Early Pregnancy Weight Gain and Arterial Stiffness in Gestational Sleep Disordered Breathing

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Abstract

Introduction: Pregnancy increases a woman's risk of developing sleep disordered breathing (SDB), with obstructive sleep apnea (OSA) affecting 8.3% of women by mid-gestation. Both comorbidities and hormonal/physiological changes associated with pregnancy, specifically weight gain and estrogen levels, may contribute to the development of SDB in pregnancy. Pregnant women with OSA are at increased risk of morbidity and mortality; OSA is associated with the development of hypertensive disorders of pregnancy (HDPs), such as preeclampsia (PrE), which can have severe detrimental effects on both mother and fetus. Recently, there have been increasing efforts to establish effective screening tools in early pregnancy, which can accurately predict the development of HDPs in the later stages of gestation.

One method that has the potential for a high degree of clinical utility is the measurement of arterial stiffness (AS). In the general population, AS has been associated with acute weight gain and is predictive of cardiovascular events later in life. Accordingly, stiffening of the central arteries is one of the major vascular changes observed in pregnant women destined to develop PrE.

Indeed, the *predictive value of arterial stiffness on the development of preeclampsia* (REVEAL), a previous study from Dr. Daskalopoulou's Lab, was conducted to evaluate the predictive ability of AS in high-risk pregnant women. In this study, they identified a changepoint in AS in early pregnancy; women who subsequently developed PrE had a higher AS than those who did not develop PrE. AS was found to predict PrE earlier and with greater predictive ability than existing predictive tools, such as blood pressure, biomarkers, and uterine artery ultrasound. Additionally, it was determined that women with SDB had higher AS throughout pregnancy than women without SDB. Informed by REVEAL, the *early prediction of preeclampsia using arterial stiffness in high-risk pregnancies: a multinational study* (PULSE) aims to confirm and validate the REVEAL findings by examining AS in a multi-model approach to PrE prediction in high-risk pregnant women. Current studies examining SDB or PrE and weight gain in pregnancy have focused on either pre-pregnancy weight or total pregnancy weight gain. However, early pregnancy weight gain in high-risk pregnancies and its impact on the development of PrE and SDB have yet to be explored.

Methodology: This project incorporates data from high-risk pregnant women in the REVEAL study (N=188) and a smaller subset of women from the ongoing PULSE study (N=118). Both REVEAL and PULSE recruited women from the obstetrics clinic between 10-13 weeks' gestation. The REVEAL study followed women throughout pregnancy until 12 weeks post-partum, whereas PULSE focuses on the first and second trimester of pregnancy. AS measurements, as well as sleep and weight-related questionnaires were gathered for each trimester visit. AS was measured non-invasively using applanation tonometry through the validated SphygmoCor System, while sleep was assessed using the Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index.

Objective: The overall objective of my project was to determine the association between early pregnancy weight gain and AS in the development of PrE and SDB in high-risk women. Specifically, my objectives were to examine 1) weight gain patterns and AS values in high-risk pregnant women in the first and second trimester of pregnancy, and 2) the impact of weight gain trajectories and AS on the development of a) PrE and b) SDB in pregnant women at high risk of developing PrE.

Hypothesis: We hypothesized that 1) high-risk pregnant women with higher pre-pregnancy body mass index (BMI) and/or excessive weight gain in early pregnancy and across gestation would have a significant increase in AS, and 2) women with higher pre-pregnancy BMI and/or excessive weight gain and higher AS would be more likely to develop a) PrE and b) SDB compared to those who gain normal amounts of weight.

Results: We first analyzed the association between AS and weight gain in each trimester during pregnancy. Through the analysis of REVEAL data, we identified that pregnancy weight gain is not associated with AS during the first, second, and third trimester ($p>0.05$). However, early pregnancy weight gain is significantly associated with increased AS from the first to second trimester ($p<0.05$). Additionally, pre-pregnancy BMI is strongly associated with increased AS throughout pregnancy ($p<0.01$). There was a graded increase in AS across BMI categories, where women in higher BMI categories had higher AS during each trimester. Despite the small sample size at the time, we confirmed a strong association between pre-pregnancy BMI and AS in early pregnancy ($p<0.05$).

Secondly, we examined the impact of AS and weight gain on the development of PrE. We identified a positive association between AS trajectories and the development of PrE ($p<0.01$). Late pregnancy weight gain is significantly associated with 1.19-fold increased odds of developing PrE ($p<0.05$); however, early pregnancy weight gain is not associated with the development of PrE ($p>0.05$). Through PULSE data, we identified that the AS trajectory in early pregnancy is non-significantly associated with 1.8-fold odds of developing PrE. However, the lack of significance in the PULSE study is likely due to the smaller sample size.

Finally, through REVEAL data, we examined the impact of AS and weight gain on the presence of SDB during pregnancy. AS trajectories throughout each trimester are significantly associated with 1.6-fold increased odds of gestational SDB ($p<0.05$). Additionally, early pregnancy weight gain is significantly associated with 0.77-fold decreased odds of gestational SDB ($p<0.05$). However, late pregnancy weight gain is not associated with gestational SDB ($p>0.05$). Accordingly, through PULSE data, we confirmed that the AS trajectory in early pregnancy is associated with a significant 1.15-fold increased odds of gestational SDB ($p<0.05$). However, first trimester AS was associated with a non-significant 1.56-fold odds for gestational SDB.

Conclusion: In summary, there is a strong association between pre-pregnancy BMI and AS, irrespective of the amount of weight gained during pregnancy. Early pregnancy weight gain is associated with an increase in AS and increased odds of gestational SDB, while late pregnancy weight gain is associated with increased odds of developing PrE. Future research should determine specific AS cut-offs based on pre-pregnancy BMI for the development of PrE and SDB.

Résumé

Introduction: La grossesse augmente le risque de développer des troubles respiratoires du sommeil (TRS), l'apnée obstructive du sommeil (AOS) touchant 8,3 % des femmes à la mi-gestation. Les comorbidités et les changements hormonaux/physiologiques associés à la grossesse, notamment la prise de poids et les niveaux d'œstrogènes, peuvent contribuer au développement des TRS pendant la grossesse. Les femmes enceintes atteintes de AOS présentent un risque accru de morbidité et de mortalité ; elles sont associées au développement de troubles hypertensifs de la grossesse, tels que la prééclampsie (PrE), qui peuvent avoir de graves effets néfastes sur la mère et le fœtus. Récemment, des efforts croissants ont été déployés pour mettre au point des outils de dépistage efficaces en début de grossesse, capables de prédire avec précision l'apparition de troubles hypertensifs de la grossesse aux stades ultérieurs de la gestation.

La mesure de la rigidité artérielle (RA) est une méthode qui pourrait avoir une grande utilité clinique. Dans la population générale, la RA a été associée à une prise de poids aiguë et permet de prédire les événements cardiovasculaires ultérieurs. En conséquence, la rigidité des artères centrales est l'un des principaux changements vasculaires observés chez les femmes enceintes destinées à développer une PrE.

En effet, *la valeur prédictive de la rigidité artérielle sur le développement de la prééclampsie* (REVEAL), une étude précédente du laboratoire du Dr Daskalopoulou, a été menée pour évaluer la capacité prédictive de la RA chez les femmes enceintes à haut risque. Dans cette étude, ils ont identifié un point de changement dans la RA en début de grossesse; les femmes qui ont ensuite développé une PrE avaient une RA plus élevée que celles qui n'ont pas développé la PrE. Il a été constaté que la RA permettait de prédire la PrE plus tôt et avec une plus grande capacité de prédiction que les outils de prédiction existants, tels que la pression artérielle, les biomarqueurs et l'échographie de l'artère utérine. De plus, il a été déterminé que les femmes souffrant des TRS présentaient une RA plus élevée tout au long de la grossesse que les femmes sans TRS. S'inspirant de l'étude REVEAL, l'étude *prédiction précoce de la prééclampsie à l'aide de la rigidité artérielle dans les grossesses à haut risque : une étude multinationale* (PULSE) vise à confirmer et à valider les résultats de l'étude REVEAL en examinant la RA dans le cadre d'une approche multi-modèle

de la prédiction de la prééclampsie chez les femmes enceintes à haut risque.. Les études actuelles portant sur les TRS ou la PrE et la prise de poids pendant la grossesse se sont concentrées sur le poids avant la grossesse ou sur la prise de poids totale pendant la grossesse. Cependant, la prise de poids en début de grossesse chez les femmes enceintes à haut risque et son impact sur le développement de la PrE et des TRS n'ont pas encore été explorés.

Méthodologie: Ce projet intègre les données des femmes enceintes à haut risque de l'étude REVEAL (N=188) et d'un plus petit sous-ensemble de femmes de l'étude PULSE en cours (N=118). Les études REVEAL et PULSE ont toutes deux recruté des femmes à la clinique d'obstétrique entre 10 et 13 semaines de gestation. L'étude REVEAL a suivi les femmes tout au long de la grossesse jusqu'à 12 semaines post-partum, tandis que l'étude PULSE se concentre sur le premier et le deuxième trimestre de la grossesse. Des mesures de la RA, ainsi que des questionnaires sur le sommeil et le poids ont été recueillis pour chaque visite trimestrielle. La RA a été mesurée de manière non invasive à l'aide d'une tonométrie par applanation grâce au système validé SphygmoCor, tandis que le sommeil a été évalué à l'aide du Epworth Sleepiness Scale et du Pittsburgh Sleep Quality Index.

Objectif: L'objectif global de mon projet était de déterminer l'association entre la prise de poids en début de grossesse et la RA dans le développement de la PrE et des TRS chez les femmes à haut risque. Plus précisément, mes objectifs étaient d'examiner 1) les trajectoires de prise de poids et les valeurs de RA chez les femmes enceintes à haut risque au cours du premier et du deuxième trimestre de la grossesse, et 2) l'impact des trajectoires de prise de poids et de la RA sur le développement de la a) PrE et des b) TRS chez les femmes enceintes à haut risque de développer un PrE.

Hypothèse: Nous avons émis l'hypothèse que 1) les femmes enceintes à haut risque ayant un indice de masse corporelle (IMC) plus élevé avant la grossesse et/ou une prise de poids excessive en début de grossesse et tout au long de la gestation présenteraient une augmentation significative de la RA, et 2) les femmes ayant un IMC plus élevé avant la grossesse et/ou une prise de poids excessive et une RA plus élevée seraient plus susceptibles de développer a) la PrE et b) des TRS par rapport à celles qui prennent un poids normal.

Résultats: Nous avons d'abord analysé l'association entre la RA et la prise de poids au cours de chaque trimestre de la grossesse. Grâce à l'analyse des données REVEAL, nous avons identifié que la prise de poids pendant la grossesse n'est pas associée à la RA Cependant, la prise de poids en début de grossesse est significativement associée à une augmentation de la RA du premier au deuxième trimestre ($p<0,05$). De plus, l'IMC avant la grossesse est fortement associé à une augmentation de la RA tout au long de la grossesse ($p<0,01$). On a observé une augmentation graduelle de la RA dans les catégories d'IMC, les femmes des catégories d'IMC supérieures présentant une RA plus élevée au cours de chaque trimestre. Malgré la petite taille de l'échantillon à l'époque, nous avons confirmé une forte association entre l'IMC avant la grossesse et la RA en début de grossesse ($p<0,05$).

Ensuite, nous avons examiné l'impact de la RA et de la prise de poids sur le développement de la PrE. Nous avons identifié une association positive entre les trajectoires de RA et le développement de la PrE ($p<0,01$). La prise de poids en fin de grossesse est significativement associée à une probabilité 1,19 fois plus élevée de développer la PrE ($p<0,05$); cependant, la prise de poids en début de grossesse n'est pas associée au développement de la PrE ($p>0,05$). Grâce aux données de l'étude PULSE, nous avons identifié que la trajectoire de la RA en début de grossesse est associée de manière non significative à une probabilité 1,8 fois plus élevée de développer une PrE. Cependant, l'absence de signification dans l'étude PULSE est probablement due à la taille plus réduite de l'échantillon.

Enfin, grâce aux données de l'étude REVEAL, nous avons examiné l'impact de la RA et de la prise de poids sur la présence de TRS pendant la grossesse. Les trajectoires de RA tout au long de chaque trimestre sont associées de manière significative à une probabilité 1,6 fois plus élevée d'avoire des TRS gestationnel ($p<0,05$). De plus, la prise de poids en début de grossesse est significativement associée à une diminution de 0,77 fois du risque d'avoire des TRS gestationnel ($p<0,05$). Cependant, la prise de poids en fin de grossesse n'est pas associée au risque de syndrome de Down gestationnel ($p>0,05$). Par conséquent, grâce aux données de l'étude PULSE, nous avons confirmé que la trajectoire de la RA en début de grossesse est associée à une augmentation

significative de 1,15 fois du risque d'avoire des TRS gestationnel ($p<0,05$). Cependant, la RA du premier trimestre est associée à un risque non significatif de 1,56 fois pour les TRS gestationnel.

Conclusion: En conclusion, il existe une forte association entre l'IMC avant la grossesse et la RA, quelle que soit la quantité de poids prise pendant la grossesse. La prise de poids en début de grossesse est associée à une augmentation de la RA et à un risque accru de TRS gestationnel, tandis que la prise de poids en fin de grossesse est associée à un risque accru de développer la PrE. Les recherches futures devraient déterminer des seuils spécifiques de RA basés sur l'IMC avant la grossesse pour le développement du PrE et des TRS.

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Contribution of Authors

Chapter 2

Sophia Bourgeois has contributed to the design of this project. Kim Phan, Yessica Haydee Gomez, and Jessica Gorgui were responsible for the recruitment, enrollment, and data collection of REVEAL participants. Sophia Bourgeois was responsible for the statistical data organization, analysis and interpretation of the results. Dr. Stella Daskalopoulou was responsible for the conception, design, implementation, and funding of the REVEAL study, and the design of this project. Additionally, Dr. Stella Daskalopoulou was responsible for the interpretation, revision, and approval of this project.

Chapter 3

Sophia Bourgeois has contributed to the design of this project. Mekayla Forrest and Sophia Bourgeois were responsible for the recruitment, enrollment, and data collection of PULSE participants. Sophia Bourgeois was responsible for the statistical data organization, analysis and interpretation of the results. Dr. Sarah Caughlin and Dr. Helena Papacostas Quintanilla were administrators of the PULSE project and were responsible for the implementation and organization of the study. Dr. Stella Daskalopoulou was responsible for the conception, design, implementation, and funding of the PULSE study, and the design of this project. Additionally, Dr. Stella Daskalopoulou was responsible for the interpretation, revision, and approval of this project.

Abbreviations

AHI	Apnea-hypopnea index
AIx	Augmentation index
AS	Arterial stiffness
BMI	Body mass index
BP	Blood pressure
cfPWV	Carotid-femoral pulse wave velocity
CI	Confidence intervals
CPAP	Continuous positive airway pressure
ESS	Epworth sleepiness scale
HDPs	Hypertensive disorders of pregnancy
IOM	Institute of Medicine
MAP	Mean arterial pressure
OR	Odds ratio
OSA	Obstructive sleep apnea
PrE	Preeclampsia
PSQI	Pittsburgh sleep quality index
PTT	Pulse transit time
PWA	Pulse wave analysis
PWV	Pulse wave velocity
SDB	Sleep disordered breathing
SOGC	Society of Obstetricians and Gynaecologists of Canada

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Chapter 1: Introduction and Literature Review

1.1 Sleep Disordered Breathing

It is estimated that Sleep disordered breathing (SDB) affects 5.4 million Canadian adults, as they are either already diagnosed with or at high risk of developing SDB(1). SDB is characterized by fragmented sleep and intermittent hypoxia(2). It encompasses a group of disorders that range in severity from minor conditions, such as snoring, to more severe disorders, such as obstructive sleep apnea (OSA)(2). Risk factors for SDB can be modifiable, such as excessive weight gain/obesity, comorbidities, and smoking, and unmodifiable, such as age, sex, and ethnicity(1, 3). Although many tools have been developed to diagnose and treat SDB, it is frequently underdiagnosed, especially in pregnancy(4-6).

OSA is a chronic condition characterized by episodes of complete or partial obstruction of the airway that leads to oxygen desaturation and arousal during sleep(2). Many patients with OSA are unaware of their apneic episodes and suffer from fragmented sleep and daytime fatigue(1). The hypoxic conditions caused by apneic events inflict stress on the cardiovascular system through sympathetic overactivation and vasoconstrictive-induced surges in blood pressure(7, 8). In the general population, OSA has been associated with a number of cardiovascular complications, such as hypertension, stroke, heart failure, and heart attacks(7).

SDB is most frequently assessed by symptom-based questionnaires, at-home sleep tests, and, most reliably, in-clinic overnight polysomnography. Polysomnography, the gold standard for diagnosing SDB, measures several indexes. The most frequently reported index, apnea-hypopnea index (AHI), is a measure of the frequency of apneic and hypopneic events per hour of sleep and is indicative of snoring and flow limitations(8). Symptoms of SDB, such as snoring, with minimal AHI, are indicative of minor SDB conditions, while an AHI of 5 events or greater per hour with symptoms or 15 events or greater per hour without symptoms is the threshold for OSA(2, 8). The severity of OSA increases with increasing apnea-hypopnea events(8).

Although polysomnography is the gold standard for diagnosing SDB, they have long waiting times, is costly, and require patients to sleep in overnight clinics. Therefore, many clinicians opt for an at-home sleep test or symptom-based questionnaires as they can be done at the patient's convenience and are cost-effective. Several questionnaires are used to determine a patient's likelihood of having SDB, such as the self-reported snoring, tiredness, observed apneas, high blood pressure, body mass index (BMI), age, neck-circumference, and gender (STOP-

BANG), Belin Questionnaire, Pittsburgh Sleep Quality Index (PSQI), and Epworth Sleepiness Scale (ESS)(9-12). Symptom-based questionnaires are not used as a diagnostic tool but rather to indicate the need for urgent polysomnography.

The PSQI and ESS are some of the most commonly used sleep-related questionnaires. The PSQI is a seven-component questionnaire that assesses patients' sleep quality (sleep quality, sleep latency, sleep duration, sleep efficiency, sleep, sleep disturbance, use of sleep medications, and daytime dysfunction) over a one-month interval(12). The PSQI has been validated in the general population and was found to have good constructive validity and reliability for sleep quality in pregnant women (Cronbach's alpha = 0.74)(10, 13). The ESS assesses a patient's daytime sleepiness, one of the most prominent symptoms of SDB(11). The ESS comprises 8 questions regarding the likelihood of dozing off in different situations. A systematic review and meta-analysis demonstrated that the internal consistency of the ESS was good in the general population(11). However, the individual-level comparison was not. In the obstetrics population, Baumgartel, Terhorst (14) demonstrated that ESS is an appropriate tool to measure daytime sleepiness and revealed moderate reliability (Cronbach's alpha = 0.75).

Importantly, patients diagnosed with OSA can be treated with continuous positive air pressure (CPAP) to increase oxygen supply and reduce apneic events(7, 8). While clinical guidelines have been established for diagnosing SDB in the general population, these, especially OSA, have yet to be defined in the pregnant population.

1.2 Pregnancy and Sleep Disordered Breathing

Mild forms of SDB, such as snoring, affect one-third of pregnant women, of which 25% are believed to have developed snoring during pregnancy. Pregnant women are particularly vulnerable to SDBs due to hormonal and physiological changes, such as acute weight gain, rhinitis, and increased estrogen levels(3, 5, 15). Interestingly, excessive weight gain and obesity are the most prominent risk factors for developing OSA(16). However, the significance of acute weight gain experienced during pregnancy on the development of SDB has not been studied. In the general population, a 10% increase in body mass is associated with a 6-fold increased risk of developing moderate to severe SDB(17). During pregnancy, women of normal body mass index are recommended to gain 25-35lbs, averaging more than 10% of their body mass(18). Additionally,

44% of these women gain excessive weight during pregnancy(19). Moreover, the rise in estrogen and progesterone levels increases the risk of edema, especially rhinitis, which may cause difficulty breathing during sleep and may predispose women to develop SDB(5, 15). Current studies have identified that pregnancy increases a woman's risk of developing severe forms of SDB, which are associated with maternal-fetal complications, such as hypertensive disorders of pregnancy (HDPs) (20-22).

