Exploring Associations between Maternal Blood Pressure, Symptoms of Depression and Anxiety, and Gestational Age at Birth using Multivariate and Functional Data Analysis.

Kristin J. Horsley

Department of Psychology

McGill University, Montreal, QC

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✦ *twinkle, twinkle little star*

how I wonder what you are

up above the world so high

like a diamond in the sky

twinkle, twinkle little star

how I wonder what you are

...and who you will become ✦

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Resumé

La grossesse est caractérisée par des changements importants de la physiologie et de la psychologie chez la mère qui peuvent mener à des problèmes de santé. Environ 7% des femmes développeront un trouble hypertensif de la grossesse et 10 à 25% rapporteront des symptômes importants de dépression ou d'anxiété. Des études antérieures démontrent que les symptômes maternels de dépression ou d'anxiété sont associés au développement ou à l'aggravation de l'hypertension pendant la grossesse, ainsi qu'à des conséquences de grossesse défavorables telles que la naissance prématurée. Cependant, la façon dont ces facteurs interagissent demeure méconnue. Cette thèse présente les résultats de trois études conçues pour: (1) examiner comment les symptômes maternels de dépression et d'anxiété interagissent avec l'hypertension pendant la grossesse pour prédire l'âge gestationnel à la naissance, (2) identifier les trajectoires de tension artérielle tout au long de la grossesse en utilisant l'analyse des données fonctionnelles et examiner comment celles-ci sont liées à l'âge gestationnel à la naissance, et (3) étudier comment les facteurs maternels, obstétricaux et psychologiques sont liés à la pression artérielle pendant la gestation en utilisant l'analyse de régression fonctionnelle.

Dans le premier manuscrit de ma thèse, j'ai effectué une analyse secondaire des données d'une étude d'une cohorte de femmes enceintes à Calgary, Alberta, Canada. Sur 2763 femmes qui ont eu une grossesse unique et une naissance vivante, 247 (9%) ont reçu un diagnostic de trouble hypertensif de la grossesse. Les résultats de cette étude reproduisent les résultats de recherches antérieures sur le lien entre les troubles hypertensifs de la grossesse et l'âge gestationnel plus jeune à la naissance. De plus, les résultats démontrent que la force de cette association dépend de la gravité des symptômes de dépression et d'anxiété, de sorte que ces

symptômes peuvent augmenter le risque de grossesse raccourcie lié aux troubles hypertensifs de la grossesse.

Dans le deuxième manuscrit, j'utilise l'analyse de données fonctionnelles pour modéliser la pression artérielle pendant la grossesse. Des données cliniques sur la pression artérielle étaient disponibles pour 370 femmes qui ont participé à une étude de cohorte longitudinale de grossesse menée à Montréal, Québec. L'analyse de données fonctionnelles a permis d'identifier les trajectoires prédominantes de changement de pression artérielle au cours de la gestation. Les résultats de l'analyse de régression multivariée montrent qu'une augmentation tardive de la pression artérielle est associée à une gestation plus courte, tandis qu'une diminution de la pression artérielle à la mi-grossesse est associé à une gestation plus longue. En utilisant l'analyse de données fonctionnelles, cette étude contribue de façon méthodologique à la littérature sur l'analyse de la pression artérielle pendant la grossesse.

Le troisième manuscrit utilise l'analyse des données fonctionnelles afin d'examiner comment les facteurs de risque de l'hypertension durant la grossesse et les symptômes de dépression et d'anxiété sont associés la pression artérielle tout au long de la grossesse. Ces résultats indiquent que la parité et l'indice de masse corporelle avant la grossesse, mais non pas les symptômes de dépression et d'anxiété, sont associés à la pression artérielle particulièrement durant certaines phases de la grossesse. Il est possible que ces résultats soient différents dans un échantillon plus «à risque» pour les maladies cardiovasculaires.

L'ensemble des études de cette thèse contribue de façon significative aux connaissances sur la façon dont la psychologie maternelle interagit avec ou influence la santé cardiovasculaire maternelle tout au long de la grossesse, et à la littérature sur les méthodologies statistiques

disponibles pour examiner les associations entre les variables indépendantes et dépendantes lorsqu’elles sont de nature fonctionnelle.

Abstract

Pregnancy is characterized by significant changes to maternal physiology and psychology that sometimes set the stage for health problems. Approximately 7% of women will develop one of the hypertensive disorders of pregnancy (HDP) and 10 to 25% will report significant symptoms of depression or anxiety. Previous researchers have shown that maternal symptoms of depression or anxiety are associated with the development or worsening HDP, and that these factors are associated with younger gestational age at birth. How maternal psychology interacts with or influences maternal cardiovascular function is unclear. This dissertation present results from three studies that were designed to: (1) examine how maternal symptoms of depression and anxiety interact with HDP to predict gestational age at birth; (2) identify trajectories of blood pressure change across pregnancy using functional data analysis and examine how these relate to gestational age at birth; and (3) to investigate how maternal, obstetrical, and psychological factors relate to blood pressure across gestation using functional regression analysis.

In Manuscript 1, the aim was to examine whether symptoms of depression or state anxiety changed the strength or nature of the association between HDP and gestational age at birth through secondary analysis of data from a large pregnancy cohort study conducted in Calgary, Alberta. Of 2763 participants, 247 (9%) were diagnosed with HDP. Women with HDP had significantly shorter gestational length relative to those without the diagnosis. Moderation analyses showed that the strength of the association between HDP and younger gestational age at birth increased alongside greater depressive symptom and state anxiety severity. Results suggest that depressive symptoms and state anxiety may add to the increased risk for shortened gestation associated with HDP.

Manuscript 2 demonstrates how functional data analysis can be used to model maternal blood pressure across gestation. Clinical blood pressure data were available from 370 women who participated in a longitudinal pregnancy cohort study conducted in Montreal, Quebec. Functional data analysis was used to identify trajectories of blood pressure change across gestation and to examine how these relate to gestational age at birth. Results from multivariate regression analysis showed that a late-increase in blood pressure was associated with younger gestational age at birth, while a mid-decrease pattern is associated with older. Through application of functional data analysis, this study makes a methodological contribution to literature on statistical modeling of blood pressure across pregnancy.

Manuscript 3 builds on the methodological work and examined how maternal risk factors for HDP and maternal symptoms of depression and pregnancy-specific anxiety relate to blood pressure across pregnancy. In this study, functional regression analysis was applied to explore the effect of each predictor on blood pressure across gestation. Results showed that parity and pre-pregnancy body mass index were more strongly associated with blood pressure at certain timepoints during gestation over others, but that symptoms of depression and pregnancy-specific anxiety were not. Whether this pattern of results looks different among a sample at greater cardiovascular risk is an intriguing question for further study.

Taken together, the contents of this dissertation contribute to original knowledge on how maternal psychology interacts or influences maternal cardiovascular health across pregnancy, or not, and to literature on statistical methodologies that can be used to examine associations between independent and dependent variables when one is functional in nature.

Acknowledgements

In the spirit of truth and reconciliation, I want to first acknowledge that the work presented in this dissertation was conducted at the University of Calgary and McGill University, institutions that are respectively situated on the traditional, ancestral, unceded territories of the people of Treaty 7 region in Southern Alberta, the Métis Nation of Alberta, Region 3, and on land which has long served as a site of meeting and exchange amongst Indigenous peoples, including the Haudenosaunee and Anishinabeg nations. Second, I want to acknowledge the Métis roots that run through my maternal line. In 2015, with the release of the Truth and Reconciliation Report, there has been noticeable shift, a warming, in how Canadians understand, acknowledge, and speak about our First Nations, Inuit, and Métis peoples. With this in mind, I want to acknowledge my maternal grandfather, Robert Bertrand Racicot, born to his Métis mother on October 15th, 1925 in Killarney, Ontario, and who died on July 7th, 2003 in Comox, British Columbia. It is my understanding that he did not acknowledge his Métis heritage because of the associated cultural stigma and so it is my wish to do so now on behalf of him and of my mother, to intentionally thread this back into our family history.

To my supervisor, Dr. Blaine Ditto, thank you for your constant and considerate support and supervision. I am grateful for quality of your mentorship, for your dedication to stretching the limits of my mind, and for your even keeled nature that I hope to emulate in my own career. Thank you to Dr. Deborah Da Costa for your generosity, guidance, and support over the last several years – without you, this work would not have been possible. I am grateful to my doctoral committee members, Drs. Barbel Knauper and Irv Binik, for their support of my clinical and research endeavours. My sincere gratitude to Dr. Jim Ramsay who provided countless hours of individual teaching and mentorship on a new statistical approach that I have come to deeply

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The purpose of life is not to be happy. It is to be useful, to be honorable, to be compassionate, to have it make some difference that you have lived and lived well.

Ralph Waldo Emerson

Contribution to Original Knowledge

Manuscript 1 contributes to knowledge on how maternal psychological factors interact with cardiovascular complications that arise during pregnancy. First, results replicated the well-established association between hypertensive disorders of pregnancy and younger gestational age at birth. Second, moderation analyses showed that this effect increased alongside greater depressive and state-anxiety severity. These results are suggestive of an additional effect of maternal psychological factors among women with a cardiovascular system that is under stress via the presence of a hypertensive disorder of pregnancy. From a clinical perspective, results from this study also indicate that women with hypertensive disorders of pregnancy *and* who reported elevated symptoms of depression or anxiety may represent a particularly "at-risk" sample of pregnant women who may benefit from psychological support.

Throughout the peer-review process of Manuscript 1, a consistent comment was that results were limited by a binary indicator of maternal cardiovascular health, namely the absence or presence of hypertensive disorders of pregnancy. As a result of this limitation, the question turned to how maternal psychological factors like symptoms of depression or anxiety might relate to continuous blood pressure observations across gestation. Unsatisfied with previous multivariate statistical methodologies, functional data analysis was identified as a useful statistical technique to model the dynamic changes in maternal blood pressure across gestation. Manuscript 2 describes how functional data analysis can be used to construct curves across time from a set of clinical blood pressure observations. Functional principal components analysis is used to identify predominant modes of variation among the curves, and multivariate statistics are reincorporated to examine how these trajectories relate to gestational age at birth. The results show the usefulness of functional data analysis for repeated observations that vary in number and

frequency, and where the interval between assessment timepoints is a potentially meaningful source of variation. Manuscript 2 makes a primarily methodological contribution to the sparse literature that has used functional data analysis within the context of pregnancy research.

The third manuscript of my dissertation builds upon findings from the second study through an examination of maternal factors relate to constructed blood pressure curves. In this study, functional regression analysis is used to examine how established risk factors for a hypertensive disorder of pregnancy (i.e., maternal pre-pregnancy body mass index, primiparity) relate to blood pressure across gestation. Beyond the methodological contribution that allows researchers to examine how the effect of a predictor changes across time, this study also is the first to examine how maternal symptoms of depression and pregnancy-specific anxiety relate to maternal cardiovascular function. Results of this study showed that among an ethnically diverse sample of relatively healthy pregnant women, these maternal psychological factors were not related to blood pressure across pregnancy. Whether this pattern of results would look different among a sample of women who are at greater risk for cardiovascular complications in the index pregnancy (e.g., history of a hypertensive disorder of pregnancy, presence of cardiovascular risk factors such as overweight/obesity, positive smoking status) remains unknown.

Beyond these contributions, the contents of this dissertation serve highlight how difficult it is to adequately measure, model, and describe the complex psychological and physiological processes that unfold across pregnancy. In the general discussion, findings from the maternal psychological and cardiovascular health literatures are synthesized. A conceptualization is proposed for why psychological distress is expected when there is a sudden change in the psychophysiology of pregnancy, and how the integration of clinical psychology into high-risk obstetrical settings is essential to increase research capacity and improve in clinical care.

Contribution of Authors

This dissertation is comprised of three manuscripts that represent my doctoral work conducted under the supervision of Dr. Blaine Ditto and in collaboration with several mentors and colleagues from the University of Calgary and McGill University.

The first study is a secondary analysis of data from the All Our Families (AOF) Cohort, a longitudinal pregnancy study conducted in Calgary, Alberta, Canada, led by Dr. Suzanne Tough. For this manuscript, I was responsible for study conceptualization, research proposal preparation and submission for internal review by the AOF study team, ethics preparation and submission, legal aspects of data acquisition and data transfer between institutions, data cleaning and preparation, formal statistical analysis and visualization, preparation and writing of manuscript drafts, and all aspects of the peer-review process. As primary investigator for the AOF study, Suzanne Tough secured grant funding for the study (Alberta Innovates Health Solutions Interdisciplinary Team Grants Program #200700595) and, with her research team, was responsible for all aspects of study design and conceptualization, participant recruitment, and data collection. Lianne Tomfohr-Madsen provided significant support with study conceptualization, data analysis, and manuscript preparation – writing and editing. Blaine Ditto provided significant support with manuscript preparation – writing and editing, and endless mentorship across the peer-review process.

The second and third study of this thesis were analyses of data collected as part of the Healthy Behaviours in Pregnancy and Postpartum Study. This longitudinal cohort study was led by Dr. Deborah Da Costa in the Department of Epidemiology at the Research Institute of the McGill University Health Center. Dr. Da Costa secured grant funding for the study (Canadian Institutes of Health Research grant #247035) and was responsible for all aspects of study design

and conceptualization and with preparation and initial cleaning of the self-report questionnaire dataset. Participants were recruited by her research team at two McGill University affiliated hospitals. Rebecca Wickett was responsible for blood pressure data extraction and data entry and provided support for data cleaning and preparation.

For manuscripts two and three, I was involved with study conceptualization, data preparation and cleaning, formal data analysis and visualization, and all aspects of manuscript preparation. Jim Ramsay provided a tremendous amount of statistical consultation and support for data analysis, interpretation, and visualization and without him this work would not have been nearly as exciting or possible. Blaine Ditto and Deborah Da Costa provided guidance with study conception, data preparation and analysis, and manuscript preparation – writing and editing, and hours of support and mentorship.

List of Abbreviations

ACOG	American College of Obstetrics and Gynecologists
AOF	All Our Families
BMI	Body mass index
CRH	Corticotropin releasing hormone
DBP	Diastolic blood pressure
DSM	Diagnostic and statistical manual
EPDS	Edinburg postnatal depression scale
FDA	Functional data analysis
***f*PCA**	Functional principal components analysis
GCV	Generalized cross validation
HDP	Hypertensive disorders of pregnancy
HPA-axis	Hypothalamic-pituitary-adrenal axis
LGTBQ	Lesbian, gay, transexual, bisexual, queer/questioning
PDQ	Pregnancy distress questionnaire
PRAQ	Pregnancy related anxiety questionnaire
SAI	State anxiety index
SBP	Systolic blood pressure

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Pregnancy, like puberty or menopause, is regarded as a period of crisis involving profound endocrine and general somatic as well as psychological changes. The crisis of pregnancy is basically a normal occurrence and indeed even essential part of growth, which must precede and prepare maturational integration. It varies, individually, however, from woman to woman, according to her personality structure, her special kind and degree of adjustment and conflict solution with which she enters pregnancy and the particular life setting and family constellation in which this event takes place.

Dr. Grete Bibring

General Introduction

Pregnancy is considered to be a natural cardiovascular stress test (Bilhartz et al., 2011; Williams, 2003). The maternal cardiovascular system must change and adapt across gestation to meet increased metabolic demands of a developing fetus (Chang & Streitman, 2012). For some, when demands exceed a maternal cardiovascular reserve, normal physiological changes such as increased cardiac output and blood volume unmask cardiometabolic vulnerabilities and lead to complications such as gestational hypertension (Bilhartz et al., 2011; Williams, 2003). Similarly, pregnancy serves as a window into a woman's psychological health. From a psychodynamic perspective, this period is understood as a maturational crisis, where underlying psychological vulnerabilities are particularly susceptible to emerge as pathological in the absence of adequate resources to resolve inner conflicts (Bibring, 1961). Current perspectives focus more on weaknesses in coping with the environment which can spring from current life situation (e.g., economic stress) as well as long-term family and other influences (e.g., education, social support). In turn, ineffective coping may lead to maternal symptoms of depression or anxiety, that are potent predictors of maternal, infant, and child health outcomes. There is an inextricable link between the physiological and psychological aspects of pregnancy. Emotion, thought, behavior, and physical sensations weft along the warp of a woman's entire life history to create a unique pregnancy experience. The resultant tapestry serves as an indicator for how her reproductive history will impact life or longevity.

In essence, pregnancy represents a persistent state of disequilibrium that requires nearly constant maternal cardiovascular and psychological adjustment (Bibring, 1959). The contents of this dissertation document my pursuit to understand how maternal psychological factors interact with or influence blood pressure across gestation, the most important and frequently assessed

clinical indicator of maternal cardiovascular function (Nathan et al., 2015; Sanghavi & Rutherford, 2014). Central to this understanding is the question of how to model dynamic changes in blood pressure that unfold over nine months. Further, if maternal psychological factors associate with blood pressure across pregnancy, when in this process might they matter most? The present work begins to take up these questions.

Taken together, the aim is to inspire an increased appreciation for how difficult it is to adequately measure and model physiological and psychological processes across time in a way that best captures the process that is unfolding. And more, to discuss some themes peripherally linked to this work: how to adequately assess and describe intricate physiological and psychological processes, the importance of sex- and gender-based analyses, and alterations to broader life meaning systems and points of self-reference that happen during pregnancy. These topics inform my work as a researcher and, coupled with my clinical training, create a broad foundation of knowledge and theoretical framework to build upon.

The first section of this dissertation begins with an introduction and brief overview of hypertensive disorders that occur during pregnancy, maternal depression and anxiety, and research that shows how these phenomena are potentially linked. Then, a brief overview of maternal cardiovascular physiology and what is known about how maternal factors influence this process. Statistical methods that have been typically used to examine change in blood pressure at some point in gestation are reviewed, and limitations of multivariate statistical methods are discussed. Finally, an introduction to functional data analysis as a novel statistical methodology that is highly suitable to examine variance in blood pressure across time.

Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy (HDP) occur in approximately 7% of pregnancies and represent the most common obstetrical complications in Canada (Nerenberg et al., 2018). HDP include a spectrum of conditions characterized by elevated systolic (SBP; >140mmHg) or diastolic (DBP; >90mmHg) blood pressure (i.e., hypertension) that is present at some point across gestation. Diagnostic criteria for HDP range in terms of timing of onset and severity. Specifically, chronic hypertension refers to hypertension diagnosed before pregnancy, gestational hypertension is elevated blood pressure that presents after 20 weeks of gestation, preeclampsia refers to hypertension with target organ involvement (i.e., proteinuria, renal/hepatic involvement, neurological or haematological complications, or restriction of foetal growth), and chronic hypertension with superimposed hypertension refers to pre-existing hypertension that progresses to preeclampsia with advancing gestation (American College of Obstetrics and Gynecologists (ACOG), 2020). Together, these disorders account for approximately 16% of maternal deaths (ACOG, 2020), 15% of all indicated preterm births, and are associated with an approximate 3-fold increase in risk for low birthweight (Roberts et al., 2003).

Unfortunately, there is limited ability to predict or prevent the development or worsening of HDP. Consideration of pregnancy-specific factors such as nulliparity, advanced maternal age, previous diagnosis of HDP, multiple pregnancy, and traditional cardiovascular disease risk factors such as overweight/obesity provide some indication of disease trajectory but, in general, disease onset and progression are difficult to predict (Berry & Atta, 2016; Townsend et al., 2016). In contrast, the consequences and impact of HDP are well-established. Research has shown that the adverse effects of HDP extend beyond the perinatal period and are highly predictive of maternal cardiovascular health outcomes later in a woman's life (Tranquilli et al.,

2012). Women with HDP are at a 3.7-fold increase in risk of chronic hypertension, 4-fold increase in risk of heart failure, and a 2-fold increase in risk of coronary heart disease and cardiovascular disease death (Wu et al., 2017). Research from the last 10 years has unequivocally shown that HDP represent an independent, sex-specific risk factor for cardiovascular morbidity and mortality (Coutinho et al., 2018; Tranquilli et al., 2012).

Aside from physical and obstetrical complications associated with HDP, there is a developing literature on the psychological aspects of these disorders, both as possible effects and causal factors. Recent research has shown associations between HDP and elevated maternal symptoms of depression and anxiety (Fairbrother et al., 2017; Melville et al., 2010), increased maternal risk for diagnosis of postpartum depression and greater depressive symptom severity (Caropreso et al., 2020), and a 16% increase in risk for hospitalization for major depressive disorder up to 28 years after birth (Auger et al., 2020). In the postpartum period, HDP is associated with lower maternal psychosocial well-being (Rep et al., 2007), including an increased risk of post-traumatic stress disorder associated with pregnancy and birth complications that are more commonly experienced among these women (Hoedjes et al., 2011; Pampus et al., 2004; Porcel et al., 2013). Thus, for most women, HDP occur in an otherwise uncomplicated first pregnancy, are often unexpected and potentially set off a cascade of events that can have a short- and long-term impact on maternal cardiovascular and psychological health (Duffy et al., 2019).

Maternal Depression and Anxiety

Mood and anxiety disorders are among the most frequently diagnosed mental illnesses in Canada. Population based data shows that up to 3.5 million or 10 percent of Canadians will consult a healthcare professional for these mental health difficulties (McRae et al., 2016).

Depressive disorders are characterized by low mood, loss of interest or pleasure, feelings of worthlessness, and by somatic symptoms such as weight changes, sleep disturbance, and fatigue (American Psychiatric Association, 2013). Symptoms of anxiety are typically defined as adverse cognitive-affective experience characterized by fear and unpredictability and marked apprehension about future outcomes. In short duration and appropriate circumstances, anxiety is considered an adaptive experience, but when symptoms are more frequent, at higher intensities and longer duration, and/or during inappropriate situations, anxiety can quickly become maladaptive (Barlow, 2004). Diagnostically, anxiety disorders are comprised of several sub-categories of psychopathology that range in frequency, intensity, duration, and situational factors and include diagnoses such as generalized anxiety disorder (i.e., frequent and persistent worry about several events or activities), panic disorder (i.e., sudden and unexpected onset of intense fear), and specific phobia (i.e., marked fear about specific objects or situations; American Psychiatric Association, 2013).

Historically, research into the complex psychological experiences associated with pregnancy has focused on the presence or absence of psychiatric diagnoses, and mainly antenatal (i.e., across gestation) and postpartum anxiety and depressive disorders (Leight et al., 2010; Ross & McLean, 2006). Results from these studies have shown that depression affects one in seven women during pregnancy and the first year postpartum (ACOG, 2018). Similarly, recent research estimates that perinatal anxiety disorders affect one in five women (Fawcett et al., 2019). Though the “true” prevalence remains unclear due to significant between-study heterogeneity and disagreement on appropriate screening tools, there is general consensus that a significant proportion of women experience symptoms of anxiety in general or anxiety related specifically to pregnancy (Dunkel Schetter & Tanner, 2012; Fawcett et al., 2019).

Depression

There has been increased interest in routine screening, diagnosis, and treatment for maternal depressive symptomology that occurred alongside introduction of the Postpartum Onset specifier for Major Depressive Disorder in the fourth edition of the Diagnostic and Statistical Manual (DSM-IV) published in 1994 (American Psychiatric Association, 1994). The specifier indicated a diagnosis of major depressive disorder that occurred within the first four to six weeks postpartum. It remained unchanged in the DSM-IV Text Revision (DSM-IV-TR; American Psychiatric Association, 2000), but in the DSM-5 was expanded to include Peripartum Onset, i.e., Major Depressive Disorder with onset during pregnancy or within the first 4-6 weeks postpartum (American Psychiatric Association, 2013). Although this change reflects findings from accumulated research on the incidence and prevalence of depression across pregnancy, the psychiatric and research community was largely dissatisfied since, in practice and regardless of the DSM-5 specifier, a diagnosis of major depressive disorder during pregnancy and the first 12 months after birth is considered to warrant the "with Peripartum Onset" specifier (O'Hara & McCabe, 2013).

