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Obesity in obstetric care

Consequences and risk prediction

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Abstract

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The incidence of obesity is increasing at an alarming rate worldwide and the epidemic has reached the pregnant population of developed countries. Obesity is associated with several obstetric complications for both the mother, the fetus and the new-born. Today, obesity risk assessment is based on body mass index (BMI). However, the majority of women considered obese based on BMI will have an event-free pregnancy and delivery. Obesity is one of the greatest challenges for obstetricians and improving prediction of risk among obese women is essential.

The overall aim of this thesis was to increase the capacity for early pregnancy prediction of obesity-related late adverse pregnancy outcomes in women with overweight and obesity.

The thesis encompassed four population-based cohort studies. The first showed that obesity in early pregnancy modulated the association between depression and infant birthweight. Women with obesity and depression gave birth to infants with higher birthweight than non-depressive obese women. The opposite pattern was seen in normal-weight women, where depressed women gave birth to infants with lower birthweight than non-depressive women. About one-third of pregnant women with obesity are metabolically unhealthy, which was the focus of the second study. Almost half of those women developed at least one obesity-related complication and the risk was higher than in women with obesity who were metabolically healthy. The difference seemed to have little clinical relevance. Further, women with metabolically unhealthy obesity have numerous risk factors for development of cardiovascular disease later in life, including altered levels of cardiovascular markers in blood samples. The third and fourth studies explored if estimation of fat distribution in the first half of pregnancy predicted preeclampsia development. It was found that waist circumference (WC) measured in the first trimester was associated with increased risk of developing preeclampsia. However, first-trimester WC was highly correlated with BMI and adding WC to a prediction model already including BMI did not improve its prediction performance. The research team also measured abdominal adipose tissue with ultrasound in the second trimester. Both subcutaneous adipose tissue (SAT) thickness and visceral adipose tissue (VAT) thickness were associated with preeclampsia development, but only SAT thickness had an association that remained after adjustment for BMI.

In conclusion, assessment of obese women in early pregnancy for detection of high risk for obesity-related complications is essential. Comorbidity of other diseases, such as depression, should be taken into account. Metabolically unhealthy obesity during pregnancy has little impact in the short term, but might be an opportunity for prevention of long-term consequences in obese women. Central obesity, measured as WC or SAT/VAT thickness, was associated with preeclampsia, but only SAT thickness seemed to improve prediction of preeclampsia in models already addressing obesity as BMI.

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To my friends and family

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I **Petursdottir Maack H**., Skalkidou A., Sjöholm A., Eurenius-Orre K., Mulic-Lutvica A., Wikström AK., Sundström Poromaa I. (2019). Maternal body mass index moderates antenatal depression effects on infant birthweight. *Scientific Reports.* 2019: 9(1):6213.

II **Pétursdóttir Maack H**., Larsson A., Axelsson O., Olovsson M., Wikström AK., Sundström Poromaa I. Pregnancy in metabolic healthy and unhealthy obese women. *Acta Obstet Gynecol Scand.* 2020 Dec;99(12):1640-1648.

III **Pétursdóttir Maack H**., Sundström Poromaa I., Segeblad B., Lindström L., Jonsson M., Junus K., Wikström AK. Waist circumference measurement for prediction of preeclampsia: a population-based cohort study. *American Journal of Hypertension.* 2021 Sep 27:hpab156. Online ahead of print.

IV **Pétursdóttir Maack H**., Sundström Poromaa I., Lindström L., Mulic-Lutvica A., Junus K., Wikström AK. Ultrasound estimated subcutaneous and visceral adipose tissue thickness and risk of preeclampsia. *Submitted, under revision*.

Contents

Abbreviations

ALAT	Alanine transaminase
AOR	Adjusted odds ratio
ApoA	Apolipoprotein A
ApoB	Apolipoprotein B
AUC	Area Under the Curve
BASIC	Biology, Affect, Stress, Imaging and Cognition in the Puerperium
BAT	Brown adipose tissue
BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
DAG	Directed acyclic graph
EPDS	Edinburgh Postnatal Depression Scale
GDM	Gestational diabetes mellitus
GFR	Glomerular filtration rate
HDL	High-density lipoprotein
HPA	Hypothalamus-pituitary-adrenal
ICD	International Classification of Disease
IL	Interleukin
IVF	*In vitro* fertilization
LGA	Large for gestational age
MAP	Mean arterial pressure
MHO	Metabolically healthy obesity
MUO	Metabolically unhealthy obesity
NICE	National Institute for Health and Clinical Excellence
NO	Nitric oxide
OGTT	Oral glucose tolerance test
OR	Odds ratio
PGF	Placental growth factor
PTX-3	Pentraxin-related protein 3
SAT	Subcutaneous adipose tissue
sFlt-1	Soluble fms-like tyrosine kinase 1
SD	Standard deviation
SGA	Small for gestational age
SLE	Systemic lupus erythematosus
TNF	Tumor necrosis factor

VAT	Visceral adipose tissue
WAT	White adipose tissue
WC	Waist circumference
WHO	World Health Organization

Introduction

Obesity

Definition and prevalence

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a health risk. For adults, the most common measurement for overweight and obesity is the body mass index (BMI). This is because of its simplicity and the fact that BMI is the same for both sexes and for all ages of adults. A person's BMI is calculated based on the individual's weight in kilograms and height in centimeters, by dividing the weight by the square of the height. BMI is usually categorized as seen in Table 1 (1).

Table 1. *World Health Organization classification of obesity (1).*

Classification	**BMI (kg/m^2)**	**Health risk**
Underweight	< 18.5	Increased
Normal weight	18.5–24.9	Least
Overweight	25.0–29.9	Increased
Obesity grade I	30.0–34.9	High
Obesity grade II	35.0–39.9	Very high
Obesity grade III	> 40	Extremely high

However, using BMI as a categorization of overweight and obesity has its downsides. BMI does not always correspond to the same degree of fatness in different individuals, and only takes weight and height into account, not muscle mass or fat distribution.

The incidence of overweight and obesity is increasing worldwide, at an alarming rate. According to the World Health Organization (WHO), obesity has nearly tripled since 1975. In 2016, 39% of adults aged 18 years or older were overweight and 13% were obese, Figure 1. Obesity is more common among women and 15% of women worldwide were obese in 2016 (1). Earlier, obesity was considered a problem only in high-income countries, but during the last decades, we also note a rise in low- and middle-income countries.

According to the Public Health Agency of Sweden, 52% of the Swedish population aged 18–84 years was overweight or obese in 2020 (2). Overweight is more common among men than among women (47% vs. 46%), but obesity is

more common among women than men (16% vs. 15%). Obesity has become one of the most common reasons for loss of healthy life years in Sweden (3). Overweight and obesity are most common in the older age categories (44–84 years of age), with 61% of this age population being overweight or obese. In the youngest age group (16–29 years), the prevalence of overweight and obesity is 23% and 8%, respectively. The largest increase in overweight and obesity between 2006 and 2018 was in this age group, rising from 22% in 2006 to 31% in 2018 (4).

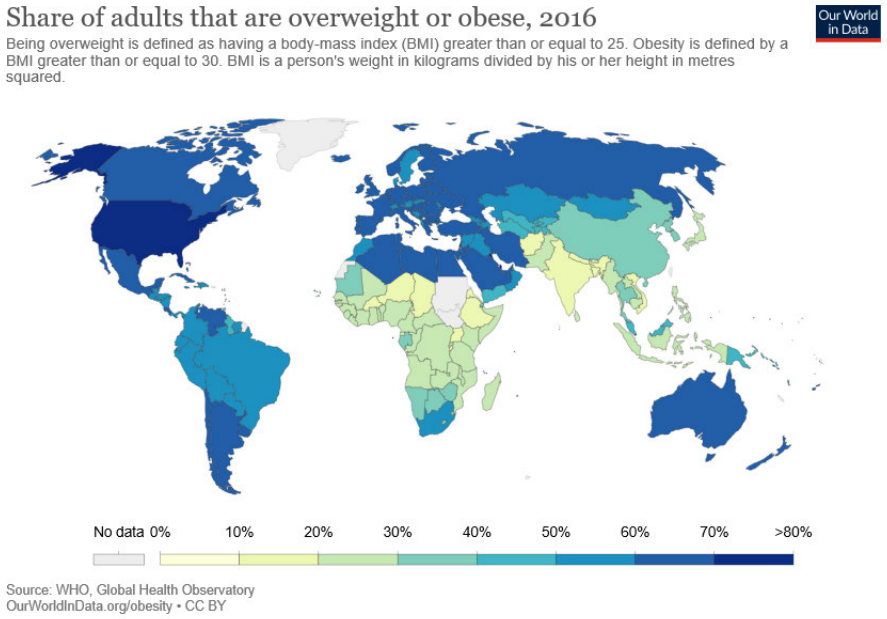

Figure 1. Prevalence of overweight and obese individuals globally (5).

Consequences of obesity

Obesity is commonly described as a major risk factor for metabolic complications such as insulin resistance, non-alcoholic fatty liver disease, high lipid levels, high blood pressure, and sleep apnea (6). These metabolic factors and obesity itself are associated with a broad range of medical diseases such as type-2 diabetes (7), cardiovascular disease (CVD) (8), dyslipidemia and hypertension (9), and various cancers (10).

BMI is a strong predictor of overall mortality, with the optimal BMI being 22.5–25.0 kg/m^2. Above this range, the absolute excess risk for every 5 kg/m^2 higher BMI is associated with 30% higher mortality on average. Mortality is mainly due to CVD, and is probably largely causal (11).

The adipose tissue is considered an endocrine organ in itself due to its ability to secrete adipokines. These are bioactive molecules that play important roles in glucose or lipid metabolism, insulin sensitivity, regulation of appetite/satiety, immune cell attraction, and endothelial function (12). The adipose tissue has been shown not only to release endocrine hormones, but also to secrete a diverse range of cytokines, proteins, and signals that have both paracrine and endocrine actions and can affect local and systemic metabolic responses (13, 14).

Metabolically healthy obesity

Definition

It has been proposed that not all individuals with overweight and obesity are unhealthy. While obesity is known to be associated with the above metabolic disturbances, a subgroup of obese individuals has a normal metabolic profile. This concept is referred to as metabolically healthy obesity (MHO). Thus, obese individuals who are not metabolically healthy may be defined as having metabolically unhealthy obesity (MUO). There are currently no universally accepted criteria for identifying MHO (or MUO) (15), but MHO is usually used to refer to individuals with BMI > 30 kg/m^2 with *no components* of the metabolic syndrome, depending on the cohort and the criteria used (16).

The concept of the metabolic syndrome is important to recognize as a syndrome, not as a defined uniform entity. Several organizations have attempted to formulate a simple criterion for its diagnosis, but again, there is no consensus on which criteria to use (17). The first group to come up with a proposal was the WHO in 1998, but their focus was mainly on insulin resistance (18).

The five established components of metabolic syndrome are the following (19):

1. Abdominal obesity defined by ethnicity-specific waist circumference
2. Elevated blood pressure
3. Impaired fasting glucose levels
4. Increased triglyceride levels
5. Decreased high-density lipoprotein (HDL) cholesterol levels

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) introduced criteria for the definition of metabolic syndrome (20). The NCEP-ATP III criteria were based on the above five components, but did not require any single risk factor for diagnosis. Rather, they made the presence of three of five factors the basis for diagnosis. The NCEP-ATP III criteria drew attention to the importance of abdominal obesity and

allowed the diagnosis of metabolic syndrome in the presence of type-2 diabetes mellitus (17).

MHO individuals have lower levels of triglycerides, inflammatory markers and higher HDL cholesterol than MUO individuals (16). Moreover, serum markers, such as low levels of high sensitivity C-reactive protein (CRP) (21), normal levels of liver enzymes (22), and high levels of adiponectin (23) have been associated with MHO. The prevalence of MHO in the general population is estimated at 20–30% among obese individuals (16). The MHO phenotype seems to protect those obese individuals against obesity-related metabolic diseases, and their adipose tissue seems to have a normal function. Further, individuals with MHO may not significantly improve their obesity-related metabolic risks by anti-obesity treatment strategies in the same way as their MUO counterparts (24). Liu et al. compared the prevalence of MHO and MUO based on five different criteria. They classified obesity both as BMI $\geq$ 28 kg/m^2 and as abdominal obesity by waist circumference (WC) $\geq$ 85 cm in men and $\geq$ 80 cm in women, based on the Chinese standard. In their results, the prevalence of MHO varied from 4% to 13% when obesity was defined by BMI, but from 14% to 40% when defined by WC. MUO prevalence was 10–20% and 22–49%, respectively (25). Overall, these findings indicate that WC might be a better marker for obesity than BMI. In addition, when identifying individuals with MUO, WC seems to be a better predictor than BMI.

MHO and long-term consequences

Studies on individuals with MHO demonstrate that the risk of all-cause mortality and cardiovascular events is lower than in those with the MUO phenotype (26), but this concept has also been questioned.

Increased mortality risk in MUO groups compared with MHO groups has been demonstrated consistently (27-29). Further, several studies have shown that MHO individuals are at lower risk of cardiovascular events than MUO individuals, and they appear to have no increased risk compared with normal-weight, metabolically healthy individuals (30-32), not even in studies with a 10-year follow-up (33).

However, the prognostic value of MHO was recently challenged by a large study reporting that MHO individuals are still at a higher risk of coronary heart disease, cerebrovascular disease and heart failure compared with normal-weight, metabolically healthy individuals (34). Further, although there was no difference in the short term, the 10-year risks of all-cause mortality and cardiovascular events in MHO individuals seemed to be increased compared with those in metabolically healthy normal-weight individuals (33, 35). Other studies, including a meta-analysis, have suggested that MHO is associated with

short-term increased risks of both cardiovascular events and diabetes compared with the risks in normal-weight, metabolically healthy individuals (36-39). The reasons for inconsistency in these studies can only be speculated on, but a probable explanation is that there is no uniform definition of MHO and different criteria were used in different studies.

Adipose tissue distribution

Central adipose tissue

In assessing obesity-related risks, evidence suggests that different body fat distribution must be taken into consideration to identify individuals with a high-risk obesity pattern (40, 41). Fat storage can be mainly in the upper abdominal body region, i.e., central fat distribution, or in the lower body region, i.e., gluteofemoral or peripheral fat distribution (42). Epidemiological studies have shown that upper and lower body fat distribution have different effects on cardiovascular and metabolic disease prevalence, even after adjustment for total body fat mass (42, 43). Central obesity correlates more strongly with most obesity-related complications, such as type-2 diabetes mellitus and coronary artery disease (44, 45).

Waist circumference

WC is an simple method for measurement of obesity, and is currently a part of the metabolic syndrome criteria instead of BMI, as it better reflects central abdominal fat deposits (20). It is strongly associated with the absolute amount of visceral fat (46). Increased WC has been associated with increased cardiovascular risk in both men and women, and with elevated blood pressure, hyperlipidemia, and raised insulin concentration (47, 48). Among younger individuals (< 55 years), WC and BMI seem to be independent and equally important predictors of elevated blood pressure (49). WC is a better predictor than BMI of non-insulin-dependent diabetes mellitus (50), as well as CVD (51). A strong relationship between WC and all-cause mortality has been shown, even after adjustment for BMI, indicating that WC is a BMI-independent risk factor. Changes in WC predict changes in visceral fat distribution and cardiovascular risk factors in women (52). Studies have shown that over time, the relative increase in WC is larger than the relative increase in BMI (53), and the variation in WC is considerable within different BMI categories. In any given BMI category, adults with higher WC values are at higher health risk (54).

Adipose tissue depots

In humans, there are two main types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT).

WAT is mainly composed of white adipocytes and functions as energy storage. Fatty acids, carried by circulating lipoproteins, are taken up by the white adipocytes. Insulin plays a central role in this process by causing uptake of both fatty acids and glucose, and by inhibiting lipolysis. The fatty acids are then converted into triglycerides, which are stored in large intracellular lipid droplets in the cells. In a catabolic state, WAT releases free fatty acids through lipolysis (55). With excess caloric intake, WAT can expand by both hypertrophy and hyperplasia of white adipocytes, which subsequently leads to obesity. Excessive expansion of WAT during obesity is followed by local inflammation and decreased response of adipocytes to insulin, causing insulin resistance and disrupted metabolism (56). Insulin resistance in adipocytes leads to insufficient lipid retention in WAT and, consequently, lipid accumulation occurs in organs such as the liver and skeletal muscle. These effects partly explain how insulin resistance contributes to metabolically unhealthy obesity. On the other hand, weight loss does not lead to any discernible change in the numbers of adipocytes, but only modifies their size (57). Thus, the number of adipocytes in adult individuals does not change only their size and function.