There are challenges in diagnosing pregnant women with SDB, as there is a lack of provider awareness, lack of research, and excessive waiting times for polysomnography which can extend beyond the duration of the pregnancy(5). Two phenotypes have been proposed for the diagnosis of SDB during pregnancy; those who had SDB pre-pregnancy but pregnancy amplified the symptoms and those who developed SDB due to pregnancy(3). However, these hypothesized phenotypes have yet to be defined as pregnant women are often excluded from studies(5, 15). Pregnant women are underdiagnosed due to the overlapping symptoms between SDB and pregnancy, the lack of pregnancy-specific SDB symptoms, the lack of institutional guidelines, and the limited data on the effects of CPAP in pregnant women(5, 23). As a result, many pregnant women with OSA do not receive CPAP treatment that could otherwise potentially reduce their risk of developing the various cardiovascular complications associated with OSA, such as hypertension.

1.3 Hypertensive Disorders of Pregnancy

HDPs include chronic hypertension, gestational hypertension, preeclampsia (PrE), and chronic hypertension with superimposed PrE. They are characterized by the presence of high blood pressure during pregnancy and differ based on the onset of hypertension and the presence or absence of other factors such as proteinuria and end-organ dysfunction(24). As per the Society of Obstetrics and Gynecology Canada (SOGC), chronic hypertension is defined as the onset of hypertension before the 20th week of pregnancy. Gestational hypertension is defined as the new onset of hypertension after 20 weeks' gestation. PrE is defined as the new-onset of hypertension after 20 weeks' gestation in combination with other factors such as proteinuria and end-organ dysfunction. Finally, chronic hypertension with superimposed PrE is defined as chronic hypertension with the development of other factors, such as proteinuria and end-organ dysfunction

20 weeks' gestation. HDPs, such as PrE, can cause severe health issues for both the mother and the developing fetus, including premature delivery, renal and hepatic complications, intracranial hemorrhage, placental abruption, and death(25). PrE is one of the leading causes of maternal and fetal deaths worldwide, accounting for 70 000 maternal and 500 000 fetal deaths yearly(25). PrE occurs in 5-8% of pregnancies, with higher rates occurring in developing countries(26). Unfortunately, one of the only successful treatment options for PrE is labour induction, regardless of gestational age(25). The impacts of PrE extend beyond the pregnancy, as PrE increases the risk for cardiovascular events later in life(25).

Although the pathogenesis and pathophysiology of PrE are still being uncovered, it is accepted that PrE, specifically early-onset PrE, begins with abnormal placentation followed by the symptoms of PrE such as hypertension and proteinuria, end-organ dysfunction or abnormal fetal growth(27). Indeed, the placentas of women who develop PrE typically have signs of impaired implantation, insufficient uteroplacental blood flow, and ischemia(27, 28). During healthy pregnancies, spiral arteries develop into large capacitance vessels of low resistance, allowing oxygen, nutrient and waste exchange for the developing fetus(28). However, the pathological reports of placentas from PrE women commonly have narrow spiral artery formation, causing insufficient blood flow and increased pressure in the uterine arteries(27, 28). Therefore, ultrasound images of uterine blood flow and placental perfusion in combination with blood pressure, ischemic biomarkers, and clinical risk factors are used in earlier stages of pregnancy to predict the development of PrE. Unfortunately, these clinical tools only predict 42.5% of term preeclampsia cases(29).

Many physicians and scientists have focused on developing clinical tools to help predict PrE as it can have detrimental consequences on mother and fetus(25). As per the Society of Obstetrics and Gynecology Canada (SOGC), risk factors for PrE include a history of PrE, chronic hypertension, diabetes mellitus, obesity, maternal age, and black race, amongst others(24). Women with a history of PrE have a 7 to 10 times increased risk of developing PrE in subsequent pregnancies; however, early aspirin intervention can be used to reduce the development of PrE(25, 30). Additionally, 60% of preeclampsia-related maternal deaths are suspected to be preventable(31). Unfortunately, predicting PrE is challenging, and physicians are still searching for more accurate and early predictive tools.

1.4 Hypertensive Disorders of Pregnancy and Sleep Disordered Breathing

There has been increasing interest in discovering the impact of SDB in pregnancy. SDB affects 3.6% of pregnant women by early pregnancy and 8.3% of pregnant women by mid-gestation(22). Several studies have reported an association between SDB and pregnancy complications (20-22). Mild forms of SDB, such as snoring, have been associated with higher rates of gestational diabetes, PrE, and gestational hypertension(3, 20, 22, 32). The association between SDB and HDPs has been identified in studies using varying methods to evaluate SDB, such as polysomnography and symptom-based questionnaires(20, 22). To date, several published systematic reviews have investigated the relationship between SDB and HDPs. In 2013, Pamidi, Pinto (33) identified an association between SDB and gestational hypertension/PrE (OR, 2.34; 95%CI, 1.60-3.09) and gestational diabetes mellitus (OR, 1.86; 95% CI, 1.30-2.42)(33). A year later, Ding, Wu (34) identified similar associations between moderate-severe SDB and gestational hypertension (OR, 2.38; 95%CI, 1.63-3.47), PrE (OR, 2.19; 95%CI, 1.71-2.80), gestational diabetes mellitus (OR, 1.78; 95%CI, 1.29-2.46), and other fetal complications. Most recently, a systematic review in 2018 by Li, Zhao (35) and one in 2021 by Lu, Zhang (36), further confirmed an association between SDB and gestational hypertension and PrE.

Although there is an evident association between SDB and PrE, the precise pathophysiology that may link them has yet to be uncovered. Causality has yet to be defined; however, SDB has been suggested as a potentially modifiable risk factor for HDPs(22). Furthermore, cases of gestational SDB and PrE are expected to increase with the rise in the obesity epidemic.

1.5 Obesity and Pregnancy Weight Gain

Interestingly, both OSA and PrE have similar risk factors and long-term maternal cardiovascular outcomes. Obesity is a prominent risk factor for SDB and is a moderate risk factor for PrE. Currently, one-third of pregnant Canadian women are overweight/obese(37). Analysis of the National Inpatient Sample database identified that women with OSA had an increased risk of developing PrE (OR, 2.5; 95%CI, 2.2−2.9) and that obesity exacerbated the adverse effects of OSA(21). Like SDB and PrE, excessive adipose tissue can impair vascular and metabolic pathways. Although many studies have found a strong association between HDPs, especially PrE,

and SDB, many have overlooked the confounding effects that BMI and gestational weight gain can have on SDB and the development of PrE(21, 35, 38). Interestingly, in a study by Wilson, Walker (39) the association between HDPs and SDB was examined while accounting for BMI as a covariate. By BMI matching participants, they found that there was no significant difference in SDB cases between women with and without gestational hypertension/PrE. However, severe SDB was two times more frequent in women with gestational hypertension/PrE than those without(39). Therefore, it is imperative to acknowledge and study the consequences of obesity in pregnant women.

Pre-pregnancy obesity increases the risk of pregnancy complications such as PrE, gestational hypertension, gestational diabetes, stillbirths, as well as labour and delivery complications(40-42). In a subset of obese women, a dose-response relationship has been observed between BMI obese class I, II, and III, and the development of PrE(43). Furthermore, there is limited success from weight management interventions during pregnancy(41). Therefore, the SOGC has encouraged clinicians to implement pre-conception and prenatal care guidelines to reduce pre-pregnancy obesity and the risk associated with it(41).

Additionally, the Institute of Medicine (IOM) has released guidelines to help ensure women gain the appropriate amount of weight during pregnancy(24). Based on their pre-pregnancy BMI, underweight, normal-weight, overweight and obese women are recommended to gain between 28-40lbs, 25-35lbs, 15-25lbs, and 11-20lbs throughout pregnancy respectively (24). Women of higher pre-pregnancy BMI are recommended to gain less weight than those of lower BMIs as they are already at higher risk of pregnancy complications(40, 42, 43). Gaining below the recommended range is associated with complications such as small for gestational age and preterm birth, while gaining above the recommended range is associated with gestational hypertension, gestational diabetes, and labour and delivery complications(19, 24, 44, 45). Analysis of data from the Canadian Maternity Experiences Survey found that more than half (59.4%) of women gained more than the recommended range(37). In this study, they identified that excessive gestational weight gain contributed more to adverse outcomes than pre-pregnancy BMI(37). However, they did not evaluate adverse outcomes such as HDPs(37).

With the rising obesity epidemic, the effects of pre-pregnancy BMI and gestational weight gain on maternal and fetal health have gained more attention. Several studies have found strong positive associations between late/total pregnancy weight gain and fetal and maternal complications(19, 37, 40, 44-47). However, studies evaluating the relationship between early pregnancy weight gain and the development of complications later in pregnancy are lacking.

To our knowledge, only two studies have investigated the relationship between early pregnancy weight gain and PrE. In 2013, Macdonald-Wallis, Tilling (45) were the first group to have reported a positive association between early pregnancy weight gain (18 weeks gestation) and the development of PrE (OR, 1.31; 95%CI, 1.07-1.62.). Similarly, Bodnar, Himes (46) reported an association between early pregnancy weight gain (16-19 weeks gestation) and the development of PrE. Interestingly, instead of analyzing absolute weight gain and the risk of PrE amongst women of all BMI categories, they standardized gestational weight gain for gestational duration using BMI-specific z-score chart(46). They reported a positive dose-response relationship between weight gain and risk of PrE in normal-weight and obese women. Additionally, Bodnar, Himes (46) identified that weight loss in obese women was associated with decreased odds of developing PrE.

Additional studies are required to confirm the findings found by Macdonald-Wallis, Tilling (45), Bodnar, Himes (46). Identifying the impacts of early pregnancy weight gain on the development of pregnancy outcomes has the potential to aid predictive tools for the development of PrE. Although PrE is a complication of pregnancy known to have severe and detrimental consequences on both mother and fetus, its prediction has remained a challenge. Many physicians and researchers are determined to find early and accurate predictions of PrE. Recently, using arterial stiffness (AS) as a predictor of PrE is of large interest.

1.6 Arterial Stiffness

In recent years, AS has developed as a new tool for predicting cardiovascular health. AS is an indicator of vascular dysfunction as it reflects the mechanical properties of arteries(48). AS represents the stiffening of central arteries and depicts the aorta's ability to expand with pressure(49). The largest artery, the aorta, starts at the left ventricle and branches off into smaller arteries and finally into capillaries(50). Large arteries are composed of endothelial cells, smooth

muscle cells and matrix proteins such as collagen and elastin, which are responsible for buffering stroke volume and controlling blood pressure and flow(50). In smaller peripheral vessels such as arterioles, there is a decrease in elastin and an increase in smooth muscle cells(48). Waves propagating from the aorta will increase in pressure as they branch into smaller vessels. With every left ventricular contraction, there is an increase in pressure exerted on the aorta. In order to control the pressure in the circulatory system, the aorta stretches and increases in diameter, thereby decreasing the pressure and flow of the blood in peripheral vessels(48, 50). The elastin allows the artery to expand while collagen protects the integrity of the aorta.

AS increases with age, obesity, and hypertension(51). As arteries increase in inelastic properties, such as collagen, they become stiffer, and their ability to compensate for the increase in blood pressure and flow declines(48). A decrease in elastin prevents the aorta's ability to expand in diameter. As such, the aorta cannot compensate for the increase in blood pressure, and the blood travels at a higher speed. AS affects arterial diameter, blood pressure, and blood flow(51, 52).

Pressure catheters can be used as a direct method of measuring aortic blood pressure. Although this method is the most reliable measure of AS, it is invasive and requires the procedure to be performed in catheterization laboratories(53). As AS has a high degree of clinical utility, several non-invasive measures have been developed(49).

AS is primarily characterized by pulse pressure wave propagation, pulse wave velocity (PWV), and pulse wave analysis (PWA). PWV is measured as the distance travelled by a pulse wave over a certain transit time(54). Importantly, PWV is recommended as a reliable measure of AS by the European Society of Hypertension European Society of Cardiology Guidelines for the Management of Arterial Hypertension, the European Network for Non-invasive Investigation of Large Arteries, amongst several other hypertension guidelines in China, Korea, and Japan(55-57). Different methods of measuring PWV exist, such as tonometry-based techniques, oscillometric devices, ultrasound imaging, and magnetic resonance imaging(49).

PWV can be measured at different sites, such as carotid-radial, ankle-brachial, carotid-femoral, and cardio-ankle vascular index(49). However, the gold standard for measuring AS is by carotid-femoral PWV (cfPWV). cfPWV is commonly measured as the indirect distance between

the carotid and femoral pulse sites divided by the propagation time; the difference in the time it takes for the foot of the pulse wave to reach the femoral site and carotid site (**Figure1.1)**(58). cfPWV is generally accepted as a reliable and direct measure of AS; an increase in cfPWV represents an increase in AS(55). cfPWV is frequently measured using a validated- tonometry-based device, while PWA is measured using a brachial cuff(58).

Figure 1.1–Diagram of cfPWV measurements

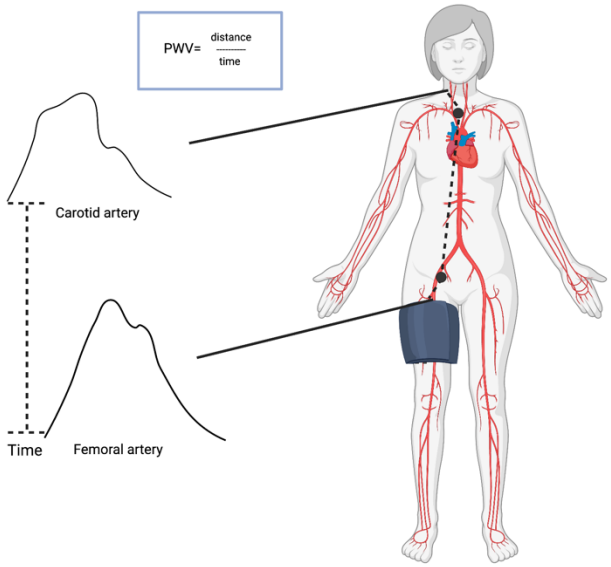

Image created with BioRender.com
cfPWV: carotid-femoral pulse wave velocity
PWV: pulse wave velocity

PWA allows for an in-depth understanding of the standard systolic and diastolic blood pressure waveforms. Using validated devices, PWA can non-invasively reconstruct central aortic blood pressure waveforms. PWA produces a composite waveform which is composed of a forward wave and a backwards wave. A forward pulse wave is generated during left ventricular ejection, and a backwards wave is created as the forward wave reflects off sites of bifurcation (**Figure 1.2**)(55, 59). In compliant arteries, the backward waves combine with the diastolic nadir. However, an increase in AS causes the forward waves to travel faster(52). The reflective waves return earlier (time to wave reflection), combining with the forward wave and results in an increase (augmentation pressure) in composite waveform (pulse pressure)(55). The pressure difference

between the original forward pulse wave and the augmented pulse wave is known as the augmentation index (AIx).

Figure 1.2–Pulse pressure composite waveform in compliant and stiffened arteries

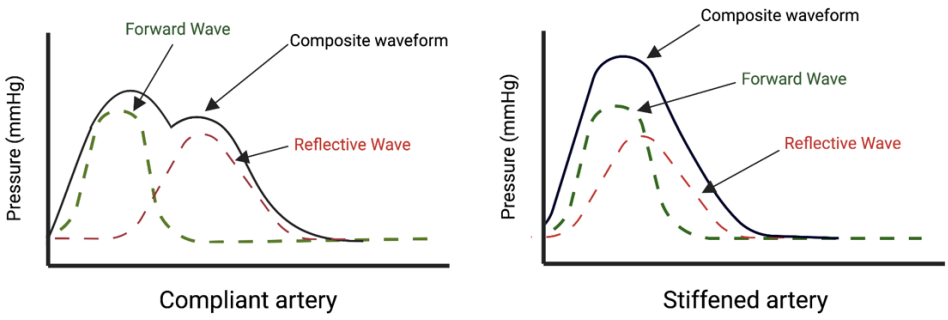

Image created with BioRender.com

The SphygmoCor devices are some of the earliest and most widely used non-invasive PWV devices (58). The most recent SphygmoCor XCEL device relies on applanation tonometry to capture the carotid pulse and a cuff-based approach to capture the femoral pulse. The XCEL device is less operator dependent as it has implemented the use of a thigh cuff. Importantly, the SphygmoCor system has been validated against invasive measurements of aortic PWV and has been employed in over 424 research studies(49). The SphygmoCor XCEL devices within-observer, between-observer, and inter-observer measures have been validated(60).

1.7 Arterial Stiffness and Obesity

Risk factors for AS can be either modifiable, such as obesity, or unmodifiable such as age(51). Obesity has been strongly associated with many comorbidities such as hypertension, dyslipidemia, glucose intolerance, and type 1 and 2 diabetes(61, 62). Using data from the Framingham study, Hubert, Feinleib (61) identified obesity as an independent predictor of cardiovascular events. In the general population, obese individuals have increased AS(63). Recently, the impacts of acute weight gain on AS has been explored by a few research groups(64-66). Benetos, Adamopoulos (66) evaluated the impacts of several variables on AS. In their 6-year longitudinal study, they did not find an association between weight gain and AS. However, in an

observational study by Wildman, Farhat (64), acute weight gain was associated with AS over a 2-year period. Additionally, in a subset of young adult men, Orr, Gentile (65) identified that diet-induced weight gain (~5kg) was associated with increased AS compared to baseline. Therefore, acute weight gain may be a potentially modifiable risk factor for AS; however, more research is required to elucidate this relationship.

In the general population, AS can be used to predict cardiovascular events such as stroke, myocardial infarction, and heart failure. In a study by Mitchell, Hwang (67), higher aortic PWV was associated with a 48% increase in cardiovascular risk in the general population. Additionally, AS is identified as a risk factor for clinical hypertension(59). AS is a better and more accurate indicator of vascular health than blood pressure alone(59, 68). Specifically, AS has a strong relative risk in young populations, which can allow for early identification and treatment(68). Although AS has proven to be useful in the general population and is implicated in clinical standards of care, its predictive capabilities in the pregnancy population are still being discovered.

Furthermore, it is anticipated that there will be a rise in cardiovascular disease, SDB and PrE cases as the obesity epidemic continues to rise(69). Interestingly, obesity-related AS is observed to affect a greater proportion of women than men(70). Obesity, SDB and PrE have each been associated with oxidative stress(7, 28, 70-72). However, the exact pathophysiological mechanisms linking weight gain, obesity, SDB and PrE have yet to be uncovered.

1.8 Arterial stiffness and Pregnancy

Pregnancy causes major hemodynamic changes to the cardiovascular system(73). In early healthy pregnancies, there is an increase in systemic vasodilation, increased cardiac output, decreased blood pressure, and decreased peripheral vascular resistance(73). These maternal cardiovascular changes compensate for a 40-45% increase in blood volume to support the growing fetus' needs(73). Recently, several studies have found that healthy pregnant women experience a decrease in AS in the early pregnancy followed by a steady incline in the second to third trimester(71, 74). However, an increase in AS during pregnancy has been associated with an increased risk of hypertension during pregnancy(74). An increase in AS has been observed not only at the time of PrE diagnosis but also proceeds the development of PrE(75).

Importantly, two independent systematic reviews have determined that PrE women have increased AS. In a meta-analysis of 23 studies, Hausvater, Giannone (74) determined that cfPWV and AIx were significantly higher in PrE women compared to both normotensive controls and women with gestational hypertension. Following the result published by Hausvater, Giannone (74), Osman, Nath (71) conducted a systematic review to determine the association between AS and the subsequent development of PrE. They identified that first-trimester AIx and second-trimester cfPWV were significantly higher in women who subsequently developed PrE compared to normotensive pregnant controls. These findings demonstrate the need to evaluate the predictive ability of AS in pregnant women.

