Examining patterns of gestational diabetes and gestational hypertension as risk indicators of cardiometabolic disease following two consecutive pregnancies

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Dedication

This doctoral thesis is dedicated to my beloved parents and cherished girlfriend, whose unwavering support and boundless love have sustained me throughout my academic journey. Their encouragement, sacrifices, and belief in my abilities have been the cornerstone of my success, providing me with the strength and motivation to persevere in the face of challenges.

To my dear parents, your constant guidance, understanding, and endless encouragement have been my guiding light. From the earliest stages of my education to the culmination of my doctoral studies, you have been my pillars of strength, always cheering me on and instilling in me the belief that I could achieve anything I set my mind to. Your support has been a source of inspiration, and I am eternally grateful for the countless sacrifices you have made to ensure my academic pursuits were realized.

To my beloved girlfriend, Kelly, your unconditional love, patience, and understanding have been my source of comfort and motivation. Your steadfast belief in me, even during moments of doubt, has propelled me forward and given me the courage to pursue my dreams. Your unwavering presence by my side, cheering me on through the highs and lows, has been a constant reminder of the love that fuels my ambitions.

These two support systems have undeniably shaped not only my academic endeavors but also my character and resilience. I am forever indebted to them for their love, guidance, and firm beliefs in me.

"Let us not become weary in doing good, for at the proper time we will reap a harvest if we do not give up." ~ Galatians 6:9 ~

"I have fought the good fight, I have finished the race, I have kept the faith." ~ 2 Timothy 4:7 ~

Abstract

Cardiometabolic disease (CMD) refers to a cluster of interrelated conditions that affect the cardiovascular system and metabolism, and arises from a combination of genetic predisposition, lifestyle factors (e.g., suboptimal dietary habits, physical inactivity, and smoking), and environmental influences (e.g., social environment, resources, neighborhood walkability, access to healthcare, etc.). Insulin resistance is a key CMD driver, contributing to elevated glucose levels, abnormal lipid levels, and elevated blood pressure, among other metabolic abnormalities. Among women of reproductive age, gestational diabetes (GDM) and gestational hypertension (GHTN) are pregnancy-related indicators of diabetes, hypertension, and cardiovascular disease (CVD), which are included under the umbrella term, CMD. However, knowledge gaps exist in terms of their implications beyond an ever occurrence/never occurrence dichotomy that is applied when performing risk assessments in clinical practice, irrespective of the number of occurrences and the number of pregnancies. This thesis focuses on women with at least two consecutive singleton livebirth pregnancies (between April 1, 1990 and December 31, 2012; followed up to April 1, 2019), to enhance comparability in terms of baseline CMD risk, which can vary with parity and is increased with infertility. The overarching aim is to examine all patterns of absence, new onset, and recurrence of GDM and/or GHTN (with or without preeclampsia) and their associations with maternal diabetes, hypertension, and CVD (myocardial infarction, stroke and unstable angina) development. Across the three retrospective cohort studies that I conducted, I used the province of Quebec's health administrative and vital statistics (birth, stillbirth, and death registries, as applicable) data from nearly half a million women, their two offspring, and their partners (fathers of the offspring pair), and evaluated outcomes over a median of 11 years (hypertension), 11.5 years (diabetes), and 16.5 years (CVD).

The **first** manuscript examined the association of GDM patterns across two pregnancies (none, first pregnancy only, second pregnancy only, both pregnancies) with the development of diabetes. I examined 431,980 Quebec women with two consecutive singleton livebirth deliveries and no history of diabetes, hypertension, or CVD before or between pregnancies. I built Cox proportional hazards (PH) models that accounted for GHTN and other pregnancy complications, among other co-variates. Limitations of Quebec's health administrative and vital statistics databases include lack of information on adiposity and health behaviors, such as smoking status. To address limitations in these health administrative data, I incorporated simple sensitivity bias analyses to perform indirect adjustments for obesity and smoking, using external cohort data from the 2004 Canadian Community Health Survey

(CCHS), Cycle 2.2. I demonstrated conclusive associations (hazard ratios [HR] and 95% confidence intervals [CI]) of GDM patterns and subsequent diabetes development that indicated increased hazards with GDM in the first pregnancy only, higher with GDM in the second pregnancy only, and highest with GDM in both (GDM_{FIRST}=4.35 [4.06-4.67]; GDM_{SECOND}=7.68 [7.31-8.07]; GDM_{BOTH}=15.8 [15.0-16.6], compared to women without GDM in either pregnancy). Furthermore, conclusive differences across exposure groups persisted when I modified the reference group to allow other direct comparisons between exposure groups to be drawn. History of a GHTN occurrence was also associated with diabetes development, as were preterm delivery, large for gestational age (LGA) offspring, and partner history of diabetes. Overall, indirect adjustments for obesity slightly attenuated HRs, while indirect adjustments for smoking did not importantly affect HRs.

I applied a similar approach using the same cohort to examine associations of GHTN with incident chronic hypertension in the **second** manuscript. GHTN represents new-onset blood pressure elevation in pregnancy and may occur with preeclampsia, which is characterized by placental and systemic vascular dysfunction causing organ injury, or without it. Therefore, in addition to examining GHTN with or without preeclampsia (combined), I also created two additional subcohorts of women, one which excluded those with GHTN without preeclampsia (N=412,735; women without any GHTN in either pregnancy, and those with preeclampsia in either pregnancy), and the other which excluded those with preeclampsia (N=414,875; women without any GHTN in either pregnancy, and those with GHTN without preeclampsia in either pregnancy). I used Cox PH models to estimate HRs, accounting for GDM and other adverse pregnancy occurrences, among other co-variates. I demonstrated conclusive associations between GHTN, with or without preeclampsia, and chronic hypertension, with elevated hazards for GHTN in the first pregnancy, higher with GHTN in the second, and highest for GHTN in both ($GHTN_{FIRST}$=2.67 [2.57-2.78]; $GHTN_{SECOND}$=4.85 [4.61-5.11]; $GHTN_{BOTH}$=7.25 [6.90-7.63], compared to women without GHTN in either pregnancy), paralleling the findings I delineated for associations between GDM and diabetes. Patterns and estimates were similar for the two subcohorts described above. History of a GDM occurrence was also associated with hypertension development, as were preterm delivery, small for gestational age (SGA) and LGA offspring, and partner history of hypertension, diabetes or CVD. Similar to Manuscript 1, indirect adjustments for obesity slightly attenuated HRs, while indirectly adjusting for smoking did not importantly influence my effect estimates.

The **third** manuscript examined the associations of GDM and GHTN (with or without preeclampsia) across two pregnancies with the development of CVD. Considering the presence or absence of GDM and of GHTN across two pregnancies resulted in 16 exposure categories. I opted to evaluate these categories as a secondary analysis and instead focused on the cumulative number of GDM and GHTN occurrences across two pregnancies in relationship to CVD for my primary analyses. I made this decision in recognition of the challenges that readers may face in interpreting 16 unique exposure categories and their respective HRs. In the same study cohort, utilizing Cox PH models, I observed that an increased number of occurrences of GDM and GHTN were associated with elevated hazards for CVD, in a stepwise pattern (1 occurrence=1.47 [1.35-1.61]; 2 occurrences=1.91 [1.68-2.17]; ≥3 occurrences=2.93 [2.20-3.90], compared to women without GDM and GHTN in either pregnancy). Indirect adjustments for obesity and smoking slightly attenuated these HRs.

In the **fourth** manuscript, I conducted a scoping review that addresses the evolving algorithms for GDM screening, by collating guidelines released by major Canadian obstetric and diabetes organizations, highlighting shifts in their recommendations over time. This scoping review documents that variations in screening and diagnostic approaches existed between Diabetes Canada and the Society of Obstetricians and Gynecologists of Canada. Through the influence of the Hyperglycemia and Adverse Pregnancy Outcome study, these disparities have diminished, and many Canadian physicians now adhere to recent recommendations, as I demonstrated through a physician survey. Furthermore, given that the use of diagnostic codes to identify GDM (in Manuscripts 1 through 3) may be influenced by these temporal trends in guideline recommendations that I identified, I conducted additional analyses to examine if including the calendar year of each pregnancy (at 20 weeks' gestation) impacted the effect estimates in each of my models. I observed no important differences in the associations of GDM with each of the assessed outcomes when attempting to account for temporal trends in the screening and diagnosis of GDM.

In conclusion, this thesis underscores that in women who have two or more singleton livebirth deliveries, representing over half of women globally, consideration of GDM and GHTN occurrences or absences in each pregnancy can further nuance estimates of future diabetes, hypertension, and CVD risk. These findings may permit personalized risk estimation, enabling clinicians and patients to determine the urgency and importance of preventive interventions and close surveillance.

Résumé

La maladie cardiométabolique (CMD) fait référence à un ensemble de conditions interdépendantes qui affectent le système cardiovasculaire et le métabolisme, et qui résultent d'une combinaison de prédispositions génétiques, de facteurs liés au mode de vie (par exemple, mauvaise alimentation, inactivité physique et tabagisme) et d'influences environnementales. Les composantes clés de la maladie cardiométabolique comprennent la résistance à l'insuline, les niveaux anormaux de lipides, l'élévation de la pression artérielle et l'obésité. Chez les femmes en âge de procréer, le diabète gestationnel (GDM) et l'hypertension gestationnelle (GHTN) sont des indicateurs liés à la grossesse du risque de développement de diabète, d'hypertension et de maladie cardiovasculaire (CVD), reconnus sous le terme générique de CMD. Cependant, il existe des lacunes de connaissances en ce qui concerne leurs implications dans ces risques au-delà de celles d'une dichotomie d'apparition antérieure (oui/non), l'implication de leurs nombres d'apparitions en dedans d'un nombre déterminé de grossesses étant inconnu. Cette thèse se concentre sur les femmes ayant eu au moins deux grossesses uniques consécutives pendant une période déterminée (entre le 1er avril 1990 et le 31 décembre 2012 ; suivi jusqu'au 1er avril 2019), afin d'améliorer la comparabilité en termes de risque de CMD de base, qui peut varier avec la parité et augmente avec l'infertilité. L'objectif principal de la thèse est d'examiner les différents profils de GDM/GHTN chez ces femmes allant de l'absence, à une première occurrence et à la récurrence du GDM/GHTN (GHTN étant avec ou sans prééclampsie) et leurs associations avec le développement du diabète, de l'hypertension et du CVD (infarctus du myocarde, accident vasculaire cérébral, angine instable) chez la mère. À travers les trois études de cohorte rétrospectives que j'ai menées, j'ai utilisé des données administratives de santé et de statistiques vitales (registres de naissance, de mortinaissance et de décès, le cas échéant) de la province de Québec provenant de près d'un demi-million de femmes, de leurs deux enfants et de leurs partenaires (pères de ces enfants), et j'ai évalué les résultats sur une période médiane d'environ 11 ans (hypertension), 11,5 ans (diabète) et 16,5 ans (CVD).

Dans le premier manuscrit j'ai examiné l'association des profils de GDM à travers deux grossesses (aucune, première grossesse seulement, deuxième grossesse seulement, les deux grossesses) avec le développement du diabète. J'ai examiné 431 980 femmes québécoises avec deux accouchements consécutifs de bébés uniques et sans antécédents de diabète, d'hypertension ou de CVD avant ou entre les grossesses. J'ai construit des modèles de risques proportionnels de Cox (PH) qui tenaient compte de GHTN et d'autres complications de la grossesse, parmi d'autres covariables. Pour pallier

les limites des données administratives de santé, j'ai utilisé des analyses de biais pour effectuer des ajustements indirects pour l'obésité et le tabagisme, en utilisant des données de cohorte externes de l'Enquête sur la santé dans les collectivités canadiennes (CCHS) de 2004, Cycle 2.2. J'ai démontré des associations concluantes (rapports de risque [HR] et intervalles de confiance à 95 % [CI]) des profils de GDM et du développement subséquent du diabète qui indiquaient des risques accrus chez les femmes avec le GDM lors de la première grossesse seulement, des risques plus élevés chez celles avec le GDM lors de la deuxième grossesse seulement, et des risques les plus élevés chez celles avec le GDM dans les deux grossesses ($GDM_{PREMIERE}$=4,35 [4,06-4,67] ; $GDM_{DEUXIEME}$=7,68 [7,31-8,07] ; GDM_{TOUS}=15,8 [15,0-16,6] par comparaison aux femmes sans GDM dans aucune des grossesses). De plus, des différences concluantes entre les groupes d'exposition ont persisté lorsque j'ai modifié le groupe de référence. L'antécédent d'une occurrence de GHTN était également associé au développement du diabète, tout comme l'accouchement prématuré, les nouveau-nés de grande taille pour l'âge gestationnel et l'antécédent de diabète du partenaire. Dans l'ensemble, les ajustements indirects pour l'obésité ont légèrement atténué les HR, tandis que les ajustements indirects pour le tabagisme n'ont pas affecté de manière importante les HR.

J'ai appliqué une approche similaire en utilisant la même cohorte pour examiner les associations du GHTN avec l'hypertension chronique incidente dans le deuxième manuscrit. Le GHTN représente une élévation nouvelle de la pression artérielle pendant la grossesse et peut survenir avec ou sans la prééclampsie, caractérisée par une dysfonction vasculaire placentaire et systémique entraînant des lésions d'organes. Par conséquent, en plus d'examiner le GHTN avec ou sans la prééclampsie (combinée), j'ai également créé deux sous-groupes supplémentaires de femmes, l'un excluant celles ayant eu une GHTN sans prééclampsie (N=412 735; femmes sans aucun GHTN dans aucune des grossesses, et femmes avec prééclampsie dans l'une ou l'autre des grossesses), et l'autre excluant celles ayant eu une prééclampsie (N=414 875; femmes sans aucun GHTN dans aucune des grossesses, et femmes avec GHTN sans prééclampsie dans l'une ou l'autre des grossesses). J'ai utilisé des modèles de risques proportionnels de Cox pour estimer les rapports de risque, en tenant compte du GDM et d'autres occurrences d'évènements indésirables de grossesse. J'ai démontré des associations concluantes entre le GHTN, avec ou sans prééclampsie, et la survenue de l'hypertension chronique, avec des risques accrus pour le GHTN lors de la première grossesse, des risques plus élevés avec le GHTN lors de la deuxième grossesse, et des risques encore plus élevés pour le GHTN dans les deux grossesses, parallèlement aux résultats que j'ai décrits pour les associations entre le GDM et le diabète

($GHTN_{PREMIERE}$=2,67 [2,57-2,78] ; $GHTN_{DEUXIEME}$=4,85 [4,61-5,11] ; $GHTN_{TOUS}$=7,25 [6,90-7,63] par rapport à l'absence du GHTN dans les deux grossesses). Les profils et les estimations étaient similaires pour les deux sous-groupes décrits ci-dessus. L'antécédent d'une occurrence de GDM était également associé au développement de l'hypertension, tout comme l'accouchement prématuré, les nouveau-nés petits ou grands pour leur âge gestationnel, et l'antécédent d'hypertension, de diabète ou de CVD du partenaire. Tout comme dans le manuscrit 1, les ajustements indirects pour l'obésité ont légèrement atténué les rapports de risque, tandis que les ajustements indirects pour le tabagisme n'ont pas influencé de manière importante nos estimations d'effet.

Dans le troisième manuscrit j'ai examiné les associations entre le GDM et le GHTN (avec ou sans prééclampsie) à travers deux grossesses avec le développement du CVD. La prise en compte de la présence ou de l'absence du GDM et du GHTN à travers deux grossesses a donné lieu à 16 catégories d'exposition. J'ai choisi d'évaluer ces catégories dans le cadre d'une analyse secondaire et me suis plutôt concentré sur le nombre d'occurrences de GDM et de GHTN à travers deux grossesses consécutives par rapport à leurs effets sur la survenue du CVD dans mes analyses principales. J'ai pris cette décision en reconnaissance des défis auxquels les lecteurs pourraient être confrontés dans l'interprétation de 16 catégories d'exposition uniques et de leurs HR respectifs. Dans la même étude de cohorte, en utilisant des modèles de risques proportionnels de Cox, j'ai observé qu'un nombre accru d'occurrences de GDM et de GHTN était associé à un risque accru de CVD, selon un schéma graduel (1 occurrence = 1,47 [1,35-1,61] ; 2 occurrences = 1,91 [1,68-2,17] ; ≥3 occurrences = 2,93 [2,20-3,90] par comparaison à l'absence de GDM et de GHTN dans les deux grossesses). Les ajustements indirects pour l'obésité et le tabagisme ont légèrement atténué ces rapports de risques.

Dans le quatrième manuscrit, j'ai mené une revue exploratoire de littérature qui aborde les algorithmes évolutifs pour le dépistage du GDM, en regroupant les lignes directrices publiées par les principales organisations obstétriques et diabétiques canadiennes, mettant en lumière les changements dans leurs recommandations au fil du temps. Cette revue exploratoire a montré que des variations dans les approches de dépistage et de diagnostic existaient entre Diabète Canada (DC) et la Société des obstétriciens et gynécologues du Canada (SOGC). Grâce à l'influence de l'étude sur l'hyperglycémie et les résultats néfastes pour la grossesse, ces disparités se sont atténuées, et de nombreux médecins canadiens adhèrent désormais aux recommandations récentes, comme je l'ai démontré à travers une enquête auprès des médecins. De plus, étant donné que l'utilisation des codes de diagnostic pour

identifier le GDM (dans les Manuscrits 1 à 3) peut être influencée par ces tendances séculaires dans les recommandations des lignes directrices que j'ai identifiées, j'ai mené des analyses supplémentaires pour examiner si l'inclusion de l'année civile de chaque grossesse (à 20 semaines de gestation) avait un impact sur les estimations d'effet dans chacun de mes modèles. Je n'ai observé aucune différence importante dans les associations du GDM avec chacun des résultats évalués après avoir essayé de prendre en compte les tendances séculaires dans le diagnostic du GDM.

En conclusion, cette thèse souligne que chez les femmes ayant eu deux ou plusieurs accouchements uniques, représentant plus de la moitié des femmes dans le monde, la prise en compte des occurrences ou des absences de GDM et de GHTN dans chaque grossesse peut nuancer davantage les estimations du risque futur de diabète, d'hypertension et de CVD. Ces résultats peuvent permettre une estimation personnalisée du risque, donnant aux cliniciens et aux patients des moyens de déterminer l'urgence et l'importance des interventions préventives et de la surveillance étroite.

Thesis Format

My thesis is a compilation of four manuscripts of which I am the first author. I have carefully organized my thesis into seven chapters. In Chapter 1, I introduce the topics of my doctoral research and present the objectives and hypotheses of my overall thesis work. I also highlight important research gaps that this thesis work addresses, discussing incorporating key novel methodological considerations in the design of each study. Moving on to Chapter 2, I review the existing body of literature on various epidemiological aspects of GDM and GHTN (e.g., their global burden and incidence, pathophysiology, traditional risk factors, screening and prevention, validity of their coding definitions using health administrative data, impact of their recurrence) in relation to CMD.

In Chapter 3, I present the results of Manuscript 1, which aimed to examine associations of GDM patterns across two pregnancies with incident diabetes. In terms of application of novel methods, I also incorporated sensitivity bias analyses to indirectly adjust for obesity and smoking, an approach I also adopted in the other studies presented in the thesis. This manuscript is published in *JAMA Network Open*.

In Chapter 4, I present Manuscript 2, through which I examined associations of GHTN patterns (with or without preeclampsia, combined in main analyses and separately in sensitivity analyses) with chronic hypertension development later in life. I was able to evaluate preeclampsia and GHTN without preeclampsia separately, by constructing subcohorts. These GHTN subgroups could not be evaluated within a single Cox PH model as this violated PH assumptions, discussed later in the thesis. I also delineated differences in hypertension risk associated with patterns of GDM across two pregnancies. This manuscript is published in the *Journal of the American Heart Association*.

Given proof of differential risks associated with specific patterns of GDM and GHTN on diabetes and hypertension risk, respectively, in Chapter 5, I examine associations between both pregnancy complications and CVD risk, as diabetes and hypertension are established CVD risk factors. I modeled both the cumulative number of conjoint occurrences of GDM and GHTN (primary analysis), as well as specific GDM/GHTN categories (16 groups, secondary analysis). CVD hazards increased across the groupings of none, one, two, and three or more cumulative GDM and GHTN occurrences. The analysis across 16 exposure groups were consistent with this. This manuscript is published in *Diabetes, Research, and Clinical Practice*.

Lastly, given variations in the definition of GDM over the years among practitioners and my usage of International Classification of Diseases (ICD) codes within Quebec's linked administrative databases to identify women with GDM, in Chapter 6, I present a scoping review that I conducted on this topic within the Canadian landscape. Given the variability in guideline recommendations over the years, I also administered a physician survey to evaluate uptake of the most recent guidelines. This manuscript is published in the *International Journal of Environmental Research and Public Health*. Furthermore, I assessed how accounting for temporal trends in the screening and diagnosis of GDM impacted the associations of GDM with diabetes (Manuscript 1), hypertension (Manuscript 2), and CVD (Manuscript 3), by including calendar years of each pregnancy across these models.

In Chapter 7, I summarize the thesis' findings, discuss important study considerations, and highlight the major novel contributions of this research towards refining risk assessment of cardiometabolic health in reproductive-aged women. Furthermore, I identify strengths and limitations of this collective body of research, and discuss areas and opportunities for future research aimed at evaluating GDM and GHTN as early risk indicators for maternal diabetes, hypertension, and CVD later in life.

Lastly, I provide additional Appendix materials that summarize the literature on recurrent occurrences of GDM/GHTN. These studies were discovered while searching the literature for studies that addressed new-onset occurrences in a second pregnancy, representing an important subgroup of women that were shown to be at increased risk of CMD in this thesis, but who have scarcely been delineated from women with only a first-affected pregnancy.

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I am extremely grateful to my supervisor, Dr. Kaberi Dasgupta, and my co-supervisor, Dr. Elham Rahme, for their unreserved support, encouragement, and guidance throughout my academic journey here at McGill University. Working with them both has been an absolute privilege. Their unwavering devotion and enthusiasm for their profession, coupled with genuine dedication towards their students and profession, was always truly inspiring. I would not change one thing about my PhD experience, and I am sincerely thankful for all the valuable lessons they both have taught me throughout these years.

I would like to express my gratitude to Dr. Nakhla from my supervisory committee for her valuable time and insightful discussions towards each of these manuscripts. Also, I would like to thank Mourad Dahhou, a statistical analyst who helped me with various important aspects of data analyses (including data preparation and cleaning) in order for each of these thesis objectives to be made possible, along with his guidance on several extracurricular research projects. Early in my PhD journey, he made challenging tasks seem possible.

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Lastly, I would like to express my sincere gratitude towards the McGill Faculty of Medicine and the Société Québécoise d'hypertension Artérielle for their generous financial assistance towards my doctoral studies. Support from their training fellowships has been invaluable, enabling me to pursue my academic aspirations with dedication and focus; these awards spanning from 2019-2022 not only lightened the financial burden, but also encouraged me to strive for excellence in my research endeavors, knowing that I had more people that believed in me.

Contributions of Authors

The research questions, study methodologies and objectives of my thesis were formulated in collaboration with my supervisors, Dr. Kaberi Dasgupta and Dr. Elham Rahme. I took the responsibility of analyzing, interpreting and writing all the different components of the thesis, including the introduction, literature review, individual manuscripts, linking preface subchapters, discussion and closing remarks. I am the lead author on all the manuscripts included in this thesis. My supervisors provided me with guidance and comments throughout the process, building the important work that I am proud to present here.

Dr. Kaberi Dasgupta, MD, MSc, FRCPC (primary supervisor) is a Full Professor of Medicine at McGill University and Physician-Scientist at the Research Institute of the McGill University Health Centre. Dr. Dasgupta oversaw all aspects of preparing each manuscript and the final thesis. She also provided the majority of guidance towards the conceptualization and design of each study, supervised my analyses, helped interpret the data, and critically reviewed all draft revisions and final deliverables.

Dr. Elham Rahme, PhD (co-supervisor) is an Associate Professor of Medicine at McGill University and Biostatistician at the Research Institute of the McGill University Health Centre. Dr. Rahme contributed to the study conception and design, engaged in frequent discussions concerning all statistical analyses and methodology, provided oversight of these analyses, and critically reviewed all manuscripts and the final thesis.

Mr. Mourad Dahhou, MSc previously worked as a statistical analyst on Dr. Dasgupta's research team at the Research Institute of the McGill University Health Centre. Mr. Dahhou contributed to dataset cleaning, variable derivation, statistical analyses, and data interpretation.

Dr. Meranda Nakhla, MD, MSc, FRCPC (thesis committee member) is an Associate Professor of Pediatrics at McGill University and Physician-Scientist at the Research Institute of the McGill University Health Centre. Dr. Nakhla critically reviewed of all these materials, providing valuable insight towards each manuscript included in the final thesis.

Contributions to Original Knowledge

CMD is the leading cause of morbidity and mortality worldwide, accounting for a third of all global deaths. CMD is not a single ailment, but rather a cluster of preventable conditions, which include diabetes, hypertension, and CVD (myocardial infarction, stroke, unstable angina). Diabetes and hypertension are themselves risk factors for myocardial infarction and stroke, and are also associated with additional complications, including renal, ophthalmological, and nerve injury. In the past decade, there has been a substantial increase in the prevalence of these chronic conditions, leading to CMD emerging as a major public health problem worldwide. To reduce the burden of CMD, it is imperative to identify high-risk populations for early assessment, prevention, and management of modifiable risk factors to reduce complication rates. GDM and GHTN are recognized as modifiable, pregnancy-related indicators of future diabetes, hypertension, and CVD among young to middle-aged women. In 2011, and more recently, in 2021, the American Heart Association issued statements recognizing that both GDM and GHTN could potentially act as early indicators of CVD in pregnant women. Guidelines from the European Society of Cardiology and the International Federation of Gynecology and Obstetrics have also recognized this accumulating evidence and have similarly updated their guidelines to reflect GDM and GHTN as pregnancy-related indicators of CVD, recommending that women are screened for hyperglycemia and elevated blood pressure early in pregnancy. A key gap in the literature is that most studies dichotomize women into never/ever categories with respect to GDM and/or GHTN history, not leveraging information across more than one pregnancy.

Women frequently experience more than one pregnancy; the global average number of offspring per women is estimated to be two. Guidance on the use of pregnancy-related information from additional subsequent pregnancies is limited; it remains unclear if the pattern of GDM/GHTN occurrences beyond one pregnancy impacts the magnitude of risk for diabetes, hypertension, and CVD.

One challenge of examining these associations is that each occurrence of GDM and/or GHTN is conditional on being pregnant; thus, women with fewer pregnancies will have fewer opportunities to develop GDM and/or GHTN. Few studies in the literature have attempted to examine the impact of new onset GDM/GHTN, following pregnancy without these conditions. Among the limited number of prior studies in the literature, most have not defined a minimum number of pregnancies, frequently including women with no previous pregnancies. Some studies opt to start the follow-up many years after the woman's last pregnancy. On the other hand, some studies begin follow-up immediately after

the last pregnancy (e.g., after one, after two, etc.), while others start after the first pregnancy affected by GDM/GHTN. These designs can complicate interpretation. The decision or ability to become pregnant, either a first time or subsequently, may be associated with factors related to insulin resistance, hormonal imbalances, stress, cardiovascular health, and/or a prior history of pregnancy complications. Thus, investigators may inherently be comparing subjects with importantly different baseline cardiometabolic risk profiles.

My thesis work specifically focused on women with at least two consecutive singleton livebirth pregnancies during the exposure definition period (1990-2012). Prior to this period, only 6% of women in the study cohort were recorded to have had a previous pregnancy in the birth registry; thus, the majority of women (94%) had their first pregnancy during the years in which these data were linked and made available to me. I consistently set the index date at 12 weeks after the second delivery for all women in my study cohort, and excluded women with a prior history of diabetes, hypertension, or CVD. I designed this approach to enhance subject comparability. The overarching aim of my thesis was to comprehensively examine patterns of GDM/GHTN absence, occurrence, and recurrence across two livebirth pregnancies and their associations with the development of maternal diabetes, hypertension, and CVD later in life.

Diabetes: In the **first** manuscript, I conducted a retrospective cohort study among 431,980 Quebec women with at least two consecutive singleton deliveries, who were free of diabetes at the first pregnancy and had not developed diabetes between pregnancies. I used data from the provincial health administrative and vital statistics databases of Quebec. I used Cox PH models to estimate associations between patterns of GDM absence, occurrence, and recurrence across two pregnancies and their associations with the onset of diabetes later in life. Although the literature on patterns of GDM beyond one pregnancy are scarce, the studies that have adopted this approach allow for a high degree of variability in the numbers of pregnancies considered during their exposure periods, thus impacting the woman's baseline cardiometabolic risk. Moreover, women with GDM recurrence are often compared to women with one occurrence of GDM, irrespective of which pregnancy was affected. I did not identify any prior studies in the literature that compared a single occurrence GDM in a first pregnancy to a single occurrence of GDM in a second, among women with two pregnancies.

I also accounted for GHTN and other adverse pregnancy occurrences, among other co-variates. In contrast to the relationship between GDM and diabetes, PH assumptions did not hold between GHTN and incident diabetes when I separated GHTN exposure as neither, first only, second only, and both pregnancies. I therefore considered a never/ever category for GHTN across two pregnancies, which resolved this issue (see **Chapter 7.1.2**). While health administrative data sets and vital statistics offer an opportunity to study a large number of individuals over a long period of time, they lack information on adiposity and health behaviors. To address this, I applied simple sensitivity bias analyses to perform indirect adjustments for obesity and smoking, which may confound the relationship between GDM and diabetes development. Although this method of indirect adjustment is well-established, indirect adjustments for obesity and smoking have not been applied by study investigators who are examining the risk between GDM and subsequent diabetes, but whose datasets are missing measures of these confounders. Previous studies have been unable to apply such adjustment methods as there are key requirements that can be challenging to fulfill, including: a) access to a large external data source that is representative of the original study population, b) inclusion of personal risk factors that are recorded or can be derived within the representative sample from the external dataset (e.g., anthropometric measures, cigarette smoking), c) ability to delineate proportions with these personal risk factors (e.g., obesity, smoking) within the external data set that are stratified by the exposure categories of interest in the main study, d) estimates of the associations between the unmeasured potential confounder (e.g., obesity, smoking) and the outcome of interest in the literature (e.g., diabetes) among a representative sample of the study population. I leveraged my access to a random sample of Canadian citizens who completed the 2004 CCHS (Cycle 2.2) and consented to probabilistic record linkage, conducted by Statistics Canada, to the 2004-2017 Discharge Abstract Database and Canadian Mortality Database. Since the completion of the 2004 survey, these women were subsequently followed-up for up to 13 years to ascertain vital status and underlying causes of hospitalization/death through linkage of the aforementioned databases. I applied specific inclusion criteria (e.g., limited to women aged 12-50 with at least two pregnancies recorded; without prior diabetes, hypertension, or CVD at baseline) attempting to mimic the inclusion criteria applied to my primary cohort to maximize subject comparability between both datasets.

As previously summarized, I demonstrated a progressively higher hazards for diabetes, moving from absence of GDM in either pregnancy, GDM in the first but not in the second, GDM in the second but not in the first, and GDM in both. My key novel finding was that women with GDM in a first

pregnancy, who do not develop either diabetes between pregnancies or GDM in the second pregnancy, have entered a lower diabetes risk trajectory than women with first-onset GDM in a second pregnancy. Thus, not all women with a single occurrence of GDM are the same. Furthermore, women with GDM in both pregnancies had the highest risk of developing diabetes, demonstrating the cumulative impact of these occurrences on long-term metabolic dysregulation.

Hypertension: In the **second** paper, I focused on associations of GHTN with hypertension development. New-onset blood pressure in pregnancy may present with either evidence of organ injury (variously termed GHTN with preeclampsia, or simply, preeclampsia), or without organ injury, termed GHTN without preeclampsia, or GHTN alone.

In these analyses, GHTN with or without preeclampsia split into the neither, first only, second only, and both pregnancies categories fulfilled PH assumptions in relationship to hypertension development. The methodological challenge was that the assumptions were not met when further divided into presence or absence of preeclampsia. Previous studies suggest that preeclampsia leads to greater perinatal morbidity and mortality than GHTN without preeclampsia, but the longer term associations of these adverse pregnancy occurrences may be more similar. I evaluated both preeclampsia and GHTN without preeclampsia, combined and separately, in association with chronic hypertension. I was able to delineate the nuances between both preeclampsia and GHTN without preeclampsia by creating two subcohorts. One included individuals without any form of GHTN and also those with preeclampsia, but excluded those who had GHTN without preeclampsia. The other subcohort included those without any form of GHTN and those with GHTN without preeclampsia, but excluded those with preeclampsia. Across models, I performed indirect adjustments for obesity and smoking in sensitivity analyses. I was able to consider GDM absence, only in first pregnancy, only in second pregnancy, and in both, in these models evaluating hypertension as an outcome, without violating PH assumptions (see **Chapter 7.2.4**).

As for GDM and diabetes, I identified a progressively higher hazards for hypertension across GHTN occurrence categories, moving from absence of GHTN in either pregnancy, GHTN in the first but not in the second, GHTN in the second but not in the first, and GDM in both. Women with GHTN in a first pregnancy, who do not develop either hypertension between pregnancies or GHTN in the second pregnancy, have entered a lower hypertension risk trajectory than both women with first-onset

GHTN in a second pregnancy, and those with GHTN recurrence in a second pregnancy. These findings applied for preeclampsia and for GHTN without preeclampsia, considered separately, and the magnitude of the increase in hazards for incident hypertension, in comparison to absence of GHTN, was similar for both GHTN subgroups. Additionally, a single occurrence of GDM in either pregnancy was associated with increased hypertension hazards, with similar estimates for GDM in the first pregnancy and for GDM in the second pregnancy only, compared to absence of GDM in either pregnancy. The highest hazards were observed among women with GDM in both pregnancies.

Thus, manuscripts 1 and 2 indicate that for the relationship of GDM with diabetes and for GHTN with hypertension in women with at least two singleton livebirth pregnancies, compared to their respective absence across two pregnancies, the presence in a first pregnancy, new onset in a second pregnancy, and occurrence in both pregnancies are associated with escalating risks. Relationships of GDM with hypertension and GHTN with diabetes, while present, did not exhibit such an escalating pattern. This may perhaps be due to the lower magnitude of their overall association with the outcome of interest.

CVD: Both diabetes and hypertension have a similar magnitude of association with CVD. In a previous study, my supervisors and their team demonstrated that among a random sample of 40,000 Quebec women with one singleton pregnancy, compared to absence of GDM or GHTN, the presence of either was associated with elevated CVD risk and the presence of both with even higher risk. In the **third** manuscript, I examined numbers of GDM and GHTN occurrences across two consecutive singleton pregnancies (none, one, two, and three or more) in relationship to CVD, focusing on myocardial infarction, stroke, and unstable angina in a composite CVD outcome measure. I used Cox PH models to examine effect measures associated with the primary exposure, and in a secondary analysis, I created 16 mutually-exclusive GDM/GHTN exposure categories to model all possible joint combinations of GDM and GHTN across two pregnancies.

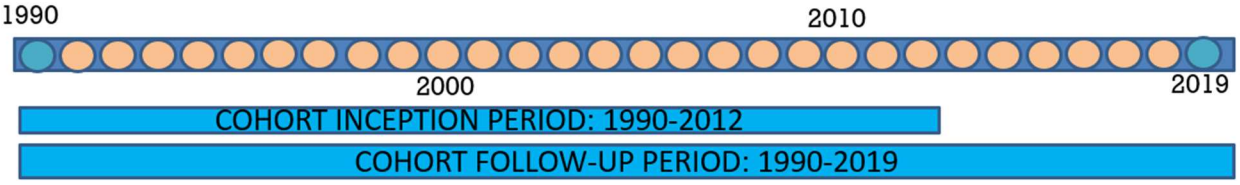
In these analyses, I demonstrated a stepwise increase in CVD hazards moving from absence of GDM or GHTN in either pregnancy, to one occurrence of GDM or GHTN, two occurrences of GDM and/or GHTN, and three or more occurrences. The numbers of GDM and GHTN occurrences are important, irrespective of the pregnancy in which they occur. Thus, having both GDM and GHTN in a single pregnancy was associated with similar hazards as having GDM in one and GHTN in the

other. Having GDM and GHTN co-occurring in both pregnancies was associated with the highest hazards. The secondary analysis with 16 exposure groups, originally my main focus, demonstrated these similarities better than the primary analysis focusing on numbers of GDM and GHTN occurrences across pregnancies. However, I felt it might be difficult for readers to appreciate patterns of risk when presented across 16 unique exposure groups, and thus I opted to present the Cox PH model depicting all 16 HRs as a secondary analysis for ease of interpretability (see **Chapter 7.3.1**). From a knowledge translation perspective, creating exposure groups based on numbers of GDM and GHTN occurrences increases comprehensibility and offers an advantage of including higher numbers of outcomes within the four exposure groups considered, compared to splitting these across 16 groups.

Prior to my studies, previous investigators examined independent effects of GDM recurrence and GHTN recurrence on CMD risk. However, there has been little previous study of GDM and GHTN together, and none that I could identify examining recurrence of both across two pregnancies. Additionally, there has been little attempt to distinguish outcomes following a single GDM or GHTN occurrence in relationship to the pregnancy in which it occurred (e.g., first pregnancy, second pregnancy, etc.). Studies considering the totality of occurrences across pregnancies have largely considered women without any pregnancies as part of the reference group, and the initiation of follow-up has also often varied across participants (e.g., after the first pregnancy, after two pregnancies, after a pregnancy affected by a GDM/GHTN occurrence [irrespective of in which pregnancy it occurred]). I have addressed these knowledge gaps, leveraging Quebec's provincial health administrative data, combined with birth, stillbirth, and death vital statistics. Quebec has a population of over 8 million individuals. Similar to other parts of Canada, hospitalizations and physician visits are funded through a public health insurance plan. The ICD codes used for administration of this plan, combined with dates and demographic data, are key assets for research. I used validated health administrative data-based definitions for exposures and outcomes. In Quebec, all mothers are obliged to complete a birth declaration that incorporates demographic and offspring data (maternal education, paternal languages and countries of birth, offspring weight and sex, among others) that are all integrated into the birth registry. I used data on nearly a half million women, and the offspring from two singleton pregnancies, as well as data available for the fathers of these offspring. Cohort inception was from April 1, 1990 to December 31, 2012 and follow-up was from 12 weeks' postpartum of the second delivery to April 1,

2019 (**Figure 1**), allowing for up to nearly three decades of follow-up (median follow-up of roughly 11 years until incident diabetes or hypertension, and a median of 16.5 years until incident CVD).

Figure 1. Visualization of cohort inception and follow-up period



Manuscript 1 is published in *JAMA Network Open*. Manuscript 2 is published in the *Journal of the American Heart Association*. Manuscript 3 is published in *Diabetes Research and Clinical Practi*ce and was presented at Vascular 2023 in Montreal; the International Diabetes Epidemiology Group biennial meeting in Porto, Portugal in 2023; and the International Diabetes Federation in Lisbon, Portugal in 2023.

While there is a long-standing international consensus on thresholds of blood pressure during pregnancy to define GHTN, establishing glucose thresholds to define GDM have been inconsistent over the years. I used physician-billing and hospitalization ICD codes in the application of GDM definitions. Notwithstanding variations in GDM definitions, in a fourth manuscript, I present a scoping review to address evolving algorithms for the screening of GDM, as recommended by different renditions of clinical practice guidelines released by Canada's largest national obstetric and diabetes organizations (Diabetes Canada and the Society of Obstetricians and Gynecologists of Canada). In my scoping review, I highlight that earlier guidelines were based on expert opinion, leading to different recommendations from these organizations regarding screening and diagnostic approaches (one-step versus two-step), recommended oral glucose tolerance test (OGTT) loads, diagnostic threshold values, etc. However, as a result of the Hyperglycemia and Adverse Pregnancy Outcome study, disparities between Diabetes Canada and the Society of Obstetricians and Gynecologists of Canada recommendations no longer exist. My review highlights that because the national guidelines recommend use of either diagnostic approach to-date, lack of consensus on a single

diagnostic threshold continues to exist, as demonstrated in a physician survey that I had circulated as part of my review; this likely explains the differing estimates of GDM prevalence across Canada to date. This scoping review is published in *the International Journal of Environmental Research and Public Health* and has been cited 16 times to date. Utilizing the findings from my scoping review, in this thesis, I also discuss additional analyses that I performed to account for these temporal trends. Through these analyses, I demonstrated that although the definition has varied somewhat across the years, accounting for the calendar year of each pregnancy did not impact my overall findings in terms of relationships between GDM and diabetes, hypertension, and CVD.

In summary, I demonstrate in this thesis that considerations for CMD risk assessment should be further nuanced in women with at least two pregnancies, in relationship to their history of GDM and GHTN. I have considered all patterns of absence, new onset, and recurrence of GDM and/or GHTN across two pregnancies, and quantified the magnitude of their associations with maternal diabetes, hypertension, and CVD risk. Such information could allow for more personalized risk estimation. These findings offer clinicians an opportunity to use this information to help identify high risk groups to ascertain the importance and urgency of preventive action. Moreover, pregnancy may also be a period where younger adults are concerned about attending to health matters to enhance the wellbeing of their family.

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List of Abbreviations

AGA = appropriate for gestational age

AOBP = Automated Blood Pressure Monitoring

ASCVD = Atherosclerotic Cardiovascular Disease

BMI = body mass index

CADRISQ = Centres for Access to Research Data

CanDIPS = Canadian Diabetes in Pregnancy

CANRISK = Canadian Diabetes Risk Assessment Questionnaire

CCHS = Canadian Community Health Survey

CCDSS = Canadian Chronic Disease Surveillance System

CGM = Continuous glucose monitoring

CI = confidence interval

CMD = cardiometabolic disease

COPD = chronic obstructive pulmonary disease

CPG = clinical practice guidelines

CVD = cardiovascular disease

DALY = disability adjusted life years

DC = Diabetes Canada

FRS = Framingham risk score

GBD = Global Burden of Disease

GCT = glucose challenge test

GDM = gestational diabetes

GHTN = gestational hypertension

GHTNa = GHTN alone

HAPO = Hyperglycemia and Adverse Pregnancy Outcome

HbA1C = glycated hemoglobin

HBPM = Home Blood Pressure Monitoring

HDP = hypertensive disorders of pregnancy

HELLP = hemolysis, elevated liver enzymes, and low platelet count

HR = hazard ratio

IADPSG = International Association of Diabetes and Pregnancy Study Groups

ICD = International Classification of Diseases

IL-6 = interleukin-6

INSPQ = Institut national de santé publique du Québec

ISQ = Institut de la statistique du Quebec

LGA = large for gestational age

N = number

NDSS = National Diabetes Surveillance

OGTT = oral glucose tolerance test

OR = odds ratio

PCOS = polycystic ovary syndrome

PH = proportional hazards

PE = preeclampsia

P_{oe} = proportion within specific GDM/GHTN category who have obesity

P_e = proportion of those with specific GDM/GHTN category among all women with two consecutive singleton pregnancies

P_o = proportion with obesity among all women with two consecutive singleton pregnancies

RAAS = renin-angiotensin-aldosterone system

RR = risk ratio

SGA = small for gestational age

SNS = sympathetic nervous system

SOGC = Society of Obstetricians and Gynecologists

TNF-α = tumor necrosis factor-alpha

VSMC = vascular smooth muscle cell.

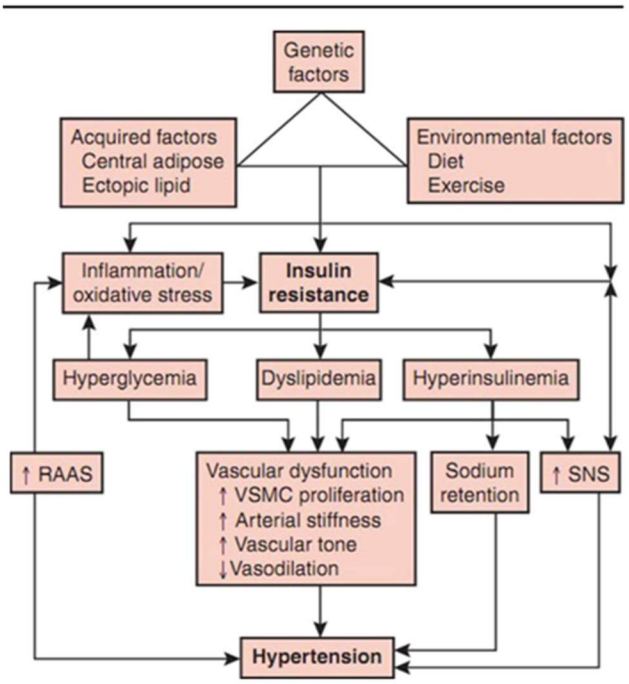
Chapter 1: Introduction

1.1 Background

CMDs are a cluster of interrelated health conditions that include diabetes, hypertension, and CVD (e.g., myocardial infarction, stroke, unstable angina). Diabetes and hypertension are risk factors for CVD,[1,2] but are also associated with other important health outcomes. For example, hyperglycemia can lead to microvascular damage, contributing to hepatic[3] and nerve injury,[4] while both hyperglycemia and elevated blood pressure are associated with renal and ophthalmological injury.[5,6] However, CVD continues to remain as a major disease associated with both conditions as a result of macrovascular complications, predominantly in the heart (coronary) and brain (cerebral). CVD is the leading cause of death globally, accounting for nearly one third of total annuals deaths as reported in a recent systematic analysis;[7] 85% of CVD deaths are attributable to myocardial infarction and stroke**.** While CVD continues to remain the leading cause of death on a global scale to date, hypertension and diabetes are recognized as its leading preventable risk factors, with most of the burden of CVD being attributable to these two conditions.[1,2] Moreover, hypertension is considered to be leading contributor to premature death globally,[1] while diabetes is recognized as the eighth leading cause of mortality worldwide.[8] Diabetes and hypertension represent separate clinical entities that commonly manifest together. Hypertension is defined by elevated systolic and/or diastolic blood pressure.[9] Diabetes is characterized by elevated levels of glucose in the bloodstream, which arise due to insufficient production of insulin and/or resistance of tissues to the effects of insulin.[10] In a non-pregnant state, the two prevailing categories of diabetes are categorized as type 1 and type 2 diabetes. Type 1 diabetes, which constitutes less than 5% of all instances of diabetes in adults,[11] primarily arises from autoimmune harm to the pancreatic insulin-producing beta cells, resulting in diminished insulin production. Type 2 diabetes, which accounts for more than 95% of diabetes cases,[11,12] arises from resistance to the action of secreted insulin.

Elevated glucose and increased blood pressure levels are both clinical manifestations of CMD (**Figure 2**). Several modifiable and non-modifiable risk factors are shared among CMDs, contributing to their development and progression. Established modifiable risk factors include obesity, physical inactivity, suboptimal dietary habits, and tobacco use.[1,13] Weight gain and physical inactivity contribute to visceral fat accumulation leading to insulin resistance, increases in glucose and blood pressure levels, and other thrombogenic changes that contribute to atherosclerosis.[14]

Figure 2. Summary of putative pathophysiologic mechanisms in the development of diabetes and hypertension (Image adapted from Mugo *et al.,* 2007[15])



RAAS—renin-angiotensin-aldosterone system; SNS—sympathetic nervous system; VSMC—vascular smooth muscle cell.

Non-modifiable risk factors such as age, biological sex at birth, ethnicity, and genetic predisposition also play significant roles in their onset. Importantly, the global epidemiological transition, characterized by urbanization, an aging population, sedentary lifestyles, and dietary changes, has led to an escalating prevalence of these risk factors.[13] While I use the terms "women" and "mothers" in sections of the thesis, I am aware that not all individuals who become pregnant self-identify as women. This terminology is employed because it is currently widely used, though I recognize and respect that gender-fluid individuals and trans men may also experience pregnancy.[16] The participants in my studies were individuals capable of becoming pregnant, defined by female sex at birth, but I acknowledge that their self-identified sex and/or gender may differ from sex at birth. Across my four manuscripts, I discussed ethnocultural background, defining it based on language and country of birth. I acknowledge that the gold standard for background is self-identified background. Unfortunately, we did not have access to such information in our data sources. Over the course of ongoing discussions with my supervisor, the terminology evolved from what was originally written in these published manuscripts.

For example, in some sections of our manuscripts, we have used the term "Europid" but more recently have changed our terminology to "of European origin," as Europid may be considered equivalent to Caucasian, an outdated race designation. I acknowledge that race and ethnicity are dynamic constructs, shaped by geographic, cultural, and sociopolitical forces.[16] My approach relied on country of birth combined with language, categorizing languages according to their place of origin. Consequently, I can only speak of origins, recognizing the potential for misclassification. Therefore, apart from the four manuscripts, I use the term "origin" in the remainder of the text. While the terms may differ across my papers due to these discussions, this approach applies consistently throughout the other sections of my thesis.

To reduce the burden of CMD, it is imperative to identify high-risk populations for early assessment and management of modifiable risk factors. Pregnancy is a pivotal period in a pregnant person's life, characterized by profound physiological changes to support fetal development. It provides a unique window and an early opportunity to assess cardiometabolic health. The interplay between a pregnant person's physiology, fetal development, and long-term health outcomes underscores the importance of understanding cardiometabolic risk factors during this critical phase. In particular, GDM and GHTN are recognized as modifiable, pregnancy-related indicators of diabetes,[17-22] hypertension,[23-26] and CVD[24,26-37] risk among young to middle aged persons who become pregnant.

There are a plethora of epidemiological studies and reviews highlighting the evidence of associations between GDM and GHTN with CMD. For example, GDM is associated with 10-fold increased risk for type 2 diabetes in the years following pregnancy.[22] GDM is also associated with 26% increased risk of women developing hypertension later in life[23] and a two-fold increase in the odds of developing maternal CVD.[33,34] In addition, GDM is a risk factor for increased carotid arterial wall thickness[38] and preeclampsia.[39]

GHTN is also an important risk factor for development of type 2 diabetes, hypertension and CVD. GHTN with preeclampsia confers a 1.8-fold risk increase for type 2 diabetes and 3.4-fold risk increase for hypertension.[26] Similar to GDM, findings from a meta-analysis[34] and umbrella review[33] also demonstrated conclusive associations between GHTN (with and without preeclampsia, separately) and CVD. Compared to those without GHTN, the odds of non-fatal CVD has been shown to be

67% higher among women with GHTN (without preeclampsia), 2.2-fold higher among women with moderate preeclampsia, and 2.7-fold higher among those with severe preeclampsia.[33]

However, there is a paucity of evidence regarding what happens to a woman's cardiometabolic risk when a woman experiences adverse pregnancy complications in more than one pregnancy. For example, clinicians may ask, among multiparous women, how are patterns of these pregnancy complications (i.e., recurring complications, absence, or new onset of complications in later pregnancies) accounted for in these risk assessments? Can this information be factored in to help estimate risk more precisely? Should women seek earlier preventative measures if these complications keep recurring? What does it mean in terms of CMD risk if these complications stop recurring (e.g., present in the first pregnancy, but absent in the second); does this mean that these women have reduced their risk to some degree, compared to those that have it recur? What about women that develop them in the second pregnancy but did not experience it in their first pregnancy; does this indicate that they have moved towards a higher risk group? These questions are all important in the era of precision medicine. It may thus be useful to use information across pregnancies to better estimate CMD risk and customize management following delivery.

Although women average two offspring globally,[40] few studies have examined patterns of GDM and/or GHTN among multiparous women, in relationship to the future development of diabetes, hypertension and CVD. The existing literature typically focuses on 'ever/never' GDM and GHTN dichotomies,[17,25-27,34,35] not harnessing the information for more than one pregnancy. Among the limited studies that have assessed the implications of GDM or GHTN beyond one pregnancy, most have allowed for variations in the numbers of pregnancies during the exposure period among the women considered, but have not accounted for parity in their analyses. This complicates the interpretation of these investigators' findings since the decision or ability to become pregnant may be dependent on cardiovascular risk factors themselves. Previous meta-regression results estimate a GDM recurrence rate of 48% (95% CI, 41%-54%) following a first GDM pregnancy[41,42] while estimates for GHTN recurrence approximate 20.7% (95% CI, 20.4-20.9%).[43,44] Among multiparous women with a uniform number of deliveries prior to the index date (ensuring similar baseline cardiometabolic risk), assessing the totality of occurrences and particular sequence of these patterns beyond one pregnancy (i.e., recurrence, absence or new onset in subsequent pregnancies), as opposed to a single dichotomous 'ever/never' measure, may help to further refine CMD assessment, with the

dual goals of prevention and early detection. Among women with more than one pregnancy, it remains unclear in the literature if the number of GDM and/or GHTN occurrences and their sequence impact the magnitude of risk for developing diabetes, hypertension, and CVD.

The aim of my thesis work was to address these key gaps in the literature to potentially further nuance cardiometabolic risk estimation in women following two consecutive, singleton pregnancies.

1.1 Research objectives and hypotheses

Among nearly half a million women with two consecutive singleton livebirth deliveries (without diabetes, hypertension, or CVD before or between pregnancies), following the delivery of the second offspring:

1) Manuscript 1: My primary aim was to compare GDM in the first only, second only, and both pregnancies, with GDM absence in both pregnancies, in terms of associations with diabetes development (**Figure 3**). I also sought to compare these GDM categories with one another in terms of diabetes development. My secondary aim was to concurrently evaluate associations of other adverse pregnancy occurrences (GHTN, LGA and SGA offspring, preterm birth), prior paternal CMD (diabetes/hypertension/CVD), and demographic factors with maternal diabetes (see directed acyclic graph in **Figure 4**).

2) Manuscript 2: My primary aim was to compare GHTN (with or without preeclampsia) in the first only, second only, and both pregnancies, with GHTN absence in both pregnancies, in terms of associations with hypertension development (**Figure 3**). I also aimed to compare these GHTN categories with one another in terms of hypertension development. I concurrently evaluated associations of other adverse pregnancy occurrences (GDM, LGA and SGA offspring, preterm birth), prior paternal CMD, and demographic factors with maternal hypertension, as my secondary objective. Finally, I aimed to evaluate associations of preeclampsia to hypertension and GHTN without preeclampsia to hypertension, using separate subcohorts.

3) Manuscript 3: My primary aim was to compare having one, two, or three or more GDM and/or GHTN occurrences during one or two pregnancies to no GDM or GHTN in either pregnancy, in terms of associations with CVD development (**Figure 3**), defined as myocardial infarction, stroke, or unstable angina. My secondary aim was to separately evaluate 16 mutually exclusive categories of

GDM/GHTN absence, occurrence, or recurrence across two pregnancies to CVD. Lastly, I sought to concurrently evaluate associations of other adverse pregnancy occurrences (LGA and SGA offspring, preterm birth), paternal CMD, and demographic factors with CVD.

Given that I and others[45] use validated health administrative definitions for GDM, but these criteria for GDM have varied over the years, my objectives for Manuscript 4 were:

4) Manuscript 4: to summarize the criteria and sequence of GDM screening algorithms recommended by Canadian diabetes and obstetrics societies over the years, specifying periods of varying guideline recommendations and their potential implications. Furthermore, I planned to demonstrate the level of adherence to the latest guideline recommendations through a physician survey. My final aim of this research was to evaluate how accounting for temporal trends may impact estimates of the association of GDM with diabetes, hypertension and CVD in the manuscripts of this thesis.

