The influence of macronutrient dietary patterns on pregnancy weight gain and birth outcomes

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Intellectual property and publication statements

The candidate confirms that the work submitted is her own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Publications and outputs

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1. Submitted a grant application to the BBMRI-LPC scientific call in 2016 for large cohort data access and was granted data access to explore three cohorts, namely MoBa (Norway), DNBC (Denmark) and LifeLines (The Netherlands) (application attached in Appendix A)

II Jai Ganesha II

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Abstract

There is limited and inconclusive evidence regarding the association between maternal dietary macronutrients (carbohydrate, protein and fat) and birth outcomes. The central aim of this project was to study maternal macronutrient dietary intakes through the generation of a unique maternal weight gain dietary pattern and its relationship to birth outcomes.

Analyses were conducted in three birth cohorts such as the CAffeine and REproductive Health study (CARE) in the U.K (N=1196), The Norwegian Mother and Child Cohort Study (MoBa) (N=85,574) in Norway and The Danish National Birth Cohort Study (DNBC) (N=63,755) in Denmark. The birth outcomes of interest were birthweight, and odds of small-for-gestational-age (SGA) and large-for-gestational-age (LGA) babies.

The thesis undertook a random-effects meta-analysis of three birth cohorts (N= 149,927 mother-infant pairs) to explore the association between maternal dietary macronutrient intakes and birth outcomes. The results showed an additional increment of 30g/day in dietary protein during pregnancy was associated with higher birthweights (20g, 95% CI 10g to 31g; I^2= 38%, combined p value<0.001) but, not with the odds of SGA and LGA babies.

Further, in MoBa, maternal dietary patterns were explored using principal component analysis (PCA). The results found that high “marine food” dietary pattern scores were associated with higher birthweights (5g; 95% CI 2g to 9g; p=0.005), and lower odds of SGA delivery (0.95; 95%CI 0.93 to 0.97; p<0.001), but not with LGA delivery. Also, high adherence to an “animal meat” dietary pattern was associated with a lower birthweight (-5g; 95%CI -9g to -1g; p=0.02) and higher odds of LGA delivery (1.06; 95% CI 1.04 to 1.09; p<0.001).

Furthermore, a unique set of gestational weight gain dietary patterns (GWGDP) were created in MoBa and DNBC using reduced rank regression (RRR) and included four risk factors. Based on previous literature from large systematic reviews, the four risk factors included for a analyses were total energy intake, smoking habits, pre-pregnancy BMI and physical activity. In MoBa, the results demonstrated that a high “fish and coffee” GWGDP score was associated with higher birthweight (6g; 95% CI -1g to 11g; p=0.01) and lower odds of LGA delivery (0.95, 95%CI 0.92 to 0.98; p<0.003). Further, high adherence to “animal meat and sugar-sweetened beverages (SSB)” dietary pattern in MoBa and “meat” dietary pattern in DNBC were associated with higher odds of LGA delivery (1.03, 95%CI 1.01 to 1.05; p<0.001) and (1.16; 95%CI 1.12 to 1.21; p<0.001), respectively.

In summary, this thesis found that no particular macronutrient appears to be associated with poorer birth outcomes such as odds of SGA and LGA babies within a well-nourished group of pregnant women. Therefore, macronutrient composition, as stated in the dietary reference

values (DRVs), is still warranted for optimised growth of the offspring. However, additional weight gain through excess energy intakes from protein and carbohydrate should be avoided.

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List of abbreviations

BCC	Bulk Centile Calculator
BMI	Body Mass Index
BW	Birthweight
CARE	Caffeine And Reproductive Health Study
CHO	Carbohydrate
CI	Confidence Interval
DHA	Docosahexaenoic Fatty Acid
DNBC	Danish National Birth Cohort
EFA	Eicosapentaenoic Fatty Acid
FAO	Food And Agriculture Organisation Of The United Nations
FFQ	Food Frequency Questionnaire
GDM	Gestational Diabetes Mellitus
GROW	Gestation Related Optimal Weight
HTN	Hypertension
LBW	Low Birthweight
LGA	Large-For-Gestational-Age
MFR	Medical Birth Registry
MoBa	The Norwegian Mother And Child Cohort Study
MUFA	Mono-Unsaturated Fatty Acid
NICE	The National Institute For Health And Care Excellence
NIPH	Medical Registry Of Norway
OR	Odds Ratio
PIH	Pregnancy Induced Hypertension
PUFA	Polyunsaturated Fatty Acid
SD	Standard Deviation
SGA	Small-For-Gestational-Age
WHO	World Health Organisation

Chapter 1 Introduction

1.1 Global burden of obesity

The WHO has defined obesity as abnormal or excessive fat accumulation that presents a risk to health and has suggested using body mass index (BMI) (weight in kg/height in metres^2) to measure it (WHO, 2016). A person with a BMI of 30 and above is classed as obese. The global burden of obesity has increased at a rapid rate in the past forty years. According to WHO, the worldwide prevalence of obesity has tripled between 1975 to 2016. In 2016, it reported that around 13% of the world's population is obese and around 40% of adults worldwide were overweight (WHO, 2016). Further, it reported that around 41 million children under 5 years of age were either overweight or obese in 2016 (WHO, 2016). Amongst global adult women, the proportion of overweight women increased by around 8% from 30% in 1980 to 38% in 2013 (Chen et al., 2018).

1.2 Maternal obesity

The role of maternal obesity in determining birth outcomes has been recently studied. Over the last decade, data from the United States (US) highlighted the prevalence of maternal obesity and suggested that nearly 39% of normal weight, 59% of overweight and 56% of obese pregnant women gain more weight during pregnancy than the recommended guidelines by the Institute of Medicine (IOM) (Dalenius et al., 2012). It is suggested that women with high pre-pregnancy BMI have a high risk of postpartum weight retention and fetal macrosomia (>4000 g) (Akgun et al., 2017; Ganer Herman et al., 2019; McDowell et al., 2019; Samura et al., 2016; Yu et al., 2013) emphasising the need to promote healthy gestational weight gain.

Further, it is suggested that maternal obesity could be positively associated with higher rates of large for gestational age (LGA) infants (>90th centile on a birth centile chart). Therefore, the maternal and neonatal obesity might represent a vicious cycle of obese women giving birth to obese children who in turn give birth to obese generations in future (Ehrenberg et al., 2004).

1.3 Birth size – an essential parameter

In the last quarter of the century, human studies have observed a steady increase in offspring birthweight with a higher prevalence of large-for-gestational-age (LGA) infants. This indicated an increase in fetal growth, i.e., birthweight for gestational age across countries, including United Kingdom (Alberman, 1991), Finland (Oja et al., 1991), India (Singhal et al., 1991), United States of America and Canada (Arbuckle and Sherman, 1989; Kramer et al., 2002). Size at birth

is used as an essential parameter for clinical evaluation of offspring. Birth weight or length represent the expression of fetal growth in the uterus and is a result of maternal factors, including parity, maternal BMI, fasting glucose and gestational weight gain (Chiavaroli et al., 2016; Roland et al., 2014).

1.4 Critical periods of fetal growth

The critical periods of fetal growth occurring in pregnancy could be summarised as follows – in the first trimester, two main processes occur: 1. organogenesis, i.e., an establishment of basic structure of organs and tissues. 2. placentation, i.e., placental growth. In the second and third trimesters, the fetus continues to grow rapidly in weight and length. In addition, the kidneys, lungs and brain continue to mature and develop during the third trimester (Hill, 2019; Okai, 1986; Rehman and Bacha, 2019).

1.5 Barker's hypothesis

The developmental origins hypothesis by Barker and colleagues (Barker, 1995; Godfrey and Barker, 1995) stated that in an effort to adjust to the adverse influences in the intrauterine environment the fetus makes permanent structural changes in physiology and metabolism. These result in lower birthweights associated with increased risk of cardio metabolic diseases, including Type 2 Diabetes Mellitus, hypertension and coronary heart disease in later life. Barker and colleagues observed that the regions in England that had the highest rates of infant mortality in the early twentieth century also had the highest rates of coronary heart diseases decades later. During this period as the most commonly registered cause of infant death was low birthweight (<2500 g) it was hypothesised that the low birthweight offspring who survived infancy and early childhood might be at a higher risk of coronary heart disease in adulthood. This was evidenced amongst men born in the first quarter of the twentieth century in two studies conducted in Sheffield and Hertfordshire (Barker et al., 1993; Barker et al., 1989). These studies suggested that lower birthweight, particularly SGA infants were associated with high mortality rates due to coronary heart disease.

In further agreement of this hypothesis, according to the Gaussian distribution of birth size, small-for-gestational-age (SGA) and large-for-gestational-age (LGA) babies are two categories of birth outcomes recognised to be at increased risk of poor perinatal outcomes and cardio metabolic diseases in adulthood (Chiavaroli et al., 2014; Weissmann-Brenner et al., 2012).

1.6 Fetal metabolic alterations

Mechanisms for adverse influences responsible for poor fetal growth or birth size include altered nutritional stimuli, both, high and low intakes, and excess fetal glucocorticoid exposure. Human and animal studies have suggested that elevated cortisol levels transferred to the fetus via the placenta could be associated with lower birthweight and increased blood pressure and glucose intolerance (Jensen et al., 2002; Nyirenda et al., 1998; Tangalakis et al., 1992). Recent studies have reported the negative association between birth size and glucose metabolism. It is suggested that lower birthweight infants have higher insulin resistance, higher fasting insulin concentrations, and increased risk of Type 2 Diabetes Mellitus (Béringue et al., 2002; van Assche and Aerts, 1979).

1.7 Fetal genetic alterations

However, genetic and epigenetic pathways are also associated with this theory (de Boo and Harding, 2006). During embryogenesis, DNA undergoes demethylation and re-methylation which subsequently is inactivated. This process of imprinting of genes is suggested to affect the genes regulating fetal and placental growth (Reik et al., 2001). Amongst offspring rats low protein diets are suggested to affect the demethylation of the fetal liver and thus changes in the intrauterine environment may lead to altered gene expressions via the alteration of the DNA demethylation, increasing the overall risk SGA infants and chronic diseases in adulthood (Rees et al., 2000; Waterland and Jirtle, 2004).

1.8 Relation between small-for-gestational age infants and morbidities

SGA babies has been consistently associated with increased morbidity amongst full term and premature infants. One study suggested that full term SGA infants were at a higher risk of morbidities, including intubation at birth, seizures on the first day of life, and sepsis (McIntire et al., 1999). Two studies suggested that full term SGA infants were at a higher risk of neonatal deaths and respiratory distress syndrome (Bernstein et al., 2000; Boghossian et al., 2018) and chronic lung disease (Boghossian et al., 2018).

1.9 Gestational weight gain guidelines

Gestational weight gain is the total weight gained during pregnancy. The 2009 guidelines by the Institute of Medicine (IOM) recommend a total gestational weight gain of about 11.3-15.8 kg for women with Normal BMI, 6.8-11.3 kg for overweight women and around 4.9-9.0 kg for obese women (includes all classes of obesity) (National Research Council Committee to Reexamine, 2009). These guidelines were updated due to increasing evidence suggesting higher

prevalence of obese women entering pregnancy and the positive association between excessive gestational weight gain and poor pregnancy outcomes.

1.10 Post-partum weight retention – an obesity risk factor

Literature has identified post-partum weight retention as a risk factor for obesity. A study suggested that around 75% women were heavier after one year of delivery and over 47% women retained a postpartum weight of around 10 lbs (Endres et al., 2015). Another study suggested that a high pre-pregnancy weight and excessive gestational weight gain are strong risk factors of post-partum weight retention(Gore et al., 2003). Further, the study found that postpartum weight retention was the highest amongst women with different ethnicities, including African American women and advised weight loss strategies to lower future risk of obesity (Gore et al., 2003). The evidence presented so far highlights that modifiable risk factors, including diet and physical activity might promote healthy gestational weight gain and improve birth outcomes.

1.11 Dietary recommendations for pregnant women

During pregnancy as there is increased metabolic activity, changes in the blood volume, formation of fetus and placenta, women require additional maternal energy and macronutrient intakes to meet the requirements for a healthy pregnancy. Dietary recommendations for a healthy population, including pregnant women, infants, and elderly are used by policy makers to make dietary guidelines. In UK, the Scientific Advisory Committee on Nutrition and Committee on Medical Aspects of Food and Nutrition Policy (SACN/COMA) report to the Department of Health in UK, the Food and Agriculture Organisation of the United Nations and World Health Organisation (FAO/UN/WHO), and the British Nutrition Foundation (BNF) have discouraged pregnant women to ‘eat for two’ and have recommended protein and energy requirements (+200 kcal/day and +6g protein/day only in the last trimester) to prevent excessive gestational weight gain for healthy birth outcomes (British Nutrition Foundation, 2015; FAO, 2018; Health, 1991). The Nordic countries use the Nordic Nutrition Recommendations for determining the additional nutrient requirements during pregnancy. Although they are similar to the dietary recommendations in UK, they recommend an additional intake of 100 kcal for trimester 1, and an additional intake of 200-300 kcal for trimester 2 and 3, with no change in protein intakes (NNR, 2012; von Ruesten et al., 2014).

1.12 Importance of diet during pregnancy

Diet during pregnancy is an important source of energy for the fetus. In order for the fetus to grow to its maximum potential, it largely depends on the placental exchange of nutrients from maternal stores (de Boo and Harding, 2006). Keeping this in view, in the last two decades, studies explored the influence of maternal nutrition to improve fetal outcomes and mainly focused on two areas: 1. Maternal micronutrient supplementation, including iron, folate and vitamin B_{12} during pregnancy (Haider and Bhutta, 2017; Kawai et al., 2011; Kim et al., 2014; Lu et al., 2014; Shah and Ohlsson, 2009). 2. Maternal malnutrition in low to middle-income countries, including energy-protein supplementation to improve fetal outcomes (Imdad and Bhutta, 2011; Imdad and Bhutta, 2012; Liberato et al., 2013; Stevens et al., 2015). However, there has been lesser focus on the impact of macronutrients, particularly dietary macronutrients on offspring outcomes. Further, appetite during pregnancy could influence the overall energy intake and placental supply to support growth because of hormonal changes (Faas et al., 2010; Ladyman et al., 2010). Hormonal changes are mainly due to estrogen and progesterone; estrogen decreases food intake whereas progesterone increases food intake. Furthermore, studies have suggested that nausea and vomiting occurring during early pregnancy amongst some women could lower food intakes or change the dietary choices (Crozier et al., 2017; Latva-Pukkila et al., 2010). Thus, it is also important to consider the role of appetite in the overall energy and macronutrient intakes.

Therefore, this makes it necessary to focus on the contributory role of maternal nutrition in the development of gestational weight gain that might subsequently be associated with birth outcomes.

1.13 Project aim and objectives

The central aim of this project is to study maternal macronutrient dietary intakes through generation of a unique maternal weight gain dietary pattern and its relationship to birth outcomes. The exploration will be conducted under specific study objectives stated below:

1. To examine the association between maternal dietary macronutrient composition (carbohydrate [CHO], protein and fat and its dietary components (starch, glucose, sucrose, fructose, lactose, mono-unsaturated fatty acids [MUFA], polyunsaturated fatty acids [PUFA] and saturated fatty acids [SFA], and birth outcomes (birthweight, odds of SGA and LGA babies) – results from the CARE study (Chapter 4).
2. To investigate the association between maternal dietary macronutrient composition (carbohydrate [CHO], protein and fat, and birth outcomes (birthweight, odds of SGA and LGA babies) – A meta-analysis of 3 birth cohorts ((CAffeine and REproductive health)

[CARE] study, Danish National Birth Cohort [DNBC] and Norwegian Mother and Child Cohort Study [MoBa]) (Chapter 5).

3. To examine the association between maternal dietary patterns using principal component analysis (PCA) and birth outcomes (birthweight, odds of SGA and LGA babies) – results from the MoBa birth cohort (Chapter 6).
4. To develop 'gestational weight gain dietary patterns [GWG-DPs]' using reduced rank regression (RRR) in DNBC and MoBa birth cohorts (Chapter 7).
5. To demonstrate associations between 'gestational weight gain dietary patterns [GWG-DPs]' and birth outcomes (birthweight, odds of SGA and LGA babies) – results from the DNBC and MoBa birth cohorts (Chapter 7).

1.14 Brief overview of the chapters

This thesis will explore and demonstrate the influence of maternal dietary macronutrient patterns during pregnancy on offspring birth outcomes amongst three birth cohorts. Chapter 2 will conduct a literature review to identify the existing gaps in the research area. Chapter 3 will describe and compare the birth cohort profiles. Chapter 4 will examine the influence of dietary macronutrient composition in pregnancy on offspring outcomes using a British birth cohort. Chapter 5 will undertake a meta-analysis of three birth cohorts to explore the association between maternal dietary macronutrient composition and birth outcomes. Chapter 6 will examine the maternal dietary patterns of a Norwegian birth cohort and study its associations with birth outcomes. Chapter 7 will create dietary patterns contributing to gestational weight gain by including the risk factors associated with gestational weight gain. In addition, it will demonstrate associations between the gestational weight gain dietary patterns and birth outcomes. Lastly, Chapter 8 will discuss and justify the overall findings of the thesis.

The next chapter will conduct a critical evaluation of the existing literature to provide a summary of the available evidence in this research area. The chapter will conclude by identifying the existing gaps in the literature in order to justify the objectives stated in this project.

Chapter 2 Review of literature

2.1 Introduction

Chapter 1 discussed the central aim and objectives of the project. This chapter will provide a detailed assessment of the previous studies in order to demonstrate the gaps in the existing literature.

The chapter will first briefly discuss the methodology used for including specific review articles within the scope of this project. Second, it will discuss the established evidence in the research area and critically evaluate the existing literature. Third, it will discuss the gaps identified and finally, will conclude with restating the project objectives addressing each gap.

However, it should be noted that this chapter is not a systematic review because the main objective of the thesis required exploring the study objectives by conducting exhaustive analysis. Therefore, due to time constraints, focus was provided on the analysis rather than conducting a complete systematic review. But, for ease of reference and presentational reasons the chapter outline and methodology are kept similar to a systematic review.

The influence of maternal nutrition on offspring outcomes is a broad research area and has been widely explored over the last two decades. The evidence generated so far has recognised maternal diet as a modifiable risk factor in the prevention of metabolic disease during early life and adulthood (de Boo and Harding, 2006). Most studies have explored the association of micronutrient status during pregnancy and offspring outcomes (Haider and Bhutta, 2017; Kawai et al., 2011; Kim et al., 2014; Lu et al., 2014; Shah and Ohlsson, 2009), as previously mentioned in Chapter 1. However, it is unclear whether there are any associations between maternal dietary macronutrient intakes and birth outcomes, including birthweight, small-for-gestational-age (SGA) and large-for-gestational-age (LGA) infants. Also, it is unclear if any dietary patterns contribute to gestational weight gain amongst women.

The association between maternal macronutrients and birth outcomes and the effect of maternal dietary intakes on gestational weight gain and offspring outcomes are unclear in the maternal nutrition – offspring outcome pathway.

This review will explore and assess the available literature mainly under 3 categories:

1. Maternal macronutrient intake and birth outcomes

2. Maternal dietary patterns and birth outcomes

3. Creation of gestational weight gain dietary patterns.

2.2 Methodology

2.2.1 Search strategy

The literature search was conducted between 2016 to 2018 using two electronic databases such as PubMed and Scopus. All the citations were stored in Endnote.

For example, to identify the dietary macronutrient intake during pregnancy and birth outcomes, the following keywords were searched in Scopus:

(TITLE-ABS-KEY (macronutrient AND composition) AND TITLE-ABS-KEY (birth AND outcomes) AND TITLE-ABS-KEY (pregnancy)). To identify studies for maternal dietary patterns and birth outcomes the search keywords used were (TITLE-ABS-KEY (maternal AND dietary AND pattern) AND TITLE-ABS-KEY (birth AND outcomes)). To identify studies for maternal dietary patterns for gestational weight gain and birth outcomes the search keywords used were (TITLE-ABS-KEY (maternal AND dietary AND pattern) AND TITLE-ABS-KEY (gestational AND weight AND gain) AND TITLE-ABS-KEY (birth AND outcomes)).

2.2.2 Eligibility criteria

Table 1 highlights the inclusion and exclusion criteria used to review the research articles. This review only included studies relevant to the study objectives of the thesis by limiting the literature search to observational studies exploring dietary macronutrient intakes amongst a well-nourished population of pregnant women and birth outcomes.

2.2.2.1 Inclusion criteria

Research articles were included if they were observational studies conducted within a birth cohort published between 1980-2018. Studies were reviewed if the exposures of interest were maternal dietary macronutrients, single macronutrients (only fat or protein or CHO) and dietary patterns during pregnancy. Articles were reviewed only if the study conducted analysis for clearly defined offspring outcomes, including birthweight, ponderal index, preterm deliveries, low birth weights, and risk of SGA and LGA infants. Only full text research articles in English language were included for review.

2.2.2.2 Exclusion criteria

Research articles reporting results of randomised controlled trials, animal studies, case reports and editorial commentaries were excluded. Although RCTs provide higher level of

evidence, they were excluded because RCT studies are well-monitored and evenly control for confounders within the case and control groups, therefore implying causality unlike observational studies. However, it should be acknowledged that this might be a limitation and it is preferable and advantageous to include RCTs in the systematic review. But it is important to note that conducting RCTs have logistical and ethical limitations particularly amongst pregnant women and children (Kaye, 2019; Roessner, 2014). Furthermore, pregnant women are excluded from RCTs because of the potential harm and consequences of teratogenicity by the consumption of the drug, nutrients or vaccines used during gestation on women and their fetus (Kaye, 2019). Therefore, keeping these reasons in view, the focus of this review was to assess and critically appraise the results generated only from observational studies; as they would be useful to conduct realistic comparisons and interpretations with the results generated in this thesis.

Studies which did not measure dietary data and birth outcomes were not assessed. Studies exploring the effects of micronutrient supplementations during pregnancy were not included. Studies examining the effects of maternal dietary micronutrient intakes as the exposure were not assessed. Also, studies presenting results for child outcomes were excluded. Studies exploring elements such as mercury and lead in food, weaning foods, breast milk, lactation, breast feeding formula, metabolic biomarkers, genomic and toxicology were excluded. Lastly, articles reporting results for pregnant women with morbidities such as gestational diabetes mellitus, pregnancy induced hypertension, preeclampsia, psychiatric illness, HIV and AIDS were excluded as study outcomes.

Table 1 Inclusion and exclusion criteria for the selection of studies

Inclusion criteria	Exclusion criteria
Studies conducted amongst high-income countries between 1980 to 2018 amongst well-nourished pregnant women	Studies published in languages other than English
Observational study design and full text articles	Maternal health conditions such as gestational diabetes mellitus, pregnancy induced hypertension, pre-existing hypertension and Diabetes Mellitus, psychiatric illness, HIV, AIDS, pre-eclampsia
Birth outcomes, including birth weight, length, ponderal index, risk of SGA and LGA infants, preterm infants and low birthweight deliveries	Animal studies, randomised controlled trials, case reports, cross-sectional studies, editorial commentaries and abstracts
Studies exploring only macronutrients intakes from the diet in pregnancy	Child health outcomes include body composition (body mass index (BMI)), respiratory and atopic outcomes, allergies,

	child intake and appetite, and cognitive and behavioural outcomes
	Studies exploring breast milk, dietary and supplementary micronutrients, metabolic biomarkers, feeding formula
	Presentational errors of the study results
	Prenatal diets, low-glycaemic index diets, Dietary Approaches to Stop Hypertension (DASH) diet

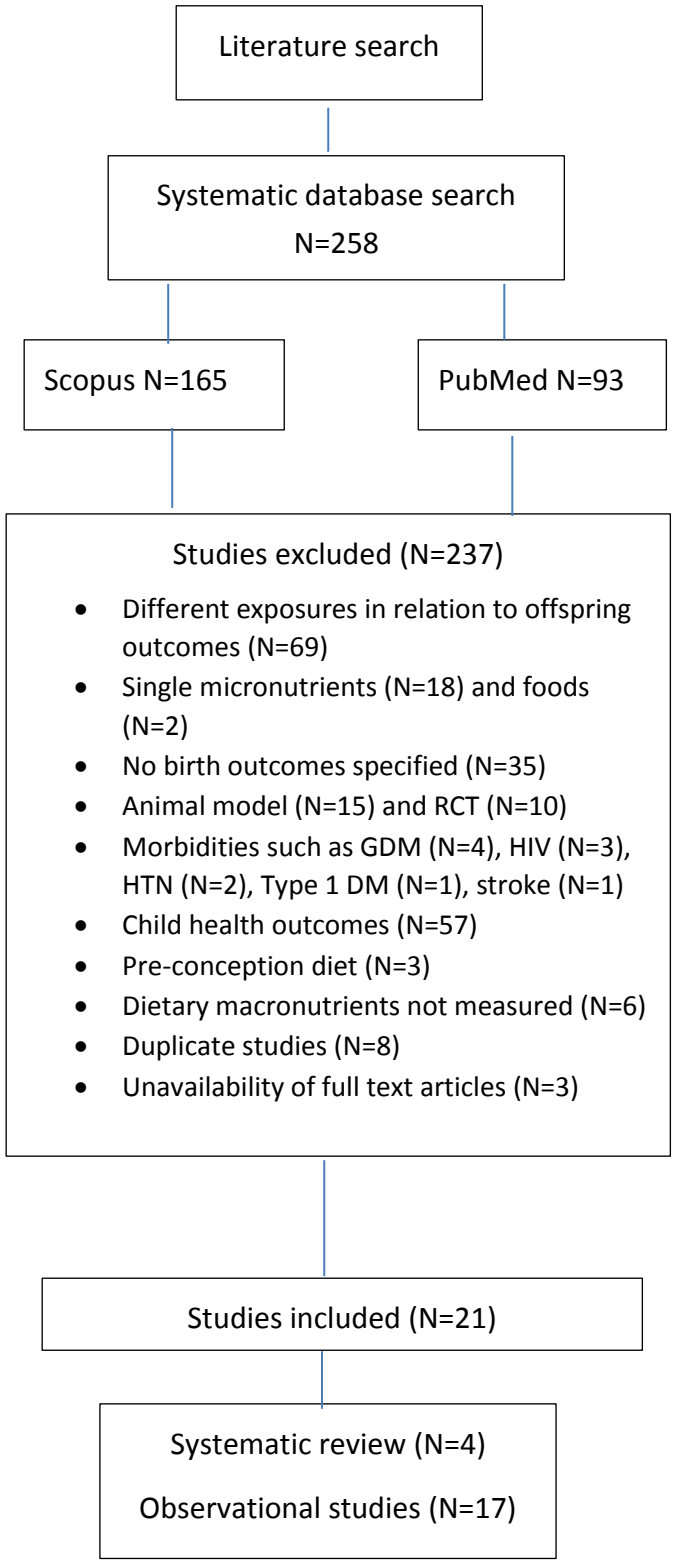
2.3 Descriptive results

In total Scopus and PubMed identified 258 studies after the original literature search. The study flow for the selection of the studies for critical evaluation is summarised in Figure 1. Scopus and PubMed each identified 17 studies for maternal dietary macronutrient intakes and birth outcomes. Further, Scopus identified 128 studies and PubMed identified 72 studies for maternal dietary patterns and birth outcomes. Finally, Scopus identified 20 studies and PubMed identified 4 studies for gestational weight gain dietary patterns and birth outcomes.

Out of the 258 studies original identified in the literature search, 237 studies were excluded as they were not relevant to the study objectives. The reasons are cited as follows.

It was observed that most studies had specified different exposures in relation to offspring outcomes(n=69), other studies explored the single micronutrients in relation to birth size (n=18), some studies did not explore any birth outcome (n=35), systematic reviews and individual studies were based on animal models (n=15) and randomised controlled trials (n=10). Further, studies were conducted amongst populations with morbidities such as gestational diabetes mellitus (GDM) (n=4), Human Immunodeficiency Virus (HIV) (n=3), pre-existing hypertension (HTN) (n=2), Type 1 Diabetes Mellitus (n=1), and stroke (n=1). Most of the studies were conducted to explore child health outcomes (n=57) and pre-conceptional diets (n=3). Some studies did not measure the dietary macronutrients despite defining clear birth outcomes (n=6), and others explored single foods (n=2). Furthermore, duplicate studies (n=8) and unavailability of full-text articles (n=3) were excluded.

Figure 1 Flowchart summarising the selection of the studies for literature review



Therefore, the current chapter included 21 studies for review, of which, 4 were systematic reviews and 17 were observational studies.

It should be noted that critical appraisal is only conducted amongst observational studies that measured dietary macronutrient intakes for well-nourished pregnant women and clearly defined offspring outcomes, including birthweight, ponderal index, preterm deliveries, low birth weights, and risk of SGA and LGA babies. This is because the central aim of this thesis is to investigate associations between maternal dietary macronutrients, dietary patterns related to gestational weight gain and birth outcomes. For ease of reference, Table 2 provides a brief review for all the studies with the corresponding references.

Table 2 Summary of the studies evaluated in the literature review

Theme: Maternal dietary macronutrient composition and birth outcomes						
Serial number	**Reference**	**Study design and population**	**Exposure**	**Outcome**	**Confounders***	**Result**
1.	(Moore et al., 2004)	An observational study of 557 women	Dietary macronutrient composition	Birthweight, ponderal index	Adjusted for smoking, maternal age and parity	A positive association between protein and birthweight
2.	(CucÓ et al., 2006)	An observational study of 77 women planning pregnancies	Dietary macronutrient composition	Birthweight	Adjusted for energy intake, maternal age, pre-conceptional body mass index, sex of the newborn, length of pregnancy, parity, physical activity in leisure time, and smoking	A positive association between protein and birthweight
3.	(Chong et al., 2015)	An observational study of 835 women	Dietary macronutrient composition	Birthweight, ponderal index and length	Models are adjusted for the child's gender, gestational age, and birth order, and the mother's BMI, ethnicity, age, education level, monthly household income, and gestational diabetes mellitus, alcohol use, and smoking statuses	No evidence of an association between macronutrients and birthweight. Lower protein intakes were associated with longer birth length and lower ponderal index in male offspring
4.	(Brei et al., 2018)	An observational study of 208 women	Maternal dietary macronutrient composition	Birthweight, length, fat mass compositio	Models adjusted for pre-pregnancy BMI, energy, sex of the baby (except zBMI model), pre-pregnancy BMI,	No evidence of an association between macronutrients and birthweight.

			n at 1, 3, and 5 years	gestational age in days, subcutaneous adipose tissue, visceral adipose tissue, BMI *z* score.	Higher fat and protein intakes were negatively associated with fat mass up to 5 years of age. High fibre intake of 10 g was associated with increased abdominal subcutaneous fat at 1, 3 and zBMI at5 years but not with birthweight
5. (Mani et al., 2016)	An observational study of 1838 women	Dietary fat and fatty acids	Birthweight, SGA infants	Models adjusted for maternal age, education, parity, height and weight at recruitment.	No evidence of an association between maternal dietary fat, saturated fatty acids, and birthweight
6. (Maslova et al., 2016)	A prospective study with 20 years follow up amongst 965 women	Dietary fat and fatty acids	Offspring anthropometry (BMI and Waist circumference) at 20 years	Adjusted for saturated/monounsaturated/polyunsaturated fatty acids, total protein, energy, maternal age, maternal education, parity, maternal prepregnancy BMI, maternal smoking during pregnancy, and sibling overweight	No evidence of an association between maternal dietary fat and female offspring anthropometry at 20 years. However, a positive association observed between high MUFA intake and high BMI and waist circumference in male offspring at 20 years.
Theme: Maternal dietary patterns and birth outcomes					
7. (Kjøllesdal and Holmboe-Ottesen, 2014)	A systematic review of 7 studies	Dietary patterns during pregnancy extracted using PCA analysis	Birthweight and SGA delivery	Studies included for review mostly adjusted for gestational age at delivery, sex of the baby, pre-pregnancy BMI, maternal age, smoking	"Protein-rich" and "nutrient-dense" dietary patterns were positively associated with birthweight. "Western", "processed", "vegetarian" and "wheat products" dietary patterns were associated with lower

				habits and socioeconomic status	birthweight. “Western” dietary pattern was associated with a high risk of SGA delivery.
8. (Brantsæter et al., 2014)	A systematic review of 19 studies within the Norwegian Mother And Child Cohort Study (MoBa)	Maternal dietary patterns extracted with PCA	Birthweight, preterm deliveries, preeclampsia, and SGA and LGA babies.	-	Results suggest pregnant women consume vegetables, fruit, whole grain, fish, dairy, and water regularly and lower the intake of sugar-sweetened beverages, processed meat products and salty snacks
9. (Sengpiel et al., 2013) Included in the (Brantsæter et al., 2014) review	An observational study of 59,123 women within the Norwegian Mother And Child Cohort Study (MoBa)	Maternal caffeine intake	Birthweight and risk of small for gestational age (SGA) delivery.	Adjustment for maternal age, pre-pregnancy body mass index, parity, history of preterm delivery, baby's sex, nausea during the second trimester, smoking habits, passive smoking, nicotine intake from other sources, alcohol consumption during pregnancy, energy intake, maternal education, marital status, household income.	Diet with higher caffeine intake (above 200mg-300mg/day) as compared to 0-50 mg/day was positively associated with high risk of SGA delivery and associated with lower birthweight
10. (Hillesund et al., 2014) Included in the (Brantsæter et al., 2014) review	An observational study of 66597 women within the Norwegian Mother And	Maternal dietary pattern adherence to the New Nordic Diet (NND) score	Risk of LGA and SGA babies.	Maternal age at delivery, parity, pre-pregnancy BMI, maternal height, educational attainment, smoking, gestational diabetes, exercise during	A higher dietary pattern adherence to the New Nordic Diet (NND) score was associated with a lower risk of SGA delivery and a higher risk of LGA delivery

	Child Cohort Study (MoBa)			pregnancy and energy intake	
11. (Borgen et al., 2012) Included in the (Brantsæter et al., 2014) review	An observational study of 32933 women within the Norwegian Mother And Child Cohort Study (MoBa)	Maternal dietary pattern of high intake of sugar-sweetened beverages	Risk of preeclampsia	Maternal age at delivery, education, prepregnant BMI, height, smoking, total energy intake and leisure exercise in the first pregnancy trimester	High consumption of "sugar-sweetened beverage" dietary pattern was positively associated with a high risk of preeclampsia
12. (Brantsæter et al., 2009) Included in the (Brantsæter et al., 2014) review	An observational study of 23423 women within the Norwegian Mother And Child Cohort Study (MoBa)	Maternal dietary pattern extracted using PCA	Risk of preeclampsia	Maternal age, maternal education, maternal height, maternal smoking, total energy intake, hypertension before pregnancy, dietary supplement use and additional adjustment for other dietary patterns in the model	High intake of "processed" dietary pattern was positively associated with a high risk of preeclampsia
13. (Englund-Ögge et al., 2012) Included in the (Brantsæter et al., 2014) review	An observational study of 60761 women within the Norwegian Mother And Child Cohort Study (MoBa)	FFQ used to record the self-reported dietary data Logistic regression models	Risk of preterm deliveries	Maternal age, prepregnancy BMI, height, and total energy intake as continuous variables and for marital status, parity, smoking, education, previous preterm delivery, and alternative beverage as categorical data	A dietary pattern rich in artificial sweetened and sugar sweetened beverages were positively associated with a high risk of preterm delivery (PTD)

14. (Brantsæter et al., 2014) Included in the (Brantsæter et al., 2014) review	An observational study of 66000 women within the Norwegian Mother And Child Cohort Study (MoBa)	Maternal dietary pattern extracted using PCA	Risk of preterm deliveries	Maternal age, pre-pregnancy body mass index, height, parity, total energy intake, maternal education, marital status, smoking, previous preterm delivery, household income, and other dietary patterns	A "traditional" dietary pattern characterised by potatoes and fish and a "prudent" dietary pattern characterised by vegetables, fruits, whole grains, oils, fibre-rich bread was associated with a lowered risk of PTD
15. (Thompson et al., 2010)	An observational study of 1714 pregnant women	Maternal dietary pattern extracted using PCA	Risk of SGA delivery	Gestation, infant sex, maternal smoking in pregnancy, maternal pre-pregnancy height and weight, parity, ethnicity and maternal hypertension	The study suggested that a "traditional" dietary pattern characterised by high intake of apple/pears, citrus fruits, kiwis, bananas, green vegetables, roots, dairy products, and peas/maize, was associated with low risk of SGA delivery.
Theme: Creation of gestational weight gain dietary patterns					
16. (Lagiou et al., 2004)	An observational study of 224 women	Maternal dietary macronutrients	Gestational weight gain, birth weight	Energy intake (except for energy models), maternal age, maternal education, parity, maternal height, pre-pregnancy BMI, pre-gravid OC use, smoking during pregnancy, exact gestational age at delivery and gender of the baby	No evidence of an association with birthweight. Maternal total energy, protein, and fat intakes were positively associated with gestational weight gain. Whereas, maternal CHO intake was associated with gestational weight gain.
17. (Streuling et al., 2011)	A systematic review included 12 studies	Maternal dietary macronutrients and energy	Gestational weight gain	-	Five studies observed a positive association between high maternal energy intake and gestational weight gain.

					Three studies did not find any evidence of association. High maternal protein and lipid intakes were positively associated with gestational weight gain. High maternal CHO intakes were negatively associated with weight gain
18. (Tielemans et al., 2015)	A systematic review included 56 studies	Maternal dietary macronutrients and energy	Gestational weight gain	-	Maternal energy intake was positively associated with gestational weight gain. Maternal dietary macronutrients were also positively associated with gestational weight gain.
19. (Shin et al., 2016)	An observational study included 391 pregnant women	Maternal dietary patterns extracted using factor analysis	Gestational weight gain	Pre-pregnancy BMI, age, race/ethnicity, family poverty income ratio, education level, physical activity, and marital status	A high dietary score for the "mixed" dietary pattern characterised by dairy products, fruit drinks, fruits, nuts, vegetables, legumes, meat, snacks and sweets were negatively associated with excessive gestational weight gain.
20. (Tielemans et al., 2015)	An observational study included 3374 pregnant women	Maternal dietary patterns extracted using PCA (*posteriori* approach) and Dutch Healthy Diet Index (*a priori* approach)	Gestational weight gain	Adjusted for pre-pregnancy BMI, age, educational level, household income, parity, smoking during pregnancy, alcohol consumption during pregnancy, stress during pregnancy, and fetal sex.	No evidence of an association between the Dutch Healthy Diet Index derived dietary patterns and gestational weight gain. Normal weight women with high adherence to the "vegetable, oil and fish" dietary pattern were positively associated to gain

					higher early pregnancy weight. Further, a higher adherence to “margarine, sugar and snacks” dietary pattern was positively associated with excessive gestational weight gain. Also, they suggested that high adherence to the “high in fibre, nuts and soy” dietary pattern were negatively associated with moderate weight gain.
21. (Starling et al., 2017)	An observational study included 764 pregnant women	Maternal dietary patterns extracted using reduced rank regression and included gestational weight gain (GWG) and fasting glucose during pregnancy	Newborn adiposity (birthweigh t, adiposity, fat mass, fat-free mass)	Maternal age, pre-pregnancy BMI, race/ethnicity, education, parity, smoking, average weekly physical activity during pregnancy, infant sex, gestational age at birth, and postnatal age at body composition measurement (for fat mass, fat-free mass, and adiposity only).	Dietary pattern 1 correlated with gestational weight gain and was characterised by a high intake of poultry, nuts, cheese, fruits, whole grains, added sugars, and solid fats. High adherence to dietary pattern 1 was positively associated only with fat-free mass. Dietary pattern 2 correlated with higher fasting glucose and was characterised by a high intake of eggs, starch vegetables, solid fats, fruits and refined grains and lower intakes of dairy foods, whole grains and green vegetables. Higher adherence to dietary pattern 2 was positively associated with higher

					birthweight, fat mass, fat-free mass and adiposity.

*not applicable for systematic reviews

2.4 Discussion of identified papers

A critical evaluation of the research articles was conducted by examining individual aspects, for example, the study objectives and design, and methodology. There is very limited and inconclusive evidence amongst observational studies exploring the association between maternal dietary macronutrient intakes (CHO, fat and protein) and birth outcomes. The following section critically evaluates the available literature and has identified few gaps.

2.4.1 Maternal dietary macronutrients and birth outcomes

Amongst maternal dietary carbohydrate (CHO), fat and protein consumption, two studies have only found an association between dietary protein during pregnancy and birth outcomes. The CucO study (CucÓ et al., 2006) and the Moore study (Moore et al., 2004) reported that increased maternal protein intakes are positively associated with increased birthweights. The Moore study (Moore et al., 2004) suggested a positive association between increased energy (%E) from dietary protein and an increase in birthweight (95% CI 3 to 29g). This study did not find any evidence of an association between %E from dietary fat and CHO, and birthweight. The inclusion criteria and the dietary data recorded were methodologically appropriate according to the study's objective. Also, the study did not adjust the dietary macronutrient analysis for total energy intake, and thus, it reduced the overall confounding error.

In theory, a variable can only be included as a confounder if it is associated with both the maternal macronutrient consumption and birth size. Gestational age is associated with birth size, but it is unclear if it is associated with maternal diet, and so the results might have confounding errors. It can only be included as a competing exposure for this analysis. However, discrepancies in reporting the confounders used for adjustment made it challenging to understand the results. It was unclear whether the study only adjusted for smoking, maternal age and parity or for maternal age, height, pre-pregnancy weight, primiparity, smoking, alcohol consumption, and recreational drug use. Also, the models did not account for physical activity. Moreover, the study suggested results based on the statistical significance of p-values and misreported results as clinically significant by providing borderline non-significant p-values. However, statistical p-values only provide the strength of evidence and do not describe whether the clinical significance is conclusive. In theory, the size of the estimates (small/large) and confidence intervals (CI) indicate this information in a study.

Although the CucO study (CucÓ et al., 2006) reported similar results, the study was conducted within a limited sample size of only 77 healthy females who were planning pregnancy as compared to the Moore study (Moore et al., 2004) (N=557). Also, in

comparison, this study used 7-day dietary recalls to record dietary data as compared to the FFQ method used in the Moore study, which could explain for the robustness and quality of the dietary data recorded as the method chosen was time-consuming. Although the study outcome was the same, i.e., birthweight, the exposure was more detailed in the CucO study (CucÓ et al., 2006). Not only did they use a detailed dietary assessment method for recording maternal macronutrient dietary intakes, but they also recorded it at four-time points during the pregnancy – before conception, 6^{th}, 10^{th}, 26^{th} weeks of pregnancy. They reported results at the rate of 1 g increment of protein during preconception, and 10^{th}, 26^{th} and 38 weeks of pregnancy were positively associated with a higher birthweight of around 8 to 11g. However, the choice of confounders included for analysis might introduce confounding errors to the results. For example, 2 confounders, including sex of the baby, gestational age at delivery were only associated with birthweight in theory, but not with dietary macronutrient consumption.

Further, the macronutrient-birthweight models were adjusted for total energy intake indicating the possibility of collinearity, where total energy intake is highly correlated with the macronutrients in the model, and each macronutrient is also mutually adjusted for the other two macronutrients. Also, they did not include maternal alcohol consumption as a confounder since they included women at preconception. However, they might not have considered it as a confounder because they included women who were planning pregnancies; therefore, they would typically avoid alcohol consumption.

In contrast to the Moore and Cuco studies, the Chong study (Chong et al., 2015) did not observe any evidence of an association between maternal dietary macronutrient composition and birthweight. This was conducted amongst the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study and explored birthweight, ponderal index (relative body mass expressed as the ratio of the cube root of body weight to height multiplied by 100) and birth length as outcomes. Amongst macronutrients, only lower protein intake was associated with longer birth lengths and lower ponderal index in male offspring. This study recorded dietary data satisfactorily using 24-hour dietary recalls and 3-day food diaries. Further, it included ethnicity as a confounder, a variable which is difficult to get access in large datasets. This was appropriate since the study was based in Singapore—culturally rich in Chinese, Indian and Malay population. However, similar to the previous two studies, the Chong study (Chong et al., 2015) had confounding errors as it adjusted the models for gestational age and sex of the baby. Both confounders were asscociated with birth outcomes but not with maternal dietary macronutrient intakes. In

particular, the issue of double-adjustment for gestational age at delivery could affect the robustness of the birth outcome models.

Another recent study (Brei et al., 2018) suggested no evidence of an association between dietary macronutrient composition in early pregnancy (at 15 weeks) amongst 208 women and offspring body composition, including birthweight and length. However, they suggested that in late pregnancy (at 32 weeks), higher fat and protein intakes in pregnancy were negatively associated with offspring body composition measures up to 5 years, including subcutaneous fat mass and zBMI scores. Amongst the influence of maternal dietary CHO on birth outcome, fibre (10 g increment) was suggested to be associated with increased abdominal subcutaneous fat at 1, 3 and zBMI at 5 years, but not with birthweight. This study used two models – partition and substitution models for analysis, which were complex to report and interpret. The results were consistent amongst both models and were interpreted at an increment of 100 kcal of macronutrient. These models were adjusted for energy, introducing the issue of collinearity. Further, gestational age at delivery as a confounder, which was not associated with maternal dietary macronutrient intakes and introduces the issue of double-adjustment in the models. The study observed residual confounding as the models did not adjust for other clinically important confounders including, alcohol intake, smoking habits, dietary supplements, physical activity and parity. However, the study used 7-day dietary recalls to measure dietary intakes and used sophisticated equipment to measure the offspring body composition at birth, 1, 3, and 5 years, for example, Holtain calliper for skinfold thickness and abdominal MRI to measure visceral fat.

In particular, the role of maternal fat amongst dietary macronutrients has been considered important amongst fetal outcomes due to its association with metabolic and cardiovascular diseases in adulthood as per Barker's hypothesis (Barker, 1995). A couple of studies have explored the role of maternal fat in offspring outcomes (Mani et al., 2016; Maslova et al., 2016). A study (Mani et al., 2016) explored the association between maternal dietary fat and fatty acids consumption, and birthweight amongst 1838 healthy South Indian women. They suggested no evidence of an association between maternal dietary fat and saturated fat intakes, and birthweight and small-for-gestational-age (SGA) infants. However, they reported borderline non-significant results ($p=0.07$) in their conclusions. Further, they only used a validated food frequency questionnaire to record dietary data and standard raw food conversion tables to extract nutrient intakes. The study did not use dietary recalls to verify the FFQ intakes, and this might be due to the longitudinal nature of the study design, where it is practically challenging to conduct

repeated dietary assessments. Also, this might have introduced the issue of underreporting and underestimation of fat intakes, a common issue when dietary data is recorded in pregnancy, especially related to fat intakes (McGowan and McAuliffe, 2012).

In agreement with this study, a longitudinal, follow-up study in Denmark (Maslova et al., 2016) suggested no evidence of an association between maternal dietary fat intake and female offspring BMI and waist circumference at 20 years. However, it suggested a positive association between higher fat intake, and higher body mass index (BMI) and waist circumference amongst 20-year-old male offspring and is partly in agreement with Barker's hypothesis (Barker, 1995). But, the regression models were not adjusted for relevant confounders, including alcohol intake in pregnancy and physical activity levels. These two confounders are directly associated with the amount of maternal dietary fat consumed and permanent impact on the fetal outcomes, which could further influence the anthropometry and metabolic health in adulthood. Also, they adjusted the regression models for sibling overweight, and they did not justify this choice, making it unclear—although the potential reason might be genetics. Also, results suggested an association between higher MUFA intakes and higher waist circumference for the male offspring at 20 years and indicated wide confidence intervals (5.87; 95% CI 0.47 to 74) and might be because the dietary MUFA might have been consumed in meagre amounts by few women. Further, the dietary data was recorded using FFQ, and the anthropometry was partly based on memory, which might have introduced potential bias and underreporting in the analysis. Lastly, although this study provided some evidence regarding the role of maternal fat and its components (MUFA and SFA), the study design and outcome chosen was longitudinal and involved 20-year-old offspring.

Therefore, it could be observed that very limited number of studies have demonstrated evidence regarding the association between dietary macronutrients in pregnancy and birth outcomes. Further, majority of the evidence is inconclusive and could be due to reasons, including low power samples, confounding bias, misreporting of results, poorly designed regression models and measurement of dietary data using different dietary assessment tools. Furthermore, there is no evidence amongst observational studies regarding the association between maternal dietary macronutrient sub-components, including mono and di-saccharides and fatty acids (PUFA, MUFA and SFA) and birth outcomes. The gaps identified in this section will be addressed in Chapters 4 and 5, where analysis will be conducted within large sample size birth cohorts and will carefully adjust the analyses to reduce confounding bias.

2.4.2 Maternal dietary patterns in relation to gestational weight gain and birth outcomes:

Individuals consume foods in combinations, and therefore, it is difficult to detect the effect of a single nutrient on a particular birth outcome (Hu, 2002). Also, these foods are highly correlated with each other, and thus, this gives the need to assess the food intakes as a component (Hu, 2002; Kjøllesdal and Holmboe-Ottesen, 2014). Statistical methods, including principal component analysis (PCA) and factor analysis, have been used to study the cumulative effect of foods consumed in combinations on birth outcomes across various populations (Hu, 2002; Jolliffe, 2011). Principle component analysis (PCA) has been commonly used in nutritional epidemiological evidence as it is used to extract uncorrelated linear combinations of the dietary variables (dietary patterns) to explain for maximum variance of the cohort's dietary intakes (Schwedhelm et al., 2018). PCA reduces the number of dietary intake variables in a large dataset while retaining its original variance as much as possible (Jolliffe, 2011). Finally, PCA generates dietary pattern scores which summarise the combined maternal dietary intakes.

To explore more, two systematic reviews and five observational studies suggested an association between maternal dietary patterns and birth outcomes including birthweight (Kjøllesdal and Holmboe-Ottesen, 2014), preterm deliveries (Englund-Ögge et al., 2014; Haugen et al., 2008), and SGA and LGA infants (Brantsæter et al., 2014; E. Hunter and Schmidt, 2002; Knudsen et al., 2007; Thompson et al., 2010). These studies are discussed in detail further in Chapter 8, under section 8.3.2

A systematic review of 7 studies by (Kjøllesdal and Holmboe-Ottesen, 2014) investigated the association between maternal dietary patterns, and birthweight and SGA offspring. It observed that five studies used PCA, and two studies used cluster analysis and logistic regression, respectively. The review suggested that the "western" diet was positively associated with a high risk of SGA baby, whereas "traditional" dietary pattern was associated with lowered SGA offspring. For birthweight outcomes, "nutrient-rich", "protein-rich", "Mediterranean", and "health-conscious" dietary patterns were positively associated with higher birthweight. These patterns were primarily characterised by a high intake of vegetables, fruit and dairy products. However, "western", "processed" and "vegetarian" dietary patterns were associated with lower birthweights. These patterns were largely characterised by high intake of sugar-rich products, fats and oils, and processed and high-fat meat.

A limitation was observed in this review– the definition of SGA infant amongst each study differed between the range <2.5 percentile to 10^{th} percentile of birthweight as

they used different standards, therefore miscategorising as SGA infants introduced bias according to the authors. Also, the cluster analysis approach used in one study requires a different interpretation as compared to the studies which used the PCA and factor analysis. Although this method is a data-driven *(posteriori)* approach where the population influences patterns, the analysis groups or finds people who share similar patterns or frequency of food consumption. Whereas the PCA and factor analysis finds and extracts similar foods that are correlated and then scores the people based on the degree of their variance in the same diets consumed (Reedy et al., 2010). Therefore, as compared to cluster analysis, PCA and factor analysis are better approaches to observe dietary patterns during pregnancy.

A review by the MoBa study group (Brantsæter et al., 2014) included 19 studies which used the validated MoBa FFQ data of 87,700 pregnancies in the MoBa cohort. The birth outcomes in the MoBa review included birthweight, preterm deliveries, preeclampsia, and SGA and LGA babies. Only six articles from this review will be evaluated as their study objectives included maternal dietary intakes as exposures, while rest of the studies included the following exposures – mercury and acrylamide exposures, antimicrobial food items (onion, garlic), probiotics in dairy products and single nutrients including folate and vitamin D in dietary supplements.

Amongst birthweight, SGA and LGA offspring as study outcomes, a study suggested that a dietary pattern with higher caffeine intake (above 200mg-300mg/day) as compared to 0-50 mg/day was positively associated with high risk of SGA baby and associated with lower birthweight (Sengpiel et al., 2013). Another study suggested that higher dietary pattern adherence to the New Nordic Diet (NND) score was associated with a lower risk of SGA baby and a higher risk of LGA baby (Hillesund et al., 2014).

Studies which explored preeclampsia as an outcome, suggested that a high consumption of “sugar-sweetened beverage” dietary pattern (Borgen et al., 2012; Brantsæter et al., 2009) were positively associated with a high risk of preeclampsia. In Norway, the diagnostic criterion for preeclampsia is high blood pressure above 140 mmHg and 90 mmHg (millimetres of mercury) after 20 weeks of gestation combined with proteinuria higher than +1 dipstick on at least two occasions (Brantsæter et al., 2014). The study also suggested that a dietary pattern with a high intake of fruits and dried fruits containing natural sugars were associated with a lower risk of preeclampsia, suggesting that foods with high content added sugars might be differently associated with preeclampsia.

Amongst preterm deliveries, a couple of studies authored by the same researcher suggested that a dietary pattern rich in artificial sweetened and sugar sweetened beverages were positively associated with a high risk of preterm delivery (PTD) (Englund-Ögge et al., 2012). Further, a "traditional" dietary pattern characterised by potatoes and fish and a "prudent" dietary pattern characterised by vegetables, fruits, whole grains, oils, fibre-rich bread was associated with a lowered risk of PTD (Englund-Ögge et al., 2014).

Although these studies adjusted for various confounders, confounding errors were observed as most studies adjusted the maternal dietary pattern models for gestational age at delivery and did not consider alcohol intake. In the Branstaer and Englund 2014 studies (Brantsæter et al., 2009; Englund-Ögge et al., 2014) they included four dietary patterns into one model, and so each pattern was also mutually adjusted for other dietary patterns. This could have slightly affected the results where the associations with risk of preeclampsia could not be entirely attributed to a specific dietary pattern. Further, it is difficult to notice any changes in the effect size of the associations between individual dietary pattern scores and the outcome of interest.

One study (Hillesund et al., 2014) used NND diet scoring index, which might have misclassified the women's dietary scores and BMI as both were self-reported and based on memory. Also, another study (Englund-Ögge et al., 2012) recorded self-reported dietary data of artificial and sugar sweetened beverages, that is generally susceptible to underreporting.

The Thompson study (Thompson et al., 2010) explored the association between maternal dietary patterns and the risk of SGA babies. The author used PCA analysis to extract the dietary patterns for 1714 pregnant women. The study suggested that a "traditional" dietary pattern characterised by high intake of apple/pears, citrus fruits, kiwis, bananas, green vegetables, roots, dairy products, and peas/maize, was associated with low risk of SGA baby.

The dietary data were self-reported, and the participants filled in two FFQ shortly after delivery. Two FFQ separately covered the frequency of food intakes in the first and last month of pregnancy, respectively, and did not justify any reason, which made the methodology seem complicated and time-consuming. Also, they used the FFQ recorded during early pregnancy (first month) for the PCA analysis instead of the FFQ for the last month of pregnancy. The study's method required them to recall their early pregnancy dietary intakes after delivery, which not only increases the chance of underreporting but also caused inconvenience for the participants (Black and Cole,

2001; McGowan and McAuliffe, 2012). Although they appropriately adjusted for maternal smoking, pre-pregnancy height and weight, ethnicity and maternal hypertension, they need not have adjusted for gestational age at delivery and infant sex as they are not associated with maternal dietary patterns (exposure). Also, they did not adjust for alcohol intake, which might have had a potential effect on the associations.

Amongst the systematic reviews and studies it can be observed that the association between maternal dietary patterns and birth outcomes, including the risk of SGA and LGA babies has not yet been fully established. Firstly, lesser number of studies have explored this association and found inconsistent results. The studies which reported an association had poor study design and confounding bias. They also had measurement error in the dietary data and under-reporting was observed. Also, inconsistent definitions were used amongst studies to define an SGA baby. Since it is a binary outcome, there is loss of data when categorical variables are used, this might have produced effects which are small to detect. The gaps identified in this section will be addressed in this thesis in Chapter 6 by using a large sample sized birth cohort, a standardised definition of SGA baby and dietary recorded during pregnancy and well-designed regression models to represent realistic changes in birth outcomes.

Most studies have explored preeclampsia and preterm deliveries and suggested a consistent evidence. Further, most have explored mercury and acrylamide exposures, single nutrients such as vitamin D and folate in dietary supplements, antimicrobial food items (onion, garlic) and probiotics in dairy products in relation to birth outcomes.

Most studies have used principal component analysis (PCA) to derive the dietary patterns and further used multivariate regression models to predict birth outcomes. Although the PCA, factor analysis and diet quality index are suitable in epidemiological studies (Hoffmann et al., 2004; Jolliffe, 2011; Venkaiah et al., 2011), they are data reduction techniques which extract uncorrelated linear combinations of components that represent the maximum variance of the predictor variable, i.e., maternal diet (Jolliffe, 2011). These methods cannot predict the dietary patterns which are related to a specific disease, for example, Type 2 Diabetes Mellitus (Hoffmann et al., 2004; McNaughton et al., 2008) and Cardiovascular disease (Jankovic et al., 2014). Therefore, the PCA approach is appropriate for describing the overall maternal dietary consumption patterns amongst different populations (Hoffmann et al., 2004; Jolliffe, 2011).

2.4.3 Creation of gestational weight gain dietary patterns

Gestational weight gain is an essential mediator between maternal diet and birth outcomes, as it is directly influenced by maternal food intakes (Lagiou et al., 2004; Streuling et al., 2011; Tielemans et al., 2015) and determines the offspring outcome(Koh et al., 2013; Nohr et al., 2009). As per studies, the appropriate amount of gestational weight gain adhering to the IOM guidelines is suggested to improve the offspring birthweight and minimise maternal postpartum weight retention (Butte et al., 2003; Nehring et al., 2013). As discussed in Chapter 1, a report observed that nearly 50% of normal, overweight and obese women gain more weight than the recommended IOM guidelines (Devlieger et al., 2016). Factors including pre-pregnancy BMI, physical activity, dietary intake and smoking contribute to gestational weight gain (Herring et al., 2012; Hui et al., 2014; Koh et al., 2013; Samura et al., 2016; Suliga et al., 2018). Since diet is an important source of energy directly affecting weight gain (Shin et al., 2016), it is necessary to focus on the dietary aspect during pregnancy in order to control gestational weight gain to support healthy birth outcomes.

There is sufficient evidence confirming that sources of energy, including CHO, fat and protein intakes during pregnancy, are important contributors to maternal weight gain. (Lagiou et al., 2004) explored the role of maternal macronutrients in relation to gestational weight gain and birth size. Although they did not observe any evidence of an association with birth size, they suggested that total maternal energy, protein, and fat intakes were positively associated with gestational weight gain. Whereas, maternal CHO intake was negatively associated with gestational weight gain. The macronutrient regression models were adjusted for energy, maternal age, smoking, oral contraceptive use, pre-pregnancy BMI, parity, maternal height, maternal education, gestational age at delivery and sex of the baby. The study was well-designed and measured dietary intakes using validated FFQ at 27 weeks of gestation, followed up with the participants through the delivery, measured weight gain around 27 weeks and mostly adjusted the models for appropriate confounders. However, the study mainly relied on self-reported dietary intakes, which might raise the issue of underreporting, especially prevalent amongst pregnant women with higher pre-pregnancy BMI (Johansson et al., 1998; McGowan and McAuliffe, 2012).

Also, the study adjusted the model for maternal height, and pre-pregnancy BMI, which might have introduced slight collinearity as height and pre-pregnancy BMI is correlated with each other. They could have ideally adjusted the model only for maternal height and maternal pre-pregnancy weight in order to lower confounding bias and measurement error (Elmståhl and Gullberg, 1997). Further, they adjusted for sex of the

baby and gestational age at delivery, which might again be incorrect as it is not associated with maternal dietary intakes. They also did not adjust for alcohol intake. However, they reasoned that only six women had consumed alcohol out of 224 and so they preferred to exclude it from the analysis.

In support of this observational study, a systematic review (Streuling et al., 2011) suggested that maternal dietary energy intakes are necessary in order to control the gestational weight gain. The review included 12 studies, out of which five studies observed a positive association between high maternal energy intake and gestational weight gain, whereas three did not find any evidence of association. Also, the review suggested that high maternal protein and lipid intakes were positively associated with high gestational weight gain. Whereas, maternal CHO intakes were associated with low weight gain, implying that it could bypass maternal weight gain and prioritise the promotion of fetal growth.

Another large systematic review of 56 studies (Tielemans et al., 2015) also explored the association between maternal energy and macronutrient intakes, and gestational weight gain. Results from the systematic review suggested that maternal energy intake and dietary macronutrients were positively associated with gestational weight gain. The (Tielemans et al., 2015) review's study design reduced publication bias by including research articles in all languages, application of a broad search strategy which focused on all nutritional exposures related to gestational weight gain and searched articles through trial registries. However, they included interventional trials from the trial registries that were not yet published, which might mean that the results of the studies included in this review were not approved and externally reviewed. Also, the selection of the articles was based on a scoring system (0 to 10, ten rated as high quality) devised by the authors and was not validated. This might have introduced bias in selecting articles for the review and might have led to the exclusion of other relevant articles. Further, the study did not perform a meta-analysis of all the articles citing the issue of heterogeneity. Instead, they used a quality scoring index and harvest plots to compile their results. However, the authors could have considered a combined meta-analysis with a random-effects model to account for the expected heterogeneity and accordingly provide combined estimates and confidence intervals (E. Hunter and Schmidt, 2002). Despite these limitations, it is a largest systematic review that provided evidence for the association between maternal macronutrients and gestational weight gain.

Although there is substantial albeit inconsistent evidence suggesting the association between maternal macronutrient intakes and gestational weight gain, only three small sample sized studies have explored maternal dietary patterns during pregnancy contributing to gestational weight gain (Shin et al., 2016; Starling et al., 2017; Tielemans et al., 2015).

The Shin study (Shin et al., 2016) explored the association between maternal dietary patterns and gestational weight gain amongst 391 pregnant women. They suggested that a high dietary score for the "mixed" dietary pattern characterised by dairy products, fruit drinks, fruits, nuts, vegetables, legumes, meat, snacks and sweets were negatively associated with excessive gestational weight gain. The study used factor analysis to extract three dietary patterns, "mixed", "healthy" and "western". Factor analysis is usually used to extract uncorrelated linear combinations of maternal food group intakes, which explain the maximum variance for exposure variable, i.e., maternal diet. A better approach would have been the use of reduced rank regression (RRR) to extract dietary patterns that explain the maximum variance of the food intakes related to the specific disease of interest (Hoffmann et al., 2004). The RRR analyses will be undertaken in Chapter 7. Also, the food group aggregation in this study were not made for similar food items, for example, the study had separate food groups for alcohol beverage/liquor, wine and beer, instead they could have had only food group, i.e., alcoholic beverages. Also, this study did not have total gestational weight gain data to use as study outcome, instead, they used the gestational weight gain recorded every month of pregnancy.

Further, the continuous variables were classified into several categories and were then included as confounders for the analysis. For example, maternal age was divided into three groups (<24, 25-34,>35 years) and prepregnancy BMI was categorised into four groups (<18.5, 18.5-24.9,25-29.9,>30). Categorising variables within a modest sample size is not the best option because there is a loss of information, high chance of measurement error and lower statistical power. If continuous variables were used as confounders, the results would demonstrate strong associations with high statistical power.

Tielemans and colleagues (Tielemans et al., 2015) conducted a PCA analysis within the Generation R Study to explore the association between maternal dietary patterns and gestational weight gain. They recorded dietary data using validated Dutch FFQ amongst 3374 pregnant women. The study design included two methods: 1. *A posteriori* approach included PCA 2. *A priori* approach included the use of a validated Dutch

Healthy Diet Index. The results in this study suggested that the three PCA-derived dietary patterns were associated with gestational weight gain. Normal weight women with high adherence to the "vegetable, oil and fish" dietary pattern were positively associated to gain higher early pregnancy weight. Further, a higher adherence to "margarine, sugar and snacks" dietary pattern was positively associated with excessive gestational weight gain. Also, they suggested that high adherence to the "high in fibre, nuts and soy" dietary pattern were negatively associated with moderate weight gain. This is one of the first studies to conduct PCA derived dietary patterns that describe dietary choices in the contribution to gestational weight gain. The study was well designed and recorded dietary data at appropriate time points during pregnancy. For easy interpretation they used the women classed under normal weight as reference category. Also they demonstrated two types of analyses to derive the dietary patterns. However, the methodology used in this study were not appropriate for the study objective.

For the *a posteriori* approach, they used PCA derived dietary patterns which explain the maximum variance for the maternal diet, as mentioned earlier. The PCA method is a good exploratory technique but is not relevant for this study objective as it does not describe or predict the food choices that are specifically related to pregnancy weight gain (Hoffmann et al., 2004; Jolliffe, 2011). This study excluded all underweight women and included the normal, overweight and obese pregnant women for analysis. However, the study prevented potential underreporting of self-reported weight gain and height by organising research centre visits for all trimesters to measure the weight gain. But it should be noted that pre-pregnancy weight and BMI was self-reported and so there could be measurement error in the associations as it would affect determining the exact gestational weight gain and potential misclassification as per the IOM guidelines (Nehring et al., 2013).

In addition, this study excluded 538 participants who had missing dietary information in the FFQ and so that could have lowered the statistical power. Instead, they could have cleaned the data with missing dietary intake values by using the "replace to '0' if missing" command in Stata based on the assumption that the participant did not consume the food items. This data cleaning method could have retained maximum sample size. However, this approach of data cleaning might not have been possible within SPSS version 21.0 as it would in Stata SE/15.1.

For an *a priori* approach, this study (Tielemans et al., 2015) used the Dutch Healthy Index to define the dietary patterns based on dietary guidelines. They suggested no

evidence of an association between the Dutch Healthy Diet Index derived dietary patterns and gestational weight gain. The limitation of this methodology could justify for this finding. The weakness of the dietary score index is that they focus on the selected aspects of the diet and not account for the correlation structure between the food and predictors of the disease (gestational weight gain). Therefore, the dietary scores derived will not explain for the overall effect of the diet on gestational weight gain, therefore, the dietary patterns cannot efficiently predict the weight gain in pregnancy (Hoffmann et al., 2004).

Another study (Starling et al., 2017), derived dietary patterns using reduced rank regression (RRR) that predicted newborn adiposity, including birthweight, adiposity, fat mass and fat-free mass. RRR is a statistical method used to create dietary patterns by including risk factors (predictors) associated with gestational weight gain which represent the maximum variance of the dietary intakes related to gestational weight gain.

The study was conducted amongst 764 pregnant women, and they used an appropriate statistical method to derive the dietary patterns. Reduced rank regression extracted dietary patterns that predicts maximum variance in the response variable. Thus, the RRR method derived maternal dietary patterns, which specifically predicted newborn adiposity. The study selected two risk factors which predict infant adiposity, namely, gestational weight gain and mid-pregnancy fasting glucose during pregnancy. This study suggested that dietary pattern 1 correlated with gestational weight gain and was characterised by a high intake of poultry, nuts, cheese, fruits, whole grains, added sugars, and solid fats. High adherence to dietary pattern 1 was positively associated only with fat-free mass. Dietary pattern 2 correlated with higher fasting glucose and was characterised by a high intake of eggs, starch vegetables, solid fats, fruits and refined grains and lower intakes of dairy foods, whole grains and green vegetables. Higher adherence to dietary pattern 2 was positively associated with higher birthweight, fat mass, fat-free mass and adiposity.

The study excluded women with gestational diabetes. Thus, the results are independent of women with diabetes, maternal obesity and physical activity. Also, the associations observed in this study are only limited to two risk factors included for the reduced rank regression analysis, and so there might be other risk factors that might also contribute in infant adiposity that was not hypothesised in this study.

It can be observed that there is very limited and inconsistent evidence amongst the studies suggesting an association between gestational weight gain dietary patterns and

birth outcomes. This could be due to using an incorrect statistical method to address the study objective. It is important to use an appropriate statistical method to examine the associations. The three studies used PCA, factor analysis and diet score index to extract dietary patterns. However, these methods have not explained the variance of the disease of interest, i.e., gestational weight gain. The gaps identified in this section will be addressed in Chapter 7, where the study will use a reduce rank regression model to extract dietary patterns contributing to gestational weight gain by including its risk factors and explore its associations with birth outcomes amongst large sample sized birth cohorts.

2.5 Identifying the gaps in the evidence

Although there are studies that explored the maternal nutrition and birth outcomes, literature is still very limited for certain aspects of the research area as demonstrated within each sub-section of the chapter.

Limited literature suggested inconsistent findings for the associations between each macronutrient and birth outcomes, including birthweight and risk of SGA and LGA infants. Also, no study has explored the maternal dietary macronutrient components, including starch, lactose, glucose, sucrose, fructose, fatty acids, animal/veg protein and their relation to fetal outcomes. This thesis will address this gap by undertaking an analysis within the CAffeine and REproductive health (CARE) study.

Few studies extracted maternal dietary patterns for exploring its association with risk of SGA and LGA outcomes. Whereas, other studies explored birth length, ponderal index, preterm deliveries, preeclampsia, birthweight. Moreover, studies examined both, birth and child outcomes (amongst children who were 1, 3 and 5 years of age) using zBMI scores and subcutaneous fat mass. Most studies explored the association between dietary maternal macronutrients and energy intakes and gestational weight gain, yet, the role of maternal dietary intakes in gestational weight gain is unclear in the maternal nutrition—fetal outcome pathway.

These certain limitations could be attributed to the inconsistent and unclear findings observed during the critical evaluation. Although the studies had relevant results, the study objectives and design of a few studies explored different exposures and outcomes. Most studies have explored the hypotheses amongst modest sample-sized cohorts. Also, the authors categorised the continuous variables in the analysis which led to a lack of statistical power, loss of information, measurement errors and lowered

the strength of the associations. Some studies have misreported their findings and reported borderline non-significant results. Others only focused on the statistical significance of the associations rather than the estimate sizes and confidence intervals. Very few studies explored the association between dietary macronutrients in pregnancy and the risk of SGA and LGA infants. Also, there was an inconsistent definition used to characterise an infant as small-for-gestational-age, most studies used the standard cut-off as <10th percentile (Clausson et al., 2001; Norris et al., 2015) while others used a cut-off as low as <2.5 percentile. Therefore, it was difficult to understand the clinical significance and interpretation of the results. Few studies designed complex regression models; therefore, interpretations were unclear and complicated. This thesis will use a standardised definition for SGA (<10th centile) and LGA (>90th centile) births based on published literature (Clausson et al., 2001; Gardosi, 2004; Norris et al., 2015; Weissmann-Brenner et al., 2012).

Some studies identified relevant and clinically important confounders to adjust the regression models, which resulted in strong associations with low bias. However, most studies adjusted for competing exposures and reported them as confounders in the methodology. In theory, the competing exposures are only associated with the birth outcomes, for example, gestational age at delivery, sex of the baby. Whereas a confounder is associated with the maternal dietary macronutrient intakes and the birth outcomes, for example, pre-pregnancy BMI, smoking, alcohol intakes, and maternal age (Shrier and Platt, 2008). Confounding errors and residual confounding were observed in other studies where they incorrectly adjusted or did not consider few factors to be included as confounders in their analysis (Schisterman et al., 2017; Shrier and Platt, 2008).

Also, collinearity was an issue amongst a few studies as they adjusted the dietary macronutrient models for total energy intake, and some adjusted for pre-pregnancy BMI and maternal height in the same model. Adjusting for confounders, which are highly correlated with each other is collinearity, and it leads to poorly constructed regression models which are less robust (Schisterman et al., 2017).