Though discordance between what exists in diagnostic manuals and what happens in practice is not inherently harmful, nor uncommon, it points to a general lack of consensus between the psychiatric and research communities on the incidence, prevalence, and course of maternal depressive symptomology during pregnancy and postpartum. In recent years, there has been a substantial increase in knowledge about maternal depressive symptoms across pregnancy, and a call to action with a recommendation for widespread depression symptom severity screening for all pregnant women and increased access to mental health services (ACOG, 2018). Despite this recommendation, depressive symptoms are not routinely assessed, and maternal mental health resources are scarcely available.

Outside the psychiatric research community, there has been a proliferation of research from other health disciplines such as behavioral medicine, health psychology, and nursing on psychosocial distress and symptoms of depression and anxiety, and how different levels of distress relate to maternal and infant health outcomes (Dunkel Schetter & Tanner, 2012). Results from this literature have shown that rates of maternal depression vary depending on type and timing of assessment (e.g., self-report vs. clinical interview) but, in general, suggest that significant depressive symptomology affects up to 25% of women, and that the rates of major depressive disorder in the antenatal and postpartum period are between 10-15% (Tebeka et al., 2016), depending on the population of interest.

Among the most commonly used self-report scales to assess depressive symptoms is the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987). The EPDS is also validated for detecting clinically significant depressive symptoms during pregnancy and is widely used to repeatedly assess depressive symptom severity across pregnancy and postpartum (Murray & Cox, 1990). Developed in the late 1980s, the scale was designed in response to concerns about whether the somatic symptoms included in more typical depression scales (e.g., Beck Depression Inventory) inflated depressive symptom severity since there is significant overlap with typical somatic changes across pregnancy and postpartum (e.g., sleep, appetite, energy levels; Cox et al., 1987). There has been some indication, however, that somatic complaints characteristic of depression in non-pregnant samples may also be relevant indicators during pregnancy and postpartum, though the literature on this topic remains sparse (O'Hara & Mc Cabe, 2013). It could also be, however, that somatic complaints of depression may be simply be unique to pregnancy, such as back or hip pain, difficulty breathing, nausea and/or vomiting. There is substantial variation in the physical experience of pregnancy that could lead to different changes

in behaviours we know are linked to mood (e.g., physical or sexual activity, eating behaviours). These symptoms are important to consider but are not captured by the EPDS because somatic symptoms are instead deleted altogether (Appendix I).

Across studies, a diagnosis of major depression or high self-reported symptoms of depression during pregnancy are now well-established as risk factors for preterm birth and low birthweight, above and beyond the contribution of sociodemographic and pregnancy-related characteristics (Dayan et al., 2006; Dunkel Schetter & Tanner, 2012; Grigoriadis et al., 2013; Grote et al., 2010). These associations have been observed cross-culturally and in low- and middle-income countries (Mochache et al., 2018; Van Ngo et al., 2018). Recent systematic reviews and/or meta-analytic studies of the literature, however, have noted differences in the effect sizes (Accortt et al., 2015; Alder et al., 2007; Bonari et al., 2004; Grote et al., 2010), suggesting that the association between maternal depression or anxiety on adverse birth outcomes is stronger in some populations or circumstances over others.

Anxiety

Anxiety affects between 15 and 23% of women during pregnancy and postpartum (Dennis et al., 2017; Heron et al., 2004). Unlike maternal depression, there is no "formalized" specifier in the DSM-5 to indicate that a diagnosis of one or more anxiety disorders is related to the pregnancy or postpartum experience. As such, prevalence estimates typically describe rates of different anxiety disorders diagnosed during pregnancy and postpartum (e.g., generalized anxiety disorder, panic disorder, specific-phobia, obsessive-compulsive disorder; Fawcett et al., 2019), or anxiety symptom severity assessed through a variety of self-report questionnaires (Sinesi et al., 2019). A recent systematic review and meta-analysis of 102 studies from 34 countries indicates that the overall prevalence for a clinical diagnosis of any anxiety disorder is

15.4% (95% CI 9.0-21.4), and for elevated self-reported anxiety symptoms is 18.2% (95% CI 13.6-22.8) in the first trimester, 19.1% (95% CI 15.9-22.4) in the second trimester, and 24.6% (95% CI 21.2-28.0) in the third trimester (Dennis et al., 2017). Research has also shown that greater self-reported maternal symptoms of anxiety tend to co-occur with mild to severe depressive symptoms, and that rates of comorbidity are more pronounced in the first trimester at 11.6% (95% CI 9.0-14.2), relative to the second trimester at 10.6% (95% CI 7.2-14.0), third trimester at 9.5% (95% CI 6.1-13.0), and postpartum at 7.6% (95% CI 3.7-11.4; Falah-Hassani et al., 2017).

Self-report scales that assess anxiety during pregnancy and postpartum have received growing attention due to the significant amount of heterogeneity across studies examining links between maternal anxiety and pregnancy/infant health outcomes (Sinesi et al., 2019). Scales used assess different constructs of more generalized forms of anxiety such as worry during pregnancy, state/trait anxiety, and general anxiety, and more pregnancy-specific constructs of anxiety such as fear of childbirth, worry during pregnancy, and pregnancy-related anxiety (for a recent review of self-report scales used in the literature, see Sinesi et al., 2019). Despite widespread use of self-report assessment of maternal anxiety symptoms, there is often limited reporting of the psychometric properties of these scales (Evans et al., 2015). This is a concern given the overlap of somatic and psychological symptoms of anxiety with what can be considered normal psychological (e.g., increased worry, discomfort, and unease) and physiological (e.g., changes in breathing, heart rate, blood pressure) adaptations to pregnancy and childbirth.

The State-Trait Anxiety Index (STAI; Spielberger et al., 1970) is perhaps the most widely used scale to assess maternal anxiety symptom severity (Sinesi et al., 2019). The scale assesses the more short-term, temporary ‘state anxiety’ and the general and long-term construct of ‘trait

anxiety', and is considered a valid and reliable scale for use during pregnancy despite some methodological issues (Gunning et al., 2010). Still, it is likely that any major life event could reliably produce increase in these indices of state-anxiety (Appendix II), and that the scale does not consider the unique, anxiety-inducing aspects of pregnancy that relate to the maternal-fetal experience, family or social adjustment, and ability to adjust to new life circumstances.

Pregnancy-specific anxiety scales have recently emerged to assess worries and concerns unique to the perinatal period (e.g., medical care, physical symptoms, bodily changes, infant health; Blackmore et al., 2016). Although there is some overlap with more generalized forms of anxiety, pregnancy-specific anxiety is a distinct and definable construct that is considered a contextually-bound emotional state (Bayrampour, Ali, et al., 2016). At this point, none of the scales used in research have been validated to reliably indicate clinically significant pregnancy-related distress. Instead, pregnancy-specific anxiety/distress scales are used exclusively in research domains (Sinesi et al., 2019). In the last 15 years, an accumulation of research suggests that pregnancy-specific anxiety and/or distress may be a more robust predictor of maternal and infant health outcomes relative to more generalized forms of anxiety that occur during pregnancy (Bayrampour, Ali, et al., 2016; Lobel et al., 2008; Westerneng et al., 2017).

Blackmore et al. (2016) conducted a prospective, longitudinal study of 345 low-income, ethnically diverse individuals to examine how pregnancy-specific anxiety is associated with more conventional symptoms measures and how it is related to birth weight and gestational age at birth. Results from this study showed that greater pregnancy-specific anxiety about the child was associated with lower infant birth weight and younger gestational age at, above and beyond generalized anxiety and depressive symptom severity. In a large Canadian study of 5,337 pregnancy women, pregnancy-related anxiety was associated with a 1.8 (95% CI 1.3, 2.4)

increase in odds of spontaneous preterm birth (Kramer et al., 2009). Similar findings have been reported across several other studies (Leach et al., 2017; Lobel et al., 2008; Orr et al., 2007), supporting the notion that pregnancy-specific anxiety may be a particularly important predictor of pregnancy outcomes.

HDP and Maternal Symptoms of Depression and Anxiety

Recent meta-analytic findings indicate that symptoms of depression and anxiety and stress are associated with a 40% increase in risk of HDP (Shay et al., 2020). For example, the experience of high levels of psychosocial stress during pregnancy (e.g., divorce/separation, unemployment, change in residence) has been associated with a 1.6-fold increased risk for HDP and, more specifically, a 2.1-fold increased risk of preeclampsia (Leeners et al., 2007). The presence of either anxiety, depression, or both anxiety and depression early in pregnancy (i.e., 10-17 weeks' gestation) has been associated with a 3.2 (95% CI 1.4, 7.4), 2.5 (95% CI 1.1, 5.4), and 3.1(95% CI 1.4, 6.9) increase in risk for preeclampsia, respectively (Kurki et al., 2000). Null findings have also been reported, most notably in a large study of 3,679 nulliparous women in the Netherlands where neither work stress, depression, or anxiety were associated with increased risk of preeclampsia or gestational hypertension (Vollebregt et al., 2008). Thus, there is some consensus that depressive and anxious symptoms are associated with HDP, but that effects may be more pronounced in some samples over others.

Among pregnant women with a cardiovascular system that is already compromised due to the presence of HDP, the added influence of depressive or anxious symptoms may be particularly detrimental, though the literature on this topic remains sparse. Recent research findings have pointed to the potential for an even greater risk for adverse birth outcomes (i.e., shortened gestation/preterm birth, low birthweight) among women with HDP and concurrent

depressive or anxious symptoms. Results have shown a significant interaction between psychosocial stress, as either a composite stress index or as self-reported childhood racism, and high diastolic blood pressure such that when stress is high, diastolic blood pressure was negatively associated with birthweight (Hilmert et al., 2008). Notably, while this effect was more pronounced among Black women, the impact of stress and blood pressure on birthweight was significant in White women as well.

A recent epidemiological study of over two million pregnant women indicated that women with depression and HDP were 3.41 times (95% CI, 3.15-3.68), and 4.10 times (95% CI, 3.89-4.32) more likely to experience intrauterine growth restriction and preterm labour, respectively, relative to women without depression and HDP (Mogos et al., 2019). The economic impact of co-occurring depression was estimated to be approximately $5 billion during the study period, though costs were primarily driven by HDP. These results highlight the importance of considering how maternal psychological factors and the maternal cardiovascular system interact or influence one another to produce differences in birth outcomes.

Maternal Cardiovascular Function Across Pregnancy

In a relatively healthy or “normal” pregnancy, the cardiovascular system changes dramatically to sustain the maternal-fetal unit. Blood volume increases significantly, such that by the end of pregnancy the heart is pumping roughly 1.5 to 2 times as much blood (Meah et al., 2016). Systemic vascular resistance falls by 40 percent to a nadir in the middle of the second trimester (Mahendru et al., 2014). To compensate, there is an increase in cardiac output via increased stroke volume in early pregnancy, and by increases in heart rate in late pregnancy when stroke volume plateaus (Sanghavi & Rutherford, 2014). This leads to high-volume, low-resistance circulation until mid-third trimester and thus an expected slight blood pressure

decrease (Sanghavi & Rutherford, 2014; Thilaganathan & Kalafat, 2019). In mid- to late-pregnancy, systemic vascular resistance increases to or beyond pre-pregnancy levels until delivery, leading to a relative blood pressure increase (Meah et al., 2016; Rurangirwa et al., 2012). These are profound cardiovascular changes that happen within the context of a woman's current cardiovascular health upon conception.

Early work that examined trajectories of blood pressure change suggested that this "mid-pregnancy" decrease was quite substantial and clinically important. Initially, researchers observed that decreases of 5-10mmHg were a hallmark feature of a "healthy" pregnancy, and the absence of this decrease to be a marker of maternal risk for HDP (Grindheim et al., 2012; Moutquin et al., 1985). This well-accepted finding has recently been challenged by results from longitudinal studies with larger sample sizes, a greater number of blood pressure observations, and more advanced statistical techniques (Nama et al., 2011). These studies have shown that, for most, this blood pressure dip is not as pronounced or indicative as initially thought, and that instead there is a relatively steady increase in blood pressure until birth (Loerup et al., 2019).

With advances in statistical modelling, there has also been increased interest in understanding how maternal factors relate to trajectories of blood pressure change across pregnancy (Farrar et al., 2019; Macdonald-Wallis et al., 2012; Macdonald-Wallis et al., 2011). Findings from this literature have shown that pregnant women with chronic hypertension, gestational hypertension, and preeclampsia tend to have higher blood pressure across pregnancy, relative to normotensive controls (Macdonald-Wallis et al., 2012). Similarly, among healthy pregnant women who remain normotensive, those with established risk factors for preeclampsia (e.g., overweight/obesity, nulliparity, maternal age >35 years, and twin pregnancy) have higher systolic and diastolic blood pressure, compared to those without (Macdonald-Wallis et al., 2011).

Other factors such as ethnicity are also related to different patterns of blood pressure change across gestation (Farrar et al., 2019).

A recent study examined how trajectories of blood pressure relate to maternal and infant heath outcomes (Guo et al., 2020). Results showed that a moderate-increasing pattern of systolic blood pressure across pregnancy, characterized by increases in blood pressure from mid-second trimester until admission for delivery, was associated with an increase in odds of low birthweight, preterm birth, and lower APGAR score (i.e., Appearance, Pulse, Grimace, Activity, and Respiration, where greater scores are associated with better infant health status) at one and five minutes (Guo et al., 2020). Taken together, these results indicate that maternal factors influence blood pressure change across pregnancy and that they may have stronger effects at some timepoints over others, though this is difficult to ascertain with group-level analyses.

Statistical Methods for Time-Series Analysis of Clinical Blood Pressure Observations

To date, most research investigating patterns of blood pressure variation across pregnancy have been conducted using clinical blood pressure observations obtained via chart review. These are time-series data with assessments that take place at each obstetrical appointment. A unique aspect of these data is that observations occur at irregularly spaced intervals and the number varies between participants. These data are difficult to model using traditional, multivariate statistical methods for the analysis of time-series data (e.g., multilevel-modelling, latent mixture modeling) due to several methodological limitations, most notably intercorrelation between observation timepoints and an inability to adequately deal with unequally spaced data (Thompson et al., 2009). To overcome these limitations, researchers must choose how to deal with these data in a way that limits bias in statistical analyses and interpretation. There are several ways this has been done.

Guo et al. (2020) applied latent mixture modeling to identify systolic blood pressure patterns that share similar trajectories across pregnancy and evaluate their associations with maternal and infant health outcomes. In this study, the authors included four observations of systolic blood pressure: one from the first antenatal appointment (8-14 weeks of gestation), the highest value observed between 20 weeks of gestation to preadmission, and the observations at hospital admission and two hours postpartum. Selection of the highest blood pressure observation between the second to last trimester of pregnancy was reportedly used because participants had a different number of antenatal care appointments. Although this choice makes sense based on statistical constraints associated with latent mixture modeling, there are obvious disadvantages and sources of bias with exclusion of potentially meaningful datapoints and inclusion of only the highest values. There are also some theoretical concerns about the use of latent mixture models to identify groups based solely on statistical results and without a strong theoretical basis for the existence of discrete groups (Bauer, 2007).

Two larger studies utilized data from the Avon Longitudinal Study of Parents and Children. MacDonald-Wallis et al. (2011, 2012) used linear spline random-effects models to model blood pressure change across pregnancy and multilevel modelling with two levels (antenatal visit within woman) to account for the correlation between blood pressure observations on the same woman. In these models, systolic and diastolic blood pressure data were divided into two-week intervals by gestational age. When women had more than one observation during the interval, one was randomly selected to prevent women with a high number of antenatal visits from having a greater influence on the statistical models. As well, although the sample size was large (n=9023), the authors report that 2,766 women were excluded from analyses due to missing blood pressure data. A similar approach was used in a recent study

that showed differences in blood pressure trajectory based on maternal ethnicity (Farrar et al., 2019).

Thompson et al. (2009) grappled specifically with the question of how to construct datasets from maternal clinical blood pressure observations and describes several sources of bias that can influence statistical analysis and interpretation. Clinical blood pressure observations were available from The Omega Study, a prospective cohort study designed to examine metabolic and dietary predictors of gestational diabetes, HDP and other pregnancy outcomes. The authors explicitly examined sources of bias in the construction of systolic and diastolic blood pressure curves, with a focus on ways to account for over- or under-representation of women who had greater or fewer number of observations, respectively. This is an important consideration since women tend to be followed more closely in late pregnancy relative to early pregnancy and are seen more frequently if the pregnancy is medically complicated. To account for this potential source of bias, the authors opted to randomly select a single observation from the source data, if available, from each three-week interval of gestational age. Results from this study confirmed that women with a greater number of observations in the source data were more likely to be diagnosed with preeclampsia, gestational diabetes, and gave birth earlier than those with the expected number of visits based on their sample. Extra datapoints that are often disregarded due to statistical constraints likely contain important sources of variation among women that researchers are interested in the most.

The construction of blood pressure trajectories is not a simple task. Since observations are repeated over time, there is an illusion that these time-series data are best handled with statistical methods designed for repeated measurements. Multivariate analytic approaches used to identify blood pressure trajectories are not overly satisfying since they rely on parsing a

continuous process into small intervals where there may or may not be an observation. Pregnancy is characterized by ongoing biological, physiological, and psychological changes across time and there are other statistical modelling techniques that capture this process in a more elegant and intuitive way.

Functional Data Analysis

Blood pressure is an inherently dynamic, physiological process that is consistently regulated through brain and body systems in response to biological (e.g., sodium concentration in the blood), psychological (e.g., emotions) and, behavioral (e.g., exercise, smoking) factors. One blood pressure observation can be considered to reflect a smooth underlying process. From this perspective, repeated clinical blood pressure observations, during pregnancy or not, can be considered functional in nature in that they could ostensibly be observed at any point in time (James & Gerber, 2018). These data contrast with clinical observations that are fundamentally discrete, such as parity, marital status, or pre-pregnancy BMI derived from body weight and height. When the data are functions, analytical approaches can be applied to explore variance in a sample of curves (Ramsay, 1982).

Functional data analysis (FDA) is not by any means a new statistical approach, but has been surprisingly underused in the fields of behavioral medicine, and indeed in medicine in general, given its widespread applicability (Ramsay, 1982; Ramsay & Silverman, 2005; Ullah & Finch, 2013). The primary advantages of FDA include that it adequately deals with a different number of irregularly spaced observations, effectively removes the issue of intercorrelation between measurement timepoints, incorporates information between observation intervals, and permits examination of how associations changes across time. Predominant modes of variation, or trajectories of change, can also be explored using functional principal components analysis

(*f*PCA), a commonly used data reduction technique (Levitin et al., 2007; Ramsay & Silverman, 2005; Ullah & Finch, 2013).

To date, there has been some interest in the application of FDA for analysis of blood pressure across pregnancy. Three studies have used the approach, though the focus has been somewhat different. Shen et al. (2017) used FDA to model blood pressure change across pregnancy and examined the role of pre-gravid blood pressure in this change. Simpkin et al. (2018) used polynomial and spline mixed models to estimate velocity and acceleration trajectories of blood pressure. Although this study was conducted with simulated data, it effectively describes how different statistically models perform for derivative estimation and provides an overview of how derivative estimation can be used to identify important regions of change. Szczesniak et al. (2016) used FDA and *f*PCA with the goal of identifying phenotypes of type 1 diabetes control, and functional regression analysis to examine associations with maternal and neonatal characteristics. The authors identified three distinct longitudinal patterns of blood pressure, insulin, and glucose control and review the potential applications of FDA in an obstetrical setting. Combined, these results highlight the applicability of FDA for repeated biological and physiological observations, but these methods have been scarcely applied.

The Present Work

This dissertation is comprised of three manuscripts that contribute to understanding of the links between maternal psychology and cardiovascular physiology as indexed by blood pressure. The first study examines whether symptoms of depression or anxiety moderate the association between HDP and gestational age at birth, with the goal of understanding whether maternal psychology matters more in some contexts or circumstances over others – i.e., when physical complications arise. Second, FDA is applied to model maternal blood pressure variation across

pregnancy, and to examine how different trajectories of blood pressure relate to gestational length. The primary contribution of the second study is methodological, with a focus on how to move toward a more nuanced, dynamic conceptualization of cardiovascular processes that are represented by curves across time. Third, building upon the methodology described in the second study, functional regression analysis is used to explore how maternal, obstetrical, and psychological risk factors for HDP relate to blood pressure across gestation, and how the effects change across time.

The following sections are scientific, based on phenomena that are observed, predicted, and described, but it is also important to consider the unobservable; the unique constellation of life circumstances that lead to each woman's pregnancy, brought her to each appointment, where she goes home to, and what inspired her to volunteer for scientific study. The broader aim of this dissertation is to engender a sense of curiosity about the process of pregnancy research and to highlight how much remains unknown about the links between maternal psychology and physiology. In addition, in the general discussion, broader issues of measurement that arise in psychological and cardiovascular health sciences, access to mental health services in the context of a medically-complicated pregnancies, and sex- and gender-differences in cardiovascular health research. These topics are intricately linked and will be taken up in the general discussion.

Manuscript 1

Hypertensive Disorders of Pregnancy and Symptoms of Depression and Anxiety as Related to Gestational Age at Birth: Findings from the All Our Families study.

Kristin J. Horsley*, B.A.; Lianne M. Tomfohr-Madsen, Ph.D.; Blaine Ditto, Ph.D.;

Suzanne C. Tough, Ph.D.

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Abstract

Objective: To investigate whether symptoms of depression or state anxiety changed the strength or nature of the association between hypertensive disorders of pregnancy (HDP) and gestational age at birth.

Methods: We conducted a secondary analysis of data from the All Our Families Cohort, a prospective pregnancy cohort study based in Calgary, Alberta, Canada. Self-reported depressive symptoms and state anxiety were assessed between three- and five-months' gestation, and obstetrical information including diagnosis of HDP, parity, type of delivery, and gestational age at birth was retrieved from the maternal discharge abstract. All models were adjusted for sociodemographic and obstetric confounders.

Results: Of 2763 women who had a singleton pregnancy and live birth, 247 (9%) were diagnosed with HDP. Women with HDP had significantly shorter gestational length relative to those without the diagnosis (M=37.87 vs. M=38.99 weeks of gestation), $t(2761)=9.43$, $p<.001$. Moderation analyses showed significant HDP by depressive symptoms and HDP by state anxiety interactions, such that the strength of the association between HDP and gestational age at birth increased alongside greater depressive symptom and state anxiety severity.

Conclusions: Results suggest that depressive symptoms and state anxiety may add to the increased risk for shortened gestation associated with HDP. Women at high risk of cardiovascular complications during pregnancy may benefit from additional resources to manage symptoms of depression or anxiety.

Keywords: Hypertension, gestational age, depressive symptoms, state anxiety, All Our Families.

Introduction

Hypertensive disorders of pregnancy (HDP; i.e., chronic hypertension, gestational hypertension, preeclampsia, and eclampsia) occur in five to 10% of pregnancies and account for approximately 15% of all preterm deliveries (Hutcheon et al., 2011; Roberts et al., 2003). Although the consequences of birth before 37 weeks of gestation include increased risk of newborn morbidities and infant mortality (Saigal & Doyle, 2008), these risks also extend into the early term period and, for this reason, birth prior to 39 weeks of gestation is discouraged unless medically indicated (Fleischman, 2010; Spong, 2013). Research has also shown that depressive symptoms and/or state anxiety are associated with shorter gestation in most, but not all studies, suggesting that the risk may be greater in some populations or circumstances (e.g., low income countries, low socioeconomic status) over others (Dunkel Schetter & Tanner, 2012; Grote et al., 2010; Shapiro et al., 2013). In addition, symptoms of depression or anxiety are more commonly reported among women with obstetrical complications(Melville et al., 2010), and some studies show that they are independent risk factors for the development or worsening of hypertension during pregnancy (Kurki et al., 2000; Qiu et al., 2007; Yu et al., 2013). Despite well-documented effects of HDP, depressive symptoms, and anxiety on gestational length, whether these factors interact or influence each other has been scarcely examined.