Figure 3. Objectives of Manuscripts 1 through 3

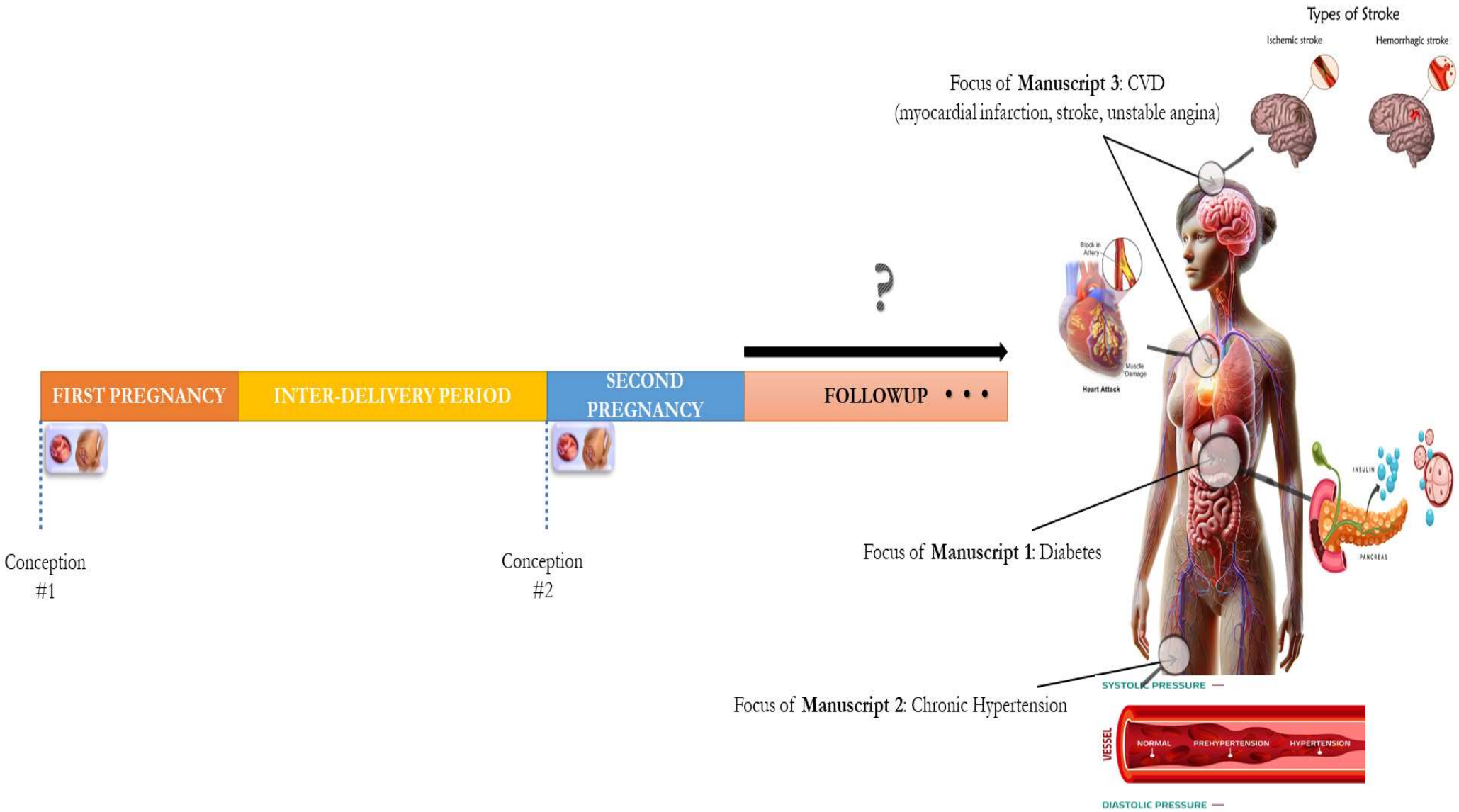
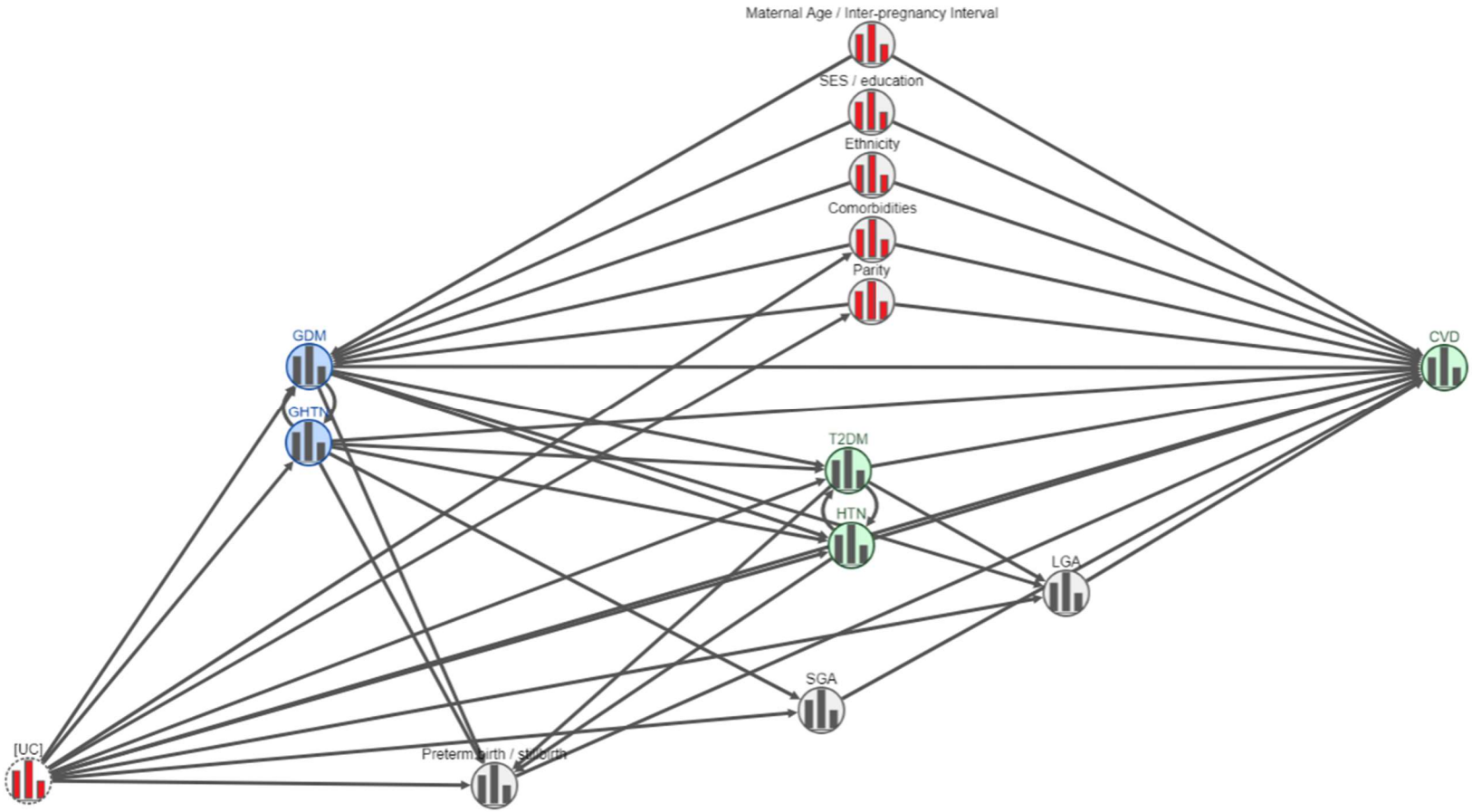


Figure 4. Directed acyclic graph depicting the relationship between gestational diabetes and gestational hypertension exposure, covariates in my models, and cardiometabolic disease



Blue = primary exposures; green = primary outcomes of interest; red = confounders addressed in my analysis. CVD = cardiovascular disease, GDM = gestational diabetes, GHTN = gestational hypertension, HTN = hypertension, LGA = large for gestational age, SES = socioeconomic status, SGA = small for gestational age, T2DM = type 2 diabetes, UC = unmeasured confounders (e.g., obesity, smoking).

Hypotheses

Manuscripts 1 and 2: In women with at least two consecutive livebirth pregnancies, I hypothesized that for the relationship of GDM with diabetes (Manuscript 1) and for GHTN with hypertension (Manuscript 2), the presence in a first pregnancy, new onset in a second pregnancy, and occurrence in both pregnancies are associated with stepwise escalating risks, compared to their respective absence across two pregnancies. For example, in Manuscript 1, I speculated that compared to women without GDM in either pregnancy, there is some diabetes risk increase in those with GDM in the first but absent in the second pregnancy, higher diabetes risk in those with GDM in the second but absent in the first pregnancy, and highest diabetes risk in those with GDM in both pregnancies. I reasoned that associations of GHTN with incident hypertension risk would parallel the escalating patterns of risk observed between GDM and diabetes.

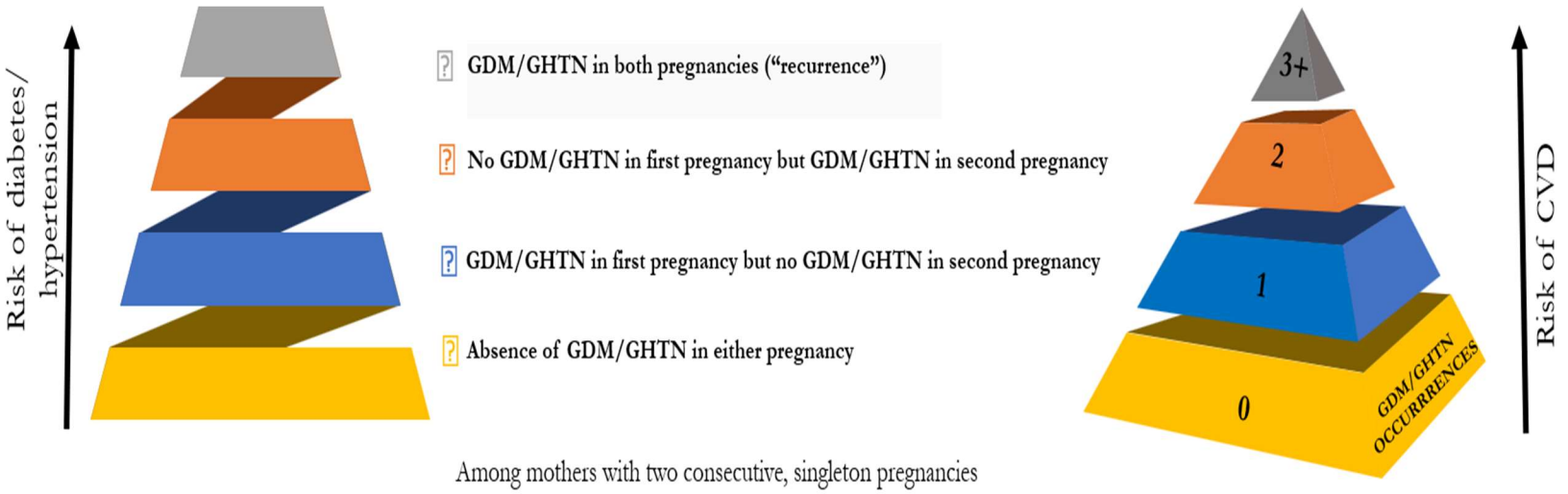
This ranking of risk was based on the notion that between pregnancies, women may adopt healthier lifestyle habits that reduce rates of recurrent GDM/GHTN in a subsequent pregnancy, and thus overall chronic diabetes/hypertension risk (**Figure 5**). For example, women with a pregnancy complication in a first pregnancy may be motivated to adopt or enhance health behaviors (increased levels of physical activity, weight optimization, healthier food intake, smoking cessation) that lower serum glucose levels, thus reducing the risk of recurrence in a second pregnancy and could signal a shift to a lower diabetes/hypertension risk trajectory. On the other hand, occurrence in a second pregnancy could indicate a shift to higher risk. This may be related to difficulty in losing excess gestational weight from the first pregnancy, stress related to parenthood, and time pressures limiting physical activity and nutritionally adequate diets. I also speculated that women with GDM/GHTN occurring in both pregnancies would inherently be women on highest risk trajectory of developing diabetes/hypertension. This rationale stems from the notion that suboptimal lifestyle behaviours (e.g., poor dietary habits, lack of physical exercise) may have stemmed years before first pregnancy, remained during the months/years between pregnancies, and thus were likely to continue to be adopted in the years following second delivery.

Manuscript 3: I hypothesized stepwise increases of cardiovascular risk associated with more cumulative occurrences of GDM and GHTN across two pregnancies. These pregnancy complications and chronic CMD conditions are believed to emerge from a similar substrate of excess weight, physical inactivity, and insulin resistance ("common soil" hypothesis). Moreover, I speculated that cumulative

impact of these pregnancy complication operating simultaneously across pregnancies may also reflect direct effects of GDM-associated hyperglycemia and GHTN-associated antiangiogenic factors that lead to vascular dysfunction, endothelial injury, and ultimately atherosclerosis (**Figure 2**). In a secondary analysis evaluating the individual impact of GDM and GHTN in each pregnancy, I hypothesized that GDM and/or GHTN occurrence(s) in a second pregnancy would indicate shift to a higher-risk trajectory group than occurrences only in a first pregnancy (similar to my hypothesis for Manuscripts 1 and 2).

Manuscript 4: I hypothesized that accounting for temporal trends by including calendar years in my Cox PH models could potentially impact estimates of the association of GDM with diabetes importantly, given the magnitude of these observed associations and the explanatory power of the GDM variable in this model. I hypothesized that adjusting for calendar years would influence the association of GDM with hypertension and with CVD to a lesser degree. Variability in the definition of GDM is expected to have influenced which criteria individual physicians were using to diagnose women in pregnancy (inter-physician variability) at a specific point in time, and also throughout the years (temporal trends, even leading to intra-physician variability) based on guideline recommendations at the time of each pregnancy.

Figure 5. Hypothesized ranking of CMD risk among women with GDM/GHTN



Chapter 2. Literature Review

2.1 The global burden of cardiometabolic diseases

2.1.1 The global burden of cardiovascular disease

CVD encompasses a broad spectrum of conditions that affect the heart and blood vessels, including myocardial infarction, stroke, and angina, often leading to premature death and disability. Myocardial infarction and stroke are recognized as CVD manifestations with the highest mortality rates, accounting for 85% of CVD deaths and responsible for most of the burden associated with CVD.[1,7] Lindstrom *et al.* recently demonstrated in their systematic analysis of the 2021 Global Burden of Disease (GBD) study that CVD was responsible for an estimated 621 million cases worldwide, contributing to 20.5 million deaths in 2021 alone.[7] Several important risk factors contribute to its onset and progression, including obesity, smoking, hyperlipidemia, physical inactivity, diabetes and hypertension. To date, diabetes and hypertension remain the leading modifiable risk factors of CVD.[1] Several recent systematic analyses of the GBD study demonstrate that the combination of diabetes and hypertension pose a synergistic effect on the burden of CVD, leading to a higher risk of cardiovascular events and its associated complications.[1,2] Although the rate of disability-adjusted life years (DALYs) and deaths from metabolic-attributed CVD have decreased by 28% and 30%, respectively, from 1990 to 2019,[2] the prevalence of these metabolic risk factors, namely diabetes and hypertension, remains high and emphasizes the need for early interventions to target them.[46]

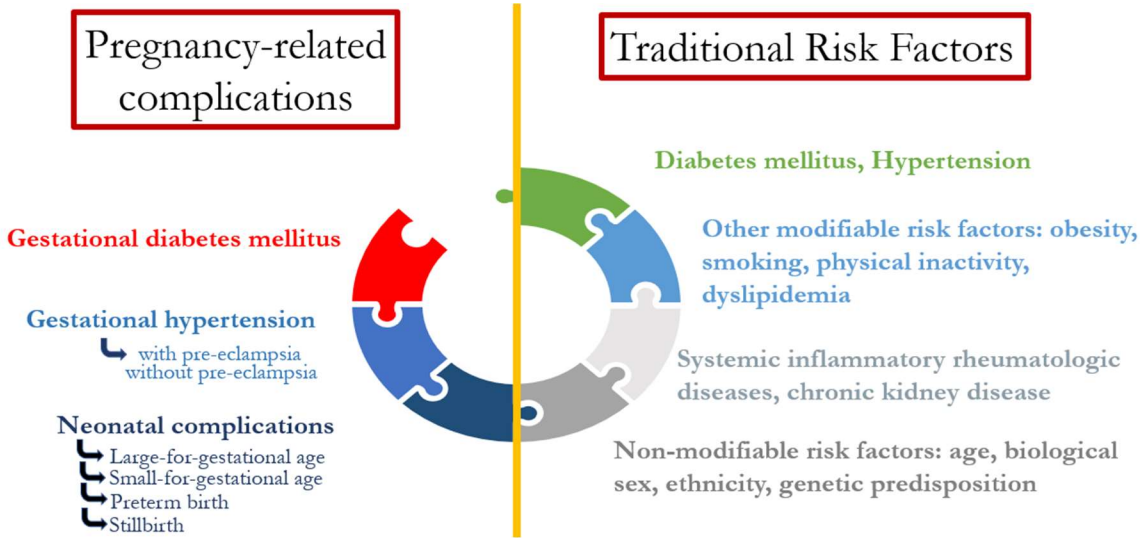
The global burden of CVD extends beyond individual health outcomes, encompassing implications on broader population health implications and posing multifaceted challenges to healthcare systems worldwide. CVD imposes substantial socioeconomic burdens through its direct implications on healthcare costs, including hospitalizations, medications, and surgeries, as well as indirect costs related to disability and loss of productivity.[1] Therefore, an integrated and synergistic approach is required to address and tackle its underlying determinants of health. Effective management of hyperglycemia and elevated blood pressure are crucial in reducing the burden of CVD and are often targeted in prevention programs.

2.1.2 Traditional risk factors for cardiovascular disease and risk prediction models

Understanding the interplay of risk factors contributing to the development of CVD is of critical importance towards designing effective prevention and management strategies. Modifiable risk factors

of CVD encompass diabetes, hypertension, dyslipidemia, obesity, tobacco use, physical inactivity, and suboptimal diets (**Figure 6**).[1,13] Additionally, non-modifiable risk factors include age, biological sex, ethnicity, and genetic predisposition.

Figure 6. CVD risk factors



The INTERHEART study[47] was one of the first international, standardized case-control studies designed to assess the importance of modifiable risk factors for CVD, highlighting that dyslipidemia, smoking, diabetes, hypertension, abdominal obesity, psychosocial factors, infrequent consumption of fruits and vegetables, regular alcohol consumption and physical inactivity could explain >90% of the population attributable risk of acute myocardial infarction risk across the world. These risk factors demonstrated associations with CVD across various socioeconomic levels and across a diverse range of ethnic populations included in the study. A recent report from the American Heart Association[13] has noted that the rising prevalence of these risk factors can be attributed to the global epidemiological transition characterized by urbanization, an aging population, sedentary lifestyles, and dietary modifications.

Briefly, dyslipidemia characterized by abnormal lipid profiles, are believed to be directly involved in the pathogenesis of atherosclerosis and coronary artery disease.[48] Statins which are effective at lowering lipids are one form of therapy shown to reduce CVD-related morbidity, highlighting the crucial role of dyslipidemia management in CVD prevention.[49] Smoking is known to exert deleterious effects on endothelial function, inflammation, and thrombosis.[50] Previous studies have consistently

shown a dose-dependent relationship between smoking and CVD incidence, emphasizing smoking cessation as an intervention to reduce the burden of CVD.[51] Weight gain, poor dietary quality, and physical inactivity contribute to visceral fat accumulation leading to insulin resistance (a hallmark of diabetes), increases in blood pressure levels (hypertension), and other thrombogenic changes that contribute to atherosclerosis, ultimately leading to CVD.[14,52]

Diabetes and hypertension are well-established as leading modifiable risk factors for CVD. Diabetes is associated with a 2-3 fold risk increased for CVD compared to those without diabetes,[53-56] with the risk rising with worsening glycemic control.[57] Hypertension is associated with a 2-4 fold increase in the risk of CVD, depending on the severity of uncontrolled blood pressure, compared to non-hypertensive individuals.[58,59] Mechanisms linking these three cardiometabolic disorders are unclear; however, there are ample evidence for two mechanisms that may explain this link. The first postulates that diabetes, hypertension, and CVD share similar predisposing risk factors contributing to their onset, and thus the independent pathologic processes underlying each of these conditions may evolve in parallel with one another (referred to as the "common soil" hypothesis).[60] While this mechanism revolves around the notion that diabetes and hypertension may be earlier expressions of cardiovascular phenotype due to shared risk factors, the second mechanism suggests that hyperglycemia (diabetes) and elevated blood pressure (hypertension) directly lead to chronic oxidative stress, inflammation and chronic vascular impairment (**Figure 2**), eventually leading to atherosclerotic CVD.

Risk Prediction Models

In order to enable timely prevention and intervention strategies, the development and utilization of accurate risk prediction models are helpful to identify high-risk individuals. The Framingham Risk Score (FRS) is one of the most widely utilized prediction models for CVD and is based on data from the Framingham Heart study, initiated in 1948.[61] The FRS and updated versions have been endorsed by various organizations, such as the Canadian Cardiovascular Society,[62] and incorporate several risk factors that have been identified as significant predictors of CVD events: age, sex, total cholesterol levels, high-density lipoprotein cholesterol levels, blood pressure, smoking status, and diabetes status. Originally designed to estimate 10-year risk of coronary heart disease, this tool was eventually adapted to predict overall CVD (coronary heart disease, stroke, peripheral vascular disease, and heart failure) risk in 2008. Over the years, several iterations of the FRS have been proposed, such as including obesity and physical activity. While obesity and physical inactivity underlie the development of lipid

abnormalities, blood pressure elevation, and diabetes, these predisposing factors are not included in traditional risk models as they have been shown to not enhance prediction when included. Although the FRS has been widely used in clinical practice, it has received criticism for relying on traditional risk factors, despite emerging evidence of other novel risk predictors (e.g., biomarkers),[63] and for its limited accuracy in certain subpopulations (e.g., younger men and women at-risk, those with diverse ethnocultural backgrounds).[64,65] A recent observation study conducted in Ontario demonstrated the traditional FRS overestimated atherosclerotic events rates by 101% among 84,000 residents in Ontario, Canada (aged 40-79). Predicted event rates were compared to observed event rates after 5 years, using linked, validated health administrative databases (EMRALD).[66]

Other risk calculators include the Atherosclerotic Cardiovascular Disease (ASCVD) risk calculator (which additionally incorporates ethnicity, medications used to treat hypertension, and the use of aspirin or statins), and was developed as part of the 2013 American Heart Association guidelines.[67] The current version, known as the ASCVD Risk Estimator Plus, incorporates changes in risk factor levels over time and requires both initial and follow-up values.[68] This allows the application to calculate a patient's previous risk for comparison, and also more precisely adjust one's recent ASCVD-assessed risk by factoring in change in a patient's risk factors over time using the Million Hearts Longitudinal Assessment tool.[69] Recently, the American Heart Association also released the PREVENT risk calculator, which estimates the 10- and 30-year risk of total CVD for adults aged as young as 30.[70] This new calculator incorporates measures of cardiovascular, kidney, metabolic health and social health determinants to estimate the risk for CVD and is sex-specific and race free, being able to be applied to any general population of primary prevention adults. The tool was validated in a total of 46 electronic medical record datasets and observational cohorts, including 6.6 million adults in the United States, aged 30 to 79 years of age. This novel model shows promising performance results in external validation testing (median C-statistics ranging from 0.76 to 0.81)

In Europe, the QRISK and SCORE risk prediction models have gained prominence for estimating cardiovascular risk among European men and women.[71-73] QRISK was developed using data from the United Kingdom's General Practice Research Database and incorporates a wide range of additional risk factors, including social deprivation, ethnicity, body mass index (BMI), and comorbidities such as rheumatoid arthritis and chronic kidney disease. Similarly, the SCORE risk tool, endorsed by the European Society of Cardiology, is currently the gold-standard in Europe for initial clinical risk

assessment and provides region-specific estimates of cardiovascular risk based on traditional risk factors, but with refinement to each region using risk factor distributions and expected incidences.[72,73] Despite their utility in European populations, the generalizability of QRISK and SCORE to other geographic regions remains uncertain, highlighting the need for further validation studies.

A systematic review published in *Circulation*[74] compared 25 different risk-scoring methods, and demonstrated a pooled average concordance of 67% agreement in risk category identification, highlighting the variability that exists between each scoring method. Similarly, a scoping review by Badawy *et al.* evaluated the key features, usability, and benefits of various CVD risk calculators.[75] Their analyses included 17 different studies, each using different algorithms for CVD risk prediction. The QRISK was found to be the most accurate prediction algorithm, whereas the World Health Organization/International Society of Hypertension risk scores were shown to be the least accurate in their study. Moreover, there are additional tools that have been calibrated for use in specific subpopulations with other clinical entities (e.g., a CVD risk calculator for those diagnosed with diabetes).[76,77] In a systematic review published in *Heart*,[76] the authors describe that these risk scores require further validation for improvement, with only a few calculators shown to have a discriminative value >0.80. With the rising interest in applying precision medicine to improve health outcomes, calculators incorporating novel prognostic factors have recently been of high interest, but continue to demonstrate limited incremental predictive utility beyond the aforementioned traditional risk factors.[78] The availability of various algorithms and the development of new calculators portray ongoing efforts to improve CVD risk assessment and management.

2.1.3 The global burden of diabetes

The prevalence of diabetes has significantly risen over the past few decades, evolving into a major public health challenge. Globally, among those aged 20-79 years, diabetes is estimated to affect 537 million adults in 2021, with projections to rise to 784 million by 2045.[79] A recent systematic analysis of the GBD study reported significant increases in rates of age-standardized incidence (117/100,000 persons in 1990 to 183/100,000 in 2019) and DALYs (106/100,000 persons in 1990 to 150/100,000 in 2019) for type 2 diabetes among young adults globally.[80] On the contrary, the global age-standardized incidence rate for type 1 diabetes has only slightly increased over the decades (5.1/100,000 persons in 1990 to 5.4/100,000 in 2017), with studies reporting a decline in the age-standardized mortality rate and DALY rate since 1990.[81]

The burden of type 2 diabetes varies across regions. While high-income countries exhibit a higher prevalence of diabetes due to factors such as obesity and genetic predisposition, the incidence is rapidly increasing in low to middle- income countries, primarily due to urbanization, socioeconomic transitions, inadequate healthcare infrastructure and Westernization of lifestyles.[79,82] Diabetes imposes a significant economic burden on healthcare systems and society, attributed to its related complications. These include peripheral neuropathy, lower limb amputations, nephropathy (e.g., chronic kidney damage), non-alcoholic fatty liver disease, retinopathy, peripheral vascular disease, and most notably, CVD, collectively leading to reduced quality of life, increased disability, and premature mortality.[83]

Diabetes manifests as a metabolic disorder primarily characterized by dysregulation in blood glucose levels, serving as a central mechanism underlying its association with various complications affecting multiple organ systems. Neuropathy in diabetes arises from prolonged exposure of peripheral nerves to high glucose levels, leading to nerve damage and ultimately, limb amputation if not managed properly. Nephropathy in diabetes results from the deleterious effects of hyperglycemia on the renal microvasculature, initiating a cascade of events culminating in diabetic nephropathy and chronic kidney disease. Insulin resistance in the liver promotes hepatic lipogenesis (fatty acid synthesis) and inhibits fatty acid oxidation, resulting in increased accumulation of triglycerides within hepatocytes, a key characteristic of non-alcoholic fatty liver disease. Furthermore, diabetes exacerbates liver injury by promoting oxidative stress, inflammation, and mitochondrial dysfunction, thereby accelerating the progression of non-alcoholic fatty liver disease to more severe liver complications. Retinopathy in diabetes is attributed to microvascular damage within the retina due to hyperglycemia-induced oxidative stress and inflammation, contributing to vision impairment and blindness. Peripheral vascular disease in diabetes is triggered by endothelial dysfunction and a pro-inflammatory state secondary to hyperglycemia, leading to impaired blood flow, tissue hypoxia, and subsequent limb complications. Lastly, cardiovascular complications in diabetes stem from the interplay of hyperglycemia, insulin resistance, and dyslipidemia, fostering the development of atherosclerosis and subsequent CVD (**Figure 2**).

In 2019, diabetes was the direct cause of 1.5 million deaths and listed as the eighth leading cause of death globally,[84] climbing up from its listed 20th rank only three decades ago. Furthermore, utilizing

data from the 2019 GBD study, the World Health Organization reported that hyperglycemia was responsible for approximately 20% of CVD deaths in 2019.[85] Treatment of this complex endocrine disease and its related microvascular and macrovascular complications is substantially costly, resulting in increased medical consultations, escalated pharmacotherapy costs, and a rise in hospital admissions.[86]

2.1.4 Traditional risk factors for type 2 diabetes and risk prediction models

Traditional risk factors of diabetes encompass a multifaceted interplay of genetic, demographic, lifestyle, and metabolic factors. These factors include genetic predispositions, obesity and body composition, physical inactivity, suboptimal dietary habits, age, sex, and ethnicity. Briefly, genetic predisposition plays a fundamental role in the pathogenesis of diabetes. Previous studies have identified specific genetic variants associated with an increased susceptibility to type 2 diabetes, such as TCF7L2 and PPARG.[87] Suboptimal dietary habits (high intake of refined carbohydrates, saturated fats, and processed foods) and physical inactivity are major risk factors for high fasting plasma glucose, leading to caloric imbalance, weight gain and visceral fat accumulation (**Figure 2**). The accumulation of visceral fat is known to contribute to the release of inflammatory cytokines and adipokines, disrupting insulin signaling and promoting insulin resistance.[88] Moreover, excess adiposity exacerbates dyslipidemia and ectopic lipid deposition, contributing to beta-cell dysfunction and impaired glucose metabolism.[89] Epidemiological studies consistently demonstrate a dose-response relationship between obesity and type 2 diabetes risk,[90] underscoring the imperative of weight management strategies in diabetes prevention.[91]

Hypertension and dyslipidemia are common comorbidities that frequently co-occur with diabetes, given their shared burden of risk factors. Hypertension manifests in around 30% of individuals with type 1 diabetes and 50-80% of individuals with type 2 diabetes within the United States.[92] Hypertension contributes to inflammation and oxidative stress, exacerbating insulin resistance and impairing glucose uptake. Similarly, dyslipidemia is believed to promote a pro-inflammatory state and impair insulin signaling pathways, thereby escalating resistance to insulin action.[14]

Risk Prediction Models

Various tools and models have been developed to predict the risk of type 2 diabetes. However, the methodologies used in developing these models vary. A systematic review was conducted to identify

studies that report the development of prediction models for the risk of prevalent or incident type 2 diabetes.[93] The authors investigated 39 studies which utilized a total of 43 different risk prediction models; however, they highlight that the majority of these risk calculators suffer from poor methodology and/or reporting of their methods, thus compromising the application of these calculators. Issues ranged from utilizing improper methods for variable selection (univariate pre-screening), categorization of continuous risk predictors, poor handling of missing data, lack of minimal sample size and statistical power (events per variable criterion) and insufficient information on the number of considered risk predictors.

Among the various existing risk calculators for diabetes, the Canadian Diabetes Risk Assessment Questionnaire (CANRISK), the American Diabetes Association Risk Test and the Finnish Diabetes Risk Score tools are among the most prominently used in Europe and North America. Focusing on the Canadian context, the CANRISK tool was created and validated in 2011 by the Public Health Agency of Canada and encompasses age, ethnicity, family history, history of high blood glucose, hypertension, physical activity, and dietary habits to estimate diabetes risk.[94] The tool comprises a series of inquiries that delineate one's risk (low: <21, moderate: 21–32, high = >32). These pre-existing score cut-off points were established by analyzing data from a cohort of 6,200 Canadians from seven provinces, where CANRISK was administered alongside the gold standard OGTT.[95] It should be noted that CANRISK was initially validated in a Canadian population (aged 40 years and older), and therefore, it is typically not used to screen diabetes risk among younger adults. Interestingly, a recent study utilizing a sample of Indigenous Peoples, discovered that CANRISK may have potential to be utilized on those below 40 years of age with an adjustment of the score cut-off to enhance sensitivity and reduce false negatives.[96]

Studies evaluating the performance of risk prediction models have reported varying degrees of discrimination and calibration, influenced by factors such as study population characteristics, follow-up duration, and outcome definition. For example, a systematic review by Noble *et al.* evaluated the performance of 145 risk prediction models for type 2 diabetes and found substantial variability in discrimination, with the c-statistic ranging from 0.60 to 0.91.[97] Calibration, however, was generally poorer and suffered from substantial variability across studies, indicating the need for recalibration or customization of models to specific populations to enhance accuracy and generalizability. The authors

also note that inclusion of genetic markers did not further enhance prediction over traditional clinical and sociodemographic factors.

2.1.5 The global burden of hypertension

The escalating prevalence of hypertension globally is well recognized as a serious public health concern. In 2019, it was approximated that this condition affected approximately 1.13 billion individuals, with a global prevalence of 24.1%.[98] Globally, hypertension is estimated to account for 218 million DALYs and over 10 million deaths annually, with the majority of this burden being attributable to CVD that it predisposes individuals to, serving as its leading risk factor.[99] The prevalence of hypertension has doubled in the last three decades,[100,101] hence, the World Health Assembly in 2013 set a target to reduce the prevalence of hypertension by 25%, as one of its global non-communicable disease goals.[102] Moreover, uncontrolled hypertension also contributes to development of renal dysfunction (e.g., chronic kidney disease), retinopathy, peripheral arterial disease, aneurysms, and cognitive impairment, further exacerbating the disease burden.[103]

Briefly, the kidneys, which are crucial regulators of blood pressure, are susceptible to damage from hypertension-induced vascular changes, leading to hypertensive nephropathy and eventual renal dysfunction or failure. Concurrently, hypertension-induced damage extends to the ocular vasculature, resulting in retinopathy, a condition characterized by retinal damage and visual impairment. Additionally, hypertension plays a pivotal role in the pathogenesis of peripheral arterial disease, impairing blood flow to the extremities and leading to symptoms such as claudication and compromised wound healing. The sustained pressure exerted by hypertension on arterial walls also weakens their integrity, increasing the risk of aneurysms. Furthermore, chronic hypertension is implicated in cognitive decline and dementia, as it compromises cerebral blood flow and oxygen delivery, ultimately contributing to neuronal damage and cognitive impairment, including Alzheimer's disease. Lastly, the chronic elevation of blood pressure contributes to the development of atherosclerosis by inducing endothelial dysfunction, promoting lipid deposition, fostering inflammation, and facilitating plaque destabilization. These processes collectively increase the risk of CVD by predisposing individuals to the formation of obstructive coronary lesions and the rupture of vulnerable plaques (**Figure 2**).

While hypertension affects individuals across all regions, there are significant disparities in its prevalence and control rates among different geographic areas and populations. Low- and middle-income countries bear a disproportionate burden of hypertension, with higher prevalence rates observed in urban compared to rural areas. Additionally, certain demographic groups, such as older adults and individuals from socioeconomically disadvantaged backgrounds, are more likely to experience hypertension and its associated complications. Despite the availability of effective lifestyle modifications and pharmaceutical treatments, the proportion of hypertension awareness, treatment, and control remains low globally. The World Health Organization has been actively involved in supporting countries to reduce hypertension and CVD as a public health priority through initiatives such as the Global Hearts Initiative,[104] which was initiated in 2017 and has demonstrated the feasibility and effectiveness of standardized hypertension control programs.

The economic burden of hypertension on healthcare systems is substantial, encompassing direct medical costs, productivity losses, and DALYs.[98] In particular, the financial burden that hypertension imposes is estimated to be about 10% of the world's healthcare expenditures, varying across regions.[105] In low to middle- income countries where healthcare resources are limited, managing and living with hypertension poses significant challenges due to inadequate infrastructure, lack of trained personnel, and limited access to essential medications.[106]

2.1.6 Traditional risk factors of hypertension and risk prediction models

The development of hypertension is multifactorial, influenced by a combination of non-modifiable risk factors (e.g., age and genetic predisposition) and modifiable behavioral factors.

Obesity, physical inactivity, excessive salt intake, low potassium consumption, alcohol consumption, tobacco use are well-established modifiable risk factors for hypertension[9,107] and the common substrate of conditions that allow hypertension to frequently co-occur with diabetes.[14] **Figure 2** details the mechanistic pathways linking elevated blood pressure and these modifiable risk factors, underscoring the importance of preventive measures and lifestyle modifications in its management.

Age, genetic predisposition, ethnicity, and sex are non-modifiable risk factors for hypertension. Briefly, age plays a significant role, as blood pressure tends to increase with advancing age due to physiological changes in blood vessels and the cardiovascular system. Additionally, family history of

hypertension contributes to the risk, indicating a genetic predisposition to the condition. For example, studies have identified several genetic variants associated with increased susceptibility to hypertension. For instance, a genome-wide association study by Ehret *et al.* identified multiple genetic loci linked to blood pressure regulation, including genes involved in renal sodium handling and vascular smooth muscle function.[108] Similarly, a meta-analysis conducted by Evangelou *et al.* confirmed the role of genetic polymorphisms in genes such as angiotensinogen, angiotensin-converting enzyme, and endothelial nitric oxide synthase in hypertension susceptibility.[109] Ethnicity is associated with differences in hypertension prevalence, with individuals of African descent having a higher risk compared to other racial or ethnic groups. The underpinnings for this association may stem from other related upstream characteristics, such as food insecurity,[110] local environments not conducive to physical activity,[111,112] structural inequity and histories of colonialism.[113] Sex also plays a role, with men generally having a higher risk of hypertension until around age 65, after which the risk becomes similar between men and women.

Furthermore, recent studies have additionally identified social determinants and environmental factors to influence hypertension risk. For example, emerging evidence shows that levels of education, air pollution, psychosocial stress and insomnia may be associated with the development of chronic hypertension.[114-116] Chronic psychological stress, arising from contemporary habits and customs, is commonly linked with physiological and psychological disruptions, and may indirectly contribute to the development of hypertension.[14] Social determinants of health, such as level of education, may inherently reflect an individual's access to healthcare services, quality of nutrition, and exposure to chronic stressors, all of which contribute to hypertension development through various pathways (including neuroendocrine dysregulation and suboptimal coping behaviors).[117] Although epidemiologic investigations have demonstrated these emerging associations, futures studies are required to investigate these mechanisms which are not completely understood.

Risk prediction models

Although several investigators have developed their own prediction tools to delineate future hypertension risk,[118-124] the most well-known calculator is the Framingham Hypertension Risk Score.[118] This risk calculator is based on the data from the landmark Framingham Heart Study, derived from 1700 individuals (20-69 years of age), who were free of CVD, hypertension and diabetes at baseline.[118] Although the tool has been shown to have good prediction when estimating the risk of developing

hypertension typically within four years (c-statistic = 0.79), its developers acknowledge that the scoring method may not be generalizable to persons of non-European origin or to persons with diabetes. Other groups of investigators have recently shown that recalibration of the model (intercept, scale parameter, coefficients) may enhance its prediction for other individuals of non-European origin (c-statistic = 0.81).[125] Currently, the tool is based on a single measurement of risk factors (age, sex, BMI, smoking status, systolic and diastolic blood pressure, and parental history of hypertension) and blood pressure.

A previous systematic review summarized the performance measures of existing hypertension risk models at the time, identifying gaps in evidence on their prognostic ability and the need for future improvement (c-statistic>0.70).[126] The best performing models were shown to be the Framingham and Hopkins risk calculator, demonstrating a c-statistic ranging from 0.71to 0.81, which indicated acceptable-to-good discriminatory capability compared to various hypertension risk models.

A recent Chinese study in 2022 demonstrated good prediction (c-statistic = 0.82) among an internal validation group of 3,000 individuals, showing a sensitivity of 83.4% and specificity of 64.3%.[127] Furthermore, within the Canadian context, a study in 2022 developed a hypertension risk prediction model that was validated among 18,000 Canadians, and demonstrated both good model performance (discrimination [c-statistic = 0.77] and calibration [Grønnesby and Borgan test statistic= 8.75]).[128]

In conclusion, to reduce the burden of diabetes, hypertension and CVD, it is essential to identify populations at high risk in order to improve modifiable risk factors and initiate early management. Risk assessment calculators have become integral tools in the era of precision medicine, which aims to utilize a combination of demographic, clinical, and lifestyle factors to estimate an individual's likelihood of developing a particular disease over a specific time frame. As discussed above, various tools are available to assess an individual's cardiometabolic risk, whose data can be incorporated in precision medicine approaches aimed at tailoring interventions to the individual; however, current risk assessment tools do not incorporate these cardiometabolic abnormalities that may manifest during pregnancy. These abnormalities are of particular interest among reproductive-aged women as they offer early indications of long-term risk and can potentially lead to more effective strategies for preventing CMD and its associated complications on an individual level.

2.2 Pregnancy: a specific window-of-opportunity for risk assessment in women

Pregnancy offers an opportunity to detect future risks for diabetes, hypertension, and CVD, as reflected by the occurrence of adverse pregnancy outcomes, the most notable of which are new onset diabetes (GDM) and new-onset hypertension (GHTN with or without preeclampsia). Despite their recognition as early indicators of CVD from the American Heart Association,[27,129] European Society of Cardiology,[31] and International Federation of Gynecology and Obstetrics,[30] none of the risk engines described above incorporate these pregnancy complications in their risk equations.

Pregnancy embodies a crucial stage in a woman's life, distinguished by significant alterations in her physiological state to accommodate the demands of the developing fetus. A mounting body of proof implies that pregnancy provides a unique opportunity to evaluate the well-being of the heart and metabolism. The interaction among the physiological processes of the mother, the development of the fetus, and the long-term health outcomes of both mother and offspring highlight the significance of understanding important pregnancy-related risk factors related to her cardiometabolic conditions during this crucial period. Pregnancy can be viewed as an early cardiometabolic "stress test" that a woman experiences in her life,[130] given that it naturally puts the mother in a pro-atherogenic metabolic state. Physiological changes, including increased insulin resistance, elevated inflammatory activity, altered lipid metabolism, increased cardiac output and hypercoagulability are central to these adaptations.[131]

Insulin is a hormone that allows the body's fuel, glucose, to enter cells. During pregnancy, insulin resistance inherently develops to allow glucose to be preferentially delivered to the fetus[132] while preserving maternal nutrient stores. In order to regulate and maintain normoglycemia in the mother, the pancreas must produce more insulin in response. Studies have demonstrated that the fasting levels of insulin in the plasma during late pregnancy are nearly two times higher compared to the levels observed after childbirth.[133] Women whose insulin resistance rises more markedly or was already elevated before pregnancy may develop GDM, because they cannot increase insulin levels high enough to counter the resistance. GDM is a type of diabetes that first manifests during pregnancy, specifically at or after 20 weeks of pregnancy; this condition affects 7-16% of Canadian pregnancies.[134] Genetic predisposition, obesity, suboptimal dietary habits, and physical inactivity may all contribute to increased insulin resistance and development of GDM. In pregnant women without pre-existing diabetes, plasma glucose levels above defined thresholds warrant a diagnosis of GDM. The latest 2018

Diabetes Canada and 2019 Society of Obstetricians and Gynecologists of Canada guidelines suggest a fasting plasma glucose=5.1 mmol/L; 1-hr post glucose loading=10.0 mmol/L; 2-hr post glucose loading=8.5 mmol/L when performing one-step testing (criteria for two-step testing are shown in **Table 1**). Specific thresholds continue to be debated, partly because glucose levels have a continuous association with fetal overgrowth and other outcomes, as demonstrated in the longitudinal Hyperglycemia and Adverse Pregnancy Outcomes study.[135]

Table 1. Defining diabetes and hypertension in pregnancy

Condition	Standard Definition
Diabetes in Pregnancy	
Pregestational diabetes (pre-existing diabetes)	Type 1 diabetes or type 2 diabetes that is present before 20 weeks' gestation of pregnancy. This can include diagnosed or undiagnosed diabetes.
Gestational diabetes mellitus	Diabetes that is diagnosed at or after 20 weeks' gestation. The following are criteria that warrant a diagnosis as endorsed by the latest 2018 Diabetes Canada and 2019 Society of Obstetricians and Gynecologists of Canada guidelines: ***1-step 75g oral glucose tolerance test:*** 1) Fasting: 5.1 mmol/L 2) 1-hr post glucose loading: 10.0 mmol/L 3) 2-hr post glucose loading: 8.5 mmol/L ***2-step 75g oral glucose tolerance test (50g glucose challenge test between 7.8-11.1 mmol/L, proceed to steps below. Greater than 11.1 mmol/L warrants immediate diagnosis):*** 1) Fasting: 5.3 mmol/L 2) 1-hr post glucose loading: 10.6 mmol/L 3) 2-hr post glucose loading: 9.0 mmol/L
Hypertensive Disorders of Pregnancy	
Gestational hypertension	
• Without preeclampsia	De novo blood pressure elevations (≥140 [systolic] / 90 [diastolic]), based on the mean of at least 2 readings (taken at least 15 min apart and using the same arm), after 20 weeks' gestation without other indicators of organ system dysfunction.
• With preeclampsia	De novo blood pressure elevations (≥140 [systolic] / 90 [diastolic]), based on the mean of at least 2 readings (taken at least 15 min apart and using the same arm), after 20 weeks' gestation, coupled with proteinuria or other indicators end-organ dysfunction. As endorsed by the International Society for the Study of Hypertension in Pregnancy, these symptoms include: Acute kidney injury (creatinine ≥90umol/L; 1 mg/dL) Liver involvement (elevated transaminases, e.g., alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain Neurological complications (examples include eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata) Hematological complications (thrombocytopenia–platelet count <150 000/μL, disseminated intravascular coagulation, hemolysis) Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth)
Chronic hypertension	Elevated blood pressure (≥140 [systolic] / 90 [diastolic]) before 20 weeks' gestation.
Chronic hypertension with superimposed preeclampsia	Elevated blood pressure (≥140 [systolic] / 90 [diastolic]) with new-onset proteinuria or other end-organ dysfunction after 20 weeks' gestation, in addition to pre-existing chronic hypertension.
Other hypertensive effects	***White-coat hypertension***: elevated blood pressure in the office (i.e., systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg), but systolic < 135 mmHg and diastolic < 85 mmHg on ambulatory or home blood pressure monitoring. ***Masked hypertension***: blood pressure that is normal in the office but elevated on ambulatory or home blood pressure monitoring (i.e., systolic ≥ 135 mmHg or diastolic ≥ 85 mmHg).

During pregnancy, blood pressure is expected to slightly fall below normal levels given the vasodilatory role of circulating peptide hormones. Reduced vascular resistance supports the increased flow of blood to the placenta for the developing fetus (optimal perfusion of the uteroplacental circulation).[132,136] However, during pregnancy, a woman's blood pressure may also rise abnormally as a result of vascular resistance stemming from physical inactivity, nutritionally inadequate diets, obesity or genetic predisposition. In some instances, blood pressure may rise due to problems with placental implantation leading to placental insufficiency; this may be related to the above factors or from other sources, such as immunological phenomena. Hypertensive disorders of pregnancy (HDP) are defined as elevated blood pressure levels of 140/90 mm Hg during pregnancy and complicate 2-8% of pregnancies. HDP includes pre-existing hypertension (diagnosis before 20 weeks' gestation; **Table 1**), GHTN without preeclampsia (new diagnosis at or after 20 weeks' gestation) or with preeclampsia (elevated blood pressure accompanied by new or worsening proteinuria or indicators of other maternal organ dysfunction [e.g., platelet count <150 000/μL]), which may be superimposed on either GHTN alone or on pre-existing hypertension.[137]

The onset of preeclampsia is closely linked to placental insufficiency, which induces a cascade of physiological changes in both the fetus and the mother, including alterations in the renin-angiotensin-aldosterone system (RAAS), endothelial dysfunction, inflammation, and sympathetic activation, all of which can contribute to elevated blood pressure (**Figure 2**).[132] Briefly, one of the primary pathways involves the RAAS, which plays a crucial role in regulating blood pressure. Placental insufficiency can result in reduced oxygen and nutrient supply to the developing fetus, leading to fetal distress. Maternal physiological responses to fetal distress include increased sympathetic nervous system activity and the release of pro-inflammatory cytokines, thus stimulating the production of angiotensin II in the maternal circulation. Angiotensin II is a potent vasoconstrictor that increases peripheral vascular resistance, thereby further exacerbating endothelial dysfunction and promoting raised blood pressure. Furthermore, placental insufficiency can lead to fetal growth restriction and intrauterine hypoxia, triggering the release of placental factors such as soluble fms-like tyrosine kinase-1 and soluble endoglin into the maternal circulation. These factors interfere with endothelial function and vasodilation, promoting vasoconstriction and endothelial dysfunction, which can contribute to elevated blood pressure in the mother.

GDM and GHTN serve as early clinical indicators of heightened cardiometabolic risk during pregnancy.[27,33,34] They generally resolve soon after delivery but are harbingers of future diabetes, hypertension, and CVD. These adverse pregnancy occurrences often coexist with metabolic dysregulation, endothelial dysfunction, and systemic inflammation, contributing to an increased risk of type 2 diabetes, hypertension, and CVD risk later in life. Recognizing these associations is an essential part of conducting a comprehensive risk assessment during pregnancy to identify those at heightened risk. Although evidence has emerged over the years demonstrating the increase in CMD risk among women with GDM or GHTN,[17,25,26,33-35,39] risk stratification tools for diabetes, hypertension, and CVD typically do not incorporate these adverse pregnancy complications in their prediction models. Ignoring their presence is a missed opportunity to further refine risk stratification among women who have been pregnant, as the postpartum period offers an opportunity for targeted interventions to mitigate these risks. Lifestyle modifications, including diet and exercise interventions, have shown promise in reducing the incidence of diabetes, hypertension, and CVD among high-risk women,[91,138,139] specifically in the case of GDM. Moreover, optimal GDM management has been shown to lower rates of preeclampsia.[140,141] Further, pregnancy and the postpartum period shortly after may also be a time where younger women are interested in tackling health issues to optimize the short- and long-term health of the family.[142]

2.3 Gestational Diabetes

2.3.1 Definition and diagnosis of gestational diabetes

GDM is a prevalent metabolic disorder characterized by glucose intolerance with onset or first recognition at or after 20 weeks' gestation of pregnancy. The definition and diagnostic criteria for GDM have evolved over time,[134] reflecting advancements in understanding its pathophysiology and the need for effective screening and management strategies. The variability in screening and diagnostic criteria are expanded upon in detail within Manuscript 4 of this thesis. Briefly, in Canada, GDM is now screened for universally among all pregnant women, typically beginning at the period of 20 weeks' gestation in persons judged to be at high risk, and onwards up to 28 weeks' gestation, with the physician either using a one-step or two-step approach (**Table 1**). In the one-step approach, a pregnant woman undergoes a single 2-hour OGTT with a 75 gram oral glucose load; blood samples are taken fasting and at 1-hour and 2-hour time points. The 2018 Diabetes Canada and 2019 Society of Obstetricians and Gynecologists of Canada guideline suggest a fasting plasma glucose=5.1 mmol/L, 1-hr post glucose loading=10.0 mmol/L, or 2-hr post glucose loading=8.5mmol/L to warrant a

diagnosis of GDM. In the two-step approach, initial screening is performed using a glucose challenge test (GCT), also known as the glucose screening test. This test involves drinking a glucose solution (50 grams), followed by measuring blood glucose levels after a specified period, typically 1 hour. If the result of the GCT is above 7.8-11.1 mmol/L, the individual proceeds to a diagnostic OGTT. If the result of the GCT is above 11.1 mmol/L, an immediate diagnosis of GDM is warranted. During the OGTT, blood glucose levels are measured at fasting and at 1-hour and 2-hour intervals after drinking a higher concentration glucose solution. The most recent Canadian guidelines unanimously suggest a fasting plasma glucose=5.3 mmol/L, 1-hr post glucose loading=10.6 mmol/L or 2-hr post glucose loading=9.0 mmol/L in order to conclude a diagnosis of GDM when using the two-step approach.

Over the years, there have been efforts to standardize diagnosis of GDM to improve short- and long-term maternal and offspring outcomes. Historically, GDM was diagnosed based on the subjective judgement of the practicing physician when assessing serum glucose levels through random glucose measurements or an OGTT. However, these methods lacked standardization and were prone to variability (i.e., number of steps required, diagnostic thresholds considered, number of abnormal values required for a diagnosis, recommended glucose loads for OGTT) leading to inconsistencies in the diagnosis, management and reported prevalence of GDM worldwide. In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) proposed new diagnostic criteria based on the Hyperglycemia and Adverse Pregnancy Outcome study, advocating for a one-step approach using OGTT with lower threshold values than were generally used at the time. Currently, the Diabetes Canada and Society of Obstetricians and Gynecologists of Canada guideline recommendations for diagnosing GDM follow these criteria suggested by IADPSG; however, also equally endorse the use of the two-step approach (**Table 1**).

2.3.2 Incidence and prevalence

Studies indicate substantial variability in the reported incidence rates of GDM worldwide (varying from 1-28%), attributed to differences in screening methods, diagnostic criteria, population demographic factors, and differences in excess weight and physical inactivity prevalence.[143,144] Aligned with these reports, a meta-analysis from International Diabetes Federation special interest group reported prevalence rates of 7% in North America and the Caribbean, 8% in Europe, 10% in South American and Central America, 15% in Africa, 21% in South Asia and 28% in the Middle East and North African regions in 2021.[145] The authors of this meta-analysis also show that the standardized

prevalence of GDM was high, irrespective of the regions being in developing or developed countries. Low-, middle- and high-income countries demonstrated standardized GDM prevalences of 12.7% (11.0-14.6%), 9.2% (9.0-9.3%) and 14.2% (14.1-14.2%), respectively, in 2021. In Canada, GDM is believed to affect 7-16% of pregnancies,[146] while globally it is estimated to occur in 14-17% of pregnancies.[145,147,148]

2.3.3 Pathophysiology

Insulin resistance and beta-cell dysfunction

During pregnancy, insulin resistance develops in the mother to allow the delivery of glucose across the placenta to the growing fetus via facilitated diffusion.[132] Insulin resistance is a hallmark of GDM's pathophysiology, occurring primarily within the woman's peripheral tissues such as the muscle, liver and adipose tissue. During pregnancy, significant changes occur in the maternal adipose tissue, including the release of adipokines (adiponectin and leptin), contributing to the development of insulin resistance.[131,149] Additionally, placental hormones, including human placental lactogen and placental growth hormone, antagonize insulin action, further exacerbating insulin resistance. Concomitant with insulin resistance, there is a decline in pancreatic beta-cell function. This dysfunction is attributed to the increased demand for insulin production during pregnancy, leading to beta-cell exhaustion and apoptosis.[150] Moreover, the placental production of cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), contributes to beta-cell dysfunction by promoting apoptosis and impairing insulin gene expression.[151,152]

Placental dysfunction

The placenta plays a pivotal role in the pathogenesis of GDM, acting as an endocrine organ that secretes hormones and cytokines influencing maternal metabolism. Placental dysfunction, characterized by abnormal trophoblast invasion and inadequate spiral artery remodeling, results in ischemia and oxidative stress, contributing to insulin resistance.[153] Inflammatory pathways are implicated in the pathophysiology of GDM, with elevated levels of pro-inflammatory cytokines, such as TNF-α, IL-6, and C-reactive protein, observed in affected individuals[151,152] These inflammatory mediators promote insulin resistance by impairing insulin signaling pathways and disrupting glucose uptake in target tissues.

Most women are able tolerate these metabolic demands of pregnancy. However, in some situations, these physiological changes may be poorly tolerated, leading to the development of GDM. These situations usually occur in women whose insulin resistance was pre-existing or rose more markedly in pregnancy as a consequence of genetic predisposition, obesity, gestational weight gain, suboptimal dietary patterns, and/or physical inactivity.

In conclusion, the pathophysiology of GDM involves complex interactions between insulin resistance, beta-cell dysfunction, placental abnormalities, inflammatory pathways, and genetic and environmental factors. A comprehensive understanding of these mechanisms is essential for the development of targeted therapeutic interventions and preventive strategies to mitigate the adverse maternal and fetal outcomes associated with GDM.

2.3.4 Maternal risk factors

Similar to the development of type 2 diabetes, risk factors influencing the onset of GDM are multifactorial and encompass shared risk factors associated with type 2 diabetes. Both type 2 diabetes and GDM stem from similar risk factors since they are both hyperglycemic conditions, with the difference being that GDM is a specific form of hyperglycemia that first manifests during pregnancy and typically resolves after pregnancy. Traditional risk factors include a family history of diabetes, nutritionally inadequate diets, obesity, physical inactivity, smoking, advanced maternal age, and ethnicity. The rising epidemic of overweight and obesity are believed to be substantial contributors to the increasing prevalence of GDM among pregnant women of reproductive age.[154,155] Weight gain (including throughout a woman's pregnancy, termed "gestational weight gain"), suboptimal dietary habits, and physical inactivity are all factors that contribute to the accumulation of visceral fat (**Figure 2**). The chronic low-grade inflammation associated with this accumulation disrupts insulin signaling pathways, leading to insulin resistance. Given that insulin resistance is already one of the inherent changes of pregnancy, women whose insulin sensitivity has already been impaired due to weight gain and physical inactivity over the years are at heightened risk of reaching a hyperglycemic threshold during pregnancy.

Maternal Age

Advanced maternal age has consistently been identified as a significant risk factor for GDM. The physiological changes accompanying aging, such as decreased insulin sensitivity and impaired

pancreatic function, may predispose older mothers to glucose intolerance during pregnancy. A recent meta-analysis demonstrated for each additional year in maternal age after the age of 18, GDM risk was shown to increase by 7.90%.[156]

Nutrition and Diet

A recent 2023 systematic review of 44 observational studies demonstrated that iron, processed meat, and low carbohydrate diets (that consist of low-quality carbohydrates) were positively associated with GDM, while consumption of fruits, vegetables, eggs, folic acid and antioxidant nutrients were protective of GDM.[157]

Family History and Genetics

A family history of diabetes, particularly a first-degree relative with type 2 diabetes mellitus, confers an increased risk of GDM. Genetic susceptibility genes associated with type 2 diabetes, such as TCF7L2 and KCNJ11, have been implicated in the pathogenesis of GDM.[158,159] Additionally, shared environmental factors within families, including dietary habits and sedentary lifestyles, contribute to familial clustering of insulin resistance.[160]

Ethnicity

Ethnic disparities in GDM prevalence highlight the influence of genetic and sociodemographic factors on disease susceptibility. Studies have consistently shown higher GDM rates among certain ethnocultural groups, including individuals from South Asian, Hispanic, and African-American origin, compared to those of European origin. Genetic predispositions, coupled with lifestyle and dietary practices, contribute to the observed ethnic variations in GDM risk.[161,162] These disparities suggest that genetic, cultural, and socioeconomic factors may play a role in the development of GDM, as well as colonial histories and structural racism, as experienced, for example, by Indigenous peoples.[163]

Pregnancy-related and Fertility-related Factors

Pregnancy-specific and fertility-related factors may also influence the risk of GDM. These include gestational weight gain, parity, polycystic ovary syndrome (PCOS) and history of a previous pregnancy with GDM or GHTN. Women with PCOS are speculated to have heightened risk of developing GDM due to the underlying metabolic abnormalities and hormonal imbalances inherent to this condition, thus leading to heightened insulin resistance.[164,165]

A Kaiser Permanente (California) study among 1145 multiethnic women demonstrated higher odds of developing GDM with increasing rates of gestational weight gain. Relative to women in the lowest tertile of gestational weight gain (<0.27 kg/week), women who gained 0.27-0.39 kg/week had 43% higher odds of GDM, while those who gained 0.40 kg/week demonstrated 74% higher odds; this association was elevated even higher among women who were already overweight/obese pre-pregnancy.[166] Aligned with these estimates, a meta-analysis of 70 studies demonstrated that compared to women with normal pre-pregnancy BMI, overweight women had 2-fold elevated risk of GDM, while obese women had 3-fold higher risk.[167]

The association between parity and GDM may be due to factors such as changes in maternal physiology with each successive pregnancy, including increased insulin resistance and alterations in glucose metabolism.[168] Independent of these factors, other theories suggest that the parity may be linked to GDM due to progressive ageing and weight gain either before or during pregnancy, particularly when the inter-delivery period extends across many years in-between.[164] Additionally, a history of GDM in previous pregnancies significantly elevates the risk of recurrence in subsequent pregnancies, with meta-analyses showing the rate of recurrence to be as high as 48%.[41,42]

Lastly, GHTN is also a risk factor for GDM. This finding was first reported by Carpenter *et al.,*[141] who reported an elevated risk of developing GDM among women diagnosed with GHTN. Fasting hyperinsulinemia in mid-pregnancy has been shown to be associated with the subsequent development of GHTN (without preeclampsia) in a Japanese cohort of 84 women[169] and development of preeclampsia in African-American women,[170] independent of BMI. Furthermore, among 3,300 nulliparous women, a secondary analysis of the Calcium for Preeclampsia Prevention trial[171] demonstrated that the relative risk of developing GHTN without preeclampsia (RR=1.48, 95%CI 0.99-2.22), or with preeclampsia (RR=1.67, 95%CI 0.92-3.05), was heightened among women with GDM, compared to those without GDM; the investigators demonstrated conclusive associations when GHTN, with or without preeclampsia, was combined (RR=1.54, 95%CI 1.28-2.11). It is believed that chronic inflammation and oxidative stress, secondary to elevated blood pressure among women with GHTN, can contribute to the development of insulin resistance, and thus development of GDM (**Figure 2**).[172]

2.3.5 Perinatal maternal and offspring complications

GDM poses significant risks not only to the maternal health, but also to fetal and neonatal outcomes. The intergenerational transmission of metabolic disturbances underscores the importance of early intervention and preventive measures targeting both maternal and offspring health.