Another observation was that most confounders were chosen based on the statistical significance level, and none of the studies used directed acyclic graphs (DAG) to select their confounders. Directed acyclic graphs (explain in detail in Chapter 6) is an *a priori* approach, and the selected confounders are clinically meaningful, reducing overall

confounding bias (Schisterman et al., 2017; Shrier and Platt, 2008). The thesis will use DAG to choose a set of covariates identified after a literature search.

Underreporting is a limitation in any study exploring dietary data. However, some study designs recorded multiple food frequency questionnaires, for example, separate FFQ for early pregnancy and late pregnancy. Moreover, dietary intakes for both FFQ were prospectively recorded after delivery, which introduced the issue of misreporting and underestimation of food intakes. One study has shown that pregnant women with high pre-pregnancy BMI have a higher tendency to underreport dietary data in pregnancy (Johansson et al., 1998; McGowan and McAuliffe, 2012).

Only two studies (Shin et al., 2016; Tielemans et al., 2015) explored the role of maternal diet as a predictor in the development of gestational weight gain by extracting maternal dietary patterns. These studies used principal component analysis and factor analysis, which extract uncorrelated linear combinations of dietary components that explain maximum variance for the maternal dietary intake. PCA and factor analysis cannot predict the associations for a specific disease outcome. However, no study has used reduced rank regression (RRR) to derive gestational weight gain specific dietary patterns by including its risk factors. This gap will be addressed in Chapter 7. Also, a detailed comparison between PCA and RRR is provided (refer section 7.4.2 of Chapter 7). RRR is relatively a new statistical technique that extracts uncorrelated linear combinations of maternal dietary patterns that explain maximum variance for the gestational weight gain (outcome of interest) (detailed explanation given in Chapter 7, in statistical methods under section 7.2.5).

Therefore, based on the gaps identified in this chapter the project objectives are restated below. In order to thoroughly investigate the maternal diet-gestational weight gain-birth outcome pathway, this thesis will explore it in four stages:

1. Examine the association between maternal dietary macronutrient composition and its components, and birth outcomes using multivariate regression models.

2. Understand the overall maternal dietary consumption in a cohort by examining the maternal dietary patterns generated using PCA.

3. Create maternal dietary patterns specifically related to gestational weight gain using RRR.

4. Finally, demonstrate an association between gestational weight gain dietary patterns and birth outcomes, including birthweight, and SGA and LGA babies using multivariate regression models.

The analyses in this thesis have been conducted within three prospective birth cohorts, namely, CAffeine and REproductive Health study (CARE), the Norwegian Mother and Child Cohort Study (MoBa), and the Danish National Birth Cohort (DNBC). The next chapter (Chapter 3) will discuss the birth cohort profiles. In addition, a detailed comparison of the three births cohorts will undertaken for a better understanding of the decisions taken in the analyses.

Chapter 3 Background and comparison of the birth cohorts

The previous chapter conducted a literature search and identified studies relevant to the project objectives. Further, the gaps in literature were identified after undertaking a critical appraisal of all the studies. The current chapter will provide a background and comparison of the three birth cohorts included for analyses, namely Danish National Birth Cohort (DNBC), The Norwegian Mother and Child Birth Cohort (MoBa) and CAffeine and Reproductive Health study (CARE).

3.1 Introduction

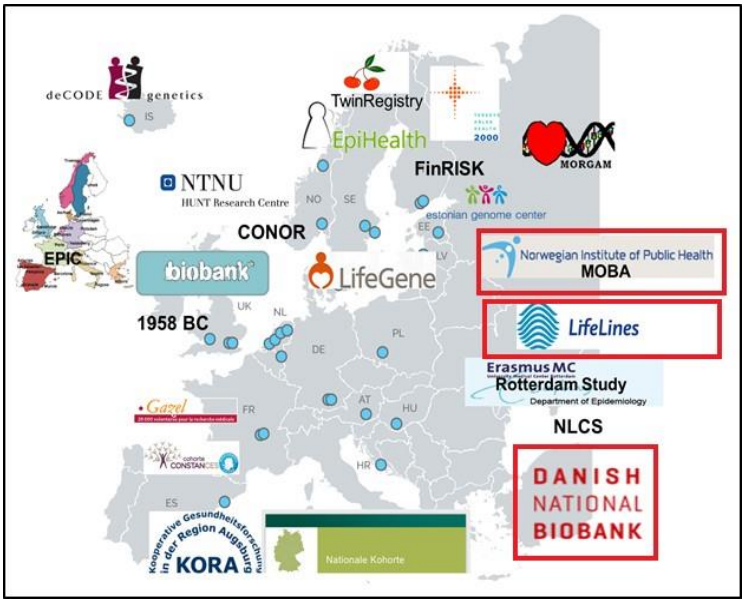
Epidemiological studies are the cornerstone of public health key for disease prevention. They mainly rely on datasets from cohorts or surveys that represent the population in order to mainly analyse the potential risk factors or determinants associated with disease outcomes related to the population. This is done while avoiding any causal implications.

In order to explore the study objectives of this thesis: to explore the impact of dietary maternal macronutrient intakes, dietary patterns contributing to gestational weight gain and birth outcomes data from birth cohorts were used to conduct an observational study. The analyses was conducted using three birth cohorts in the thesis. Data access to two birth cohorts were provided after applying for a scientific grant at the Biobanking and Biomolecular Resources Infrastructure: Large Prospective Cohorts (BBMRI-LPC), a part of the FP7 project (GA no. 313010) and was a consortium of 22 Trans-European cohorts. (Figure 2 shows a map representing the 22 cohorts in the European continent). Of which, only two were birth cohorts, namely DNBC and MoBa, and were chosen because their study population was pregnant women and offspring. Further, they recorded dietary data during pregnancy and birth outcomes, and had baseline information which were necessary for the current study. Other cohorts in the consortium mainly included national biobanks, cohorts with data available for genome studies, cancer research, and adult and elderly populations to explore co-morbidities and aging.

The third birth cohort was the CAffiene and REproductive Health (CARE) study from Leeds, UK. This birth cohort was included for analyses for the same reasons given above. A justification for choosing the three birth cohorts for the analysis is given in section 3.6.

However, it should be noted that although data access was also given for the LifeLines cohort from The Netherlands, the cohort was not included for analysis because it excluded pregnant women at baseline.

Figure 2 Map representation of the 22 cohorts participating in the BBMRI-LPC consortium in the European continent [source: (www.BBMRI-LPC.org, 2015)]



The following sections include a brief description of the cohort profiles and baseline information for the three birth cohorts included for analyses.

3.1.1 Norwegian Mother and Child Cohort (MoBa) study (1999-2008)

The Norwegian Mother and Child Cohort Study (MoBa) was set up by a group of researchers from the National Institute of Public Health (NIPH), Norway and from the Medical Birth Registry of Norway (MBRN).

3.1.1.1 Aim of the cohort

The main objective was to test specific aetiological hypotheses by estimating the associations between exposures and diseases, aiming at prevention (Magnus et al., 2016). The birth cohort recorded data on parental disease exposures and outcomes to study offspring health, and also study the aetiological factors of these diseases that occur among themselves (Magnus et al., 2006).

3.1.1.2 Participant recruitment

The target population of the cohort was to include all women who give birth in Norway. All hospitals and maternity units who delivered more than 100 birth annually were invited to participate. The recruitment rates in MoBa were 42%. Sampling frame comprised of women who attended routine ultrasound examination. Postal invitations were sent along with appointments for ultrasound scanning. The invitation included an informed consent form, a baseline questionnaire and a brochure having general information. The data in MoBa were recorded using self-administered questionnaires, hence, under-reporting and missing data was

expected. This was accounted for during the data cleaning process in the analyses. The MoBa recruited a total sample size of 100,000 mothers and 114,247 infants. The cohort largely recruited primiparous women in their study (91%). Therefore, the study population in MoBa were included for analysis as the main aim of the thesis required pregnant women and their offspring.

3.1.1.3 Exclusion criteria

The cohort had no exclusion criteria.

3.1.1.4 Follow-up period

Baseline data was recorded during 13-17 weeks of pregnancy, dietary data was recorded around 22 week of gestational. In addition, four questionnaires were sent at post-pregnancy and child's growth at 6 months of age, at 3 years, at 5 years and finally at 7 years of age. However, questionnaire 3 also included few questions regarding the maternal weight, physical activity levels, alcohol and smoking habits during trimester three. This data has been used in the analysis chapters of this thesis.

From MoBa the baseline information (15-17 weeks of gestation) and dietary data (around 22 weeks of gestation) were used for maternal exposures in the analyses.

3.1.1.4.1 Baseline questionnaire (13-17 weeks)

This was sent around the 13 to 17 weeks of gestation and primarily consisted of baseline information regarding the mothers' previous pregnancies and outcomes, stress levels at work, diseases, occupation, anthropometric measurements (height, weight before and start of pregnancy), physical activity, mental health, and lifestyle habits. For the analyses, data regarding maternal age, pre-pregnancy BMI, maternal smoking habits, alcohol intake, physical activity levels, use of dietary supplements and parity were used. This baseline data were used because they are known to be associated with maternal diet and offspring outcomes. Thus, covariates from retrospective data were used for model adjustment.

3.1.1.4.2 Maternal dietary exposures: recorded around 22 weeks of gestation

A semi-quantitative food frequency questionnaire (FFQ) was sent out to all participating mothers which record their daily food intake, dietary changes after pregnancy, food choices, portion sizes and dietary supplements. The FFQ covers the mother's diet from start of pregnancy. The data recorded was favourable for the analyses as the dietary data covers the dietary intakes for a longer period of time and therefore, might represent consistent dietary patterns in the results. For the development of the FFQ, the MoBa cohort conducted a stepwise regression analyses using Norwegian food intake data to identify the most varied food items.

This helped in framing an FFQ that covered all the major food items and food groups consumed by the Norwegian population. Also, the FFQ included questions regarding consumption of new/modern foods, citing the increased consumption of westernised foods including pizza, ciabatta, burritos that are not commonly consumed in a traditional Norwegian diet.

The FFQ (Brantsæter et al., 2008) contained 340 questions organised into 40 groups based on the Norwegian meal pattern. Three groups included questions regarding the dietary patterns and 23 groups asked questions regarding the 255 specific food items to monitor the daily nutrient intake, food groups, and energy intake.

The FFQ did not include food portion sizes for all of its food items. They included portion sizes only for fruits (piece), bread (slices) and liquids (cups/glasses) to include more number of questions possible with a specific aim to capture the intake of non-nutrients more accurately. In the initial stages of the MoBa inclusion period, a previous version of the FFQ included questions on portion sizes thus lowering the response rates citing complexities related to answering the FFQ. Omitting portion sizes from the new FFQ (Brantsæter et al., 2008) enabled MoBa to capture larger number of food questions which described the food patterns and food habits in a better way. The FFQ was validated using reference measures including 4-day weighted food diary, motor sensor for measuring total energy expenditure, one 24-hour urine sample to measure iodine and nitrogen excretion, and a venous blood specimen to analyse plasma 25-hydroxy-vitamin D and serum folate. It reported that the FFQ provided consistent intake estimates (Brantsæter et al., 2008).

The reported food and supplement intakes were converted into daily intakes using FoodCalc software and the Norwegian Food Composition Table (NFCT).

Therefore, it can be observed that a detailed high quality dietary data (22 weeks) was recorded by MoBa and was used for analyses. The nutrient intakes data will enable to explore associations between maternal dietary macronutrient intakes and birthweight, and odds of SGA and LGA babies. Further, the food frequencies data will enable to examine the dietary patterns during pregnancy.

3.1.1.4.3 Pregnancy and birth outcomes

The Medical Birth Registry of Norway (MBRN) contains records for all the maternal health and pregnancy outcomes and is linked with the MoBa database, this included birth outcomes for the analysis. The birth outcomes data included information on the type of delivery, postpartum health of the mother, maternal health including maternal age, birth weights (grams), ultrasound scan measurements, gestational age at delivery (days and in weeks), preterm pregnancies, parity, sex of the baby, and crown to rump lengths. From the MBRN data the regression analyses

used birthweights as the study outcome and maternal age as a covariate. Also, Chapter 5, 6 and 7 will explore secondary outcomes such as odds of SGA and LGA babies. For this, birthweight, gestational age at delivery, sex of the baby, parity, maternal height, and weight data will be used to extract birth centiles.

3.1.2 Danish National Birth Cohort (DNBC) (1996-2002)

3.1.2.1 Aim of the cohort

The DNBC was established to investigate the causal link in exposures in early life and disease later on and the possibilities of disease prevention (Olsen et al., 2001).

3.1.2.2 Participant recruitment

The DNBC recruited around 95% participants for the study through all the general practitioners (GP) in Denmark. Invitations to pregnant women during their first pregnancy visit, around 6-12 weeks were given by their respective GPs. The DNBC study recruited 101,042 women with singleton pregnancies. Therefore, the study population in DNBC were included for analysis as the main aim of the thesis required pregnant women and their offspring. Also, the analyses explored the dietary maternal data on singleton pregnancies. The data of DNBC and MoBa are included in the meta-analysis and to derive the maternal dietary patterns as they have a high sample size. Therefore, including these two birth cohorts will increase the statistical power. The benefits of including high sample sized birth cohorts for individual patient data meta-anlaysis is given under section 5.4.2 of Chapter 5.

3.1.2.3 Exclusion criteria

The candidates should be able to speak Danish well enough to take part in the telephonic interviews and should reside in Denmark. No other exclusion criteria were used.

3.1.2.4 Follow-up period

Computerised telephonic interviews were conducted to record data of the pregnant women using baseline questionnaires (around 12 weeks), at 30 weeks, and when the infants are six and 18 months old. Therefore, it could be observed that the study design of the cohort lowered the chances of under-reporting and misreporting of baseline information through interviewer administered questionnaires.

3.1.2.5 Baseline questionnaire

The maternal information, including work status, education, maternal age, marital status, occupation, maternal height and weight, pre-pregnancy BMI, weight at each trimester, physical activity levels, lifestyle habits (smoking status and alcohol intakes), use of dietary supplements and parity were recorded.

For the analyses, baseline data regarding maternal age, height, weight, pre-pregnancy BMI, physical activity levels, alcohol intake, smoking habits, use of dietary supplements and parity was used as covariates in the regression analyses as they are known to be associated with maternal diet and offspring outcomes. This is described in detail in Chapter 5 under section 5.2.6. The DNBC study design enabled to record high quality and reliable baseline data through telephonic interviews, therefore lowering the overall missing data caused by under-reporting or misreporting.

3.1.2.6 Maternal dietary exposures: recorded around 25 weeks of gestation

Dietary data was recorded using self-reported validated food frequency questionnaire (FFQ) which contained 360 items (Mikkelsen et al., 2007). The DNBC captured dietary intakes during pregnancy by including questions for the past one month of pregnancy. The FFQ recorded information regarding vitamin and dietary supplements consumed during pregnancy.

For estimation of food intakes, standard portion sizes and standard recipes were developed for all items in the questionnaires. All the food intake frequencies were converted to per day frequency consumption, for example, if the tea was consumed 2/week then the data was divided by 7 days per week for a per day consumption value. In order to avoid overestimation of food and nutrient intakes, the cohort used standard portion sizes and new recipes that matched the food descriptions reported by the participants. A total of 615 new standard recipes were made based on the participant descriptions, and 475 individual recipes. This approach accounted for new recipes and foods available in markets that were not mentioned or included in the Danish Food Composition Tables, which otherwise generally included traditional Nordic dishes. The food and nutrient intakes were computed using FoodCalc and Danish food composition tables. Maternal dietary data was taken from DNBC because it recorded high quality data that captured intakes of the last one month during pregnancy. The FFQ data was included for analysis to study maternal dietary patterns from the food frequencies. Nutrient data was used to explore the impact of macronutrients on offspring outcomes.

3.1.2.7 Pregnancy and birth outcomes

The DNBC extracted pregnancy and birth outcomes data through the pregnancy discharge registration data linked within the National Hospital Discharge Registry. The data included diseases during pregnancy leading to hospitalisation, birth weight, birth length, gestational age at birth, sex of the baby, birth complications and delivery methods.

For the analyses in this thesis, the baseline and dietary data from DNBC were used as covariates and study exposures. This comprised participant demographic characteristics such as maternal height, weight, pre-pregnancy BMI, parity, maternal age, alcohol intake, smoking habits, physical activity, and maternal dietary exposures, respectively. Further, the analyses in this

thesis, Chapters 5 and 7 will use birthweight data. Also, in order to explore secondary outcomes such as odds of SGA and LGA baby, birth centiles will be extracted using the data of birthweight, maternal height, weight, parity, gestational age at delivery and sex of the baby.

3.1.3 CAffiene and REproductive Health (CARE) study (2003-2006)

The Caffeine and Reproductive Health (CARE) study was a prospective longitudinal observational study in Leeds, UK.

3.1.3.1 Aim of the cohort

The cohort was formed to explore maternal caffeine intakes on fetal outcomes (Boylan S, 2010; Boylan et al., 2008).

3.1.3.2 Cohort objective

The cohort used a caffeine assessment tool (CAT) tool to set safe upper limits for caffeine consumption during pregnancy in relation to adverse fetal outcomes.

3.1.3.3 Recruitment period

The recruitment was conducted in two large teaching hospital maternity units in Leeds, UK. The total number of women recruited in the CARE study composed of 2635 pregnant women with singleton pregnancies. The CARE data will be included for analysis to explore associations between maternal dietary macronutrient data and outcomes of singletons. The pre-booking notes at the hospital maternity units were checked for eligible participants. An invitation was then sent to these potential participants attaching an information booklet and informed consent form. They were asked to return the written (signed) consent forms and invitation slips if they agreed to participate. Personal contact was then made for ones who consented to take part.

3.1.3.4 Inclusion criteria

The CARE study recruited women who were between 18-45 years of age with low-risk singleton pregnancies which were accurately dated by ultrasound scan.

3.1.3.5 Exclusion criteria

Women with concurrent medical disorders, psychiatric illness, HIV infection, or hepatitis B infection were excluded.

3.1.3.6 Follow-up period

The participants were followed up once every trimester in order to measure their caffeine intakes in pregnancy. A robust validated caffeine assessment tool (CAT) was developed to quantify the maternal caffeine intake for all trimesters(Boylan et al., 2008).

3.1.3.7 Baseline questionnaire

Baseline questionnaire was used to record maternal information such as maternal age parity, maternal height, pre-pregnancy weight, marital status, socioeconomic status, education and gestational age at delivery, physical activity levels, use of dietary supplements, smoking habits and alcohol intakes. The first questionnaire was filled in by a midwife around 8-12 weeks of gestation at the hospital after the participants were recruited into the study or at the participant's home.

The analyses used baseline information such as maternal age, physical activity levels, smoking, alcohol intake, use of dietary supplements, parity, ethnicity, height, weight and pre-pregnancy BMI as covariates for adjusting the regression models for trimester 1 and 2. This data was high quality as the data was interview-administered and therefore, lowered under-reporting and missing data.

Chapter 4 will explore the association between maternal dietary macronutrient intakes in trimester 2 and birth outcomes (see methods in Chapter 4) and will require covariates measured during the second trimester. For this, maternal data recorded for trimester 2 such as physical activity levels, smoking habits, alcohol intake were taken from the CAT used between 13-28 gestational weeks.

3.1.3.8 Maternal dietary exposures

Dietary intakes were recorded using a 24-hour dietary recall by a trained midwife at home twice; between 8-12 weeks of gestation and again around 13-28 weeks of gestation (Boylan et al., 2008). The dietary intakes were then entered into a nutrient analysis package- 'DANTE' (Diet And Nutrition Tool for Evaluation). The nutrient analysis computed by this dietary software was based on the standard UK food composition tables by the Royal College of Chemistry. For the analyses in this thesis in Chapters 4 and 5, the dietary macronutrient intakes will be used for exploring the association between dietary macronutrients and offspring outcomes.

3.1.3.9 Pregnancy and birth outcomes

The cohort recorded the offspring outcomes including birth weight, sex of the baby, gestational age at delivery, preterm delivery, pregnancy complications, adverse pregnancy outcomes (stillbirth, neonatal deaths, termination of pregnancies). This information was obtained from the hospital maternity records.

Chapters 4 and 5 will include the birthweight data as the birthweight is the primary outcome. In addition, only Chapter 4 will include data of the sex of the baby and gestational age at delivery as covariates to adjust the birthweight models. Also, in order to examine secondary outcomes

such as odds of SGA and LGA babies, birth centiles will be extracted using data of maternal height, weight, birthweight, gestational age at delivery, ethnicity, sex of the baby and parity.

This following section will conduct a detailed comparison between the three birth cohorts.

As the birth cohorts had different study designs it is important to observe the differences between their cohort profiles and data recorded for proper interpretations of the results. Table 3 compares the cohort profiles of the three births cohorts included for analyses.

Table 3 Cohort profiles comparison of of MoBa, DNBC and CARE study

Category	MoBa	DNBC	CARE study
Country	Norway	Denmark	UK
Recruitment period	1999-2008	1996-2002	2003-2006
Sample size	100,000 mothers and 114,247 infants	101,042 women with singleton pregnancies	2635 pregnant women with singleton pregnancies
Exclusion criteria	None	None	Medical disorders, psychiatric illness, hiv infection, or hepatitis B infection
Baseline data recording method	Self-administered	Telephonic interviews	Interview-adminstered by trained research midwife
Baseline data (weeks of pregnancy)	Between 13-17 weeks of gestation	Between 12 weeks of gestation	Between 8-12 weeks of gestation
Dietary assessment tool	Self-adminsitered validated FFQ	Self-adminsitered validated FFQ	Interview-adminstered 24-hour dietary recalls
Dietary data (weeks of pregnancy)	Around 22 weeks	Around 25 weeks	Around 8-12 weeks for trimester 1 intakes, around 13-28 weeks for trimester 2 intakes
Data available for maternal characteristics	Maternal age, pre-pregnancy BMI, maternal smoking habits, alcohol intake, physical activity levels, use of dietary supplements and parity were used	Maternal height, weight, pre-pregnancy BMI, parity, maternal age, alcohol intake, smoking habits, physical activity, use of dietary supplements	Data recorded for trimester 1: Maternal age, physical activity levels, smoking, alcohol intake, use of dietary supplements, parity, ethnicity, height, weight and pre-pregnancy BMI Data recorded for trimester 2:

			Physical activity levels, smoking habits, alcohol intake
Data available for birth outcomes	Birthweight, gestational age at delivery, sex of the baby, parity, maternal height, and weight.	Birthweight, maternal height, weight, parity, gestational age at delivery and sex of the baby.	Maternal height, weight, birthweight, gestational age at delivery, ethnicity, sex of the baby and parity

The three birth cohorts are compared based on:

1. Study design
2. Maternal and offspring characteristics
3. Dietary data
4. Dietary intakes

3.2 Comparison of the study designs

The total number of pregnancies varied between the three cohorts; MoBa had the highest sample size (mothers= 95,200), followed by DNBC (mothers=91,827) and CARE (mothers=1196 in trimester 1 and 598 in trimester 2).

CARE recruited the participants from the maternity wards of two hospitals in Leeds. Whereas, DNBC participants were invited by their general practitioner around the 6-10th week of gestation, while MoBa recruited the participants after they signed up for an ultrasound examination at the hospital during similar gestational weeks of DNBC.

The MoBa and DNBC included all pregnant women in Norway and Denmark, respectively. However, the CARE birth cohort only included participants between 18-45 years with low-risk singleton pregnancies.

There were no exclusion criteria for MoBa. However, DNBC excluded participants who could not speak Danish. Whereas, the CARE cohort excluded participants with concurrent medical disorders, psychiatric illness, HIV infections, and Hepatitis B infection.

The data collection amongst all three cohorts varied widely. In DNBC, four computer-assisted telephone interviews were conducted during gestational weeks 12 and 30, and again at 6 and 18 months postpartum. In MoBa, the participants were mailed the questionnaires around gestational weeks 15 and 30, and 6 and 18 months postpartum. Whereas, in CARE, interview-administered questionnaires were used for the first trimester (8-12 weeks) and second

trimester (13 to 28 weeks), and another for the third trimester (29 to 40 weeks). The trained research midwives recorded the baseline data at the hospital during trimester 1 and visited the participants' residence during trimester 2.

Participation response rates for returning FFQ also varied amongst DNBC and MoBa; MoBa had a 90% response rate as compared to 74% of DNBC. Therefore maternal dietary data included for analyses was available for higher number of participants from MoBa (n=85,391) as compared to DNBC (n=68,123).

In CARE, in trimester 2, the 24-hour dietary recalls were only available for 598 participants because a case-control approach was used to recruit women in the second and third trimester including women who delivered a LBW infant as "case" and matched to a "control" who did not. Also, because there were limited resources to conduct home visits for all the participants.

The baseline data in each cohort were recorded in the following gestational periods: around 15 weeks of gestation in MoBa, around 12 weeks of gestation in DNBC and around 13-27 weeks of gestation in CARE. The covariates in the baseline data were recorded differently in each cohort because they used different questionnaires. Therefore, this will be accounted while conducting the meta-analysis of the three birth cohorts (Chapter 5) as the results combined from the cohort-specific analysis might influence the heterogeneity levels. A detailed comparison of the covariates recorded within the three cohorts is given in Chapter 5 under section 5.2.6.1.

3.3 Comparison of the maternal and offspring characteristics

A total of 203,676 mother-infant pairs were available for analysis from DNBC (N=92,458) in Denmark, MoBa (N=110,022) in Norway, and CARE (N=1196) in the UK. The CARE study analyses originally included 1196 women in trimester 1, amongst which trimester 2 (13-28 weeks) included 598 women. Only for the comparison of the dietary intakes, 598 participants in CARE are included in this chapter because they were recorded around similar gestational periods as the MoBa (22 weeks) and DNBC (25 weeks).

The demographic characteristics of the mother and infants in CARE, MoBa and DNBC are given in Tables 4 and 5, respectively.

Maternal baseline characteristics were similar amongst the three cohorts such as the mean maternal age, mean pre-pregnancy BMI, and proportion of primiparous women.

Amongst differences observed in the cohorts, a more substantial proportion of women in DNBC were unemployed (20%, n=17,331) as compared to MoBa (4%, n=3825) and CARE (5%, n=25).

This might be due to the difference in the definition used for “employment status” in DNBC as compared to MoBa and CARE.

The DNBC categorised employment status in 4 categories, such as Employed (one job), Employed (two jobs), Employed (more than two jobs), No employment. This might be possible that there was misreporting during the baseline data recording. They did not specify the definition of unemployed or type of job in the questionnaire and the categories did not include categories which could also be termed as employed for example, self-employment or intern. Whereas MoBa included 10 categories such as student, at home, intern, military service, unemployed or laid off, rehabilitation or disabled, employed in public sector, employed in private sector and self-employed. However, CARE defined work as “hours of work/week”, “paid job= yes or no” and “describe your work.” Therefore, CARE and MoBa allowed participants to describe their work status appropriately while recording the baseline data as compared to DNBC.

Women in the Norwegian cohort were more physically active in their leisure time during pregnancy, i.e. at week 15 (59%, n=55,217) and week 30 weeks of gestation (59%, n=50671) as compared to DNBC and CARE cohorts. The CARE defined physical activity in three categories such as no physical activity, light or moderate physical activity in most weeks and vigorous physical activity (>20 minutes/week or <20 minutes/week). MoBa defined physical activity as “Frequency of being currently so active in your leisure that you get out of breath or sweat - during pregnancy”, therefore those who answered “yes” were considered physically active. In DNBC, participants were considered to be physically active if they answered “yes” to “Do you get any kind of exercise during pregnancy”, (1=Yes, 0=No). Therefore, physical activity was recorded in three different formats in the cohorts and the duration of exercise was not quantified in the MoBa and DNBC as it was done in the CARE study. This might have misclassified the women who were physically active during their pregnancy. Also, the regression models in Chapters 4, 5, 6 and 7 have been adjusted for physical activity and might have contributed to the heterogeneity levels observed in the meta-analysis in Chapter 5.

However, there were obvious differences in lifestyle habits such as smoking habits and alcohol intakes between Norwegian and Danish women during pregnancy. Danish women smoked in higher proportions at 12 weeks of gestation (26%, n=22,481) than Norwegian women around 15 weeks of gestation (9%, n=8315). Also, almost 45% of the Danish participants were more likely to get passively exposed to the tobacco fumes, even if they were non-smokers (45%, n=24738) than Norwegian participants (6%, n=5658). Whereas, in CARE, more than half of the cohort were non-smokers during pregnancy (57%, n=470), which were the lowest as compared

to the DNBC and MoBa. The European Union presented prevalence rates of current smokers in 2014 (Eurostat, 2014) and reported that women smokers prevalent in both Norway (12.3%) and Denmark (11.9%) were similar, but slightly lower than the prevalence rates observed in UK (13%). Therefore it is observed that the smoking rates of the three birth cohorts are higher than the overall prevalence rates of their respective countries. This might be due to the steady decline observed in the prevalence of smoking in the Europe, as suggested by one (Graham, 1996) study. Two studies suggested that smoking rates in Denmark were higher between 1960-early 2000 and have gradually lowered in the past two decades (Graham, 1996; Osler et al., 1998). As the three cohorts recorded the data between 1995-2005 the results in this chapter might represent the prevalence rates during that period. Another reason for this difference might be that the current prevalence rates have lowered in the EU by 5 to 7% due to the increased tax of 10% on cigarettes in the EU (Jackson et al., 2018).

This proportions observed might affect the overall associations with birth outcomes, as smoking habits are included as covariates in the regression models in Chapters 4,5,6, and 7. This might also contribute to heterogeneity levels observed in the meta-analysis results in Chapter 5. Further, based on previous literature smoking habits were chosen as risk factors of gestational weight gain (refer Chapter 7 methodology 7.2.5). This difference might potentially influence the variance explained by the extracted dietary patterns.

When mean alcohol consumption was examined, high intakes were observed amongst the Danish participants during pregnancy (mean alcohol 20 g/day, SD 11) as compared to the Norwegian (mean alcohol 1g/day, SD 8) and the British (mean alcohol 10g/day, SD 33) cohorts. This was based on the assumption that one standard alcohol unit (500 ml of beer) in Denmark has 12 grams or 10 ml of pure alcohol. However, Denmark and Norway had same standard alcohol units (12 g per day) but, not UK. The standard unit of alcohol in UK is 8g which is much lesser than the alcohol units in the Nordic countries. As alcohol is included as a covariate in the birthweight and odds of SGA and LGA models, this difference observed might influence the overall associations with birth outcomes in DNBC and the overall heterogeneity levels in the meta-analysis in Chapter 5. This observation meant that most of the Danish women in this cohort who consumed alcohol had almost 1.6 standard alcoholic units (1.6 multiplied by 12g (the standard alcohol content in 500 ml of beer)=19.2 g of alcohol) per day during pregnancy as compared to no alcohol consumption in MoBa and only around one standard drink (around 10g of alcohol/day) in UK.

These observations were also reported by Olsen et al. where they acknowledged the prevalence rates of alcohol and smoking habits were generally higher in Denmark as compared to Norway

when the cohort recruited the participants (Mackenbach et al., 2015; Olsen et al., 2014). In agreement with this result a study exploring Nordic countries suggested that Denmark had the highest prevalence rates of self-reported alcohol consumption (80% amongst men, 58% amongst women) as compared to Norway and Sweden (69% amongst men, 40-44% amongst women) (Östergren et al., 2019).

The differences observed in recording data of smoking and alcohol intake will be taken into account for the regression models in Chapters 4,5,6 and 7. These differences might change the interpretation of the results within cohort-specific results as each cohort recorded alcohol and smoking in different formats as described above. However, although adjusting for similar covariates in the the analyses might remove the effect in the models, residual confounding might still occur even after adjustment.

Table 4 Demographic characteristics of the pregnant women in DNBC, MoBa and CARE

Characteristic	DNBC[a] N=92,458		MoBa[b] N=110,022		CARE[c] N=1196	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	30	4	30	5	30	5
Self-reported weight (kg)						
Pre-pregnancy weight	67	13	68	13	67	14
At 12 weeks in DNBC/ At 15 weeks in MoBa	71	13	71	13	-	-
At 30 weeks of gestation	77	12	77	13	-	-
Total gestational weight gain (kg)	10	4	9	4		
Weight gain between pre-pregnancy weight and week 12 DNBC/ Weight gain between pre-pregnancy weight and week 15 in MoBa	3	3	3	3	-	-
Weight gain between weeks 12 and 30 in DNBC/ Weight gain between weeks 15 and 30 in MoBa	7	4	6	3	-	-
Maternal BMI (kg/m^2)						
Pre-pregnancy	24	4	24	4	25	5
At 12 weeks of gestation in DNBC/ At 15 weeks in MoBa	25	4	25	4	-	-
At 30 weeks of gestation	27	4	27	4	-	-
	n	**%**	**n**	**%**	**n**	**%**
Primigravida	40,623	47	48,229	44	497	42
Employment status						
No	17,331	20	3,825	4	25	2
Yes	69,228	80	84,989	96	1171	98
Physical activity status, (Yes)						

[a] DNBC collected data at baseline (at 12 weeks of gestation) and around 30 weeks of gestation

[b] MoBa collected data at baseline (at 15 weeks of gestation) and around 30 weeks of gestation

[c] CARE collected data at baseline (around 8-12 weeks of gestation) and around 13-27 weeks of gestation

At week 12 in DNBC/ At week 15 in MoBa	31,762	37	55,217	59	-	-
At week 30	25,640	30	50,671	59	-	-
Dietary supplement users						
Yes	50,714	55	81,990	88	988	83
Yes, but not quantified (only in DNBC)	12,682	14	-	-	-	-
Smoking status at 12 weeks in DNBC/ At 15 weeks in MoBa					-	-
No	64,073	74	79,979	91	-	-
Yes	22,481	26	8,315	9	-	-
Smoking status for trimester 1 in CARE (n=1118)						
Non-smoker	-	-	-	-	585	52
Occasional smoker	-	-	-	-	342	31
Current smoker	-	-	-	-	191	17
Smoking status for trimester 2 in CARE (n=821)						
Non-smoker	-	-	-	-	470	57
Occasional smoker	-	-	-	-	252	31
Current smoker	-	-	-	-	99	12
Physical activity during pregnancy for trimester 1 in CARE (n=1102)						
No weekly physical activity	-	-	-	-	240	22
Light to moderate physical activity	-	-	-	-	753	68
Vigorous physical activity (above and upto 20 minutes, 1-2 times/week)	-	-	-	-	109	10
Physical activity during pregnancy for trimester 2 in CARE (n=824)						
No weekly physical activity	-	-	-	-	65	8
Light to moderate physical activity	-	-	-	-	642	78
Vigorous physical activity (above and up to 20 minutes, 1-2 times/week)	-	-	-	-	117	14

Amongst offspring characteristics, the birthweights amongst all three cohorts were similar. However, there was a notable difference in the proportion of large-for-gestational-age infants (LGA), where MoBa had a larger proportion of LGA infants (22%, n=23,775) as compared DNBC (8%, n=7,715), and CARE (9%, n=109). A possible reason could be a positive association between maternal dietary patterns and birth outcomes using PCA, given in Chapter 6 under section 6.4.2. The results in Chapter 6 demonstrated that a high adherence to "animal meat" and "potato and cereal" dietary patterns were associated with high odds of LGA baby in MoBa. Thus, the maternal dietary choices might possibly explain the high rates of LGA babies in MoBa. However, the SGA babies were highest within the CARE cohort (13%, n=155) as compared to MoBa (10%, n=11,025) and DNBC (9%, n=8513).

Table 5 Demographic characteristics of the offspring in DNBC, MoBa and CARE

Offspring characteristics	DNBC		MoBa		CARE	
	Mean	SD	Mean	SD	Mean	SD
Birthweight (g)	3585	564	3,590	583	3434	559
Gestational age at delivery (weeks)	40	2	39	2	40	2
	n	%	n	%	n	%
Sex of the baby						
Male	47,391	51	56,338	51	602	50
Female	45,067	49	53,476	49	594	50
Preterm delivery (<37 weeks)	4,381	5	5,383	5	51	4
LBW infants (<2500 g)	2,764	3	3,495	3	51	4
LGA infants (>90th percentile)	7,715	8	23,775	22	109	9
SGA infants (<10th percentile)	8,513	9	11,025	10	155	13

3.4 Comparison of the dietary data

The dietary data in CARE, MoBa and DNBC was recorded at different gestational weeks of pregnancy. MoBa recorded the maternal dietary intakes around 22 weeks but DNBC recorded around 25 weeks using self-reported validated FFQ. In contrast the CARE study recorded dietary data twice using 24-hour dietary recalls administered by a trained research midwife, once in trimester 1 (8-12 weeks), and again in trimester 2 (13-27 weeks) at the participant's residence.

Although both methods are widely used to measure dietary intakes studies have suggested that the both methods could produce different results (Schatzkin et al., 2003). Also, studies suggested that the FFQ could underestimate actual intakes as compared to dietary recalls (Mertens et al., 2019). Also studies suggest that in comparison with FFQ, 24-hour dietary recalls provide more accurate dietary intake on a given day thus lowering measurement error (Shim et al., 2014; Wark et al., 2018). FFQ is a common a dietary assessment tool used to measure dietary

data amongst large populations and is more cost effective than an expensive and time-consuming method like 24-hour dietary recalls (Shim et al., 2014). This is a better tool than 24-hour dietary recall because a single dietary recall cannot capture day-to-day variations of the intake amongst a large population(Wark et al., 2018). Also, it cannot predict the dietary patterns consumed within a cohort. These advantages and disadvantages of both methods might impact the results because the dietary assessment tools such as FFQ and 24-hour dietary recall used in the three birth cohorts could be prone to under-reporting, measurement error and missing data(Black and Cole, 2001; Elmståhl and Gullberg, 1997; Shim et al., 2014) .

In the CARE cohort, the 24-hour dietary recall included a meal wise description of food items and portion sizes, and the nutrient intake analysis was later computed using the DANTE software, which was based on McCance and Widdowson's standard UK food composition tables (Holland B, 1992). Whereas, the dietary intakes were computed using Norwegian food composition tables in MoBa (Blaker and Aarsland, 1989) and Danish food composition tables in DNBC (Mikkelsen et al., 2007). However, both used the same software called FoodCalc to extract the nutrient intakes and therefore, similar mean dietary intakes in the two cohorts could be observed.

The MoBa FFQ included 300 food items which were aggregated into 33 food groups such as added sugar, fruits and dried fruit, nuts and oilseed, potato (boiled, baked and cooked), whole and low-fat yogurt, rice and millet, creams and mayonnaise, unrefined bread, refined bread, fruit juices, jams and syrups, other milk, tea, coffee, alcoholic beverages, colas, whole milk, low-fat milk, breakfast cereals, desserts, sweets and chocolate, fats and oil, cheese spread, pasta, spaghetti and noodles, vegetables, fatty fish, lean fish, seafood and molluscs, fish products, egg and poultry, red meat, pork, offal, beef and veal, and miscellaneous foods (popcorn, pizza, sauces, ketchups, chips).

The DNBC included 360 food items in the validated semi-quantitative FFQ. The questionnaire included frequencies for 40 pre-defined food groups such as low fat dairy, high fat dairy, ice cream, breakfast cereals, whole grains, refined rains, fruit, offal, processed meat, red meat, fish, shellfish, poultry, eggs, animal fats, vegetable fats, margarine, sweets and desserts, tea, coffee, high energy drinks, low energy drinks, alcoholic beverages, snacks, vegetables juice, fruit juice, fruit syrups and jams, nuts, other vegetables, potato products, green leafy vegetables, tomatoes, soy products, dried fruit, dressings, beans and lentil, cheese, and added sugar.

In DNBC and MoBa the food items were converted into grams per day by multiplying the standard portion sizes with daily frequencies. Further, the nutrient intakes were estimated using similar methods such as summing the nutrients from all food items in the questionnaire

using standard portion size assumptions in MoBa (Blaker and Aarsland, 1989) and DNBC (Andersen LT, 1996). However, DNBC used Danish food composition tables version 6.02 (databank, 2007) and MoBa used Norwegian food composition tables (Rimestad AH and K, 2005) to refer the nutrient component in the food items and recipes. Further, both cohorts calculated the daily nutrient intakes of the participants by using the same software: FoodCalc.

One principle difference between the nutrient calculations of DNBC and MoBa is that the DNBC food database does not have data on mixed recipes and only includes individual food items (Andersen LT, 1996). Whereas, the Norwegian food database has the data available for mixed dishes. Therefore, the DNBC uses predefined food recipes to describe mixed dishes and aggregates all the nutrient content of individual food items in a mixed dish by referring the Danish food composition table (Olsen et al., 2014). For example, mixed dishes such as pizza and tacos were not available in DNBC database. Therefore, the individual standard portion sizes of the food items (ingredients) in the FFQ such as flat bread, tomato sauce, vegetables, cheese and olive oil had to be aggregated and Danish food composition tables were used to extract the nutrient values for the ingredients. This did not account for the possibility of adding other food items (ingredients) or added amounts. Therefore, in DNBC the nutrient intake calculations might have measurement error, under and overestimation of food portions while aggregating the nutrient intakes from individual food items belonging to a recipe. This must be accounted while exploring the impact of macronutrient during pregnancy on offspring outcomes, as the macronutrient intakes in DNBC might be measurement error.

Also, the MoBa FFQ included certain food items only consumed in Norway and not in Denmark, which might help in describing the maternal dietary patterns of the Norwegian population inclusive of the native foods such as certain types of cheese and fish.

Also, the MoBa dietary intakes capture the mothers' diets for the past 3 to 4 months before filling the FFQ. Therefore, the dietary intakes and dietary patterns extracted from MoBa would represent consistent dietary choices which could making the results more reliable. This is better in contrast to DNBC and CARE, as maternal dietary choices are captured only for the past one month of pregnancy (DNBC) and actual intakes of one day (CARE). This could also help in understanding the results from a clinical perspective after considering the metabolic changes which occur in pregnancy and how they are linked with the maternal nutrition intakes, for example, the protein, fat and carbohydrate (CHO) metabolism.

3.5 Comparison of the dietary intakes

The three cohorts had similar mean macronutrient (CHO, protein and fat) and mean micronutrient (iron, folate, vitamin B12 and calcium) intakes during pregnancy (refer Table 6). This shows that despite using different dietary methods and nutrient analysis software amongst the three cohorts (FFQ and FoodCalc in MoBa and DNBC, and 24-hour dietary recalls and DANTE in CARE) the mean maternal dietary intakes were consistent. However, the CARE participants' mean sugar intake per day (149g, SD 69) was relatively higher than MoBa (63g, SD 47) and DNBC (49g SD 35). This might be due to the misreporting of dietary intakes in the 24-hour dietary recall in the CARE study.

Amongst mean micronutrient intakes during pregnancy, slight differences were observed in mean calcium and mean folate. The mean dietary calcium consumption was higher by 365mg in DNBC (1426 mg/day, SD 577 mg) than MoBa (1061 mg/day, SD 498 mg), and the calcium intakes in CARE were the lowest (1033 mg/day, SD 488 mg). Mean dietary folate was higher in DNBC (357 µg/day, SD 117) than CARE (290 µg/day, SD 120) and MoBa (280 µg/day, SD 116).

A DNBC study (Olsen et al., 2014) compared the mean dietary intakes between DNBC and MoBa and suggested that the pregnant women in MoBa consumed higher intakes of fish, potato, rice and added sugar. This might be due to the high adherence to Nordic diets within the Norwegian population (Hillesund et al., 2014; von Ruesten et al., 2014). Whereas, women in DNBC consumed higher intakes of milk, butter and whole grain products.

Table 6 Mean maternal nutrient intakes in DNBC, MoBa and CARE

Trimester 2		**DNBC[d] (*n* = 68,123)**		**MoBa[e] (*n* = 85,391)**		**CARE[f] (*n*=598)**	
Mean macronutrient intake	Unit/day	Mean	SD	Mean	SD	Mean	SD
Total energy	kJ	10047	3061	9812	3244	9535	2652
Total energy	kcal	2392	639	2315	658	2279	634
Total carbohydrate	g	331	100	312	114	300	92
Total protein	g	91	27	88	25	81	28
Total fat	g	83	34	81	29	91	36
Carbohydrate	%	54	6	53	5	52	8
Protein	%	15	2	15	2	14	4
Fat	%	30	6	31	5	35	8
Monosaccharide and disaccharide	g	-	-	154	77	142	95
Starch	g	110	40	146	51	146	52
Added sugar	g	49	35	63	47	149	69
Total dietary fibre	g	27	10	31	12	16	7

[d] Dietary data available for only 68,123 participants in DNBC

[e] Dietary data available for only 85,391 participants in MoBa.

[f] Dietary data available for only 598 participants in CARE

MUFA	g	26	11	26	10	27	12
PUFA	g	12	5	15	7	14	9
SFA	g	35	16	31	12	34	17
Alcohol	g	20	11	1	8	10	33
Mean micronutrient intake							
Iron	mg	11	4	11	4	13	5
Calcium	mg	1426	577	1061	498	1033	488
Vitamin B_{12}	µg	6	3	6	3	4	4
Folate	µg	357	117	280	116	290	120
Iodine	µg	275	116	-	-	-	-

In summary, this chapter has provided the cohort profiles of MoBa, DNBC and CARE study, and has highlighted the differences within each birth cohort based on factors such as study design, maternal and offspring characteristics, measurement of dietary data and mean dietary intakes. This will be useful for justifying the results of the analyses within the three birth cohorts.

3.6 Justification for choosing DNBC, MoBa and the CARE study for analyses

High sample sized birth cohorts recruit pregnant women during pregnancy or at birth within a defined period of time and conduct follow ups of the infants through infancy, early childhood and adolescence through a well-constructed study design. It is undertaken to record all possible exposures and disease outcomes in order to monitor early life exposures such as dietary intakes, alcohol intake and smoking habits in relation to diseases in later life such as Type 2 DM, HTN and cardiovascular diseases. This is conducted by collecting samples such as blood and urine, recording participant data such as anthropometry, diet, maternal characteristics, lifestyle habits, medical history, medication, morbidities, birth outcomes and pregnancy related diseases and outcomes. Some birth cohorts include all types of exposures and outcomes, whereas others include specific health outcomes or exposure related research questions (Richmond et al., 2014).

This thesis has used birth cohorts such as MoBa, DNBC and CARE study to explore the association between maternal dietary macronutrients and dietary patterns, and birth outcomes such as birthweight, and odds of SGA and LGA babies. The following section explains the reasons for selecting the three birth cohorts for analyses.

The project objectives aimed at exploring the associations within a well-nourished population of pregnant women, because as demonstrated in section 2.4.1 of the literature review in Chapter 2, the association between maternal energy and macronutrient status and birth outcomes have been well established amongst low to middle income countries. Therefore, the birth cohorts from high income countries were used as they included dietary intakes

representative of a well-nourished population. It was an advantage to include birth cohorts from the same geographical region because relevant and consistent research implications specific to the region could be made.

The analyses did not include the birth cohorts from South East Asia and Eastern Mediterranean regions as they were from middle income countries. Also, these cohorts were not considered suitable for the study objectives because most birth cohorts explored single exposures of interest for conducting research, mainly relating to growth and infectious diseases limiting the choice of data available for selection (McKinnon and Campbell, 2011).

It could be argued that birth cohorts from low to middle income groups could have been additionally used for analyses however, certain issues need to be considered for realistic comparisons such as, dietary recommendations are made specific to the population of a country or a geographical region (*European Food Safety Authority (EFSA)- online database*, 2018). Therefore, it might be possible that the recommendation for food based dietary intakes for could differ between countries (Del Gobbo et al., 2015; Herforth et al., 2019). It is important to consider that the maternal malnutrition status of pregnant women in the birth cohorts of low-income countries would influence the results of the association between dietary macronutrient intakes and offspring outcomes. Moreover, women belonging to low to middle-income countries might be at a higher risk of poorer pregnancy outcomes such as higher risk of SGA baby, low birthweight infants and preterm deliveries (Parker et al., 1994; Perez-Escamilla et al., 2018; Stevens et al., 2015; Unger et al., 2016).

Also, including birth cohorts from high and middle-income countries could introduce heterogeneity in the results in two ways. 1. They might differ in maternal characteristics such as maternal age, ethnic groups, pre-pregnancy BMI, parity, lifestyle habits such as smoking habits and alcohol intakes, physical activity levels(Matijasevich et al., 2012; Raum et al., 2001). 2. The affordability to purchase food could influence the disparity of the amount of food consumed between high and low income countries, as high income countries could afford to buy more foods which are nutrient dense (Darmon and Drewnowski, 2008).

Further, a systematic review suggested that birth cohorts from middle income countries were smaller in sample size (N=100-500 participants) compared to birth cohorts of high income countries such as UK and Europe, for example, the ALSPAC cohort (N=10,000), CARE study (N=2635), MoBa (N=110,114) and DNBC (N=100,000) participants (McKinnon and Campbell, 2011).

As discussed in the previous sections of this chapter, the three birth cohorts recruited participants using a well-structured study design to record as many maternal exposures during and post pregnancy possible that could be linked to fetal outcomes and diseases in adulthood.

So far, there are three national cohorts that are largely recognised: The National Children's Study (NCS) in USA (Knox and Echeveria, 2009), DNBC in Denmark and MoBa in Norway (Lawlor et al., 2009). However, due to expensive costs involved in setting up the cohort on a national scale, the National Children's study was discontinued in 2014. However, in contrast, the biggest advantage of using data from Nordic birth cohorts as compared to other birth cohorts is that the two birth cohorts are linked to the national medical registry database in Denmark and Norway. Therefore, recruitment in large numbers was possible because all the hospitals in Denmark and Norway provide patient data access to MoBa and DNBC. High participant recruitment rates of the Nordic birth cohorts therefore, could produce robust results for large sample sized studies with high statistical power (Magnus et al., 2006; Olsen et al., 2001). It is therefore, ideally favourable to undertake analyses within a national birth cohort to predict associations between maternal dietary exposures and offspring outcomes, provided there is funding availability.

Another birth cohort in UK such as The Born in Bradford study (BiB) in UK (N=12453) (Wright et al., 2012) recruited participants in Bradford which largely composed of a multi-ethnic group of pregnant women. They recorded data for ethnicity, lifestyle factors, physical and mental health, anthropometric assessment, biological samples such as blood and urine and physical activity levels and measured birthweights. However, the BiB study recruited participants at a much later duration of pregnancy, i.e., around 26-28 weeks of gestation and then recorded baseline data in this period. In contrast, all three birth cohorts in this thesis recruited participants who were in trimester 1 in order to record as many dietary and maternal characteristics possible to make assumptions in relation to offspring health. Since the gestational duration chosen to recruit participants in BiB study was later than MoBa, DNBC and the CARE study, this could have affected the quality of dietary data and baseline data recorded using interviewer administered questionnaires. Because it would largely rely on memory and introduce measurement errors and underreporting. Most importantly, the study design of BiB did not capture the early life exposures in the first trimester such as diet or changes in maternal characteristics, including pre-pregnancy BMI, weight gain, physical activity levels, and lifestyle habits. Moreover, although the BiB study used an interviewer administered questionnaire at baseline, potential under-reporting or misreporting could have introduced measurement errors due to language barriers because the cohort included non-English speaking participants.

Further, despite recruiting 12453 participants in the BiB study, only a sub-set of the whole cohort completed the FFQ at baseline, therefore lowering the final sample size available for analyses to 5083 participants (Marvin-Dowle et al., 2018). Unlike the CARE study, the Born in Bradford cohort did not capture the dietary exposures in the first trimester but only recorded dietary data of participants who were almost into their third trimester (around 27 to 30 weeks of gestation) (Wright et al., 2012). The MoBa although recorded dietary data around 22 weeks of gestation, the questions included in the FFQ covered the dietary intakes and choices from the start of the pregnancy. Further, though DNBC captured dietary intakes around 25 weeks, their questions included consumption for last one month of pregnancy. This was useful to make appropriate assumptions between maternal nutrition and fetal outcome from the start of pregnancy. For these reasons, including BiB study was not considered appropriate for the project objectives of this thesis.

The Avon Longitudinal Study of Parents and Children (ALSPAC), also known as the Children of the 90s in UK is a population based study and was considered for including in the analysis. It has followed almost 14,500 families in Bristol, UK. It is a transgenerational cohort which studies the impact of biological, psychological, genetic, social and environmental exposures in relation to health and developmental outcomes.

The recruitment period of ALSPAC (1990-92) (Fraser et al., 2013) was shorter in comparison to CARE (2003-2006) DNBC (1996-2002) and MoBa (1999-2008) which might have been the reason that it had a lower sample size as compared to DNBC and MoBa, yet it was a large study when considered on its own. In comparison to DNBC, MoBa and CARE recruitment procedures, the ALSPAC recruited pregnant women directly from the community by organising community visits for the recruitment staff, and from antenatal and maternity health services. However, few disadvantages of the quality of the maternal data that possibly influence the overall results of the analyses are discussed below.

The ALSPAC recorded data through self-reported baseline and FFQ questionnaires. This might have introduced measurement errors and potential under-reporting of dietary intakes. Missing data could be an issue to consider during analysis as the ALSPAC used self-reported questionnaires at baseline in contrast to DNBC and the CARE study. MoBa also used self-reported questionnaires similar to ALSPAC but the MoBa study design included data quality checks to make sure the data entry matches the information given the questionnaires.

The ALSPAC recorded dietary data of pregnant women using self-reported FFQ (Emmett, 2009). The FFQ recorded 56 food groups and 12 beverage groups in the latest FFQ and included questions on portion sizes. However they did not conduct any data quality checks which might

increase the chances of over and under estimation of actual intakes. In comparison, DNBC and MoBa used standardised food portion sizes to convert food frequency data into measured intakes (g/day). Additionally, although the ALSPAC study design recorded more data and is well-structured than the BiB study, the dietary data recorded in ALSPAC is later than that of the BiB study, CARE study, MoBa and DNBC. The ALSPAC recorded dietary data around 32-34 weeks of gestation, increasing the chances of under-reporting, measurement error, missing data. This is because the FFQ largely relies on memory-recall and it might have been possible that the women misunderstood the questions or entered incorrect information. Also, the ALSPAC FFQ could not capture the maternal dietary exposures for the first two trimesters of pregnancy making it difficult to explore the link between maternal exposures in early pregnancy and offspring growth.

Most importantly, the ALSPAC FFQ used to record the dietary data for the 14000 women during pregnancy was not validated citing funding issues. This might have introduced measurement errors in the actual intakes which needs to be ideally compared against another dietary assessment tool such as a 24-hour dietary recall, which is a cheaper method for large cohorts, and ideally with a 3-day or a 7-day dietary records (Emmett, 2009). This is important because incorrect information might lead to making false associations between maternal dietary exposures and offspring health outcomes (Cade et al., 2004).

Another birth cohort – Generation R study in the Netherlands was considered for including in the analyses. This birth cohort is a prospective population based study designed for exploring early environmental and genetic influences identifies during fetal life that could be associated with diseases in young adulthood (Jaddoe et al., 2006). Similar to the CARE study the Generation R study recruited participants from 2002 to 2006. The total sample size included 9778 pregnant women. Similar to the CARE study, DNBC and MoBa the Generation R study had a well-structured study design that recorded prenatal data using questionnaires, physical examinations and biological samples. The Generation R study data was recorded during early pregnancy <18 weeks of gestation, mid-pregnancy 18-25 weeks of gestation and late pregnancy <25 week of gestation. This was favourable because it is possible to observe potential associations between early to mid-pregnancy dietary exposures on the offspring outcomes as it is suggested that the associations seem to weaken or disappear after the second trimester (Kroener et al., 2016; Roberts, 2010; Smith, 2004). Therefore, in comparison with the ALSPAC and the BiB study the data recorded within the CARE, DNBC, MoBa and the Generation R study are favourable in exploring the maternal dietary exposures of interest. However, the cohort recorded dietary data only for 4097 women of Dutch origin (Heppe et al., 2013). This is because they used a FFQ that was validated for the assessment of dietary intake in a Dutch population,

which conducted amongst an elderly population (Klipstein-Grobusch et al., 1998). Whereas, DNBC and MoBa conducted a validation study amongst pregnant women to assess their dietary intakes (Haugen et al., 2008; Mikkelsen et al., 2007). Conducting a validation study amongst the elderly might have introduced chances of measurement errors and could lead to underestimation of dietary intakes. This might be due to the lower intakes of food consumed amongst the elderly as compared a healthy population (Morley, 2001). Also, since the FFQ largely relies on memory, certain degree of under-reporting might have occurred. Therefore, using a FFQ validated within pregnant women would have been preferable as it would have estimated the true intakes during pregnancy (Haugen et al., 2008; Mikkelsen et al., 2007).

Also, the Generation R study FFQ included only 170 food items in comparison to the DNBC (360 food items) and MoBa (340 food items) FFQ, therefore covering a lesser range of dietary intakes and food choices consumed during pregnancy (Klipstein-Grobusch et al., 1998). Including a lesser range of food related questions in the FFQ cannot extract whole information describing the participants consumption patterns and preferences. This could further limit the scope of interpreting the results in the analyses, for example, in the maternal dietary patterns analyses. Lesser number of food items might not completely represent the maternal food intakes, or explain all the possible food items that could be associated in contributing to gestational weight gain or offspring outcomes (Brantsæter et al., 2008). However, it is also suggested avoid using a too detailed FFQ as it increases the chances of participant drop out (Cade et al., 2002; Willett, 2012).

Another reason is the availability of scientific grants to fund data access of birth cohorts. This was available for two birth cohorts, DNBC and MoBa. As described in section 3.1 of the Introduction, the BBMRI-LPC scientific grant was available in 2015 during the initial stages of the project. This access included 22 cohorts of which only 2 were birth cohorts. As data access for large sized birth cohorts is expensive the scientific grants support the cost of data access in research projects. Therefore, available funding enabled data access to MoBa and DNBC.

Lastly, the CARE study was formed by the Nutritional Epidemiology Group in Leeds and therefore it was readily accessible. Most importantly, it had the required maternal dietary and offspring data to conduct the analyses.

The next chapter will commence the analysis of the study objectives. The chapter will explore the association between maternal dietary macronutrients and birth outcomes, including birthweight, and odds of SGA and LGA babies in the CARE study.

Chapter 4 : The association between maternal dietary macronutrient composition and offspring outcomes – results from the CARE study

Chapter 3 provided an outline of the birth cohort profiles and included a detailed comparison to help understand the decisions taken in all the analyses included in this chapter and in chapters 5, 6 and 7.

The current chapter will investigate the association between maternal dietary macronutrient composition and birth outcomes amongst a UK birth cohort: CAffeine and REproductive health (CARE) study.

4.1 Introduction

There is increasing evidence elucidating the role of diet during pregnancy on the growing fetus (Blumfield et al., 2012; Moore and Davies, 2005) and subsequently, in the offspring metabolic health in adulthood (Maslova et al., 2016). Maternal diet in pregnancy is suggested to contribute in the alteration of fetal outcomes (Kjøllesdal and Holmboe-Ottesen, 2014), including birthweight (von Ruesten et al., 2014), preterm delivery (Englund-Ögge et al., 2014), low birthweight infants (<2500 g)(Chen et al., 2014) and small for gestational age (SGA) births (Thompson et al., 2010).

Meta-analyses (Haider et al., 2011; Klemmensen et al., 2009; Lu et al., 2014) have examined the role of micronutrients in the maternal diet, including vitamin C (Klemmensen et al., 2009), iron (Alwan et al., 2011) and folate (Fekete et al., 2012; Kawai et al., 2011) in the development of poor birth outcomes.

Amongst dietary macronutrients, evidence has been restricted to exploring the use of protein-energy supplementation in pregnancy for improving offspring birthweight amongst low-income countries (Imdad and Bhutta, 2012; Liberato et al., 2013; Stevens et al., 2015). However, amongst high-income countries the prevalence of maternal and infant protein-energy under-nutrition is low due to sufficient macronutrient consumption during pregnancy (Blumfield et al., 2012).

Although during pregnancy, in well-nourished women, the recommended dietary allowances of protein, carbohydrate (CHO) and fat are largely met (Blumfield et al., 2012; von Ruesten et al., 2014), the influence of the source of energy intake: macronutrients during pregnancy on birth outcomes including birthweight remains unclear.

The specific source of energy (dietary protein, fat and CHO) consumed may also have an impact on birth outcomes (Chong et al., 2015; CucÓ et al., 2006; Lagiou et al., 2004; Moore and Davies, 2005; Moore et al., 2004). Evidence remains inadequate and conflicting from previous

observational studies (Chong et al., 2015; CucÓ et al., 2006; Lagiou et al., 2004; Moore and Davies, 2005; Moore et al., 2004) that investigated the potential association between energy composition of food consumed during pregnancy and birthweight. Studies have also explored the effect of macronutrient/energy-dense dietary patterns in pregnancy (Englund-Ögge et al., 2014; Knudsen et al., 2007; Thompson et al., 2010) on birth outcomes. These "western" or "junk" dietary patterns in the studies, included energy-dense food items, for instance, sweet snacks, desserts, bakery products and processed foods, were suggested to have negative implications on the quality of birth outcome.

Amongst macronutrient sub-components, results remain conflicting in studies which explored the effect of fatty acids, including long chained polyunsaturated fatty acids (LC-PUFA) on birth outcomes (De Giuseppe et al., 2014; Imhoff-Kunsch et al., 2012; Mani et al., 2016; Oken et al., 2004; Szajewska et al., 2006).

In addition, no studies, according to the knowledge of the author, have explored the effect of dietary saccharides (mono-saccharides, di-sachcharides, dietary fibres) during pregnancy on birth outcomes including birth weight or "customised" birthweight centiles− computer generated antenatal growth charts for individual pregnancies that allow variation in the maternal characteristics, taking birthweights from previous pregnancies into consideration (Gardosi et al., 1992). Customised birthweight centiles are used in this study as they set individual standards for fetal growth that allow better differentiation between optimal and abnormal growth *in utero* (Gardosi, 2004). This method adjusts for a number of variables including maternal height, weight, parity, sex of the baby, ethnicity, and across all gestational ages. Using this external adjustment is particularly useful for some categories, such as minor ethnic groups which require large numbers to derive precise model coefficients.

The aim was to investigate the association between intakes of specific dietary macronutrients (carbohydrate [CHO], fat and protein, and their sub-components such as saccharides and fatty acids) during pregnancy in a well-nourished population and birth outcomes: birthweight, birth centile, small-for-gestational-age (SGA) infants and large-for-gestational-age (LGA) infants.

4.2 Methodology

4.2.1 Study population

The CARE (CAffeine and REproductive health) study prospectively recruited low risk pregnant women from two large teaching hospital maternity units in Leeds, UK from September 2003 to June 2006 (Boylan S, 2010; Greenwood et al., 2010). This study was designed to explore diet with a focus on maternal caffeine intake in relation to fetal growth. The inclusion criteria were pregnant women aged between 18-45 years and carrying singleton pregnancies accurately

dated by ultrasound. Women with concurrent medical disorders, psychiatric illness, HIV infection, or hepatitis B infection were excluded. Participants completed a consent form indicating their willingness to participate in the study. They were interviewed by research midwives during their booking appointment in the antenatal clinic. Questionnaires for trimester 1 (8-12 weeks of gestation) and 3 (from 28 weeks of gestation) were interviewer-administered, and the questionnaire for trimester 2 (13-27 weeks of gestation) was self-administered (Alwan et al., 2010). Their demographic details (age, parity, maternal height, weight, socioeconomic status, and gestational age) were self-reported by means of an interviewer-administered questionnaire. Ethical approval was obtained from Leeds West Local Research Ethics Committee (LREC) Ref 7260. A grant from the Food Standards Agency, United Kingdom (Contract number T01032/33) was obtained to enable conduct the study.

4.2.2 Dietary data

Out of 1,289 participants in the original study, dietary information was available for 1,196 women in trimester 1 and 598 women in trimester 2. The dietary intake was recorded at home twice in a 24-hour dietary recall (Alwan et al., 2010; Boylan et al., 2008; Greenwood et al., 2010) administered by a trained research midwife; once during trimester 1 (8-12 weeks of gestation) and again during trimester 2 (13-27 weeks of gestation). Trained personnel entered the 24-hour dietary recalls by using nutrient analysis package– 'DANTE' (Diet and Nutrition Tool for Evaluation). The nutrient analysis computed by this software package was based on the standard UK food composition tables (5^{th} edition) by the Royal Society of Chemistry (Holland B, 1992).

4.2.3 Study exposures

Primary exposures were macronutrients: protein, fat and CHO and their sub-components including fatty acids and saccharides. The carbohydrate sub-components included mono-saccharides (glucose, fructose), di-saccharides (sucrose, maltose and lactose), and complex sugars (starch, soluble fibre). The dietary fat sub-components included saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA). However, total protein was considered for sub-component analyses as the data for animal and vegetable protein, and amino acid contents were unavailable.

4.2.4 Covariates

The analyses adjusted for the following covariates – maternal height, weight, gestational age at delivery, sex of the baby, ethnicity, parity, alcohol intakes, smoking habits and physical activity. The covariates data was used from the baseline questionnaires administered by trained midwives that included information on confounders such as smoking habits and alcohol

consumption. Further, additional data was extracted from the three questionnaires used for the original CARE study. These were developed to determine lifestyle behaviours with a focus on caffeine intake in pregnancy from four weeks before pregnancy until recruitment into the study–at 8-12 weeks of pregnancy; the second covered the period 13-27 weeks; and the third included the period from 28-40 weeks of pregnancy (Alwan et al., 2010).

The covariates included in the CARE analysis were associated with both the exposure and the outcomes of the study, i.e., the maternal dietary macronutrient intakes and the birth outcomes (Shrier and Platt, 2008).

A detailed explanation for including the covariates in the analyses is provided in the meta-analysis study in Chapter 5 under covariates section 5.2.6. However, a brief justification is provided for each covariate in turn below.

Smoking has been suggested to affect the appetite centres of the brain by lowering the hunger levels thus leading to reduced maternal dietary intakes. Also, it has been suggested to be associated with low birthweight (Suzuki et al., 2016) and high risk of SGA babies (Nohr et al., 2009).

Smoking status for trimesters 1 and 2 listed the frequency of smoking and was categorised into three: 'non-smoker', 'current smoker' and 'occasional smoker − previously smoked everyday but do not smoke now'.

Studies have shown that *alcohol consumption* is usually paired with unhealthy foods high in fat which might affect the overall quality of dietary choices (Rangan et al., 2008). Also it has been suggested to be associated with high risk of SGA births (Chiaffarino et al., 2006) and fetal alcohol syndrome (FAS) which alter the facial structure of the fetus (Das et al., 2004; de Sanctis et al., 2011). The participant's average alcohol consumption (unit/day) (continuous variable) was measured during trimester 1 and 2.

Physical activity has been suggested to be associated with increased appetite levels and healthy dietary choices (Faas et al., 2010). It has also been suggested that women who were physically active in pregnancy were more likely to have healthy pregnancy outcomes (Varrassi et al., 1989) and not lower birthweight infants (Leiferman and Evenson, 2003).

Physical activity was self-reported and was recorded into 3 categories: 'no weekly physical activity', 'light/moderate physical activity' and 'vigorous physical activity (up to <20 minutes 1-2/week).'

Ethnicity has been suggested to be associated with dietary choices in pregnancy and studies have shown that women from ethnic minorities might have higher energy dense dietary intakes than Caucasian women (Diana et al., 2018; Rahman et al., 2009), which might be subsequently linked to lower birthweight infants (Dominguez et al., 2008).

Parity has been suggested to affect the maternal dietary intakes, as multiparous women would consume lower energy intakes as compared to primiparous women in order to feed their older children (Herring et al., 2012).

Maternal height and weight were included as confounders in this study instead of pre-pregnancy BMI. This was chosen to keep consistency with the customised birth centile charts. Nevertheless, studies have suggested that women with higher BMI are more likely to have unhealthy dietary choices as compared to women with normal BMI (Hirschberg, 2012; Sullivan et al., 2011). It has also been suggested that women with high pre-pregnancy BMI are more likely to deliver LGA infants, whereas underweight women are likely to give birth to low birthweight infants (Bhattacharya et al., 2007; Pan et al., 2016; Yu et al., 2013).

Also, it should be noted that two confounders 1. gestational age at delivery and 2. sex of the baby were included for the birthweight analyses. Gestational age at delivery has been suggested to be associated in determining the pregnancy outcome, for example, preterm deliveries (<37 weeks) thus influencing the overall fetal growth (Goldenberg et al., 2008).

Finally, it has been observed that male infants weigh heavier than female offspring, therefore suggesting that the *sex of the baby* is associated with differing birthweights (Di Renzo et al., 2007). Also it has been suggested that mothers delivering male offsprings are at higher risk of gestational diabetes mellitus, macrosomia and caesarean sections (Di Renzo et al., 2007).

Gestational age at delivery and sex of the baby might not be associated with the maternal dietary macronutrient intakes, this is because adjusting for gestational age at delivery could introduce the issue of double-adjustment in birth outcome models. However, they were included in order to keep consistent with the birth centile analysis, because birth centiles were derived from birthweights. In addition, the centiles extracted from the customised birth centile charts included for analyses were pre-adjusted for a certain covariates including, sex of the baby, gestational age at delivery, maternal height, weight, ethnicity and parity (Gardosi, 2004; Perinatal-Institute, 2017).

4.2.5 Study outcome

The primary outcomes in this study were birthweight and birth centile. Birthweight was recorded in grams (g) in the electronic maternity database. The information on antenatal pregnancy complications and delivery details (gestational age at delivery, birth weight, and sex of the baby) were obtained from the electronic maternity databases. The customised birth centiles of the CARE data were computed by using customised centile charts (Gardosi, 2004; Perinatal-Institute, 2017) which accounted for the following factors: maternal weight, height, ethnicity, parity, gestational age at delivery and sex of the baby. A more detailed explanation of the customised birth centile charts is provided in the meta-analysis study in Chapter 5 under

the Methods section 5.2.7.1. However, in brief, the centile calculators were developed according to the principles of the Gestation Related Optimum Weight (GROW) method of the Perinatal Institute, specifically for research purposes with large datasets (Gardosi, 2004; Gardosi et al., 1992). The country-specific centile calculators in the GROW software individually customises anonymous databases according to a particular country. Depending on the availability of the databases from which the coefficients are extracted the centile chart calculators are regularly updated and are developed according to the different populations and countries. The database of each country is then analysed to derive centiles and coefficients of certain variables including, maternal weight, height, ethnicity, parity, gestational age at delivery and sex of the baby. The software with the updated centile calculators from the Perinatal Institute was then installed and used to derive the birth centiles from the birthweight data within the CARE study.

Other outcomes additionally explored were small-for-gestational-age (SGA) births and large-for-gestational-age (LGA) births. These particular definitions were chosen as they are clinically relevant amongst at-risk infant groups. On the customised centile chart, SGA birth was defined as birth weight <10th centile (Clausson et al., 2001; Gardosi, 2004; Gardosi et al., 1992), and an LGA birth was defined as birthweight >90th centile (Gardosi et al., 1992; Pasupathy et al., 2011). Both of these outcomes accounted for the following variables: maternal height, weight, ethnicity, parity, gestational age at delivery and sex of the baby (Gardosi, 2004). Population centiles were not used for this analysis as they cannot fundamentally differentiate between abnormal growth and consititutionally large or small, but only healthy fetuses. In contrast, customised centiles overcome these limitations by accounting for certain variables known to affect the fetal growth (Chiossi et al., 2017; Gardosi, 2004; Reeves and Bernstein, 2008).

4.2.6 Statistical methods

The means and standard deviations (mean[SD]), and absolute frequency distributions with percentages (n (%)) are calculated for the demographic characteristics of interest in both birth cohorts (see Tables 4 and 5 in Chapter 3).