BAT is mainly composed of brown adipocytes and functions to generate heat. During a process called adaptive (non-shivering) thermogenesis, fatty acids and glucose are metabolized for the production of heat (56). Brown adipocytes differ from white adipocytes as they have multiple lipid droplets and their mitochondria contain uncoupling protein 1, which is essential for the heat-producing process (58). Although BAT depots are small, they have exceptionally high metabolic activity. BAT usually decreases with increased age and increasing body weight (56).

Visceral versus subcutaneous fat distribution

More than 80% of the overall body fat mass is stored in the subcutaneous adipose tissue, defined as the upper abdominal subcutaneous adipose tissue and the lower body gluteofemoral fat deposit, with the remaining fat being stored in the visceral adipose tissue (42). Of the intra-abdominal fat deposit, visceral fat accounts for 10–20% in men and 5–8% in women, and the amount of visceral fat increases with age (59, 60). There are several differences between visceral and subcutaneous adipose tissue. Visceral adipose tissue is more vascular and innervated than subcutaneous adipose tissue. The adipocytes in the visceral adipose tissue are larger and more dysfunctional and in-

sulin-resistant than the smaller adipocytes in the subcutaneous tissue. The adipocytes in the subcutaneous tissue avidly absorb free fatty acids and triglycerides. The visceral adipose tissue has a higher density of androgen receptors than the subcutaneous adipose tissue, which has a higher density of estrogen receptors with greater binding capacity. Deficiency in estrogen contributes to the shift in increased visceral adipose tissue seen with age in postmenopausal women (59).

Both visceral adipose tissue and subcutaneous adipose tissue volumes are correlated with metabolic risk factors, but some studies suggest that visceral adipose tissue is a stronger indicator (61). Visceral adiposity is closely associated with insulin resistance, hyperinsulinemia, dyslipidemia, hypertension and the metabolic syndrome in the general population (62). In contrast to subcutaneous adipose tissue, which drains through systemic veins, visceral adipose tissue is drained directly to the portal system. Thus, higher concentration of molecules and lipids secreted from WAT in this region reach the liver. This is believed to be one of the reasons behind the stronger association between visceral adipose tissue, fatty liver disease and metabolic diseases (59, 63).

Obesity and pregnancy

The obesity epidemic has also reached the pregnant population of developed countries. In 2019, 27.2% and 15.7% of Swedish pregnant women were overweight and obese, respectively, at the beginning of their pregnancies (64), see Figure 2.

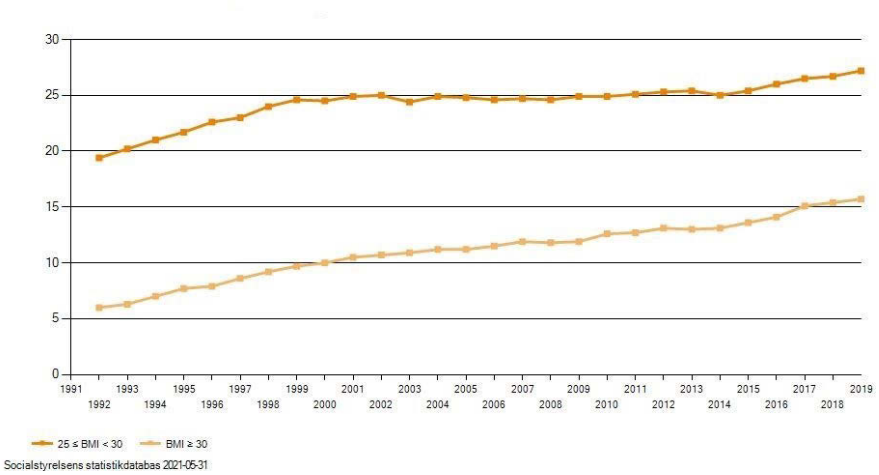

Figure 2. Proportion of women with overweight and obesity at the beginning of their pregnancies in Sweden from 1992 to 2019 (65).

Overweight and obesity are associated with a number of adverse outcomes for both mother and fetus during pregnancy. The risks of spontaneous miscarriage and even late miscarriage are increased (66). Maternal obesity is also associated with increased risks of a number of structural birth defects such as neural tube defects and cardiac defects (67, 68). Moreover, maternal obesity is associated with impaired antenatal ultrasound detection of congenital anomalies (69).

During pregnancy and childbirth, the risks of gestational hypertension, preeclampsia, intrauterine growth restriction, spontaneous preterm birth (before gestational week 37+0), shoulder dystocia, heavy postpartum bleeding (> 1000 ml), large for gestational age (LGA), stillbirth, low Apgar score (< 7 at 5 minutes), meconium aspiration, neonatal asphyxia, and neonatal metabolic disturbances increase with increasing early pregnancy BMI (70-78).

While these obesity-associated consequences are well known, the underlying mechanisms for some of them are likely complex, especially in light of pregnancy-induced changes in metabolism and inflammatory response. The mechanisms are probably multifactorial and involve alterations in glucose and lipid metabolism, as well as impaired endothelial function and upregulated markers of inflammation (79). For example, obesity during pregnancy leads to maternal insulin resistance and fetal hyperinsulinemia, in turn causing increased fetal growth, even in the absence of gestational diabetes mellitus (GDM) (80). This may contribute to the increase in LGA infants. Heavy postpartum bleeding is potentially explained by larger area of implantation of the placenta, typically associated with LGA fetuses (81).

Epidemiologic evidence has linked maternal obesity to preeclampsia (82, 83). Obesity and preeclampsia have a number of biochemical and physiological changes in common, such as oxidative stress, inflammation, and endothelial dysfunction. In spite of this, the exact mechanism behind how maternal adiposity leads to preeclampsia remains unclear (83).

A causal relationship between BMI and the above pregnancy complications was strengthened by findings in a large population-based Swedish study. The study showed that an increase in BMI by 3 kg/m^2 between two consecutive pregnancies increased the risk of gestational hypertension, preeclampsia, GDM, caesarean delivery, stillbirth, and LGA. This risk increase could also be seen in women with a normal BMI in both pregnancies (84).

Although the risks of obesity during pregnancy are well known, obstetric complications are relatively rare. Most overweight and obese women will have event-free pregnancies, and will not be in need of extra surveillance or interventions during their pregnancies or deliveries. These circumstances make

prediction of obstetric complications challenging, even in high-risk individuals with obesity.

MHO and pregnancy

During a normal pregnancy, the maternal metabolism changes substantially. In the beginning of the pregnancy, the mother is in an anabolic state, with increased maternal fat stores and a small increase in insulin sensitivity. Late pregnancy is better described as a catabolic state, with increased insulin resistance (85). Accumulation of fat in maternal depots during early pregnancy and later development of hyperlipidemia are the two main changes in lipid metabolism during pregnancy (86). The hyperlipidemia of pregnancy is further exaggerated by obesity, with higher serum triglyceride and very low-density lipoprotein (VLDL) cholesterol concentrations, together with lower HDL cholesterol, noted in normal-weight pregnant women (87).

While the concept of MHO has been questioned in the long term in the non-pregnant population, this thesis hypothesizes that, in the short-term perspective of a pregnancy, MHO may still be of relevance. To date, no studies have estimated the prevalence of MHO and MUO in pregnant women, or investigated if this distinction can be useful for identifying women with obesity at greater risk of obesity-associated adverse outcomes in pregnancy.

Waist circumference and pregnancy

WC is a simple measurement that can easily be incorporated at the first antenatal visit and can be used as part of a risk assessment at the beginning of pregnancy.

Surprisingly, very little effort has been made to establish if WC is a valid measure to distinguish between healthy and unhealthy obesity in pregnancy. Only a few studies have been done on the predictive value of WC for adverse obstetric and neonatal outcomes. As a marker for central obesity, WC is a BMI-independent risk factor for GDM (88, 89), and appears to be an independent risk factor for giving birth to infants with macrosomia (90) and for preterm birth (91). Only a few studies have been published on the association between WC and pregnancy hypertensive disorders, including preeclampsia (88, 92-95). Most of these studies are relatively modest in size, and further replication is needed to demonstrate the usefulness of WC measurements in obstetric practice. Further, although WC is associated with central adipose tissue distribution and visceral fat, no study has claimed to investigate if WC is a BMI-independent risk factor for pregnancy hypertension disorders and if it can improve preeclampsia prediction models as compared with BMI.

Fat distribution in pregnancy

Several methods are established for estimating fat distribution in non-pregnant populations. Of those, computed tomography (CT) and magnetic resonance imaging (MRI) seem to provide the best estimates of visceral fat (96, 97). However, these methods are not practical during pregnancy; CT due to potentially harmful radiation for the fetus and because it is time-consuming and expensive. The use of ultrasonography to measure visceral and subcutaneous adiposity has been shown to be an alternative, non-invasive, risk-free method to the standard measurement with (98). It is also easy to incorporate in clinical practice at a routine gestational ultrasound, in the first or second trimester.

Thus far, ultrasound measurements of abdominal fat distribution during pregnancy have been performed only in small series. Abdominal fat distribution is usually measured as either subcutaneous adipose tissue (SAT) thickness or visceral adipose tissue (VAT) thickness, with different approaches in different studies. According to the studies at hand, visceral adiposity seems to be correlated with metabolic outcomes during pregnancy, such as GDM and glucose intolerance (99-101). Studies on the association between abdominal adipose tissue distribution and risk of hypertensive disorders in pregnancy have shown an association between central adipose tissue distribution, both SAT thickness and VAT thickness, and hypertensive disorders in pregnancy, including preeclampsia (101-103). SAT thickness has also been shown to be superior to BMI in predicting obesity-related pregnancy outcomes such as GDM, LGA and caesarean section (44). One large study suggested SAT thickness was an independent predictor of adverse pregnancy outcomes, even after adjustment for age, parity, smoking, and BMI (104). Lastly, during early pregnancy, an ultrasound measurement of visceral adiposity seems to correlate better than subcutaneous adiposity and BMI with metabolic risk factors, such as elevated blood pressure, insulin resistance, and hyperlipidemia (100). As most of the studies on ultrasound measurements of abdominal adipose tissue have been performed only in small series, and conflicting results have been found, this is an area in need of further research. Measuring fat distribution in pregnancy has a potential to identify obese women at higher risk of obesity-associated complications.

Obesity-associated pregnancy complications

Gestational hypertension

Gestational hypertension is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on two occasions at least 4 hours apart (105). Further, gestational hypertension starts at ≥ 20 weeks of gestation,

and should remit ≤ 12 weeks after delivery. The prevalence of gestational hypertension is estimated at 1.8–4.4% (106), but approximately 10% of women will have a blood pressure above normal recorded at some point before delivery (107). Up to half of all women who start with mild gestational hypertension will progress to preeclampsia during their pregnancies. If progression to preeclampsia occurs, it is highly related to gestational age at onset of hypertension (105).

Preeclampsia

Preeclampsia is defined as gestational hypertension in combination with one or more of the following conditions at or after 20 weeks of gestation: i) Proteinuria (i.e., ≥ 300 mg protein per 24 hours; ≥ 30 mg/mmol protein:creatinine ratio; or ≥ 2 + dipstick); ii) Maternal organ dysfunction, including acute kidney injury, liver involvement, neurological complications, or hematological complications; iii) Uteroplacental dysfunction (108, 109). Preeclampsia complicates about 1.2–4.3% of pregnancies (106), but incidence rates as high as 8% have been reported (107). The most severe form of preeclampsia is eclampsia. Many risk factors for developing preeclampsia are known, such as nulliparity, high BMI, maternal age, previous history of preeclampsia, and family history of preeclampsia (106). Paradoxically, smoking during pregnancy has been associated with reduced risk of preeclampsia (110).

Preeclampsia can have devastating complications for both the mother and the fetus. Hypertensive conditions during pregnancy account for 14–18% of all maternal deaths worldwide, with a great variation both across and within geographical regions (111, 112). Where maternal mortality is high, eclampsia seems to be the leading cause of death (107). Moreover, for every woman who dies, it is estimated that 20 others suffer severe morbidity (111). Preeclampsia is a multi-organ disease, as the central nervous system, lungs, liver, kidney, systematic vasculature, coagulation, and heart are all susceptible to excessive inflammation and endothelial damage (113).

Preeclampsia is nowadays often grouped into preterm and term preeclampsia, based on when birth occurs (< 37 gestational weeks or ≥ 37 gestational weeks). It has been speculated that the pathogeneses of preterm and term preeclampsia may differ (114). Preterm preeclampsia is more strongly associated with poor placentation, i.e., impaired remodeling of the spiral arteries, than term preeclampsia. Systematic maternal disease develops later during pregnancy, with an exaggerated endothelial activation and generalized hyper-inflammatory state compared with normal pregnancy. On the other hand, predisposing cardiovascular or metabolic risk of endothelial dysfunction, as part of an exaggerated systemic inflammation response, might dominate the origins of term preeclampsia (113).

Obesity is a well-established risk factor for preeclampsia, and substantial evidence shows that obesity confers a two- to ten-fold higher risk of developing preeclampsia (109, 115). Although obesity is a risk factor for both preterm and term preeclampsia, the association is stronger with term preeclampsia (116). The increasing prevalence of obesity has been linked to the increase in preeclampsia (117).

Preeclampsia is associated with intrauterine growth restrictions, as the blood flow to and over the placenta might be affected, and can precipitate preterm birth. International studies have estimated that preeclampsia is a causal factor for 12% of infants born small for gestational age (SGA) and 20% of preterm births (107).

Women with preeclampsia, in addition to being subject to the aforementioned risks during pregnancy, are at increased risk of developing CVD later in life (118). A large systematic review showed increased risk of chronic hypertension, ischemic heart disease, stroke, and venous thromboembolism (119). The risk of type-2 diabetes is also increased (120).

Preterm birth and fetal growth

Preterm birth is defined as birth before 37 gestational weeks. The incidence of preterm birth in the USA is about 12–13%, whereas in Europe and other high-income countries, the incidence is about 5–9% (121). Preterm birth can have a spontaneous onset or be iatrogenic with induced labor or caesarean delivery for maternal or fetal indication. Preeclampsia, gestational hypertension, and fetal growth restriction are well-known risk factors for iatrogenic preterm birth (122). The mechanism of spontaneous preterm birth is usually unknown, but there are a few known risk factors, including both high and low pre-pregnancy BMI (123, 124). Obese pregnant women have a higher risk of both spontaneous and iatrogenic preterm birth, with an increased risk of induced preterm birth of 30% (125). It remains uncertain if metabolic abnormalities in obese women contribute to this increased risk. Preterm births account for 75% of perinatal mortality and more than half of long-term morbidity (126).

Fetal growth during pregnancy is a sign of wellbeing and surveillance of fetal growth is an important part of antenatal care. When estimating birthweight, it is important to take gestational length into account. Low birthweight usually refers to infants who weight < 2,500 g at birth, and macrosomia to infant > 4,000 g. When poor growth is detected between two ultrasound measurements during pregnancy, intrauterine growth restriction is noted (127).

SGA is a statistical term that describes infants who have lower than expected weight in relation to gestational length and sex (127). The exact definition of

SGA is unclear, and multiple criteria have been used, most commonly the 10th, 5th, or 3rd percentile or 2 standard deviations (SDs) below the mean. The most common cause of SGA is inadequate nutrient supply caused by vascular insufficiency (128). However, most SGA infants are not growth-restricted at birth, and some infants with intrauterine growth restriction are born with weight appropriate for gestational age (AGA) (129). Large for gestational age (LGA) is a term similar to SGA, but describes infants with higher than expected weight. Usually, the definition of LGA refers to neonatal birthweight greater than the 90th percentile or 2 SDs above expected weight in relation to gestational length and sex. Maternal obesity has been associated with a more than two-fold increased risk of having an LGA infant (115), and high BMI, maternal diabetes mellitus, and excessive weight gain during pregnancy are the most common causes of LGA infants. Being born LGA or SGA have both been associated with increased risk of metabolic complications both early and late in life (128). Further, customized and conditional charts have been proposed as an alternative to population-based or reference charts, which are currently used for estimation of SGA and LGA (130). Such charts are based on ultrasound estimates of fetal growth, with adjustment for variables known to affect fetal weight and growth.