Among pregnant women with a cardiovascular system that is already under strain (i.e., via HDP), the added influence of depression or anxiety on birth outcomes may be particularly detrimental due to shared physiological pathways. For example, previous research has shown that HDP are associated with autonomic nervous system alterations reflected by reduced parasympathetic control of the heart (Schobel et al., 1996), and by increased sympathetic activity directed at the heart and vasculature (Yang et al., 2000). More recently, researchers have shown

that elevated depressive symptoms are also associated with decreased parasympathetic tone during pregnancy (Rouleau et al., 2016; Shea et al., 2008), and suggest that autonomic nervous system changes may represent a plausible biological pathway through which psychological factors influence adverse birth outcomes (Dunkel Schetter, 2011; Rouleau et al., 2016; Shapiro et al., 2013). Thus, within the context of HDP, it is possible that elevated symptoms of depression or anxiety exacerbate a state of autonomic dysregulation and contribute to an even greater risk for shorter gestational length.

The purpose of the present study was to investigate if depressive symptoms or state anxiety assessed in the first half of pregnancy moderated the association between HDP and gestational length in a community-sample of pregnant women. Specifically, we hypothesized that (1) consistent with previous research, HDP would be associated with shorter gestational length, and (2) we predicted that there would be a significant interaction such that the association between HDP and gestational length would be stronger among women with greater depressive symptom or state anxiety severity.

Methods

The present study was a secondary analysis of data collected in the All Our Families Study (AOF), a prospective pregnancy cohort of approximately 3300 women that were recruited between 2008 to 2011 in Calgary, Alberta, Canada. The study was approved by the Conjoint Health Research Ethics Board of the University of Calgary and informed consent was provided at time of study enrolment. A detailed description of the study methods and sample characteristics has been previously published (McDonald et al., 2013). Briefly, pregnant women who were <25 weeks' gestation and at least 18 years of age (*M*=31.16, *SD*=4.47, Range=18-47) were recruited from the community, with most (69%) women identified through city-wide single

provider public health laboratory services (i.e., Calgary Laboratory Services; https://www.calgarylabservices.com/). Women who agreed to be contacted were provided with study details and, after informed consent, were asked to complete questionnaires twice during pregnancy (at <25 weeks' and approximately 36 weeks' gestation). Questionnaire packages were mailed to participants and returned to the research team by regular post, and the self-report information was linked to the obstetric electronic medical records. Participants who returned incomplete self-report questionnaires were contacted by a trained research assistant to obtain the missing information. Women were also asked to consent for access to their electronic medical health records to retrieve prenatal and birth data, obstetric history, infant health data, and any complications related to the index pregnancy. For present study purposes, self-report questionnaire data from the assessment at <25 weeks' gestation was used given that it captured *prenatal* depressive symptoms and state anxiety for all women in the sample, whereas at the second assessment timepoint (i.e., ~36 weeks' gestation), depressive symptoms and state anxiety were postpartum for approximately one third (57/174) of women who delivered before 37 completed weeks of gestation.

Study Variables

Clinical and sociodemographic background. For this study, women with singleton pregnancies and who had a live birth were included in analyses (N=2763). Demographic and health related characteristics were retrieved from the self-report questionnaire completed between three and five months' gestation (M=16.14, SD=4.00, Range=5-24) and included maternal age, marital status (i.e., married/common-law, single), education (i.e., high-school or less, some or completed postsecondary), household income (i.e., <$40,000; $40,000-$79,999; ≥$80,000), ethnicity (i.e., white, non-white), pre-pregnancy body mass index (preBMI;

calculated as maternal self-reported pre-pregnancy weight (kg) divided by height (m) squared). Obstetric characteristics of the index pregnancy were retrieved from medical records that were reviewed following delivery and included parity (i.e., nulliparous, multiparous), cardiovascular complications (i.e., pre-existing hypertension, gestational hypertension, preeclampsia, or preeclampsia with severe features), type of delivery (i.e., vaginal, emergency caesarean, planned caesarean), and gestational age at birth.

Pregnancy outcomes. Information regarding the presence of HDP was retrieved from the maternal discharge abstract. HDP diagnosis was based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Version: 2008, Canada. Accordingly, gestational hypertension was defined as hypertension (i.e., systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) that develops for the first time after 20 weeks' gestation (code 013), and preeclampsia as gestational hypertension with significant proteinuria that can range from moderate to severe (code 014). HDP was considered present if codes 013 or 014 were listed on the maternal discharge abstract from labour and delivery of the index pregnancy; the date of diagnosis was not available. Gestational age was calculated in completed weeks of gestation at birth. Type of delivery was coded as vaginal, an emergency caesarean, or a planned caesarean.

Depressive Symptoms. The Edinburgh Postnatal Depression Scale (EDPS) was used to measure depressive symptoms during the perinatal period(Cox et al., 1987). The EPDS is a 10 item self-report questionnaire, with each item rated on a 4-point scale to produce a summative score ranging from 0 to 30; higher scores indicate greater depressive symptom severity. A cut-off score of ≥10 has been used to identify women with clinically significant depressive symptoms in community samples (Cox et al., 1987). The EPDS has been validated against standardized

interview schedules and other self-report instruments (Bergink et al., 2011). Within the AOF cohort, the EPDS has high internal consistency, with values that are comparable previously published results (Cronbach's alpha=.84 to .86) (Bayrampour, Tomfohr, et al., 2016) .

State Anxiety. The state anxiety subscale (SAI) of the Spielberger State-Trait Anxiety inventory was used to assess symptoms of anxiety (Spielberger et al., 1970). The scale consists of 20 items rated on a 4-point scale, for a total score ranging from 20 to 80, with higher scores reflecting greater levels of anxiety, and scores ≥40 corresponding to clinically significant state anxiety. The SAI has been validated during the perinatal period (Meades & Ayers, 2011), and has demonstrated adequate internal consistency within the AOF cohort (Cronbach's alpha = 0.92; Benediktsson et al., 2016).

Statistical Analyses

First, *t*-tests and chi-square analyses were performed to compare women with and without HDP on the study variables. Regression analyses were performed to examine the association between HDP and gestational age at birth. To determine whether maternal depressive symptoms or state anxiety influenced the association, two separate moderation analyses were conducted using the macro PROCESS (Hayes, 2013). For significant interactions, an analysis of conditional effects was conducted to examine the association between HDP and gestational length at each quintile of depressive symptom severity and state anxiety. For moderation analyses, we report bias-corrected accelerated confidence intervals (CI; 95%) based on 5000 re-samples which are robust to violations in normality. Regression coefficients are presented as unstandardized beta coefficients (*b*) that denotes the change in completed weeks of gestation at birth associated with a one-unit change in HDP [i.e., going from absent (0) to present (1)] at each quintile of the moderator (Meyers et al., 2006). The value for statistical significance was set at

$p<.05$. Statistical analyses were performed using SPSS 22.0 (IBM Corporation, Armonk, NY) and RStudio (RStudio Team, 2016).

All models were adjusted for covariates that were selected a priori based on previous research and theoretical relevance, namely: maternal age, parity (0=nulliparous, 1=multiparous), preBMI, ethnicity (0=white, 1=non-white), education (0=high school, 1=some post-secondary), and income (Hilmert et al., 2008). Only participants with complete data on all variables of interest were included which resulted in the exclusion of less than 5% of participants across all regression analyses. The value for statistical significance was set at $p<.05$.

Results

Participants were predominately white, highly educated, married women who were pregnant with their first child and reported an annual household income of ≥$80,000. Overall, the sample mean for depressive symptoms was M =5.18, SD=4.32, and state anxiety was M=30.93, SD=8.77. Clinically meaningful depressive symptoms (i.e., EPDS total score ≥10) were present in 16.3% (n=449) of participants, and 15.0% (n=415) reported elevated levels of state anxiety (i.e., SAI total score ≥40).

Approximately 9% (n=247) of participants were diagnosed with HDP (Table 1.1). Independent samples t-tests revealed that participants with HDP had greater preBMI (M=27.95 kg/m^2, SD=6.81 vs. M=24.07 kg/m^2, SD=4.78, $t(2724)=-11.58$, $p<.001$) and reported greater depressive symptom severity (M=6.00, SD=4.71 vs. M=5.09, SD=4.27, $t(2755)=-3.16$, $p=.002$) and state anxiety (M=33.29, SD=9.70 vs. M=30.70, SD=8.64, $t(2674)=-4.38$, $p<.001$) relative to those without the diagnosis. Chi-square analysis indicated that women with HDP were more likely to be nulliparous, $\chi^2=28.92$, $p<.001$. There was no difference between those with and without HDP on the variables of age, ethnicity, income, or education ($ps > .05$).

The mean gestational age at birth was 38.89 (*SD*=1.80) weeks. With respect to delivery, 73.7% (*n*=2037) delivered vaginally, 13.6% (*n*=375) had an emergency caesarean section, and 12.7% (*n*=351) were admitted for a planned caesarean section. HDP were associated with significantly earlier gestational age at birth relative to those without the diagnosis (*M*=37.87 vs. *M*=38.99 weeks of gestation), $t(2761)=9.43$, $p<.001$.

Moderation analyses examined if there was an interaction between HDP and depressive symptoms or state anxiety in the prediction of gestational age at birth. In the first model involving depressive symptom severity as the moderator, after adjustment for maternal age, parity, pre-pregnancy BMI, ethnicity, education, and income, the model significantly predicted gestational age at birth, $F(9, 2623)=14.98$, $p<.001$, $R^2=.05$, and the HDP x depressive symptoms interaction term was statistically significant, $F(1, 2623)= 10.56$, $p=.001$. The analysis of conditional effects showed that the effect of HDP on gestational age increased with greater depressive symptom severity in a dose-response fashion. The association between HDP and gestational age was statistically significant at the 10th (EPDS=0; *b*=-.58, 95% CI [-.97, -.19]), 25th (EPDS=2; *b*=-.75, 95% CI [-1.07, -.43]), 50th (EPDS=4; *b*=-.92, 95% CI [-1.18, -.65]), 75th (EPDS=8; *b*=-1.25, 95% CI [-1.51, -.99), and 90th (EPDS=11; *b*=-1.49, 95% CI [-1.85, -1.15) percentiles of depressive symptom severity (Figure 1.1).

In the second model that involved state anxiety as the moderator, the HDP x state anxiety interaction term was also statistically significant, $F(1, 2547)= 6.27$, $p=.01$. The analysis of conditional effects indicated that HDP was negatively associated with gestational age at all percentiles of state anxiety, and that the strength of the association increased with greater anxiety symptom severity in a dose-response fashion (Figure 1.2). Specifically, the association was significant at the10th (SAI=22; *b*=-.73, 95% CI [-1.10, -.37]), 25th (SAI=24; *b*=-.80, 95% CI [-

1.13, -.47]), 50th (SAI=29; *b*=-.96, 95% CI [-1.22, -.69]), 75th (SAI=36; *b*=-1.17, 95% CI [-1.43, -.92]), and 90th (SAI=43; *b*=-1.39, 95% CI [1.74, -1.05]) percentiles of state anxiety.

Discussion

Results from this study indicated that in a large, community-based sample of pregnant women, depressive symptoms and state anxiety assessed before 25 weeks of gestation interact with HDP in the prediction of gestational age at birth. Specifically, the association between HDP and earlier gestational age at birth increased alongside greater depressive symptom severity and state anxiety. Results of our study extend upon previous work suggesting that psychosocial stress may have a detrimental impact on gestational length among women with elevated blood pressure during pregnancy (Hilmert et al., 2008, 2014). Although a recent meta-analysis concluded that psychological factors make negligible contributions to increased risk of adverse birth outcomes (Littleton et al., 2010), our results suggest that the investigation of psychological factors as moderators in the context of established medical predictors may reveal stronger associations – depression and/or anxiety may add incremental risk among women with cardiovascular complications during pregnancy. If the observed results are confirmed in other samples, women with elevations in blood pressure who report elevated symptoms of depression or anxiety may represent a specific patient group to target for psychosocial interventions aimed at improving birth outcomes.

Among the proposed mechanisms that may account for a synergistic effect of maternal psychological factors and HDP on birth outcomes is the impact symptoms of depression or anxiety have on central mechanisms regulating blood pressure, neuroendocrine, inflammatory, and immune processes (Alder et al., 2007; Christian, 2012). During pregnancy, the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis undergo profound changes that

are necessary for adaptation to the developing fetus. Changes to the HPA-axis are marked by a disruption to the negative feedback loop that results in sustained hyperactivity (i.e., a feed-forward loop) and steady increases in circulating corticotrophin-releasing hormone (CRH) that peak at the onset of labour and delivery (Hobel et al., 2008; Smith et al., 2009). It has been hypothesized that psychological stress and HDP may both influence the timing of delivery through their impact on HPA-axis functioning, specifically through their associations with increased levels of circulating maternal CRH (Hobel et al., 2008; Perkins et al., 1995). In support of this hypothesis, researchers have found significantly higher concentrations of CRH in umbilical cord blood and infants born to mothers with a hypertensive disorder (Goland et al., 1995), and significant associations between psychological stress and elevated levels of CRH (Hobel et al., 1999). Thus, the shared physiological and psychological influences on the stress response system may be responsible for associations between both and timing of delivery.

Some methodological factors strengthen our results. Longitudinal study design allowed for assessment of psychological distress in early pregnancy, and a large sample size allowed for the detection of small effects. Moreover, the incidence of HDP observed in this sample was comparable to established prevalence rates (Hutcheon et al., 2011). The sample was primarily white, married women with high socioeconomic status and low psychological distress, which serves as both a strength and limitation. Since we observed a significant interaction in this sample, it is reasonable to expect that the effects may be more pronounced in more diverse, distressed samples. Although the results may not generalize to women living in rural areas, or those without access to prenatal care, they suggest that the combination of elevated depressive symptoms or state anxiety and hypertension during pregnancy has important implications for birth outcomes among the population of women cared for in primary health care settings.

Despite the strengths of our study, there are several limitations that may be useful to guide future research. First, it would have been beneficial to obtain blood pressure parameters continuously throughout pregnancy and, if possible, before conception. The expansion to include both normal, high-normal, and abnormal blood pressure elevations in a research setting could be particularly fruitful given the finding that blood pressure increases in pregnancy are associated with reduced gestational length even in women whose blood pressure does not cross threshold for a diagnosis of HDP (Macdonald-Wallis et al., 2014). Whether psychological factors interact with systolic or diastolic blood pressure, or with other blood pressure parameters (e.g., cardiac output, total peripheral resistance) to predict maternal or infant health outcomes is an opportunity for further study and may help elucidate potential mechanisms of risk.

Second, depressive symptoms and state anxiety were measured only twice during pregnancy, at approximately 24 and 36 weeks of gestation. It is therefore possible that questionnaire completion occurred beyond 20 weeks of gestation and after the diagnosis of HDP. Within the present study, we proposed that psychological factors may change the strength of the association between HDP and birth outcomes, but it could be that depressive or anxious symptoms play a mediating role in the association between HDP and gestational age at birth. Although we were unable to investigate temporal relationships between depressive symptoms, state anxiety, and HDP, future researchers could build upon our results through studies designed to reduce depression and anxiety in those with HDP to see if those reductions confer a benefit to gestational length.

Third, though we assessed state anxiety and depressive symptoms with reliable and well validated measures, we did not have an assessment of pregnancy anxiety. There has been considerable interest in the construct of pregnancy anxiety over the last 10 years, and a

convergence of research suggests that pregnancy anxiety is associated with elevated risk of adverse birth outcomes which may be beyond the contribution of state/trait anxiety (Dunkel Schetter & Tanner, 2012). Since depressive symptom severity and state anxiety were examined separately, it is possible that there is an underlying construct related to both that accounts for our observed effects. In future research studies, it would be helpful to include not only measures of depressive symptoms and state anxiety, but also measures that capture specific worries and concerns related to the index pregnancy to see whether they influence the impact of HDP on birth outcomes.

Finally, the presence or absence of HDP was defined in accordance with the American College of Obstetrics and Gynecology guidelines for the diagnosis and treatment of hypertension during pregnancy present in 2008. These guidelines differ from those published in 2012 that expanded criteria for HDP diagnosis to include, for example, elevated systolic blood pressure and a preeclampsia diagnosis without significant proteinuria but with other associated features (Roberts et al., 2012). It is therefore possible that, with current guidelines applied, the incidence of HDP in this sample would be greater than reported.

This study contributes to limited work that has examined how psychosocial factors interact with blood pressure elevations to influence birth outcomes. Overall, results suggest that pregnant women at high risk of cardiovascular complications during pregnancy may benefit from additional strategies to support mental health during the perinatal period. Further, women who report increased depressive symptoms or state anxiety, and who have HDP may represent a population that could benefit from additional, psychosocial interventions.

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Table 1.1

Sample Characteristics (N=2763)

	Hypertensive Disorder of Pregnancy[a]	
	Absent	Present
Maternal characteristics, *M*(SD)	*n*=2516	*n*=247
Age (years)	31.16 (4.46)	31.13 (4.56)
Pre-pregnancy body mass index	24.07 (4.78)	27.95 (6.81)
Depressive symptoms	5.09 (4.27)	6.00 (4.71)
State anxiety	30.70 (8.64)	33.29 (9.70)
Gestational age at birth	38.99 (1.72)	37.87 (2.24)
Parity, *n*(%)		
Nulliparous	1189 (47.3)	161 (65.2)
Primi/Multiparous	1327 (52.7)	86 (34.8)
Type of Delivery, *n*(%)		
Vaginal	1874 (74.5)	163 (66.0)
Emergency caesarean	316 (12.6)	59 (23.9)
Planned (scheduled) caesarean	326 (13.0)	25 (10.1)
Marital status, *n*(%)		
Married/Common law	2396 (95.2)	226 (91.5)
Other	115 (4.6)	21 (8.5)
Missing	5 (0.2)	0 (0.0)

continued

Ethnicity, *n*(%)		
White	1988 (79.0)	202 (81.8)
Chinese	124 (4.9)	2 (0.8)
South Asian	109 (4.4)	5 (2.0)
Latin American	57 (2.3)	4 (1.6)
Filipino	42 (1.7)	8 (3.2)
African American	34 (1.4)	5 (2.0)
Indigenous	19 (0.8)	4 (1.6)
Other	138 (5.5)	16 (6.5)
Missing	5 (0.2)	1 (0.4)
Education, *n*(%)		
High school	261 (10.4)	23 (9.3)
Some postsecondary	2250 (89.4)	224 (90.7)
Missing	5 (0.2)	-
Income, *n*(%)		
<$40,000	192 (7.6)	20 (8.1)
$40,000 to $79,999	526 (20.9)	52 (21.1)
≥$80,000	1720 (68.4)	166 (67.2)
Missing/Undisclosed	78 (3.1)	9 (3.6)

[a]Participants diagnosed with pre-existing (chronic) hypertension (*n*=25), gestational hypertension (*n*=196), pre-eclampsia (*n*=182), and eclampsia (*n*=25).

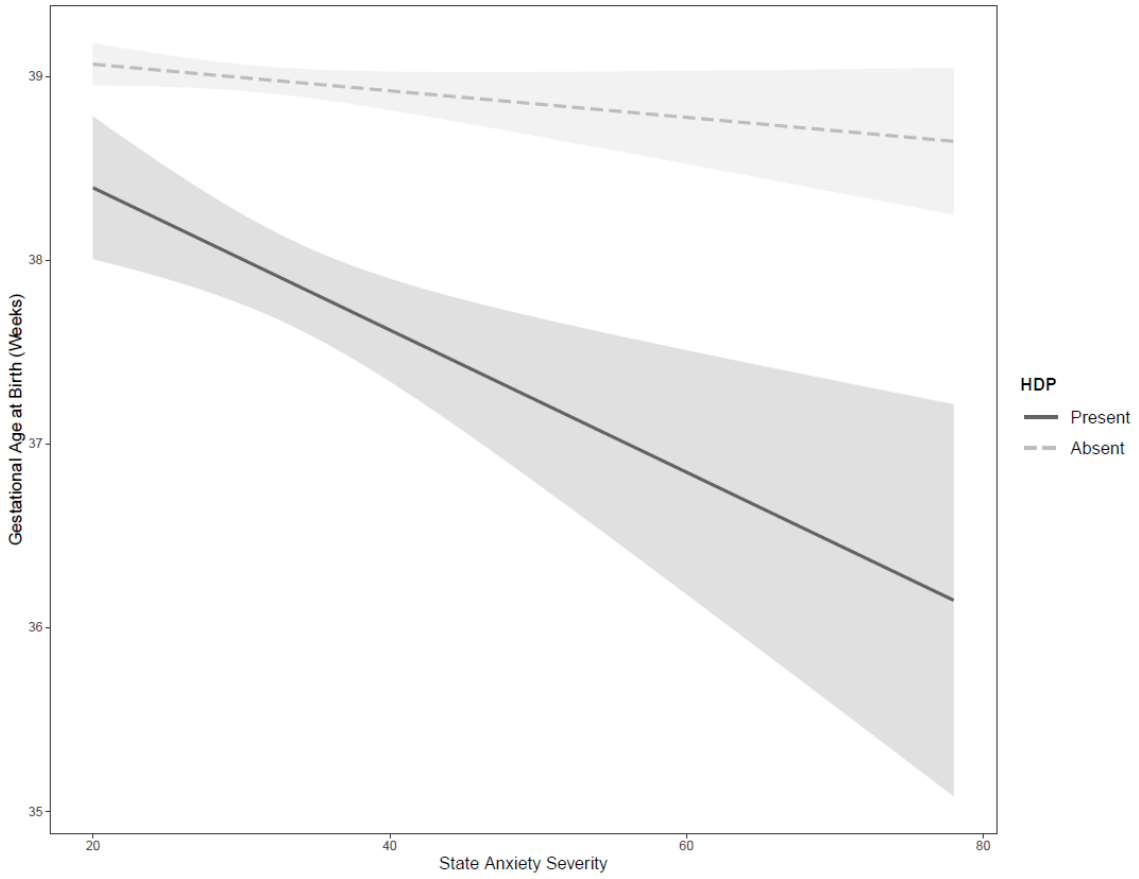

Figure 1.1 The moderating role of depressive symptom severity on gestational age at birth among women with (solid line) and without (dashed line) hypertensive disorders of pregnancy (HDP). The association between HDP and gestational age at birth increased alongside greater depressive symptom severity. Shading indicates 95% confidence intervals.

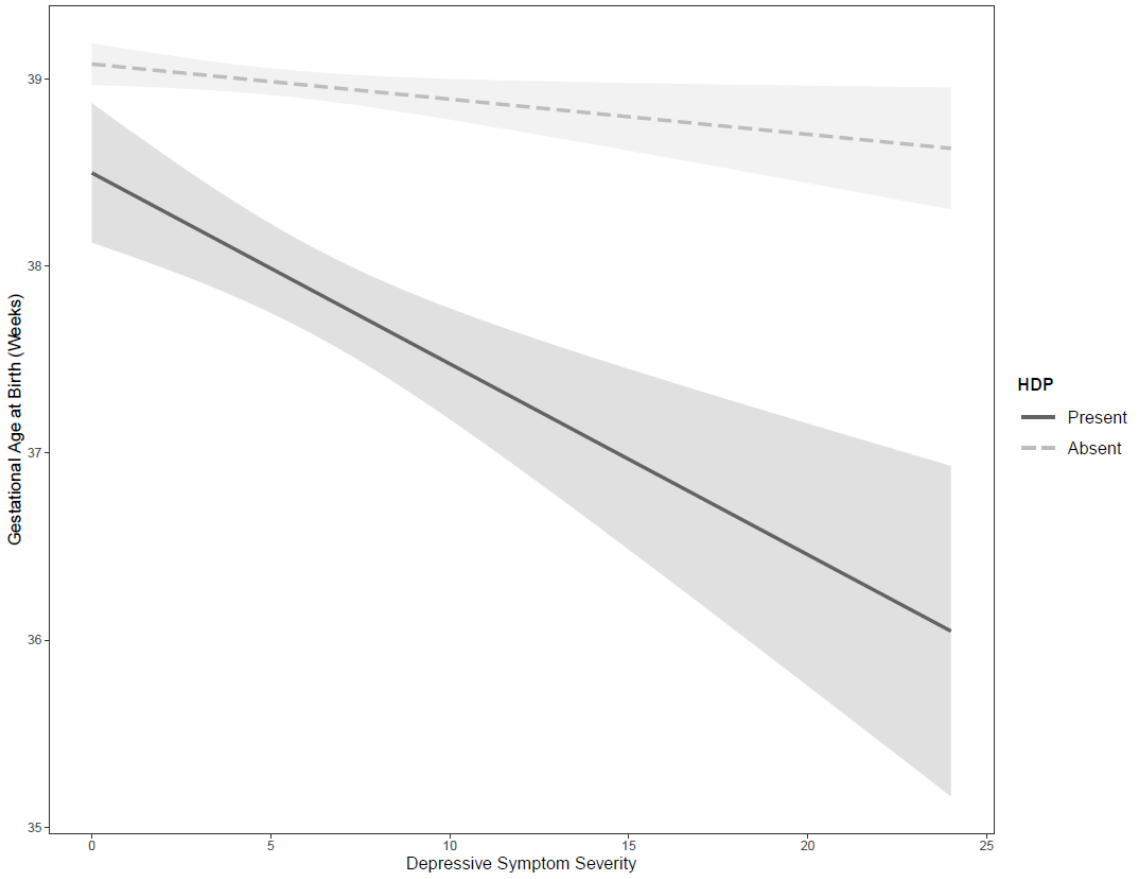

Figure 1.2 The moderating role of state anxiety on gestational age at birth among women with (solid line) and without (dashed line) hypertensive disorders of pregnancy (HDP). The association between HDP and gestational age at birth increased alongside greater state anxiety severity. Shading indicates 95% confidence intervals.