To examine associations between macronutrients or their sub-components, and birthweight/centile; multiple linear regression models (Model 1 and Model 2) were designed for trimesters 1 and 2 separately. This was designed for clear interpretation of the results per trimester. Also, the data format at baseline was recorded for each trimester and so it was not possible to present overall results for both trimesters. Each macronutrient and its sub-component model were adjusted for physical activity, other energy contributing macronutrients and sub-components within the model. In order to help with the interpretation

of birth centiles, results have been additionally presented in actual birthweight in grams. In the centile model (Model 1) customised centile charts (Gardosi, 2004; Perinatal-Institute, 2017) were used which automatically accounted for these variables: maternal height, weight, parity, ethnicity, gestational age at delivery and sex of the baby.

The birthweight model (Model 1) was adjusted for maternal height, weight, parity, ethnicity, physical activity, gestational age at delivery and sex of the baby to keep consistent with the pre-adjusted customised birth centile charts. All regression models (birthweight/centile models) under Model 2 were additionally adjusted for participants' alcohol consumption and smoking habits in pregnancy. Although gestational age at delivery and sex of the baby are associated with birth outcomes, they are not associated with the maternal dietary intake. Therefore, a sensitivity analyses was conducted within the birthweight model to observe if the results changed after excluding two covariates including, sex of the baby and gestational age at delivery. The results remained unchanged for CHO and but changed slightly for fat.

Logistic regression analyses was conducted to explore the odds ratio (OR) for delivering an SGA/LGA infant. In the logistic regression models, SGA and LGA births were binary outcomes, where "0" is control and "1" is case. The estimates derived from the logistic regression models were interpreted as odds ratios (OR). As the SGA and LGA variables were derived from the customised centiles they were pre-adjusted for the same confounders in the centile model. Therefore Model 1 accounted for these variables: maternal height, weight, parity, ethnicity, gestational age at delivery and sex of the baby (Gardosi, 2004; Perinatal-Institute, 2017).

Model 2 additionally adjusted for alcohol intake and smoking habits. The analyses results under the results section are mostly for Model 2 after full adjustment for covariates.

Since very limited evidence has explored the association between the exposures and outcomes of interest in this study, the results of the macronutrient consumption (CHO, fat and protein) were presented at the rate of 10g/day increments, and their respective sub-components at the rate of 1g/day increments. But, couple of sub-components consumed in higher amounts: starch and glucose intakes were also presented for 10g/day increments. The statistical significance level for the results was set at 5%. All analyses were performed using Stata SE, version 13.1 (StataCorp 1985-2013, TX USA).

4.3 Results

4.3.1 The relation between maternal dietary macronutrients, and birth centile/birthweight

There were associations between trimester 1 macronutrient intake and both birth centile and birthweight (Table 7). In trimester 1, there was a positive association between CHO consumption and birth centile/birthweight. The fully adjusted models (Model 2) indicated that a higher intake of CHO (10g/day increment) was associated with a higher birth centile (0.2; 95% CI 0.1 to 0.4; P=0.002) and a higher birthweight (4g; 95% CI 1g to 7g; P=0.003). Conversely, a higher total fat intake (10 g/day increment) at this stage of pregnancy was negatively associated with birth centile (-0.7; 95% CI -1.2 to -0.1; P=0.008) on the customized centile chart. However, on further adjusting the model for alcohol intake and smoking habits (Model 2), higher fat intake (10g/day increment) was not associated with birth centile (-0.5; 95% CI -1.0 to 0.0; P=0.06) in spite of narrow confidence intervals. When we explored its relation with birthweight, fat consumption (10g/day increment) was negatively associated with birthweight (-8g; 95% CI -16g to -0.3; P=0.04) in the fully adjusted model (Model 2). Amongst other macronutrients, protein intake was not associated with birth centile or birthweight after adjusting for smoking status and alcohol intake, but it had wide confidence intervals.

In Table 8, the results are shown for energy percentages (%E) from macronutrients and their association with birthweight. In Model 2, per unit higher %E from carbohydrates was positively associated with higher birthweights (3g; 95% CI 0.1g to 5g; P=0.04). Whereas, per unit higher %E from fat was associated with lower birthweight (-4g; 95% CI -7g to 1g; P=0.01) in the fully adjusted model (Model 2).

Table 7 Association between macronutrients (g) in trimester 1 and 2, and birth centile/birthweight

Macronutrient*intake[7] 10 g/day increment	Birth centile, Model 1			Birth centile, Model 2		
Trimester 1 n=1196	**Centile[a]**	**95% CI**	***P* value**	**Centile[a,c]**	**95% CI**	***P* value**
Total carbohydrate	0.3	0.1 to 1	0.001	0.2	0.1 to 0.4	0.002
Total fat	-0.7	-1 to 0	0.008	-0.5	-1 to 0	0.06
Protein	0.6	0 to 1	0.07	0.4	-0.2 to 1	0.22
Trimester 2 n=598						
Total carbohydrate	0.2	0 to 1	0.06	0.2	0 to 1	0.07
Total fat	-0.3	-1 to 0.4	0.37	-0.3	-1 to 1	0.43
Protein	-0.2	-1 to 1	0.70	-0.3	-1 to 1	0.48
	Birthweight (g), Model 1			**Birthweight (g), Model 2**		
Trimester 1 n=1196	**Birthweight[b]**	**95% CI**	***P* value**	**Birthweight[b,c]**	**95% CI**	***P* value**
Total carbohydrate	4	2 to 7	0.002	4	1 to 7	0.003
Total fat	-10	-18 to -3	0.006	-8	-16 to -0.3	0.04
Protein	10	1 to 20	0.04	8	-2 to 19	0.12
Trimester 2 n=598						
Total carbohydrate	4	-0.3 to 8	0.07	3	-1 to 7	0.09
Total fat	-2	-14 to 9	0.64	-1	-13 to 10	0.76
Protein	-6	-20 to 8	0.40	-6	-22 to 8	0.38

[7][a]Adjusted using customised growth charts for maternal weight, height, ethnicity, parity, gestational age at delivery, sex of baby [b] Adjusted for maternal weight, height, ethnicity, parity,physical activity, gestational age at delivery, sex of baby [c]Additional adjustment for average alcohol intake and smoking status *Mutually adjusted for other energy contributing macronutrients

Table 8 Association between energy percentages (%E) from macronutrients (g) in trimester 1 and 2, and birthweight.

Macronutrient intake[8] (%E increment)	Birthweight (g), Model 1			Birthweight (g), Model 2		
Trimester 1 n=1196	**Birthweight[a]**	**95% CI**	***P* value**	**Birthweight[a,b]**	**95% CI**	***P* value**
%E (Carbohydrate)	3	1 to 6	0.01	3	0.1 to 5	0.04
%E (Fat)	-4	-7 to -2	0.002	-4	-7 to 1	0.01
%E (Protein)	2	-3 to 8	0.38	1	-5 to 7	0.73
Trimester 2 n=598						
%E (Carbohydrate)	3	0 to 7	0.08	3	-1 to 7	0.10
%E (Fat)	-2	-7 to 2	0.25	-2	-7 to 2	0.29
%E (Protein)	-7	-16 to 2	0.13	-7	-16 to 2	0.12[9]

8 [a]Adjusted for maternal weight, height, ethnicity, parity, physical activity, gestational age at delivery, sex of baby [c]Additional adjustment for average alcohol intake and smoking status

4.3.2 The relation between maternal dietary macronutrient sub-components, and birth centile/birthweight

In trimester 1 (Model 2) (Table 9 and 10), among the complex CHO sub-components, higher starch intake (10g/day increment) was positively associated with birth centile (0.3; 95% CI 0.0 to 0.7; P=0.05) but not with birthweight (5g; 95% CI -0.6g to 10g; P=0.08). Amongst saccharides, higher lactose intake (1g/day increment) was associated with a higher birth centile (0.1; 95% CI 0.0 to 0.2; P=0.03) and not with higher birthweight (2g; 95% CI -0.1g to 4g; P=0.06). In trimester 2 (Model 2), higher glucose (10g/day increment) consumption was positively associated with a higher birthweight (52g; 95% CI 4g to 100g; P=0.03). Lactose intake (1 g/day increment) was positively associated with a higher birth centile (0.2; 95% CI 0.0 to 0.4; P=0.01) and birthweight (5g; 95% CI 2g to 7g; P<0.001). Amongst fat sub-components in trimester 1 (Model 2), a higher PUFA intake (1 g/day increment) was negatively associated with birthweight (-4g; 95% CI -8g to 0.1g; P=0.05) but not with birth centile.

Table 9 Association between macronutrient sub-components during trimester 1 and 2, and birthweight.

Macronutrient sub-components[10] (g/day increment)	Birthweight (g), Model 1			Birthweight (g), Model 2		
Trimester 1 n=1196	**Birthweight[a]**	**95% CI**	***P* value**	**Birthweight[a,]**	**95% CI**	***P* value**
Sources of total carbohydrate[†‡]						
Starch (10g)	4	-1 to 9	0.13	5	-1 to 10	0.08
Glucose (10g)	13	-20 to 45	0.43	13	-20 to 47	0.43
Fructose (1g)	0.4	-1 to 2	0.62	0	-2 to 2	0.83
Sucrose (1g)	-1	-1 to 0	0.11	0	-1 to 0.4	0.40
Lactose (1g)	2	0 to 4	0.07	2	0 to 4	0.06
Maltose (1g)	5	-4 to 15	0.28	2	-8 to 13	0.66
Soluble fibre (1g)	6	-4 to 15	0.23	2	-8 to 12	0.67
Sources of total fat[†*]						
Saturated fatty acid (1g)	-2	-4 to 1		-1	-4 to 2	0.46
Monounsaturated fatty acid (1g)	2	-2 to 6	0.28	1	-2 to 5	0.44
Polyunsaturated fatty acid (1g)	-4	-8 to -4	0.02	-4	-8 to 0.1	0.05
Protein[*‡] (10g)	10	1 to 20	0.04	8	-2 to 19	0.12

[10] [a]Adjusted for maternal weight, height, ethnicity, parity, physical activity, gestational age at delivery, sex of baby [b]Additional adjustment for average alcohol intake and smoking status [*]Adjusted for carbohydrate intakes [†]Adjusted for dietary protein intakes [‡]Adjusted for dietary fats intakes

Macronutrient sub-components[11] g/day increment	Birthweight (g), Model 1			Birthweight (g), Model 2		
Trimester 2 n=598	**Birthweight[a]**	**95% CI**	***P* value**	**Birthweight[a,b]**	**95% CI**	***P* value**
Sources of total carbohydrate[†‡]						
Starch (10g)	4	-4 to 12	0.34	4	-4 to 12	0.32
Glucose (10g)	42	-6 to 90	0.09	52	4 to 100	0.03
Fructose (1g)	-1	-4 to 2	0.40	-2	-5 to 1	0.20
Sucrose (1g)	-1	-2 to 0	0.14	-1	-2 to 0	0.08
Lactose (1g)	3	1 to 6	0.005	5	2 to 7	<0.001
Maltose (1g)	-1	-15 to 14	0.94	0	-14 to 14	0.99
Soluble fibre (1g)	2	-12 to 16	0.78	-1	-14 to 13	0.94
Sources of total fat[†*]						
Saturated fatty acid (1g)	2	-2 to 6	0.35	3	-1 to 7	0.14
Monounsaturated fatty acid (1g)	-2	9 to 4	0.46	-4	-11 to 2	0.19
Polyunsaturated fatty acid (1g)	-2	-7 to 3	0.51	0	-1 to 0	0.12
Protein[*‡] (10g)	-6	-21 to 8	0.40	0	-5 to 6	0.93

11 [a]Adjusted for maternal weight, height, ethnicity, parity, physical activity, gestational age at delivery, sex of baby [b]Additional adjustment for average alcohol intake and smoking status [*]Adjusted for carbohydrate intakes [†]Adjusted for dietary protein intakes [‡]Adjusted for dietary fats intakes

Table 10 Associations between macronutrient sub-components in trimester 1 and 2, and birth centile.

Macronutrient sub-components[12] g/day increment	Birth centile, Model 1			Birth centile, Model 2		
Trimester 1 n=1196	**Centile[a]**	**95% CI**	***P* value**	**Centile[a,b]**	**95% CI**	***P* value**
Sources of total carbohydrate[†‡]						
Starch (10g)	0.4	0 to 1	0.03	0.4	0 to 1	0.05
Glucose (10g)	2	0 to 4	0.07	2	0 to 4	0.09
Fructose (1g)	0	0	0.60	0	0	0.52
Sucrose (1g)	0	0	0.15	0	0	0.48
Lactose (1g)	0.1	0 to 0.2	0.04	0.1	0 to 0.3	0.03
Maltose (1g)	0	0	0.82	0	-1 to 1	0.96
Soluble fibre (1g)	0	0	0.33	0	0	0.67
Sources of total fat[†*]						
Saturated fatty acid (1g)	0	0	0.22	0	0	0.56
Monounsaturated fatty acid (1g)	0	0	0.60	0	0	0.74
Polyunsaturated fatty acid (1g)	0	0	0.11	0.2	-0.5 to 0	0.12
Protein[*‡] (10g)	1	0 to 1	0.07	0.5	-0.2 to 1	0.22

[12] [a]Adjusted using customised growth charts for maternal weight, height, ethnicity, parity, physical activity, gestational age at delivery, sex of baby
[b]Additional adjustment for average alcohol intake and smoking status [*]Adjusted for carbohydrate intakes [†]Adjusted for dietary protein intakes
[‡]Adjusted for dietary fats intakes

Macronutrient sub-components[13] g/day increment	Birth centile, Model 1			Birth centile, Model 2		
Trimester 2 n=598	**Centile[a]**	**95% CI**	***P* value**	**Centile[a,b]**	**95% CI**	***P* value**
Sources of total carbohydrate[†‡]						
Starch (10g)	0.3	0 to 1	0.16	0.3	0 to 1	0.18
Glucose (10g)	2	0 to 6	0.16	3	-1 to 6	0.09
Fructose (1g)	0	0	0.45	0	0	0.29
Sucrose (1g)	-0.5	0	0.30	0	0	0.23
Lactose (1g)	0	0	0.05	0.2	0 to 0.4	0.01
Maltose (1g)	-0.2	-1 to 1	0.75	0	-1 to 1	0.94
Soluble fibre (1g)	0.2	-1 to 1	0.68	0	-1 to 1	0.97
Sources of total fat[†*]						
Saturated fatty acid (1g)	0	0	0.57	0	0	0.44
Monounsaturated fatty acid (1g)	-0.2	-1 to 0	0.31	-0.3	-1 to 0	0.25
Polyunsaturated fatty acid (1g)	0	0	0.84	0	0 to 1	0.67
Protein[*‡] (10g)	-0.2	-1 to 1	0.70	0	-1 to 1	0.48

[13] [a]Adjusted using customised growth charts for maternal weight, height, ethnicity, parity, physical activity,gestational age at delivery, sex of baby [b]Additional adjustment for average alcohol intake and smoking status [*]Adjusted for carbohydrate intakes [†]Adjusted for dietary protein intakes [‡]Adjusted for dietary fats intakes

4.3.3 The relation between maternal dietary macronutrient, sub-components, and odds of SGA and LGA babies

In Table 11, the odds of delivering a SGA infant were positively associated with a high fat consumption (10g/day increment) in trimester 1, unadjusted OR 1.05 (95% CI 1.00 to 1.10; P=0.03). However, after adjusting the model (Model 2) the odds of delivering a SGA infant (adjusted OR 1.03, 95% CI 0.98 to 1.09; P=0.14) were not associated with a high fat intake (10g/day increment). This analyses showed no evidence of an association between macronutrient intake, and the risk of giving birth to LGA infants (Table 11). However, in Table 14, amongst sub-components of CHO, the odds of delivering a LGA infant was positively associated with high starch intake in trimester 1 (Adjusted OR 1.05, 95% CI 1.01 to 1.10: P=0.01). There was no evidence of an association between the sub-components of dietary macronutrients and the risk of SGA babies in this cohort (Table 12 and 13).

Table 11 Association between macronutrient intakes in trimester 1 and 2 and odds of giving birth to SGA and LGA infants

Macronutrient*intake[14] 10 g/day increment	Odds of SGA, Model 1			Odds of SGA, Model 2		
Trimester 1 n=1196	**OR[a]**	**95% CI**	***P* value**	**OR[a,c]**	**95% CI**	***P* value**
Total carbohydrate	0.99	0.97 to 1.01	0.63	0.99	0.97 to 1.01	0.67
Total fat	1.05	1.00 to 1.10	0.03	1.03	0.98 to 1.09	0.14
Protein	0.97	0.90 to 1.05	0.54	0.99	0.92 to 1.07	0.99
Trimester 2 n=598						
Total carbohydrate	0.98	0.95 to 1.01	0.27	0.98	0.95 to 1.01	0.30
Total fat	1.03	0.95 to 1.11	0.44	1.02	0.93 to 1.11	0.61
Protein	1.01	0.91 to 1.12	0.73	1.03	0.92 to 1.15	0.54
	Odds of LGA, Model 1			**Odds of LGA, Model 2**		
Trimester 1 n=1196	**OR[b]**	**95% CI**	***P* value**	**OR[b,c]**	**95% CI**	***P* value**
Total carbohydrate	1.00	0.98 to 1.02	0.34	1.00	0.98 to 1.02	0.47
Total fat	0.97	0.91 to 1.03	0.36	0.97	0.91 to 1.03	0.35
Protein	1.04	0.96 to 1.13	0.24	1.04	0.96 to 1.13	0.27
Trimester 2 n=598						
Total carbohydrate	0.99	0.96 to 1.03	0.82	0.99	0.96 to 1.02	0.77
Total fat	0.96	0.88 to 1.06	0.52	0.96	0.87 to 1.06	0.46
Protein	1.00	0.89 to 1.12	0.95	1.01	0.89 to 1.15	0.81

[14][a]Adjusted using customised growth charts for maternal weight, height, ethnicity, parity, physical activity, gestational age at delivery, sex of baby [b]Adjusted using customised growth charts for maternal weight, height, ethnicity, parity, gestational age at delivery, sex of baby [c]Additional adjustment for average alcohol intake and smoking status
*Mutually adjusted for other energy contributing macronutrients

Table 12 Association between macronutrient sub-components in trimester 1 and odds of giving birth to small-for-gestational-age infants (SGA <10th centile)

Macronutrient sub-components[15] g/day increment	Odds of SGA, Model 1			Odds of SGA, Model 2		
Trimester 1 n=1,196	**OR[a]**	**95% CI**	***P* value**	**OR[a,b]**	**95% CI**	***P* value**
Sources of total carbohydrate[†‡]						
Starch (10g)	1.01	0.98 to 1.05	0.34	1.01	0.98 to 1.05	0.32
Glucose (10g)	0.95	0.71 to 1.28	0.77	0.99	0.74 to 1.32	0.99
Fructose (1g)	0.99	0.97 to 1.01	0.59	0.99	0.97 to 1.01	0.54
Sucrose (1g)	1.00	0.99 to 1.01	0.06	1.00	0.99 to 1.00	0.24
Lactose (1g)	0.99	0.97 to 1.00	0.32	0.99	0.97 to 1.00	0.29
Maltose (1g)	0.96	0.88 to 1.04	0.35	0.96	0.89 to 1.04	0.44
Soluble fibre (1g)	0.94	0.88 to 1.01	0.11	0.95	0.88 to 1.02	0.16
Sources of total fat[†*]						
Saturated fatty acid (1g)	1.01	0.99 to 1.03	0.05	1.01	0.99 to 1.02	0.16
Monounsaturated fatty acid (1g)	0.98	0.96 to 1.01	0.25	0.98	0.96 to 1.01	0.26
Polyunsaturated fatty acid (1g)	1.02	0.99 to 1.04	0.08	1.02	0.99 to 1.04	0.06
Protein[*‡] (10g)	0.97	0.90 to 1.05	0.54	0.99	0.92 to 1.07	0.99

15 [a]Adjusted using customised growth charts for maternal weight, height, ethnicity, parity, physical activity, gestational age at delivery, sex of baby [b]Additional adjustment for average alcohol intake and smoking status [*]Adjusted for carbohydrate intakes [†]Adjusted for dietary protein intakes [‡]Adjusted for dietary fats intakes

Table 13 Associations between macronutrient sub-components in trimester 2, and odds of giving birth to small-for-gestational-age infants (SGA <10th centile)

Macronutrient sub-components[16] g/day increment	Odds of SGA, Model 1			Odds of SGA, Model 2		
Trimester 2 n=598	**OR[a]**	**95% CI**	***P* value**	**OR[a,b]**	**95% CI**	***P* value**
Sources of total carbohydrate[†‡]						
Starch (10g)	0.99	0.94 to 1.04	0.88	0.99	0.93 to 1.04	0.74
Glucose (10g)	0.95	0.63 to 1.39	0.80	0.87	0.60 to 1.28	0.49
Fructose (1g)	0.99	0.96 to 1.02	0.79	1.00	0.97 to 1.02	0.86
Sucrose (1g)	1.00	0.99 to 1.01	0.31	1.00	0.99 to 1.01	0.29
Lactose (1g)	0.98	0.96 to 1.00	0.20	0.98	0.96 to 1.00	0.13
Maltose (1g)	1.00	0.91 to 1.11	0.84	1.02	0.92 to 1.13	0.66
Soluble fibre (1g)	0.96	0.87 to 1.06	0.48	0.98	0.88 to 1.09	0.78
Sources of total fat[†*]						
Saturated fatty acid (1g)	1.01	0.98 to 1.04	0.36	1.00	0.97 to 1.03	0.58
Monounsaturated fatty acid (1g)	0.97	0.93 to 1.02	0.38	0.98	0.94 to 1.03	0.62
Polyunsaturated fatty acid (1g)	1.02	0.98 to 1.05	0.22	1.01	0.97 to 1.04	0.53
Protein[*‡] (10g)	1.01	0.91 to 1.12	0.73	1.03	0.92 to 1.15	0.54

16 [a]Adjusted using customised growth charts for maternal weight, height, ethnicity, parity, physical activity, gestational age at delivery, sex of baby [b]Additional adjustment for average alcohol intake and smoking status [*]Adjusted for carbohydrate intakes [†]Adjusted for dietary protein intakes [‡]Adjusted for dietary fats intakes

Table 14 Associations between macronutrient sub-components in trimester 1, and odds of giving birth to large-for-gestational-age infants (LGA >90th centile)

Macronutrient sub-components[17] g/day increment	Odds of LGA, Model 1			Odds of LGA, Model 2		
Trimester 1 n=1,196	**OR[a]**	**95% CI**	***P* value**	**OR[a,b]**	**95% CI**	***P* value**
Sources of total carbohydrate[†‡]						
Starch (10g)	1.05	1.01 to 1.09	0.01	1.05	1.01 to 1.10	0.01
Glucose (10g)	1.05	0.80 to 1.38	0.70	1.09	0.82 to 1.43	0.53
Fructose (1g)	0.99	0.98 to 1.01	0.87	0.99	0.97 to 1.01	0.59
Sucrose (1g)	0.99	0.98 to 1.00	0.33	0.99	0.99 to 1.00	0.54
Lactose (1g)	1.00	0.98 to 1.02	0.52	1.00	0.99 to 1.02	0.49
Maltose (1g)	0.98	0.90 to 1.06	0.65	0.97	0.88 to 1.06	0.51
Soluble fibre (1g)	0.98	0.91 to 1.06	0.73	0.96	0.88 to 1.04	0.33
Sources of total fat[†*]						
Saturated fatty acid (1g)	0.99	0.97 to 1.01	0.56	0.99	0.97 to 1.01	0.78
Monounsaturated fatty acid (1g)	1.00	0.97 to 1.02	0.94	0.99	0.96 to 1.02	0.71
Polyunsaturated fatty acid (1g)	1.00	0.97 to 1.02	0.98	1.00	0.97 to 1.03	0.72
Protein[*‡] (10g)	1.04	0.96 to 1.13	0.24	1.04	0.96 to 1.13	0.27

17 [a]Adjusted using customised growth charts for maternal weight, height, ethnicity, parity, physical activity, gestational age at delivery, sex of baby
[b]Additional adjustment for average alcohol intake and smoking status [*]Adjusted for carbohydrate intakes [†]Adjusted for dietary protein intakes [‡]Adjusted for dietary fats intakes

Table 15 Associations between macronutrient sub-components in trimester 2, and odds of giving birth to large-for-gestational-age infants (LGA >90th centile)

Macronutrient sub-components[18] g/day increment	Odds of LGA, Model 1			Odds of LGA, Model 2		
Trimester 2 n=598	**OR[a]**	**95% CI**	***P* value**	**OR[a,b]**	**95% CI**	***P* value**
Sources of total carbohydrate †‡						
Starch (10g)	1.00	0.95 to 1.06	0.76	1.00	0.94 to 1.06	0.94
Glucose (10g)	1.28	0.82 to 1.97	0.26	1.32	0.85 to 2.05	0.20
Fructose (1g)	0.98	0.95 to 1.02	0.43	0.98	0.95 to 1.01	0.38
Sucrose (1g)	0.99	0.98 to 1.00	0.10	0.99	0.97 to 1.00	0.09
Lactose (1g)	1.01	0.99 to 1.03	0.14	1.01	0.99 to 1.03	0.12
Maltose (1g)	0.98	0.87 to 1.11	0.86	1.00	0.89 to 1.12	0.95
Soluble fibre (1g)	1.05	0.94 to 1.16	0.34	1.04	0.93 to 1.16	0.44
Sources of total fat†*						
Saturated fatty acid (1g)	1.02	0.98 to 1.05	0.18	1.02	0.98 to 1.05	0.22
Monounsaturated fatty acid (1g)	0.96	0.90 to 1.01	0.18	0.96	0.90 to 1.02	0.22
Polyunsaturated fatty acid (1g)	1.00	0.96 to 1.05	0.80	1.00	0.95 to 1.05	0.80
Protein*‡ (10g)	1.00	0.89 to 1.12	0.95	1.01	0.89 to 1.15	0.81

[18] [a]Adjusted using customised growth charts for maternal weight, height, ethnicity, parity, physical activity, gestational age at delivery, sex of baby [b]Additional adjustment for average alcohol intake and smoking status *Adjusted for carbohydrate intakes †Adjusted for dietary protein intakes ‡Adjusted for dietary fats intakes

4.4 Discussion

This analysis has shown that dietary macronutrient composition and its sub-components could be associated with birth outcomes. To the knowledge of the author, it is the first observational study to explore relationships between dietary macronutrient sub-components in pregnancy and birth outcomes, including birthweight and birth centile. These associations were mostly observed in trimester 1. A possible explanation for this might be that placentation is established and the fetal growth is programmed in trimester 1 (Kroener et al., 2016; Roberts, 2010; Smith, 2004). Up to 11 weeks of gestation, the embryo develops in a stable nutritional environment. This may explain why the associations seem to weaken or disappear in trimester 2. Early pregnancy reflects infant organ developmental stages, where the overall energy intake may be less important than the quality of diet. So it might be that the diets high in carbohydrate and fat might just reflect poorer quality diets. Additionally, 45% women in trimester 2 (n=598) were lost to follow-up as fewer women responded to the request for a second 24-hour dietary recall, since communication at this point with the women was by post rather than a study visit. Despite this, the size of the estimates and confidence intervals were similar between trimesters 1 and 2. In trimester 2, glucose and lactose were associated with increasing birthweight, this might be attributed to the increased availability of free maternal glucose ready to be utilised as a primary source of energy to meet fetal demands required for organ growth during this period (Brantsæter et al., 2012; Gabbe and Quilligan, 1977; Hay, 2006; Hay and Sparks, 1985; Walsh et al., 2011).

4.4.1 Comparison with other studies

Higher intakes of total CHO during trimester 1 was associated with higher birthweight and an increase in birth centile. This particular finding in the study is in agreement with literature. A study reported similar associations between low contribution of CHO to total energy during pregnancy and thinness at birth (Langley-Evans and Langley-Evans, 2003). Another study reported that high percentage (%E) of energy from CHO in the diet could be associated with high offspring birthweight (Moore et al., 2004). This particular finding is in support of the current analysis which also examined the energy percentages (%E) of macronutrients where, a higher %E from carbohydrate intake was positively associated with higher birthweight. However, it also demonstrated that a higher %E from dietary fat was associated with lower birthweight after further adjustment for alcohol intake and smoking habits.

Interestingly, amongst mono-saccharides, it was observed that in trimester 2 additional consumption of dietary glucose was associated with heavier birthweight. A similar association was observed in a study (Kerssen et al., 2007) amongst pregnant women with type 1 diabetes

mellitus. They reported an association between increased maternal glucose levels amongst diabetic pregnant women and LGA offspring. In this study, it was observed that high intake of starch was associated with increased odds of delivering LGA infants. According to a study (Butte, 2000) which compared normal versus pregnant women with gestational diabetes mellitus (GDM), participants who consumed a CHO-rich diet were likely to have high blood glucose levels, and an increased risk of delivering LGA offspring. Randomised controlled trials (RCTs) have reported possible effects of a high CHO intake vs a low CHO intake amongst women with GDM and increased risk of macrosomia (Combs et al., 1992; Walsh et al., 2012). A possible explanation for these results could be that high CHO intakes could lower maternal insulin sensitivity, making higher levels of free glucose available for placental circulation, subsequently activating fetal glycogenesis (Clapp, 2002). Pedersen(Pedersen, 1961) attributed the role of maternal hyperglycaemia to this birth outcome which reportedly caused increase in fetal insulin levels and led to fetal hyperglycaemia.

A high lactose intake might be attributed to high milk and dairy product intake by the women. The Danish National Birth Cohort (DNBC) study (Olsen et al., 2007) explored the association between maternal milk and dairy products consumption with birthweight among 50,117 mother-infant pairs and found that higher dairy consumption promoted higher birthweight. Another study came to a similar conclusion suggesting a decreased risk of SGA (Olmedo-Requena et al., 2016). Additional lactose consumption (in the form of dairy products) leading to a higher birthweight could also be related to higher iodine levels found in milk and dairy sources in the UK (Bath et al., 2017; Yang and Huffman, 2011). Iodine levels could influence birthweight(Andersen et al., 2013; Rydbeck et al., 2014) through a role in controlling metabolic rate and development of body structures (Xiao et al., 2017). The lactose association observed may also be indirectly attributed to the level of placental calcium transferred to the fetus (Kovacs, 2014), increasing bone calcification during skeletal development, and overall birthweight (Sabour et al., 2006).

Unlike previous studies (Blumfield et al., 2012; CucÓ et al., 2006; Moore et al., 2004) which reported an association with protein, this study did not find any evidence of an association between protein and birthweight/centile, and LGA/SGA babies. Although there was a positive association between protein intake and birthweight under model 1 during trimester 1, no association was observed after adjusting for alcohol and smoking habits, but the confidence intervals were wide. Also, there was no evidence of an association between the dietary macronutrient intakes in trimesters 1 and 2 and the risk of SGA and LGA babies. CARE study participants were adequately nourished, hence this might be the reason no effects were noticed. A study (Moore et al., 2004) suggested that the energy contribution from protein in

the diet is associated with increased birthweight and placental weight. They considered the type of protein such as animal/ vegetable protein and suggested that higher dairy protein consumption was positively associated with higher birthweight. But their results were of low statistical power, and did not adjust for mother's alcohol consumption. However, in support of this chapter's finding, a study (Chong et al., 2015) in Asia found no evidence of an association between protein intake in pregnancy and offspring weight.

The current study's analyses suggest that total fat intake and its sub-components such as PUFA were associated with lower birthweight and birth centile. However, this result conflicts with a South-Asian study (Mani et al., 2016) which reported a positive association between dietary fat intake in pregnancy and increased birthweight. Contradicting results from other studies (Chong et al., 2015; Lagiou et al., 2004; Moore et al., 2004) reported no association between them; an observational study (Moore et al., 2004) explored the relation between energy percentage (%) from total dietary fat and birthweight, and suggested no evidence of an association after adjusting for other energy contributing nutrients. This analysis adjusted for alcohol, as it is associated with increased risk of lower birthweight (Chiaffarino et al., 2006; Nykjaer et al., 2013; Windham et al., 1995) and fat-rich foods are often consumed with alcohol. Conversely, the study by Moore et al. (Moore et al., 2004) did not adjust for alcohol consumption during pregnancy. However, amongst randomised controlled trials (RCTs) on animal models, there is no evidence suggesting an association between a high fat diet in pregnancy and changes in birthweight. Previous studies (Khan et al., 2005; White et al., 2009) based on animal models explored the effect of a high-fat diet in pregnancy on the development of offspring metabolic disorders including hyperinsulinemia, blood pressure, and changes in serum leptin levels. An RCT (White et al., 2009) amongst pups, explored the effects of high-fat diet on offspring and suggested that maternal adiposity and not dietary fat per se, was associated with increased offspring weight, and metabolic disorders such as hyperinsulinemia which could further persist through adulthood. During trimester 1, higher PUFA intake was associated with lower birthweight of infants. Three studies (Blumfield et al., 2012; Newman et al., 2002; Nuernberg et al., 2011) discussed the "anti-obesogenic" property of PUFA during pregnancy which reportedly prevented extra fat mass deposits in the fetus. Ethical issues make studies of this nature challenging in humans such as acidosis and ketosis in response to low CHO-high fat diets, alterations in cholesterol and free fatty acid metabolism in pregnancy. Further studies are needed to validate this result.

The CARE cohort was a well-nourished group; the participants' average dietary macronutrient intake/day during trimesters 1 and 2 largely met the estimated average requirements of energy (EAR) recommended during pregnancy in the Committee on Medical Aspects of Food Policy

(COMA) report by the Department of Health, UK (Health, 1991), and the intakes were similar to those found in other studies involving pregnant women (Chen et al., 2016; Langley-Evans and Langley-Evans, 2003; Moore et al., 2004). The previous publication of results conducted within the CARE cohort made use of the specially designed questionnaire to capture caffeine intake, which demonstrated that maternal caffeine intake was inversely associated with birthweight(Boylan S, 2010).

According to the CARE study cohort profile, a decision was taken to use the 24-hour dietary recall which was also collected, to measure the whole dietary intake of participants in detail on a specific day. Alternative approaches such as a food frequency questionnaire were not available for the whole diet in this sample and require participants to subjectively average out a potentially varied diet over a longer period of time. A number of validation studies (Beer-Borst and Amadò, 1995; Hartman et al., 1990; Karvetti and Knuts, 1985; Sharma et al., 1998) have shown that 24-hour dietary recall is a well-established method which correlates well with true usual intake, and are adequate and suitable to large populations rather than individuals. Though this method is less suited to episodically consumed foods, it has been shown to work well for commonly consumed foods and nutrients, particularly macronutrients, present in most food items that are the subject of this current research (Beer-Borst and Amadò, 1995; Hartman et al., 1990).

The estimates of change in birthweight by macronutrient intake are small because a small macronutrient increment/day (10g is 1/10th of a standard deviation) was chosen. Using a larger increment for all macronutrients, such as 100g/day, equivalent to 1 SD, would be associated with an increase in birthweight of around 40 g. Such a change in birthweight might have a modest impact on preterm infants or those already having low birthweight, but need not be of great concern to infants with a better starting point. However, although these results demonstrate statistical significance in their association with birthweight, it is important to note that they have no clinical significance. Furthermore, it is essential to consider that small effects on a population level could be important (Rose, 2001), through shifting the whole distribution of birthweights, higher or lower depending on the type of macronutrient consumed.

4.4.2 Strengths and weaknesses

The strength of the study is that it is a large cohort comprising of 1196 pregnant women. Hence this cohort had a large sample size with high statistical power. Considering the logistics associated with recording data in a cohort, this study had high quality dietary data recorded twice during pregnancy by trained research midwives i.e. in trimesters 1 and 2. This is more advantageous as compared to other birth cohorts including, MoBa (22 weeks of gestation),

DNBC (25 weeks of gestation) and ALSPAC (32 weeks of gestation) which recorded dietary data at one time point during pregnancy (Magnus et al., 2016; Magnus et al., 2006; Olsen et al., 2001; Rogers and Emmett, 1998).

Diet was assessed using an interviewer led 24-hour dietary recall; allowing detail of food types and amounts to be recorded. Although it might be argued that 24-hour recall is less efficient than a FFQ, both dietary assessment tools produce similar results. Previous studies compared other dietary assessment tools including FFQ, 3-day and 7-day dietary recalls with a 24-hour dietary recall and suggested that 24-hour dietary recall is a well-established method which correlates well with the daily dietary intakes and can be used within large populations (Beer-Borst and Amadò, 1995; Hartman et al., 1990; Karvetti and Knuts, 1985; Sharma et al., 1998).

The regression models were carefully adjusted for potential confounders: alcohol intake, smoking habits, maternal height, weight, parity, ethnicity and sex of the baby and were kept consistent with the covariates pre-adjusted for the customised centile charts in the GROW software from the Perinatal Institute.

There was detailed dietary information available, including values of macronutrient sub-components including saccharides and fatty acids. These are were advantageous as no other cohort according to the knowledge of the author has explored and demonstrated associations between saccharides and fatty acids consumed in pregnancy, and birth outcomes. Large birth cohorts usually do not have detailed dietary data for all the macronutrient components (Brantsæter et al., 2008; Mikkelsen et al., 2007; Rogers and Emmett, 1998).

There are few limitations to any study which explores nutritional intake. For sub-components, the nutrient values computed in the software using the food composition database(Holland B, 1992) may not be accurate or complete. A couple of studies (Cowin, 1999; Deharveng et al., 1998) reported issues of missing values for nutrients in databases, including McCance and Widdowson's food composition database (Cowin, 1999).

Determination of the increment rates for the macronutrients was a challenge since there was very limited evidence. In this study bite size amounts estimated at an increment rate of 10 grams per macronutrient, i.e., approximately two teaspoons was considered appropriate for easier interpretation and demonstrate associations which represented realistic changes in birthweights. Although this might seem a small amount, it was appropriate in comparison with the increment rate used in previous studies, for example, per gram or per %E from a macronutrient (Chen et al., 2016; CucÓ et al., 2006; Moore and Davies, 2005; Moore et al., 2004).

The increment rates could have been expressed as per SD to cover a larger range of the dietary macronutrients (exposure) similar to the Lagiou study (Lagiou et al., 2004). This decision could have increased the overall estimates of the change in birthweights and odds of the SGA and LGA babies; which might have represented realistic changes in birthweights that are clinically significant.

Energy intake estimations from food items and beverages of the participants were based on memory recall and are subjected to mis/under-reporting (Black and Cole, 2001; Brantsæter et al., 2008; Meltzer et al., 2008). This was especially likely amongst women with higher pre-pregnancy weight. Studies suggested that women with higher pre-pregnancy BMI (>25) were more likely to underreport their overall dietary choices and intakes thus introducing potential bias in the interpretation of the overall results (Johansson et al., 1998; McGowan and McAuliffe, 2012). Therefore, these results need to be duplicated to test for consistency.

Some studies suggest the use of a combination of dietary assessments to cross check the dietary information for correct quantity estimation, measurement uniformity and frequency of consumption(Byers, 2001; Hebert et al., 1995), however, this is more common where food frequency questionnaires are the main dietary measure.

Dietary data in this study was recorded only for trimesters 1 and 2 and not trimester 3 as per the study design. Also due to the study design there was a higher rate of loss to follow up cases observed due to lack of response during the second trimester as postal communication was used instead of study visits.

The birthweight models were adjusted for gestational age at delivery and sex of the baby. These two factors are known to be associated with birthweight but might not be associated with maternal dietary macronutrient intakes, hence they cannot be theoretically included as covariates. However, the two variables were included in the analyses in order to include similar covariates which were included in the birth centile model and maintain consistency. This was because the birth centiles were extracted from birthweights.

A sensitivity analyses was performed by excluding the two variables from the birthweight model, and the results remained statistically significant for CHO (positive trend), and no evidence of an association for protein, but changed for fat. Original results presented a statistically significant negative association between dietary fat and birthweight, but after excluding the two variables there was no evidence of an association observed. Nevertheless, the negative trend, estimates and the confidence intervals of dietary fat remain unchanged. Therefore, it could be justified that the results in the sensitivity analyses remained consistent because it is important to observe the estimate and confidence intervals rather than depending

only on the p values representing the statistical significance levels. However, it is meaningful to include covariates which are clinically important and associated with both, the exposure and outcome. Furthermore, two clinically important covariates including, maternal age and use of dietary supplements in pregnancy were not included in the regression analyses.

Hence, it should be acknowledged that these decisions might have affected the results of this study. The regression models in the next chapter have been reconstructed by accounting for the limitations observed in this study. The section 5.2.6 of methodology in the next chapter provides an explanation and justification for including important covariates based on *a priori* knowledge in order to increase robustness of the statistical models.

Data were unavailable for investigating the type of protein (animal/vegetable), which finally led to include total protein in the regression models. Therefore, differential associations of the type of maternal protein with birth outcomes could be further explored amongst other cohorts which have the relevant data available.

The analysis could not include other covariates, including medications, pregnancy-related hypertension, gestational Diabetes Mellitus (GDM) and pre-eclampsia as the data were unavailable.

4.5 Overall implications

These results show that dietary macronutrient composition during pregnancy is associated with birthweight outcomes. Carbohydrate and its sub-components such as lactose, glucose and starch were associated with higher offspring birthweight. Conversely dietary fat and its sub-component− PUFA were associated with lower birthweight. The results in this study represent the associations mostly observed in trimester 1. Therefore, this might highlight the importance of monitoring diets during the initial months of pregnancy. There is sufficient evidence suggesting the role of preconception diets and its positive association with healthy birth outcomes (CucÓ et al., 2006; King, 2016; Potdar et al., 2014; Ramakrishnan et al., 2012). In addition to these, the results in this study could imply the need to maintain adequate balance of macronutrients and follow healthy dietary choices during the first trimester which are described as the critical periods of development in pregnancy. Finally, this could in turn support offspring birthweight through a carefully balanced intake of fat and carbohydrate during pregnancy.

The next chapter (Chapter 5) will examine the association between maternal dietary macronutrients and birth outcomes in a meta-analysis study of three international birth cohorts. Replication of the analyses of the current study will be done amongst the following

birth cohorts (2 international birth cohorts: DNBC and MoBa from Denmark and Norway respectively, and CARE study).

Chapter 5 : Association between dietary macronutrient composition in pregnancy and birth outcomes: a meta-analysis of three birth cohorts (CARE, DNBC and MoBa)

The previous chapter examined the association between maternal dietary macronutrients and birth outcomes amongst the CAffeine and REproductive health study (CARE) in U.K. This chapter will examine these associations amongst three birth cohorts in the Northern Europe and compare their results.

5.1 Introduction

Recent studies have demonstrated that maternal nutrition influences fetal growth and could be associated with diseases in adulthood (Blumfield et al., 2012; Brantsæter et al., 2014; Englund-Ögge et al., 2014; Knudsen et al., 2007; Oken et al., 2004); by permanent alteration of metabolism and organ structures (de Boo and Harding, 2006; Delisle, 2002; Kelleher et al., 2014; Roseboom et al., 2001). Recent studies have linked the development of co-morbidities including Diabetes Mellitus, hypertension, and coronary heart disease (CHD) in adulthood to the quality of the *in-utero* nutrition(de Boo and Harding, 2006; Delisle, 2002; Kelleher et al., 2014; Roseboom et al., 2001). It is also suspected that the nutrient intake in the second and third trimesters have more influence on fetal growth than the first trimester, with the reasoning that high levels of nutrients transferred via the placental pathway are utilised for the fetal growth which is peak during these periods(Chen et al., 2016; CucÓ et al., 2006; Kerssen et al., 2007; Marangoni et al., 2016).

In the past, a large number of meta-analysis studies have explored the impact of micronutrients including iron, folate, vitamin B12, calcium important in relation to optimum fetal growth (Blumfield et al., 2013; Fekete et al., 2012; Haider et al., 2011; Kawai et al., 2011; Kirke et al., 1993). However, focus on maternal dietary macronutrients has been limited in the literature, especially amongst meta-analysis studies. Also, little is known regarding the individual contribution of a particular macronutrient (carbohydrate (CHO), protein and fat) in the maternal diet on size at birth.

Hence, I have undertaken the first pooled cohort study using a random-effects meta-analysis model to combine three birth cohorts to explore the impact of maternal dietary macronutrient composition consumed during the second trimester on birth outcomes including birthweight, and SGA and LGA babies. The justification for this method is provided in section 5.2.8 of statistical methods under 5.2 methodology. Three observational studies have examined this association amongst modest sample sizes (Chong et al., 2015; CucÓ et al., 2006; Moore et al.,

2004) (Chong et al., 2015; CucÓ et al., 2006; Moore et al., 2004) but the results appear to be inconclusive. The Chong study suggested that there was no evidence of an association between any maternal dietary macronutrient and birthweight (Chong et al., 2015). However, in contrast the Moore study suggested a positive association between higher dairy protein consumption in pregnancy and higher birthweight (Moore et al., 2004). Further, the results from the CucO study were in agreement with the Moore study and suggested that amongst CHO, fat and protein, the maternal protein intakes had a positive association with birthweight (CucÓ et al., 2006). Therefore, it can be observed that apart from inconsistent results, none of the studies suggested an evidence of an association between maternal CHO and fat, and birthweight.

In Chapter 4, the analysis explored this association within the CAffeine and REproductive Health study (CARE) in U.K. This analysis is replicated amongst The Danish National Birth Cohort (DNBC) from Denmark and The Norwegian Mother and Child Cohort Study (MoBa) from Norway along with the CARE study from the U.K. The current study, therefore, aims to increase the strength and robustness by examining the meta-analysis results of three birth cohorts.

The study objective was to investigate the association between dietary macronutrient composition during pregnancy and birth outcomes after combining the results of three international birth cohorts (CARE, DNBC and the MoBa) using a meta-analysis approach.

The birth outcomes included in this study are birthweight (g), and the odds of small-for-gestational-age (SGA) and large-for-gestational-age (LGA) babies.

5.2 Methodology

5.2.1 Baseline data

The Individual participant data (IPD) meta-analysis included cohort-specific results of three birth cohorts – CAffeine and REproductive Health study (CARE), U.K., The Danish National Birth Cohort (DNBC), Denmark and The Norwegian Mother and Child Cohort Study (MoBa), Norway.

Since it is a meta-analysis, the purpose was to include variables recorded at baseline which were as uniform as possible in the statistical modelling. For which, the study design of all birth cohorts were first referred to select appropriate data. The details of the study design of all three birth cohorts are given between sections 3.1.1 to 3.1.3 in Chapter 3.

According to the individual birth cohort profiles (Boylan et al., 2008; Magnus et al., 2006; Olsen et al., 2001), the baseline data were collected around 12 weeks of gestation in DNBC, around 15 weeks of gestation in MoBa, and between 8-12 weeks of gestation in CARE.

The variables recorded at baseline necessary for analysis included, maternal age, weight gain in trimesters 1, 2 and 3, pre-pregnancy body mass index (BMI) [weight (kg)/height (m^2)], parity, smoking habits, alcohol consumption, dietary supplements, and physical activity levels.

5.2.2 Study inclusion criteria

The initial sample size of the DNBC and MoBa datasets were (N=92,646) and (N=114,700) pregnant women, respectively. There were two exclusion criteria for the meta-analysis (refer Figure 3 and Figure 4 for inclusion flow charts of MoBa and DNBC): 1) Pregnant women above 45 years and below 18 years of age were excluded from the DNBC (n=188) and MoBa (n=712) birth cohorts. CARE study already included women who were in this age bracket in their study design since the original CARE study also used similar exclusion criteria (refer Figure 5). The meta-analysis was designed for an adult population who were above 18 years and under 45 years of age. 2) Multiple births, including twins, triplets and quadruplets were excluded from MoBa (n=3966). DNBC and CARE cohorts only recruited participants with singleton pregnancies in their study design. Multiple births, including twins and triplets, were excluded because interpretations for singleton pregnancies are more straightforward, and there could be other reasons for different outcomes related to multiple births.

5.2.3 Data cleaning procedure for the cohort datasets

Data cleaning was conducted in the initial stages of the analysis for certain variables in both MoBa and DNBC datasets and aimed to keep as many observations as possible in the analysis. Also, some variables in both the datasets had outliers, which were corrected after setting them to 'missing' instead of entirely excluding participants from the analysis.

For example, energy consumption outliers (>6000 kcal/day and <600 kcal/day) were corrected by setting the energy intakes to missing in the DNBC (n=349) and MoBa (n=286) datasets. These cut points were set because they were considered to be extreme and unrealistic intakes (Olsen et al., 2007; Samuel-Hodge et al., 2004) possibly due to misreporting in the FFQ. The CARE dataset had already set the required cut-off for energy consumption (>6000 kcal/day and <600 kcal/day) in the study design.

Data cleaning (variable values replaced to missing) was required in the MoBa dataset for the following variables: Unknown sex of the baby (n=35), height below 140 centimetres (n=223) and height in metres (n=226), weight above 200 kilograms (n=2 in trimester 1 [T1], n=3 in T2) and below 35 kilograms (n=29 in T1, n=60 in T2 and n=10 in T3), and BMI above 90 (n=203 in T1, n=198 in T2 and n=179 in T3). Apart from the requirement to include as many participants

as possible in the analysis, data cleaning also prevents any potential outliers from hampering the analysis.

Hence, after excluding participants and cleaning the datasets, the cohort size was n=110,022 mother-infant pairs in MoBa, n=92,458 mother-infant pairs in DNBC, and n=598 mother-infant pairs in the CARE study.

Also, dietary data was not available for the entire cohort and were available only for 89,345 participants in MoBa, and 68,236 participants in DNBC. Due to funding limitations, MoBa and DNBC cohorts recorded the dietary data only once around 22 weeks and 25 weeks of gestation, respectively. CARE recorded the dietary data twice according to their study design, once at recruitment, i.e. during 8-12 weeks of gestation, and again during the 13-28 weeks of gestation. Hence for the cohort-specific analysis within the CARE study, the second trimester's dietary data (n=598) were included for the meta-analysis in order to be consistent with the DNBC and MoBa cohorts' dietary data recording period.

5.2.4 Study population

After data cleaning, the cohort-specific sample sizes included for dietary analysis in this study were as follows: (N = 85,574) in MoBa, (N=63,755) in DNBC, and (N=598) in CARE. In total, the meta-analysis study results will represent a sample size of 149,927 mother-infant pairs.

Figure 3 Inclusion criteria flow chart for MoBa cohort

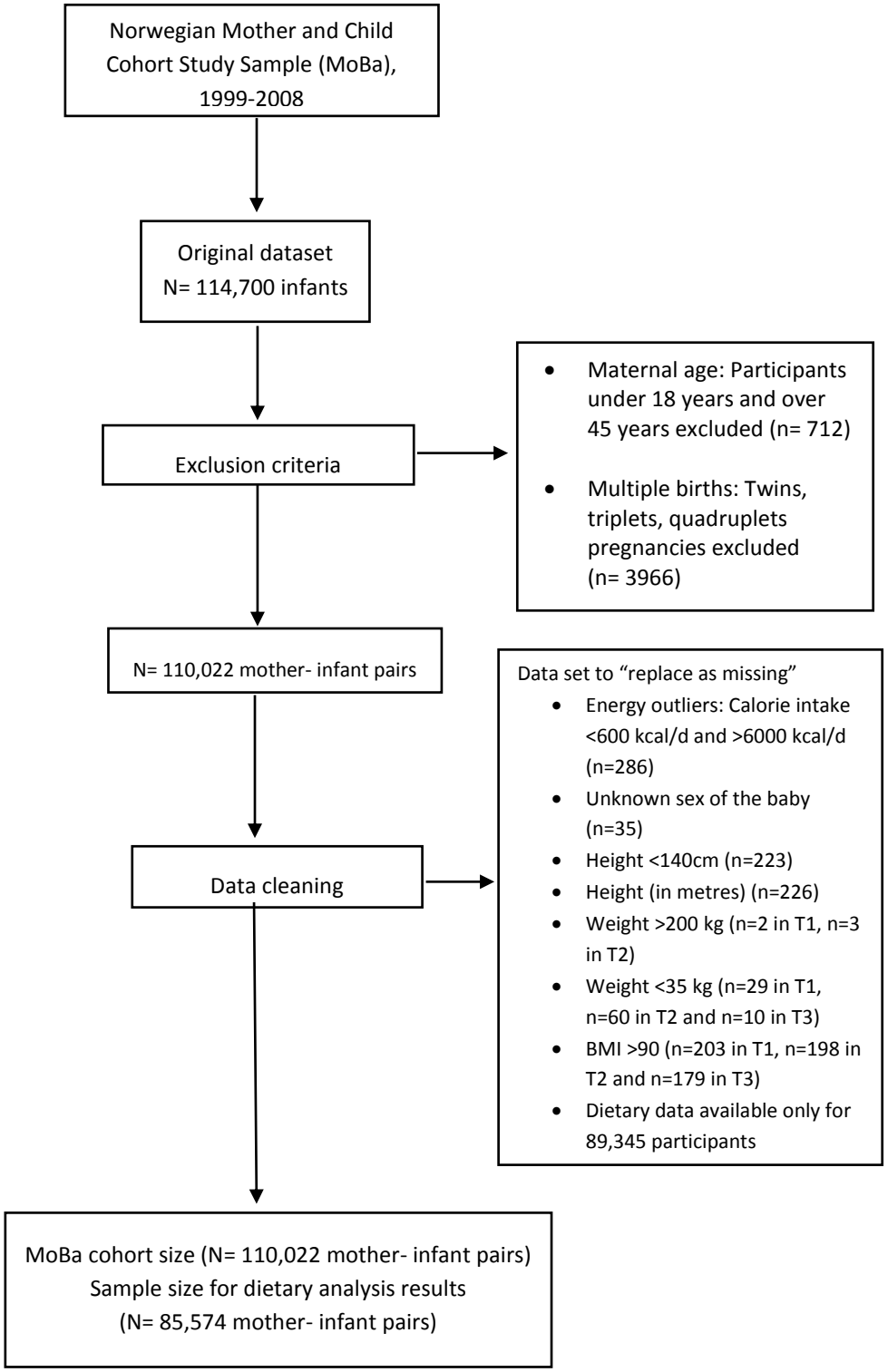


Figure 4 Inclusion criteria flow chart for DNBC cohort

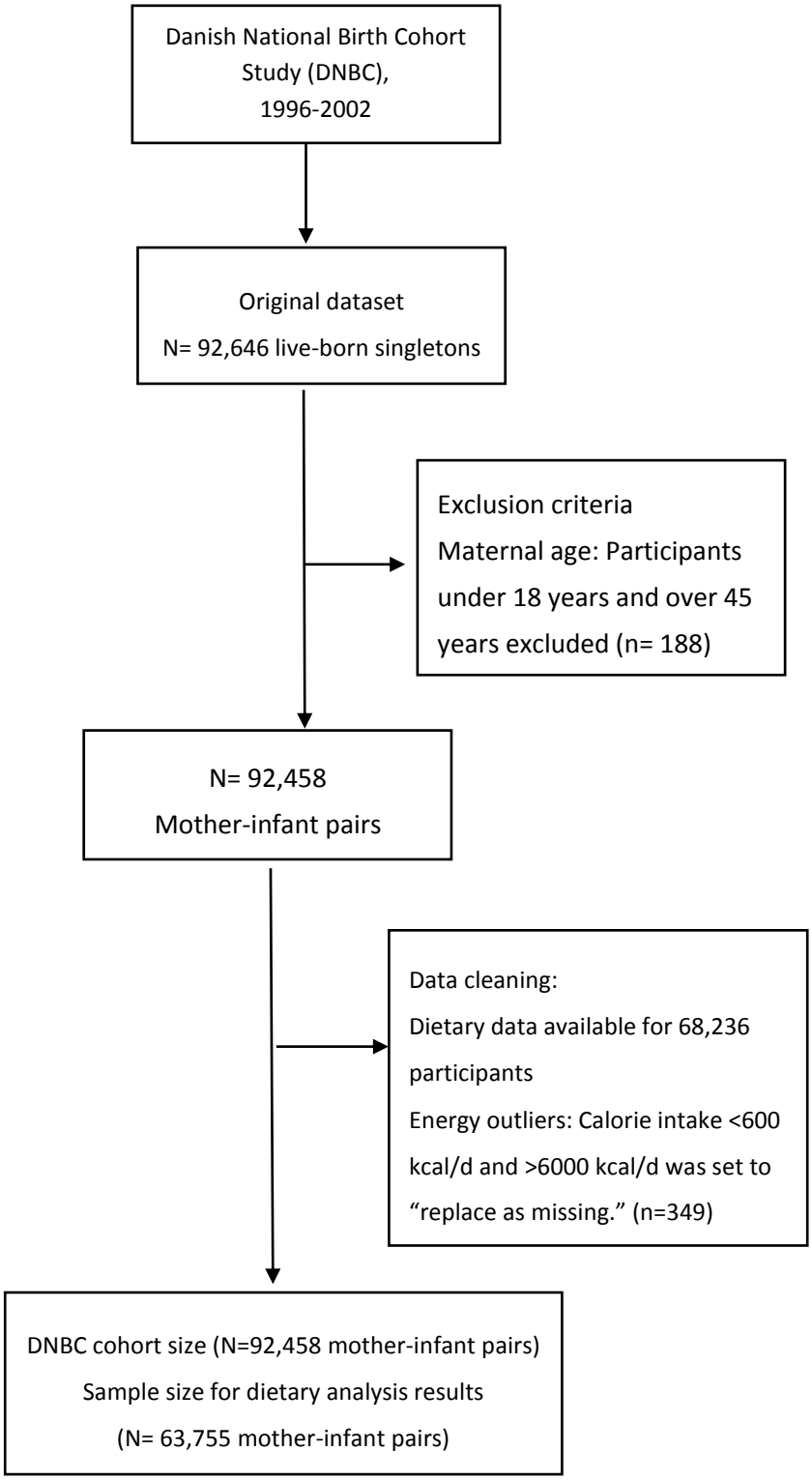
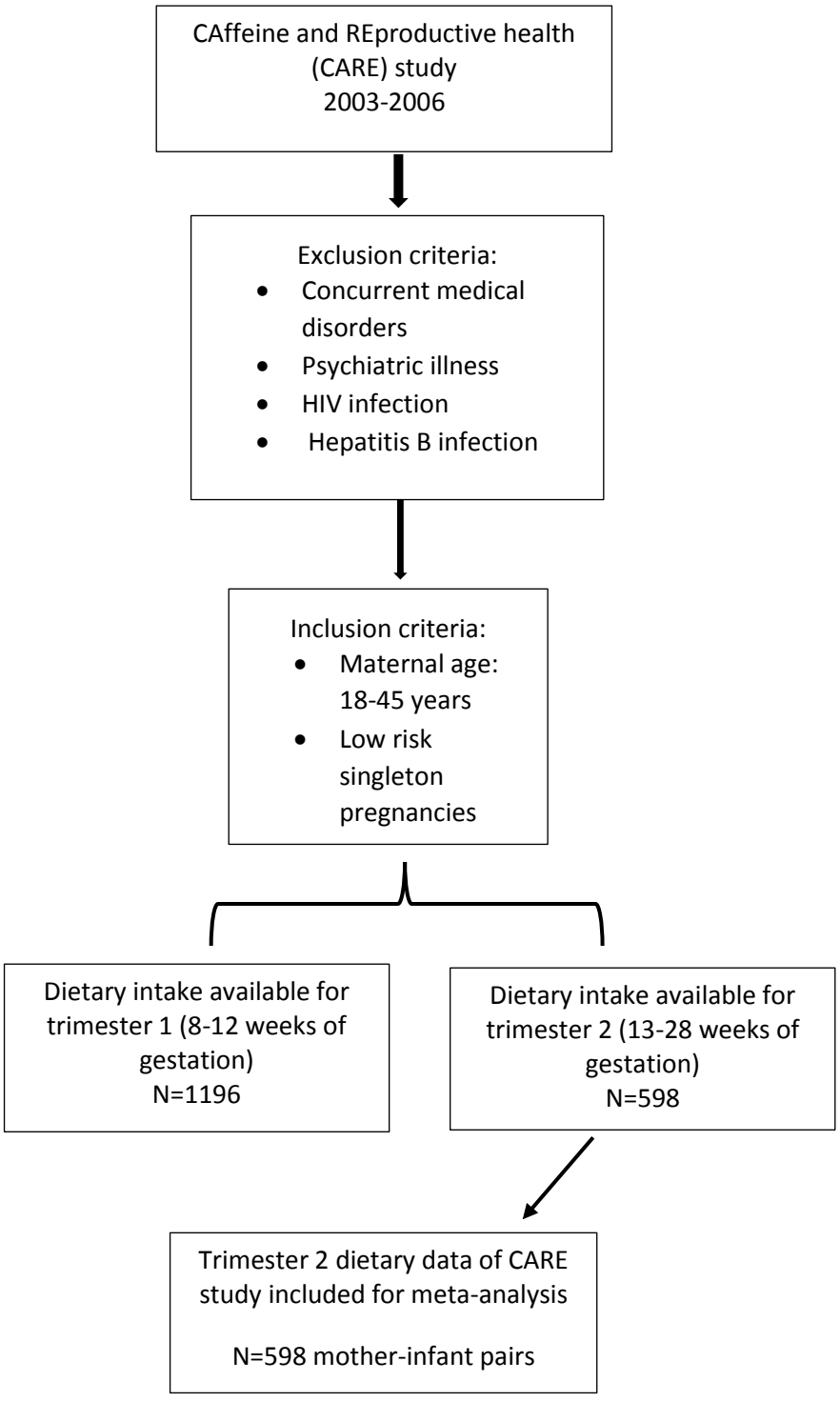


Figure 5 Inclusion criteria flow chart for the CARE study



5.2.5 Dietary data

The four dietary exposures in this analysis are CHO, protein, fat and total energy intake. DNBC and MoBa birth cohorts used a self-administered semi quantitative food frequency questionnaire (FFQ) (Brantsæter et al., 2008; Meltzer et al., 2008; Mikkelsen et al., 2007), and CARE recorded dietary data using a self-administered 24-hour dietary recall (Boylan S, 2010; Boylan et al., 2008). Nutrient intakes were computed using dietary software: FoodCalc in MoBa and DNBC and DANTE in CARE. As discussed in section 3.5 of Chapter 3, the dietary data in MoBa was recorded around 22 weeks of gestation, around 25 weeks of gestation in DNBC, and between 13 to 28 weeks in the CARE study.

The macronutrients (carbohydrate [CHO], fat and protein) were expressed in grams per day (g/day), and total energy intakes in kilocalorie per day (kcal/day).

5.2.6 Study covariates

In order to include a covariate in the regression models, it must cause (or be a marker for a cause) of both, the exposure (maternal dietary macronutrient intake) and the outcome (birthweight, odds of SGA and LGA births). Causal effect identification was made using directed acyclic graph (DAG) by mapping out causal diagrams which include all the potential variables which could be causes or markers for the cause of the maternal dietary macronutrients and birthweight, SGA and LGA births, thus minimising bias. The DAG software (Textor et al., 2011) is primarily based on *a priori* literature, with selected variables entered into the causal diagram. The DAG algorithm then produces minimal sufficient adjustment sets of confounders for estimating the effects which are causes or markers of causes of the macronutrient intakes in pregnancy and the birth outcomes. The primary purpose of using the DAG software for selection of confounders was to reduce the confounding bias when the estimation of the causal effect was made between the maternal macronutrient intakes and birth outcome, for example, birthweight, due to a confounder, such as alcohol consumption (Shrier and Platt, 2008).

In the DAG model, the grey circles represent unavailability of data, red circles represent the covariates included in the model, the green circle represents the dietary macronutrients (exposure) and the blue circle represents the birth outcome. There are three separate DAGs, for birthweight (refer Figure 6), and odds of SGA (in Figure 7) and LGA babies (in Figure 8). Although the three DAGs seem similar, minor differences can be observed. In the DAG for the odds of SGA baby, it can be observed that preeclampsia is linked with the outcome through gestational age at delivery along with pregnancy induced hypertension and pre-existing hypertension, and does not include gestational Diabetes Mellitus. However, in the DAG for the odds of LGA baby, there is no pre-eclampsia included and GDM is directly linked to gestational

age at delivery, which is subsequently linked to odds of LGA baby. Also, dietary micronutrients are linked to both gestational age at delivery, and odds of SGA baby and birthweight, but in the LGA baby DAG, it is only linked with gestational age at delivery.

For the models in this chapter, the confounders were included based on the minimal sufficient adjustment sets of confounders presented by the DAG algorithm (shown in red circles in Figure. 6, 7 and 8).

The minimal sufficient adjustment set for regression models of the three birth outcomes were alcohol intake, parity, physical activity, pre-pregnancy BMI, smoking, socio-economic status, ethnicity, dietary supplements and maternal age. However, two confounders in the DAG adjustment set were not included in the analysis, namely, ethnicity and socioeconomic status. In DNBC and MoBa data for ethnicity was unavailable because of data security issues. Also, socioeconomic status variable was incorrectly recorded in MoBa.

A detailed justification is provided for all the covariates included in the DAG model in turn below:

The *pre-pregnancy body mass index (BMI)* of women is suggested to be associated with both the energy intake during pregnancy and birth size. Underweight and normal BMI women might be more aware and self-conscious about their energy intakes and dietary choices before pregnancy and therefore might continue to have better diet quality through pregnancy(Laraia et al., 2007). Whereas, overweight and obese women who might usually have unhealthy dietary choices before pregnancy, could consume higher amounts of energy-dense foods with low nutrient value in their pregnancy due to hormonal influences on their appetite(Hirschberg, 2012; Sullivan et al., 2011). Also, mothers with high BMI are given pre-natal dietary counselling as a part of the nutritional intervention programs aiming at weight control strategies for a healthy pregnancy, possibly influencing energy consumption(Rogozinska et al., 2017). Also, ethnicity could influence the mothers' BMI, as women from Asian and African ethnic groups have a higher pre-pregnancy BMI, which could, in turn, influence their diet in pregnancy(Rahman et al., 2009). Most of the studies suggest that underweight women have a higher risk of delivering low birthweight offspring, and overweight and obese women tend to deliver LGA offspring(Bhattacharya et al., 2007; Pan et al., 2016; Yu et al., 2013).

Dietary supplements, including multivitamins, help increase the overall appetite during pregnancy, which influences the overall maternal energy intake. It is reported that consuming dietary supplements help restore the energy and protein metabolisms to normal and help reduce weakness and fatigue thus improving the overall feeling of wellbeing, resulting in

increased appetite (Major et al., 2008; 1958). Dietary supplement consumption has been associated with improving fetal outcomes including preterm birth, small for gestational age babies and low birthweight by supplying adequate micronutrients, including iron and folate(Haider and Bhutta, 2017; Kim et al., 2014; Shah and Ohlsson, 2009), vitamin B12 (Rogne et al., 2017), and calcium(Imdad and Bhutta, 2012) for optimum protein metabolism necessary for fetal growth.

Alcohol intake can influence dietary choices generally. Energy-dense and high-fat food products are usually consumed with alcohol(Rangan et al., 2008). Alcohol consumption during pregnancy is also associated with alteration of fetal outcomes; for example, the possibility of Fetal Alcohol Syndrome (FAS)(Das et al., 2004; de Sanctis et al., 2011; Hanson et al., 1978; Weinberg, 1985). It is also suggested to be associated with increased pre-pregnancy BMI and psychosocial stress, which causes women to increase their alcohol intake, thus indirectly leading to higher caloric intake(Beulens et al., 2012).

Maternal smoking can alter dietary choices by suppressing energy intake. The nicotine content in cigarettes alters the appetite; by suppressing the hypothalamus gene receptors controlling appetite lowering the overall caloric intake(Chen et al., 2012; Mineur et al., 2011). Also, in some women, smoking could be associated with a higher appetite, which could influence the dietary choices and energy intakes in pregnancy. Studies suggest that maternal smoking is associated with reduced birthweight due to hypoxic effects causing the offspring to weigh lesser by approximately 100-130 g at birth(Abraham et al., 2017; Cnattingius, 2004; Cogswell et al., 2003; Suzuki et al., 2016).

Maternal age could affect macronutrient dietary choices and intakes. Younger women usually consume higher amounts of processed foods, which are often high in saturated fat, salt and refined CHO, as compared to older women(Escoto et al., 2012; Shiraki et al., 2017). Maternal age is an essential factor to consider for determining the birth outcome, as older mothers are likely to be at higher risk for pregnancy complications, including Caesarean section delivery, pre-eclampsia, gestational diabetes mellitus, pregnancy induced hypertension, and preterm delivery, fetal distress (Cavazos-Rehg et al., 2015; Dietl et al., 2015; Kenny et al., 2013; Lamminpää et al., 2012; Lampinen et al., 2009).

Women who are physically active are thought to have an increased appetite to keep up with the body's energy expenditure, which increases their macronutrient dietary intakes. Studies suggest that women who were physically active before and during pregnancy had better birth outcomes, with optimum birthweights than women who had low physical activity levels (Domenjoz et al., 2014; Leiferman and Evenson, 2003; Varrassi et al., 1989). Studies have suggested that physical activity controls stress levels thus reducing the likelihood of binge

eating amongst mothers (generally opting for energy-dense foods) during pregnancy(Rogozinska et al., 2017).

Parity is important to consider, as multiparous mothers might have different diets and energy intakes as compared to primiparous women. The difference in energy intakes might be because the mother might cut down on her energy intake before and during pregnancy in order to feed her other children; which is a common phenomenon amongst lower to middle socio-economic groups(Herring et al., 2012). Whereas, a primiparous woman might be extra cautious with her diet and will maintain optimum energy intakes required for fetal(Nohr et al., 2009).

Socioeconomic status (SES) in the form of employment rates determine the generation of income in the family; hence this could affect the dietary choices of the women while pregnant, mainly it could be that they might choose high energy dense foods with low nutrient value as they are usually more affordable(Drewnowski and Specter, 2004). SES is also directly associated with the birth outcomes, where offspring birthweights are generally at a better starting point amongst developed countries than those belonging to lower to middle-income groups(Nasreen et al., 2010). SES also causes maternal psychosocial stress, which could affect their appetite, in turn affecting their macronutrient intakes (Nasreen et al., 2010). However, the variables in MoBa were incorrect, and this confounder was not included in the analyses.

The dietary choices and caloric intake during pregnancy vary amongst women belonging to different *ethnic groups*. Also, this could indirectly be influenced by the women's pre-pregnancy BMI levels, partially contributed by genetics. Women in some ethnic groups, for example, Asian, Middle Eastern and African ethnic groups weigh heavier than women from other ethnicities, as they consume energy-dense foods and believe in the 'eat for two' phenomenon(Diana et al., 2018; Rahman et al., 2009). The dietary choices could, in turn, be associated with the birth outcome; where offspring of these ethnic groups with poor dietary choices are suggested to weigh less than the Caucasian population(Dominguez et al., 2008). Hence ethnicity can play both direct and indirect roles in influencing the dietary intake during pregnancy and birth outcomes. However, this variable was unavailable from DNBC and MoBa cohorts due to data privacy issues and was not included as a confounder in the models.