Gestational diabetes

GDM is the most common metabolic pregnancy disorder, with a prevalence of 3–15%, depending on which criteria are used for diagnosis (131). The protocols for screening for GDM differ between countries. In some countries, all pregnant women undergo an oral glucose tolerance test (OGTT), whereas in others, an OGTT is performed only in women with risk factors for GDM. In Sweden, the criteria have been strict and about 3% of pregnancies are considered to be complicated by GDM (132). GDM is defined as the type of glucose intolerance that develops in the second or third trimester of pregnancy, resulting in hyperglycemia of varying severity (133). Because of the increase in obesity, the prevalence of GDM is also rising. Women with hyperglycemia detected during pregnancy are at greater risk of many pregnancy complications, such as development of preeclampsia and macrosomia of the infant (131). GDM also raises the risk of long-term consequences, with increased risk of type-2 diabetes mellitus and CVD later in life (133, 134). According to WHO guidelines from 2006, GDM should be diagnosed if any of the following criteria are met:

- Fasting plasma glucose 5.1–6.9 mmol/l
- 1-hour plasma glucose ≥ 10.0 mmol/l following a 75 g oral glucose load
- 2-hour plasma glucose 8.5–11.0 mmol/l following a 75 g oral glucose load

In earlier guidelines from WHO (from 1999), the criteria for fasting plasma glucose was ≥ 7.0 mmol/l, which is universally considered to be too high (135). The prior WHO guidelines did not include any 1-hour plasma glucose measurement and the 2-hour plasma glucose reference was ≥ 7.8 mml/l. Unfortunately this older definition of GDM was used in the studies in this thesis, as the new guidelines had not been implemented into clinical practice when the studies were performed.

Depression

Obesity is associated not only with somatic conditions during pregnancy, but also with mental health problems. Depression and obesity are both widespread medical conditions with major public health implications. These two conditions often occur in the same individuals, with approximately one in four obese women also being depressed (136). A large systematic review and meta-analysis showed that being obese increased the risk of becoming depressed by 55% and individuals with depression had a 58% risk of becoming obese (137). A large meta-analysis examined whether depression was predictive of the development of overweight and obesity, and if overweight and obesity were predictive of the development of depression (137). It confirmed a reciprocal link between those two conditions, but it remains unclear what the mechanism of this causal relation is. It has been speculated that depressive individuals develop obesity over time via a dysregulated stress system or unhealthy lifestyles (138). On the other hand, obesity might lead to depressive symptoms over time through its negative effect on self-image or its somatic consequences. Notably, the association between obesity and depression is strongest among the most obese individuals (139).

The definition of peripartum depression is based on the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5): a major depressive disorder with peripartum onset, i.e., symptom onset during pregnancy or in the four weeks following delivery (140). From an endocrine and metabolic perspective, this definition is imperfect. A number of endocrine disturbances, which are ultimately very different between the pregnant and the postpartum states, may influence development or severity of depression. For research purposes, it is still relevant to consider the antenatal and postpartum depression disorders separately. In this thesis, antenatal depression refers to depressive symptoms during pregnancy. The estimates of the prevalence vary widely between studies, from 5% to 25% (141, 142). A large systematic review has estimated the prevalence to 11.9% (143) and a Swedish study by Rubertsson and colleagues suggested that 13.4% of women had signs of depression during pregnancy (144). The diagnosis of depression in pregnant women can be complicated due to overlap with normal pregnancy symptoms, such as sleep disturbances, fatigue, and changes in appetite. Studies have demonstrated that

depression is most likely underrecognized and undertreated in perinatal care (145, 146).

Increasing numbers of reports suggest that obesity is common among women with antenatal depression (147, 148). Despite the co-prevalence of obesity and depression, and the known risks of adverse pregnancy outcomes, their combined effects on maternal and neonatal health have not been widely studied. Two studies on this co-prevalence have suggested that maternal overweight/obesity and depression, when combined, have a greater impact on the risk of adverse maternal and neonatal outcomes, such as preterm birth, macrosomia, LGA, gestational hypertension, and preeclampsia (149, 150). One of them, a large Canadian study, showed that the prevalence of macrosomia and LGA infants was highest among overweight and obese women with comorbid depression (149).

Depression during pregnancy is associated with several adverse neonatal outcomes, including preterm birth and low birthweight (151). These complications may partly be explained by the fact that antenatal mental health problems are associated with a number of characteristics that increase the risk of low birthweight such as low socioeconomic status, smoking, and drug abuse (152-154). Indeed, a recent meta-analysis described a multifaceted picture, where socioeconomic status also influenced the relationship between antenatal depression and birthweight (151). The meta-analysis suggested that the relationship between birthweight and depression was stronger in women with a clinical diagnosis of depression than in women who merely reported depressive symptoms. However, conflicting findings regarding the relationship between antenatal depression and birthweight have also been noted. One Swedish report showed a borderline significant association between antenatal depressive disorder and increased birthweight, but no differences in other neonatal outcomes (155).

Preeclampsia prediction and prevention

One of the major challenges in obstetric care is predicting and preventing preeclampsia. As mentioned above, many individual risk factors for developing preeclampsia are known, although their individual predictive values are low. In screening for preeclampsia, evaluating individual factors is the traditional way to identify women at high risk of preeclampsia. According to guidelines from the National Institute for Health and Clinical Excellence (NICE) (156), women should be considered to have high risk of developing preeclampsia if they have any one high risk factor or any two moderate risk factors as described below:

High risk factors	Moderate risk factors
• Hypertensive disorder during a previous pregnancy • Chronic kidney disease • Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome • Diabetes type 1 or 2 • Chronic hypertension	• First pregnancy • Age ≥ 40 years • Pregnancy interval > 10 years • BMI ≥ 35 kg/m^2 at first visit • Family history of preeclampsia • Multiple pregnancy

To address this problem, efforts have been made to develop prediction models for preeclampsia, based on maternal characteristics and medical history (157). Most existing models also include various biophysical and biochemical markers (158). The most commonly used model is the one created by the Fetal Medicine Foundation, and is based on a survival time model for the time of delivery due to preeclampsia (Bayes' theorem) (159). This approach assumes that, if the pregnancy were to continue indefinitely, all women would experience preeclampsia and that whether they do so or not before a specified gestational age depends on competition between delivery before or after development of preeclampsia (157). In this model, the maternal demographic variables are maternal age, weight, height, race, smoking, conception by *in vitro* fertilization (IVF), chronic hypertension, diabetes mellitus type 1 or 2, systemic lupus erythematosus (SLE) or antiphospholipid syndrome, history of preeclampsia in previous pregnancy, and family history of preeclampsia. The model can be expanded to include mean arterial pressure (MAP), as well as uterine artery pulsatility index (PI), serum pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) (159). The full model detects preeclampsia at a screen-positive rate of 10%, with an area under the curve (AUC) of 0.777 for preeclampsia at ≥ 37 weeks, and 0.916 for preeclampsia at < 37 weeks.

The effect of aspirin in preventing preeclampsia was first noted as early as in 1979 (160). In 2017, a large placebo-controlled trial, using the full Fetal Medicine Foundation prediction model (158), studied the effect of low-dose aspirin in women at high risk of preeclampsia. The study showed that low-dose aspirin from 11 to 14 weeks of gestation until 36 weeks of gestation reduced the risk of preterm preeclampsia by 62% compared with placebo (161).

In Sweden, during the period when this thesis was written, prophylactic treatment with aspirin was only recommended to women with high risk of preeclampsia, based on individual predictors. Currently, aspirin prophylaxis

is also considered for women with moderate risk factors, but the use of an established prediction model based on maternal characteristics, biophysical and biochemical markers has not yet been implemented into clinical routine.

Why does obesity cause preeclampsia?

Obesity is a well-established risk factor for both preeclampsia and CVD. Increased BMI, even within the normal range, progressively increases the risk of preeclampsia. In fact, given the global epidemic of obesity, one might see obesity as one of the largest attributable and potentially modifiable risk factors for preeclampsia (162).

The mechanism that links obesity to preeclampsia is complicated and not completely understood. Many different mechanisms are found to explain the physiopathology of preeclampsia, and some of them are also seen in obesity. Of those, insulin resistance, inflammation, oxidative stress, and vascular dysfunction are the most studied (162, 163). Data suggest that the obese pregnant women with the greatest metabolic abnormalities have the highest incidence of preeclampsia (164).

Inflammation

In women with preeclampsia, altered invasion of cytotrophoblast cells into the uterus, leading to decreased remodeling of spiral arteries, causes lower perfusion of the placenta. This hypoxic condition in the placenta then causes release of various factors into the mother's blood circulation, such as tumor necrosis factor alpha (TNF-α) and anti-angiogenic soluble fms-like tyrosine kinase 1 (sFlt-1) factors (163). Circulating pro-inflammatory cytokines, such as TNF-α and interleukin 6 (IL-6), are elevated in women with preeclampsia (165). Both TNF-α and IL-6 are produced in adipose tissue. Elevated levels of TNF-α and IL-6 lead to a pro-inflammatory state characterized by insulin resistance and may contribute to endothelial dysfunction and oxidative stress associated with preeclampsia (163, 165). Studies on placental expression of TNF-α and IL-6 have not indicated any difference between women with or without preeclampsia, which could indicate that adipose tissue production of these cytokines contributes to the elevated plasma levels shown in women with preeclampsia (166).

CRP is an acute phase protein produced in the liver and in adipose tissue (167). Its production is stimulated by TNF-α and IL-6, and it is a sensitive index of systemic inflammation due to its relatively short half-life (168). Wolf et al. showed an association between CRP levels in the first trimester and

preeclampsia, but when BMI was added to their multivariable model, the association disappeared (168). As BMI has been associated with higher levels of CRP, this might indicate that obesity and CRP share a common pathway through inflammation to preeclampsia (169).

sFLt-1 is an anti-angiogenic factor that works though binding to placental growth factor (PGF) and preventing its interaction with endothelial receptors, thereby inducing endothelial dysfunction (170). Levels of PGF are lower in women with preeclampsia (162). Results in studies of levels of sFlt-1 in obese pregnant women have not been consistent. An association between higher BMI and higher sFlt-1 levels has been shown (171), but other studies have shown lower levels of both PGF and sFlt-1 with increasing BMI (172). Such a change in the angiogenic environment contributes to the development of preeclampsia, but how obesity influences this change remains uncertain.

Leptin and adiponectin

Leptin and adiponectin are adipocytokines or hormones produced mainly by adipocytes in WAT. They are currently the only endocrine hormones generally accepted as such (56). Their function is in regulation of lipid metabolism, angiogenesis, insulin sensitivity, and in inflammatory processes (173). It has been speculated that adipocytokines might be involved in the mechanism of implantation during pregnancy, and thereby play a role in the pathogenesis of preeclampsia (174).

Leptin is a peptide hormone secreted mainly by adipocytes and has a pro-inflammatory activity (175). Higher levels of serum leptin are found in obese individuals and circulating levels of leptin reflect adipose tissue size (163, 175, 176). Leptin is produced in large amounts from the placenta during pregnancy. Elevated levels of leptin are seen in pregnant women compared with non-pregnant women, and the levels are even higher in pregnant women who develop preeclampsia (177). These higher levels of leptin in women with preeclampsia have been shown even after adjustment for BMI, indicating that leptin can be a potential mediating factor between BMI and preeclampsia (178). The role of leptin in the pathogenesis of preeclampsia is, however, not obvious. Reduced placental perfusion, causing a hypoxic state, increases placental expression of leptin, potentially as a coping mechanism to increase nutrition delivery to the fetus (178). Increased levels of leptin can be seen even before clinical manifestation of preeclampsia (175).

Adiponectin has an anti-inflammatory activity and insulin-sensitizing effect and is inversely associated with obesity (162, 163, 174). During normal pregnancy, a progressive increase in insulin resistance is normal, and plasma adi-

ponectin levels subsequently decrease during pregnancy (179). Conflicting results have been reported regarding the association between adiponectin and preeclampsia, as some have stated that lower adiponectin can predict preeclampsia (180), whereas others have shown elevated levels of adiponectin in women with manifest preeclampsia (181). Lower adiponectin levels are associated with GDM independently of BMI. Adiponectin may thus represent an alternative process for insulin resistance, as a link between obesity and preeclampsia (182).

Oxidative stress and the role of nitric oxide

Nitric oxide (NO) is a gas produced from arginine by NO synthases (183). It plays an important role in increasing blood flow through relaxation of vascular smooth muscle. Endothelial dysfunction associated with obesity is partly mediated through reduced endothelial NO production (163). Leptin, produced in adipose tissue, activates nicotinamide adenine dinucleotide phosphate oxidase, which impairs endothelium-dependent vasodilation by increasing NO degradation (184). Both these mechanisms lead to decreased NO levels, which affects the function of the endothelium. Increased production of NO in vascular endothelial cells during normal pregnancy causes peripheral vasodilation (185). Studies have shown that endothelial NO synthase is expressed in the placenta and thus production of NO from the placenta plays an important role in vascular adaption during pregnancy (186). Generalized peripheral vasoconstriction is seen in the development of preeclampsia, and lower production and increased inactivation of NO is an important part of this process (185). Further study of the biological links between obesity and development of preeclampsia is clearly needed.

Aims

The overall aim of this thesis was to increase the capacity for early pregnancy prediction of development of obesity-related late adverse pregnancy outcomes in women with overweight and obesity based on BMI.

The specific aims of the studies were:

I To investigate if maternal BMI in early pregnancy moderated antenatal depression effects on infant birthweight.

II To investigate if the MHO/MUO classification of women with obesity at the beginning of pregnancy could be used for prediction of obesity-related late adverse pregnancy outcomes in pregnancy.

III To investigate the association between early pregnancy WC and preeclampsia, taking early pregnancy BMI into account.

IV To investigate if VAT thickness or SAT thickness at the routine ultrasound in gestational week 17–19 could be used as a predictor of preeclampsia.

Materials and methods

Overview of the studies

This thesis consists of four studies described in Table 2.

Table 2. *Overview of the studies.*

Study	Study design	Study population	Exposure	Outcome
I	Retrospective population-based cohort study	3,965 pregnant women in Uppsala	Depression and BMI	Birthweight
II	Retrospective population-based cohort study	547 pregnant women with obesity in Uppsala	MHO/MUO	Pregnancy complications *
III	Prospective population-based cohort study	4,696 pregnant women in Uppsala	Waist circumference	Preeclampsia
IV	Prospective population-based cohort study	3,777 pregnant women in Uppsala	Visceral and subcutaneous adipose tissue	Preeclampsia

* Gestational hypertension, preeclampsia, gestational diabetes, preterm birth (< 37 weeks), spontaneous preterm birth, postpartum hemorrhage, small for gestational age, large for gestational age, asphyxia, or a composite outcome of any of the aforementioned complications.

Ethics

All studies were approved by the Ethical Review Board of Uppsala, Sweden; Study I, Dnr 2009/171; Study II, Dnr 2007/181 and Dnr 2014/353; Study III, Dnr 2014/363 and Dnr 2015/366; and Study IV, Dnr 2014/353.

Data sources

The BASIC study

The BASIC project (Biology, Affect, Stress, Imaging and Cognition in the Puerperium) is a population-based, longitudinal study of psychological well-being during pregnancy and the postpartum period in Uppsala County, Sweden. It has been ongoing since 2009. The main aim of the study is to investigate social and biological parameters in relation to peripartum depression. An invitation to the BASIC study is sent out together with the invitation for the routine ultrasound examination at around 17 weeks of gestation. Exclusion criteria for the BASIC study are (1) inability to communicate adequately in Swedish, (2) having confidential personal data, (3) having a pathologic pregnancy, as diagnosed by routine ultrasound (miscarriage or congenital malformation), and (4) being younger than 18 years. The participation rate in the BASIC study is approximately 22%. In general, there seems to be an overrepresentation of older mothers with higher education compared with the general female Swedish population.

At gestational weeks 17 and 32, all women who gave informed consent to participate in the study receive web-based, self-administered structured questionnaires containing questions on demographic variables, smoking, prior psychiatric history, ongoing medication, and the Swedish validated version of the Edinburgh Postnatal Depression Scale (EPDS). They also filled out the same questionnaires at 6 weeks, 6 months, and 12 months postpartum. The EPDS is an internationally used 10-item self-report questionnaire, designed to identify depressive symptoms in the peripartum period (187). While the sensitivity of the EPDS scale is relatively low, between 0.47–0.71, the specificity as regards depressive disorders is excellent (pooled specificity 0.94–0.98) (188). The BASIC database is regularly updated with information from the standardized antenatal and obstetric medical records, including clinical variables like BMI and weight, obstetric diagnoses, and information on infant sex and birthweight.

