan for future research will be outlined.

7.4.2 Proposed study background

General Practitioner's (GPs) often have the first contact with women on confirmation of pregnancy. Research shows they are most trusted source of information during pregnancy and are therefore well placed to provide early advice about lifestyle (38). However, GP's time is limited (39). At confirmation of pregnancy there are a multitude of competing clinical priorities needing to be covered by the GP, including genetic risks, smoking, vaccinations, folic acid, cervical screening, psychosocial health, toxoplasmosis, listeriosis, mercury as well as monitoring their health and arranging scans etc (40). Given the breadth of information that needs to be covered at this time, it is recommended that GPs refer to women to

appropriate accessible resources and services to help support lifestyle change for a healthy pregnancy (40).

It is now argued that access to the internet should be considered a human right (41). This highlights how ingrained the internet has become in our lives. Furthermore, in Chapter 6, the Sleeping Mums Study showed that pregnant women constantly connected to devices such as smart phones. Unsurprisingly, the interest in delivering health services over the internet is growing in popularity. Tele-health is now a service utilised by providers needing to cover large geographical and/or remote areas (42). Online platforms have been successfully utilised to reduce excessive GWG at a lower cost than traditional face-to-face methods (43).

Therefore, it is proposed that future research should consider an intervention to be delivered via a centralised online, user-friendly and evidence-based platform. There are many documented factors that influence translation of research into the clinical setting including but not limited to; competing demands, limited resources and limited organisational support (44). Interventions that are not scalable have limited ability to be translated and have reduced capacity to make the leap from academia to changing clinical best practice (45). Assuming success, this model would provide a method that could be easily scaled-up and incorporated as an adjunct to standard care. The approach provides the ability for women to access information and support at a time that suits them regardless of their geographical location, without adding additional burden to the healthcare system.

7.4.3 Proposed study design for future research

Aim: To determine if a multi-component lifestyle early intervention can influence glucose tolerance at the point of routine clinical screening for gestational diabetes (GDM) which

occurs between 24- and 28-weeks' gestation, compared to an active control.

Hypothesis to be tested: Women with unlimited and free access to an online interactive multi-component lifestyle advice will have improved glucose tolerance compared to those exposed to standard information online information (active control).

Participants eligible for inclusion would be primipara women with a singleton, non-complicated pregnancy with access to the internet.

The proposed intervention would be an online platform made available to women by GP's at confirmation of their pregnancy. Findings from this thesis and current literature recommend an intervention that will target glycaemic control by utilising the following lifestyle strategies; i) a sleep component for participant and bed partner which supports healthy sleep during pregnancy (including addressing barriers to sleep, managing sleep disturbance and light exposure including screen time) and ii) adoption of a low GI dietary pattern which will be themed to ensure that culturally specific advice is provided.

To ensure acceptability it is recommended that the intervention be developed using the principals of co-design (46). Co-design is a methodology by which the end-user in the process of designing the intervention to ensure acceptability and feasibility (46). The participants engaged in co-design would be required to be from a range of education levels, cultural and socio-economic backgrounds. This form of intervention development has been recommended to ensure information is accessible to the layperson and include culturally specific information to ensure that the diverse multicultural groups (including Chinese and Indian in Australia) are catered for with cultural learning orientation as cultural acceptability impacts intervention efficacy (47). Feasibility and acceptability would be assessed using the Bowens et al framework (45) as well as the Technology Acceptance Model (48). This

proposal presents an immediately scalable approach to fill the literature gaps raised by the work presented in this thesis.

7.5 Overall conclusion

In conclusion, sleep quality may be a useful strategy to optimise pregnancy outcomes. This thesis investigated the impact of sleep in pregnancy from a theoretical, observational and interventional approach. Previous research has not leveraged sleep during pregnancy as an intervention target to improve outcomes such as GWG, GDM or infant anthropometrics. Results show that optimal sleep length (approximately 8 hours/night), without significant disturbance may positively influence dietary intake and pregnancy outcomes. However, the intervention trialled, which increased time in bed and decreased light exposure, was not considered acceptable by participants. This feasibility study provided important insights for future research. Interventions targeting sleeping behaviour in pregnancy are recommended to consider the significant barriers (family and work commitments and TV/streaming services) identified. Supporting women to improve sleeping behaviour in pregnancy may provide a novel and accessible method of improving the health of both mother and baby and should be a priority for future clinical trial.

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Appendix 1 –Interventions designed to reduce excessive gestational weight gain can reduce the incidence of gestational diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials (Publication)

Appendix 2 – Medline search strategy for systematic reviews (Chapters 2 & 3)

1. pregnan*.tw.
2. exp Pregnancy/
3. gestational diabetes.tw.
4. exp Diabetes, Gestational/
5. antenatal.tw.
6. exp Prenatal Care/
7. 1 or 2 or 3 or 4 or 5 or 6
8. intervention*.tw.
9. exp Early Medical Intervention/
10. diet*.tw.
11. nutrition*.tw.
12. exp Diet/ or exp Diet Therapy/
13. pharmacotherap*.tw.
14. exp Drug Therapy/
15. exp Text Messaging/
16. exp Telemedicine/
17. Exercis*.tw.
18. (physic* adj1 activ*).tw.
19. exp Exercise/ or exp Exercise Therapy/
20. sleep*.tw.
21. (nap or naps or napping*).tw.
22. (eHealth or eHealth or mHealth or mhealth).tw.
23. (smartphone or SMS or text messag*).tw.
24. snor*.tw.
25. apn?ea.tw.
26. exp Sleep/
27. counsel*.tw.
28. exp Counseling/
29. exp Behavior Therapy/
30. lifestyle.tw.

31. life style.tw.
32. exp Life Style/
33. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. weight.tw.
35. exp body weight/ or exp birth weight/ or exp body weight changes/ or exp weight gain/ or exp weight loss/
36. 34 or 35
37. 7 and 33 and 36
38. Randomi#ed controlled trial.pt.
39. controlled clinical trial.pt.
40. randomi#ed.ab.
41. placebo.ab.
42. clinical trials as topic.sh.
43. randomly.ab.
44. trial.ti.
45. 38 or 39 or 40 or 41 or 42 or 43 or
46. Animals/
47. Humans/
48. 46 not 47
49. 45 not 48
50. 37 and 49

**Appendix 3 –Attenuation of gestational weight gain SLR
(Publication)**

Appendix 4 - Monounsaturated fat intake is associated with improved sleep quality in pregnancy (Publication)