Macrosomia / Large for Gestational Age

One of the most well-documented complications of GDM is fetal overgrowth, leading to macrosomia and/or LGA offspring.[173-175] Increased maternal glucose levels cross the placenta, resulting in fetal hyperinsulinemia and subsequent excessive growth. Studies have consistently shown a positive correlation between poor glycemic control during pregnancy and the risk of macrosomia. A systematic review of 12 studies demonstrated that the mothers with GDM had 1.7-fold higher odds of delivering a macrosomic offspring compared to non-GDM mothers.[174] In a randomized control trial conducted by Landon *et al.,*[175] it was demonstrated that tighter glycemic control during pregnancy significantly reduced the incidence of macrosomia. Moreover, GDM in previous pregnancy may influence the risk of fetal overgrowth in a woman's subsequent pregnancy, even if unaffected by GDM. For example, in a retrospective study conducted by Kim *et al.,*[176] the investigators only included women who had two consecutive live births and examined how a woman's diabetes status (no diabetes, GDM, or chronic diabetes) in one pregnancy affected the offspring outcomes in the other pregnancy, even if the diabetes status changed between the two pregnancies. Compared to women without GDM in either pregnancy, women with GDM only affecting their first pregnancy had a higher prevalence of macrosomia (17.2% versus 12.3%) and LGA offspring (18.2% versus 12.3%) during their second delivery. Similarly, relative to those without GDM, women with GDM only affecting their second pregnancy were shown to have a higher prevalence of macrosomic (14.9% versus 9.7%) and LGA offspring (15.1% versus 8.5%) in their first pregnancy. Although prepregnancy BMI and gestational weight gain were not measured in the study, the authors suggest women with GDM, even in one pregnancy, may have higher glucose levels during other pregnancies, even if they do not meet the full criteria for a GDM diagnosis at that time. This highlights the importance of monitoring glucose levels and managing diabetes across all pregnancies, not just the current one, to optimize maternal and infant health.

Birth Trauma

Macrosomic infants born to mothers with GDM are at higher risk of birth trauma due to their increased size. Shoulder dystocia, brachial plexus injury, and fractures are common complications observed during delivery. A retrospective cohort study by Weissmann-Brenner *et al.* found a significant linear association between LGA offspring (birthweight: 90-94.9th, 95-98.9th to ≥ 99th percentiles) and shoulder dystocia, (OR= 2.61, 3.35 and 5.11, respectively), emphasizing the need for meticulous prenatal monitoring and delivery planning (e.g., cesarean delivery) in affected pregnancies.[177] Moreover, cohort studies have shown that treatment of mild GDM significantly reduces the incidence of shoulder dystocia.[175] GDM in a one pregnancy may also have associations with outcomes in other pregnancies, irrespective of whether the affected pregnancy precedes or follows. In the Kim *et al.* study described above,[176] the authors also examined the incidence of cesarean section across a first and second pregnancy among women various patterns of GDM occurrence. Women with GDM only affecting their first pregnancy showed a higher incidence of cesarean delivery (37.9% versus 27.0%) in their second pregnancy compared to those without GDM in either pregnancy. Likewise, women with GDM only in their second pregnancy also demonstrated increased rates of cesarean delivery (31.3% versus 24.7%) in their first pregnancy, relative to the group in which GDM was absent in both pregnancies.

Preterm Birth

Research has shown that pregnant women with GDM are at higher risk of delivering prematurely (before 37 weeks of gestation), compared to those without GDM. In a population-based retrospective cohort study, Hedderson *et al.*[178] demonstrated increasing levels of maternal glucose intolerance to be associated with stepwise elevated incidence rates and odds for spontaneous preterm birth. In women with normal glucose screening values (1-hour plasma glucose less than 7.8 mmol/L), the age-adjusted incidence of spontaneous preterm birth was 4.0%, while among those with abnormal glucose screening values (1-hour plasma glucose of at least 7.8 mmol/L with a normal diagnostic 100-g 3-hr OGTT), it was 5.0%. Similarly, the incidence was 6.7% in those meeting the Carpenter-Coustan criteria for GDM (at least two values higher than the following cutoffs during 100g OGTT: fasting, 5.3 mmol/L; 1 hour, 10.0 mmol/L; 2 hour, 8.6 mmol/L; 3 hour, 7.8 mmol/L) and also 6.7% in those meeting the National Diabetes Data Group criteria (fasting, 5.8 mmol/L; 1 hour, 10.6 mmol/L; 2 hour, 9.2 mmol/L; 3 hour, 8.1 mmol/L). Compared to those with normal glucose values (reference group), women with abnormal results had 23% increased odds (OR=1.23, 95%CI, 1.08-1.41), those meeting the Carpenter-Coustan criteria for GDM had 53% elevated odds (OR=1.53, 95%CI, 1.16-

2.03), and those meeting the National Diabetes Data Group criteria for GDM had a 42% increase in odds (OR=1.42, 95%CI, 1.15-1.77).

There is also evidence that preterm delivery in a first pregnancy is associated with GDM in a subsequent pregnancy, indicating that this relationship may also operate across pregnancies. In a study by Kim *et al.*[176] the investigators found that compared to those with absence of GDM in two consecutive pregnancies, women with GDM only in their second pregnancy had a higher incidence rate of preterm deliveries in their first pregnancy (12.9% versus 7.7%).

The exact mechanism underlying this association is not fully understood, but it is believed that factors such as insulin resistance, inflammation, and vascular dysfunction associated with GDM may contribute to an increased risk of preterm birth. Additionally, GDM is often associated with other risk factors for preterm delivery, such as maternal obesity and hypertensive disorders (see **Chapter 2.4.5**), which can further increase the likelihood of preterm birth. Therefore, women with GDM should be closely monitored for signs of preterm labor and receive appropriate medical care to reduce the risk of adverse outcomes for both the mother and their offspring.

Hypoglycemia

While fetal hyperinsulinemia contributes to macrosomia, it also predisposes the newborn to hypoglycemia after birth. Postnatal glucose levels in infants born to mothers with GDM depend on maternal glucose concentrations during pregnancy, with GDM posing a higher risk for neonatal hypoglycemia. The study conducted by Hyperglycemia and Adverse Pregnancy Outcome Study Cooperative Research Group (2008) established a clear link between maternal glucose levels and neonatal hypoglycemia.[135] Findings from this study demonstrated that an increase of 1.7mmol/L in 1-hour glucose levels were attributed to a 13% increased odds of neonatal hypoglycemia.

Hypocalcemia

Transient neonatal hypocalcemia is another complication observed in infants born to mothers with GDM. Maternal hyperglycemia stimulates fetal pancreatic beta-cells to produce excess insulin, leading to fetal hyperinsulinemia. This hyperinsulinemic state suppresses fetal parathyroid hormone secretion, impairing calcium homeostasis. A study by Demarini *et al.* demonstrated a lower incidence of neonatal hypocalcemia among diabetic women with tighter glycemic control during pregnancy.[179]

Congenital Heart Disease

Emerging evidence has linked GDM with congenital heart disease in the offspring. This was demonstrated in a recent large retrospective cohort study conducted in France that evaluated 796,346 deliveries in which 7.24% were complicated by GDM.[180] There were 30% higher odds of cardiac malformations in the offspring of mothers with GDM compared to the offspring of mothers without diabetes in pregnancy (OR=1.3, 95%CI 1.1-1.4) after adjusting for maternal age, birthweight and gestational age. All cardiac malformations were grouped together; there was also evidence of higher rates of cardiac malformations in those with GDM requiring insulin therapy than in those who had GDM but did not require insulin treatment. A Danish retrospective cohort study[181] determined that GDM in the third trimester was associated with a 36% risk increase for congenital heart disease (RR=1.36, 95% CI 1.07, 1.69) compared to no diabetes in pregnancy. The authors adjusted for delivery year, maternal age, and birth order. A similar study conducted in Norway reported a 47% (RR=1.47, 95% CI 1.26-1.71) risk increase for congenital heart disease in the offspring after adjusting for year of birth, maternal age, and parity.[182] The specific congenital heart defects observed to be elevated in GDM were isolated septal defects (adjusted R=1.27, 95% CI 1.01, 1.60) and isolated patent ductus arteriosus (RR=1.83, 95% CI 1.31, 2.55); other heart defects had elevated RRs but inconclusive 95% CIs. Findings from a recent retrospective cohort study that utilized the Texas Birth Defects Registry and statewide birth records from 2005-2009 also demonstrated a 30% (OR=1.30, 95%CI 1.21-1.40) increase in the odds of the offspring developing congenital heart disease among women with GDM, compared to those without GDM.[183] The authors adjusted for maternal age, ethnicity, previous live births, smoking, BMI and hypertension. More recent findings from a population-based register study of 620,751 individuals in Finland, published in 2024, have estimated more modest associations of GDM with congenital heart disease.[184] After adjusting for maternal smoking, maternal age, child birth year, first parity, and highest parental education level, the investigators estimated only a 7% increase in odds (OR=1.07, 95%CI 1.01-1.14) among women with GDM, compared to those without GDM. While the onset of hyperglycemia and clinical manifestations of GDM and preeclampsia often occur beyond the period of fetal organogenesis, it is possible that other factors related to insulin resistance that predate GDM may contribute to the pathogenesis of congenital heart disease.

Additionally, there is also evidence with GDM being associated with long-term offspring complications in life. Studies have demonstrated a higher prevalence of obesity,[173,185,186]

diabetes,[173,185,187-191], and hypertension[192] in children born to mothers with GDM, predisposing them to early-onset cardiometabolic complications.

2.3.6 Maternal type 2 diabetes risk associated with gestational diabetes

Numerous longitudinal studies have established a strong association between GDM and subsequent development of type 2 diabetes in affected mothers. Bellamy *et al.* published one of the early meta-analyses on this topic, involving over 675,000 women. They reported that women with a history of GDM had a sevenfold higher risk of developing type 2 diabetes compared to those with normoglycemic pregnancies.[17] Furthermore, although the risk of developing diabetes persists over decades, findings from a systematic review showed that a significant proportion of women with GDM are expected to develop type 2 diabetes within 5-10 years postpartum.[20] More recently, a 2020 meta-analysis of 1.3 million women used a random effects model to estimate the pooled association across twenty different studies. The overall risk was shown to increase 9.5-fold among women with GDM compared to those without GDM.[22] Several investigators have suggested that in women with GDM, beta-cell exhaustion coupled with insulin resistance, accelerates the progression to diabetes in the postpartum period.[150-152]A Dutch study[193] using the European Prospective Investigation into Cancer and Nutrition database illustrates this concept showing that women who were diagnosed with diabetes those with a GDM history were diagnosed 7.7 years earlier (95% CI, 5.8-9.6) than women without a history of GDM. Although the cumulative risk of type 2 diabetes has been reported to be highest in the initial five years following a pregnancy affected by GDM,[20] previous Canadian cohort studies have demonstrated that 3.7% of women with GDM are diagnosed with type 2 diabetes as early as nine months postpartum, increasing to 19% by nine years.[19]

2.3.7 Maternal hypertension risk associated with gestational diabetes

Findings from a large prospective cohort study[23] have investigated the association between GDM and hypertension among 23,000 women from the Nurses' Health Study II, showing 1.26-fold higher hazards (95% CI 1.11–1.43) for chronic hypertension among women with GDM, compared to those without GDM. These associations were independent of pre-pregnancy BMI, HDPs and subsequent development of type 2 diabetes in the follow-up period. Previous studies have shown similar associations between GDM and hypertension, also independent of HDPs, obesity and future diabetes, with the increased risk for hypertension rising as high as 2.7-fold among GDM mothers compared to non-GDM mothers,[24] indicating that transient hyperglycemia in pregnancy may pose direct persistent

implications on vascular health and/or lipid profiles. Aligned with this, a Scandinavian prospective cohort study conducted by Lekva *et al.* demonstrated that five years after an index pregnancy, those with GDM had increased arterial stiffness relative to those without GDM.[194] Women with an index pregnancy affected by GDM were shown to have significant higher pulse wave velocity (measuring arterial stiffness [6.9m/s versus 6.6m/s]) and more severe dyslipidemia (higher triglycerides/high-density lipoprotein cholesterol ratio [0.65 versus 0.45]), than women with normoglycemic pregnancies, even after adjustments for age, BMI and smoking status. GDM contributes to systemic inflammation, oxidative stress, and endothelial dysfunction, which are central mechanisms in the development of hypertension (**Figure 2**). Persistent insulin resistance is hypothesized to lead to endothelial dysfunction by decreasing vasodilation and increasing arterial stiffness, vascular tone, vascular smooth muscle cell proliferation and carotid arterial wall thickness,[38] ultimately leading to atherosclerosis. Additionally, the activation of RAAS may further exacerbate vascular dysfunction in those with GDM, predisposing these individuals to hypertension.

2.3.8 Cardiovascular disease risk associated with gestational diabetes

In 2011,[28] and more recently, in 2021,[27] the American Heart Association released statements acknowledging that GDM may serve as an early, pregnancy-related indicator of CVD in young to middle aged women. These recommendations are also highlighted in guidelines from the European Society of Cardiology[31] and the International Federation of Gynecology and Obstetrics,[30] and have been emphasized in a recent commentary published in *Circulation*.[195] Whether these conditions stem from the shared burden of risk factors, as postulated from the common soil theory, remains unclear. Additionally, there is some evidence of direct links between GDM and CVD, including pathways related to chronic inflammation, endothelial dysfunction, and dyslipidemia (**Figure 2**).

A recent 2020 umbrella review[33] that summarized 20 previous meta-analyses estimated the association between GDM and future CVD risk to be two-fold (RR=1.98, 95%CI 1.57-2.50) when compared to women without GDM. Also recently, as reported in a meta-analysis conducted by Grandi *et al.,*[34] the pooled odds ratio for fatal or non-fatal CVD was 1.30 (95%CI 1.22-1.37) among those with GDM compared to those without GDM. Eight studies were included in this pooled analysis; however, the investigators note that variability exists on whether these studies accounted for subsequent development of diabetes. Among those with GDM, it also remains unclear whether the long-term risk of CVD is dependent upon developing type 2 diabetes.

Previous studies have suggested that type 2 diabetes partly mediates the association between GDM and CVD.[17,36,196] For example, in a population-based retrospective cohort study using health administrative data from Ontario, Shah *et. al* demonstrated a 1.71-fold increase in CVD hazards among women with GDM compared to those without; however, when the multivariable model adjusted for subsequent type 2 diabetes in the follow-up, this estimate became inconclusive and was attenuated to 1.13 (95%CI 0.67-1.89). Other studies have suggested that women with GDM may have markedly higher CVD risk even without the manifestation of diabetes prior to CVD development.[24,35,37] In a recent 2019 meta-analysis, Kramer *et al.*[35] demonstrated a two-fold higher risk for 10-year postpartum CVD incidence in women with GDM, compared to women without GDM. Results from this meta-regression analysis demonstrated GDM to be associated with maternal CVD, not entirely dependent on the development of type 2 diabetes. When the analysis was restricted to cohorts of women who did not subsequently develop type 2 diabetes, the reported risk ratio (RR) among women with GDM was found to be 1.56 (95% CI 1.04-2.32), compared to women without GDM. However, while GDM may, in some cases, be directly associated with CVD, in most cases, type 2 diabetes is expected to occur first. As noted, the effect estimate became two-fold (RR among women with GDM = 1.98, 95% CI 1.57-2.50) when women with diabetes development in the follow-up were included in the study cohort, indicating that the significant contribution that diabetes has towards future maternal CVD. Similarly, in a retrospective cohort study conducted in Ontario,[37] 1.5 million women who delivered between 1994-2014 were stratified into four groups and compared after adjusting for age, income, and rurality (adjusted HRs for CVD shown in brackets): no GDM and no subsequent diabetes (reference group), no GDM but subsequent diabetes development (2.01 [95%CI 1.82-2.20]), GDM and no subsequent diabetes (1.30 [95%CI 1.07-1.59]), and GDM and subsequent diabetes (2.82 [95%CI 2.41-3.30)]. Women with GDM and subsequent diabetes were shown to be at the highest risk of developing CVD; however, GDM was shown to be conclusively associated with greater CVD odds, independent of diabetes. A previous population-based cohort study published in 2016 demonstrated a similar effect estimate (HR=1.25, 95%CI 1.09-1.43) among those with GDM only compared to non-GDM mothers, after adjustment for HDPs, obesity and subsequent diabetes development) compared to non-GDM mothers.

2.4 Gestational hypertension, with and without preeclampsia

2.4.1 Definition and diagnosis of gestational hypertension, with and without preeclampsia

HDPs encompass a spectrum of conditions, each with distinct characteristics and implications. The hallmark criteria for diagnosing HDPs include systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on two readings at least 15 minutes apart (**Table 1**). GHTN without preeclampsia is characterized by new-onset elevated blood pressure after 20 weeks of gestation without the presence of proteinuria or other systemic complications in previously normotensive women, differentiating it from chronic hypertension or GHTN with preeclampsia,[137,197] which all fall under the broad categorization of HDPs. Preeclampsia is a multisystem disorder characterized by hypertension and signs of organ dysfunction, commonly involving the kidneys and liver, that develops after 20 weeks of gestation. It is usually accompanied by proteinuria (≥300 mg in a 24-hour urine collection or protein/creatinine ratio ≥0.3), indicating kidney damage, although proteinuria is not always required for a diagnosis.[137] The International Society for the Study of Hypertension in Pregnancy define other indicators of maternal organ dysfunction as a) acute kidney injury (creatinine ≥90 μmol/L), b) liver involvement (elevated transaminases [e.g., alanine aminotransferase or aspartate aminotransferase >40 IU/L]) with or without right upper quadrant or epigastric abdominal pain, c) neurological complications (examples include eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata), d) hematological complications (thrombocytopenia–platelet count <150 000/μL, disseminated intravascular coagulation, hemolysis), or e) Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth).[137] Preeclampsia can be categorized as mild (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) or severe (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg), although recent guidelines suggest not categorizing preeclampsia in this manner.[137] Preeclampsia includes eclampsia (preeclampsia in the presence of seizures), HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, and can lead to maternal and fetal mortality, if left untreated. Chronic hypertension may predate pregnancy or is recognized as elevated blood pressure diagnosed before 20 weeks of gestation. Women with pre-existing chronic hypertension may also develop new-onset proteinuria or exacerbation of hypertension with signs of organ dysfunction after 20 weeks of gestation, termed chronic hypertension with superimposed preeclampsia.[137]

Accurate diagnosis of GHTN relies on regular blood pressure monitoring and clinical assessment throughout pregnancy. Guidelines recommend measuring blood pressure at each antenatal visit using standardized techniques (**Table 1**).[137,197] Diagnosis typically involves confirming elevated blood readings across two separate readings that are 15 minutes apart, in order to rule out transient spikes or measurement errors. Additionally, clinicians may perform laboratory tests to exclude secondary causes of hypertension and assess end-organ damage, such as renal function tests and urinalysis. Despite established diagnostic criteria, several challenges persist in accurately identifying GHTN. Variability in blood pressure measurements due to factors like "white-coat hypertension" or patient anxiety can complicate diagnosis, necessitating multiple assessments for confirmation. Moreover, distinguishing new-onset GHTN from chronic hypertension with superimposed preeclampsia remains clinically challenging, emphasizing the need for comprehensive clinical evaluation and longitudinal monitoring. Advancements in technology and biomarker research offer promising avenues for improving the diagnosis of GHTN. Ambulatory blood pressure monitoring and home blood pressure monitoring (HBPM) provide more comprehensive assessments of blood pressure patterns, enhancing diagnostic accuracy and prognostic stratification.[198] Additionally, biomarkers such as placental growth factor and soluble fms-like tyrosine kinase-1 have been shown to aid early prediction and distinguish between different types of HDPs, including GHTN.[199]

2.4.2 Incidence and prevalence

Studies have reported varying incidence rates of GHTN globally, with the variation stemming from different populations and time periods. Longitudinal studies have shown an increasing trend in the incidence of GHTN over the past few decades, mirroring the rise in obesity rates and maternal age.[13] A recent publication in the *Journal of American Heart Association* demonstrated that the incidence of new-onset HDPs doubled from 2007 to 2019, with accelerating rates of annual incidence since 2014.[200] A meta-analysis by Abalos *et al.* revealed an overall incidence rate ranging from 6% to 8% worldwide.[201] However, substantial heterogeneity was observed across different geographical regions and populations, with higher rates reported in developed countries compared to developing nations. In Hypertension Canada's 2018 guidelines,[202] GHTN is reported to affect 7% of pregnancies in Canada.

Ethnocultural background also plays a crucial role in the prevalence of GHTN. Studies have consistently reported higher prevalence rates among women of African-American and Hispanic origin compared to those of European origin.[203-205] Socioeconomic factors such as access to prenatal care

and quality of healthcare services further contribute to disparities in the management of GHTN among different demographic groups.[206]

2.4.3 Pathophysiology

GHTN is a multifactorial disorder characterized by placental malperfusion, endothelial dysfunction, immune dysregulation, RAAS dysregulation, and interactions with genetic and environmental factors. GHTN with or without preeclampsia typically resolves after delivery; however, women can remain at risk for postpartum preeclampsia up to six weeks after delivery. A comprehensive understanding of the pathophysiological mechanisms underlying GHTN is crucial for the development of targeted therapeutic strategies aimed at mitigating maternal and fetal complications associated with this condition.

Placental Malperfusion and Ischemia

One of the primary mechanisms implicated in the pathogenesis of preeclampsia is placental malperfusion and ischemia. Studies have demonstrated that inadequate trophoblast invasion and remodeling of uterine spiral arteries lead to reduced placental perfusion, resulting in hypoxia and oxidative stress within the placenta.[132,207] This hypoxic environment triggers the release of vasoactive factors such as soluble fms-like tyrosine kinase-1 and soluble endoglin, which antagonize the actions of vascular endothelial growth factor and placental growth factor, leading to endothelial dysfunction and systemic vasoconstriction.

Endothelial Dysfunction and Vasoconstriction

The imbalance between vasodilatory and vasoconstrictive factors disrupts vascular homeostasis, contributing to increased vascular resistance and elevated blood pressure.[208,209] Moreover, impaired endothelial function results in reduced nitric oxide bioavailability, augmented production of vasoconstrictors such as endothelin-1, and enhanced sensitivity to antihypotensive agents, further exacerbating levels of elevated blood pressure in pregnancy, leading to GHTN onset.

Inflammatory Mediators and Immune Dysregulation

Mounting evidence suggests that an exaggerated maternal inflammatory response to placental factors contributes to endothelial activation and dysfunction. Pro-inflammatory cytokines, including IL-6 and TNF-α, disrupt vascular integrity and promote vasoconstriction, thereby exacerbating GHTN with or

without preeclampsia.[151] Moreover, activation of the innate immune system and recruitment of immune cells to the placenta further amplify the inflammatory cascade, perpetuating endothelial injury and hypertension.[210]

Renin-Angiotensin-Aldosterone System Dysregulation

Normal pregnancy is distinguished by the capacity to resist the vasoconstrictive impacts of angiotensin II. The levels of renin, angiotensin, and aldosterone experience are increased despite a general decrease in systemic vascular resistance. However, in women with who develop preeclampsia, this resistance is attenuated, leading to heightened sensitivity to angiotensin II in comparison to normotensive pregnant women.[207] Increased production and sensitivity to renin and angiotensin II, coupled with decreased clearance of aldosterone, leads to enhanced sodium retention, volume expansion, and systemic vasoconstriction.[210] Additionally, angiotensin II stimulates the release of aldosterone and endothelin-1, exacerbating endothelial dysfunction and rises in blood pressure. The dysregulated RAAS not only contributes to maternal hypertension but also impairs placental perfusion and fetal growth, highlighting its significance in the pathogenesis of preeclampsia.

Genetic and Environmental Factors

Genetic and environmental factors also play a significant role in the pathophysiology of GHTN. Genome-wide association studies have identified several susceptibility loci associated with GHTN, implicating genetic predisposition in disease susceptibility.[63,211] Research into the genetic origins of preeclampsia has revealed connections to seven genetic variations, a substantial number of which have also been linked to onset of CVD. Meta-analyses have discovered seven genetic variants in or near the following six genes (ACE, CTLA4, F2, FV, LPL, and SERPINE1) that demonstrated conclusive association with preeclampsia.[212] Furthermore, maternal factors such as obesity and advanced maternal age may contribute to an increased risk of GHTN by exacerbating underlying vascular and metabolic dysfunction.

2.4.4 Maternal risk factors

GHTN represents a complex multifactorial condition influenced by various maternal, fetal, and environmental factors. The onset of GHTN shares common risk factors with chronic hypertension given that GHTN is a form of elevated blood pressure that specifically presents during pregnancy and typically resolves at delivery or within 12 weeks after childbirth. Traditional risk factors for both

GHTN and chronic hypertension encompass suboptimal dietary habits, physical inactivity, obesity smoking, advanced maternal age, and ethnicity. A thorough understanding of these risk factors is essential for risk stratification, early intervention, and tailored management strategies to mitigate the adverse outcomes associated with GHTN.

Maternal Age

Advanced maternal age has been consistently identified as a significant risk factor for GHTN. Research by Dietl *et al.* demonstrated a positive association between maternal age and the incidence of GHTN, with women aged 35-39 years being at 22% higher risk, and those aged 40-45 being at 63% higher risk, compared to women aged 25-30.[213] The underlying mechanisms may involve age-related changes in vascular function and increased susceptibility to endothelial dysfunction.[214]

Obesity

Obesity is recognized as a major modifiable risk factor for GHTN. Several studies have reported a strong association between maternal obesity and the development of GHTN.[132,215] The mechanisms linking obesity to GHTN include chronic inflammation, insulin resistance, and adipokine dysregulation, which contribute to endothelial dysfunction and vascular complications (**Figure 2**).

Ethnicity

Ethnic disparities in the prevalence of GHTN have been well-documented, with certain ethnic groups exhibiting a higher susceptibility to this condition. For instance, studies have shown that women of African and Hispanic origin have a significantly elevated risk of GHTN compared to other racial/ethnic groups.[203-205] Furthermore, in a prospective cohort study conducted from 2018-2019,[204] 1077 women with an HDP were enrolled in a blood pressure monitoring program and followed for up to 6 weeks' postpartum. Although elevated blood pressure is expected to resolve by 12 weeks' postpartum of a woman's affected pregnancy, the investigators report a significant difference in the trajectory of this blood pressure decline with both systolic and diastolic pressure decreasing significantly slower among Black women (mean peak systolic/diastolic blood pressure at 3 weeks postpartum=136/91mm Hg) compared to women of European origin (mean peak systolic/diastolic blood pressure at 3 weeks postpartum=129/84 mm Hg). Genetic factors, socio-economic determinants, and differential access to healthcare services may contribute to these disparities, highlighting the need for targeted interventions and culturally sensitive care approaches.

Pregnancy-specific and Fertility-related Factors

Pregnancy-specific and fertility-related factors may also influence the risk of GHTN. These include gestational weight gain, multifetal pregnancies, a history of a previous pregnancy with GHTN, or the occurrence of GDM. Multiple gestation pregnancies, such as twins or higher-order multiples, confer an increased risk of GHTN compared to singleton pregnancies. A retrospective study conducted by Sibai *et al.* demonstrated a higher prevalence of GHTN among women carrying multiple fetuses, attributed to greater hemodynamic changes, placental insufficiency, and enhanced RAAS activation.[216] Additionally, a history of GHTN in previous pregnancies significantly elevates the risk of GHTN occurring in subsequent pregnancies, with meta-analyses showing the rate of GHTN recurrence to be as high as 21%.[44,217] Women with a history of GHTN in a first pregnancy may have underlying risk factors predisposing them to hypertensive disorders in subsequent pregnancies (e.g., gestational weight gain from the first pregnancy, physical inactivity, suboptimal dietary habits, stress related to parenthood), especially if this burden has been amplified during the year(s) between pregnancies. Aligned with this notion, a case-control study conducted by Bryson *et al.* utilized 60,000 linked maternal records from the 1992-1998 Washington State birth certificate and hospital discharge records, and demonstrated that GDM confers a 1.4-fold (95%CI 1.2-1.6) increase in odds for GHTN alone, 1.5-fold (95%CI 1.3-1.8) increased odds for mild preeclampsia, and a 1.5-fold (95%CI 1.1-2.1) elevated odds for severe preeclampsia, compared with women without GDM.[218] The authors adjusted for age, ethnicity, BMI, parity, and prenatal care. Other investigators have shown that the risk of developing preeclampsia among women with GDM may be closer to two-fold (OR=1.9, 95%CI 1.7-2.1), as demonstrated in a retrospective cohort study of nearly 500,000 Alberta women.[39] Women with GDM typically demonstrate higher degrees of postpartum insulin resistance, beta-cell dysfunction, central obesity and BMI, and hyperlipidemia.[141]As a result of such, bidirectional associations may exist between GDM and GHTN, a hypothesis first described by Vorzimer *et al.* in 1937.[219]

2.4.5 Perinatal maternal and offspring complications

Fetal Growth Restriction / Small for Gestational Age

Fetal growth restriction, often observed in pregnancies complicated by GHTN, poses a substantial risk to neonatal health. Findings from a Norwegian case-control study have demonstrated a clear association between preeclampsia and SGA, with findings showing a 4.2-fold higher risk (95%CI 2.2-8.0) among women with preeclamptic pregnancies compared to the normotensive control group.

Mechanistically, impaired placental perfusion secondary to HDPs contributes to inadequate fetal nutrient and oxygen delivery, culminating in suboptimal fetal growth.

Preterm Birth

GHTN is linked with preterm birth, a leading cause of neonatal morbidity and mortality worldwide. A large case-control study conducted in Scotland[220] corroborated this association, indicating a 4.4-fold (95%CI 3.80-5.16) increased risk of preterm delivery in pregnancies complicated by preeclampsia, adjusting for BMI and pre-existing diabetes and hypertension. Furthermore, a large prospective cohort study conducted in China demonstrated the risk for preterm birth in women with GHTN alone (RR=1.04, 95%CI 0.98-1.11) and preeclampsia (RR=1.39, 95% CI 1.25-1.55), compared to women without each of these respective conditions.[221] Notably, the investigators found stronger, conclusive associations with both GHTN alone (RR=2.13, 95%CI 1.71-2.65) or preeclampsia (RR=8.47, 95%CI 5.59-12.8), when occurred earlier in pregnancy (<28 weeks' gestation). The authors adjusted for maternal age, BMI, educational level, occupation, parity, ethnicity and folic acid use.

Preeclampsia is characterized by abnormal placental development and function, leading to reduced blood flow to the fetus and fetal distress. This compromised blood flow can result in inadequate oxygen and nutrient supply to the growing fetus, which may trigger unplanned preterm labor and delivery. Additionally, significantly elevated blood pressure in women with GHTN (with or without preeclampsia) is linked to oxidative stress, endocrine disruption, and chronic inflammation. Such can potentially lead to placental abruption if not properly managed, which may necessitate planned preterm delivery to prevent harm to both the mother and the fetus.[222,223]

Stillbirth

Elevated maternal blood pressure during pregnancy confers a heightened risk of stillbirth, underscoring the gravity of GHTN as a potentially life-threatening condition for the fetus. A population-based cohort study of half a million Norwegian women reported a 1.45-fold (95%CI 1.20-1.76) elevated risk of stillbirth among women with preeclampsia compared to those with normotensive pregnancies.[224] Plausible mechanisms include impaired placental function, resulting in fetal hypoxia and fetal morbidity, as well as increased susceptibility to placental thrombosis in hypertensive pregnancies.

Congenital Heart Disease

A Quebec-based study demonstrated an association between preeclampsia and congenital heart defects, adjusting for maternal age, parity, comorbidity, multiple birth, socioeconomic deprivation, and calendar period.[225] Preeclampsia in this study included both GHTN with preeclampsia as well as preeclampsia superimposed on pre-existing hypertension. There was an overall higher prevalence of congenital heart defects with preeclampsia (Prevalence Ratio=1.57, 95% CI, 1.48-1.67). Higher prevalence was observed for all site-specific defects (septum, valve, and aorta/pulmonary artery) and for multiple defects. Analyses accounted for pre-existing diabetes but not for GDM.

2.4.6 Maternal hypertension risk associated with gestational hypertension

Pooled findings from thirteen studies published in a meta-analysis[26] have demonstrated that preeclampsia is associated with a 3.7-fold (95%CI 2.70-5.05) risk increase for incident chronic hypertension later in life, compared to women without preeclampsia. The comparison group are women who did not have preeclampsia, but may have had GHTN without preeclampsia; thus, the pooled findings may underestimate the risk relative to women who are normotensive. It should be noted that the authors also clarify that they had limited their search strategy to only include studies where the exposure was *de novo* preeclampsia, but acknowledge that studies published before 2001 (that were included in their pooled estimate) may have misclassified some women as having preeclampsia given lacking definitive criteria for its diagnosis during these earlier years. Only one of the 13 included studies reported adjustments for subsequent type 2 diabetes developed in the postpartum period and none accounted for GDM. More recently, a Swedish retrospective study[25] using linked health administrative databases to examine the link between preeclampsia and hypertension at 40 years of age, among approximately 16,000 parous women without any diagnosis of hypertension prior to their pregnancy. History of preeclampsia was found to be associated with 3.1-fold (95%CI 2.6-3.7) increased odds of hypertension compared to women without preeclampsia, even after adjustments for other pregnancy complications (e.g., GDM, stillbirth, placental abruption), BMI, lifestyle factors (e.g., smoking, alcohol consumption) and socioeconomic status. Furthermore, a Dutch study utilizing the European Prospective Investigation into Cancer and Nutrition database reported that women with HDPs in their cohort of 22,000 women were diagnosed with hypertension 7.7 years earlier (95% CI 6.9-8.5) than women without HDPs.[193]

A Danish retrospective cohort study of approximately 700,000 women has teased out the nuances of hypertension risk associated with the various HDP subtypes.[21] Compared to women without HDP, women with a history of GHTN (without preeclampsia) had a 5.3-fold (95%CI 4.9-5.8) increased risk for hypertension, those with mild preeclampsia had a 3.6-fold (95%CI 3.4-3.8), and those with severe preeclampsia had 6.1-fold (95%CI 5.5-6.8) risk increase. The authors adjusted for year of delivery, maternal age, preterm delivery, SGA offspring, placental abruption, stillbirth, and subsequent development of type 2 diabetes after the index pregnancy. They did not account for GDM. Chronic low-grade inflammation, characterized by elevated levels of pro-inflammatory cytokines and oxidative stress markers, has been hypothesized to play a key role in endothelial dysfunction and beta-cell damage, promoting the transition from GHTN to hypertension.

2.4.7 Maternal type 2 diabetes risk associated with gestational hypertension

Accumulating evidence underscores the significant association between GHTN and the subsequent risk of type 2 diabetes, given their shared risk factors ("common soil" hypothesis). Additionally, underlying direct mechanisms linking GHTN to the development of diabetes mellitus are multifactorial and complex, and are primarily attributed to chronic low-grade inflammation and oxidative stress (as a result of dysregulation of adipokines, such as adiponectin and leptin) contributing to beta-cell dysfunction and insulin resistance (**Figure 2**). Lykke *et al.* demonstrated elevated risk of incident diabetes during the subsequent postpartum years among women with GHTN without preeclampsia (HR=3.4, 95%, CI 3.0-4.0) also in those with severe preeclampsia (HR=4.1, 95% CI 3.5-4.8) in multivariable models adjusted for age, SGA, preterm delivery, still births and placental abruptions.[21]. More recently, a meta-analysis published in *Diabetologia*[18] demonstrated that among a pooled cohort of 2.8 million women, preeclampsia was associated with a more than 2-fold (pooled RR= 2.37, 95%CI 1.89-2.97) increase in type 2 diabetes risk, persisting even after additional adjustments for BMI and GDM. These findings persisted, but were slightly attenuated, when the cohort was limited to women with less than 1 year of postpartum follow-up (pooled RR= 1.95, 95%CI 1.28-2.97), indicating that effective postpartum screening and management may be critical in these high-risk women.

2.4.8 Maternal cardiovascular disease risk associated with gestational hypertension

Epidemiological evidence consistently demonstrates an association between GHTN (with and without preeclampsia) and increased risk of hypertension and CVD later in life.[26,33,34] A meta-analysis published

in 2007 compared women with preeclampsia to those without preeclampsia and demonstrated pooled relative risks for ischemic heart disease [myocardial infarction, angina, heart failure] (RR=3.7; 95% CI, 2.7-5.1), and fatal, (RR=2.3; 95% CI, 1.9-2.5) and non-fatal stroke [hemorrhagic and ischaemic] (RR 1.8; 95% CI 1.5-2.3) after a mean follow-up for 10 years.[26] Among the studies included, some investigators also opted to also adjust for subsequent development of type 2 diabetes, while only two account for GDM. More recently, findings from a 2019 meta-analysis also demonstrated conclusive associations between GHTN and CVD; among women with GHTN without preeclampsia (nine pooled studies), the risk of CVD was 67% higher compared to those without GHTN (RR=1.67, 95% CI 1.28-2.19).[34] Among women with moderate preeclampsia (sixteen pooled studies), the risk was elevated to 2.2-fold (RR=2.24, 95%CI 1.72-2.93) compared to women without preeclampsia. Those with severe preeclampsia (six pooled studies) were shown to be at the highest risk of CVD, showing a 2.7-fold (RR=2.74, 95%CI 2.48-3.04) risk increase compared to women without preeclampsia. These findings are highlighted in a 2020 umbrella review that summarized the evidence across previous meta-analyses examining various pregnancy complications and their associations with CVD.[33] Aligned with evidence from these studies, guidelines from the American Heart Association,[27,226] European Society of Cardiology[31] and the International Federation of Gynecology and Obstetrics[30] recommend that pregnant women should be screened for GHTN early in pregnancy for the prevention of CVD; however, the mechanisms linking these conditions remains unclear to date. The "common soil" hypothesis suggests that the burden of shared predisposing risk factors may also evolve in parallel with one another, implying that GHTN serves as an early phenotype of this burden. In support of this, a Norwegian prospective cohort study[227] measured unfavorable cardiovascular risk factors (BMI, serum lipids, and blood pressure) before and after the pregnancies of 3,200 women. The authors found that associations of GHTN (with or without preeclampsia) with each of these risk factor (post-pregnancy measurements) was significantly attenuated after adjustment for their prepregnancy measurements, suggesting that the association between GHTN and CVD likely stems from shared prepregnancy risk factors more than direct pathophysiological implications of GHTN itself (**Figure 2**). Nonetheless, previous studies have shared mechanistic insights that suggest that systemic inflammation, persistent endothelial dysfunction, and metabolic dysregulation related to GHTN directly contribute to atherosclerosis.[63,207,228]

2.5 Individual and joint associations of gestational diabetes and gestational hypertension with cardiometabolic outcomes in women

Researchers have now begun to investigate the combined impact of GDM and GHTN on cardiovascular health, although the literature on this topic remains scarce. Given the shared factors underlying some aspects of GDM and GHTN, the effects of these conditions may not be completely independent given their common soil. An emerging body of studies suggest their co-occurrence to heighten diabetes, hypertension, and CVD risk.

A large retrospective cohort study that was conducted in 2013,[229] examined the combined effects of GDM and GHTN (with or without preeclampsia) on postpartum diabetes risk among approximately one million Canadian women, adjusting for age, income quintile, prior hypertension, and co–morbidity. The investigators concluded that GDM alone led to a 13-fold risk increase (HR=12.8; 95%CI 12.4-13.1), with increasing effect measures observed when co-occurring with GHTN (without preeclampsia; HR=18.5; 95%CI 17.1-20.0) or preeclampsia (HR=15.8; 95% CI 14.5-17.1).

Although GDM and GHTN have been shown to be associated with each other (discussed in Chapters 2.3.4 and 2.4.4),[39,218] and both GDM and GHTN to be associated with CVD when considered alone, a 2017 retrospective cohort study by my supervisors and their former student (Pace *et al.*) assessed joint effects of GDM/GHTN on CVD risk (over a 22 year follow up period) by grouping these exposures into 'neither,' 'either,' and 'both GDM and GHTN' categories. Relative to women with neither GDM nor GHTN (reference group), either GDM or GHTN was associated with increased risk of diabetes (HR=14.7 [95% CI 12.9-16.6]), hypertension (HR= 1.9 [95% CI 1.8-2.0]) and CVD/mortality (HR= 1.4 [95% CI 1.2-1.7]) in mothers. The combination GDM and GHTN together demonstrated an even greater risk of diabetes (HR=36.9 [95% CI 26.0-52.3]), hypertension (HR=5.7 [95% CI 4.9-6.7]), and CVD/mortality (HR=2.4 [95% CI 1.6-3.5]), in mothers compared to the reference group with neither GDM nor GHTN. The authors adjusted for maternal age, gestational age and size of infants at birth, deprivation level, ethnocultural background, co-morbid conditions, prior pregnancy in partner, and living with partner at time of delivery.

Recently in 2022, a population-based retrospective cohort study of 880,000 pregnant women residing in Ontario (Canada), [230] also examined the impact of GDM and GHTN occurrence on CVD risk over

a mean follow-up of 12 years. The investigators report that after the initial 5-year postpartum period, compared to women without GDM/GHTN, women with a GHTN affected pregnancy demonstrated at 1.41-fold (95%CI 1.12-1.76) increase in CVD risk, while those with GDM and GHTN co-occurring in their pregnancy had even higher risks (HR=2.43, 95%CI 1.60-3.67). The authors report adjustments for age, parity, rurality, socioeconomic status, preterm delivery, chronic kidney disease, GDM/GHTN in prior pregnancies, pre-existing circulatory disease, postpartum diabetes and postpartum hypertension (the latter two covariates treated as time-varying covariates).

These findings collectively suggest that the concurrent presence of GDM and GHTN amplifies the cardiovascular risk conferred by each condition individually, emphasizing the need for comprehensive risk assessment and management strategies in affected women. Research aimed at examining joint effects of these pregnancy complications on maternal CVD incidence are scarce. Future research directions should aim to assess the joint impact of GDM and GHTN, along with its implications across consecutive pregnancies.

2.6 Screening and prevention strategies for gestational diabetes and gestational hypertension

2.6.1 Strategies for early detection

Early detection and intervention are paramount in the management of GDM and GHTN to minimize maternal and fetal morbidity and mortality. Glucose and blood pressure monitoring, biomarkers, and predictive models facilitate the early identification of at-risk pregnancies, while lifestyle modifications, pharmacological interventions, and close monitoring contribute to optimal maternal and neonatal outcomes. Collaborative efforts between healthcare providers, researchers, and pregnant individuals are essential to implement effective strategies for the early detection and interventions for GDM and GHTN.

Gestational Diabetes

Early detection of GDM is fundamental to enable timely intervention and management. Historically, the OGTT has been the gold standard for diagnosing GDM. This test requires the patient to remain at the test centre for at least two hours, and to consume a sugary drink that can be perceived as unpleasant. This inconvenience has led to the exploration of alternative screening methods. One such method is the use of glycated hemoglobin (HbA1c) levels in early pregnancy. A study by Hughes *et al.*

demonstrated that elevated HbA1c levels in the first trimester were associated with an increased risk of GDM development later in pregnancy, suggesting its potential as an early screening tool.[231]

Furthermore, advancements in technology have led to the exploration of non-invasive methods for GDM screening. Continuous glucose monitoring (CGM) systems have emerged as promising tools for early detection of abnormal glucose levels throughout pregnancy, providing real-time data and serving a comprehensive testing tool in pregnant women. A recent Australian prospective cohort study[232] demonstrated that among 87 recruited women, a CGM device (Freestyle Libre Pro 2) that was worn for one week between 24-28 weeks' gestation was rated as more acceptable among women diagnosed with GDM (compared to OGTT, the gold standard; conducted before CGM removal). Furthermore, triangulation analysis of CGM results with observed OGTT values demonstrated that the relying on solely the OGTT lead to identification of several false positives (positive OGTT but total risk score and CGM both below the cut-offs) and negatives (negative OGTT with both total risk score and CGM above the respective cut-offs) in this cohort of women. Future studies are required to further elucidate the full potential of implementing CGMs for GDM diagnosis in routine care.

Gestational Hypertension: Automated Blood Pressure Monitoring (AOBP)

Early detection of GHTN often begins with regular blood pressure monitoring during prenatal visits. According to a meta-analysis by Bo *et al.,*[233] pooled estimates from 26 observational studies and demonstrated that AOBP (digital blood pressure monitors) led to few cases of white-coat hypertension (**Table 1**) than routine measurements (7% versus 14%), but 13% had masked hypertension. The width of the limit of agreement in measurements was found to be comparable among: (i) AOBP and ambulatory blood pressure measurement (ABPM; diagnostic reference) and (ii) manual office blood pressure measurements (MOBP) and ABPM. A previous comparative study[234] found that among 202 individuals, the average MOBP was 145.6/76.4 mmHg, while AOBP was 135.3/70.1 mmHg, indicating a mean paired difference of 10.3/6.3 mmHg. Routine manual office blood pressure measurements combined with AOBP monitoring may potentially enhance the detection of HDPs, including GHTN. Regular screening enables healthcare providers to identify elevated blood pressure levels early in pregnancy, facilitating timely intervention.

Gestational Hypertension: Home Blood Pressure Monitoring

HBPM offers a promising approach for early detection and continuous monitoring of GHTN. A meta-analysis by Albadrani *et al.* suggests that HBPM, when integrated into prenatal care, improves the detection of HDPs, including GHTN.[235] Pooled estimates from this analysis demonstrated that compared to AOBP, HBPM was superior in reducing the risk of induced labor and postpartum readmission. Empowering pregnant individuals to monitor their blood pressure at home enhances patient engagement and enables timely detection of abnormal readings between clinic visits.

Gestational Hypertension: Biomarkers and Predictive Models

Emerging research explores the potential of biomarkers and predictive models for early detection of GHTN. A systematic review by Antwi *et al.*[236] reviewed the literature, highlighting that among 40 eligible studies, most prediction models attempt to incorporate maternal characteristics and biomarkers (e.g., plasma protein-A, placental growth factor and soluble fms-like tyrosine kinase-1) to predict the onset of GHTN; however, the majority suffer from poor methodology and/or reporting of these methods, thus compromising their model development and applicability. Furthermore, although some investigators showed good (>0.70) to strong (>0.80) c-statistic scores, external validation is lacking. Implementing such models in clinical practice has the potential to enable refined risk stratification and targeted monitoring of high-risk pregnancies.

2.6.2 Lifestyle modifications

Early intervention strategies in GDM and GHTN primarily focus on lifestyle modifications as first-line therapies to optimize glycemic and blood pressure control during pregnancy. Regular exercise, weight management and dietary interventions (e.g., medical nutrition therapy and dietary counseling), are among key guideline recommendations from Diabetes Canada[237] and others to manage these pregnancy complications, alongside insulin therapy and antihypertensive agents safe in pregnancy, as needed.

Evidence from cohort studies indicate that incorporating nutritionally adequate diets (e.g., low intakes of red/processed meats, high intakes of nuts, fish, fruits and vegetables) up to three years before conception is associated with reduced risk of GHTN/GDM.[238] The Dietary Approaches to Stop Hypertension diet has been associated with lowering blood pressure to a greater extent than other dietary patterns,[239] and among women with GDM, randomized control trials have shown its

incorporation to lower the use of insulin.[240] Diabetes Canada recommends low-glycemic index diets, which have been shown to lower postprandial blood glucose in recent randomized controlled trials.[237]

In conjunction with dietary intervention, the incorporation of physical activity seems to yield greater efficacy in the management of GDM as opposed to its prevention. A recent review[241] revealed that five out of the seven studies (consisting of five randomized controlled trials, one case-control study, and one self-enrollment study), demonstrated improved GDM management through implementing physical activity interventions. Positive impacts of these interventions were observed through reduced use of insulin and improved glycemic control among women diagnosed with GDM.[237] The optimal type of physical activity intervention for women with GDM/GHTN remains unclear, as successful programs vary in their recommendations for the type, intensity, frequency and duration exercise. It should be noted that walking interventions, aimed to increase total daily steps/day (with pedometer monitoring) are gaining prominence for improving glucose control during pregnancy. A recent randomized trial has shown that 151 women with GDM were able to improve their glycemic control (fasting 1-hr and 2-hr postprandial glucose levels decreased significantly [$p< 0.001$]) by incorporating recreational walking and pedometer monitoring, which also reduced the risk of adverse neonatal outcomes by 70%. A recent meta-analyses of 5,000 women with a previous pregnancy demonstrated that combining exercise with diet (within 2 years postpartum) was associated with greater average weight reduction in the years following pregnancy, compared to exercise-only interventions.[242] Aligned with this notion, my supervisors completed a pilot feasibility trial evaluating steps/day and gestational weight gain, measured by digital weighing scales (at home) and pedometer-based tracking in 227 women with GDM (ACTIVE PATIENT GDM, ACTIVating and Engaging PAtients Through clinical Interaction redesign and Electronically-integrated Novel Technologies in Gestational Diabetes; Clinicaltrials.gov NCT03802877; registered January 10, 2019; first participant recruited August 29, 2019).

In regard to weight management, a subgroup analyses of the American Diabetes Prevention Program among women with a GDM history demonstrated that healthful diet-induced weight loss and higher physical activity levels in the years following a GDM pregnancy could reduce type 2 diabetes risk,[138] although the women in this trial averaged 10 years following a GDM pregnancy. Supporting the importance of loss of excess weight sooner after pregnancy, a recent cohort study demonstrated that among women without GDM in their first pregnancy, weight loss between pregnancies was associated

with reduced risk for new occurrence of GDM in a subsequent pregnancy.[166] Similarly, among women without GDM in their first pregnancy, higher levels of weight gain between pregnancies were associated with stepwise increases in the risk of new occurrence of GDM in second pregnancy. In another study[243] among women with excess weight and GDM in a first pregnancy, weight loss between pregnancies lowered the risk for GDM recurrence in a second pregnancy.

Ongoing studies investigating the role of lifestyle modifications towards mitigating/managing the risk of GDM/GHTN underscore the importance of comprehensive perinatal care and patient education in optimizing maternal and fetal outcomes.

2.7 Validity of diagnoses in administrative databases

The validity of diagnostic codes found within administrative databases has been assessed in many studies, with several reporting moderate levels of sensitivity and specificity for accurate identification of different conditions. To carry out the studies presented in this thesis, I applied validated health administrative database definitions to define my exposures of interest (GDM and GHTN) and the outcomes of interest (diabetes, hypertension, and CVD).

2.7.1 Validation of gestational diabetes definition

Previous studies have been conducted to validate the definition of GDM, comparing several methods to identify and monitor GDM prevalence using health administrative data.[244-250] These algorithms typically demonstrate moderate sensitivity and excellent specificity when used in various large databases across Canada.[244-247] The sensitivity of these codes has improved over the years with the implementation of GDM-specific codes. A validation report conducted by Bowker *et al.* compared two validated algorithms (National Diabetes Surveillance [NDSS] algorithm and GDM-specific ICD codes) for identifying GDM using administrative data specifically among 411,390 deliveries recorded.[245] The authors compared the NDSS case definition and GDM-specific ICD codes with Alberta's Perinatal Health Program database definition, serving as the reference standard. The Alberta Perinatal Health Program routinely collects detailed maternal and obstetric information during the perinatal period for all deliveries in the province (crude prevalence of GDM: 3.9%). Briefly, the NDSS definition of GDM incorporates the Canadian Chronic Disease Surveillance System (CCDSS) definition of chronic diabetes (requiring one hospitalization for diabetes [ICD-9: 250, ICD-10: E10-E14] or two physician claims for diabetes within a 2-year period), but requires fulfilment of additional

criteria in order to re-classify chronic diabetes as GDM. Diabetes is ruled to be GDM by the NDSS algorithm if an obstetrical claim is available either a) 120 days after this date of diabetes diagnosis or b) diabetes diagnosis preceded by an obstetrical claim within 180 days (crude prevalence of GDM: 1.3%).

The second GDM-specific algorithm did not require any obstetrical ICD records, but rather necessitated a record of GDM-specific codes (ICD-9: 648.8, ICD-10: O24.4, O24.8) applied in any diagnosis field of the delivery-related hospitalization (crude prevalence of GDM: 4.0%). Relative to the reference standard, the authors concluded that the NDSS algorithms severely underestimated the prevalence of GDM cases within the database (sensitivity: 25%, specificity: 100%), while the use of GDM-specific ICD codes was shown to improve sensitivity (86%) while maintaining excellent specificity (99%), suggesting this algorithm to be a more valid and accurate method to monitor and capture GDM using health administrative data. In another report by Bowker *et al.*, algorithms using GDM-specific ICD-10 codes (O24.8) from delivery-related hospitalizations and/or outpatient clinic visits were compared to laboratory data measurements of glucose levels in pregnancy as the gold standard (GDM diagnosis warranted by a 50-g GCT ≥10.3 mmol/l or ≥2 abnormal values on a 2-step 75-g OGTT [**Table 1**]).[244] The algorithm that applied GDM-specific codes required GDM-specific codes to be available within 270 days preceding the delivery for the purposes of their study. The authors demonstrated these GDM-specific ICD-10 codes to be highly sensitive (92%) and specific (97%), especially when these specific codes are applied in databases combining both inpatient and outpatient data. Sensitivity varied from 83-86% when these databases were consulted separately, while specificity remained excellent (98%). GDM-specific ICD-10 codes have demonstrated sensitivity as high as 98% in a smaller-scale validation study conducted in British Colombia;[247] however, it is important to note that differences in code structure and usage exist across provincial healthcare systems in Canada.

In a more recent validation study by Shah *et al.*,[246] the authors determined the accuracy of algorithms using hospitalization and physician claims data to identify GDM among 120,000 pregnant women residing in Ontario (Canada) in 2019. The gold reference standard was a GDM definition based on glucose screening laboratory results, which they tested against 214 algorithms using various combinations of diagnostic codes for GDM (ICD-10: O24.4, O24.8) *and* diabetes (ICD-9: 250, ICD-10: E10-E14, O24.*) in hospitalization and/or physician claims data (applying various lookbacks [30,

60-, 90- or 120-day] before delivery). The authors concluded that compared to the gold standard, sensitivity was maximized (95.9%) in an algorithm which required any GDM-specific/general diabetes codes on the delivery hospitalization record or at least one outpatient record with a diabetes diagnosis at least 90-days before delivery, while maintaining excellent specificity (99.2%). Specificity was maximized (99.5%) in another algorithm that applied the same set of codes, but required at least two outpatient records at least 120-days before delivery; this algorithm also demonstrated excellent measures of sensitivity (94.1%).

2.7.2 Validation of gestational hypertension definition

The majority of validation studies in the literature are discussed in the context of HDPs as a broad term, encompassing GHTN (with and without preeclampsia) and pre-existing chronic hypertension. Only two studies have examined the validation of HDPs using Canadian databases. In a study conducted by Joseph *et al.*,[251] the authors compared diagnostic codes available in the Canadian Institute for Health Information hospitalization database to the Nova Scotia Atlee Perinatal Database, which served as the reference standard. Among 6,100 mothers residing in Nova Scotia in 2002, ICD-10 codes for severe preeclampsia were found to have a sensitivity of 75% and a specificity of 99%. The authors demonstrated that sensitivity was increased to 88% when diagnostic codes ICD codes for mild preeclampsia were included in this case definition. In another Canadian study, ICD-10 diagnostic codes from the Ottawa Hospital Discharge Databases were compared to medical chart review (reference standard) among women who participated in the Ottawa and Kingston Birth Cohort Study and delivered at The Ottawa Hospital Civic or General Campus. The author demonstrated that the sensitivity for any form of HDP (GHTN with and without preeclampsia and chronic hypertension) was found to be 72% with a specificity of 99%. Sensitivity was 36% when examining preeclampsia alone, but specificity (100%) remained high.