The Uppsala Biobank

The Uppsala Biobank of Pregnant Women is a population-based biobank. Blood samples are collected in conjunction with routine ultrasound screenings when a research nurse is available. Eligible women are 18 years or older, Swedish speaking, and without blood-borne disease. In Uppsala County, all routine ultrasound examinations are performed at Uppsala University Hospital, which is the only delivery ward in the county. Women are invited to participate in the biobank at the time of their routine ultrasound screening in gestational week 17–19. The biobank is considered population-based as 97% of the

pregnant population participates in the routine ultrasound examination (189). Approximately 70% of the respondents consent to participation, and it is estimated that the biobank covers approximately half of the pregnant population of Uppsala County (a research nurse is not always available) (190). Upon inclusion, brief demographic data are collected, including ongoing chronic disorders, medication, smoking, and height and weight. The blood samples are collected in ethylenediaminetetraacetic acid (EDTA)-containing tubes and centrifuged at 1,500 g for 10 min. Plasma and buffy coat are separated within two hours and stored at -70 °C.

National registers

The Swedish National Board of Health and Welfare provided access to information from the Swedish Medical Birth Register. The Medical Birth Register contains data on 98% of all births at gestational week 22 or later in Sweden and includes prospectively collected data from the standardized antenatal, obstetric, and pediatric medical records, including reproductive history, smoking status, and complications that occur during pregnancy, delivery, or the neonatal period. Complications during pregnancy and delivery are classified based on the International Classification of Disease 10th revision (ICD-10), as noted by the obstetrician in charge at discharge from the hospital.

Statistics Sweden provided data on educational level and maternal origin from the Education Register and the Register of the Total Population, respectively. Individual record linkage between registers was made possible by the use of the unique personal registration numbers assigned to Swedish residents at birth or upon immigration (191, 192).

Study populations and exposures

Study I

For Study I, the research team used information from the population-based BASIC study. A total of 3,965 pregnant women with complete information on BMI and child's birthweight were included. Women were considered to suffer from antenatal depression if they reported EPDS scores ≥ 17, either in gestational week 17 or in gestational week 32. The relatively high cut-off was based on a recent report from the Postpartum Depression: Action Towards Causes and Treatment Consortium, suggesting an EPDS score ≥ 17 as being indicative of moderate to severe depression (193). A previous meta-analysis on neonatal outcomes in women with antenatal depression suggested that the relationship between child's birthweight and depression was stronger in women with a clinical diagnosis of depression (151).

Information on maternal clinical variables, pregnancy complications, and perinatal outcomes was extracted from the standardized antenatal, obstetric, and pediatric medical records. Obstetric diagnoses based on ICD-10 codes are recorded in the obstetric medical records.

The BASIC project has a relatively low response rate and is thus susceptible to selection bias. To ensure that the outcomes (birthweight and LGA) were equally common as in the remaining population, information from the Medical Birth Register was used. The study included all mothers with singleton pregnancies, giving birth between January 1 2009 and December 31 2014, in Uppsala County (n = 23,352) and the rest of Sweden (n = 625,118).

Study II

Data for this retrospective cohort study were derived from the population-based Uppsala Biobank of Pregnant Women. For this study, women with singleton pregnancies and obesity (BMI > 30.0 kg/m^2) at the first antenatal visit in gestational week 10–12 were included. We included all women with morbid obesity (BMI ≥ 35 kg/m^2, n = 257), and a random selection of women with obesity (BMI 30–34.99 kg/m^2, n = 343), yielding a study population of 600 women. We further excluded women with obesity who had pre-pregnancy hypertension (n = 21), pre-pregnancy diabetes (n = 4), SLE (n = 2), and previous history of preeclampsia (n = 25) because of their known risk of maternal and fetal adverse outcomes (194-197). One blood sample could not be retrieved, leaving a study population of 547 women with obesity.

All blood samples were analyzed for the following known cardiovascular markers: leptin, endostatin, cathepsin S, TNF R1, pentraxin-related protein 3 (PTX-3), adiponectin, calprotectin, alanine transaminase (ALAT), high-sensitive CRP, cystatin C, apolipoprotein A1 (apoA1) and apolipoprotein B (apoB).

During the same time-period, 9,989 women with singleton pregnancies and BMI 18.5–29.99 kg/m^2 had been included in the biobank. After application of the same exclusion criteria as for the women with obesity, a comparison group of 8,154 women remained. Of these, 5,852 (67.3%) were normal weight (BMI 18.5–24.99 kg/m^2) and 2,302 (26.5%) were overweight (BMI 25.0–29.99 kg/m^2).

Information on maternal clinical variables, pregnancy complications, and perinatal outcomes was obtained from the standardized antenatal, obstetric, and pediatric medical records. Maternal BMI, blood pressure, and non-fasting capillary glucose levels at the first antenatal visit were noted. Lastly, obstetric

diagnoses based on ICD-10 codes, as recorded in the obstetric medical records by the discharging obstetrician, were noted.

Women were defined as having a metabolic factor if they had any one of following:

i) systolic blood pressure > 130 mmHg at the first antenatal visit,
ii) diastolic blood pressure > 85 mmHg at the first antenatal visit,
iii) non-fasting capillary glucose > 6.8 mmol/l at first antenatal visit, or
iv) dyslipidemia defined as an apolipoprotein B/apolipoprotein A1 (apoB/apoA1) ratio > 0.8, analyzed in the stored biobank sample.

Women were classified as MUO if they had *at least one* metabolic factor.

The cut-off for hypertension was based on the US NCEP-ATPIII criteria (17). The cut-off for non-fasting capillary glucose corresponded to the 97.5th percentile of all non-fasting glucose values from the first visit among normal-weight women in the biobank database (n = 5191). The apoB/apoA1 ratio was used instead of plasma cholesterol or triglycerides levels, as lipoproteins are less affected by food intake (198). The cut-off for the apoB/apoA1 ratio was based on literature, suggesting that a ratio above 0.8 is associated with high risk of developing cardiovascular events (199). The research team chose non-fasting glucose and apoB/apoA1 ratio, as women in the biobank had donated blood samples at different times during the day, and most were non-fasting.

Study III

WC measurements during pregnant women's first antenatal visits were implemented and data for this prospective population-based cohort study were collected between 5 January 2015 and 29 December 2017. During that time, WC was measured in 5,827 pregnancies. Women with miscarriage, abortion, or missing information on delivery (n = 590) were excluded. The data were linked to the Medial Birth Register, and 60 pregnancies were excluded because linkage failed. The team also excluded pregnancies with missing data on BMI (n = 49), pregnancies with multiple births (n = 155), and pregnancies in women already included in the cohort during the study period (n = 277). The final study population consisted of 4,969 singleton pregnancies in women with available information on early pregnancy BMI and WC, which resulted in birth after 22 gestational weeks or more (see Figure 3).

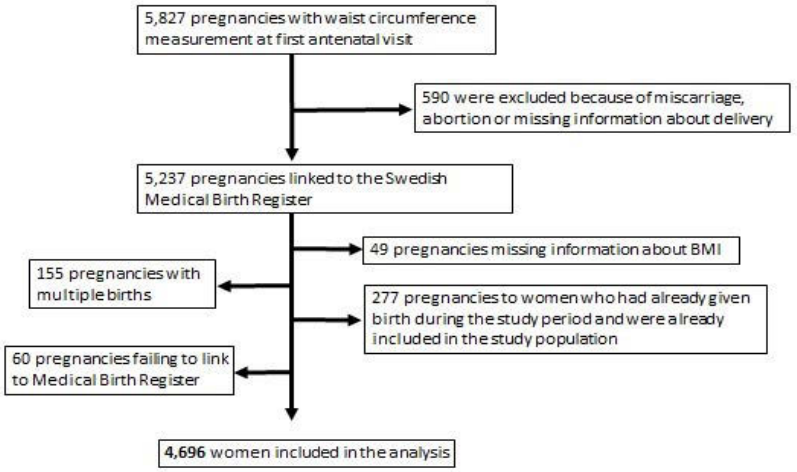

Figure 3. Study population in Study III.

WC was measured at the first antenatal visit. The mean time-point for measurement was 9.1 gestational weeks (SD 2.2 weeks). The measurement was done with a standardized tape, midway between the lower rib margin and the iliac crest, with the woman in a standing position. All midwives making measurements were given verbal and written information on how to perform the measurements.

Study IV

Data for this study were prospectively collected from women who did their routine ultrasound at Uppsala University Hospital from 2 January 2015 to 17 January 2019, n = 4,038. The research team excluded women in whom measurement was not possible because of lack of visualization of the rectus musculature (n = 12), women who could not be followed up because of temporary or confidential medical records (n = 11), and women who moved during the study time or did not give birth in Uppsala (n = 191). Women with late miscarriages (n = 4), twin pregnancies (n = 8), chronic hypertension (n = 9), pre-pregnancy diabetes type 1 or 2 (n = 22), or SLE (n = 4) were also excluded. That left a study population of 3,777 pregnant women (see Figure 4).

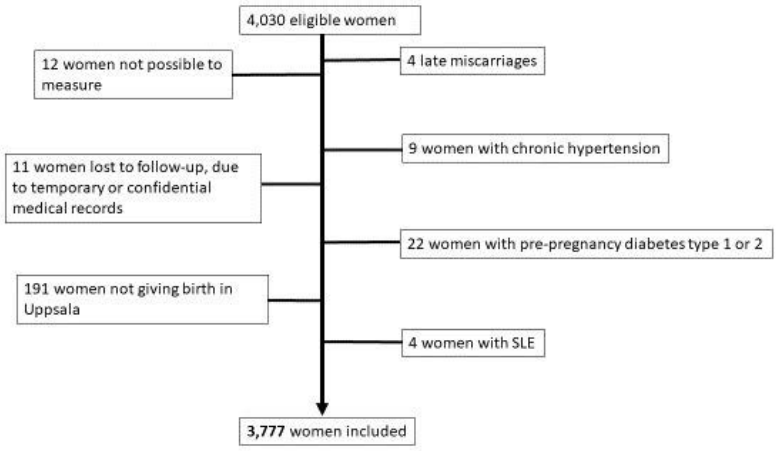

Figure 4. Study population in Study IV.

Information on maternal clinical variables, pregnancy complications, and perinatal outcome was obtained from the standardized antenatal, obstetric, and pediatric medical records. Maternal BMI and blood pressure at first antenatal visit were noted. In addition, obstetric diagnoses based on ICD-10, as recorded in the obstetric medical records by the discharging obstetrician, were noted.

During the routine ultrasound at gestational week 17–19, the ultrasound midwife also measured and registered the women's abdominal subcutaneous and visceral fat. The midwives were trained to perform those measurements based on the method described by Armellini and colleagues (200) (see Figure 5). As described, the ultrasound measurements were made at 10 cm above the level of the umbilicus. The SAT thickness was measured from the inner border of the skin down to linea alba, the connecting part between the abdominal rectus musculature in midline. VAT thickness was measured from the posterior edge of the linea alba to the anterior aortic wall. The measurements were documented in millimeters and ultrasound images were saved in an ultrasound data program. The VAT/SAT ratio was calculated based on the measurements.

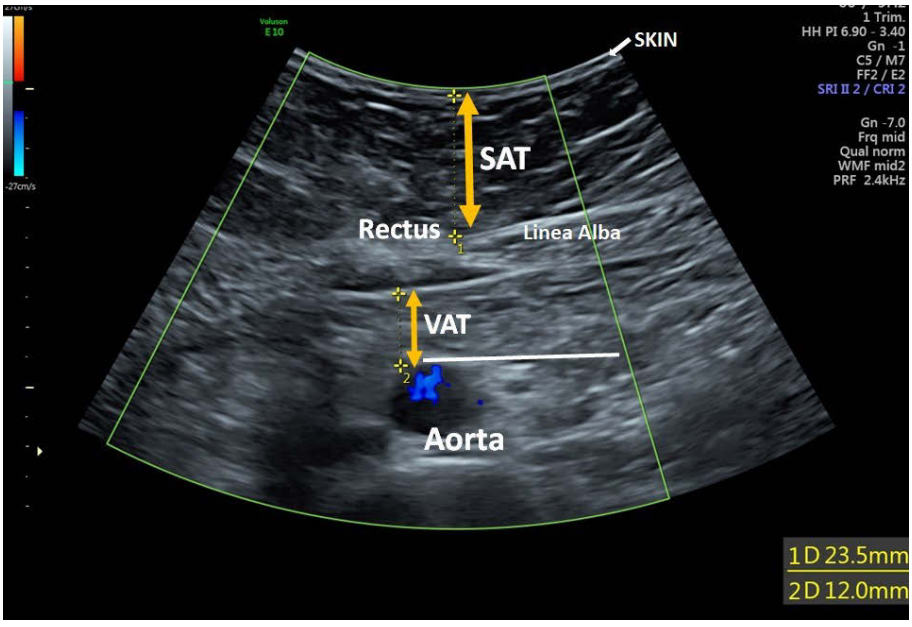

Figure 5. Adipose tissue measurement made 10 cm below the umbilicus. The subcutaneous adipose tissue thickness (SAT) was measured from the inner border of the skin down to linea alba. The visceral adipose tissue thickness (VAT) was measured from the posterior edge of the linea alba to the anterior aortic wall.

Definition of outcomes

Study I

Standardized birthweight scores were calculated based on gestational age and sex-specific Swedish birthweight curves (201). SGA and LGA were defined as a birthweight of more than two SDs below or above the mean weight for gestational age, respectively, based on the ultrasonically estimated fetal weight reference curve (201).

Study II

The obesity-associated outcomes were gestational hypertension (*de novo* hypertension after 20 weeks gestation), preeclampsia (gestational hypertension in combination with proteinuria), and GDM (based on the WHO criteria from 1999). Further, preterm birth (< 37 weeks of gestation), spontaneous preterm birth, postpartum hemorrhage (> 1,000 ml blood loss during delivery or within the first 2 hours after delivery), SGA (< 5^{th} percentile), LGA (> 5^{th} percentile), asphyxia (Apgar score < 7 after 5 minutes or pH in umbilical artery ≤ 7.05),

or a composite outcome consisting of *any of the aforementioned* complications. Definitions of gestational hypertension, preeclampsia, and GDM are described in detail in the background.

All laboratory analyses were performed at the Clinical Chemistry Laboratory, Uppsala University Hospital. ALAT, apoA1, apoB, and hsCRP were analyzed on BS380 instrument (Mindray) with reagents from Abbott Laboratories. Calprotectin and cystatin C were analyzed on Mindray BS-380 with reagents from Gentian. Adiponectin, cathepsin S, endostatin, leptin, PTX-3, and TNF R1 were analyzed with sandwich ELISA kits from R&D Systems.

Studies III and IV

The main outcome was preeclampsia defined as *de novo* hypertension after 20 weeks of gestation in combination with proteinuria. Hypertension was defined as systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg measured on two subsequent occasions, at least 6 hours apart, and proteinuria was defined as ≥ 2+ on a dipstick or ≥ 300 mg/24 h in a urine collection.

Preeclampsia was further defined as being preterm (< 37 weeks) or term (≥ 37 weeks), based on when birth occurs.

Statistical methods

Demographic and clinical variable comparison

In all four studies, comparisons of demographic and clinical variables between women with and without the outcome were performed using independent t-tests or chi-squared tests.

Study I

Comparisons between depressed and non-depressed women were performed using independent t-tests and chi-squared tests. Correlations were analyzed using Spearman's rank correlation, as self-rated depression scores failed to meet the assumption of normal distribution.

The influence of maternal BMI and antenatal depression on standardized birthweight (continuous, and LGA [yes/no]) was evaluated by analysis of covariance (ANCOVA) or logistic regression. In both analyses, BMI (categorized as BMI < 25.0 kg/m^2 vs. BMI ≥ 25.0 kg/m^2) and depression status (yes/no) were entered as fixed factors, evaluating the main effects of BMI and

depressive symptoms as well as the interaction between these two factors. The BMI cut-off was chosen to capture overweight and obesity, and to yield relatively comparable group sizes.

The analysis of covariance and logistic regression models were adjusted for age (continuous), parity (nulliparous vs. parous), maternal height (continuous), maternal education (more or less than 12 years of education), maternal origin (Nordic vs. non-Nordic), and smoking (yes/no), and in a second step with BMI as a continuous variable. These covariates were chosen based on the findings in the bivariate analyses, whereas smoking and age were forced to the models based on previous literature (152).

A follow-up linear regression model was created using dummy variables corresponding to 1) normal-weight, non-depressed women (reference), 2) normal-weight women with depressive symptoms, 3) overweight non-depressed women, and 4) overweight women with depressive symptoms. The regression model was devised in two steps: model 1 incorporating potential confounders as described above, and model 2 incorporating weight gain in gestational week 32 as a potential mediator.