Bridge to Manuscript 2

Findings from Manuscript 1 show that maternal symptoms of depression and anxiety may interact with elevated blood pressure to influence birth outcomes. A significant limitation highlighted throughout the peer-review process was that there were no observations of systolic and diastolic blood pressure across pregnancy, but rather a binary diagnosis of HDP that was based on medical chart review data. Thus, it could not be ascertained whether symptoms of depression and anxiety interacted with blood pressure in a dose-response manner. Questions also remained about whether maternal psychological factors influence blood pressure across pregnancy and, if so, at what magnitude and when?

Repeated measurements of blood pressure are routinely collected across pregnancy and are considered a key marker of maternal health during the perinatal period. In the last 20 years, clinical blood pressure observations have been used to identify trajectories of blood pressure change and how these differ among women who develop a hypertensive disorder of pregnancy. While these studies have provided useful information on differences in maternal cardiovascular adaptation, there are several limitations to the statistical methods employed to model blood pressure variation across gestation. Repeated, clinic blood pressure data are unique in that observations vary between participants in frequency and interval. These factors complicate statistical modelling using more traditional, multivariate methods. In Manuscript 2, FDA is proposed as a useful, statistically elegant way to model and visualize variation across time that is highly applicable for repeated blood pressure observations across pregnancy.

Manuscript 2

Maternal Blood Pressure Trajectories Across Pregnancy and Associations with Gestational Age at Birth: A Functional Data Analytic Approach

*Kristin J. Horsley, BA[1]; James O. Ramsay, PhD[1]; Blaine Ditto, PhD[1]; Deborah Da Costa, PhD[2]

[1]Department of Psychology, Faculty of Science, McGill University; [2]Department of Epidemiology, Faculty of Medicine, McGill University.

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Abstract

Background: Research has revealed group-level differences in maternal blood pressure trajectories across pregnancy. These trajectories are typically constructed using clinical blood pressure data and multivariate statistical methods that are prone to bias and ignore the functional, dynamic process underlying a single blood pressure observation. The aim of this study was to use functional data analytic techniques to explore blood pressure variation across pregnancy, and multivariate methods to examine whether trajectories related to gestational age at birth.

Methods: Clinical blood pressure observations were available from 370 women who participated in a longitudinal pregnancy cohort study conducted in Montreal, Quebec, Canada. Functional data analysis was used to smooth blood pressure data and then to conduct a functional principal component analysis to examine predominant modes of variation.

Results: Three eigenfunctions explained >95% of the total variance in blood pressure. The first accounted for approximately 80% of the variance and was characterized by a prolonged-decrease trajectory in blood pressure; the second explained 10% of the variance and captured a late-increase trajectory; and the third accounted for approximately 7% of the variance and captured a mid-decrease trajectory. The prolonged-decrease trajectory of blood pressure was associated with older gestational age at birth, and late-increase with younger gestational age at birth.

Conclusion: Functional data analysis is a useful method to model repeated maternal blood pressure observations and many other time-related cardiovascular processes across pregnancy. Results add to previous research investigating blood pressure trajectories across pregnancy through identification of additional, potentially clinically important modes of variation.

Keywords: blood pressure, pregnancy, functional data analysis, gestational age at birth

Introduction

Over the last 10 years, there has been increased interest in modeling maternal blood pressure trajectories and how these relate to maternal (e.g., hypertensive disorders of pregnancy) and infant (e.g., gestational age at birth, birth weight) health outcomes (Bakker et al., 2010; Farrar et al., 2019; Gaillard et al., 2011; Guo et al., 2020; Macdonald-Wallis et al., 2012; Macdonald-Wallis et al., 2011, 2014; Salles et al., 2015; Simpkin et al., 2018). Most of this research has been conducted using clinical blood pressure data obtained via maternal chart review. Clinical blood pressure data are typically considered time-series data given that repeated assessments occur at each obstetrical appointment. These data present unique problems for analysis with multivariate statistical methods due to methodological limitations such as intercorrelation between observations and an inability to adequately deal with unequally spaced observations (Levitin et al., 2007; Thompson et al., 2009; Ullah & Finch, 2013). Methodological and statistical constraints lead to the exclusion of blood pressure observations that fall outside preselected or statistically determined boundaries (e.g., random sampling in each trimester of pregnancy (Gaillard et al., 2011), random selection from defined gestational age intervals (Farrar et al., 2019; Macdonald-Wallis et al., 2012; Macdonald-Wallis et al., 2011; Salles et al., 2015), selection of highest value (Guo et al., 2020). The result is a loss of potentially meaningful datapoints, and the dynamic functional process underlying these data is largely ignored.

Blood pressure is under constant regulation through brain and body systems and is therefore functional in nature since it could ostensibly be observed at any point in time (James & Gerber, 2018; Shahoud & Aeddula, 2019). During pregnancy, the interval between observation timepoints is a meaningful source of information. For example, women tend to have a greater number of observations in late pregnancy when they are followed more closely, and those with

pregnancy complications (e.g., gestational hypertension, preeclampsia) tend to have more observations than those without (Thompson et al., 2009). As such, maternal blood pressure observations are best represented by a single functional datum, or curve across time, that incorporates information from the interval rather than treating it as random effect. When data represent functions, functional data analysis (FDA) can be applied to explore variance in a sample of curves (Ramsay, 1982; Ramsay & Silverman, 2005).

FDA is a relatively novel statistical approach that addresses limitations of multivariate statistical methods used to analyze time-series data. Instead of a set of discrete datapoints, FDA models time-series data as functional data objects, such that an individual set of blood pressure observations becomes a single curve representative of the underlying function that gives rise to a single blood pressure observation (Ramsay et al., 2009; Ramsay et al., 2018). The most significant advantages of FDA are that it eliminates the issue of intercorrelation, nicely deals with unequally spaced observation timepoints, there is limited loss of information, and there can be a different number of observations between participants (Ramsay et al., 2009; Wang et al., 2016). Dominant modes of variation in the constructed curves can be explored using functional principal components analysis (*f*PCA), a commonly used data reduction technique (Ullah & Finch, 2013; Wang et al., 2016). Although there are significant advantages to this approach, FDA remains an underused statistical method (Levitin et al., 2007; Ullah & Finch, 2013) that is highly suitable for the analysis of repeated blood pressure observations across pregnancy.

Given the advantages of FDA for the analysis of time-series data, the aim of this study was to apply an FDA approach to explore dominant modes of blood pressure variation (i.e., trajectories) using *f*PCA in a community sample of pregnant women. Further, we used

multivariate methods to examine whether these trajectories are associated with a clinical outcome, gestational age at birth, for a subset of participants who had this data available.

Methods

Study design

Data were available from women who participated in the Healthy Behaviours During Pregnancy and Postpartum Study, a prospective, longitudinal cohort study. The primary aim of the study was to examine the influence of behavioural and psychosocial factors on gestational weight gain. Ethics approval was granted by McGill Faculty of Medicine Institutional Review Board and the ethics review boards of participating hospitals.

Sample

Convenience sampling was used to recruit 754 women who were ≥18 years of age with a singleton pregnancy who were less than 20.0 weeks of gestation, able to communicate in English or French, and able to access the internet. At study entry, exclusion criteria were pre-existing Type 1 or 2 diabetes and gestational diabetes mellitus due to dietary requirements and restrictions that may influence weight gain across pregnancy.

Data from medical charts were available for 395 (53% of total sample) women that attended appointments at two obstetrical clinics associated with the two McGill University affiliated hospitals. Participants were included in analyses if they had at least four blood pressure observations, and at least one in each trimester of pregnancy (i.e., 13 weeks, between 14- and 26-weeks, and ≥27 weeks), resulting in the exclusion of n=25 and a final sample of N=370.

Data Collection

Pregnant women were recruited from two McGill University affiliated hospitals that cater to a large heterogenous and multiethnic population. Potential participants were approached by a researcher who explained the study aims and determined whether they would be interested in participating. If so, they were emailed a link to complete an online informed consent form that provided them with a description of the research project.

Following informed consent, participants received a link to a secure website address where they could access and complete online, self-report questionnaires at five timepoints (13, 24, and 36 weeks gestation, and 6-weeks and 6-months postpartum) that were available using FluidSurveys and Survey Monkey (www.surveymonkey.com). The questionnaires measured demographic information, emotional well-being, dietary knowledge, and lifestyle behaviours and took approximately 30 to 45 minutes to complete. Participants were given one-week to complete questionnaires and reminder phone calls were made, if necessary. To encourage ongoing study participation, participants were compensated through a lottery system at each data collection timepoint. Participant data was anonymized, and all data were stored securely on a password protected server.

Measures

Demographics. Data on maternal demographics (age, ethnicity, education, pre-pregnancy height and weight, pre-existing health conditions, health behaviors) and pregnancy characteristics (parity, multifetal pregnancy, assisted reproductive technologies) were obtained through online self-report questionnaires. Maternal self-reported height and weight were converted to metric units to obtain pre-pregnancy body mass index (BMI) in kg/m^2.

Obstetrical variables. Pregnancy complications (i.e., gestational hypertension, preeclampsia, gestational diabetes) were obtained by medical chart review data from the first postpartum visit. Details regarding the onset and severity of the hypertensive disorder were not available. Gestational age at birth was available for a subset of participants (*n*=255) who completed the 6-week postpartum self-report questionnaire and reported their infant's birthdate. For this subset, gestational age at birth was derived from the appointment date and weeks of gestation recorded in the medical chart at the first obstetrical appointment, and the infants date of birth reported by participants at the 6-week postpartum assessment.

Blood pressure measurements. Systolic blood and diastolic blood pressure were measured by clinical staff at each obstetrical appointment using automated oscillometric blood pressure monitors (HEM-7320T-CACS; Omron Healthcare, Kyoto, Japan; Lifesource Model UA-787 AC, A&D Medical, San Jose, CA) with an appropriately sized cuff as part of routine prenatal care. Clinic staff reported that their standard protocol is to obtain blood pressure from the left upper arm while at heart level and supported. The number of readings was not standardized across participants nor routinely recorded, and there was no way to ascertain whether clinic staff had a standardized assessment protocol.

Data Preparation and Statistical Analyses

Statistical analyses were performed using RStudio (RStudio Team, 2016) using the BaylorEdPsych (Beaujean, 2012) and Functional Data Analysis (fda; Ramsay et al., 2018) packages. Participant characteristics were described using means and standard deviations for continuous variables and percentage for categorical variables.

A total of 3387 systolic and 3384 diastolic blood pressure observations were available from the sample. To prepare data for functional analysis, a lower boundary timepoint was

selected by taking the average weeks of gestation at the first blood pressure observation (*M*=11.81 weeks), and an upper boundary by taking the average weeks of gestation for blood pressure measurements that occurred between 38 and 40 weeks of gestation (*M*=39.04 weeks). Functional data objects from discrete systolic and diastolic blood pressure observations were constructed using an Order four B-spline basis function with 7 basis coefficients, corresponding to three equally spaced interior knots over the time interval of 11.81 to 39.04 weeks of gestation. The number of knots corresponds to order of the polynomial (4) subtracted from the number of basis functions (7). A smoothing parameter was selected by examination of the generalized cross-validation (GCV) criterion and visual observation of the constructed curves at log10(λ) of -2, -1, 1, and 2 (Ramsay et al., 2018). The GCV score was minimized at $\lambda=10^{-1}$ for systolic blood pressure, and $\lambda=10^{1}$ for diastolic blood pressure. The GCV value did not change substantially when a smoothing parameter of $\lambda=10^{1}$ was applied to systolic blood pressure data, and visual inspection of the curves smoothed at $\lambda=10^{-1}$ indicated that there were several cases where the approximating function displayed erratic changes between data timepoints. Thus, we opted to set the smoothing parameter at $\lambda=10^{1}$ for both systolic and diastolic blood pressure. As a result, each set of discrete blood pressure observations was transformed and represented by a single curve with 7 basis coefficients.

Mean and standard deviation functions and the covariance structure were estimated based on the smoothed data objects from all participants. Then, a *f*PCA was used to characterized the principal types of blood pressure variation among the observed curves (Ramsay et al., 2009). A *f*PCA extracts a limited number of functional principal component curves, referred to as *harmonics* (ξ), that best capture temporal patterns of variation while retaining as much of the total variation as possible (Ramsay & Silverman, 2005). The goal of *f*PCA is to reduce the

number of blood pressure curves to a smaller number of variables to examine latent structure in the relation between curves (Levitin et al., 2007). For computational details, see publications by Ramsay et al (Ramsay et al., 2009; Ramsay & Silverman, 2005).

The number of harmonics retained was based on evaluation of the covariance structure and scree plots, on a satisfactory amount of variance explained (i.e., >90%), and on the components being interpretable (Jolliffe, 2002; J. Ramsay et al., 2009). In this case, the selected harmonics were then rotated using the VARIMAX criterion, a tool borrowed from multivariate analyses that maximizes variation and aids with interpretation (Ramsay & Silverman, 2005). Each harmonic was then plotted as a perturbation of the mean by adding or subtracting a suitable multiple to examine each pattern of blood pressure variation.

Since gestational age at birth was available for a subset of participants (*n*=255), two exploratory regression analyses were conducted to examine whether the three harmonics were related to this clinical outcome. For each model, regression coefficients (*b*) represent the change in gestational age at birth associated with a one-unit increase in harmonic score.

Results

Participants were primarily white, married women who were pregnant with their first child (Table 2.1). Gestational diabetes was reported by 3.8% (*n*=14) of the sample and 5.7% (*n*=21) of participants reported were diagnosed with a hypertensive disorder of pregnancy (i.e., gestational hypertension or preeclampsia). Participants had an average of 7.88 (*SD*=0.99, *Range*=4-11) and 7.89 (*SD*=0.99, *Range* 4-11) systolic and diastolic blood pressure measurements across pregnancy, respectively. Functional descriptive statistics are presented in Figure 1. On average, the trajectory of systolic blood pressure was characterized by a negligible decrease in systolic blood pressure (~2mmHg) from 11 to 18 weeks of gestation, followed by a

gradual increase across pregnancy. Similarly, diastolic blood pressure showed a small decrease (~4mmHg) from 11 to 22 weeks of gestation, and then gradually increased in late pregnancy (Figure 2.1A). The standard deviation function for systolic and diastolic blood pressure is shown in Figure 1B. Perspective plots of the variance-covariance structure are presented in Figure 2.1C and provide a more detailed, visual representation of blood pressure variation.

Results from the *f*PCA are presented in Figure 2.2. After evaluation of the scree plots (Figure 2.2A), the first three harmonics were selected to represent these data given that they accounted for >95% of the variance and corroborated the pattern of variation observed in the variance-covariance structure. Figure 2.2B displays the weight functions for the first three harmonics that characterize the principal types of variation among the sample of blood pressure curves.

Harmonic one accounted for 78.07% and 80.01% of variation in systolic and diastolic blood pressure, respectively. This harmonic captures a “prolonged-decrease” in blood pressure followed by an increase to or beyond pre-pregnancy levels (Figure 2.3A). Harmonic two accounted for 10.87% and 9.62% of the variance in systolic and diastolic blood pressure, respectively. This harmonic captures a negligible decline earlier in pregnancy, followed by a steeper “late-pregnancy increase” in blood pressure (Figure 2.3B). Harmonic three accounted for 6.42% and 6.18% of the variance in systolic and diastolic blood pressure, respectively, and captured a more pronounced “mid-pregnancy decrease” in blood pressure, followed by an increase slightly beyond pre-pregnancy levels (Figure 2.3C).

Multiple linear regression analyses were conducted to examine whether blood pressure trajectories were associated with gestational age at birth. Results are presented in Table 2.2. In the model involving systolic blood pressure, the combination of harmonics accounted for

approximately 6% of the variance in gestational age at birth, $F(3, 251) = 6.74$, $p < .001$, $R^2=0.06$. Of the harmonics, the prolonged-decrease trajectory was associated with significantly older gestational age at birth, $b=.014$, $SE=0.01$, $p=.008$ (Figure 2.4A), while the late-increase trajectory was significantly associated with younger gestational age at birth, $b=-0.014$, $SE= 0.01$, $p=.015$ (Figure 2.4B). There was no association between the mid-decrease trajectory and gestational age at birth. In the second regression model involving diastolic blood pressure, the combination of harmonics accounted for 2% of the variance in gestational age at birth, $F(3, 251)=2.57$, $p=0.05$, $R^2=.02$. Of the harmonics, the late-increase trajectory was the only significant predictor of gestational age at birth, such that a higher score on this harmonic was associated with younger gestational age at birth, $b=-0.02$, $SE=0.01$, $p=.044$ (Figure 2.4C).

Discussion

In this study, we used FDA to construct a sample of curves from discrete clinical blood pressure observations, and *f*PCA to model dominant modes of blood pressure variation across pregnancy. Multiple regression analysis was used to examine associations between these trajectories and gestational age at birth. The statistical approach adequately addresses limitations of multivariate analyses for time-series data that are collected as part of routine obstetrical care, and our results suggest that *f*PCA represents a useful data reduction technique to identify trajectories of blood pressure change across pregnancy. Multiple regression analyses showed that the prolonged-decrease trajectory of systolic and diastolic blood pressure was associated with older gestational age at birth, while the late-increase trajectory was associated with younger.

In this sample, mean trajectories of systolic and diastolic blood pressure were characterized by negligible decrease in early pregnancy followed by a gradual increase. This finding is consistent with those reported in a recent systematic review and meta-analysis by

Loerup et al. (2019). The authors analyzed blood pressure and heart rate data from 39 studies undertaken from 1967 to 2017 in an effort to establish gestation-specific norms for these parameters. Results of their study are in contrast with the commonly espoused theory of a "mid-pregnancy dip" for systolic and diastolic blood pressure, but are consistent with more recent research indicating that the mid-pregnancy drop may be smaller than previously thought (Loerup et al., 2019; Nama et al., 2011).

Although mean blood pressure trajectories are informative, by definition they represent the mode of variation shared by most curves. In the present study, three additional trajectories of blood pressure were identified that capture potentially important modes of maternal blood pressure variation. The prolonged-decrease trajectory (harmonic one) was associated with older gestational age at birth and may represent a particularly adaptive pattern with respect to this clinical outcome. This finding is similar to results from a longitudinal study that examined the association between trajectories of ambulatory blood pressure in a sample of pregnant adolescents (i.e., age 14-20) and showed that a subtle U-shape blood pressure trajectory was associated with birth at 39 weeks of gestation (Spicer et al., 2019).

The late-increase trajectory (harmonic two) is pattern that has been described in previous research and has been shown to characterize pregnancies complicated by a hypertensive disorder (i.e., essential hypertension, gestational hypertension, preeclampsia; Macdonald-Wallis et al., 2012), or by pre-existing preeclampsia risk factors (Macdonald-Wallis et al., 2011). A recent study by Guo et al. (2020) also showed that an increase in systolic blood pressure from 8 to 14 weeks to 20 weeks of gestation was predictive of adverse maternal and fetal outcomes, including an increase in odds of preterm birth (OR=2.99, 95% CI 2.40-3.71). Combined with our results that showed a small, but statistically significant association between the mid-increase trajectory

and younger gestational age at birth, we hypothesize that it may capture an “at-risk” blood pressure trajectory. Although we did not observe an association between the mid-decrease trajectory (harmonic three) and gestational age at birth, it is possible this pattern is linked with maternal pregnancy outcomes not assessed in this study. Relative to literature on the consequences of high blood pressure during pregnancy, the impact of prolonged decreases and/or low blood pressure on maternal and infant health outcomes has been relatively unexplored and is an opportunity for further research (Warland & McCutcheon, 2002).

To date, there has been some interest in the application of FDA for analysis of blood pressure and other maternal characteristics across pregnancy which speaks to the potential applicability of this approach. Shen et al. (2017) used FDA to model blood pressure change across pregnancy and examined the role of pre-gravid blood pressure in this change. Simpkin et al. (2018) used polynomial and spline mixed models to examine velocity and acceleration trajectories of blood pressure through derivative estimation. Although this study was conducted with simulated data, the researchers describe how different statistically models perform for derivative estimation and provides an overview of how derivative estimation can be used to identify important regions of blood pressure change. Szczesniak et al. (2016) used FDA and *f*PCA with the goal of identifying phenotypes of type 1 diabetes control, and functional regression analysis to examine associations with maternal and neonatal characteristics. The authors identified three distinct patterns of blood pressure, insulin, and glucose control and review the potential applications of FDA in an obstetrical setting. Similarly, a recent study applied an *f*PCA to examine trajectories of weight gain during pregnancy and describe how this method more accurately captured deviations from the mean trajectory, relative to multivariate methods (i.e., nonlinear mixed-effects models) that are prone to bias (Che et al., 2017). Like

blood pressure, gestational weight is observed at sparse (i.e., 3 to 5 observations), unequal intervals and thus FDA represents a useful statistical approach.

Strengths and Limitations

Clinical blood pressure data increases the ecological validity of our study, particularly since these assessments are used in practice to monitor maternal cardiovascular health. Nonetheless, there are several disadvantages to these data that have been reported in previous research and are present in this study (Farrar et al., 2019; Guo et al., 2020; Macdonald-Wallis et al., 2011, 2014). Clinical blood pressure assessments are subject to substantial measurement error, particularly without adherence to a strict assessment protocol (Nathan et al., 2015). A recent systematic review empirically identified 29 patient-, device-, and procedure-related sources of error for blood pressure assessment in clinical settings (Kallioinen et al., 2017). These sources of error can lead to over- and under-approximations of blood pressure that have obvious implications for clinical care, but also for statistical analysis and interpretation.

The quality of individual curves relies on the reliability and validity of discrete observations. With this in mind, results of this study should be interpreted with caution and future research designed to investigate patterns of blood pressure variation would benefit from standardized assessment protocols with monitors validated for the population of interest. Notably, this is not a limitation of only this study, but also of the wider literature on blood pressure trajectories across pregnancy where device information and assessment protocols are not available (Farrar et al., 2019; Macdonald-Wallis et al., 2012; Macdonald-Wallis et al., 2011, 2014). When protocols are available, studies are limited by a small number of observations (e.g., one in each trimester ;Bakker et al., 2010, 2011; Guo et al., 2020).

Despite the advantages of FDA, there are some limitations. Recent research has shown that women with preeclampsia may display greater mean arterial pressure volatility (i.e., more "erratic swings" in blood pressure across time) relative to normotensive controls (Zhu & Dunson, 2017). This finding has important implications for the use of FDA to analyse repeated blood pressure observations across pregnancy when the same smoothing parameter is applied to all participants, as done in this study. As a result, a set of observations with greater volatility may have been over-smoothed, while those with relatively lower volatility may be under-smoothed, potentially obscuring important sources of variation. Although data-smoothing using B-splines common, the approach is researcher driven so that the level of "smoothness" is appropriate for the application (Ramsay & Silverman, 2005). As values of $\lambda(>0)$ increase, curvature is penalized and there is increased risk of glossing over important sources of variation; but, with smaller values of $\lambda(<0)$, the fit will prioritize crossing through discrete datapoints, sometimes at the expense of extreme variation in the approximating function (Ramsay et al., 2009). Ramsay, Hooker & Graves (2009) recommend a "cautious and considered" approach to data smoothing that includes subjective examination of each constructed curve, rather than relying solely on a numerical indicator of fit.