Indeed, a previous study from Dr. Daskalopoulou's lab, REVEAL, was conducted to evaluate the predictive ability of AS in pregnant women at high risk of developing PrE. In this longitudinal study of 235 high-risk pregnant women, AS was found to be increased in women who subsequently developed PrE. Interestingly, a change point in AS was identified in early pregnancy (14-17 weeks' gestation). Women who did not develop PrE had a decrease in AS from 14-17 weeks' gestation with a nadir between 22-33 weeks' gestation. Whereas women who subsequently developed PrE had an increase in AS between 14-17 weeks' gestation with a peak at 22-25 weeks' gestation; cfPWV was 1.2m/s higher in women who develop PrE compared to those who did not. By the end of the third trimester, there was no significant difference between the two groups. Most importantly, they found that AS better predicted PrE earlier and with greater accuracy than current clinical tests (blood pressure, blood biomarkers, and ultrasound imaging)(75). Findings from REVEAL emphasize the potential clinical utility of AS in high-risk pregnant women.

1.9 Arterial Stiffness and Sleep Disordered Breathing

As previously discussed, SDB is significantly associated with cardiovascular disease(7). Recent studies have identified OSA as an independent risk factor for cardiovascular disease(61). Additionally, patients with SDB, especially OSA, frequently have additional risk factors for cardiovascular diseases, such as obesity, diabetes, and hypertension(61). Accordingly, SDB has been associated with AS in the general population(76-78).

The precise pathophysiologic changes associated with SDB that influence AS have yet to be established. However, the oxidative stress, sympathetic overactivation, and inflammation

experienced during apneic events are believed to contribute to AS(77, 78). During a hypopneic/apneic event, there is an obstruction to the airway that prevents proper airflow, leading to oxygen desaturation, sleep disruption and arousal. Episodes of hypopnea are associated with oxidative stress, endothelial dysfunction, and inflammation(72). Changes in cardiovascular hemodynamics, such as an increase in heart rate and blood pressure, are observed in response to prolonged hypopneic events(72). Therefore, several studies have investigated the association between SDB and AS(76-78).

In a systematic review of 24 studies, AS was consistently significantly associated with OSA in the included studies(78). AS was higher in patients with OSA compared to those without OSA. Most studies supported the association between OSA severity and the severity of AS. Additionally, the relationship between OSA and AS was further supported by several studies that found reduced AS in patients treated with CPAP treatment. Results from this systematic review suggest that there is a strong relationship between OSA and AS; however, women were underrepresented. Furthermore, SDB has been associated with increased AS in children and in premenopausal women(79, 80). However, its relationship in pregnant women remains elusive.

High-risk pregnancies, such as those with pre-pregnancy obesity, increase not only the risk of developing PrE but also SDB during pregnancy, which has also been associated with an increase in AS(32, 81). Specifically, a study conducted by Link, Eid (81), investigated the use of pulse transit time (PTT) in detecting SDB compared to AHI captured by polysomnography. PTT is inversely correlated to AS and is measured by the time it takes for a pulse wave propagated from the left ventricle to reach a peripheral site. It was noted that many women experienced airflow limitations that did not meet the threshold criteria for AHI established in the general population. However, PTT was better at identifying these airflow limitations in pregnant women than AHI(81).

Indeed, in the REVEAL study, SDB was assessed in high-risk pregnant women using a symptom-based questionnaire. Phan, Pamidi (32), determined that cfPWV was elevated throughout pregnancy compared to non-SDB women, independent of BP and BMI. Furthermore, daytime sleepiness, a hallmark of SDB, was associated with increased cfPWV in SDB women. Through the REVEAL study, Phan, Pamidi (32) determined that cfPWV was associated with the development of PrE as well as SDB, and that SDB was associated with increased odds of

developing PrE. Findings from this study clearly indicate a need to further evaluate the relationship between AS, PrE, and SDB, and potential covariates that may be involved. There is currently a knowledge gap regarding the risks associated with early pregnancy weight gain on AS and the development of SDB. Thus, exploring the impact of first-trimester weight gain on AS could help understand its potential link with the development of SDB.

1.10 Aims and Hypothesis

The overall aim of this thesis was to determine the association between early pregnancy weight gain and AS in the development of SDB and PrE in high-risk women. Specifically, we aimed to 1) Examine weight gain patterns and AS values in high-risk pregnant women in the first and second trimester of pregnancy, and 2) to examine the impact of weight gain trajectories and AS on the development of a) PrE and b) SDB in pregnant women at high risk of developing PrE.

We hypothesized that 1) high-risk pregnant women with higher pre-pregnancy body mass index (BMI) and/or excessive weight gain in early pregnancy and across gestation would have a significant increase in AS. 2) Women with higher pre-pregnancy BMIs and/or excessive weight gain and higher AS would be more likely to develop a) PrE and b) SDB compared to those who gain normal amounts of weight.

Chapter 2: Longitudinal Analysis of the REVEAL Study

Early Pregnancy Weight Gain and Arterial Stiffness in Gestational Sleep Disordered Breathing

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2.1 Abstract

Objective: Pregnancy characteristics, such as weight gain, increase a woman's risk of sleep disordered breathing (SDB). SDB is associated with increased arterial stiffness (AS) and, during pregnancy, is associated with preeclampsia (PrE). Furthermore, late pregnancy weight gain is associated with PrE. However, whether early pregnancy weight gain is associated with AS and the development of PrE and SDB is unknown.

Methods: carotid-femoral pulse wave velocity (cfPWV) was measured in high-risk pregnant women every four weeks throughout pregnancy. Women completed sleep-related questionnaires during each trimester. Weight was recorded during each obstetrics visit. Participants were monitored until 12 weeks post-partum for PrE.

Results: Of the 235 women enrolled, 188 participants successfully completed the study, 14 developed PrE, and 41 had SDB during pregnancy. We identified that pregnancy weight gain is not associated with AS during the first, second, and third trimester ($p>0.05$). However, early pregnancy weight gain is significantly associated with increased AS from the first to second trimester ($p<0.05$). Additionally, pre-pregnancy body mass index (BMI) is strongly associated with increased AS throughout pregnancy ($p<0.01$). There was a graded mean AS across BMI categories, where women of higher BMI categories had higher AS during each trimester.

We identified a positive association between AS trajectories and the development of PrE ($p<0.01$). Late pregnancy weight gain was significantly associated with 1.19-fold increased odds of developing PrE ($p<0.05$); however, early pregnancy weight gain was not associated with the development of PrE ($p>0.05$).

Finally, AS trajectories throughout each trimester were significantly associated with 1.6-fold increased odds for gestational SDB ($p<0.05$). Additionally, early pregnancy weight gain was significantly associated with 0.77-fold decreasing odds for gestational SDB ($p<0.05$), however, late pregnancy weight gain is not associated with gestational SDB ($p>0.05$).

Conclusion: In summary, there is a strong association between pre-pregnancy BMI and AS, irrespective of the amount of weight gained during pregnancy. Early pregnancy weight gain is associated with an increase in AS and increased odds for gestational SDB, while late pregnancy weight gain is associated with increased odds for developing PrE. Future research should determine specific AS cut-offs based on pre-pregnancy BMI for the development of PrE and SDB.

2.2 Introduction

It is estimated that 5.4 million Canadian adults are either already diagnosed with or at high risk of developing sleep disordered breathing (SDB)(1). SDB is a disorder characterized by fragmented sleep and intermittent hypoxia(2). It encompasses a group of disorders that range in severity from minor conditions, such as snoring, to more severe disorders, such as obstructive sleep apnea (OSA)(2). Risk factors for SDB included excessive weight gain/obesity and craniofacial features(2). The clinical implications of SDB, especially OSA, have been extensively studied and are well established in the general population; SDB has been linked to the development of cardiovascular complications, such as hypertension, stroke, heart failure, and heart attacks(7). Unfortunately, there is a lack of research on SDB in the pregnant population.

Pregnancy increases a woman's risk of developing SDB, with SDB affecting 3.6% of women in early pregnancy and 8.3% of women by mid-pregnancy(3, 22). Both comorbidities and hormonal/physiological changes associated with pregnancy, specifically weight gain and estrogen levels, are suspected to be responsible for the development of SDB in pregnancy(3). In the general population, excessive weight gain is a major risk factor for developing SDB, where a 10% body weight gain results in a 6-fold increase odds of developing moderate to severe SDB(17). Interestingly, during pregnancy, normal-weight women are recommended to gain more than 10% of their body weight(18).

Notably, pregnant women with SDB, especially OSA, are at increased risk of morbidity and mortality; it is associated with the development of gestational diabetes as well as hypertensive disorders of pregnancy (HDPs), such as preeclampsia (PrE)(21). PrE is characterized as the new onset of high blood pressure and end-organ dysfunction, such as proteinuria, after the 20th week of gestation; however, it is most frequently diagnosed in the third trimester(24). Unfortunately, one of the only treatments for PrE is to induce labour as it can have severe detrimental effects on both mother and fetus(24). Furthermore, SDB and PrE have similar risk factors, such as obesity, and increase the risk of cardiovascular events later in life(20, 38, 62, 77).

In Canada, 34% of pregnant women are overweight or obese(37). The prevalence of SDB amplifies with increasing body mass index (BMI), particularly in high-risk pregnancies(21). Current studies examining SDB and weight gain in pregnancy have focused on either pre-

pregnancy weight or total pregnancy weight gain; however, early pregnancy weight gain in high-risk pregnancies and its impact on the development of PrE and SDB, have yet to be explored(3). Recently, early pregnancy weight gain has been associated with the development of HDPs such as PrE(47, 82). However, more research is needed to validate this potentially critical predictive link.

There have been increasing efforts to establish effective screening tools in early pregnancy which can accurately predict the development of HDPs in the later stages of gestation. One method which has shown a high degree of clinical utility in the general population is the measurement of arterial stiffness (AS)(67). Stiffening of the central arteries is one of the major vascular changes observed in pregnant women destined to develop PrE(75). In the general population, even modest weight gain is directly correlated with increased AS(64). Interestingly, increased AS is predictive of cardiovascular events such as stroke, myocardial infarction, and heart failure(67). Research studies have found that pregnancy causes major changes in the mothers' vascular system(73). Indeed, a systematic review and meta-analysis identified that women with PrE had significantly higher AS throughout pregnancy compared to women who did not develop PrE(71, 74). A more recent study found that both pregnant women who snored and women with SDB have increased pulse transit time, an index of AS, compared to pregnant women without SDB(81). There is currently a knowledge gap regarding the risks associated with early pregnancy weight gain on AS and the development of SDB. Thus, exploring the impact of early pregnancy weight gain on AS could help understand its potential link with the development of SDB.

Therefore, our overall aim was to determine the association between early pregnancy weight gain and AS in the development of SDB and PrE in high-risk women. Specifically, we aimed to 1) Examine weight gain patterns and AS values in high-risk pregnant women in the first and second trimester of pregnancy, and 2) to examine the impact of weight gain trajectories and AS on the development of a) PrE and b) SDB in pregnant women at high risk of developing PrE.

We hypothesized that 1) high-risk pregnant women with higher pre-pregnancy body mass index (BMI) and/or excessive weight gain in early pregnancy and across gestation would have a significant increase in AS. 2) Women with higher pre-pregnancy BMIs and/or excessive weight gain and higher AS would be more likely to develop a) PrE and b) SDB compared to those who gain normal amounts of weight.

2.3 Methods

Ethical approval of this project was granted by the McGill University Health Center Research Ethics Board. Consent was obtained after a complete explanation of the study objectives and procedures.

Study Population

In this prospective longitudinal study, high-risk pregnant women in their first trimester, between 10 and 13 weeks' gestation, were recruited from the obstetrics clinic at the Jewish Hospital and Royal Victoria Hospital in Montreal, Canada. Women were identified as high-risk if they met the established clinical criteria for preeclampsia. Study visits were held every 4 weeks from 10^{th} week of gestation until delivery (i.e. 10^{th}, 14^{th}, 18^{th}, 22^{nd}… 38^{th} and 40^{th}) with one visit 6 weeks post-partum.

The inclusion criteria for high-risk pregnancies consisted of a history of PrE, chronic hypertension, diabetes mellitus, family history of PrE, body mass index (BMI) $\geq$25 kg/m^2, advanced maternal age (>35 years old), and those who conceived via in vitro fertilization. Women were excluded from the study if they had autoimmune disorders, coagulopathies, history of cigarette or illicit drug use, alcohol abuse and arrhythmias.

Anthropometric measurements and medical information

Study visits were held in conjunction with scheduled hospital appointments. Study visits consisted of AS measurements, blood draws, and questionnaires. Chart reviews were conducted for each trimester of pregnancy. Medical information obtained included participants' height, weights, obstetrics medical history and family medical history. Maternal and fetal outcomes, including the diagnosis of PrE was gathered once the participant completed the study 12 weeks postpartum. PrE diagnosis was adjudicated by an appointed study physician, Dr. Robert Gagnon.

AS was measured non-invasively by cfPWV using the validated tonometry-based SphygmoCor System. Participants completed sleep related questionnaires (Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index) at each trimester in-clinic visit.

Hypertensive Disorders of Pregnancy Diagnosis

Hypertensive disorders of pregnancy were diagnosed according to the Society of Obstetricians and Gynecologist of Canadian guidelines(24). Chronic hypertension was defined as hypertension diagnosed before pregnancy or before 20 weeks of pregnancy without the onset of proteinuria. Gestational hypertension was defined as the onset of hypertension (systolic >140 mmHg and diastolic > 90 mmHg) after 20 weeks of pregnancy without the onset of proteinuria. PrE was defined as the onset of hypertension coupled with one or more of the following: proteinuria, maternal organ dysfunction or hematological involvement, and/or uteroplacental dysfunction, including fetal growth restriction or abnormal uteroplacental blood flow from doppler ultrasounds. Finally, chronic hypertension with superimposed PrE occurs when PrE occurs in the context of pre-existing chronic hypertension.

Screening for Sleep Disordered Breathing

Participants complete the Pittsburgh Sleep Quality Index (PSQI) questionnaires during each trimester. Within the PSQI, participants were asked to how frequently they snored loudly or have long pauses between breaths while sleeping (i.e. apneas). Participants that experienced loud snoring or had long pauses between breaths ≥3 times a week were classified as having SDB.

Arterial Stiffness

AS was defined by carotid-femoral pulse wave velocity (cfPWV). AS measurements were gathered every 4 weeks from the 10^{th} week of gestation until delivery and included one measurement 6 weeks post-partum. cfPWV was measured using the SphygmoCor, AtCorMedical applanation tonometer. Participants were required to lay in the supine position for 10 minutes prior to AS measurements. A cuff was placed on the participants right tight to obtain the femoral pulse, while the tonometer was used to obtain a carotid pulse. The direct distance between the carotid and femoral pulse was used to obtain the cfPWV. Two cfPWV measurements were obtained for measurements within 0.5m/s. If the two measures were greater than 0.5m/s apart, a third measure was obtained, and the three cfPWV values were averaged.

cfPWV is measured as the distance travelled by a pulse wave over a certain transit time. Therefore, higher cfPWV values represent greater stiffening of the central arteries.

Pregnancy Weight Gain

Participants' weights were recorded at every obstetrics visit. Study staff members gathered participant weight measurements from pre-pregnancy until delivery from the medical charts.

Statistical Analysis

The baseline maternal characteristics of participants were tabulated. Histograms and tests of skewness and kurtosis were used to assess the normality of the data. Normally distributed continuous variables were reported as means and standard deviations, while those not normally distributed were reported as medians and interquartile ranges. Categorical variables were reported as frequency and proportions.

Comparison of continuous variables between PrE and non-PrE women, as well as between SDB and non-SDB women, were analyzed using Students T-test or Wilcoxon Ranksum. Categorical variables were analyzed using Fisher's exact test. Multiple group comparisons of continuous variables, such as in the case of BMI, were analyzed using ANOVA and post-hoc Tukey's test or Kruskal Wallis and Dunn's Test, while categorical variables were analyzed using Fisher's exact test.

The primary analysis was to measure the association between weight gain and AS during pregnancy. Weight gain and AS measurements were analyzed using simple linear regression. Continuous non-normally distributed data were transformed for linear regression.

The secondary analysis explores the association between weight gain and AS measurements in women who develop PrE compared to non-PrE women. Logistic regression was used to analyze the association between weight gain and/or AS during each trimester in women who subsequently developed PrE compared to those that did not. Mixed random effects model were used to analyze the association between weight gain and AS trajectories in women with and without PrE.

The tertiary analysis explored the association between weight gain and AS measurements in women who had SDB during pregnancy compared to non-SDB women. Logistic regression was used to analyze the association between weight gain and/or AS during each trimester in women with SDB compared those without SDB. Mixed random effects model was used to analyze the association between weight gain and AS trajectories in women with and without SDB. Analyses were adjusted for confounding variables, such as maternal age and black race as they were found to have a direct impact on AS. A two-sided p-value>0.05 was considered statistically significant. 95% confidence was used for linear regressions. Statistical analysis was performed using STATA 17.0.

2.4 Results

Sample demographics and characteristics

Of the 235 women recruited for the study, 21 women did not complete the study, 188 participated in the AS measurements, and 167 participated in the sleep-related questionnaires during at least one trimester (**Figure 2.1**). Of those included in the analysis, 14 women developed preeclampsia, and 41 had SDB at some point during pregnancy. The mean maternal age was 37.21 $\pm$ 4.11 years old, while the mean BMI was 24.74 [21.83, 29.74] (**Table 2.1**). As AS was measured every 4 weeks from the first trimester until 12 weeks throughout pregnancy, measurements from weeks 10, 22, and 34 were used as first, second, and third trimester measurements, respectively. Measurements from week 34 were used instead of week 38 as many women delivered prior to the 38th week of gestation. If the participant's measurements were missing for the respective weeks, the prior week's measurements were selected.

Of the women recruited, 8(4.5%) were underweight, 86(48.3%) were normal-weight, 43 (24.2%) were overweight, and 41 (23.0%) were obese. Pre-pregnancy BMI was based on recalled pre-pregnancy weight and height. BMI <19 was considered underweight, 19-25 normal-weight, 25-35 overweight, and >35 obese (**Table 2.2**). As seen in **Table 2.2,** underweight, normal-weight, and obese women gained weight within the recommended by the IOM range, while overweight women gained on average greater weight than the recommended range(18).

2.4.1 Pre-pregnancy body mass index, weight gain, and arterial stiffness

Kruskal Wallis Test was used as continuous variables were not normally distributed. We subcategorized women by pre-pregnancy and identified that there was no difference in early pregnancy weight gain, from the first to the second trimester, between women of different BMI categories (underweight, normal-weight, overweight, and obese) ($p>0.05$). However, there was a significant difference in late pregnancy ($p=0.035$) and total pregnancy weight gain between women of different BMI categories($p=0.016$). Women with higher pre-pregnancy BMIs were gaining less weight than those with lower pre-pregnancy BMI (**Table 2.2**).

Interestingly, pre-pregnancy BMI has a strong positive association with AS at all time points throughout pregnancy (**Figure 2.2**. first trimester: $\beta=0.084$, 95%CI: 0.059– 0.109, $p<0.01$, second trimester cfPWV: $\beta=0.060$, CI: 0.036– 0.084, $p<0.01$, and third trimester cfPWV: $\beta=0.058$, CI: 0.027–0.089, $p<0.01$). Baseline mean arterial pressure (MAP) was significantly higher in women with higher BMI compared to those with lower BMIs (**Table 2.2**). There was a steadily higher MAP from underweight to obese women (**Table 2.2**).