Figure 6: Directed acyclic graph (DAG model) for maternal dietary macronutrient intakes and change in birthweight

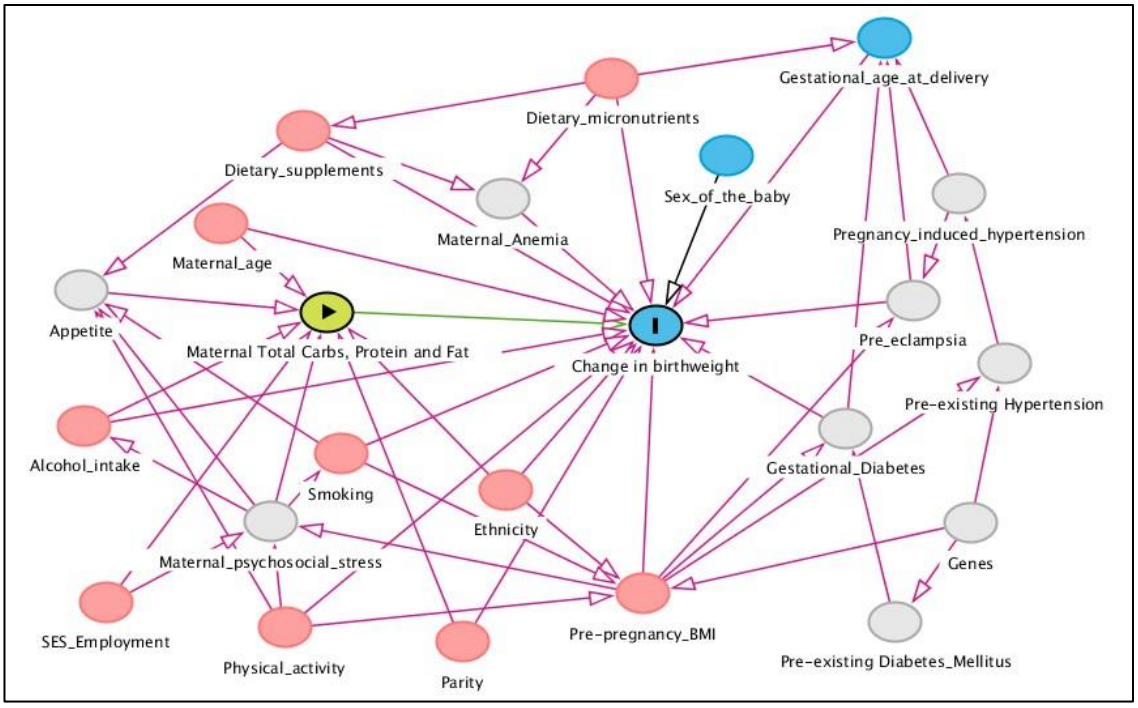


Figure 7: Directed acyclic graph (DAG model) for maternal dietary macronutrient intakes and odds of SGA babies

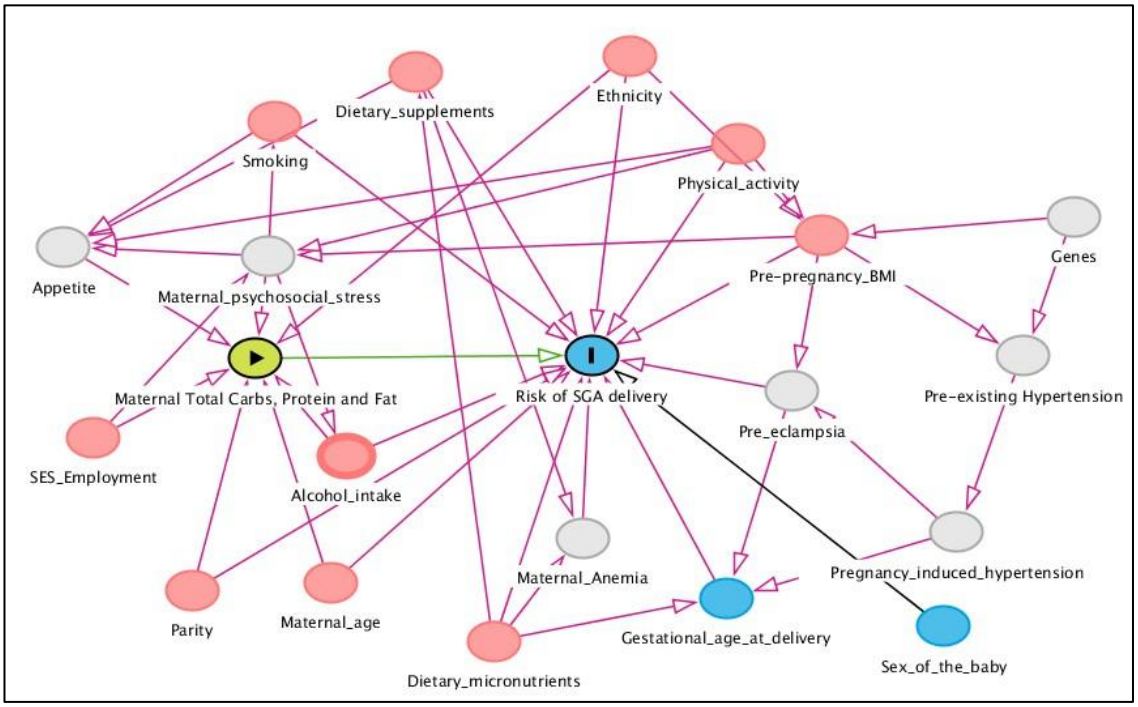
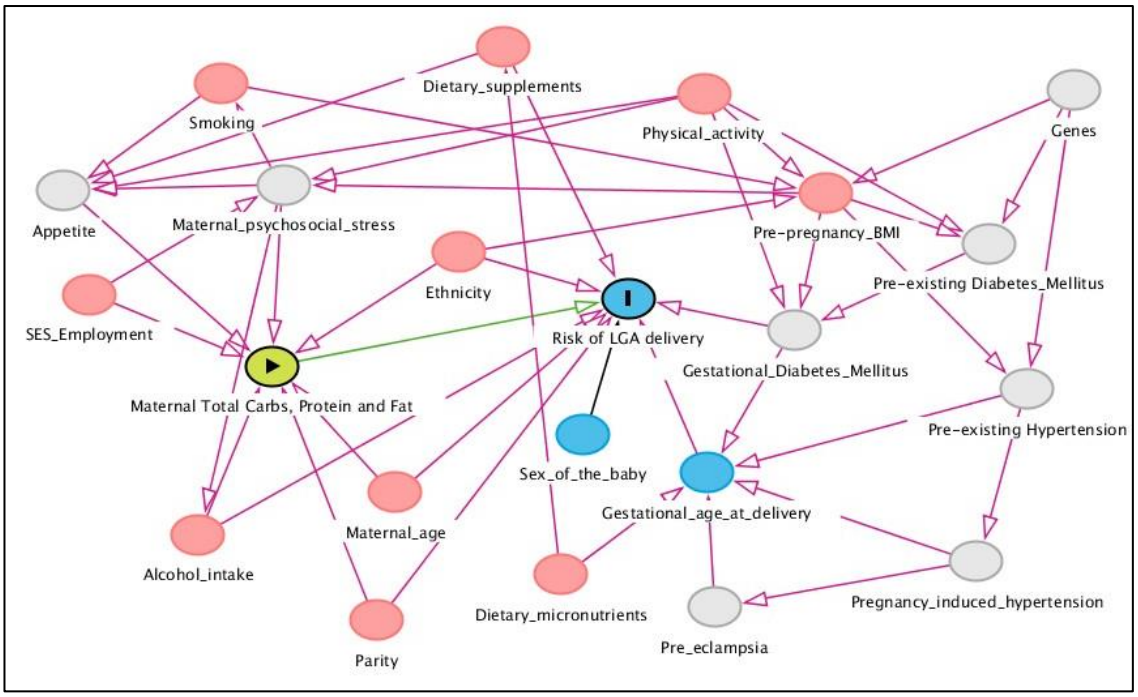


Figure 8: Directed acyclic graph (DAG model) for maternal dietary macronutrient intakes and odds of LGA babies



5.2.6.1 Data cleaning and harmonisation

Based on the set of confounders computed by DAG, variables which best represented the data of a given confounder were extracted from all three cohorts and were included as confounders for modelling. Since there are three outcomes of interest in this study: birthweight (g), odds of SGA and LGA babies, the regression models for all the outcomes are adjusted for the same set of confounders to maintain consistency, aid in better interpretation and because similar mechanisms were involved. The lowest common denominator approach was used where most common variables available in all three cohorts recorded in their simplest form were used for cohort-specific and meta-analysis. Further, categorical variables recorded with multiple categories were then simplified into lesser categories. For example, in the MoBa cohort, data on smoking variable was recorded as frequencies in 7 categories, which was then recoded and reduced to a 'yes/no' variable to match with the smoking variables available in the CARE and DNBC cohorts.

Certain variables used as confounders in the cohorts were 'recoded' (categories were combined into lesser categories) using Stata to make the inclusion of these variables consistent between cohorts for analyses. The description of the covariates after recoding is provided in turn below:

1. **Alcohol intake:** In MoBa, alcohol was recoded as a 'yes/no' question (categorical variable). In the CARE study, alcohol was recorded as alcohol units/day (continuous variable). In DNBC alcohol was recorded in glasses/week (continuous variable).
2. **Smoking habits:** In MoBa and DNBC smoking habits were recoded as a 'yes/no' question. In the CARE study, smoking habits were categorised into three categories: 'non-smoker', 'current smoker' and 'occasional smoker- previously smoked every day but do not smoke now.'
3. **Physical activity:** DNBC and MoBa recorded physical activity as a 'yes/no' variable. In CARE, physical activity was self-reported and recorded in three categories: 'no physical activity', 'light to moderate physical activity' and 'vigorous physical activity <20 minutes/day'.
4. **Use of dietary supplements:** Dietary supplements were comprised of iron, calcium, B12, and folate. In DNBC, the dietary supplements (categorical variable) were an aggregate of the individual dietary supplements which included both (yes, quantities known + yes, but quantities unknown). For unknown quantities of dietary supplements in DNBC, the mean quantities of the participants who reported the amounts were considered, assuming that their dietary supplement quantities would be similar. In

MoBa and CARE, the dietary supplements were recoded as a 'yes/no' question (categorical variable).

5. **Other continuous variables:** Maternal age (years), parity and pre-pregnancy BMI were recorded as continuous variables across all three cohorts.

5.2.7 Study outcomes

The analysis explored the association of maternal dietary macronutrients with three birth outcomes and was available amongst the three birth cohorts. The primary outcome is birthweight (g). Secondary outcomes are the odds of small-for-gestational-age (SGA) and large-for-gestational-age (LGA) babies. The results of the associations within the birthweight models will be interpreted in grams (g). A 'small-for-gestational-age' baby is characterised when an offspring is under $<10^{th}$ centile on the customised centile chart (Faraci et al., 2011). Whereas, a large-for-gestational-age baby is characterised when an offspring is above $>90^{th}$ centile on the customised centile chart (Aye et al., 2010; Norris et al., 2015).

5.2.7.1 Centile calculators

Exploring odds of SGA and LGA baby required the conversion of birthweight to centiles. Bulk centile calculators (BCC) from the GROW software by the Gestation Network (Perinatal-Institute, 2017) were used. The centiles calculators were developed according to the principles of the Gestation Related Optimum Weight (GROW) method, specifically for research purposes with large datasets(Gardosi, 2004; Gardosi et al., 1992). These free to use BCC are available in two forms: region-specific and country-specific centile calculators. Region-specific centile calculators are usually used for multiple large datasets having similar regional backgrounds, e.g., Northern/Southern Europe, and North/South America. Country-specific centile calculators are individually customised according to a particular country, which is available for 30 countries so far.

Global bulk centile calculators are computed from an international database with around 3 million births submitted from over 30 countries and 113 ethnic groups. The Perinatal Institute has anonymised databases from over 120 countries, including 104 ethnic groups. The chart calculators are regularly updated and are developed according to the different populations and countries depending on the availability of the databases from which coefficients are extracted. Database of each country was analysed to obtain a constant (centile) and coefficients for maternal height and weight, parity, gestational age at delivery, ethnicity and sex of the baby, using multiple regression techniques. According to the gestational network (Perinatal-Institute, 2017), coefficients for the respective regional analysis are provided for use as an approximation

if the coefficients are insufficient for the countries an ethnic groups. In cases where no ethnic/country of origin information is available, the application applies a global average coefficient.

For the SGA and LGA analysis in this chapter, region-specific bulk centile calculator (BCC) v8.0.2 (Northern Europe) was used to extract centiles, because the birth cohorts are from the U.K., Norway and Denmark. Keeping in mind the large sample size of three cohorts (CARE, DNBC and MoBa) in this analysis, it is necessary to use bulk centile calculators to determine if the offspring size at birth is at odds of an SGA or LGA baby based on the centile categorisation. The primary reason for using region-specific BCC is the study's primary objective: to explore results of the meta-analysis using three cohorts located in UK, Norway and Denmark in the North European region.

5.2.8 Statistical methods

Multiple linear regression models were used to explore the association between maternal dietary macronutrients as the exposure and birthweight (g) as the outcome as it was a continuous variable. For birthweight models, there were two models, Model 1 and Model 2. Model 1 adjusted for maternal age. Model 2 additionally adjusted for alcohol intake, smoking habits, parity, physical activity, dietary supplements, and pre-pregnancy BMI.

Multiple logistic regression models were used to investigate the association between maternal dietary macronutrient intake and the odds of SGA and LGA babies because SGA and LGA babies were binary outcomes. In the cohorts, the SGA and LGA data were recorded as categorical variables and were coded as '0' for control and '1' for case (case represents SGA or LGA baby). The logistic regression models will be interpreted as odds ratios. For odds of SGA and LGA baby models, there were two models, Model 1 and Model 2. Model 1 adjusted for maternal age. Model 2 additionally adjusted for smoking habits, alcohol intake, physical activity, and dietary supplements. However, Model 2 did not account for pre-pregnancy BMI and parity as the bulk centile charts already account for the two covariates in the GROW software. The estimates of the odds of SGA and LGA baby models will be expressed as odds ratio (OR).

The multiple linear and logistic regression models for each dietary macronutrient and birth outcomes were mutually adjusted for other energy contributing macronutrients. Also, models exploring maternal energy and birth outcomes did not adjust for alcohol intake as all the birth cohorts included energy from alcohol while computing total energy intake.

In order to better interpret the results and represent realistic changes in birthweight, increment units were determined for maternal dietary macronutrients. The increment units for the

maternal dietary macronutrients were as follows – CHO (an additional intake of 100 g/d), protein (an additional intake of 30 g/d), fat (an additional intake of 30 g/d), and total energy intake (an additional intake of 600 Kcal/d). The CHO increment (100g/d) was equivalent to 1SD, and protein and fat increments covered almost quarter of the SD range of the exposure. The standard deviations of the dietary macronutrients and energy were consistent across the three cohorts. The increment units of the dietary exposures were kept uniform amongst the cohort-specific analysis of the three cohorts, to combine the results using the meta-analysis method.

The study did not pool the data using data harmonisation techniques, instead only the common variables required for analyses were harmonised using the lowest common denominator approach to keep variables as similar as possible.

In this study a meta-analysis was undertaken by combining individual results from three birth cohorts. The analysis was conducted using the two-step individual participant data (IPD) meta-analyses. The two steps include: 1. conducting analyses within each birth cohort separately. 2. combining the individual results using the standard meta-analysis technique, i.e., a random effects model. This technique generated a combined estimate and a p value by including weights (odds ratios for SGA and LGA babies, and estimates and the standard errors for the birthweights) from all the cohort-specific results, therefore, providing an unbiased representation of the results. This is a more straightforward approach as it lowers the complexity of separating the variability within and in between each birth cohort, and therefore assists in interpreting the results more clearly. A detailed comparison between the one-step and two-step approach is given in the Discussion section under 5.4.2.

Combining the results can be conducted using two types of meta-analysis: 1. fixed effects models 2. random effects models. In this meta-analysis, random effects assumption was used for combining the cohort-specific results because the effect sizes of the birthweight, and odds of SGA and LGA regression models within each birth cohort were different from each other(Bravata and Olkin, 2001). Whereas, the fixed effects models would have been suitable if the effect sizes of the birthweight, and SGA and LGA models were the same amongst all three cohorts(E. Hunter and Schmidt, 2002).

Secondly, random effects model accounted for heterogeneity between the three birth cohorts. The heterogeneity in meta-analysis is the variation observed in study outcomes between birth cohorts. The I^2 statistic provides the percentage of variation across birth cohorts which is due to heterogeneity rather than by chance, and represents the overall inconsistency in between birth cohorts (Higgins and Thompson, 2002; Higgins et al., 2003).

The meta-analysis results are presented individually for each macronutrient and total energy intake with a combined estimate (95% confidence interval) and p value. Also, the heterogeneity between the cohort-specific estimates was assessed using the I^2 statistic (%). The forest plots are presented for each macronutrient result and denote the weights contributed by each birth cohort.

The DNBC, MoBa and CARE datasets satisfied the validity of the assumptions of normality and variance. Due to the large sample size the datasets were not formally tested for assumption. However, the test of normality was conducted using histogram plots which showed a normal distribution (a bell shaped curve) for the dietary macronutrients, energy and birthweights in the three birth cohort datasets.

The statistical significance was set at $p<0.05$. All analyses in this chapter were done using Stata SE/14.2 version.

5.3 Results

The meta-analysis results of the adjusted models are presented for a total sample of 149,927 mother-infant pairs. In addition, the cohort-specific results are presented individually for the associations between dietary macronutrient intakes during the second trimester of pregnancy and birth outcomes amongst the DNBC, MoBa and CARE birth cohorts. Also, amongst cohort-specific results, within the CARE cohort, there was no evidence of an association observed between maternal dietary macronutrients and energy, and birth outcomes.

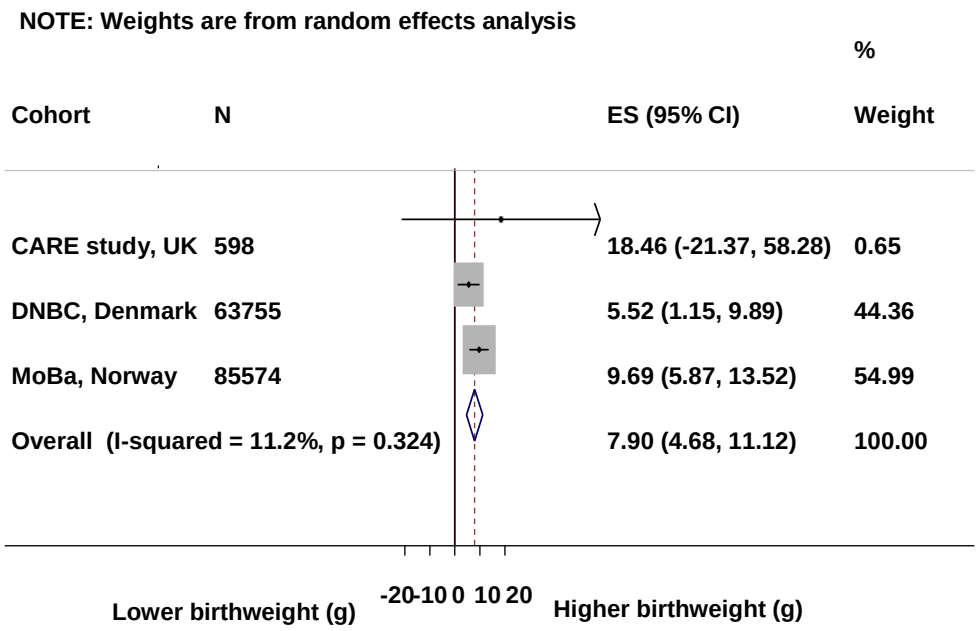
5.3.1 Meta-analysis results for the adjusted associations between maternal dietary macronutrient consumption and birthweight

5.3.1.1 Maternal energy intake and birthweight

In the combined-effect size meta-analysis results for DNBC, MoBa and CARE an additional energy intake of 600 kcal/d was positively associated with a higher birthweight (8g, 95% CI 5g to 11g; I^2= 11%, combined p value<0.001) (Refer Figure 9 for forest plot).

Amongst cohort-specific results, an additional intake of 600kcal/d was positively associated with high birthweight in DNBC (6g, 95% CI 1g to 10g; p value=0.01) and MoBa (10g, 95%CI 6g to 14g; pvalue <0.001), but not in CARE.

Figure 9 Forest plot for the association between maternal energy and birthweight

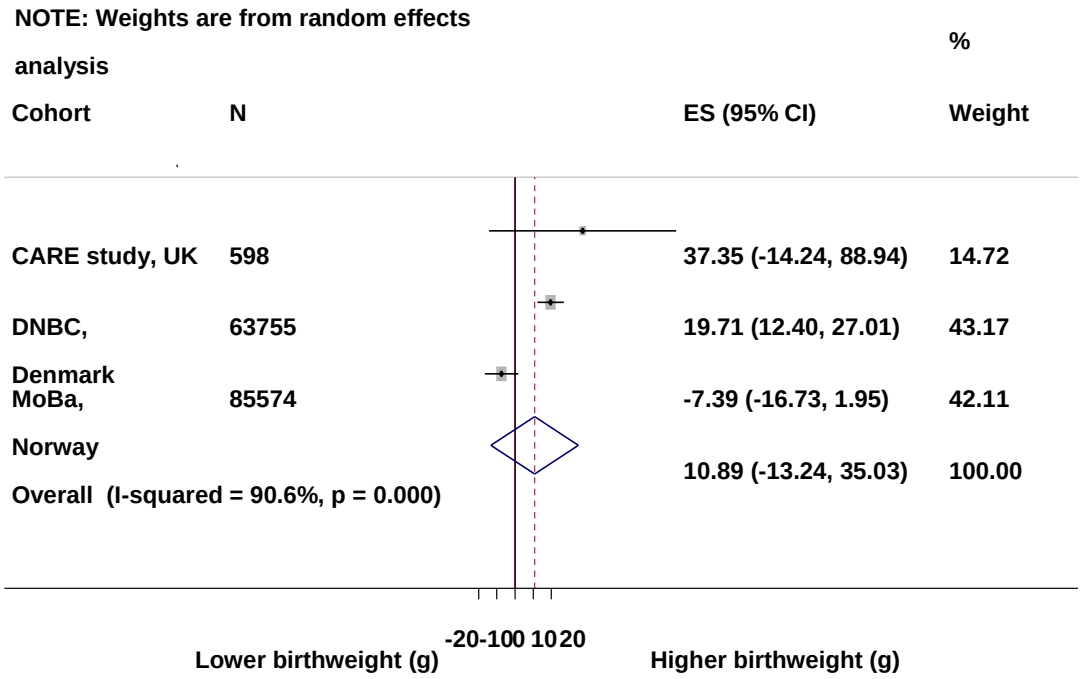


5.3.1.2 Maternal dietary CHO and birthweight

Amongst the meta-analysis results of the maternal CHO intakes, there was no evidence of an association between an additional CHO intake of 100g/d and change in birthweight (11g, 95% CI -13g to 35g; I^2= 91%, combined p value=0.37) (Refer Figure 10 for forest plot).

Amongst cohort-specific results for maternal dietary CHO, within DNBC, an additional CHO intake of 100g/d was positively associated with higher birthweight (20g, 95% CI 12g to 27g; p value<0.001).

Figure 10 Forest plot for the association between maternal CHO and birthweight

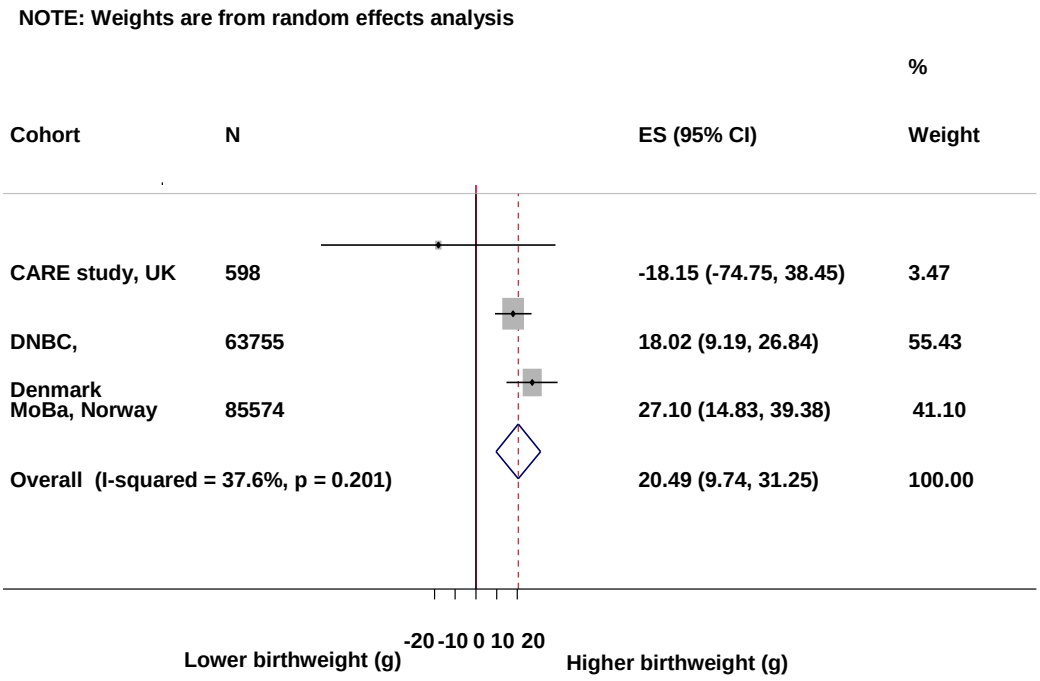


5.3.1.3 Maternal dietary protein and birthweight

Amongst the meta-analysis results for maternal dietary protein, an additional protein intake of 30g/ was positively associated with higher birthweight (20g, 95% CI 10g to 31g; I^2= 38%, combined p value<0.001) (Refer forest plot in Figure 11).

Amongst cohort-specific results, there was a positive association observed between an additional protein intake of 30g/d and high birthweight amongst DNBC (18g, 95% CI 9g to 27g; p value<0.001) and MoBa (27g, 95% CI 15g to 40g; p value<0.001)

Figure 11 Forest plot for the association between maternal protein and birthweight

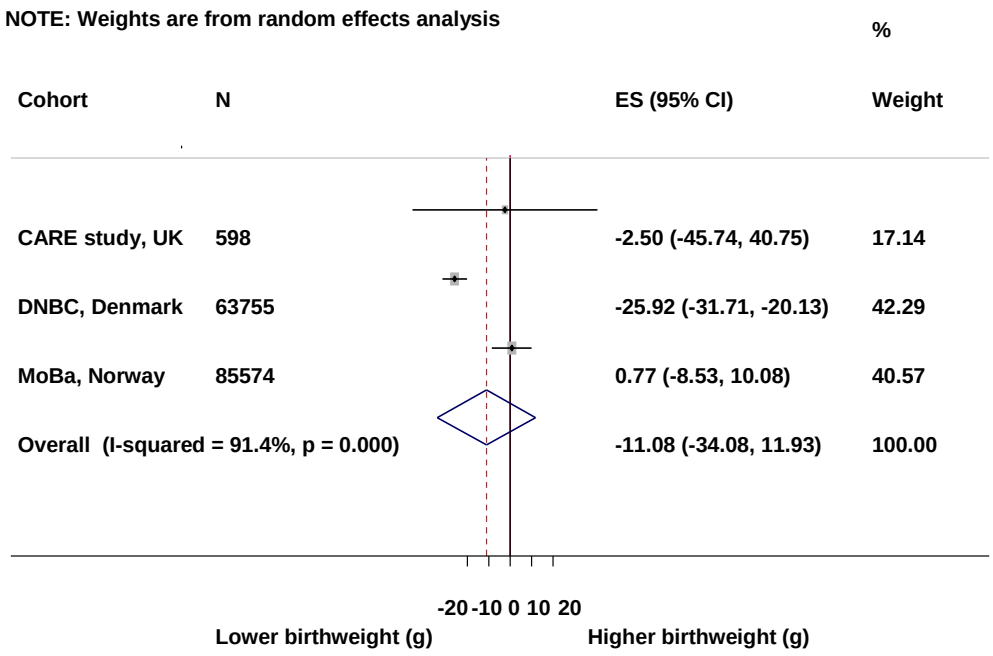


5.3.1.4 Maternal dietary fat and birthweight

The combined effect size for maternal fat intakes gave no evidence of an association between an additional fat intake of 30g/d and change in birthweight (11g, 95% CI -34g to 12g; I^2= 91%, combined p value=0.34) (Refer forest plot in Figure 12).

Amongst cohort-specific results, in DNBC, an additional fat intake of 30g/d was negatively associated with birthweight (26g, 95% CI 20g to 32g; p value<0.001).

Figure 12 Forest plot for the association between maternal fat and birthweight

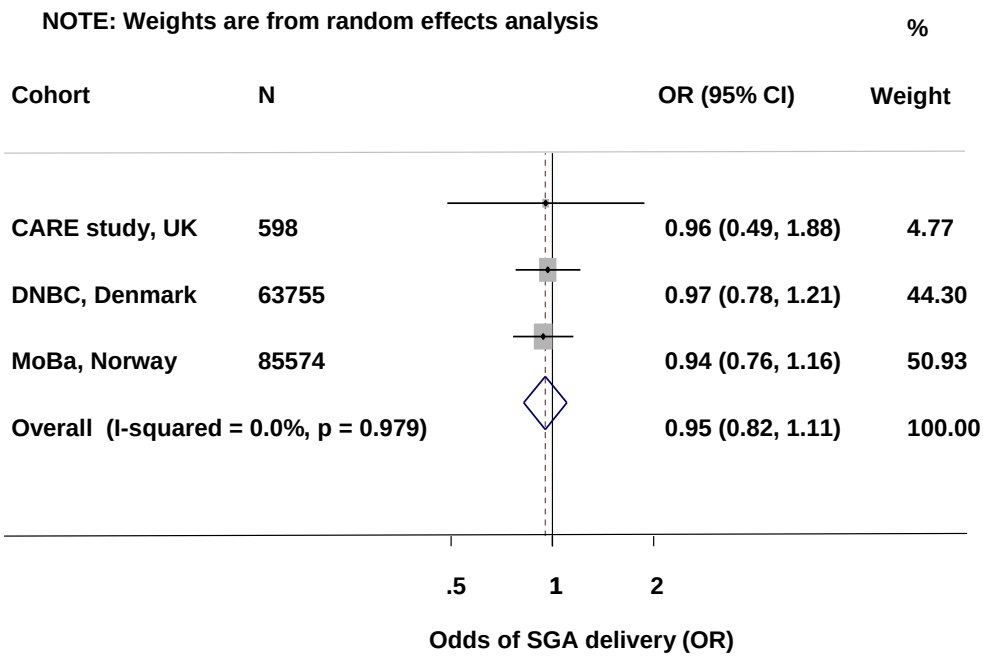


5.3.2 Meta-analysis results for the associations between maternal dietary macronutrient consumption and odds of SGA baby

5.3.2.1 Maternal energy and odd of SGA baby

In the meta-analysis, there was no evidence of an association observed between the additional energy consumption of 600 kcal/day and odds of SGA baby (Refer forest plot in Figure 13). Amongst cohort-specific results for odds of SGA baby, a negative association was observed between additional energy intakes of 600 kcal/d and odds of SGA baby in DNBC (adjusted OR 0.97, 95% CI 0.94 to 0.99; p value=0.01) and MoBa (adjusted OR 0.93, 95% CI 0.91 to 0.96; p value<0.001), respectively (Refer Table 20 and forest plot in Figure 13).

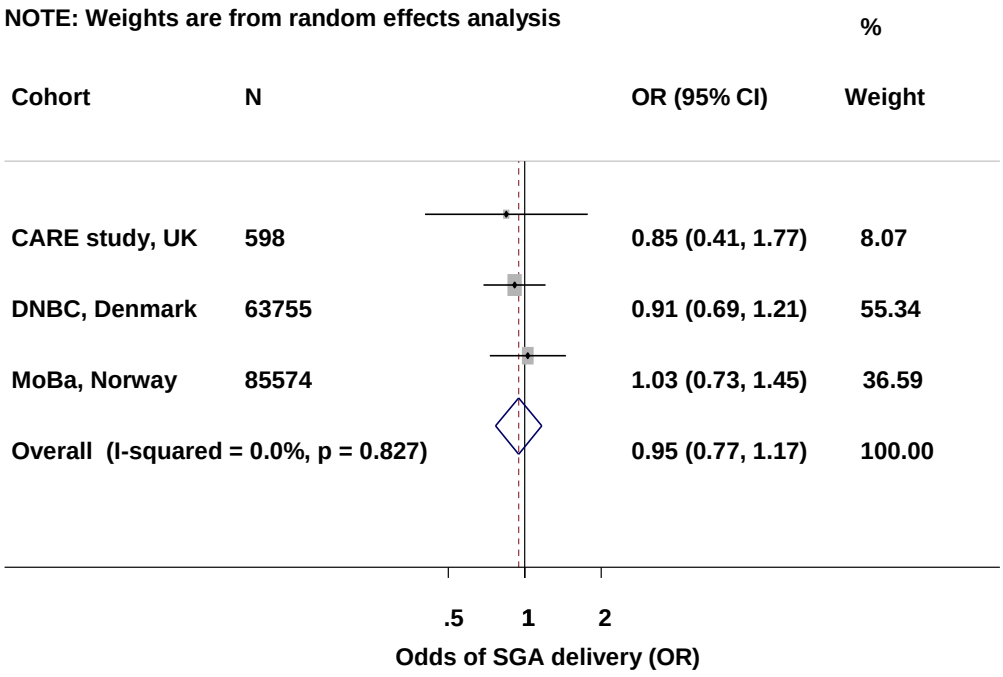
Figure 13 Forest plot for the association between maternal energy and odds of SGA delivery



5.3.2.2 Maternal dietary CHO and odds of SGA baby

In the meta-analysis, there was no evidence of an association observed between an additional CHO intake of 100 g/day and odds of SGA baby (Refer forest plot in Figure 14). However, in DNBC, an additional CHO intake of 100g/d was negatively associated with low odds of SGA baby (adjusted OR 0.91, 95% CI 0.87 to 0.95; p value<0.001).

Figure 14 Forest plot for the association between maternal CHO and odds of SGA delivery

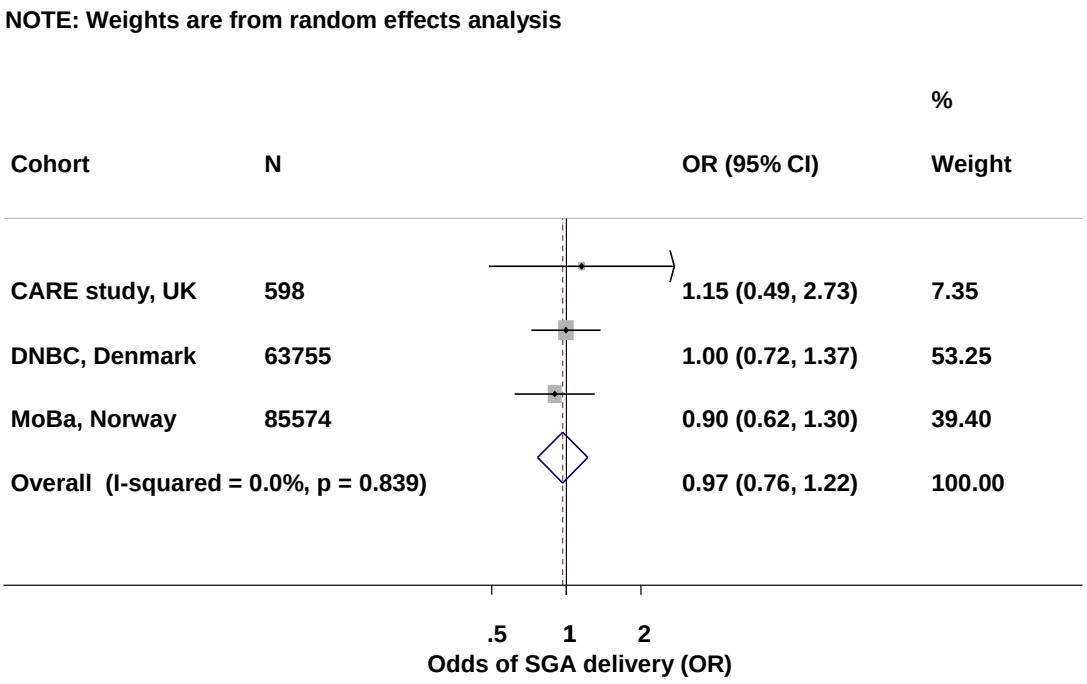


5.3.2.3 Maternal dietary protein and odds of SGA baby

In the meta-analysis, there was no evidence of an association observed between an additional protein intake of 30 g/day and odds of SGA baby (Refer forest plot in Figure 15).

However amongst cohort-specific results, in MoBa an additional protein intake of 30g/d was negatively associated with low odds of SGA baby (adjusted OR 0.89, 95% CI 0.82 to 0.96; p value=0.006).

Figure 15 Forest plot for the association between maternal protein and odds of SGA delivery

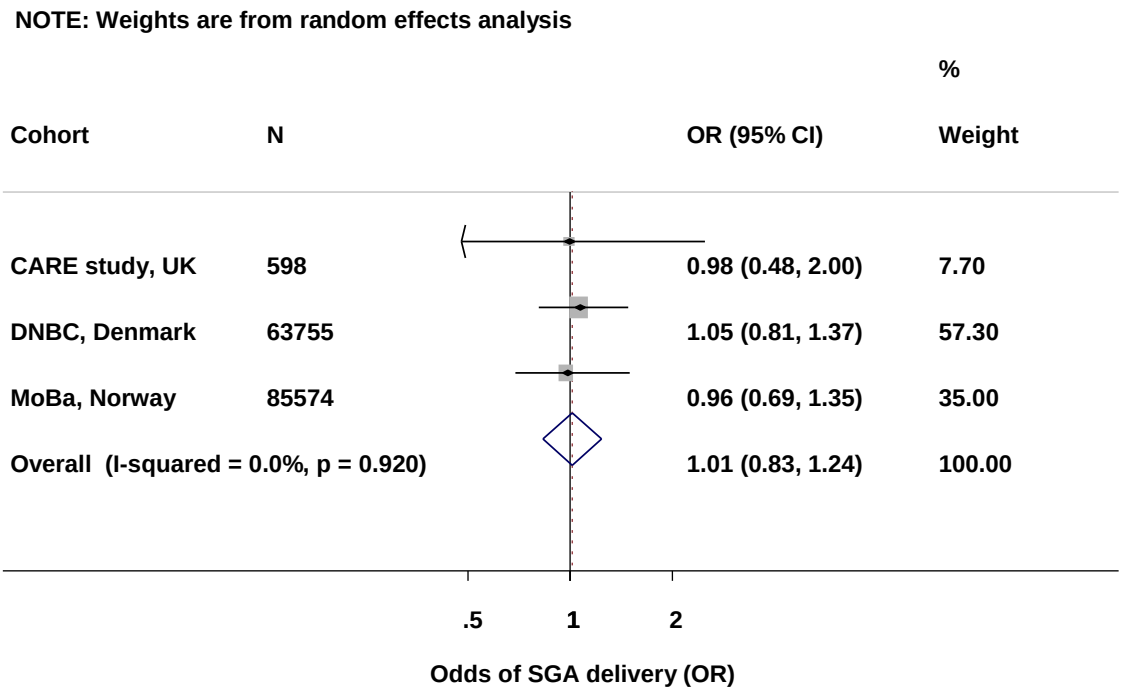


5.3.2.4 Maternal dietary fat and odds of SGA baby

There was no evidence of an association between an additional intake of fat 30g/d and the odds of SGA baby in the meta-analysis (Refer forest plot in Figure 16).

However amongst cohort-specific results, in DNBC, an additional fat intake of 30g/d was positively associated with a high odds of SGA baby (adjusted OR 1.05, 95% CI 1.01 to 1.08; p value=0.004).

Figure 16 Forest plot for the association between maternal fat and odds of SGA delivery

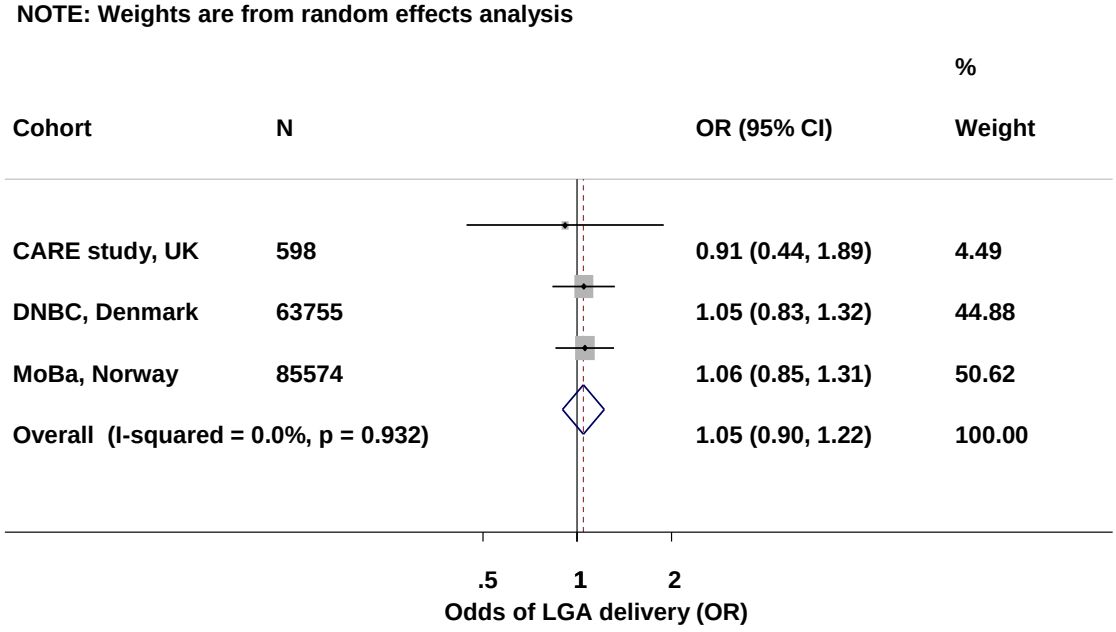


5.3.3 Meta-analysis results for the adjusted associations between maternal dietary macronutrient consumption and odds of LGA baby

5.3.3.1 Maternal energy and odds of LGA baby

In the meta-analysis results, there was no evidence of an association observed between an additional energy consumption of 600 kcal/day and odds of LGA baby (Refer forest plot in Figure 17). Amongst cohort-specific results for the odds of LGA baby, a positive association was observed between an additional energy intake of 600 kcal/d and odds of LGA baby in DNBC (adjusted OR 1.04, 95% CI 1.02 to 1.07; p value<0.001) and MoBa (adjusted OR 1.05, 95% CI 1.03 to 1.08; p value<0.001), respectively.

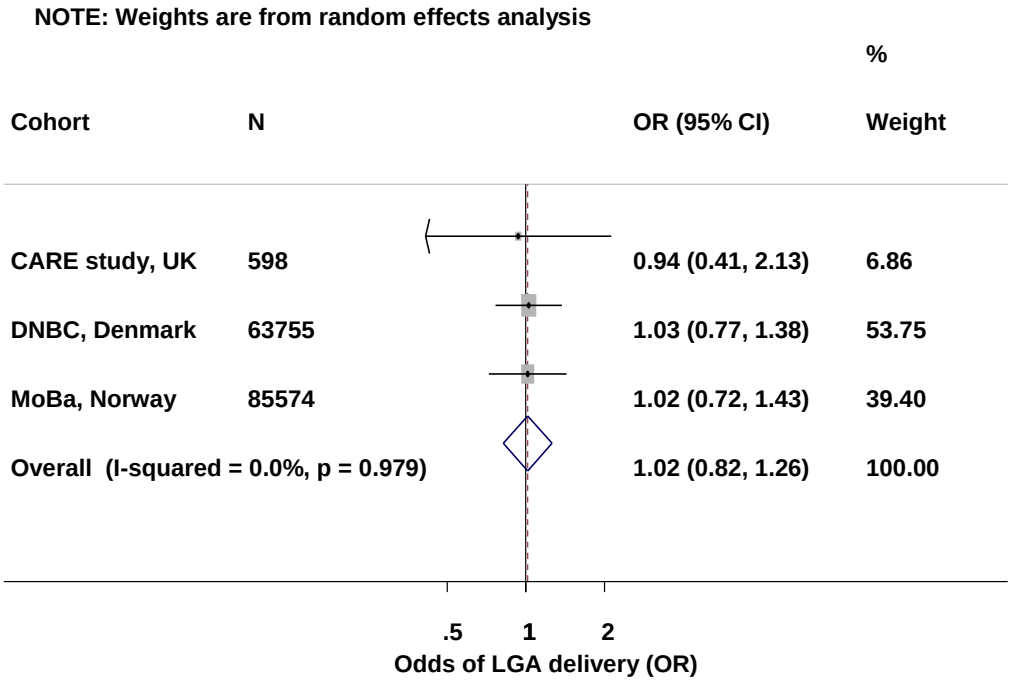
Figure 17 Forest plot for the association between maternal energy and odds of LGA delivery



5.3.3.2 Maternal dietary CHO and odds of LGA baby

Amongst the meta-analysis results, there was no evidence of an association observed between an additional CHO intake of 100 g/day and odds of LGA baby (Refer forest plot in Figure 18). Also, amongst the cohort-specific results, there was no evidence of an association between higher CHO intakes and odds of LGA baby.

Figure 18 Forest plot for the association between maternal CHO and odds of LGA delivery

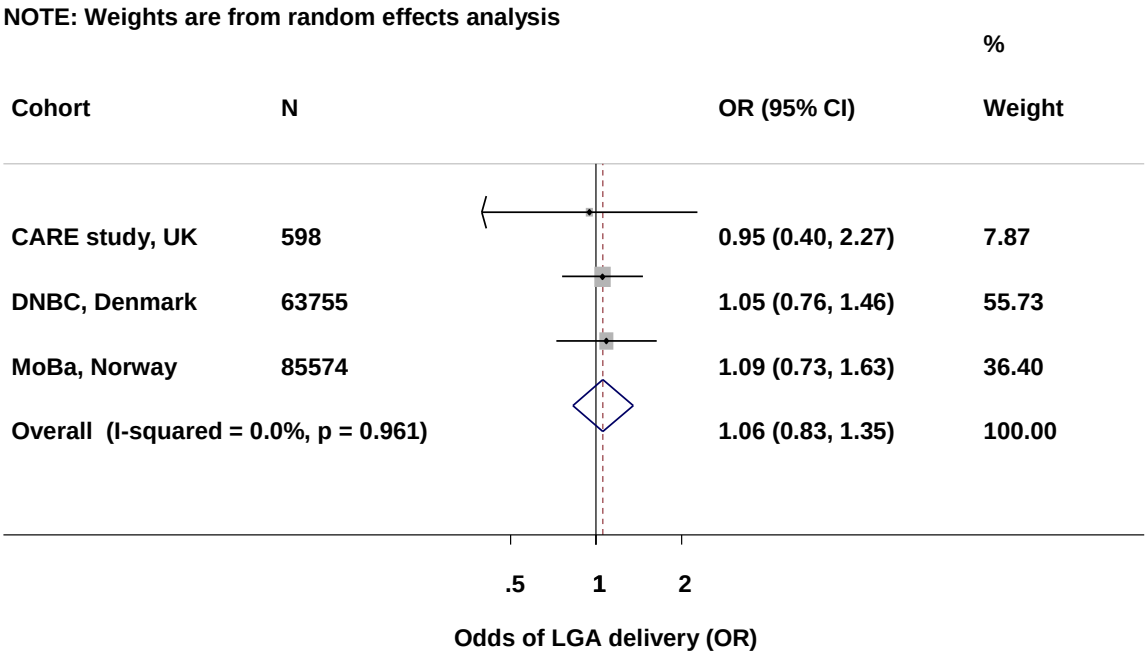


5.3.3.3 Maternal dietary protein and odds of LGA baby

Amongst the combined results for the odds of LGA baby, there was no evidence of an association observed between an additional protein intake of 30 g/day and odds of LGA baby (Refer forest plot in Figure 19).

However amongst cohort-specific results, additional protein intakes of 30g/d was positively associated with high odds of LGA baby in DNBC (adjusted OR 1.05, 95% CI 1.00 to 1.11; p value=0.04) and (adjusted OR 1.08, 95% CI 1.00 to 1.17; p value=0.03) MoBa.

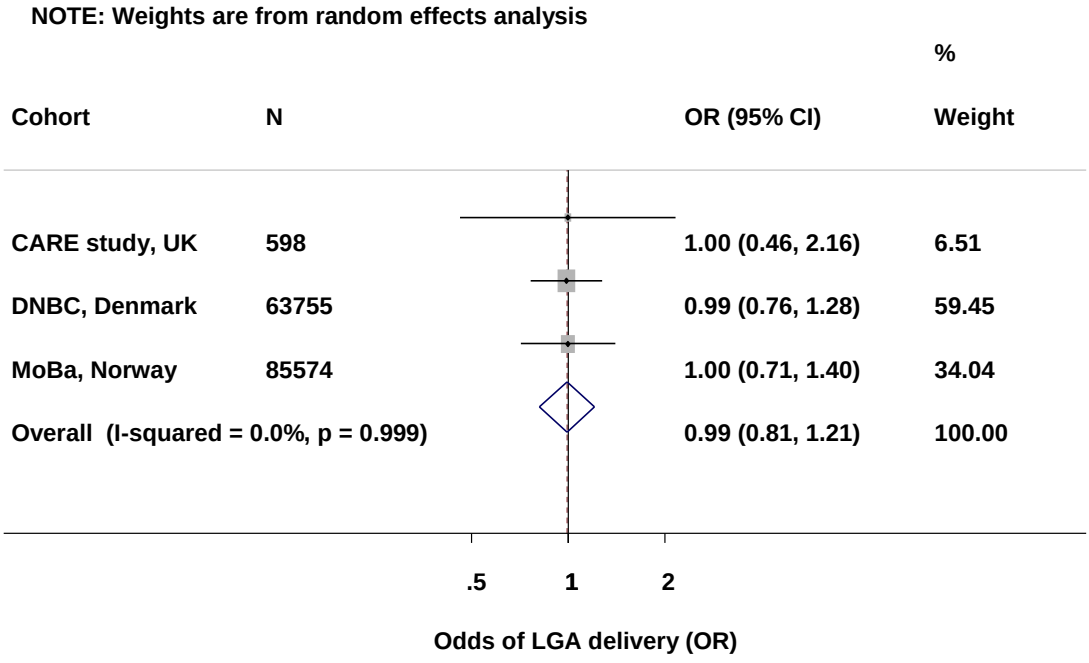
Figure 19 Forest plot for the association between maternal protein and odds of LGA delivery



5.3.3.4 Maternal dietary fat and odds of LGA baby

There was no evidence of an association between an additional intake of fat 30g/d and the odds of LGA baby in the meta-analysis and in the cohort-specific results (Refer forest plot in Figure 20).

Figure 20 Forest plot for the association between maternal fat and odds of LGA delivery



5.4 Discussion

The current study explored and demonstrated the associations between maternal dietary macronutrient intake and birth outcomes amongst a large meta-analysis cohort study, which consisted of 149,927 mother-infant pairs. The results apply to the Northern European region as the study included birth cohorts from Denmark, Norway and the United Kingdom.

The meta-analysis results demonstrated that amongst macronutrients, additional intakes of protein was associated with heavier offspring. It must be noted that these results had statistical significance and no clinical significance. When total energy intake was examined, it could be inferred that higher energy intakes were associated with heavier offspring at birth. The positive direction of the association of the combined energy intake with birthweight was only supported with the results of protein.

5.4.1 Comparison with other studies

Previous meta-analyses of cohort studies were based on individual food intakes in the diet example, fish intakes in pregnancy and child outcomes (Stratakis et al., 2016), individual micronutrients, including folate intakes in pregnancy and health outcomes (Fekete et al., 2012) or have explored maternal diseases including maternal Malaria and its fetal effects(Unger et al., 2016). But so far there is no meta-analysis exploring the maternal dietary macronutrient intake in pregnancy on birthweight.

This is the meta-analysis of cohort studies to demonstrate associations between maternal dietary macronutrients and offspring birth outcomes using large sampled birth cohorts across the Northern parts of the European continent. The exploration of this study provides advanced understanding regarding the individual contributions of macronutrients eaten during pregnancy on fetal outcome.

The combined effect size observed in this study for protein are consistent with previous observational studies. Similar results have been observed in an Australian study (Moore et al., 2004) of 557 pregnant women where the study suggested that adequate amounts of protein is required to support rapid fetal growth during the second and third trimesters. They also adjusted their regression models for similar confounders and presented results for protein as a percentage of energy (%E). Also, a Spanish study (CucÓ et al., 2006) of 77 pregnant women suggested that higher protein intake was positively associated with fetal growth size around 10^{th}, 26^{th} and 30^{th} weeks of pregnancy after adjusting for a similar set of covariates. Moreover, this further supported the results observed from the current meta-analysis because the

maternal protein intakes were assessed using FFQ with similar gestational periods, i.e., around 23rd-26th weeks of pregnancy amongst the three cohorts.

However, one study (Lagiou et al., 2004) of 224 pregnant women suggested no association between macronutrient increments and birth size, but this could be partly because of their choice of covariates added in the regression models. They adjusted the macronutrient models for gestational age at delivery, sex of the baby and oral contraceptive pills which are indirectly associated with only the birth size and not the maternal macronutrient intakes, and can be termed as 'competing exposures' introducing confounding bias.

One of the reasons for the result observed in the current study could be the metabolic adaptations of the mother's protein stores in order to enable adequate placental amino acid utilisation and amino acid transport to the fetus. During pregnancy, the maternal liver breaks down the protein into amino acids, which are then placentally transferred to the fetus for cell growth promoting tissue formation. Higher protein intake could mean that higher circulation of amino acids, for example, glutamine (important for the gut and the immune function) could get placentally transferred. Fetal hepatic uptake of glutamine is the highest of any other amino acid. Almost, 45% of glutamine is converted to glutamate in the fetal liver and returns to the placenta where it is used as a source of energy to support rapid growth (Robinson and Prendergast, 1996).

Further, dietary protein is necessary to support the physiological functions in the mother and the fetus for healthy birth outcomes. These include the tissue and muscle formation of the fetus, generation of the placenta and amniotic sac, where it helps in hematopoiesis, i.e., the formation of blood cells in the mother and the fetus, which is in turn required for the increased maternal blood volume. Also, it is essential for the production of maternal hormones including estrogen, progesterone, human placental lactogen (hPL) and human chorionic gonadotropin (hCG), fetal skeletal formation, and strengthening the fetal immunity.

Amongst meta-analysis results for dietary CHO and fat, there was no evidence of an association with birth outcomes. However, there were associations amongst cohort-specific results.
In DNBC, additional intakes of CHO were associated with bigger babies and low risk of SGA babies, whereas, additional intakes of fat were associated with smaller babies and a high risk of SGA babies. These results in DNBC are consistent with the previous results of the CARE study in section 4.3.1 of Chapter 4. The common perception that if the mothers eat foods high in fat, they are more likely to deliver heavier babies could be questioned after the results in this study. However, various explanations could be given for this phenomena to occur. Women with higher pre-pregnancy BMI might under-report their dietary fat intakes in the dietary recalls and FFQ

and therefore, this might have contributed to lower birthweights (Black and Cole, 2001; Johansson et al., 1998; McGowan and McAuliffe, 2012).

Further, the type of dietary fat also plays an important role in the association with offspring weight. The CARE study examined the role of dietary fat components, including PUFA, MUFA and SFA, and observed that dietary PUFA and SFA were associated with lowered birthweights (refer Chapter 4 under section 4.3.2 of results). Previous studies have suggested that the type of fat affects the direction of the association and reported that PUFA's 'anti-obesogenic' mechanism might explain for the negative association (Blumfield et al., 2012; Newman et al., 2002; Nuernberg et al., 2011).

Furthermore, it might be that during the second trimester the mother's hepatic stores of fatty acids cater to the mother's lipid requirement and immediately transfer the fatty acids to the mother and lower the rate of placental transfer of fatty acids to the fetus. This might be due to the action of the important role of the hormone- human placental lactogen (hPL)(Butte, 2000; Kumar and Magon, 2012).

In the meta-analysis, the CARE results did not demonstrate any evidence of any association because it had a small sample size (n=598) as compared to DNBC and MoBa, therefore it might be unlikely to influence the overall results. and the CARE confidence intervals were wider as compared to the DNBC (n=63,755)and MoBa (n=85,574) results. The CARE study the associations in the meta-analysis were consistent with the results in Chapter 5, despite adjusting for a different set of covariates in the current study as compared to the individual analysis in Chapter 5.

It is important to acknowledge that the meta-analysis results had high heterogeneity, despite including birth cohorts with similar study designs, dietary intakes and populations from the North European region. It is essential to consider it by measuring the overall variance across the birth cohorts rather than assume that it occurred by chance. According to (Higgins et al., 2003), heterogeneity of meta-analysis studies has been classified in 4 categories (I^2 =25% is low, I^2 = 50% is moderate, I^2 = 75% and above is high). The heterogeneity levels for combined maternal energy (I^2 =11%) and protein (I^2 =38%) intakes have low to moderate heterogeneity levels. The I^2 statistic was as high as 92% in some combined regression models describing the large variance of the dietary macronutrient consumptions, for example, fat (I^2 = 91%) and CHO (I^2 = 92%) across each birth cohort. The Higgins study (Higgins et al., 2003) suggested that nearly a quarter of the meta-analysis from the Cochrane database had heterogeneity (I^2) over 50%. Although random effects models were used in the meta-analysis, which accounted for large variance between the birth cohorts and were based on the assumption that each cohort will have

different estimate sizes, high heterogeneity (I^2) was observed (DerSimonian and Laird, 1986). Heterogeneity is inevitable when several birth cohorts are combined to give a combined result, and it would be otherwise surprising to observe low heterogeneity levels with similar estimates and low variance between each birth cohort.

This might have occurred due to different reasons. According to Haidich (Haidich, 2010), results from a combined meta-analysis with lesser number of individual studies have high levels of heterogeneity. The current study included only three birth cohorts for the meta-analysis. Therefore, lower heterogeneity could have been observed if more cohorts were included. However, data was only available for the three birth cohorts to conduct analyses.

Further, there might be other reasons relating to the cohort methodologies. First, the dietary data was recorded in different ways amongst all three birth cohorts. DNBC and MoBa recorded diets through self-administered FFQ, and CARE recorded diets via a self-administered 24-hour dietary recall. The nutrient intakes were computed and extracted using different software, MoBa and DNBC used FoodCalc, whereas CARE extracted nutrient intakes using DANTE software. Also, each birth cohort used country-specific dietary composition tables varying in standard portion sizes and types of foods and recipes included. Using traditional dietary recording methods might have resulted in inaccurate estimates of nutrient intakes with problems including estimations of portions sizes and limited availability of food composition tables as compared to computerised dietary techniques (Cade et al., 2017; Eldridge et al., 2018).

Second, the FFQ structure differed within MoBa and DNBC where MoBa' FFQ included food items questions which were extensive and recorded the data in detail. Although both cohorts designed the FFQ around the same period considering the scope of future collaborations, the MoBa FFQ included generic foods and recorded the food items in frequencies, omitting portion sizes for most foods. Whereas, DNBC did not include generic foods and only included new recipes and estimated the portion sizes based on the participants' description. The gestational periods within DNBC and MoBa were also different when study design is considered (details of comparison available under section 3.2 of Chapter 3). The CARE data's study design was different from the MoBa and DNBC. In CARE the diets were recorded twice, in trimester 1 and 2 using 24-hour dietary recalls administered by a trained research midwife.

Third, the size of the CARE study was small, with a sample size for trimester 2 (n=598) as compared to the DNBC (n=63,755) and MoBa (n=85,574) cohorts.

Fourth, the covariates were measured in different formats within each birth cohort requiring the lowest common denominator approach to be used to tackle it.

This analysis was undertaken for women with a healthy pregnancy with no co-morbidities and pregnancy risks. Considerations were given whether to include 'pregnancy risk' including pregnancy-induced hypertension (PIH) and gestational diabetes mellitus (GDM) as a covariate, but they were not considered appropriate for this analysis. This was because women with pregnancy risks, for example, gestational diabetes require special dietary attention and have other factors which could influence the results, for example, medications. Even if these variables were included as covariates, it would have introduced the risk of confounding bias for the same reason. Also, pregnancy risk data was only available within the MoBa cohort. DNBC cohort did not disclose this data, and so it was not possible to include these as a variable in the meta-analysis.

Replacing missing values to '0' was used instead of multiple imputations. meta-analysis. Cleaning the energy consumption variable by keeping the range broad, i.e. 600-6000 kilocalories was appropriate to account for pregnancy conditions that influence the dietary intakes amongst pregnant women including, morning sickness, hormones (leptin and cortisol) that influence low and high appetite levels, gastric-oesophagal reflux and heartburn. If a narrower calorie intake range was considered for analysis, for example, 1720-2800 kcal/day (Moore and Davies, 2005; Moore et al., 2004) and 1000-4000 kcal/day (Knudsen et al.,2013)DNBC, then the energy intake range would be too tight and the analysis sample size would have lost around 40% of the participants.

Directed acyclic graphs (DAG) were considered in the analysis in order to include relevant covariates for increasing the robustness of the regression models and preventing confounding bias. This was a suitable method over the traditional methods which are less efficient in identifying a correct set of potential confounders because they invariably introduce the risk of bias and imply causality to results. In an attempt to reduce the potential bias, DAG models have been introduced to have a logical and directed approach which lessens the chances of overestimation or bias while interpreting the results (Shrier and Platt, 2008). This technique was useful amongst this study as it is a large sample size where there is always a potential likelihood for assuming causality which could be controlled and minimised, in order to interpret the results as associations.

The birth outcomes- the birthweights (g) and odds of an SGA and LGA baby were selected in the analysis because they are easier for interpretation through the statistical models, and have relevant clinical significance. The risk of SGA and LGA babies were selected because of two reasons: 1. They represent and cover birth outcomes on both extreme ends of the birth size spectrum. Thus, the presentation of results for odds of SGA and LGA babies provide a broad

representation and the results presented as odds ratios (OR) could be clinically important. Further, they might be important especially in the SGA baby risk cases where the offspring has to undergo a 'catch-up growth' phase where it has to make up for the lost time and grow at a higher velocity for optimum growth levels as compared to the normal birthweight offspring who are at a better starting point (Prader, 1978). 2. Association between maternal dietary macronutrient intakes and odds of SGA and LGA baby outcomes has not been widely explored. Most studies have explored birthweights (Brantsæter et al., 2012; Chong et al., 2015; CucÓ et al., 2006; Lagiou et al., 2004; Moore et al., 2004; Olsen et al., 1986), ponderal index(Andreasyan et al., 2006; Chong et al., 2015; Moore et al., 2004), birth length (Chong et al., 2015; Lagiou et al., 2004) and neonatal adiposity (Chen et al., 2016).

The data from the three birth cohorts was harmonised by using the lowest common denominator approach but was not pooled together. The cohort-specific results were combined using the random effects meta-analysis.

MoBa and DNBC used the North European region-specific bulk centiles calculators. However, the CARE study used the UK region-specific bulk centile calculators to extract birth centiles. Despite this fact, it might be argued that given the geographical location of U.K, the centile coefficients might not be too different from its Northern European counterparts: Norway and Denmark. Also, for CARE centiles, the centile coefficient would be approximate of other regional specific countries and considering the sample size of CARE (n=578), the contributing effect of this cohort's centile approximation would be considerably low in the combined SGA and LGA results.

Also, by using the regional specific BCC (Northern Europe), we assumed the mean macronutrient intakes and the characteristics of the participants in both cohorts were similar. In addition, they were similar to the CARE cohort's participants. Moreover, the mean birthweights and absolute percentages of SGA and LGA babies were similar amongst all three birth cohorts. Hence based on the assumption that the macronutrient dietary intakes and birth outcomes are more or less similar across the Scandinavian region and the U.K region, it was thought to be appropriate to consider using regional specific centile charts instead of country-specific centile charts to combine results from all three birth cohorts.

5.4.2 Strengths and limitations

Actual data from large sample sized cohorts of DNBC and MoBa were available for analyses instead of using published values. Also, reasonable steps were undertaken to minimise excluding participants from the analyses.

The combined results of this study could indirectly represent the remaining countries from the Northern Europe as it included birth cohorts of high statistical power from Norway, Denmark and UK. The choice of birth outcomes in this study covers both extreme ends of the birth size spectrum.

This study presented results using appropriate increment rates which represented realistic and achievable changes in birthweight which could be clinically important. The increment rates for CHO and energy were equivalent to 1SD, and the increment rates of protein and fat covered more than quarter of the range of the dietary exposure. The increment rates of the current study's results were better than the CARE study analysis as they provided a SD range to allow for reasonable comparison of the differing maternal macronutrient intakes (Lagiou et al., 2004).

Despite logistical constraints amongst the birth cohorts maternal dietary data were adequately analysed using validated FFQ and 24-hour dietary recalls, and nutrient intakes were extracted using dietary software and updated country-specific food composition tables.

Individual participant data (IPD) meta-analysis was used in this study with three birth cohorts as compared to a systematic review of the aggregated data meta-analysis. This was preferred because the regression models using actual data could be standardised across all birth cohorts with directly deriving the information required to conduct analyses. The inclusions, exclusions could be kept consistent across all cohorts, and missing data could be dealt at individual cohort level. Further, the IPD meta-analysis is flexible as it facilitates in-depth analysis by considering more number of outcome variables as compared to published data meta-analysis, and avoids reliance on published results. Furthermore, conducting an IPD meta-analysis is suitable if there is direct access to raw data of high sample sized cohorts. However, IPD meta-analysis has two disadvantages: 1. it is time-consuming and 2. It requires extensive data cleaning within each birth cohort (Riley et al., 2010).

The IPD meta-analysis could be conducted using two methods: 1. one-step approach. 2. two-step approach. In the one-step IPD approach, data pooled from three birth cohorts is included in a single mixed effects model to separate within and in between study variability (Riley et al., 2010). This study did not pool the data from three birth cohorts. Instead the study used a two-step IPD meta-analysis to combine individual cohort results from a random effects model. The method for two-step IPD approach is described under Section 5.2.8 in Statistical methods. However, previous studies have suggested that both methods produce similar results, particularly when the meta-analysis aims to explore single associations between an exposure (dietary macronutrient) and an outcome of interest (birthweight, and odds of SGA and LGA babies) (Mathew and Nordstrom, 1999; Olkin and Sampson, 1998; Riley et al., 2010; Riley et al.,

2008; Stewart et al., 2012; Tierney et al., 2015). Stewart et al., and Tierney et al., suggested that the one-step and two-step approaches usually give similar results. The Stewart study explored effects of anti-platelets on pre-eclampsia in pregnancy and reported that the results of the two stage approach (relative risk = 0.90, 95% CI = 0.83 to 0.96) and one step approach (relative risk = 0.90, 95% CI = 0.83 to 0.97) were almost similar (Stewart et al., 2012; Tierney et al., 2015). Further, both approaches are suggested to present results of clinical importance by describing how the combined estimates and p values get modified by different study characteristics, including design, baseline data, dietary data (Riley et al., 2010).

In contrast a study by Burke and colleagues (Burke et al., 2017) suggested that one-step and two-step IPD approach might produce different summary results and explained that most differences were due to different modelling assumptions. Further, the Burke study reported that unbalanced sample sizes might be a reason for different results. In addition, it suggested that the choice of fixed-effects or random-effects assumption could also give different results in the one-step and two-step approach. However, they also suggested that in most studies both approaches give identical results but certain factors including, clinical question, sample size of the cohorts and parameters of interests must be considered in order to choose the right method. Finally, they summarised that one-step approach is only used amongst studies exploring rare diseases and conditions, and amongst small studies (Burke et al., 2017). Another study by Kontopantelis and colleagues (Kontopantelis, 2018) compared one-step and two-step approaches by generating 1000 datasets with different IPD sizes. They suggested that the one-step approach could be used to specifically explore multiple interactions between the predictor and response variables instead of the two-step approach (Kontopantelis, 2018).

In comparison with the one-step IPD, the two-step IPD method is elaborate because it requires analysing each cohort separately and then provides combined estimates using the random effects model in the meta-analysis. Despite the limitation, two-step IPD was conducted in this study as it is complex to differentiate and interpret the in between and within study variances using the one-step IPD (Riley et al., 2010).

Although there is no straightforward method for conducting the IPD meta-analysis, based on the available evidence the two-step approach is usually preferred. Therefore, by accounting for these reasons the two-step approach IPD meta-analysis was undertaken in this study by keeping as much consistency and similarity as possible within the three birth cohorts enabling it to account for in-between and within study variances. This method was suitable for this study because it analysed models of high sample sized birth cohorts and produced results for single

interactions between maternal dietary macronutrients and common outcomes of interest, including birthweight, and odds of delivering SGA and LGA infants.

The covariates inlcuded for anlayses were chosen based on Directed acyclic graphs (DAG) for increasing the robustness of the regression models and preventing confounding bias.

The birth centiles were extracted from birthweights using bulk centile calculators— a unique method for calculating centiles for large datasets specifically catering to the ethnic background and nationality of the cohorts.

One limitation could be that there were only three birth cohorts in this meta-analysis. Had there been at least two more birth cohorts, the associations observed within the regression models could have been more pronounced over a large majority with lower heterogeneity levels. However, in the current study, it could not be observed because combined results represent the average of the three cohort-specific results derived using the random effects meta-analysis method.

In the regression models, socioeconomic status was not included as a covariate because data were incorrect in MoBa. DNBC cohort used the food composition tables which have limited food items available for computation of nutrients and made new recipes according to the participant descriptions introducing potion size overestimations. This study had a high heterogeneity of (I^2=91%) for maternal CHO and fat intakes due to differing study designs and dietary methods.

Although the three birth cohorts used adequate dietary assessment tools to record dietary data, under-reporting of the dietary intakes needs to be accounted. Also, during pregnancy it is possible that women with higher pre-pregnancy BMI are more likely to under-report their overall energy intakes (Johansson et al., 1998; McGowan and McAuliffe, 2012). Further, most of the dietary assessment tools rely on memory and could be time-consuming (Black and Cole, 2001).

5.4.3 Overall implications

The current meta-analysis study of three birth cohorts has demonstrated that additional maternal energy intake is associated with higher birthweight. Amongst the macronutrients, maternal dietary protein is positively associated with higher birthweight. In line with previous literature, the results suggest a positive role of adequate protein consumption during pregnancy necessary for optimum fetal growth. Although the western population largely consumes adequate dietary protein it is important to further investigate the type of protein that might be associated in influencing the birth outcome. While the meta-analysis has not evidenced the associations between maternal dietary CHO and fat, and birth outcomes, the

individual cohort results have demonstrated important associations which could be essential for further investigation.

The next chapter will extract maternal dietary patterns using principal component analysis (PCA) in MoBa and will demonstrate associations between the maternal dietary patterns and birth outcomes, including birthweight, and odds of delivering SGA and LGA infants.

Chapter 6 : Association between maternal dietary patterns and birth outcomes within MoBa

The previous chapter demonstrated associations between maternal macronutrient intakes and birth outcomes in a meta-analysis of three birth cohorts, including MoBa, DNBC and CARE. The current chapter will extract maternal dietary patterns and explore its associations with birth outcomes, including birthweight, and risk of SGA and LGA babies within the MoBa cohort.

6.1 Introduction

Recent evidence has created awareness regarding the impact of diet in pregnancy on fetal growth such as birthweight and organogenesis (de Boo and Harding, 2006; Moore et al., 2004; Obermann-Borst et al., 2011). Although studies have indicated that maternal dietary choices could affect pregnancy outcomes such as preterm deliveries, birthweight and risk of SGA babies, the evidence remains inconclusive (Haugen et al., 2008; Kjøllesdal and Holmboe-Ottesen, 2014)

Literature from traditional analysis attempted to demonstrate the associations between single nutrients and foods, and outcomes of interest, but these have certain methodological concerns. Firstly, foods or nutrients are eaten in a combination, making it difficult to examine their separate effects on a specific outcome (Research, 1989). This is because there is a marked reduction in the degree of independent variance of dietary intakes when the foods or nutrients are simultaneously entered into the models. Secondly, the individual effect of a particular food may be too small to detect, but when many foods are considered together in a dietary pattern, the overall effect size might be sufficiently large to detect in large populations (Hu, 2002). Also, a further challenge is to conduct accurate and appropriate characterisation of dietary intake (McCann et al., 2001).