Typically, erratic changes in blood pressure are chalked up to measurement error or other extraneous variable, but are now recognized as a meaningful source of variation rather than something to be overcome with more stringent assessment protocols (Muntner et al., 2015). For example, in recent years, visit-to-visit blood pressure variability has been identified as a potential independent risk factor for adverse cardiovascular health outcomes, beyond the contribution of mean blood pressure, highlighting the importance of haemodynamic stability over time as an index of cardiovascular health (Muntner et al., 2015; Stevens et al., 2016). These findings

underscore the importance of developing a greater foundation of knowledge on maternal blood pressure variation. This could be achieved with more densely sampled blood pressure across gestation (e.g., daily or weekly) and adherence to assessment protocols, and recruitment of healthy and at-risk samples. FDA could then be used to evaluate whether blood pressure volatility represents a signal to identify a pregnancy at risk for averse maternal cardiovascular health outcomes.

The use of a novel statistical method to examine patterns of blood pressure variation represents the most significant strength of this study. Some additional strengths of this study include an online self-report questionnaire procedure that reduced participant burden. Although the sample was ethnically diverse, generalizability of these results is limited by a small sample size that lacked sociodemographic diversity. Future researchers could apply FDA to investigate patterns of variation in other indices of maternal cardiovascular function that are commonly assessed in clinical and/or research settings (e.g., cardiac output, systemic vascular resistance, mean arterial pressure, pulse wave velocity, and uterine artery resistance (Flo et al., 2010; Franz et al., 2013; Han et al., 2014; Lim et al., 2012; Meah et al., 2016; Sallis & Saelens, 2000), or to explore how two cardiovascular measures covary across pregnancy. In short, an FDA approach to the analysis of repeated measurements has the potential to yield a more nuanced and dynamic understanding of maternal cardiovascular risk during the perinatal period.

Conclusions

In summary, we applied an FDA to model blood pressure variation across pregnancy and, through *f*PCA, identified three blood pressure trajectories that best capture blood pressure variation among a community-sample of pregnant women. The statistical approach is novel and addresses limitations of multivariate methods that have previously been applied to model blood

pressure trajectories across gestation. Our results demonstrate the usefulness for *f*PCA to identify common blood pressure trajectories and suggest that a late-increase pattern of systolic and diastolic blood pressure is associated with shorter gestation, while a prolonged-decrease pattern of systolic blood pressure is associated with older gestational age at birth. When discrete datapoints represent smooth, underlying dynamic processes, FDA is an applicable statistical approach to model variance across time and has widespread applicability within the field of maternal cardiovascular health.

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Table 1.1

Participant Characteristics (*N*=370)

	M (SD)
Age	32.7 (4.56)
Pre-pregnancy BMI	23.71 (5.01)
	n (%)
Smoking in pregnancy	8 (2.2)
Primiparous	235 (63.5)
Multifetal pregnancy	2 (0.5)
Pregnancy Complications	
Gestational hypertension	11 (2.9)
Preeclampsia	14 (3.8)
Gestational diabetes	14 (3.8)
Ethnicity*	
White	226 (61.6)
Latin American	25 (6.8)
Arab	25 (6.8)
Chinese	20 (5.4)
Black	18 (4.9)
Other	56 (15.1)
Marital status	
Married	280 (75.7)

continued

Co-habiting	68 (18.4)
Single	19 (5.1)
Separated	2 (0.5)
Widowed	1 (0.3)
Employment status†	
Full-time	224 (60.5)
Part-time	33 (8.9)
Student	27 (7.3)
Unemployed	31 (8.4)
Maternity leave	14 (3.8)
Other	40 (10.8)
Missing	1 (0.3)
Secondary education only	31 (8.4)
Income	
More than $120,000	84 (22.7)
81,000 - $120,000	58 (15.7)
41,000 - $80,000	98 (26.5)
Less than $40,000	72 (19.5)
Did not disclose	6 (1.6)

Note. BMI = Body Mass Index. *Participants that identified as a part of an ethnic group that represented <5% of the total sample were included in the 'Other' category of ethnicity.

†Participants that listed a type of employment that represented <5% of the sample were included in the 'Other' category of employment.

Table 2.2

Results from multiple linear regression analyses predicting gestational age at birth from harmonic scores representing trajectories of blood pressure across gestation (*n*=255).

Model 1 Systolic Blood Pressure				Model 2 Diastolic Blood Pressure			
Predictor	*b*	95% CI [LL, UL]	Fit	Predictor	*b*	95% CI [LL, UL]	Fit
(Intercept)	39.63**	[39.43, 39.82]		(Intercept)	39.64**	[39.44, 39.84]	
Harmonics				Harmonics			
Prolonged-decrease	0.01**	[0.00, 0.02]		Prolonged-decrease	0.00	[-0.01, 0.02]	
Late-increase	-0.01*	[-0.02, -0.00]		Late-increase	-0.02*	[-0.03, -0.00]	
Mid-decrease	0.01	[-0.01, 0.02]		Mid-decrease	-0.00	[-0.02, 0.02]	
			R^2 = .058** 95% CI [.01,.11]				R^2 = .030 95% CI [.00,.07]

Note. A significant *b*-weight indicates the beta-weight and semi-partial correlation are also significant. *b* represents unstandardized regression weights. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively.

* indicates $p < .05$. ** indicates $p < .01$.

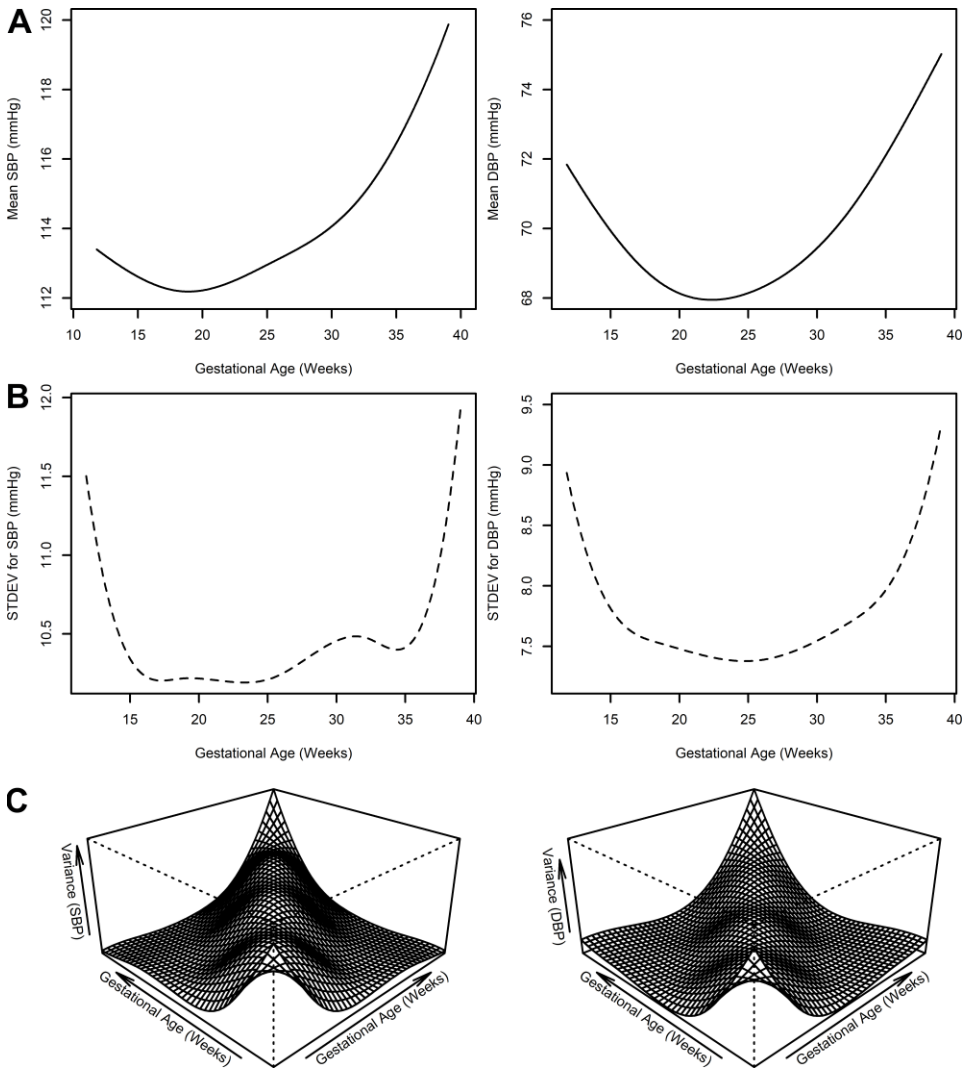

Figure 2.1. Functional descriptive statistics derived from the sample of curves (*N*=370). **A,** represents the mean functional curve of the systolic and diastolic blood pressure data across gestation (11.81-39.04 weeks of gestation). **B,** represents the standard deviation function of systolic and diastolic blood pressure. **C**, represents the variance-covariance perspective plots and shows the variance in systolic and diastolic blood pressure across gestation. The plots indicate that variance is maximized at three timepoints during pregnancy (early, mid, and late gestation).

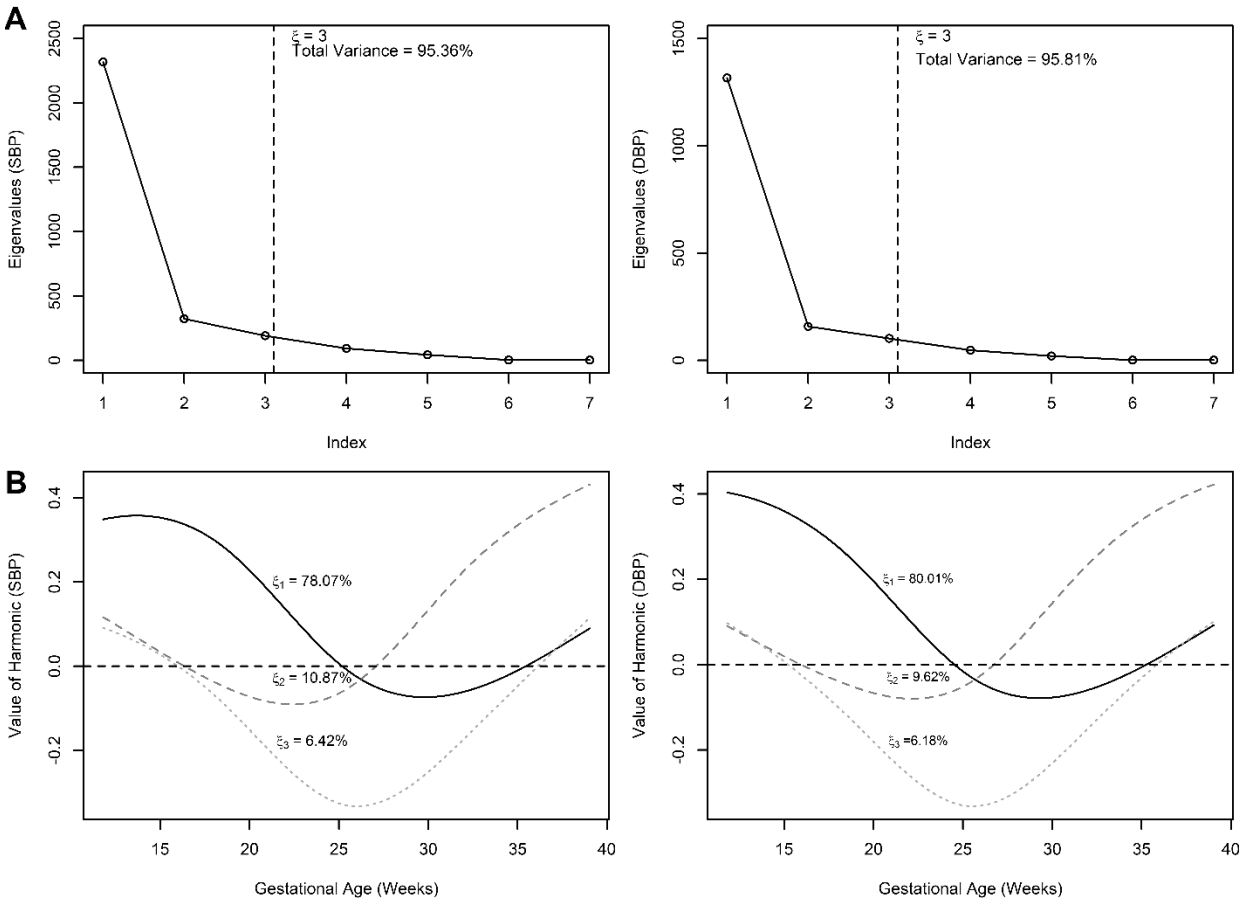

Figure 2.2 Results from a functional principal components analyses. **A,** Scree plots that display the final number of harmonics (ξ) retained from the functional principal components analysis for systolic (SBP) and diastolic (DBP) blood pressure. **B,** The first three weight functions for the rotated harmonics are displayed for SBP and DBP and capture successively decreasing proportions of variation. The first harmonic (ξ_1) is represented by the solid black line, second harmonic (ξ_2) by the long-dashed grey line, and third harmonic (ξ_3) by the short-dashed grey line.

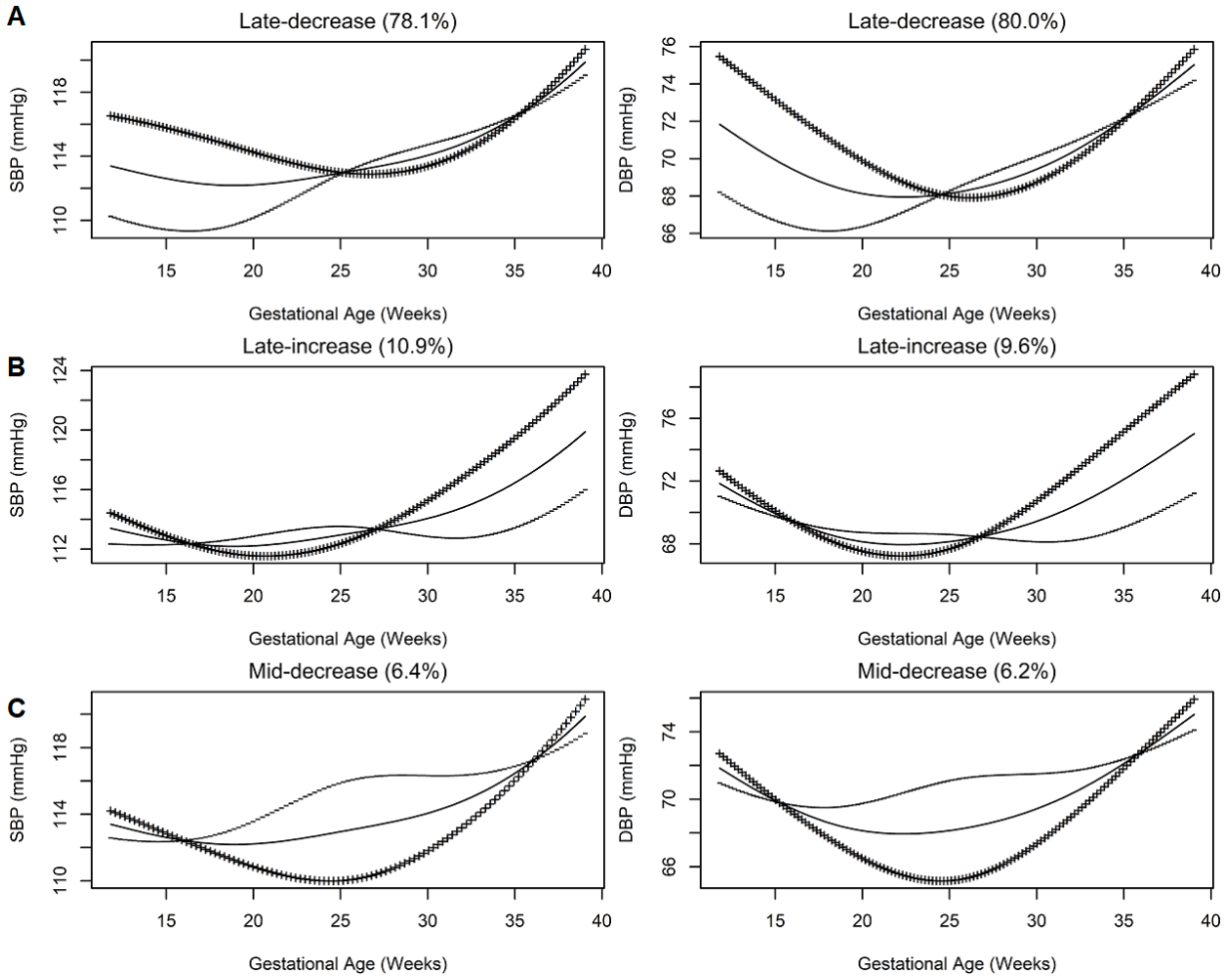

Figure 2.3. The first three harmonics for systolic (SBP) and diastolic (DBP) blood pressure displayed as perturbations of the mean trajectory, represented by the solid line. The plus and minus icons represent the variability captured by each harmonic when a multiple of the component score is added (++) or subtracted (--) from the mean curve. **A,** the prolonged-decrease trajectory characterized by relatively higher blood pressure in early pregnancy a later decline, relative to the mean trajectory. **B,** shows the late-increase trajectory characterized by a negligible initial decline and greater blood pressure increase in late pregnancy. **C,** shows the mid-decrease trajectory characterized by a more pronounced, prolonged blood pressure decline in mid-pregnancy, relative to the mean trajectory.

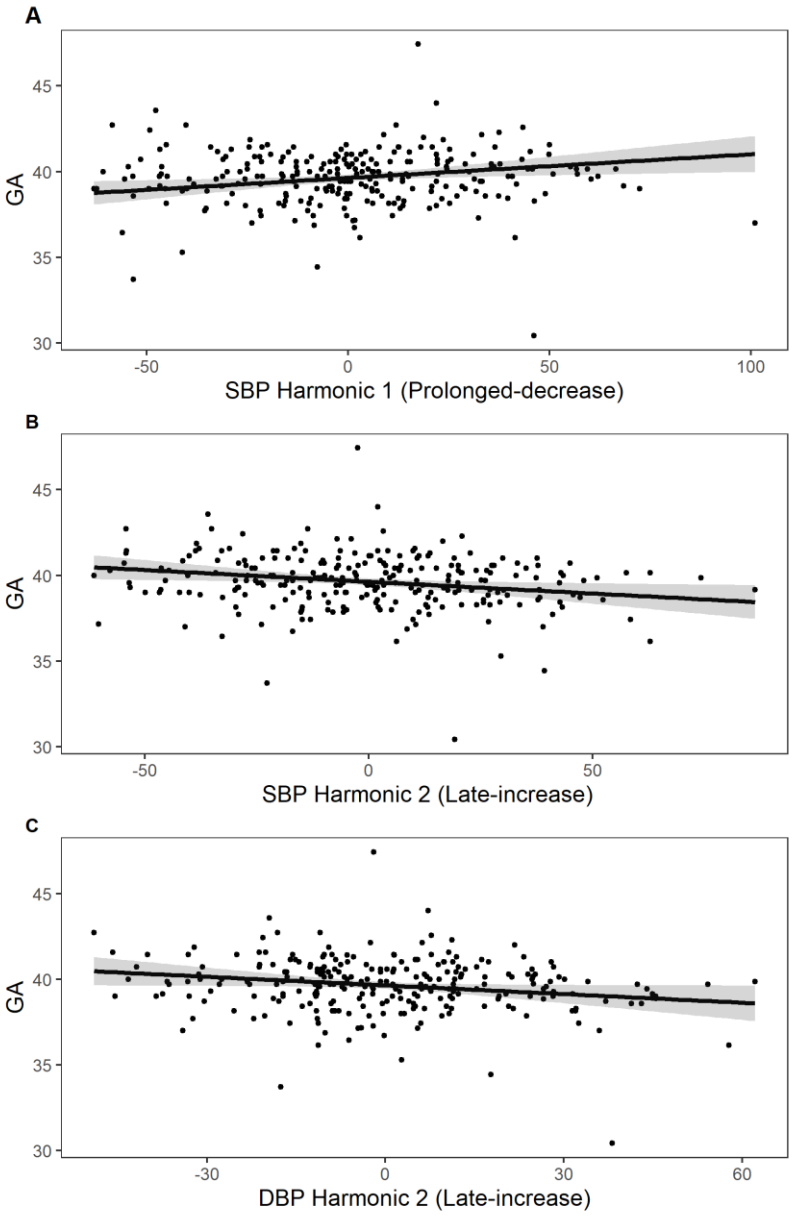

Figure 2.4. Effect plots of results from multiple linear regression analyses predicting gestational age at birth from systolic and diastolic blood pressure trajectories. Shading indicates 95% confidence intervals. **A,** prolonged-decrease systolic blood pressure trajectory was significantly associated with older gestational age at birth. Late-increase blood pressure trajectory was significantly associated with younger gestational age at birth for systolic (**B**) and diastolic (**C**) blood pressure.

Bridge to Manuscript 3

Results from Manuscript 2 showed that FDA represents a useful tool for the analyses of repeated blood pressure observations across pregnancy, and hint at how this approach can be used to better understand associations across time. In Manuscript 3, functional linear regression analysis is used to examine the association between maternal behavioral, obstetrical, and psychological factors and blood pressure across gestation. This paper builds on the methodology described in Manuscript 2 by using the functional data objects created from discrete systolic and diastolic blood pressure observations as the primary, functional outcome variables.

Among the advantages of using functional linear regression analyses is the ability to visualize the effects in a more intuitive way. Blood pressure, and many other cardiovascular processes, are typically represented by repeated observational data that are often displayed with straight lines that connect points across time. Blood pressure is fundamentally dynamic in nature, changing from moment to moment in response to a person's internal and external environment. With use of FDA, it is possible to model physiological processes in a way that more accurately reflects the underlying, smooth, moment-to-moment variation. In this way, the researcher can begin to think differently about these data and ask more nuanced questions about not only if an independent predictor is associated with a physiological process, but when this association has the strongest effect.

Manuscript 3

Maternal Cardiovascular Risk Factors, Symptoms of Depression and Pregnancy-Specific Anxiety, and Blood Pressure Across Gestation

*Kristin J. Horsley, BA[1], Blaine Ditto, PhD[1], James Ramsay, PhD[1], Deborah Da Costa, PhD[2]

[1]Department of Psychology, Faculty of Science, McGill University; [2]Department of Epidemiology, Faculty of Medicine, McGill University

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Abstract

Objective: To examine the association between general cardiovascular risk factors (e.g., pre-pregnancy body mass index, visible minority identification), obstetrical factors (i.e., nulliparity) and psychological factors (i.e., symptoms of depression and pregnancy-specific anxiety) and systolic and diastolic blood pressure across gestation using a functional data analytic approach.

Methods: Data on maternal sociodemographic, obstetrical, and psychological variables were assessed with self-report questionnaires in early pregnancy, and clinical blood pressure data from across gestation were available from 370 women who participated in a prospective, longitudinal study in Montreal, Quebec, Canada. Functional data analysis was used to construct blood pressure curves across gestation from each participant's set of blood pressure observations, and functional regression analysis was used to examine how maternal factors related to blood pressure across gestation.

Results: Consistent with previous research, pre-pregnancy body mass index and nulliparity were associated with higher systolic and diastolic blood pressure across gestation, but the effects were more pronounced at some timepoints. Visible minority status was associated with lower systolic blood pressure in late, but not early pregnancy, and with lower diastolic blood pressure in mid, but not late pregnancy. Maternal depressive symptoms and pregnancy-specific anxiety were not associated with blood pressure across gestation.

Conclusions: These findings replicate and extend upon previous research that has identified maternal and obstetrical factors as important predictors of blood pressure across gestation. More research is needed to determine whether symptoms of depression and pregnancy-specific anxiety relate to blood pressure across pregnancy among more "at-risk" samples.