Other studies have previously shown the specificity of diagnostic codes for HDPs to be high in other national administrative databases, but typically suffer from low to moderate sensitivity, depending on the subtype of HDP considered. Using the Danish National Patient Registry, Klemmensen *et al.* compared ICD-10 diagnostic codes of HDPs (ICD-10 codes: O139-O143, O149-O150) to detailed chart reviews (serving as the reference standard and using criteria from the American College of Obstetricians and Gynecologists) of 3,000 women who delivered between 1998 and 2002.[252] Compared to detailed chart review, the use of diagnostic codes for HDPs as a whole demonstrated

excellent specificity (99%), but low sensitivity (49%). When examining subtypes of HDPs, the lowest sensitivity (10%) in this study was demonstrated when relying on codes that just pertained to GHTN without preeclampsia (O139), but showed improvement when identifying those with preeclampsia (69%); both subtypes showed excellent maintenance of sensitivity (99%). In another validation study by Roberts *et al.,*[253] the investigators examined the reporting of HDPs (ICD-10: O11-O16) from birth and hospital discharge data with detailed review of medical charts (reference standard) among 1,200 Australian women giving birth in 2002. The application of diagnostic codes for all HDPs demonstrated good sensitivity (81%) and excellent specificity (99%). While preeclampsia-specific codes demonstrated excellent sensitivity (99%) and specificity (95%), GHTN-specific codes (without preeclampsia) were shown to have poorer sensitivity (48%).

On the contrary, other studies in the United States (85%)[254] and Australia (80%)[249] have shown high sensitivity when examining GHTN without preeclampsia, with both studies maintaining specificity >97%. Currently, there is no universally standardized set of codes specifically designated for HDPs in medical coding systems. A systematic review by Johnson *et al.*[255] highlighted that the reported sensitivity among the studies they reviewed reported this metric to vary anywhere from 3-100%. This variation can likely be attributed to diagnostic (misclassification) error by the physician when differentiating between types of HDPs,[256] along with varying reference standards and different ICD codes used in various geographic regions among the studies reviewed.

2.7.3 Validation of diabetes definition

The CCDSS is a collaborative network composed of established provincial and territorial surveillance systems that collects data on all Canadian residents who are eligible for health insurance in Canada. Use of this data enhances the scope of monitoring chronic diseases in Canada and includes the capture of persons living with diabetes; however, ICD codes cannot accurately differentiate between type 1 and type 2 diabetes. Given that 95% of diabetes onset among adults is type 2 diabetes,[11,12] new onset diabetes in adults is often considered to be type 2 diabetes. The CCDSS definition of diabetes requires one hospitalization with an ICD code for diabetes (ICD-9: 250, ICD-10: E10-E14) or at least two outpatient (physician billing) claims within the span of two years.[257] These definitions have been validated in a previous meta-analysis[257] by Leong *et al.* (my supervisors and their former student) that compared the CCDSS case definition for diabetes to cases reported from population-based or primary care medical chart reviews (reference standard). The authors determined that compared to the

reference standard, the CCDSS definition accurately captured cases from these health administrative databases, with a reported sensitivity of 82% and a specificity of 98%. In another study by Leong *et al.*,[258] the authors (my supervisors and a former student) demonstrated that the CCDSS case definition had a sensitivity of 84% and specificity of 98% among 6,200 women in Quebec when compared to telephone-survey data (reference standard). Findings demonstrating the validity of the CCDSS case definition have also been reported in earlier validation studies.[259,260]

2.7.4 Validation of hypertension definition

Similar to the validated diabetes case definition, the CCDSS requires one hospitalization with an ICD code for hypertension (ICD-9: 401-405, ICD-10: I10-13, I15) or at least two physician billing claims within the span of two years to define chronic hypertension using health administrative databases. Several studies conducted in Canada have confirmed this definition by comparing data from different provinces using both charts and surveys.[259,261-263] These studies have reported various sensitivities (69-75%) and specificities (93-95%), which have been shown to be suitably sensitive and specific for most research and surveillance purposes. Briefly, a meta-analysis by Pace *et al.*[263] (my supervisors and their former student) evaluated the validity of this definition compared self-report from surveys or medical chart reviews (reference standard) used among studies in the literature. Using a random-effects bivariate regression model, the investigators concluded that the pooled sensitivity of the CCDSS case definition of hypertension was 71%, with a specificity of 95% when compared to the reference standard.

2.7.5 Validation of cardiovascular disease definition

Administrative databases are used often in CVD research, particularly in the areas of cerebrovascular disease and coronary heart disease (specifically myocardial infarction and unstable angina). Systematic reviews published by McCormick *et al.* have assessed the validity of diagnostic codes pertaining to myocardial infarction[264] and cerebrovascular disease.[265] Findings from these studies have shown that the sensitivity of diagnostic codes related to myocardial infarction to be >86% across most studies included in their review, with a specificity of >89%.[264] Diagnostic codes related to cerebrovascular disease have yielded a sensitivity of >82% in most studies, with specificity shown to be >89%. A previous study by Austin *et al.*[266] conducted among patients admitted to cardiac care units in Ontario also compared diagnostic codes from the Canadian Institute for Health Information's hospital discharge abstracts to discharge diagnoses from the cardiac care unit (reference standard),

demonstrating high sensitivity for conditions like acute myocardial infarction (93%), and moderate sensitivity for unstable angina (73%).

2.8 Overview of recurrent occurrences of gestational diabetes and gestational hypertension

There are few epidemiological studies that assess the implications of GDM/GHTN patterns of recurrence or absence or new onset across two consecutive pregnancies, as I have approached these analyses. Therefore, most studies discuss the implications of recurrent GDM or GHTN on diabetes, hypertension, and CVD risk, drawing comparisons to women without these complications or only a single occurrence. Previous meta-regression results estimate a GDM recurrence rate of 48% (95% CI, 41%-54%)[41,42] following a first GDM pregnancy while estimates for GHTN recurrence approximate 20.7% (95% CI, 20.4-20.9%).[44,217]

2.8.1 Limited epidemiological studies on type 2 diabetes risk following gestational diabetes recurrence

Numerous longitudinal studies have established a strong association between GDM and the development of type 2 diabetes later in life. Studies that examine the impact of its recurrence on type 2 diabetes risk are limited.[267-273] Among these , I found two studies[269,270] in the literature that attempted to improve subject comparability by fixing the number of pregnancies during the exposure window, requiring women to have had two pregnancies prior to their study's index date (**Appendix A**). Compared to women with GDM in a first pregnancy followed by a normoglycemic pregnancy, those with GDM recurrence in both studies were shown to have a 2.4-fold (95%CI 1.6-2.7;[269] 95%CI 1.3-4.3[270]) increase in type 2 diabetes risk. Both studies adjusted for maternal age, ethnic background, inter-delivery period, and maternal age, among several other confounders, but did not account for GHTN in relation to type 2 diabetes risk. I identified a single study that evaluated hazards of postpartum type 2 diabetes in relationship to numbers of prior GDM pregnancies.[271] After adjusting for BMI, race, education and time since last GDM diagnosis (as a time-dependent covariate), the investigators concluded that women with a history of two GDM pregnancies experienced a 6.2-fold higher hazards for type 2 diabetes in middle age, compared to women with no GDM pregnancies. Interpretation of these findings is complicated given that the investigators allowed the number of pregnancies to vary across exposure groups, only counting the cumulative number of pregnancies affected by GDM.

2.8.2 Limited epidemiological studies on hypertension risk following gestational hypertension recurrence

GHTN represents not only a significant obstetric complication but also a harbinger of heightened hypertension risk later in life. These associations persist whether GHTN presents with or without preeclamspsia.[21] Although the relationship between these two conditions is well-established, less than a dozen studies have examined associations of recurrent HDPs, or its subtypes, and future development of hypertension.[21,43,274-281] Among these studies, investigators have opted to focus on recurrent patterns of overall HDPs, or specifically on preeclampsia (**Appendix B**). In a previously reported individual participant data meta-analysis,[217] van Oostward *et al.* demonstrated that women with recurrent HDP had almost a 4-fold increase (HR=3.7, 95%CI 2.3-6.1) for hypertension later in life compared to those with only a first HDP-affected pregnancy followed by a normotensive pregnancy (no mention of adjustments made). In a more recent cohort study conducted in Quebec (Canada), Auger *et al.*[275] compared women without any history of HDP to women with a first affected pregnancy (followed by a normotensive pregnancy) to those with recurrent HDPs. Compared to women without any history, women with an HDP occurrence in their first pregnancy had a 3.7-fold increase (95%CI 3.5-3.9) in hypertension risk, and women with recurrent HDP had a 7.2-fold increase (6.6-7.8). The authors adjusted for age at first delivery, pre-existing diabetes, pre-existing CVD, socioeconomic deprivation, and time period. I note that findings from these two studies are difficult to interpret, and likely inflated, given that these investigators opted to include preeclampsia superimposed on pre-existing chronic hypertension in their definitions of the exposure. Both studies appeared to have included women with pre-existing hypertension, examining impacts of superimposed preeclampsia and preeclampsia, but it is unclear how the hypertension outcome could be evaluated in this context, if some women had preexisting hypertension. The main focus of the van Oostward *et al.* study was aimed at identifying rates of HDP recurrence,[217] while Auger *et al.* focused on CVD risk as the primary outcome, evaluating the risk of chronic hypertension as a secondary outcome.[275] Given that assessing hypertension risk was not the main focus of both studies, perhaps both investigators did not consider this potential methodological shortcoming.

A Nurses' Health Study II analysis[277] examined first pregnancy GHTN (with or without preeclampsia) and conducted a secondary analysis for GHTN in 'second or later' pregnancies, rather than focusing on the second pregnancy. Compared to women with no history of GHTN, those with GHTN (with

or without preeclampsia): only in the first pregnancy had 1.85-fold (95%CI 1.73-1.98) increased risk, only in the second or later pregnancies had 2.24-fold (95%CI 2.01-2.49) increased risk, and in the first pregnancy and at least one more occurrence in subsequent pregnancies had 3.53-fold (95%CI 3.17-3.93) increased risk. The authors adjusted for physical activity, smoking, BMI, alcohol consumption, healthy eating index, oral contraceptive use, and family history of hypertension/diabetes. The investigators did not account for or examine GDM or other adverse pregnancy outcomes in relationship to hypertension development. They also did not report on preeclampsia and GHTN without preeclampsia separately.

Other investigators have focused specifically on preeclampsia. Brouwers *et al.* conducted a meta-analysis[278] and demonstrated that compared to women with a first preeclamptic pregnancy, those with recurrent preeclampsia had a 2.33-fold (95%CI 1.86-1.92) higher risk for chronic hypertension. Within the literature, I identified only a single 2009 Danish study[21] that distinguished first pregnancy preeclampsia from second pregnancy preeclampsia. Compared to absence of any form of GHTN, preeclampsia only in the first pregnancy was associated with a 2.7-fold (95%CI 2.5-2.9) increase in hazards for hypertension, preeclampsia only in the second pregnancy with a 4.3-fold (95%CI 4.0-4.7) increase, and preeclampsia in both with a 6.0-fold (95%CI 5.4-6.7) increase. The authors adjusted for preterm delivery, SGA, placental abruption, and stillbirth, and subsequent development of type 2 diabetes, but did not account for GDM.

2.8.3 Limited epidemiological studies on cardiovascular disease risk following gestational diabetes or gestational hypertension recurrence

There is evidence that women with recurrent GHTN are at increased risk of CVD onset later in life (**Appendix C**).[33,278] All of the evidence in the literature focuses on associations between GHTN with preeclampsia and CVD. In a recent meta-analysis by Brouwers *et al.*,[278] the investigators used a random-effects model to pool RRs across studies that addressed this relationship. They concluded that in comparison to women with a single occurrence of preeclampsia followed by a normotensive pregnancy, recurrent preeclampsia was associated with elevated risk of CVD as a composite outcome (RR=1.57, 95%CI 1.31-1.90), ischemic heart disease (pooled RR=2.40, 95%CI 2.15-2.68), stroke (RR=1.69, 95%CI 1.21-2.35) and heart failure (RR=2.88, 95%CI 2.23-3.72). The investigators emphasize that studies on this topic are limited with only two to three studies included in each of their

pooled analyses, often conducted by the same investigators across the evaluated outcomes. These findings are also highlighted and summarized in a recent umbrella review published in 2020.[33] To my knowledge, no studies have investigated the impact of recurring patterns of GDM on CVD risk.

In summary, studies that address occurrences of GDM/GHTN beyond one pregnancy are scarce and often limited in their interpretation as a result of their study design. Firstly, the majority of the literature often has drawn comparisons between (a) women with recurrent GDM/GHTN to those with one occurrence in a first pregnancy, or (b) women with recurrent events to those with no occurrences. I did not identify any prior studies in the literature that compared a single occurrence GDM in a first pregnancy to a single occurrence of GDM in a second, among women with two pregnancies, in relationship to diabetes, hypertension or CVD risk, as my approaches did. Similarly, as described in **Chapter 2.8.2**, I found only one study in the literature that designed their GHTN exposure categories to draw these important comparisons between a first- versus second-affected pregnancy, but the investigators were limited to only evaluating the risk of chronic hypertension with patterns of preeclampsia across two pregnancies.[21] They were unable to assess the association of chronic hypertension with patterns of GHTN alone, as my approach has done. Additionally, I also simultaneously accounted for GHTN (along with other adverse pregnancy outcomes) when assessing the association of GDM patterns with diabetes, and simultaneously accounted for GDM (and other adverse pregnancy outcomes) in models evaluating the association of GHTN patterns with chronic hypertension. Previous investigators have often failed to account for these frequently co-occurring complications which stem from the similar predisposing risk factors and have been shown to be associated with each other (see **Chapter 2.3.4 and 2.4.4**) Furthermore, other studies have often allowed for variations in the numbers of pregnancies during the exposure period among the women considered, essentially comparing women with different baseline cardiometabolic risk profiles.

I have addressed these knowledge gaps in this thesis, leveraging Quebec's provincial health administrative data, linked with birth, stillbirth, and death vital statistics. Using these linked datasets, I studied nearly half a million women (and their two offspring, and their partners), with at least two consecutive singleton pregnancies in Quebec from 1990 to 2012. I, alongside my supervisors, designed these studies to enhance subject comparability by commencing the index date after the second delivery for all women, in addition to ensuring that all subjects were free of diabetes, hypertension or CVD prior to the index date.

2.9 Methodological framework of thesis research

2.9.1 Thesis study methodologies: An overview

Manuscript 1: In this retrospective cohort study, I examined the association between patterns of GDM across two pregnancies and the subsequent development of type 2 diabetes. The study utilized health administrative databases and vital statistics from Quebec, Canada, linked by the Quebec Statistical Institute. The cohort included 431,980 women with at least two consecutive singleton deliveries between April 1, 1990, and December 31, 2012, excluding those with diabetes or hypertension before or between pregnancies. GDM was categorized based on its absence, presence in the first pregnancy, presence in the second pregnancy, and presence in both pregnancies. The primary outcome was incident diabetes, identified using the CCDSS definition. Covariates included gestational hypertension, preterm delivery, small- and large-for-gestational-age status, time between deliveries, co-morbid conditions, maternal age, deprivation level, paternal diabetes and hypertension, and ethnocultural background. I employed multivariable Cox proportional hazards models to estimate hazard ratios (HRs) for type 2 diabetes, with various sensitivity analyses to address temporal trends, stillbirths, miscarriages, and indirect adjustments for obesity and smoking. Statistical analyses were conducted using SAS version 9.4.

Manuscript 2: In this retrospective cohort study, I investigated the relationship between patterns of GHTN, with or without preeclampsia, across two pregnancies and the subsequent development of chronic hypertension. The study utilized linked data from public healthcare insurance administrative databases and birth, stillbirth, and death registries in Quebec, Canada. The cohort included 431,980 women with two consecutive singleton deliveries between April 1990 and December 2012, excluding those with pre-existing hypertension or diabetes before or between pregnancies. GHTN was categorized into four mutually exclusive groups: absence of GHTN, GHTN in the first pregnancy only, GHTN in the second pregnancy only, and GHTN in both pregnancies. I employed multivariable Cox proportional hazards models to estimate HRs for incident chronic hypertension, adjusting for covariates such as GDM, preterm delivery, SGA and LGA status, time between deliveries, maternal age, material and social deprivation, ethnocultural background, and chronic paternal conditions (diabetes, hypertension, and cardiovascular disease). Sensitivity analyses included indirect adjustments for obesity and smoking using external cohort data. We also created two subcohorts to separately analyze the effects of GHTN with and without preeclampsia. Statistical analyses were conducted using SAS version 9.4.

Manuscript 3: In this Quebec-based retrospective cohort study, I investigated the relationship between the number of occurrences of GDM and GHTN/preeclampsia across two pregnancies and the subsequent development of CVD. The study utilized health administrative and vital statistics databases from Quebec, Canada, including the public health insurance registry, physician claims data, hospitalization discharge data, and birth, stillbirth, and death registries. The cohort comprised 431,980 women with two consecutive singleton deliveries between April 1990 and December 2012, excluding those with pre-existing diabetes or hypertension before or between pregnancies. GDM and GHTN were defined using validated diagnostic codes and categorized into four main exposure groups: no occurrences, one occurrence, two occurrences, and three or more occurrences.

We examined a composite outcome of fatal and nonfatal myocardial infarction, stroke, and angina, requiring hospitalization or causing death. Follow-up continued until the first CVD event, death, or the end of the study period (April 1, 2019). Covariates included preterm birth, small- and large-for-gestational-age status, maternal age, time between deliveries, material deprivation level, ethnocultural background, and co-morbid conditions (e.g., mood disorders, alcohol/drug dependence, cancer, arthritis, HIV/chronic hepatitis, asthma/chronic obstructive pulmonary disease).

Statistical analyses included computing baseline characteristics, assessing for multicollinearity and interactions, calculating CVD incidence, and constructing Kaplan-Meier curves. I used Cox proportional hazards models to estimate HRs for CVD, comparing various GDM/GHTN occurrence categories. Sensitivity analyses involved indirect adjustments for obesity and smoking using external cohort data. In secondary analyses, I created 16 mutually exclusive GDM/GHTN exposure categories and modified inclusion criteria to include women who developed diabetes or hypertension between pregnancies. Statistical analyses were conducted using SAS version 9.4.

Manuscript 4: In this scoping review, I examined the evolving algorithms for the screening and diagnosis of GDM in Canada over the last three decades, as recommended by Diabetes Canada and the Society of Obstetricians and Gynecologists of Canada. The review included a comprehensive search of five electronic bibliographic databases (The Cochrane Library, PubMed, CINAHL, Web of Science, and SCOPUS) for clinical practice guidelines (CPGs) from January 1964 to November 2020. The search strategy used specific subject headings and key MeSH terms related to national recommendations, clinical practice guidelines, diabetes mellitus, pregnancy, gestational diabetes

mellitus, screening, and diagnosis, with restrictions to English and French materials and a geographic focus on Canada. The eligibility of the guidelines was independently assessed by two reviewers, and data were extracted on publication year, screening population, method/test for screening and diagnosis, glucose thresholds, and estimated GDM prevalence.

Additionally, a voluntary online survey was distributed to members of the Canadian Diabetes in Pregnancy (CanDIPS) study group to assess current GDM screening practices among Canadian physicians. The survey captured information on the screening approaches used, glucose thresholds applied, and any changes in practice due to the COVID-19 pandemic.

The scoping review also included interviews with a co-author to discuss the history of GDM screening in Canada. Data extraction from eligible CPGs involved capturing recommendations for screening and diagnosing GDM, including the number of abnormal values required for diagnosis and glucose thresholds for fasting and post-load glucose levels. The findings highlighted the evolution of national CPGs, the degree of variability in screening practices, and the impact of varying diagnostic criteria on GDM prevalence in Canada.

2.9.2 Data source, ethics, and analytical considerations

Data Collection and Access: The data for this research were derived from the Régie de l'assurance maladie du Québec and Institut de la statistique du Québec linked administrative databases. These databases provide comprehensive health information for residents of Quebec, including physician claims, hospital discharge summaries, and vital statistics. The data encompass a wide range of variables including demographic information, diagnoses, procedures, and health outcomes. Access to these data required approvals from multiple governing bodies. The protocol for data access and linkage, written by my supervisors, was approved by the McGill University Health Centre's Research Ethics Board (2019-5029; 2018/12/11) and the Quebec Access to Information Commission (1019371-S; 2019/11/18).

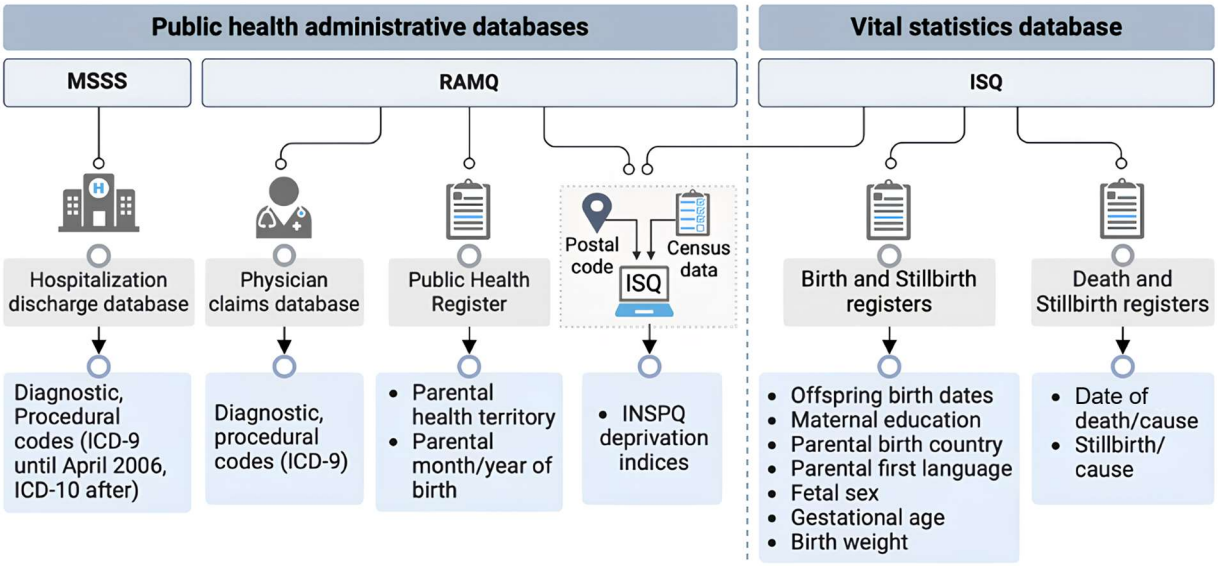


Figure 7. Data Sources

Ethical Considerations: Ethical approval was essential for this research due to the use of sensitive health information. McGill University Health Centre's research ethics board reviewed the protocol to ensure that the study design adhered to ethical standards, particularly concerning participant confidentiality and data security. Additionally, the Quebec Access to Information Commission evaluated the protocol to ensure proper handling and linkage of administrative data. These bodies waived informed consent because it involved deidentified data, analyses at the Quebec Statistical Institute's secure data centres, and rounded frequencies to multiples of 5. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Data Environment and Analysis: The linked data were accessed and analyzed within a trusted research environment to maintain data security and participant confidentiality. Data were not exported outside of this secure environment. Analysis was conducted using SAS version 9.4, with stringent data handling procedures to ensure the integrity and confidentiality of the information. All final tables, figures and listings required vetting and approval from a coordinator at the secured research data centre prior to release.

Data Cleaning and Missing Data: The data underwent rigorous cleaning processes by Mr. Dahhou (statistical analyst) and me to prepare it for analysis. This involved:

a) Validation and Standardization: Ensuring that all variables adhered to acceptable value ranges. For example, maternal age and birth weights were checked against standard medical thresholds.

b) Handling Missing Data: Given that our study utilizes large, linked health administrative databases, most variables included in our Cox regression model do not have missing data. I used ICD codes to ascertain the presence or absence of maternal diabetes, hypertension, and CVD from linked hospitalization and outpatient records during the defined lookback period. In the case of a stillbirth, it is not possible to identify the father since there is an absence of paternal information in the Stillbirth registry (registry is linked only to mothers); thus, information on the partner's diabetes/hypertension/CVD status was complete, as we excluded women with stillbirths (431,980 mothers linked to 431,980 fathers) in the primary analysis. The only variables with missing data were material and social deprivation (assigned by the Institut national de santé publique du Québec; 7335 women missing deprivation indices) and offspring size patterns (150 offspring missing birthweight information in the Birth registry). Individuals with missing data for these variables were excluded from the models. Overall, missing data in our models accounted for only 1.7% of the entire cohort of 431,980 women. According to our SAS outputs, the Cox proportional hazards model used 424,495 out of the 431,980 (98%) observations when generating the reported hazard ratios.

c) Inclusion Criteria: The study included all eligible women with at least two consecutive singleton pregnancies, excluding those with pre-existing diabetes or hypertension. This criterion ensured a uniform study population and minimized biases.

Strengths of the Data

a) Large and Comprehensive Coverage Using Longitudinal Data: The RAMQ and ISQ databases provide extensive coverage of the Quebec population, capturing a wide range of health services and outcomes. The use of health administrative datasets provides long-term follow-up data, which is crucial for studying the development of chronic conditions over time. The study leveraged Quebec's provincial health administrative data, linked with birth, stillbirth, and death vital statistics, covering nearly half a million women with at least two consecutive singleton pregnancies. This large sample size increases the study's power and generalizability.

b) Validated ICD codes: The use of validated ICD codes and algorithms ensures accurate identification GDM, GHTN, preeclampsia, diabetes, hypertension, and CVD.

c) Capture of Gestational Age for Each Respective Pregnancy: Most health administrative databases in Canada do not record gestational age, but linkage with the Quebec Birth Registry allowed for the inclusion of gestational age data in this study. This precise adjustment ensured accurate definition of the pregnancy-specific period for identifying GDM and GHTN/preeclampsia in each respective pregnancy.

Limitations of the Data

a) Data Accuracy: The use of ICD codes, despite being validated, may still lead to some instances of misclassification. While the administrative data are comprehensive, there may be inaccuracies in coding or recording that could impact the capture of the exposures and outcomes of interest. Additionally, the definitions and screening algorithms for GDM have evolved over time, leading to potential inconsistencies in the identification of GDM. While the study accounted for temporal trends, this variability remains a limitation.

b) Lack of Information on Adiposity and Health Behaviors: Health administrative datasets and vital statistics lack detailed information on adiposity (e.g., body mass index) and health behaviors (e.g., diet, physical activity, smoking status), which are important confounders in studies examining the relationships between pregnancy complications and long-term health outcomes. The use of indirect adjustment methods for unmeasured confounders like obesity and smoking, using data from the CCHS cycle 2.2 enhanced the robustness of my findings.

c) Some Missing Data: Few variables had missing values due to non-reporting or recording errors.

Steps to Gain Access to the Data: These data were obtained from the Heart and Stroke Foundation through a grant awarded to my supervisors, who drafted the initial protocol for which the grant was awarded. Under their supervision, I revised the analytical approach while exploring and working with the data. Specifically, I developed the detailed analytical and statistical methodologies presented in this thesis, tailoring them to fit the specific objectives of my research. The following steps were performed

by my supervisors and ensured that the research was conducted ethically and in compliance with all regulatory requirements, maintaining the integrity and confidentiality of the data throughout the study.

a) Protocol Development: Drafting a detailed research protocol that outlines the study design, data requirements, and ethical considerations.

b) Ethics Approval: Submitting the protocol to the McGill University Health Centre's REB and obtaining approval.

c) Data Access Approval: Submitting the approved protocol to the Quebec Access to Information Commission for authorization to access and link the administrative data.

d) Data Linkage and Access: Working with the Quebec Statistical Institute to perform the probabilistic linkage of the datasets and secure access to the linked data in a trusted research environment.

Chapter 3: Manuscript 1

3.1 Preface

As previously discussed in Chapter 1.1, the overarching goal of this dissertation is to evaluate how the absence of GDM and/or GHTN, their presence in a first pregnancy, new onset in a second pregnancy, and occurrence in both pregnancies are associated with differential magnitudes of CMD hazards, among women with at least two pregnancies. Research to date has consistently shown that women with a history of GDM are at increased risk of future diabetes; however, these studies typically do not leverage information across more than one pregnancy, despite the global average birth rate estimated to be two offspring per woman.[40] Although rates of GDM recurrence are estimated to be at 48%,[41,42] there is a dearth of empirical data on a woman's diabetes risk when she encounters GDM beyond a single pregnancy. In this first manuscript, I conducted a retrospective cohort analysis that focused on the relationship between patterns of GDM across two pregnancies (order and number of occurrences: GDM_{NONE}, GDM_{FIRST}, GDM_{SECOND}, GDM_{BOTH}) and their impact on the onset of type 2 diabetes. As described, previous studies evaluating GDM beyond occurrences in a single pregnancy have examined risks with diabetes in relationship to the cumulative number of pregnancies complicated by GDM (often times allowing the number of pregnancies for each woman to vary, without adjustments for parity[267,268,271-273]), or compared women with GDM occurrence in a first pregnancy to those with recurrent exposure in the first and second pregnancy (see **Appendix A**). Among women with two pregnancies, no previous literature was found wherein a comparison was made between the occurrence of GDM in a first pregnancy and a single incidence of GDM in a second pregnancy. As I describe in this paper, not all women with a single occurrence of GDM are on the same trajectory to developing diabetes later in life.

Additionally, in my analyses, I also accounted for GHTN and other gestational complications (i.e., SGA, LGA, preterm births), among other covariates. Previous researchers have frequently overlooked the need to account for these commonly co-occurring complications, which arise from shared predisposing risk factors and have been shown to be associated with one another. In contrast to the association observed between GDM and diabetes, the PH assumption was not met in the case of GHTN when categorized similarly to patterns of the GDM exposure. Consequently, I opted to categorize GHTN exposure across two pregnancies into a binary "never/ever" category, which effectively addressed this issue (see **Chapter 7.1.2**).

I also introduce methods of bias analyses to perform indirect adjustments for obesity and smoking, which have not been applied in previous studies assessing this relationship when direct measures of these confounders have not been made available in their primary datasets. While health administrative datasets and vital statistics afford the opportunity to examine a large cohort of individuals over an extended period, they lack comprehensive data on factors such as adiposity and health-related behaviors. To mitigate this limitation, I conducted simple sensitivity analyses to indirectly adjust for potential biases arising from obesity and smoking, which could confound the relationship between GDM and the subsequent development of diabetes. Although this method of indirect adjustment is established, previous researchers investigating the association between GDM and subsequent diabetes have not applied indirect adjustments for obesity and smoking, particularly when datasets lack measures of these confounders. Leveraging access to a random sample of Canadian citizens who participated in the 2004 Canadian Community Health Survey (Cycle 2.2) and consented to probabilistic record linkage, conducted by Statistics Canada, to link to the 2004-2017 Discharge Abstract Database and Canadian Mortality Database, I conducted follow-up investigations on these individuals for up to 13 years to ascertain vital status and underlying causes of hospitalization/death. While this sample is inherently designed by Statistics Canada to represent the Canadian population, I applied specific inclusion criteria (e.g., restricted to women aged 12-50 with at least two recorded pregnancies; absence of prior diabetes, hypertension, or cardiovascular disease at baseline) to emulate the inclusion criteria utilized in my primary cohort, thereby enhancing comparability between both datasets.

This manuscript entitled "Incident Diabetes in Women With Patterns of Gestational Diabetes Occurrences Across 2 Pregnancies" is published in *JAMA Network Open*.

Incident Diabetes in Women With Patterns of Gestational Diabetes Occurrences Across 2 Pregnancies

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Key Points

Question: Across 2 pregnancies, are the order and number of gestational diabetes occurrences linked to maternal diabetes risk in the years after second pregnancy?

Findings: In this retrospective cohort study of 431,980 women, those with a first occurrence of gestational diabetes in a second pregnancy had 76% higher risk for diabetes development than women who had gestational diabetes in the first pregnancy but not in the second, a statistically significant difference. The highest risk was in women with gestational diabetes in both pregnancies.

Meaning: These findings suggest that considering gestational diabetes history in each pregnancy results in more accurate diabetes risk estimation than a simple yes/no dichotomy of past gestational diabetes occurrence.

Abstract

Importance: Gestational diabetes is a type 2 diabetes risk indicator, and recurrence further augments risk. In women with a single occurrence across two pregnancies, it is unclear whether first- versus second-pregnancy gestational diabetes differ in terms of risk.

Objective: To compare the hazards of incident diabetes among those with gestational diabetes in the first, in the second, and in both pregnancies with women without gestational diabetes in either.

Design, Settings and Participants: This was a retrospective cohort study with cohort inception from April 1, 1990, to December 31, 2012. Follow-up was April 1, 1990, to April 1, 2019. Participants were mothers with 2 singleton deliveries between April 1, 1990, and December 31, 2012, without diabetes before or between pregnancies, who were listed in public health care insurance administrative databases and birth, stillbirth, and death registries in Quebec, Canada. Data were analyzed from July to December 2023.

Exposure: Gestational diabetes occurrence(s) across 2 pregnancies.

Main outcomes and measures: Incident diabetes from the second delivery until a third pregnancy, death, or the end of follow-up period, whichever occurred first.

Results: The 431,980 women with 2 singleton deliveries studied had a mean (SD) age of 30.1 (4.5) years at second delivery, with a mean (SD) of 2.8 (1.5) years elapsed between deliveries; 373 415 (86.4%) were of European background, and 78 770 (18.2%) were at the highest quintile of material deprivation. Overall, 10 920 women (2.5%) had gestational diabetes in their first pregnancy, 16 145 (3.7%) in their second, and 8255 (1.9%) in both (12 205 incident diabetes events; median [IQR] follow-up 11.5 [5.3-19.4] years). First pregnancy–only gestational diabetes increased hazards 4.35-fold (95% CI, 4.06-4.67), second pregnancy–only increased hazards 7.68-fold (95% CI, 7.31-8.07), and gestational diabetes in both pregnancies increased hazards 15.8-fold (95% CI, 15.0-16.6). Compared with first pregnancy–only gestational diabetes, second pregnancy–only gestational diabetes increased hazards by 76% (95% CI, 1.63-1.91), while gestational diabetes in both pregnancies increased it 3.63-fold (95% CI, 3.36-3.93).

Conclusions and relevance: In this retrospective cohort study of nearly half a million women with 2 singleton pregnancies, both the number and ordinal pregnancy of any gestational diabetes occurrence increased diabetes risk. These considerations offer greater nuance than an ever or never gestational diabetes dichotomy.

Keywords: Adverse pregnancy outcomes, gestational diabetes, maternal health, recurrence, risk estimation, type 2 diabetes

Introduction

Gestational diabetes (GD) affects 14% of pregnancies globally.[1] A recent meta-analysis[2] estimates its occurrence is associated with a 10-fold risk increase for type 2 diabetes. Whether risks vary with the order of GD occurrences is not well-studied. We hypothesized that new GD occurrence in a second pregnancy implies transition to a higher risk profile, while a single occurrence in a first pregnancy implies the converse.

One challenge is that GD is conditional on pregnancy (ie, cannot occur without pregnancy) and the number of pregnancies itself is associated with type 2 diabetes risk. The lowest risk occurs in those with 1 pregnancy.[3] Two previous studies[4,5] tried to improve comparability among participants by requiring that all have at least 2 pregnancies. Both reported a 2.4-fold increase in hazards with GD recurrence compared with its absence in the second pregnancy. They did not include women without any GD or women with a new occurrence of GD in a second pregnancy.

In the longer term, first-pregnancy GD may motivate some to adopt behaviors demonstrated to reduce diabetes risk,[6,7] lowering GD recurrence rates and type 2 diabetes development. In contrast, some women without GD in the first pregnancy may enter a higher risk trajectory, related to excess gestational weight gain,[8] postpartum weight retention,[9] weight gain between pregnancies,[10,11] and parenthood demands impeding nutritionally adequate diets and physical activity.[12] The delineation of differences in future incident type 2 diabetes risk between GD occurrence in a first pregnancy compared with new occurrence in a second could allow further personalization of approaches to type 2 diabetes prevention.[13] We therefore examined patterns of GD absence, occurrence, and recurrence across 2 pregnancies and their associations with diabetes.

Methods

The McGill University Health Centre's research ethics board and Quebec Access to Information Commission approved the protocol. These bodies waived informed consent because the study involved deidentified data, analyses at the Quebec Statistical Institute's secure data centres, and rounded frequencies to multiples of 5. This cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Design and Data Sources

We conducted a retrospective cohort study in Quebec, Canada. We examined health administrative databases of the public health insurance plan linked to birth, stillbirth, and death registries by the Quebec Statistical Institute (probabilistic linkage). We obtained mothers' residential territory and month and year of birth from the public health insurance registry. The Physician Services Claims and Hospitalization Discharge Databases include diagnostic codes (eTable 1 in Supplement 1) and hospitalization dates; we used these to define outcomes, exposures, and other variables alongside data from birth and stillbirth registries (offspring birthdates, gestational age at birth, birthweight, parental country of birth and first language, and years of maternal education). We also had access to the mothers' Institut national de santé publique du Québec (INSPQ) material and social deprivation indices, derived from the 6-digit postal code in the public health registry.[14] The INSPQ material and social deprivation indices are computed from small area census data. Specifically, the material indices are derived from average income, proportions without high school diploma, and employment to population ratio among those 15 years and older. The social indices are derived from the proportion of the population who are single-parent families, aged 15 years and older living alone, and aged 15 years and older who are separated, divorced, or widowed. To assign the INSPQ index for each woman, we first checked availability of this variable in the index year (year of second delivery).

Study Population

We considered women with 2 or more consecutive singleton deliveries between April 1, 1990, and December 31, 2012, who were alive at 12 weeks following the second delivery (index date) (eFigure 1 in Supplement 1). We excluded mothers with missing offspring gestational age (required to distinguish diabetes from GD),[15] and those with diabetes or hypertension before or between pregnancies. We applied the validated Canadian Chronic Disease Surveillance System (CCDSS) diabetes[16,17] and hypertension[18] definitions of 2 outpatient or 1 hospitalization diagnostic code(s) to (1) the 2-year period before 20 weeks' gestation in first pregnancy and (2) the period from 12 weeks after the first delivery until 20 weeks' gestation in the second pregnancy. All required an opportunity to develop GD for both of the pregnancies considered, thus gestation 20 or more weeks was required. In the primary analysis, we required the same partner for each offspring to minimize heterogeneity of within-household factors.[19-21] This resulted in the removal of stillbirths, for whom paternal data were unavailable; in a sensitivity analysis, we removed the paternal data requirement. Lastly, we excluded

those with 2 outpatient visits or 1 hospitalization for cardiovascular disease, the most common diabetes consequence, before the index date.

Exposure

We adapted a validated health administrative database GD definition[22] that applies diabetes and GD diagnostic codes to a pregnancy-specific period. We started this period at 20 weeks' gestation instead of the 120-day predelivery date used in the validation study, as the information we had on gestational age allowed us to conform with clinical definitions, which considers type 2 diabetes before 20 weeks' gestation as preexisting.[15] We extended the period beyond delivery to 12 weeks postpartum, as screening for type 2 diabetes after pregnancy is generally advised by this time.[23,24] We required 2 outpatient and/or 1 hospitalization code to maximize specificity (99.5%) and maintain sensitivity (94.1%), as recommended in the validation study.[22] Our 4 mutually exclusive exposure categories were absence of GD, its presence in only first pregnancy, in only the second, and in both.

Outcome

Our primary outcome was incident diabetes, using the previously described CCDSS definition.[16,17] These diagnostic codes cannot differentiate between type 1 and type 2 diabetes, but because 95% of incident diabetes among adults is type 2 diabetes, they primarily capture incident type 2 diabetes. Follow-up was until the first of incident diabetes, the 120-day time point before a third delivery (we did not have gestational age data for any third pregnancy), death, or the end of the study period (April 1, 2019).

Covariates

For both the first and second pregnancies, we considered other pregnancy and offspring-related factors associated with type 2 diabetes development, specifically, gestational hypertension (with or without preeclampsia), preterm delivery (<37 weeks), and small-for-gestational-age (SGA) and large-for-gestational-age (LGA) status.[25,26] For gestational hypertension, we applied the CCDSS hypertension definition to the same pregnancy periods for which we defined GD, and we also considered diagnostic codes for gestational hypertension and preeclampsia.

We considered time between deliveries, comorbid conditions, maternal age at index date, deprivation level (see Table 1 footnotes),[14] preexisting paternal diabetes and hypertension (validated CCDSS

definitions[16,17] applied from 2 years before 20 weeks' gestation in the first pregnancy to 12 weeks following the second delivery), and ethnocultural background (African/Caribbean [if born in West/South/East/Central Africa or first language was of Caribbean or African descent], Arabic [if born in the Arab league or first language was of Arabic or other North African or South-West Asian descent], Asian [if born in West/East/Central/South/Southeast/Pacific Asia or first language descends from these regions], European [if born in North America, South America, Central America, Mexico, East/South/Southern/West Europe, or Australia and first language was English, French, or other European language], and other [if first language was of Indigenous descent) based on participant-reported place of birth and primary language recorded on the mandatory birth declaration and incorporated into the birth registry. Ethnocultural background was assessed in this study because those with background other than European have a higher baseline risk for diabetes.

Statistical Analyses

We computed baseline characteristics (counts and proportions for categorical variables and mean [SD] for continuous variables) and compared them across exposure groups (Pearson $\chi 2$ tests for proportions; 1-way analysis of variance for means, as applicable). We calculated type 2 diabetes incidence rates (IR). We assessed for interactions ($P < .05$ for interaction terms) and multicollinearity (Cramer $V > 0.10$) among exposures and covariates. We constructed Kaplan-Meier curves and compared these through log-rank testing. We evaluated proportional hazards assumptions (log-minus-log survival plots, Schoenfeld residuals) and performed some transformations to fulfill these (age as a spline variable and binary gestational hypertension category defined as presence in either or both pregnancies vs neither).

We constructed multivariable Cox proportional hazards models to compute hazard ratios (HR) for type 2 diabetes, first with GD absence in either pregnancy as the reference group. We then examined models with GD in only the first pregnancy as the reference group and finally with GD in only the second as the reference group. We retained covariates based on univariate association with type 2 diabetes where $P \leq .25$, multivariable association (stepwise selection) where $P \leq .05$, and reduced bayesian information criteria values with inclusion (see eMethods in Supplement 1 for omitted variables).

In a sensitivity analysis, we evaluated the change in associations when including calendar years

of each pregnancy in our models to account for temporal trends in the screening and diagnosis of GD over the years.[27] In another sensitivity analysis, we retained women with stillbirth deliveries and accounted for stillbirths in the model, along with miscarriages between pregnancies. In a third sensitivity analysis, we applied indirect adjustments for obesity and smoking status to our main results, using established methods.[28,29] This bias analysis required external estimates for the HRs of obesity and of smoking with incident type 2 diabetes in women, which we respectively estimated as 3.90 (obesity vs no obesity)[30] and 1.13 (smoking vs not smoking).[31] This method also required external cohort data for obesity and smoking prevalence in groups of women corresponding to our main exposure categories. We used the Canadian Community Health Survey (Cycle 2.2) for this purpose[32]; 13% were in the obesity category and 24% smoked cigarettes. We applied the following formula for the indirect obesity adjustment: $HR_{(\text{corrected for obesity})} = HR_{(\text{from our analysis})} / HR_{(\text{related to obesity, from literature})}^{Poe-Pe*Po}$ (see eMethods in Supplement 1, similar formula applied for smoking; Poe = proportion within specific GD category who have obesity; Pe = proportion of those with specific GD category among all women with 2 consecutive singleton pregnancies; Po = proportion with obesity among all women with 2 consecutive singleton pregnancies). We performed analyses with SAS version 9.4 (SAS Institute). Data were analyzed from July 2023 to December 2023.

Results

The 431 980 women analyzed (Figure 1) had a mean (SD) age of 30.1 (4.5) years, and a mean (SD) of 2.8 (1.5) years elapsed between deliveries. Overall, 8550 women were African or Caribbean, 17 315 were from Arab-speaking regions, 14 615 were Asian, 373 415 were of European background, 78 770 (18.2%) at the highest material deprivation level (INSPQ deprivation index: quintile 5), 62 605 (14.5%) had 1 or more SGA offspring, 64 195 (14.9%) had 1 or more LGA offspring, 35 290 (8.2%) had 1 or more preterm delivery, and 34 145 (7.9%) had 1 or more gestational hypertension occurrence. In terms of the main exposure, 10 920 (2.5%) had GD in only their first pregnancy, 16 145 (3.7%) had GD in only their second, and 8255 (1.9%) in both (eFigure 2 in Supplement 1). Those without GD in either pregnancy (396 660 participants) (Table 1) were younger with higher proportions of European background and lower proportions with deprivation, comorbid conditions, LGA offspring, preterm births, and partners with diabetes and hypertension.

Associations of main exposure groups with incident type 2 diabetes

Over a median (IQR) of 11.5 (5.3-19.4) years (5 298 940 total person years), 12 205 mothers developed type 2 diabetes. The IRs per 1000 person-years rose across the no GD (IR, 1.4), GD in first pregnancy only (IR, 6.7), GD in second pregnancy only (IR, 12.4), and GD in both pregnancies (IR, 25.5) categories. Kaplan-Meier curves suggested significant differences in event-free survival across groups (Figure 2). The proportional hazards assumption applied. We did not detect interactions or multicollinearity

In adjusted models, compared with those without GD, those with GD in first pregnancy had a 4.35-fold higher hazard for type 2 diabetes (95% CI, 4.06-4.67) (Figure 3A), those with GD in the second pregnancy had a 7.68-fold increase (95% CI, 7.31-8.07), and those with GD in both pregnancies demonstrated a 15.80-fold increase (95% CI, 15.00-16.61). Compared with those with GD in the first pregnancy, women with GD in the second had 76% higher hazards (95% CI, 1.63-1.91) (Figure 3B) and those with GD in both pregnancies had a 3.63-fold increase (95% CI, 3.36-3.93). Hazards were 2.06-fold higher among women with GD in both pregnancies (95% CI, 1.94-2.19) (Figure 3C) compared with those with GD in the second pregnancy.

Sensitivity analyses

Inclusion of calendar years for each pregnancy did not importantly alter HRs (eTable 2 in Supplement 1). In another sensitivity analysis including women with stillbirth pregnancies in our study cohort (435 685 participants; 12 415 events), stillbirths were associated with 19% increased hazards (HR, 1.19; 95% CI, 1.04-1.38), compared with women without stillbirth deliveries (eTable 3 in Supplement 1). Miscarriages between pregnancies were not conclusively associated with incident diabetes (HR, 1.03; 95% CI, 0.97-1.09). Furthermore, retaining stillbirths among the 2 pregnancies examined and considering miscarriages between pregnancies did not importantly alter the association between GD occurrences and incident diabetes.

Indirect adjustments for obesity (no GD: reference; GD in first pregnancy HR, 2.72; 95% CI, 2.46-2.83; GD in second pregnancy HR, 5.48; 95% CI, 5.22-5.76; GD in both pregnancies HR, 9.62; 95% CI, 9.15-10.10) (see eMethods in Supplement 1 for other comparisons) somewhat attenuated the HRs for the incident type 2 diabetes outcome. Indirect adjustments for smoking (no GD: reference; GD

in first pregnancy HR, 4.23; 95% CI, 3.94-4.53; GD in second pregnancy HR, 7.44; 95% CI, 7.09-7.83; GD in both pregnancies HR, 15.50; 95% CI, 14.70-16.21) did not significantly alter the HRs.

Other associations observed

Gestational hypertension in either or both pregnancies was associated with a 65% increase in hazards for diabetes development (Table 2). Compared with appropriate size for gestational age of both offspring, LGA was consistently associated with diabetes development, with a 60% increase in hazards whether it occurred in the first or second pregnancies, and a doubling when it occurred in both pregnancies or when LGA occurred in 1 pregnancy and SGA in the other. Preterm delivery in 1 or both pregnancies was associated with a 10% to 20% increase in hazards of diabetes compared with full-term delivery in both pregnancies. Deprivation levels were associated with a stepwise increase in hazards. All ethnocultural groups other than European had higher diabetes hazards compared with European women, and all comorbid conditions considered were associated with increased hazards. Paternal diabetes was associated with a 43% increase in hazards for maternal diabetes development.

Discussion

Among nearly half a million mothers with 2 consecutive singleton pregnancies, our analyses demonstrate that GD in only the second pregnancy was associated with higher hazards for type 2 diabetes development than GD in only the first pregnancy. The highest hazards are with GD occurrence in both pregnancies. Compared with women without GD in either pregnancy, there were 4.35-fold, 7.68-fold, and 15.80-fold greater hazards for type 2 diabetes with GD in the first, in the second, and in both pregnancies, respectively. Indirect adjustments for obesity somewhat attenuated these values to 2.72-fold, 5.48-fold, and 9.62-fold, respectively, but the magnitude remained high, and the differences persisted. Direct comparisons between GD groups were also conclusive. For example, compared with first pregnancy–only GD, second pregnancy–only GD increased hazards by 76%, while GD in both pregnancies increased hazards 3.63-fold.

We did not identify any prior study that compared GD in a first pregnancy with GD in a second among women with 2 pregnancies. Our specific estimate for the increase in hazards associated with GD recurrence (HR, 3.63; HR, 2.21 with indirect adjustment for obesity) compared with women with a GD occurrence in only a first pregnancy was similar to the greater than 2-fold increase in hazards reported in 2 previous studies[4,5] that restricted analyses to women with at least 2 pregnancies. Other

studies that examined GD recurrence had a higher degree of variability in numbers of pregnancies. One reported a 16% increase in hazards with GD recurrence[33] while the other estimated a 2-fold increase.[34] We identified a single study that examined hazards of type 2 diabetes after pregnancy in relationship to numbers of prior GD pregnancies (Sister Study).[35] It differed in several other respects from ours. As such, its interpretation applies to an older group of women, several years beyond pregnancy. In the Sister Study, women with a history of 2 GD pregnancies experienced 6.2-fold higher hazards for type 2 diabetes in middle age compared with women with no GD pregnancies. The reference group included women without pregnancies. The investigators accounted for time since last GD pregnancy and self-reported weight. In our study, women with 2 pregnancies and GD in both had a 15.8-fold increase in hazards for type 2 diabetes development between their 30s and 40s, starting soon after their second pregnancy, compared with women without GD in either pregnancy. We indirectly adjusted for obesity and demonstrated that the association was attenuated to a 10-fold increase in hazards.

Our key discovery is that a single GD occurrence in a first pregnancy is associated with lower hazards for type 2 diabetes than a single GD occurrence in a second pregnancy. A subgroup analysis of the American Diabetes Prevention Program among women with a GD history showed that healthful diet-induced weight loss and higher physical activity levels could reduce type 2 diabetes risk.[6,7] Women with a first GD pregnancy may be motivated to adopt behavioral changes that both prevent GD in a second pregnancy and lower hazards of incident type 2 diabetes development thereafter. Supporting this, a recent cohort study[11] determined that among women without GD in their first pregnancy, weight loss between pregnancies was associated with reduced risk for new occurrence of GD in a subsequent pregnancy. In another study[10] among women with excess weight and GD in a first pregnancy, weight loss between pregnancies lowered the risk for GD recurrence in a second pregnancy. In our analyses, the women without GD in the first pregnancy who developed GD in the second may have gained excess weight in the first pregnancy and had difficulty losing it[9] or gained weight between pregnancies.[10,11] In an Australian investigation11 among women without GD in their first pregnancy, higher levels of weight gain between pregnancies were associated with stepwise increases in the risk of new occurrence of GD in second pregnancy. For many women, the additional responsibilities of parenthood[12] may challenge efforts to engage in behaviors to enhance personal health. Furthermore, the metabolic stresses inherent to pregnancy may impair their β-cell function,[36]

making them more susceptible to developing GD in the second pregnancy, and ultimately to type 2 diabetes development.

Alongside health behaviors and physiological changes, our analyses reinforce the importance of social factors, including material and social deprivation and non-European background. The underpinnings of such associations likely stem from other related upstream characteristics, such as food insecurity,[37] local environments not conducive to physical activity,[38,39] and structural inequity.[40] Partner diabetes was another risk indicator for maternal type 2 diabetes development in our analyses, with a 43% increase in hazards. This is consistent with our prior studies[41,42] demonstrating increases in hazards for the development of diabetes in fathers whose partners had GD compared with those whose partners did not. Shared partner type 2 diabetes risk may be related to shared health behaviors, resources, social factors, and household environments.[20,43-46] Assortative mating (similar demographics, attitudes, behaviors, and traits at the outset) may also play a role.[46-49]

Strengths and Limitations

Our large sample size of nearly half a million women was possible through linkage of Quebec's health administrative and vital statistics databases. Limitations to these data include lack of information on GD management, prepartum weight status, gestational weight gain, smoking status, and laboratory values. GD and weight excess are intimately associated. However, all of our models accounted for LGA in both the first and second pregnancies, a strong correlate of prepregnancy and gestational weight gain.[50,51] Furthermore, we performed indirect adjustments for obesity using established methods.[28,29] We could not corroborate International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revision–coded diagnoses of diabetes with laboratory data, but to mitigate for misclassification, we applied validated definitions of GD and diabetes.[16,17] The diagnostic codes do not reliably distinguish between type 1 and type 2 diabetes, but given that 95% of diabetes onset among adults is type 2 diabetes, the majority of events captured with our codes are type 2 diabetes. We acknowledge that women with more than 1 GD occurrence may already be undergoing more frequent screening for diabetes than women with only 1 occurrence, perhaps partly accounting for their higher diabetes hazards. We also acknowledge potential misclassification of ethnocultural background, as second- and third-generation women and/or Indigenous women would have been classified as European if their first language was English, French, or another European language. Lastly, we did not examine women without pregnancies or women with a single pregnancy, but our

focus was women with 2 consecutive deliveries; restriction to women with 2 or more deliveries overcame some methodological challenges, as discussed.

Conclusions

Our retrospective cohort study suggests that among women with 2 consecutive singleton pregnancies, without diabetes before or between pregnancies, the absence of GD in a second pregnancy following GD in the first suggests that the mother is taking effective diabetes prevention measures. If confirmed, she should be encouraged to continue. New onset GD or recurrent GD in a second pregnancy, however, should inspire urgent action for prevention or adjustments to ongoing efforts. We also confirmed the importance of material deprivation and ethnocultural background in type 2 diabetes risk estimation, and we identified paternal diabetes as a factor associated with risk for type 2 diabetes development in mothers. Our results provide a personalized medicine–oriented pathway to diabetes risk estimation in women. This should be coupled with tailored prevention programs and equitable referral pathways to reduce the burden of type 2 diabetes and its complications.

Declarations

Acknowledgements: The authors thank the Quebec Statistical Institute (Institut de la statistique du Québec) for data linkage and hosting us at their secured Centres for Access to Research Data.

Ethics approval and consent to participate: The McGill University Health Centre's Research Ethics Board (2019-5029; 2018/12/11) and Quebec Access to Information Commission (1019371-S; 2019/11/18) approved the protocol. These bodies waived informed consent because it involved deidentified data, we performed analyses at the Quebec Statistical Institute's data centres, and we rounded frequencies to multiples of 5. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Access to Data Statement: The data that support the findings of this study are available only through Quebec's Statistical Institute Centres for Access to Research Data (CADRISQ), secure environments available to accredited researchers in Quebec for research purposes, and so are not publicly available. Restrictions apply to the availability of these data and data requests must be made with permission from the Quebec Statistical Institute (https://statistique.quebec.ca/recherche/). K.D. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of Interests Disclosure: The authors declare that they have no competing interests.