Citing these issues, evidence has supported the use of dietary patterns for studying the combination of foods in the diets eaten in different populations (Huijbregts et al., 1997; Huijbregts et al., 1995; Kant, 1996). It is suggested that conducting analysis of a group of foods in the form of dietary patterns within various cohorts is an appropriate approach as compared to exploring the influence of single food intakes. This was because the extracted dietary patterns provided a broad representation and description of people's dietary habits belonging to a certain population (Englund-Ögge et al., 2014). Furthermore, the dietary patterns indicate certain factors that might influence habitual diets, for example, socioeconomic culture, ethnicity, dietary preferences, weather conditions and geographical location.

Dietary patterns have been investigated using two types of analyses – 1. Hypothesis-based or *a priori* approach where the dietary patterns are defined based on previous literature and does not use the dietary intake data from the cohort to create the dietary patterns. The evidence to extract dietary patterns is from diet quality scores based on recommended diets, for example Mediterranean diets (Cade et al., 2011), or dietary guidelines (Hoffmann et al., 2004; Tielemans et al., 2015). However, the scores in this method do not account for correlation between the different dietary components and so it does not reflect the overall effect of the maternal diet but only gives an unadjusted sum of single effects.

2. Exploratory analyses or *a posteriori* approach use dietary data within a cohort for dietary pattern extraction and does not account for prior knowledge. Previous studies have used exploratory analyses including, cluster analysis, factor analysis (FA) and principal component analysis (PCA) to derive patterns. Cluster analysis has been used to derive dietary patterns previously, but the results extracted are based on the participants who share similar frequency patterns of dietary intakes during pregnancy and not their dietary intakes (Reedy et al., 2010). In contrast, the patterns extracted from factor analysis are based on foods which are correlated to each other and participants are scored based on their adherence to observe intake variations (Reedy et al., 2010).

Factor analysis (FA) and PCA are similar statistical methods although they are fundamentally different. FA determines the number or the nature of latent variables that account for the observed variation amongst a set of dietary intake variables and extract a set of correlated patterns, known as factors explaining it (Bédard et al., 2015; Hoffmann et al., 2004). For example, a latent variable could be behavioural intervention, including diet and physical activity amongst obese pregnant women that accounts for the observed variation of the dietary intakes and extracts factors explaining the effectiveness of the intervention (Flynn et al., 2016).

In comparison to these methods, principle component analysis (PCA) has been commonly used in nutritional epidemiological evidence as it is used to extract uncorrelated linear combinations of the dietary variables (dietary patterns) to explain for maximum variance of the cohort's dietary intakes (Schwedhelm et al., 2018). PCA reduces the number of dietary intake variables in a large dataset while retaining its original variance as much as possible (Jolliffe, 2011). Finally, PCA generates dietary pattern scores which summarise the combined maternal dietary intakes.

The purpose of this study was to observe the overall maternal dietary intakes within the MoBa cohort, therefore, PCA was used since this method derived dietary patterns that explained maximum variance for a predictor variable, i.e., maternal dietary intakes. The study had two objectives – 1. To extract maternal dietary patterns using PCA in MoBa 2. To demonstrate

associations between maternal dietary patterns and birth outcomes, including birthweight, and risk of SGA and LGA babies.

6.2 Methodology

6.2.1 Study population

In this chapter the PCA analyses will be conducted within the MoBa birth cohort (N=85,574 mother-infant pairs) because the MoBa FFQ asked questions regarding the dietary intakes of women for the past 4 to 5 months of pregnancy(Brantsaeter et al., 2008; Olsen et al., 2014). This was more appropriate to generate usual intake patterns compared to DNBC because the Danish FFQ asked questions on dietary intakes only for the past 4 weeks of pregnancy (Olsen et al., 2001; Olsen et al., 2014). Factors including hormonal changes and morning sickness in trimester 1 could affect the appetite levels amongst some women, therefore, influencing the overall dietary choices and intakes during pregnancy (Crozier et al., 2017; Hirschberg, 2012; Ladyman et al., 2010; Orloff et al., 2016). Hence using an FFQ which has captured dietary intakes for long durations would extract dietary patterns representing consistent dietary choices and therefore, could be clinically important.

6.2.2 Dietary data

The participants filled in a 300-food item FFQ around 22 weeks of gestation which assessed the dietary intakes from the start of pregnancy. Participants were asked to provide information regarding consumption frequencies, dietary changes after pregnancy, food preparations and portion sizes, and dietary supplements. Self-administered FFQ is susceptible to missing data and hence, data cleaning was conducted by replacing all the missing values in the food item variables with '0', instead of excluding participants from the cohort. Therefore, it was assumed that a food item was missing because the participant had not consumed it.

However, from the MoBa data, out of 300 food items, data of only 206 food items were available for analyses. These 206 food items were pre-defined as frequencies (number of times consumed per week) and were converted to daily food intakes (grams/day) to derive dietary patterns in g/day. The quantification of food items was preferred to frequencies as it is clinically important to observe the dietary patterns representing the amount of food consumed per day during pregnancy than frequencies in order to make realistic interpretations of the results. However, the MoBa cohort did not use portion sizes, except for liquids (glass/cup), fruits (per piece) and bread (slice) in their FFQ and the explanation to not include portion sizes was provided in an FFQ validation study(Brantsæter et al., 2008). Hence Norwegian food composition tables were used to extract standard food portion sizes (g) for the 206 food

items(Blaker and Aarsland, 1989). Further, per week intakes for all food items were derived by multiplying the standard portion size (g) times the frequency. Lastly, food intakes per day were derived dividing by 7.

Furthermore, the 206 food items (g/day) were also aggregated into 33 non-overlapping food groups. This was conducted for clearer interpretation of the PCA results as smaller number of food group variables made it easy to describe the extracted dietary patterns. For example, the standard Norwegian portion size (g) of Mackerel, Herring, Salmon, Trout were multiplied with their respective frequency intakes (per week) and were then divided by 7 for gram per day intakes. The sum of these individual fish intakes (g/day) were then aggregated under the "fatty fish" food group. Another example, the standard Norwegian portion size (g) of wholemeal bread, dark rye bread, fibre crispbread were multiplied with their respective frequency intakes (per week) and were then divided by 7 for gram/day intakes. Finally, the sum of these individual variety of breads (g/day) consumed were then aggregated under the "unrefined bread" food group. **Table 16** has listed 33 food groups that were categorised according to the MoBa food groups listed in the Olsen study (Olsen et al., 2014).

Table 16 List of individual food items and the aggregated food groups in the MoBa dataset

Serial number	Food group	Food items under these food groups	Serial number	Food group	Food items under these food groups
1.	Fruits and dried fruit	Orange, grapefruit, plum, banana, apple, grapes, peach, mango, melon, papaya, pear, strawberries, other berries, apricots, raisin, prune fig and date	18.	Fats and oil	Butter slice, brelett, soft margarine, light margarine, melted butter, melted margarine, butter, soft margarine, hard margarine, soy margarine, olive margarine, other margarine, soya oil, cooking oil, olive oil, corn oil, other oil
2.	Nuts and oilseed	Peanuts, almond and cashew	19.	Cheese spreads (includes other spreads)	Whey cheese, low-fat whey cheese, hard cream cheese, low-fat hard cream cheese, blue cheese, other cheese, cheese in pasta, roe spread, mackerel sardine spread, sardine spread, smoked salmon trout spread, herring spread, liver spread, peanut butter spread, other nut spread, other sweet spread
3.	Potato (baked, cooked and boiled)	Potatoes, cream potato casserole	20.	Pasta, noodles, spaghetti	Meat pasta, fish pasta, vegetable pasta, tomato sauce pasta, spaghetti and noodles
4.	Low-fat and whole yoghurt	Low-fat yoghurt, Gomorgen yoghurt, whole yoghurt	21.	Added sugar	Added sugar was given in the dataset, computed from the dietary software (FoodCalc) accounting for sugar in tea coffee, honey on bread and cereals.
5.	Rice and millet	Rice (cooked), couscous	22.	Miscellaneous food	Pizza, soups, potato chips, popcorn, salted snacks, white and brown sauce, bearnaise sauce, ketchup
6.	Unrefined bread	Wholemeal bread, dark rye bread, fibre crispbread	23.	Vegetables	Cucumber, aubergine, peas, onion leek, onion leek(boiled) garlic, carrot, carrot (boiled), swede, swede (boiled), corn cob, pepper, Brussel sprouts, lettuce, celery, mushroom (raw), mushroom, spinach, squash, tomato, vegetable spreads, cauliflower, cauliflower (boiled), broccoli, broccoli (boiled), cabbage, cabbage (boiled)

7.	Refined bread	White bread, crispbread, crackers	24.	Fatty fish	Mackerel, Herring, Salmon, Trout
8.	Juices, jams and fruit syrup	Orange juice, other juice, tomato juice, jam in cereal, jam on bread, fruit syrup, light fruit syrup	25.	Lean fish	Cod, Haddock, Tuna Fish
9.	Other milk	Chocolate milk, rice milk, soymilk	26.	Seafood and molluscs	Shrimps, mussels, crab
10.	Tea	Tea, green tea, herbal tea	27.	Fish products	Fish products, fishcake, fish finger
11.	Coffee	Filter coffee, instant coffee, pressed coffee, café latte, espresso, decaffeinated coffee, fig barley coffee	28.	Poultry and egg	Egg, chicken turkey fillet, fried chicken, baked and boil chicken turkey, chicken schnitzels and nuggets, chicken turkey sausage
12.	Alcoholic beverage	Wine, spirits, non-alcoholic beer, pilsner beer	29.	Red meat	Meat products, meat products (grilled), meatball, mincemeat. lamb roast, lamb stew
13.	Colas	Coke, other colas, energy drink, diet coke, other diet colas	30.	Pork	Hotdog, meat pork sausage, pork chop, pork fillet, pork loins, pork belly bacon, bacon
14.	Whole milk	Whole milk, milk in tea and coffee	31.	Offal	
15.	Low-fat milk	Low-fat milk, extremely low-fat milk, skimmed milk, cultured milk, bio milk and yoghurt	32.	Beef and veal	Hamburger, beef, veal beef, venison
16.	Breakfast cereals	Unsweetened cereals, porridge, sweetened muesli, cornflakes	33.	Potato fried	
17.	Desserts, chocolates and cake	Pudding, ice cream, frozen yoghurt, ice sherbets, vanilla sauce, whip-cream, sweet bun, Danish pastry, doughnut, waffle, chocolate cake, cookie, plain chocolate, fancy chocolate, caramel, jelly, pastille, sugar-free pastille, marzipan			

6.2.3 Statistical methods

The means and standard deviations (mean[SD]), and absolute frequency distributions with percentages (n (%)) are calculated for the demographic characteristics of interest within the MoBa cohort (see Tables 4 and 5 in Chapter 3).

6.2.3.1 Maternal dietary pattern extraction using principal component analysis (PCA)

Principal component analysis was used in this chapter because it is a data-reduction method that extracts linear combinations of uncorrelated food groups/food items which explain the maximum variance of the maternal dietary intakes (predictor) in MoBa (Hoffmann et al., 2004; Jolliffe, 2011) (detailed comparison with other types of analyses is discussed in Introduction under section 7.1).

The output of PCA produces factor loadings for the dietary intake variables (food item or food group) under each component. The factor loadings describe the strength of the correlation between the food groups and each maternal dietary pattern (component)(Tielemans et al., 2015). A positive loading describes a positive correlation between the food group and the maternal dietary pattern, whereas a negative loading describes a negative correlation.

The PCA was conducted using a correlation matrix, and not covariance matrix because it is a suitable method that accounts for differing variance levels of food group consumption and food group variables measured in different units, for example in glasses, cups and slices. Factor loadings included for analysis were rotated using orthogonal varimax rotation (Kline, 1994). Orthogonal rotation is usually conducted for uncorrelated linear combinations of food groups. This procedure in PCA simplifies the dietary component structure and makes the interpretation of the factor loadings under maternal dietary patterns easier to interpret and more reliable, which could be replicated amongst other birth cohorts (Abdi and Williams, 2010; Kline, 1994). This is because food group variables lie at different points on a plane formed by the components. The factor loadings which represent the correlation between the components and the food group variable are signified as the coordinates of the plane. In a component extraction which is not rotated, the axes of the components may not be in proper alignment with the factor loadings and so they might not represent a clear dietary pattern. Therefore, an orthogonal rotation will rotate the axes more closely to the corresponding food group factor loadings and provide clear interpretation of the dietary patterns defined (Jolliffe, 2011).

Dietary pattern extraction from the PCA model was based on their eigenvalues (above 1.0) (Jolliffe, 2011; Venkaiah et al., 2011) and a scree plot which showed the total variance

associated with each dietary pattern (component). Further, dietary pattern scores of the participants will represent the degree of adherence to a specific dietary pattern; for example, high dietary pattern score represented high adherence and vice versa. These scores will explain the variation of food groups correlated with the maternal dietary patterns. The scores were derived by computing the individual sum of food groups, weighted with their factor loadings, and standardising the weighted sums to a mean of zero and standard deviation score of 1 (SD score).

Dietary patterns were extracted separately from two PCA models – 1. 206-food item PCA model in which 206 individual food intakes (g/day) were included to extract maternal dietary pattern (components) comprising of food items 2. 33-food group PCA model in which 33 food groups (g/day) to extract maternal dietary patterns (components) comprising of food group intakes.

6.2.3.2 Regression models to explore associations between PCA dietary pattern scores and birth outcomes

6.2.3.2.1 Exposures

Dietary patterns extracted from the 33-food group PCA model were included as exposures in the regression analysis instead of dietary patterns based on the 206 single food items. This was because these dietary patterns used food groups, for example, dairy products, desserts and sweets, fats and oils; implying better representation of the overall maternal dietary intakes in MoBa. Therefore, its associations with birth outcomes could be more easily interpreted and clinically important as compared to dietary patterns with a wider range of individual food items, for example, banana, dark rye bread, rice and chocolate milk.

6.2.3.2.2 Covariates

Covariates included in the PCA analysis are associated with both the exposure (maternal dietary patterns) and outcome (offspring birthweight, and risk of SGA and LGA babies) (Shrier and Platt, 2008). The covariates were recorded at baseline around 15 weeks of gestation in MoBa, and include maternal age, alcohol intake, smoking habits, pre-pregnancy BMI, parity, physical activity in pregnancy and use of dietary supplements (for detailed description of the covariates refer Data cleaning section in Chapter 5 under section 5.2.3).

The selection of covariates was *a priori* as they were based on previous literature. *Maternal age* is suggested to be associated with influencing maternal dietary choices as younger women have less healthy choices as compared to older women(Escoto et al., 2012; Shiraki et al., 2017). Studies have also suggested the negative association between maternal age and birth outcomes as older women have higher pregnancy risks including, stillbirth, preterm births and

macrosomia (birthweight >4000 grams)(Dietl et al., 2015; Kenny et al., 2013). Studies have suggested that women who *consume alcohol* tend to have unhealthy dietary choices including fried foods which is likely to increase their overall energy consumption (Rangan et al., 2008). Also, it is well established that alcohol intakes during pregnancy could be negatively associated with fetal alcohol syndrome (Das et al., 2004; de Sanctis et al., 2011) and SGA baby risk (Chiaffarino et al., 2006). *Smoking* during pregnancy is suggested to lower the appetite levels and the overall dietary intakes which are necessary for fetal growth (Chen et al., 2012; Mineur et al., 2011). In addition, studies have also suggested that smoking is associated with lower birthweight (Suzuki et al., 2016) and risk of SGA baby (Nohr et al., 2009). *Pre-pregnancy BMI* is also suggested to be associated with maternal dietary intakes as overweight and obese women might have unhealthy dietary choices and higher energy intakes as compared to women classed as normal and underweight(Laraia et al., 2007). Studies have suggested that pre-pregnancy BMI is positively associated with unhealthy birth outcomes, for example, overweight and obese women could be associated with high risk of low birthweight and large for gestational age infants (Pan et al., 2016; Yu et al., 2013). Women who *were physically active* during pregnancy were suggested to have better appetite levels and overall dietary intakes (Faas et al., 2010). Also, women who had light to moderate physical activity levels were suggested to have healthier pregnancy outcomes as compared to women who had no physical activity (Leiferman and Evenson, 2003; Varrassi et al., 1989). *Use of dietary supplements* in pregnancy has been suggested to improve the appetite levels and improve overall nutrient absorption (Major et al., 2008; Nutrition, 1958). Also, studies have suggested that prenatal and antenatal use of dietary supplements high in micronutrients are associated with healthy pregnancy outcomes including improved birthweight, full term pregnancies and low risk of SGA and LGA babies (Lu et al., 2014). *Parity* is suggested to affect the dietary choices and overall intakes as multigravida women could compromise the dietary intakes during pregnancy by ensuring sufficient food supply for the children as a priority (Herring et al., 2012). Studies have suggested that multigravida women are associated with high risk of SGA and LGA pregnancies and prolonged postnatal weight retention (Nohr et al., 2009).

6.2.3.2.3 Outcomes

The primary outcome of the regression analysis is offspring birthweight in grams (g). Secondary outcomes include the risk of small-for-gestational-age (SGA) and large-for-gestational-age (LGA) babies. An SGA baby is characterised when an offspring is <10th centile on the customised centile chart. An LGA baby is characterised when an offspring is >90th centile in the customised centile chart (Chiavaroli et al., 2016; Clausson et al., 2001; Norris et al., 2015).

6.2.3.2.4 Statistical methods for regression models

In the regression models the dietary pattern scores of the participants were expressed at an increment unit of 1 standard deviation (SD) to allow for comparability amongst the intakes within the differing dietary patterns, and to represent realistic changes in the birthweight which could make the associations clinically relevant (Lagiou et al., 2004).

The associations between maternal dietary patterns and birthweight, and risk of SGA and LGA baby were explored using two models: Model 1 and Model 2. Model 1 in all three outcomes only adjusted for maternal age. In the birthweight analysis, Model 2 additionally adjusted for pre-pregnancy BMI, alcohol intake, smoking habits, parity, physical activity and dietary supplements. However, in the SGA and LGA baby analyses, Model 2 only adjusted for alcohol intake, physical activity, smoking habits and dietary supplements. This was because the customised birth centiles used to extract the LGA and SGA outcomes were pre-adjusted for parity and pre-pregnancy BMI in the GROW software (Perinatal-Institute, 2017).

Multiple linear regression models were used to explore the change in birthweight (g) as it is a continuous variable and will be interpreted as birthweight estimates (g). Multiple logistic regression analyses were conducted to explore the risk of SGA and LGA babies as they are binary outcomes, in which 0 is “control” and 1 is “case” and were interpreted as odds ratio (OR).

The statistical significance was set $p<0.05$. All analyses in this chapter were performed using the Stata SE/15.1 version. The PCA code applied for the analyses in Stata is attached in the Appendix 8.11.2.

6.4 Results

6.4.1 Results of the PCA for 206-food items

From the PCA model of 206-food items five dietary patterns (principal components) were extracted based on the eigenvalues and scree plot (see **Figure 21**) and represented maximum variance of the food item intakes in MoBa. Dietary pattern 1 explained the highest variance in the PCA (variance=8%, eigenvalue=30.22) followed by dietary pattern 2 (variance=5%, eigenvalue=4.70), dietary pattern 3 (variance=4%, eigenvalue=3.82), dietary pattern 4 (variance=3%, eigenvalue=3.37), and lastly, dietary pattern 5 (variance= 2%, eigenvalue=2.78). The PCA model of 206-food items explained a total variance of 22% in the dietary intakes in MoBa.

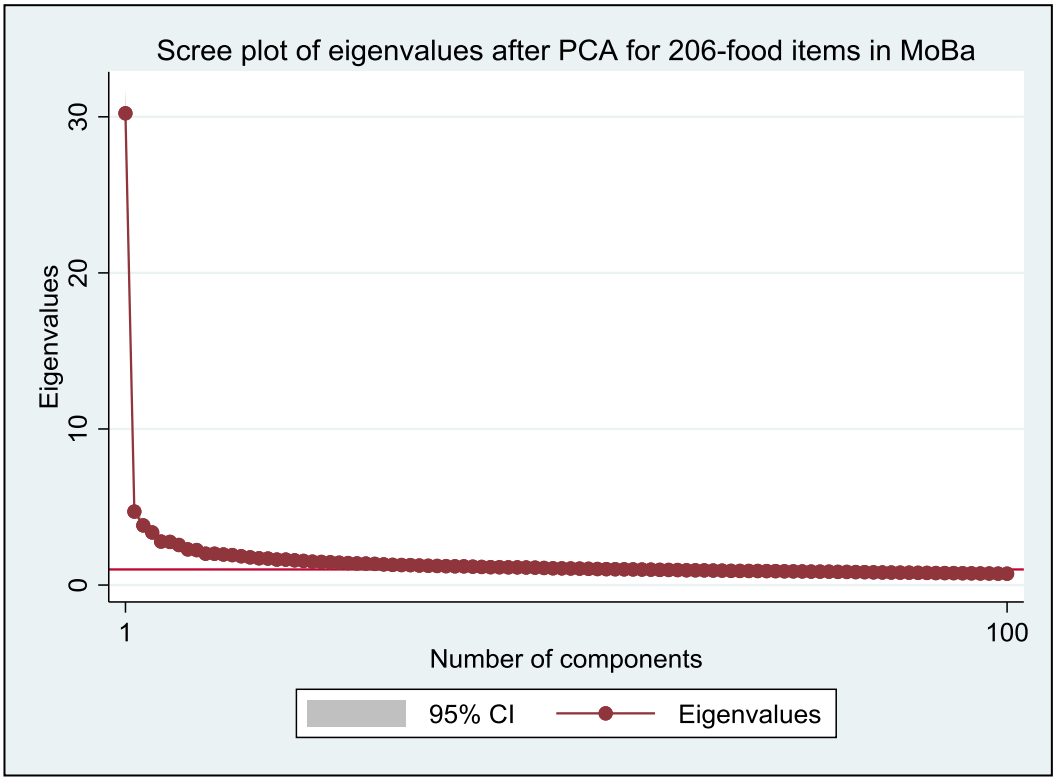


Figure 21 Scree plot after PCA for 206-food items in MoBa

The dietary patterns extracted from the PCA were labelled based on the factor loadings of the food items under each dietary pattern. The PCA factor loadings for all 206 food items are appended in a table under Appendix B. Dietary pattern 1 was labelled as *"mixed" dietary pattern* as it was characterised by high intakes of papaya, couscous, beverages (soy milk, rice milk, expresso, fig barley tea), alcoholic beverages (wine, pilsner beer, spirits), frozen yogurt, wild and regular mushroom, broccoli, mussels, venison and low intakes of white sauce.

Dietary pattern 2 was labelled as *"vegetarian" dietary pattern* as it included only vegetarian food items and was characterised by high intakes of vegetables (corncob, pepper, brussels sprouts, cauliflower, onion leeks boiled), white and bearnaise sauces, cooked rice, spaghetti and fresh cream, and low intakes of venison, green and herbal teas, and pilsner beer.

Dietary pattern 3 was labelled as *"high sugar" dietary pattern* as it was characterised by high intakes of chocolate cake, caramel, jelly, doughnut, sweet bun, pudding, pastille, vanilla sauce, cookies, waffles, savouries including popcorn, potato chips and low intakes of soy oil, cooking oil, wild mushroom, chicken fillet, vegetable pasta, broccoli, mussels and crab.

Dietary pattern 4 was labelled as *"animal meat" dietary pattern* as it was characterised by high intakes of pork loins, pork fillet, pork belly, hamburger, pizza, beef and veal, meat balls, bacon, hot dog and low intakes of apricots, prunes and figs, almond and cashew, cooking margarine, pepper and tomato.

Dietary pattern 5 was labelled as *"fish and high fibre" dietary pattern* as it was characterised by high intakes of cod, haddock, fish products, orange, banana, orange, banana, apple, grapes, hard cheese, cucumber, tomato, vegetable spreads and low intakes of added sugar, cola, melted butter and ketchup.

6.4.2 Results of the PCA for 33 food groups

From the PCA model of 33 food groups five maternal dietary patterns were extracted based on the eigenvalues and scree plot (see **Figure 22**) within the MoBa cohort. The dietary patterns (principal components) explained for a total variance of 28% in the maternal food group intakes (exposure), amongst which dietary pattern 1 explained for maximum variance (variance=10%, eigenvalue=3.23), followed by dietary pattern 2 (variance=5%, eigenvalue=1.72), dietary pattern 3 (variance=5%, eigenvalue=1.55), dietary pattern 4 (variance=4%, eigenvalue=1.35) and dietary pattern 5 (variance=4%, eigenvalue=1.20). In comparison, the total variance in the maternal dietary intakes explained by the food group PCA (27%) was higher than that of the food item PCA (22%) within MoBa.

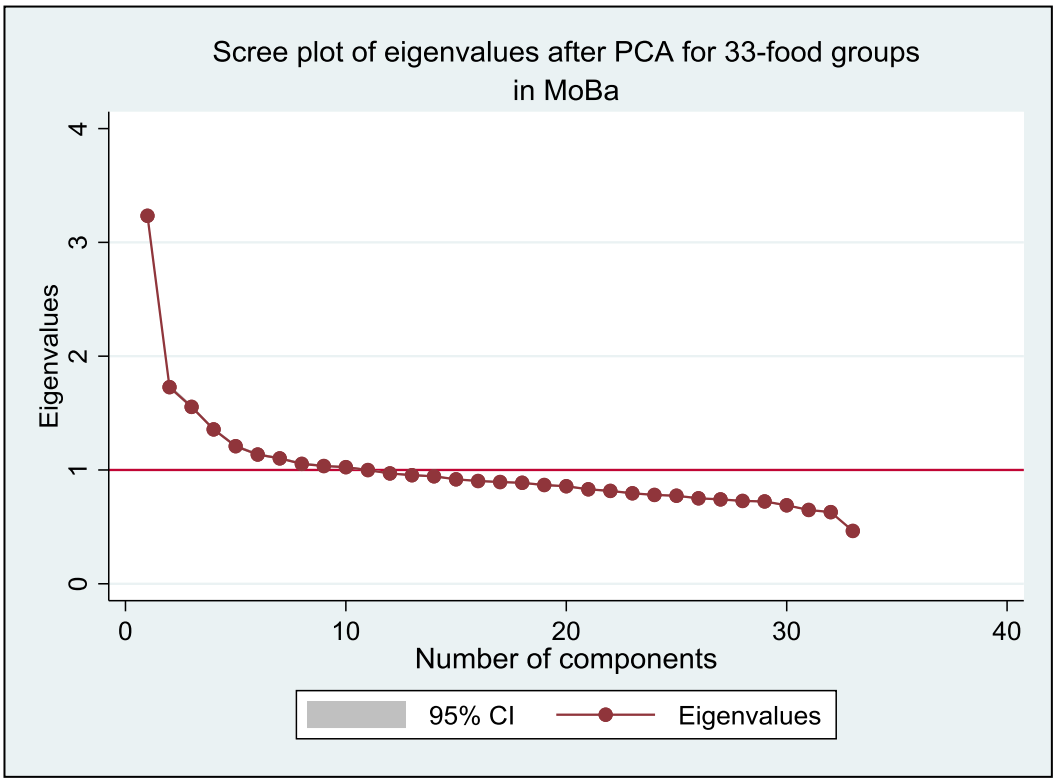


Figure 22 Scree plot after PCA for 33-food groups in MoBa

The dietary patterns were labelled based on the PCA factor loadings for all food groups (see **Table 17)**. Dietary pattern 1 was labelled as *"high sugar" dietary pattern* as it was characterised by high factor loadings of carbohydrate rich foods (desserts, sweets and chocolate, SSBs, added sugar, fruit juices, jams and syrup, breakfast cereals), miscellaneous foods including snacks, pizza, chips, popcorn, ketchup, whole and low-fat yogurt, and low factor loadings of fish products, fatty fish and lean fish, unrefined bread, rice and millet, and potato.

Dietary pattern 2 was labelled as *"marine food" dietary pattern* as it was characterised by high factor loadings of fish (lean and fatty fish, fish products), egg and poultry, fruits and dried fruits, pasta, spaghetti and noodles, and tea, and low factor loadings of carbohydrate rich foods

(added sugar, refined bread, potato, rice and millet, desserts, sweets and chocolate), fats and oil, and beef and offal.

Dietary pattern 3 was labelled as *"animal meat" dietary pattern* as it was characterised by high factor loadings of protein rich foods (pork, red meat, beef and veal, egg and poultry, seafood and molluscs), miscellaneous foods (snacks, popcorn, ketchup, pizza), refined bread, SSB and low factor loadings of fruits and dried fruit, nuts and oilseed, added sugar, beverages (tea, coffee, alcoholic beverages), dairy products (whole and low-fat milk and yogurt, cheese spreads), breakfast cereals and vegetables.

Dietary pattern 4 was labelled as *"potato and cereal" dietary pattern* as it was characterised by high factor loadings of carbohydrate rich foods (rice and millet, potato, desserts, sweets and chocolate, fruits and dried fruit), and fibre rich foods (vegetables and nuts and oilseed), and low factor loadings of dairy products (whole and low-fat yogurt, low-fat milk), bread (refined and unrefined), SSB, fruit juices, jams and syrups, tea, pasta, spaghetti and noodles.

Dietary pattern 5 was labelled as *"fats and bread" dietary pattern* as it was characterised by high factor loadings of bread (unrefined and refined), fats and oils, creams and mayonnaise, dairy products (cheese spreads, whole and low-fat milk) and low factor loadings of miscellaneous foods (snacks, ketchups, pizza, popcorn), pasta, spaghetti and noodles and protein rich foods (egg and poultry, nuts and oilseed).

Table 17 PCA factor loadings of the 33 food groups in the maternal dietary patterns within MoBa

Food groups	PCA factor loadings[1]				
	High sugar pattern	**Marine food pattern**	**Animal meat pattern**	**Potato and cereal pattern**	**Fats and bread pattern**
Added sugar	0.50	-0.09	-0.08	-0.01	0.01
Fruits and dried fruit	0.12	0.25	-0.10	0.15	-0.05
Nuts and oilseed	0.10	0.08	-0.14	0.24	-0.12
Potato (baked, cooked and boiled)	-0.07	-0.01	0.09	0.45	0.07
Whole and low-fat yogurt	0.33	0.12	-0.14	-0.07	0

[1] Factor loadings in the PCA model represent the correlation coefficients between the dietary pattern and the food groups.

Rice and millet (Couscous)	-0.05	-0.04	0.02	0.53	-0.02
Creams and mayonnaise	0.10	0.05	-0.02	0.04	0.21
Unrefined bread	-0.05	0.04	-0.03	-0.06	0.53
Refined bread	0.08	-0.13	0.15	0	0.40
Fruit juices, jams and syrup	0.31	0.10	-0.06	-0.18	0.10
Other milk (soya, rice and chocolate)	0.26	-0.05	-0.03	0.06	-0.02
Tea	0	0.20	-0.16	-0.02	0.08
Coffee	0.01	0.13	-0.08	0.05	0.12
Alcoholic beverages	0.13	0.01	-0.06	0.11	0.01
Cola	0.33	-0.16	0.15	-0.08	-0.03
Whole milk	0.05	0	-0.02	0.15	0.15
Low fat milk	0.08	0.15	-0.12	-0.04	0.16
Breakfast cereals	0.21	0.10	-0.20	0.02	-0.07
Desserts, sweets and chocolate	0.30	-0.06	0.01	0.28	-0.07
Fats and oil	-0.02	-0.06	0.05	0.09	0.46
Cheese spreads	0.12	0.22	-0.08	-0.01	0.30
Pasta, spaghetti and noodles	0.09	0.27	0.16	-0.14	-0.10
Vegetables	0.06	0.13	-0.08	0.40	0
Fatty fish	-0.05	0.38	0	0	-0.08
Lean fish	-0.13	0.40	0.04	0.03	0.02
Seafood and molluscs	0.01	0.11	0.12	0.15	-0.06
Fish products	-0.11	0.39	0.12	-0.02	0.05
Egg and poultry	0.05	0.30	0.14	-0.05	-0.12
Red meat	0	0.12	0.42	-0.03	0.06
Pork	0.02	0.04	0.47	0.05	0.03
Beef and veal	0.05	0	0.45	0.03	-0.01
Offal	-0.01	-0.02	0.13	0.13	0.06

Miscellaneous food (ketchup, sauces, pizza, popcorn, chips)	0.22	0.02	0.21	-0.02	-0.14

6.4.3 Association between maternal dietary pattern scores and change in birthweight

Amongst birthweight results (Table 18), in model 2, high "marine food" and "fats and bread" dietary pattern scores per 1SD increment were positively associated with higher birthweights (5g; 95% CI 2g to 9g; p=0.005) and (8g; 95%CI 3g to 12g; p=0.001), respectively. However, a high "animal meat" dietary pattern score per 1SD increment was associated with a lower birthweight (5g; 95%CI 1g to 9g; p=0.02).

Table 18 Association between maternal dietary pattern (DP) scores in the second trimester and birthweight in MoBa

Maternal dietary pattern scores (increment per 1SD)	Change in birthweight (g), Model 1			Change in birthweight (g), Model 2		
Trimester 2 n=85,574	BW[a]	95% CI	*p* value	BW[b]	95% CI	*p* value
High sugar	-7	-10 to -5	<0.001	1	-3 to 4	0.92
Marine food	4	2 to 8	<0.001	5	2 to 9	0.005
Animal meat	5	3 to 8	<0.001	-5	-9 to -1	0.02
Potato and cereal	-11	-14 to -8	<0.001	-4	-9 to 2	0.21
Fats and bread	6	2 to 9	0.001	8	3 to 12	0.001

[a]Adjusted for maternal age

[b]Additionally adjusted for pre-pregnancy body mass index (BMI), alcohol intake, smoking, parity, physical activity, dietary supplements

6.4.4 Association between maternal dietary pattern scores and the odds of SGA baby

Amongst SGA baby results (Table 19), in model 2, high "marine food" and "potato and cereal" dietary patterns scores per 1SD increment were associated with lower odds of SGA baby (0.95; 95%CI 0.93 to 0.97; p<0.001) and (0.95; 95%CI 0.92 to 0.99; p=0.02), respectively.

Table 19 Association between maternal dietary pattern (DP) scores in the second trimester and the odds of SGA baby

Maternal dietary pattern scores (increment per 1SD)	Odds of SGA[†] (OR), Model 1			Odds of SGA[†] (OR), Model 2		
Trimester 2 n=85,574	OR[a]	95% CI	*p* value	OR[b]	95% CI	*p* value
High sugar	1.02	1.00 to 1.03	0.002	0.99	0.96 to 1.01	0.45
Marine food	0.96	0.95 to 0.98	<0.001	0.95	0.93 to 0.97	<0.001
Animal meat	1.01	0.99 to 1.03	0.05	0.99	0.96 to 1.02	0.67
Potato and cereal	1.01	0.99 to 1.02	0.13	0.95	0.92 to 0.99	0.02
Fats and bread	0.98	0.96 to 1.00	0.10	0.97	0.94 to 1.00	0.09

[a]Adjusted for maternal age

[b]Additionally adjusted for alcohol intake, smoking, physical activity, dietary supplements

[†]Bulk centile calculators (BCC) for North European region in GROW software was used to derive centiles after adjusting for maternal height, weight, parity, ethnicity, gestational age at delivery and sex of the baby

6.4.5 Association between maternal dietary pattern scores and odds of LGA baby

Amongst LGA results (see Table 20), in model 2, high "animal meat" and "potato and cereal" dietary pattern scores per 1SD increment were positively associated with higher odds of LGA baby (1.06; 95% CI 1.04 to 1.09; p<0.001) and (1.04; 95%CI 1.00 to 1.07; p=0.01), respectively (Table 32).

Table 20 Association between maternal dietary pattern (DP) scores in the second trimester and the odds of delivering large-for-gestational-age (LGA) infants in MoBa

Maternal dietary pattern scores (increment per 1SD)	Odds of LGA† (OR), Model 1			Odds of LGA† (OR), Model 2		
Trimester 2 n=85,574	**OR[a]**	**95% CI**	***p* value**	**OR[b]**	**95% CI**	***p* value**
High sugar	1.01	0.99 to 1.02	0.17	1.02	0.99 to 1.04	0.09
Marine food	0.99	0.98 to 1.01	0.48	0.99	0.97 to 1.02	0.84
Animal meat	1.05	1.03 to 1.07	<0.001	1.06	1.04 to 1.09	<0.001
Potato and cereal	1.01	1.00 to 1.03	0.03	1.04	1.00 to 1.07	0.01
Fats and bread	1.00	0.98 to 1.02	0.88	1.01	0.98 to 1.04	0.27

[a]Adjusted for maternal age

[b]Additionally adjusted for alcohol intake, smoking, physical activity, dietary supplements

†Bulk centile calculators (BCC) for North European region in GROW software was used to derive centiles after adjusting for maternal height, weight, parity, ethnicity, gestational age at delivery and sex of the baby

6.5 Discussion

The current study conducted principal component analysis (PCA) of the dietary intakes of 85,574 women during pregnancy within the MoBa cohort. To observe the maternal dietary intakes, separate dietary patterns were extracted using two approaches in PCA– 1. 33-food groups 2. 206-food items. The five dietary patterns extracted from the PCA of food groups were labelled as “high sugar” dietary pattern, “marine food” dietary pattern, “animal meat” dietary pattern, “potato and cereal” dietary pattern and “fats and bread” dietary pattern. Further, five dietary patterns extracted from the PCA of individual food items were labelled as “mixed” dietary pattern, “vegetarian” dietary pattern, “high sugar” dietary pattern, “animal meat” dietary pattern and “fish and high fibre” dietary pattern. Three dietary patterns extracted within the two PCA models were observed to be similar – amongst the PCA of food items, “high sugar”, “animal meat” and “fish and high fibre” dietary patterns were mostly similar with the dietary patterns extracted within the PCA of food groups namely, “marine food”, “animal meat” and “high sugar” dietary patterns. The food group based dietary patterns explained for higher variance of the maternal dietary intakes (27%) than that of individual food items (22%), therefore it could be implied that food group based dietary patterns explained for wider variance of dietary intakes in this study. In addition, including smaller number of food intake variables in the form of food groups for the PCA and the regression analysis made it possible to easily describe the extracted dietary patterns and conduct clearer interpretations.

This study explored the associations between the food group based dietary patterns extracted from PCA and birth outcomes, including birthweight, and odds of SGA and LGA babies within MoBa. The results suggested that a high adherence to “marine food” and “fats and bread” dietary patterns during pregnancy was positively associated with high birthweight. It must be noted that these results had high statistical significance and no clinical significance. Further, amongst odds of SGA babies the results demonstrated that a high adherence to “marine food” dietary pattern was associated with lower odds of SGA baby. Amongst odds of LGA babies, the results suggested that a high adherence to “animal meat” and “potato and cereal” dietary patterns were positively associated with high odds of LGA babies.

Amongst the 33-food group PCA models, the first five components (dietary patterns) were examined in detail. Although, 10 components (dietary patterns) were observed to be above the eigenvalue cut-off the limit (>1.0) on the scree plot (Kaiser, 1958; Rasmussen et al., 2014), it was observed that components between six to ten had similar eigenvalues and variance that explained for maternal dietary intakes. Therefore, for easier interpretations of the results only

the first five components were extracted from PCA because they explained maximum variance in the maternal dietary intakes of MoBa.

6.5.1 Comparison with other studies

The association between a high animal meat dietary pattern and lower birthweight observed in this chapter is in agreement with the meta-analysis results of the Kjøllesdal study (Kjøllesdal and Holmboe-Ottesen, 2014). Interestingly, the PCA result is also in contrast to the meta-analysis results for dietary protein in the previous chapter. In Chapter 5 under section 5.3.1, the meta-analysis results demonstrated that high maternal protein intake was associated with higher birthweight. A possible reason for the difference in the results could be the differential impact of the type of protein (animal meat and fish protein) on birthweight and odds of SGA and LGA babies. The results in this chapter showed that high adherence to an animal meat dietary pattern was associated with lower birthweight, whereas high adherence to a "fish" dietary pattern was associated with improving birthweight and preventing poorer birth outcomes. In agreement, the Kjøllesdal study observed that high adherence to "western" dietary pattern characterised by high intakes of high-fat meat products, refined grain products and sugar-sweetened beverages were associated with lower birthweights. The food items characterised in the "western" dietary pattern were similar to the "animal meat" dietary pattern in this chapter.

Furthermore, it could be possible that a high adherence to a dietary pattern with high intake of protein and refined CHO foods might have simultaneously lowered the intake of other food groups necessary for fetal growth. The Kjøllesdal study suggested that it is important to consume healthy foods including, fruits and dried fruit, nuts and oilseed, dairy products (whole and low-fat milk and yoghurt, cheese spreads), breakfast cereals and vegetables for higher birthweights (Kjøllesdal and Holmboe-Ottesen, 2014; Olsen et al., 2007). Another possible reason could be that pregnant women who tend to consume 'junk' foods might not only eat less healthily but might consume more of the unhealthy foods (Thompson et al., 2010).

Previous studies suggested that "nutrient dense", "protein rich", and "health conscious" maternal dietary patterns were positively associated with higher birthweights and low risk of SGA baby (Kjøllesdal and Holmboe-Ottesen, 2014). Although the dietary patterns were named differently in previous studies (Chia et al., 2016; Hillesund et al., 2014; Kjøllesdal and Holmboe-Ottesen, 2014), they characterised the food items similarly to the dietary patterns in the current study. Further, studies which suggested high adherence to the "nutrient dense", "protein rich", and "health conscious" dietary patterns had characterised dairy products, low fat meats, bread (refined and unrefined), pasta, rice and fish similar to the "fats and bread", "potato and cereal"

and “marine food” dietary patterns in this study. Therefore, the results in the current study are in line with the previous literature, as it suggests that a high adherence to “fats and bread” and “marine food” maternal dietary patterns are positively associated with higher birthweight (Northstone et al., 2008; Wolff and Wolff, 1995). Possible reasons for these results could be that the cohorts conducted analyses amongst a well-nourished population within developed countries, who mostly consumed a traditional Nordic diet high in potatoes, fish, meat and poultry, vegetables and fruits, dairy products and cereals.

In this study, it was observed that a high adherence to “potato and cereal” dietary pattern was associated with both, lowered risk of SGA and increased risk of LGA babies. In agreement with the SGA baby result observed in this study, previous studies suggested that a dietary pattern high in cereals and millets, potatoes, fruits and vegetables, dairy products and animal protein were associated with lowered risk of SGA babies as they promoted adequate fetal growth (Brantsaeter et al., 2012; Imhoff-Kunsch et al., 2012; Kjøllesdal and Holmboe-Ottesen, 2014).

There is very limited evidence suggesting a positive association between high carbohydrate and risk of LGA babies amongst a non-diabetic population of pregnant women. In agreement with the results of this study, a couple of studies that suggested that a high consumption of CHO rich food groups including, potatoes, vegetables, cereals and fruits was associated with high risk of LGA infants (Chia et al., 2016; Hillesund et al., 2014). Although both studies observed different ethnic and cultural backgrounds, and geographical locations, the results demonstrated were in line with the current study.

The Growing Up in Singapore Towards healthy Outcomes (GUSTO) study and extracted three dietary patterns from PCA and recorded dietary data using 3-day food dairies. The study suggested that a “vegetable, fruit and white rice” dietary pattern was positively associated with risk of LGA baby amongst an Asian population (Chia et al., 2016). The Norwegian study by Hillsund and colleagues demonstrated similar results within the MoBa cohort (Hillsund 2014) and reported that a high New Nordic Diet (NND) score was positively associated with risk of LGA baby (Hillesund et al., 2014). The NND diet was characterised by high intakes of potatoes, vegetables and fruits, whole grains, milk, and was partially similar to the “potato and cereal” dietary pattern in this study. Possible reasons for these results could be that the Hillsund study was also conducted within MoBa who mostly consumed a Nordic diet, although culturally different, both birth cohorts, i.e., the MoBa and the GUSTO study shared similar maternal and offspring characteristics and consumed similar food groups including cereal, vegetables and fruits. Moreover, the studies were conducted within a well-nourished and non-diabetic population and accounted for ethnicity hence making the results widely applicable amongst

other cohorts. However, these results are inadequate and require further exploration amongst other cohorts to test for consistency.

Based on the awareness of the author, this is the first study to suggest that an “animal meat” dietary pattern is positively associated with risk of LGA babies amongst a non-diabetic population of women. A systematic review and meta-analysis by Chia and colleagues (Chia et al., 2019) included 36 studies and explored the association between maternal dietary patterns and birth outcomes, including birthweight and risk of SGA and LGA babies, of which only five studies had explored the association with risk of LGA babies. The systematic review suggested that no study included in the meta-analysis had explored the association between “unhealthy” dietary patterns and the risk of LGA babies (Chia et al., 2019). The “unhealthy dietary pattern” in the review was characterised by high intakes of refined grain, processed meats, and food high in saturated fat or sugar that was similar to the “animal meat” dietary patterns in the current study. The “animal meat” dietary pattern was characterised by high factor loadings of protein-rich foods (pork, red meat, beef and veal, egg and poultry, seafood and molluscs), miscellaneous foods (snacks, popcorn, ketchup, pizza), refined bread, and SSBs (Chia et al., 2019). In addition, the meta-analysis results in the Chia study suggested that there was no evidence of an association between high adherence to a “healthy” dietary pattern and the risk of LGA babies. Furthermore, in line with the Chia study, another observational study also suggested that a “healthy” dietary pattern was not associated with the risk of LGA infants (Poon et al., 2013). Both studies characterised a “healthy” dietary pattern by high intakes of vegetables, fruits, low-fat dairy, wholegrains and lean protein food (Chia et al., 2019; Poon et al., 2013). However, the statistical methods primarily chosen to extract dietary patterns might have affected the resulting associations amongst the studies. In comparison to the dietary patterns extracted using PCA in the current study and the Chia study, the Poon study extracted dietary patterns using diet quality score index questionnaires which would not provide the correlations between the food groups and the components therefore, might not present the overall effect of the maternal diet on the risk of LGA babies.

Another meta-analysis of seven studies (Kjøllesdal and Holmboe-Ottesen, 2014) explored dietary patterns in relation to size at birth (birthweight and risk of SGA babies) suggested that a maternal diet high in processed and high fat meat products, confectionary, sweets, soft drinks and sugar, and refined grains were positively associated with high risk of SGA babies and lower birthweights (Kjøllesdal and Holmboe-Ottesen, 2014). However, the meta-analysis did not explore its associations with risk of LGA babies. In similarity with the current study all the individual studies included in the meta-analysis were conducted within high-income countries and used self-reported FFQ to record dietary intakes and mostly used PCA for dietary pattern

extraction. However, the studies included in the meta-analyses had certain disadvantages including, confounding errors and bias, incorrectly definition of SGA infants and inappropriate use of statistical methods (Kjøllesdal and Holmboe-Ottesen, 2014). For instance, Knudsen and colleagues (Knudsen et al., 2007) suggested that a "western" diet high in red and processed meat, potatoes and high dairy fat and low intakes of fruits and vegetables were associated with high SGA baby risk. However, the dietary patterns were extracted using factor analysis and not PCA, because the study's primary objective was to detect underlying common variables to detect the highly correlated dietary variables within DNBC. In addition, the Danish study had characterised infants with birthweights <2.5 percentile as SGA babies. This was opposite to this study because the current study used a standard reference of birthweights <10 percentile to characterise SGA infants (Chiavaroli et al., 2016; Clausson et al., 2001; Norris et al., 2015). Also, a confounding error was observed in the SGA models of the DNBC study as it had adjusted for father's height which was associated with the SGA baby but could not be associated with maternal dietary intakes.

Interestingly, the current study has highlighted the protective effect of a "marine food" dietary pattern in pregnancy on birth outcomes. It was observed that high intake of "marine food" dietary pattern was positively associated with high birthweight but not with risk of LGA babies (Brantsaeter et al., 2012; Imhoff-Kunsch et al., 2012). However, the "marine food" dietary pattern was protective against SGA baby in this study. The MoBa cohort was primarily comprised of participants who consumed a Nordic diet high in marine foods and both high and low-fat animal meat products (Hillesund et al., 2014; NNR, 2012; von Ruesten et al., 2014). In support of the results for this association a study suggested that higher dietary pattern adherence to the New Nordic Diet (NND) score was protective against SGA babies (Hillesund et al., 2014). Also, a pooled analysis of 15 cohorts suggested that a high fish intake (3 times a week) during pregnancy was positively associated with rapid infant growth (Stratakis et al., 2016). Furthermore, a DNBC study suggested that high intakes of marine fat in the form of omega 3 fatty acids during pregnancy is associated with increased birthweight (Imhoff-Kunsch et al., 2012; Olsen et al., 1986). This result is clinically important as it demonstrates a positive, yet potentially preventive effect of a high adherence to a fish diet on birthweight and SGA baby risk, while simultaneously preventing excessive offspring weight gain >4000 grams (LGA infant). A high fish diet is rich in polyunsaturated fatty acids (PUFA), especially in omega 3 fatty acids. These are suggested to prolong gestation by interfering with the prostaglandin production in the uterus by blocking the dienoic prostaglandins, in particular mediators including PGE2 and PGF2 which are responsible for initiating labour through uterine contractions and ripening of the cervix (Olsen et al., 1986). In addition, it contains docosahexaenoic acid, an important

component of the nervous system cell membranes necessary for vision and fetal brain development (Hanebutt et al., 2008), therefore increasing the overall birthweight. This underlying pathway might explain for the observed associations.

The associations observed could be linked to metabolism in the maternal macronutrient-fetal pathway. Previous studies have suggested the a hyperinsulinemic effect of amino acids in the form of protein rich dietary intakes, implying that dietary patterns high in animal meat, poultry, marine foods, nuts and oilseeds, and dairy products are susceptible to increase the overall insulin levels and therefore transfer excessive amino acids to the fetus causing accelerated growth. Further, in relation to high CHO dietary patterns characterised by high intakes of potatoes, cereal (rice and couscous), bread (refined and wholegrain), studies suggested that excessive amounts of CHO during pregnancy get absorbed as glucose and is metabolically transferred to promote fetal glycogenesis. While optimum glucose levels are required for fetal growth, it could be implied that excessive CHO intakes through such dietary patterns could expose the fetus to free glucose and could be associated with increased risk of LGA baby. (Buschur E, 2000; Jolly et al., 2003).

Furthermore, the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study (Group, 2009) suggested that almost 80% of the infants were born to non-GDM mothers and hence the results in this chapter might be clinically important amongst well-fed, normal pregnancy populations . This was similar to the MoBa cohort as the demographic results for birth outcomes described particularly high rates of around 22% (n=23,775) of LGA infants born to non-diabetic women (refer Chapter 4 under section 4.4.3 and Table 4). Further, through the PCA and regression analysis it is suggested that a high adherence to “animal meat” and “potato and cereal” dietary patterns during pregnancy were positively associated with higher risk of LGA babies. Therefore, evidence demonstrated in this study could potentially explain these high rates of LGA babies.

6.5.2 Strengths and limitations

The principal component analysis was conducted amongst a large sample size of 85,574 participants within the MoBa cohort. This not only gave a high statistical power to the study but also provided robustness to the observed associations between the dietary patterns and birth outcomes. The MoBa birth cohort recorded dietary data in semi quantitative food frequency questionnaires that were initially validated before initiation of recording dietary data in the whole sample (Brantsaeter et al., 2008). The validation of FFQ improved the overall quality of the dietary data recorded during pregnancy as it made it easier for the participants to answer and hence, increased their overall response rates and lowered missing data issues. This in turn

was useful for the current study as it used high quality dietary data in the form of maternal dietary intakes for analyses. Further, due to the MoBa study design, it was possible to use the dietary data which captured the dietary intakes of the women from the start of the pregnancy until 22 weeks of gestation (Magnus et al., 2006). Therefore, the results observed in the PCA analysis represent the overall dietary patterns consumed through the first 5 to 6 months of pregnancy. This could highlight the appropriate choice of conducting the PCA analysis within MoBa as compared to DNBC. It would have been a potential weakness if the study was conducted within the DNBC because then the observed results would only represent dietary intakes for the 4th month of pregnancy, as the DNBC FFQ (recorded around 25 weeks of gestation) only captured dietary data for the past 4 weeks of pregnancy (Olsen et al., 2001). Another strength was the quality of the baseline data recorded around 15 weeks of gestation using detailed questionnaires. Since the MoBa used detailed baseline questionnaires around 15 weeks of gestation it was possible to account for appropriate covariates required for regression analyses (Magnus et al., 2006). The issue of missing data in the FFQ was dealt appropriately by replacing the missing food intakes to "0" based on the assumption that the participant had not consumed the respective food items. This decision prevented the unnecessary exclusion of participants from the birth cohort.

The regression models adjusted for appropriate covariates and were based on previous literature (*a priori* approach). The covariates were chosen only if they were associated with both the maternal dietary patterns and birth outcomes and if they were clinically important (Shrier and Platt, 2008). This was methodologically correct as compared to previous studies that adjusted for covariates based on statistical significance and if they were associated only with the study outcome.

Since a confounder needs to be an independent variable associated with both the exposures and the outcome, total maternal energy intake was not included as a confounder in this study because it was derived from the daily dietary intake of food groups in the FFQ (Knudsen et al., 2007).

Increment units at the rate of 1SD were chosen appropriately for interpreting the associations between dietary pattern adherence and birth outcomes. This range of increment allowed for comparability amongst differing dietary patterns to make realistic changes in birthweight and make the results clinically significant (Lagiou et al., 2004; Thompson et al., 2010).

The PCA factor loadings of all the food groups and items within the dietary patterns were presented in the results for an unbiased observation of the correlations of the food groups or items with the dietary patterns. The presentation of all the PCA factor loadings is necessary

because each factor loading is important in the computation and formation of a dietary pattern in the PCA model. Previous studies had set cut-off limits for factor loadings of the extracted dietary patterns in PCA, for example, >0.20 or 0.10 (Batis et al., 2016; Englund-Ögge et al., 2014; Knudsen et al., 2007; Shin et al., 2016; Tielemans et al., 2015).

The food items were quantified using Norwegian standard portion sizes from the Norwegian food composition tables and so the dietary intakes specifically represented Norwegian dietary intakes and patterns. However, a limitation to this could be that these results might be restricted specifically to the Norwegian population and it, therefore, requires replication of the observed results amongst other cohorts in order to test for consistency of the dietary patterns and associations with birth outcomes.

The MoBa FFQ did not provide portion sizes for most of the food items included and it could be a possible limitation as additional steps were required to compute gram per day intakes for all the food items required for PCA. However, in agreement with the MoBa authors (Brantsæter et al., 2008), it is appropriate not to use portion sizes in the FFQ as it could have lowered the participant response rates and affected the overall quality of the dietary data as the MoBa FFQ with portion sizes in the validation study was reported to be extensive and time consuming by the participants (Brantsæter et al., 2008).

Another weakness could be that MoBa only used semi quantitative FFQ to record maternal dietary data which introduces the issue of under-reporting and measurement errors. This is especially prevalent amongst overweight and obese pregnant women as they are susceptible to under report unhealthy dietary intakes in the FFQ (Black and Cole, 2001; Johansson et al., 1998; McGowan and McAuliffe, 2012). Therefore, it is likely that the women would have underestimated the self-reported food intakes and frequencies. However, the use of multiple dietary assessment tools, for example, an FFQ and a 3-day diet recall or 24-hour recall would not be realistic and logistically possible. This is because MoBa's study design was at a national level and therefore included women from all of Norway, although new technologies currently available might make it possible (Carter et al., 2015; Wark et al., 2018).

The dietary patterns extracted from principal component analysis do not explain maximum large proportion of the variance of specific outcomes of interest, for example, risk of SGA and LGA babies or change in birthweight. Hence it cannot predict the dietary patterns consumed in relation to birth outcomes (Hoffmann et al., 2004). PCA fundamentally forms linear uncorrelated combinations of dietary patterns that explain maximum variance in the exposure of interest, for example, maternal dietary intakes. Although, PCA is an appropriate method to explore the dietary patterns consumed during pregnancy as compared to other methods

including cluster analysis and factor analysis (Reedy et al., 2010) (detailed comparison given in section 7.1 under Introduction), it not an *a priori* approach and hence PCA method does not account for previous literature (Reedy et al., 2010). Therefore, the PCA results observed in this study was limited only to the available data. This could reduce the overall applicability of the observed results as compared to another statistical method used to extract *a priori* based dietary patterns such as reduced rank regression (DiBello et al., 2008; Hoffmann et al., 2004) (detailed comparison of both methods provided in Chapter 8 section 8.7 under Discussion).

Although the regression models adjusted for clinically important confounders it was not possible to adjust for certain confounders including, medications used in pregnancy, episodes of vomiting, ethnicity, glucose tolerance test, pregnancy induced hypertension and Diabetes Mellitus as data was unavailable. However, the birth centiles extracted for LGA and SGA babies in the GROW software had pre-adjusted for ethnicity (Gardosi et al., 1992; Perinatal-Institute, 2017). Since this is an observational study the observed results are associations and do not imply causality and therefore, the associations must be replicated amongst other cohorts and the study's findings must be tested amongst well-designed high sample sized randomised controlled trials.

6.5.3 Overall implications

Based on these results observed in this study it could be implied that while maternal dietary patterns high in fish could be associated with higher birthweight, it might have a protective effect towards preventing adverse pregnancy outcomes including risk of SGA and LGA babies. Further, it might be suggested that maternal dietary patterns high in protein and CHO might be associated with high risk of LGA babies and therefore, could possibly explain the high prevalence rates of LGA infants within this cohort. These results could further encourage and promote women to have appropriate dietary choices that enable healthy pregnancy outcomes.

The next chapter will examine maternal dietary choices contributing to gestational weight gain by creating dietary patterns for gestational weight gain. Additionally, it will investigate its associations with birth outcomes, including birthweight, and risk of SGA and LGA babies.

Chapter 7 Creation of gestational weight gain dietary patterns and its association with birth outcomes—results from the MoBa and DNBC cohort

The previous chapter demonstrated the association between maternal dietary patterns extracted using principal component analysis (PCA), and birth outcomes within MoBa. This chapter will create gestational weight gain dietary patterns (GWGDP) using reduced rank regression (RRR) and explore the associations with birth outcomes within MoBa and DNBC.

7.1 Introduction

Obesity has been rapidly increasing in recent years and is prevalent amongst high and middle-income countries, especially within urban settings. According to a study (Devlieger et al., 2016) in 2014, nearly 40% women who were of childbearing age were overweight, and 15% of women were obese, indicating that pre-pregnancy BMI has an independent association with increased risk of adiposity and cardio metabolic disorders amongst offsprings.

In Europe, most countries do not report data on pre-pregnancy body mass index and gestational weight gain, and so no comprehensive representation of maternal obesity is possible (Devlieger et al., 2016). In the UK, one amongst five women has been classed as obese at antenatal booking according to (O'Reilly and Reynolds, 2013). A longitudinal study between 1989-2007 in Middlesbrough, UK represented data from 34 maternity units (N=619,323) and showed a significant double-fold increase of pre-pregnancy BMI of women from 8% to 16% (Heslehurst et al., 2007).

Lack of European guidelines for maternal weight gain cut-offs in order to prevent maternal obesity makes it necessary to depend on international guidelines, such as the Institute of Medicine (IOM; currently known as National Academy of Medicine)(Devlieger et al., 2016). Over the last decade, data from the United States of America (USA) had suggested that nearly 39% of normal weight, 59% of overweight and 56% of obese pregnant women gain more weight during the pregnancy than the recommended IOM guidelines (Dalenius et al., 2012). In 2009, the IOM guidelines (Table 21) were updated due to higher prevalence rates of overweight women entering pregnancy and increased evidence of gestational weight gain (GWG) and poor offspring outcomes (National Research Council Committee to Reexamine, 2009).

Table 21 The 2009 Institute of Medicine (IOM) recommendations for gestational weight gain

		Recommended range of total weight gain[1]	
Pre-pregnancy weight category	**Body mass index (BMI)**	**In pounds (lb)**	**In kilograms (kg)**
Underweight	Less than 18.5	28-40 lb	12.7-18.0 kg
Normal weight	18.5 to 24.9	25-35 lb	11.3-15.8 kg
Overweight	25-29.9	15-25 lb	6.8-11.3 kg
Obese (all classes included)	30 and greater	11-20 lb	4.9-9.0 kg

[1] Adapted from the 2009 Institute of Medicine guidelines

Evidence states that insufficient or excessive weight gain have differential effects on pregnancy and offspring outcomes. Excessive maternal weight gain could be associated with pregnancy-induced hypertension (McDowell et al., 2019), higher risks of congenital malformations including neural tube defects (OR, 1.87; 95% CI 1.62-2.15), spina bifida (OR, 2.24; 95% CI 1.86-2.69), cardiovascular anomalies (OR, 1.30; 95% CI 1.12-1.51), septal anomalies (OR, 1.20; 95% CI 1.09-1.31), and cleft palate (OR, 1.23; 95% CI 1.03-1.47) (Stothard et al., 2009). Others studies suggested a higher risk of macrosomia (OR, 1.67; 95% CI, 1.42–1.97) (Yu et al., 2013), and stillbirths (overall HR 8.55; 95%CI 7.12,-10.20) (Yao et al., 2014). Whereas, insufficient gestational weight gain could be linked to preterm birth or low birthweight(Wen and Lv, 2015). Systematic reviews suggest that certain risk factors, including maternal pre-pregnancy BMI, smoking, total energy intake, and physical activity, affect the rate of the GWG (Jebeile et al., 2016; Khan, 2017; King, 2007; Samura et al., 2016; Streuling et al., 2011; Suliga et al., 2018; Vargas-Terrones et al., 2019).

The weight gain during pregnancy is mainly due to three physiological components 1. maternal tissues: uterus, mammary glands and blood volume 2. products of conception: fetal weight, placenta, and amniotic fluid and 3. high maternal fat stores which comprise of 30% of the total gestational weight gain (Butte et al., 2003). The components can also be divided into 65% water, 30% fat and 5% protein (Kopp-Hoolihan et al., 1999). Although diet is the primary source for replenishing the maternal and fetal nutrient stores, it is complex to differentiate its contribution towards gestational weight gain and the subsequent offspring outcomes, making it necessary to investigate the role of gestational weight gain as an intermediate variable between maternal diet and offspring outcomes.

Recent evidence suggested that reduced rank regression (RRR) technique had been widely used to extract dietary patterns related explicitly to diseases of particular interest, for example, cardiovascular diseases (by exploring the biomarkers as risk factors), including metabolic syndrome (Bahari et al., 2018), and Type 2 Diabetes Mellitus (Jacobs et al., 2017). However,

RRR-derived dietary patterns for pregnancy have only been restricted to gestational diabetes mellitus (Shin et al., 2015), Spinabifida (Vujkovic et al., 2009) and congenital heart defect (Obermann-Borst et al., 2011). Limited studies have suggested that individual food choices and macronutrients are associated with contributing to pregnancy weight gain (Tielemans et al., 2015). One study included GWG and mid-pregnancy fasting glucose as the risk factors in the reduced rank regression (RRR) analysis and extracted dietary patterns to predict new born adiposity (Starling et al., 2017). However, no study to the knowledge of the author has created dietary patterns using RRR analysis by including risk factors (predictors) associated with gestational weight gain which represent the maximum variance of the dietary intakes related to gestational weight gain. It is also unknown whether these dietary patterns are associated with the offspring outcomes, including birthweight, and odds of SGA and LGA babies.

Hence, the main objectives of this study are 1. to create gestational weight gain dietary patterns (GWGDP) using reduced rank regression (RRR). 2. to demonstrate the association between the GWGDP and offspring outcomes, including birthweight, and odds of SGA and LGA babies within the MoBa and DNBC birth cohorts.

7.2 Methods

7.2.1 Study population

The analysis will use data from the Norwegian Mother and Child Birth Cohort (MoBa) (N=85,574 mother-infant pairs) and the Danish National Birth Cohort (DNBC) (N=67,803 mother-infant pairs). However, the results within the cohorts will not be compared in this study, because they had separate study designs and recorded baseline data differently, and used separate FFQ and country-specific food composition tables to record dietary data. A detailed description of the two cohorts is provided in Chapter 3 in section 3.2 and 3.4.

7.2.2 Dietary data

The dietary data recorded by both birth cohorts has been described in Chapter 3 under section 3.4. But briefly, according to the study designs, the MoBa and DNBC recorded the dietary data using self-reported FFQ around 22 and 25 weeks of gestation, respectively. The dietary data in MoBa captured dietary intakes for the last 4 to 5 months of pregnancy, whereas, the DNBC FFQ covered dietary intakes for the last one month of pregnancy. Since the two birth cohorts recorded dietary data differently using separate FFQ formats, MoBa FFQ was more heterogeneous than the DNBC FFQ as it recorded the dietary data in detail and included modern foods and traditional Norwegian foods specifically consumed within the Nordic population. Hence there was a slight difference observed in the number of aggregated food groups within

both cohorts. In DNBC, there were 40 pre-defined food groups recorded in grams per day (g/day) (see Table 3 further in results). The following food groups were included in DNBC – Low fat dairy, high fat dairy, ice cream, breakfast cereals, whole grains, refined rains, fruit, offal, processed meat, red meat, fish, shellfish, poultry, eggs, animal fats, vegetable fats, margarine, sweets and desserts, tea, coffee, high energy drinks, low energy drinks, alcoholic beverages, snacks, vegetables juice, fruit juice, fruit syrups and jams, nuts, other vegetables, potato products, green leafy vegetables, tomatoes, soy products, dried fruit, dressings, beans and lentil, cheese, and added sugar.

In MoBa, 206 food items were aggregated into 33 food groups (see methodology in Chapter 6 under section 6.2.2). The food groups included in MoBa were as follows – Added sugar, fruits and dried fruit, nuts and oilseed, potato (boiled, baked and cooked), whole and low-fat yogurt, rice and millet, creams and mayonnaise, unrefined bread, refined bread, fruit juices, jams and syrups, other milk, tea, coffee, alcoholic beverages, colas, whole milk, low-fat milk, breakfast cereals, desserts, sweets and chocolate, fats and oil, cheese spread, pasta, spaghetti and noodles, vegetables, fatty fish, lean fish, seafood and molluscs, fish products, egg and poultry, red meat, pork, offal, beef and veal, and miscellaneous foods (popcorn, pizza, sauces, ketchups, chips).

In MoBa the dietary data was pre-defined as food frequencies (per week format), and were subsequently converted into grams per day. The MoBa food groups were quantified in g/day to keep consistent with DNBC and for straightforward interpretation of the results. The food item variables in MoBa were aggregated into food groups as it was easier to describe the results for a smaller number food groups.

7.2.3 Covariates

Covariates included in this analysis are associated with both the exposure (gestational weight gain dietary pattern scores) and outcome (offspring birthweight, and odds of SGA and LGA babies). The covariates were recorded at baseline around 12 weeks of gestation in MoBa and 15 weeks of gestation in DNBC, and include maternal age, total energy intake, alcohol intakes, smoking habits, pre-pregnancy BMI, physical activity in pregnancy and use of dietary supplements (for detailed description of the covariates refer Data cleaning and harmonisation in Chapter 5 under section 5.2.6.1).

Firstly, *women's age* during pregnancy influences their dietary intakes as younger mothers might have poorer dietary choices and might consume energy-dense foods with low nutrient quality which contribute to excessive weight gain, as compared to older women(Escoto et al., 2012; Shiraki et al., 2017). Women above 35 years of age are included in the high-risk category

and are likely to develop pregnancy complications with poor offspring outcomes including stillbirth, preterm births and macrosomia (birthweight >4000 grams) (Dietl et al., 2015; Kenny et al., 2013).

Energy intake could directly affect weight gain in pregnancy, and this could partially be due to the influence of the appetite and sex hormones (Ladyman et al., 2010). This could, in turn, affect the intakes represented by the dietary patterns in this analysis, for example, women with high energy intakes will have high dietary patterns scores because they would have consumed a varied number of food components more frequently as compared to those with low energy intakes (Togo et al., 2001). Total energy intakes are suggested to be positively associated with better birth outcomes, and this has also been demonstrated previously in the combined meta-analysis of the three cohorts (see Chapter 6) (Abu-Saad and Fraser, 2010).

Smoking habits during pregnancy affect the maternal dietary intakes due to the nicotine effect on the appetite control centres in the brain, which might lower the hunger levels, and subsequently lower the overall energy intakes and pregnancy weight gain (Chen et al., 2012; Mineur et al., 2011). The harmful effect of smoking on the fetal growth has been demonstrated through studies thus observing that higher frequency levels of smoking are associated with lower birthweight infants(Suzuki et al., 2016) and increased risk of SGA baby (Nohr et al., 2009).

Gestational alcohol intakes affect the dietary choices of women as they prefer energy-dense foods which are generally high in dietary fat as compared to wholesome foods (Rangan et al., 2008). Studies also suggest that alcohol consumption in pregnancy have harmful effects on the fetal growth including SGA births (Chiaffarino et al., 2006), and fetal alcohol syndrome (FAS) which alter the morphological structure of the fetus (Das et al., 2004; de Sanctis et al., 2011). *Pre-pregnancy BMI* affects dietary choices as women classed under normal BMI have healthier food choices as compared to overweight and obese women(Laraia et al., 2007). It also suggested to be associated with offspring outcomes, as women who belong to overweight and obese BMI categories at the start of their pregnancy are more likely to have poor fetal outcomes including low birthweight and large for gestational age infants (Pan et al., 2016; Yu et al., 2013), and women who are underweight by BMI are more likely to give birth to low birthweight and SGA infants (Yu et al., 2013).

It is suggested that women who maintained low to moderate *physical activity levels* in pregnancy had healthier dietary choices with improved appetite levels, as compared to women who were not physically active (Faas et al., 2010). Also, two studies suggested that physically active women were more likely to have healthy pregnancy outcomes (Varrassi et al., 1989).

Whereas, those who were not physically active during pregnancy were at a high risk of delivering low birthweight infants (Leiferman and Evenson, 2003).

Lastly, *dietary supplements* consumption, including iron, folate, calcium and vitamin B_{12} in pregnancy could influence the appetite levels of the pregnant women and increase their energy intakes, thus promoting weight gain(Major et al., 2008; Nutrition, 1958). Also, there is a positive association between high maternal micronutrient intakes and healthy birth outcomes (Lu et al., 2014).

7.2.4 Study outcome

The primary outcome of this analysis is offspring birthweight in grams (g). Secondary outcomes include the odds of small-for-gestational-age (SGA) and large-for-gestational-age (LGA) babies. An SGA baby is characterised when an offspring is $<10^{th}$ centile on the customised centile chart (Clausson et al., 2001). An LGA baby is characterised when an offspring is $>90^{th}$ centile in the customised centile chart (Pasupathy et al., 2011). The bulk centile calculators (BCC) from the Perinatal Institute were used to extract the centiles for the birthweight data in DNBC and MoBa (Gardosi, 2004; Gardosi et al., 1992) (refer Methods in Chapter 5).

7.2.5 Statistical methods

The means and standard deviations (mean[SD]), and absolute frequency distributions with percentages (n (%)) are calculated for the demographic characteristics of interest in both birth cohorts (see Table 4 in Chapter 3).

7.2.5.1 Reduced rank regression derived dietary patterns

In order derive dietary patterns related to the disease of interest, i.e. gestational weight gain this study has used reduced rank regression (RRR), by including its risk factors (response variables) (for a detailed justification refer 7.4.2 in Discussion).

The RRR was conducted using the PROC PLS in SAS 9.4 because PROC PLS minimises sample response prediction error by extracting linear combinations of uncorrelated food groups that explain maximum variance of the risk factors related to gestational weight gain.

The statistical analysis in this chapter was performed separately within MoBa and DNBC because both cohorts had different study design, constructed and recorded data in baseline questionnaires differently, their FFQ covered maternal dietary intakes for different gestational periods, and used country specific food composition tables to extract the dietary variables.