Introduction

Hypertensive disorders of pregnancy (i.e., chronic hypertension, gestational hypertension, preeclampsia, and eclampsia; HDP) occur in approximately seven to 10% of pregnancies and are a leading cause of perinatal morbidity and mortality (Hutcheon et al., 2011; Magee et al., 2014; Magnussen et al., 2007). Over the last 10 years, there has been increased interest in the identification of blood pressure trajectories across pregnancy in an effort to better understand the development of HDP, and to examine factors that predict the degree of blood pressure elevation among women at greater cardiovascular risk. Results from these studies have shown that women diagnosed with HDP tend to have higher blood pressure across gestation, and steeper blood pressure increases in late pregnancy, relative to normotensive controls (Macdonald-Wallis et al., 2012). Among pregnant women who remain normotensive, those with established risk factors for preeclampsia (e.g., overweight/obesity, nulliparity, maternal age >35 years, and twin pregnancy) have higher systolic and diastolic blood pressure, compared to those without (Macdonald-Wallis et al., 2011). These differences can be observed as early as 8 weeks of gestation, but also appear to change over the course of pregnancy, suggesting that maternal factors may have a more pronounced effect at some timepoints over others.

Symptoms of depression and anxiety are commonly reported by pregnant women and are among the risk factors associated with development or worsening of HDP (Cripe et al., 2011; Mogos et al., 2019; Thombre et al., 2015). For example, results from a recent systematic review and meta-analysis of 44 studies concluded that symptoms of maternal depression and anxiety across pregnancy are associated with an up to 39% increase in risk for the development of HDP (RR = 1.30, 95% CI 1.25, 1.54). Although the mechanisms of risk remain unclear, research has shown that symptoms of depression and anxiety can lead to changes in central mechanisms

involved in blood pressure regulation such as decreased parasympathetic control of the heart, and that these changes may lead to increases in blood pressure over time (Mizuno et al., 2017; Rouleau et al., 2016; Shea et al., 2008). Whether symptoms of depression or anxiety relate to blood pressure across pregnancy has not been examined.

Clinical blood pressure observations are routinely collected as part of prenatal care and represent the most frequently assessed markers of maternal cardiovascular health across gestation. To date, most research has utilized clinic blood pressure observations and multivariate statistical methods to describe group-level differences in blood pressure change across pregnancy (Farrar et al., 2019; Guo et al., 2020; Macdonald-Wallis et al., 2012; Macdonald-Wallis et al., 2011, 2014; Simpkin et al., 2018). Clinical data from pregnancy are unique in that they are typically sparse, unequally spaced observations that vary between participants in terms of timing and frequency. Previous researchers have used multivariate statistical analyses (e.g., multilevel modeling, latent growth curve analysis) to identify blood pressure trajectories, but these methods are prone to statistical bias given they do not adequately deal with unequally spaced data or account for intercorrelations between repeated assessments (Levitin et al., 2007; Ullah & Finch, 2013). Further, multivariate methods ignore the continuous physiological processes that underlie a single blood pressure observation. Since repeated clinical blood pressure observations can be observed at any point in time, these data can be considered functional in nature (James & Gerber, 2018).

When data are best represented as a curve across time, functional data analysis (FDA) can be applied to examine blood pressure variability across gestation as functions, rather than as discrete observations (Ramsay & Silverman, 2005). Among the advantages of using FDA to model time-series data is that it allows for an examination of the smooth, underlying function

that gives rise to a single blood pressure observation and eliminates the issue of intercorrelation between assessment timepoints (Ramsay et al., 2018). Further, functional linear regression analysis can be used to examine associations between explanatory and predictor variables where at least one is functional in nature, and yields regression coefficient functions that show how the effect of a predictor changes across time (Ramsay et al., 2009; Ullah & Finch, 2013). Although there are significant advantages, FDA remains an underused statistical method (Levitin et al., 2007; Ullah & Finch, 2013) that is highly suitable for the investigation of how maternal factors relate to blood pressure across pregnancy.

In light of previous research that has shown links between maternal symptoms of depression and anxiety and HDP, and the usefulness of FDA to examine how maternal factors influence blood pressure across gestation, the aim of the present study was to explore associations between maternal risk factors for HDP, symptoms of depression and pregnancy-specific anxiety, and systolic and diastolic blood pressure across pregnancy using a functional data analytic approach.

Methods

Study design

Data were available from women who participated in the Healthy Behaviours During Pregnancy and Postpartum Study. This was a prospective, longitudinal study designed to collect data at several timepoints across the pregnancy and postpartum period. Data from medical charts were available from a subset of participants. The primary aim of the study was to examine the influence of behavioural and psychosocial factors on gestational weight gain. Ethics approval

was granted by McGill Faculty of Medicine Institutional Review Board and the ethics review boards of participating hospitals.

Sample

Convenience sampling was used to recruit women who were ≥18 years of age with a singleton pregnancy who were less than 20.0 weeks of gestation, able to communicate in English or French, and able to access the internet. Exclusion criteria were pre-existing Type 1 or 2 diabetes and gestational diabetes mellitus due to dietary requirements and restrictions that may influence weight gain across pregnancy.

At study entry, 754 participants completed the online questionnaires. Of these, medical chart data were available for 395 (53%) women that attended appointments at two obstetrical clinics associated with the two McGill University affiliated hospitals. Participants were included in analyses if they had at least four blood pressure observations, and at least one in each trimester of pregnancy (i.e., ≤12 weeks gestation, between 13- and 26-weeks gestation, and ≥27 weeks gestation), resulting in the exclusion of *n*=25 and a final sample of 370.

Measures

Demographics

Data on maternal socio-demographics (age, ethnicity, education, pre-pregnancy height and weight) and pregnancy characteristics (parity, multifetal pregnancy, assisted reproductive technologies) were obtained through online self-report questionnaires. Maternal self-reported height and weight were converted to metric units to obtain pre-pregnancy body mass index (BMI) in kg/m^2.

Depressive symptoms

The Edinburgh Postnatal Depression Scale (EDPS) was used to assess depressive symptoms during the perinatal period (Cox et al., 1987). The EPDS is a 10-item self-report questionnaire, with each item rated on a 4-point scale to produce a summative score ranging from 0 to 30; higher scores indicate greater depressive symptom severity (Cox et al., 1987). The EPDS has also been validated against standardized interview schedules and other self-report instruments for use during pregnancy (Bergink et al., 2011). In this sample, the EPDS demonstrated adequate reliability (i.e., Cronbach's $\alpha>0.80$) in the first, second, and third trimesters of pregnancy. Depressive symptoms were assessed concurrently with pregnancy-specific anxiety in each trimester of pregnancy. For present study purposes, only depressive symptom severity assessed in the first trimester of pregnancy was included due to rates of missing self-report data in the second (12%) and third (22%) trimesters of data.

Pregnancy-specific anxiety

The Prenatal Distress Questionnaire Revised (PDQ) is a 17-item self-report questionnaire that asks women to indicate the degree to which they feel bothered, upset, or worried about pregnancy-specific stressors (e.g., medical care, physical symptoms, parenting, bodily changes, and infant health) on a 3-point scale (i.e., not at all, somewhat, very much; Lobel et al., 2008) with total scores ranging from 0 to 34. In the present study, the PDQ demonstrated high internal consistency in the first (Cronbach's $\alpha=0.82$), second (Cronbach's $\alpha=0.82$), and third (Cronbach's $\alpha=0.83$) trimesters of pregnancy and are comparable to those reported in previous research (Alderdice et al., 2012; Lobel et al., 2008). The PDQ has been associated with birth outcomes (i.e., preterm birth) and poor health behaviours (i.e., smoking; Lobel et al., 2008). The PDQ has not been examined in relation to blood pressure across pregnancy, but represents a potentially

important construct to assess given that it has been found to be a robust predictor of adverse maternal and infant health outcomes (Blackmore et al., 2016; Westerneng et al., 2017). For present study purposes, only pregnancy-specific anxiety assessed in the first trimester of pregnancy was included due to rates of missing self-report data in the second (12%) and third (22%) trimester data. The questionnaire is available in Appendix III.

Blood pressure measurements

Systolic blood pressure and diastolic blood pressure were measured by trained clinical staff at each obstetrical appointment using validated automated oscillometric blood pressure monitors (HEM-7320T-CACS; Omron Healthcare, Kyoto, Japan; Lifesource Model UA-787 AC, A&D Medical, San Jose, CA) with an appropriately sized cuff as part of routine care. The left upper arm was at heart level and supported. The number of readings was not standardized across participants and was not routinely recorded.

Data Preparation and Statistical Analyses

Statistical analyses were performed using RStudio (RStudio Team, 2016). Participant characteristics were described using means and standard deviations for continuous variables and percentage for categorical variables. The fda (Ramsay et al., 2018) package was used for all functional data analyses described below. For reviews of the methodology and specific computational details, see publications by Ramsay et al. (Levitin et al., 2007; Ramsay et al., 2009; Ramsay & Silverman, 2005).

A total of 3387 systolic and 3384 diastolic blood pressure observations were available from the sample. To prepare data for functional analysis, a lower boundary timepoint was selected by taking the average weeks of gestation at the first blood pressure observation

(*M*=11.81 weeks), and an upper boundary by taking the average weeks of gestation for blood pressure measurements that occurred between 38 and 40 weeks of gestation (*M*=39.04 weeks). Functional data objects were created from each set of systolic and diastolic blood pressure observations using a 7 Order four B-spline basis function, corresponding to three equally spaced interior knots over the time interval of 11.81 to 39.04 weeks of gestation, and a smoothing parameter set at λ=10 (Ramsay et al., 2009). Through creation of functional data objects, each participant's repeated blood pressure data is transformed and represented by a single curve with 7 basis coefficients. This transformation makes it possible to extract information from the whole temporal process of gestation rather than only at the observation timepoints.

Mean and standard deviation functions were estimated based on the smoothed data objects from all participants. A linear model was built from the functional data objects to examine effects of maternal depressive symptom severity and pregnancy-specific anxiety on blood pressure variation across gestation. Since systolic and diastolic blood pressure are represented as functional data objects, the resulting regression coefficients are curves rather than scalars and allow for determination of how the effect of a predictor changes across time. Regression coefficients are presented as unstandardized beta coefficients (*b*) that represent the change in blood pressure associated with a one-unit increase in the predictor. The regression analysis also yields pointwise standard error functions to calculate 95% confidence intervals of the regression coefficients. A predictor is considered statistically significant if the 95% confidence interval for the regression coefficient function does not contain 0. For in depth computational details and scripts for R, see Ramsay et al. (2009, 2005).

Additional predictors for the model were selected based on previous research and theoretical relevance, namely: maternal age, ethnicity, parity, pre-pregnancy BMI, and smoking

status. Only covariates that were significant predictors of systolic or diastolic blood pressure at some timepoint in pregnancy were retained in the final models, resulting in the exclusion of maternal age and smoking status.

Thus, the systolic and diastolic functional linear models are represented by

$$bp_{i(t)} = \beta_0(t) + \beta_1(t)\,\mathrm{Eth}_i + \beta_2(t)\,\mathrm{Par}_i + \beta_3(t)\,\mathrm{Bmi}_i + \beta_4(t)\,\mathrm{Dep}_i + \beta_5(t)\,\mathrm{PAnx}_i + \varepsilon_i(t).$$

Ethnicity (Eth) and parity (Par) were coded such that $\mathrm{Eth}_i = 0$ if the *i*th participant was white/Caucasian, and 1 if identified as a visible minority, and $\mathrm{Par}_i = 0$ if the *i*th participant had ≥ one previous birth (i.e., multiparous), and 1 if it was their first child (i.e., nulliparous). Pre-pregnancy BMI (Bmi), depressive symptoms severity (Dep), and pregnancy-specific anxiety (PAnx) were treated as continuous variables where regression coefficients indicate the change in systolic or diastolic blood pressure associated with a one-unit increase in the predictor variable. Missing data for the predictors were handled with mean and mode replacement for continuous and categorical variables, respectively. Across all predictors, the percentage of missing data did not exceed 2.1% (8/370 missing values).

Results

Maternal characteristics are presented in Table 1. Most participants were white (61%), married (76%) women who were pregnant with their first child (64%). Pre-pregnancy BMI ranged from 12.99 to 60.57 kg/m^2 and, on average, fell within the normal range (*M*=23.70, *SD*=4.98). On average, the sample reported low depressive symptom severity (*M*=7.18, *SD*=4.59, *Range*=0-23). Scores on the pregnancy-specific anxiety scale ranged from 0 to 26 (*M*=10.79, *SD*=5.44).

Functional descriptive statistics for systolic and diastolic blood pressure are presented in Figure 3.1. On average, systolic and diastolic blood pressure decreased from 11.81 weeks of gestation to mid-second trimester. The standard deviation functions indicate that, on average, blood pressure showed greater variability in early and late pregnancy, relative to mid-pregnancy.

The functional equivalent to the F-test for systolic and diastolic blood pressure is plotted in Figure 3.2 and shows the pointwise and maximal *F*-statistic (highest value of the red line) and the corresponding permutation critical values (dashed blue line, determined using 200 permutations) for the models. For the model involving systolic blood pressure, the test yields a maximum observed statistic of 0.13 with a corresponding critical value of 0.03, and a minimum observed statistic of 0.05 with a corresponding critical value of 0.03, indicating that the model was significant across gestation. For the model involving diastolic blood pressure, the test yields a maximum observed statistic of 0.15 with a corresponding critical value of 0.03, and a minimum observed statistic of 0.08 with a corresponding critical value of 0.03, again indicating that the model was significant across gestation.

Figures 3.3 and 3.4 display the regression coefficient and 95% pointwise confidence interval functions for the intercept and the effects of pre-pregnancy BMI, parity, ethnicity, depressive symptoms, and pregnancy-specific anxiety on systolic and diastolic blood pressure. The effect of a predictor is considered statistically significant if the 95% pointwise confidence interval does not include zero which is represented by the horizontal dashed line in each regression coefficient function. For each model, the intercept function represents the mean trend in systolic (Figure 3.3A) and diastolic (Figure 3.4A) blood pressure.

For the model involving systolic blood pressure, a one-unit increase in pre-pregnancy BMI was associated with a 0.42 to 0.63 mmHg increase in systolic blood pressure across gestation. Figure 3.3B shows how the effect of pre-pregnancy BMI changed across gestation. Specifically, the effect was greater in early pregnancy at 11.81 weeks of gestation (*b*=0.63, *SE*=0.12, 95% CI 0.40-0.87), declines to a nadir at 18.62 weeks (*b*=0.59, *SE*=0.10, 95% CI 0.39, 0.76), increases to a peak at 27.05 weeks (*b*=0.65, *SE*=0.10, 95% CI 0.44, 0.85), and then declines to the minimum value at 39.04 weeks of gestation (*b*=0.42, *SE*=0.13, 95% CI 0.16, 0.67).

Nulliparous women had significantly higher systolic blood pressure across pregnancy relative to multiparous women, but the effect was more pronounced in early and late pregnancy relative to mid pregnancy (Figure 3.3C). Specifically, the effect was greatest in early pregnancy at 11.81 weeks of gestation (*b*=3.90, *SE*=1.29, 95% CI 1.32, 6.49), declined to a nadir at 26.78 weeks (*b*=2.21, *SE*=1.10, 95% CI 0.02, 4.41), and then increases in late pregnancy to a peak at 37.95 weeks of gestation (*b*=2.77, *SE*=1.25, 95% CI 0.27, 5.27). The effect of ethnicity is shown in Figure 3.3D and shows that participants identifying as a visible minority had significantly lower systolic blood pressure in late pregnancy, relative to women who identified as white. The effect becomes statistically significant at 29.78 weeks of gestation (*b*=-2.17, *SE*=1.07, 95% CI -4.26, 0.30) and is greatest in late pregnancy at 39.04 weeks of gestation (*b*=-3.04, *SE*=1.31, 95% CI -5.65, -0.43). The effect of depressive symptom severity and pregnancy-specific anxiety are presented in Figures 3.3E and 3.3F and show that there was no significant association between these variables and systolic blood pressure across gestation.

For the model involving diastolic blood pressure, a one-unit increase in pre-pregnancy BMI was again associated 0.42 to 0.60 mmHg increase in diastolic blood pressure (Figure 3.4B.

Specifically the effect was again higher in early pregnancy (*b*=0.55, *SE*=0.12, 95% CI 0.31, 0.49), decreased to a nadir at 22.16 weeks of gestation (*b*=0.10, *SE*=0.20, 95% CI 0.20, 0.61), increased until 31.96 weeks (*b*=0.48, *SE*=0.11, 95% CI 0.27, 0.69), and then decreased until 39.04 weeks (*b*=0.42, *SE*=0.13, 95% CI 0.17, 0.68). Nulliparous women had 1.9 to 3.20 mmHg higher blood across gestation (Figure 3.4C). The effect, however, was only significant in early pregnancy, between 12.35 (*b*=1.94, *SE*=0.96, 95% CI 0.03, 3.85) and 16.71 weeks of gestation (*b*=1.63, *SE*=0.81, 95% CI 0.01, 3.26). The effect was again significant at 23.25 weeks of gestation (*b*=1.62, *SE*=0.80, 95% CI 0.02, 3.21), rose to a peak at 32.51 weeks (*b*=3.20, *SE*=0.82, 95% CI 1.57, 4.83), and then decreased until 39.04 weeks of gestation (*b*=2.46, *SE*=1.07, 95% CI 0.33, 4.59). Women who identified as a visible minority has lower blood pressure in mid pregnancy (Figure 3.4D), between 18.89 weeks (*b*=-1.56, *SE*=0.77, 95% CI -3.11, -0.02) and 25.70 weeks of gestation (*b*=-1.47, *SE*=0.75, 95% CI, -2.98, -0.03). There was no significant effect of depressive symptom severity and pregnancy-specific anxiety on diastolic blood pressure across gestation (Figure 3.4E and 3.4F).

To further aid with visualization of these results and compare with previous research (Macdonald-Wallis et al., 2011), mean systolic and diastolic blood pressure trajectories were plotted for participants based on their pre-pregnancy BMI category (i.e., underweight, normal weight, overweight, obese; Figure 3.5), parity (i.e., nulliparous, multiparous; Figure 3.6A), and visible minority status (i.e., visible minority, white; Figure 3.6B).

Discussion

The present study used functional regression analysis to examine the effect of pre-established risk factors for HDP and maternal symptoms of depression and anxiety across

gestation. Our results are consistent with previous research that documented effects of pre-eclampsia risk factors on blood pressure trajectories across gestation (Macdonald-Wallis et al., 2011), and extends this work by statistically modelling how the effect changes across time. Although previous research has shown that symptoms of depression and anxiety are associated with development of worsening of hypertension during pregnancy, results from this study indicate no significant link between these variables and maternal blood pressure across gestation. Despite null results, the present study makes a significant methodological contribution to the literature by demonstrating the usefulness of functional regression analysis to examine the effect of maternal factors on blood pressure across time.

Recent research has shown that symptoms of depression or anxiety may exacerbate risk of adverse birth outcomes associated with HDP (Horsley et al., 2019; Mogos et al., 2019), suggesting that these factors may have a more detrimental impact for women with a cardiovascular system already under strain via the presence of HDP. In the present study, only 21 participants were diagnosed with HDP and so we could not statistically examine whether depressive symptoms or pregnancy-specific anxiety were associated with blood pressure changes across pregnancy for this group of women. Previous research on the association between symptoms of depression and anxiety on birth outcomes has been somewhat equivocal, with a recent systematic reviews and meta-analysis studies showing conflicting results (Accortt et al., 2015; Alder et al., 2007; Bonari et al., 2004; Grote et al., 2010). One potential explanation for these inconsistent findings is that perhaps maternal psychological factors matter more in some populations or circumstances over others. Within the context of HDP, for example, symptoms of depression and anxiety may have a more detrimental impact among women who are “at risk”,

such as those women with established cardiovascular risk factors or who have had a previous pregnancy complicated by a hypertensive disorder.

Another consideration is that we included only maternal symptoms of depression and pregnancy-specific anxiety assessed in the first trimester of pregnancy. Two other assessment timepoints were included in this study (i.e., between 13- and 26-weeks gestation, and ≥27 weeks gestation), but rates of missing data at the second and third assessment timepoints were 12 to 22%, thus requiring imputation methods might bias statistical results (Bennett, 2001). From a methodological standpoint, the goal of the present study was also to examine how maternal factors influence blood pressure across pregnancy, and therefore it also made more sense to include predictor variables from early pregnancy. Ideally, future researchers could incorporate assessments of maternal depressive and anxiety symptoms into prenatal care such that they occur at the same frequency as clinical blood pressure observations. This would permit analysis of dynamic changes in maternal psychology and physiology and allow for a more ecological examination of how these factors relate to across pregnancy.

Relative to research on the association between symptoms of depression and anxiety and the development or worsening of HDP, few studies have investigated underlying physiological mechanisms that could account for these observations. In non-pregnant samples, converging research suggests that autonomic nervous system alterations may represent a plausible biological pathway that links depressive symptoms with adverse cardiovascular health outcomes (Grippo & Johnson, 2009). Similar findings are also emerging among samples of pregnant women. For example, in a Canadian sample, Rouleau et al. (2016) showed an indirect effect of maternal self-reported depressive symptoms on gestational hypertension through lower high-frequency heart rate variability, representing reduced parasympathetic control of the heart, in late but not early

pregnancy. Mizuno et al. (2017) reported similar results among a small Japanese sample (*N*=65), where greater state- and trait-anxiety at 20 weeks of gestation was associated with lower high-frequency heart rate variability at 30 and 36 weeks of gestation. There is a significant opportunity for researchers to investigate the cooccurrence of psychological and physiological problems that arise in pregnancy, and when these factors may have the greatest impact across the perinatal period.

A strength of the present study is that the sample was ethnically diverse, with 40% of women identifying as a visible minority. A somewhat surprising finding is that these women also had lower blood pressure across gestation, relative to women who identified as white. These results are in line with recent research that showed lower blood pressure during the first two trimesters of pregnancy among Pakistani women relative to white British women (Farrar et al., 2019). Results must be interpreted with caution given that the visible minority group is comprised of several different ethnic and racial minorities and so it is not possible to ascertain for whom this finding matters most. More research on how maternal blood pressure trajectories differ by race or ethnicity is certainly warranted.

The use of functional data analytic methods to examine how maternal factors relate to blood pressure change across pregnancy represents the most significant strength of this study. Functional data analysis is a particularly useful statistical approach when repeated observations vary between participants in terms of timing, frequency, and interval as is the case for clinical blood pressure observations (Ramsay & Silverman, 2005). Relative to multivariate methods, functional data analysis more adequately deals with sources of statistical bias present in clinical blood pressure datasets (Thompson et al., 2007), and functional regression analysis allows for an examination of how the effect of a predictor changes across time. These methods have important

implications for understanding when a particular biological, psychological, or social factor may influence maternal blood pressure and represent a statistical technique that can be used to better understand pathophysiological processes across gestation.

In sum, this study replicates what is known about the association between maternal risk factors for HDP (i.e., pre-pregnancy BMI, parity) and blood pressure across gestation, and adds to this literature by using functional regression analysis to examine the effect of these predictors across time. Depressive symptoms and pregnancy-specific anxiety were not associated with blood pressure across gestation, but further research is needed to examine whether these links may be present in more at-risk samples. Functional data analysis represents a useful statistical method to model clinical blood pressure observations and for the examination of when across the course of gestation predictors matter most. These methods have applicability for the analysis of blood pressure across pregnancy and many other time-related cardiovascular processes.