Author Contributions: J.M. contributed to the study design, interpreted the data, prepared the first draft of the manuscript and revised based on co-authors' comments, and approved the final manuscript as submitted. E.R. contributed to the study conception and design, provided oversight of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. M.D. contributed to dataset cleaning, variable derivation, statistical analyses, data interpretation and approved the final manuscript as submitted. M.N. critically reviewed the manuscript

and approved the final version as submitted. K.D. conceptualized and designed the study, supervised analyses, interpreted the data, critically reviewed the manuscript and supervised draft revisions, and approved the final manuscript as submitted. K.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Table 1. Baseline covariates, stratified by gestational diabetes (GD) occurrence(s) in each respective pregnancy

N (%)[a]	**No GD** (N=396,660)	**GD in 1st pregnancy** (N=10,920)	**GD in 2nd pregnancy** (N=16,145)	**GD in both pregnancies** (N=8,255)
Prior history of gestational hypertension in either or both pregnancies[b]				
Yes (N=34,145)	29,550 (7.5)	1,275 (11.7)	2,160 (13.4)	1,160 (14.1)
Age of mother at 2nd delivery[c]				
Mean age, years (SD)	30.0 (4.5)	30.9 (4.6)	31.6 (4.7)	32.0 (4.7)
Time between deliveries: years				
<2 (N=134,910)	124,800 (31.5)	3,525 (32.3)	4,055 (25.1)	2,530 (30.6)
2-<2.5 (N=88,110)	81,610 (20.6)	2,250 (20.6)	2,705 (16.8)	1,545 (18.7)
2.5-<3.5 (N=112,005)	103,195 (26.0)	2,710 (24.8)	4,010 (24.8)	2,090 (25.3)
≥3.5 (N=96,955)	87,050 (21.9)	2,435 (22.3)	5,380 (33.3)	2,090 (25.3)
Material deprivation index: Quintiles[d]				
1 (N=87,645)	81,265 (20.5)	2,005 (18.4)	2,900 (18.0)	1,475 (17.9)
2 (N=91,140)	83,975 (21.2)	2,285 (20.9)	3,250 (20.1)	1,630 (19.7)
3 (N=85,660)	78,870 (19.9)	2,135 (19.6)	3,095 (19.2)	1,560 (18.9)
4 (N=81,430)	74,525 (18.8)	2,125 (19.5)	3,155 (19.5)	1,625 (19.7)
5 (N=78,770)	71,280 (18.0)	2,195 (20.1)	3,455 (21.4)	1,840 (22.3)
Social deprivation index: Quintiles[d]				
1 (N=95,755)	88,545 (22.3)	2,305 (21.1)	3,145 (19.5)	1,760 (21.3)
2 (N=92,740)	85,620 (21.6)	2,250 (20.6)	3,255 (20.2)	1,615 (19.6)
3 (N=88,355)	81,225 (20.5)	2,200 (20.1)	3,325 (20.6)	1,605 (19.4)
4 (N=79,930)	72,980 (18.4)	2,110 (19.3)	3,155 (19.5)	1,685 (20.4)
5 (N=67,870)	61,545 (15.5)	1,885 (17.3)	2,975 (18.4)	1,465 (17.7)
Background[e]				

America, Australia or Europe (N=373,415)	346,230 (87.3)	8,865 (81.2)	12,280 (76.1)	6,040 (73.2)
Africa or Caribbean (N=8,550)	7,565 (1.9)	260 (2.4)	465 (2.9)	260 (3.2)
Arab-speaking Regions (N=17,315)	14,840 (3.7)	600 (5.5)	1,210 (7.5)	665 (8.1)
Asia (N=14,615)	12,040 (3.0)	640 (5.9)	1,190 (7.4)	745 (9.0)
Other (N=18,085)	15,980 (4.0)	555 (5.1)	1,005 (6.2)	545 (6.6)
Co-morbid conditions				
Mood disorders, alcohol or drug dependence (N=18,010)	16,315 (4.1)	440 (4.0)	850 (5.3)	405 (4.9)
Thyroid disorder (N=15,010)	13,185 (3.3)	450 (4.1)	895 (5.5)	480 (5.8)
Arthritis (N=9,180)	8,265 (2.1)	270 (2.5)	435 (2.7)	210 (2.5)
Asthma or COPD (N=8,650)	7735 (2.0)	250 (2.3)	425 (2.6)	240 (2.9)
Small for gestational age[f]				
Neither pregnancy (N=369,225)	338,405 (85.3)	9,465 (86.7)	14,120 (87.5)	7,235 (87.6)
1st pregnancy only (N=26,115)	24,225 (6.1)	630 (5.8)	815 (5.1)	445 (5.4)
2nd pregnancy only (N=26,145)	24,240 (6.1)	580 (5.3)	890 (5.5)	435 (5.3)
Both pregnancies (N=10,345)	9,650 (2.4)	240 (2.2)	320 (2.0)	135 (1.6)
Large for gestational age[f]				
Neither pregnancy (N=367,635)	339,910 (85.7)	8,735 (80.0)	12,635 (78.3)	6,355 (77.0)
1st pregnancy only (N=26,160)	23,290 (5.9)	845 (7.7)	1,315 (8.1)	710 (8.6)
2nd pregnancy only (N=26,070)	23,145 (5.8)	865 (7.9)	1,370 (8.5)	690 (8.4)
Both pregnancies (N=11,965)	10,175 (2.6)	470 (4.3)	825 (5.1)	495 (6.0)
Preterm birth				
Neither pregnancy (N=392,290)	361,365 (91.1)	9,725 (89.1)	14,040 (87.0)	7,160 (86.7)
1st pregnancy only (N=20,330)	18,155 (4.6)	595 (5.5)	1,050 (6.5)	530 (6.4)
2nd pregnancy only (N=14,630)	13,050 (3.3)	450 (4.1)	720 (4.5)	410 (5.0)

Both pregnancies (N=4,730)	4,085 (1.0)	150 (1.4)	340 (2.1)	155 (1.9)
Prior history of paternal diabetes[g]				
Yes (N=3,645)	3170 (0.8)	110 (1.0)	225 (1.4)	140 (1.7)
Prior history of paternal hypertension[g]				
Yes (N=9,420)	8385 (2.1)	305 (2.8)	480 (3.0)	250 (3.0)

COPD = chronic obstructive pulmonary disease; GDM = gestational diabetes mellitus; SD = standard deviation

[a] Values are randomly rounded up or down to a multiple of '5' (for patient confidentiality purposes). Therefore, column sums for each baseline characteristic may not equal the total number of women in each level of the exposure due to this random rounding process.

[b] Gestational hypertension was collapsed as a binary variable (absent or present in either/both pregnancies) as a measure to ensure the proportional hazards assumption was met when tested. When GHTN status was categorized into four levels, similar to the primary GDM exposure, the assumption was violated. The capture period for this co-morbidity was between 20 weeks' gestation to 12 weeks' postpartum of each respective pregnancy.

[c] Age was not categorized and instead kept as a continuous variable. Thus, we report the mean age in years and its standard deviation for women in each exposure category.

[d] Range from 1 (least deprived) to 5 (most deprived). The Institut national de santé publique du Québec (INSPQ) material and social deprivation index is computed from small-area census data. Specifically, the material indices are derived from average income, proportions without high school diploma, and employment to population ratio among those 15 years and older. The social indices are derived from the proportion of the population: who are single-parent families, aged 15 and over living alone, and aged 15 and over who are separated, divorced or widowed. In order to assign the INSPQ index for each woman, we first checked availability of this variable in the index year (year of 2nd delivery). 7335 women were missing an assigned INSPQ index score.

[e] Ethnocultural background based on the mother's region of birth and reported preferred language. We categorized women as: i) "Europid" if born in North America, South America, Central America, Mexico, East/South/Southern/ West Europe or Australia and first language is English, French, or other European language; ii) "African or Caribbean" if born in West/South/East/Central Africa or first language is of Caribbean or African descent; iii) "Arabic" if born in the Arab league or first language is of Arabic or other North African/South-West Asian descent; iv) "Asian" if born in West/East/Central/South/Southeast/Pacific Asia or first language descends from these regions; or v) "Other" (does not fit into any other category), or if first language is of Indigenous descent (N=1,680).

[f] 150 offspring were missing birthweight required to derive offspring size.

[g] Prior history in the father was defined as ≥ 1 inpatient and/or ≥ 2 outpatient ICD codes for any form of diabetes or hypertension, respectively, that occurred during the period from two years prior to 20 weeks' gestation of their partner's first pregnancy to 12 weeks' postpartum in relationship to the second pregnancy.

Table 2. Association of incident diabetes with covariates included in the final model

	Covariate[a]	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
	Gestational hypertension affecting either pregnancy or both pregnancies[b]	2.14 (2.04-2.25)	1.65 (1.57-1.73)
Offspring indicators	**Offspring size[c]**		
	AGA: both offspring	*Reference*	*Reference*
	SGA: 1st offspring only	0.97 (0.90-1.05)	0.94 (0.87-1.02)
	SGA: 2nd offspring only	0.96 (0.89-1.04)	0.91 (0.84-1.00)
	SGA: both offspring	1.00 (0.89-1.13)	0.97 (0.86-1.10)
	LGA: 1st offspring only	1.82 (1.71-1.94)	1.60 (1.50-1.70)
	LGA: 2nd offspring only	1.86 (1.75-1.98)	1.60 (1.50-1.70)
	LGA: both offspring	2.77 (2.57-2.98)	2.01 (1.86-2.17)
	SGA: 1st offspring , LGA: 2nd offspring	2.85 (2.02-4.01)	2.14 (1.51-3.02)
	LGA: 1st offspring , SGA: 2nd offspring	2.75 (1.95-3.87)	1.94 (1.38-2.73)
	Gestational age of offspring at birth[d]		
	Term birth: both offspring	*Reference*	*Reference*
	Preterm birth: 1st offspring only	1.33 (1.23-1.44)	1.11 (1.03-1.20)
	Preterm birth: 2nd offspring only	1.50 (1.38-1.63)	1.19 (1.09-1.29)
	Preterm birth: both offspring	1.71 (1.49-1.95)	1.21 (1.06-1.39)
Paternal	**Prior history of paternal diabetes[e]**	2.09 (1.80-2.42)	1.43 (1.24-1.66)
	Prior history of paternal hypertension[e]	1.34 (1.20-1.49)	1.12 (1.00-1.25)
Maternal indicators	**Age of mother at 2nd delivery, years[f]**		
	Not applicable as a result of spline.		
	Time between deliveries, years		
	<2	*Reference*	*Reference*
	2-2.5	0.85 (0.81-0.90)	0.90 (0.86-0.95)
	2.5-3.5	0.82 (0.78-0.86)	0.84 (0.80-0.88)
	≥3.5	1.06 (1.01-1.11)	0.94 (0.89-0.98)
	Material deprivation index, quintiles[g]		
	1 (least deprived)	*Reference*	*Reference*
	2	1.25 (1.17-1.32)	1.24 (1.17-1.32)
	3	1.38 (1.30-1.47)	1.35 (1.27-1.43)
	4	1.56 (1.47-1.66)	1.44 (1.36-1.53)
	5 (most deprived)	1.99 (1.87-2.10)	1.67 (1.58-1.78)
	Social deprivation index, quintiles[g]		
	1 (least deprived)	*Reference*	*Reference*
	2	1.08 (1.02-1.14)	1.08 (1.02-1.14)
	3	1.14 (1.08-1.21)	1.10 (1.04-1.17)
	4	1.32 (1.25-1.40)	1.16 (1.10-1.23)

	5 (most deprived)	1.53 (1.45-1.62)	1.26 (1.19-1.34)
	Background[h]		
	America, Australia or Europe	*Reference*	*Reference*
	Africa or Caribbean	2.68 (2.44-2.95)	1.90 (1.72-2.10)
	Arab-speaking regions	2.24 (2.07-2.42)	1.60 (1.48-1.74)
	Asia	2.50 (2.33-2.69)	1.62 (1.50-1.74)
	Other	2.00 (1.86-2.15)	1.46 (1.35-1.58)
	Co-morbid conditions[j]		
	Mood disorders, alcohol or drug dependence	1.50 (1.39-1.62)	1.40 (1.29-1.51)
	Thyroid disorder	1.82 (1.68-1.98)	1.40 (1.29-1.53)
	Arthritis	1.49 (1.35-1.65)	1.26 (1.14-1.40)
	Asthma or COPD	1.95 (1.77-2.15)	1.67 (1.52-1.84)

AGA = appropriate for gestational age; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; LGA = large for gestational age; SGA = small for gestational age

[a] The Cox proportional hazards model adjusted for the GDM occurrences across pregnancies, as well as each of the variables listed.

[b] Gestational hypertension was collapsed as a binary variable (absent or present in either/both pregnancies) as a measure to ensure the proportional hazards assumption was met when tested. When GHTN status was categorized into four levels (similar to the primary GDM exposure), the assumption was violated. The capture period for this co-morbidity was between 20 weeks' gestation to 12 weeks' postpartum of each respective pregnancy.

[c] We observed a stepwise increase in type 2 diabetes hazards with increasing occurrences of LGA offspring. Compared to AGA offspring in both pregnancies, LGA in the first (HR=1.60, 95%CI 1.50-1.70) or second (HR=1.60, 95%CI 1.50-1.70) only was associated with an identical increase in type 2 diabetes hazards, while LGA in both pregnancies was associated with nearly a doubling of type 2 diabetes hazards (HR=2.01, 95%CI 1.86-2.17). 150 offspring were missing birthweight required to derive offspring size.

[d] Compared to women without preterm delivery, preterm in the first (HR=1.11, 95%CI 1.03-1.20), second (HR=1.19, 95%CI 1.09-1.29) , or both pregnancies (HR=1.21, 95% CI 1.06-1.39) was associated with a similar increase in type 2 diabetes hazards.

[e] Prior history in the father was defined as ≥ 1 inpatient and/or ≥ 2 outpatient ICD codes for any form of diabetes or hypertension, respectively, that occurred during the period from two years prior to 20 weeks' gestation of their partner's first pregnancy to 12 weeks' postpartum in relationship to the second pregnancy.

[f] No point estimate of the hazard ratio available for variables that have a spline applied.

[g] We observed a stepwise increase in type 2 diabetes hazards with increasing material and social deprivation (as defined by the Institut national de santé publique du Québec [INSPQ]) . 7335 women were missing a value for the INSPQ material deprivation index.

[h] Compared to women of Europid descent, those from other ethnic origins demonstrated increased hazards of developing type 2 diabetes, respectively, during the follow-up period.

[i] The reference group are women with the absence of each condition, respectively. The presence of each co-morbid condition was associated with higher type 2 diabetes hazards. Co-morbid conditions were defined in accordance with the Chronic Disease Surveillance System's definition of chronic disease, requiring ≥1 inpatient or ≥2 outpatient ICD codes to be present within 2 years prior to the index date.

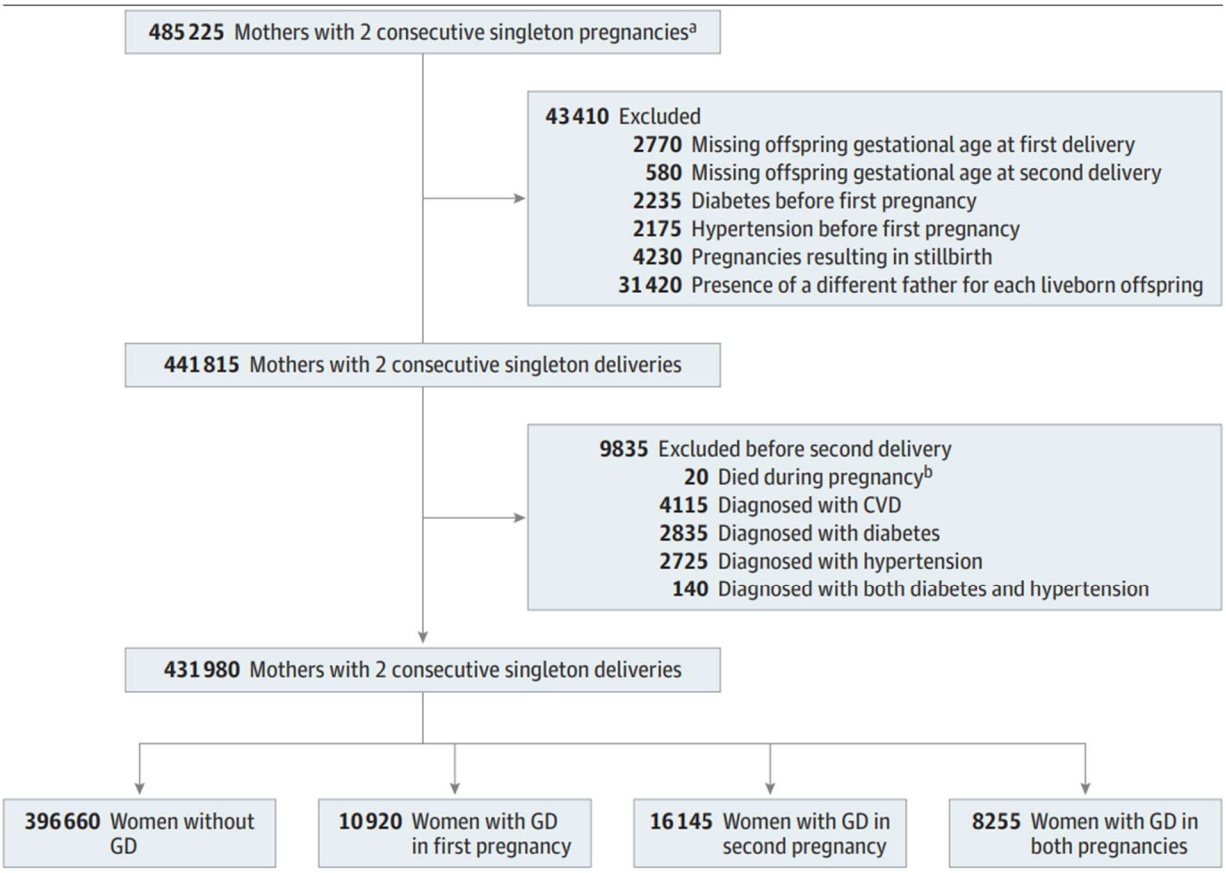
Figure Legend

Figure 1: Cohort construction.

Figure 2: Kaplan-Meier curves for diabetes-free survival. The log-rank test indicated significant differences in event-free survival across exposure groups ($p < 0.02$).

Figure 3: Associations of incident diabetes with gestational diabetes in first, second, or both pregnancies, from adjusted multivariable models. The corresponding unadjusted hazard ratios among women with no GDM, GDM in first pregnancy, GDM in second pregnancy and GDM in both pregnancies, in Panel A are: 1.00 (reference group), 4.80 (95%CI 4.48-5.14), 9.09 (95%CI 8.67-9.53) and 19.05 (95%CI 18.10-19.91), respectively. The corresponding unadjusted hazard ratios among those in Panel B are: 1.00 (reference group), 1.89 (95%CI 1.75-2.05) and 3.96 (95% CI 3.66-4.28), respectively. The corresponding unadjusted hazard ratios among those in Panel C are: 1.00 (reference) and 2.09 (95%CI 1.97-2.22), respectively. When the adjusted hazard ratios (shown in the Figure) were additionally indirectly adjusted for obesity, the following hazard ratios were obtained for those in Panel A: 1.00 (reference), 2.72 (95%CI 2.46-2.83), 5.48 (95%CI 5.22-5.76) and 9.62 (95%CI 9.15-10.10), respectively. Indirect adjustments for obesity resulted in the following hazard ratios for those in Panel B: 1.00 (reference), 1.26 (95%CI 1.17-1.37) and 2.21 (95%CI 2.05-2.39), respectively. The following results were obtained for this indirect adjustment among those in Panel C: 1.00 (reference) and 1.25 (95%CI 1.18-1.33). When the adjusted hazard ratios (shown in the Figure) were additionally indirectly adjusted for smoking, the following hazard ratios were obtained for those in Panel A: 1.00 (reference), 4.23 (95%CI 3.94-4.53), 7.44 (95%CI 7.09-7.83) and 15.50 (95%CI 14.70-16.21), respectively. Indirect adjustments for smoking resulted in the following hazard ratios for those in Panel B: 1.00 (reference), 1.71 (95%CI 1.58-1.85) and 3.55 (95%CI 3.29-3.85), respectively. The following results were obtained for this indirect adjustment among those in Panel C: 1.00 (reference) and 2.01 (95%CI 1.89-2.13).

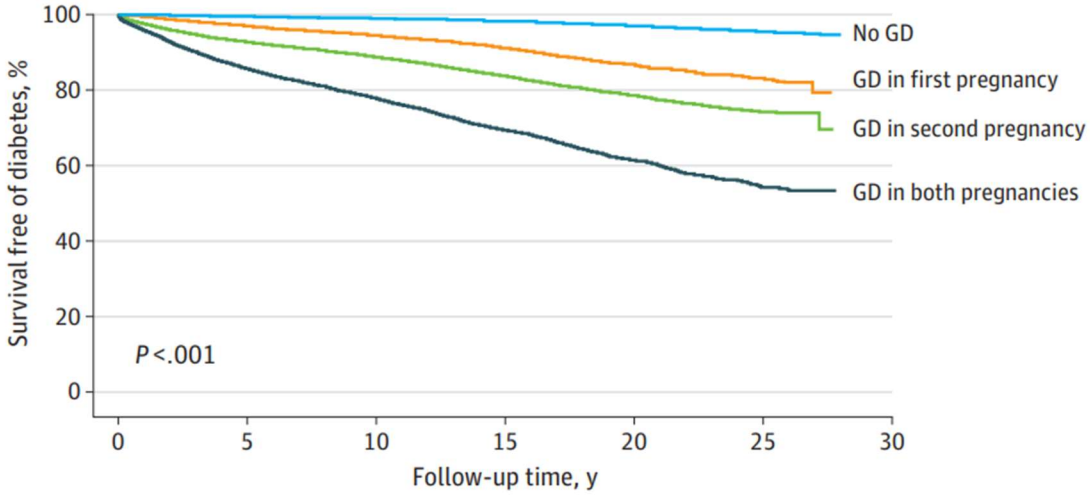
Figure 1. Cohort construction



[a]Values are rounded either up or down to a multiple of 5 for patient confidentiality purposes.

[b]Fatal events occurring at any point between 20 weeks' gestation in the second pregnancy and 12 weeks post partum. Five deaths were related to a fatal cardiovascular disease (CVD) event while the remaining 15 fatalities were related to obstetrical complications related to childbirth, major trauma, and suicide.

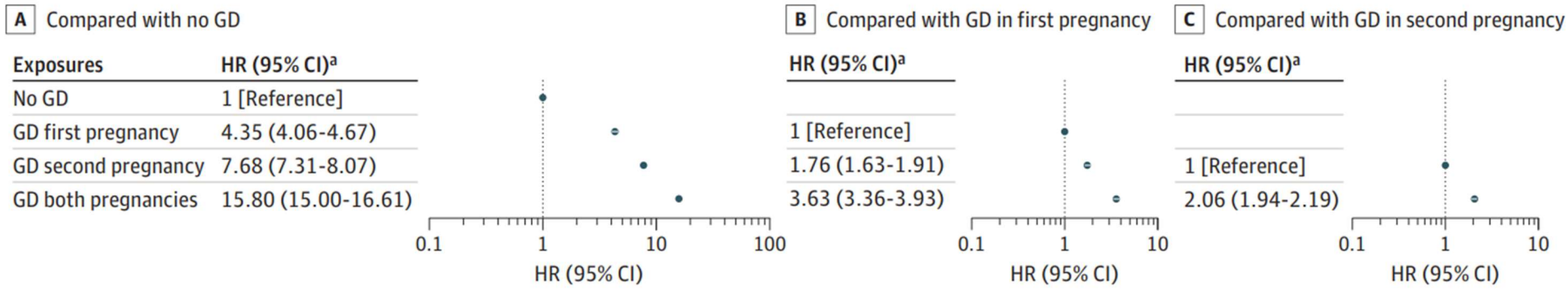
Figure 2. Kaplan-Meier curves for diabetes-free survival



No. at risk							
No GD	396660	300890	222735	154015	92115	20025	0
GD in first pregnancy	10920	8245	6160	4325	2450	440	0
GD in second pregnancy	16145	12045	8070	5205	2815	530	0
GD in both pregnancies	8255	5750	3795	2250	1100	215	0

The log-rank test indicated significant differences in event-free survival across exposure groups ($p < 0.02$).

Figure 3. Associations of incident diabetes and gestational diabetes (GD) in first, second, and both pregnancies, from adjusted multivariable models



The corresponding unadjusted hazard ratios (HRs) among women with no GD, GD in first pregnancy, GD in second pregnancy and GD in both pregnancies, in Panel A were 4.80 (95% CI, 4.48-5.14), 9.09 (95% CI, 8.67-9.53), and 19.05 (95% CI, 18.10-19.91) for GD in first pregnancy, GD in second pregnancy, and GD in both pregnancies, respectively. The corresponding unadjusted HRs among those in panel B were 1.89 (95% CI, 1.75-2.05) and 3.96 (95% CI, 3.66-4.28) for GD in second pregnancy and GD in both pregnancies, respectively. The corresponding unadjusted HR among those in panel C was 2.09 (95% CI, 1.97-2.22) for GD in both pregnancies.

3.3 Supplementary Materials, Manuscript 1

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eTable 1. ICD codes

Condition	ICD-9	ICD-10	Capture period
Prior cardiovascular disease or circulatory system disease conditions (mother; exclusion criteria)[a]	325, 410-415, 427-444, 451-453, 6396, 671, 673, 6740, 7943, 9971-9972, 2506	I20-I26, I46-I52, I60-I70, I73-I74, I79-I82, I86, I97, R9430-R9431, E105, E115, E145, G08, G45-G46, H34, O882, O994, T817	2 years prior to 12 weeks' postpartum of second delivery (index date) – *2 outpatient diagnoses, 1 inpatient diagnosis or 1 related surgical procedure (angioplasty, endarterectomy or coronary artery bypass surgery)*
Prior diabetes (mother; exclusion criteria)	250, 6480, 6488	E10-14, O245-O248	2 years prior to 20 weeks' gestation of first pregnancy (preexisting condition) or codes occurring between 12 weeks' postpartum of the first pregnancy and 20 weeks' gestation of the second pregnancy (condition developed during interpregnancy interval) – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
Prior hypertension (mother; exclusion criteria)	401-405, 642	I10-I13, I15, O10-O11, O13-O16	2 years prior to 20 weeks' gestation of first pregnancy (preexisting condition) or codes occurring between 12 weeks' postpartum of the first pregnancy and 20 weeks' gestation of the second pregnancy (condition developed during interpregnancy interval) – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
Prior diabetes (father; covariate)	250, 6480, 6488	E10-14, O245-O248	2 years prior to 20 weeks' gestation of first pregnancy to 12 weeks' postpartum of second pregnancy – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
Prior hypertension (father; covariate)	401-405, 642	I10-I13, I15, O10-O11, O13-O16	2 years prior to 20 weeks' gestation of first pregnancy to 12 weeks' postpartum of second pregnancy – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
Gestational diabetes	250, 6480, 6488	E10-14, O248	20 weeks' gestation of each respective pregnancy to 12 weeks' postpartum – *2 outpatient diagnoses or 1 inpatient diagnosis*
Gestational hypertension (collapsed as a binary variable)[b]	401-405, 642	I10-I13, I15, O10-O11, O13-O16	20 weeks' gestation of each respective pregnancy to 12 weeks' postpartum – *2 outpatient diagnoses or 1 inpatient diagnosis*
Diabetes outcome	250, 6480, 6488	E10-14, O245-O248	After 12 weeks' following the second delivery (index date) – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
Pregnancy after the index date (censor at 120 days prior)	630-676, 763, 767-768, 779 V22-V24, V27-V39	O00-O99, Z32-Z39, P95, P964, P968-P969	After 12 weeks' following the second delivery (index date) – *1 inpatient diagnosis*

Miscarriages between pregnancies	630-638	O03-O05	12 weeks' postpartum of the first delivery to conception date of the second pregnancy - *1 outpatient or 1 inpatient diagnosis*
Mood disorders, alcohol or drug dependence	291-292, 295-305, 311 V11 V654	F10-F25, F30-F34, F38-F45, F48, F53, F99 R457 Z914 Z915 X65 Z714 Z864-Z865	2 years prior to 12 weeks' postpartum of the second delivery (index date) – *2 outpatient diagnoses or 1 inpatient diagnosis*
Thyroid disorders	240-246 0175, 1222, 2513, 6481, 7753, 7758, 7945, V770	E01-E07 A188, B673, E350, E890-E891, O905, P720-P722, R946, Z138, O9920	2 years prior to 12 weeks' postpartum of the second delivery (index date) – *2 outpatient diagnoses or 1 inpatient diagnosis*
Arthritis	274 6960, 710-721, 724	M05-M19, M32, M43, M46-M48, M53-M54, L405	2 years prior to 12 weeks' postpartum of the second delivery (index date) – *2 outpatient diagnoses or 1 inpatient diagnosis*
Asthma or COPD	491-493, 496, 5181-5182	J44-J45	2 years prior to 12 weeks' postpartum of the second delivery (index date) – *2 outpatient diagnoses or 1 inpatient diagnosis*

COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; HIV = human immunodeficiency virus

[a]The CVD-related exclusion criteria included codes related to both hospitalization and outpatient clinic visits for myocardial infarction, stroke, angina, and additionally considered other circulatory system disease conditions (atrial fibrillation, heart failure, other ischemic disease, other cardiac dysrhythmias, peripheral vascular disease and venous thromboembolism. We also excluded those with the following ***procedure codes*** related to pacemaker implantation, angioplasty, endarterectomy or coronary artery bypass surgery: 00460, 00631, 00662, 04022, 04030, 04031, 04037, 04046, 04601-04608, 04610-04612, 04661, 04662, 04665-04668, 04669, 04689, 04692-04699, 04701-04704, 04707-04709, 04710, 04713-04716, 04721-04723, 04725-04727, 04732-04737, 04740-04058, 09302, 20123, 20124, 20186, 20191, 20194, 20195, 20531, 20532, 20577-20583-20590.

eTable 2. Comparing effect estimates of the diabetes outcome, with and without inclusion of years of pregnancy, to account for temporal trends in the screening and diagnosis of gestational diabetes

Exposure	Excluding years of pregnancy in model	Including years of pregnancy in model[a]	Absolute Δ HR for incident diabetes
No GD	Reference	Reference	
GD in first pregnancy	4.35 (4.06-4.67)	4.36 (4.07-4.68)	+0.01
GD in second pregnancy	7.68 (7.31-8.07)	7.64 (7.28-8.03)	-0.04
GD in both pregnancies	15.80 (15.00-16.61)	15.80 (15.10-16.72)	0.00
GD in first pregnancy	Reference	Reference	
GD in second pregnancy	1.76 (1.63-1.91)	1.75 (1.62-1.90)	-0.01
GD in both pregnancies	3.63 (3.36-3.93)	3.63 (3.36-3.93)	0.00
GD in second pregnancy	Reference	Reference	
GD in both pregnancies	2.06 (1.94-2.19)	2.07 (1.95-2.20)	+0.01

GD = gestational diabetes; HR = hazard ratio

[a] These analyses include all of the baseline characteristics shown in Table 2, in addition to calendar years for pregnancy #1 and pregnancy #2 (as two separate variables).

eTable 3. Associations of incident diabetes with gestational diabetes occurrences when including women with stillbirth pregnancies in cohort (N=435,685)

	Variable	Hazard ratio (95% CI) from sensitivity analysis
Exposure	Gestational diabetes (GD) occurrences	
	No GD	*Reference*
	GD in first pregnancy	4.34 (4.05-4.65)
	GD in second pregnancy	7.65 (7.28-8.03)
	GD in both pregnancies	15.80 (15.00-16.61)
	Gestational hypertension affecting either pregnancy or both pregnancies	1.63 (1.55-1.72)
Offspring indicators	Offspring size	
	AGA: both offspring	*Reference*
	SGA: 1st offspring only	0.94 (0.87-1.02)
	SGA: 2nd offspring only	0.91 (0.84-1.00)
	SGA: both offspring	0.99 (0.88-1.11)
	LGA: 1st offspring only	1.61 (1.51-1.71)
	LGA: 2nd offspring only	1.60 (1.50-1.70)
	LGA: both offspring	2.01 (1.87-2.17)
	SGA: 1st offspring , LGA: 2nd offspring	2.13 (1.51-3.02)
	LGA: 1st offspring , SGA: 2nd offspring	1.94 (1.38-2.73)
	Gestational age of offspring at birth	
	Term birth: both offspring	*Reference*
	Preterm birth: 1st offspring only	1.09 (1.01-1.17)
	Preterm birth: 2nd offspring only	1.19 (1.09-1.29)
	Preterm birth: both offspring	1.19 (1.05-1.36)
Paternal	Prior history of paternal diabetes[a]	- -
	Prior history of paternal hypertension[a]	- -
Maternal indicators	Age of mother at 2nd delivery, years	
	Not applicable as a result of spline.	
	Stillbirth delivery[b]	
	Yes	1.19 (1.04-1.38)
	Miscarriage between pregnancies[c]	
	Yes	1.03 (0.97-1.09)
	Time between deliveries, years	
	<2	*Reference*
	2-2.5	0.90 (0.85-0.95)
	2.5-3.5	0.84 (0.80-0.88)
	≥3.5	0.94 (0.90-0.98)

	Material deprivation index, quintiles	
	1 (least deprived)	*Reference*
	2	1.24 (1.17-1.32)
	3	1.34 (1.26-1.43)
	4	1.44 (1.36-1.53)
	5 (most deprived)	1.67 (1.57-1.77)
	Social deprivation index, quintiles	
	1 (least deprived)	*Reference*
	2	1.07 (1.02-1.14)
	3	1.10 (1.04-1.17)
	4	1.16 (1.10-1.23)
	5 (most deprived)	1.26 (1.19-1.33)
	Background	
	America, Australia or Europe	*Reference*
	Africa or Caribbean	1.89 (1.72-2.08)
	Arab-speaking regions	1.59 (1.47-1.72)
	Asia	1.63 (1.51-1.75)
	Other	1.46 (1.36-1.58)
	Co-morbid conditions	
	Mood disorders, alcohol or drug dependence	1.39 (1.29-1.50)
	Thyroid disorder	1.41 (1.30-1.53)
	Arthritis	1.26 (1.14-1.39)
	Asthma or COPD	1.67 (1.52-1.84)

[a] Prior history of paternal diabetes and hypertension were removed from the Cox proportional hazards model in this sensitivity analysis, as linked paternal information is unavailable for stillbirths.

[b] 3,705 women had a first and/or second pregnancy that resulted in a stillbirth.

[c] 51,360 women with miscarriage between pregnancies. We required at least one outpatient and hospitalization record of miscarriage/abortion (ICD-9: 630-638, ICD-10: O03-O05) occurring from 12 weeks postpartum of the first pregnancy and 20 weeks' gestation of the second pregnancy to define a miscarriage between pregnancies. This variable was removed from our primary analysis because it did not meet our criteria for variable inclusion (see Statistical Analysis).

Supplemental Methods

Omitted variables from primary analysis (variable selection): Other variables that we considered but ultimately did not meet thresholds for inclusion in statistical models (see Statistical Analysis for inclusion criteria) were several paternal variables (age, ethnicity), parental co-habitation, years of maternal education, offspring congenital anomalies, offspring sex, history of cancer, history of HIV or chronic hepatitis, placental abruption and miscarriages between pregnancies.

Sensitivity analysis (adjusting for unmeasured confounders): Shin *et al.,* 2014 (1); Lash *et al.,* 2014 (2)

$$HR_{(\text{corrected for smoking})} = \frac{HR_{(\text{from our analysis})}}{HR_{(\text{related to smoking, from literature})}^{P_{se}-P_e P_s}}$$

Notation

P_{se} = proportion within specific exposure category who smoke

P_e = proportion of those corresponding to specific exposure category among all women with two consecutive singleton pregnancies

P_s = proportion who smoke among all women with two consecutive singleton pregnancies

$HR_{(\text{related to smoking, from literature})} = 1.13$ (3)

$HR_{(\text{related to obesity, from literature})} = 3.90$ (4)

GD occurrences from CCHS-derived cohort				
	No GD	**GD in 1st pregnancy**	**GD in 2nd pregnancy**	**GD in both pregnancies**
P_{se}: Proportion of Smokers (%, N)	24.34 (266/1093)	25.00 (8/32)	27.03 (20/74)	18.75 (6/32)
P_{oe}: Proportion of Obese (%, N)*	12.35 (74/599)	35.00 (7/20)	25.64 (10/39)	36.84 (7/19)

*554 women missing BMI measures in CCHS, cycle 2.2

Methods for applying indirect adjustment: We performed a bias analysis that indirectly adjusted for obesity and smoking status using data from the Canadian Community Health Survey (CCHS) with established methods. [1,2] CCHS 2004-2005 incorporated direct measurements of height and weight and queried smoking status (never, occasional, and daily). These data were linked to hospital discharge diagnoses and mortality data. We applied specific inclusion criteria (e.g., limited to women aged 12-50 with at least two pregnancies recorded between 2004-2017; without prior diabetes, hypertension, or CVD at baseline) in an attempt to mimic the inclusion criteria applied to our primary cohort. This was performed to maximize subject comparability between both datasets. We classified the 1,231 women who met these inclusion criteria by GD status, and computed proportions smoking (occasional smoker and daily smoker vs. non-smoker) and/or with obesity at baseline. We then adjusted the hazard ratios (HRs) and confidence intervals (CIs) corresponding to

the primary GD exposures in the present study, with these proportions. The methods for indirect adjustment for smoking and obesity (using data available in the CCHS), proposed by Shin and associates, were previously validated with CVD outcomes and are described in detail elsewhere.[1,2] Adjusting for unmeasured confounders using this method requires the model to adjust for one unmeasured variable at a time and for the unmeasured variable to be dichotomous.

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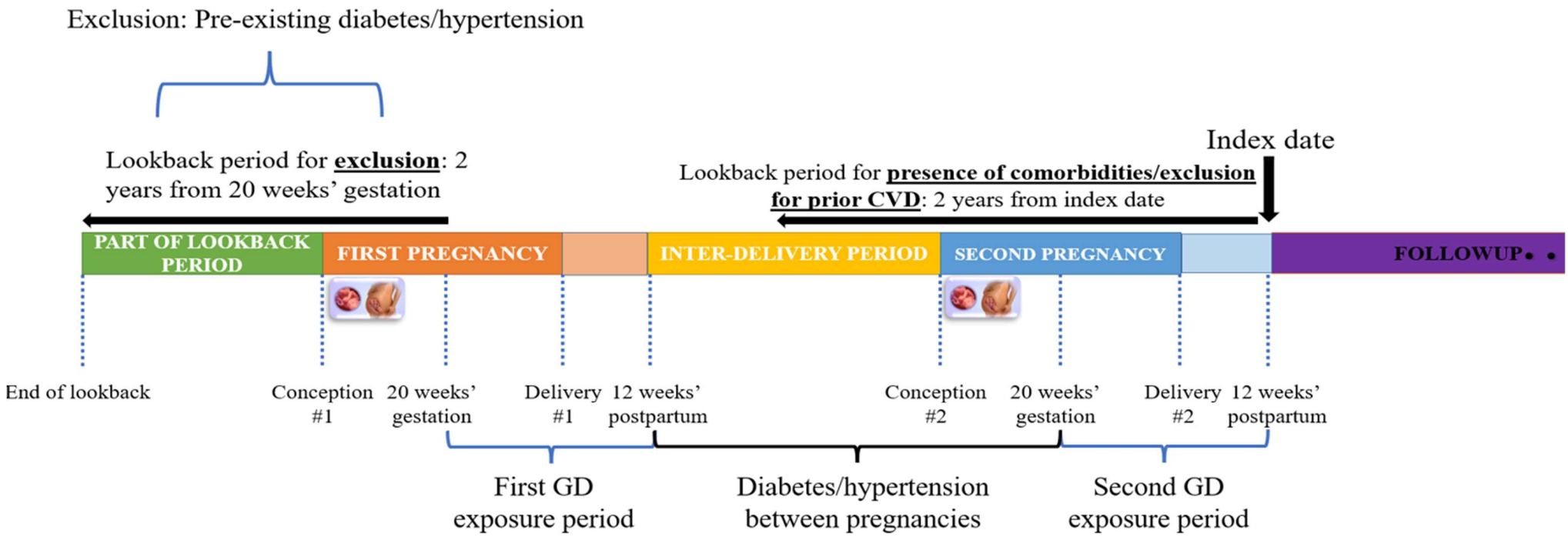
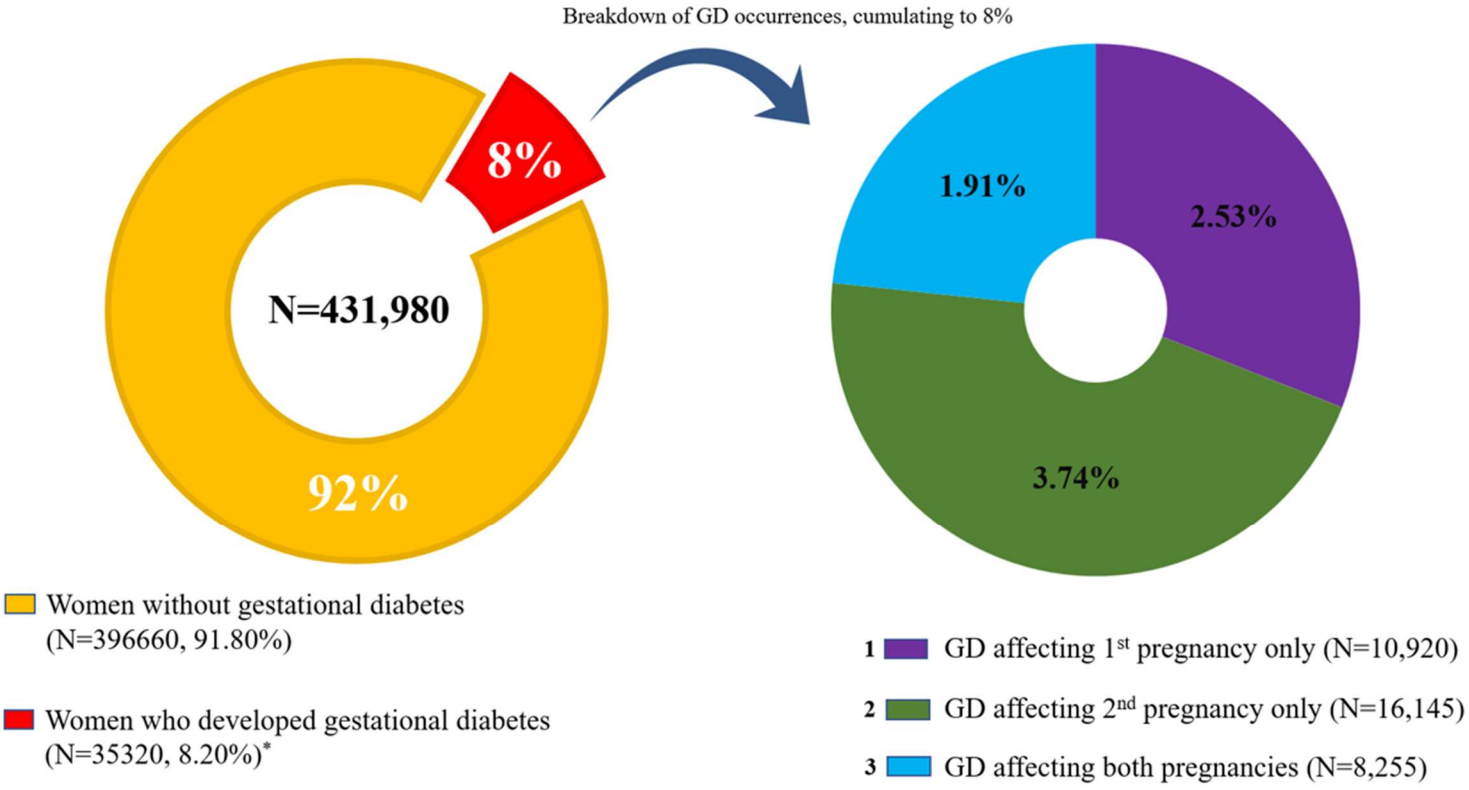
eFigure 1. Timeline of applied exclusions and exposure ascertainment windows



eFigure 2. Distribution of gestational diabetes exposure categories



Chapter 4: Manuscript 2

4.1 Preface

Although women affected with new-onset hypertension during pregnancy experience hypertension resolution soon after delivery, many studies demonstrate that these women remain at increased predisposed risk of developing hypertension later in life (**see Chapter 2.4.6**). These associations persist whether or not GHTN presents with or without preeclampsia. Previous research has estimated GHTN to recur in approximately 21% of pregnancies if a woman's first pregnancy is affected.[41,42] Most of the existing literature[21,43,274-281] often overlook their specific patterns of onset and tend to focus on 'ever/never' dichotomies for GHTN or preeclampsia, failing to consider subsequent pregnancies as useful opportunities to gain early insight into a woman's risk of developing hypertension.

Diabetes and hypertension, and thus GDM and GHTN, are intimately linked. Building on our findings from Manuscript 1, which elucidated the differential impacts that the sequence of GDM poses on future diabetes risk, this paper aimed to explore analogous patterns in the context of GHTN and hypertension risk. Manuscript 1 highlighted that the sequence in which GDM initially manifests (whether in the first or second pregnancy) significantly influences the long-term risk of developing type 2 diabetes among those with a single occurrence. These findings underscore the importance of comprehensively considering cumulative occurrences of gestational complications and their sequences, in order to delineate their differential ramifications on maternal health beyond the perinatal period. Similarly, this critical knowledge gap exists in the context of GHTN occurrences and its impact on future hypertension risk. In Manuscript 2, we aimed to build upon insights from Manuscript 1, and extend our understanding to another prevalent gestational complication, GHTN, and its association with future hypertension. Given the substantial overlap of their shared risk factors, extending my findings from Manuscript 1 may further refine and guide targeted holistic risk assessments and preventative approaches during the postpartum period. Importantly, in these analyses, I also simultaneously adjusted for GDM (GDM_{NONE}, GDM_{FIRST}, GDM_{SECOND}, $GHDM_{BOTH}$; PH assumption satisfied), which previous investigators have often not accounted for, yet has been shown to be associated with both GHTN and hypertension.

Previous studies have examined instances of GHTN recurrence (as a whole)[43,274,275,277,282] or preeclampsia recurrence (see **Appendix B**),[21,278-281] but have not comprehensively explored all patterns

of absence, new onset and recurrence of GHTN and their associations with maternal hypertension. Only a single study in the literature[21] was found to adopt similar exposure categories as those presented in this manuscript, but the investigators did not examine associations of chronic hypertension with patterns of GHTN without preeclampsia, nor did they account for GDM. In order to gain deeper insight on the relationship between patterns of GHTN and their impact on future hypertension risk, I conducted retrospective cohort analyses to examine associations of GHTN patterns (with or without preeclampsia, combined) across two pregnancies with subsequent chronic hypertension. In these analyses, GTHN with or without accompanying preeclampsia, when collapsed into four categories ($GHTN_{NONE}$, $GHTN_{FIRST}$, $GHTN_{SECOND}$, $GHTN_{BOTH}$) met PH assumptions. However, a methodological challenge arose when attempting to divide these categories based on the presence or absence of preeclampsia, as this grouping violated the PH assumption (see **Chapter 7.2.2**). Thus, I also created two additional subcohorts (after checking that the PH assumption was satisfied) to delineate differences in hypertension risk associated with patterns of GHTN, with or without preeclampsia, separately. I note that although these subgroup analyses do not allow for direct comparisons between GHTN alone and preeclampsia due to the exclusion criteria set, these analyses allowed me to indirectly compare the two by observing the magnitude of increased hazards associated with their patterns relative to the same reference group (absence of GHTN in both pregnancies). This subgroup analysis also addresses an important knowledge gap, given that I did not identify any studies in the literature examining the associations of GHTN (without preeclampsia) and its recurrence on hypertension risk.

This manuscript entitled "Patterns of gestational hypertension or preeclampsia across 2 pregnancies in relationship to chronic hypertension development: A retrospective cohort study" is published in the *Journal of the American Heart Association*.

Patterns of gestational hypertension or preeclampsia across 2 pregnancies in relationship to chronic hypertension development: A retrospective cohort study

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Abstract

Background: Gestational hypertension (GHTN) and preeclampsia are established risk indicators for chronic hypertension. While recurrence is associated with a greater risk, it is unclear whether there are differences in risk when these gestational complications occur for the first time in an earlier pregnancy versus first occurrence in a subsequent one. We hypothesized that the absence of recurrence reflects a transition toward a lower hypertension risk trajectory, whereas a new occurrence in a later pregnancy indicates a transition toward elevated risk.

Methods and Results: We analyzed linked data in Quebec, Canada, from public health care insurance administrative databases and birth, stillbirth, and death registries. Our retrospective cohort study included mothers with 2 singleton deliveries between April 1990 and December 2012. The primary exposure was patterns of GHTN or preeclampsia across 2 pregnancies (GHTN/preeclampsia in neither, first only, second only, or both). The outcome was incident chronic hypertension. We performed an adjusted multivariable Cox regression analysis. Among 431980 women with 2 singleton pregnancies, 27755 developed hypertension during the follow-up period. Compared with those without GHTN/preeclampsia, those with GHTN/preeclampsia only in the first pregnancy had a 2.7-fold increase in hazards (95% CI, 2.6–2.8), those with GHTN/preeclampsia only in the second had a 4.9-fold increase (95% CI, 4.6–5.1), and those with GHTN/preeclampsia in both pregnancies experienced a 7.3-fold increase (95% CI, 6.9–7.6). Patterns and estimates were similar when we considered GHTN and preeclampsia separately.

Conclusions: The magnitude of hypertension risk is associated with the number and sequence of GHTN/preeclampsia-affected pregnancies. Considering both allows more personalized risk estimates.

Keywords: chronic hypertension, gestational hypertension, preeclampsia, pregnancy, recurrence

Clinical Perspective

What is new?

- In women with 2 singleton pregnancies, without chronic hypertension before or between pregnancies, those who developed gestational hypertension or preeclampsia for the first time in the second pregnancy were at higher risk for future chronic hypertension, compared with those who had gestational hypertension or preeclampsia in the first pregnancy but not in the second.

- Our findings were similar when we considered gestational hypertension alone and when we considered preeclampsia alone.

- Gestational diabetes was independently associated with chronic hypertension, with the highest chronic hypertension risk among those with gestational diabetes in both pregnancies

What are the clinical implications?

- In gauging chronic hypertension risks, health care providers should ask not only about previous history of gestational hypertension and preeclampsia but also about the number of pregnancies and specifically in which pregnancies these adverse pregnancy outcomes did or did not occur; the number of gestational diabetes occurrences should also be queried.

List of abbreviations:

AGA = appropriate for gestational age; CCDSS = Canadian Chronic Disease Surveillance System; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; GDM = gestational diabetes; GHTN = gestational hypertension; HR = hazard ratio; ICD = International Classification of Diseases; INSPQ = Institut national de santé publique du Québec; LGA = large for gestational age; N = number; P_{oe}=proportion within specific GDM category who have obesity; P_e=proportion of those with specific GDM category among all women with two consecutive singleton pregnancies; P_o=proportion with obesity among all women with two consecutive singleton pregnancies; SGA = small for gestational age

Introduction

Globally, >1 billion people have hypertension.[1] Its prevalence has doubled over the past 3 decades[1,2] due to population aging, higher obesity rates, and lower physical activity levels.[3] Chronic hypertension–induced vascular injury contributes to heart disease and stroke in the longer term,[4] as well as the development of renal disease, retinopathy, dementia, and peripheral vascular disease.[5] In the shorter term, hypertensive disorders of pregnancy can lead to organ injury during pregnancy itself, in the form of preeclampsia (new-onset blood pressure elevation at or after 20weeks' gestation, accompanied by proteinuria or other maternal organ dysfunction).[6] Beyond its urgent importance during pregnancy, preeclampsia predicts the future development of chronic hypertension.[7,8] Gestational hypertension (GHTN) without preeclampsia is also a hypertension risk marker.[8,9] Although women average 2 offspring globally,[10] few studies have examined patterns of GHTN/preeclampsia across pregnancies, in relationship to future development of hypertension. Such information could allow further refinement of hypertension risk assessment, with the dual goals of prevention and early detection. We hypothesized that many women with GHTN/preeclampsia in a first pregnancy but not in a second pregnancy had modified their dietary or physical activity behaviors in response to their experiences in the first pregnancy. These behaviors could both reduce their risks for another GHTN/preeclampsia recurrence and their longer-term hypertension risk.

A 2022 meta-analysis[8] across 13 studies estimated that preeclampsia confers a 3-fold risk increase for chronic hypertension; the estimate across 3 studies that specifically evaluated GHTN was similar or higher.[8,9,11] Some studies have examined risks associated with preeclampsia recurrence[12–16]; a 2018 meta-analysis across 7 studies reported a doubling of chronic hypertension risk with recurrence, compared with 1 occurrence.[12] A single 2009 Danish study[13] distinguished first-pregnancy preeclampsia from second pregnancy preeclampsia. Compared with absence of preeclampsia, preeclampsia only in the first pregnancy was associated with a 2.7-fold increase in risk for hypertension, preeclampsia only in the second pregnancy with a 4.3-fold increase, and preeclampsia in both with a 6-fold increase. This suggests an upwards risk trajectory in women with a first preeclampsia occurrence in a second pregnancy, and a downward risk trajectory in those with preeclampsia only the first pregnancy.

Now, more than a decade later, we build on these Danish findings[13] using a large Canadian database in women with at least 2 consecutive pregnancies. We evaluated both GHTN and preeclampsia,

combined and separately, in relationship to the development of chronic hypertension. In contrast to other studies, we concurrently accounted for patterns of gestational diabetes (GD),[17–19] along with other adverse pregnancy complications associated with hypertension development (preterm delivery[2,20] and small [SGA] or large [LGA] for gestational age offspring[21,22]). Pregnancy is a time when younger adults are interested in addressing health issues, to optimize the short- and long-term health of the family.[23] Our overarching goal is to generate precision medicine-oriented clinical and social measures to refine risk estimates and stimulate action.

Methods

The McGill University Health Centre's Research Ethics Board (2019–5029; 12/11/2018) and Quebec Access to Information Commission (1019371-S; 11/18/2019) approved the protocol. These bodies waived informed consent because we used deidentified data, performed analyses at the Quebec Statistical Institute's secured research data centres, and rounded frequencies to multiples of 5. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

The data that we analyzed are available only through Quebec's Statistical Institute Centres for Access to Research Data, secure environments available to accredited researchers in Quebec for research purposes. Data requests must be made through the Quebec Statistical Institute (https://statistique.quebec. ca/recherche/) and are subject to ethical and scientific review.

Design and Data Sources

We conducted a retrospective cohort study in Quebec, Canada, where residents are publicly insured for physician services and hospitalization. We examined health administrative databases of the public health insurance plan, linked to birth, stillbirth, and death registries. We obtained mothers' health territory of residence and month and year of birth from the public health insurance registry. The Physician Services Claims (International Classification of Diseases, Ninth Revision [ICD-9]: Table S1) and Hospitalization Discharge Databases (ICD-9 codes to April 1, 2006; International Classification of Diseases, Tenth Revision [ICD-10] codes thereafter) include diagnostic codes, hospitalization dates, medical services, and surgical procedure codes; we used these to define outcomes, exposures, and covariables, alongside data from birth/ stillbirth registries. Variables from these registries include offspring birthdates, gestational age at birth, birth weight, fetal sex, parental country of birth and first

language, and years of maternal education. Where applicable, we obtained ICD-coded cause of death from the stillbirth and death registries (ICD-9 codes until December 31, 1999; ICD-10 codes thereafter). We had mothers' Institut national de santé publique du Québec material and social deprivation indices, derived from the 6-digit postal code in the public health registry and corresponding small-area census data.[24] The Quebec Statistical Institute performed probabilistic database linkage based on multiple identifiers (G-link software, Statistics Canada).

Study Population

We studied women with ≥2 consecutive singleton deliveries between April 1, 1990, and December 31, 2012, who were alive at 12weeks after the second delivery (index date). We accessed follow-up data to April 1, 2019, for these women, their offspring, and, for liveborn offspring, the fathers. We excluded mothers from families with missing gestational age in either offspring (required to distinguish chronic hypertension from GHTN/ preeclampsia[25]), those with preexisting hypertension or diabetes before 20weeks' gestation of first pregnancy, and those who developed these conditions between pregnancies. To exclude women with these preexisting conditions, we applied the validated Canadian Chronic Disease Surveillance System (CCDSS) hypertension definition[26] of 2 outpatient or 1 hospitalization diagnostic code(s) to (1) the 2-year period before 20 weeks' gestation in the first pregnancy and (2) the period from 12 weeks after delivery of the first pregnancy to 20 weeks' gestation of the second pregnancy (between pregnancies). We applied a validated parallel diabetes definition[27,28] to the same time periods.

We removed those with a different partner for each offspring to minimize the heterogeneity of paternal or within-household factors that could influence health behaviors and subsequent maternal outcomes,[29–31] or baseline preeclampsia risk.[6,32,33] Using available diagnostic codes, we also excluded those with 2 outpatient visits or 1 hospitalization for cardiovascular disease (CVD) and/or other circulatory system diseases before the index date.

Exposure

Following exclusion of preexisting hypertension as described above, we defined GHTN/preeclampsia as a composite exposure, applying validated codes for both hypertension[26,34] and preeclampsia[34] to a pregnancy-specific period. This period started at 20 weeks' gestation[34] and ended at 12 weeks after delivery, by which point any blood pressure elevation related to GHTN/preeclampsia should have

resolved. We required 2 outpatient and/or 1 hospitalization code(s), similar to the validated CCDSS hypertension definition.[26] Our 4 mutually exclusive exposure categories were absence of GHTN/preeclampsia, GHTN/preeclampsia only in the first pregnancy, GHTN/preeclampsia only in the second pregnancy, and GHTN/ preeclampsia in both pregnancies. In subgroup analyses, we considered occurrences of GHTN and preeclampsia separately.

Outcome

We examined incident chronic hypertension as the primary outcome, applying the validated CCDSS definition, which requires at least 2 outpatient codes or 1 hospitalization code with a 2-year period.[26] Follow-up was until the first of the following: incident chronic hypertension (using the date of the first component of the definition fulfilled), the date coinciding with 120 days before a third delivery (we did not have gestational age data for pregnancies after the second), death, or the end of the study period (April 1, 2019), as applicable.

Covariates

We accounted for other pregnancy- and offspring related factors previously shown to be associated with hypertension, specifically, GD, preterm delivery (<37weeks), SGA (<10th percentile) and LGA (>90th percentile) offspring.[35,36] We examined these variables for both the first and second pregnancies (4 categories of GDM; 4 categories of preterm delivery; 9 categories of offspring size). To define GD, we applied the CCDSS diabetes definition to the same pregnancy period for which we defined GHTN/preeclampsia, in accordance with a validated GD definition[37] that we used in a previous study.[38]

We also accounted for other covariates associated with hypertension development, including time between deliveries (<2, 2–<2.5, 2.5–<3.5, ≥3.5years), maternal age at the index date (<25, 25–29, 30–34, ≥35years), material and social deprivation level recorded in the index year (1 [least deprived] to 5 [most deprived]),[24] race or ethnicity based on participant-reported region of birth and first language (Europid, African/Caribbean, Arabic, Asian, Other [Indigenous language or language unspecified]), presence of comorbid conditions (mood disorders, alcohol/drug dependence; thyroid disorder; arthritis; asthma/chronic obstructive pulmonary disease; defined as ≥1 hospitalization or≥2 outpatient diagnostic codes occurring within 2 years before the index date) and preexisting paternal diabetes, hypertension, and CVD (validated CCDSS definitions[27,28] applied from 2 years before 20

weeks' gestation of the first pregnancy to 12 weeks following the second delivery). We accounted for preexisting spousal diabetes, hypertension, and CVD, given spousal concordance for these conditions, likely related to shared behaviors and environments.[17,39–41]

We considered other covariates (eg, placental abruption, stillbirth, cancer, offspring sex, offspring congenital anomalies), but these did not meet our variable inclusion criteria (see Statistical Analysis), as described in Data S1.