Study II

The impact of the metabolic factors on obesity-associated outcomes was evaluated using logistic regression. The research team estimated adjusted odds ratios (AORs) and corresponding 95% confidence intervals (CIs) for adverse obstetric and neonatal outcomes, with adjustment for parity and smoking in the models that incorporated the normal- and overweight comparison groups. Additional adjustment for maternal first-trimester BMI was incorporated into the models comparing women with MUO and MHO. Nagelkerke values from the logistic regression analyses are presented as estimates of the predictive powers of the models.

Linear regression analyses were used to compare the cardiovascular risk markers between women with MUO and MHO. These analyses were adjusted for BMI. PTX-3, calprotectin, ALAT, and high-sensitive CRP were not normally distributed and were log-transformed prior to the analyses.

Study III

Correlation between BMI and WC was visualized in a scatterplot and calculated using Pearson's t-tailed correlation test.

The association between WC in early pregnancy and risk of preeclampsia was estimated with logistic regression analyses. The research team estimated crude

odds ratios (ORs) and AORs and corresponding 95% CIs. Established predictors from the NICE guidelines (156) and the Fetal Medicine Foundation model (159) for preeclampsia were used as confounders. Variables included in the adjusted model were maternal BMI, age, parity, smoking, country of birth, chronic hypertension, diabetes mellitus type 1 or 2, SLE, chronic kidney disease, history of preeclampsia in past pregnancy, conception with ovarian stimulation or IVF, and MAP. Models were created in two steps, first without BMI, and then with the addition of BMI.

To predict the influence of adding WC to the model, c-statistical analyses were performed by generating receiver operating characteristic (ROC) curves. The AUC was used to compare the models. The likelihood ratio test was used to estimate if WC statistically influenced the models.

Study IV

Correlations between BMI and SAT thickness and VAT thickness, respectively, were calculated with Person's t-tailed correlation test.

The risk of developing preeclampsia in relation to SAT thickness and VAT thickness was evaluated through multiple logistic regression analyses. AORs and corresponding 95% CIs were estimated. Possible confounders were identified by drawing a directed acyclic graph (DAG). The minimal sufficient adjustment sets for estimating the direct effects of SAT thickness and VAT thickness on preeclampsia suggested adjustment for age, BMI, country of origin, smoking, and parity.

Across all studies, the statistical analyses were done using IBM SPSS Statistics, versions 24, 25, and 27. The likelihood ratio test in Study III was performed using R 4.0.5.

Results

Study I

The study population differed from the general female population of Uppsala County and the rest of Sweden in that it had a higher educational level and a lower rate of women with non-Nordic origin. Maternal BMI, child's birthweight, and prevalence of LGA infants were similar to those in the general female population.

Overall, 178 (4.5%) women were classified as depressed, with the remaining women (n = 3,787) classified as non-depressed. Depressed women were younger, less often cohabiting, had a lower educational level, and were less often of Nordic origin. They had a similar BMI distribution and similar standardized birthweight of their infants as the non-depressed women, although they gave birth to infants with lower birthweight.

Following adjustment for confounders, a significant interaction between BMI and depression status was noted, $F(1.3840) = 6.82$; $p = 0.009$. This interaction remained unchanged when BMI, as a continuous variable, was also entered into the model, $F(1.3839) = 6.32$; $p = 0.012$, Figure 6.

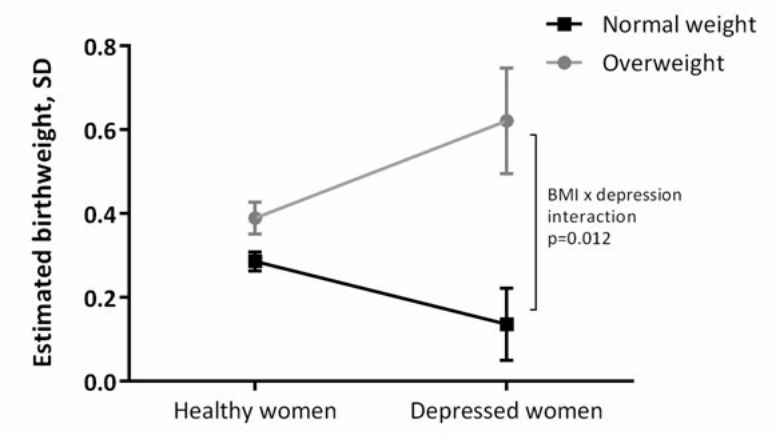

Figure 6. Interaction between maternal BMI and antenatal depression on standardized birthweight.

The interaction was primarily driven by depressed women with BMI of ≥ 25 kg/m^2, who gave birth to infants with greater birthweight than non-depressed overweight women, whereas the opposite pattern was noted in normal-weight women, Table 3 (model 1). When weight gain was entered into the linear regression analysis on the influence of BMI and depressive symptoms on standardized birthweight, the estimates were only marginally changed, Table 3 (model 2).

When using LGA as an outcome instead of standardized birthweight, a significant interaction between antenatal depression and maternal BMI was also noted: AOR 3.73 (95% CI 1.62–8.51). This interaction did not remain following adjustment for BMI as a continuous variable: AOR 2.09 (95% CI 0.98–4.98).

Table 3. *Multivariable linear regression analysis on the interaction between maternal BMI, antenatal depression, and standard birthweight scores in the primary study population. Model 1 adjusted for known confounding factors, Model 2 adjusted also for gestational weight gain as a potential mediator of the relationship.*

Model 1	Unstandardized β (95% CI)	*P*
Normal BMI, depressive	-0.14 (-0.31–0.30)	0.106
Overweight, non-depressive	0.32 (0.25–0.38)	< 0.001
Overweight, depressive	0.59 (0.34–0.83)	< 0.001
Model 2	Unstandardized β (95% CI)	*P*
Normal BMI, depressive	-0.15 (-0.32–0.02)	0.094
Overweight, non-depressive	0.35 (0.28–0.42)	< 0.001
Overweight, depressive	0.64 (0.40–0.88)	< 0.001
Weight gain in gestational week 32	0.04 (0.04–0.05)	< 0.001

Study II

Among the pregnant women with obesity, 366 (66.9%) were categorized as MHO and 181 (33.1%) as MUO. The most common metabolic factor in the MUO women was high blood pressure (n = 118, 65.2%), while one-third had dyslipidemia (n = 60, 33.1%), and 24 (13.3%) had elevated non-fasting capillary glucose levels. Women with MUO had higher first-trimester BMI and more often had polycystic ovary syndrome than women with MHO.

Overall, 45.9% of women with MUO developed at least one obesity-associated adverse obstetric outcome. The corresponding proportion in women with

MHO was 35.0%, in women with overweight 27.6%, and in normal-weight women 21.2%. Prior to adjustment for BMI, women with MUO had a greater risk of gestational hypertension, preeclampsia, GDM, preterm birth, and delivering LGA infants in comparison with women with MHO, overweight or normal weight.

Following adjustment for BMI, parity, and smoking, the overall risk of any adverse obesity-associated obstetric or perinatal outcome in women with MUO was increased in comparison with women with MHO, AOR 1.49 (95% CI 1.03–2.15), Table 4. Among the individual obstetric and perinatal outcomes, only the risk of preterm birth (all causes) was increased in women with MUO compared with MHO women, AOR 2.47 (95% CI 1.15–5.28). The predictive power of the MUO classification was low in all models, with Nagelkerke values ranging from 3.1% to 13.2%.

Women with MHO had increased risk compared with overweight women of any adverse obstetric or perinatal outcome, AOR 1.43 (95% CI 1.13–1.81). Among the individual obstetric and perinatal outcomes, the risk of gestational hypertension (AOR 2.52, 95% CI 1.50–4.22), GDM (AOR 6.33, 95% CI 2.49–16.11), and LGA (AOR 1.72, 95% CI 1.27–2.32) was increased in women with MHO compared with women with overweight, Table 4.

Table 4. *Multivariable logistic regression analyses on pregnancy complications in women with MHO and MUO in comparison with overweight and normal-weight women.*

		Cases, n (%)	AOR[a] (95% CI)	AOR[a] (95% CI)	AOR[b] (95% CI)	Nagelkerke[c]
Any obesity-associated complication	Normal weight	1241 (21.2)	1			
	Overweight	636 (27.6)	**1.45 (1.29–1.62)**	1		
	MHO	128 (35.0)	**2.07 (1.65–2.59)**	**1.43 (1.13–1.81)**	1	
	MUO	83 (45.9)	**3.20 (2.37–4.33)**	**2.24 (1.65–3.04)**	**1.49 (1.03–2.15)**	0.041
Specific obesity-associated complications						
Gestational hypertension	Normal weight	101 (1.7)	1			
	Overweight	57 (2.5)	**1.54 (1.11–2.14)**	1		
	MHO	21 (5.7)	**3.93 (2.42–6.39)**	**2.52 (1.50–4.22)**	1	
	MUO	22 (12.2)	**8.47 (5.18–13.86)**	**5.49 (3.26–9.25)**	1.82 (0.95–3.51)	0.132
Preeclampsia	Normal weight	137 (2.3)	1			
	Overweight	87 (3.8)	**1.76 (1.34–2.32)**	1		
	MHO	17 (4.6)	**2.27 (1.35–3.81)**	1.28 (0.75–2.19)	1	
	MUO	17 (9.4)	**4.52 (2.65–7.70)**	**2.56 (1.48–4.43)**	1.91 (0.94–3.89)	0.066

Gestational diabetes	Normal weight	15 (0.3)	1			
	Overweight	9 (0.4)	1.44 (0.63–3.30)	1		
	MHO	9 (2.5)	**9.01 (3.89–20.87)**	**6.33 (2.49–16.11)**	1	
	MUO	10 (5.5)	**22.34 (9.85–50.69)**	**15.59 (6.23–39.05)**	2.46 (0.97–6.28)	0.069
Preterm birth (< 37 weeks)	Normal weight	261 (4.5)	1			
	Overweight	87 (3.8)	0.85 (0.66–1.09)	1		
	MHO	14 (3.8)	0.83 (0.48–1.43)	0.97 (0.55–1.74)	1	
	MUO	15 (8.3)	**1.86 (1.08–3.20)**	**2.23 (1.26–3.95)**	**2.47 (1.15–5.28)**	0.043
Spontaneous preterm birth	Normal weight	162 (2.9)	1			
	Overweight	57 (2.5)	0.90 (0.66–1.22)	1		
	MHO	10 (2.7)	0.96 (0.50–1.83)	1.05 (0.53–2.08)	1	
	MUO	7 (3.9)	1.39 (0.64–3.01)	1.56 (0.70–3.49)	1.71 (0.63–4.65)	0.048
LGA	Normal weight	366 (6.2)	1			
	Overweight	267 (11.6)	**1.89 (1.60–2.24)**	1		
	MHO	66 (18.0)	**3.25 (2.43–4.34)**	**1.72 (1.27–2.32)**	1	
	MUO	29 (16.0)	**2.97 (1.96–4.51)**	**1.58 (1.03–2.41)**	0.80 (0.49–1.32)	0.085

[a]Adjusted for parity and smoking.
[b]Adjusted for maternal BMI, parity, and smoking.
[c]Nagelkerke value reported for the comparison between MHO and MUO individuals.

Women with MUO had higher levels of cathepsin S, and lower levels of adiponectin, compared with women with MHO. Women with MUO also had increased cystatin C and decreased estimated GFR compared with women with MHO, Figure 7.

Figure 7. Cathepsin S, adiponectin, and cystatin C serum concentrations in women with MUO (n = 181) and MHO (n = 366). Adjusted for BMI. P-values presented in relation to each biomarker.

Study III

Among the 4,696 women in the study population, 209 (4.5%) developed preeclampsia. The women who developed preeclampsia were younger, more often nulliparous, and had a higher BMI in early pregnancy. They had higher mean arterial pressure in early pregnancy and more often had a history of preeclampsia and pre-pregnancy diabetes mellitus. Pregnancies complicated with preeclampsia had shorter mean gestational length at birth, and the women with preeclampsia gave birth to smaller infants.

WC had a strong positive correlation with BMI, $r = 0.82$, $p \leq 0.001$ (Figure 8).

Women with preeclampsia had a larger WC (85.8 ± 12.6 cm) compared with women without preeclampsia (82.3 ± 11.3 cm), $p < 0.001$. Risk of preeclampsia increased by 2% for every centimeter increase in WC. Stratified by cut-offs of WC, women with WC over 80 cm had a 69% increased risk of preeclampsia and women with WC over 88 cm had a 68% increased risk. After adding known risk factors into the model (model 1), the association between WC and preeclampsia showed a similar pattern, but when BMI was added into the model (model 2), the association was lost, Table 5.

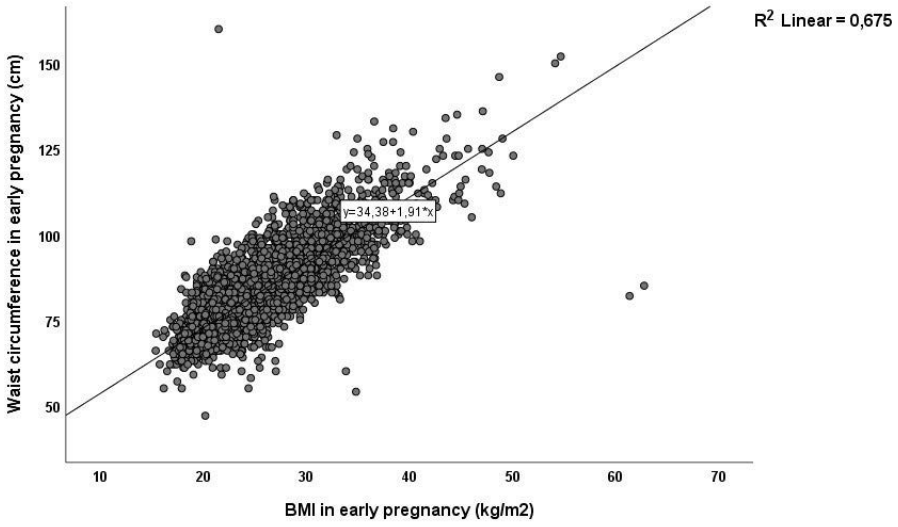

Figure 8. Correlation between BMI and waist circumference in early pregnancy.

Following the logistic regression, comparisons of AUC values for models including BMI, with and without adding WC, were 0.738 (95% CI 0.704–0.771) and 0.739 (95% CI 0.705–0.773), respectively, $p = 0.318$. When excluding BMI from the model, testing only the model with WC, the AUC remained unchanged at 0.739 (95% CI 0.705–0.773).

Table 5. *Association between waist circumference in early pregnancy and risk of developing preeclampsia. Risk is presented as odds ratios (ORs) and illustrates increased risk of preeclampsia for each centimeter increase in waist circumference, and stratified by waist circumference cut-offs > 80 cm and > 88 cm.*

	OR (95% CI)	*P*	Model 1 AOR (95% CI)[a]	*P*	Model 2 AOR (95% CI)[b]	*P*
Waist circumference (cm)	1.02 (1.01–1.04)	**< 0.001**	1.02 (1.01–1.03)	**0.001**	1.01 (0.99–1.04)	0.318
Waist circumference > 80 cm	1.69 (1.27–2.25)	**< 0.001**	1.59 (1.16–2.17)	**0.005**	1.32 (0.90–1.93)	0.155
Waist circumference > 88 cm	1.68 (1.26–2.25)	**0.001**	1.50 (1.08–2.08)	**0.015**	1.12 (0.72–1.73)	0.629

AOR = adjusted odds ratio; CI = confidence interval.

[a]Model 1: Adjusted for age (continuous), parity (nulliparous/multipara), smoking (yes/no), origin (born inside/outside European Union), chronic hypertension (yes/no), pre-pregnancy diabetes (yes/no), systemic lupus erythematosus (yes/no), chronic kidney disease (yes/no), history of preeclampsia (yes/no), conception with ovarian stimulation (yes/no), conception with *in vitro* fertilization (yes/no), mean arterial pressure (continuous).

[b]Model 2: Adjusted for the same variables as model 1 and for body mass index (continuous).

Study IV

Among the 3,777 women in the study population, 138 (3.7%) developed preeclampsia. Women with preeclampsia were more often nulliparous and had a higher BMI compared with women without preeclampsia. Their gestational length was shorter, and they gave birth to infants with lower birthweight. The risk of preterm birth was higher in women with preeclampsia. Of the women with preeclampsia, 116 (84.1%) had term preeclampsia and only 22 (15.9%) had preterm preeclampsia. 55 women (1.5%) were treated with prophylactic aspirin, of those nine women were nulliparous and six of the women treated with aspirin developed preeclampsia.