The relationship between weight gain and AS was assessed during each trimester of pregnancy. Using linear regression and adjusting for maternal age and black race, there was no association between weight gain and absolute cfPWV values at any timepoint in pregnancy (first trimester: $\beta=0.18$, 95%CI: -0.59, 0.96, $p=0.641$, second trimester: $\beta=-0.07$, CI: -0.44–0.30, $p=0.706$, third trimester: $\beta=-0.40$, CI: -0.84–0.04, $p=0.072$). There was a significant association between late trimester weight gain and third trimester cfPWV; however, this association was insignificant after adjusting for maternal age ($\beta=0.07$, CI: -0.14–0.01, $p=0.067$). As depicted in **Figure 2.3** early pregnancy weight gain is associated with an increase in cfPWV from the first to the second trimester (**Figure 2.3,** $\beta=0.09$, 95%CI: 0.01– 0.18, $p=0.033$). However, there was no significant association between late and total pregnancy weight gain and change in cfPWV (late pregnancy: $\beta=-0.01$, CI: -0.08–0.07, $p=0.853$, total pregnancy: $\beta=0.04$, CI: -0.14–0.09, $p=0.149$). Further analysis showed that the association between AS and weight gain remained insignificant even after adjusting for pre-pregnancy BMI ($p>0.05$).

Additionally, while adjusting for maternal age and black race, we found that relative weight gain was significantly negatively associated with absolute cfPWV values in each trimester (early pregnancy: $\beta=-5.39$, 95%CI: -10.67– -0.10, $p=0.046$, late pregnancy: $\beta=-6.78$,

CI: -11.30– -2.26, p<0.01). However, relative weight gain was not associated with a change in cfPWV between each trimester (early pregnancy: β=4.75, CI: -0.63–10.15, p=0.083; late pregnancy: β=1.14, CI: -3.44–5.73, p=0.623, total pregnancy: β=1.76, CI: 0.70, 4.21, p=0.160).

2.4.2 Weight Gain, arterial stiffness and preeclamptic patients

Of the women who participated in the REVEAL study, 14 developed PrE, while 174 did not develop PrE. **Table 2.3** outlines the difference in baseline characteristics between PrE women and non-PrE women. MAP is higher in women who develop PrE compared to those who do not (**Table 2.3, p=0.049**). Women who developed PrE had a significantly higher presence of pre-pregnancy diabetes (p=0.047) and history of PrE (**Table 2.3**, p=0.016). There was no difference in early, late, nor total pregnancy weight gain between women who developed PrE compared to those that did not develop PrE (p>0.05).

Using mixed random effects models, there was no association between early pregnancy weight gain and the development of preeclampsia; however, an increase in late pregnancy weight gain was associated with a 1.19 fold-increase in the odds risk of developing preeclampsia (**Table 2.4**, p=0.037). This remained significant even after adjusting for maternal age and black race. Additionally, cfPWV trajectories throughout each trimester was significantly associated with a 1.67-fold increased odds risk of developing PrE (**Table 2.4**).

2.4.3 Weight gain, arterial stiffness and sleep disordered breathing

Of the women who participated in REVEAL, 41 had some type of SDB during pregnancy, while 126 did not have SDB. **Table 2.5** describes the baseline characteristics of women with and without SDB. Baseline MAP was higher in SDB women than non-SDB women (**Table 2.5, p=0.028**). Women with SDB had significantly higher pre-pregnancy BMI compared to those that did not have SDB (**Table 2.5, p<0.01**). Although slightly insignificant, women with SDB were younger than those who did not develop SDB (p=0.05).

Using an unpaired students T-test, women with SDB gained significantly less weight in early pregnancy, from pre-pregnancy to second trimester, than those without SDB (p<0.01).

Interestingly, there was no difference in late nor total pregnancy weight gain between SDB and non-SDB women (**Table 2.5**, p>0.05).

Using mixed random effects models, an increase in early pregnancy weight gain decreased the predicted odds of having SDB during pregnancy by 0.77 (p=0.005). Interestingly, there was no association between late nor total pregnancy weight gain and SDB during pregnancy (**Table 2.6, p>0.05**). This remained insignificant even after adjusting for maternal age and black race. Additionally, cfPWV trajectories throughout each trimester was significantly associated with a 1.60-fold increased odds risk of having SDB during pregnancy (**Table 2.6, p=0.077**).

2.5 Discussion

In this study, we evaluated the relationship between weight gain, AS, PrE and gestational SDB in high-risk pregnant women from the REVEAL study. We identified a strong positive association between pre-pregnancy BMI and cfPWV throughout pregnancy. cfPWV was steadily higher from underweight to obese women throughout each trimester. We found that only in early pregnancy was there a positive association between weight gain and change in AS. Additionally, relative weight gain was negatively associated with absolute AS values. Despite gaining less weight, women of greater BMI have higher AS. Results from our study suggest that women with higher pre-pregnancy BMI have increased AS throughout pregnancy, regardless of the amount of weight gained during pregnancy.

The clinical application of AS measurements has been widely discussed amongst the scientific and medical communities. It is believed that AS will help guide future therapeutic decision-making. Therefore, many have tried to uncover the risk factors associated with AS and establish guides to reduce the prevalence of the modifiable risk factors. In the general population, risk factors for AS are age, obesity, diabetes mellitus, hypertension(52, 54, 67). Although it is known that obesity increases the risk of having stiffer arteries, the direct impact of acute weight gain on AS has only been explored by a few studies in the general population(64, 66). In a longitudinal analysis of young adults, acute weight gain was associated with an increase in AS, while weight loss was associated with a decrease in AS(64). Accordingly, we found that early pregnancy weight gain was associated with an increase in cfPWV in early pregnancy. However,

we did not find that late pregnancy weight gain was associated with late pregnancy change in AS. Relative weight gain was negatively associated with AS throughout pregnancy. In accordance with the IOM guidelines, women of higher pre-pregnancy BMI are recommended to gain less weight than women of lower BMI as they are already at higher risk of pregnancy complication(18). Therefore, the relationship between pregnancy weight gain and AS is likely influenced by pre-pregnancy BMI.

Additionally, obesity is a prominent risk factor for HDPs; PrE is almost 3 times more prevalent in obese women than normal-weight women(18). However, the impacts of pregnancy weight gain on the development of PrE have resulted in contradicting findings as the direct impact of weight gain on the outcome of PrE is not sufficiently studied. A meta-analysis by Voerman, Santos (40), found that pre-pregnancy BMI was associated with maternal complications, such as PrE and gestational hypertension, regardless of weight gain during pregnancy. Unlike Voerman, Santos (40), we did not find an association between pre-pregnancy BMI and PrE. We found that late pregnancy weight gain was associated with increased odds for PrE as found in other studies(45). Most studies have focused on late or total pregnancy weight gain and its association with the development of PrE; however, the direct relationship is unclear as PrE causes edema and weight gain. Recently, two studies have identified a positive association between early pregnancy weight gain and the development of PrE(47, 82). Unlike Ruhstaller, Bastek (47) and Bodnar, Himes (82), we did not find an association between early pregnancy weight gain and the development of PrE. Due to the lack of studies and contradicting findings, more research is needed to explore and define the potential link between early pregnancy weight gain and PrE.

Several studies have determined that women with PrE have impaired vascular adaptation during pregnancy(71, 74, 75). In contrast, women with uncomplicated pregnancies exhibit a decrease in AS to compensate for the increased blood volume during pregnancy(73, 75). Two meta-analyses' identified that women with PrE have an increase in cfPWV as well as other as indices such as augmentation index and a decrease in time to wave reflection(71, 74). Furthermore, previous work from our lab determined that early markers of AS better predicted the development of PrE later in pregnancy than clinical tests(75). However, the impacts of early pregnancy weight gain and AS on the development of PrE was unknown. In this study, we

identified that early pregnancy weight gain in combination with AS does not increase the predicted odds risk of developing PrE.

Furthermore, it has been long suspected that excessive weight gain during pregnancy is associated with gestational SDB. Although BMI is a major risk factor for SDB, the impact of early weight gain during pregnancy and AS on gestational SDB has not been established. In a study conducted by Pien, Pack (3), total gestation weight gain was not associated with SDB, while pre-pregnancy BMI was significantly associated with SDB. Similar to Pein, Pack (4), we evaluated the association between pregnancy weight gain and SDB; however, we focused on early pregnancy weight gain as well as late and total pregnancy weight gain. Contrary to their findings, our results suggest that early pregnancy weight gain is associated with decreasing odds risk for SDB. As seen in **Table 2.2**, women of greater pre-pregnancy BMI gain less weight during pregnancy, which is in accordance with current IOM guidelines(18). Additionally, BMI is a major risk factor for SDB(7). Therefore, our results suggest that despite gaining less weight, women of greater BMI are at increased odds risk of SDB.

In the general population, SDB is associated with excessive weight gain/obesity, AS, and cardiovascular events later in life(7). Unfortunately, studies exploring the association between AS and SDB in pregnancy are lacking. Link, Eid (81), identified a positive association between pulse transit time, an index of AS, and apnea/hypopnea events in women with gestational SDB. To our knowledge, our lab is the only group to have explored the association with gestational SDB and cfPWV, the gold standard non-invasive measurement of AS. Phan, Pamidi (32) identified that cfPWV was significantly higher in women with SDB compared to non-SDB women. Additionally, SDB was associated with an odds ratio of 3.4 for developing PrE(32). In accordance with previous work from our lab, results from this study confirmed that cfPWV was significantly higher throughout pregnancy in SDB women compared to non-SDB women(32). However, the combined odds of cfPWV and weight gain trajectories did not increase the odds risk of having gestational SDB. It should be noted that our cohort of women has several comorbidities and are at high risk of developing PrE. Therefore, future studies should evaluate the association between early pregnancy weight gain, AS and the development of SDB during pregnancy in a cohort that includes low-risk pregnant women.

The limitations of this study should be addressed. As previously mentioned, only high-risk women were included in our study; future studies should compare the associates between

weight gain, AS, PrE, and SDB in low-risk pregnant women. Although the SphygmoCor System is validated for and we imposed strict protocols, it requires the operator to identify and capture the carotid pulse with a tonometer which could lead to variability between assessors. There was a small sample size of underweight women. Additionally, only a small portion of women developed PrE. Therefore, a larger sample size would represent women of all BMI categories.

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2.7 Tables

Table 2.1 –Baseline characteristics of REVEAL participants

N=188	**Mean± SD, median [IQR] or frequency (%)**
Maternal age (years)	37.21 ± 4.11
MAP (mmHg)	80.99 ± 9.00
Pre-pregnancy BMI (kg/m^2)	24.74 [21.83, 29.74]
BMI category	
Underweight	8 (4.5%)
Normal-weight	86 (48.3%)
Overweight	43 (24.2%)
Obese	41 (23.0%)
Total gestational weight gain (kg)	11 [8.4, 14.15]
Chronic hypertension	15 (8.8%)
Pre-pregnancy diabetes	21 (11.5%)
Black race	25 (13.8%)
Nulliparous	94 (50.5%)
Assisted reproductive technology	85 (45.2%)
History of preeclampsia	8 (4.3%)
Family history of preeclampsia	13 (7.2%)
History of gestational hypertension	1 (0.5%)
History of gestational diabetes	11 (5.9%)

Data presented as mean ± standard deviation, median [IQR] or frequency (%). BMI: body mass index, MAP: mean arterial pressure.

Table 2.2 – Comparison of outcomes based on pre-pregnancy BMI category

	Underweight n= 8	**Normal-weight** n= 86	**Overweight** n= 43	**Obese** n= 41	**p-value**
Maternal age (years)	39.25 ± 1.78	37.55 ± 3.72	37.19 ± 4.87	36.22 ± 4.43	0.189
MAP (mmHg)	72.24 ± 6.39¥¤	78.91 ± 8.37*‡	83.55 ± 7.77	84.45 ± 9.78	<0.01
Gestational diabetes mellitus	0 (0%)	13 (15.12%)	7 (16.28%)	8 (19.51%)	0.579
Early pregnancy weight gain (kg)	4.82 ±0.87	5.28 ± 2.59	5.69 ± 3.05	4.05± 2.46	0.167
Late pregnancy weight gain (kg)	6.97±2.17	6.65±3.1*	6.25±3.0	4.80±2.5	0.043
Total pregnancy weight gain (kg)	13.23 [10.35, 16.15]	13.98 [11.34, 16.70]*	14.50 [10.55, 18.20]†	8.46 [4.46, 13.53]	<0.01
First trimester cfPWV (m/s)	5.6±0.72¥	6.1±0.77*	6.54±1.12†	7.14±0.87	<0.01
Second trimester cfPWV (m/s)	5.90±0.776	6.01±0.92*‡	6.63±1.17	6.91±1.33	<0.01
Third trimester cfPWV (m/s)	5.59 [5.05, 6.2] ¥¤ϕ	6.20 [5.6, 7.15]* ‡	7.05 [6.2, 7.51]	7.09 [6.46, 8.6]	<0.01
Preeclampsia	1 (12.5%)	4 (4.6%)	5 (11.6%)	4 (9.7%)	0.307
SDB	0 (0%)	11 (13.9%)	11 (28.2%)	18 (51.4%)	<0.01

Data presented as mean ± standard deviation, median [IQR] or frequency (%). Analyzed using ANOVA or Kruskal Wallis and Chi-square or Fisher's exact test.
cfPWV: carotid-femoral pulse wave velocity, MAP: mean arterial pressure, SDB: sleep disordered breathing.
* is for a difference between obese women and normal-weight women
‡ is for a difference between overweight women and normal-weight women
† is for a difference between obese and overweight women
¥ is for a difference between obese and underweight women
¤ is for a difference between overweight and underweight women
ϕ is for a difference between normal-weight and underweight women

Table 2.3 – Baseline characteristics of participants that developed PrE compared to those who did not develop PrE

	Preeclampsia n= 14	**Non-preeclampsia** n= 174	**p-value**
Maternal age (years)	36.17 ± 4.08	37.29 ± 4.12	0.356
Pre-pregnancy BMI (kg/m^2)	26.89 [24.12, 31.47]	24.56 [21.66, 29.58]	0.168
MAP (mmHg)	87.85 ± 11.42	80.47 ± 8.62	0.049
Chronic hypertension	3 (2.5%)	12 (7.7%)	0.078
Pre-pregnancy diabetes mellitus	4 (30.7%)	17 (10.05%)	0.047
Early pregnancy weight gain (kg)	4.93 ± 3.29	5.06 ± 2.57	0.894
Late pregnancy weight gain (kg)	8.16 ± 3.72	6.10± 3.08	0.087
Total gestational weight gain (kg)	14.47± 6.10	12.97± 6.52	0.432
Nulliparity	10 (71.42%)	72 (48.8%)	0.163
History of preeclampsia	3 (21.4%)	5 (2.9%)	0.016
History of gestational diabetes	1 (7.1%)	10 (5.9%)	0.592
SDB	5 (45.5%)	36 (23.1%)	0.140

Data analyzed using Students T-test or Wilcoxon Ranksum, and Chi-square or Fisher's exact test.
BMI: body mass index, MAP: mean arterial pressure, SDB: sleep disordered breathing.

Table 2.4.– Adjusted odds ratio of developing preeclampsia based on weight gain and cfPWV

	OR	95% CI	P-value
Early pregnancy weight gain (kg)	0.98	0.78 – 1.23	0.866
Late pregnancy weight gain (kg)	1.19	1.01– 1.40	0.037
Across trimester weight gain (kg)	1.04	0.93 – 1.15	0.498
Trimester cfPWV (m/s)	1.67	1.29 – 2.17	<0.01

Data analyzed using logistic regression and mixed random effects model. Adjusted for maternal age and black race.
cfPWV: carotid-femoral pulse wave velocity, MAP: mean arterial pressure.

Table 2.5 – Baseline characteristics of REVEAL participants with SDB compared to those without SDB during pregnancy

	Sleep disordered breathing n= 41	**No sleep disordered breathing** n= 126	**p-value**
Maternal age (years)	35.96 ± 4.57	37.54 ± 3.87	0.052
Pre-pregnancy BMI (kg/m^2)	28.28 [24.56, 33.05]	26.95 [24.19, 35.17]	<0.01
MAP (mmHg)	84.26 ± 9.93	80.30 ± 8.43	0.028
Chronic hypertension	3 (7.7%)	10 (8.7%)	1.000
Pre-pregnancy diabetes mellitus	6 (14.6%)	13 (10.6%)	0.570
Early pregnancy weight gain (kg)	3.84± 2.41	5.27 ± 2.33	<0.01
Late pregnancy weight gain (kg)	5.54± 3.08	6.31± 0.31	0.200
Total gestational weight gain (kg)	11.99± 5.96	13.04± 6.04	0.359
Nulliparity	21 (51.22%)	58 (46.4%)	0.719
History of preeclampsia	1 (2.5%)	6 (4.8%)	1.000
History of gestational diabetes mellitus	4 (10%)	7 (5.64%)	0.465

Data analyzed using students T-test, assuming unequal variance, and Chi-square or Fisher's exact test.

BMI: body mass index, MAP: mean arterial pressure, SDB: sleep disordered breathing.

Table 2.6 – Adjusted odds ratio for SDB during pregnancy by weight gain and cfPWV

	OR	95% CI	P-value
Early pregnancy weight gain (kg)	0.77	0.64 – 0.92	<0.01
Late pregnancy weight gain (kg)	0.92	0.80 – 1.05	0.195
Weight gain trajectory	0.95	0.89 – 1.00	0.077
cfPWV trajectory	1.60	1.32 – 1.94	<0.01

Data analyzed using logistic regression and mixed random effects model. Adjusted for maternal age and black race.
cfPWV: carotid-femoral pulse wave velocity, MAP: mean arterial pressure.