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Table 3.1

Participant Characteristics (*N*=370)

	M (SD)
Age	32.7 (4.56)
Pre-pregnancy BMI	23.71 (5.01)
Depressive symptoms	7.18 (4.59)
Pregnancy-specific anxiety	10.79 (5.44)
	n (%)
Smoking in pregnancy	8 (2.2)
Nulliparous	235 (63.5)
Multifetal pregnancy	2 (0.5)
Pregnancy Complications	
Gestational hypertension	11 (2.9)
Preeclampsia	14 (3.8)
Gestational diabetes	14 (3.8)
Gestational age at birth	
Ethnicity*	
White	226 (61.6)
Latin American	25 (6.8)
Arab	25 (6.8)
Chinese	20 (5.4)

(*continued*)

Black	18 (4.9)
Other	56 (15.1)
Marital status	
Married	280 (75.7)
Co-habiting	68 (18.4)
Single	19 (5.1)
Separated/widowed	3 (0.8)
Employment status†	
Full-time	224 (60.5)
Part-time	33 (8.9)
Student	27 (7.3)
Unemployed	31 (8.4)
Maternity leave	14 (3.8)
Other	40 (10.8)
Missing	1 (0.3)
Secondary education only	31 (8.4)
Income	
More than $120,000	84 (22.7)
81,000 - $120,000	58 (15.7)
41,000 - $80,000	98 (26.5)
Less than $40,000	72 (19.5)
Did not disclose	6 (1.6)

Note. BMI = Body Mass Index. *Participants that identified as a part of an ethnic group that represented <5% of the total sample were included in the 'Other' category of ethnicity. †Participants that listed a type of employment that represented <5% of the sample were included in the 'Other' category of employment.

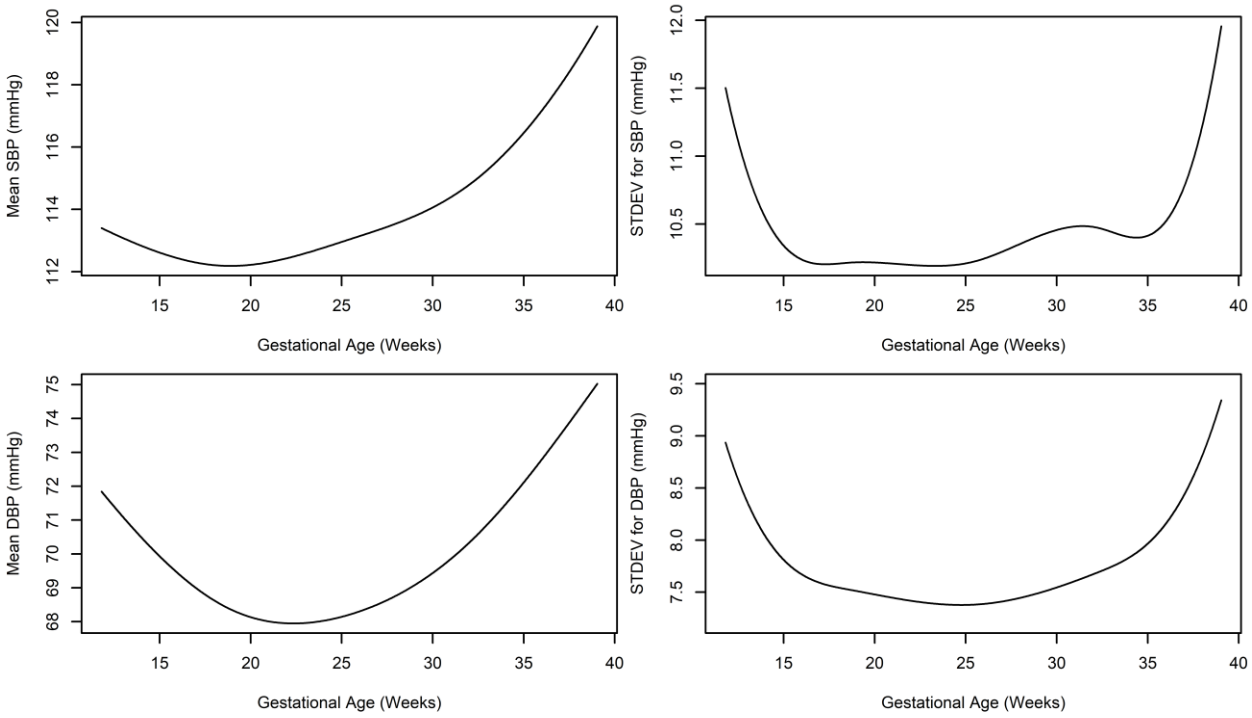

Figure 3.1. Functional descriptive statistics derived from the sample of curves (N=370). A, represents the mean functional curve of the systolic and diastolic blood pressure data across gestation (11.81-39.04 weeks of gestation). B, represents the standard deviation function of systolic and diastolic blood pressure and suggests that blood pressure has greater variability in early and late pregnancy, as compared to mid-pregnancy.

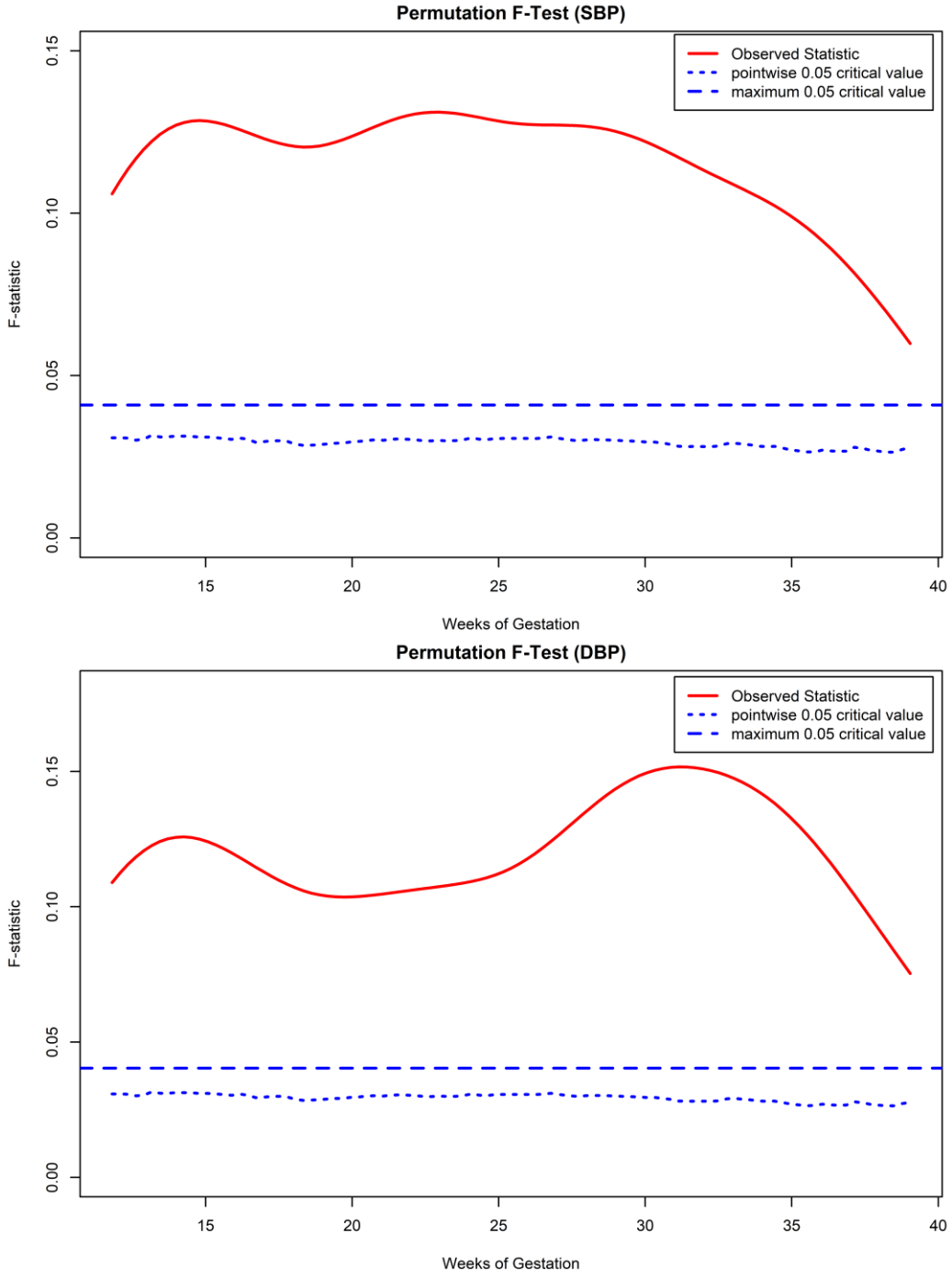

Figure 3.2. Results from the functional F-test for systolic (top) and diastolic blood pressure (bottom), and shows the maximum value of the observed test statistic (red line); pointwise critical value (dotted blue line), and the overall critical value based on the maximum of the test statistic (dashed blue line, determined using 200 permutations).

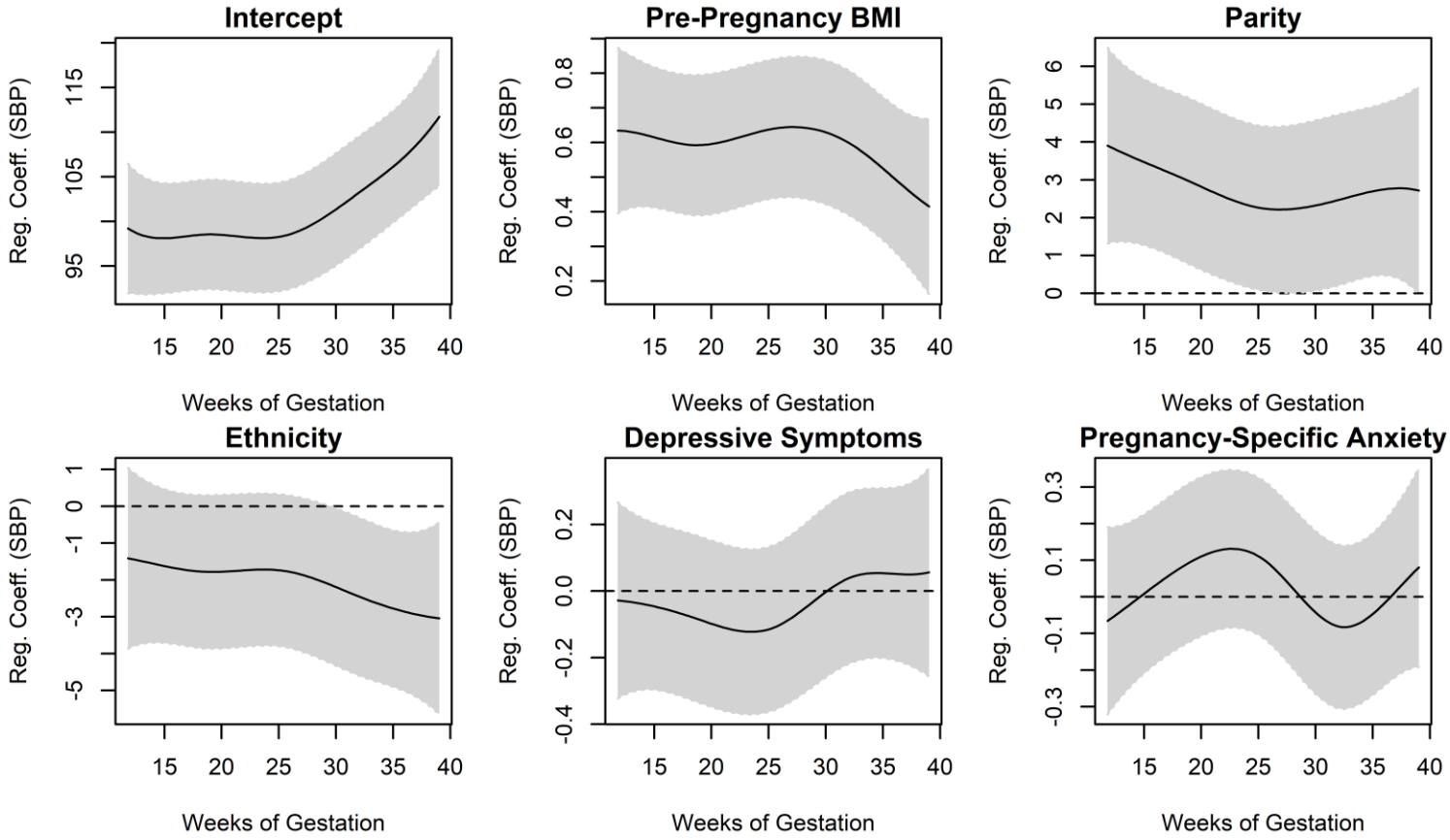

Figure 3.3. Regression coefficient functions predicting systolic blood pressure across gestation. **A,** greater pre-pregnancy BMI, and **B,** nulliparity was associated with higher blood pressure across gestation, but the effect was greater in early pregnancy. **C,** visible minority women had significantly lower blood pressure in late pregnancy. **D**, depressive symptoms and **E,** pregnancy-specific anxiety was not associated with systolic blood pressure.

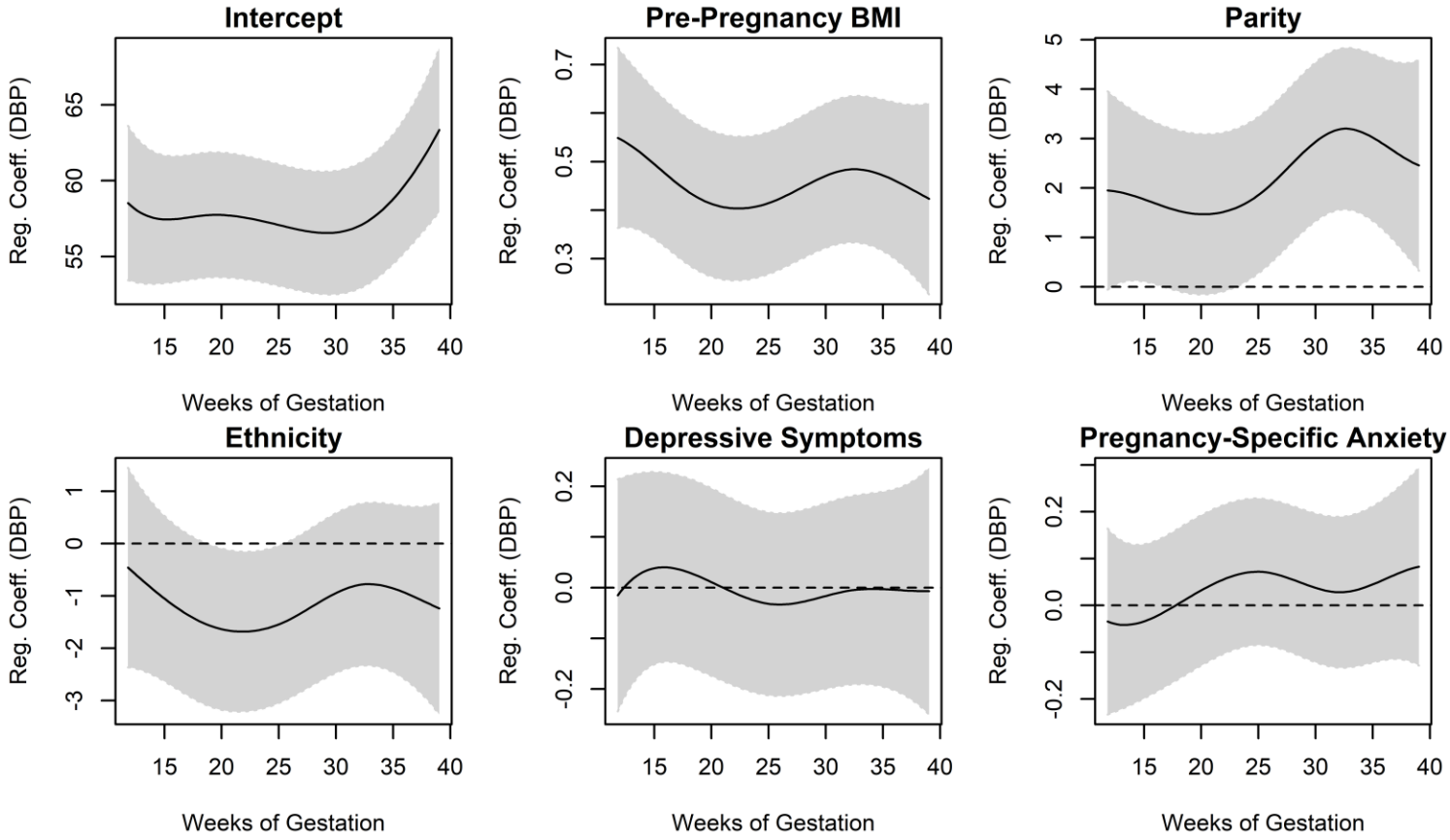

Figure 3.4. Regression coefficient functions predicting diastolic blood pressure across gestation. **A,** greater pre-pregnancy BMI was associated with significantly higher blood pressure, but the effect was greater in early and late gestation. **B,** primiparous women had significantly higher blood pressure in the second half of pregnancy. **C**, visible minority women had significantly lower blood pressure in mid-pregnancy. **D**, depressive symptoms and **E,** pregnancy-specific anxiety was not associated with diastolic blood pressure.

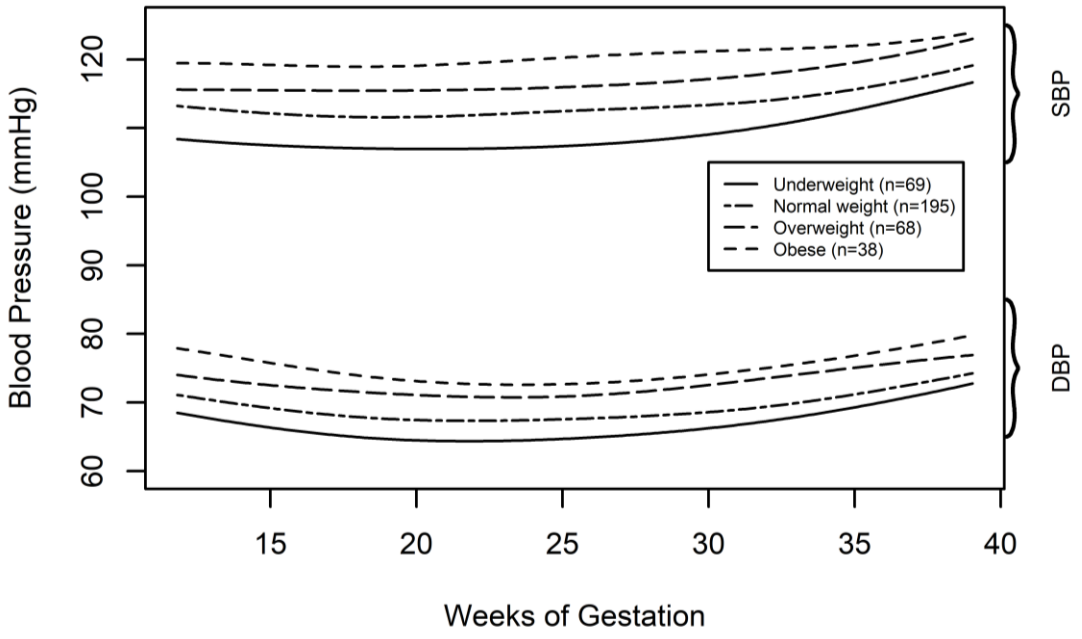

Figure 3.5. Mean systolic and diastolic blood pressure trajectories across gestation by pre-pregnancy BMI category (*N*=370).

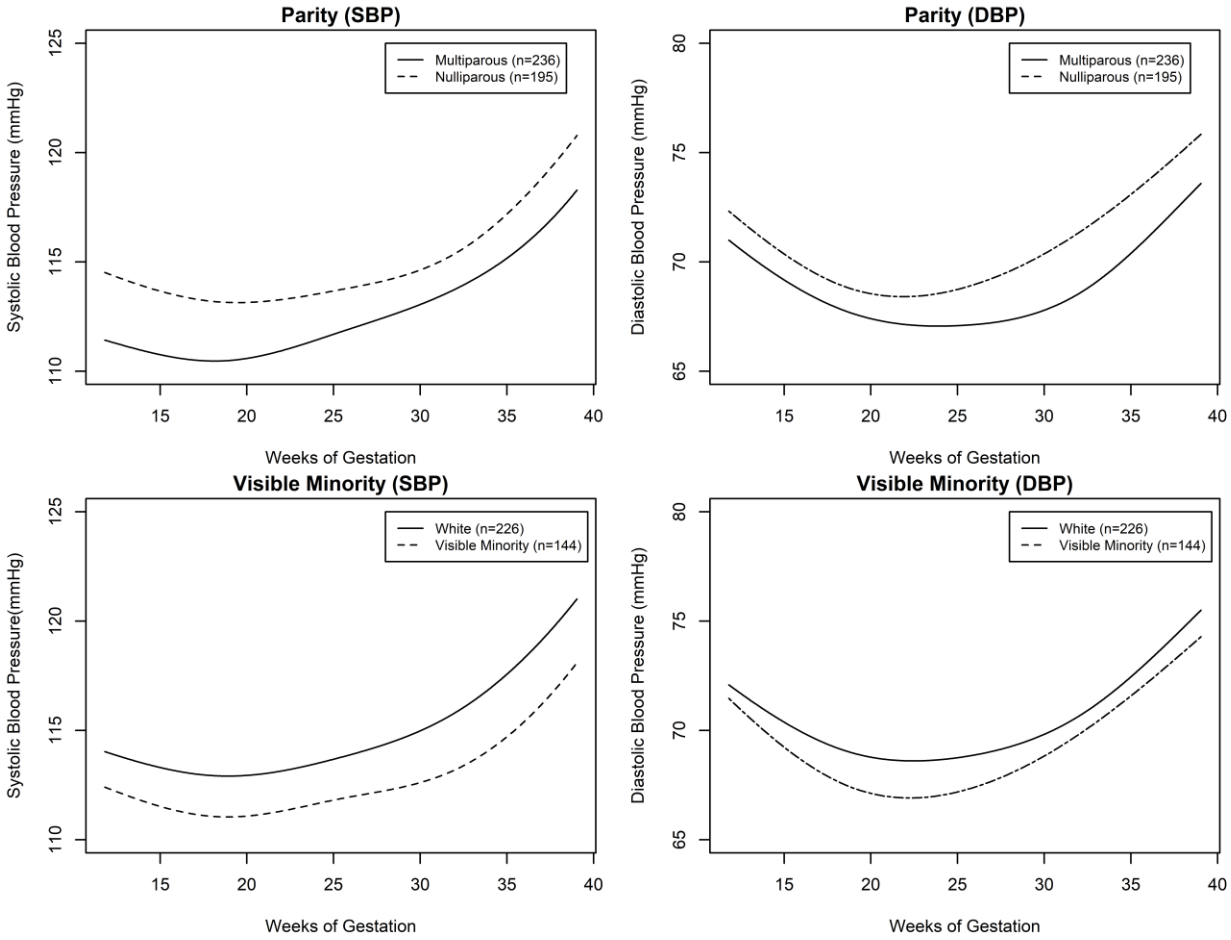

Figure 3.6. Mean systolic and diastolic blood pressure trajectories across gestation by parity and visible minority status (*N*=370).

General Discussion

Pregnancy is characterized by substantial change in maternal psychology and cardiovascular physiology. Despite links between maternal symptoms of depression and anxiety and HDP, and the overlap between these factors and risk for shorter gestational length, how they interact or influence one another in the prediction of birth outcomes, and whether symptoms of depression or anxiety impact blood pressure across gestation is not clear. Findings presented in this dissertation contribute to knowledge on the intersection of maternal psychological and cardiovascular health, and on statistical methodologies that can be applied to better model and describe dynamic, functional cardiovascular processes that unfold across gestation. Results from the present work are of particular relevance to obstetricians or clinical psychologists involved with clinical care of women with HDP, and to researchers who are interested in the construction and analysis of clinical health datasets. A summary of the main findings is presented below.

Summary of Results

In Manuscript 1, a secondary analysis of data available from the All Our Families Cohort was conducted and showed that the association between HDP and younger gestational age at birth increased alongside greater depressive symptom severity and state anxiety. These findings contribute to understanding on how maternal psychology interacts with maternal cardiovascular health during pregnancy to influence birth outcomes. Clinically, results also suggest that women with HDP and who report elevations in symptoms of depression or anxiety may represent a specific sub-group of women who may benefit from psychological services designed to alleviate distress related to a medically high-risk pregnancy. Although it is likely that psychological

services will help to reduce depressive or anxious symptoms, whether these interventions also lead to more favorable obstetrical outcomes is an intriguing question for future research.