BMI was positively correlated with SAT thickness $r = 0.68$, $p < 0.001$, and VAT thickness $r = 0.46$, $p < 0.001$, Figures 9 and 10.

Women with greater SAT thickness more often developed preeclampsia, OR 1.79 (95% CI 1.48–2.17), i.e., with every centimeter increase in SAT, the risk of preeclampsia increased by 79%. Women with greater VAT thickness also had increased risk of developing preeclampsia, OR 1.23 (95% CI 1.11–1.35), suggesting that every centimeter increase in VAT increased the risk by 23%. After adjustment for confounders, the association between SAT thickness and preeclampsia remained, AOR 1.35 (95% CI 1.02–1.79), but the association for VAT thickness weakened, AOR 1.11 (95% CI 0.99–1.24). Table 6. When the analyses were repeated after exclusion of women treated with prophylactic aspirin, the estimates were only marginally changed for both SAT and VAT.

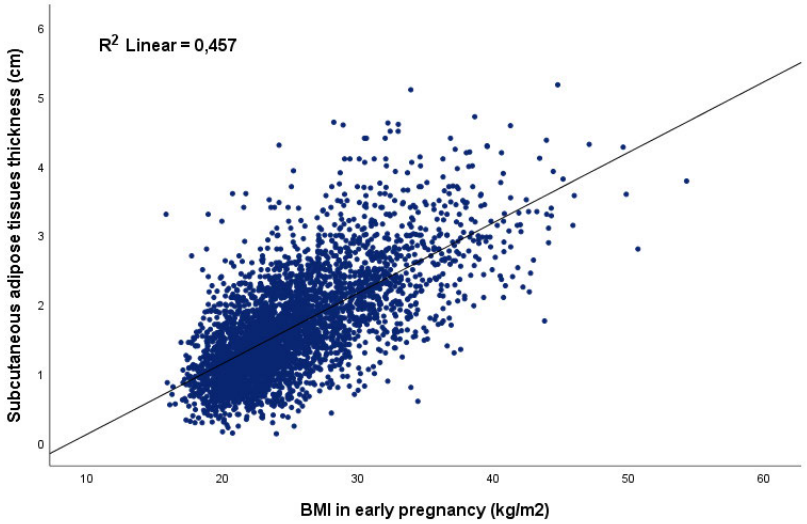

Figure 9. Correlation between BMI and subcutaneous adipose tissue thickness.

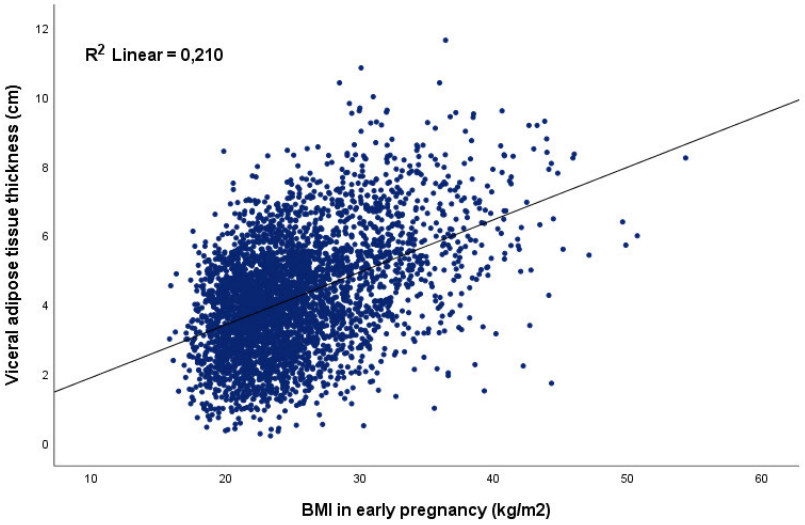

Figure 10. Correlation between BMI and visceral adipose tissue thickness.

Table 6. *Visceral adipose tissue (VAT) thickness and subcutaneous adipose tissue (SAT) thickness in patients with or without preeclampsia.*

	Preeclampsia (n = 138)	Non preeclampsia (n = 3639)	OR (95% CI)	*p*	AOR (95% CI)[a]	*p*
SAT (cm)	2.04 ± 0.89	1.65 ± 0.73	1.79 (1.48–2.17)	**0.000**	1.35 (1.02–1.79)	**0.037**
VAT (cm)	4.75 ± 1.79	4.16 ± 1.63	1.23 (1.11–1.35)	**0.000**	1.11 (0.99–1.24)	0.080
VAT/SAT ratio	2.69 ± 1.60	2.94 ±1.71	0.90 (0.80–1.02)	0.090	0.99 (0.88–1.12)	0.923

Data on SAT measurement missing for 2 patients and data on VAT measurement missing for 6 patients.
OR = odds ratio; AOR = adjusted odds ratio; CI = confidence interval; VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue.
[a]Adjusted for maternal age, parity, BMI, smoking, and country of birth.

Discussion

The occurrence of obesity is rapidly increasing at an alarming rate worldwide, and has reached women of childbearing age in developed countries (202). Today, obesity is one of the greatest challenges for obstetricians and is associated with a number of obstetric risks that can have both short- and long-term consequences for mother and fetus. Still, the majority of overweight and obese women will have uncomplicated, normal pregnancies and deliveries. Hence, maternity health care needs to improve the general risk assessment in order to identify the obese women at highest risk, to offer closer surveillance and better interventions during their pregnancies. Identifying obese women at increased risk at the beginning of their pregnancies has the potential to be useful in several ways. Clinicians could increase surveillance during the pregnancies of women identified as being at high risk and under certain circumstances provide treatment, such as aspirin for prevention of preeclampsia. Pregnancy is a period when most women have high motivation for lifestyle changes, with more than 50% of smokers giving up smoking during the beginning of pregnancy (203). Further, studies of dietary and lifestyle interventions in obese women during pregnancy have shown reduced maternal gestational weight gain, improved outcomes for both mother and baby, and a lower BMI 12 months postpartum (204, 205). Pregnant women with obesity might also benefit from surveillance/intervention as regards their future risk of developing CVD after their pregnancies. The studies in this thesis have focused on risks associated with obesity and identification of high-risk individuals. Population-based cohorts were used to improve generalizability.

Methodological considerations

All four studies in this thesis were population-based cohort studies. Epidemiological cohort studies aim to identify and evaluate associations between predetermined exposures and outcomes. Several issues must be considered when designing and interpreting cohort studies.

Findings in cohort studies may be subject to bias related to the information used and the selection of covariates associated with both the exposure and the outcome (mediators, confounders, colliders). Causal interference can be chal-

lenged in such studies. To improve the models and obtain a systematic overview of possible causal pathways, DAGs were constructed. The DAGs were created using the DAGitty web application available at *www.dagitty.net*. DAGs can be used to identify possible confounders by drawing arrows from one factor to another. In that way, each factor can be identified as a confounder, a mediator, or a collider, Figure 11. In analysis of associations, non-causal pathways must be blocked, which is done be adjusting only for confounders.

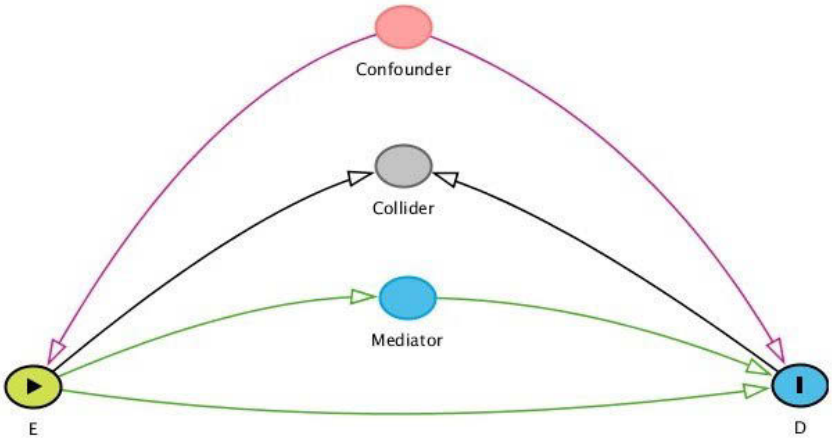

Figure 11. Example of a directed acyclic graph (DAG) showing the relationship of a confounder, a collider, and a mediator to exposure (E) and outcome (D).

One disadvantage of cohort studies is that rare outcomes are difficult to study. Most complications during pregnancies are rare, and studying individual complications requires large datasets, which can both be time-consuming and costly to obtain. Reaching sufficient power for a given study can therefore be challenging. For example, to increase the power in Study II, the main outcome chosen was the association between MUO/MHO and risk of developing *any* obesity-associated complication, although analyses were performed on individual complications as well.

In Studies III and IV, the main outcome was preeclampsia. The prevalence rates of preeclampsia in the study populations were 4.5% and 3.6%, respectively. This is consistent with other register studies on Swedish population of pregnant women (206, 207), indicating representative study groups. The aim of the studies was to improve prediction of women with the highest risk of preeclampsia, i.e., to identify those suitable for prophylactic aspirin treatment, so as to minimize their risk. The benefit of aspirin use in lowering the inci-

dence of preterm preeclampsia had already been demonstrated in a large randomized placebo-controlled trial by Rolnik and colleagues (161). However, in both Study III and Study IV, only 0.6% of the study population developed preterm preeclampsia. Because preterm preeclampsia was such a rare outcome, it was not possible to explore term and preterm preeclampsia separately, although this would have been of great interest.

In Study I, information was obtained from the larger population-based BASIC cohort study, to which all women undergoing ultrasound examination at approximately gestational week 17 in Uppsala were invited to participate. As mentioned in the methods section, women not speaking Swedish, women with confidential personal data, women with pathological pregnancies, and women younger than 18 years of age were excluded. The participation rate was rather low, about 22%. The results of the comparison with the general female population showed that study participants were younger, more often nulliparous, had higher educational level, and more often were of Nordic origin. This bias could in part be due to the exclusion of women not speaking Swedish, but also the general higher educational level and higher level of Nordic inhabitants within Uppsala County. This selection bias of the study population must be taken into account in assessing the generalizability of the study. When recruiting participants to Studies I and II, there was also some risk of selection bias. Women who chose to participate in the biobank might have a higher educational level and higher socioeconomic status than women refusing participation. This might be due to higher awareness of the importance of scientific research within the more highly educated population and among those with higher socioeconomic status.

A large challenge to the study design in Studies I and II was information bias regarding the exposure. In Study I, information on clinical diagnosis of depression based on DSM-5 criteria was not available. Instead, information on depression status was obtained using the EPDS scale, a self-reported screening questionnaire for antenatal depression. The EPDS scale is validated, with high sensitivity but somewhat lower specificity for detection of a major depressive episode (188). The EPDS might therefore result in falsely high prevalence estimates (208). Therefore, a certain degree of misclassification of depression was assumed. To address this issue, a higher cut-off (17 or more) was used, which yielded a prevalence of antenatal depression within the range reported in the literature (209).

In Study II, the definition of MHO (and MUO) as exposure was a major limitation. As there are currently no universally accepted criteria for MHO (15), the definition used was based on the main criterion that MHO usually refers to individuals with BMI > 30 kg/m^2 with *no components* of the metabolic syndrome, depending on the cohort and the criteria used (16). A lean definition

was used, requiring only one metabolic factor for MUO diagnosis. Furthermore, the research team did not have access to fasting blood samples or OGTT, but depended on non-fasting blood samples and capillary glucose levels. It is thus possible that a stricter definition would have been of greater value, or that inclusion of other variables, like fasting lipid levels and the results of an OGTT, would have produced better predictive power and reduced measurement bias of the exposure.

Measurement errors in Studies III and IV need to be taken into consideration as a possible information bias. In Study III, measurement of WC was implemented into clinical practice, being performed at the first antenatal visit to a midwife. Measurements were done by different midwives at different health care centers. To minimize the measurement errors, midwives were provided with standardized measurement tapes and all received the same education on how to perform the measurement, with both verbal and written information. In Study IV, the SAT and VAT ultrasound measurements were performed by certified obstetric ultra-sonographers, but their identities differed. As measurement error risk is large in ultrasound measurements, a quality review was performed, measuring the interclass correlation coefficient of the inter-examiner variation; this indicated good reliability. To further minimize measurement bias, a standardized, well-established measurement technique was used. As Studies III and IV were both prospective cohort studies, the measurement of the exposure was not influenced by knowledge of the outcome.

General discussion

Study I

The results of Study I showed that overweight and obesity modulate the effect that depression had on infant birthweight. Conflicting results have been published on the relation between depression and birthweight. Most previous studies have suggested an association with lower birthweight (151), but other studies have found higher prevalence of macrosomia and LGA infants among overweight and obese women with comorbid depression (149). The interaction found in this study, that women who were both overweight/obese and had depression gave birth to infants with greater birthweight than non-depressed overweight/obese women, and that the opposite pattern was seen in normal-weight women, may help to explain the discrepancies between these results and the prior results.

Potentially, in populations with a high proportion of normal-weight or underweight women, the tendency towards lower birthweight, as noted in this study, may be amplified. This would be consistent with the results from a large meta-

analysis by Grote et al. (151), in which the association between antenatal depression and low birthweight was stronger in studies from developing countries and studies from the US on women with low socioeconomic status. Low birthweight may be the result of undeveloped or unequal maternal health care, whereas optimized maternal surveillance can counteract the depressogenic effects leading to low birthweight. In the study population in Study I, risk factors for low birthweight, such as smoking and low educational levels, were less prevalent than in the general female Swedish population. The study population was thus selected towards more favorable socioeconomic factors, which would contribute to driving the association in the opposite direction.

According to the results of Study I, the infant's birthweight was lower among women classified as depressed, but importantly the standardized birthweight did not differ. Most previous studies have only addressed the association between depression and birthweight, but not addressed the birthweight in relation to gestational length. The low birthweight reported in prior research might therefore simply be a result of a depression-induced increased prevalence of preterm birth (151).

As both increase and decrease in appetite are known symptoms of depression (210), the research team speculated that deviating weight gain during pregnancy would explain the results. When adding weight gain in gestational week 32 to the model, the estimates were only marginally changed. Thus, the mechanism behind the results can only be speculated on and is probably multifactorial. Indeed, there is evidence indicating that obesity and depression have multifactorial shared biological mechanisms. Hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis and glucocorticoid receptor dysfunction leading to a non-adaptive unabated release of cortisol is one of the most consistent findings in biological psychiatry and is also found in nearly half of all adult obese individuals (211). In depressed pregnant women this HPA alterations seem to be regulated differently than in non-depressive pregnant women. Prenatal stress or depression during pregnancy might thus cause release of stress hormones, resulting in placental hypo-perfusion, leading to fetal growth restriction (151, 212, 213). A possible association between cortisol to cortisone ratio and infant birthweight has recently been reported in women with psychiatric morbidity (214, 215).

Obesity itself is a condition associated with a chronic inflammatory state (211) and associated with maternal insulin-resistance and fetal hyperinsulinemia during pregnancy (80), both positively influencing fetal growth. Inflammation and oxidative stress are associated with the onset of depressive symptoms (216), but how these two conditions interact and influence birthweight remains unclear.

There is evidence that the association between obesity and depression is stronger for abdominal obesity, and obese individuals with MHO had only a slightly increased risk of depression compared with non-obese individuals, while depression risk was higher for MUO individuals (217, 218).

Study II

The overall risk of having any obstetric or perinatal complication due to obesity was high, as shown by the results that 35.0–45.9% of women with obesity (depending on absence/presence of metabolic factors) and 27.6% of overweight women had at least one adverse obstetric or perinatal complication.

Non-pregnant individuals with MUO have a higher risk of morbidity and mortality than those with MHO, at least in the short-term perspective (26, 33). Therefore, the research team wanted to evaluate if classifying obese women in early pregnancy as MHO or MUO would be useful for prediction of obesity-associated obstetric and perinatal complications. The overall risk of complications in women with MUO was higher than that in women with MHO, overweight, or normal weight, before adjustment for BMI. This points to the fact that metabolic state can influence the risk of obstetric complications. However, it seems that this adds only modest information to the risk already known through assessment based on BMI in early pregnancy. In maternal health care, information on BMI is already collected in early pregnancy. Although BMI has limitations, it is an easy way to identify women at higher risk of complications. As the predictive power of the models was low, defining obese women as metabolically healthy or unhealthy in early pregnancy seems to have little clinical impact.