In the RRR model, there were two sets of variables: predictors and response variables, respectively. The 33 food groups (in MoBa analysis) and 40 food groups (in DNBC analysis) were

predictors, and the risk factors that contributed in gestational weight gain were *response variables*. The number of dietary patterns extracted is determined by the number of response variables included in the RRR model as the RRR initiates linear function from the correlation matrix of the response variables. The loadings produced from this model represent the correlation coefficients between the food groups and the dietary patterns. A positive loading describes a positive correlation between the food group and a pattern, whereas a negative loading describes a negative correlation. Further, to determine the degree of adherence to a particular dietary pattern of each participant, patterns scores were computed by using the RRR loadings. The scores are derived by the sum of food group variables weighted by their loadings. Therefore, the dietary pattern scores will represent the degree of adherence to a specific dietary pattern by explaining maximum variance of the dietary intakes correlated with the GWG risk factors; for example, high dietary pattern score represented high adherence and vice versa.

7.2.5.2 Definition of response variables

The response variables that were known to be associated with the contribution of gestational weight gain were chosen for the RRR analyses. These were identified based on high statistical power studies and systematic reviews. The response variables included pre-pregnancy BMI, total energy intake, smoking and physical activity during pregnancy. A detailed justification is provided for each response variable in turn below.

The first response variable is *pre-pregnancy body mass index* because it has been suggested that women with high pre-pregnancy BMI have a high risk of postpartum weight retention and fetal macrosomia (Ganer Herman et al., 2019) (Akgun et al., 2017; McDowell et al., 2019; Samura et al., 2016).

The second response variable is *total energy intake* because it is suggested to be positively associated with gestational weight gain; women who consume higher energy intakes are more likely to gain more weight during pregnancy, in an effort to maintain adequate energy supply for the fetal growth (Jebeile et al., 2016; King, 2007; Streuling et al., 2011; Tielemans et al., 2015).

The third response variable is *maternal physical activity*. As per literature women who maintained light to moderate physically activity levels during their pregnancies had controlled weight gain and better pregnancy outcomes including lower risk of caesarean section, and risk of SGA and LGA babies as compared to women who had low physical activity levels (Hui et al., 2014; Khan, 2017; Vargas-Terrones et al., 2019).

Finally, the fourth response variable was *maternal smoking habits* as it is suggested to influence the maternal weight gain; the nicotine content in cigarettes are likely to affect the appetite levels in pregnancy, thus being associated with lower caloric intakes in pregnant women (Chen et al., 2012; Mineur et al., 2011). According to the (Lindberg et al., 2016)study, current smokers were more likely to gain less gestational weight, whereas former smokers were more likely to gain excessive weight during pregnancy(Suliga et al., 2018).

7.2.5.3 Regression models for the association between GWGDP scores and birth outcomes

For interpretation of the RRR model results, the dietary pattern scores of the participants were expressed at an increment unit of 1SD to allow for comparability amongst the intakes within the differing dietary patterns, and to represent realistic changes in the birthweight which could make the associations clinically relevant (Lagiou et al., 2004). This decision was taken in order to derive achievable increments representing realistic changes in birthweight.

The associations between the gestational weight gain dietary pattern scores (exposure) and birthweight (g) were examined using multiple linear regression models, and the odds of SGA and LGA babies (outcomes) were examined using multiple logistic regression models

Regression analyses was conducted using two models: Model 1 and Model 2. Model 1 only adjusted for maternal age. Model 2 additionally adjusted for smoking habits, alcohol intake, physical activity, use of dietary supplements, pre-pregnancy BMI and total energy intake. However, the SGA and LGA baby models were not adjusted for pre-pregnancy BMI because the customised birth centile charts were pre-adjusted for maternal height and weight in the GROW software (Perinatal-Institute, 2017). As previously discussed in Chapter 4,5 and 6, the SGA and LGA data were binary outcomes. The estimates provided in the logistic regression models were interpreted as odds ratios (OR).

The statistical significance was set at $p<0.05$. All analyses in this chapter were performed using the Stata SE/15.1 version. The reduced rank regression procedure was conducted using PROC PLS in SAS 9.4 (SAS Institute, Inc.). The SAS code applied to this analysis is attached in the Appendix C.4.

7.3 Results

7.3.1 Explained variations of the predictors and response variables in MoBa and DNBC

There were four gestational weight gain dietary patterns (GWGDP) extracted from the reduced rank regression analysis separately from MoBa and DNBC. The dietary patterns explained for 17% and 19% of the total variance in the predictors (food groups) in MoBa and DNBC, respectively (refer Table 22).

Four risk factors of GWG were identified *a priori* and then included in the RRR model to extract dietary patterns for predicting gestational weight gain. The number of dietary patterns is determined by the number of risk factors included. Therefore, there were four dietary patterns extracted. The GWGDPs are labelled as follows: GWGDP 1 represents the risk factor: pre-pregnancy BMI and is labelled as "mixed" in MoBa and "cereals and animal fat" in DNBC. GWGDP 2 represents the risk factor: total energy intakes and is labelled as "fish and coffee" in MoBa and "beverage" in DNBC. GWGDP 3 represents the risk factor: physical activity and is labelled as "added sugar" in MoBa and "meat" in DNBC. Lastly, GWGDP 4 represents the risk factor: smoking and is labelled as "animal meat and SSB" in MoBa and "healthy, low fat" in DNBC.

Therefore, after using the RRR analyses amongst MoBa and DNBC, the total variance explained by the four risk factors in the GWGDP is 18% (in MoBa) and 31% (in DNBC). Further, the table provides the variance explained by each risk factor within each GWGDP in order to provide the total explained variance in the risk factors. For example, the highest percentage (%) of explained variance in the risk factors was in GWGDP 3 in MoBa (15.33%) and GWGDP 1 in DNBC (25%). In addition, observing the maximum variance explained by each risk factor within each GWGDP helps to understand the highest % of variance explained by GWG risk factors in the two birth cohorts. In this RRR analyses, smoking in MoBa (59%) and total energy intake in DNBC (98%) explained for the highest % of explained variance in each GWGDP which therefore, contributed to the cumulative percentage of the total % of explained variance in MoBa (18%) and DNBC (31%). This will help in interpreting and better understanding the GWGDP that explains the maximum variation of the GWG risk factor. The percentages of explained variation are necessary to explore the associations between GWGDP and birth outcomes as dietary patterns scores represent the dietary patterns explaining maximum variance for the GWG risk factors. The percentages provided for the explained variances of the food groups and risk factors under each GWGDP is a cumulative aggregate out of the total variance explained by all the food groups and risk factors in the cohort.

For example, in Table 23 and 24, a high adherence to “animal meat and SSB” dietary pattern (GWGDP 4 represented the risk factor: smoking) was associated with lower birthweight and higher odds of SGA baby. Its implications could be that it might not be the food items in the dietary patterns per se but could also be due to the association between maternal smoking and lower birthweights, and high risk of SGA babies (Abraham et al., 2017; Pollack et al., 2000; Suzuki et al., 2016; Vardavas et al., 2010).

Table 22 Explained variations of the food group intakes and risk factors (response variables) within MoBa and DNBC cohorts

		Gestational weight gain dietary patterns (GWGDP)				Total explained variance (%)
		1	**2**	**3**	**4**	
Explained variation in food groups (%)	MoBa	3.36	3.54	6.05	4.26	17.21
	DNBC	7.18	5.24	3.18	3.72	19.32
Explained variation in risk factors (%) within MoBa	Pre-pregnancy BMI	0.92	1.80	0	0.79	
	Total energy intake	6.47	6.64	1.41	6.05	
	Physical activity	4.14	4.14	0.42	2.89	
	Smoking	59.56	59.57	59.49	59.52	
	Total Y variation	0.45	0.26	15.33	1.98	18.02
Explained variation in risk factors (%) within DNBC	Pre-pregnancy BMI	1.24	3.26	8.87	8.98	
	Total energy intake	98.03	98.03	98.13	98.13	
	Physical activity	0.15	3.35	3.41	4.77	
	Smoking	0.21	11.29	12.58	12.81	
	Total Y variation	24.91	4.07	1.76	0.42	31.16

7.3.2 GWG dietary patterns in MoBa

In MoBa (see Table 23), GWGDP 1 was labelled as “mixed” pattern as it was characterised by high factor loadings of colas, low fat milk, fruits and dried fruit, red meat, pork, poultry, unrefined bread, vegetables, cheese spreads, fish products, and whole and low fat yogurt, and low factor loadings of added sugar, refined bread, desserts and sweets, whole milk, beverages (tea, coffee, and soy, rice and chocolate milks), breakfast cereals, and fats and oils. GWGDP 2 was labelled as “fish and coffee” pattern and was characterised by high factor loadings of coffee, marine food (lean fish and fish products), vegetables, and fruits and dried fruits and low factor loadings of cereals (rice and millet, refined bread), creams and mayonnaise, fruit juices, jams and syrups, animal meat (pork, beef and veal, and offal), miscellaneous food products (popcorn, potato crisps, ketchups and sauces), fats and oils, and desserts and sweets. GWGDP 3 was labelled as “added sugar” pattern as it was characterised by high factor loadings of added sugar, refined carbohydrate foods (refined bread, desserts and confectionery), fruit and fruit products (dried fruits, fruit juices and syrups), and cheese spreads. However, there were no negative factor loadings observed in GWGDP 3. Finally, GWGDP 4 was labelled as “animal meat

and sugar-sweetened beverages (SSB)" pattern and was characterised by high factor loadings of colas, animal meats (pork, beef and veal), and fruits and dried fruit and low factor loadings of dairy products (low fat milk and yogurt, cheese spreads), cereals (unrefined bread, rice and millets, breakfast cereals, pasta, spaghetti and noodles), creams and mayonnaise, fruit juices and syrups, vegetables, and high protein foods (lean and fatty fish, fish products, molluscs, eggs and poultry, nuts and oilseed).

Table 23 Factor loadings of the food groups in the four gestational weight gain dietary patterns (GWGDP) within MoBa

Food groups	**Factor loadings[2]**			
	GWGDP 1 Mixed	GWGDP 2 Fish and coffee	GWGDP 3 Added sugar	GWGDP 4 Animal meat and SSB*
Added sugar	-0.10	0.21	0.60	0.14
Fruits and dried fruit	0.28	0.24	0.21	0.28
Nuts and oilseed	0	0.04	0.08	-0.13
Potato (baked, cooked and boiled)	0.01	0.05	0.11	0.16
Whole and low-fat yogurt	0.13	0.07	0.20	-0.07
Rice and millet (Couscous)	-0.10	-0.25	0.04	-0.02
Creams and mayonnaise	0	-0.11	0.12	-0.01
Unrefined bread	0.17	0.13	0.10	-0.21
Refined bread	-0.02	-0.11	0.20	0.17
Fruit juices, jams and syrup	0.02	-0.14	0.20	-0.18
Other milk (soya, rice and chocolate)	-0.09	-0.07	0.10	0.02
Tea	-0.10	0.05	0.06	-0.27
Coffee	-0.50	0.57	0.09	0.10
Alcoholic beverages	0.03	0.01	0.03	0.01
Colas	0.31	0.09	0.11	0.48
Whole milk	-0.23	0.05	0.15	0.04

[2] Factor loadings in the RRR model represent the correlation coefficients between the dietary pattern and the food groups.

*Sugar sweetened beverages

Low fat milk	0.29	0.08	0.16	-0.13
Breakfast cereals	-0.07	0.02	0.10	-0.16
Desserts, sweets and chocolate	-0.04	-0.21	0.24	0.01
Fats and oil	-0.08	-0.24	0.12	0.01
Cheese spreads	0.19	0.1	0.23	-0.16
Pasta, spaghetti and noodles	0.09	0.12	0.12	-0.11
Vegetables	0.13	0.24	0.11	-0.10
Fatty fish	0.05	0.19	0.05	-0.22
Lean fish	0.09	0.33	0.09	-0.11
Seafood and molluscs	0	0.08	0.06	0
Fish products	0.17	0.25	0.13	-0.13
Egg and poultry	0.17	0	0.07	-0.23
Red meat	0.25	0.03	0.16	0.16
Pork	0.22	-0.02	0.18	0.34
Beef and veal	0.14	0	0.13	0.22
Offal	0.05	0	0.04	0.07
Miscellaneous food (ketchup, sauces, pizza, popcorn, chips)	0.19	-0.07	0.15	0.10

[1] Factor loadings in the RRR model represent the correlation coefficients between the dietary pattern and the food groups.

7.3.3 GWG dietary patterns in DNBC

In DNBC (see Table 24), GWGDP 1 was labelled “cereals and animal fats” pattern and was characterised by high factor loadings of whole and refined grains, animal fats, added sugar, margarine, and potato products. Only low energy drinks had a negative factor loading in this dietary pattern. GWGDP 2 was labelled “beverage” pattern and was characterised by high factor loadings of coffee and high energy drinks, and low factor loadings of fibrous foods (whole grains, breakfast cereals, fruit, green leafy vegetables, other vegetables, tomatoes, dried fruit), beverages (vegetable and fruit juice), dairy products (ice cream, low fat dairy, cheese), high protein foods (fish, poultry nuts, beans and lentil) soy products, sweets and dessert, and margarine. GWGDP 3 was labelled as “meat” pattern and was characterised by high factor

loadings of red meat, processed meat and low energy drinks and low factor loadings of added sugar, breakfast cereals, fibrous foods (soy products, dried fruit, beans and lentil, green leafy vegetables, tomatoes, nuts, other vegetables, fruit), sweets and dessert, fats and oils (animal and vegetable fats, margarine), ice cream and high fat dairy, beverages (tea, coffee and vegetable juice), and protein foods (eggs and fish). Finally, GWGDP 4 was labelled as "healthy, low fat" pattern and was characterised by high factor loadings of fish, low-fat dairy, beverages (coffee and low energy drinks), and fibrous foods (fruit, tomatoes, beans and lentil, dried fruit, other vegetables), and low factor loadings of added sugar, high fat dairy and ice cream, fats and oils (animal and vegetable fat, margarine), refined grains, tea, snacks, potato products, processed and red meats, and dressings.

Table 24 Factor loadings of the food groups in the four gestational weight gain dietary patterns (GWGDP) within DNBC

Food group	**Factor loadings[3]**			
	GWGDP 1 Cereals and animal fat	GWGDP 2 Beverage	GWGDP 3 Meat	GWGDP 4 Healthy, low fat
Low fat dairy	0.17	-0.01	0.20	0.28
High fat dairy	0.15	0.05	-0.20	-0.27
Ice cream	0.08	-0.03	-0.01	-0.03
Breakfast cereals	0.10	-0.27	-0.16	0.09
Wholegrains	0.30	-0.17	0.05	0.04
Refined grains	0.25	0.151	0.17	-0.12
Fruit	0.11	-0.30	-0.05	0.26
Offal	0.04	0.04	0.04	0.02
Processed meat	0.24	0.16	0.29	-0.07
Red meat	0.21	0.18	0.35	-0.20
Fish	0.17	-0.12	-0.05	0.26
Shellfish	0	0	0	0
Poultry	0.07	-0.15	0.04	0.23
Eggs	0.21	0.01	-0.11	0.10
Animal fats	0.33	0.23	-0.21	-0.32
Vegetable fats	0.19	0.07	-0.16	-0.05

[3] Factor loadings in the RRR model represent the correlation coefficients between the dietary pattern and the food groups.

Margarine	0.23	-0.04	-0.06	-0.15
Sweets and dessert	0.22	-0.04	-0.15	-0.11
Tea	0.04	-0.11	-0.09	0
Coffee	0.07	0.42	-0.42	0.28
High energy drinks	0.11	0.27	0.01	0.02
Low energy drinks	-0.01	0.13	0.30	0.255
Alcoholic beverages	0.02	0.04	0	0.09
Snacks	0.11	0.18	0.04	-0.01
Vegetable juice	0.01	-0.01	-0.04	0.04
Fruit juice	0.15	-0.07	0.05	0.11
Fruit syrups and jams	0.14	0.07	0.19	0.02
Nuts	0.08	-0.06	-0.11	0.07
Other vegetables	0.13	-0.19	-0.06	0.26
Potato products	0.23	0.15	0.17	-0.01
Green leafy vegetables	0.06	-0.21	-0.11	0.12
Tomatoes	0.10	-0.18	-0.09	0.21
Soy products	0	-0.03	-0.04	0.03
Dried fruit	0.08	-0.25	-0.11	0.15
Dressings	0.03	0.02	0.14	-0.03
Beans and lentil	0.03	-0.21	-0.26	0.23
Cheese	0.20	-0.04	0	0.11
Added sugar	0.28	0.11	-0.04	-0.100

7.3.4 Association between gestational weight gain dietary pattern (GWGDP) and change in birthweight in MoBa and DNBC

In MoBa (See Table 23), the four GWGDPs were labelled as “mixed” GWGDP, “fish and coffee” GWGDP, “added sugar” GWGDP and “animal meat and sugar-sweetened beverage (SSB)” GWGDP. In Table 25, Model 2, an each additional 1SD of a “fish and coffee” GWGDP score was positively associated with higher birthweight (6g; 95% CI -1g to 11g; p=0.01). Whereas, an each additional 1SD of an “animal meat and SSB” GWGDP score was associated with lower birthweight (3g; 95% CI 0.25g to 5g;p=0.03).

In DNBC (See Table 24), the four GWGDPs were labelled as “cereals and animal fat” GWGDP, “beverage” GWGDP, “meat” GWGDP, and “healthy and low fat” GWGDP. In Table 25, Model 2, each additional 1SD of a “beverage” GWGDP score was associated with lower birthweight (41g; 95% CI 33g to 47g; p<0.001). Further, an each additional 1SD of a “meat” GWGDP score was positively associated with higher birthweight (20g;95% CI 14g to 27g; p<0.001).

Table 25 Association between gestational weight gain dietary patterns (GWGDP) and change in birthweight in MoBa and DNBC

RRR dietary pattern GWGDP) (increment per 1SD)	**BW(g), Model 1**			**BW (g), Model 2**		
MoBa (n=85574)	**BW[4]**	**95% CI**	***p* value**	**BW [3,5]**	**95% CI**	***p* value**
Mixed	5	-3 to 7	<0.001	2	-1 to 5	0.17
Fish and coffee	-1	-4 to 3	0.64	6	-1 to 11	0.01
Added sugar	1	-1 to 3	0.28	2	-1 to 6	0.19
Animal meat and SSB[6]	-0.2	-2 to 2	0.80	-3	-5 to -0.2	0.03
DNBC (n=67,803)	**BW[3]**	**95% CI**	***p* value**	**BW [3,4]**	**95% CI**	***p* value**
Cereals and animal fat	9	2 to 15	0.01	-7	-22 to 8	0.35
Beverage	-57	-63 to -51	<0.001	-41	-47 to -33	<0.001
Meat	52	46 to 58	<0.001	20	14 to 27	<0.001
Healthy, low fat	11	6 to 17	<0.001	6	0 to 13	0.05

[4] Adjusted for maternal age

[5] Additionally adjusted for pre-pregnancy body mass index, alcohol intake, smoking, physical activity, dietary supplements

[6] Sugar sweetened beverages (SSB)

7.3.5 The relation between gestational weight gain dietary pattern (GWGDP) and odds of small-for-gestational-age (SGA) baby in MoBa and DNBC

In Table 26, in MoBa under Model 2, an each additional 1SD of an "animal meat and SSB" GWGDP score was associated with higher odds of SGA baby (1.01, 95%CI 1.00 to 1.03; p=0.04). In DNBC, Model 2, an each additional 1SD of a "beverage" GWGDP score was associated with higher odds of SGA baby (1.26;95% CI 1.21 to 1.31; p<0.001). Whereas, an each additional 1SD of a "meat" GWGDP score was associated with lower odds of SGA baby (0.88; 95%CI 0.85 to 0.91; p<0.001).

Table 26 Association between gestational weight gain dietary patterns (GWGDP) and odds of small-for-gestational-age (SGA) baby in MoBa and DNBC

RRR dietary pattern (DP) (increment per 1SD)	Odds of SGA[7] (OR), Model 1			Odds of SGA (OR), Model 2		
MoBa (n=85574)	**OR[2]**	**95% CI**	***p* value**	**OR[2,3]**	**95% CI**	***p* value**
Mixed	0.97	0.96 to 0.99	<0.001	0.99	0.97 to 1.01	0.92
Fish and coffee	1.01	0.99 to 1.03	<0.001	0.98	0.95 to 1.01	0.38
Added sugar	0.99	0.97 to 1.00	0.21	0.98	0.96 to 1.00	0.24
Animal meat and SSB[8]	1.02	1.01 to 1.03	<0.001	1.01	1.00 to 1.03	0.04
DNBC (n=67,803)	**OR[2]**	**95% CI**	***p* value**	**OR[2,3]**	**95% CI**	***p* value**
Cereals and animal fat	0.99	0.95 to 1.03	0.64	1.08	0.99 to 1.18	0.07
Beverage	1.38	1.34 to 1.43	<0.001	1.26	1.21 to 1.31	<0.001
Meat	0.79	0.76 to 0.81	<0.001	0.88	0.85 to 0.91	<0.001
Healthy, low fat	0.99	0.96 to 1.02	0.58	1.00	0.96 to 1.04	0.80

[6] Bulk centile calculators (BCC) for North European region in GROW software was used to derive centiles after adjusting for maternal height, weight, parity, ethnicity, gestational age at delivery and sex of the baby

[2] Adjusted for maternal age

[3] Additionally adjusted for alcohol intake, smoking, physical activity, dietary supplements

[8] Sugar sweetened beverages (SSB)

7.3.6 The relation between gestational weight gain dietary pattern (GWGDP) and odds of large-for-gestational-age (LGA) baby in MoBa and DNBC

In Table 27, in MoBa under Model 2, an each additional 1SD of "mixed" GWGDP and "animal meat and SSB" GWGDP scores were both positively associated with higher odds of LGA baby (1.03, 95%CI 1.01 to 1.05; p<0.001). Whereas, an additional increment per 1SD of "fish and coffee" GWGDP score was associated with lower odds of LGA baby (0.95, 95%CI 0.92 to 0.98; p<0.003). In DNBC, Model 2, an each additional 1SD of a "beverage" GWGDP score was associated with lower odds of LGA baby (0.86;95% CI 0.82 to 0.90; p<0.001). Whereas, an each additional 1SD of a "meat" GWGDP score was positively associated with higher odds of LGA baby (1.16; 95%CI 1.12 to 1.21; p<0.001).

Table 27 Association between gestational weight gain dietary patterns (GWGDP) and odds of large-for-gestational-age (LGA) baby in MoBa and DNBC

RRR dietary pattern (DP) (increment per 1SD)	**Odds of LGA[6] (OR), Model 1**			**Odds of LGA (OR), Model 2**		
MoBa (n=85574)	**OR[2]**	**95% CI**	***p* value**	**OR[2,3]**	**95% CI**	***p* value**
Mixed	1.00	0.99 to 1.01	0.32	1.03	1.01 to 1.05	<0.001
Fish and coffee	0.96	0.94 to 0.98	<0.001	0.95	0.92 to 0.98	0.003
Added sugar	1.02	1.00 to 1.03	<0.001	1.01	0.98 to 1.03	0.36
Animal meat and SSB[9]	1.02	1.01 to 1.03	<0.001	1.03	1.01 to 1.05	<0.001
DNBC (n=67,803)	**OR[2]**	**95% CI**	***p* value**	**OR[2,3]**	**95% CI**	***p* value**
Cereals and animal fat	1.05	1.01 to 1.09	0.01	1.00	0.91 to 1.09	0.94
Beverage	0.82	0.79 to 0.85	<0.001	0.86	0.82 to 0.90	<0.001
Meat	1.21	1.17 to 1.25	<0.001	1.16	1.12 to 1.21	<0.001
Healthy, low fat	1.02	0.98 to 1.05	0.20	1.01	0.98 to 1.05	0.30

[9] Sugar sweetened beverages (SSB)

[6] Bulk centile calculators (BCC) for North European region in GROW software was used to derive centiles after adjusting for maternal height, weight, parity, ethnicity, gestational age at delivery and sex of the baby

[2] Adjusted for maternal age

[3] Additionally adjusted for alcohol intake, smoking, physical activity, dietary supplements

7.4 Discussion

The current study separately conducted analysis within MoBa and DNBC, and identified four gestational weight gain dietary patterns (GWGDPs) that represented the maximum variance of the response variables associated with gestational weight gain. In MoBa, the four GWGDPs were labelled as “Mixed” GWGDP, “Fish and coffee” GWGDP, “Added sugar” GWGDP and “Animal meat and sugar-sweetened beverage (SSB)” GWGDP. In DNBC, the four GWGDPs were labelled as “Cereals and animal fat” GWGDP, “Beverage” GWGDP, “Meat” GWGDP, and “Healthy and low fat” GWGDP.

The GWGDPs in MoBa explained a total variance of 18% in the risk factors. Whereas, the GWGDP in DNBC explained a total variance of 31%. Amongst the risk factors included in the reduced rank regression, maximum variance was explained by maternal smoking(60%) in MoBa and total energy (98%) in DNBC.

In MoBa, a high adherence to a “fish and coffee” GWGDP was positively associated with birthweight, whereas, a high adherence to an “animal meat and SSB” GWGDP was negatively associated with birthweight. In DNBC, a high adherence to “meat” and “healthy, low fat” GWGDPs were associated with birthweight, whereas, a high adherence to a “beverage” GWGDP was negatively associated with birthweight. It must be noted that these results had high statistical significance and no clinical significance.

Amongst the odds of SGA babies, in MoBa, high adherence to an “animal meat and SSB” GWGDP was associated with higher odds of SGA baby. In DNBC, a high adherence to “beverage” and ”meat” GWGDPs were associated with higher and lower odds of SGA baby, respectively.

Amongst LGA babies, in MoBa, a high adherence to “mixed” and “animal meat and SSB” GWGDPs were associated with higher odds of LGA baby, whereas, a high adherence to a “fish and coffee” GWGDP was negatively associated with odds of LGA baby. In DNBC, a high adherence to a “meat” GWGDP was positively associated with higher odds of LGA baby, whereas, a high adherence to a “beverage” GWGDP was negatively associated with lower odds of LGA baby.

7.4.1 Comparison with other studies

According to the knowledge of the author, this is the first study to identify dietary patterns related to gestational weight gain risk factors in a reduced rank regression analysis and explore its association with birth outcomes amongst two large cohorts. One study had included gestational weight gain, and mid-pregnancy fasting glucose as the risk factors and derived two dietary patterns associated with fetal adiposity (response variable) using the reduced rank regression approach (Starling et al., 2017). Although their dietary pattern results were

associated with gestational weight gain as the risk factor, their results for fetal adiposity were independent of alcohol, smoking, physical activity, and pre-pregnancy BMI. They suggested that higher maternal glucose and infant adiposity was associated with high adherence of the dietary pattern characterised by poultry, potato and other starchy vegetables, and unrefined grains. The Starling study's result is not in line with the results observed in this study and might be because the dietary pattern extracted in the Starling study was based on maternal glucose as a risk factor. In this study, maternal glucose was not included because data was not available, the study objectives would differ, and dietary requirements and guidelines, especially for CHO intakes are separate than non-diabetic women.

However, the second risk factor in the Starling study, maternal GWG was associated with high adherence to a dietary pattern characterised by high intakes of poultry, nuts and oilseeds, fruits, whole grains, and cheese. However, the dietary pattern was not associated with the study's response variable- infant adiposity. This pattern was similar to the "Mixed" GWGDP in MoBa characterised by high factor loadings of fruits and dried fruit, red meat, colas, pork, poultry, unrefined bread, vegetables, and cheese spreads. However, the Mixed GWGDP in this study had a positive association with higher birthweight after covariate adjustment (see Covariates section in this chapter).

In this study, the dietary patterns extracted associated with gestational weight are similar to previous studies. A study identified dietary patterns related to gestational weight gain and used factor analysis to extract them. While factor analysis extracts linear combinations of uncorrelated dietary patterns of the participants, the patterns explain the maximum variance of the food groups (predictors) and not the response variable of interest, i.e., gestational weight gain (Shin et al., 2016). However, the food groups extracted associated in preventing excessive gestational weight gain in the (Shin et al., 2016) study are similar to the food groups in this study, which include high in meat, dairy products, fruits, vegetables, and nuts and seeds.

Another Finnish study (Uusitalo et al., 2009) conducted a PCA analysis and suggested a positive association between high adherence to "fast food" dietary pattern and higher gestational weight gain of 10 grams/week. Their pattern was characterised by high intakes of soft drinks, fruit juices, processed meats, desserts, and refined bread. It was similar to the 2 dietary patterns in MoBa associated with gestational weight gain, including "animal meat and SSB" and "added sugar" GWGDPs which are together characterised by high factor loadings of pork, beef and veal, colas, fruit juices, desserts and sweets, fruits and dried fruits, fruit juices, jams and syrups, and refined bread.

In this study the Animal meat GWGDP and Mixed GWGDP in MoBa, and Meat GWGDP in DNBC had positive associations with higher odds of LGA baby. The two GWGDPs in MoBa mainly consisted of high protein food groups including animal meats (pork, beef and veal, red and processed meat) and free sugars through sugar-sweetened beverages, fruits and dried fruits; however, the GWGDP in DNBC mainly consisted of red and processed meats. Additionally, the Meat GWGDP in DNBC and Fish and coffee GWGDP in MoBa were also positively associated with higher offspring birthweights (refer to Table 25 in section 7.3.4 in the results section of this chapter). Hence higher participant scores for Animal meat and SSB GWGDP and Beverage GWGDP may explain the association with a higher odds of large-for-gestational-age babies (Tzanetakou et al., 2011).

The food groups in the GWGDPs listed above have high protein content which is placentally transferred for fetal growth (organs, muscle mass)(Robinson and Prendergast, 1996). In DNBC, it was observed a high adherence to a Meat GWGDP was positively associated with higher odds of LGA baby. This might imply that a high protein dietary pattern might improve the fetal outcome. However, cautious care must be taken to avoid overconsumption of protein as it could be associated with heavier offsprings. This is because amino acids, a basic form of protein help produce high insulin levels. Maternal consumption of food groups high in CHO, including SSBs, fruits and dried fruits, refined bread are assimilated into their basic form – glucose and are placentally transferred for fetal glycogenesis. Therefore, if high protein and carbohydrate intakes are consumed, a high maternal glucose and amino acids are placentally transferred and will be associated with fetal hyperinsulinemia and accelerated growth, which could mean an increased odds of LGA baby (Buschur E, 2000; Jolly et al., 2003). According to the Buscher et al. suggested that in the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) trial, almost 78% offsprings were born to non-GDM women. Therefore, the results in this study are in agreement with this evidence (Group, 2009) and might further explain the association and the need to observe the dietary choices of non-GDM women in relation to the odds of LGA babies.

An interesting result in this study was that the two GWGDPs namely, “animal meat and SSB” (MoBa) and “beverage” (DNBC) were associated with lower birthweight and a higher odds of SGA baby. These patterns were characterised by high factor loadings of sugar-sweetened beverages, fruits and dried fruits, animal meat (pork, beef and veal) in MoBa, and sugar-sweetened beverages and coffee in DNBC. The “animal meat and SSB” GWGDP represented the risk factor-maternal smoking, which could partially explain that smoking habits prevent weight gain during pregnancy (Chen et al., 2012) and increase pregnancy complications, including low birthweight and preterm deliveries(Pollack et al., 2000). Studies have suggested a positive

association between maternal smoking and low birthweight (Pollack et al., 2000) and high SGA baby risk (Vardavas et al., 2010). In DNBC the “beverage” GWGDP represented the risk factor – total energy intake and was associated with lower birthweight and high odds of SGA baby, implying that low maternal energy intakes are associated with lower gestational weight (Tielemans et al., 2015) and subsequently affect the fetal growth with higher odds of SGA baby (Abu-Saad and Fraser, 2010).

Another explanation could be the negative effect of maternal caffeine on fetal growth. Both GWGDPs in the two cohorts had sugar-sweetened beverages in common, with a high factor loading for coffee in DNBC, which are primary sources of caffeine (Verster and Koenig, 2018). Studies have suggested that high maternal caffeine intake above 200 mg are associated with low birthweight (LBW) (Chen et al., 2014) and high risk of SGA baby(Bakker et al., 2010). Also, the CARE study suggested a similar result that high maternal caffeine consumption (200-299mg/day) was associated with an increased odds of SGA baby (Boylan S, 2010). Further, according to two studies, fetal growth is largely dependent on the speed of the caffeine metabolism in the mother’s body, meaning slower the metabolism and renal clearance more fetal exposure(Nawrot et al., 2003; Okubo et al., 2015). Previously the cut-off limit was <300mg/day and has been recently limited to <200mg/day by the European Food Safety Authority and American Institute of Medicine (European Food Safety Authority (EFSA) Panel on Dietetic Products and Allergies, 2015) (Pray et al., 2014). However, in MoBa, there was no evidence of an association between the “Fish and Coffee” pattern and odds of SGA baby, but there was a negative trend observed.

The result for the Fish and Coffee GWGDP is in line with previous literature (Brantsaeter et al., 2012; Imhoff-Kunsch et al., 2012) suggesting that the high maternal fish consumption improved poor birth outcomes such as the odds of SGA baby and birthweight. This is because fish and fish products are a major source of omega-3 polyunsaturated fatty acids, in particular, docosahexaenoic acid (DHA, 22:6n-3) are placentally transferred for fetal neural and visual development and accrete the maximum after the second trimester (Amezcua-Prieto et al., 2018; Hanebutt et al., 2008; Imhoff-Kunsch et al., 2012; Koletzko et al., 2007). Another study in MoBa explored the associated between maternal marine food intake and birth weight, length and head circumference and suggested that higher seafood consumption, especially lean fish, is positively associated with higher birthweight. This is in agreement with this study as the “Fish and Coffee” dietary pattern in MoBa was characterised by a high factor loading of lean fish (Brantsaeter et al., 2012).

The decision to include four risk factors in the reduced rank regression analysis was based on *a priori* literature. According to previous studies (Akgun et al., 2017; Brantsaeter et al., 2012; Chen et al., 2012; Ganer Herman et al., 2019; Hui et al., 2014; Jebeile et al., 2016; Khan, 2017; King, 2007; McDowell et al., 2019; Mineur et al., 2011; Samura et al., 2016; Streuling et al., 2011; Tielemans et al., 2015; Vargas-Terrones et al., 2019), risk factors including smoking, total energy intake, physical activity and pre-pregnancy BMI were suggested to determine the degree of gestational weight gain.

The results in this study suggest that smoking and total energy intake explained maximum variance amongst the four GWGDP identified in MoBa and DNBC. During pregnancy conditions, including high or low appetite levels(Orloff et al., 2016), morning sickness (Crozier et al., 2017), and gastroesophageal reflux (Vazquez, 2015) affect the maternal energy intakes, which might consequently determine the weight gained. Smokers have lower dietary intakes than non-smokers because of the negative effect of nicotine on the appetite centres in the brain(Chen et al., 2012). In this study, around 26% and 9% of women were smokers at the start of the pregnancy within DNBC and MoBa, respectively (see Chapter 3 under section 3.3 for demographic characteristics).

In comparison the other two risk factors – physical activity and pre-pregnancy BMI explained low variance for the gestational weight gain dietary patterns and this might explain that most women had almost very light physical activity levels around 15 and 12 gestational weeks in MoBa (yes=59%) and DNBC (yes=37%), respectively (see Chapter 3 for demographic characteristics given in Table 4). Pre-pregnancy BMI explained low variance for the gestational weight gain dietary patterns because the mean pre-pregnancy BMI was 24 (SD 4) in both the cohorts which is classed under the 'normal BMI (18.5 to 24.9)' category by the World Health Organisation (WHO)(Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults, 1998; Seidell and Flegal, 1997).

This study found no evidence of an association between two GWGDPs with birth outcomes. Both GWGDPs explained for the low variance of their risk factors, "Added sugar" GWGDP for physical activity in MoBa explained the low variance of 0.42% and "Cereals and fat" GWGDP for pre-pregnancy BMI in DNBC explained the low variance of 1.24%.

It might be argued that the two GWGDPs consisted of food groups high in carbohydrate and fats possibly linked with the metabolic pathways affecting fetal growth, however, few food groups in both patterns including, fruits and dried fruits, fruit juices, syrups and jams, refined and unrefined bread, potato products, fish products, pork and sugar-sweetened beverages were in common with the other GWGDPs of the risk factors associated with birth outcomes. It

might mean that in comparison with total energy intake (Streuling et al., 2011; Tielemans et al., 2015) and maternal smoking habits (Lindberg et al., 2016; Suliga et al., 2018) as GWG risk factors, physical activity (in MoBa) and pre-pregnancy BMI (in DNBC) might not have thoroughly predicted the contribution of the gestational weight gain as an intermediate in the maternal diet-birth outcome pathway in this study.

7.4.2 Comparison between RRR approach with statistical methods including PCA and factor analysis

The RRR method was used in this study as it extracts linear combinations of food groups, which are outcome specific. The patterns explain maximum variance in the risk factors of gestational weight gain (response variable). This was demonstrated in the (Hoffmann et al., 2004) (Batis et al., 2016) studies, where they compared the RRR and PCA methods to extract dietary patterns related to Type 2 Diabetes Mellitus and observed that the dietary patterns explained for maximum variance in RRR and lesser in the PCA analysis.

According to the Hoffman study (Hoffmann et al., 2004), the RRR method is *a posteriori* method- a mix of *a priori* and exploratory statistical method because it uses information from both the dietary data from a cohort and published literature for selecting risk factors of gestational weight gain. However, a limitation of RRR is that the coefficients of the factor scores are limited to the data in hand and cannot be reproduced with other cohort datasets. This implies that coefficients of the risk factor scores of one study cannot be used as a template in other cohort datasets to duplicate the RRR analysis (Imamura et al., 2009) (Hoffmann et al., 2004).

In contrast, PCA and factor analysis are data reduction techniques that provide a snapshot of a large dataset by producing components of dietary intakes (dietary patterns) describing the maximum variance of the maternal dietary intakes (predictor) of a cohort (refer Chapter 6 under section 6.4.1 for PCA dietary patterns within MoBa) (DiBello et al., 2008; Shin et al., 2016). The dietary patterns extracted in factor analysis and PCA do not explain the importance or the potential contribution of specific food intakes in the GWG pathway. Another difference is that the RRR reduces the dimension of the food group variables to the dimension of the number of risk factors included in the model (Hoffmann et al., 2004). In the sense, the number of dietary patterns extracted depends on the number of risk factors included. However, in PCA and factor analysis, this is not applicable, because the extracted dietary patterns (components) depend on the number of food group variables included in the model. The Hoffman study (Hoffmann et al., 2004) tested the first 10 components (dietary patterns) of a PCA model and found no association between dietary patterns and risk of Diabetes Mellitus. However, on including specific risk factors of Diabetes Mellitus which were based on literature in the RRR model, the

dietary patterns not only explained the variance in Diabetes Mellitus but also were specific in number, easier for a thorough examination.

Finally, compared to RRR, the PCA analysis is advantageous because it helps in exploratory analysis for understanding the data more clearly. However, the objective of this study required RRR to extract dietary patterns specific for GWG risk factors.

Also, it might be argued that the current study could have used the variable for gestational weight gain (GWG) itself to extract dietary patterns. However, this approach was not possible because the main objective of the analysis was to create and explore the dietary patterns contributing to weight gain in pregnancy using RRR. Therefore, in order to adequately derive maternal dietary patterns, the RRR analysis fundamentally includes GWG risk factors contributing to GWG, instead of using the GWG variable itself. Thus the main advantage of RRR is that the correlation matrix of the RRR makes use of the risk factors or biomarkers of a disease/outcome of interest to derive dietary patterns explaining maximum variance in the outcome variable, i.e., GWG. Therefore, GWG variable was not used in the analysis.

7.4.3 Strengths and limitations

The gestational weight gain dietary patterns have been extracted from a total sample size of 153,377 mothers-infant pairs from two prospective birth cohorts (MoBa=85574) and (DNBC= 67803).

The systematic study design of both cohorts recorded dietary data in high detail using validated food frequency questionnaires to capture mid-pregnancy dietary intakes (Brantsæter et al., 2008; Mikkelsen et al., 2007). Further, the required data was available in MoBa and DNBC for the RRR, and multiple linear and logistic analyses including, dietary data, response variables, covariates and birth outcomes (Magnus et al., 2006; Olsen et al., 2001).

In this study, the GWGDPs explained a total variance of 18% and 31% in the risk factor variables, which is comparatively higher than other pregnancy-related studies that had extracted RRR-dietary patterns. The Oberman Hurst study extracted two maternal dietary patterns in association with congenital heart defects and reported a total variance of 15% (Obermann-Borst et al., 2011). Another study extracted maternal dietary patterns in association with infant adiposity, which explained for a total variance of 5% in the risk factors, including gestational weight gain and mid-pregnancy fasting glucose (Starling et al., 2017).

The factor loadings for all the food groups presented in the results of this chapter had no cut-offs as opposed to other studies which had the respective cut-offs, (Starling et al., 2017), (Jacobs et al., 2017) and (Shin et al., 2015) had a >0.20 cut-off, and (Jankovic et al., 2014) set a <0.10

cut-off limit. Presenting factor loadings for all food groups advantageous because it gave an unbiased observation regarding the correlations between all food groups and patterns, rather than the partial presentation of selected food groups with notable factor loadings. Also, there is no appropriate cut-off limit in the RRR analysis, and each factor loading is important in the computation of linear combinations in the RRR matrix for the formation of a dietary pattern that represent the maximum variance of the risk factors related to gestational weight gain, therefore lowering potential bias. Further examination of the correlations which were initially anticipated to occur might not be possible if the loadings below cut-offs are eliminated.

In the regression models, increments units at the rate of 1SD were chosen which covered about quarter of the range of exposure. Further, a 1SD increment allowed for fair comparison between the differing dietary patterns consumed within both cohorts in order to make realistic changes in the birthweight that is more easier to interpret and which might be clinically significant (see Regression models under Statistical analysis section under 7.2.5.3 of this chapter). Also, this provides a better understanding of the resulting implications in the maternal dietary patterns-birth outcome pathway. Furthermore, previous studies also conducted RRR analyses at an increment rate of 1 SD (Batis et al., 2016; de Haas et al., 2018; Tielemans et al., 2015).

First limitation is that the reduced rank regression model did not allow for direct adjustment for covariates associated with the maternal food group intakes (predictors) and GWG risk factors (response variables). However, the analysis in this study did not include pre-adjusted residuals of the predictors and response variables because the same covariates used for pre-adjustment were included as risk factors in the RRR model.

Second limitation was the residual methods. According to one study, the use of the residual method by including energy-adjusted dietary intakes in the RRR is study-specific and should be relevant to the analysis (Batis et al., 2016). Few studies have used the residual method by Willett et al. (Willett et al., 1997) where the energy-adjusted residuals of dietary data are included into the RRR model, but they included a different set of risk factors for the related disease outcome, for example, the (Lamichhane et al., 2014) study included risk factors for arterial stiffness, (Starling et al., 2017) study included risk factors for infant adiposity, and (Obermann-Borst et al., 2011) study included risk factors for a congenital heart defect. Further, in contrast to the studies which adopted this method, two studies, namely the Zutphen Elderly Study (Jankovic et al., 2014) and the McNaughton study (McNaughton et al., 2008) reported that the energy-adjusted dietary patterns using the residual method were similar to the RRR- unadjusted dietary patterns for the risk factors of cardiovascular disease and Type 2 Diabetes Mellitus, respectively.

Another weakness of this study could be that the dietary patterns identified in the RRR analysis only represent the risk factors chosen *a priori*, implying that these results do not account for other risk factors, including metabolic or genetic risk factors possibly involved in gestational weight gain (Obermann-Borst et al., 2011). Hence further exploration of the genetic and metabolic risk factors must be conducted using RRR to understand their contribution in GWG.

Covariates included in the regression models were limited to the data available. The analysis could not include other covariates, including medications, pregnancy-related hypertension, gestational Diabetes Mellitus (GDM) and pre-eclampsia as they were unavailable.

Finally, since this study has used dietary data, underreporting of the food intakes remain a limitation (see Chapter 6 under section 6.5.2 of Discussion for details) although the MoBa and DNBC used validated semi quantitative FFQ to record dietary data. This is of concern, especially amongst women with high pre-pregnancy BMI (Johansson et al., 1998). The McGowan study suggested that around 45% of pregnant women could be underreporting their total energy intakes during pregnancy and a high BMI of >25 was an important predictor of underreporting of energy intakes (McGowan and McAuliffe, 2012). Underreporting might have influenced the dietary patterns and their associations with birth outcomes in both cohorts and therefore, requires duplication of results amongst other cohorts to test for consistency.

7.4.4 Overall implications

This study has explored the contribution of gestational weight gain as an intermediate variable in the maternal dietary intake and birth outcome pathway. This was possible by examining the maternal dietary choices related to the individual risk factors of gestational weight gain, including total energy intakes, maternal smoking habits, pre-pregnancy BMI and physical activity.

In this study, the dietary patterns of two GWG risk factors – maternal smoking in MoBa and total energy intake in DNBC were predominantly associated with a change in birthweight and odds of SGA and LGA babies.

The overall results could imply that particular maternal food group intakes are positively associated with gestational weight gain risk factors, mainly belonging to two categories, protein-rich foods (cheese spreads, red meat, processed meats, pork, beef and veal, marine food [lean fish and fish products]) and carbohydrate and fibre rich foods (fruits and dried fruits, vegetables, sugar-sweetened beverages, unrefined bread). Finally, it highlights the requirement of abstinence from smoking and cautious dietary choices contributing to energy intakes for adequate gestational weight gain to support fetal growth.

This was the last chapter amongst the main analysis chapters of the thesis. The next and final chapter will be discussion and conclusions which will summarise, discuss and provide concluding remarks for the overall findings in this thesis.

Chapter 8 Discussion and conclusion

The individual chapters in this thesis (Chapter 4, 5, 6 and 7) provide separate discussion, including strengths, limitations and implications of the reasearch findings.

This chapter provides a general discussion for the whole thesis and includes the following sections.

Firstly, the chapter will discuss the general findings of the thesis achieved under each objective, listed Chapter 1 of Introduction under section 1.13. Secondly, it will identify the overall strengths and limitations of this project. Thirdly, it will include a brief discussion regarding the implications of the research findings. Finally, the chapter will provide recommendations for future research and an overall conclusion.

8.1 Central aim of the project

The central aim of this project was to study maternal macronutrient dietary intakes through generation of a unique maternal weight gain dietary pattern and its relationship to birth outcomes. This was conducted using data from three large birth cohorts, including CAffeine and REproductive Health study (CARE) in U.K, The Norwegian Mother and Child Cohort study (MoBa) in Norway and the Danish National Birth Cohort Study (DNBC) in Denmark. The birth outcomes of intrest in this thesis were birthweight, and odds of small-for-gestational-age (SGA) and large-for-gestational-age (LGA) infants.

8.2 Fulfilment of the project objectives

A detailed literature review was conducted in Chapter 2 and the study objectives were formed after identifying the gaps in the existing literature. The overall findings of the analyses fulfilling each study objective are stated in turn below:

1. *To examine the association between maternal dietary macronutrient composition and its dietary sub-components (starch, glucose, sucrose, fructose, lactose, mono-unsaturated fatty acids [MUFA], polyunsaturated fatty acids [PUFA] and saturated fatty acids [SFA]), and birth outcomes – results from the CARE cohort*

   Chapter 4 addressed this project objective and suggested the following research findings–

   i. Higher maternal dietary carbohydrate intake in firth trimester was positively associated with heavier offspring, and amongst CHO sub-components, higher intakes of starch, lactose and glucose were positively associated with higher birthweight.

ii. In contrast, higher maternal dietary fat intake was associated with lower birthweights, and amongst fat sub-components, only higher dietary PUFA intake was associated with lower birthweight.

iii. Based on the knowledge of this thesis it was the first observational study to suggest associations between maternal dietary macronutrient sub-components and birthweight.

iv. In this study there was no evidence of an association between maternal dietary macronutrient composition and odds of SGA and LGA babies since they were included as categorical variables in the logistic regression models. This might have lowered the statistical power because unlike continuous variables, the categorical variables do not use the complete data for regression analyses.

2. *Investigation of the association between maternal dietary macronutrient composition and birth outcomes– Meta-analysis results from 3 birth cohorts (CAffeine and REproductive health cohort [CARE], Danish National Birth Cohort [DNBC] and Norwegian Mother and Child Cohort Study [MoBa]).*

   Chapter 5 addressed this project objective and suggested the following research findings–

   i. Higher maternal total energy intake was positively associated with higher birthweight.

   ii. Amongst the combined results for maternal macronutrients, only higher maternal dietary protein intake was positively associated with heavier offspring.

   iii. The meta-analysis suggested no evidence of an association between maternal dietary macronutrient composition and odds of SGA and LGA offspring because they were included as binary outcomes in logistic regression models. Unlike continuous variables, categorical variables do not use complete information therefore, it might have lowered the statistical power to detect any overall associations.

   iv. Based on the knowledge of this thesis it was the first meta-analysis study of three birth cohorts to demonstrate the associations between maternal dietary macronutrient composition and birth outcomes.

3. *To study the association between maternal dietary patterns using PCA (Principal Component Analysis) and birth outcomes– results from the MoBa birth cohort*

Chapter 6 addressed this project objective and suggested the following research findings–

i. The results indicated that maternal protein intakes from seafood and animal meat might have different associations with birth outcomes.
ii. The study used PCA to extract 5 dietary patterns which explained the maximum variance for the maternal dietary intakes.
iii. This is the first study to demonstrate an association between an "animal meat" dietary pattern in pregnancy and higher odds of LGA baby.
iv. The "marine foods" dietary pattern characterised by high intakes of fatty and lean fish, fish products, fruits and dried fruits, poultry, and low intake of sugar sweetened beverages were associated with higher birthweight, but not with high odds of SGA babies. The overall results in the PCA demonstrated that dietary patterns high in marine foods could have protective effects during pregnancy.
v. Interestingly, no evidence of an association between the "marine foods" dietary pattern and odds of LGA baby, which could highlight the "anti-obesogenic" effect of PUFA found in fish and fish products.

4. *To develop 'gestational weight gain dietary patterns [GWG-DPs]' using reduced rank regression (RRR) and to study the association between GWGDPs and birth outcomes– results from the DNBC and MoBa birth cohorts.*

Chapter 7 addressed this objective and suggested the following research finding–

i. Findings suggested a key contribution of gestational weight gain as an intermediate variable in the maternal dietary intake – birth outcome pathway. This was demonstrated by examining the maternal dietary choices related to the individual risk factors of gestational weight gain, including total energy intakes, maternal smoking habits, pre-pregnancy BMI and physical activity.
ii. Maternal food group intakes were positively associated with gestational weight gain risk factors and mainly belonged to two categories, protein-rich foods (cheese spreads, red meat, processed meats, pork, beef and veal, marine food [lean fish and fish products]) and carbohydrate and fibre rich foods (fruits and dried fruits, vegetables, sugar-sweetened beverages, unrefined bread).
iii. In association with birth outcomes, dietary patterns of two GWG risk factors – maternal smoking in MoBa and total energy intake in DNBC were

predominantly associated with a change in birthweight, and odds of SGA and LGA babies.

iv. Based on the knowledge of this thesis it was the first study to create dietary patterns related to gestational weight gain risk factors in a reduced rank regression analysis and demonstrate its association with birth outcomes amongst two large birth cohorts.

8.3 Comparison of the findings with previous literature

The study objectives of this thesis set out to explore the association between maternal dietary macronutrients and birth outcomes such as birthweight, and odds of SGA and LGA babies amongst a well-nourished population of pregnant women. This was conducted in two parts. First, the analyses investigated the association between maternal dietary macronutrients and its components and birth outcomes within the CARE study. Second, the analysis was duplicated using data from three birth cohorts, MoBa, DNBC and the CARE study and a meta-analysis of the individual participant data was undertaken. In addition, the thesis extracted maternal dietary patterns using PCA and examined its associations with birth outcomes within MoBa. Finally, the thesis explored the dietary choices contributing to gestational weight gain by creating a unique set of gestational weight gain dietary patterns and demonstrated its associations with offspring outcomes. A flow chart summarising the project analysis is provided for ease of reference in Figure 23.

8.3.1 Comparison of the meta-analysis results with other studies

As identified through the critical evaluation conducted in Chapter 2, there is inconclusive evidence suggesting that there is an association between dietary macronutrient intakes in pregnancy and offspring weight, and odds of delivering and SGA and LGA infants. Studies have suggested an association between protein intakes in pregnancy and higher birthweight (CucÓ et al., 2006; Godfrey et al., 1997; Moore et al., 2004) (refer section 2.4.1 in Chapter 2). In agreement with their findings, in Chapter 5 the meta-analysis results of the three birth cohorts demonstrated an association between maternal protein intake and higher birthweight; a 30g/d protein increment was associated with higher birthweights of 20g (95% CI 10g to 31g). Although the two studies used %E and 1g increment to express the results, the estimates sizes and confidence intervals were similar to the current study. In the Moore study, an increase of 16g in birthweight was observed (95% CI 3g to 35g) amongst 577 participants.

Similarly, the CuCo study suggested that a 1g protein increment was associated with higher birthweights between 8 to 11 grams. In comparison the CuCo was a well design study because it recorded dietary intakes at 4 different episodes in pregnancy, at preconception, 6^{th}, 10^{th}, 26^{th} and 38^{th} weeks of gestation using a 7 day food diary records amongst 77 pregnant women, whereas the Moore study, DNBC and MoBa in the meta-analysis recorded using FFQ. Only the CARE study used 24-hour dietary recall.

Although there is, a difference in the dietary assessment tools to record maternal dietary data, it could be implied that the method did not affect the effect estimates and the confidence intervals largely. However, in theory, the CuCo study results could be considered more reliable

as the dietary data was one week and might represent more consistency in dietary intakes and portion sizes as compared to other methods. However, the sample size in this study was the smallest amongst the three studies, and therefore, using FFQ as a dietary assessment tool could be thought practical within the study's setting. This cannot be considered the best approach amongst large birth cohorts because it is not feasible due to lack of time, logistics, and shortage of trained personnel. Therefore, despite the choice of FFQ used by the birth cohorts in the meta-analysis results seem to be consistent with the existing literature.

Interestingly, similar to the results of the meta-analysis in Chapter 5, both studies did not observe any association between maternal dietary CHO and fat, and birthweight (CucÓ et al., 2006; Moore et al., 2004). This was observed although the studies had different study designs, confounders and recorded using dietary assessment tools. Another observation within the findings was that none of the maternal macronutrients was associated with the odds of SGA and LGA babies. This might be due to the use of binary outcomes in the analysis. The SGA and LGA variables were categorical variables: "0" as control and "1" as case. It might be possible that including categorical variables might have led to using less information in the dataset. This might have lowered the overall statistical power and showed no evidence of an association. Perhaps if continuous variables of SGA and LGA were included in the regression models, it would have used complete information in the dataset and might have shown associations. In agreement, one study explored the association between macronutrient intakes on risk of SGA infants by sex of the offspring in trimester 1 (Mukhopadhyay et al., 2018). They suggested no evidence of an association between dietary protein and risk of SGA infants.

Although the associations within the individual birth cohorts differed (refer section 5.3.1 in Chapter 5), the results in the meta-analysis are considered to be more important in this thesis as they provide a precise estimate from the individual studies after accounting for heterogeneity to resolve uncertainty of varying results from the individual studies. Therefore, using the results of a meta-analysis advantageous and preferable because it increases statistical power to detect an effect and make it more applicable to a general population (Haidich, 2010).

Therefore, based on these reasons it could be implied that within a large population, amongst the dietary macronutrients, dietary protein during pregnancy is most important for higher birthweights, but not with odds of LGA babies. In addition, no particular dietary macronutrient was associated with poorer birth outcomes such as odds of SGA and LGA babies.

8.3.2 Comparison of the PCA results with other studies

Amongst maternal dietary patterns, it was observed that marine food and animal meat patterns were associated with birth outcomes (refer Chapter 6 under section 6.5). In Chapter 6, maternal

dietary patterns were extracted using PCA to explore the maternal dietary choices within MoBa. The study used MoBa because the FFQ captured dietary intakes from the start of pregnancy, therefore representing consistent dietary intakes and choices of pregnant women.

The study suggested that pregnant women with high adherence to an “animal meat” dietary pattern were associated with higher odds of delivering LGA infants in a non-diabetic population. This result in Chapter 6 was unexpected and has not been suggested by previous literature. A systematic review of 36 studies explored maternal dietary patterns and birth outcomes such as birthweight, and risk of SGA and LGA babies (Chia et al., 2019). Studies from the systematic review included animal meat in an “unhealthy” dietary pattern and suggested that no study had explored the association between “unhealthy” dietary patterns and risk of LGA infants. In similarity to the Chia study, the “unhealthy dietary pattern” in the review was characterised by high intakes of refined grain, processed meats, and foods high in saturated fat or sugar that was similar to the “animal meat” dietary patterns in the current study.

In contrast to the positive association observed between an animal meat dietary pattern and higher odds of LGA infants, previous studies have suggested a negative association. Moreover, a meta-analysis of 7 studies (Kjøllesdal and Holmboe-Ottesen, 2014) suggest that high adherence to an “animal meat” dietary pattern is associated with higher odds of SGA infants. There could be possible reasons for observing a difference. The studies included in the meta-analysis reporting the results had confounder bias and errors, incorrect definition of an SGA infant and improper use of statistical methods.

One such study was conducted by Knudsen and colleagues (Knudsen et al., 2007). The study suggested that western diet high in processed and red meat was associated with a high risk of SGA baby. However, the study methodology was unsuitable to extract dietary patterns representing dietary choices of a population. Factor analysis was used to extract dietary patterns. Although FA and PCA are similar statistical methods, they have a fundamental difference. FA determines the number or the nature of latent variables that account for the observed variation amongst a set of dietary intake variables and extract a set of correlated patterns, known as factors (Bédard et al., 2015; Hoffmann et al., 2004). For example, a latent variable could be behavioural intervention, including diet and physical activity amongst obese pregnant women that accounts for the observed variation of the dietary intakes and extracts factors explaining the effectiveness of the intervention (Flynn et al., 2016). Whereas, PCA extract dietary patterns that explain maximum variance of the maternal diet and describe the correlation between the food groups and the components (Hoffmann et al., 2004). Also, the study adjusted for fathers height in the regression models, that made it challenging to interpret the possible reason, and might have introduced confounding error. This study defined SGA

(infants <2.5 percentile) differently and lower than that the standardised definition of infants <10th centile (Chiavaroli et al., 2016; Clausson et al., 2001; Norris et al., 2015), therefore it might be possible that the western dietary patterns might be associated with infants of a very low birthweight category. However, this difference might have changed the interpretation of the results within the Knudsen study (Knudsen et al., 2007).

The study in Chapter 6 also highlighted the protective role of fish and fish products in lowering the odds of SGA births by a high adherence to a "marine food" dietary pattern in pregnancy. The dietary pattern mainly consisted of lean and fatty fish and fish products such as fish cakes and fish fingers. Lean and fatty fish are high sources of PUFA and contain EPA and DHA which improve visual and fetal brain growth in the offspring, thus improving overall birthweight (refer Chapter 6 under section 6.5.1) (Hanebutt et al., 2008).

Interestingly, the results suggested no evidence of an association between a high adherence of a "marine food" dietary patterns and odds of LGA baby but was only associated with higher birthweight. Therefore, highlighting the "anti-obesogenic" effect of the PUFA found in fish and fish products. This is in agreement with studies that suggested that PUFA could prevent excessive deposits of fat mass in the fetus (Blumfield et al., 2012; Newman et al., 2002; Nuernberg et al., 2011). The results for a "marine food" dietary pattern observed in this study agree with other studies (Brantsaeter et al., 2012; Imhoff-Kunsch et al., 2012) which suggested that a high fish intake during pregnancy is associated with higher birthweight. However, in contrast to the results observed in this study, (Brantsaeter et al., 2012; Imhoff-Kunsch et al., 2012) studies found no evidence of an association with risk of SGA baby. This probably might be because of the demographics of the birth cohorts. The dietary patterns observed in MoBa might be because it represented a traditional Nordic diet comprised of fish, potatoes, dark fibre bread, cheese, fruits and vegetables (Hillesund et al., 2014; NNR, 2012; Northstone et al., 2008; von Ruesten et al., 2014; Wolff and Wolff, 1995).

In support of the findings, a pooled study 15 cohorts suggested that consuming fish thrice a week was positively associated with higher fetal growth. The study used a random-effects model in the meta-analysis and adjusted the individual analyses for maternal age, pre-pregnancy BMI, sex of the baby, gestational weight gain, birthweight, maternal smoking and maternal education. They used an FFQ specifically designed to record marine food intakes within all cohorts. However, there was confounding error by including birthweight, sex of the baby as covariates. Nevertheless, it is a well-structured pooled study with high statistical power, and are important to consider because the pooled estimates of the fish intakes could represent a large population (Stratakis et al., 2016).

Another study (Hillesund et al., 2014) conducted within MoBa assessed the Nordic diets using a health index score assessment – the New Nordic Diet (NND) score amongst 66597 women and suggested that a high fish intake could lower risk of SGA babies and increase risk of LGA infants. In contrast, in this thesis, there was no evidence of an association observed between a high fish pattern adherence and higher odds of LGA infants. This might be because of the confounders selected for the dietary pattern model. The Hillsund study chose gestational diabetes mellitus as a confounder for the fetal growth model, and this might have potentially affected the results due to confounding error. As it is well established that GDM women have a higher odds of delivering LGA infants (Reece, 2010), the resulting associations might have represented this link and not necessarily influence of the Nordic diet scores (Hillesund et al., 2014). In addition, the methodology used in the Hillsund study differed; the study used NND to score the intakes of the participants and conducted regression analyses to explore their associations with fetal outcomes.

Whereas, the study in Chapter 6 used PCA to extract the maternal dietary patterns. Using PCA is a better approach to extract dietary patterns because it extracts uncorrelated linear combinations of maternal dietary components which explain for maximum variance in the maternal diet (predictor variable)(Jolliffe, 2011). This is better than using a diet score index because it creates a dietary pattern based on the correlations between food group and components. The diet score index method does not account for correlation between the different dietary components, and so it does not reflect the overall effect of the maternal diet but only gives an unadjusted sum of single effects (Hoffmann et al., 2004).

Therefore, the results suggest that the type of animal protein eaten in pregnancy could be important in predicting associations with birth outcomes, especially with poorer birth outcomes such as SGA and LGA births.

8.3.3 Comparison of the RRR results with other studies

In Chapter 7 the maternal dietary data from MoBa and DNBC were used to create a unique set of gestational weight gain dietary patterns and explored their associations with birth outcomes such as birthweight, and odds of SGA and LGA infants. Studies and systematic reviews have explored the impact of macronutrients consumed during pregnancy on gestational weight gain (Lagiou et al., 2004; Streuling et al., 2011; Tielemans et al., 2015). However, there was limited literature to suggest that certain foods consumed during pregnancy contribute to gestational weight gain and might be associated with birth outcomes. One study investigated the association between maternal dietary patterns and gestational weight gain amongst 391 pregnant women and recorded dietary data using FFQ (Shin et al., 2016). The results suggested

that a high dietary score for the “mixed” dietary pattern characterised by dairy products, fruit drinks, fruits, nuts, vegetables, legumes, meat, snacks and sweets were negatively associated with excessive gestational weight gain. However, the study reported no evidence of an association between “healthy” and “western” dietary patterns, and gestational weight gain. The study used factor analysis to extract uncorrelated linear combinations of dietary patterns explaining maximum variance in the maternal diet. This methodology differed to the methodology applied in Chapter 7. Also, the study used categorical variables in the regression models, for example maternal age was divided into three groups (<24, 25-34,>35 years). Using a categorical variable might not be preferable amongst a modest sample size as it could lead to loss of information and could have lower the statistical power and introduce measurement errors. Instead using a continuous variable would have used all the information and resulted in strong associations with high statistical power. Also, this study did not examine its association with birth outcomes, therefore its potential relations with the offspring outcomes are unknown.

Another study conducted similar analyses within a Dutch population of 3374 pregnant women using the validated Dutch FFQ and a Dutch healthy diet index to explore the associations between maternal dietary patterns and gestational weight gain (Tielemans et al., 2015). However, the study used PCA to extract dietary patterns and suggested that “vegetable, oil and fish” and “margarine, sugar and snack” dietary patterns were positively associated with gestational weight gain. Although it was a well-designed study and recorded maternal dietary data in two dietary assessment tools, the study methodology used PCA, which was an inappropriate choice to measure the study outcome. Further, the study found no evidence of an association between the dietary patterns extracted from the healthy diet index and gestational weight gain. A possible reason could be that extracting dietary patterns using the healthy diet index does not provide information regarding the correlation coefficients between the food groups and the dietary patterns, but only gives an unadjusted sum of single effects. Therefore, these results might not reflect the overall effect of the maternal diet (Hoffmann et al., 2004). Another difference in the methodology was that the study excluded around 538 participants with missing data. This might have lowered the statistical power of the study. Overall the methodologies used to extract the dietary patterns in the two studies (Shin et al., 2016; Tielemans et al., 2015) were not ideal for exploring the dietary patterns contributing to gestational weight gain.

Whereas, the analyses in this thesis did not exclude the participants based on missing data in order to prevent the loss of statistical power. Instead, the missing data in the FFQ was cleaned and was replaced to “0” if missing, assuming that the participants did not consume any

particular food item in FFQ. This was an appropriate method to retain the maximum sample size.

Furthermore, the study in Chapter 7 used reduced rank regression analyses (RRR) to extract maternal dietary patterns. This is a better method because the method extracts uncorrelated linear combinations of dietary patterns that explain maximum variance in the response variable. i.e., gestational weight gain (Jacobs et al., 2017; Lamichhane et al., 2014; Weikert and Schulze, 2016). This is a method used to extract dietary patterns that best describe dietary choices related to or contributing to a disease of interest (Hoffmann et al., 2004). Whereas, the PCA and diet quality index and FA derived dietary patterns explain the maximum variance in the exposure variable, i.e., maternal diet, and so the patterns cannot predict the patterns related a disease outcome.

The risk factors known to be associated with the disease of interest were entered into the RRR model. This study included 4 GWG risk factors, namely maternal smoking, total energy intakes, physical activity and pre-pregnancy BMI (refer section 7.2.5.2 in Chapter 7 for the definition of response variables) based on previous literature. Therefore, these were entered into the RRR model to extract uncorrelated linear combinations of dietary patterns that explained maximum variance in the gestational weight gain. Amongst the risk factors, maternal smoking (MoBa) and total energy intakes (DNBC) explained for maximum variance amongst response variables. The results in this study suggested that maternal food group intakes were positively associated with gestational weight gain risk factors, predominantly with maternal smoking and total energy intake. The dietary patterns mainly comprised of foods from two categories, protein-rich foods (cheese spreads, red meat, processed meats, pork, beef and veal, marine food [lean fish and fish products]) and carbohydrate and fibre rich foods (fruits and dried fruits, vegetables, sugar-sweetened beverages, unrefined bread). This could mean that, in addition to exploring the dietary patterns related to gestational weight gain, it is also necessary to observe the role of maternal smoking and energy intake as gestational weight gain risk factors.

The food groups contributing to gestational weight gain in this study differed from the Shin study (Shin et al., 2016) and the Tielemans study (Tielemans et al., 2015) possibly due to different statistical methods used to extract dietary patterns. Therefore, the results from the two studies (Shin et al., 2016) (Tielemans et al., 2015) might imply that the dietary patterns explain the variance of the maternal diet, but not of gestational weight gain. Based on the results from the RRR study in this thesis it could be suggested that maternal food intakes high in protein (animal and marine sources) and carbohydrate (refined and unrefined sources) contribute to gestational weight gain and are associated with birth outcomes such as higher birthweight, and odds of SGA and LGA babies.

However, one study (Starling et al., 2017) derived dietary patterns using reduced rank regression (RRR) to predict newborn adiposity, including birthweight, adiposity, fat mass and fat-free mass amongst 764 pregnant women. Further, the dietary patterns extracted were associated with two risk factors: gestational weight gain and mid-pregnancy fasting glucose during pregnancy. However, the study excluded gestational diabetic women; therefore this made the results more generalizable for a non-diabetic population. Although the dietary pattern correlated with gestational weight gain and was characterised by a high intake of poultry, nuts, cheese, fruits, whole grains, added sugars, and solid fat, the dietary pattern explained maximum variance for the response variable of the study, i.e., fat-free mass. Thus, the results implied that the foods in the dietary patterns were associated with contributing to fat free mass, and considered gestational weight gain as its predictor/risk factor. This was the difference between the current study in the thesis and the Starling study (Starling et al., 2017). Although the study used an appropriate method, it specifically predicted newborn adiposity and not gestational weight gain. Whereas, the current study explored and included risk factors predicting gestational weight gain as the response variable in the RRR model and extracted maternal dietary patterns associated with gestational weight gain. In addition, the GWG dietary patterns, in particular of two risk factors, namely maternal smoking and total energy intakes were associated with birthweight and odds of SGA and LGA babies.

8.3.4 Physiological adjustments during pregnancy

Pregnancy consists of continuous physiological adjustments, which affects the metabolism of the nutrients. This varies from woman to woman, amongst different populations, pre-pregnancy BMI and nutrition (King, 2000). Few metabolic adjustments occurring during pregnancy might further explain the results of the impact of macronutrients on birth outcomes.

One of the reasons for the meta-analysis suggesting that a higher protein intake could be associated with higher birthweight is the metabolic adaptations of the mother's protein stores in order to enable adequate placental amino acid utilisation and amino acid transport to the fetus. During pregnancy, the maternal liver breaks down the protein into amino acids and is transferred through the placenta for fetal cell growth, thus promoting tissue formation. This could imply that a higher protein intake might lead to a higher placental transfer of amino acids, for example, glutamine (important for the gut and the immune function). Fetal hepatic uptake of glutamine is the highest than any other amino acid. Almost, 45% of glutamine is converted to glutamate in the fetal liver and returns to the placenta where it is used as a source of energy to support rapid growth (Robinson and Prendergast, 1996).

This thesis did not observe any evidence of an association between maternal fat and birth outcomes in the meta-analysis. This might be due to the underreporting of fat amongst pregnant women while self-reporting the FFQ (Black and Cole, 2001; Johansson et al., 1998; McGowan and McAuliffe, 2012). Therefore, a large effect on birthweight might not have been detected in the analyses. However, in Chapter 4, the CARE analyses suggested that a high maternal dietary fat was associated with lower birthweights, but not with odds of SGA and LGA infants. On further exploring the type of fatty acids that could be linked to this association, it was observed that higher PUFA intakes were associated with lower birthweights. There might be a few possible explanations for this.

Firstly, higher PUFA intakes linked to lower birthweight might be due to the role of the maternal hormone – human placental lactogen (hPL). During the second trimester under the influence of hPL, the mother's hepatic stores of fatty acids cater to the mother's lipid requirement and immediately transfer the fatty acids to the mother and lower the rate of placental transfer of fatty acids to the fetus (Butte, 2000; Kumar and Magon, 2012). Therefore, the hepatic stores during pregnancy prioritise the circulation of maternal fatty acids over the fetus deposit of around 2 to 2.5 kg of adipose tissue as an energy reserve for lactation (Health, 1991).

Secondly, the results in the gestational weight gain dietary patterns suggested that a high intake of marine food during pregnancy was positively associated with higher birthweight, but not with high odds of LGA infants. In addition, this study highlighted the protective effect of high fish intakes to be associated with low risk of poorer birth outcomes such as SGA babies. This is because lean and fatty fish are a major source of omega-3 polyunsaturated fatty acids, in particular, docosahexaenoic acid (DHA, 22:6n-3). DHA is placentally transferred for fetal neural and visual development. Furthermore, accretion of DHA is the maximum after the second trimester, thus preventing the risk of SGA babies (Amezcua-Prieto et al., 2018; Hanebutt et al., 2008; Imhoff-Kunsch et al., 2012; Koletzko et al., 2007).