In Manuscript 2, the aim was to identify a statistical method to adequately model and depict the dynamic changes in blood pressure across gestation that reduce sources of statistical bias in analysis and interpretation and made use of the largest proportion of available data. FDA was identified as a useful method that addressed limitations of multivariate analyses and was used to construct trajectories of maternal blood pressure from discrete blood pressure observations so that blood pressure was represented by curves across time. Results from a *f*PCA yielded three trajectories of blood pressure that captured >95% of variation among the curves. Two trajectories demonstrated some clinical utility among a subsample of participants for whom gestational age at birth was available. Consistent with previous research, a late-increase pattern of blood pressure was associated with younger gestational age at birth, while a prolonged-decrease pattern was associated with older gestational age at birth. Results of this study contribute to limited research demonstrating the usefulness of FDA for the analysis of blood pressure across pregnancy and many other cardiovascular processes.

One of the unique advantages of FDA is that functional regression analysis can be applied to examine how the effect of independent predictor variables changes across time. In Manuscript 3, functional regression was used to examine how maternal factors with established links to HDP (i.e., pre-pregnancy BMI, parity, and visible minority status) relate to blood pressure across gestation and contributed to this literature through inclusion of maternal symptoms of depression and anxiety. Results from functional regression analyses indicated that greater pre-pregnancy BMI and nulliparity were associated with higher blood pressure across

gestation, but that the effect was more pronounced at some timepoints over others. Visible minority status was associated with lower blood pressure, but only at specific timepoints in gestation relative to others. Maternal depressive symptoms and pregnancy-specific anxiety were not related to blood pressure across gestation, though based on previous research, further research is needed to examine whether this pattern of results is different in samples with pre-existing cardiovascular disease risk factors. These results contribute to knowledge on how maternal factors are implicated in blood pressure change across pregnancy and demonstrate how functional regression analysis could be applied to examine when in pregnancy maternal factors may exert the greatest influence on the maternal cardiovascular system.

Broader Strengths and Limitations

In combination, findings presented in this dissertation provide a more nuanced understanding of how maternal psychological and cardiovascular health relate across pregnancy. Results also highlight how much remains unknown about the complex processes that unfold across gestation. Strengths of the presented studies include large sample sizes, ecological validity through use of clinical diagnosis of HDP and clinical blood pressure data, and participant burden was reduced with use of self-report questionnaire assessments completed at home by paper (Manuscript 1) or online (Manuscripts 2 and 3). Although FDA improves on multivariate statistical methods used to construct maternal blood pressure trajectories, limited information can be extracted from curves with sparse, irregularly spaced observations across several months. Blood pressure curves that are constructed with, high quality, densely sampled blood pressure data are more useful and can be further analyzed with, for example, derivative estimations to identify important regions of blood pressure change. Similarly, more densely sampled data on

maternal mood, depression, or anxiety could be used to model the dynamic changes in maternal psychology across pregnancy.

Clinical blood pressure observations

In Manuscripts 2 and 3, there is some discussion about the limitations associated with clinical blood pressure data, but this topic warrants further discussion given the importance of observer training and standardized protocols for accurate blood pressure assessment in a clinical setting (Muntner et al., 2019). Issues related to measurement and data quality must be thoughtfully considered given the substantial sources of bias from the patient, observer, device, or recording (Kallioinen et al., 2017; Tolonen et al., 2015). When a researcher obtains clinical blood pressure data, many sources of bias are not able to be controlled or accounted for unless they are routinely recorded (e.g., time of assessment, baseline rest, participant mood, time of last meal). Devices used to assess blood pressure in pregnancy are also not typically validated for this sample (Bello et al., 2018). Many sources of measurement error can be addressed when blood pressure is measured in a laboratory setting with adherence to a strict protocol; in a clinical setting, these assessments can be quite different (James & Gerber, 2018; Kallioinen et al., 2017).

When bias estimates and measurement error combine with data selection or exclusion that in turn bias statistical analysis and results, it becomes essential for researchers to comment more thoroughly on these limitations. There is a tendency to minimally acknowledge the downsides of clinical blood pressure data, but how sources of measurement error and statistical bias may impact assessment, dataset construction, and statistical choices is not typically discussed at length (Farrar et al., 2019; Macdonald-Wallis et al., 2012; Macdonald-Wallis et al., 2011, 2014). One solution to overcome these limitations is to recruit samples of pregnant women

to participate in research studies where blood pressure observations can be obtained in a more controlled, laboratory environment. Although this is an attractive approach, the trade-off is less ecologically valid data that may not generalize back to a clinical setting where decisions about clinical care are made. A better alternative is to implement standardized assessment protocols for blood pressure assessment into obstetrical settings at the outset of a research study, to use validated and calibrated devices, and to incorporate observer training as a way to mitigate sources of bias (Muntner et al., 2019; Padwal et al., 2019). These are critical and relatively inexpensive solutions that will also lead to better clinical care.

Sex and gender differences in cardiovascular health research

Blood pressure is a complex phenomenon and it has only been 81 years since the American Heart Association and Cardiac Society of Great Brittan endorsed Nikolai Korotkoff's non-invasive, reproducible technique for blood pressure assessment as the standard for clinical practice (A Joint Report of the Committees Appointed by the Cardiac Society of Great Britain and Ireland and the American Heart Association, 1939). Since then, a proliferation of research has ensued across health disciplines and the predictive utility of blood pressure, as an index of cardiovascular health in the moment and later in the lifespan, has been solidified (James & Gerber, 2018). An accumulation of research on the adverse effects of hypertension on cardiovascular morbidity and mortality has led to widespread improvements in secondary prevention programs (e.g., antihypertensive medication, cardiac rehabilitation) that have been associated with decreased deaths due to cardiovascular disease in Canada (Campbell et al., 2009). These benefits, however, have been shown to disproportionately benefit men, and especially so during the reproductive years.

Cardiovascular disease research has a long history of excluding women from what was considered to be primarily a man's disease. Only in the last 25 years have researchers begun to understand the role of sex and gender in disease development, diagnosis, treatment, rehabilitation, and prevention (Garcia et al., 2016; Oosenbrug et al., 2016). Although there has been a substantial increase in understanding of sex differences in cardiovascular disease, today women remain under-researched, under-diagnosed, under-treated, and more likely to die prematurely of cardiovascular disease relative to men (Norris et al., 2020). A recent population based study on Canadian trends in hospitalization rates for cardiovascular disease and stroke from 2007 to 2016 showed that women aged 20 to 39 had a 25% relative increase in stroke hospitalization and were the only group to not show a statistically significant decline in hospitalization rate for coronary artery and vascular disease during the study period (Botly et al., 2020). The authors suggest that findings can be explained in part by increased rates of obesity and other cardiovascular risk factors (e.g., smoking, physical inactivity, type 2 diabetes), but that incidence of pregnancy-related stroke has also increased and likely contributes—approximately 30 per 100,000 pregnant women are affected by stroke, a rate three times higher than in young adulthood (Swartz et al., 2017). Other observed trends in the 20 to 39 age group include an increase in hospitalization for heart failure among men (+55% for men, +25.1% for women), and for acquired valvular heart disease in women (+65.7% for women, +15% for men). Although there are overall improvements, analysis of sex differences shows changing patterns of cardiovascular disease and stroke, and in particular among younger women during the reproductive years.

Gender and Sexual Orientation

There is a notion that sex and gender-based considerations are somewhat "cleaner" in pregnancy research, since the condition requires participants to be biologically female. Missing from this literature, however, are considerations of gender and sexual orientation. In the present work, mothers are referred to as women and she/her pronouns are used. This is because there was no assessment of gender identity in the self-report questionnaires. Similarly, there was no assessment of sexual orientation. We now know that members of the lesbian, gay, bisexual, transgender, queer/questioning (LGBTQ) community are disproportionately affected by mental health difficulties, including increased rates of depression and anxiety among sexual minority women (Steele et al., 2009). Research has also shown that sexual minority women specifically are more likely to exhibit greater cardiovascular risk factors such as higher BMI, current or former smoking, and to report a family history of cardiovascular disease (Boehmer et al., 2007; Caceres et al., 2017; Farmer et al., 2013). Recent population-based research from the United States documented disparities in birth outcomes among bisexual and lesbian couples, such that these women were more likely to report preterm birth (OR=1.84, 95% CI 1.11, 3.04) and low birthweight (2.64, 95% CI 1.38, 5.07), relative to heterosexual women (Everett et al., 2019). In light of psychological and cardiovascular health inequities among sexual minority women, it is prudent for pregnancy researchers to incorporate sex- *and* gender-based considerations into research design, analysis, and interpretation.

Perspectives on Maternal Psychology

Canadians with cardiovascular disease are twice as likely to experience concurrent depression, and the link between depression and adverse cardiovascular health outcomes is

graded such that increasing severity is associated with even greater risk (Hare et al., 2014). Likewise, meta-analytic studies show that baseline anxiety in initially healthy adults is associated with a 26% increased risk of incident coronary heart disease, and a 48% increased risk of cardiac death over 11 years, after accounting for demographic, biological, and health behaviours (Roest, Martens, de Jonge, & Denollet, 2010). Hypertension that develops during pregnancy a potent risk factor for adverse maternal psychological and cardiovascular health outcomes. Maternal symptoms of depression and anxiety have been linked with the onset of hypertensive disorders during pregnancy (Shay et al., 2020), and women who develop these complications are at a 2-fold increase in risk of coronary heart disease and cardiovascular disease death, and 1.8-fold increase in risk of stroke (Wu et al., 2017). Women with hypertensive disorders and co-occurring depression are at even greater risk for adverse obstetrical outcomes, relative to women who have hypertension but not depression (Mogos et al., 2019). Integration of these data suggests that women diagnosed with hypertensive disorders and who report greater symptoms of depression or anxiety represent a subsample of pregnant women at even greater cardiovascular risk across their lifespan. These women may also stand to benefit substantially from integration of psychological services into their obstetrical care.

Assessment of maternal symptoms of depression and anxiety

Across the three studies presented in this manuscript, a significant limitation is that maternal symptoms of depression, state anxiety, and pregnancy-specific anxiety were assessed at only two to three timepoints, and that these timepoints differed from when blood pressure was observed or the diagnosis of HDP was made. Although self-report questionnaires provide a snapshot of maternal mental health at one point in time, symptoms of depression and anxiety are known to differ over the course of gestation (Bayrampour, Tomfohr, et al., 2016; McCall-

Hosenfeld et al., 2016; Tomfohr et al., 2015). Studies designed to assess patterns of depression and anxiety across pregnancy suffer much of the same limitations as clinical blood pressure observations. Self-report or diagnostic assessments are typically conducted at relatively sparse, unequally spaced intervals and at different timepoints across gestation, usually once in each trimester. Additionally, prospective, longitudinal questionnaire studies designed to assess maternal psychological symptoms are expensive, prone to selection bias (i.e., low-risk samples), and subject to greater participant attrition as time goes on.

Like blood pressure, mood and anxiety are functional in nature—these processes can also ostensibly be observed at any point in time and thus are probably best represented by curves across time, too. Measures of maternal symptoms of depression or anxiety, general ratings of mood, affect or stress, and distress all reflect underlying, dynamic processes that are under constant psychological and physiological regulation. These processes are inextricably and necessarily linked. Ideally, observations of maternal mood or anxiety and cardiovascular function occur at the same frequency and timepoints across gestation. Then, FDA can be used to model how these factors change or covary across time, what biopsychosocial factors relate to changes in maternal psychological or cardiovascular function across pregnancy, and when they matter most. Current assessment tools such as those used in the present study are insufficient. Commonly used measures such as the EPDS and SAI only scratch the surface of what is going on psychologically during pregnancy and leave out important physical changes that vary dramatically between women. Although pregnancy-related distress questionnaires seem to better capture the unique psychophysiological changes that occur, these measures are only used in research settings. Despite measurement and assessment limitations in this literature, researchers have uncovered small, but significant effects of symptoms of depression or anxiety on maternal

cardiovascular health and these findings contribute to a useful foundation of knowledge to build upon.

There is another conceptualization to consider. The fields of behavioral medicine and health psychology typically examine the downstream effects of higher-order emotional functioning on health behaviours and physical disease states. Within the context of pregnancy, there is more evidence to suggest that maternal physical health and medical complications produce reliable disruptions in maternal psychological functioning. This slight shift in thinking alters the theoretical framework and has implications for research methodology and sample selection. For example, instead of identifying participants based on elevations in symptoms of depression or anxiety, select those at high risk for medical complications due to pre-existing cardiovascular or psychological risk factors, or with new onset of hypertension. Within this framework, there is also a shift from intervention to prevention, since researchers will be more likely to capture women before onset or recurrence of psychological difficulties like depression or anxiety. Clinicians can then work to temper distress as it arises—strike when the iron is cold, or at least warm—and help women integrate pregnancy complications into their broader psychology and systems of meaning.

Some considerations of the psychology of pregnancy

The section heading is the title of an article published by Dr. Grete L. Bibring (b. Vienna, Austria 1899, d. Boston, MA 1977), a medical doctor and psychoanalyst who trained at the University of Vienna in 1918 and went on to become the first woman appointed as Full Clinical Professor at Harvard Medical School in 1961. The title was stolen on purpose and with affection,

to honour her seminal work on the psychology and physiology of pregnancy (Bibring, 1959). In this manuscript, Dr. Bibring exquisitely describes pregnancy as a maturational crisis:

> Pregnancy is a crisis that affects all expectant mothers, no matter what their state of psychic health. Crises, as we see it, are turning points in the life of the individual, leading to acute disequilibria which under favorable conditions result in specific maturational steps toward new functions. We find them as developmental phenomena at points of no return between one phase and the next when decisive changes deprive former central needs and modes of living of their significance, forcing the acceptance of highly charged new goals and functions. Pregnancy as a major turning point in the life of the woman represents one of these normal crises, especially for the primigravida who faces the impact of this event for the first time. We believe that all women show what looks like remarkable, far-reaching psychological changes while they are pregnant. The outcome of this then, has profound effects on the early mother-child relationship. (p. 119).

Pregnancy is not rare, but it is psychologically and physiologically unique. A woman's mind and body effortfully adapt to constant states of change and new ways of being within the context of a broader shift in life meaning. A woman must begin to reconcile this maturational crisis almost immediately as she begins to psychologically invest and prepare for motherhood. In contrast with situational crises such as a near-death experience—where time leads to psychological distance from injury or trauma—there is also a state of permanency, an inevitability that comes with pregnancy in that a woman will now always be a mother. Self-concept and identity are reformed and redefined by how she sees herself through the eyes of a child who knows nothing about her. These are profoundly complex, referential processes for women without psychopathology or medical complications.

In the face of identification of actual or threatened maternal or fetal life-limiting conditions, the pregnancy experience is transformed and intensity of emotion is amplified with greater fear, shame, guilt, anger, hopelessness, anxiety, and depression (Wool, 2013). Findings from qualitative literature describe how maternal hypertensive disorders have a 'whole person' impact on a woman (Duffy et al., 2019). Importantly, women with lived experience of hypertension during pregnancy report that obtaining help to reduce the emotional burden is an important part of recovery, but that emotional aspects are rarely reported as treatment outcomes (Duffy et al., 2019; Duffy et al., 2017). Common psychological themes in the literature that does exist include feeling fearful of dying; guilt and frustration in relation to separation from infants and loved ones; disrupted parent and baby bonding; elevated symptoms of post-traumatic stress disorder; and reduced confidence about being a mother (Duffy et al., 2019; East et al., 2011; Kehler et al., 2016; Leeners et al., 2008, 2015; Mukwenda et al., 2017; Værland et al., 2018; Værland et al., 2016). Note that these emotions are impressed upon the already delicate process of maternal identity development.

When the process of pregnancy is augmented by a medical complication and matters of life meet matters of disease or potential death, greater psychological complexity is to be expected. In this case, a woman must navigate maturational and situational crises that coalesce immediately upon identification of a pregnancy complication. The resolution of these crises relies solely on an existing psychological reserve stockpiled by her past and present life circumstances. Referential processes that create new life meaning through the maternal-fetal experience—intertwining of object, thought, sensory perception, and emotional states that belong to one another—suddenly unfold differently. Systems of meaning are thwarted; the paradigm shifts. In the face of this *referential crisis*, psychological investment into new goals and functions

may cease, dampen, or intensify depending on the pre-existing maternal psychological foundation and current psychosocial supports. These are essentially perfect conditions for increased distress that, in absence of effective coping and support, may lead to long-term psychological disruption.

What does this mean for clinical care? Although a broader discussion of access to psychological services in Canada is beyond the scope of this dissertation, it is of particular relevance within the context of a medically high-risk pregnancy and especially for women with a hypertensive disorder. Despite increased attention and awareness, decreased stigma, and screening recommendations for depressive symptoms (ACOG, 2018), there is a devastating lack of mental health resources available for these women. During the reproductive years (i.e., aged 25 to 44), women are twice as likely to be diagnosed with mood disorders compared to men (Pearson et al., 2013). Psychological services are not systematically integrated into provincial healthcare systems, so most Canadians will have to pay out of pocket for these services, with minimal contributions from employee benefit programs. This system contributes to mental health inequities because there is unequal access to services, and women may be disproportionately affected by the lack of available mental healthcare during the reproductive years, a time when they are more likely to be diagnosed with depression and to ask for help (Eid et al., 2019).

Historically and presently, pregnant women and women with cardiovascular disease are under-researched and underserved populations (Arnott et al., 2020; Norris et al., 2020). To address the important role of sex and gender in health research, there has been a push from funding agencies such as the Canadian Institutes of Health Research to ensure that researchers consider sex-specific factors in study design and statistical analysis and reporting. Across Canada, there is increased awareness of women's heart health through campaigns with the Heart

& Stroke Foundation of Canada (www.heartandstroke.ca), and through the development of the Canadian Women's Heart Health Alliance (https://cwhhc.ottawaheart.ca/national-alliance/cwhha). These government and non-profit initiatives to improve women's heart health are combined with calls to action from grass-roots organizations like the Canadian Perinatal Mental Health Collaborative (https://cpmhc.ca/) who recently petitioned the Federal Government to develop a National Perinatal Mental Health Strategy, but to no avail.

There is an unquestionable need to identify a point of entry for clinical health psychologists in high-risk obstetrical settings. Women with medically high-risk pregnancies, and perhaps especially those who develop a hypertensive disorder, are a population that stands to benefit from integrated psychological services into their prenatal and postpartum care. The combination of clinical and research skills of a psychologist can be leveraged to better understand the psychophysiological nexus of pregnancy and organize access to psychological services for women who want them. Questions about how psychology changes in the face of medical complications, as cause or consequence, can be more efficiently asked and answered from within rather than alongside a healthcare system. Embedment of researchers into a clinical setting leads to improved clinical care, knowledge generation and translation, and increased organizational research capacity (Vindrola-Padros et al., 2017). Whether integration of clinical psychologists lead to short- or long-term improvements in maternal psychological and cardiovascular health during pregnancy and postpartum is an intriguing question. It is difficult to imagine that incorporation of clinical psychology into high-risk obstetrical settings will do harm or produce no benefit at all, and nearly impossible to consider all the ways improved maternal mental health services could benefit women's health across the lifespan.

Conclusion

This dissertation contributes to knowledge on the inextricable link between maternal psychology and physiology. Findings from the presented research studies suggest that maternal symptoms of depression or anxiety augment the physiological process of pregnancy and lead to shorter gestation among women with a hypertensive disorder of pregnancy. Functional data analytic techniques are described and applied as a useful statistical method that better captures the dynamic process of maternal blood pressure regulation that occurs as a woman's heart and vasculature adapt to the developing fetus. Then, functional regression is used to understand how different factors relate to cardiovascular processes over time. Combined, this work makes a theoretical contribution to the fields of clinical psychology, obstetrical medicine, and women's cardiovascular health through a broader discussion of the links among them. The importance of maternal psychology during the reproductive years is underscored, and issues related to assessment of maternal depression, anxiety, and distress are discussed. A conceptualization is proposed for how life meaning systems inform the transition to motherhood, and for why psychological distress will arise when there is a sudden change in referential processes required for maternal identity development. With integration of clinical psychology into obstetrical settings, research studies to understand how maternal psychology interacts with cardiovascular health during pregnancy can be better designed and executed, and access to psychological services will improve. Repeated observations of maternal psychological constructs and cardiovascular function can then be assessed at the same time, and modelled more elegantly, to better understand how psychophysiological experiences weave together and what happens to the tapestry when internal systems are disrupted.

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Appendix I

EDINBURGH SCALE
Cox, Holden, Sagovsky, University of Edinburgh

As you are expecting a baby, or have recently had a baby, we would like to know how you are feeling. Please indicate the answer which comes the closest to how you have felt IN THE PAST 7 DAYS, not just how you feel today.

IN THE PAST 7 DAYS

1. Have you been able to laugh and see the funny side of things:

_____ as much as I always could
_____ not quite so much now
_____ definitely not so much now
_____ not at all

2. Have you looked forward with enjoyment to things:

_____ as much as I ever did
_____ rather less than I used to
_____ definitely less than I used to
_____ hardly at all

3. Have you blamed yourself unnecessarily when things went wrong:

_____ yes, most of the time
_____ yes, some of the time
_____ not very often
_____ no, never

4. Have you been anxious or worried for no good reason:

_____ no, not at all
_____ hardly ever
_____ yes, sometimes
_____ yes, very often

5. Have you felt scared or panicky for no very good reason:

_____ yes, quite a lot
_____ yes, sometimes
_____ no, not much
_____ no, not at all

6. Have you felt like things have been getting on top of you:

_____ yes, most of the time I haven't been able to cope at all
_____ yes, sometimes I haven't been coping as well as usual
_____ no, most of the time I have coped quite well
_____ no, I have been coping as well as ever

7. Have you been so unhappy that you have had difficulty sleeping:

_____ yes, most of the time
_____ yes, sometimes
_____ not very often
_____ no, not at all

8. Have you felt sad or miserable:

_____ yes, most of the time
_____ yes, quite often
_____ not very often
_____ no, not at all

9. Have you been so unhappy that you have been crying:

_____ yes, most of the time
_____ yes, quite often
_____ only occasionally
_____ no, never

10. Has the thought of harming yourself occurred to you:

_____ yes, quite often
_____ sometimes
_____ hardly ever
_____ never

Appendix II

State Anxiety Inventory (SAI)

Directions: Please read the statements below and then circle the number that corresponds with how you feel right now, that is at this moment. There are no right c wrong answers. Use the following scale

1 = Not at all
2 = Somewhat
3 = Moderately
4 = Very much

1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I am regretful	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel rested	1	2	3	4
9. I feel anxious	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel “high strung”	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel over-excited and “rattled”	1	2	3	4
19. I feel joyful	1	2	3	4
20. I feel pleasant	1	2	3	4

Appendix III

Revised Prenatal Distress Questionnaire

At this point in your pregnancy, are you feeling bothered, upset, or worried about....:

		Not at all	Somewhat	Very much
1.	... the effect of ongoing health problems such as high blood pressure or diabetes on your pregnancy?	0	1	2
2.	...feeling tired and having low energy during your pregnancy?	0	1	2
3.	...pregnancy related medical costs	0	1	2
4.	...changes in your weight and body shape during pregnancy?	0	1	2
5.	...whether you might have an unhealthy baby?	0	1	2
6.	...physical symptoms of pregnancy such as vomiting, swollen feet, or backaches?	0	1	2
7.	...the quality of your medical care during pregnancy?	0	1	2
8.	...working or caring for your family during pregnancy?	0	1	2
9.	...whether the baby might be affected by alcohol, cigarettes, or drugs that you have taken?	0	1	2
10.	... whether the baby might come too early?	0	1	2
11.	...changes in your relationships with other people due to having a baby?	0	1	2
12.	...paying for the baby's clothes, food, or medical care?	0	1	2
13.	...taking care of a newborn baby?	0	1	2
14.	...pain during labor and delivery?	0	1	2
15.	...what will happen during labor and delivery?	0	1	2
16.	...working at a job after the baby comes?	0	1	2
17.	...getting day care, babysitters, or help to watch the baby after it comes?	0	1	2

whole-heartedness

(n.) a referential process to create meaning where there may initially be none.

pronunciation /ˌhəʊlˈhɑːtɪdnəs/