There are differing opinions regarding if the comparison of MHO and MUO should be adjusted for BMI or not. The main purpose of this thesis was to identify which obese women were at the highest risk of complications. Therefore, it was considered important to adjust for BMI. The main reasons for this in Study II were threefold. First, women with MUO had higher BMI than women with MHO. Secondly, BMI was considered to be a predictor of MUO and therefore a cofounder of the association between MUO and the obstetric complications. Third, the aim was to evaluate if the MUO classification provided any additional information to that offered by BMI. BMI is already measured in maternal health care, and if further measurements are to be imposed in clinical care, they need to be of value for the patients and health care providers.

Regrettably, the research team did not have blood sample measurements for the comparison groups of normal-weight and overweight women. It was therefore not possible to identify the comparison groups as metabolically healthy or metabolically unhealthy. Studies on all-cause mortality using only standard

BMI categories have shown increased risk in case of obesity (all categories), grade 2 and 3 obesity, but not grade 1 obesity compared with normal weight. Overweight was associated with lower all-cause mortality (219). Studies on life expectancies have also shown no association between overweight or mild obesity and reduction in life expectancy compared with normal-weight individuals (220). These conflicting results can probably be explained by the fact that the metabolic status of the control group was not taken into consideration, which reveals the importance of metabolic status in both normal-weight and overweight individuals.

Women with certain pregnancy complications, like preeclampsia, gestational hypertension, and GDM have a higher risk of CVD later in life (221-223), and preterm birth has been associated with metabolic dysregulation later in life (224). Early detection of women with CVD risk is paramount for reducing this risk. With better risk assessment of women with obesity during pregnancy, it would be possible to identify women who have more subtle or subclinical variables that jointly speak for an increased risk of CVD in the future. By focusing the post-pregnancy follow-up only on women who develop certain pregnancy complications, more than half of all women with obesity would go undetected, as shown by the results in Study II, that only 45% of women with MUO developed a pregnancy-related adverse outcome.

The above reasoning is supported by the increased levels of cathepsin S and cystatin C in women with MUO. Cathepsin S is a protease of the cathepsin family that has been implicated in metabolic disturbances such as obesity, diabetes, and dyslipidemia. It has been suggested that cathepsin S, through adipose tissue-derived inflammatory activity, can be a part of the link between obesity and development of CVD (225). It is also known that cystatin C is the most abundant and potent endogenous inhibitor of cathepsin S (226). Cystatin C reflects changes in GFR during pregnancy and can be used to diagnose renal impairment in pregnant women, independent of weight (227). Cystatin C is an independent predictor of cardiovascular events in non-pregnant populations (228). Adiponectin is the most abundant adipose tissue-specific protein and has anti-inflammatory, antiatherogenic, and insulin-sensitizing properties. The concentration of adiponectin decrease in insulin-resistant states, such as obesity. Clinical studies suggest that maternal adiponectin levels are decreased in GDM (229), but unchanged in pregnancies complicated with preeclampsia (230). Women with MUO had lower adiponectin levels, and earlier studies have pointed to an association between low serum adiponectin levels and CVD risk (231), although this association has also been questioned (232). Given the elevated cardiovascular risk factors at first antenatal visit among MUO individuals, the findings in Study II may have greater relevance for the long-term health in these women.

Although the definition of MUO used in Study II creates a risk of measurement bias of the exposure, as discussed in greater detail under methodological considerations, it also has strengths. Using non-fasting blood samples and information already collected in maternal health care, makes it easier to implement this definition of the metabolic state of pregnant women in clinical practice.

Study III

According to the findings in Study III, greater WC measured in early pregnancy was associated with preeclampsia development. However, a strong correlation was seen between WC and BMI in early pregnancy in the study population. Thus, adding WC to established prediction models that included BMI did not improve their performance in predicting preeclampsia.

Evidence suggests that metabolic abnormalities, such as increased leptin, glucose, insulin, and lipids, may play a role in the causal pathway between obesity and preeclampsia (164). As WC is a known risk factor for CVD (233, 234) and predicts metabolic abnormalities (235), the research team hypothesized that WC would improve performance of a prediction model for preeclampsia. Most studies on WC in the general population are on older study populations than the relative young study population of pregnant women. WC increases with age, and this increase is larger than one can expect based on an individual's BMI (236). With increasing age, redistribution of fat tissue from subcutaneous to visceral fat occurs, contributing to metabolic dysfunction not seen in the younger population (237). The stronger association between SAT thickness and preeclampsia seen in Study IV underlines that this shift in metabolically unhealthy fat distribution had probably not occurred in the young population of pregnant women.

With almost 5,000 women included, this is the largest study to date on the association between WC and preeclampsia. As its prediction performance was based on a well-established and commonly used prediction model (157) and WC is a simple, inexpensive, and reliable tool for central obesity, one of its largest strengths was its clinical potential.

The only study to my knowledge comparing the performance of BMI and WC in a prediction model for preeclampsia is one by Wendland et al. (95). Their results were consistent with the results of Study III, showing similar capacity of BMI and WC in predicting preeclampsia. They measured WC in gestational weeks 20 to 28, and used only maternal age, education, and parity in their prediction model. Study III expanded this finding as the measurements on WC were performed in early pregnancy and used in a prediction model including the most established maternal characteristics and medical history. The results

were also in agreement with other studies on the association between WC and gestational hypertensive disorders (88, 92-94).

A limitation of the study was the lack of knowledge on aspirin treatment in the study population. However, the influence of this on the results was assumed to be minimal, as aspirin use was restricted during the study period, with only about 1.1% of nulliparous women treated with aspirin in Sweden during 2008–2013 (238). We could verify this result in Study IV, were 1.5% of the total study population was treated with aspirin and in a sensitivity analysis excluding women on aspirin prophylaxis, the association we found there remained unchanged. Another limitation was that information on uterine artery PI and biomarkers commonly used in predication models for preeclampsia was not available.

Study IV

Increased abdominal adipose tissue thickness, measured with ultrasound, was associated with preeclampsia. This association was stronger for SAT thickness than VAT thickness, as the association remained after adjustment for confounders, including BMI. After adjustment, the association between VAT thickness and preeclampsia barely lost its significance.

Abdominal adipose tissue distribution is associated with adverse metabolic risk profile. Both SAT thickness and VAT thickness correlate with metabolic risk factors, although VAT thickness seems to have a stronger association (61, 239). As mentioned earlier, the causal pathway between obesity and preeclampsia is poorly understood, but abdominal obesity in early pregnancy could be a part of the link. Existing literature suggests that metabolic abnormalities may play a substantial role in this pathway and that both obesity and preeclampsia have several pathophysiological alterations in common. Those pathophysiological alterations include oxidative stress, inflammation, and endothelial dysfunction (83). VAT is more infiltrated with inflammatory cells than SAT and is capable of generating higher amounts of pro-inflammatory proteins, such as TNF-α and IL-6 (240, 241). Both TNF-α and IL-6 levels are increased in abdominal obesity (59). Because of its anatomical location, venous blood from the VAT, with increased levels of pro-inflammatory proteins, drains directly into the portal system. Thus, a hepatic immune response is activated with production of inflammatory markers, such as CRP. CRP levels are significantly correlated with both increased WC and VAT thickness (59).

As VAT thickness seems to be a stronger indicator of metabolic factors than SAT, the research team anticipated that VAT thickness would be a better predictor of preeclampsia than SAT. In addition, Bartha et al. showed that ultra-

sound measurement of VAT thickness during early pregnancy correlated better with metabolic risk factors than either SAT thickness or BMI (100). In contrast, the association with preeclampsia found in Study IV was stronger for SAT thickness. The results are consistent with previous reports showing that SAT thickness can predict a higher number of adverse outcomes than BMI (44, 104). As discussed in the section above on Study III, deposition in visceral areas may not yet have started in the comparatively young study group of pregnant women, explaining this stronger association to SAT thickness, at least in part.

The prevalence of preeclampsia was 3.7%, which is comparable with that in other large Swedish cohort studies. Of the women with preeclampsia, only 15.9% had preterm preeclampsia, which is lower than expected compared with a large Swedish cohort study, where the prevalence of preterm preeclampsia was about 20% (242). This might be a limitation, as it suggests that the study population might be healthier that the general pregnant Swedish population, It would be of interest to measure SAT thickness and VAT thickness in a larger population sample and perform sub-analyses on term and preterm preeclampsia, to investigate if there is a stronger association with either of the groups.

With a study population of almost 3,800 women, this is the largest study to date on the association between adipose tissue thickness and risk of preeclampsia. Most previous reports have studied the association with hypertensive disorders in pregnancy, not specifically preeclampsia, which has a somewhat different pathophysiology and clinical outcome (243, 244). Overall, the results of Study IV are in agreement with these reports (101, 103, 104). The only study specifically on preeclampsia showed similar results as Study IV: a significant association between VAT thickness and preeclampsia only in unadjusted models (103). Unfortunately, my research team did not have information on history of preeclampsia in previous pregnancies, which is one of the strongest risk factors for preeclampsia in multiparous women (245).

Clinical implications and future perspectives

Obesity is known to be associated with several obstetric risks that can have devastating consequences for both the mother and the infant. One of them is preeclampsia. As the incidence of obesity is rising at an alarming rate all over the world, obesity is becoming one of the greatest challenge for obstetricians in clinical practice. While the risk of developing obesity-associated obstetric complication is as high as 35–46%, as shown by the results in Study II, the majority of obese women will have an event-free pregnancy. It remains unknown which subgroup of obese women has a higher risk, meaning that there

is a great need to develop risk assessment models for this large group of pregnant women.

Most prediction models for obstetric complications, including the one most commonly used for preeclampsia (159), use BMI as a marker of obesity. In my thesis, the aim was to identify a subgroup of obese individuals with an even higher risk, using various markers of obesity. As the strongest evidence in the non-pregnant population shows that abdominal obesity seems to have the strongest correlation with metabolic abnormalities and morbidity, the studies have focused on various markers of abdominal obesity in the pregnant population. From a clinical perspective, it is important that the methods or markers used to identify high-risk groups in general are simple and easy to apply. They need to be cost-effective and easy to both perform and interpret. In this thesis, markers that could be implemented in clinical practice (Studies III and IV) without any major organizational changes in the antenatal health care were used, as well as non-fasting biomarkers that are easy to collect and therefore could be practical to use in risk assessment (Study II).

In low- and middle-income countries, preeclampsia is a major cause of morbidity and mortality (107). Obesity is rising not only in high-income countries, but globally (1). As the availability of health care and public hospitals with neonatal intensive care can be limited in lower-income countries, prevention of preeclampsia would be highly cost-effective. Low-dose aspirin is the only current treatment, shown to decrease the prevalence of preterm preeclampsia (161). NICE guidelines for preeclampsia prevention consider only maternal characteristics and are simple and easy to use, but have a much lower prediction rate than the combined method recommended by the International Federation of Gynecology and Obstetrics (109). Improving both these models and increasing the prediction rate could enable the use of prophylactic aspirin from early pregnancy and improve surveillance of women at high risk of preeclampsia worldwide. WC is one marker that would be easy to incorporate into maternal antenatal care, but the results of Study III showed no beneficial effects of WC measurement where BMI was already measured. Study II showed that a simple blood marker for identifying obese pregnant women with MUO had little relevance in prediction beyond that of BMI. Further research into identifying groups at high risk of obstetric complications within the obese group of pregnant women is therefore needed. Research adding both WC and ultrasound measurements of SAT thickness and VAT thickness to the Fetal Medicine Foundation model, including both uterine artery PI and biomarkers, would be of great interest.

Ultrasound is a valuable diagnostic tool for fetal surveillance during pregnancy and for use in risk assessment. Ultrasound measurements of uterine ar-

tery PI are already included in prediction models for preeclampsia (159). Implementing measurement of adipose tissue thickness with ultrasound into clinical practice as a part of routine ultrasound screening for fetal abnormalities might improve risk assessment. Since it is becoming more common to offer women in high-income countries a first trimester ultrasound, measuring SAT thickness in early pregnancy has the potential to be an effective, quick, and highly cost-effective method for identifying the women at highest risk of preeclampsia. As earlier studies have shown that both increased SAT thickness and increased VAT thickness are associated with both gestational hypertensive disorder and GDM (44, 101), it remains uncertain if measuring both SAT thickness and VAT thickness would be beneficial for risk assessment. Thus, further studies are needed. A meta-analysis of the use of aspirin in prevention for preeclampsia has shown benefits only when treatment is started before gestational week 16 (246). In Study IV, the ultrasound measurements on SAT thickness and VAT thickness were performed in gestational weeks 17–19, instead of earlier in pregnancy. Abdominal adipose tissue distribution changes in the third trimester compared with in the first and second trimesters, but such changes are not seen between the first and second trimester (247). Therefore, the results of Study IV can likely be transferred to measurements in the first trimester, but future studies on this are needed.

In Study I, overweight/obesity was found to modulate the effect that depression has on infant birthweight. It remains to determine if the results can be transferred to other populations and settings. Depression and obesity are two conditions with a reciprocal relationship and many shared biological mechanisms. Further insights on the potential mechanisms underlying the findings in Study I are needed. Nevertheless, the results underscore the need to address both those conditions in maternal health care for prevention, diagnosis, and treatment and thus minimize the potential complications for mother and infant.

The increased risk of CVD later in life among obese women in early pregnancy is of high clinical relevance. In this thesis, I have shown that obese women with MOU have higher levels of cathepsin S and cystatin C, and lower adiponectin levels. Increased WC and increased SAT thickness and VAT thickness are associated with increased cardiovascular risk in the general population. As prevention of metabolic diseases and CVD is paramount, maternal health care has the possibility to identify women with increased risk of CVD later in life. Those women should receive lifestyle intervention in the same way as women with pregnancies complicated with gestational hypertension, preeclampsia, or GDM. Most women are highly motivated for lifestyle changes during pregnancy, and this can be an advantage for motivating these women to start the dietary and lifestyle changes necessary to decrease this risk. Given the elevated cardiovascular risk identified within this group of obese

women during early pregnancy, the findings of Study II may have greater relevance for long-term health in these women. This could be an opportunity for lifestyle intervention, education, and follow-up for prevention of CVD later in life and for improvement of general health in this group.

Conclusions

- First-trimester maternal BMI seems to modulate the association between antenatal depressive symptoms and birthweight. Depressed women with overweight/obesity gave birth to infants with significantly higher standardized birthweight than non-depressed overweight/obese women. The opposite pattern was noted in normal-weight women. The increased birthweight in women with both overweight/obesity and depressive symptoms was not explained by increased weight gain during the pregnancy (Study I).

- One-third of pregnant women with obesity were metabolically unhealthy, according to the definition used in Study II. Almost half of the women with MUO developed at least one obesity-associated adverse obstetric outcome. These women were at overall increased risk of developing obesity-associated obstetric and neonatal complications in comparison with their metabolically healthy counterparts. Despite this, the classification of MUO and MHO had little clinical relevance for risk prediction beyond that of BMI, due to the low predictive power in the models (Study II).

- Women with MUO have numerous risk factors for future CVD, including altered levels of cardiovascular risk markers. Women with MUO had higher levels of cathepsin S and cystatin C compared with women with MHO. They also had lower levels of adiponectin and decreased estimated GFR (Study II).

- Large WC, measured in early pregnancy, was associated with higher risk of preeclampsia. However, first-trimester WC was highly correlated with first-trimester BMI. Adding WC to a well-established prediction model for preeclampsia that already incorporated BMI did not improve its prediction performance (Study III).

- Increased abdominal adipose tissue, measured through second-trimester ultrasound, was associated with risk of developing preeclampsia. This association was seen with both SAT thickness and VAT thickness, but was stronger for SAT thickness, as the association remained significant after adjustment for BMI, smoking, country of birth, and parity (Study IV).

Summary in Swedish – Sammanfattning på svenska

Övervikt och fetma ökar i hela världen, även i Sverige. Andelen svenska kvinnor som var överviktiga (kroppsmasseindex, BMI ≥ 25 kg/m^2) eller hade fetma (BMI ≥ 30 kg/m^2) i början av sin graviditet år 2019 var 27,2 % respektive 15,7 %. Fetma (obesitas) har blivit ett av de största hälsoproblemen som läkare och barnmorskor står inför inom obstetriken, då obesitas är associerat med en rad komplikationer under graviditeten för både den gravida kvinna och hennes foster. Dock har de allra flesta gravida kvinnor med övervikt eller obesitas normala graviditeter och förlossningar. Sjukvården behöver därför utveckla strategier för att tidigt i graviditeten hitta de kvinnorna med övervikt eller obesitas som löper risken att utveckla komplikationer under graviditeten. Kvinnor med hög risk skulle då kunna få skräddarsydd övervakning under graviditeten eller förebyggande behandling mot komplikationer. Idag finns prediktionsmodeller för att förutspå vilka kvinnor som riskerar att utveckla havandeskapsförgiftning. Övervikt eller obesitas, baserat på mammans BMI, är en vanlig riskfaktor i dessa modeller. Denna avhandling har utforskat mätvariabler och markörer som är associerade med hjärtkärlsjukdomar i den allmänna befolkningen, för att förbättra förutsägelseförmågan hos dessa prediktionsmodeller och identifiera de överviktiga/obesa gravida kvinnorna som löper högst risk för komplikationer under graviditeten.