Statistical Analysis

We computed baseline characteristics (numbers and percentages for categorical variables) and compared them across exposure groups (Pearson $\chi 2$ tests for proportions). We constructed Kaplan–Meier curves, calculated the incidence of hypertension by the primary exposure categories, derived crude hazard ratios (HRs; see Tables S2 and S3), and examined for interactions ($P<0.05$ for interaction terms) and multicollinearity (Cramer's V >0.10) among exposures and covariates. We evaluated applicability of the proportional hazards assumptions (Schoenfeld residuals test and visual inspection of log-minus-log survival plots). We constructed multivariable Cox proportional hazards models to compute HRs for incident chronic hypertension. In the first set of models, the reference group was the absence of GHTN/preeclampsia in either pregnancy. We compared GHTN/preeclampsia in the first pregnancy only, GHTN/preeclampsia in the second pregnancy only, and GHTN/preeclampsia in both pregnancies to this reference category. In other analyses, we compared the GHTN/preeclampsia exposure groups directly to one another. Specifically, we next set GHTN/preeclampsia only in the first pregnancy as the reference group and compared GHTN/preeclampsia in the second pregnancy only and GHTN/preeclampsia in both pregnancies to this group. Then, we set GHTN/preeclampsia only in the second pregnancy as the reference group and compared GHTN/ preeclampsia in both pregnancies to this. We considered including covariates in our final statistical models if their univariate associations with hypertension had a P value ≤ 0.25 and we opted to retain them on the basis of demonstration of a multivariable association with hypertension of $P \leq 0.05$ (stepwise selection), and reduced Bayesian information criteria values with inclusion of each additional variable.

The proportional hazards assumptions held when GHTN and preeclampsia were combined as a composite exposure variable and divided into 4 categories (absence of GHTN/preeclampsia, presence

in the first pregnancy only, in the second pregnancy only, and in both). These assumptions did not hold within the model when stratified further into 9 categories that distinguished GHTN from preeclampsia (eg, absence of GHTN/preeclampsia in either pregnancy, GHTN in first only, preeclampsia in first only). Therefore, we created 2 subcohorts of women to separately examine GHTN and preeclampsia, in comparison with women without either of these conditions. In 1 subcohort, we removed all women with GHTN in 1 or both pregnancies; in this subcohort, we compared preeclampsia in the first pregnancy only, second pregnancy only, and in both pregnancies, with women who did not have preeclampsia in either pregnancy. In another subcohort, we removed all women with preeclampsia in 1 or both pregnancies; in this subcohort, we compared GHTN in the first pregnancy only, second pregnancy only, and in both pregnancies, with women who did not have GHTN in either pregnancy.

In a sensitivity analysis, we performed indirect adjustments for obesity and smoking status (separately), using established methods of bias analyses.[42] This approach required external estimates for the HRs of obesity and of smoking with incident hypertension in women, which we respectively estimated as 1.85 (obese versus not obese)[43] and 1.02 (smoking versus not smoking).[44] This method also required external cohort data to estimate obesity and smoking prevalence in groups of women with no GHTN/preeclampsia, GHTN/preeclampsia in first pregnancy, GHTN/preeclampsia in second pregnancy, and GHTN/preeclampsia in both pregnancies. We used the Canadian Community Health Survey (cycle 2.2) to estimate these prevalence values, as we had access to these data for another study[45]; 13% were in the obesity category, and 24% smoked cigarettes. We applied the following formula for the indirect obesity adjustment: $HR_{(\text{corrected for obesity})} = HR_{(\text{from our analysis})} / HR_{(\text{related to obesity, from literature})}^{Poe-Pe*Po}$ (P_{oe}=proportion within specific GHTN/preeclampsia category who have obesity; P_e=proportion of those with specific GHTN/preeclampsia category among all women with 2 consecutive singleton pregnancies; P_o=proportion with obesity among all women with 2 consecutive singleton pregnancies; see Data S2, similar formula applied for smoking). All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

Among the 431980 women with 2 singleton pregnancies following exclusions (Figure 1), 4.9% (n=21335) had GHTN/preeclampsia only in their first pregnancy, 1.6% had GHTN/preeclampsia in only their second pregnancy (n=6980), and 1.3% had GHTN/preeclampsia in both pregnancies

(n=5830; Figure S1). In those with GHTN/preeclampsia in the first, second, and both pregnancies, the following proportions of women had preeclampsia, respectively: 51% (n=10820), 36% (n=2540), and 64% (n=3750). The distribution of baseline characteristics (numbers and percentages presented) were similar (P>0.05) across each of the exposure groups (Table 1); most percentage differences across these groups were within 1% to 5%.

Associations between GHTN/preeclampsia and incident hypertension

Over a median 11.0years (interquartile range, 4.96– 18.7; 5147250 total person years), a total of 27755 mothers developed chronic hypertension during the follow-up period. Kaplan–Meier curves indicated significant differences in event-free survival across exposure groups (P<0.001; Figure 2). The incidence rates per 1000 person-years rose across the no GHTN/preeclampsia (4.49), GHTN/preeclampsia in the first pregnancy only (12.0), GHTN/preeclampsia in the second pregnancy only (23.6), and GHTN/preeclampsia in both pregnancies (32.1) categories. Schoenfeld residuals test and visual inspection of log-minus-log survival plots indicated that the proportional hazards assumptions applied. There was no significant multicollinearity/interaction detected in our models. In adjusted Cox regression models, compared with absence of GHTN/preeclampsia, those with GHTN/preeclampsia in first pregnancy had 2.67-fold higher hazards for hypertension (95% CI, 2.57–2.78; Figure 3A), those with GHTN/preeclampsia in the second pregnancy had a 4.85-fold increase (95% CI, 4.61–5.11), and those with GHTN/preeclampsia affecting both pregnancies demonstrated a 7.25-fold increase (95% CI, 6.90–7.63). When the reference group was changed to those with GHTN/preeclampsia in the first pregnancy, women with GHTN/preeclampsia in the second pregnancy had an 82% higher hazards (95% CI, 1.71–1.93), and those with GHTN/preeclampsia in both pregnancies had a 2.71-fold increase (95% CI, 2.55–2.88). Finally, risk for incident hypertension was 1.50-fold higher among women with GHTN/preeclampsia in both pregnancies (95% CI, 1.37–1.60) compared with those with GHTN/preeclampsia occurring only in the second pregnancy.

Associations between preeclampsia and incident hypertension

When we removed those with GHTN from the original cohort, 412735 women remained. Compared with absence of preeclampsia in either pregnancy, those with preeclampsia in the first pregnancy had 2.48-fold increased hazards for hypertension (95% CI, 2.35–2.61; Figure 3B), those with preeclampsia in the second pregnancy had a 4.08-fold increase (95% CI, 3.76–4.43), and those with preeclampsia in

both pregnancies had a 5.74-fold increase (95% CI, 5.22–6.31). When women with preeclampsia in the first pregnancy served as the reference group, those with preeclampsia in the second pregnancy had their hazards for hypertension increase by 65% (95% CI, 1.50–1.81), and those with preeclampsia in both pregnancies had a 2.32-fold increase (95% CI, 2.08–2.58). Finally, compared with those with preeclampsia occurring only in the second pregnancy, risk for incident hypertension was 1.41-fold higher among women with preeclampsia in both pregnancies (95% CI, 1.25–1.59).

Associations between GHTN and incident hypertension

Removal of women who had preeclampsia in either or both pregnancies (n=17105) resulted in a sample of 414875 women. Compared with absence of GHTN in either pregnancy, those with GHTN in the first pregnancy demonstrated 2.92-fold (95% CI, 2.76–3.09; Figure 3C) increased hazards for subsequent hypertension development, those with GHTN in the second pregnancy had 5.39-fold (95% CI, 5.06–5.74) increase, and those with GHTN affecting both pregnancies had an 8.59-fold (95% CI, 7.90–9.34) increase. When the reference group was changed to those with GHTN in the first pregnancy, women with GHTN in the second pregnancy had an 84% higher hazards (95% CI, 1.70–2.00), and those with GHTN in both pregnancies had a 2.94-fold increase (95% CI, 2.67–3.25). Finally, compared with those with GHTN affecting only the second pregnancy, hazards for incident hypertension was 1.59-fold higher among women with GHTN in both pregnancies (95% CI, 1.44–1.77).

Bias analyses: Indirect adjustments for obesity and smoking

Indirect adjustments for obesity (no GHTN/preeclampsia: reference; GHTN/preeclampsia in first pregnancy: HR, 2.36 [95% CI, 2.27–2.46]; GHTN/preeclampsia in second pregnancy: HR, 4.31 [95% CI, 4.10–4.54]; GHTN/preeclampsia in both pregnancies: HR, 6.44 [95% CI, 6.13–6.77]); and smoking (no GHTN/preeclampsia: reference; GHTN/preeclampsia in first pregnancy: HR, 2.66 [95% CI, 2.56–2.77]; GHTN/ preeclampsia in second pregnancy: HR, 4.83 [95% CI, 4.81–5.09]; GHTN/preeclampsia in both pregnancies: HR, 7.21 [95% CI, 6.87–7.60]) slightly attenuated the reported HRs for incident chronic hypertension from our primary analysis.

Associations between patterns of other pregnancy complications and incident hypertension

GD was also found to be associated with elevated hazards of developing incident hypertension later in life. Compared with those without GDM, this condition conferred an increase of 40% to 45% if

occurring in a first or in a second pregnancy alone, and 76% if occurring in both pregnancies (Table 2).

SGA and LGA, compared with appropriate for gestational age; and preterm delivery status, compared with term delivery, each elevated hypertension risk by 5% to 15% compared with women without each of these conditions. SGA in a single pregnancy was independently associated with an ≈5% increase in hypertension hazards, which rose to a 15% increase when occurring in both pregnancies, compared with women delivering appropriate for gestational age offspring in both pregnancies. Any occurrence of LGA independently demonstrated 7% to 10% increased hypertension hazards compared with appropriate for gestational age offspring size in both pregnancies. Having SGA in 1 pregnancy and LGA in another (or vice versa) was an infrequent occurrence, with no conclusive associations for such combinations. Preterm delivery status was also independently associated with increased hazards for incident hypertension. Compared with women with 2 term deliveries, those with preterm delivery only in a first pregnancy demonstrated a 6% increase in hypertension hazards, rising to a 12% to 15% increase when occurring only in a second pregnancy or in both pregnancies.

Associations between paternal risk indicators and other maternal risk indicators with incident hypertension

Paternal diabetes, hypertension, and CVD were each independently associated with roughly a 20 to 25% increase in hazards for incident hypertension in the mother, compared with mothers with partners in which these conditions were absent (Table 2). Maternal age was associated with a stepwise increase in risk of hypertension, as was material deprivation. Ethnicity and comorbid conditions were also conclusively associated with increased hypertension hazards.

Discussion

Our analyses demonstrated that in women with at least 2 singleton pregnancies, the future risk for chronic hypertension is associated with the cumulative number of GHTN/preeclampsia-affected pregnancies, and the ordinal pregnancy in which it occurs, in the case of a single occurrence. The risk for chronic hypertension doubled with GHTN/preeclampsia in the first pregnancy alone, rose >4-fold with occurrence only in the second, and >7-fold higher with GHTN/preeclampsia in both pregnancies, compared with their absence in either pregnancy. We observed similar patterns for preeclampsia and for GHTN when modeled separately. GD was also independently associated with

an increase in hazards for hypertension, at 40% to 45% for GD in the first or second pregnancy alone, and 76% with GD in both. SGA, LGA, and preterm status each conferred a 5% to 15% increase in hazards, similar for 1 or both pregnancies. Paternal diabetes, hypertension, and CVD were each associated with a roughly 20% to 25% increase in hazards for hypertension in the mother. Age at second delivery, material deprivation, ethnicity, and the presence of comorbidities were also associated with chronic hypertension development.

As previously noted, a 2009 Danish study[13] reported higher hypertension risk for a second pregnancy with preeclampsia alone than for a first pregnancy with preeclampsia alone; specifically, a >2-fold increase in risk with first pregnancy preeclampsia, a roughly 4-fold increase with second pregnancy preeclampsia, and a 6-fold increase with preeclampsia in both. Our findings are consistent with this but demonstrate similar patterns and similar risk increases both for preeclampsia and for GHTN, separately. Specifically, compared with absence of GHTN/preeclampsia in either pregnancy, we determined first pregnancy preeclampsia to be associated with a 2.5-fold increase in risk for chronic hypertension, second pregnancy preeclampsia with a 4-fold increase, and preeclampsia in both pregnancies with a 5.7-fold increase. Compared with absence of GHTN/preeclampsia in either pregnancy, GHTN in the first pregnancy was associated with a nearly 3-fold increase in risk, in the second pregnancy with a 5.4-fold increase, and in both with an 8.6-fold increase. A Nurses' Health Study II analysis[11] examined first pregnancy GHTN/preeclampsia and conducted a secondary analysis for GHTN/preeclampsia in "second or later" pregnancies, rather than focusing on the second pregnancy. Their findings were consistent with ours, but their estimates were lower (HR, 1.85 GHTN/ preeclampsia in the first pregnancy; HR, 2.40 GHTN/ preeclampsia in second or later pregnancy; HR, 3.53 GHTN/preeclampsia in both first pregnancy and in second or later pregnancy). This is likely because they commenced follow-up at the age of 40 years, rather than soon after the second delivery, and required women to be free of CVD and other risk factors (including hypertension) by the age of 40 years. Additionally, their "second or later" exposure group likely included women with lower risk trajectories (eg, absence of GHTN/preeclampsia in either the first or second pregnancy and presence only in a third pregnancy).

The primary focus of the Nurses' Health Study II analysis[11] was to compare the presence of GHTN or preeclampsia in a first pregnancy versus its absence. In their main analysis, the investigators examined GHTN and preeclampsia, separately, and reported similar associations for both with chronic hypertension development. Consistent with this, in our analyses, we demonstrated that

GHTN and preeclampsia have similar patterns of associations with chronic hypertension. Women with severe organ injury related to preeclampsia in a first pregnancy may opt to not have a second pregnancy. Those with a milder course may be similar to women with GHTN, and thus more likely to have a second pregnancy. It is also important to note that while heterogeneity in the pathophysiological processes and clinical phenotypes exist between GHTN and preeclampsia, both conditions share maternal endothelial dysfunction as a central phenomenon.[46–49]

Among women with 2 consecutive singleton pregnancies who have not yet developed chronic hypertension by the second delivery, there thus appears to be a downward shift in risk profile among women with GHTN/preeclampsia occurring only in a first pregnancy. First-pregnancy GHTN/preeclampsia may motivate some to adopt or enhance health behaviors that lower blood pressure (higher physical activity levels, healthier food intake, optimized weight, smoking cessation). These actions may prevent recurrence in a second pregnancy. The 21% recurrence rate that we observed is similar to that reported in other studies,[12,50,51] suggesting that a large proportion of women take preventive action, possibly including health behavior change, aspirin therapy before 20 weeks' gestation, and/or calcium supplementation in those at risk for deficiency.[6] Also consistent with some preventive action following a first pregnancy complicated by preeclampsia is a prior study that suggested that even when preeclampsia recurs, it tends to be a milder subtype.[52] Women with GHTN/preeclampsia restricted to the first pregnancy subsequently experience lower risk for chronic hypertension, as we additionally demonstrated for both GHTN and preeclampsia separately, and as reported for preeclampsia in a prior study.[13]

While women without recurrence entered a lower risk trajectory, we observed that women with a first GHTN/preeclampsia occurrence in a second pregnancy had entered a higher one. This may be related to difficulty in losing excess gestational weight from the first pregnancy, stress related to parenthood, and time pressures limiting physical activity and nutritionally adequate dietary habits.[53] Additionally, we demonstrated that women with any form of recurrent GHTN/preeclampsia had the highest risk of developing chronic hypertension. As previously discussed, in contrast with our study, no other studies have assessed associations between recurrent GHTN and long-term hypertension risk, as conducted in our study. However, previous investigators have hypothesized that the potential mechanism underlying associations of recurrent preeclampsia with increased chronic hypertension risk may stem from persistent vascular alterations, dysregulated inflammatory responses, and cumulative metabolic abnormalities.[12,14,54] Whether these women have a stronger predisposition for

chronic hypertension as a result of a more unfavorable cardiovascular risk profile, or if recurrent GHTN/preeclampsia induces direct, cumulative impacts on endothelial dysfunction remains to be elucidated. Understanding these mechanisms is crucial for informing targeted preventive strategies and therapeutic interventions aimed at mitigating long-term hypertension risk.

We also demonstrated that compared with those without GD, the presence of GD in either a first or second pregnancy conferred 40% to 45% increased risk of developing hypertension, which rose to 76% with GD in both pregnancies. Although GD is a recognized risk marker for chronic hypertension,[17–19] we did not identify any prior study that evaluated GD and GHTN/preeclampsia patterns concurrently across 2 pregnancies, in relationship to hypertension development. Like diabetes and hypertension, both GD and GHTN/preeclampsia emerge from an interplay of genetic factors alongside modifiable household, social, economic, and behavioral factors. These conditions collectively contribute to the emergence of vascular injury and complications. In a previous study,[38] we demonstrated that the risk of CVD increased with the number of GD and GHTN/preeclampsia occurrences across 2 pregnancies, suggesting a cumulative effect over multiple pregnancies.

Preeclampsia results in part from uteroplacental insufficiency that can lead to impaired fetal growth, preterm labor, placental abruption, and stillbirth. Such insufficiency could result in SGA and preterm delivery. Even after accounting for GHTN/preeclampsia, in our analyses, SGA in a single pregnancy was associated with a roughly 5% increased risk for chronic hypertension, and in both pregnancies with a 15% increase, compared with offspring of appropriate size in both pregnancies. Preterm status was also independently associated with a small increase in risk of hypertension, at 6% for the first pregnancy alone and at 12% to 15% for the second pregnancy or both pregnancies.

We also identified a 20% to 25% increase in hypertension hazards for each of hypertension, diabetes, and CVD in the father. Previous studies have demonstrated that spousal concordance exists for type 2 diabetes, hypertension, and CVD,[39,40,55,56] likely as a result of shared behaviors and environments.[31] We previously demonstrated that GD and GHTN/preeclampsia in mothers predict diabetes and CVD development in fathers.[17,41] The importance of these associations lies in untapping the potential for couple collaboration in reducing CVD risk, stimulated by their shared risk.

Linkage of Quebec's health administrative and vital statistics databases allowed us to leverage data from nearly half a million women, a population-based sample with up to 29 years of follow-up. These databases are designed for administrative purposes and thus have limitations. We could not corroborate ICD-coded diagnoses of hypertension with direct clinical measurement or medication use, but to mitigate the potential for misclassification, we applied validated definitions. To offset the potential for confounding by obesity and smoking, we performed indirect adjustments for these factors using data from an external cohort in sensitivity analyses, and we observed little impact on our estimates.[42] Further, we accounted for LGA in both pregnancies, a variable that correlates with both maternal prepregnancy obesity and gestational weight gain.[57,58] We did not have information on medication use and thus do not know to what degree second pregnancy GHTN recurrence was influenced by implementation of aspirin early in pregnancy or calcium supplementation.

Conclusions

In women with two singleton pregnancies, the risk for chronic hypertension associated with new-onset blood pressure elevation at or after 20 weeks' gestation increases when this elevation occurs in the first pregnancy, is higher when it occurs in the second, and is highest when it complicates both pregnancies. This is true for both preeclampsia and for GHTN without preeclampsia. The risk for hypertension rises further with GDM, preterm delivery, and SGA or LGA. Lack of GHTN recurrence in a second pregnancy provides some indication that hypertension prevention efforts may be working and should continue. Conversely, GHTN recurrence or new-onset GHTN in a second pregnancy should stimulate preventive action and careful postpartum monitoring (e.g., regular blood pressure assessments and comprehensive cardiovascular evaluations) to facilitate early detection and intervention for chronic hypertension. Our findings support a precision medicine-oriented pathway to hypertension prevention in relationship to GHTN history in women with at least two pregnancies.

Declarations

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Contribution statement: J.M. contributed to the study design, interpreted the data, prepared the first draft of the manuscript and revised based on co-authors' comments, and approved the final manuscript as submitted. E.R. contributed to the study conception and design, provided oversight of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. M.D. contributed to dataset cleaning, variable derivation, statistical analyses, data interpretation and approved the final manuscript as submitted. M.N. critically reviewed the manuscript and approved the final version as submitted. K.D. conceptualized and designed the study, supervised analyses, interpreted the data, critically reviewed the manuscript and supervised draft revisions, and approved the final manuscript as submitted. K.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Table 1. Baseline characteristics, stratified by GHTN/preeclampsia status

N (%)*	**No GHTN/preeclampsia** (N=397,835)	**GHTN/preeclampsia in first pregnancy** (N=21,335)	**GHTN/preeclampsia in second pregnancy** (N=6,980)	**GHTN/preeclampsia in both pregnancies** (N=5,830)
Maternal characteristics				
History of gestational diabetes (GD) across 2 pregnancies				
No GD (N=396,660)	367,105 (92.3)	18,640 (87.4)	5,985 (85.7)	4,930 (84.6)
GD in first pregnancy (N=10,915)	9,645 (2.42)	785 (3.68)	265 (3.80)	220 (3.77)
GD in second pregnancy (N=16,150)	13,990 (3.52)	1,280 (6.00)	460 (6.59)	420 (7.20)
GD in both pregnancies (N=8,255)	7,095 (1.78)	630 (2.95)	270 (3.87)	260 (4.46)
Maternal age at second delivery: years				
<25 (N=56,460)	52,135 (13.1)	2,885 (13.5)	715 (10.2)	725 (12.4)
25-30 (N=156,305)	143,700 (36.1)	8,185 (38.4)	2,295 (32.9)	2,125 (36.4)
30-35 (N=157,740)	145,640 (36.6)	7,480 (35.1)	2,530 (36.2)	2,090 (35.8)
>35 (N=61,485)	56,360 (14.2)	2,785 (13.1)	1,450 (20.8)	890 (15.3)
Time between deliveries: years				
<2 (N=134,915)	125,065 (31.4)	6,580 (30.8)	1,565 (22.4)	1,705 (29.2)
2-<2.5 (N=88,105)	81,120 (20.4)	4,550 (21.3)	1,215 (17.4)	1,220 (20.9)
2.5-<3.5 (N=112,000)	103,145 (25.9)	5,530 (25.9)	1,790 (25.6)	1,535 (26.3)
≥3.5 (N=96,955)	88,500 (22.2)	4,675 (21.9)	2,415 (34.6)	1,365 (23.4)
Material deprivation index : Quintiles‡				
1 = least deprived (N=87,645)	81,450 (20.5)	3,885 (18.2)	1,260 (18.1)	1,050 (18.0)
2 (N=91,135)	83,965 (21.1)	4,485 (21.0)	1,440 (20.6)	1,245 (21.4)
3 (N=85,660)	78,865 (19.8)	4,275 (20.0)	1,365 (19.6)	1,155 (19.8)
4 (N=81,430)	74,725 (18.8)	4,190 (19.6)	1,385 (19.8)	1,130 (19.4)
5 = most deprived (N=78,765)	72,140 (18.1)	4,105 (19.2)	1,395 (20.0)	1,125 (19.3)

Social deprivation index: Quintiles[‡]				
1 = least deprived (N=95,755)	88,110 (22.1)	4,895 (22.9)	1,450 (20.8)	1,300 (22.2)
2 (N=92,735)	85,195 (21.4)	4,695 (22.0)	1,525 (21.8)	1,320 (22.6)
3 (N=88,345)	81,100 (20.4)	4,520 (21.2)	1,525 (21.8)	1,200 (20.6)
4 (N=79,930)	73,890 (18.6)	3,715 (17.4)	1,260 (18.1)	1,065 (18.3)
5 = most deprived (N=67,865)	62,845 (15.8)	3,115 (14.6)	1,085 (15.5)	820 (14.1)
Ethnicity[§]				
America, Australia or Europe (N=373,415)	343,050 (86.2)	19,175 (89.9)	5,965 (85.5)	5,225 (89.6)
Africa or Caribbean (N=8,550)	7,680 (1.93)	430 (2.02)	285 (4.08)	155 (2.66)
Arab-speaking regions (N=17,315)	16,525 (4.15)	480 (2.25)	210 (3.01)	100 (1.72)
Asia (N=14,620)	13,875 (3.49)	435 (2.04)	200 (2.87)	110 (1.89)
Other (N=18,080)	16,705 (4.20)	815 (3.82)	325 (4.66)	235 (4.03)
Co-morbid conditions				
Mood disorders, alcohol or drug dependence (N=18,010)	16,340 (4.11)	955 (4.48)	400 (5.73)	315 (5.40)
Thyroid disorder (N=15,015)	13,525 (3.77)	900 (4.22)	330 (4.73)	260 (4.46)
Arthritis (N=9,180)	8,305 (2.09)	505 (2.37)	220 (3.15)	150 (2.57)
Asthma or COPD (N=8,650)	7,695 (2.17)	545 (2.55)	225 (3.22)	185 (3.17)
Offspring characteristics				
Small for gestational age[‖]				
Neither pregnancy (N=369,230)	341,695 (85.9)	17,390 (81.5)	5,550 (79.5)	4,595 (78.8)
First pregnancy only (N=26,110)	23,375 (5.88)	1,675 (7.85)	590 (8.45)	470 (8.06)
Second pregnancy only (N=26,145)	23,415 (5.89)	1,680 (7.87)	555 (7.95)	495 (8.49)
Both pregnancies (N=10,350)	9,210 (2.32)	580 (2.72)	290 (4.15)	270 (4.63)
Large for gestational age[‖]				

Neither pregnancy (N=367,635)	339,380 (85.3)	17,555 (82.3)	5,845 (83.7)	4855 (83.3)
First pregnancy only (N=26,155)	23,810 (5.98)	1,475 (6.91)	475 (6.81)	395 (6.78)
Second pregnancy only (N=26,070)	23,725 (6.72)	1,485 (6.96)	465 (6.66)	395 (6.78)
Both pregnancies (N=11,965)	10,785 (2.91)	805 (3.77)	200 (2.87)	175 (3.00)
Preterm birth				
Neither pregnancy (N=392,290)	363,555 (91.4)	18,510 (86.8)	5,715 (81.9)	4,510 (77.4)
First pregnancy only (N=20,330)	17,315 (4.35)	1,820 (8.53)	490 (7.02)	705 (12.1)
Second pregnancy only (N=14,630)	12,890 (3.24)	750 (3.52)	635 (9.10)	355 (6.09)
Both pregnancies (N=4,730)	4,080 (1.03)	255 (1.20)	145 (2.08)	260 (4.46)
Paternal characteristics				
Prior history of paternal diabetes[#]				
Yes (N=3,650)	3,305 (0.83)	205 (0.96)	75 (1.07)	65 (1.11)
Prior history of paternal hypertension[#]				
Yes (N=9,420)	8505 (2.14)	545 (2.55)	210 (3.01)	160 (2.74)
Prior history of paternal cardiovascular disease[**]				
Yes (N=1,610)	1455 (0.37)	100 (0.47)	35 (0.50)	20 (0.34)

COPD = chronic obstructive pulmonary disease; GDM = gestational diabetes mellitus; GHTN = gestational hypertension; SD = standard deviation

* Values are randomly rounded up or down to a multiple of '5' (for patient confidentiality purposes). Therefore, column sums for each baseline characteristic may not equal the total number of women in each level of the exposure due to this random rounding process.

‡ Range from 1 (least deprived) to 5 (most deprived). The Institut national de santé publique du Québec (INSPQ) material and social deprivation index is computed from small-area census data. Specifically, the material indices are derived from average income, proportions without high school diploma, and employment to population ratio among those 15 years and older. The social indices are derived from the proportion of the population: who are single-parent families, aged 15 and over living alone, and aged 15 and over who are separated, divorced or widowed. In order to assign the INSPQ index for each woman, we first checked availability of this variable in the index year (year of second delivery). 7335 women were missing an assigned INSPQ index score.

§ Ethnicity based on the mother's region of birth and reported preferred language. We categorized women as: i) "Europid" if born in North America, South America, Central America, Mexico, East/South/Southern/West Europe or Australia and first language is English, French, or other European language; ii) "African or Caribbean" if born in West/South/East/Central Africa or the Caribbean or African language; iii) "Arabic" if born in the Arab league or language Arabic or of other North African/South-West Asian language; iv) "Asian" if born in West/East/Central/South/ Southeast/Pacific Asia or language from this region; or v) "Other" (does not fit into any other category, including Indigenous languages.

|| 150 offspring were missing birthweight required to derive offspring size.

Prior history in the father was defined as ≥ 1 inpatient and/or ≥ 2 outpatient ICD codes for any form of diabetes or hypertension, respectively, that occurred during the period from two years prior to 20 weeks' gestation of their partner's first pregnancy to 12 weeks' postpartum in relationship to the second pregnancy.

** Prior history of cardiovascular disease in the father was defined as ≥ 1 inpatient, ≥ 1 related surgical procedure (angioplasty, endarterectomy or coronary artery bypass surgery), and/or ≥ 2 outpatient ICD codes for any form of myocardial infarction, stroke and angina, that occurred during the period from two years prior to 20 weeks' gestation of their partner's first pregnancy to 12 weeks' postpartum in relationship to the second pregnancy.

Table 2. Associations of covariates with incident hypertension

Covariate*	Adjusted hazard ratio (95% CI)
Maternal characteristics	
History of gestational diabetes (GDM) across two pregnancies	
No GDM	*Reference*
GDM in first pregnancy	1.40 (1.31-1.49)
GDM in second pregnancy	1.44 (1.37-1.52)
GDM in both pregnancies	1.76 (1.65-1.88)
Age of mother at second delivery, years	
< 25	*Reference*
25 – 29	1.24 (1.18-1.30)
30 – 34	1.58 (1.50-1.66)
≥ 35	2.22 (2.11-2.34)
Time between deliveries, years	
< 2	*Reference*
2 – < 2.5	0.96 (0.92-0.99)
2.5 – < 3.5	0.97 (0.94-1.00)
≥3.5	1.08 (1.05-1.12)
Material deprivation index, quintiles†	
1 (least deprived)	*Reference*
2	1.15 (1.11-1.20)
3	1.17 (1.13-1.22)
4	1.25 (1.20-1.29)
5 (most deprived)	1.32 (1.27-1.38)
Social deprivation index, quintiles†	
1 (least deprived)	*Reference*
2	1.01 (0.97-1.05)
3	1.05 (1.01-1.09)
4	1.08 (1.04-1.12)
5 (most deprived)	1.07 (1.03-1.11)
Ethnicity‡	
Europid-descent: America, Australia or Europe	*Reference*
Africa or Caribbean	2.20 (2.07-2.35)
Arab-speaking regions	0.82 (0.76-0.89)
Asia	1.14 (1.07-1.22)
Other	0.99 (0.93-1.05)
Co-morbid conditions§	
Mood disorders, alcohol or drug	1.21 (1.14-1.28)
Thyroid disorder	1.06 (1.00-1.14)
Arthritis	1.24 (1.15-1.33)
Asthma or COPD	1.38 (1.29-1.49)

Offspring characteristics	
Offspring size[‖]	
AGA: both offspring	*Reference*
SGA: first offspring only	1.05 (1.00-1.10)
SGA: second offspring only	1.06 (1.01-1.11)
SGA: both offspring	1.15 (1.07-1.23)
LGA: first offspring only	1.08 (1.03-1.14)
LGA: second offspring only	1.07 (1.02-1.12)
LGA: both offspring	1.10 (1.02-1.18)
SGA: first offspring , LGA: second	1.16 (0.87-1.56)
LGA: first offspring , SGA: second	0.92 (0.68-1.26)
Gestational age of offspring at birth	
Term birth: both offspring	*Reference*
Preterm birth: first offspring only	1.06 (1.00-1.11)
Preterm birth: second offspring only	1.15 (1.09-1.22)
Preterm birth: both offspring	1.12 (1.01-1.23)
Paternal characteristics	
Prior history of paternal diabetes[#]	1.25 (1.12-1.41)
Prior history of paternal hypertension[#]	1.21 (1.13-1.30)
Prior history of paternal cardiovascular disease[**]	1.21 (1.03-1.42)

AGA = appropriate for gestational age; CI = confidence interval; COPD = chronic obstructive pulmonary disease; GDM = gestational diabetes; HR = hazard ratio; LGA = large for gestational age; SGA = small for gestational age

[*] The Cox proportional hazards model adjusted for the GHTN occurrences (with or without preeclampsia) across pregnancies, as well as each of the variables listed. See Supplemental Tables 2 and 3 for unadjusted associations.

† 7335 women were missing a value for the Institut national de santé publique du Québec (INSPQ) material deprivation index.

‡ Compared to women of Europid descent, those from African or Arabic ethnic origins demonstrated increased hazards of developing hypertension, respectively, during the follow-up period.

§ The reference group are women with the absence of each condition, respectively. The presence of each co-morbid condition was associated with higher hypertension hazards. Co-morbid conditions were defined in accordance with the Chronic Disease Surveillance System's definition of chronic disease, requiring ≥ 1 inpatient or ≥ 2 outpatient ICD codes to be present within 2 years prior to the index date.

‖ 150 offspring were missing birthweight required to derive offspring size.

[#] Prior history in the father was defined as ≥ 1 inpatient and/or ≥ 2 outpatient ICD codes for any form of diabetes or hypertension, respectively, that occurred during the period from two years prior to 20 weeks' gestation of their partner's first pregnancy to 12 weeks' postpartum in relationship to the second pregnancy. The reference group are those without diabetes or hypertension, respectively.

[**] Prior history of cardiovascular disease in the father was defined as ≥ 1 inpatient, ≥ 1 related surgical procedure (angioplasty, endarterectomy or coronary artery bypass surgery), and/or ≥ 2 outpatient ICD codes for any form of myocardial infarction, stroke and angina, that occurred during the period from two years prior to 20 weeks' gestation of their partner's first pregnancy to 12 weeks' postpartum in relationship to the second pregnancy. The reference group are those without cardiovascular disease.

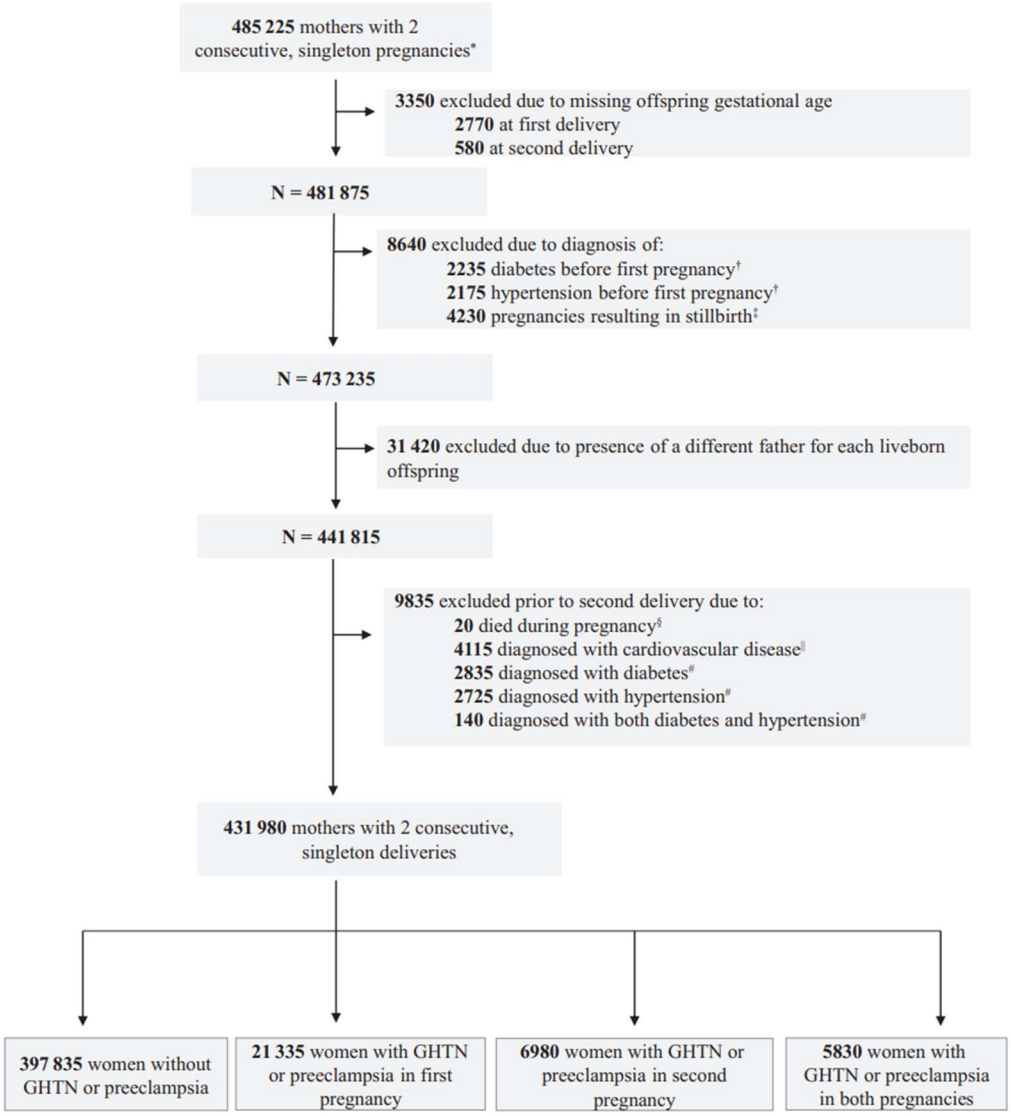
Figure Legend

Figure 1: Cohort construction.
[*] Values are rounded either up or down to a multiple of '5' (for patient confidentiality purposes).
[†] Preexisting diabetes or hypertension in the mother, defined as ≥ 1 inpatient and/or ≥ 2 outpatient ICD codes for any form of diabetes or hypertension in the two years prior to 20 weeks' gestational age of the first pregnancy.
[‡] Fatal events occurring at any point between 20 weeks' gestation of the second pregnancy and 12 weeks' postpartum. Five deaths were related to a fatal cardiovascular disease (CVD) event while the remaining 15 fatalities were due to obstetrical complications related to childbirth, major trauma and suicide.
[§] The CVD-related exclusion criteria included codes related to both hospitalization and outpatient clinic visits for myocardial infarction (N=55, 1.3%), stroke (N=1030, 25%) and angina (N=60, 1.5%), and additionally considered other circulatory system disease conditions (atrial fibrillation [N=60, 1.5%], heart failure [n=75, 1.8%], other ischemic disease [N=530, 13%], other cardiac dysrhythmias [N=25, 0.6%], peripheral vascular disease [N=40, 1.0%] and venous thromboembolism [N=2230, 54%]). We required ≥ 1 inpatient diagnosis/surgical procedure (angioplasty, endarterectomy or coronary artery bypass surgery), or ≥ 2 outpatient diagnoses, occurring 2 years prior to 12 weeks' postpartum of the second pregnancy (index date), to define prior CVD events.
[||] Defined as ≥ 1 inpatient and/or ≥ 2 outpatient (within 2 years) diabetes-related or hypertension-related ICD codes occurring between 12 weeks' postpartum of the first pregnancy and 20 weeks' gestation of the second pregnancy.
[#] With or without preeclampsia.

Figure 2: Kaplan-Meier curves for hypertension-free survival, by GHTN or preeclampsia status. The log-rank test indicated significant differences in event-free survival across exposure groups ($p < 0.02$). GHTN indicates gestational hypertension.

Figure 3: Associations of GHTN or preeclampsia in first and second pregnancies with incident chronic hypertension. A: Primary analysis. B: Subgroup analysis (excluding women with GHTN). C: Subgroup analysis (excluding women with preeclampsia).

Figure 1. Cohort construction



*Values are rounded either up or down to a multiple of '5' (for patient confidentiality purposes).

†Preexisting diabetes or hypertension in the mother, defined as ≥1 inpatient and/or ≥2 outpatient ICD codes for any form of diabetes or hypertension in the 2 years before 20 wks' gestational age of the first pregnancy.

‡Stillbirths were identified from the stillbirth registry. In the case of a stillbirth, it is not possible to identify the father since there is an absence of paternal information in the stillbirth registry (registry is linked only to mothers).

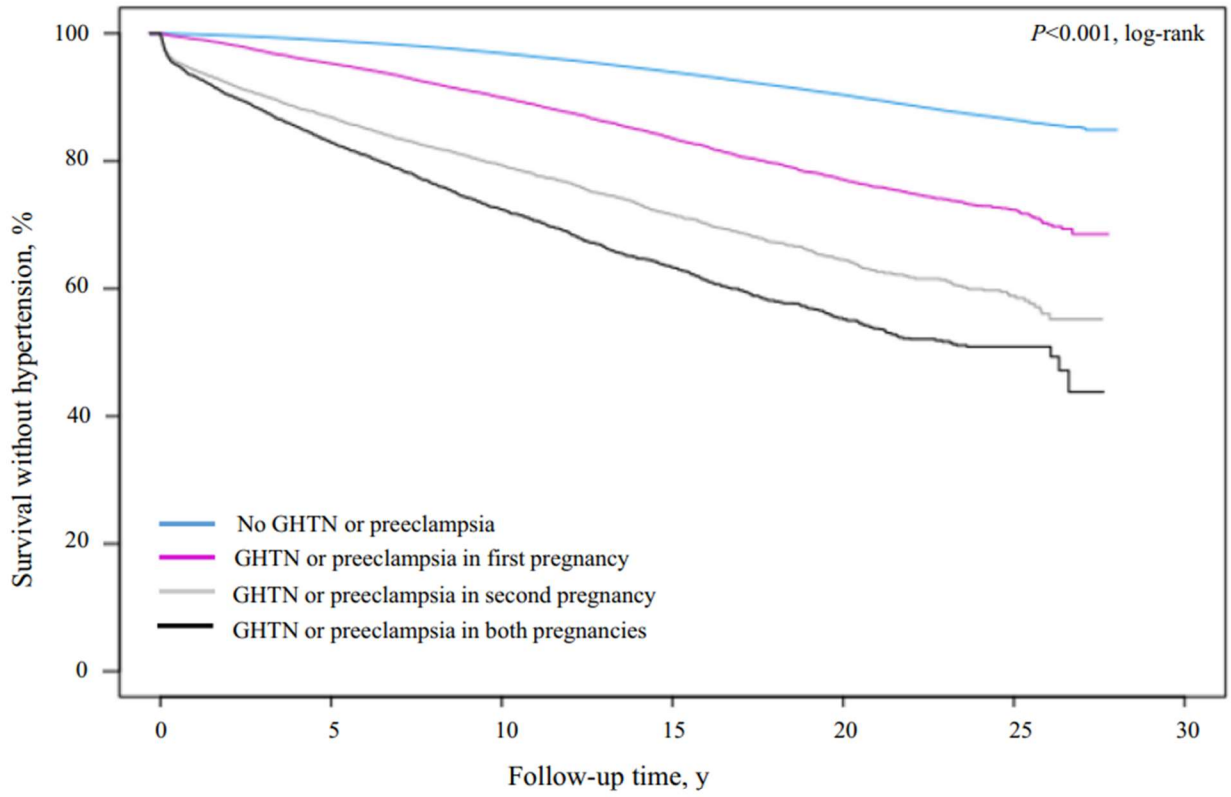
§Fatal events occurring at any point between 20 wks' gestation of the second pregnancy and 12weeks' postpartum. Five deaths were related to a fatal CVD event while the remaining 15 fatalities were related to obstetrical complications related to childbirth, major trauma and suicide.

||The CVD-related exclusion criteria included codes for myocardial infarction, stroke, angina, and other circulatory system disease conditions (atrial fibrillation, heart failure, other ischemic disease, other cardiac dysrhythmias, peripheral vascular disease, and venous thromboembolism). We required ≥1 inpatient diagnosis, 1 related surgical procedure (angioplasty, endarterectomy, or coronary artery bypass surgery), or ≥2 outpatient diagnoses, occurring 2y before 12 wks' postpartum of the second pregnancy (index date), to define prior CVD events.

#Defined as ≥1 inpatient and/or≥2 outpatient (within 2years) diabetes-related or hypertension-related ICD codes occurring between 12 wks' postpartum of the first pregnancy and 20 wks' gestation of the second pregnancy.

CVD indicates cardiovascular disease; ICD, International Classification of Diseases; and GHTN, gestational hypertension.

Figure 2. Kaplan Meier curves for hypertension-free survival, by GHTN or preeclampsia status

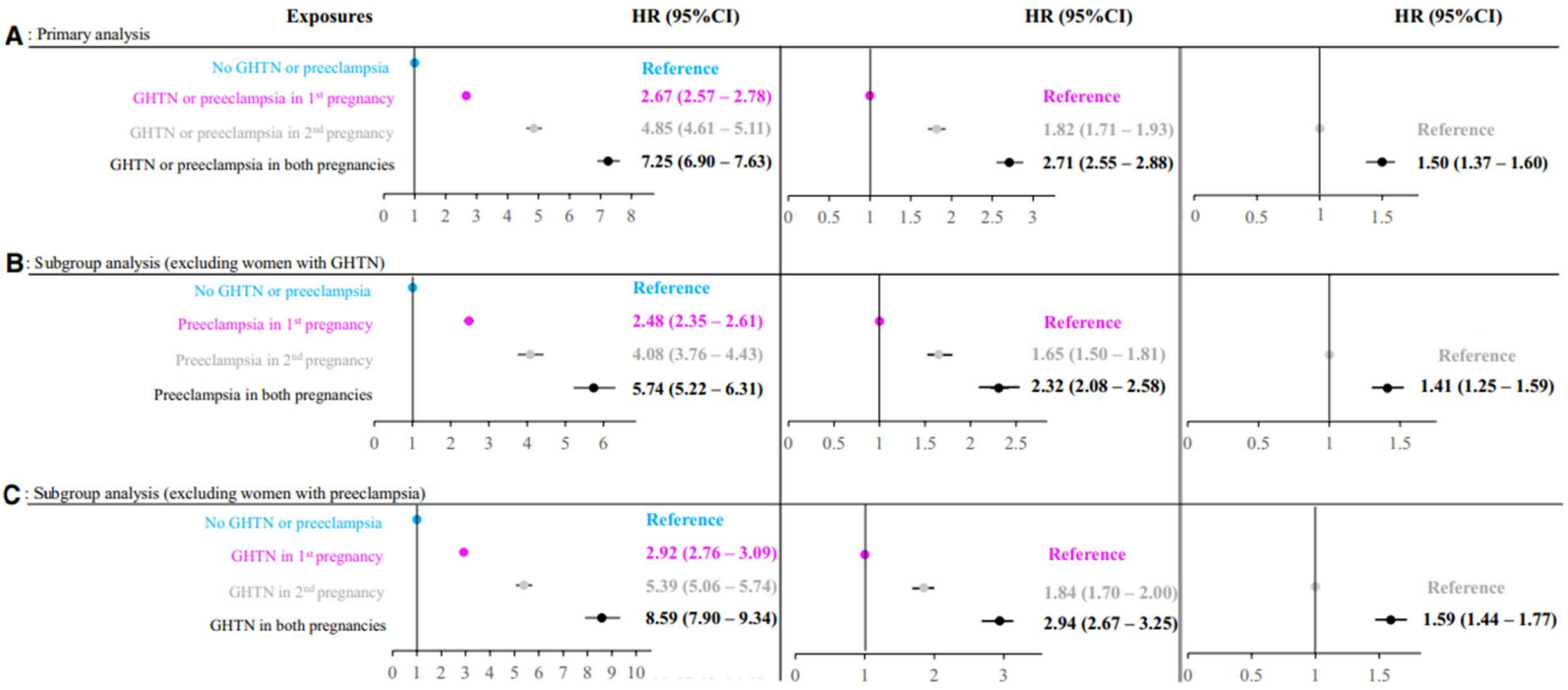


Number at risk

	397650	299540	217575	146645	85195	17825	0
	21320	15450	10690	6745	3640	760	0
	6980	4820	3180	1910	920	175	0
	5825	3775	2315	1315	595	110	0

The log-rank test indicated significant differences in event-free survival across exposure groups ($p < 0.02$). GHTN indicates gestational hypertension.

Figure 3. Associations of gestational hypertension in first and second pregnancies with incident chronic hypertension



(A) Primary analysis. (B) Subgroup analysis (excluding women with GHTN). (C) Subgroup analysis (excluding women with preeclampsia). CI indicates confidence interval; GHTN, gestational hypertension; and HR, hazard ratio.

4.3 Supplementary Materials, Manuscript 2

Supplemental Data

Data S1: Omitted variables from statistical models (variable selection): Other variables that we considered but ultimately did not meet thresholds for inclusion in statistical models (see Statistical Analysis for inclusion criteria) were several paternal variables (age, ethnicity), parental co-habitation, years of maternal education, offspring congenital anomalies, offspring sex, history of cancer, history of HIV or chronic hepatitis, placental abruption, and stillbirth (many stillbirths excluded based on our inclusion criteria requiring the same father for both offspring; there is an absence of paternal information in the Stillbirth registry).

Data S2: Sensitivity analysis (adjusting for unmeasured confounders):

Shin et al., 2014 (reference 42)

$$HR_{(\text{corrected for smoking})} = \frac{HR_{(\text{from our analysis})}}{HR_{(\text{related to smoking, from literature})}^{P_{se}-P_eP_s}}$$

Notation

P_{se} = proportion within specific exposure category who smoke

P_e = proportion of those corresponding to specific exposure category among all women with two consecutive singleton pregnancies

P_s = proportion who smoke among all women with two consecutive singleton pregnancies

$HR_{(\text{related to obesity, from literature})} = 1.85$ (reference 43)

$HR_{(\text{related to smoking, from literature})} = 1.02$ (reference 44)

GHTN/preeclampsia occurrences from CCHS-derived cohort				
	No GHTN/ preeclampsia	**GHTN/preeclampsia in first pregnancy**	**GHTN/preeclampsia in second pregnancy**	**GHTN/preeclampsia in both pregnancies**
P_{se}: Proportion of Smokers (%, N)	24.4 (242/990)	23.3 (21/90)	23.8 (24/101)	26.0 (13/50)
P_{oe}: Proportion of Obese (%, N)*	12.9 (70/541)	21.2 (11/52)	20.4 (11/54)	20.0 (6/30)

CCHS = Canadian Community Health Survey (Cycle 2.2), GHTN = gestational hypertension, HR = hazard ratio, N = number

*554 women missing BMI measures in CCHS, cycle 2.2

Table S1. ICD codes

Condition	ICD-9	ICD-10	Capture period
Prior cardiovascular disease or circulatory system disease conditions (mother; exclusion criteria)*	325, 410-415, 427-444, 451-453, 6396, 671, 673, 6740, 7943, 9971-9972, 2506	I20-I26, I46-I52, I60-I70, I73-I74, I79-I82, I86, I97, R9430-R9431, E105, E115, E145, G08, G45-G46, H34, O882, O994, T817	2 years prior to 12 weeks' postpartum of second delivery (index date) – *2 outpatient diagnoses, 1 inpatient diagnosis or 1 related surgical procedure (angioplasty, endarterectomy or coronary artery bypass surgery)*
Prior diabetes (mother; exclusion criteria)	250, 6480, 6488	E10-14, O245-O248	2 years prior to 20 weeks' gestation of first pregnancy (preexisting condition) or codes occurring between 12 weeks' postpartum of the first pregnancy and 20 weeks' gestation of the second pregnancy (condition developed during interpregnancy interval) – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
Prior hypertension (mother; exclusion criteria)	401-405, 642	I10-I13, I15, O10-O11, O13-O16	2 years prior to 20 weeks' gestation of first pregnancy (preexisting condition) or codes occurring between 12 weeks' postpartum of the first pregnancy and 20 weeks' gestation of the second pregnancy (condition developed during interpregnancy interval) – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
Prior diabetes (father; covariate)	250, 6480, 6488	E10-14, O245-O248	2 years prior to 20 weeks' gestation of first pregnancy to 12 weeks' postpartum of second pregnancy – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
Prior hypertension (father; covariate)	401-405, 642	I10-I13, I15, O10-O11, O13-O16	2 years prior to 20 weeks' gestation of first pregnancy to 12 weeks' postpartum of second pregnancy – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
Prior cardiovascular disease (father; covariate)	325, 3623, 410, 41190, 413, 430-438, 6740	I20-21, I60-I66, I69, R9430-R9431,G08, G45-G46, H34, O882	2 years prior to 20 weeks' gestation of first pregnancy to 12 weeks' postpartum of second pregnancy – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
Gestational diabetes	250, 6480, 6488	E10-14, O248	2 years prior to 20 weeks' gestation of first pregnancy to 12 weeks' postpartum of second pregnancy – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
Gestational hypertension†	401-405, 642	I10-I13, I15, O10-O11, O13-O16	20 weeks' gestation of each respective pregnancy to 12 weeks' postpartum – *2 outpatient diagnoses or 1 inpatient diagnosis*
Hypertension (outcome)	401-405, 642	I10-I13, I15, O10-O11, O13-O16	After 12 weeks' following the second delivery (index date) – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
Pregnancy after the index date (censor at 120 days prior)	630-676, 763, 767-768, 779 V22-V24, V27-V39	O00-O99, Z32-Z39, P95, P964, P968-P969	After 12 weeks' following the second delivery (index date) – *1 inpatient diagnosis*
Mood disorders, alcohol or drug dependence	291-292, 295-305, 311 V11 V654	F10-F25, F30-F34, F38-F45, F48, F53, F99 R457 Z914 Z915 X65 Z714 Z864-Z865	2 years prior to 12 weeks' postpartum of the second delivery (index date) – *2 outpatient diagnoses or 1 inpatient diagnosis*
Thyroid disorders	240-246 0175, 1222, 2513, 6481, 7753, 7758, 7945, V770	E01-E07 A188, B673, E350, E890-E891, O905, P720-P722, R946, Z138, O9920	2 years prior to 12 weeks' postpartum of the second delivery (index date) – *2 outpatient diagnoses or 1 inpatient diagnosis*
Arthritis	274 6960, 710-721, 724	M05-M19, M32, M43, M46-M48, M53-M54, L405	2 years prior to 12 weeks' postpartum of the second delivery (index date) – *2 outpatient diagnoses or 1 inpatient diagnosis*
Asthma or chronic obstructive pulmonary disease	491-493, 496, 5181-5182	J44-J45	2 years prior to 12 weeks' postpartum of the second delivery (index date) – *2 outpatient diagnoses or 1 inpatient diagnosis*

* The cardiovascular-related exclusion criteria included codes related to both hospitalization and outpatient clinic visits for myocardial infarction, stroke, angina, and additionally considered other circulatory system disease conditions (atrial fibrillation, heart failure, other ischemic disease, other cardiac dysrhythmias, peripheral vascular disease and venous thromboembolism). We also excluded those with the following ***procedure codes*** related to pacemaker implantation, angioplasty, endarterectomy or coronary artery bypass surgery: 00460, 00631, 00662, 04022, 04030, 04031, 04037, 04046, 04601-04608, 04610-04612, 04661, 04662, 04665-04668, 04669, 04689, 04692-04699, 04701-04704, 04707-04709, 04710, 04713-04716, 04721-04723, 04725-04727, 04732-04737, 04740-04058, 09302, 20123, 20124, 20186, 20191, 20194, 20195, 20531, 20532, 20577-20583-20590

† The following codes were used to capture preeclampsia: 6424-6427 (ICD-9) and O11, O14-O15 (ICD-10). The remaining codes were used to capture GHTN (without preeclampsia).