However, in Chapter 7, there was no evidence of an association between high marine food dietary patterns and odd of LGA babies. In contrast, in Chapter 4, the CARE study suggested a negative association between high PUFA and birthweight. This might be due to the preventive effect of PUFA in preventing the additional placental fat transfer to the fetus (Hillesund et al., 2014). The association observed in the CARE study is supported by previous studies that have suggested that the type of fat affects the direction of the association. Studies suggested the PUFA's 'anti-obesogenic' mechanism might explain for the negative association, implying that PUFA reportedly prevented extra fat mass deposits in the fetus (Blumfield et al., 2012; Newman et al., 2002; Nuernberg et al., 2011). Although the results in this thesis are from an observational

study, it could be of clinically importance. Furthermore, in agreement, studies have suggested that a high PUFA intake could improve birthweights, yet simultaneously have preventive effects of on SGA baby risk and excessive offspring weight gain >4000 grams (LGA infant) (Imhoff-Kunsch et al., 2012; Olsen et al., 1986).

Therefore, it could be implied that although there was no evidence of an association between dietary fat and birth outcomes, dietary fat components such as PUFA appear to have a protective effect in preventing poorer birth outcomes such as odd of SGA and LGA babies, while improving birthweights. In addition, a high fish diet rich in PUFA from omega 3 fatty acids suggested to prolong gestation by interfering with the prostaglandin production in the uterus by blocking the dienoic prostaglandins, in particular mediators including PGE2 and PGF2 which are responsible for initiating labour through uterine contractions and ripening of the cervix (Olsen et al., 1986).

Amongst results exploring the odds of LGA babies, in Chapter 7, it was observed that foods high in protein and CHO contributed to gestational weight gain and were positively associated with LGA babies. Further implying that cautious care must be taken to avoid overconsumption of protein and CHO as it could be associated with additional gestational weight gain and heavier offsprings. This is because high maternal consumption of food groups high in CHO, including SSBs, fruits and dried fruits, refined bread are assimilated into their basic form – glucose and are placentally transferred for fetal glycogenesis. Further, mothers who consume protein-rich dietary patterns are susceptible to have an hyperinsulinemic effect of amino acids, subsequently supplying excessive amino acids through the placenta causing accelerated fetal growth, implying increased odds of LGA baby (Buschur E, 2000; Jolly et al., 2003). Therefore, this result could be of clinical importance for non-diabetic pregnant women. Moreover, evidence from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) trial suggested that almost 78% of offsprings were born to non-diabetic women (Group, 2009).

It could also be possible that the confounding effect of a dietary supplement could have contributed to the result (Mousa et al., 2019). However, a sensitivity analysis was conducted to explore this possibility, but the results did not change after removing the covariate from the regression models.

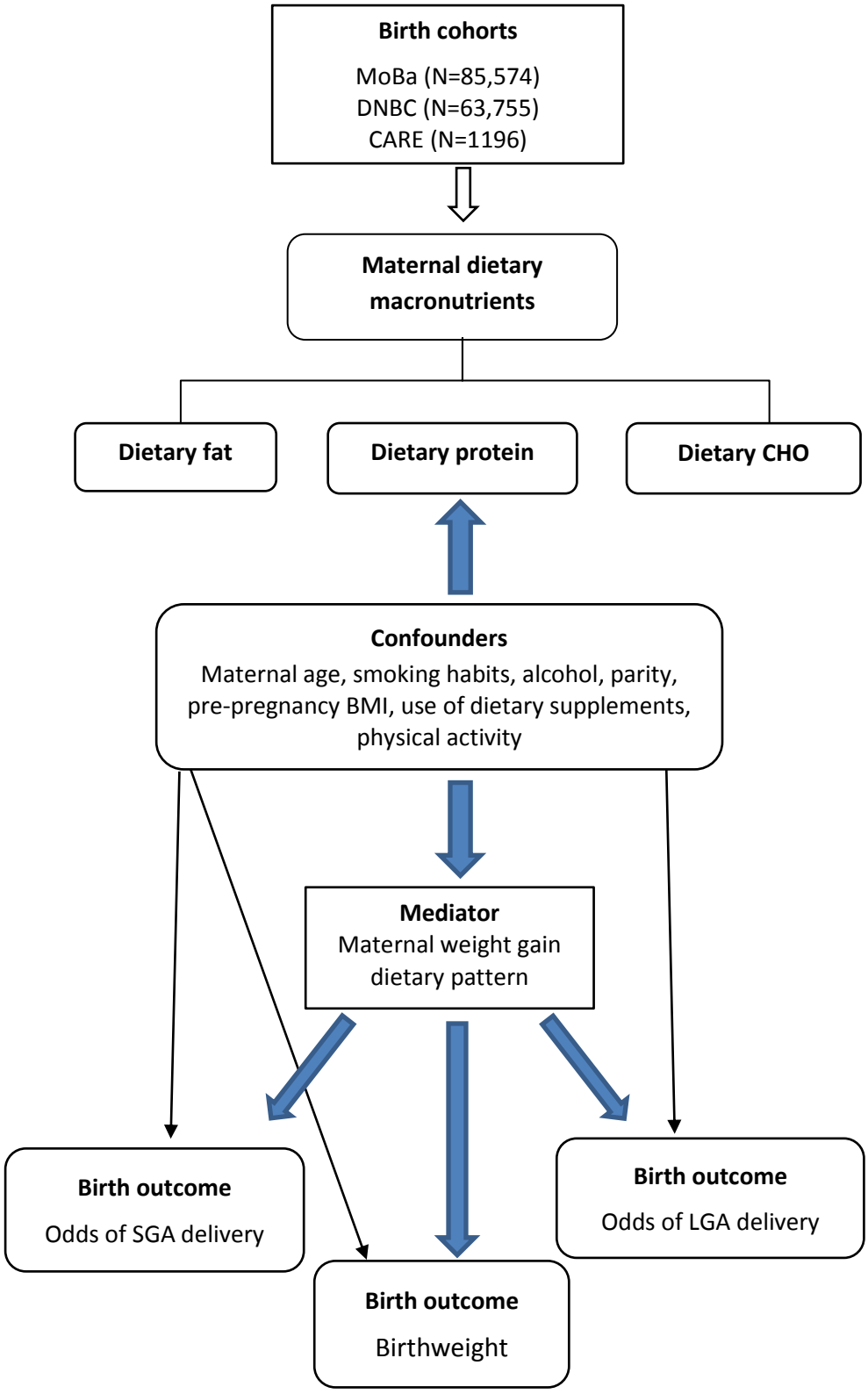
Therefore, it could be implied that amongst the macronutrients, protein consumed during the second trimester was positively associated with increasing birthweight. However, in the CARE study, there was no evidence of an association observed in trimester 1. This might suggest that the protein metabolism changes gradually from early pregnancy to mid-pregnancy so that

nitrogen conservation occurs in full potential during the last four months of the gestation period to support optimal fetal growth (King, 2000).

It is also suggested that biological effects of the nutrients on fetal growth could vary during pregnancy because fetal growth and nutritional needs are structured during gestation. Studies have suggested the changes in nutritional requirement even during early pregnancy in the embryonic stage (Moore et al., 2004). The embryonic growth is majorly dependent on simple molecular products of the metabolic pathway such as pyruvate followed by the fetus largely depending on amino acid to grow to its maximum potential (Martin et al., 2003). Furthermore, glucose is largely used by the fetus in the late pregnancy phase (Harding, 2001).

Finally it is challenging to suggest if any particular macronutrient is consistently associated with gestational weight gain and birth outcomes due to inconsistent evidence this thesis and from large systematic reviews (Streuling et al., 2011; Tielemans et al., 2015). The Streuling study (Streuling et al., 2011) suggested that high maternal protein and fat intakes were positively associated with gestational weight gain. Whereas, maternal CHO intakes were associated with gestational low weight gain implying that it could bypass gestational weight gain and prioritise fetal growth. However, the Tielemans study suggested that only maternal fat might be associated with gestational weight gain, particularly animal fat, but evidence was inconclusive for protein and CHO intakes (Tielemans et al., 2015).

Figure 23 A flow chart summarising the project analysis



- High protein associated with high BW in the meta-analysis
- High CHO and components (starch, glucose and lactose) associated with high BW, whereas high PUFA intakes associated with low BW in the CARE study
- Maternal dietary patterns high in fish are associated with preventing poorer birth outcomes

8.4 Comparison of maternal macronutrient intakes in the cohorts with national dietary reference values

Dietary reference values (DRV) are reference values that are quantitative estimates of nutrient intakes used for planning and assessing diets of a healthy population. In addition, the DRV provides guidance in determining the nutrient intake requirements by accounting for age, gender and nutritional requirements during pregnancy (Trumbo et al., 2002). Policymakers use DRVs to make national dietary guidelines for a population. Independent organisations including European Food Safety Agency (EFSA) and the Committee on Medical Aspects of Food Policy (COMA) report by the Department of Health, in the UK, provide updated scientific evidence on nutrient intakes to the policy makers in Europe and UK, respectively (*European Food Safety Authority (EFSA)- online database*, 2018; Health, 1991).

During pregnancy, there is increased metabolic activity, changes in the tissue comprised of increased mass of uterus, the formation of the fetus and the placenta, increased blood volume and a deposit of around 2 to 2.5 kg of adipose tissue as an energy reserve for lactation. For the same reasons, based on scientific evidence from RCTs and observational studies, DRV account for additional nutrient intakes during pregnancy (Health, 1991).

The analyses used maternal dietary macronutrient data of participants who were well-nourished and belonged to cohorts of developed countries, UK, Norway and Denmark. In the CARE cohort, participants' average dietary macronutrient intake/day during trimesters 1 and 2 largely met the estimated average requirements of energy (EAR) recommended during pregnancy in the Committee on Medical Aspects of Food Policy (COMA) report by the Department of Health, UK (Health, 1991; Williamson, 2006). Similarly, the participants in MoBa and DNBC belonged to a well-nourished population and hence, their dietary macronutrient intakes around the second trimester largely met the overall macronutrient recommendations by the Nordic Nutrient Recommendations (Lundqvist et al., 2014; NNR, 2012; von Ruesten et al., 2014).

Table 28 Daily dietary reference values for macronutrient intake during pregnancy for UK, and Nordic countries

Nutrients	UK[1]	Nordic countries[2,3]
Additional energy intake during pregnancy (kcal/day)	+200 kcal (only during last trimester)	+100 kcal/day for trimester 1 +200-300 kcal (for trimesters 2 and 3)

	Mean energy intake of the CARE study: 2279 kcal (SD 634)	Mean energy intake of DNBC: 2392 kcal (SD 639) MoBa: 2315 kcal (SD 658)
Dietary CHO (E%)	50-65 E% mean CHO of CARE: 300 g (SD 92)	45-60 E% mean CHO intake of DNBC: 331 g (SD 100) MoBa: 312 g (SD 114)
Dietary protein (E%)	10-35% 45 g/d +6 grams/day mean protein intake of CARE: 81g (SD 28)	10-20 E% mean protein intake of DNBC: 91g (SD 27) MoBa: 88g (SD 25)
Dietary fat (E%)	15-35 E% mean fat intake of CARE: 91g (SD 36)	25-35 E% mean fat intake of DNBC: 83g (SD 34) MoBa: 81g (SD 29)

[1]DRV based on COMA 1991 and SACN 2015 recommendations [2]Nordic countries include Norway, Denmark, Iceland, Sweden and Finland [3]based on Nordic Nutrient Recommendations

The dietary recommendations for additional energy intakes for pregnancy differed between NNR and the COMA and SACN reports of the Department of Health in the UK (refer Table 28). The NNR recommended additional energy intake of +100kcal/day for trimester 1 and +200-300 kcal/day for trimesters 2 and 3. However, the SACN report in the UK recommended additional energy intake of +200 kcal only for trimester 3.

Further, NNR recommended no change in protein, i.e., an intake of 0.8 to 1.1 g/kg body weight similar to that of non-pregnant women. However, the UK DRV recommended an additional requirement of 6 grams/day during pregnancy. The NNR justified that the dietary protein content in western diets, including Nordic and English diets are generally above 12% of the total energy intake (%E) and hence, meet the overall protein requirements. Therefore, the dietary macronutrient recommendations for pregnant women in western countries are not increased much as compared to non-pregnant women because most are able to cover their macronutrient needs through a normal diet (NNR, 2012). Also, the UK and Nordic countries recommended similar DRV for CHO and fat intakes. Furthermore, the maternal dietary intakes in CARE, DNBC and MoBa were similar to those found in other studies involving pregnant women (Chen et al., 2016; Langley-Evans and Langley-Evans, 2003; Moore et al., 2004).

In agreement with these observations, Blumfield and colleagues (Blumfield et al., 2012) conducted a systematic review of 90 studies and compared energy and macronutrient intakes

of pregnant women from developed countries including, USA/Canada, the UK, Europe, Australia/New Zealand and Japan. The results from the systematic review suggested that UK and European countries had similar daily dietary reference values which are listed as follows – an extra total energy intake of 360 kcal/day in trimester 2 and 475 kcal/day in trimester 3, 10-35 E% from protein, 55-75 E% from carbohydrate and 15-30 E% from fat (Blumfield et al., 2012). The results of the systematic review suggested that the mean energy intakes differed by geographical location. However, it should be noted that the Blumfield study compared the mean macronutrient dietary intakes with DRV recommended for pregnancy by the World Health Organization/Food and Agriculture Organization of the United Nations (WHO/FAO) population nutrient intake goals for preventing diet-related chronic diseases (WHO, 2003). Therefore the recommendations might differ with the DRV recommended by the SACN in UK and NNR.

In addition, comparisons were made between the mean maternal dietary intakes of the birth cohorts (CARE study, DNBC and MoBa), and maternal dietary intakes of the systematic review with the international recommendations by the World Health Organization/Food and Agriculture Organization of the United Nations (WHO/FAO) population nutrient intake goals for preventing diet-related chronic diseases (WHO, 2003). Therefore, it could be suggested that although the mean energy and protein intakes of CARE, DNBC and MoBa largely met the current dietary recommendations of the WHO/FAO/UN (WHO, 2003). But, dietary fat were above (5%) and CHO were below (20%) the recommendations, respectively which might be due to misreporting (Black and Cole, 2001; Johansson et al., 1998; McGowan and McAuliffe, 2012).

Also compared to USA/Canada and Australia, the mean dietary macronutrient intakes were consistently lower in UK and Europe by the WHO/FAO/UN (WHO, 2003).

The thesis used the dietary data of birth cohorts from UK, Norway and Denmark and this could have possibly influenced the associations with birth outcomes. Perhaps other birth cohorts from different geographical regions, for example, USA/Canada or Australia/NZ with higher maternal macronutrient intakes would demonstrate a different effect on the birth outcomes (Blumfield et al., 2012).

8.5 Overall strengths

The analyses in this thesis were conducted within high sample-sized birth cohorts, including CARE (N=1,289), MoBa (N=85,391) and DNBC (N=68,123) and produced robust results with high statistical power. Also, the models were well constructed to make simple and clear

interpretations. Further, it was possible to test the results for their consistency by replicating the analyses amongst the birth cohorts separately.

Large sample-sized studies were better for exploring the project objectives as they provide a more precise estimate of the effect size of the birth outcomes such as birthweight. Also, the results produced from high sample-sized birth cohorts such as DNBC and MoBa are representative of the sample and therefore, increase the generalisability of results demonstrated. However, a small effect size may not prove to be of clinical significance (Biau et al., 2008; Roessner, 2014).

Studies with high statistical power have a higher probability of detecting a difference in birth outcomes, such as birthweight. It is important to consider the statistical power of a study to draw meaningful conclusions related to the impact of maternal diet on offspring birth size if there is no change in birthweight observed in the regression models. Therefore, it is necessary to consider the power of a birth cohort while undertaking analyses; an ideal power of 80% or 90% will mean that only 10% of the difference in the birth outcome, for example, change in birthweight would be undetected by the analyses(Biau et al., 2008). So, the project objectives were addressed using large size birth cohorts. Given these reasons, the findings observed in this thesis are of high statistical power and could be generalised amongst a similar population because of the robustness of the associations. Additional reasons for choosing DNBC, MoBa and the CARE study are given in section 8.6 of this chapter.

In this thesis, all the birth outcome models were structured to improve the interpretation value of the resulting associations. Results from complex regression models of the birth outcomes could be confusing to interpret. Therefore, the models were carefully adjusted for a finite number of confounders based on their association with both maternal diet and offspring outcomes. Model 1 adjusted for a factor with no erratic changes such as maternal age. Model 2 was additionally adjusted for the covariates associated with the maternal diet and birth outcomes, therefore enabling a structured pattern of reporting the results ensuring meaningful interpretations. A complex model which best fits the data might result in poor generalisation of the results achieved this is because although a complex model is a good fit it might not provide any useful interpretations of the possible reasons (Myung, 2000).

Raw data from the birth cohorts was available to undertake the meta-analysis, which was advantageous as it helped to conduct in-depth analysis and adjust for similar covariates across all the cohorts. This was better than conducting a systematic review of published data which could introduce measurement errors and confound bias from the individual studies.

Data harmonisation techniques were not used to pool the data of the three birth cohorts in the meta-analysis study. Instead, a two-step IPD approach, a simpler method was undertaken to conduct analyses individually within the cohorts and were then entered into a random-effects model of the meta-analysis. This, therefore, produced combined effect estimates and p values for the individual associations in the meta-analyses. It was possible to also explore the heterogeneity levels between the cohorts by providing an I^2 statistic and explained possible reasons for high heterogeneity.

High quality maternal dietary data was recorded using validated semiquantitative FFQ (MoBa and DNBC) and 24-hour dietary recall (CARE) and adequate measures were undertaken to prevent participant drop-out (Boylan S, 2010; Boylan et al., 2008; Brantsæter et al., 2008; Meltzer et al., 2008; Mikkelsen et al., 2007). In the CARE study, the maternal dietary data was recorded twice, in trimester 1 and again in trimester 2 by trained research midwives. Also, DNBC and MoBa did not use portion sizes in the FFQ to avoid low response rates.

Many birth cohorts use FFQ to estimate dietary intakes of the pregnant women and the children because FFQ has certain advantages over other dietary assessment tools such as 24-hour, 3-day or a 7- day dietary recalls. Measuring dietary intakes using FFQ is cheaper and time-saving when used amongst large cohorts since it is challenging to conduct repeated dietary assessments through follow up, thus resulting in higher participant dropout rates. Also, it does relatively easier to fill and does not require trained personnel (Steinemann et al., 2017). Also, it is logistically challenging to employ trained personnel for study community visits nationally to record data from the recruited participants. Given these reasons, FFQ is mailed to the participants using a self-administered questionnaire. Although this has disadvantages of under-reporting and misreporting, especially amongst high-pregnancy BMI women (Black and Cole, 2001; Johansson et al., 1998; McGowan and McAuliffe, 2012), it is still suitable for large populations to measure actual intakes, provided the FFQ is validated amongst a group of pregnant women (Meltzer et al., 2008; Steinemann et al., 2017). Validation studies have suggested that the actual intakes reported in the FFQ were in moderate to high correlation to other dietary assessment tools such as 4-day weight dairy (Steinemann et al., 2017), 7-day weighed food diary (Mikkelsen et al., 2007; Yuan et al., 2017) and 24-hour dietary recall (Yuan et al., 2017) and a motion sensor measuring total energy expenditure, one 24-hour urine sample for analysis of nitrogen and iodine excretion, and venous blood sample for serum folate and 25 hydroxy-vitamin D (Brantsaeter et al., 2008; Meltzer et al., 2008).

Semi-quantitative FFQ record the food portion sizes as standardised portion sizes or include choices of portions sizes for the participants to enter (Dehghan et al., 2005; Mouratidou et al.,

2006). This structure of FFQ helps to account and prevent measurement error while reporting actual food intakes (Meltzer et al., 2008; Mikkelsen et al., 2007). Further, the MoBa and DNBC covered a varied number of food questions capturing maternal dietary choices during pregnancy. MoBa FFQ included 340 questions, and DNBC included 360 questions related to food consumption as compared to FFQ with lesser food items, for example, the Generation R study used a 170 food item FFQ to recorded maternal diets in the Netherlands (Klipstein-Grobusch et al., 1998). FFQ with a higher number of food item questions could better cover a large range of maternal dietary exposures and could provide a maximum representation of the study population's dietary choices in the dietary patterns extracted (Meltzer et al., 2008). However, it should be noted that a too detailed FFQ could increase dropout rates and increase under-reporting by the participants (Cade et al., 2002; Meltzer et al., 2008; Willett, 2012). Nevertheless, the dietary data thus recorded by the two birth cohorts, i.e., DNBC and MoBa were of high quality and demonstrated associations between macronutrients and birth outcomes, and extracted maternal dietary patterns that explained maximum variance in the maternal diets and the gestational weight gain risk factors. Also, all three cohorts used food composition tables for converting the standardised food portion sizes of the FFQ into nutrient intakes. The CARE study used McCance and Widdowson's standard UK food composition tables (Holland B, 1992). Whereas, the dietary intakes were computed using Norwegian food composition tables in MoBa (Blaker and Aarsland, 1989) and Danish food composition tables in DNBC (Mikkelsen et al., 2007). A strength of using food composition tables is that it makes the extraction of single nutrients possible for conducting analyses. Availibility of the single nutrients are largely based on the completeness of the food composition tables. All three cohorts used food composition tables which were updated regularly; therefore the nutrient intakes could be considered representative of the actual intakes in the birth cohorts. Because, if there is incomplete information in the food composition tables, then it might lead to biases, underestimation of the overall dietary intakes and might lead to false associations (Sacco and Tarasuk, 2013). However, the limitations of the food composition tables must also be considered while interpreting the results of macronutrient components, including glucose, starch, lactose, maltose, galactose, fructose, sucrose, and fatty acids (PUFA, SFA and MUFA). Because it might be possible that not all food composition tables would provide this data to conduct analyses, and, therefore the large gaps in the coverage of the nutrients must also be considered.

For the analyses, this was a strength because analyses was possible using the maternal dietary macronutrients components as the exposure for exploration in Chapter 4 within the CARE study. But it should be noted that the results of the composition tables which provide nutrient

values for such components might differ, for example total fibre might be provided in all the food composition tables but its values might differ according to the chemical analysis used (Aldwairji et al., 2014; Cade et al., 2017).

Also, dietary measurement error was lowered in this thesis by excluding participants who reported unrealistic energy intakes. This was dealt by setting cut-off limits of <600 kcal/day and >6000 kcal/day for energy outliers in CARE study, MoBa and DNBC. This was dealt in the initial stages of the analyses as outliers in a dataset could significantly influence the process of estimating the estimates, odds or mean and SD of a cohort, which, therefore lead to overestimation or underestimation of the results, for example, the mean maternal macronutrient intakes of the birth cohort. This can occur due to errors by the participants or during data entry. Therefore, it is essential to data clean the outliers because it could introduce bias in the birthweight estimates of the birth outcomes leading overestimating actual results (Kwak and Kim, 2017).

A detailed analysis exploring the association between dietary maternal macronutrient components and birth outcomes was possible using the CARE study as it measured dietary macronutrient components, for example, glucose, fructose, lactose, sucrose, MUFA, PUFA and SFA.

The thesis explored maternal dietary choices using principal components analysis (PCA) within MoBa by extracting dietary patterns explaining maximum variance in the maternal diets. These dietary patterns also demonstrated to be associated with birth outcomes. As discussed in Chapter 6 under section 6.1 the PCA extracted uncorrelated linear combinations of dietary patterns which are not based on previous literature and are exploratory; therefore, they are useful in describing the dietary patterns specific to any population (Jolliffe, 2011; Schwedhelm et al., 2018).

Dietary patterns contributing to gestational weight gain were explored in this thesis. Gestational weight dietary patterns were created using reduced rank regression analyses, which is an appropriate method as it extracted dietary patterns that explained maximum variance in the gestational weight gain risk factors (Hoffmann et al., 2004). The study included risk factors affecting gestational weight gain in the RRR model based on previous literature. These included smoking, total energy intakes pre-pregnancy BMI and physical activity levels. Further, the dietary patterns contributing to gestational weight gain were observed to be associated with birth outcomes.

The study outcomes in the thesis were recognised with the help of a literature search of 258 studies and a critical evaluation of the evidence available from 24 studies. However, there was inconclusive evidence for three birth outcomes, namely birthweight, and odds of SGA and LGA babies. Therefore, the three outcomes were clearly defined for further exploration in order to demonstrate results for both ends of the birthweight spectrum. As evidenced in Chapter 2 under section 2.5, there is evidence available for other birth outcomes of interest such as preterm deliveries, birth length (Chong et al., 2015), ponderal index (Chong et al., 2015; Moore et al., 2004) and preeclampsia (Brantsæter et al., 2014).

Confounders were only included for analyses if they were associated with both maternal dietary intakes and birth outcomes, thus reducing overall confounding bias. Directed acyclic graph (DAG) – an *a priori* approach was used to select a final set of confounders (Shrier and Platt, 2008). The potential confounders included in the DAG were based on previous literature and their clinical importance but not their statistical significance. The traditional approach suggested that a confounder should be an independent cause of an outcome. However, it has led to confounding bias in many studies, as evidenced during the critical evaluation in Chapter 2. Therefore, DAG is a simple method which helps to graphically represent whether the bias is reduced or not in a causal pathway, for example, if maternal diet is the exposure and birthweight is the outcome, the DAG could visually help determine if a covariate, for example, smoking is associated with both (maternal diet and birthweight) or either of them, with the help of arrows and coloured circles (this is illustrated in Figures 6, 7, and 8 in Chapter 5 under section 5.2.6). It should be noted that the logarithm provides a minimum adjustment set of confounders based on the direction of arrows, i.e., if the arrows from the covariates are pointing towards, both, the exposure (maternal diet) and outcome (birthweight). The process only includes manual entry of confounders into the electronic DAG; therefore, the choice of confounders entered are entirely based on previous literature that suggests that a confounder is associated with both exposure and outcome (Shrier and Platt, 2008).

Finally, larger increments for maternal dietary macronutrients (100g fo CHO and 30g each for protein and fat) and dietary patterns (1SD) were used to make the resulting associations more clinically relevant and represent more realistic changes in birthweight. This allowed comparing birthweight estimates amongst the macronutrient variables which had different ranges of intake (Lagiou et al., 2004).

Therefore, even if the difference in birthweight estimates and confidence intervals seemed smaller than expected, it is essential to consider that small effects on a population level could be important (Rose, 2001) through shifting the whole distribution of birthweights, higher or lower depending on the type of macronutrient consumed.

8.6 Overall weaknesses

The results in this thesis cannot establish causal relationships between maternal dietary macronutrient intakes and maternal dietary patterns and birth outcomes. This is because the analyses were conducted using an observational study design and might introduce bias in assuming there is a causal pathway (Grimes and Schulz, 2002; Roessner, 2014). There might be two possible reasons influencing the associations in the observational study, 1. Using self-reported data for conducting analysis and 2. The influence of other possible factors such as biological and genetic exposures and mechanisms that might have contributed to the associations implying multi causality. Thus, the conclusions will need to be drawn cautiously (Rothman and Greenland, 2005). Therefore, studies suggest that it might be favourable to consider reliable results from a well-monitored RCT (Kaye, 2019); however, it is challenging due to the reasons cited further.

According to the Centre for Reviews and Dissemination (CRD) (Tacconelli, 2009), randomised controlled trials (RCT) present highest form of clinical evidence, therefore, these findings warrant further research amongst well-designed RCT. But, conducting RCTs have logistical and ethical limitations particularly amongst pregnant women and children (Kaye, 2019; Roessner, 2014). Pregnant women are excluded from RCTs because of the potential harm and consequences of teratogenicity by the consumption of the drug, nutrients or vaccines used during gestation on women and their fetus (Kaye, 2019). Therefore, they are limited to conducting animal studies of short durations and smaller sample size, making it challenging to capture the associated effects of maternal diet on offspring outcome (Kaplan, 2018; Macklin, 2010). Also, there is a disadvantage of using observational studies because if there are less number of variables or the quality of the data recorded is poor then the analyses is prevented from confounder adjustment. This is not the case with RCTs because all potential confounders, whether known or unknown are expected to be evenly distributed between the case and control groups (Roessner, 2014). However, in nutrition research within a study population of pregnant women, conducting RCTs are less feasible and have ethical constraints.

Further, an animal model study used mice and conducted 2 observational studies to observe the impact of food consumption on weight gain and rigorously controlled the food intakes supplied to the mice in both studies. Study 1 randomised the mice into three groups and in Study 2, the mice were paired and divided into two groups and followed a 2-week feeding regime. The study reported different results amongst both the observational studies conducted using mice even under rigorous and well-monitored environment. This could suggest that in nutrition research associations observed in the observational studies might not be reliable and

appropriate indicators of causality, even in the most rigorous and supervised environment (Ejima et al., 2016).

However, as all the birth cohorts were of prospective design, the maternal dietary data were recorded and measured before the birth outcomes and so this allowed for temporality to unfold in the causal relationship and lowered measurement error(Grimes and Schulz, 2002). Also, the dietary data recorded by the three birth cohorts are of high quality as they have been either interviewer administered (24 hr dietary recall in CARE) or the FFQ (in DNBC and MoBa) have been validated against other dietary assessment tools to test for validity. Moreover, rigorous quality checks were conducted within the cohorts to lower participant and data entry errors in the dietary and baseline data recorded therefore, lowering the overall measurement error and bias in the results produced.

In large birth cohorts, it is a methodological challenge to use sophisticated equipment for dietary and anthropometric measurements due to logistical and workforce constraints (Emmett, 2009). Hence, most cohorts resort to depending on memory-based dietary assessment tools, including 24-hour recalls and food frequency questionnaires (Black and Cole, 2001; Byers, 2001; Cade et al., 2017; Elmståhl and Gullberg, 1997) (refer section 8.4 for more details). However, FFQ and 24-hour dietary recalls are considered better options for large populations because it is inexpensive and do not require trained personnel(Brantsæter et al., 2008). Previous studies have conducted validation assessments for FFQ and 24-hour dietary recalls and have suggested that FFQ have been demonstrated to correlate well with 24-hour dietary recall (overall r= 0.62)(Yuan et al., 2017), 4-day food diaries (r=0.55 for protein and r=0.27 for CHO) (Steinemann et al., 2017) and 7-day food diaries (r=0.62 for fruits and vegetables) (Mikkelsen et al., 2007) and an overall r=0.63 in the Yuan study (Yuan et al., 2017). This could imply that FFQ is a suitable dietary assessment tool for large populations. In MoBa, amongst a validation study of 119 pregnant women, the FFQ correlation coefficients showed that the food groups and food intakes were strongly correlated with 4-day food diaries than nutrient intakes (r=0.48 vs 0.36) (Brantsæter et al., 2008). In DNBC, FFQ was validated against 7-day food diaries amongst 88 participants to test for validity for fruits and vegetable consumption and suggested that the FFQ strongly correlated against 7-day food dairies (r=0.62 for fruits and vegetables [combined], and r=0.39 for total protein) (Mikkelsen et al., 2007). Therefore, the results produced for the maternal dietary data and birth outcome could be considered reliable as the possibilities over measurement errors and overestimation of food intakes were tested for validity in the cohorts. In agreement, another study suggested that validation of FFQ against other dietary recalls with repeated measures usually have a correlation between r=0.4 to 0.7 (Byers, 2001).

The CARE study used an interview administered 24-hour dietary recall to measure dietary intakes of pregnant women on a specific day during trimesters 1 and 2. This was used in the CARE study as alternative approaches such as FFQ were not available in this sample. A number of validation studies (Beer-Borst and Amadò, 1995; Hartman et al., 1990; Karvetti and Knuts, 1985; Sharma et al., 1998) have suggested that using a 24-hour dietary recall is a well-established method that correlates well with actual intake and are an adequate tool to measure dietary intakes in a large population. Although this method might not capture occasional consumed foods and nutrients, it still is suitable for macronutrients, which are present in most foods (r=0.3 to 0.7) (Beer-Borst and Amadò, 1995; Hartman et al., 1990).

Also, it might be argued that the cohorts could have used two dietary assessment tools simultaneously as an approach to crosscheck dietary intakes, for instance, use of FFQ and 24-hour or 3-day dietary recalls but, it is challenging to recruit trained research personnel to conduct interviews and could introduce higher loss to follow up rates. Also, it puts an extra burden on the participants to report food intakes, and this could introduce participant level errors in data recording, and lower the response rate and overall statistical power(Brantsæter et al., 2008).

Although validated semiquantitative FFQ (MoBa and DNBC) and 24-hour dietary recall (CARE) was used to record dietary data, the issue of underreporting of dietary intakes remained a consistent limitation in this thesis. Studies have suggested that in nutrition research, despite high-quality dietary assessment tools used to estimate the dietary intake measurements it is challenging to estimate the actual usual intake in a large population (Black and Cole, 2001; Johansson et al., 1998). Moreover, it is also suggested that most pregnant women underreport their total energy intakes, making it further challenging to estimate true actual intakes that could influence the fetus and subsequent offspring outcomes. A study (McGowan and McAuliffe, 2012) used 3-day food dairies to measure the food intakes on three consecutive days, including one weekend and were checked for errors by the research team. The study used Goldberg's method to predict the estimated underreporting of energy intakes by using the ratio of energy intake (EI) to estimated basal metabolic rate (BMR) (Black et al.). Schofield equations were used to calculate the BMR using the participant's age and weight (kg) (Schofield, 1985). As per (Black et al.), a ratio of <1.2 may indicate underreporting and a ratio lower than <0.9 is definite underreporting (Goldberg et al., 1991). The results of the study suggested that around 45% of pregnant women could be underreporting their total energy intakes during pregnancy and a high BMI of >25 was an important predictor of underreporting of energy intakes. Since the analyses in this thesis was conducted using secondary data, there was no data available for the BMR of the participants. BMR is required to calculate to the EI ratios.

Nevertheless, the authors recommended an alternate solution to lower underreporting, i.e., to exclude participants with extreme energy intakes. In agreement with the McGowan study and other evidence (Olsen et al., 2007; Samuel-Hodge et al., 2004), a broad energy range of <600 kcal/d and >6000 kcal/d was chosen for analysis in this thesis (refer section 5.2.3 in Chapter 5). This range was set because it included extreme low intakes that might have been caused during early pregnancy such as nausea and vomiting, and higher energy intakes due to hormonal influence (Crozier et al., 2017; Faas et al., 2010; Hirschberg, 2012; Latva-Pukkila et al., 2010). It could be argued that other energy cut-off limits could have been considered. Other studies set narrow cut off limits for energy outliers such as 1000-4000 kcal/d (Brantsæter et al., 2014) and 1720-2800 kcal/d (Moore and Davies, 2005; Moore et al., 2004). These cut-offs for energy were not considered for the thesis as they would have led losing a large quantity of the sample size and lowered statistical power, and would not have covered a wide range of energy intakes during pregnancy.

Underreporting might have influenced the resulting associations with birth outcomes in the analyses and therefore, requires exploration of results amongst other birth cohorts including, the Generation R study (Jaddoe et al., 2006) and Avon Longitudinal Study of Parents and Children (ALSPAC) (Fraser et al., 2013) to test for consistency of findings. However, it is possible that the results in the two cohorts would be different as their study designs largely differ from DNBC, MOBa and the CARE study (refer section 8.6 for a detailed discussion). The ALSPAC used a non-validated FFQ to recorded dietary data from the pregnant women during late pregnancy (around 32-34 weeks), this might give different results from the findings of this thesis. The maternal dietary data might be overestimated and not present close to actual dietary intakes as it was not validated (Emmett, 2009). Therefore, this could introduce measurement errors and bias in the observed associations (Streppel et al., 2013) and could result in making false associations (Cade et al., 2004).

There was no evidence of an association observed between the maternal dietary macronutrient intakes and odds of SGA and LGA babies. They were mostly associated with birthweight, which was analysed as a continuous variable. This might be because odds of SGA and LGA babies were binary outcomes and were analysed as categorical variables which do not use complete information, unlike continuous variables. All three birth cohorts mostly included well-nourished women with healthy birth outcomes. However, in order to investigate associations between maternal dietary macronutrient composition and risk of LGA infants, it could be necessary to account for certain maternal factors as confounders, including gestational diabetes mellitus (GDM), oral glucose tolerance test and history of Type 1 and Type 2 Diabetes Mellitus (DM). The analyses in this thesis could not adjust the regression models for these confounders because

the data was unavailable. However, the participants with GDM and or Type 1 and 2 DM require medical nutrition therapy (MNT) such as low-glycaemic index diets (GI), and diabetic counselling, thereby lowering the risk of hyperglycaemia or hypoglycaemia and lower risk of macrosomia babies (>4000 g) (Dolatkhah et al., 2018; Moses et al., 2009; Wei et al., 2016). Since they require these additional considerations, it is preferable to design regression models specific to these populations to lower confounding bias, multi-causality and complexity for the models for interpretations. Most importantly analysing both groups, i.e., pregnant women with GDM and pregnant women with no GDM would change the implications of the results demonstrated. Therefore, this thesis chose to conduct analyses amongst a healthy, well-nourished group of pregnant women because they are proportionately larger in a general population, thus making the results of the thesis more generalisable.

8.7 Overall implications and recommendations for clinical practise

It is evidenced that regular weighing during pregnancy is not currently recommended in many countries but is suggested to control gestational weight gain (Allen-Walker et al., 2016; Daley et al., 2015; Daley et al., 2016). In the UK and Europe, there are no formal, evidence-based guidelines for weight gain in pregnancy. The National Institute of Health and Care Excellence (NICE) (NICE, 2010) guidelines in the UK have prescribed a range of 10-12.5 kg total weight gain during pregnancy, and this is followed by the NHS England (NICE, 2014). A study by Allen-Walker and colleagues (Allen-Walker et al., 2016) addressed this longstanding issue and reported that routine weight gain check-ups during pregnancy were regularly conducted between 1940-1970 as the evidence suggested that maternal nutrition was associated with infant weight. Following criticisms relating to routine weight gain check-ups, in 2003, the NICE guidelines prescribed that women with normal pre-pregnancy BMI were to be weighed only at booking (Allen-Walker et al., 2016). In 2010, however, a joint guideline by the Royal College of Obstetrics and Gynaecology (RCOG) and Centre for Maternal and Child Enquiries (CMACE) stated that only obese women were to be measured at booking and trimester 3 (Modder and Fitzsimons, 2010). The NICE PH27 update (2014) stated that evidence-based UK guidelines on pregnancy weight gain continued to remain an urgent research need (*Annual Report of the Chief Medical Officer, 2014—The Health of the 51%: Women*, 2015).

Similar practises are observed in Europe, where only pre-pregnancy weight is recorded at booking. Whereas in Scandinavian countries, including Norway and Denmark the pre-pregnancy weight is recorded at booking, and they additionally record trimester wise weight gain during antenatal check-ups (Magnus et al., 2006; Olsen et al., 2001). This data is linked to national health registries and is accessible by birth cohorts for further research, however, despite these

measures taken, there is a lack of evidence-based guidelines for pregnancy weight gain (Devlieger et al., 2016).

The results generated in this thesis contribute to the evidence-base as they present findings suggesting an association between maternal dietary macronutrients and offspring outcomes. In particular, the evidence demonstrated the contribution of maternal dietary choices in relation to gestational weight gain by accounting for its risk factors, including pre-pregnancy BMI, maternal smoking, physical activity levels and total energy intake. The dietary patterns derived using PCA and RRR were mostly characterised by high maternal intakes of CHO and protein-rich foods and were associated with healthy gestational weight gain and birth outcomes. Further, these research findings have accounted for confounders, including maternal age, smoking habits, alcohol intake, physical activity levels, dietary supplements and parity.

Previous studies (Arabin and Baschat, 2017; Rogozinska, 2017; Shapira, 2008) have identified the prenatal period as a 'window for change' amongst overweight and obese women as they have higher adherence levels to adopt lifestyle changes for healthy pregnancy outcomes. In addition to the available evidence, the results in this thesis present associations between maternal dietary intakes recorded around 22-25 weeks of gestation and birth outcomes.

Furthermore, although the NICE guidelines do not currently recommend community midwives or any health care professional to routinely provide information on optimal gestational weight gain, data from non-pregnant populations suggest that regular weighing is associated with improved weight control (Burke et al., 2011; Madigan et al., 2013).

In need of evidence-based pregnancy weight gain guidelines, a study conducted by the NHS in Nottingham (Swift et al., 2016) further stressed the requirements for clinical practise. It suggested that over 50% of the women were overweight and obese at booking. The study found that most obese and overweight women expected more health counselling engagement, including nutrition and lifestyle management from the healthcare professionals in order to have healthy pregnancies (Swift et al., 2016). The results in this study highlighted the urgent requirement for appropriate weight gain guidelines to control maternal obesity rates in UK.

The reference guide published by the NICE and the National Health Service (NHS) (*Weight management before, during and after pregnancy*, 2010) advices overweight and obese pregnant women not to try to lose weight during pregnancy by calorie reductions. However, evidence has suggested that dietary interventions during pregnancy might support healthy gestational weight gain and offspring outcomes (Craemer et al., 2019; Thangaratinam et al., 2012; Tielemans et al., 2015). A large systematic review of 88 studies (56 experimental studies

including RCTs) and (32 observational studies) explored the effectiveness of dietary, physical activity and lifestyle interventions on maternal weight related outcomes and fetal outcomes. The results of the meta-analysis suggested that pregnant women in the dietary intervention group observed an overall reduction in weight gain with a reduced trend of exceeding the IOM recommendations for pregnancy weight gain. Amongst fetal outcomes, the review suggested that pregnant women in the dietary intervention group were associated with lower risk of LGA infants with a reduction of 27% lower birthweight (Rogozinska et al., 2017; Thangaratinam S, 2012). Another meta-analysis of 31 studies suggested that dietary interventions for overweight and obese pregnant women are indeed effective in controlling excessive gestational weight gain and suggested the clinicians and midwives to conduct active dietary counselling sessions in order to ensure a healthy weight gain (Craemer et al., 2019).

In this thesis, the results for the association between maternal dietary macronutrients and birth weight, and odds of SGA and LGA babies have suggested that dietary protein is associated with higher birthweights. Nevertheless, there was no evidence of an association observed for poorer outcomes such as odds of SGA and LGA babies. This could be due to usage of categorical variables that do not use complete information like continuous variables. This might suggest that there was no particular maternal source of energy associated with poorer offspring outcomes amongst a well-nourished population. Amongst macronutrients, the impact of maternal protein and CHO on offspring outcomes was observed in the results. The general assumption that higher maternal dietary fat intakes are associated with heavier offspring were not demonstrated in this thesis. A possible reason could be under-reporting of actual dietary fat intakes by the participants, especially amongst women with higher pre-pregnancy BMI (Black and Cole, 2001; Johansson et al., 1998; McGowan and McAuliffe, 2012).

Due to high variability in the results presented amongst the birth cohorts, it is challenging to reach a consensus of a definite answer for an ideal maternal macronutrient composition (%E) to ensure healthy weight gain and offspring outcomes. This was because there was not sufficient evidence from studies recommending macronutrient composition ensuring healthy weight gain. A recent study reviewed the current evidence available for macronutrient and micronutrient requirement during pregnancy and suggested that amongst macronutrients, a 10-25 E% from protein appeared to be safe for consumption. However, the study did not specify if it was adequate to support a health gestational weight gain. Although there were no recommendations given for % of energy from dietary fat and CHO, the study suggested that around 175g of CHO through low glycaemic diets might be beneficial for GDM women and lower risk of LGA babies. However, the study specified that there was no evidence available to support the recommendation for %E from CHO for pregnancy. Further, the study also did not specify

any range for the %E from fat (Mousa et al., 2019). Tielemans and colleagues(Tielemans et al., 2015) explained that maternal macronutrient intakes were not consistently associated with gestational weight gain. Also, it is unclear if maternal macronutrient intakes are associated with excessive or inadequate gestational weight gain (Tielemans et al., 2015).

Based on the dietary recommendations of SACN/COMA in UK and NNR in Nordic countries (refer section 9.3) (Health, 1991; NNR, 2012) a macronutrient composition of approximately 50-60 E% from CHO, 10-30 E% from protein and 15-25 E% from fat might be an appropriate energy balance for ensuring healthy weight gain in an European population of pregnant women. This is suggested while additionally accounting for important maternal characteristics such as age, pre-pregnancy BMI, physical activity levels, parity, ethnicity and lifestyle habits including smoking and alcohol intake. In support of this suggestion, a study exploring the effect of diet during pregnancy to control excessive gestational weight gain recommended that dietary advice must be given based on the pre-pregnancy BMI of women (Tobias and Bao, 2014).

In order to control excessive gestational weight gain, a study suggested that evidence from most interventional studies provided similar nutritional advice of reducing the food high in fat and carbohydrate (Craemer et al., 2019). In addition to this evidence, the gestational weight gain dietary pattern results from this thesis suggest that the source of animal protein such as animal meat (including red and processed meat, marine protein and poultry could be differentially associated with the gestational weight gain and offspring outcome, particularly amongst LGA infants. Therefore, focusing on maternal dietary choices and lifestyle habits while accounting for pre-pregnancy BMI at booking might be beneficial to lower the odds of LGA babies. Further, in addition to women with GDM having an increased risk of LGA babies, it has been evidenced that 78% of LGA infants were born to non-GDM women in the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) trial (Group, 2009). Therefore, this might mean that non-GDM women might equally need dietary attention to lower the risk of LGA infants. These small yet achievable changes in maternal macronutrient consumption might control excessive gestational weight gain, thereby lowering overall maternal obesity rates and potentially be useful in contributing to the existing literature required to form official evidence-based guidelines. However, it should be noted that these results are observational and cannot imply causality.

8.8 Novelty of the results

This thesis has demonstrated novel findings after using the data of three large sample-sized birth cohorts and sophisticated statistical methods for analyses.

- This thesis is the first to undertake an individual participant data meta-analysis using three birth cohorts and demonstrate an association between maternal protein intake and birthweight.
- The findings from this thesis are the first to demonstrate that higher intakes of macronutrient components such as starch, lactose and glucose are associated with higher birthweight within the CARE study.
- It was possible to explore maternal dietary patterns and their association with offspring outcomes. Although it has been widely explored, the findings from the PCA analyses are the first to suggest that maternal dietary patterns high in animal meat are linked to higher odds of LGA babies.
- It is the first to create a unique set of 'gestational weight gain dietary patterns' through RRR, a statistical method used to evidence dietary patterns that explain maximum variance in the gestational weight gain risk factors. This is also the first to evidence that gestational weight gain dietary patterns high in protein and CHO are associated with offspring outcomes.

8.9 Planned future publications

There are three chapters planned for publication. The tentative titles and their target journals are given in turn below:

1. Association between dietary macronutrient composition in pregnancy and birth outcomes: a meta-analysis of three birth cohorts (CARE, DNBC and MoBa). The target journal is the International Journal of Epidemiology (IJE).
2. Association between maternal dietary patterns and birth outcomes using PCA – results from the MoBa birth cohort. The target journal is the International Journal of Epidemiology (IJE) or the European Journal of Epidemiology.
3. Creation of gestational weight gain dietary patterns and its association with birth outcomes—results from the MoBa and DNBC cohort. The target journal is the International Journal of Epidemiology (IJE) or the BJOG: International Journal of Obstetrics and Gynaecology.

8.10 Potential for further research

Although evidence in this thesis has demonstrated associations between maternal dietary macronutrient composition and dietary patterns, and birth outcomes, they are observational studies which cannot imply causality.

Further studies could replicate the analyses on maternal macronutrient composition and sub-component intakes, and birth outcomes by adjusting for similar confounders amongst other birth cohorts. However, this is dependent on the availability of such data in other birth cohorts. Also, evidence from RCT is required to explore the recommended macronutrient composition for pregnancy, ensuring healthy pregnancy weight gain.

The results in this thesis evidenced an association between an "animal meat" dietary pattern and higher odds of LGA baby. Also, the meta-analysis evidenced that total maternal protein intakes were positively associated with higher birthweights. Further studies could investigate the type of protein influencing these associations. A re-analyses of MoBa and DNBC data could be undertaken in order to explore the association between animal and plant-based proteins consumed in pregnancy with odds of SGA and LGA babies.

Studies could investigate associations between maternal dietary macronutrient composition and risk of LGA infants and possibly account for certain maternal factors as confounders, including gestational diabetes mellitus (GDM), oral glucose tolerance test and history of Type 1 and Type 2 Diabetes Mellitus (DM). Also, high sample-sized cohorts could explore the associations by conducting sub-group analyses amongst women with GDM or Type 1 or 2 DM.

Moreover, studies including women at high risk could generate gestational weight gain dietary patterns for gestational diabetes mellitus, and further investigate the impact of these dietary patterns in relation to birth outcomes, especially LGA infants. This might be necessary because the dietary macronutrient requirements for GDM are different as compared to a healthy, non-diabetic population. This exploration could provide explanations for the potential effects of CHO metabolism amongst women with GDM on risk of delivering LGA infants.

Also, high sample sized studies including RCTs and observational studies could classify their cohort based on BMI and investigate the association between maternal dietary macronutrient composition and birth outcomes amongst underweight, normal, overweight and obese pregnant women. However, the findings of this thesis have been adjusted for pre-pregnancy BMI.

8.11 Concluding remarks

The results in this thesis have demonstrated an association between maternal dietary macronutrient intakes and birth outcomes, including birthweight, and odds of SGA and LGA babies. In particular, findings from the meta-analysis study of DNBC, MoBa and CARE suggested an association between maternal dietary protein intake and higher offspring birthweight,

although not with odds of LGA babies. However, the findings from the PCA and RRR analysis suggest the positive association between maternal dietary patterns high in animal protein and odds of LGA babies. Although small effect sizes of birthweight were observed, it could have clinical implications on a population level.

The thesis created a unique set of gestational weight gain dietary patterns, demonstrating that patterns which mainly consisted of protein and carbohydrate-rich foods were associated with higher birthweight. These maternal dietary patterns explained maximum variance for two gestational weight gain risk factors, namely maternal smoking and total energy intakes.

Finally, based on the evidence in this thesis, it could be suggested that no particular macronutrient seems to be associated with poorer birth outcomes such as odds of SGA and LGA babies. Therefore, macronutrient composition, as stated in the dietary reference values (DRVs) is still warranted for optimised growth of the offspring. However, additional weight gain through excess energy intakes from protein and carbohydrate should be avoided.

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Appendix A Grant application to the BBMRI-LPC cohort data access

Biospecimen/Data Access Request Form

[The Word template is provided as an alternative should you experience any difficulty to complete the online Access Request form. The Word template should be limited to the Research Proposal section (items 1 to 7 below). Additional information about investigator, institution, biosample/data, variables and type of analysis must be completed using the online form. Please contact the helpdesk (bbmrilpc-call-helpdesk@iarc.fr) if you experience further difficulties.]

Project Title [title]

The influence of macronutrient dietary patterns on pregnancy weight gain, birth outcomes and child health- a pooled cohort study

Project narrative [limited to 300 words]

Barker's hypothesis explored the relationship between pregnancy complications such as low birth weight, intrauterine growth restriction (IUGR), preterm birth and the incidence of hypertension, coronary heart diseases and non-insulin dependent diabetes mellitus in middle age (de Boo and Harding, 2006). Poor maternal dietary intakes such as energy, protein and micronutrients have shown to contribute to adverse birth outcomes such as low birthweight and have been associated with an increased risk of developing adult obesity in the offsprings (Berkowitz et al., 2010). A review inferred that low intakes of maternal protein-energy supplementation during pregnancy increases birth complications such as still birth, small for gestational age and low birth weight (Imdad and Bhutta, 2012).

An association between total energy intake consumed in pregnancy with the subsequent birth outcomes and child's health is not completely established. Little is known about the specific and individual effects of energy sources (fats, protein and carbohydrates) on mother's BMI (body mass index) and birth outcomes (Yu et al., 2013). We will investigate the impact of the maternal dietary pattern linked to weight gain in pregnancy; and energy sources consumed (fats, protein and carbohydrates) in pregnancy on maternal BMI and its effect on birth outcomes and health of the children aged 3-7 years.

This analysis will utilise existing birth cohort studies in the BBMRI consortium. We will pool 3 cohorts. The Lifelines Cohort Study and Biobank from the Netherlands; the Norwegian Mother and Child Cohort Study from Norway; and the Danish National Birth Cohort from Denmark. Following data harmonisation, we will explore associations between total dietary energy intake and sources of energy (fats, carbohydrates and proteins) during pregnancy on maternal BMI (body mass index). We will then generate a 'pregnancy weight gain dietary pattern' using reduced rank regression and explore the link between this dietary pattern and birth outcomes such as preterm birth, birth weight, small for gestational age and IUGR. The final stage of

analysis will link the pregnancy weight gain dietary pattern to physical, dietary, and anthropometric parameters of 3-7 year old children.

Overarching aim and specific objectives

[The overarching aim of the project should be briefly summarized, along with the specific objectives (in bullet points) that are foreseen to achieve the overarching aims. This should reflect the most important aspects of the overall application and serve as project summary. Limited to 500 words]

The central aim of our project is to study maternal macronutrient dietary intake through generation of a unique maternal weight gain dietary pattern and its relationship to birth outcomes; and subsequent nutrition in early childhood. We will explore, the relationship between total dietary energy intake and its food and nutrient sources in pregnancy on pregnant women's BMI (body mass index) and its effects on birth outcomes. Through pooling of maternal dietary data among large cohorts we will investigate the consistency of this relationship across the cohorts. Identifying whether specific energy sources or total energy intake is most strongly linked to maternal pre-pregnancy weight and weight gain during pregnancy. A 'pregnancy weight gain dietary pattern' will be developed using a reduced rank regression model, including dietary components such as total energy consumption and energy sources (fats, carbohydrates and protein) and other core lifestyle variables such as smoking, exercise. For example, a pregnancy weight gain dietary pattern will be, "total dietary energy consumption patterns of overweight pregnant women who were smokers and ate high amount of fastfood in their first trimester." Then, we will explore the impact of this dietary pattern on birth outcomes, and dietary and physical activity habits observed in children between 3- 7 years of age.

Study objectives :

- To study the association between total dietary energy intake and sources of macronutrients on maternal BMI (both pre-pregnant and during pregnancy)
- To develop a 'pregnancy weight gain dietary pattern' using reduced rank regression model, including macronutrient dietary patterns and its sources and gestational weight gain as components.
- To study the impact of 'pregnancy weight gain dietary pattern' on birth outcomes: preterm, SGA, birthweight, IUGR
- To investigate the impact of different energy sources such as fats, protein and carbohydrates during pregnancy on birth outcomes such as preterm, SGA, birthweight, IUGR
- To study the association between the 'pregnancy weight gain dietary pattern' with dietary habits, physical activity and anthropometric measures amongst their 3-7 year old children.

Prospective and pan-European study design

[The core aim of the BBMRI-LPC is to facilitate studies that require prospectively collected data/bio samples from multiple cohorts across Europe. Any approved project must therefore show that the research question requires a study design where the research participants were

recruited prior to the endpoint of interest, and that the study will benefit significantly by including data/samples from multiple European countries (at least two countries). Only studies fulfilling these initial criteria will be considered for support by BBMRI-LPC. Limited to 300 words]

We will pool data from three large birth cohorts from Norway, Denmark and the Netherlands. To our knowledge, no other study has explored maternal dietary patterns leading to weight gain and birth outcomes in a pooled cohort analysis. We require an estimated number of 2,07,000 mother-1,86,500 child pairs.

The research question relates maternal nutrition to infant outcomes, requiring participants who were recruited prior to these endpoints of interest in keeping with a core aim of the BBMRI-LPC.

Pooling multiple cohorts from across Europe will ensure diets (and derived dietary patterns) are more representative than found in just one country, and therefore improve generalisability of our findings. Dietary measures are prone to error and vary by country and culture. Therefore, the pooling of 3 large cohorts will, to some extent, allow us to also assess the robustness to measurement error of any relationships we find between maternal dietary patterns and infant outcomes. The final benefit of pooling multiple cohorts is that the increased number of participants should lead to greater power to detect modest-sized associations between diet and infant outcomes. We would anticipate that any relationships we find would not be very large; otherwise they would be detectable in individual cohorts. Data pooling will substantially enhance this aspect of the study. For these reasons (representativeness, robustness and power), the study will benefit significantly by including data from multiple cohorts from multiple European countries, in keeping with a core aim of the BBMRI-LPC.

The cohort details are described in the following table:

Country – Cohort	**Participants-** **Mother/Child pairs**	**Baseline data** **(years)**	**Follow up data:** **3-7 year old children**
Norway- The Norwegian Mother and Child Cohort Study	95,000 &114,000	1999-2008	October,2012
Denmark- The Danish National Birth Cohort	100,000 &60,000	1997-2002	2005-2010
Netherlands- The LifeLines Cohort Study and Biobank	12,000 & 12,500 (estimated count)	Initiated in 2007-2013	1.5 years: 2010-2014 3 years: 2012-2015

Significance

[The proposed project must address an important biomedical research question. Are there questions relevant to specific disease endpoints that will be addressed by the research? Are there methodological obstacles that need to be overcome before further progress can be made in the field? If the aims of the project are achieved, how will the results benefit patients and/or the research community? Limited to 1200 words

Background

A meta-analysis states that the pre pregnancy obesity increases the risks of small for gestational age, low birth weight and macrosomia and subsequent off spring obesity (Yu et al., 2013). A high maternal BMI in pregnancy increases metabolic rates in pregnancy and cause further complications such as impaired glucose intolerance and hyperlipidaemia among obese mothers(King, 2006).

A review stated substituting dietary fat for carbohydrates (per each 1% of total calories) led to a higher risk of gestational diabetes and impaired glucose intolerance(Saldana et al., 2004). Blumfield et al reported in a review that pregnancy consumption patterns of dietary energy intake in pregnancy was lower than the prescribed guidelines, total fat intake was above the prescribed limits and carbohydrates intake was at border level (Blumfield et al., 2012). It is unclear whether these *dietary patterns in pregnancy can help us understand the long term health of offspring.* Further research is required that compares *maternal dietary intake with short term and long term offspring health outcomes.* Liberato et al stated a balanced protein-energy supplementation, of which 20% energy from protein would reduce the incidence of low birth weight and improve foetal growth(Liberato et al., 2013). There is lack of consensus suggesting the *correct amount and time to initiate protein-energy supplementation in pregnancy.* Regnault et al report a high number of infants are getting exposed to prenatal high fructose consumption through sweetened foods and beverages such as high fructose corn syrup (HFCS) found in breakfast cereals. These energy rich foods have shown detrimental effects on the birth outcomes such as preterm births and infantile hyperglycaemia in rats. We need to explore the prescribed *total energy intake from added sugar as it is one of the risk factors for pregnancy complications* (Regnault et al., 2013).

High calorie intakes of carbohydrates (refined sources) and total saturated fatty acids in pregnancy have harmful effects on maternal BMI in pregnancy causing impaired glucose intolerance, insulin resistance and hyperlipidaemia in women (King, 2006; Poston, 2012). A large cohort has linked gestational weight gain and pre pregnancy BMI with birth size as an outcome(Nohr et al., 2008). However, there is lack of literature that has studied the maternal weight gain or the body mass index, dietary patterns and pregnancy outcomes together. The role of dietary patterns in increasing the BMI leading to pregnancy complications has to be addressed.

Associations of prenatal mother-offspring fats and protein intakes were higher than postnatal mother-offspring intake(Brion et al., 2010). Dietary patterns vary by education, income and age. Studies have shown higher intakes of a range of nutrients including total saturated fatty acid, fructose (Regnault et al., 2013) among pregnant women. Vegetables, meat and fish, and dietary iron and folate intakes (Bodnar and Siega-Riz, 2002) were higher among well educated, older women from a higher income background. Studies have observed the effect of the maternal obesity on the birth outcomes(Nohr et al., 2008; Thangaratinam et al., 2012; Yang and Huffman, 2013), but have *not studied the effects of the individual sources of energy intake (protein, fat, CHO)* on the birth outcomes mediated through maternal BMI.

Effects of macronutrient sources (protein, fats and carbohydrates) have not been completely investigated in relation to birth outcomes such as the preterm birth, SGA, IUGR and low birth weight. There is sparse evidence suggesting the percentage of energy from carbohydrate intake and a specific influence of protein from dairy sources in early and late pregnancy were negatively associated with the birth outcomes such as ponderal index of the baby(Brion et al., 2010; Moore et al., 2004). Another study shows a positive link between balanced protein-energy supplementation in maternal diet on the birth weight and small for gestational age births (Abu-Saad and Fraser, 2010; Imdad and Bhutta, 2012; Ota et al., 2012). But, protein alone has been shown to have no particular influence on birth outcomes (Chong et al., 2015) although two studies have shown its positive impact on birthweight and preterm birth(CucÓ et al., 2006; Grieger et al., 2014).

Increased maternal BMI affects the caloric intake of the children with a higher risk of becoming overweight and obese in adulthood (Adegboye et al., 2012; Andersen et al., 2015; Berkowitz et al., 2010; Yang and Huffman, 2013) and affects the glucose intolerance amongst children (Brion et al., 2010; Murrin et al., 2013). The ALSPAC study and a German cohort (Ambrosini et al., 2014; Pei et al., 2014) tracked the diets of adolescent children aged between 7-13 years. Children with higher adiposity had a higher calorie and meat intake and poorer fruit and vegetable consumption which was associated with higher pre pregnancy maternal BMI (Ambrosini et al., 2014). However, *little is known* about the *tracking of macronutrients* in the mother's diet *through pregnancy* and how this reflects on her *child's dietary and lifestyle habits.*

We propose to use a novel approach to link the association of macronutrient consumption in mothers' diets with weight gain patterns. This new dietary pattern will be linked with birth outcomes such as preterm birth, SGA, IUGR and low birth weight; and subsequently linked with the child's later diet and lifestyle habits. Amongst the available evidence, there is no study to our knowledge that has designed a specific 'pregnancy weight gain dietary pattern' that combines maternal BMI and other factors (smoking, work, age and exercise) and total macronutrient consumption and its sources in its methodology to assess the birth outcomes. We hypothesise that the relationship between maternal energy intake on birth outcomes is mediated through maternal BMI both before and during pregnancy in terms of pregnancy

weight gain. Also, will explore whether the sources of energy (fats, protein and carbohydrates) have a differential effect on the maternal BMI and its impact on birth outcomes.

Methodological challenges

Dietary assessment is challenging and subject to a range of potential biases (Byers, 2001; Hebert et al., 1995; Livingstone et al., 2004). A recent systematic review has found that pre-pregnancy underweight increases the risk of SGA and LBW; pre-pregnancy overweight/obesity increases the risk of large for gestational age births, higher birth weight, macrosomia, and subsequent offspring overweight/obesity (Yu et al., 2013). Potential effect modification by maternal age, maternal energy intake, ethnicity and gestational weight gain needs further exploration. High weight gain during pregnancy is also associated with heavier babies (Ehrenberg et al., 2004; Gross et al., 1980; Kim et al., 2007). It is not known whether the source of energy in the diet during pregnancy is linked to the amount of weight gained or subsequent birth outcomes.

Although a range of variables have been associated with weight gain in pregnancy such as dietary fats and proteins, physical activity, food group consumption, smoking, age, hypertension (Abrams et al., 1995; Guelinckx et al., 2010; Hediger et al., 1989) a robust pattern of variables related to weight gain in pregnancy incorporating diet and other lifestyle factors (such as activity, smoking, age) has yet to be defined.

Further challenges will be to explore the mediating effect of maternal BMI when describing the relationships between maternal diet and birth and later child outcomes.

Challenges undertaken in this study will be to identify the components required for reduced rank regression analysis to predict outcomes such as a pregnancy weight gain dietary pattern and testing these across the cohorts included. Characterising maternal dietary energy patterns leading to gestational weight gain and birth outcomes will be undertaken by creating a pregnancy weight gain dietary pattern that observes the extent to which energy consumption in pregnancy mediated by weight gain has an impact on the birth outcomes.

Impact for patients and researchers

1. Future research studies can test the novel dietary pattern; the ‘weight gain dietary pattern’ developed in our study amongst these birth cohorts. Generating the potential for worldwide applicability and generalisability.
2. Obstetricians will be able to guide pregnant women regarding dietary intake and pregnancy weight gain linking it to the birth outcomes.
3. The potential effects of energy consumption and sources of energy (fats, protein and carbohydrates) on birth outcomes for example: birthweight, preterm births will be established.

Scientific excellence / Approach

[How will the research question be addressed practically? Outline details of the study design and how it benefits from the prospective nature of the data/samples. The investigator must briefly describe all methodical considerations and explain how they will address and achieve

the specific objectives of the project. The investigator should particularly describe the type of samples, and exposure and endpoints variables needed, as well as the proposed harmonisation approach. Are the laboratory and statistical methods proposed appropriate? Will the study design and proposed sample numbers bring sufficient statistical power to answer the overarching aims? Limited to 1200 words]

The study design is a pooled cohort involving pregnant women aged 18-40 years at the time of filling the questionnaires and their infants and will include follow up information of infants who are 3-7 years old from Denmark, Netherlands and Norway cohorts.

We have our own birth cohort CARE (Caffeine and Reproductive Health) study at the University of Leeds, that has involved women in pregnancy and led to UK government policy changes around caffeine intake (Boylan et al., 2008; Greenwood et al., 2010). To test the applicability of the results achieved through this pooled cohort and make it generalizable to the UK population, we plan to use the CARE study in our future analysis.

Maternal Anthropometric and Dietary assessment design:

We will require anthropometric data such as the height and weight measures of the mothers to calculate the BMI (body mass index) from the baseline data, both pre-pregnancy and weight during pregnancy. All the food frequency questionnaires will be used from these three cohorts as the source of maternal dietary pattern evaluation. Total energy intake in the diet will be calculated and computed after assessing the total number of serve sizes and frequencies listed for each food group and source of macronutrient, calculating the percentage of energy from protein, fat and carbohydrate.

Confounders or mediators:

Confounders or mediators will include information about smoking, employment, physical activity, marital status, age.

Birth outcomes and measurements:

We will require endpoint variables regarding the birth outcomes such as birth weight, preterm births, small for gestational age births and anthropometric measures such as head circumferences, birth length. We are interested to acquire endpoint variables such as follow up data regarding the child's dietary habits, anthropometric measures such as the height, weight, BMI of children and physical activity patterns. This information provided would be able to tackle each objective of our study.

See table below:

Norway:	**Denmark:**	**Netherlands:**
	The Danish National Birth Cohort	**The LifeLines Cohort Study and Biobank**

	The Norwegian Mother and Child Cohort Study		
Exposure variables:	Height & weight before & during pregnancy, gravidity, miscarriages, stillbirths. Blood pressure, gestational diabetes mellitus, elevated cholesterol levels in pregnancy.		Physical examination and questionnaires **every 18 months.**
Birth outcomes	Height/length, head circumference, birthweight, IUGR, SGA, preterm, stillbirths.		
Child outcomes	Child diet, physical activity, head circumference, height and weight **at 3, 5, 7 years.**	Child diet, physical activity, head circumference, height and weight **at 7 years.**	Child diet, physical activity, head circumference, height and weight **every 18 months to 7 years.**
Dietary data Mothers	Mothers' diet (FFQ) at **17, 22, 30 weeks gestation.** Following information required: Salt and food supplement Meat, eggs, fish and alternatives Vegetables and fruits Milk products Beverages (other than water or alcohol) Cereals, bread and starches Fat intake Sweet and baked goods Caffeine Water intake	Mothers' diet (FFQ) at **12, 30 weeks gestation.** Following information required Salt and food supplement Meat, eggs, fish and alternatives Vegetables and fruits Milk products Beverages (other than water or alcohol) Cereals, bread and starches Fat intake Sweet and baked goods Caffeine Water intake	Mothers' diet (FFQ) during pregnancy.

Dietary data Child's	Child's diet (FFQ) at **6 and 18 months.**	Child's diet (FFQ) at **18 months & 5 years.**
Confounders or mediators	Smoking, medical history, employment, physical activity, work stress, marital status, age. Maternal comorbidities: gestational diabetes mellitus & CVD, blood pressure and hypercholesterolemia.	

Statistical methods:

A 'pregnancy weight gain' dietary pattern will be created using a reduced rank regression model. Using this method, we will extract a number of linear combinations of predictor variables (i.e. components) that explain as much of the variation as possible in the response variables. In this way will identify independent (i.e. uncorrelated) dietary patterns that collectively account for different outcomes, or at least which are associated with those outcomes. We will use response variables that we have identified in advance from the literature as potentially important in the development of weight gain during pregnancy, including total energy intake, macronutrients [5-7], maternal age, pre-pregnancy BMI, smoking, previous medical history, physical activity, education, and employment status. The proposed model is therefore hypothesis-led rather than data driven, incorporating *a priori* information to characterise the dietary pattern(s) related to specific outcomes of interest.

Each study participant will then be scored to quantify the degree to which their reported dietary intake reflects the dietary pattern(s) identified. Generalised linear models (multiple linear regression for continuous outcomes and multiple logistic regression for binary outcomes) will then be used to investigate possible associations between the scores on the dietary pattern identified and outcome variables such as birth outcomes (IUGR, SGA, preterm births and low birth weight).

Finally, we will examine any association between the dietary pattern(s) identified and outcome variables relating to the child's dietary habits, physical activity levels and anthropometric measures (weight, height and head circumference).

Separately from the dietary patterns work, we will also test the differential impact of sources of energy (fats, protein and carbohydrates) on the birth outcomes using multiple linear regression models adjusting for key confounders and taking into account potential mediation by maternal BMI.

For all analyses, we will attempt to account for the effect of incomplete data by using multiple imputation, using as many imputed datasets as feasible with the large cohorts planned, and including appropriate outcome and predictor variables in the imputation models. All analyses will be performed using Stata SE, version 13.1 (StataCorp 1985-2013, TX USA), with the reduced

rank regression implemented using PROC PLS (Partial Least Squares) in SAS 9.2, called from within Stata 13.1.

Data harmonisation:

We have previous experience of cohort pooling projects, data harmonisation and dietary patterns work. For example, Prof Cade was a Co-I with the MRC Centre for Nutritional Epidemiology in Cancer Prevention and Survival (CNC), led by late Prof Sheila Bingham (University of Cambridge). This was a collaboration of 7 UK Cohorts, including dietary patterns work using pre-defined indices, principal components analysis, and reduced rank regression. We are also currently contributing to Prof Gita Mishra's (University of Sydney) InterLACE international cohort pooling project of over 20 studies.

We will carry out the data harmonisation in 2 stages:

- 1A. For dietary patterns: We will combine and harmonise the data generated by cohorts using information related to nutrients from the FFQs because although the food items and portion sizes may differ across the cohorts, the total energy consumption and nutrients estimated will be in the same format irrespective of the questionnaire structure differing among cohorts.
- 1B. For demographic patterns: We will harmonise the categories wherever necessary and will simplify by using the 'lowest common denominator' wherever necessary.
- 2. Data analysis: Once dietary patterns are identifed, we will prospectively model their association with maternal and child outcomes using generalised linear models. We anticipate undertaken the analysis separately within each cohort, using the best data available from each cohort, then pooling the results using a meta-analysis approach. We anticipate this will be the most appropriate method because it will not be possible to fully harmonise some data. For example, an important confounder such as smoking status may have a number of different ways of measuring it, but we would like to use all the information available to minimise the bias from uncontrolled confounding.

We will adhere to the University of Leeds data management policy, respecting principles of secure data storage and transfer, confidentiality, patient identiability, etc. We would adhere to the data management policies of the separate cohorts.

Innovation

[The peer-review will favour research projects that seek to challenge existing methodological paradigms and move the field of research forward. How is the proposed project different from previous studies in the same field and why will it answer questions that previous studies have failed to answer? Are there novel study designs or technological approaches involved in the project? Limited to 300 words\

- Pooling cohort data to study the effects of macronutrient dietary patterns mediated through pregnancy weight gain on birth outcomes is novel.
- The dietary pattern developed using reduced rank regression will help characterise weight gain in pregnancy, making a unique contribution because it is necessary to understand the effects of macronutrient nutrition in pregnancy on birth and child outcomes.