Syftet med delarbete I var att undersöka om mammans BMI i början av graviditeten påverkade sambandet mellan depression under graviditet och barnets födelsevikt. I denna retrospektiva kohortstudie användes information från BASIC-studien och studiepopulationen bestod av 3965 gravida kvinnor. En uppdelning gjordes beroende på om mamman var överviktig (BMI ≥ 25 kg/m^2 i början av graviditeten) eller normalviktig (BMI under 25 kg/m^2) och om de var deprimerade (17 poäng eller mer på EPDS-skalan under graviditeten) eller ej (under 17 poäng på EPDS-skalan). Studien visade att kvinnorna som var både överviktiga och deprimerade födde barn som vägde mer än barn till överviktiga kvinnor utan depression. Däremot tenderade normalviktiga kvinnor med depression att föda barn som vägde mindre än barnen till normalviktiga kvinnor utan depression. Dessa resultat förklarades inte av skillnader i viktuppgång under graviditeten mellan grupperna, eftersom estimaten i den linjära

regressionsmodellen ändrades endast marginellt när viktuppgång togs med i analysen.

Delarbete II undersökte om uppdelning av kvinnor med obesitas i grupper med metabolt hälsosam obesitas (MHO) respektive metabolt ohälsosam obesitas (MUO) skulle underlätta riskbedömning av vilka obesa kvinnor som löpte högst risk att utveckla komplikationer under graviditeten. Blodprover från 547 obesa kvinnor analyserades med avseende på flera olika metabola markörer. Därefter delades kvinnorna upp i grupperna MHO och MUO, där kvinnor som hade en eller fler av följande faktorer klassades som MUO: (i) systoliskt blodtryck över 130 mmHg eller diastoliskt blodtryck över 85 mmHg vid första mödravårdsbesöket, (ii) lätt förhöjt blodsockervärde vid första mödravårdsbesöket (icke-fastande kapillärt glukosvärde > 6.8 mmol/L), (iii) förekomst av blodfettsrubbning (apolipoprotein B/apolipoprotein A1 kvot > 0.8). Resultaten visade att en tredjedel av alla kvinnor med obesitas i början av sin graviditet hade MUO. Andelen kvinnor med MUO som utvecklade någon komplikation under graviditet var högre än den bland kvinnor med MHO, 45,9 % kontra 35,0 %. Kvinnor med MUO hade förhöjd risk för graviditetshypertoni, havandeskapsförgiftning, graviditetsdiabetes, förtidsbörd och att föda ett barn stort för tiden (LGA) jämfört med kvinnor med MHO, överviktiga och normalviktiga kvinnor. Riskökningarna bestod även om hänsyn togs till skillnader mellan grupper gällande om kvinnan fött barn tidigare och rökvanor under graviditet. Om hänsyn togs till BMI-skillnader försvann flera av riskökningarna. Slutsatsen var därför att uppdelning av kvinnor med fetma i MUO- eller MHO-grupper hade föga klinisk relevans för riskbedömning under graviditet, utöver den information som BMI ger.

I det tredje delarbetet infördes mätning av midjemått på alla kvinnor vid första besöket hos barnmorska under tidig graviditet. Syftet med studien var att se om midjemått hade samband med ökad risk för havandeskapsförgiftning, oberoende av mammans BMI. I studien undersöktes också om en riskbedömningsmodell för havandeskapsförgiftning med etablerade faktorer skulle förbättras om midjemått lades till i den. Studiepopulationen bestod av 4 696 kvinnor. Av dessa utvecklade 209 kvinnor (4,5 %) havandeskapsförgiftning under graviditeten. Kvinnor som utvecklade havandeskapsförgiftning hade större midjemått än de som inte fick havandeskapsförgiftning: 85,8 ± 12,6 cm jämfört med 82,3 ± 11,3 cm. Mammans midjemått i början på graviditeten var starkt och positivt korrelerat med mammans BMI. Sambandet mellan midjemått och havandeskapsförgiftning undersöktes genom att midjemått lades till i en riskbedömningsmodell som innehöll mammans ålder, antal tidigare födda barn, rökning, födelseland, förhöjt blodtryck, diabetes typ 1 eller 2, lupus, eller kronisk njursjukdom innan graviditeten, tidigare graviditet med havandeskapsförgiftning, graviditet genom ägglossningsstimulering eller provrörsbe-

fruktning och mammans blodtryck vid inskrivning i mödravården. Ett samband mellan midjemått och havandeskapsförgiftning märktes, justerad oddskvot (95 % konfidensintervall) 1,02 (1,01–1,03), men när BMI fördes in i riskbedömningsmodellen förstärkte det inte modellens förmåga att förutspå risken för havandeskapsförgiftning. Slutsatsen blev att midjemått i början på graviditet är associerat med ökad risk för havandeskapsförgiftning, men att lägga till midjemått till en tidigare etablerad prediktionsmodell, som redan inkluderar mammans BMI, förbättrar inte dess prestanda.

Syftet med det fjärde delarbetet var att undersöka om fettvävstjocklek, mätt med ultraljud som tjockleken på subkutant fett (underhudsfett, SAT) och visceralt fett (bukfett, VAT), hade samband med ökad risk för havandeskapsförgiftning. Ultraljudmätningar av SAT- och VAT-tjocklek infördes som en del i rutinultraljudsundersökningen runt graviditetsvecka 18. Studiepopulationen bestod av 3 777 gravida kvinnor och sambanden mellan SAT-tjocklek, VAT-tjocklek och risk för havandeskapsförgiftning undersöktes med logistisk regression. Analysen justerades för mammans ålder, antal barn, BMI i tidig graviditet, rökning och födelseland. Resultaten visade att risken för havandeskapsförgiftning ökade med 79 % för varje centimeters ökning av SAT-tjocklek (oddskvot 1,79; 95 % konfidensintervall 1,48–2,17) och med 23 % för varje centimeters ökning i VAT-tjocklek (oddskvot 1,23; 95 % konfidensintervall 1,11–1,35). Efter justering för förväxlingsfaktorer, inklusive BMI, kvarstod sambandet mellan SAT-tjocklek och havandeskapsförgiftning (justerad oddskvot 1,35; 95 % konfidensintervall 1,02–1,79), medan sambandet mellan VAT-tjocklek och havandeskapsförgiftning försvann. Att lägga till SAT-tjocklek mätt med ultraljud skulle kunna förbättra riskbedömningsmodeller för havandeskapsförgiftning.

Summary in Icelandic – Samantekt á íslensku

Ofþyngd og offita er i stöðugum vexti á heimsvísu. Það á líka við um Svíþjóð. Fjöldi sænskra kvenna sem voru i ofþyngd (líkamsþyngdarstuðull ≥ 25 kg/m^2) eða þjást af offitu (líkamsþyngdarstuðull ≥ 30 kg/m^2) í byrjun meðgöngu árið 2019 var 27,2% og 15,7%. Offita hefur verið tengd við fjölda fylgikvilla á meðgöngu fyrir bæði móður og barn og er hún því eitt stærsta heilsufarsvandamálið sem læknar og ljósmæður standa frammi fyrir á meðgöngu. Þessir fylgikvillar geta einnig leitt til heilsufarsvandamála síðar á lífsleiðinni. Þrátt fyrir þetta gengur stærsti hluti kvenna i ofþyngd eða með offitu í gengum meðgöngu og fæðingu án vandkvæða. Því hefur það mikla þýðingu að þróa aðferðir til að finna út hverjar af þessum konum í ofþyngd eða með offitu munu þjást af fylgikvillum á meðgöngu. Þeim konum sem eru í mestri áhættu er hægt að veita aukið, sérsniðið eftirlit á meðgöngunni eða þær geta fengið fyrirbyggjandi meðferð gegn vissum fylgikvillum. Í dag eru til módel sem hafa verið þróuð til að spá fyrir um hvaða konur eru í mestri áhættu á að þróa með sér meðgöngueitrun á meðgöngunni. Ofþyngd og offita er algengur áhættuþáttur í þessum módelum, og er þá stuðst við mælingar á líkamsþyngdarstuðli. Í þessari doktorsritgerð höfum við notast við aðferðir og mælingar sem eru þekktar fyrir að spá fyrir um auknar líkur á hjarta- og æðasjúkdómum hjá almenningi til að bæta spágildi þessara módela og til að finna þær konur í ofþyngd eða með offitu sem eru í aukinni hættu á fylgikvillum á meðgöngu.

Markmiðið með fyrstu rannsókninni var að skoða hvort líkamsþyngdarstuðull móður í byrjun meðgöngu hafði áhrif á sambandið milli þunglyndi móður á meðgöngu og fæðingarþyngd barnsins. Í þessari afturskyggnu ferilrannsókn var notast vid upplýsingar frá BASIC rannsókninni og rannsóknahópurinn samanstóð af 3965 ófrískum konum. Við skiptum hópnum upp eftir því hvor konurnar voru í ofþyngd (líkamsþyngdarstuðull ≥ 25 kg/m^2)í byrjun meðgöngu eða í eðlilegri þyngd (líkamsþyngdarstuðull < 25 kg/m^2) og hvort þær voru þunglyndar (17 stig eða fleiri á EPDS skala á meðan á meðgöngu stóð) eða ekki þunglyndar (minna en 17 stig á EPDS skalanum). Niðurstöður rannsóknarinnar sýndu að konurnar sem voru bæði í ofþyngd og þunglyndar fæddu börn sem voru þyngri en börn kvennanna som voru í ofþyngd en ekki þunglyndar. Öfugt þá fæddu konur í eðlilegri þyngd sem voru þunglyndar börn sem voru léttari en konur í eðlilegri þyngd sem ekki voru þunglyndar. Þessi munur var ekki útskýrður af mun á þyngdar-aukningu á meðgöngu, þar sem

niðurstöðurnar frá línulegu aðhvarfsgreiningunni breyttist eingöngu lítillega þegar þyngdaraukning á meðgöngu var bætt við módelið.

Í annarri rannsókninni skoðuðum við hvort flokkun á konum með offitu með eða án efnaskiptavillu gæti hjálpað til við að spá fyrir um hverjar af konunum með offitu væru í aukinni hættu á fylgikvillum á meðgöngu. Við skoðuðum blóðprufur frá 547 konum med offitu í byrjun meðgöngu og mældum ólíka þætti sem tengjast efnaskiptavillum. Við skiptum síðan þessum hóp upp í offitu með eða án efnaskiptavillu, þar sem konur með offitu voru skilgreindar med efnaskiptavillu ef þær voru með einn eða fleiri af eftirfarandi þáttum: (i) systólískan blóðþrýsting yfir 130 mmHg eða díastólískan blóðþrýsting yfir 85 mmHg við fyrstu mælingu í mæðravernd, (ii) létt hækkaðan blóðsykur við fyrstu mælingu í mæðravernd (ekki fastandi mæling á blóðsykri frá háræð med gildi > 6.8 mmol/L) eða (iii) blóðfituhækkun (skilgreind sem apolipoprotein B/apolipoprotein A1 kvóti > 0.8). Niðurstaðan sýndi að þriðjungur allra kvenna með offitu í byrjun meðgöngu þjáist af efnaskiptavillu. Fjöldi kvenna með offitu með efnaskiptavillu sem fengu einhvern fylgikvilla á meðgöngunni var hærri en þeirra kvenna som voru með offitu án efnaskiptavillu, 45,9% á móti 35,0%. Konurnar med offitu og efnaskiptavillu voru í aukinni hættu á að þróa með sér háan blóðþrýsting á meðgöngu, meðgöngueitrun, sykursýki á meðgöngu, fyrirburafæðingu og að fæða barn sem er stórt fyrir meðgöngulengd samanborið við konur með offitu án efnaskiptavillu, konur í ofþyngd og konur í eðlilegri þyngd. Þessi áhættuaukning var ennþá til staðar eftir leiðréttingu fyrir fjölda fyrri fæðinga og reykinga á meðgöngu, en þegar við leiðréttum fyrir mun á líkamsþyngdarstuðli þá hvarf að mestu áhættuaukningin. Lokaniðurstaðan var því að flokkun kvenna með offitu með tillit till efnaskiptavillu virðist hafa litla klíniska þýðingu fyrir að spá fyrir um fylgikvilla á meðgöngu fram yfir það sem líkamsþyngdarstuðullinn gefur.

Í þriðju rannsókninni mældum við mittismál á öllum konum við fyrstu heimsóknina hjá ljósmóður snemma á meðgöngu. Tilgangurinn með rannsókninni var að sjá hvort aukið mittismál væri tengt aukinni hættu á meðgöngueitrun, óháð líkamsþyngdarstuðli móðurinnar. Við skoðuðum líka hvort módel sem notuð eru til að spá fyrir um meðgöngueitrun myndu bæta spágildi sitt ef við bættum við mittismáli í módelin. Rannsóknarhópurinn samanstóð af 4696 ófrískum konum. 209 af þeim, eða 4,5% fengu meðgöngueitrun. Konurnar sem fengu meðgöngueitrun voru með stærra mittismál en þær konur sem ekki fengu meðgöngueitrun; 85,8 ± 12,6 cm miðað við 83,2 ± 11,3 cm. Mittismál móður í byrjun meðgöngu hafði sterka fylgni við líkamsþyngdarstuðul móðurinnar í byrjun meðgöngu. Við skoðuðum tengslin milli mittismáls og meðgöngueitrunar með því að leggja til mittismál í módel sem inniheldur aldur móður, fjölda barna, reykingar, fæðingarland, króníska háþrýsting, sykursýki af gerð 1 eða 2, rauða úlfa, króníska nýrnasjúkdóm, sögu um meðgöngueitrun á fyrri meðgöngu, þungun efter örvun á egglosi eða

tæknifrjóvgun og blóðþrýsting móður í byrjun meðgöngu. Við fundum marktæk tengsl á milli mittismáls og meðgöngueitrunar; leiðrétt gagnlíkindahlutfall (95% öryggismörk) 1,02 (1,01-1,03), en eftir að við lögðum til líkamsþyngdarstuðul í byrjun meðgöngu í módelið þá hvarf tengingin. Lokaniðurstaðan er að mittismál í byrjun meðgöngu tengist aukinni hættu á meðgöngueitrun, en það að bæta mittismáli við módel sem spá fyrir um meðgöngueitrun og innihalda líksamsþyngdarstuðul, bætir ekki spágildi þess.

Í fjórðu rannsókninni var tilganngurinn að skoða hvort þykkt fituvefjar, mældur með sónar sem þykkt fitulags undir húðinni (SAT) eða iðrafita (VAT) tengist aukinni hættu á meðgöngueitrun. Mælingar með sónarskoðun á fitulagi undir húð og iðrafitu voru framkvæmdar í sambandi með fósturskimun í kringum 18. viku meðgöngunnar. Rannsóknarhópurinn samanstóð af 3777 ófrískum konum. Sambandið á milli fitulags undir húð annars vegar og iðrafitu hins vegar og áhættunnar á meðgöngueitrun var metið með lógístískri aðhvarfsgreiningu. Greiningin var leiðrétt fyrir aldri móður, fjölda barna, líkamsþyngdarstuðli í byrjun meðgöngu, reykingum og fæðingarlandi. Niðurstaðan sýndi að áhættan á meðgöngueitrun jókst um 79% fyrir hvern sentimetra af fitulagi undir húð (gagnlíkindarhlutfall 1,79; 95% öryggisbil 1,48-2,17) og um 23% fyrir hvern sentimetra af iðrafitu (gagnalíkindahlutfall 1,23; 95% öryggisbil 1,11-1,35). Eftir leiðréttingu fyrir blöndunarþáttum, þar á meðal líkamsþyngdarstuðli, var tengingin milli fitulags undir húð og meðgöngueitrunar ennþá til staðar (leiðrétt gagnlíkindarhlutfall 1,35; 95% öryggismörk 1,02-1,79) en tengingin milli iðrafitu og meðgöngueitrunar hvarf. Lokaniðurstaðan er að aukið fitulag undir húð mælt með sónar tengist aukinni hættu á meðgöngueitrun á meðgöngu. Mæling á fitulagi undir húð með sónar gæti þannig mögulega bætt forspárgildi módela sem spá fyrir um meðgöngueitrun.

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