Table S2. Unadjusted associations of gestational hypertension in first and second pregnancies with incident hypertension

History of occurrences across two pregnancies	Unadjusted hazard ratio for incident hypertension (95% CI)		
GHTN (with or without preeclampsia)			
No GHTN or preeclampsia	*Reference*		
GHTN or preeclampsia in first pregnancy	2.73 (2.63-2.84)	*Reference*	
GHTN or preeclampsia in second pregnancy	5.52 (5.26-5.81)	2.02 (1.90-2.15)	*Reference*
GHTN or preeclampsia in both pregnancies	7.75 (7.38-8.14)	2.84 (2.67-3.01)	1.40 (1.31-1.50)
Preeclampsia			
No GHTN or preeclampsia	*Reference*		
Preeclampsia in first pregnancy	2.53 (2.40-2.67)	*Reference*	
Preeclampsia in second pregnancy	4.71 (4.35-5.11)	1.86 (1.69-2.04)	*Reference*
Preeclampsia in both pregnancies	6.06 (5.52-6.65)	2.40 (2.16-2.66)	1.29 (1.14-1.45)
GHTN			
No GHTN or preeclampsia	*Reference*		
GHTN in first pregnancy	3.03 (2.87-3.21)	*Reference*	
GHTN in second pregnancy	6.20 (5.83-6.59)	2.05 (1.89-2.22)	*Reference*
GHTN in both pregnancies	9.14 (8.42-9.93)	3.02 (2.74-3.33)	1.48 (1.33-1.63)

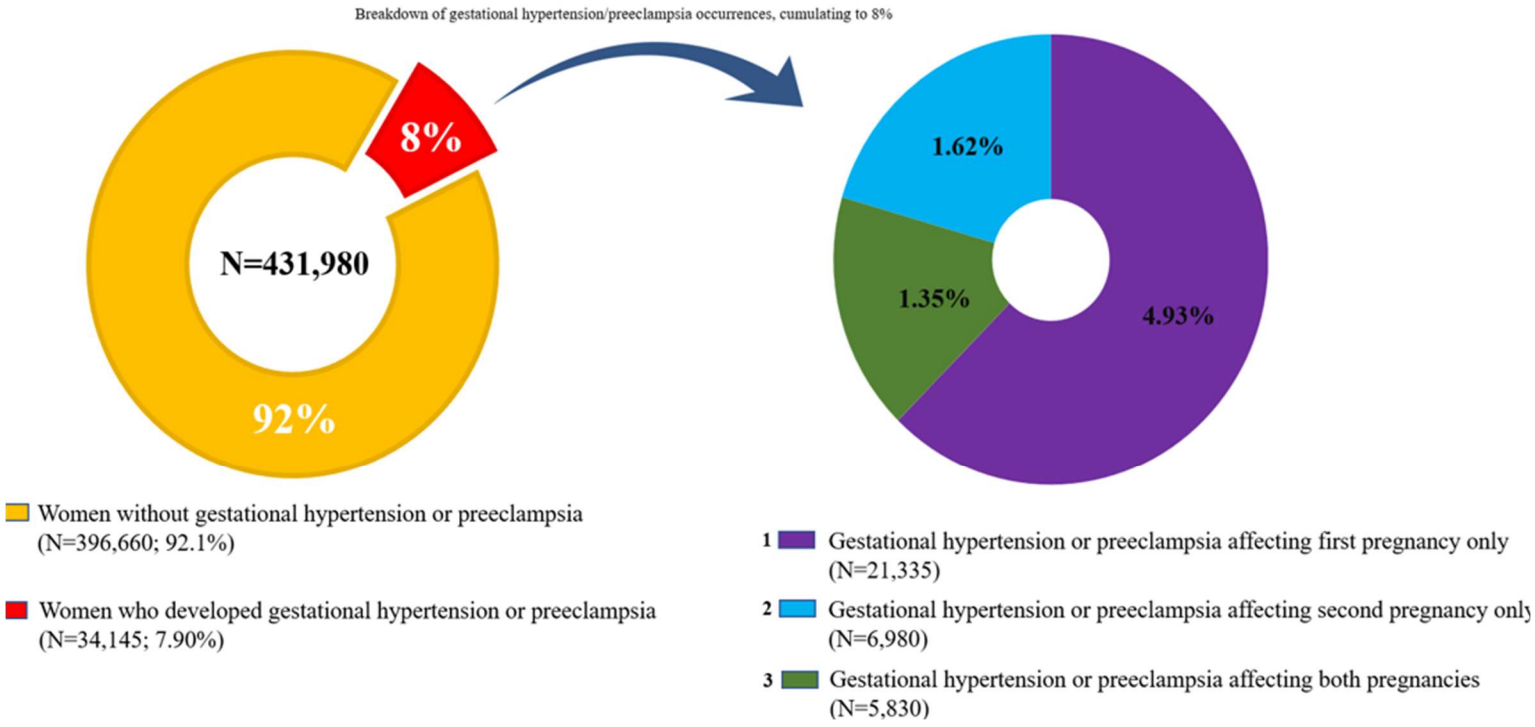
GHTN = gestational hypertension

Table S3. Unadjusted associations of covariates with incident hypertension

Covariate	Unadjusted hazard ratio (95% CI)
Maternal characteristics	
History of gestational diabetes (GD) across two pregnancies	
No GD	*Reference*
GD in first pregnancy	1.60 (1.50-1.70)
GD in second pregnancy	1.86 (1.77-1.96)
GD in both pregnancies	2.32 (2.18-2.47)
Age of mother at second delivery, years	
< 25	*Reference*
25 – 29	1.21 (1.15-1.27)
30 – 34	1.54 (1.47-1.61)
≥ 35	2.29 (2.18-2.41)
Time between deliveries, years	
<2	*Reference*
2 - <2.5	0.99 (0.95-1.02)
2.5 - <3.5	1.03 (1.00-1.07)
≥ 3.5	1.32 (1.28-1.36)
Material deprivation index, quintiles	
1 (least deprived)	*Reference*
2	1.11 (1.06-1.15)
3	1.10 (1.06-1.14)
4	1.17 (1.13-1.22)
5 (most deprived)	1.26 (1.21-1.31)
Social deprivation index, quintiles	
1 (least deprived)	*Reference*
2	1.01 (0.97-1.05)
3	1.05 (1.02-1.09)
4	1.11 (1.07-1.15)
5 (most deprived)	1.11 (1.07-1.15)
Ethnicity	
Europid-descent: America, Australia or Europe	*Reference*
Africa or Caribbean	2.79 (2.63-2.97)
Arab-speaking regions	0.91 (0.84-0.98)
Asia	1.30 (1.23-1.39)
Other	1.10 (1.04-1.17)
Co-morbid conditions	
Mood disorders, alcohol or drug dependence	1.32 (1.25-1.40)
Thyroid disorder	1.20 (1.12-1.28)
Arthritis	1.37 (1.28-1.47)
Asthma or COPD	1.51 (1.40-1.62)

Offspring characteristics	
Offspring size	
AGA: both offspring	*Reference*
SGA: first offspring only	1.15 (1.09-1.20)
SGA: second offspring only	1.16 (1.10-1.21)
SGA: both offspring	1.34 (1.25-1.43)
LGA: first offspring only	1.16 (1.10-1.21)
LGA: second offspring only	1.14 (1.09-1.20)
LGA: both offspring	1.23 (1.15-1.31)
SGA: first offspring , LGA: second offspring	1.54 (1.15-2.07)
LGA: first offspring , SGA: second offspring	1.35 (1.00-1.84)
Gestational age of offspring at birth	
Term birth: both offspring	*Reference*
Preterm birth: first offspring only	1.29 (1.22-1.36)
Preterm birth: second offspring only	1.41 (1.33-1.49)
Preterm birth: both offspring	1.52 (1.38-1.67)
Paternal characteristics	
Prior history of paternal diabetes	1.57 (1.40-1.76)
Prior history of paternal hypertension	1.44 (1.34-1.55)
Prior history of paternal cardiovascular disease	1.39 (1.18-1.63)

Figure S1. Distribution of gestational hypertension/preeclampsia occurrences across two pregnancies



Chapter 5: Manuscript 3

5.1 Preface

Both diabetes and hypertension are leading modifiable risk factors for CVD. Studies have shown that both these conditions demonstrate a similar magnitude of association with the development of CVD later in life (**see Chapter 2.1.2**). My findings from Manuscripts 1 and 2 suggest that the magnitude of the association between GDM and diabetes, as well as GHTN and hypertension in women with at least two singleton pregnancies, is impacted by the totality and sequence of their onset across pregnancies. Manuscript 3 is an extension of the previous two manuscripts as it serves to improve the understanding of the relationship between co-occurring GDM and GHTN patterns and future CVD risk. In addition to guidelines from the American Heart Association now recognizing GDM and GHTN as early indicators of CVD, Manuscripts 1 and 2 collectively build on this evidence by suggesting that GDM and GHTN are associated with earlier cardiovascular phenotype (type 2 diabetes and hypertension). These findings provide the rationale for the consideration of both GDM and GHTN as early, pregnancy-related indicators of maternal CVD development in Manuscript 3. To better understand these gestational complications in the context of CVD, I conducted retrospective cohort analyses to carefully evaluate co-occurring patterns of GDM and GHTN (totality of conjoint occurrences [primary analysis] and all possible combinations of their co-occurrence [secondary analysis]) across two pregnancies. Although the secondary analysis was able to investigate the sequential occurrences of GDM/GHTN and their relationship with CVD development much more in-depth (16 exposure categories), I believe modelling the cumulative occurrences (four exposure categories) is advantageous for improving the interpretation and uptake of my findings from a knowledge translation standpoint.

Only two recent studies[230,283] have emerged in the literature to assess the co-occurrence and joint associations of GDM and GHTN, in relation to its impact on CVD risk (**see Chapter 2.5**); one of these studies was conducted by my supervisor, who was the first investigator to examine their co-occurrence in a single pregnancy.[283] These two studies have similarly demonstrated that compared to the absence of GDM or GHTN, the presence of either is associated with increased CVD risk, and the presence of both confers the highest risk when assessing their co-occurrence in a single pregnancy. To the best of my knowledge, no previous study in the literature has examined these joint associations beyond a single pregnancy, a key methodological approach that I have adopted in the following manuscript.

This manuscript entitled "Considering gestational diabetes and gestational hypertension history across two pregnancies in relationship to cardiovascular disease development: A Retrospective Cohort Study" is published in *Diabetes Research and Clinical Practice.*

Considering gestational diabetes and gestational hypertension history across two pregnancies in relationship to cardiovascular disease development: A Retrospective Cohort Study

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Abstract

Aims: Gestational diabetes (GDM) and hypertension (GHTN) occurrences signal elevated cardiovascular disease (CVD) risk. There is little study of occurrence and recurrence of these conditions in relationship to CVD. Among women with two singleton pregnancies, we aimed to quantify CVD risk in relationship to the number of GDM/GHTN occurrences.

Methods: In this Quebec-based retrospective cohort study (n=431,980), we ascertained the number of GDM/GHTN occurrences over two pregnancies and assessed for CVD over a median of 16.4 years (cohort inception 1990-2012, outcomes 1990-2019). We defined CVD as a composite of myocardial infarction, stroke, and angina, requiring hospitalization and/or causing death. We adjusted Cox proportional hazards models for offspring size, preterm/term birth status, maternal age group, time between deliveries, ethnicity, deprivation level, and co-morbid conditions.

Results: Compared to absence of GDM/GHTN in either pregnancy, one GDM/GHTN occurrence increased CVD hazards by 47% (hazard ratio [HR]=1.47, 95% confidence interval [CI] 1.35-1.61), two occurrences nearly doubled hazards (HR=1.91, 95%CI 1.68-2.17), and three or more approximately tripled CVD hazards (HR=2.93, 95%CI 2.20-3.90). Individual components of the composite demonstrated similar findings.

Conclusions: Health care providers and mothers should consider a complete history of GDM/GHTN occurrences to ascertain the importance and urgency of preventive action.

Keywords: myocardial infarction, stroke, angina, diabetes, hypertension, adverse pregnancy outcomes

1. Introduction

Myocardial infarction and cardiovascular disease (CVD) mortality are rising in younger women, [1] with impacts on workplaces and young families. Gestational diabetes (GDM) and gestational hypertension (GHTN), with or without preeclampsia, are key early CVD risk indicators. [2-6] Although clinical care guidelines recommend that healthcare providers query about GDM and GHTN as part of CVD risk assessment in younger women, guidance on the use of this information is limited to an upgrading of risk category on a conventional CVD risk engine[2-6] for those with any GDM/GHTN history. It is unclear if the number of GDM/GHTN occurrences impacts the magnitude of CVD risk.

The existing literature focuses on 'ever/never' dichotomies for GDM/GHTN,[5,7-9] generally not incorporating information beyond one pregnancy. One challenge is that the number of pregnancies itself and CVD have a J-shaped relationship, with the lowest risk in women with two pregnancies.[10] Some researchers have focused on this group of parous women to enhance comparability among those examined. Specifically, three previous studies evaluated GHTN occurrence, absence, or recurrence across two consecutive pregnancies. [11-13] One considered GHTN with or without preeclampsia, [11] a second focused on GHTN with preeclampsia, [12] and the third on GHTN without preeclampsia. [13] All estimated some CVD risk increase with a single GHTN occurrence and more than a doubling with two occurrences, compared to absence of GHTN in either pregnancy. None, however, concurrently examined GDM occurrences.

We previously demonstrated[14] that within a single pregnancy, compared to women without GDM/GHTN, the presence of either was associated with a 40% increase in CVD hazards while the presence of both doubled hazards, as corroborated recently.[15] In the present study, we aimed to evaluate the cumulative number of GDM and GHTN occurrences across two pregnancies and its relationship to the incidence of CVD.

2. Materials and Methods

2.1 Ethics Approval

The McGill University Health Centre's Research Ethics Board (2019-5029; 2018/12/11) and Quebec Access to Information Commission (1019371-S; 2019/11/18) approved the protocol. We randomly rounded frequencies up or down to multiples of 5, as required.

2.2 Design and Data Sources

Our retrospective cohort study used health administrative and vital statistics databases from Quebec. We accessed mothers' health territory and month/year of birth (public health insurance registry); the Institut national de santé publique du Québec material deprivation index;[16] service, procedural, and diagnostic codes (International Classification of Diseases, ICD-9: Supplemental Table 1) from physician claims data; hospitalization dates and related diagnostic codes (ICD-9 codes to April 1, 2006; ICD-10 thereafter); offspring birthdates, gestational age at birth, birthweight, fetal sex, parental country of birth and first language, and years of maternal education (Birth and Stillbirth registries); and cause of death, where applicable (Stillbirth and Death Registries, ICD-9 codes until December 31, 1999; ICD-10 thereafter). The Quebec Statistical Institute performed probabilistic database linkage based on multiple identifiers (G-link software, Statistics Canada).

2.3 Study Population

We studied women with two or more consecutive singleton deliveries between April 1, 1990-December 31, 2012 alive at 12 weeks after the second pregnancy (index date). We accessed follow-up data to April 1, 2019 for these women, their offspring, and, for liveborn offspring, the fathers.

We excluded those with missing gestational age (used to distinguish diabetes and hypertension from GDM and GHTN), those with diabetes or hypertension prior to first pregnancy, and those who developed these conditions between pregnancies. We applied the validated Canadian Chronic Disease Surveillance System (CCDSS) diabetes definition[17,18] of two outpatient or one hospitalization diagnostic code(s) to (a) the 2-year period prior to 20 weeks' gestation in first pregnancy and (b) the period from 12 weeks' post-delivery first pregnancy to 20 weeks' gestation of second pregnancy. We applied a validated parallel hypertension definition[19] to the same time periods. We removed those with a different partner for each offspring, given partner influences on health behaviors. [20-22] We excluded those with one hospitalization or two outpatient visits with CVD diagnostic codes (myocardial infarction, stroke, and angina) and/or other circulatory system diseases prior to the index date.

2.4 Exposures

We adapted a validated health administrative database GDM definition[23] that applies diabetes and GDM diagnostic codes to a pregnancy-specific period. Instead of the 120-day predelivery period, we used 20 weeks' gestation to 12 weeks postpartum, as we had information on gestational age. Diabetes

prior to 20 weeks' gestation is considered pre-existing.[24] We included 12 weeks' postpartum in our definition, given that screening for diabetes after pregnancy generally occurs at or after this time point.[25,26] We required two outpatient and/or one hospitalization code to maximize specificity (99.5%) and maintain sensitivity (94.1%), as recommended in the validation study. We used a similar approach to define GHTN, using both validated GHTN codes[27] and hypertension codes.[19] Our four main exposure categories were no GDM/GHTN occurrence, one occurrence, two occurrences, and three or more occurrences.

As discussed under Statistical Analyses, in a secondary analysis, we created 16 mutually-exclusive GDM/GHTN exposure categories. In other secondary analyses, we redefined the cohort to retain those who developed diabetes and those who developed hypertension between pregnancies; we then expanded the 'GDM second pregnancy' and 'GHTN second pregnancy' groups to be 'GDM second pregnancy or diabetes between pregnancies' and 'GHTN second pregnancy or hypertension between pregnancies'.

2.5 Outcomes

We examined a composite of fatal and nonfatal myocardial infarction, stroke (thromboembolic and hemorrhagic) and angina. Follow-up was to first CVD event, death from other causes, or the end of the study period (April 1, 2019). We used validated diagnostic codes for myocardial infarction, [28] stroke,[29] and angina,[28] and some additional Quebec-specific codes. We required hospitalization or death for our CVD outcome definition[30] and/or a related surgical procedure codes (angioplasty, endarterectomy, or coronary artery bypass surgery), consistent with other studies.[31-33]

2.6 Covariates

Preterm birth (<37 weeks' gestation), small- (<10th percentile birthweight for sex and gestational age, SGA), and large- (>90th percentile, LGA) for-gestational-age also signal CVD risk. [5] Our adjusted models included nine categories of offspring size and four preterm/term birth patterns across two pregnancies, as well as maternal age category (<25, 25-29, 30-34, ≥35 years), time between deliveries (<2, 2-<2.5, 2.5-<3.5, ≥3.5 years), material deprivation level (1 [least] to 5 [most]) [16], ethnocultural background (based on region of birth or first language; Europid, African/Caribbean, Arabic, Asian, Other), and co-morbid conditions (mood disorders, alcohol/drug dependence; cancer; arthritis; HIV/chronic hepatitis; asthma/chronic obstructive pulmonary disease; defined as ≥1 hospitalization

or ≥2 outpatient diagnostic codes occurring within two years prior to the index date). We considered other covariates, but these did not meet our variable inclusion criteria (see Statistical Analysis) and are noted in the Supplemental Methods.

2.7 Statistical Analyses

We computed baseline characteristics, assessed for multicollinearity (Cramer's V) and interactions, calculated CVD incidence, and constructed Kaplan Meier curves. We tested the proportional hazards assumption (Schoenfeld's residuals). In Cox proportional hazards models, we compared *one*, *two*, and *three or more* GDM/GHTN occurrence categories with none; *two* or *three or more* categories with *one*; and the *three or more* occurrences category with *two* occurrences. We retained covariates based on univariate association with CVD $p \leq 0.25$, multivariable association (stepwise selection) $p \leq 0.05$, and reduced Bayesian Information Criteria values with inclusion.

In a sensitivity analysis, we separately performed indirect adjustments for obesity and smoking status, using established methods. [34] This required an external estimate of the associations of obesity and smoking with CVD in women, which we respectively estimated as a hazard ratio (HR) of 1.60 (obesity vs. no obesity)[35] and HR of 1.58 (smoking vs. not smoking).[36] This method also required external cohort data to estimate obesity and smoking prevalence in groups of women with none, one, two, and three or more GDM/GHTN occurrences across two pregnancies. We used the Canadian Community Health Survey (Cycle 2.2) to estimate these prevalence values, as we had access to these data for another study. [37] We applied the following formula for the obesity adjustment: $HR_{(\text{corrected for obesity})} = HR_{(\text{from our analysis})} / HR_{(\text{related to obesity, from literature})}^{Poe-Pe*Po}$ (P_{oe}=proportion within specific GDM/GHTN category who have obesity; P_e=proportion of those with specific GDM/GHTN category among all women with two consecutive singleton pregnancies; P_o=proportion with obesity among all women with two consecutive singleton pregnancies; Supplemental Methods). We applied a similar approach for the indirect adjustment of smoking.

In a secondary analysis, we assessed HRs for 16 exposure categories (including the reference group, no GDM/GHTN) based on specific combinations of GDM and GHTN across two pregnancies (Supplemental Figure 1) among the women in the primary study cohort. In another secondary analysis, we modified our study inclusion criteria to retain women who had developed diabetes and/or hypertension between pregnancies, and collapsed diabetes between pregnancies with GDM in second

pregnancy and hypertension between pregnancies with GHTN in second pregnancy. We also examined HRs for the total number of GDM/GHTN occurrences and for the specific 16 GDM and GHTN exposure categories in this secondary cohort. We performed all analyses with SAS version 9.4.

3. Results

Among the 431,980 women (Figure 1) studied following exclusions, 11% (N=48,260) had one GDM/GHTN occurrence, 3% experienced two (N=14,815), and <0.5% had three or more occurrences (N=1,800). Approximately half of all GHTN cases (16,495/34,050) involved preeclampsia. Those without GDM/GHTN were the youngest and least materially deprived; with the lowest number of co-morbid conditions and SGA, LGA, and preterm births; the shortest time between deliveries; and the highest proportion of Europid background (Table 1). Those with three or more GDM/GHTN occurrences were at the opposite end of the spectrum with respect to all of these characteristics.

3.1 Associations of maternal CVD with GDM/GHTN occurrences

Over a median 16.4 years, 4,228 mothers developed CVD. The incidence rates per 1,000 person-years rose across the *none* (0.53), *one* (0.82), *two* (1.07), and *three or more* (1.71) GDM/GHTN occurrence categories. Kaplan Meier curves indicated significant differences in event-free survival across exposure groups ($p< 0.02$; Figure 2).

There was no significant multicollinearity/interaction and Schoenfeld's tests indicated that the proportional hazards assumption applied. In adjusted models, compared to those without GDM/GHTN, those with one occurrence had 47% higher CVD hazards (HR=1.47, 95% confidence interval [CI], 1.35-1.61; Figure 3), those with two occurrences had approximately 2-fold higher hazards (HR=1.91, 95%CI 1.68-2.17), and those with three or more experienced nearly 3-fold increased hazards (HR=2.93, 95%CI 2.20-3.90). Compared to those with one GDM/GHTN occurrence, those with two occurrences had 30% increased hazards (HR=1.30, 95%CI 1.12-1.50) and those with three or more had a 2-fold increase (HR=1.99, 95%CI 1.48-2.67). Finally, CVD hazards were 54% higher among those with three or more GDM/GHTN occurrences compared to those with two (HR=1.54, 95%CI 1.13-2.09).

Indirect adjustments for obesity (No occurrences: reference; 1 occurrence HR=1.36; 2 occurrences 1.71; 3 or more occurrences 2.21) and smoking (1 occurrence HR=1.36; 2 occurrences 1.69; 3 or more occurrences 2.72) attenuated the HRs for the CVD composite outcome, but overall results were similar. HRs for myocardial infarction and for angina paralleled the composite and were conclusive (Figure 3). For the one occurrence and two occurrence categories, HRs for stroke were similar to HRs for the composite outcome.

In a secondary analysis with 16 distinct GDM/GHTN exposure categories, findings aligned with our main analyses discussed above (Table 2); for example, the various subcategories of 'two occurrences' (e.g., GDM first and GHTN first; GDM both; etc.) had HRs in a range similar to the overall 'two occurrences' category in our main model. HR estimates were slightly higher in other secondary analyses where we retained diabetes between pregnancies and hypertension between pregnancies and respectively collapsed them with GDM second and GHTN second categories (Supplemental Figure 2, Supplemental Table 2).

4. Discussion

Among women with two singleton pregnancies (without diabetes, hypertension, or CVD before or between these pregnancies), there was a 47% increase in CVD hazards with one GDM/GHTN occurrence, a doubling of hazards with two occurrences, and a tripling of hazards with three or more, compared to not having GDM or GHTN in either pregnancy, over a median follow-up of 16.4 years. Further, having two occurrences signaled 30% higher hazards than a single occurrence and having three or more GDM/GHTN occurrences was associated with 54% higher hazards than two occurrences. These findings demonstrate that consideration of the totality of GDM/GHTN occurrences offers greater nuance in CVD risk estimation than an 'ever/never' occurrence dichotomy.

As previously discussed, three prior studies[11-13] evaluated women with two consecutive pregnancies in terms of GHTN associations with CVD outcomes. A study examining GHTN with preeclampsia[12] reported 40% increased hazards for ischemic heart disease with GHTN in the first pregnancy, a 2.2-fold increase with GHTN in the second, and a 3.3-fold increase with GHTN in both. A second evaluated GHTN without preeclampsia, [13] reporting higher CVD hazards with two GHTN occurrences in the presence of SGA or preterm (absence: $GHTN_{first}$ HR=1.7, $GHTN_{second}$ HR=2.4, $GHTN_{both}$ HR=1.9; presence: $GHTN_{first}$ HR=2.0, $GHTN_{second}$ HR=3.0, $GHTN_{both}$ HR=3.6). A third

study combined GHTN with and without preeclampsia,[11] and also demonstrated higher CVD hazards with two GHTN occurrences ($GHTN_{first}$ HR=1.9, $GHTN_{second}$ HR=2.4 second, $GHTN_{both}$ HR=2.8 both). None studied GDM. We not only considered GDM but also SGA and preterm status as independent variables (Supplemental Table 3); we observed a 22 to 28% increased hazards with one SGA offspring and a doubling with two SGA offspring, as well as increased hazards with more preterm deliveries (26% with preterm in first pregnancy, 38% with second, 63% with both).

In a previous study,[14] we demonstrated that within a single pregnancy, GDM/GHTN alone are associated with a 40% increase in CVD hazards while occurrence of both in a single pregnancy was associated with a 2.4-fold increase. Our current analyses demonstrate comparable risk increases when GDM and GHTN occur in two different pregnancies. Previous studies suggest that hypertension and type 2 diabetes mellitus partly mediate the association of GDM/GHTN with CVD.[38-40] In our analyses, the proportions of women who developed diabetes before a CVD event rose from 6.75% in those without a GDM/GHTN occurrence to between 48 and 83% in those with one or more occurrence(s). The proportions who developed hypertension before a CVD event rose from 20% among those without a GDM/GHTN occurrence to between 40 and 100% in those with one or more GDM/GHTN occurrence(s). The path from GDM/GHTN to CVD also likely reflects direct effects of GDM-associated hyperglycemia and GHTN-associated antiangiogenic factors that cause endothelial injury, particularly with preeclampsia.[41-46] The cumulative impact of GDM and GHTN operating simultaneously and/or across pregnancies likely contributes to the 'dose-response' impact we observed between GDM/GHTN occurrences and CVD hazards.

Our findings contribute to a precision-medicine oriented approach to CVD risk assessment in younger women, an approach that must ultimately be distilled into a CVD risk engine that focuses on younger women and incorporates pregnancy-related factors.[47] Future studies need to develop a corresponding precision-medicine oriented prevention and management approach. There is strong evidence that diet and physical activity-focused interventions reduce type 2 diabetes mellitus risk in women averaging 10 years since a GDM diagnosis,[42] but the evidence for reduction in CVD risk in younger women is still emerging, remains limited for women with GHTN, and there are no current trials evaluating outcomes in women defined in relationship to GDM/GHTN patterns. To address rising rates of myocardial infarction and CVD mortality in young women, one of the key messages from the *Lancet Women and Cardiovascular Disease Commission* is to "educate health-care providers and patients regarding early

detection and prevention of cardiovascular disease in young women".[48] Research to build tailored risk engines and corresponding evidence-based prevention approaches are important to achieve this goal.

We leveraged large sample sizes and long follow-up periods made possible by using health administrative data sources, but we did not have laboratory, electrocardiogram, or imaging information that could corroborate ICD-coded diagnoses. To limit misclassification, we applied validated health administrative database definitions. Pre-existing obesity, excess gestational weight gain, smoking history, and low physical activity levels can lead to GDM and/or GHTN and may have independent associations with CVD.[49] We did not have individual level data for obesity, smoking, or physical activity, but we did demonstrate that indirect adjustments for obesity and for smoking history did not importantly change our results. Additionally, our main analysis included LGA, a correlate of both maternal prepartum obesity and gestational weight gain.[50]

In conclusion, among women with two consecutive singleton pregnancies without a CVD event, the number of GDM and GHTN occurrences across these pregnancies is relevant to CVD risk assessment. Healthcare providers should carefully query GDM and GHTN history and use this information to make decisions in collaboration with mothers about frequency of follow-up, health behavior optimization strategies, and enrollment in trials aiming to reduce CVD risk.

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List of abbreviations

CCDSS = Canadian Chronic Disease Surveillance System; CI = confidence interval; CVD = cardiovascular disease; GDM = gestational diabetes; GHTN = gestational hypertension; HR = hazard ratio; ICD = International Classification of Diseases; LGA = large for gestational age; N = number; P_{oe}=proportion within specific GDM/GHTN category who have obesity; P_e=proportion of those with specific GDM/GHTN category among all women with two consecutive singleton pregnancies; P_o=proportion with obesity among all women with two consecutive singleton pregnancies; SGA = small for gestational age

Declarations

Ethics approval and consent to participate: The McGill University Health Centre's Research Ethics Board (2019-5029; 2018/12/11) and Quebec Access to Information Commission (1019371-S; 2019/11/18) approved the protocol. We randomly rounded frequencies up or down to multiples of 5, as required. Informed consent was waived because of the retrospective nature of the study.

Availability of data and materials: The data that support the findings of this study are available only through Quebec's Statistical Institute Centres for Access to Research Data (CADRISQ), secure environments available to accredited researchers in Quebec for research purposes, and so are not publicly available. Restrictions apply to the availability of these data and data requests must be made with permission from the Quebec Statistical Institute (https://statistique.quebec.ca/recherche/).

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: J.M. contributed to the study design, interpreted the data, prepared the first draft of the manuscript and revised based on co-authors' comments, and approved the final manuscript as submitted. E.R. contributed to the study conception and design, provided oversight of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. M.D. contributed to dataset cleaning, variable derivation, statistical analyses, data interpretation and approved the final manuscript as submitted. M.N. critically reviewed the manuscript and approved the final version as submitted. K.D. conceptualized and designed the study, supervised

analyses, interpreted the data, critically reviewed the manuscript and supervised draft revisions, and approved the final manuscript as submitted. K.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Baseline maternal and offspring characteristics, stratified by the totality of GDM/GHTN occurrences across two pregnancies

N (%)	**No occurrences** (N=367,105)	**1 occurrence** (N=48,260)	**2 occurrences** (N=14,815)	**≥3 occurrences** (N=1,800)
Age group of mother at 2nd delivery: years				
<25 (N=134,915)	116,200 (31.7)	13,845 (28.7)	4,350 (29.4)	520 (28.9)
25-29 (N=88,110)	75,455 (20.6)	9,450 (19.6)	2,865 (19.3)	340 (18.9)
30-34 (N=112,005)	95,525 (26.0)	12,175 (25.2)	3,850 (26.0)	455 (25.3)
≥35 (N=96,950)	79,925 (21.8)	12,790 (26.5)	3,750 (25.3)	485 (26.9)
Time between deliveries: years				
<2 (N=56,460)	49,590 (13.5)	5,325 (11.0)	1,395 (9.42)	150 (8.33)
2-<2.5 (N=156,300)	134,675 (36.7)	16,435 (34.1)	4,650 (31.4)	540 (30.0)
2.5-<3.5 (N=157,735)	133,670 (36.4)	17,760 (36.8)	5,615 (37.9)	690 (38.3)
≥3.5 (N=61,485)	49,170 (13.4)	8,740 (18.1)	3,155 (21.3)	420 (23.3)
Material deprivation index: Quintiles*				
1 (N=87,640)	75,820 (20.7)	8,865 (18.4)	2,670 (18.0)	285 (15.8)
2 (N=91,130)	77,655 (21.2)	10,110 (20.9)	3,045 (20.6)	320 (17.8)
3 (N=85,665)	72,995 (19.9)	9,435 (19.6)	2,875 (19.4)	360 (20.0)
4 (N=81,435)	68,735 (18.7)	9,440 (19.6)	2,885 (19.5)	375 (20.8)
5 (N=78,775)	65,705 (17.9)	9,550 (19.8)	3,080 (20.8)	440 (24.4)
Background†				
America, Australia or Europe (N=373,415)	319,625 (87.1)	40,445 (83.8)	11,880 (80.2)	1,465 (81.4)
Africa or Caribbean (N=8,545)	6,865 (1.87)	1,190 (2.47)	410 (2.77)	80 (4.44)
Arab-speaking Regions (N=17,315)	14,225 (3.87)	2,215 (4.59)	810 (5.47)	65 (3.61)
Asia (N=14,620)	11,510 (3.14)	2,150 (4.46)	870 (5.87)	90 (5.00)

Other (N=18,085)	14,880 (4.05)	2,260 (4.68)	845 (5.70)	100 (5.56)
Co-morbid conditions				
Mood disorders, alcohol or drug dependence (N=18,015)	14,915 (4.06)	2,250 (4.66)	735 (4.96)	115 (6.39)
Cancer (N=1,845)	1,535 (0.42)	230 (0.48)	65 (0.44)	15 (0.83)
Arthritis (N=9,185)	7,535 (2.05)	1,200 (2.49)	395 (2.67)	55 (3.06)
HIV or chronic Hepatitis (N=770)	580 (0.16)	135 (0.28)	45 (0.30)	10 (0.56)
Asthma or COPD (N=8,655)	6,950 (1.89)	1,205 (2.50)	410 (2.77)	90 (5.00)
Small for gestational age‡				
Neither pregnancy (N=369,220)	314,685 (85.7)	40,590 (84.1)	12,470 (84.2)	1,475 (81.9)
1st pregnancy only (N=26,115)	21,820 (5.94)	3,200 (6.63)	960 (6.48)	135 (7.50)
2nd pregnancy only (N=26,150)	21,855 (5.95)	3,180 (6.59)	970 (6.55)	145 (8.06)
Both pregnancies (N=10,345)	8,620 (2.35)	1,270 (2.63)	410 (2.77)	45 (2.50)
Large for gestational age‡				
Neither pregnancy (N=367,635)	315,130 (85.8)	39,360 (81.6)	11,795 (79.6)	1,350 (75.0)
1st pregnancy only (N=26,160)	21,340 (5.81)	3,505 (7.26)	1,150 (7.76)	165 (9.17)
2nd pregnancy only (N=26,065)	21,245 (5.79)	3,485 (7.22)	1,165 (7.86)	170 (9.44)
Both pregnancies (N=11,970)	9,265 (2.52)	1,890 (3.92)	700 (4.72)	115 (6.39)
Preterm birth				
Neither pregnancy (N=392,295)	336,360 (91.6)	42,130 (87.3)	12,395 (83.7)	1,410 (78.3)
1st pregnancy only (N=20,325)	15,575 (4.24)	3,310 (6.86)	1,250 (8.44)	190 (10.6)
2nd pregnancy only (N=14,630)	11,605 (3.16)	2,125 (4.40)	765 (5.16)	135 (7.50)
Both pregnancies (N=4,730)	3,565 (0.97)	695 (1.44)	405 (2.73)	65 (3.61)

COPD = chronic obstructive pulmonary disease; GDM = gestational diabetes mellitus; GHTN = gestational hypertension; HIV = human immunodeficiency virus. Values randomly rounded up or down to multiple of '5' (for patient confidentiality purposes).

*Range from 1 (least deprived) to 5 (most deprived). The Institut national de santé publique du Québec INSPQ material deprivation index is computed from small-area census data (average income, proportions without high school diploma, employment to population ratio among those 15 years and older.) In order to assign the INSPQ index for each woman, we first checked availability of this variable in the index year (year of 2nd delivery). 7335 women were missing an assigned INSPQ index score.

†Ethnocultural background based on the mother's region of birth and reported preferred language. We categorized women as: i) "Europid" if born in North America, South America, Central America, Mexico, East/South/Southern/West Europe or Australia and first language is English, French, or other European language; ii) "African or Caribbean" if born in West/South/East/Central Africa or the Caribbean or African language; iii) "Arabic" if born in the Arab league or language Arabic or of other North African/South-West Asian language; iv) "Asian" if born in West/East/Central/South/ Southeast/Pacific Asia or language from this region; or v) "Other" (does not fit into any other category, including Indigenous languages.

‡150 offspring were missing birthweight required to derive offspring size.

Table 2. Adjusted CVD hazard ratios for specific combinations of GDM/GHTN exposures across two pregnancies

A) Specific GDM/GHTN exposure categories across two pregnancies, excluding those with development of diabetes and/or hypertension between pregnancies (N=431,980)				
Adjusted hazard ratios for CVD (95% CI)	**No GDM in either pregnancy**	**GDM only in 1st pregnancy**	**GDM only in 2nd pregnancy**	**GDM in both pregnancies**
No GHTN in either pregnancy	Reference*	1.38 (1.15-1.65)	1.41 (1.21-1.65)	1.69 (1.39-2.06)
GHTN only in 1st pregnancy	1.53 (1.35-1.74)	2.00 (1.20-3.32)	1.82 (1.17-2.83)	2.71 (1.63-4.50)
GHTN only in 2nd pregnancy	1.60 (1.30-1.98)	1.51 (0.57-4.02)	2.42 (1.34-4.39)	2.43 (1.09-5.43)
GHTN in both pregnancies	2.19 (1.79-2.68)	2.49 (1.04-6.00)	2.60 (1.40-4.85)	4.73 (2.68-8.35)
B) Specific GDM/GHTN exposure categories across two pregnancies, including those with development of diabetes and/or hypertension between pregnancies (N=437,680)				
Adjusted hazard ratios for CVD (95% CI)	**No GDM in either pregnancy**	**GDM only in 1st pregnancy**	**GDM in 2nd pregnancy or diabetes between pregnancies**	**GDM in both pregnancies or GDM in 1st pregnancy and diabetes between pregnancies**
No GHTN in either pregnancy	Reference*	1.38 (1.15-1.65)	1.40 (1.20-1.63)	1.86 (1.56-2.20)
GHTN only in 1st pregnancy	1.53 (1.35-1.74)	2.00 (1.20-3.32)	1.83 (1.19-2.81)	2.71 (1.73-4.26)
GHTN in 2nd pregnancy or hypertension between both pregnancies	1.77 (1.46-2.13)	1.68 (0.70-4.04)	3.12 (1.98-4.90)	3.21 (1.86-5.54)
GHTN in both pregnancies or GHTN in 1st pregnancy and hypertension between pregnancies	2.31 (1.93-2.76)	2.68 (1.28-5.63)	3.55 (2.30-5.45)	5.73 (3.86-8.50)

CI = confidence interval; CVD = cardiovascular disease; GDM = gestational diabetes; GHTN = gestational hypertension; N = number

*The reference group are women without GDM or GHTN in either pregnancy. CVD refers to the composite outcome which includes myocardial infarction, stroke, or angina, requiring hospitalization or resulting in death. We derived hazard ratios from a single model. In addition to the variables

above, other variables included in the models were appropriateness of offspring size, preterm/term birth status, maternal age category at baseline, time between deliveries, material deprivation index quintile (5 = most deprived; small area-based index incorporating metrics of education, employment, and income), ethnocultural background (extrapolated from country of birth and primary language), and co-morbid conditions (mood disorders, alcohol or drug dependence; cancer, arthritis, HIV, chronic hepatitis, asthma or chronic obstructive pulmonary disease).

Figure 1. Cohort construction

CVD = cardiovascular disease

Figure 1 legend:

[a]Values are rounded either up or down to a multiple of '5' (for patient confidentiality purposes).

[b]Pre-existing diabetes or hypertension in the mother, defined as ≥ 1 inpatient and/or ≥ 2 two outpatient ICD codes for any form of diabetes or hypertension in the two years prior to 20 weeks' gestational age of the 1st pregnancy.

[c]Fatal events occurring at any point between 20 weeks' gestation of the 2ndpregnancy and 12 weeks' postpartum. Five deaths were related to a fatal CVD event while the remaining 15 fatalities were related to obstetrical complications related to childbirth, major trauma and suicide.

[d]The CVD-related exclusion criteria included codes related to both hospitalization and outpatient clinic visits for myocardial infarction, stroke and angina, and additionally considered other circulatory system disease conditions such as atrial fibrillation and heart failure. The exclusion criteria breakdown were as follows: myocardial infarction (n=55, 1.3%), stroke (N=1,040, 25%), angina (N=60, 1.5%), other ischemic disease (N=530, 13%), heart failure (N=75, 1.8%), atrial fibrillation (N=60, 1.5%), other cardiac dysrhythmias (N=25, 0.6%), peripheral vascular disease (N=40, 1.0%), venous thromboembolism (N=2,230, 54%). We required ≥ 2 outpatient diagnoses, ≥ 1 inpatient diagnosis or ≥ 1 related surgical procedure (angioplasty, endarterectomy or coronary artery bypass surgery), occurring 2 years prior to 12 weeks' postpartum of the second pregnancy (index date), to define prior CVD events.

[e]Defined as ≥ 1 inpatient and/or ≥ 2 two outpatient (within 2 years) diabetes-related or hypertension-related ICD codes occurring between 12 weeks' postpartum of the first pregnancy and 20 weeks' gestation of the 2nd pregnancy. In a secondary analysis, we retained women who had developed diabetes and/or hypertension between pregnancies and collapsed diabetes between pregnancies with GDM in second pregnancy and hypertension between pregnancies with GHTN in second pregnancy.

Figure 2. Kaplan Meier curves for CVD-free survival. Y-axis 0%-100% (A) and 90%-100% (B).

Figure 2 legend:

The log-rank test indicated significant differences in event-free survival across exposure groups ($p < 0.02$).

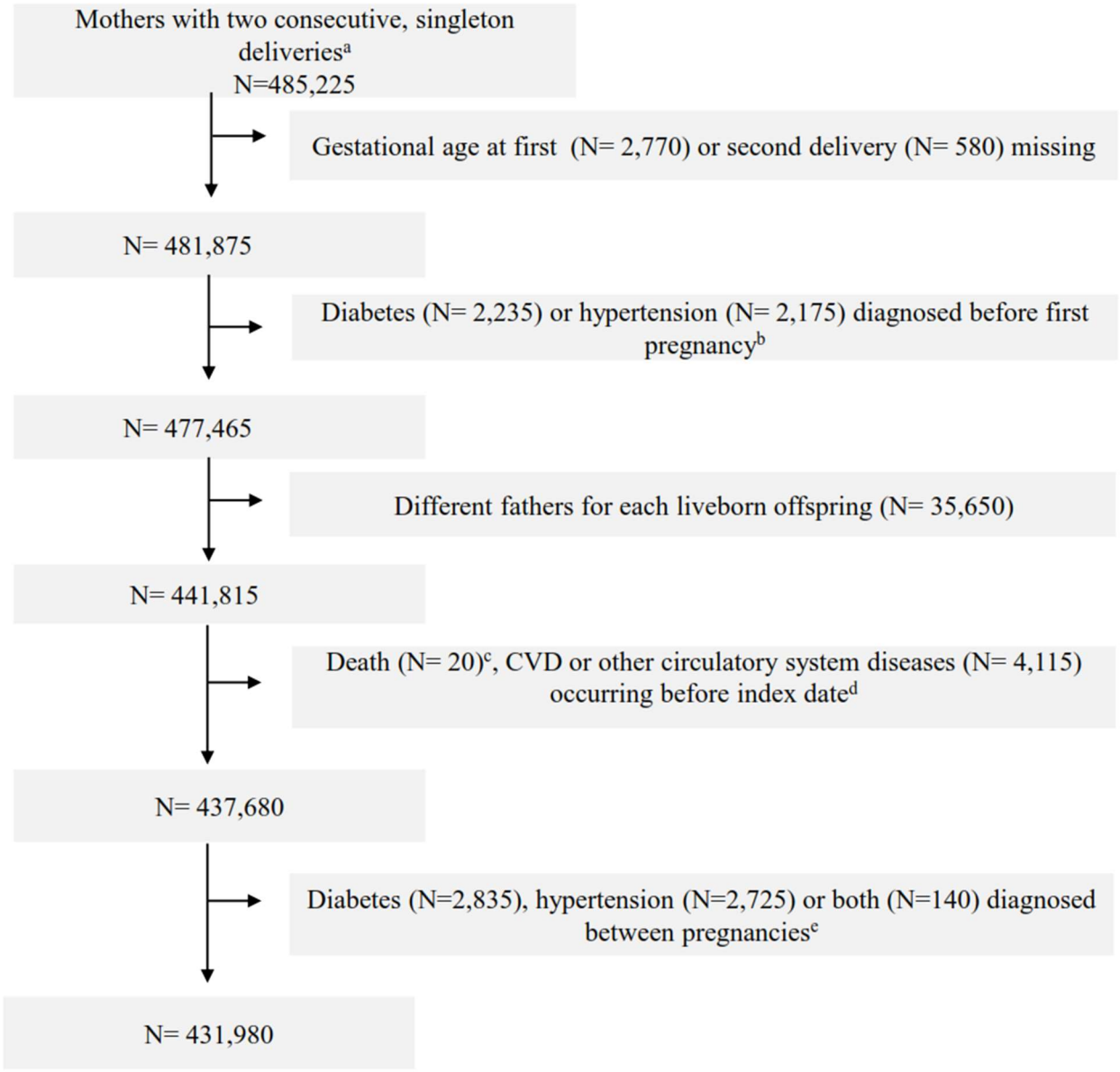
Figure 3. Associations between CVD outcomes and number of gestational diabetes and gestational hypertension occurrences

CI = confidence interval; CVD = cardiovascular disease; GDM = gestational diabetes; GHTN = gestational hypertension; HR = hazard ratio; Ref = reference group

Figure 3 legend:

Each plot represents a separate model. The first column of HRs considers absence of GDM or GHTN across two pregnancies as the reference category. In the second column, the reference category are women with a single occurrence of GDM or GHTN in across two pregnancies. In the third column, the reference category are women with two occurrences of GDM and/or GHTN across two pregnancies. Each model is adjusted for appropriateness of offspring size, preterm/term birth status, maternal age category at baseline, time between deliveries, material deprivation index quintile (5 = most deprived; small area-based index incorporating metrics of education, employment, and income), ethnocultural background (extrapolated from country of birth and primary language spoken), and co-morbid conditions (mood disorders, alcohol or drug dependence; cancer, arthritis, human immunodeficiency virus or chronic hepatitis, asthma or chronic obstructive pulmonary disease.

Figure 1. Cohort construction



CVD = cardiovascular disease

[a]Values are rounded either up or down to a multiple of '5' (for patient confidentiality purposes).

[b]Pre-existing diabetes or hypertension in the mother, defined as ≥ 1 inpatient and/or ≥ 2 two outpatient ICD codes for any form of diabetes or hypertension in the two years prior to 20 weeks' gestational age of the 1st pregnancy.

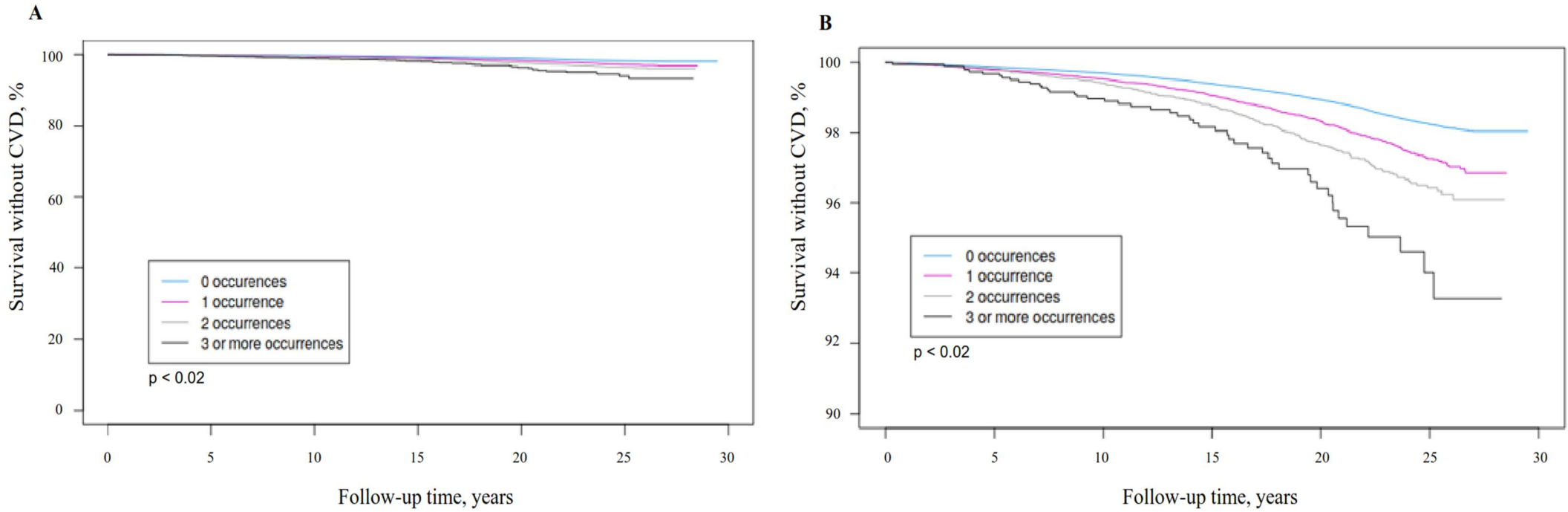
[c]Fatal events occurring at any point between 20 weeks' gestation of the 2ndpregnancy and 12 weeks' postpartum. Five deaths were related to a fatal CVD event while the remaining 15 fatalities were related to obstetrical complications related to childbirth, major trauma and suicide.

[d]The CVD-related exclusion criteria included codes related to both hospitalization and outpatient clinic visits for myocardial infarction, stroke and angina, and additionally considered other circulatory system disease conditions such as atrial fibrillation

and heart failure. The exclusion criteria breakdown were as follows: myocardial infarction (n=55, 1.3%), stroke (N=1,040, 25%), angina (N=60, 1.5%), other ischemic disease (N=530, 13%), heart failure (N=75, 1.8%), atrial fibrillation (N=60, 1.5%), other cardiac dysrhythmias (N=25, 0.6%), peripheral vascular disease (N=40, 1.0%), venous thromboembolism (N=2,230, 54%). We required = 2 outpatient diagnoses, ≥ 1 inpatient diagnosis or ≥ 1 related surgical procedure (angioplasty, endarterectomy or coronary artery bypass surgery), occurring 2 years prior to 12 weeks' postpartum of the second pregnancy (index date), to define prior CVD events.

[e]Defined as ≥ 1 inpatient and/or ≥ 2 two outpatient (within 2 years) diabetes-related or hypertension-related ICD codes occurring between 12 weeks' postpartum of the first pregnancy and 20 weeks' gestation of the 2nd pregnancy. In a secondary analysis, we retained women who had developed diabetes and/or hypertension between pregnancies and collapsed diabetes between pregnancies with GDM in second pregnancy and hypertension between pregnancies with GHTN in second pregnancy.

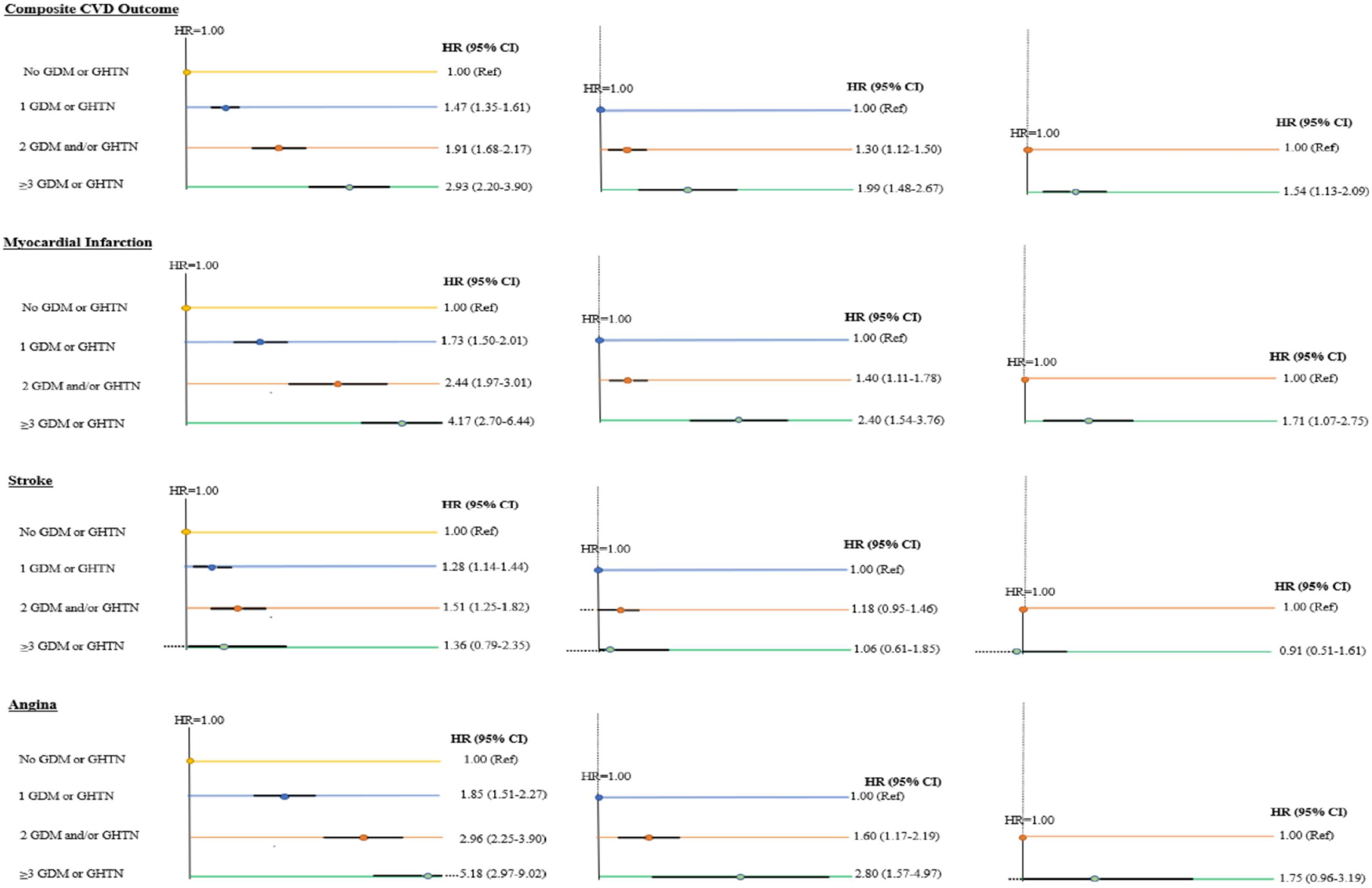
Figure 2. Kaplan Meier curves for CVD-free survival. Y-axis 0%-100% (A) and 90%-100% (B).



CVD = cardiovascular disease

The log-rank test indicated significant differences in event-free survival across exposure groups ($p < 0.02$).

Figure 3. Associations between CVD outcomes and number of gestational diabetes and gestational hypertension occurrences



CI = confidence interval; CVD = cardiovascular disease; GDM = gestational diabetes; GHTN = gestational hypertension; HR = hazard ratio; Ref = reference group

Each plot represents a separate model. The first column of HRs considers absence of GDM or GHTN across two pregnancies as the reference category. In the second column, the reference category are women with a single occurrence of GDM or GHTN in across two pregnancies. In the third column, the reference category are women with two occurrences of GDM and/or GHTN across two pregnancies. Each model is adjusted for appropriateness of offspring size, preterm/term birth status, maternal age category at baseline, time between deliveries, material deprivation index quintile (5 = most deprived; small area-based index incorporating metrics of education, employment, and income), ethnocultural background (extrapolated from country of birth and primary language spoken), and co -morbid conditions (mood disorders, alcohol or drug dependence; cancer, arthritis, HIV or chronic hepatitis, asthma or chronic obstructive pulmonary disease.

5.3 Supplementary Materials, Manuscript 3

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Supplemental Table 1. ICD codes

Condition	ICD-9	ICD-10	Capture period
Prior diabetes	250, 6480, 6488	E10-14, O245-O248	2 years prior to 20 weeks' gestation of first pregnancy – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
Prior hypertension	401-405, 642	I10-I13, I15, O10-O11, O13-O16	2 years prior to 20 weeks' gestation of first pregnancy – *2 outpatient diagnoses (within 2 years) or 1 inpatient diagnosis*
GDM	250, 6480, 6488	E10-14, O248	20 weeks' gestation of each respective pregnancy to 12 weeks' postpartum – *2 outpatient diagnoses or 1 inpatient diagnosis*
GHTN	401-405, 642	I10-I13, I15, O10-O11, O13-O16	20 weeks' gestation of each respective pregnancy to 12 weeks' postpartum – *2 outpatient diagnoses or 1 inpatient diagnosis*
Prior CVD[a]	325, 410-415, 427-444, 451-453, 6396, 671, 673, 6740, 7943, 9971-9972, 2506	I20-I26, I46-I52, I60-I70, I73-I74, I79-I82, I86, I97, R9430-R9431, E105, E115, E145, G08, G45-G46, H34, O882, O994, T817	2 years prior to index date (12 weeks' postpartum of 2nd delivery) – *2 outpatient diagnoses, 1 inpatient diagnosis or 1 related surgical procedure (angioplasty, endarterectomy or coronary artery bypass surgery)*
MI[b]	410	I21, R9430-R9431	After 12 weeks' following the 2nd delivery (index date) – *1 inpatient diagnosis or 1 related surgical procedure*
Stroke[b]	325, 3623, 430-438, 6740	I60-I66, I69, G08, G45-G46, H34, O882	After 12 weeks' following the 2nd delivery (index date) – *1 inpatient diagnosis or 1 related surgical procedure*
Angina	41190, 413	I20	After 12 weeks' following the 2nd delivery (index date) – *1 inpatient diagnosis or 1 related surgical procedure*
Mood disorders, alcohol or drug dependence	291-292, 295-305, 311 V11 V654	F10-F25, F30-F34, F38-F45, F48, F53, F99 R457 Z914 Z915 X65 Z714 Z864-Z865	2 years prior to index date (12 weeks' postpartum of 2nd delivery) – *2 outpatient diagnoses or 1 inpatient diagnosis*
Cancer	140-208, 230-234 V10 V167	C00-C97 D00-D09 D37-D48 Z85	2 years prior to index date (12 weeks' postpartum of 2nd delivery) – *2 outpatient diagnoses or 1 inpatient diagnosis*
Arthritis	274 6960, 710-721, 724	M05-M19, M32, M43, M46-M48, M53-M54, L405	2 years prior to index date (12 weeks' postpartum of 2nd delivery) – *2 outpatient diagnoses or 1 inpatient diagnosis*
HIV or chronic hepatitis	042-044, 7958 070, 5731-5733, 5714	B24, R75 Z21, F024, O987 B17-B19, K714-K715, K73, K77, O984, P353	2 years prior to index date (12 weeks' postpartum of 2nd delivery) – *2 outpatient diagnoses or 1 inpatient diagnosis*
Asthma or COPD	491-493, 496, 5181-5182	J44-J45	2 years prior to index date (12 weeks' postpartum of 2nd delivery) – *2 outpatient diagnoses or 1 inpatient diagnosis*

COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; GDM = gestational diabetes; GHTN= gestational hypertension; HIV = human immunodeficiency virus; MI = myocardial infarction

[a]Our definition of 'prior CVD' applied a broader series of ICD-codes than for the composite CVD outcome. While the composite outcome focused specifically on hospitalization or death related to myocardial infarction, stroke, or angina, the CVD-related exclusion criteria included codes related to both hospitalization and outpatient clinic visits and considered myocardial infarction, stroke, or angina, in addition to other CVD-related conditions, including atrial fibrillation, heart failure, other ischemic disease, other cardiac dysrhythmias, peripheral vascular disease and venous thromboembolism. We also excluded those with the following ***procedure codes*** related to pacemaker implantation, angioplasty, endarterectomy or coronary artery bypass surgery: 00460, 00631, 00662, 04022, 04030, 04031, 04037, 04046, 04601-04608, 04610-04612, 04661, 04662, 04665-04668, 04669, 04689, 04692-04699, 04701-04704, 04707-04709, 04710, 04713-04716, 04721-04723, 04725-04727, 04732-04737, 04740-04058, 09302, 20123, 20124, 20186, 20191, 20194, 20195, 20531, 20532, 20577-20583-20590

[b]The following procedure codes related to angioplasty, endarterectomy or coronary artery bypass surgery were included in our outcome definition of CVD: 00622, 00631, 04022, 04037,04601-08, 04610-12, 04710, 04725-27, 09302, 20123-24, 20186

Supplemental Methods

Omitted variables from statistical models (variable selection): Other variables that we considered but ultimately did not meet thresholds for inclusion in statistical models (see Statistical Analysis for inclusion criteria) were several paternal variables (age, ethnicity, diabetes, hypertension, and prior CVD), parental co-habitation, offspring congenital anomalies, offspring sex, the Institut national de santé publique du Québec (INSPQ) social deprivation index (as distinct from the material deprivation index; this index is based on the proportion of the population that are: [i] single-parent families, [ii] aged ≥15 years and living alone, and [iii] separated, divorced or widowed), placental abruption, and stillbirth (many stillbirths excluded based on our inclusion criteria requiring the same father for both offspring; there is an absence of paternal information in the Stillbirth registry).