2.8 Figures

Figure 2.1 –Flow-chart of REVEAL participant enrollment and analysis

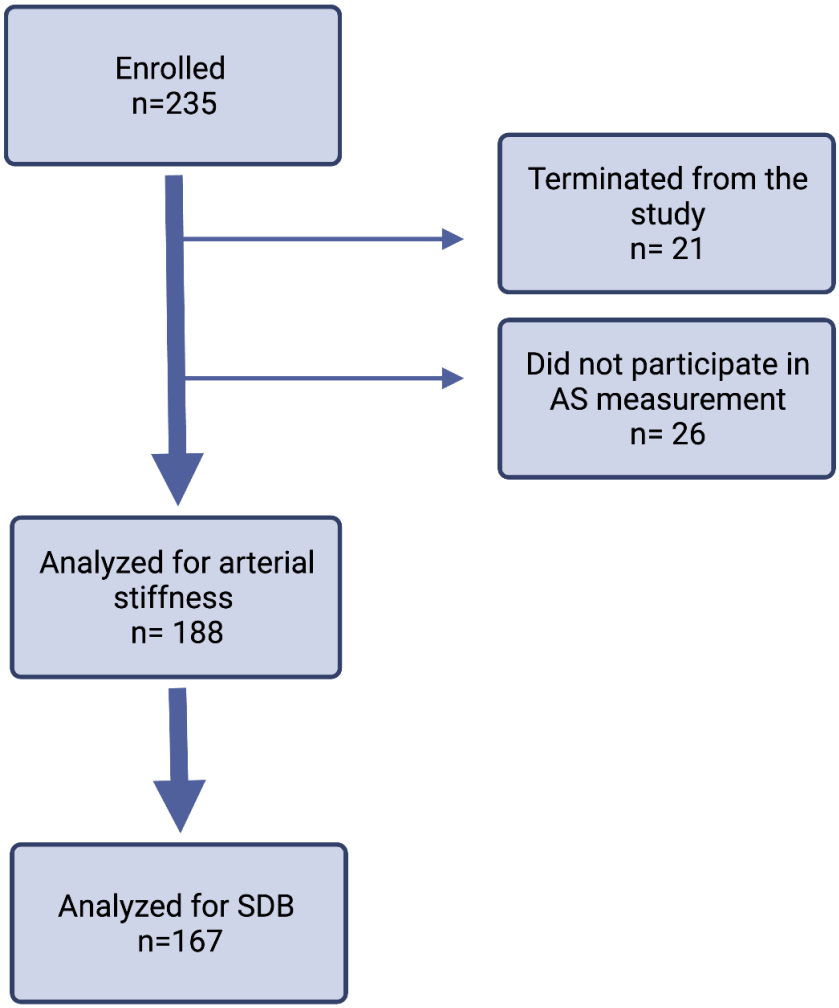
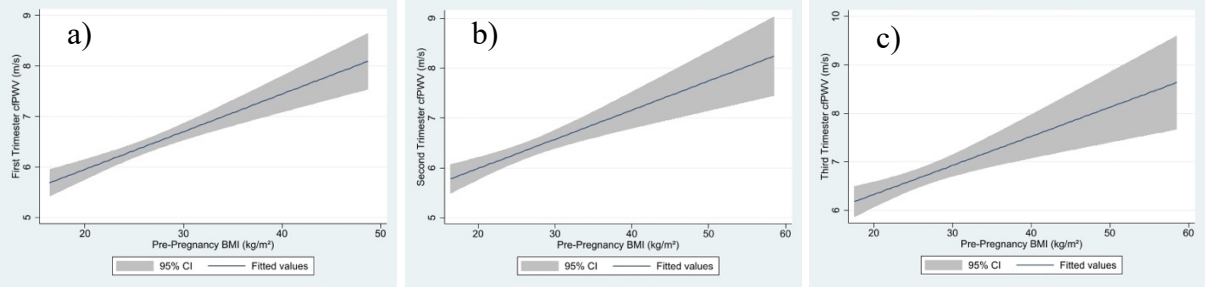


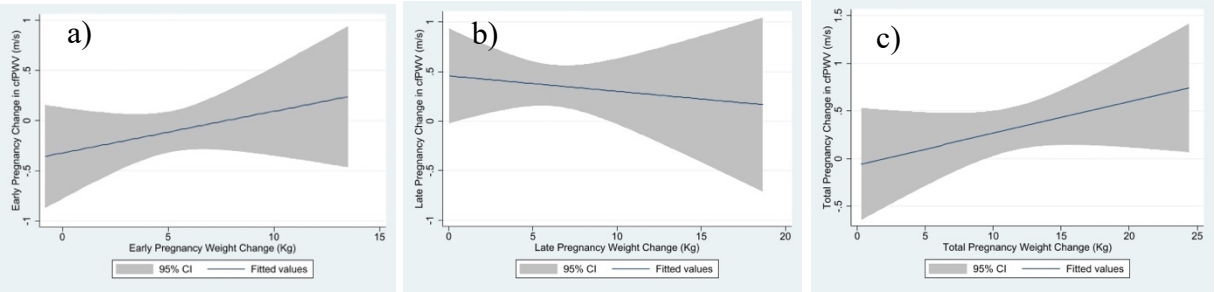
Image created with BioRender.com.

Figure 2.2 – Linear regression analyzing the association between pre-pregnancy BMI and change in cfPWV



Pre-pregnancy BMI is positively associated with a) first trimester cfPWV (β=0.084, 95%CI: 0.059– 0.109, p<0.01) b) second trimester cfPWV (β=0.060, CI: 0.036– 0.084, p<0.01), and c) third trimester cfPWV (β=0.058, CI: 0.027–0.089, p<0.01).
cfPWV: carotid-femoral pulse wave velocity.

Figure 2.3 – Linear regression analyzing the association between weight gain and change in cfPWV



There is a positive association between a) early pregnancy weight gain and early pregnancy change in cfPWV (β=0.091, 95%CI: 0.007– 0.175, p=0.033). There is no association between b) late pregnancy weight gain and change in cfPWV (β=- 0.007, CI: -0.080–0.066, p=0.853), and c) total pregnancy weight gain and change in cfPWV (β=0.039, CI: -0.140–0.091, p=0.149).
cfPWV: carotid-femoral pulse wave velocity.

Bridging Text Between Chapters

Recently, studies have documented that AS is elevated not only at the time of PrE diagnosis but also in the weeks prior to its diagnosis(71, 74, 81, 83). Importantly, Dr. Kim Phan, a previous Ph.D. student in Dr. Daskalopoulou's lab, has worked on the REVEAL study, with the goal of examining whether AS can be used as a predictor of PrE in high-risk pregnant women. They identified a change point in cfPWV between 14-17 weeks' gestation. Importantly, they identified that cfPWV could predict PrE earlier (in the first trimester) and with a greater predictive ability than current clinical standards (blood pressure, biomarkers, and ultrasound imaging).

Furthermore, several studies have observed an association between late or total pregnancy weight gain and PrE(19, 44, 46). However, only two other studies have investigated the association between early pregnancy weight gain and PrE(46, 64). The relationship between late and total pregnancy weight gain and PrE is complex, as PrE can be associated with edema and weight gain(37, 73, 84). Therefore, it is imperative that we analyze early pregnancy weight gain prior to the development of PrE. Additionally, several studies have identified an association between SDB and PrE(3, 20, 21, 33). However, work from Dr. Kim Phan was the first to report an association between cfPWV and SDB in high-risk pregnant women(32). Using the same REVEAL cohort, we aimed to analyze the impact of early pregnancy weight gain on AS, and the impact of both early pregnancy weight gain and AS on the development of PrE and SDB (**Chapter 2**).

In **Chapter 3**, we replicate similar analyses as found in **Chapter 2** with a new cohort of women from PULSE. PULSE was designed as a validation study to confirm the findings of REVEAL, with the overall goal of changing clinical standards of care for high-risk pregnant women.

While designing PULSE, we were able to focus specifically on early pregnancy measurements of AS and designed a weight history questionnaire. As evident in results from REVEAL, pre-pregnancy BMI is significantly associated with AS. Additionally, we saw that women of higher BMI categories gain significantly less weight throughout pregnancy compared to women of lower BMI. Therefore, a weight history questionnaire was designed to retrieve additional data on participant weights prior to pregnancy.

Additionally, PULSE is a validation study and not an explorative one. We had strict protocols, including the proper and timely completion of patient questionnaires. Therefore, we had

a higher number of women fill in the PSQI, allowing us to determine which women developed SDB mid-gestation compared to those who already had it in the first trimester. Finally, the inclusion criteria for PULSE were based on the United States Preventive Services Task Force guidelines for risk of PrE(56). Therefore, we noticed a greater proportion of PULSE participants developing PrE than in the previous REVEAL study.

Chapter 3: Longitudinal Analysis of the PULSE Study

Early Pregnancy Weight Gain and Arterial Stiffness in Gestational Sleep Disordered Breathing

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3.1 Abstract

Objective: Pregnancy increases a woman's risk of developing sleep disordered breathing (SDB). Pregnant women with SDB are at increased risk of morbidity and mortality; it is associated with pregnancy complications such as preeclampsia (PrE). Both SDB and PrE are associated with increased arterial stiffness (AS). Pregnancy characteristics, such as weight gain, are also associated with SDB and PrE. However, whether early pregnancy weight gain is associated with AS and the development of PrE and SDB is unknown.

Methods: Weight and carotid-femoral pulse wave velocity (cfPWV), a measure of AS, were measured in high-risk pregnant women in the first and second trimester of pregnancy. Women completed sleep and weight-related questionnaires during each visit. Participants were monitored until 6 weeks post-partum for PrE.

Results: PULSE is an ongoing study. Of the 118 women enrolled in the study, 10 developed PrE and 30 had SDB during pregnancy. Body mass index (BMI) was strongly associated with increased AS regardless of early pregnancy weight gain ($P<0.05$). Early pregnancy weight gain was not associated with the development of PrE nor SDB ($p>0.05$). However, cfPWV trajectories were associated with the development of PrE (OR: 1.84, CI:0.97 – 3.49, $p=0.06$) and SDB (OR: 1.15, CI: 1.06-2.06, $p=0.023$).

Conclusion: Results from this study suggest that AS trajectories are associated with complications of pregnancy, such as PrE and SDB. More focus should be placed on pre-conception care as AS is strongly associated with pre-pregnancy BMI regardless of early pregnancy weight gain.

3.2 Introduction

Hypertensive Disorders of Pregnancy (HDPs) can be categorized into four different types: chronic hypertension, gestational hypertension, preeclampsia, and chronic hypertension with superimposed preeclampsia. Preeclampsia is one of the leading causes of maternal and fetal death worldwide, and is characterized by the development of high-blood pressure and end-organ damage after the 20th week of gestation(24). Clinical factors, such as diabetes, obesity, chronic hypertension, autoimmune disease (antiphospholipid syndrome), and sleep disordered breathing, have been associated with an increased risk of developing preeclampsia(22, 24). Current practices used for screening to accurately predict or exclude the early development of preeclampsia are largely insufficient(29). As a result, the diagnosis of preeclampsia is made only after the onset of signs and symptoms. The consequences of late diagnosis are dire for both mother and child, with expedited delivery the only recommended management plan to avoid the significant risk of life-threatening complications. This makes research to identify early predictive tools for preeclampsia worth exploring.

AS is used with a high degree of clinical utility for predicting cardiovascular events in the general population (54, 67). AS represents the ability of an artery to expand and contract in response to fluctuations in cardiac output(51). In the general population, risk factors for AS include age, hypertension and obesity; while acute weight gain has been associated with increased AS(51, 64). AS has been extensively studied in the general population; however, its predictive ability in the pregnant population is still being uncovered(54).

Several studies have evaluated the relationship between AS and the development of PrE, given the major maternal cardiovascular changes that occur during pregnancy(71, 73, 74). One such change is the stiffening of the central arteries, observed in pregnant women with a higher risk of developing PrE(75). Most notably, two systematic reviews and meta-analyses identified that women with PrE had significantly higher AS throughout pregnancy compared to women who did not develop PrE (71, 74). A previous study, REVEAL, from our lab was conducted to evaluate the predictive ability of AS in pregnant women at high-risk of developing PrE. We identified early pregnancy changepoint in AS, where women who subsequently developed PrE had higher AS than non-PrE women. Importantly, we found that AS better predicted PrE, earlier and with greater accuracy than current clinical tests (blood pressure, biomarkers, and ultrasound). Additionally, we

found that women who had sleep disordered breathing (SDB) during pregnancy had an increase in AS compared to non-SDB women.

SDB is a broad condition encompassing a group of disorders causing airway restrictions during sleep, ranging in severity from minor conditions, such as snoring, to more severe disorders, such as obstructive sleep apnea (OSA)(8). Excessive weight gain/obesity, comorbidities, and smoking are prominent modifiable risk factors for SDB(1). In the general population, SDB, especially OSA, has been linked to the development of cardiovascular complications, such as hypertension, stroke, heart failure, and heart attacks(7). Although SDB has been well studied in the general population, SDB in the pregnant population is underdiagnosed and understudied (15).

Excessive weigh gain/obesity are major risk factors for developing SDB(16). A 10% body weight gain results in a 6-fold increase in severe OSA in the general population(17). Interestingly, normal-weight women are expected to gain more than 10% of their body weight during pregnancy(18). As seen by O'Brien, Bullough (20), 34% of pregnant women snore, of which 66% started snoring during pregnancy. It is suspected that comorbidities as well as hormonal/physiological changes associated with pregnancy, specifically weight gain and estrogen levels, are responsible for the development of SDB in pregnancy(3).

There is an increased risk of morbidity and mortality in women with SDB during pregnancy, especially OSA(20, 21). OSA is associated with the development of gestational diabetes as well as HDPs, such as PrE, which can have severe detrimental effects on both mother and fetus(21, 22).The consequences of SDB on both the mother and fetus during and after pregnancy have yet to be fully elucidated. Thus, there is a need for more research on SDB in pregnancy, as pregnancy may mask some of the symptoms.

Current studies examining SDB and weight gain in pregnancy have focused on pre-pregnancy or total pregnancy weight gain. However, there is currently a knowledge gap regarding the risks associated with early pregnancy weight gain on AS and the development of SDB. Thus, exploring the impact of early pregnancy weight gain on AS could help understand its potential link with the development of SDB. To date, only two studies have reported an association between early pregnancy (16-19 weeks gestation) weight gain and the development of PrE(82). Early pregnancy weight gain in high-risk pregnancies and its impact on the development of SDB and HDPs, have yet to be explored.

Informed by REVEAL, our current PULSE study aims to confirm and validate REVEAL findings by examining AS as a multi-model approach to PrE prediction in high-risk pregnant women. The PULSE study focuses specifically on evaluating early pregnancy measures of AS in high-risk women.

Therefore, our overall aim was to determine the association between early pregnancy weight gain and AS in the development of SDB and PrE in high-risk women. Specifically, we aimed to 1) Examine weight gain patterns and AS values in high-risk pregnant women in the first and second trimester of pregnancy, and 2) to examine the impact of weight gain trajectories and AS on the development of a) PrE and b) SDB in pregnant women at high risk of developing PrE.

We hypothesized that 1) high-risk pregnant women with higher pre-pregnancy body mass index (BMI) and/or excessive weight gain in early pregnancy and across gestation would have a significant increase in AS. 2) Women with higher pre-pregnancy BMIs and/or excessive weight gain and higher AS would be more likely to develop a) PrE and b) SDB compared to those who gain normal amounts of weight.

3.3 Methods

Ethical approval of this project was granted by the McGill University Health Center Research Ethics Board. Consent was obtained after a complete explanation of the study objectives and procedures.

Study Population

High-risk pregnant women were recruited in the first trimester, between 10- and 13-weeks' gestation. Women were identified as high-risk for PrE based on the United States Preventive Services Task Force(56). In this multinational study, participants were recruited from several obstetrics clinics in Canada and the United Kingdom. Canadian participating sites consisted of the Royal Victoria Hospital and St. Justine Hospital in Montreal and the Laval University Health Center in Quebec City. The participating site in the United Kingdom was the Glasgow Health Center in Ireland.

Women were considered high-risk for PrE if they had one major risk factor or two moderate risk factors as per the United States Preventive Services Task Force(85). High risk factors for PrE included a history of PrE, chronic hypertension, type 1 or 2 diabetes mellitus, renal disease, and autoimmune disease. Moderate risk factors included nulliparity, obesity (BMI ≥35 kg/m^2), advanced maternal age (>35 years old), family history of PrE, black race, and personal risk factors (ie. Low birth weight or small for gestational age, previous adverse pregnancy outcome, > 10 year pregnancy interval). Women were excluded from the study if they were <18 years old, had multiple gestations, were > 14 weeks gestation, had cardiovascular disease, peripheral artery disease, or had a current infectious disease such as HIV, Hepatitis B/C, and COVID-19.

Anthropometric measurements and medical information

Study visits were held in conjunction with scheduled hospital appointments. Study visits consisted of AS measurements, blood draws, and questionnaires. Chart reviews were conducted for each trimester of pregnancy. Medical information obtained included participants' height, weight, blood pressure, obstetrics medical history and family medical history. Maternal and fetal outcomes, including the diagnosis of PrE were gathered after the completion of the study, 12 weeks postpartum. PrE diagnosis was adjudicated by an appointed study physician, Dr. Amira El-Messidi.

Hypertensive Disorders of Pregnancy Diagnosis

HDPs were diagnosed according to the SOGC guidelines(24). Chronic hypertension was defined as hypertension diagnosed before pregnancy or before 20 weeks of pregnancy without the onset of proteinuria. Gestational hypertension was defined as the onset of hypertension (systolic >140 mmHg and diastolic > 90 mmHg) after 20 weeks of pregnancy without the onset of proteinuria. PrE was defined as the onset of hypertension coupled with one or more of the following: proteinuria, maternal organ dysfunction or hematological involvement, and/or uteroplacental dysfunction, including fetal growth restriction or abnormal uteroplacental blood flow from doppler ultrasounds. Finally, chronic hypertension with superimposed PrE occurs when PrE occurs in the context of pre-existing chronic hypertension.

Arterial Stiffness

AS was defined by cfPWV. AS measurements were gathered once during the first obstetrics visit 10-13 weeks gestation and once during their ultrasound anatomy scan visit at 20-22 weeks gestation. cfPWV was measured using the SphygmoCor Xcel, AtCorMedical applanation tonometer. Participants were required to lay in the supine position for 10 minutes prior to AS measurements. A cuff was placed on the participant's right tight to obtain the femoral pulse, while the tonometer was used to obtain a carotid pulse. The indirect distance between the carotid and femoral pulse was used to obtain the cfPWV. Two cfPWV measurements were obtained for measurements within 0.5m/s, and the average value was calculated. If the two measures were greater than 0.5m/s apart, a third measure was obtained, and the three cfPWV values were averaged.

Weight Gain

Participants' weights were recorded at every obstetrics visit. Study staff members gathered all participant weight measurements from pre-pregnancy until delivery. Early pregnancy weight was recorded as the weight at their first visit (10-13 weeks gestation) minus pre-pregnancy weight (kg). Second trimester weight gain was calculated as their weight at their second visit (20-22 weeks' gestation) minus the first visit weight. A weight history questionnaire was completed by participants during their second study visit. The weight history questionnaire includes patients' height and weight at 13, 18, and 25 years old, as well as additional information on the patient's history of weight fluctuations.

Statistical Analysis:

Baseline maternal characteristics of participants were tabulated. Histograms and test of skewness and kurtosis were used to assess the normality of data. Normally distributed continuous variables were reported as means and standard deviations while those not normally distributed were reported as medians and interquartile range. Categorical variables were reported as frequency and proportions. Comparison of continuous variables between PrE and non-PrE women, as well

as between SDB and non-SDB women, were analyzed using Students T-test or Wilcoxon Ranksum. Categorical variables were analyzed using Fisher's exact test. Multiple group comparisons, such as in the case of BMI, were analyzed using ANOVA and post-hoc Tukey's test or Kruskal Wallis and Dunn's Test for continuous variables, while categorical variables were analyzed using Fisher's exact test.

The primary analysis was to measure the association between weight gain and cfPWV during pregnancy. Weight gain and cfPWV measurements were analyzed using simple linear regression.

The secondary analysis explored the association between weight gain and cfPWV measurements in women who develop PrE compared to non-PrE women. Logistic regression was used to analyze the association between weight gain and/or cfPWV during each trimester each trimester in women who subsequently developed PrE compared to those who did not. Mixed random effects model was used to analyze the association between weight gain and cfPWV trajectories in women with and without PrE.

The tertiary analysis explored the association between weight gain and cfPWV measurements in women with SDB during pregnancy compared to non-SDB women. Logistic regression was used to analyze the association between weight gain and/or cfPWV during each trimester in women with SDB compared to those without SDB. Mixed random effects model was used to analyze the association between weight gain and cfPWV trajectories in women with and without SDB. Analyses were adjusted for confounding variables, such as maternal age and black race as they have been shown to have a direct impact on AS. A two-sided p-value>0.05 was considered statistically significant. 95% confidence was used for linear regressions. In our sample size of 53 women, the two-sided logistic regression test had 70.83% power to detect a cfPWV difference of 1.2. Statistical analysis was performed using STATA 17.0.

3.4 Results

Sample demographics and characteristics

Of the 118 women recruited for the study, 5 women were terminated from the study, 100 participated in the AS measurements in both the first and second trimester, 113 participated in the

sleep-related questionnaires, and 53 women completed the study until 6 weeks post-partum (**Figure 3.1**). Of those included in the analysis, 10 women developed PrE, and 19 women had SDB in the first trimester, while 9 women developed SDB by the second trimester. The mean maternal age was 36.19± 4.59, while the mean BMI was 28.82 ± 8.07 (**Table 3.1**).

Of the women recruited, 3 (2.54%) were underweight, 41 (34.75%) were normal-weight, 37 (31.36%) overweight, and 37 (31.36%) were obese. Pre-pregnancy BMI was based on recalled pre-pregnancy weight and height. BMI <19 was considered underweight, 19-25 normal-weight, 25-35 overweight, and >35 obese (**Table 3.1**).