- Dietary pattern created ‘pregnancy weight gain dietary patterns’ will be tested across three cohorts for stability and applicability. Thus contributing to produce new research using this pattern as one of the many predictors in future work.
- This study will produce results that will characterise any differential impact of energy sources (protein, fats and carbohydrates) on birth outcomes.

Another gap will be covered observing the association between the ‘weight gain dietary pattern’ in pregnancy (includes maternal BMI and dietary energy consumption) and the child’s dietary and lifestyle patterns. This diet and lifestyle tracking of children will be done right from child’s infancy period.

A.1 Grant approval letter by the BBMRI-LPC scientific review committee

bbmri-lpc

The influence of macronutrient dietary patterns on pregnancy weight gain, birth outcomes and child health- a pooled cohort study

PI:
Prof. Janet Cade

Institute:
Nutritional Epidemiology Group, School of Food Science and Nutrition, University of Leeds

Disease of interest:
Maternal nutrition, pregnancy complications and child health

Biosamples required:
Only data is requested.

Cohorts required:
Danish National Birth Cohort (DNBC), LifeLines, Norwegian Mother and Child Cohort Study (Moba)

Analyses required:
None

Summary of Scientific Review Committee evaluation:

Overall, the application was rated as very good with an average score of 4.4. All five criteria were rated as very good. No specific comments were raised. As a conclusion, the Review Committee strongly supports this application.

Average review scores

Overall average score	**4.4**
Significance	4.3
Scientific excellence / Approach	4.2
Innovation	4.3
Study design	4.5
Investigators and research environment	4.8

Appendix B PCA factor loadings of the 206-food items in the maternal dietary patterns within MoBa

206 food items Variables	PCA factor loadings[10]				
	Mixed dietary pattern	Vegetarian dietary pattern	High sugar dietary pattern	Animal meat dietary pattern	Fish and high fibre dietary pattern
Added sugar	0.0121	0.0059	0.1401	0.1651	-0.0817
Orange	-0.0301	0.0136	0.0262	0.0156	0.1581
Grapefruit	0.0907	0.0332	-0.0041	0.0399	0.0534
Plum	0.0374	0.0153	0.0359	0.0156	0.0737
Banana	-0.0395	0.0033	0.0394	0.0287	0.1848
Apple	-0.039	0.0025	0.0285	-0.0026	0.2137
Grapes	-0.032	0.0048	0.0404	0.0485	0.1535
Peach	-0.0263	0.0484	0.0416	0.0239	0.0945
Mango	0.104	0.0681	-0.0451	0.0354	0.0295
Melon	-0.022	0.0436	0.0725	0.0045	0.1
Papaya	0.1927	-0.0123	-0.0211	0.0287	0.0213
Pear	-0.012	0.0241	0.0441	-0.0101	0.1381
Strawberry	-0.0002	0.0406	0.0731	0.0408	0.0231
Other berries	0.0451	0.0063	0.0748	0.0444	0.049
Apricots	0.102	-0.021	0.089	-0.103	0.1167
Raisin	0.0513	-0.0147	0.0904	-0.1129	0.1368
Prunes and figs	0.0854	-0.0313	0.0911	-0.1048	0.1384
Peanuts	0.0838	-0.018	0.1306	-0.0632	0.075
Almond and cashew	0.063	0.0145	0.0822	-0.0832	0.1203
Potatoes	-0.0682	0.0853	0.054	0.0493	0.0416
Cream of potato	0.0463	0.0978	0.084	-0.0043	-0.0489
Potato cooked	0.0132	0.1217	0.0861	0.0132	-0.051
Low fat yogurt	0.0665	0.005	0.0034	0.025	0.0605
Gomorgen yogurt	0.0196	-0.0008	0.081	0.0142	0.0622
Whole yogurt	-0.0008	-0.0212	0.0285	0.0314	0.116
Rice cooked	-0.0318	0.1588	0.0593	0.0081	0.0121
Couscous	0.1934	-0.03	0.0269	-0.0467	0.031
Mayonnaise	-0.0189	0.0867	0.1291	-0.0133	-0.0512
Mayonnaise cream	-0.0189	0.0867	0.1291	-0.0133	-0.0512
Fresh cream	-0.0033	0.1575	0.104	-0.0099	-0.0501
Mayonnaise, remoulade	0.0101	0.0133	-0.0198	0.0645	0.0884
Mayonnaise light	0.0657	0.0398	-0.0007	0.0865	0.0018
Whole meal bread	0.0012	-0.0275	-0.0067	0.0677	-0.0246
Dark rye bread	0.0025	0.0086	-0.0315	0.0128	0.1065

[10] Factor loadings in the PCA model represent the correlation coefficients between the dietary pattern and individual food items.

Fibre crisp bread	0.0088	0.0007	-0.0091	0.0703	0.0528
White bread	-0.0142	-0.0192	0.0168	0.132	-0.0112
Crisp bread	-0.0181	-0.0008	-0.0033	0.0562	0.0921
Crackers	-0.0118	-0.0083	0.013	0.122	0.0437
Orange juice	-0.0207	-0.0175	0.0328	0.022	0.1213
Other juices	-0.0086	-0.0155	0.0264	0.0494	0.0662
Tomato juice	0.076	0.0316	0.0084	0.0323	-0.0185
Jam in cereal	0.076	0.0459	0.0487	-0.0182	-0.0068
Jam on bread	-0.0036	-0.0125	0.0288	0.0013	0.1259
Fruit syrup	-0.0079	-0.0101	0.0332	0.0571	0.0058
Fruit syrup light	0.0156	-0.0012	0.0142	0.0155	0.027
Chocolate milk	0.0051	-0.0086	0.043	0.1033	-0.0533
Rice milk	0.174	0.0241	-0.0456	0.0292	-0.0492
Soy milk	0.1884	0.0134	-0.057	0.0256	-0.0538
Tea	0.0158	-0.0176	0.0003	-0.0252	0.1132
Green tea	0.0517	-0.0457	0.0219	-0.0113	0.1012
Herbal tea	0.0512	-0.0453	0.0334	0.0122	0.0862
Filter coffee	0.0189	-0.0127	-0.0108	-0.0202	0.0988
Instant coffee	0.0582	-0.0351	0.0218	-0.0362	0.0895
Pressed coffee	0.0441	-0.0311	0.025	-0.0009	0.0367
Café latte	0.0293	0.0129	0.0091	0.0145	0.052
Expresso	0.1603	-0.0149	0.0429	-0.0154	-0.0359
Decaf coffee	0.1084	-0.0644	0.0512	-0.0398	0.0329
Fig barley tea	0.2083	-0.074	0.0689	-0.0532	0.0065
Wine	0.2128	-0.0466	0.0162	-0.0449	0.0158
Spirits	0.2308	-0.0623	0.0271	-0.0519	0.0102
Non-alcoholic beer	0.0848	-0.0343	0.0794	-0.0086	-0.0113
Pilsner	0.2054	-0.0675	0.0713	-0.0516	-0.0017
Cola	-0.0344	-0.0143	0.08	0.1342	-0.0992
Other cola drinks	-0.0123	-0.0123	0.0561	0.1279	-0.0866
Energy drinks	0.095	-0.023	0.0603	0.0486	-0.0217
Diet coke	0.018	0.0087	0.0234	0.0291	-0.005
Other diet colas	0.0496	-0.0134	0.0327	0.0395	-0.025
Whole milk	-0.0137	-0.0115	0.0758	0.0435	0.05
Milk in tea	0.0389	-0.0216	0.0039	-0.0183	0.1087
Low fat milk	-0.0025	-0.0139	0.014	0.0429	0.0074
Extra low-fat milk	0.031	0.0029	-0.0104	0.0028	0.0463
Skimmed milk	0.0456	0.0095	-0.0319	-0.0267	0.0564
Cultura milk	0.0541	-0.0096	-0.0066	0.0198	0.0804
Biola milk	0.0534	-0.0086	-0.0151	0.0108	0.0608
Unsweetened cereals	0.0437	0.0082	0.0608	-0.046	0.0658
Porridge	0.0547	0.0476	0.0688	-0.0463	0.0408
Sweet muesli	0.0423	0.0258	0.0565	0.012	0.0231
Cornflakes	0.006	0.055	0.0762	-0.0084	0.0056
Pudding	0.0269	0.0269	0.1966	-0.0386	0.0137

Ice cream	0.0005	0.0583	0.1277	-0.0023	-0.0142
Frozen yogurt	0.1603	0.0263	0.034	-0.0194	-0.0336
Ice sherbet	0.0725	-0.0585	0.1397	-0.0078	0.0059
Vanilla sauce	0.0789	-0.0106	0.1795	-0.0334	0.0031
Whipped cream	0.1177	-0.0313	0.1579	-0.0191	0.0044
Sweet bun	-0.0283	0.0136	0.1678	0.0327	0.0347
Doughnut	0.0531	-0.0034	0.1848	-0.0058	0.0289
Waffle	-0.014	0.0375	0.1838	-0.0239	0.0466
Chocolate cake	-0.0213	0.0246	0.2607	-0.0577	0.0654
Cookies	-0.0028	-0.0066	0.1719	-0.0316	0.0673
Plain chocolate	-0.0481	-0.052	0.1534	0.0735	-0.0137
Fancy chocolate	-0.0041	-0.0565	0.1558	0.0559	0.0128
Caramel	-0.0162	-0.0422	0.181	0.0694	-0.0415
Jelly	0.0004	-0.0509	0.1612	0.0866	-0.0576
Pastille	0.0046	-0.0541	0.1436	0.0759	-0.0239
Pastille sugarfree	-0.0199	-0.0252	0.113	0.0179	0.0408
Marzipan	0.0969	-0.0396	0.0941	0.029	-0.0076
Butter	0.009	0.0144	-0.0093	0.0339	0.0003
Margarine	0.0384	-0.0084	0.0023	0.0782	-0.0481
Brelett	0.0061	0.0048	0.0087	0.0074	0.0124
Soft margarine	0.0156	-0.0208	0.0062	0.0092	0.0016
Light margarine	0.0082	0.0034	-0.0019	0.0252	0.0009
Melted butter	-0.017	0.1122	0.0698	0.0875	-0.0807
Melted margarine	-0.0383	0.1315	0.0485	0.0789	-0.0799
Cooking butter	-0.0119	0.0125	0.0208	0.0982	-0.0277
Cooking soft margarine	0.0324	0.0206	-0.0062	0.0539	-0.0008
Cooking margarine	0.0381	0.0024	-0.0545	-0.0736	0.0438
Soya margarine	0.0266	0.0042	0.001	0.0658	-0.0184
Oilive margarine	0.0589	0.0683	-0.0075	0.0092	0.021
Other margarine	0.0863	0.031	0.0128	0.0276	-0.0445
Soy oil	0.0449	0.0242	-0.0509	0.0395	0.0446
Cooking oil	0.0463	0.0262	-0.0442	0.058	0.0426
Olive oil	0.024	0.0479	-0.0496	-0.0188	0.1037
Corn oil	0.0762	0.082	-0.0311	-0.0134	0.0207
Other oil	0.0845	0.0545	-0.04	-0.0029	-0.0019
Whey cheese	-0.0207	0.0273	-0.0085	0.0219	0.1432
Whey low fat cheese	0.0121	0.0246	0.0136	0.0679	0.0313
Hard cheese	0.0002	-0.003	-0.0157	-0.0051	0.1597
Hard cheese low fat	0.0345	-0.0009	-0.0111	0.074	0.0387
Blue cheese	0.0954	0.0257	-0.0002	0.0677	-0.0236
Other cheese	0.0477	-0.0051	0.0036	0.0732	-0.0072
Cheese in pasta	0.0168	0.0004	-0.0273	0.0714	0.0542
Roe spread	0.0085	0.0018	0.0085	0.0375	0.1131
Mackerel spread	0.0084	-0.0002	-0.0156	0.0683	0.1177

Sardine spread	0.1006	0.0263	0.0573	0.0577	-0.0083
Smoke salmon spread	0.0631	0.012	-0.0348	0.0988	0.02
Herring spread	0.1017	0.0205	0.0067	0.0427	-0.0113
Liver spread	-0.0138	-0.0145	0.0128	0.0223	0.1238
Peanut butter spead	0.0644	0.0287	0.0009	0.0615	-0.0222
Other nuts spread	0.0161	0.006	0.0216	0.0796	-0.037
Other sweet spread	0.0381	0.0103	0.0008	0.0728	-0.0145
Meat pasta	-0.0156	-0.0138	-0.0418	0.1185	0.0841
Fish pasta	0.1157	-0.0175	-0.0568	0.0701	0.0371
Vegetable pasta	0.0476	-0.0147	-0.0657	0.0806	0.0884
Potato pasta	0.0377	-0.02	-0.0387	0.1077	0.0121
Spaghetti	-0.0154	0.1521	0.0265	0.034	-0.0229
Pizza	-0.0375	-0.0155	-0.0086	0.1869	0.0069
Soups	-0.0186	-0.0138	-0.0004	0.1008	0.082
Potato chips	-0.0048	-0.0415	0.1665	0.0468	-0.0179
Popcorn	-0.0085	-0.0148	0.2157	0.024	-0.0314
Salted snacks	0.0728	-0.0243	0.1473	0.0487	-0.0433
White sauce	-0.1152	0.1638	0.1491	0.0354	-0.0196
Barnaise sauce	-0.0657	0.1888	0.1207	-0.0069	-0.0507
Ketchup	-0.0585	0.1199	0.1649	-0.0128	-0.0767
Cucumber	-0.0336	0.0748	-0.0227	-0.0137	0.1705
Aubergine	0.1498	0.1058	-0.0573	-0.0026	-0.0265
Green peas	0.0249	0.1336	0.0251	0.0056	-0.0128
Onion leeks	0.0118	0.1588	-0.0306	-0.009	0.0328
Onion boiled	-0.0178	0.2313	-0.0622	-0.0068	0.0294
Garlic	-0.0087	0.1628	-0.0006	-0.02	0.0248
Carrot	-0.0403	0.1369	0.001	-0.0378	0.1233
Carrot boiled	-0.0517	0.1867	-0.0144	-0.0284	0.0776
Swede	0.0379	0.1419	-0.027	0.0127	0.027
Swede boiled	0.0428	0.1625	-0.0201	0.016	-0.0023
Corncob	-0.0117	0.2161	-0.0122	-0.0169	0.0133
Pepper	-0.0303	0.1534	-0.0026	-0.0638	0.1414
Brussel sprouts	0.0733	0.1553	-0.0228	0.0394	-0.0352
Lettuce	-0.0519	0.1879	-0.0132	-0.0224	0.0724
Celery	0.1042	0.1458	-0.0248	0.0135	-0.0551
Wild mushroom	0.1599	0.1263	-0.0918	-0.0011	-0.0242
Button mushroom	0.1884	0.0894	-0.0494	-0.0015	-0.0662
Spinach	0.1197	0.1084	0.008	-0.0038	-0.0493
Squash	0.1378	0.1062	-0.0314	-0.0119	-0.0512
Tomato	-0.0219	0.1358	-0.0453	-0.0607	0.1687
Vegetable spreads	-0.0101	-0.0085	0.0042	-0.0121	0.1859
Cauliflower	0.0987	0.1298	-0.0486	0.0088	-0.0136
Cauliflower boiled	-0.0231	0.2055	0.0171	-0.0212	0.0295
Broccoli	0.1701	0.0895	-0.0662	-0.0111	-0.0158

Broccoli boiled	-0.0082	0.2244	-0.0271	-0.0404	0.0309
Cabbage	0.0505	0.1676	-0.0191	0.0528	-0.0634
Cabbage boiled	-0.0201	0.1954	0.056	0.0587	-0.0543
Mackerel	0.0638	-0.0091	-0.0282	0.0959	0.0369
Salmon, trout	0.0072	-0.0022	-0.0328	0.0707	0.1355
Cod, haddock	-0.0093	-0.0121	-0.0254	0.0564	0.1845
Tuna	0.0727	-0.0158	0.0153	0.0461	0.0495
Shrimps	0.0322	0.0178	-0.0641	0.1323	0.0456
Mussels	0.1618	0.0121	-0.0944	0.0839	-0.0059
Crab	0.1289	0.0082	-0.0815	0.1101	0.0133
Fish products	-0.0038	-0.0114	-0.0242	-0.0113	0.1667
Fish cake	-0.0134	-0.0286	-0.0213	0.0966	0.1451
Fish fingers	-0.0193	-0.0233	-0.0055	0.1403	0.1032
Eggs	-0.0221	0.0204	0.0621	0.0211	0.0532
Chicken fillet	0.0066	0.0046	-0.0511	0.0707	0.0908
Fried chicken	-0.0159	0.0183	-0.0382	0.1441	0.0626
Baked or boiled chicken	0.0393	0.0194	-0.0364	0.0823	0.0281
Chicken schnitzel	0.0497	0.0249	-0.0168	0.1136	0.0214
Chicken sausage	0.0244	-0.0068	0.0265	0.0697	0.0186
Meat products	0.0108	-0.0237	-0.0212	-0.0165	0.1091
Meat products grilled	-0.0139	-0.0047	-0.0133	0.1235	-0.0144
Meat balls	-0.0416	-0.0256	0.0118	0.1791	0.0294
Minced meat	-0.0104	-0.0287	-0.021	0.1024	0.0541
Lamb roast	0.0257	0.0146	-0.022	0.1157	0.0686
Lamb stew	0.0151	0.0019	0.0253	0.1458	0.0222
Hot dog	-0.0302	-0.0018	0.0054	0.159	-0.0537
Meat pork chop	-0.0195	-0.0076	-0.019	0.1357	0.0183
Pork chop	-0.0242	0.0156	-0.0331	0.1714	0.039
Pork fillet	-0.0011	0.0265	-0.0249	0.1536	-0.0181
Pork loin	-0.003	0.0074	0.0017	0.1848	-0.0131
Pork belly	0.0122	-0.0294	0.018	0.1869	-0.0009
Bacon	-0.0135	-0.0233	-0.0054	0.1601	0.0113
Offal	0.039	0.0128	0.003	0.0556	0.0024
Hamburger	-0.0378	-0.0232	0.026	0.1958	-0.0148
Beef and veal roast	-0.0049	0.0216	-0.0073	0.1538	0.0234
Beef	-0.0219	0.0128	-0.0003	0.1377	-0.0143
Venison	0.214	-0.0776	0.0176	0.0352	-0.0003

Appendix C Stata codes of the analyses

C.1 Chapter 4

C.1.1 Birth centile model

INCREMENT UNITS OF MACRONUTRIENTS: 10 GRAMS, COMPONENTS: STARCH 10G, GLUCOSE 10G MODEL

*TRIMESTER 1: MACRONUTRIENT CUSTOMISED BIRTH CENTILE MODEL

regress customized_centile5 choodds10 fatodds10 proteinodds10

regress customized_centile5 choodds10 fatodds10 proteinodds10 avalc1 i.smokdesc

*TRIMESTER 2:

regress customized_centile5 t2choodds10 t2fatodds10 t2proteinodds10

regress customized_centile5 t2choodds10 t2fatodds10 t2proteinodds10 avalc2 i.c2smokdesc

* UNADJUSTED MODEL * TRIMESTER 1 MACRONUTRIENT COMPONENTS CUSTOMISED BIRTH CENTILE MODEL

regress customized_centile5 proteinodds10 fatodds10 starchodds10 T1_SumOfFructose glucoseodds10 T1_SumOfLactose T1_SumOfMaltose T1_SumOfSolNc T1_SumOfSucrose

regress customized_centile5 proteinodds10 choodds10 T1_SumOfPoly_FattyAcid T1_SumOfMono_FattyAcid T1_SumOfSat_FattyAcid

*TRIMESTER 2 MACRONUTRIENT COMPONENTS CUSTOMISED BIRTH CENTILE MODEL

regress customized_centile5 t2proteinodds10 t2fatodds10 t2starchodds10 T2_SumOfFructose t2glucoseodds10 T2_SumOfLactose T2_SumOfMaltose T2_SumOfSolNc T2_SumOfSucrose

regress customized_centile5 t2proteinodds10 t2choodds10 T2_SumOfSat_FattyAcid T2_SumOfMono_FattyAcid T2_SumOfPoly_FattyAcid

*TRIMESTER 1: ADJUSTED MACRONUTRIENT COMPONENTS CUSTOMISED BIRTH CENTILE MODEL

regress customized_centile5 proteinodds10 fatodds10 starchodds10 T1_SumOfFructose glucoseodds10 T1_SumOfLactose T1_SumOfMaltose T1_SumOfSolNc T1_SumOfSucrose avalc1 i.smokdesc

regress customized_centile5 proteinodds10 choodds10 T1_SumOfPoly_FattyAcid T1_SumOfMono_FattyAcid T1_SumOfSat_FattyAcid avalc1 i.smokdesc

*TRIMESTER 2: ADJUSTED MACRONUTRIENT COMPONENTS CUSTOMISED BIRTH CENTILE MODEL

regress customized_centile5 t2proteinodds10 t2fatodds10 t2starchodds10 T2_SumOfFructose t2glucoseodds10 T2_SumOfLactose T2_SumOfMaltose T2_SumOfSolNc T2_SumOfSucrose avalc2 i.c2smokdesc

regress customized_centile5 t2proteinodds10 t2choodds10 T2_SumOfSat_FattyAcid T2_SumOfMono_FattyAcid T2_SumOfPoly_FattyAcid avalc2 i.c2smokdesc

C.1.2 Birthweight model

*MACRONUTRIENT BIRTHWEIGHT MODEL FOR TRIMESTER 1 AND 2, UNADJUSTED AND ADJUSTED

regress weight_of_baby___grams proteinodds10 fatodds10 choodds10 weight_k height_c ethnicit parity gestation sex

regress weight_of_baby___grams proteinodds10 fatodds10 choodds10 weight_k height_c ethnicit parity gestation sex avalc1 i.smokdesc

regress weight_of_baby___grams t2proteinodds10 t2fatodds10 t2starchodds10 weight_k height_c ethnicit parity gestation sex

regress weight_of_baby___grams t2proteinodds10 t2fatodds10 t2starchodds10 weight_k height_c ethnicit parity gestation sex avalc2 i.c2smokdesc

UNADJUSTED MODELS

*TRIMESTER 1: MACRONUTRIENT COMPONENT BIRTHWEIGHT MODELS

regress weight_of_baby___grams proteinodds10 fatodds10 starchodds10 T1_SumOfFructose glucoseodds10 T1_SumOfLactose T1_SumOfMaltose T1_SumOfSolNc T1_SumOfSucrose weight_k height_c ethnicit parity gestation sex

regress weight_of_baby___grams proteinodds10 choodds10 T1_SumOfPoly_FattyAcid T1_SumOfMono_FattyAcid T1_SumOfSat_FattyAcid weight_k height_c ethnicit parity gestation sex

*TRIMESTER 2: MACRONUTRIENT COMPONENT BIRTHWEIGHT MODELS

regress weight_of_baby___grams t2proteinodds10 t2fatodds10 T2_SumOfFructose t2glucoseodds10 T2_SumOfLactose T2_SumOfMaltose T2_SumOfSolNc T2_SumOfSucrose weight_k height_c ethnicit parity gestation sex

regress weight_of_baby___grams t2proteinodds10 t2choodds10 T2_SumOfSat_FattyAcid T2_SumOfMono_FattyAcid T2_SumOfPoly_FattyAcid weight_k height_c ethnicit parity gestation sex

ADJUSTED MODELS

*TRIMESTER 1 MACRONUTRIENT COMPONENT BIRTHWEIGHT MODEL

regress weight_of_baby___grams proteinodds10 fatodds10 starchodds10 T1_SumOfFructose glucoseodds10 T1_SumOfLactose T1_SumOfMaltose T1_SumOfSolNc T1_SumOfSucrose weight_k height_c ethnicit parity gestation sex avalc1 i.smokdesc

regress weight_of_baby___grams proteinodds10 choodds10 T1_SumOfPoly_FattyAcid T1_SumOfMono_FattyAcid T1_SumOfSat_FattyAcid weight_k height_c ethnicit parity gestation sex avalc1 i.smokdesc

*TRIMESTER 2 MACRONUTRIENT COMPONENT BIRTHWEIGHT MODEL

regress weight_of_baby___grams t2proteinodds10 t2fatodds10 t2starchodds10 T2_SumOfFructose t2glucoseodds10 T2_SumOfLactose T2_SumOfMaltose T2_SumOfSolNc T2_SumOfSucrose weight_k height_c ethnicit parity gestation sex avalc2 i.c2smokdesc

regress weight_of_baby___grams t2proteinodds10 t2choodds10 T2_SumOfSat_FattyAcid T2_SumOfMono_FattyAcid T2_SumOfPoly_FattyAcid weight_k height_c ethnicit parity gestation sex avalc2 i.c2smokdesc

C.1.3 SGA and LGA models: macronutrients and components

*ODDS RATIO

generate sga_logisticSS= customized_centile5 <10

label variable sga_logisticSS "Logistic customised centile5<10 odds ratio-SGA outcome SS"

*OUTCOME=1, CASE=0 (SGA=1, OTHERS=0)

*UNADJUSTED MODELS

*TRIMESTER 1: SGA MODEL FOR MACRONUTRIENTS AND COMPONENTS

logistic sga_logisticSS choodds10 fatodds10 proteinodds10

logistic sga_logisticSS proteinodds10 fatodds10 starchodds10 T1_SumOfFructose glucoseodds10 T1_SumOfLactose T1_SumOfMaltose T1_SumOfSolNc T1_SumOfSucrose

logistic sga_logisticSS proteinodds10 choodds10 T1_SumOfPoly_FattyAcid T1_SumOfMono_FattyAcid T1_SumOfSat_FattyAcid

*TRIMESTER 2: SGA MODEL FOR MACRONUTRIENTS AND COMPONENTS

logistic sga_logisticSS t2choodds10 t2fatodds10 t2proteinodds10

logistic sga_logisticSS t2proteinodds10 t2fatodds10 t2starchodds10 T2_SumOfFructose t2glucoseodds10 T2_SumOfLactose T2_SumOfMaltose T2_SumOfSolNc T2_SumOfSucrose

logistic sga_logisticSS t2proteinodds10 t2choodds10 T2_SumOfSat_FattyAcid T2_SumOfMono_FattyAcid T2_SumOfPoly_FattyAcid

ADJUSTED MODELS

*TRIMESTER 1: SGA MODEL FOR MACRONUTRIENTS AND COMPONENTS

logistic sga_logisticSS choodds10 fatodds10 proteinodds10 avalc1 i.smokdesc

logistic sga_logisticSS proteinodds10 fatodds10 starchodds10 T1_SumOfFructose glucoseodds10 T1_SumOfLactose T1_SumOfMaltose T1_SumOfSolNc T1_SumOfSucrose avalc1 i.smokdesc

logistic sga_logisticSS proteinodds10 choodds10 T1_SumOfPoly_FattyAcid T1_SumOfMono_FattyAcid T1_SumOfSat_FattyAcid avalc1 i.smokdesc

*TRIMESTER 2: SGA MODEL FOR MACRONUTRIENTS AND COMPONENTS

logistic sga_logisticSS t2choodds10 t2fatodds10 t2proteinodds10 avalc2 i.c2smokdesc

logistic sga_logisticSS t2proteinodds10 t2fatodds10 t2starchodds10 T2_SumOfFructose t2glucoseodds10 T2_SumOfLactose T2_SumOfMaltose T2_SumOfSolNc T2_SumOfSucrose avalc2 i.c2smokdesc

logistic sga_logisticSS t2proteinodds10 t2choodds10 T2_SumOfSat_FattyAcid T2_SumOfMono_FattyAcid T2_SumOfPoly_FattyAcid avalc2 i.c2smokdesc

*LARGE FOR GESTATIONAL AGE LGA(1= OUTCOME, 0=CASE)

generate lga_logisticSS= customized_centile5 >90

*UNADJUSTED MODELS

*TRIMESTER 1: LGA MODEL FOR MACRONUTRIENTS AND COMPONENTS

logistic lga_logisticSS choodds10 fatodds10 proteinodds10

logistic lga_logisticSS proteinodds10 fatodds10 starchodds10 T1_SumOfFructose glucoseodds10 T1_SumOfLactose T1_SumOfMaltose T1_SumOfSolNc T1_SumOfSucrose

logistic lga_logisticSS proteinodds10 choodds10 T1_SumOfPoly_FattyAcid T1_SumOfMono_FattyAcid T1_SumOfSat_FattyAcid

*TRIMESTER 2: LGA MODEL FOR MACRONUTRIENTS AND COMPONENTS

logistic lga_logisticSS t2choodds10 t2fatodds10 t2proteinodds10

logistic lga_logisticSS t2proteinodds10 t2fatodds10 t2starchodds10 T2_SumOfFructose t2glucoseodds10 T2_SumOfLactose T2_SumOfMaltose T2_SumOfSolNc T2_SumOfSucrose

logistic lga_logisticSS t2proteinodds10 t2choodds10 T2_SumOfSat_FattyAcid
T2_SumOfMono_FattyAcid T2_SumOfPoly_FattyAcid
*ADJUSTED MODELS
*TRIMESTER 1: LGA MODEL FOR MACRONUTRIENTS AND COMPONENTS
logistic lga_logisticSS choodds10 fatodds10 proteinodds10 avalc1 i.smokdesc
logistic lga_logisticSS proteinodds10 fatodds10 starchodds10 T1_SumOfFructose glucoseodds10
T1_SumOfLactose T1_SumOfMaltose T1_SumOfSolNc T1_SumOfSucrose avalc1 i.smokdesc
logistic lga_logisticSS proteinodds10 choodds10 T1_SumOfPoly_FattyAcid T1_SumOfMono_FattyAcid
T1_SumOfSat_FattyAcid avalc1 i.smokdesc
*TRIMESTER 2: LGA MODEL FOR MACRONUTRIENTS AND COMPONENTS
logistic lga_logisticSS t2choodds10 t2fatodds10 t2proteinodds10 avalc2 i.c2smokdesc
logistic lga_logisticSS t2proteinodds10 t2fatodds10 t2starchodds10 T2_SumOfFructose
t2glucoseodds10 T2_SumOfLactose T2_SumOfMaltose T2_SumOfSolNc T2_SumOfSucrose avalc2
i.c2smokdesc
logistic lga_logisticSS t2proteinodds10 t2choodds10 T2_SumOfSat_FattyAcid
T2_SumOfMono_FattyAcid T2_SumOfPoly_FattyAcid avalc2 i.c2smokdesc

C.1.4 Energy percentage of macronutrient models

* TRIMESTER 1: *UNADJUSTED MODELS*
regress weight_of_baby___grams Epc_Fat weight_k height_c ethnicit parity gestation sex
regress weight_of_baby___grams Epc_CHO weight_k height_c ethnicit parity gestation sex
regress weight_of_baby___grams Epc_Protein weight_k height_c ethnicit parity gestation sex
* TRIMESTER 2:
regress weight_of_baby___grams T2Epc_Fat weight_k height_c ethnicit parity gestation sex
regress weight_of_baby___grams T2Epc_CHO weight_k height_c ethnicit parity gestation sex
regress weight_of_baby___grams T2Epc_Protein weight_k height_c ethnicit parity gestation sex
* TRIMESTER 1: *ADJUSTED MODELS*
regress weight_of_baby___grams Epc_Fat avalc1 i.smokdesc weight_k height_c ethnicit parity
gestation sex
regress weight_of_baby___grams Epc_CHO avalc1 i.smokdesc weight_k height_c ethnicit parity
gestation sex
regress weight_of_baby___grams Epc_Protein avalc1 i.smokdesc weight_k height_c ethnicit parity
gestation sex
* TRIMESTER 2: *ADJUSTED MODELS*
regress weight_of_baby___grams T2Epc_Fat avalc2 i.c2smokdesc weight_k height_c ethnicit parity
gestation sex
regress weight_of_baby___grams T2Epc_CHO avalc2 i.c2smokdesc weight_k height_c ethnicit parity
gestation sex
regress weight_of_baby___grams T2Epc_Protein avalc2 i.c2smokdesc weight_k height_c ethnicit parity
gestation sex

C.2 Chapter 5

C.2.1 Meta-analysis codes

```
*BIRTHWEIGHT METAN COMMANDS*
metan bw_energy_est bw_energy_se, randomi
metan bw_cho_est bw_cho_se, randomi
metan bw_protein_est bw_protein_se, randomi
metan bw_fat_est bw_fat_se, randomi
**ENERGY PERCENTAGES BIRTHWEIGHT MODELS**COMMANDS POOLED RESULTS
metan epc_cho_est epc_cho_se, randomi
metan epc_protein_est epc_protein_se, randomi
metan epc_fat_est epc_fat_se, randomi
*SGA METAN COMMANDS*
metan lnor_sga_cho selnor_sga_cho,  randomi eform
metan lnor_sga_protein selnor_sga_protein ,  randomi eform
metan lnor_sga_fat selnor_sga_fat ,  randomi eform
metan lnor_sga_energy selnor_sga_energy ,  randomi eform
*LGA METAN COMMANDS*
metan lnor_lga_cho selnor_lga_cho,  randomi eform
metan lnor_lga_protein selnor_lga_protein ,  randomi eform
metan lnor_lga_fat selnor_lga_fat ,  randomi eform
metan lnor_lga_energy selnor_lga_energy ,  randomi eform
*BIRTHWEIGHT FOREST PLOTS*
metan bw_energy_est bw_energy_se, randomi xlab(-20,-10,10,20) xline(0) lcols (Cohort N) texts(110)
astext(70) aspect(0.4) favours(Lower birthweight (g) # Higher birthweight(g))
metan bw_cho_est bw_cho_se, randomi xlab(-20,-10,10,20) xline(0) lcols (Cohort N) texts(110)
astext(70) aspect(0.4) favours(Lower birthweight (g) # Higher birthweight(g))
metan bw_protein_est bw_protein_se, randomi xlab(-20,-10,10,20) xline(0) lcols (Cohort N) texts(110)
astext(70) aspect(0.4) favours(Lower birthweight (g) # Higher birthweight(g))
metan bw_fat_est bw_fat_se, randomi xlab(-20,-10,10,20) xline(0) lcols (Cohort N) texts(100) astext(80)
aspect(0.4) favours(Lower birthweight (g) # Higher birthweight(g))
*BIRTHWEIGHT ENERGY PERCENTAGES FOREST PLOTS
metan epc_cho_est epc_cho_se, randomi xlab(-10,-5,5,10) xline(0) lcols (Cohort N) texts(110)
astext(70) aspect(0.4) favours(Lower birthweight (g) # Higher birthweight(g))
metan epc_protein_est epc_protein_se, randomi xlab(-10,-5,5,10) xline(0) lcols (Cohort N) texts(110)
astext(70) aspect(0.4) favours(Lower birthweight (g) # Higher birthweight(g))
metan epc_fat_est epc_fat_se, randomi xlab(-10,-5,5,10) xline(0) lcols (Cohort N) texts(100) astext(80)
aspect(0.4) favours(Lower birthweight (g) # Higher birthweight(g))
*SGA FOREST PLOTS*
metan lnor_sga_cho selnor_sga_cho, randomi eform xlab(0.5,1,2) lcols (Cohort N) texts(100) astext(80)
aspect(0.4) b1title(Risk of SGA delivery (OR))effect (OR)
```

metan lnor_sga_protein selnor_sga_protein, randomi eform xlab(0.5,1,2) lcols (Cohort N) texts(100) astext(80) aspect(0.4) b1title(Risk of SGA delivery (OR))effect (OR)

metan lnor_sga_fat selnor_sga_fat, randomi eform xlab(0.5,1,2) lcols (Cohort N) texts(100) astext(80) aspect(0.4) b1title(Risk of SGA delivery (OR))effect (OR)

metan lnor_sga_energy selnor_sga_energy , randomi eform xlab(0.5,1,2) lcols (Cohort N) texts(100) astext(80) aspect(0.4) b1title(Risk of SGA delivery (OR))effect (OR)

LGA FOREST PLOTS

metan lnor_lga_cho selnor_lga_cho, randomi eform xlab(0.5,1,2) lcols (Cohort N) texts(100) astext(80) aspect(0.4) b1title(Risk of LGA delivery (OR))effect (OR)

metan lnor_lga_protein selnor_lga_protein, randomi eform xlab(0.5,1,2) lcols (Cohort N) texts(100) astext(80) aspect(0.4) b1title(Risk of LGA delivery (OR))effect (OR)

metan lnor_lga_fat selnor_lga_fat, randomi eform xlab(0.5,1,2) lcols (Cohort N) texts(100) astext(80) aspect(0.4) b1title(Risk of LGA delivery (OR))effect (OR)

metan lnor_lga_energy selnor_lga_energy , randomi eform xlab(0.5,1,2) lcols (Cohort N) texts(100) astext(80) aspect(0.4) b1title(Risk of LGA delivery (OR))effect (OR)

C.2.2 Cohort specific analyses

C.2.2.1 CARE analyses models

***UNADJUSTED MODEL* CARE*MACRONUTRIENTS AND BIRTHWEIGHT*

regress birthweight carbSD_SS mothersage

regress birthweight proteinSD_SS mothersage

regress birthweight fatSD_SS mothersage

regress birthweight energykcalSD_SS mothersage

ADJUSTED MODEL

regress birthweight carbSD_SS proteinSD_SS fatSD_SS mothersage bmi_pre T2_alcoholunits i.smoker1 i.parity i.T2_pa i.c2sup

regress birthweight energykcalSD_SS mothersage bmi_pre i.smoker1 i.parity i.T2_pa i.c2sup

*ODDS RATIO**SGA DELIVERY* *UNADJUSTED MODEL*

logistic sga_logisticSS carbSD_SS mothersage

logistic sga_logisticSS proteinSD_SS mothersage

logistic sga_logisticSS fatSD_SS mothersage

logistic sga_logisticSS energykcalSD_SS mothersage

*ODDS RATIO**SGA DELIVERY* *ADJUSTED MODEL*

logistic sga_logisticSS carbSD_SS proteinSD_SS fatSD_SS mothersage T2_alcoholunits i.smoker1 i.T2_pa i.c2sup

logistic sga_logisticSS energykcalSD_SS mothersage i.smoker1 i.T2_pa i.c2sup

*ODDS RATIO**LGA DELIVERY* *UNADJUSTED MODEL*

logistic lga_logisticSS carbSD_SS mothersage

logistic lga_logisticSS proteinSD_SS mothersage

logistic lga_logisticSS fatSD_SS mothersage

logistic lga_logisticSS energykcalSD_SS mothersage

*ODDS RATIO**LGA DELIVERY* *ADJUSTED MODEL*

logistic lga_logisticSS carbSD_SS proteinSD_SS fatSD_SS mothersage T2_alcoholunits i.smoker1 i.T2_pa i.c2sup

logistic lga_logisticSS energykcalSD_SS mothersage i.smoker1 i.T2_pa i.c2sup

*ENERGY PERCENTAGE MODELS*CARE*

UNADJUSTED ENERGY PERCENTAGE BIRTHWEIGHT MODELS

regress birthweight T2Epc_CHO mothersage

regress birthweight T2Epc_Protein mothersage

regress birthweight T2Epc_Fat mothersage

ADJUSTED ENERGY PERCENTAGE BIRTHWEIGHT MODELS

regress birthweight T2Epc_CHO mothersage bmi_pre T2_alcoholunits i.smoker1 i.parity i.T2_pa i.c2sup

regress birthweight T2Epc_Protein mothersage bmi_pre T2_alcoholunits i.smoker1 i.parity i.T2_pa i.c2sup

regress birthweight T2Epc_Fat mothersage bmi_pre T2_alcoholunits i.smoker1 i.parity i.T2_pa i.c2sup

UNADJUSTED ENERGY PERCENTAGE SGA MODELS

logistic sga_logisticSS T2Epc_CHO mothersage

logistic sga_logisticSS T2Epc_Protein mothersage

logistic sga_logisticSS T2Epc_Fat mothersage

ADJUSTED ENERGY PERCENTAGE SGA MODELS

logistic sga_logisticSS T2Epc_CHO mothersage T2_alcoholunits i.smoker1 i.T2_pa i.c2sup

logistic sga_logisticSS T2Epc_Protein mothersage T2_alcoholunits i.smoker1 i.T2_pa i.c2sup

logistic sga_logisticSS T2Epc_Fat mothersage T2_alcoholunits i.smoker1 i.T2_pa i.c2sup

UNADJUSTED ENERGY PERCENTAGE LGA MODELS

logistic lga_logisticSS T2Epc_CHO mothersage

logistic lga_logisticSS T2Epc_Protein mothersage

logistic lga_logisticSS T2Epc_Fat mothersage

ADJUSTED ENERGY PERCENTAGE LGA MODELS

logistic lga_logisticSS T2Epc_CHO mothersage T2_alcoholunits i.smoker1 i.T2_pa i.c2sup

logistic lga_logisticSS T2Epc_Protein mothersage T2_alcoholunits i.smoker1 i.T2_pa i.c2sup

logistic lga_logisticSS T2Epc_Fat mothersage T2_alcoholunits i.smoker1 i.T2_pa i.c2sup

C.2.2.2 DNBC analyses models

UNADJUSTED MODEL DNBC*MACRONUTRIENTS AND BIRTHWEIGHT*

regress birthweight carbSD_SS mage

regress birthweight proteinSD_SS mage

regress birthweight fatSD_SS mage

regress birthweight energykcalSD_SS mage

ADJUSTED MODEL

regress birthweight carbSD_SS proteinSD_SS fatSD_SS mage bmi_pre i.parity i.pa_w12 alcohol_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

regress birthweight energykcalSD_SS mage bmi_pre i.parity i.pa_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

*ODDS RATIO**SGA DELIVERY* *UNADJUSTED MODEL*

logistic sga_logisticSS carbSD_SS mage

logistic sga_logisticSS proteinSD_SS mage

logistic sga_logisticSS fatSD_SS mage

logistic sga_logisticSS energykcalSD_SS mage

ADJUSTED MODEL

logistic sga_logisticSS carbSD_SS proteinSD_SS fatSD_SS mage i.pa_w12 alcohol_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

logistic sga_logisticSS energykcalSD_SS mage i.pa_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

*ODDS RATIO**LGA DELIVERY* *UNADJUSTED MODEL*

logistic lga_logisticSS carbSD_SS mage

logistic lga_logisticSS proteinSD_SS mage

logistic lga_logisticSS fatSD_SS mage

logistic lga_logisticSS energykcalSD_SS mage

ADJUSTED MODEL

logistic lga_logisticSS carbSD_SS proteinSD_SS fatSD_SS mage i.pa_w12 alcohol_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

logistic lga_logisticSS energykcalSD_SS mage i.pa_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

ENERGY PERCENTAGE MODELS FOR DNBC

UNADJUSTED ENERGY PERCENTAGE BIRTHWEIGHT MODELS

regress birthweight carbep mage

regress birthweight proteinep mage

regress birthweight fatep mage

ADJUSTED ENERGY PERCENTAGE BIRTHWEIGHT MODELS

regress birthweight carbep mage bmi_pre i.parity i.pa_w12 alcohol_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

regress birthweight proteinep mage bmi_pre i.parity i.pa_w12 alcohol_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

regress birthweight fatep mage bmi_pre i.parity i.pa_w12 alcohol_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

UNADJUSTED ENERGY PERCENTAGE SGA MODELS

logistic sga_logisticSS carbep mage

logistic sga_logisticSS proteinep mage

logistic sga_logisticSS fatep mage

ADJUSTED ENERGY PERCENTAGE SGA MODELS

logistic sga_logisticSS carbep mage i.pa_w12 alcohol_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

logistic sga_logisticSS proteinep mage i.pa_w12 alcohol_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

logistic sga_logisticSS fatep mage i.pa_w12 alcohol_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

UNADJUSTED ENERGY PERCENTAGE LGA MODELS

logistic lga_logisticSS carbep mage

logistic lga_logisticSS proteinep mage

logistic lga_logisticSS fatep mage

ADJUSTED ENERGY PERCENTAGE LGA MODELS

logistic lga_logisticSS carbep mage i.pa_w12 alcohol_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

logistic lga_logisticSS proteinep mage i.pa_w12 alcohol_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

logistic lga_logisticSS fatep mage i.pa_w12 alcohol_w12 i.smoke_yesno SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

C.2.2.3 MoBa analyses models

UNADJUSTED MODEL MoBa*MACRONUTRIENTS AND BIRTHWEIGHT*

regress Offspring_weight_gram carbSD_SS Mother_age

regress Offspring_weight_gram proteinSD_SS Mother_age

regress Offspring_weight_gram fatSD_SS Mother_age

regress Offspring_weight_gram energykcalSD_SS Mother_age

*ADJUSTED MODEL

regress Offspring_weight_gram carbSD_SS proteinSD_SS fatSD_SS Mother_age i.Parity_cat i.pa_w15 T1_bmi i.smoke_yesno alcoholunits_w15 i.supplement_yesno

regress Offspring_weight_gram energykcalSD_SS Mother_age i.Parity_cat i.pa_w15 T1_bmi i.smoke_yesno i.supplement_yesno

*ODDS RATIO**SGA DELIVERY* *UNADJUSTED MODEL*

logistic sga_logisticSS carbSD_SS Mother_age

logistic sga_logisticSS proteinSD_SS Mother_age

logistic sga_logisticSS fatSD_SS Mother_age

logistic sga_logisticSS energykcalSD_SS Mother_age

*ADJUSTED MODEL

logistic sga_logisticSS carbSD_SS proteinSD_SS fatSD_SS Mother_age i.pa_w15 i.smoke_yesno alcoholunits_w15 i.supplement_yesno

logistic sga_logisticSS energykcalSD_SS Mother_age i.pa_w15 i.smoke_yesno i.supplement_yesno

*ODDS RATIO**LGA DELIVERY* *UNADJUSTED MODEL*

logistic lga_logisticSS carbSD_SS Mother_age

```
logistic lga_logisticSS proteinSD_SS Mother_age
logistic lga_logisticSS fatSD_SS Mother_age
logistic lga_logisticSS energykcalSD_SS Mother_age
*ADJUSTED MODEL
logistic lga_logisticSS  carbSD_SS proteinSD_SS fatSD_SS Mother_age i.pa_w15 i.smoke_yesno
alcoholunits_w15 i.supplement_yesno
logistic lga_logisticSS  energykcalSD_SS Mother_age i.pa_w15 i.smoke_yesno i.supplement_yesno
*ENERGY PERCENTAGE MODELS FOR MoBa*
*UNADJUSTED ENERGY PERCENTAGE BIRTHWEIGHT MODELS*
regress Offspring_weight_gram cho_energypc Mother_age
regress Offspring_weight_gram protein_energypc Mother_age
regress Offspring_weight_gram fat_energypc Mother_age
*ADJUSTED MODEL
regress Offspring_weight_gram cho_energypc Mother_age i.Parity_cat i.pa_w15 T1_bmi
i.smoke_yesno alcoholunits_w15 i.supplement_yesno
regress Offspring_weight_gram protein_energypc Mother_age i.Parity_cat i.pa_w15 T1_bmi
i.smoke_yesno alcoholunits_w15 i.supplement_yesno
regress Offspring_weight_gram fat_energypc Mother_age i.Parity_cat i.pa_w15 T1_bmi i.smoke_yesno
alcoholunits_w15 i.supplement_yesno
*UNADJUSTED ENERGY PERCENTAGE SGA MODELS*
logistic sga_logisticSS cho_energypc Mother_age
logistic sga_logisticSS protein_energypc Mother_age
logistic sga_logisticSS fat_energypc Mother_age
*ADJUSTED MODEL
logistic sga_logisticSS  cho_energypc Mother_age i.pa_w15 i.smoke_yesno alcoholunits_w15
i.supplement_yesno
logistic sga_logisticSS  protein_energypc Mother_age i.pa_w15 i.smoke_yesno alcoholunits_w15
i.supplement_yesno
logistic sga_logisticSS  fat_energypc Mother_age i.pa_w15 i.smoke_yesno alcoholunits_w15
i.supplement_yesno
*UNADJUSTED ENERGY PERCENTAGE LGA MODELS*
logistic lga_logisticSS cho_energypc Mother_age
logistic lga_logisticSS protein_energypc Mother_age
logistic lga_logisticSS fat_energypc Mother_age
*ADJUSTED MODEL
logistic lga_logisticSS  cho_energypc Mother_age i.pa_w15 i.smoke_yesno alcoholunits_w15
i.supplement_yesno
logistic lga_logisticSS  protein_energypc Mother_age i.pa_w15 i.smoke_yesno alcoholunits_w15
i.supplement_yesno
```

logistic lga_logisticSS fat_energypc Mother_age i.pa_w15 i.smoke_yesno alcoholunits_w15 i.supplement_yesno

C.3 Chapter 6

C.3.1 206 Food items PCA code

pca FFQaddedsugar ffqorange ffqgrapefruit ffqplum ffqbanana ffqapple ffqgrapes ffqpeach ffqmango ffqmelon ffqpapaya ffqpear ffqstrawberries ffqotherberries ffqapricots ffqraisin ffqprunfigdate ffqpeanuts ffqalmcashaz ffqpotatoes ffqcreampotatocassro FFQpotato_fried ffqlowfatyogurt ffqgomorgenyogurt FFQyogurtwhole FFQricecooked FFQcouscousmillet ffqmayo FFQmayoremolade ffqcremefraiche ffqmayosprd ffqmayosprdyog ffqwholemealbread ffqdarkryebread ffqfibercrispbread ffqwhitebread ffqcrispbread ffqcrackers ffqorangejuice ffqotherjuice fqqtomatojuice ffqjamncereal ffqjamonbread ffqfruitsyrup ffqfruitsyrplite FFQchocmilk FFQricemilk FFQsoymilk ffqtea ffqgreentea ffqherbaltea ffqfiltcoffee ffqinstacoffee ffqpresscoffe ffqcafelatte ffqexpresso ffqdecafcoff ffqfigbarleycoff ffqwine ffqspirits ffqnonalcbeer ffqpilsnerbeer ffqcoke ffqothercolas ffqenergydrink ffqdietcoke ffqotherdietcola ffqfulmilk ffqmilkteacoff ffqlowfatmilk ffqexlowfatmilk ffqskimmilk ffqculturemilk ffqbiomilkyog ffqunsweetcereals ffqporridge ffqsweetmuesli ffqcornflakes ffqpudding ffqicecream ffqfroyo ffqicesherbets ffqvanilasauce ffqwhipcream ffqsweetbun ffqdanishpastry ffqdoughnut ffqwaffle ffqchoccake ffqcookie ffqplainchoc ffqfancychoc ffqcaramel ffqjelly ffqpastille ffqsugarfreepastil ffqmarzipan ffqbutterslice ffqmargerine ffqbrelett ffqsoftmarg ffqlightmarg ffqmeltbutter ffqmeltmarg ffqbuttercook ffqmargsoftcook ffqmarghardcook ffqsoyamargcook ffqolivmargcook ffqothermar ffqsoyaoil ffqcookoil ffqoliveoil ffqcornoil ffqotheroil ffqwheycheese ffqwheylowfatcheese ffqhardcreamcheese ffqhardcheescreamlowfat ffqbluecheese ffqothercheese ffqcheeseinpasta ffqroesprd ffqmacksardsauce ffqsardinesprd ffqsmoksalmtrout ffqherringsprd ffqliversprd ffqpeanutbuttersprd ffqothernutsprd ffqothersweetsprd ffqpastameat ffqpastafish ffqpastaveg ffqpastatomatosauce ffqspagettinoodle FFQpizza FFQsoups ffqpotatochips ffqpopcorn ffqsaltsnacks ffqwhitebrownsauce ffqbarnaisesauce ffqketchup ffqcucumberveg ffqaubergineveg ffqpeasveg ffqonionleekveg ffqonionleekboilveg ffqgarlicveg ffqcarrotveg ffqcarrotboilveg ffqswedeveg ffqswedeboilveg ffqcorncobveg ffqpepperveg ffqbrusssproutsveg ffqlettuceveg ffqceleryveg ffqmushroomrawveg ffqmushroomveg ffqspinachveg ffqsquashveg ffqtomatoveg ffqvegspreads ffqcauliflowerveg ffcauliflowerboilveg ffqbrocoliveg ffqbrocoliboilveg ffqcabbageveg ffqcabbageboilveg ffqmackherring ffqsalmontrout ffqcodhaddock ffqtunafish ffqshrimps ffqmussels ffqcrabm ffqfishprod ffqfishcake ffqfishfinger FFQegg ffqchickturkfilletmp ffqfriedchickmp ffqbakboilchickturmp ffqchickshnuggmp ffqchickturksausgmp ffqmeatprod ffqmeatprodgrill ffqmeatballmp ffqmincemeatmp ffqlambroastmp ffqlambstewmp ffqhotdog ffqmeatporksausagemp ffqporkchopmp ffqporkfillmp ffqporkloinsmomp ffqporkbelbaconmp ffqbaconmp FFQoffal ffqhamburgermp ffqbeefvealmp ffqbeef ffqvenisonlivkid, comp (5)

rotate

predict pc1 pc2 pc3 pc4 pc5, score

screeplot, yline(1) ci(het)

C.3.2 33 food group PCA code

pca FFQaddedsugar FFQfruitsndryfruit FFQnutsoilseed FFQpotato_bbc FFQlowfatwholeyogurt ///FFQricemillet FFQmayocreams FFQunrefinedbread FFQrefinedbread FFQjuicesandjamsyrup ///FFQothermilk FFQtea FFQcoffee FFQalcbev FFQcolas FFQwholemilk FFQlowfatmilk ///FFQbreakfastcereals FFQdessertschoccake FFQfatsoil FFQcheesespreads FFQpastanoodlespag ///FFQveg FFQfattyfish FFQleanfish FFQseafoodmollusc FFQfishprods FFQpoultryegg ///FFQredmeat FFQpork FFQbeefveal FFQoffal FFQmiscfood , comp (5)

rotate

predict pc1 pc2 pc3 pc4 pc5, score

screeplot, yline(1) ci(het)

C.3.3 Regression analyses between 33 food group dietary patterns scores and birth outcomes

PCA scores and birthweight models*unadjusted*

regress Offspring_weight_gram pc1 Mother_age

regress Offspring_weight_gram pc2 Mother_age

regress Offspring_weight_gram pc3 Mother_age

regress Offspring_weight_gram pc4 Mother_age

regress Offspring_weight_gram pc5 Mother_age

ADJUSTED

regress Offspring_weight_gram pc1 Mother_age i.Parity_cat i.pa_w15 T1_bmi i.smoke_yesno i.alcohol_yesno i.supplement_yesno

regress Offspring_weight_gram pc2 Mother_age i.Parity_cat i.pa_w15 T1_bmi i.smoke_yesno i.alcohol_yesno i.supplement_yesno

regress Offspring_weight_gram pc3 Mother_age i.Parity_cat i.pa_w15 T1_bmi i.smoke_yesno i.alcohol_yesno i.supplement_yesno

regress Offspring_weight_gram pc4 Mother_age i.Parity_cat i.pa_w15 T1_bmi i.smoke_yesno i.alcohol_yesno i.supplement_yesno

regress Offspring_weight_gram pc5 Mother_age i.Parity_cat i.pa_w15 T1_bmi i.smoke_yesno i.alcohol_yesno i.supplement_yesno

PCA scores and SGA models*unadjusted*

logistic sga_logisticSS pc1 Mother_age

logistic sga_logisticSS pc2 Mother_age

logistic sga_logisticSS pc3 Mother_age

logistic sga_logisticSS pc4 Mother_age

logistic sga_logisticSS pc5 Mother_age

ADJUSTED

logistic sga_logisticSS pc1 Mother_age i.pa_w15 i.smoke_yesno i.alcohol_yesno i.supplement_yesno

logistic sga_logisticSS pc2 Mother_age i.pa_w15 i.smoke_yesno i.alcohol_yesno i.supplement_yesno

logistic sga_logisticSS pc3 Mother_age i.pa_w15 i.smoke_yesno i.alcohol_yesno i.supplement_yesno

logistic sga_logisticSS pc4 Mother_age i.pa_w15 i.smoke_yesno i.alcohol_yesno i.supplement_yesno

logistic sga_logisticSS pc5 Mother_age i.pa_w15 i.smoke_yesno i.alcohol_yesno i.supplement_yesno

PCA scores and LGA models*unadjusted*

logistic lga_logisticSS pc1 Mother_age

logistic lga_logisticSS pc2 Mother_age

logistic lga_logisticSS pc3 Mother_age

logistic lga_logisticSS pc4 Mother_age

logistic lga_logisticSS pc5 Mother_age

ADJUSTED

logistic lga_logisticSS pc1 Mother_age i.pa_w15 i.smoke_yesno i.alcohol_yesno i.supplement_yesno

logistic lga_logisticSS pc2 Mother_age i.pa_w15 i.smoke_yesno i.alcohol_yesno i.supplement_yesno

logistic lga_logisticSS pc3 Mother_age i.pa_w15 i.smoke_yesno i.alcohol_yesno i.supplement_yesno

logistic lga_logisticSS pc4 Mother_age i.pa_w15 i.smoke_yesno i.alcohol_yesno i.supplement_yesno

logistic lga_logisticSS pc5 Mother_age i.pa_w15 i.smoke_yesno i.alcohol_yesno i.supplement_yesno

C.4 Chapter 7

C.4.1 RRR analyses code for DNBC

plssas, y (bmi_pre energy_kcal pa_w12 smoke_yesno) ///

x (lowfat_dairy highfat_dairy icecream breakfstcereal wholegrain refgrains fruit offal procesmeat redmeat fish shellfish poultry eggs animalfat vegfats margarine sweetsdessert tea coffee highenergydrink lowenergydrink alcobeverge snacks vegjuice fruitjuice fruitsyrupjam nuts otherveg potatonprods glv tomatoes soyprods driedfruit dressings beanslentils cheese addsugar) ///

*DNBC gestational weight gain model *Computation of the X loadings from the rrr model

*analysis for pattern score variable creation:

gen rrrscore1= lowfat_dairy* 0.176896 + highfat_dairy* 0.156922+ icecream* 0.083277 + breakfstcereal * 0.105659 + wholegrain * 0.309009 + refgrains* 0.254462+ fruit * 0.112071 + offal* 0.048754 + procesmeat * 0.24724 + redmeat* 0.210065+ fish * 0.170341 + shellfish * 0 + poultry * 0.071277 + eggs * 0.217375 + animalfat * 0.339288 + vegfats * 0.195057 + margarine* 0.231533 + sweetsdessert * 0.221295 + tea * 0.044949 + coffee* 0.070371+ highenergydrink * 0.119603 + lowenergydrink * -0.01581+ alcobeverge* 0.020338 + snacks * 0.118595 + vegjuice* 0.016513+ fruitjuice* 0.151286 + fruitsyrupjam* 0.142904 + nuts* 0.081496 + otherveg * 0.136299 + potatonprods* 0.236691 + glv* 0.060691+ tomatoes* 0.109201+ soyprods* 0.002192+ driedfruit* 0.088689+ dressings* 0.034298+ beanslentils* 0.034767+ cheese* 0.200114+ addsugar* 0.285876

gen rrrscore2= lowfat_dairy* -0.01723+ highfat_dairy* 0.055603+ icecream* -0.03232+ breakfstcereal * -0.27459+ wholegrain * -0.17158+ refgrains* 0.15112+ fruit * -0.2995+ offal* 0.043876+ procesmeat * 0.162164+ redmeat* 0.184786+ fish * -0.12234+ shellfish * 0 + poultry * -0.15066+ eggs * 0.016802+ animalfat * 0.232046+ vegfats * 0.077096+ margarine* -0.04665+ sweetsdessert * -0.04406+ tea * -0.11035+ coffee* 0.423821+ highenergydrink * 0.278367+ lowenergydrink * -0.137107+ alcobeverge* 0.043483+ snacks * 0.183498+ vegjuice* -0.01584+ fruitjuice* -0.0746+ fruitsyrupjam*0.074854+ nuts* -0.06873+ otherveg * -0.19571+ potatonprods* 0.15964+ glv* -0.21796+ tomatoes* -0.18108+ soyprods* -0.03296+ driedfruit* -0.25557+ dressings* 0.022665+ beanslentils* -0.21834+ cheese* -0.04958+ addsugar* 0.11422

gen rrrscore3= lowfat_dairy* 0.209792+ highfat_dairy* -0.20784+ icecream* -0.01913+ breakfstcereal * -0.16415+ wholegrain * 0.050245+ refgrains* 0.17048+ fruit * -0.05106+ offal* 0.046469+ procesmeat * 0.294786+ redmeat* 0.35918+ fish * -0.05845+ shellfish * 0 + poultry * 0.048457+ eggs * -0.11845+ animalfat * -0.21069+ vegfats * -0.16477+ margarine* -0.06156+ sweetsdessert * -0.15295+ tea * -0.0942+ coffee* -0.42929+ highenergydrink * 0.018284+ lowenergydrink * 0.306023+ alcobeverge* 0.00161+ snacks * 0.042632+ vegjuice* -0.04754+ fruitjuice* 0.057208+ fruitsyrupjam* 0.192668+ nuts* -0.11774+ otherveg * -0.06878+ potatonprods* 0.177166+ glv* -0.11772+ tomatoes* -0.09955+ soyprods* -0.04481+ driedfruit* -0.11192+ dressings* 0.142379+ beanslentils* -0.26903+ cheese* 0.004435+ addsugar* -0.04614

gen rrrscore4= lowfat_dairy* 0.285847+ highfat_dairy* -0.27244+ icecream* -0.03141+ breakfstcereal * 0.091255+ wholegrain * 0.04322+ refgrains* -0.12641+ fruit * 0.262883+ offal* 0.024083+ procesmeat * -0.07067+ redmeat* -0.20528+ fish * 0.267801+ shellfish * 0 + poultry * 0.235968+ eggs * 0.102061+ animalfat * -0.32975+ vegfats * -0.0529+ margarine* -0.15511+ sweetsdessert * -0.11528+ tea * -0.003+ coffee* 0.281661+ highenergydrink * 0.02111+ lowenergydrink * 0.255235+ alcobeverge* 0.097116+ snacks * -0.0135+ vegjuice* 0.049537+ fruitjuice* 0.111595+ fruitsyrupjam* 0.026373+ nuts* 0.078948+ otherveg * 0.266504+ potatonprods* -0.01591+ glv* 0.125506+ tomatoes* 0.21034+ soyprods* 0.037668+ driedfruit* 0.156227+ dressings* -0.03813+ beanslentils* 0.233053+ cheese* 0.118232+ addsugar* -0.10079

gen rrr1prebmi_200= rrrscore1/200

gen rrr2energy_200 = rrrscore2/200

gen rrr3pal_200= rrrscore3/200

gen rrr4smoke_200= rrrscore4/200

*RRR SCORES AND BIRTHWEIGHT MODELS*UNADJUSTED*

regress birthweight rrr1prebmi_200 mage

regress birthweight rrr2energy_200 mage

regress birthweight rrr3pal_200 mage

regress birthweight rrr4smoke_200 mage

ADJUSTED

regress birthweight rrr1prebmi_200 mage energy_kcal i.smoke_yesno alcohol_w12 bmi_pre i.pa_w12 SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

regress birthweight rrr2energy_200 mage energy_kcal i.smoke_yesno alcohol_w12 bmi_pre i.pa_w12 SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

regress birthweight rrr3pal_200 mage energy_kcal i.smoke_yesno alcohol_w12 bmi_pre i.pa_w12 SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

regress birthweight rrr4smoke_200 mage energy_kcal i.smoke_yesno alcohol_w12 bmi_pre i.pa_w12 SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

*RRR SCORES AND SGA MODELS*UNADJUSTED*

logistic sga_logisticSS rrr1prebmi_200 mage

logistic sga_logisticSS rrr2energy_200 mage

logistic sga_logisticSS rrr3pal_200 mage

logistic sga_logisticSS rrr4smoke_200 mage

ADJUSTED

logistic sga_logisticSS rrr1prebmi_200 mage energy_kcal i.smoke_yesno alcohol_w12 i.pa_w12 SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

logistic sga_logisticSS rrr2energy_200 mage energy_kcal i.smoke_yesno alcohol_w12 i.pa_w12 SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

logistic sga_logisticSS rrr3pal_200 mage energy_kcal i.smoke_yesno alcohol_w12 i.pa_w12 SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

logistic sga_logisticSS rrr4smoke_200 mage energy_kcal i.smoke_yesno alcohol_w12 i.pa_w12 SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

*RRR SCORES AND LGA MODELS*UNADJUSTED*

logistic lga_logisticSS rrr1prebmi_200 mage

logistic lga_logisticSS rrr2energy_200 mage

logistic lga_logisticSS rrr3pal_200 mage

logistic lga_logisticSS rrr4smoke_200 mage

ADJUSTED

logistic lga_logisticSS rrr1prebmi_200 mage energy_kcal i.smoke_yesno alcohol_w12 i.pa_w12 SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

logistic lga_logisticSS rrr2energy_200 mage energy_kcal i.smoke_yesno alcohol_w12 i.pa_w12 SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

logistic lga_logisticSS rrr3pal_200 mage energy_kcal i.smoke_yesno alcohol_w12 i.pa_w12 SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

logistic lga_logisticSS rrr4smoke_200 mage energy_kcal i.smoke_yesno alcohol_w12 i.pa_w12 SDsupp_vitB12SS SDsupp_folateSS SDsupp_ironSS SDsupp_calciumSS

C.4.2 RRR analyses code for MoBa

plssas, y (pa_w15 smoke_yesno t1_bmi energy_kcal) ///

x(ffqaddedsugar ffqfruitsndryfruit ffqnutsoilseed ffqpotato_bbc ffqlowfatwholeyogurt ffqricemillet ffqmayocreams ffqunrefinedbread ffqrefinedbread ffqjuicesandjamsyrup ffqothermilk ffqtea ffqcoffee ffqalcbev ffqcolas ffqwholemilk ffqlowfatmilk ffqbreakfastcereals ffqdessertschoccake ffqfatsoil ffqcheesespreads ffqpastanoodlespag ffqveg ffqfattyfish ffqleanfish ffqseafoodmollusc ffqfishprods ffqpoultryegg ffqredmeat ffqpork ffqbeefveal ffqoffal ffqmiscfood) ///

*MoBa gestational weight gain model *Computation of the X loadings from the rrr model

*analysis for pattern score variable creation:

gen rrrscore1= FFQaddedsugar_g*0.609866 + FFQfruitsndryfruit* 0.211634 + FFQlowfatwholeyogurt * 0.201948 + FFQrefinedbread*0.209567 + FFQjuicesandjamsyrup*0.209816 +FFQwholemilk*0.153034 + FFQlowfatmilk*0.165619 + FFQdessertschoccake*0.246685 + FFQcheesespreads*0.233646 + FFQredmeat*0.160886 + FFQpork*0.188683 + FFQmiscfood*0.152782

```
gen rrrscore2= FFQaddedsugar_g* 0.149948 + FFQfruitsndryfruit* 0.285253+ FFQpotato_bbc*
0.164999+ FFQunrefinedbread* -0.212583 + FFQrefinedbread* 0.175604+ FFQjuicesandjamsyrup* -
0.181193+ FFQtea* -0.276638 + FFQcolas * 0.484284 + FFQlowfatmilk* -0.137677 +
FFQbreakfastcereals* -0.168606 + FFQcheesespreads* -0.166385 + FFQfattyfish* -0.228646 +
FFQpoultryegg* -0.231621 + FFQredmeat* 0.163309 + FFQpork* 0.342271 + FFQbeefveal* 0.226313
gen rrrscore3= FFQfruitsndryfruit* 0.285253 + FFQunrefinedbread* 0.17695 + FFQcoffee* -0.499205 +
FFQcolas* 0.313856 + FFQlowfatmilk* 0.294185 + FFQcheesespreads* 0.195175 + FFQfishprods*
0.179306 + FFQpoultryegg* 0.175619 + FFQpork* 0.220775 + FFQbeefveal* 0.149601 + FFQmiscfood*
0.199226
gen rrrscore4= FFQaddedsugar_g* 0.211634 + FFQfruitsndryfruit* 0.241907 + FFQricemillet* -0.256356
+ FFQcoffee* 0.573939 + FFQdessertschoccake* -0.215214 + FFQfatsoil* -0.240569 + FFQveg*
0.245577 + FFQfattyfish* 0.1972 + FFQleanfish* 0.331626 + FFQfishprods* 0.252625
gen rrr1pal_200= rrrscore1/200
gen rrr2smoke_200= rrrscore2/200
gen rrr3prebmi_200= rrrscore3/200
gen rrr4energy_200= rrrscore4/200
*RRR SCORES AND BIRTHWEIGHT MODELS*UNADJUSTED*
regress Offspring_weight_gram rrr1pal_200 Mother_age
regress Offspring_weight_gram rrr2smoke_200 Mother_age
regress Offspring_weight_gram rrr3prebmi_200 Mother_age
regress Offspring_weight_gram rrr4energy_200 Mother_age
*ADJUSTED*
regress  Offspring_weight_gram rrr1pal_200 Mother_age Energy_kCal i.smoke_yesno i.alcohol_yesno
T1_bmi i.pa_w15 i.supplement_yesno
regress  Offspring_weight_gram rrr2smoke_200 Mother_age Energy_kCal i.smoke_yesno
i.alcohol_yesno T1_bmi i.pa_w15 i.supplement_yesno
regress  Offspring_weight_gram rrr3prebmi_200 Mother_age Energy_kCal i.smoke_yesno
i.alcohol_yesno T1_bmi i.pa_w15 i.supplement_yesno
regress  Offspring_weight_gram rrr4energy_200 Mother_age Energy_kCal i.smoke_yesno
i.alcohol_yesno T1_bmi i.pa_w15 i.supplement_yesno
*RRR SCORES AND SGA MODELS*UNADJUSTED*
logistic sga_logisticSS rrr1pal_200 Mother_age
logistic sga_logisticSS rrr2smoke_200 Mother_age
logistic sga_logisticSS rrr3prebmi_200 Mother_age
logistic sga_logisticSS rrr4energy_200 Mother_age
*ADJUSTED*
logistic sga_logisticSS rrr1pal_200 Mother_age Energy_kCal i.smoke_yesno i.alcohol_yesno  i.pa_w15
i.supplement_yesno
```

```
logistic sga_logisticSS rrr2smoke_200 Mother_age Energy_kCal i.smoke_yesno i.alcohol_yesno
i.pa_w15 i.supplement_yesno
logistic sga_logisticSS rrr3prebmi_200 Mother_age Energy_kCal i.smoke_yesno i.alcohol_yesno
i.pa_w15 i.supplement_yesno
logistic sga_logisticSS rrr4energy_200 Mother_age Energy_kCal i.smoke_yesno i.alcohol_yesno
i.pa_w15 i.supplement_yesno
*RRR SCORES AND LGA MODELS*UNADJUSTED*
logistic lga_logisticSS rrr1pal_200 Mother_age
logistic lga_logisticSS rrr2smoke_200 Mother_age
logistic lga_logisticSS rrr3prebmi_200 Mother_age
logistic lga_logisticSS rrr4energy_200 Mother_age
*ADJUSTED*
logistic lga_logisticSS rrr1pal_200 Mother_age Energy_kCal i.smoke_yesno i.alcohol_yesno  i.pa_w15
i.supplement_yesno
logistic lga_logisticSS rrr2smoke_200 Mother_age Energy_kCal i.smoke_yesno i.alcohol_yesno
i.pa_w15 i.supplement_yesno
logistic lga_logisticSS rrr3prebmi_200 Mother_age Energy_kCal i.smoke_yesno i.alcohol_yesno
i.pa_w15 i.supplement_yesno
logistic lga_logisticSS rrr4energy_200 Mother_age Energy_kCal i.smoke_yesno i.alcohol_yesno
i.pa_w15 i.supplement_yesno
```