3.4.1 Pre-pregnancy body mass index, weight gain, and arterial stiffness

Primary Analysis

Table 3.2. depict the comparison of baseline characteristics between women of different pre-pregnancy BMI categories. Obese and overweight women had significantly higher baseline mean arterial pressure (MAP) compared to normal-weight women ($p<0.01$)**.** There is a significant difference in second trimester weight gain and first and second trimester cfPWV amongst women of different BMI categories (**Table 3.3, $p<0.05$**). However, there is no difference in first trimester weight gain amongst women of different BMI categories ($p>0.05$). Obese women gain significantly less weight in the second trimester compared to participants of lower BMI's($p<0.01$), and overweight women gain significantly less weight in the second trimester compared to normal-weight women($p<0.01$). Overweight and obese women had significantly higher cfPWV in the first and second trimester of pregnancy compared to normal-weight women ($p<0.01$). However, there was no difference in the change in cfPWV from the first to the second trimester amongst BMI categories ($p>0.05$).

We analyzed the relationship between pre-pregnancy BMI and cfPWV during the first and second trimester of pregnancy. While adjusting for maternal age and black race, we identified a significant association between pre-pregnancy BMI and cfPWV in the first ($\beta=0.05$, 95%CI: 0.02–0.08, $p<0.01$) and second ($\beta=0.06$, CI:0.04– 0.09, $p<0.01$) trimester of pregnancy (**Figure 3.2**). However, there is no association between pre-pregnancy BMI and the change in cfPWV from the first to the second trimester of pregnancy ($\beta=0.01$, 95%CI: -0.02–0.04, $p>0.05$).

The relationship between AS and weight gain was assessed during the first and second trimester of pregnancy, as shown in **Figure 3.3**. Using linear regression and adjusting for maternal age and black race, there was no association between weight gain and cfPWV in the first trimester of pregnancy (β=-0.01, 95%CI: -0.09, 0.063, p>0.05). There was a significant negative association between second trimester weight gain and second trimester cfPWV (β= -0.06, 95%CI: -0.11– -0.00, p=0.03); however, adjusting for pre-pregnancy BMI resulted in an insignificant association (β= -0.03, 95%CI: -0.08–0.02, p>0.05). Additionally, there was no association between weight gain and change in cfPWV from the first to the second trimester of pregnancy (β= 0.00, 95%CI: -0.02–0.03, p>0.05).

While adjusting for maternal age and black race, we found that relative weight gain was significantly negatively associated with absolute cfPWV values in the second trimester (β=-4.84, 95%CI: -8.29– -1.40, p<0.01). However, relative weight gain was not associated with either cfPWV in the first trimester (β=-2.41, CI: -7.72–2.90, p=0.370), or change in cfPWV between the first and second trimester (β=0.15, CI: -0.37–0.67, p=0.569).

Secondary Analysis

As we observed that pre-pregnancy BMI was significantly associated with cfPWV, we were interested in exploring if BMI trajectories from adolescents until 1 year before pregnancy were associated with cfPWV during pregnancy. Adolescent (13 years old) BMI was not associated with first trimester cfPWV. However, it is significantly associated with cfPWV in the second trimester (p=0.02), although it became insignificant after adjusting for pre-pregnancy BMI (p=0.191). BMI at 18 years old was not associated with cfPWV in the first nor second trimester of pregnancy (p>0.05). Interestingly, BMI at 25 years old was significantly associated with an increase in cfPWV in both the first and second trimester of pregnancy (p<0.01). Accordingly, BMI one year before the current pregnancy is strongly associated with an increase in cfPWV in both the first and second trimester of pregnancy (p<0.01). The change in cfPWV from the first to the second trimester was not associated with any BMI history (p>0.05).

Furthermore, we were interested in investigating if there was a difference between women who were chronically obese since adolescence (13 years old to pre-pregnancy) compared to those who were only obese as adults. Using an unpaired Students T-test, we determined that there was

no significant difference in cfPWV in women who were chronically obese since adolescence compared to those who were only obese as adults ($p>0.05$).

3.4.2 Weight gain, arterial stiffness and preeclampsia

Of the 53 women who completed the study until 6 weeks post-partum, 10 developed PrE, while 4 developed gestational hypertension. Baseline characteristics were compared between PrE participants and non-PrE participants (**Table 3.4**). Baseline MAP was significantly higher in women who subsequently developed PrE compared to non-PrE women ($p<0.01$). Although insignificant, a greater proportion of women who developed PrE had a history of PrE than those who did not develop PrE ($p=0.05$). PrE women did not have a significantly different pre-pregnancy BMI compared to non-PrE women ($p=0.228$). However, a greater proportion of non-PrE women had a significant weight loss (>4.5kg) at some point in their life, whereas PrE women did not have a significant weight loss ($p=0.047$).

Using logistic regression, neither first nor second trimester weight gain was associated with increased adjusted odds of developing PrE (**Table 3.5**, $p>0.05$). Similarly, neither first nor second trimester cfPWV was associated with increased odds of developing PrE ($p>0.05$). However, using mixed random effect models, cfPWV trajectories, from the first to second trimester, were non-significantly associated with 1.84-fold odds for developing PrE (**Table 3.5**, CI:0.97 – 3.49, $p=0.06$). Additionally, the combined odds risk of weight gain and cfPWV in the first trimester were not associated with the development of PrE (**Table 3.6**, $p>0.05$). The combined odds risk of weight gain and cfPWV in the second trimester were associated with a non-significant increase for developing PrE ($p=0.057$).

3.4.3 Weight gain, arterial stiffness, and sleep disordered breathing

Primary Analysis

Of the 113 women who completed the sleep-related questionnaires, 30 had SDB in the first or second trimester of pregnancy, 9 of which developed SDB by mid-gestation. **Table 3.7** describes the baseline characteristics of SDB women compared to non-SDB women. Baseline MAP was significantly higher in SDB women than in non-SDB women ($p=0.023$). SDB women

did not have a significantly different pre-pregnancy BMI compared to non-SDB women (p=0.110). However, a greater proportion of women with gestational SDB had a significant weight gain (>4.5kg) at some point in their life compared to non-SDB women (p=0.02).

The adjusted odds for SDB during pregnancy based on weight gain and cfPWV values were analyzed using logistic regression (**Table 3.8**). Neither first nor second trimester weight gain was associated with increased odds of having SDB during pregnancy (p>0.05). As depicted in **Table 3.8**, first trimester cfPWV was associated with a non-significant 1.56-fold odds for gestational SDB, while second trimester cfPWV was not associated with increased odds for gestational SDB (first trimester: p=0.052, second trimester: p=0.241). Additionally, cfPWV trajectory, from the first to the second trimester, was associated with a non-significant 0.60-fold odds increase for gestational SDB (CI: 0.35– 1.00, p=0.053). Futhermore, the combined odds ratio of weight gain and cfPWV in the first trimester were non-significantly associated with gestational SDB (p=0.57). The combined odds ratio of weight gain and cfPWV in the second trimester were not associated with gestational SDB (**Figure 3.9**. p=0.180).

Secondary Analysis

The baseline characteristics of participants were compared between groups based on SDB status (**Table 3.10**). Baseline MAP was significantly higher in women with SDB in the first trimester compared to women who did not develop SDB (**Table 3.10**, p<0.05). Women who had SDB in the first trimester had significantly higher pre-pregnancy BMI than those who developed mid-gestation SDB and non-SDB women (p=0.03). A greater proportion of patients with SDB in the first trimester, as well as those with mid-gestation SDB, had a significant weight gain (>4.5kg) at some point in their life compared to non-SDB participants (p<0.05).

The odds ratio for developing SDB was analyzed using logistic regression and was adjusted for maternal age and black race (**Table 3.11**). Neither first nor second trimester weight gain was associated with increased odds for SDB in the first trimester (p>0.05). Accordingly, neither first nor second trimester weight gain was associated with increased odds of developing SDB mid-gestation (p>0.05).

In the first and second trimester, cfPWV was not associated with increased odds of SDB in the first trimester nor with the development of SDB mid-gestation (p>0.05). In contrast, cfPWV

trajectories from the first to the second trimester, were associated with a non-significant 1.42-fold increased odds of first trimester SDB (p=0.078). However, cfPWV trajectories were not associated with increased odds of developing SDB mid-gestation (p>0.05). As depicted in **Table 3.12**, the combined odds risk of weight gain and cfPWV in the first and second trimester were not associated with an increase in first trimester SDB nor the development of SDB mid-gestation(p>0.05).

3.5 Discussion

In this study, we evaluated the relationship between weight gain, AS, PrE and SDB in high-risk pregnant women from the PULSE study. We identified a strong positive association between pre-pregnancy BMI and AS in early pregnancy. Although obese women gained less weight than normal-weight women, they continuously had higher AS in the first and second trimester. We observed that there was no association between weight gain and absolute AS values in the first trimester. However, there was a significant negative association between weight gain and absolute AS values in the second trimester. Interestingly, we observed that although obese women gained less weight than normal-weight women, they experienced a similar change in AS from the first to the second trimester. These results suggest that pregnancy weight gain does not affect AS in early pregnancy, but rather it is their pre-pregnancy BMI that potentially impacts AS.

Although it is known that obesity increases the risk of having stiffer arteries, the direct impact of acute weight gain on AS, specifically during pregnancy, is not known(51, 54). Wildman, Farhat (64), are one of the only groups to have examined the association between acute weight gain and AS. In their longitudinal analysis of young adults, acute weight gain was associated with an increase in AS, while weight loss was associated with a decrease in AS(64). Similarly, we evaluated the impacts of acute pregnancy weight gain on AS. In contrast to their findings, we found that weight gain was negatively associated with absolute AS values in the second trimester. However, after adjusting for BMI, there was no association between second trimester weight gain and AS. This relationship is likely influenced by pre-pregnancy BMI rather than a direct relationship between weight gain and AS. As seen in **Table 3.2**, women of higher pre-pregnancy BMI gain less weight during pregnancy, which is in accordance with the Institute of Medicine (IOM) guidelines(18).

The IOM pregnancy weight gain guidelines are designed to inform physicians and patients of the complications associated with insufficient or excessive weight gain during pregnancy and to reduce its occurrence(18). Several studies and meta-analyses have identified an association between excessive weight gain and pregnancy complications such as gestational diabetes and labour and delivery complications. Nevertheless, the impacts of pregnancy weight gain on the development of PrE are contradicting(18, 22, 37, 40, 86). Total pregnancy weight gain has been associated with an increased risk for PrE. However, the interpretation of these results is unclear, as PrE can cause edema and rapid weight gain(84, 86). Interestingly, in a study by Bodnar, Himes (82), a positive association between early pregnancy weight gain (16-19 weeks gestation) and the development of PrE in normal-weight women was observed. Furthermore, they identified a negative association between weight loss and the development of PrE in obese women(82). Unlike Bodnar et al, we did not find an association between early pregnancy weight gain and the development of PrE. However, 32.56% of non-PrE women in our study had a significant weight loss in their life, whereas none of the women who developed PrE had a significant weight loss in their life. Interestingly, these findings support the importance of implementing pre-conception weight management guidelines.

AS is a tool that has shown a high degree of clinical utility in the general population and has recently been associated with PrE in the pregnant population(54, 67, 71, 74). While several studies have identified that AS is increased at the time of PrE diagnosis, others have found that AS is also increased prior to the development of PrE and in PrE women post-partum (71, 74, 83). In our pilot project, REVEAL, Phan, Schiller (75) identified a change point in AS in early pregnancy (14-17 weeks gestation) and found that AS was elevated throughout pregnancy in PrE women compared to non-PrE women(75). Interestingly, AS was found to predict PrE earlier and with greater accuracy than current clinical standards (blood pressure, biomarkers, ultrasounds)(75). Findings from our current study, PULSE, are similar to previous work in the field; however, we focused specifically on early pregnancy factors that may help predict PrE. Although insignificant, we identified a positive association between AS trajectories in early pregnancy and the development of PrE. It is important to note that the PULSE study is ongoing, which resulted in a small sample size. The lack of significance is most likely a result of low power. These findings suggest that early pregnancy AS trajectories may indeed predict PrE. Its predictive ability should be explored in the PULSE study cohort once a larger sample size has been achieved.

Although several studies support the association between AS and PrE, there is a lack of research evaluating the association between AS and SDB during pregnancy. AS has been associated with SDB in both the general adult population and in children, where a positive trend is identified between AS and the severity of OSA (78, 80). Unfortunately, research evaluating the relationship between AS and SDB in pregnant women is lacking. Interestingly, Link, Eid (81) identified a positive association between pulse transit time, an index of AS, and SDB in the pregnant population. To our knowledge, the work contributed by Phan, Pamidi (32), a previous PhD student working on the REVEAL study, is the only group to have evaluated cfPWV in pregnant women with SDB. In our findings from REVEAL, we identified a positive association between AS and SDB throughout pregnancy. Through our results from PULSE, we confirmed an association between AS trajectories in early pregnancy and the presence of SDB during pregnancy. However, we did not find an association between AS and the development of SDB mid-gestation. These results suggest that two separate phenotypes of gestational SDB may exist. More work is needed to explore the difference between women who unknowingly have SDB prior to pregnancy, but pregnancy amplifies the symptoms, compared to women who only develop SDB due to pregnancy.

Although obesity and excessive weight gain are major risk factors for SDB, the impacts of early pregnancy weight gain on the development of SDB during pregnancy remains elusive. To our knowledge, our study is the first to report that early pregnancy weight gain is not associated with SDB. In our study, pregnant women who developed SDB in the second trimester had similar pre-pregnancy BMI to non-SDB women and significantly lower pre-pregnancy BMI compared to women with SDB in the first trimester. Furthermore, there was no significant different in weight gain amongst these women. Therefore, our study suggests that having SDB by the first trimester is associated with pre-pregnancy BMI. However, developing SDB by mid-gestation is not associated with BMI nor early pregnancy weight gain. Future studies should evaluate other potential risk factors for SDB in combination with pre-pregnancy BMI to better predict the development of SDB during pregnancy.

The following limitation to our study should be considered. Firstly, our study included a small sample size of underweight and obese women from the ongoing PULSE study. Therefore, the PULSE data should be revaluated once a larger proportion of the sample size has completed the study. Secondly, the PULSE study focused specifically on early pregnancy weight gain.

Late/total pregnancy weight gain and AS could not be evaluated in this group of participants. Thirdly, there was a small sample size of women who developed PrE. Fourth, there was a small sample size of women who developed SDB. Fifth, there is potential recall bias as the weight history questionnaire relied on patient-recalled weight. Sixth, we did not standardize the time of day in which we measured AS as we were only authorized to see patients during their obstetrics appointments. Seventh, SDB was determined using symptom-based questionnaires (PSQI) instead of the gold standard polysomnography. Finally, we were unable to capture cfPWV in several severely obese patients as their thighs were too large to fit in our standard thigh cuff.

There are several strengths to this study. First, we gathered AS data in pregnancy prior to the development of PrE. The greater aim of PULSE is to contribute to the early prediction of PrE. Secondly, we included data from our multinational sites, which broadened our participants' dynamic cultural and racial backgrounds. Third, AS was measured using the validated gold-standard non-invasive measurements. Fourth, we adjusted for maternal age and black ethnicity as both risk factors for PrE and SDB. Fifth, study visits were completed during waiting times at the obstetrics clinic which likely helped increase our recruitment rate. Sixth, although we determined SDB using symptom-based questionnaires, which are not the gold standard, they are the most accessible and applicable tool in-clinic for our cohort of women. Seventh, to our knowledge, we are the first study to have gathered information of participants' weight trajectories from adolescents to pre-pregnancy. Finally, we evaluated women at high risk of developing PrE, which allowed us to have a greater proportion of PrE cases (18.87%) than seen in the general pregnant population (5-8%).

In conclusion, AS trajectories are associated with the development of PrE and SDB. To our knowledge, this is the first study to report that early pregnancy weight gain is not associated with a change in AS, PrE and SDB. It may be more advantageous to focus on pre-conception interventions for BMI and AS rather than weight gain during early pregnancy. This study cannot assume causality nor the predictive ability of weight gain and AS on the development of PrE and SDB. Future studies should investigate the impact of weight loss, prior to pregnancy, in women at high risk of developing PrE and SDB.

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3.7 Tables

Table 3.1 – Baseline characteristics of PULSE participants

N=118	**Mean± SD or frequency (%)**
Maternal age (years)	36.19± 4.59
Pre-pregnancy BMI (kg/m^2)	28.82 ± 8.07
BMI category	
Underweight	3 (2.54%)
Normal-weight	41 (34.75%)
Overweight	37 (31.36%)
Obese	37 (31.36%)
MAP (mmHg)	87.67 [81.5, 94.5]
First trimester weight gain (kg)	1.84 [0.09, 3.64]
Second trimester weight gain (kg)	2.87 ± 3.44
Chronic hypertension	13 (11.02%)
Diabetes mellitus	16 (13.56%)
Type 1	6 (5.08%)
Type 2	5 (4.24%)
Gestational	5 (4.24%)
Black Race	14 (11.86%)
Nulliparous	59 (50%)
Assisted reproductive technology	40 (33.89%)
History of preeclampsia	22 (18.64%)
Family history of preeclampsia	39 (33.05%)
History of fetal growth restriction	8 (6.78%)
History of gestational hypertension	13 (11.02%)
History of gestational diabetes mellitus	10 (8.47%)
History of small for gestational age	14 (11.86%)

Normally distributed data are presented as mean ± SD. Non-normally distributed data are presented as median [IQR]. BMI: body mass index, MAP: mean arterial pressure.

Table 3.2 – Comparison of baseline characteristics between BMI categories

	Underweight n= 3	**Normal-weight** n= 41	**Overweight** n= 37	**Obese** n= 37	**p-value**
Maternal age (years)	34.67 ± 4.04	36.49 ± 4.84	36.78 ± 4.48	36.38 ± 4.47	0.521
MAP (mmHg)	81.5 [81.5, 117]	83 [78, 87.5]*‡	88.67 [82.5, 93.5] †	95.58 [87.83, 104.75]	<0.01
Significant weight gain (>4.5 kg)	1 (33.33%)	7 (17.10%)*	14 (37.84%)	19 (51.35%)	<0.01
Significant weight loss (>4.5 kg)	1 (33.33%)	13 (31.71%)	12 (32.43%)	13 (35.14%)	0.990
13-year-old BMI (kg/m^2)	18.06 [17.99, 18.55]	19.66 [18.31, 21.26]	22.21 [20.41, 23.77]	24.31 [20.22 31.97]	<0.01
18-year-old BMI (kg/m^2)	19.10 ± 1.10	20.58 ± 2.84	21.72 ± 2.49	27.50 ± 7.14	<0.01
25-year-old BMI (kg/m^2)	18.96 ± 1.50	20.87 ± 1.63	23.13 ± 4.17	29.54 ± 7.08	<0.01

Data analyzed using ANOVA, post-hoc Tukeys test, Kruskal Wallis, Dunn's test, and Chi-square test or Fisher's exact test.

BMI: body mass index, cfPWV: carotid-femoral pulse wave velocity, MAP: mean arterial pressure.

* is for a difference between obese women and normal-weight women

‡ is for a difference between overweight women and normal-weight women

† is for a difference between obese and overweight women

¥ is for a difference between obese and underweight women

Table 3.3 – Comparison of weight gain and AS outcomes between BMI categories

	Underweight n= 3	**Normal-weight** n= 41	**Overweight** n= 37	**Obese** n= 37	**p-value**
First trimester weight gain (kg)	2.86 [0, 8.23]	1.90 [0.82, 3.50]	2.32 [0.18, 3.41]	1.18 [0, 4.23]	0.925
Second trimester weight gain (kg)	4.92± 2.25	4.01 ± 3.14*	2.85 ± 3.61	1.44 ± 3.19	<0.01
First trimester cfPWV (m/s)	5.90 ± 0.90	5.96 ± 0.79‡*	6.79±1.20	6.68 ±0.97	<0.01
Second trimester cfPWV (m/s)	5.65 [5.15, 6.95]	5.78 [5.4, 6.15]‡*	6.45 [6.0, 7.40]	6.78 [6, 7.4]	<0.01
Change in cfPWV (m/s)	0.02 ± 0.14	-0.17 ± 0.93	-0.32 ± 0.99	-0.07 ± 0.80	0.736
Preeclampsia	0 (0%)	4 (18.18%)	1 (8.33%)	5 (29.41%)	0.573
Gestational diabetes mellitus	0 (0%)	2 (9.09%)	3 (27.27%)	7 (41.18%)	0.099
First trimester SDB	0 (0%)	4 (9.75%)	6 (16.2%)	10 (27.03%)	0.227
Developed mid-gestation SDB	0 (0%)	4 (10.53%)	2 (5.56%)	3 (8.11%)	0.928

Data analyzed using ANOVA, post-hoc Tukeys test, Kruskal Wallis, Dunn's test, and Chi-square or Fisher's exact test.
cfPWV: carotid-femoral pulse wave velocity, SDB: sleep disordered breathing.
* is for a difference between obese women and normal-weight women
‡ is for a difference between overweight women and normal-weight women
† is for a difference between obese and overweight women
¥ is for a difference between obese and underweight women

Table 3.4 – Baseline characteristic of participants who developed PrE compared to those who did not develop PrE

	Preeclampsia n= 10	**Non-preeclampsia** n= 43	**p-value**
Maternal age (years)	34.9± 4.55	36.65 ± 4.87	0.298
Pre-pregnancy BMI (kg/m^2)	32.49 ± 12.15	27.15 ± 6.91	0.228
MAP (mmHg)	102 [79. 5, 96.66]	85.83 [82, 93]	0.004
Chronic hypertension	2 (10.00%)	5 (11.63%)	0.604
Pre-pregnancy diabetes mellitus	2 (4.65%)	2 (20.00%)	0.157
First trimester weight gain (kg)	2.84 [0.23, 4.55]	1.91 [0.09, 3.09]	0.524
Second trimester weight gain (kg)	2.04 ± 1.22	3.22 ± 3.79	0.398
Nulliparity	6 (60.00%)	20 (46.51%)	0.501
History of preeclampsia	5 (50.00%)	8 (18.60%)	0.052
History of gestational diabetes mellitus	0 (0%)	7 (16.28%)	0.171
First trimester SDB	3 (30.00%)	7 (9.00%)	0.356
Mid-gestation SDB	1 (10.00%)	6 (15.00%)	0.684
OSA	0 (0%)	1 (1.20%)	0.626
Significant weight loss (>4.5kg)	0 (0%)	14 (32.56%)	0.047
Significant weight gain (>4.5kg)	4 (40.00%)	15 (34.88%)	1.000

Data analyzed using Students T-test, assuming unequal variance, Man Whitney U test, and chi-square/fisher's exact test.

BMI: body mass index, MAP: mean arterial pressure, OSA: obstructive sleep apnea, SDB: sleep disordered breathing.

Table 3.5 – Adjusted odds ratio for PrE based on weight gain and cfPWV measurements

	OR	95% CI	p-value
First trimester weight gain (kg)	1.07	0.827 – 1.390	0.599
Second trimester weight gain (kg)	0.93	0.775 – 1.115	0.432
Weight gain trajectory (kg)	0.99	0.93 – 1.06	0.846
cfPWV trajectory(m/s)	1.84	0.972 – 3.49	0.061
First trimester cfPWV (m/s)	1.68	0.688 – 4.10	0.255
Second trimester cfPWV (m/s)	2.07	0.8179 – 5.22	0.125
Change in cfPWV (m/s)	1.46	0.502 – 4.23	0.489

Data analyzed using logistic regression and mixed random effects model. Adjusted for maternal age and black race.
cfPWV: carotid-femoral pulse wave velocity.

Table 3.6 – Combined odds ratio for PrE by trimester specific weight gain and cfPWV values

	OR	95%CI	p-value
First Trimester	1.87	0.74 – 4.71	0.183
Second Trimester	2.21	0.818 – 5.96	0.118

Data analyzed using logistic regression. Adjusted for maternal age and black race.
cfPWV: carotid-femoral pulse wave velocity.

Table 3.7 – Baseline characteristics of participants with SDB compared to those who did not have SDB

	Sleep disordered breathing n= 30	**No sleep disordered breathing** n= 83	**p-value**
Maternal age (years)	36.80±3.90	35.89 ±4.83	0.300
Pre-pregnancy BMI (kg/m^2)	31.14±8.17	28.33 ± 7.98	0.110
MAP (mmHg)	93.5 [84, 104.5]	86 [81.5, 93.33]	0.023
Chronic hypertension	4 (13.33%)	6 (7.14%)	0.304
Pre-pregnancy diabetes	5 (16.67%)	5 (5.95%)	0.075
First trimester weight gain (kg)	2.16 [0.18, 3.41]	1.84 [0.05, 3.95]	0.634
Second trimester weight gain (kg)	2.81 ± 3.17	2.86 ± 3.61	0.941
Nulliparity	15(50.00%)	42 (50.00%)	1.000
History of preeclampsia	6 (20.00%)	15 (17.86%)	0.789
History of gestational diabetes	1 (3.33%)	11 (13.10%)	0.135
Family history of preeclampsia	8 (21.62%)	29 (78.38%)	0.430
Significant weight loss (>4.5kg)	13 (43.33%)	25 (29.76%)	0.176
Significant weight gain (>4.5kg)	16 (53.33%)	25 (29.76%)	0.021

Normally distributed data were analyzed using Students T-test, assuming unequal variance, while non-normally distributed data were analyzed using Man Whitney U test. Categorical variables were analyzed by Chi-square test or fisher's exact test.
BMI: body mass index, MAP: mean arterial pressure.

Table 3.8. – Adjusted odds ratio of SDB based on weight gain and cPWV

	OR	95% CI	p-value
First trimester weight gain (kg)	0.91	0.765 – 1.08	0.277
Second trimester weight gain (kg)	0.99	0.877 – 1.12	0.907
Weight gain trajectory (kg)	0.98	0.94 – 1.03	0.461
cfPWV trajectory (m/s)	1.15	1.06 – 2.06	0.023
First trimester cfPWV (m/s)	1.56	1.00 – 2.42	0.052
Second trimester cfPWV (m/s)	1.36	0.81 – 2.28	0.241
Change in cfPWV (m/s)	0.60	0.35, – 1.01	0.053

Data analyzed using logistic regression and mixed random effects model. Adjusted for maternal age and black race.
cfPWV: carotid-femoral pulse wave velocity, SDB: sleep disordered breathing.

Table 3.9 – Combined odds ratio for SDB by trimester-specific weight gain and cfPWV values

	OR	95%CI	p-value
First Trimester	1.55	0.99 – 2.45	0.057
Second Trimester	1.45	0.84 – 2.51	0.182

Data analyzed using logistic regression. Adjusted for maternal age and black race,
cfPWV: carotid-femoral pulse wave velocity, SDB: sleep disordered breathing.

Table 3.10 – Comparison of baseline characteristics based on SDB status

	First trimester sleep disordered breathing n= 19	**Mid-gestation sleep disordered breathing** n= 9	**No sleep disordered breathing** n= 85	**p-value**
Maternal age (years)	36.47±3.90	36.66 ±3.94	35.99 ± 4.84	0.859
Pre-pregnancy BMI (kg/m^2)	32.93 ± 9.10	27.77±5.63‡	27.52±7.49*	0.027
MAP (mmHg)	96.67 [82, 113.5]	87 [84, 93.5]	86 [80.83, 93]*	0.033
Chronic hypertension	4 (21.05%)	0 (0%)	6 (7.06%)	0.094
Pre-pregnancy diabetes mellitus	6 (31.58%)	4 (44.44%)	30 (35.30%)	0.368
First trimester weight gain (kg)	1.18 [0.18, 2.91]	3.09 [-0.45, 3.59]	1.68 [0.91, 3.77]	0.733
Second trimester weight gain (kg)	2.28 ± 3.26	4.08 ± 2.90	2.82 ± 3.60	0.453
Nulliparity	9 (47.37%)	6 (66.67%)	44 (51.76%)	0.680
History of preeclampsia	4 (21.05%)	2 (22.22%)	14 (16.47%)	0.835
History of gestational diabetes mellitus	5 (26.32%)	3 (33.33%)	2 (2.35%)	0.368
Significant weight loss (>4.5 kg)	9 (47.37%)	4 (44.44%)	24 (28.24%)	0.203
Significant weight gain (> 4.5kg)	11 (57.89%)	5 (55.56%)	23 (27.06%)*	0.015
13-year-old BMI (kg/m^2)	24.26 ± 9.90	22.84 ± 4.55	22.54 ± 6.14	0.412
18-year-old BMI (kg/m^2)	24.86 ± 5.17	22.08 ± 3.86	22.61 ± 5.52	0.148
25 -year-old BMI (kg/m^2)	26.06 ± 5.38	24.40± 4.16	23.53 ± 6.10	0.0534
BMI 1 year before pregnancy (kg/m^2)	31.55 ± 7.80	27.52± 5.81	26.55± 7.01*	0.023

Normally distributed data were analyzed using ANOVA and post-hoc Tukey's test. Non-normally distributed data were analyzed using Kruskal Wallis and Dunn's test. Categorical data were analyzed using Chi-square or Fisher's exact test.

BMI: body mass index, MAP: mean arterial pressure, SDB: sleep disordered breathing.

* is for a significant difference between first-trimester SDB and non-SDB.

‡ is for a significant difference between first-trimester SDB and mid-gestation SDB

Table 3.11 – Adjusted odds ratio for developing SDB

		OR	95%CI	p-value
First trimester sleep disordered breathing	First trimester weight gain (kg)	0.96	0.73 – 1.12	0.876
	Second trimester weight gain(kg)	0.95	0.82 – 1.10	0.456
	Across trimester weight gain (kg)	0.98	0.94 – 1.04	0636
	First trimester cfPWV (m/s)	1.45	0.88 – 2.39	0.146
	Second trimester cfPWV(m/s)	1.50	0.77 – 2.92	0.234
	Change in cfPWV (m/s)	0.65	0.37 – 1.16	0.144
	cfPWV trajectory (m/s)	1.42	0.96 – 2.10	0.078
Developed mid-gestation sleep disordered breathing	First trimester weight gain (kg)	0.98	0.75 – 1.28	0.876
	Second trimester weight gain (kg)	1.12	0.91 – 1.36	0.279
	Weight gain trajectory (kg)	1.02	0.96 – 1.10	0.442
	First trimester cfPWV (m/s)	1.56	0.87 – 2.79	0.132
	Second trimester cfPWV (m/s)	1.18	0.55 – 2.53	0.674
	Change in cfPWV (m/s)	0.70	0.35 – 1.35	0.284
	cfPWV trajectory (m/s)	1.44	0.89 – 2.31	0.132

Data analyzed using logistic regression and mixed random effects model. Adjusted for maternal age and black race.
cfPWV: carotid-femoral pulse wave velocity, SDB: sleep disordered breathing.

Table 3.12 – Combined odds ratio for developing SDB by trimester-specific weight gain and cfPWV values

	Grouping	**OR**	**95%CI**	**p-value**
First trimester sleep disordered breathing	First Trimester	1.48	0.89 – 2.47	0.133
	Second Trimester	1.45	0.84 – 2.51	0.182
Developed mid-gestation sleep disordered breathing	First Trimester	1.57	0.88 – 2.80	0.130
	Second Trimester	1.29	0.58 – 2.87	0.531

Data analyzed using logistic regression and mixed random effects model. Adjusted for maternal age and black race.
cfPWV: carotid-femoral pulse wave velocity, SDB: sleep disordered breathing.

3.8 Figures

Figure 3.1 – Flow-chart of participant enrollment and analysis

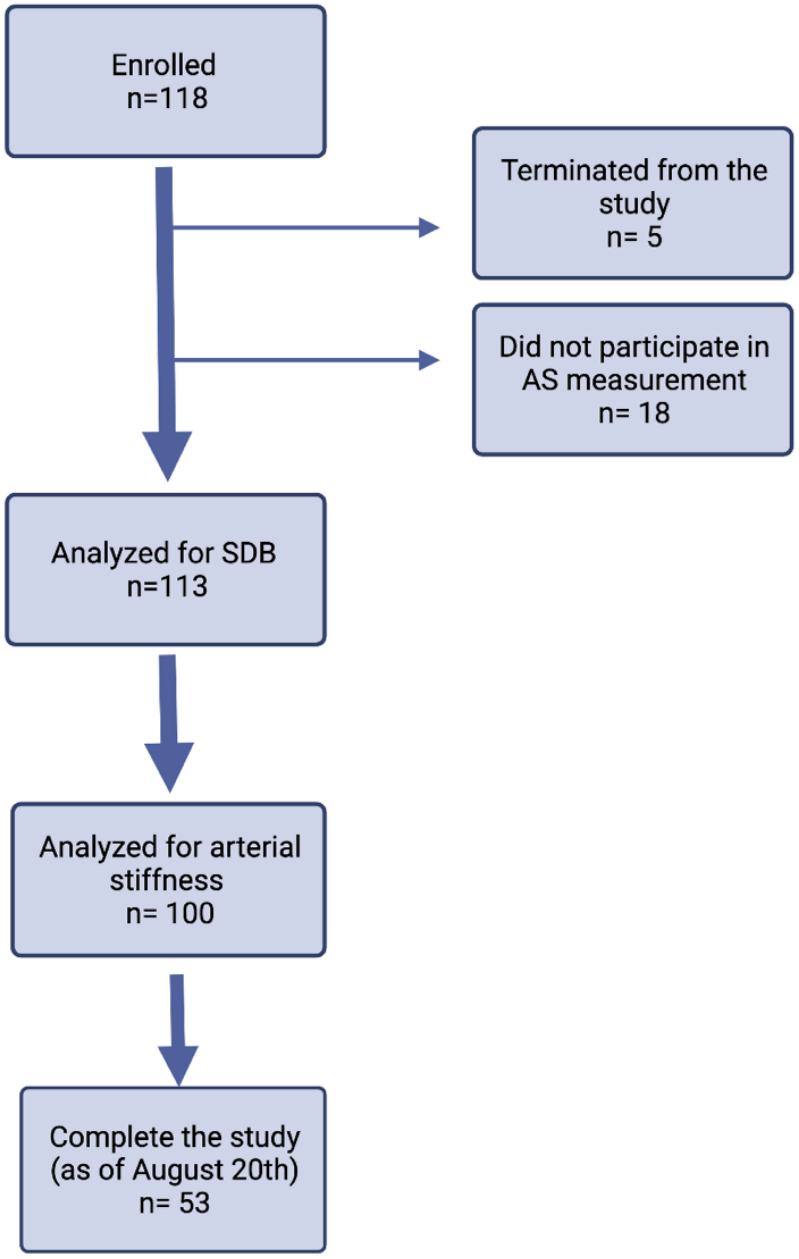
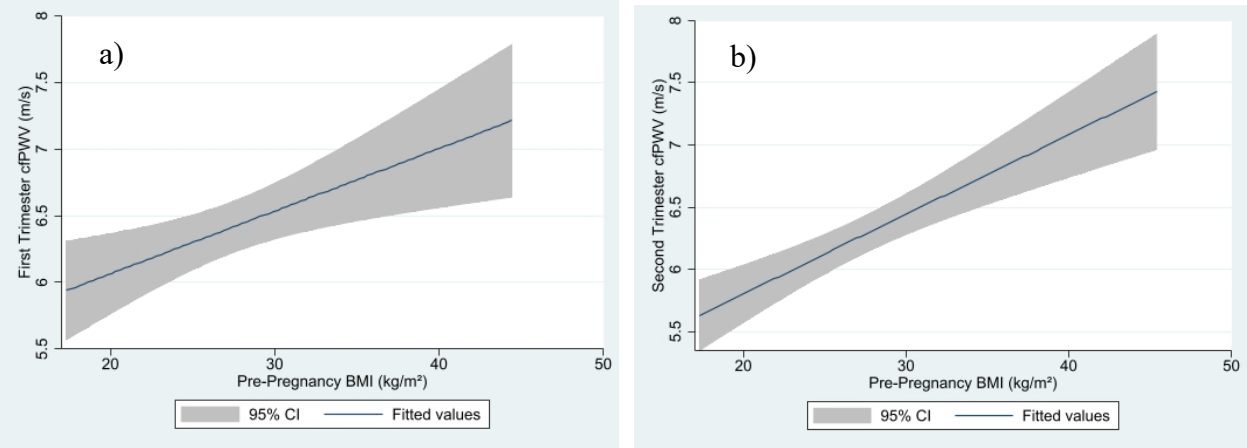


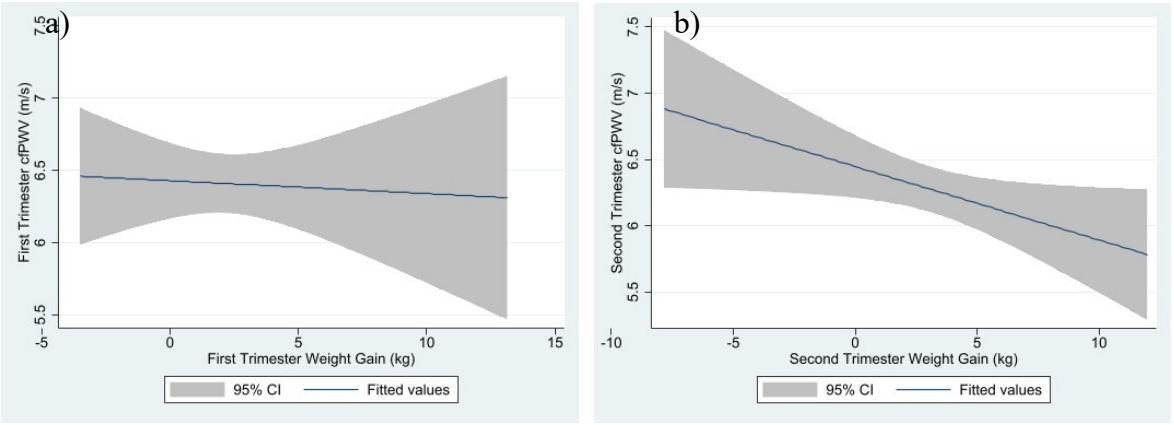
Image created with BioRender.com.

Figure 3.2 – Linear regression analyzing the association between pre-pregnancy BMI and cfPWV



There is a significant association between pre-pregnancy BMI and cfPWV in a) the first (β= 0.05, 95%CI: 0.02 – 0.08, p<0.01) and b) second (β= 0.06, CI:0.04 – 0.09, p<0.01) trimester of pregnancy.

Figure 3.3 – Linear regression analyzing the association between weight gain and cfPWV



There was no association between a) weight gain and cfPWV in the first trimester of pregnancy ((β=-0.01, 95%CI: -0.09, 0.063, p>0.05) and b) there was a significant negative association between second trimester weight gain and second trimester cfPWV (β= -0.06, 95%CI: -0.11– -0.00, p=0.03).

Chapter 4: Discussion and Conclusion

4.1 Summary of Findings

In this study, we evaluated the relationship between weight gain, AS, PrE and SDB in high-risk pregnant women from the REVEAL and PULSE study. These findings are of particular interest to both scientists and clinicians as they aim to improve our understanding of the impact of early pregnancy weight gain and AS on the development of PrE and SDB. Importantly, our study aims to contribute to research on pregnant women as they are often underrepresented in studies of cardiovascular disease and SDB.

4.1.1 Weight gain and arterial stiffness

In our populations of high-risk pregnant women, BMI was consistently significantly associated with AS throughout pregnancy. Women of different BMI categories gained a similar amount of weight in the first trimester. However, in the second and third trimester, women of larger BMI gained less weight than those of lower BMI, as per the IOM guideline(18). As seen in the general population, women of higher BMI had higher AS throughout pregnancy compared to those of lower BMI. Therefore, our results depicted a significant negative association between relative weight gain and AS.

Furthermore, using data from REVEAL, pregnancy weight gain was associated with increased AS from the first to the second trimester of pregnancy. However, these findings were not replicated in PULSE. Therefore, more studies are needed to further evaluate this association.

These findings suggest that pre-pregnancy BMI has a large impact on AS during pregnancy regardless of the amount of weight gained during pregnancy. Although more studies are needed to support these findings, it suggests that clinicians should focus on pre-conception interventions rather than antepartum strategies. Especially in cases of women seeking assisted reproductive technologies, where 22.9% of women are obese(87).

Furthermore, results from the weight history questionnaire suggest that there is no difference in AS between pregnant women with chronic or acute obesity. As suggested by other studies that evaluated AS in children, AS can be influenced by acute weight gain and does not require long-term effects from obesity(62, 80). Weight loss strategies should be a large focus in obese women before pregnancy, as suggested by Maxwell and et al. (88) Pre-Conception and Prenatal Care guidelines.

4.1.2 Weight gain, arterial stiffness, and preeclampsia

In these same populations, we evaluated the association between weight gain, AS, and PrE. Many groups have aimed to evaluate the impacts of pregnancy weight gain on pregnancy complications(19, 37, 44, 46, 47). Although several studies have determined that weight gain is associated with an increased risk of pregnancy complications such as PrE, they have primarily evaluated late or total pregnancy weight gain. These results are complex as PrE can cause weight gain, and we are therefore unable to determine if weight gain's association precedes the onset of PrE. By investigating early pregnancy weight gain, we were able to identify that there was no association with the development of PrE. Our findings contrast those of Macdonald-Wallis, Tilling (46), and Wildman, Farhat (64), the only two other groups to have reported investigating the association between early pregnancy weight gain and the development of PrE. More studies are needed to establish the association between early pregnancy weight gain and PrE as the current minimal evidence is contradicting.

As determined by Dr. Kim Phan, the previous PhD student studying the REVEAL project in Dr. Daskalopoulou's lab, AS is higher in PrE women than non-PrE women and has greater predictive ability than current clinical standards. Similar to other published studies, we found a positive association between AS trajectories throughout pregnancy and the development of PrE. However, there was no association between absolute AS in the first trimester, implying that although AS has great potential clinical utility in high-risk pregnant women, it is limited to hemodynamic changes that occur between the first trimester and second trimester.

4.1.3 Weight Gain, arterial stiffness, and sleep disordered breathing

The association between weight gain and AS during pregnancy was prospectively compared between women with and without SDB. Further analysis subdivided women with SDB into those with SDB first trimester and those who developed SDB mid-gestation (second trimester). In the REVEAL study, we determined that early pregnancy weight gain was negatively associated with SDB, while early pregnancy AS was positively associated with SDB. Furthermore, in PULSE, we determined that women with SDB in the first trimester had significantly higher BMI and MAP than those who developed SDB mid-gestation and non-SBD women. Interestingly, compared to non-SDB women, both women who had SDB in the first trimester and women who

developed mid-gestation SDB had a significantly greater proportion of excessive weight gain (>4.5kg) pre-pregnancy. Our results suggest that despite gaining less weight, women of higher pre-pregnancy BMI are more likely to have SDB than women of lower BMI's. Although pregnancy weight gain was not associated with increased odds risk of developing SDB during pregnancy, the relationship between excessive weight gain and weight fluctuations should be explored. Results from this study suggest that there are differences in hemodynamic and weight gain characteristics between women who had SDB by the first trimester compared to those who develop SDB by mid-gestation. Further studies should be deployed to explore the potential different phenotypes suggested by Pain et al.

Interestingly, while several studies have identified an association between SDB and PrE, results from neither REVEAL nor PULSE have shown a significant difference in SDB cases in women who did and did not develop PrE. Although both PrE and SDB were associated with cfPWV trajectories in pregnancy, these results suggest that they may be associated through different pathophysiologic mechanisms.

4.2 Justification and strengths of the approach

The greater aim of this study is to contribute important research findings in high-risk pregnancies. There are several strengths to this study that support the findings herein. Our study focuses specifically on PrE women, yet it only occurs in 5-8% of pregnancies; therefore, we selectively included only those at high risk of developing PrE. A larger proportion of our population developed PrE (18.87%) than in the general pregnant population, which allowed us to properly represent and study PrE women.

Additionally, women at high risk of PrE are more frequently followed in-clinic, putting a larger burden on the healthcare system and on patients. Therefore, by analyzing only high-risk pregnant women, we hope to contribute research to aid reduce unnecessary clinic visits and bring focus to factors that put women at higher risk of developing PrE. Additionally, all data gathered through this study are observational and did not harm the mother or fetus.

AS was measured non-invasive using the gold standard cfPWV. Importantly, we used the SpyghmoCor device, which has been validated against many different populations, has been used in over 424 studies, and has low inter- and intra-operator variability(49, 54, 55, 59, 67, 68). In the

PULSE study, we measured AS using the most recent version of SpyghmoCor device, the XCEL, which captures the femoral artery using a femoral cuff while the operator uses the tonometer to capture the carotid pulse. This most recent version is more user friendly and requires less training than the previous versions. All AS operators were trained and certified prior to recruiting patients.

In our study, we defined SDB as snoring or long pauses between breaths 3 or more times a week. Although this measure is not the gold standard, polysomnography, has been used in large population studies and has a good correlation with objective evaluation(22). Using symptom-based questionnaires is more clinically relevant and applicable to the pregnant population; pregnant women often have other children to care for, and polysomnography has waiting times that exceed the duration of pregnancy, making polysomnography unfeasible. Furthermore, we performed study visits in conjunction with obstetrics appointments, which likely helped contribute to our recruitment success.

Importantly, this paper included data from two separate studies, REVEAL, the pilot project, and PULSE, the ongoing validation study. Although there were some contradicting findings between the two studies, most of PULSE findings had similar associations as seen in REVEAL but lacked significance, most likely due to the sample size. Therefore, the analysis put forth in this thesis should be replicated once PULSE has recruited a larger proportion of its sample and stronger power.

As age is a confounder for arterial stiffness, SDB, and PrE, we adjusted for maternal age in all analyses. Furthermore, black race populations are at higher risk of hypertension, cardiovascular disease, SDB, and PrE; therefore, we also adjusted for black race in all analyses.

A key importance to our study design is that we evaluated patient characteristics, starting at the first obstetrics clinical appointment, prior to the development of PrE. Therefore, results from our studies will allow us to analyze the predictive ability of many other variables. Additionally, the measurements of exposure could not have impacted the outcome and PrE diagnosis was adjudicated by an appointed obstetrician.

There is a small potential of selection bias as patients who are Native Canadians only have their first obstetrics visit in their second trimester. Our inclusion criteria require women to be in their first trimester. Therefore, we were unable to recruit any women who identified as Native Canadian and lived in Northern remote regions. Volunteer bias is unlikely in our study as we screened (inclusion/exclusion criteria and interest in being approached by research) all pregnant

women coming for their first obstetrics appointment. There is a possibility of self-selection bias as patients who were familiar with research or had a history of PrE and wanted additional tests might be more likely to participate than those who refused. Unfortunately, recall bias should be accounted for as patients were assessed for SDB through a questionnaire, and the weight history questionnaire reordered weight and height from 13 years old onwards. Additionally, we excluded 9 women who miscarried as we were unable to identify when the women had miscarried (before or after our first study visit). Operator bias is unlikely in this study as we adhered to strict protocols.

There may be some non-response bias as several patient did not complete the SDB component of the PSQI. To determine if a patient has SDB, the participants asked their bedroom partners if they (partner) witnessed them (participants) snore or have long pauses in their breath 3 or more times a week. If women do not have a bedroom partner and were unsure if they snored or had long pauses in breath, they were unable to answer the questionnaire. Therefore, we were unable to include these women in the SDB analysis. Using at-home sleep tests or different methods to assess SDB, such as Facco, Parker (22) , would help prevent missing patient SDB data. Furthermore, at-home sleep test would allow for the analysis of SDB severity.

4.3 Limitations

There are certain limitations to this study that should be addressed. First, although we recruited a large sample of women, underweight and obese women were underrepresented. Future studies should aim to include a larger proportion of underweight women and properly represent women of different obesity categories (class I, II, and III). Secondly, we recruited only women at high-risk of developing PrE. Therefore, our results are not applicable to low-risk pregnancies. Thirdly, we did not differentiate early-onset PrE from term PrE as we had a limited sample of women who developed early-onset PrE. As early-onset PrE has a high rate of morbidity and mortality compared to term, future studies should independently analyze the association of early pregnancy weight gain and AS in early-onset and term PrE. Fortunately, PULSE is ongoing and has a larger proportion of women developing PrE than in the general pregnant population; therefore, these analyses should be run once PULSE is complete.

Fourth, although cfPWV is a tool with great clinical utility, has been validated against many populations, and is the gold-standard measurement of AS, it is not ideal for all clinical

practices. Tonometry-based cfPWV requires a great amount of user experience when it comes to obese women. As experience by Protogerou, Laaban (1), we were unable to obtain cfPWV measurement of several patients as they were severely obese, and the SpygmoCor device could not obtain a femoral pulse that reached the minimum threshold for analysis.

Fifth, we evaluated AS in women of different BMI's as it is a standard measurement used in clinics to represent a patient's level of adiposity. However, BMI classifications can oversimplify patients' body composition as it does not differentiate weight attributed to muscle, fat, or bone. Several studies have identified that both visceral and subcutaneous adiposity are associated with increased AS(62, 89). Therefore, evaluating body composition in combination with BMI may provide additional information regarding the relationship between pre-pregnancy BMI/body composition, weight gain, and AS.

Finally, SDB was determined using a portion of the PSQI that asked patients if their partners had witness them snore or have long pauses between breaths 3 or more times a week. As previously mentioned, several women were unable to answer these questions as they did not have a bedroom partner. Furthermore, determining SDB by symptom-based questionnaire is limiting to our study as the gold-standard for measuring SDB is by polysomnography. Symptom-based questionnaires have moderate specificity and sensitivity in the pregnant population(1, 10, 22, 90). It should be noted that polysomnography's are not easily accessible. Therefore, using other tools such as at-home sleep tests would be more practically relevant and provide more accurate assessments of SDB than questionnaires.

4.4 Implications of the Findings

The major implication of this study is the attribution of knowledge linking BMI, weight gain, and AS to PrE and SDB. The relationship between most of these topics have been explored individually. However, to our knowledge, we were the first study to have analyzed the dynamic relationship between all variables.

Currently, AS is known to be associated with BMI and acute weight gain in the general population(62). Additionally, AS can predict cardiovascular events and cut offs for AS have been established in the general population(62). However, AS and the hemodynamic changes in high-risk pregnancies are still being uncovered. The impacts of early pregnancy weight gain on AS are

unknown. Findings from our study suggest that there is a potential association between weight gain and AS in early pregnancy. Although more studies are needed to further evaluate these findings, the predictive ability of weight gain for developing cardiovascular diseases specific to the pregnant population, such as PrE, should be explored. Furthermore, weight gain is an easy marker to measure, and most obstetrics clinics are already monitoring patient weights.

Although results from REVEAL were not replicated in our preliminary analysis of PULSE, they share common patterns. We identified that obese women have higher AS throughout pregnancy compared to normal-weight women, regardless of the amount of weight gained during pregnancy. Our findings determined that pre-pregnancy BMI is significantly associated with AS throughout pregnancy and that early pregnancy weight gain does not impact the risk of PrE, and SDB. Furthermore, AS trajectories are associated with increased odds risk of developing PrE and SDB. These findings suggest that there is a need to improve the execution and implementation of pre-conception interventions, especially with those who are obese or have SDB. Furthermore, these findings support the potential use of AS in predicting the development of PrE.

Interestingly, if other studies observe that SDB during pregnancy is strongly associated with an increase in AS, an indicator of vascular dysfunction, it would support other studies advocating for the implementation and benefit of CPAP devices in the pregnant population.

4.5 Future Directions

In a previous study conducted by Phan, Schiller (75), AS was shown to better predict PrE than current clinical tests. Additionally, she discovered that AS was associated with SDB. Following their findings, this thesis focused on the impacts of early pregnancy weight gain on AS, PrE and SDB. As seen in our analyses of REVEL and PULSE, BMI is consistently associated with AS throughout pregnancy. Currently, normal value ranges of AS in the pregnant population do not exist. Therefore, future work should aim to identify normal AS value ranges in high-risk pregnant women by BMI category.

Obese/overweight women are at higher risk of developing pregnancy complications and are therefore followed more closely in clinic. However, in a study by Zutshi, Santhosh (91), more than half of overweight and obese women had uncomplicated pregnancies. Excessively following patients in-clinic is not only costly and cumbersome for the health care system, but it is also tiring for patients. Therefore, several groups have sought out other methods of measuring body

composition. In a systematic review and metanalysis by Gao, Yan (92), waist circumference, and waist to hip ratio were significantly associated with gestational diabetes and HDPs, while fat mass, neck circumference, skinfolds, and visceral fat were associated with other complications of pregnancy. Therefore, future studies should evaluate the association between AS and other measures of body compositions such as the once investigated in Heslehurst, Ngongalah (89).

As seen in our evaluation of the relationship between weight gain, AS and PrE, REVEAL and PULSE had mixed findings. Only two other groups have investigated the association between early pregnancy weight gain and PrE. Therefore, more studies are needed to assess this potential relationship. As PULSE is an ongoing study, these analyses should be explored once the study is completed.

In accordance with Tantrakul and et al. (90), symptom-based questionnaires are not most reliable way of assessing SDB. Using an at-home sleep test would prove beneficial in providing more knowledge on the association between weight gain, AS and SDB. Many studies evaluating at-home sleep tests and polysomnography in pregnancy are currently ongoing. Results from these studies will help guide future research on SDB in pregnancy.

Most importantly, recording patient baseline measurements prior to pregnancy would enhance our understanding of hemodynamic changes in high-risk pregnancies. Although hemodynamic changes, such as an increase in blood volume, do not occur in the first trimester, having measurements prior to pregnancy would be helpful in pre-conception clinics. Pre-pregnancy and inter-pregnancy care are often lacking and should become a larger focus as these baseline measurements could help inform us of patients' potential complications based on AS and BMI. Moreover, longitudinal studies recording patient weight and AS measurements from adolescence to pregnancy would significantly enhance our understanding of the hemodynamic response to weight fluctuations.

As mentioned in Chapter 1, pregnant women are at an increased risk of developing SDB due to the physiological changes that occur during pregnancy, such as weight gain, rhinitis and estrogen levels. Future studies should investigate estrogen levels in high-risk pregnant women throughout pregnancy. It may prove beneficial to determine if there is an association between weight gain and estrogen levels in women who develop SDB during pregnancy compared to those who have SDB prior to pregnancy and to those without SDB.

Finally, this study focused on the clinical aspects of the association between weight gain, AS, PrE and SDB. However, obesity, AS, PrE and SDB are all linked to inflammation, oxidative stress, and endothelial dysfunction(8, 28, 52, 84). Identifying the mechanistic link between each of these variables would prove particularly useful in understanding their pathophysiology.

4.6 Conclusion

The findings of this thesis aimed to help elucidate the relationship between weight gain, AS, PrE and SDB in high-risk pregnant women. In the general population weight gain has been associated with AS, SDB is associated with AS and cardiovascular events, and AS is predictive of cardiovascular events. However, as commonly seen, pregnant women are often excluded from research, and research on the association between these variables in pregnant women is lacking. Recent studies have found that AS is associated with PrE. Several studies have found that a relationship between SDB and PrE. Although several studies have found weight gain to be associated with PrE, they have focused on late or total pregnancy weight gain, neither of which would help predict PrE. The greater aim of both REVEAL and PULSE are to find ways to better predict PrE in high-risk pregnant women in early pregnancy. Our aim in this thesis was to to 1) examine weight gain patterns and AS values in high-risk pregnant women in the first and second trimester of pregnancy, and 2) to examine the impact of weight gain trajectories and AS on the development of a) PrE and b) SDB in pregnant women at high risk of developing PrE. In this thesis, we demonstrated that 1) early pregnancy weight gain has a potential impact on AS; however, 2) it is not associated with the development of PrE or SDB. Significantly, we found AS trajectories to be associated with the development of PrE and SDB in both REVEAL and PULSE. The findings support the theory that AS may be a potential effective clinical tool for the early prediction of PrE.

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Appendix

Figure 4.1–REVEAL study timeline

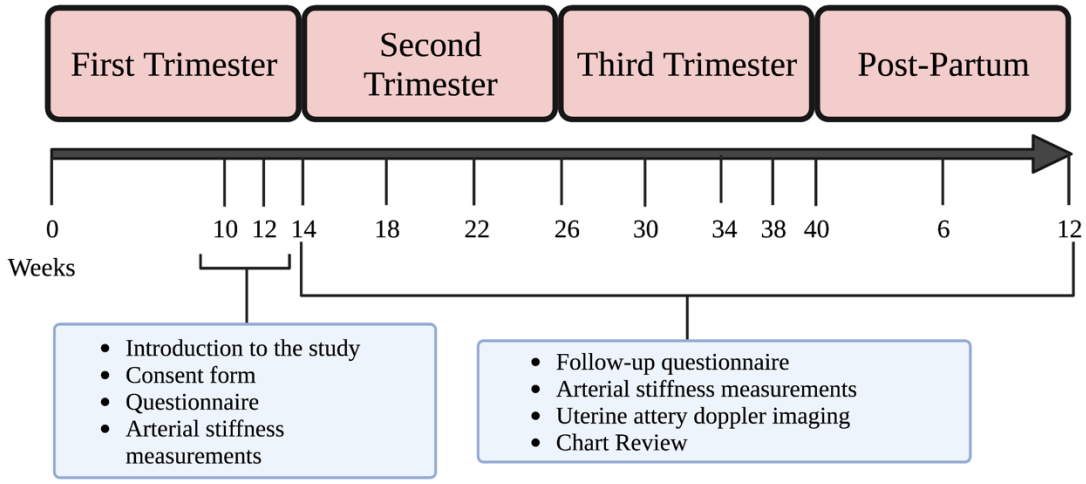

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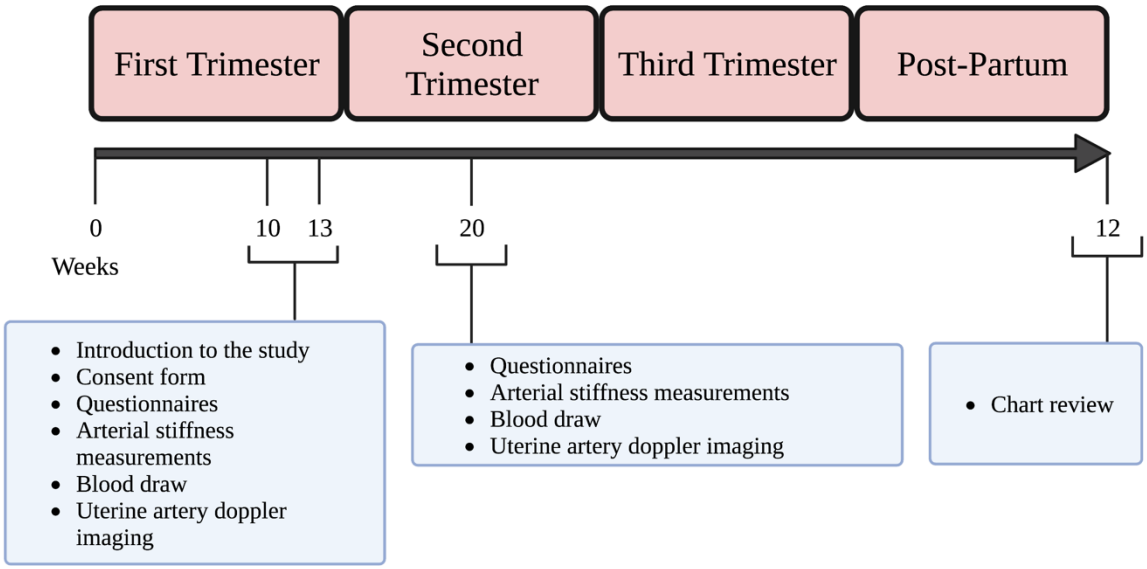
Figure 4.2–PULSE study timeline



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