Sensitivity analysis (adjusting for unmeasured confounders): Shin *et al.,* 2014 (1), Lash *et al.*, 2014 (2)

$$HR_{(\text{corrected for smoking})} = \frac{HR_{(\text{from our analysis})}}{HR_{(\text{related to smoking, from literature})}^{\,P_{se}-P_eP_s}}$$

Notation

P_{se} = proportion within specific GDM/GHTN category who smoke

P_e = proportion of those with specific GDM/GHTN category among all women with two consecutive singleton pregnancies

P_s = proportion of smokers among all women with two consecutive singleton pregnancies

$HR_{(\text{related to smoking, from literature})} = 1.58$ (3)

$HR_{(\text{related to obesity, from literature})} = 1.60$ (4)

GDM/GHTN occurrences from CCHS-derived cohort				
	No occurrences	**1 occurrence**	**2 occurrences**	**≥3 occurrences**
P_{se}: Proportion of Smokers (%, N)	24.6 (218/885)	22.6 (56/248)	27.9 (24/86)	16.7 (2/12)
P_{oe}: Proportion of Obese (%, N)*	11.3 (54/479)	19.9 (28/141)	25.0 (13/52)	60.0 (3/5)

*554 women missing BMI measures in CCHS, cycle 2.2

References

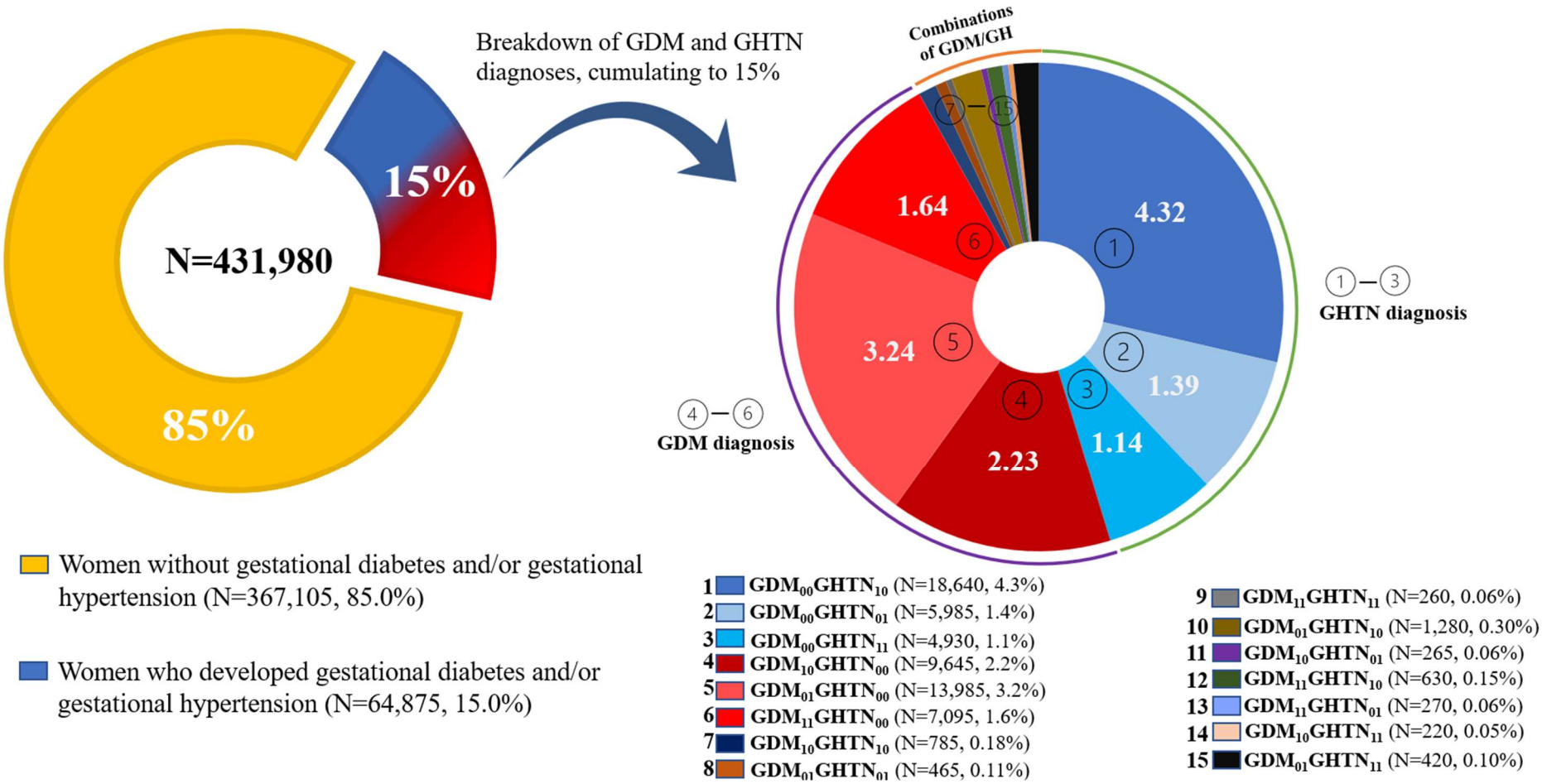
(1) Shin HH, Cakmak S, Brion O, Villeneuve P, Turner MC, Goldberg MS, Jerrett M, Chen H, Crouse D, Peters P, Pope CA 3rd, Burnett RT. Indirect adjustment for multiple missing variables applicable to environmental epidemiology. Environ Res. 2014 Oct;134:482-7. doi: 10.1016/j.envres.2014.05.016. Epub 2014 Jun 24. PMID: 24972508.

(2) Lash TL, Fox MP, MacLehose RF, Maldonado G, McCandless LC, Greenland S. Good practices for quantitative bias analysis. Int J Epidemiol. Dec 2014;43(6):1969-85. doi:10.1093/ije/dyu149

(3) Khan SS, Ning H, Sinha A, Wilkins J, Allen NB, Vu THT, Berry JD, Lloyd-Jones DM, Sweis R. Cigarette Smoking and Competing Risks for Fatal and Nonfatal Cardiovascular Disease Subtypes Across the Life Course. J Am Heart Assoc. 2021 Dec 7;10(23):e021751. doi: 10.1161/JAHA.121.021751. Epub 2021 Nov 17. PMID: 34787470; PMCID: PMC9075374.

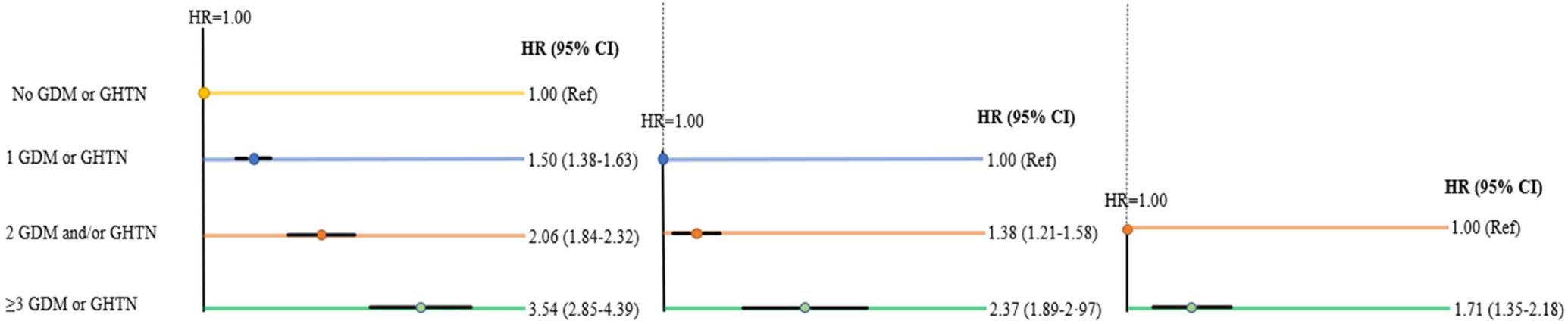
(4) Mongraw-Chaffin ML, Peters SAE, Huxley RR, Woodward M. The sex-specific association between BMI and coronary heart disease: a systematic review and meta-analysis of 95 cohorts with 1·2 million participants. Lancet Diabetes Endocrinol. 2015 Jun;3(6):437-449. doi: 10.1016/S2213-8587(15)00086-8. Epub 2015 May 7. PMID: 25960160; PMCID: PMC4470268.

Supplemental Figure 1. Distribution of specific gestational diabetes and gestational hypertension exposure categories



We created 16 exposure categories, labelled as GDMXYGHTNXY where a 1 in the subscript indicates condition present, 0 indicates absence, and the order of the digits corresponds to first (X) or second (Y) pregnancy: GDM$_{00}$GHTN$_{00}$ [reference], GDM$_{00}$GHTN$_{10}$, GDM$_{00}$GHTN$_{01}$, GDM$_{00}$GHTN$_{11}$, GDM$_{01}$GHTN$_{00}$, GDM$_{01}$GHTN$_{10}$, GDM$_{01}$GHTN$_{01}$, GDM$_{01}$GHTN$_{11}$, GDM$_{10}$GHTN$_{00}$, GDM$_{10}$GHTN$_{10}$, GDM$_{10}$GHTN$_{01}$, GDM$_{10}$GHTN$_{11}$, GDM$_{11}$GHTN$_{00}$, GDM$_{11}$GHTN$_{10}$, GDM$_{11}$GHTN$_{01}$, GDM$_{11}$GHTN$_{11}$.

Supplemental Figure 2: Associations between CVD outcomes and number of gestational diabetes and gestational hypertension occurrences in secondary cohort (N=437,680), including those with development of diabetes and/or hypertension between pregnancies



We redefined the cohort to retain those who developed diabetes and those who developed hypertension between pregnancies (secondary cohort). We then expanded the 'GDM second pregnancy' and 'GHTN second pregnancy' groups to be 'GDM second pregnancy or diabetes between pregnancies' and 'GHTN second pregnancy or hypertension between pregnancies' before collapsing by the total number of occurrences.

Supplemental Table 2: Adjusted CVD hazard ratios for specific combinations of GDM/GHTN exposures across two pregnancies in secondary cohort (N=437,680), including those with development of diabetes and/or hypertension between pregnancies

Adjusted hazard ratios for CVD (95% CI)	**No GDM in either pregnancy**	**GDM only in 1st pregnancy**	**GDM in 2nd pregnancy or diabetes between pregnancies**	**GDM in both pregnancies or GDM in 1st pregnancy and diabetes between pregnancies**
No GHTN in either pregnancy	Reference[a]	1.38 (1.15-1.65)	1.40 (1.20-1.63)	1.86 (1.56-2.20)
GHTN only in 1st pregnancy	1.53 (1.35-1.74)	2.00 (1.20-3.32)	1.83 (1.19-2.81)	2.71 (1.73-4.26)
GHTN in 2nd pregnancy or hypertension between both pregnancies	1.77 (1.46-2.13)	1.68 (0.70-4.04)	3.12 (1.98-4.90)	3.21 (1.86-5.54)
GHTN in both pregnancies or GHTN in 1st pregnancy and hypertension between pregnancies	2.31 (1.93-2.76)	2.68 (1.28-5.63)	3.55 (2.30-5.45)	5.73 (3.86-8.50)

We redefined the cohort to retain those who developed diabetes and those who developed hypertension between pregnancies (secondary cohort); we then expanded the 'GDM second pregnancy' and 'GHTN second pregnancy' groups to be 'GDM second pregnancy or diabetes between pregnancies' and 'GHTN second pregnancy or hypertension between pregnancies'.

Supplemental Table 3. Adjusted hazard ratios for covariates included in the final model

Covariate[a]	HR (95% CI)
Offspring size[b]	
AGA: both offspring	**Reference**
SGA: 1st offspring only	1.22 (1.09-1.38)
SGA: 2nd offspring only	1.28 (1.14-1.44)
SGA: both offspring	1.98 (1.72-2.27)
LGA: 1st offspring only	0.93 (0.81-1.07)
LGA: 2nd offspring only	1.00 (0.87-1.14)
LGA: both offspring	1.12 (0.93-1.34)
SGA: 1st offspring , LGA: 2nd offspring	0.77 (0.29-2.05)
LGA: 1st offspring , SGA: 2nd offspring	1.06 (0.47-2.35)
Gestational age of offspring at birth[c]	
Term birth: both offspring	**Reference**
Preterm birth: 1st offspring only	1.26 (1.11-1.44)
Preterm birth: 2nd offspring only	1.38 (1.20-1.59)
Preterm birth: both offspring	1.63 (1.30-2.04)
Age of mother at 2nd delivery, years[d]	
<25	**Reference**
25-30	0.94 (0.85-1.03)
30-35	1.09 (0.99-1.21)
≥35	1.50 (1.34-1.68)
Time between deliveries, years	
<2	**Reference**
2-2.5	0.97 (0.89-1.06)
2.5-3.5	0.90 (0.83-0.98)
≥3.5	1.02 (0.93-1.11)
Material deprivation index, quintiles[e]	
1 (least deprived)	**Reference**
2	1.22 (1.11-1.36)
3	1.26 (1.13-1.39)
4	1.39 (1.25-1.54)
5 (most deprived)	1.70 (1.54-1.88)
Background[f]	
America, Australia or Europe	**Reference**
Africa or Caribbean	1.10 (0.91-1.35)
Arab-speaking regions	0.71 (0.59-0.87)
Asia	0.64 (0.52-0.78)
Other	1.02 (0.88-1.19)
Co-morbid conditions[g]	
Mood disorders, alcohol or drug dependence	1.41 (1.23-1.62)
Cancer	1.95 (1.35-2.81)
Arthritis	1.37 (1.15-1.64)
HIV or chronic hepatitis	2.58 (1.64-4.06)
Asthma or COPD	1.52 (1.27-1.81)

CI = confidence interval COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; HR = hazard ratio

[a]The model adjusts for the totality of GDM/GHTN occurrences across pregnancies, as well as each of the variables listed.

[b]We observed a stepwise increase in CVD hazards with increasing occurrences of SGA offspring. Compared to AGA offspring in both pregnancies, SGA in the first (HR=1.22, 95%CI 1.09-1.38) or second (HR=1.28, 95%CI 1.14-1.44) only was associated with a similar increase in CVD hazards, while SGA in both pregnancies was associated with nearly a doubling of CVD hazards (HR=1.98, 95%CI 1.72-2.27). Having SGA in one pregnancy and LGA in another was an infrequent occurrence with no conclusive associations for such combinations. CVD incidence also rose in tandem with the number of SGA offspring (no SGA offspring, 0.55/1000 person years; SGA 1st, 0.71/1000 person years; SGA 2nd, 0.74/1000 person years; SGA both, 1.19/1000 person years). 150 offspring were missing birthweight required to derive offspring size.

[c]Compared to women without preterm delivery, preterm in the first (HR=1.26, 95%CI 1.11-1.44) or second (HR=1.38, 95%CI 1.20-1.59) only was associated with some increase in CVD hazards, while preterm delivery in both pregnancies was associated with the greatest increase (HR=1.63, 95%CI 1.30-2.04). CVD incidence also rose in tandem with the number of preterm births (no preterm, 0.56/1000 person years; preterm 1st, 0.75/1000 person years; PTB 2nd, 0.86/1000 person years; PTB both, 1.01/1000 person years). The incidence rates were also higher with more LGA offspring, but over a more restricted range (no LGA, 0.55/1000 person years; LGA 1st, 0.52/1000 person years; LGA 2nd, 0.57/1000 person years; LGA both, 0.66/1000 person years).

[d]Women who were 35 years of age or older at baseline had 50% higher hazards for CVD (HR=1.50 [95%CI 1.34-1.68) than those under 25 years of age.

[e]We observed a stepwise increase in CVD hazards with increasing material deprivation. Hazards were at least 22% higher for the 2nd (HR=1.22 [95%CI 1.11-1.36]) and 3rd quintiles (HR=1.26 [95%CI 1.13-1.39]); 39% higher for the 4th quintile (HR=1.39 [95%CI 1.25-1.54]) and 70% higher for the 5th (HR=1.70 [95%CI 1.54-1.88]). 7335 women were missing a value for the INSPQ material deprivation index.

[f]Compared to women of Europid descent, those from Arab-speaking regions (HR=0.71 [95%CI 0.59-0.87]) or of Asian descent (HR=0.64 [95%CI 0.52-0.78]) demonstrated 29% and 36% lower hazards of developing CVD, respectively, during the follow-up period.

[g]The reference group are women with the absence of each condition, respectively. The presence of each co-morbid condition was associated with higher CVD hazards. Co-morbid conditions were defined in accordance with the Chronic Disease Surveillance System's definition of chronic disease, requiring ≥1 inpatient or ≥2 outpatient ICD codes to be present within 2 years prior to the index date.

Chapter 6: Manuscript 4

6.1 Preface

There is a well-established global agreement regarding the levels of blood pressure that indicate GHTN during pregnancy. However, there has been a lack of consistency in determining the glucose levels that define GDM over the years, resulting in the reported prevalence to fluctuate between 2-16% in Canada. Given the utilization of diagnostic codes from health administrative databases to identify women with GDM as components of my primary exposure in Manuscripts 1 and 3, I conducted a scoping review that addresses the developing algorithms for the screening of GDM over the last three decades, as recommended by different renditions of clinical practice guidelines released by Diabetes Canada and the Society of Obstetricians and Gynecologists of Canada, the nation's largest obstetric and diabetes organizations. Findings from my scoping review discuss the various screening and diagnostic approaches that were recommended and practiced by physicians across Canada over the years, reasons for why this discrepancy existed, and levels of uptake of the most recent GDM guideline recommendations among Canadian physicians (physician survey). Building on my previous thesis objectives, I also discuss the implications of accounting for these temporal trends when including calendar years within Cox PH models for each outcome of interest (diabetes, hypertension, and CVD; see **Chapter 7.4)**.

This manuscript entitled "Trends in National Canadian Guideline Recommendations for the Screening and Diagnosis of Gestational Diabetes Mellitus over the Years: A Scoping Review" was published in 2021 and has been cited 16 times to date (Mussa J, Meltzer S, Bond R, Garfield N, Dasgupta K. Trends in National Canadian Guideline Recommendations for the Screening and Diagnosis of Gestational Diabetes Mellitus over the Years: A Scoping Review. *Int J Environ Res Public Health*. 2021 Feb 4;18(4):1454.)

Trends in National Canadian Guideline Recommendations for the Screening and Diagnosis of Gestational Diabetes Mellitus over the Years: A Scoping Review

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Abstract

Canada's largest national obstetric and diabetology organizations have recommended various algorithms for the screening of gestational diabetes mellitus (GDM) over the years. Though uniformity across recommendations from clinical practice guidelines (CPGs) is desirable, historically, national guidelines from Diabetes Canada (DC) and the Society of Obstetricians and Gynecologists of Canada (SOGC) have differed. Lack of consensus has led to variation in screening approaches, rendering precise ascertainment of GDM prevalence challenging. To highlight the reason and level of disparity in Canada, we conducted a scoping review of CPGs released by DC and the SOGC over the last thirty years and distributed a survey on screening practices among Canadian physicians. Earlier CPGs were based on expert opinion, leading to different recommendations from these organizations. However, as a result of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, disparities between DC and the SOGC no longer exist and many Canadian physicians have adopted their recent recommendations. Given that Canadian guidelines now recommend two different screening programs (one step vs. two step), lack of consensus on a single diagnostic threshold continues to exist, resulting in differing estimates of GDM prevalence. Our scoping review highlights these disparities and provides a step forward towards reaching a consensus on one unified threshold.

Keywords: clinical practice guidelines; gestational diabetes mellitus; pregnancy; diabetes mellitus; neonatal complications; national; screening; diagnosis; one step; two step; prevalence

1. Introduction

In Canada, gestational diabetes mellitus (GDM) is the most frequent endocrinopathy of pregnancy [1]. It is defined as glucose intolerance resulting in hyperglycemia with first recognition or new onset during pregnancy, but the specific glycemic thresholds for its diagnosis are a persistent subject of debate. Notwithstanding differences in definitions and their application over the last three decades, the prevalence of GDM is rising around the world [2]. Increases in obesity rates, maternal age, and ethnic diversity and changes in diagnostic thresholds have likely contributed to this shift.

In Canada, as in much of the world, there has been debate concerning: (a) the appropriate timing and method for screening, specifically the utility of a 50 g glucose challenge test (GCT) prior to an oral glucose tolerance test (OGTT) with a higher glucose load (one step vs. two step approach); (b) what constitutes the most appropriate glucose load (e.g., 75 g vs. 100 g in glucose tolerance testing); (c) the specific glucose threshold values above which a test is considered abnormal at different time points following the glucose load; and (d) the number of abnormal values required to warrant a GDM diagnosis [3]. Although the hyperglycemia observed in GDM typically resolves post-partum, GDM history is a risk factor for incident diabetes mellitus [4], hypertension [5], and cardiovascular disease later in life [6]. The original definitions of GDM were conceived with a focus on the future risk of maternal diabetes mellitus [7]. However, GDM is associated with other short-term and long-term health outcomes in both the mother and her offspring that are now considered in selecting diagnostic thresholds [3,8].

Since the initiation of the 2008 Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [8], there have been a growing number of epidemiological analyses based on HAPO data and other data sources demonstrating compelling evidence of associations between GDM and a wide array of adverse neonatal complications [9–13]. In the shorter term, several analyses have demonstrated that maternal glucose intolerance may increase risk of pre-term delivery, perinatal morbidity and mortality, neonatal hypoglycemia, macrosomia, neonatal hyperinsulinemia, and congenital malformations [8–10]. In the longer term, GDM is also associated with offspring complications such as childhood obesity, dyslipidemia, and future diabetes mellitus later in life [11–13].

Given the consequences that GDM may have on both the health of the mother and her offspring, it is important to detect its presence in pregnancy as early as possible. Though uniformity across recommendations from Canadian clinical practice guidelines (CPGs) is desirable and would be less

confusing for practitioners, historically, national guidelines from two key organizations, Diabetes Canada (DC) and the Society of Obstetricians and Gynecologists of Canada (SOGC) have differed. In this scoping review, we discuss: (1) the evolution of national recommendations for the screening of GDM in Canada over the last thirty years by both DC (formerly known as the Canadian Diabetes Association) and the SOGC; (2) the degree of variability in screening practices adopted by Canadian health care providers in their practice; and (3) the impact of varying diagnostic criteria on the estimates of GDM prevalence in Canada.

2. Study Design and Methods

We conducted a scoping review of CPGs from DC and the SOGC and a voluntary, online survey of health care providers dedicated to GDM care.

2.1 Search Strategy

Published literature was retrieved through searches in five electronic bibliographic databases (The Cochrane Library, PubMed, CINAHL, Web of Science and SCOPUS) from 1 January 1964 to 30 November 2020. Subject headings and key MeSH terms included "national recommendations", "clinical practice guidelines", "diabetes mellitus", "pregnancy", "gestational diabetes mellitus", "screening", "diagnosis", "one step" and "two step". The search strategy was based on three key concepts: (1) pregnancy (study population); (2) GDM (exposure); and (3) screening and diagnostic parameters (outcome). Restrictions for language (limited to English and/or French materials) and geographic location (Canada; limited to national-level recommendations) were applied. In addition, the reference lists of all identified CPGs were examined to identify other Canadian national guidelines not captured in our search. The electronic search and the eligibility of the guidelines were independently assessed by two reviewers (JM, KD) and discrepancies were resolved through discussion.

In addition, several interviews were conducted with one of the co-authors (SM) to discuss the history of GDM screening and aid in the identification of key Canadian guidelines over the years. SM served as the Steering committee co-chair in the development of the 1998 DC CPG for the management of diabetes in Canada; she holds extensive, substantive knowledge on the diagnostic criteria recommended by Canadian CPGs over the years.

2.2 CPG Selection and Data Extraction

CPG recommendations were retained if they met the following criteria: (1) CPGs included recommendation for screening, diagnosing, and managing diabetes mellitus during pregnancy; (2) recommendations were made at the national level (CPGs specific to a local region of Canada were excluded). Abstracts, case reports, study protocols, commentaries, observational studies, reviews, randomized controlled trials, and meta-analyses were excluded. The full-text articles of all relevant guidelines were reviewed (JM).

Data extraction captured the following information from CPGs retained: (1) year of publication; (2) recommended population for GDM screening; (3) method/test for screening and diagnosis; (4) number of abnormal values required for diagnosis; (5) glucose thresholds to warrant a GDM diagnosis after initial screening test and/or diagnostic testing (fasting glucose, 1 h after loading, 2 h after loading, 3 h after glucose load); (6) estimated prevalence of GDM. One author (JM) extracted data from all eligible CPGs which underwent review by another (KD). Discrepancies were resolved through discussion.

2.3 Survey Distribution

We also conducted a survey among physicians from the Canadian Diabetes in Pregnancy (CanDIPS) study group to determine what GDM screening practices they are currently using in clinical practice (Figure A1). The survey link was distributed to CanDIPS members via electronic mail by one of the co-authors (RB).

3 Results

3.1 Search Results

The initial search identified 38 CPGs. A total of nine CPGs were screened for eligibility after removal of duplicates ($n = 6$) and local CPGs specific to a region in Canada ($n = 23$). In total, nine national CPGs were retained (Figure 1).

3.2 CPG Characteristics

National guidelines were published by the SOGC [14–17], the largest national obstetrical society, and DC [18–22], the largest national society of diabetology. Since the release of the first Canadian

CPGs to address diabetes during pregnancy by the SOGC in 1992 [14], this organization released subsequent, updated versions of its guidelines in 2002 [15], 2016 [16] and 2019 [17]. DC released five national guidelines on screening, diagnosing and managing GDM in Canada; these include the first release in 1998 [18] followed by revised guidelines published in 2003 [20], 2008 [20], 2013 [21] and 2018 [22].

Several key differences in recommendations regarding the necessity and benefits of universal screening, the appropriate method for GDM screening, and appropriate glucose cut-off thresholds exist between national guidelines published from each of these societies.

3.3 The Origin of Defining GDM

The increased risk of obstetrical complications associated with GDM was first detailed in an issue of *Diabetes* authored by Dr. J.P. Hoet in 1954 [23]. Shortly after the release of this publication, the National Institutes of Health (US) initiated a program focused on the epidemiology of chronic disease, a program joined by Dr. John O'Sullivan in the late 1950s [24]. During the era following World War II, there was widespread interest and controversy around the globe regarding the method of diagnosing GDM among pregnant women. At this time, Canadian physicians relied on "elevated" glucose values following a 100 g OGTT to warrant a diagnosis of GDM; thresholds were defined vaguely and left to the interpretation of the individual physician.

To generate evidence, Dr. O'Sullivan conducted a prospective cohort study (New York, NY, USA) [7]. He challenged 752 pregnant women in their second or third trimester ("pregnancy cohort") with 100 g oral glucose loads and measured whole blood glucose levels, at baseline, 1 h, 2 h, and 3 h after the load, using the Nelson–Somogyi method and rounding to the nearest whole number. He calculated the means and standard deviations (SD) at each of these time points, considering two SD above the mean to be elevated, such that 5% of the pregnancy cohort would be considered abnormal. Applying only one SD and corresponding glucose thresholds would have resulted in a higher proportion of women to have been considered to have GDM [25]. O'Sullivan believed that this would lead to psychologic ill effects (i.e., depression, anxiety, eating disorders) and unnecessary long-term follow up of patients with only mild glucose intolerance [7]. These concerns were expected to pose significant increases in economic burden, while only offering minimal benefit towards preventing maternal diabetes mellitus later in life. Similar concerns are part of today's debates concerning optimal screening methods.

Subsequently, O'Sullivan and statistician, Dr. Mahan, defined GDM as two or more elevated values of glucose among the four time points. This definition was published as the first set of statistically-based criteria to define glucose intolerance during pregnancy in 1964 (fasting, 5.0 mmol/L; 1 h, 9.2 mmol/L; 2 h, 8.1 mmol/L; 3 h, 6.9 mmol/L) [7]. O'Sullivan conducted several follow-up studies during the 1960s and re-applied his pre-defined thresholds of "elevated glucose" to define GDM among a different group of 1013 women tested during pregnancy. Women were followed for 5–10 years post-partum and results indicated that 22% of women with GDM in the cohort later developed diabetes mellitus within 7–8 years after their pregnancy [26]. These findings were consistent with several holding theories at the time explaining that GDM may be associated with post-partum maternal diabetes mellitus; shortly after publication, his criteria were accepted on the basis of risk assessment for future maternal diabetes mellitus [18,26,27].

3.4 Evolution in Screening Approaches: Early Adoption of the 50 g GCT

Some physicians in Canada had slowly begun to adopt thresholds proposed by O'Sullivan due to their increasing recognition in the late 1960s to early 1970s [12,24]. Individual physicians used their own discretion to decide who required a 100 g OGTT. At this time, the physician's decision was based on the presence of known risk factors for GDM during this period, which were predominantly limited to renal glycosuria during pregnancy, previous history of large infants at birth, and family history of diabetes mellitus [25]. However, in the pregnancy cohort followed by O'Sullivan, restricting screening to those defined as "at risk" by these risk factors demonstrated insufficient sensitivity (63%) and specificity (57%) for the detection of GDM [28]; 37–50% of women with GDM would remain undiagnosed [28,29]. In 1973, O'Sullivan and Mahan recommended the use of a screening test in all pregnant women, the 50 g 1 h glucose challenge test (GCT), to improve the detection of women with GDM without the need to subject all of these women to a longer 100 g tolerance test [28]. Using the Nelson–Somogyi method, a threshold of 7.2 mmol/L at one hour post-ingestion of the 50 g glucose load was 79% sensitive and 87% specific for GDM in his pregnancy cohort [7]. Although O'Sullivan demonstrated the positive predictive value (PPV) of the 50 g GCT to be merely 14%, the negative predictive value (NPV) was 99.4%; these results indicate that 50 g GCT screening tests produced an excess of false positives but minimal false negative results [12]. Since the pregnancy cohort underwent both the 50 g GCT screening test followed by a 100 g OGTT, O'Sullivan's proposed method allowed for strong GDM case ascertainment, which quickly became adopted as the gold standard.

3.5 Evolution of O'Sullivan's Proposed Criteria

In the late 1970s, the US National Diabetes Data Group (NDDG) endorsed O'Sullivan's criteria with several slight modifications, but determined that plasma glucose should be used instead of whole blood values [30]; therefore, they increased the diagnostic thresholds (to FPG 5.8 mmol/L; 1 h 10.6 mmol/L; 2 h 9.2 mmol/L; 3 h 8.0 mmol/L) given that the glucose content present in whole blood is less than that found in plasma (Table 1). With endorsement from the NDDG, widespread screening for GDM using these modified criteria grew rapidly across the globe, including application in clinical practice among many Canadian physicians during the mid 1980s. In 1982, Drs. Carpenter and Coustan proposed replacing the Nelson–Somogyi method with more accurate enzyme-based assays [31]. The Nelson–Somogyi method measures all reducing substances present in whole blood and is not specific for glucose; this typically results in glucose measurements 11–15% higher than more specific enzyme-based assays [25]. With these assays, Drs. Carpenter and Coustan lowered the diagnostic cut off for GDM relative to values proposed by the NDDG (Table 1). In Canada during the 1980s, physicians variously implemented the O'Sullivan, NDDG, and Carpenter–Coustan criteria. These reference thresholds were an improvement over the more subjective approaches to GDM diagnosis that had previously been used, yet there remained a wide variation in clinical practice.

3.6 Universal vs. Selective Screening

The 1992 SOGC CPG [14] recommended universal screening at 24 to 28 weeks with the 50 g GCT and progression to a 100 g OGTT if glucose values met or exceeded 7.8 mmol/L (1 h post-glucose ingestion). In fact, 84% of Canadian physicians at this time had adopted this approach even prior to the 1992 SOGC guidelines, given the validation of the 50 g GCT screening test (improved sensitivity and specificity) by O'Sullivan twenty years prior [15]. Several years later, the second Canada-wide CPG to encompass diabetes mellitus in pregnancy was published by DC in 1998 [18]. Emerging evidence at this time suggested that women at low risk could be exempt from screening [32]. Selective screening was endorsed in the 1998 DC CPGs and subsequently adopted by the 2002 SOGC guidelines. Advantages of selective screening were reductions in the burden of screening on pregnant women and the health care system. Low-risk individuals were defined as those 25 years of age or younger, pre-pregnancy BMI <27 kg/m2 (the SOGC) or "non-obese" (DC), Caucasian ethnicity or other ethnic group with low diabetes mellitus prevalence, no previous history of GDM or glucose intolerance, no history of GDM-associated adverse pregnancy outcomes (i.e.,

macrosomia) and no family history of diabetes mellitus in first-degree relatives [15,18]. Despite these recommendations, many physicians in Canada still chose to practice universal screening since the majority of pregnant women do not meet all criteria needed to be considered low-risk [12,33]. In 2003, DC revised their national guidelines to recommend universal screening [19]. Since the release of their 2003 CPG, DC have consistently advocated for universal screening in their 2008, 2013 and 2018 CPGs because the expert panel holds that: (a) selective screening allows for undiagnosed cases of GDM among women who do not have risk factors [34]; (b) most Canadian women (90%) do not meet the criteria to be considered low risk, rendering selective screening complicated and unnecessary (supported by evidence from a cohort of 1655 pregnant women in Australia [35]); and (c) although more expensive in the short-term, universal screening for GDM may reduce the long-term costs and burden of future complications in the mother and offspring [18–21,36]. After its 2002 CPGs, the SOGC did not provide an update until 2016. The 2002 guidelines had recommended selective screening and the physicians' choice between a 75 and 100 g OGTT. In 2016, the SOGC aligned with the 2013 DC CPGs, recommending that all pregnant women be screened at 24 to 28 weeks' gestation with a 75 g OGTT [16].

3.7 Diagnostic Approaches: Variations in the Testing Times and Recommended Glucose Loads to Be Administered for OGTT

The 1992 SOGC guidelines recommended the 50 g GCT followed by a 100 g 3 h OGTT with at least two abnormal values to warrant a diagnosis of GDM. During this time, the application of a 50 g GCT (screening test) followed by a 100 g 3 h OGTT (diagnostic test) was commonly practiced in most countries [12]. The 1998 DC guidelines advocated the 75 g 2 h OGTT with at least two abnormal values as the preferred diagnostic method following a 50 g GCT screening test. The recommendation for a 75 g OGTT was based on the fact that:
(a) non-pregnant criteria for diabetes mellitus were based on a standardized 75 g OGTT and (b) the test allows for less blood sampling, less time for testing, lower costs, and less nausea as a result of the lower glucose load administered [18]. However, they retained the 100 g 3 h OGTT as an alternative option given its widespread application in North America but with specification of Carpenter–Coustan thresholds. Carpenter–Coustan thresholds are more inclusive with lower values of 5.3, 10.0, 8.6 and 7.8 mmol/L (Table 1).

Similarly, in 2002, the SOGC adopted the 75 g 2 h OGTT as a diagnostic tool with at least two abnormal values [15], in addition to the 100 g OGTT that its previous guidelines had endorsed [14]. The adoption of the 75 g OGTT approach was consistent with recommendations from the 1998 DC, 1998 American Diabetes Association, 1999 World Health Organization and 2001 American Congress of Obstetricians and Gynecologists guidelines available at the time. Both options were included due to an "absence of clear, comparative trials" [15]. The 2002 SOGC guidelines applied Carpenter–Coustan criteria to the 75 g OGTT while recommending both NDDG or Carpenter–Coustan thresholds for the 100 g OGTT (Table 1), the latter test having higher test sensitivity for GDM relative to the 75 g OGTT. Eventually, the 100 g 3 h OGTT alternative was removed in the revised 2003 DC guidelines due to the inconvenience, poor tolerance and costs associated with the three hour test [19]. DC guidelines continued to require all women to be screened via 50 g GCT and at least two abnormal values of plasma glucose during an OGTT to identify GDM in their 2003 guidelines. Similarly, upon the SOGC's recent updates in 2016 and 2019, their guidelines also have removed recommendations for the 100 g OGTT and endorse that Canadian providers apply the 75 g OGTT for diagnostic purposes [16,17].

3.8 Variation in Screening and Diagnostic Approaches: Debates on Glucose Thresholds Prior to Efforts for International Consensus in 2008

All of the 1992/2002 SOGC and 1998/2003/2008 DC recommendations were based on substantive expert opinion due to a scarcity of high-quality evidence at this time [33]. The early versions of the SOGC (1992, 2002) and DC (1992, 2003, 2008) share consensus on several criteria including: (a) applying the 50 g GCT screening technique; (b) the requirement of plasma glucose levels > 7.8 mmol/L (at 1 h post-ingestion) following a 50 g GCT to allow for progression towards an OGTT; (c) the requirement of plasma glucose levels >10.3 mmol/L (at 1 h post-ingestion) following a 50 g GCT to warrant an immediate diagnosis of overt diabetes mellitus; and (d) two abnormal OGTT values to conclude a diagnosis. However, over the years, there has been uncertainty about the specific levels of plasma glucose required to prevent complications in the mothers and offspring. Therefore, the cut-off thresholds warranting a diagnosis of GDM following a 100 g and 75 g OGTT have typically differed across these organizations over the years.

In terms of diagnostic approaches using the 100 g OGTT approach, guidelines from the 1992/2002 SOGC differ slightly from those proposed by the 1998 DC guideline. The early SOGC guidelines [14,15] suggested application of both Carpenter–Coustan and NDDG criteria when conducting the 100 g OGTT (Table 1) and were based on earlier guidelines from American Congress of Obstetricians and Gynecologists. They suggested that physicians consider either threshold, given insufficient evidence demonstrating clear benefit of one set of criteria over another. In contrast, the 1998 DC guideline [18] recommended only Carpenter–Coustan criteria be applied to define glucose thresholds following administration of the 100 g OGTT (alternative approach), as also recommended by the 1998 American Diabetes Association. Application of Carpenter–Coustan criteria generally leads to increased test sensitivity, given that the thresholds are lower relative to NDDG criteria and thus more inclusive.

Although both the 2002 SOGC and 1998/2003/2008 DC guidelines allowed for diagnostic testing using the 75 g OGTT, cut-off thresholds using this approach differed across guidelines published from these two organizations. The 2002 SOGC's recommendations for 75 g OGTT thresholds [15] are based primarily on Carpenter–Coustan criteria as applied to the 100 g OGTT with no inclusion of upper NDDG criteria, given that women are administered a smaller glucose load relative to the 100 g OGTT (Table 1). Meanwhile, the guidelines from the 1998/2003/2008 DC guidelines had suggested higher thresholds relative to the lower thresholds from the 2002 SOGC guidelines when testing with a 75 g OGTT (Table 1). The DC expert panel argue that the previous Carpenter–Coustan and NDDG criteria are based on O'Sullivan's original data from the pregnancy cohort; the mean fasting levels of glucose found in two prospective, multicentre studies (~4000 pregnant women) were slightly different [37,38]. The derivation of 2 SD above the mean plasma glucose in these cohort of women leads to thresholds that lie between the Carpenter–Coustan and NDDG criteria, as suggested in their proposed thresholds.

3.9 The HAPO Study and Application of Its Results by the International Association of Diabetes and Pregnancy Study Groups (IADPSG)

Although estimates of GDM prevalence can be derived from health administrative database definitions for GDM that rely on physician billing and hospitalization diagnostic codes, the widespread variations in screening approaches result in varying definitions of GDM over the years

(based on available guidelines at this time) and across physicians (Table 1). The 2008 HAPO study [8] was conducted in response to the persistent need for a standardized, internationally-agreed-upon GDM diagnostic criteria that took into account both maternal and offspring outcomes. The original investigation was a multicentre, five-year, prospective cohort study. The investigators recruited more than 25,000 pregnant women in nine countries between July 2000 and April 2006 willing to undergo a 75 g OGTT between 24 and 32 weeks of gestation. Participants were ethnically diverse, consisting of 48% European origin, 29% Asian origin, 12% African origin, and 8% Hispanic origin [8]. The four primary outcomes included cesarean delivery, clinical neonatal hypoglycemia (as noted in medical records),
LGA status (defined as birth weight > 90th percentile for gestational age, sex, ethnicity, parity) and hyperinsulinemia (cord serum C-peptide >90th percentile for the study group as a whole). Secondary outcomes included pre-term birth, shoulder dystocia, preeclampsia, admission for neonatal intensive care, percent body fat and hyperbilirubinemia.

For categorical analyses, fasting plasma glucose (FPG) levels were classified a priori into seven different categories each in 0.2775 mmol/L increments representing the SD of that value. A similar method was applied to categorize plasma glucose septiles corresponding to 1 and 2 h post-75 g glucose loading. These analyses demonstrated that the association between categorized maternal glucose and frequency of each of the primary outcomes was linear and continuous across time points. The HAPO investigators did not conclude any specific recommendations, given that their analyses demonstrated no clear threshold at which to define GDM, further fuelling controversies around appropriate cut-off points to guide systems of care. Subsequently, a meeting was convened in Pasadena under the umbrella of the IADPSG to develop a consensus regarding the appropriate diagnostic criteria, given findings from the HAPO study. During the workshop conference in 2008, the IADPSG panel agreed that several of the adverse outcomes initially studied were not equally important for devising diagnostic criteria; the panel concluded that hyperinsulinemia based on C-peptide, neonatal body fat and LGA outcomes should comprise the basis for determining diagnostic thresholds, considered as one composite primary outcome [9]. At each time point, individuals with blood glucose within the third septile (representing the mean) were chosen as the reference and compared to those with mean glucose higher by 1 SD (0.38 mmol/L for FPG, 1.71 mmol/L for 1 h PG, 1.30 mmol/L for 2 h PG) to produce ORs for the composite outcome developed by the IADPSG. The IADPSG considered ORs of 1.5, 1.75 and 2.0, and ultimately focused on an OR of

1.75, defining diagnostic thresholds (fasting glucose: 5.1 mmol/L, 1 h glucose: 10.0 mmol/L, 2 h glucose: 8.5 mmol/L) in terms of correspondence to 75% increased odds (OR = 1.75) of cord serum C-peptide > 90th percentile, neonatal body fat > 90th percentile, and LGA at each time point. Setting thresholds based on an OR = 1.5 was believed to lead to a diagnostic test with low PPV (generating an excess of false positives) with 20% being diagnosed with GDM [9]. Of note, the 2 h glucose threshold corresponding to OR = 1.5 was 7.8 mmol/L which was also the 2 h glucose threshold used to diagnose GDM in other earlier guidelines (i.e., 1999 World Health Organization). Glucose thresholds corresponding to an OR = 2.0 were believed by the IADPSG to lack sensitivity. Thresholds corresponding to an OR = 1.75 identified 16.1% incidence in the HAPO cohort [9].

In addition to the glucose thresholds, the IADPSG investigators also decided that only one abnormal OGTT value should be required to conclude a diagnosis of GDM, given that the corresponding glucose thresholds were modelled independently across each time point. They further recommended directly conducting a 75 g OGTT without the necessity for a 50 g GCT screening test (one-step approach) since women in the cohort did not undergo 50 g GCT screening and glucose thresholds corresponding to 75% increased odds of the primary outcome were modelled solely considering OGTT values. In addition, a one-step test was endorsed as the preferred method by the IADPSG due to the ease of administrating the test, given that a woman may not always return to the clinic for an OGTT following screening. The IADPSG task force has also endorsed universal screening and recommended that a fasting plasma glucose > 7 mmol/L or HbA1c > 6.5% discovered in the early stages of pregnancy (before 24 weeks) should be identified as pre-existing diabetes mellitus. These recommendations are published in the 2010 IADPSG guidelines [9].

3.10 Uniform CPG Recommendations: Recent Trends in Glucose Thresholds and Updated CPGs in Response to the 2008 HAPO Trial and the 2010 IADPSG Guidelines

The plasma glucose cut off suggested in the 2013 DC recommendations were the first Canadian guidelines to adopt the findings from the IADPSG expert panel [21]. These new guidelines introduced the notion of two different but acceptable approaches to identifying GDM:

(A) A two-step approach (preferred by DC) which involves screening (50 g GCT) and diagnostic testing (75 g OGTT) similar to previous guidelines but basing thresholds on HAPO values signaling an OR of 2.0, rather than 1.75 as adopted by the IADPSG [9]. The higher OR

corresponds to less inclusive glucose thresholds, aimed to somewhat offset increases in workload, patient burden (glucose monitoring) and associated costs [21].

(B) one-step approach (alternative approach) as endorsed by the IADSPG and using the IADSPG thresholds based on the OR of 1.75 as discussed previously. The IADPSG has endorsed one-step testing as the only approach to diagnosing GDM and have concerns that many women are unable to return following a 50 g GCT. Ancillary data, along with previous retrospective studies [39], have demonstrated that most women (82%) return to complete a 75 g OGTT following a screening test and that this is not a major concern in Canada.

Recommendations from earlier versions of DC guidelines (1998/2003/2008) also suggested that plasma glucose levels > 10.3 mmol/L following a 50 g GCT were sufficient to conclude a diagnosis of GDM. Currently, no high-quality evidence exists to endorse a specific glucose threshold at which the 50 g GCT can be used for diagnostic purposes. Although Carpenter–Coustan's original work in the 1980s demonstrated that a threshold of 10.1 mmol/L had a PPV of 95% [31], recent evidence has demonstrated equivocal findings. For example, in a retrospective cohort study of 14,771 women screened for GDM between 1988 and 2001, a 50 g GCT threshold of 11.1 mmol/L only demonstrated 84% PPV while >12.8 mmol/L demonstrated 100% PPV [40]. Furthermore, pregnant women with GCT values >11.1 mmol/L in the cohort were more than twice as likely to have caesarean delivery than women below this cut off (OR = 2.24, 95% CI 1.19–4.21). Given these findings, the 2013 DC expert panel agreed that increasing this threshold to >11.1 mmol/L was warranted in order to avoid additional testing for women with markedly elevated levels of glucose and to minimize delays to treatment [21,33]. While a higher glucose threshold increases specificity (lowering the risk of a false-positive results), the trade-off is reduced sensitivity which allows women with severe hyperglycemia to remain untreated for some period of time (until administered a diagnostic test).

While DC has consistently updated its GDM recommendations over the years, the SOGC provided its most recent updates in 2016 and 2019, more than a decade after its last release in 2002. The 2016/2019 SOGC CPGs have now reached a consensus with the 2013/2018 DC Canada CPGs, proposing similar methods of screening and diagnosis with the release of DC's latest guidelines. This includes the recommendation of universal screening, abandoning the 100 g OGTT, shifting the

values required for an immediate diagnosis following a 50 g GCT to higher thresholds (>11.1), adopting the one-step and two-step approach with DC-endorsed cut-off thresholds, and identifying new risk factors for GDM that warrant earlier screening (i.e., PCOS, corticosteroid use) since its last update [16,17]. While the 2013/2018 DC expert panel classifies this recommendation for early screening among women with multiple clinical risk factors as based on expert consensus opinion [21,22], the 2016/2019 SOGC panel considers this recommendation to be based on evidence from well-designed cohort studies [16,17].

3.11. The Impact of Changing Diagnostic Criteria on Prevalence across Canada

The current prevalence of GDM in Canada has seen a drastic rise, with quadruple the number of women diagnosed with GDM over the last two decades (Table 1). Apart from increases in obesity rates, maternal age and ethnic diversity, changes to the diagnostic criteria for GDM over the years have largely contributed to the observed rise in GDM prevalence [41]. Findings from a large, population-based study (1,109,605 women delivering between 1996 and 2010 in Ontario), conducted by Feig *et al.* [42], revealed that the age-adjusted incidence rates of both GDM (2.7% to 5.6%, $p < 0.001$) and pre-GDM (0.7% to 1.5%, $p < 0.001$) doubled from 1996 to 2010. Since the Canada-wide adoption of the 2010 IADPSG CPG recommendations for one-step testing, first initiated in the 2013 DC and 2016 SOGC CPGs, the national prevalence of GDM has shifted from approximately 3.7–6.5% to now 7–16% (Table 1). Traditionally in Canada, GDM was diagnosed using the two-step approach; however, following the release of guidelines from the IADPSG in 2010, the current criteria now recommends both two-step testing (preferred approach) and one-step testing (alternative approach).

As previously mentioned, DC had re-calculated their 2013 thresholds [21] for the two-step approach to correspond with an OR = 2.0 from the HAPO study [8], leading to thresholds similar to those proposed since their 2003 guidelines. However, the prevalence of GDM in the Canadian population ascertained through these two guidelines will differ due to changes in sensitivity from the revised criteria for testing. The reason for this disparity stems from another modification implemented in their 2013 guidelines: only one abnormal value during the post-load time is required to determine a diagnosis of GDM (as opposed to two abnormal values required previously), thus increasing the test sensitivity of these new diagnostic criteria [41]. Furthermore, an increase in the nationwide prevalence of GDM over the last decade can be attributed to the updated Canadian guidelines now

recommending one-step testing as an alternative approach with lower thresholds that are more diagnostically sensitive for GDM (5.1, 10.0, and 8.5 mmol/L; Table 1).

In a previous prospective cohort study of 2500 pregnant women, conducted by Agarwal *et al.* [43], the investigators aimed to compare the differences between several international expert panel diagnostic criteria for GDM and the implications of switching to the one-step approach as endorsed by the IADPSG. Agarwal *et al.* demonstrated that switching from DC's two-step preferred approach to the one-step approach led to a 15.3% increase in the prevalence of GDM among the study group. In comparison to the 2003 DC CPGs, applying the IADPSG's one-step approach led to a 36.1% increase in the prevalence of GDM among the women. Similarly, in another retrospective study conducted in Ontario by Pouliot *et al.* [44], they found switching from two-step to one-step testing increased the prevalence of GDM from 10.8% to 17.6% among the study cohort. This substantial variability in screening practices adds to the complexity of calculating the true prevalence of GDM in Canada.

3.1.2. The Impact of Changing Diagnostic Criteria on Health Care Economic Costs

In terms of the impact on resources within the Canadian context, application of the one-step approach is believed to decrease the laboratory workload, yet pose more immediate costs to the patient and health care system [45]. In another cost minimization analysis [46], Meltzer *et al.* compared the cost implications of switching from the two-step approach to the one-step approach among a subset of 1500 pregnant, Canadian women attending tertiary care (Royal Victoria Hospital, Montreal, Quebec). Women who presented for GDM screening and consented to participation in the study were randomized to Group 1 (1 h, 50 g GCT + 3 h, 100 g OGTT with 2002 SOGC NDDG criteria), Group 2 (1 h, 50 g GCT + 2 h, 75 g OGTT with 2013/2018 DC criteria) and Group 3 (2 h, 75 g OGTT alone with 2013/2018 DC criteria for the 1 step approach). Meltzer *et al.* demonstrated that the two-step approach, using either a 75 or 100 g OGTT, was found to be less costly with similar diagnostic sensitivity to the one-step approach. While GDM prevalence was found to be similar across all three groups (3.7%, 3.7% and 3.6%, respectively), the total costs per woman screened were as follows: Group 1, $91.61 CAN; Group 2, $89.03 CAN; Group 3, $108.3 CAN. Total costs included direct medical costs, direct transportation costs and indirect time costs. The higher total costs of one-step testing were attributed to increased medical costs (blood draws

and laboratory analysis) and the indirect time costs, which involved women spending more time at the test centre [46].

3.1.3. The Impact of Changing Diagnostic Criteria on Obstetric and Neonatal Outcomes

With the steadily increasing prevalence of GDM, and the serious nature of obstetrical and neonatal outcomes associated with its condition, the burden of these high-risk pregnancies continue to rise. Although we have come a long way towards improving the delivery of GDM care for women with diabetes mellitus in pregnancy, the role of screening and diagnostic criteria continues to remain controversial to date. Over the years, the diagnosis of GDM has evolved from criteria initially developed to predict future maternal diabetes mellitus to recent criteria centred on adverse neonatal outcomes. Evidence from the 2008 HAPO study [8] has demonstrated that the incidence of adverse outcomes occurs on a continuum, as oppose to a definitive inflection point. This has led to great controversy and lack of international unity on setting one global, standard diagnostic threshold for GDM. Although adverse neonatal outcomes are the basis of the IADPSG's one-step approach, there remains a lack of randomized clinical trials that demonstrate that its application leads to improvements in neonatal outcomes relative to the two-step approach.

Fuelling the controversy, several studies have compared these adverse pregnancy outcomes across the two approaches with divergent findings [44,46–50]. In a retrospective cohort study conducted by Pouliot *et al.* [44], the investigators compared pregnant women who were screened for GDM using the two-step approach (pre-IADPSG group) to women who were screened using the one-step approach (post-IADPSG group). The authors found that women in the post-IADPSG group were observed to have lower rates of labour induction, preeclampsia and offspring admission to the neonatal intensive care unit and concluded that one-step testing was associated with improved pregnancy outcomes. Similarly, in another retrospective cohort study conducted by Sacks *et al.* [48], the authors compared pregnancy outcomes among women without GDM during pregnancy, untreated women who only met the criteria for the IADPSG's one-step approach and women who met DC's criteria for their preferred two-step approach. Women with more severe GDM (higher glucose levels) were treated and excluded in this study. Relative to those without GDM, untreated women who were diagnosed with the two-step approach demonstrated significant increased risk of

shoulder dystocia, preeclampsia, pre-term births, delivering large-for-gestational age offspring, and delivering offspring with hypoglycemia. Compared to women without GDM, untreated women diagnosed with the one-step approach only demonstrated increased risk of delivering large-for-gestational offspring but none of the other obstetric and neonatal outcomes.

In contrast, Meltzer *et al.* demonstrated, in a clinical trial of 5142 Canadian women (total sample size) randomized to a GDM screening approach (described earlier), that higher rates of preeclampsia (Group 1, 3.5%; Group 2, 3.3%; Group 3, 5.4%; $p < 0.05$) and neonatal hypoglycemia (Group 1, 3.5%; Group 2, 4.2%; Group 3, 6.5%; $p < 0.05$) were observed among women in Group 3 undergoing one-step testing (applying 2013/2018 DC threshold values), relative to those in Groups 1 and 2 that underwent two-step testing for GDM [46,49]. Maternal data were obtained from the McGill Obstetric and Neonatal Database. Furthermore, in a recent population-based cross-sectional study conducted by Shah and Sharifi [47], the authors assessed 90,140 pregnant women in Ontario who underwent a 75 g OGTT between 2007 and 2015. Women were classified as those who met the 2013 DC criteria for the two-step approach and were treated, those who were untreated but would have only met the IADPSG criteria for the one-step approach (but not the two-step thresholds), and those who did not meet the criteria for GDM. Women diagnosed with the two-step approach demonstrated a significant increase in the risk of pre-term births (RR= 1.25, 95% CI 1.15–1.36), primary caesarean section (RR= 1.07, 95% CI 1.03–1.12), and neonatal intensive care unit admissions (RR= 1.21, 95% CI 1.14–1.28) relative to those who would have been diagnosed with GDM using the one-step approach. In contrast, rates of large-for-gestational-age offspring (RR= 0.87, 95% CI 0.82–0.91) and shoulder dystocia (RR-0.80, 95% CI 0.71–0.90) were lower in women who were diagnosed using the two-step approach relative to the one-step approach. In summary, the absence of robust evidence on GDM diagnostic thresholds and their associated short-term and long-term implications on maternal and neonatal outcomes continues to exist to date. Future research should continue to aim towards comparing these serious perinatal outcomes across women undergoing different screening approaches.

3.1.4. Changes to Screening and Diagnosing GDM in the Context of the Coronavirus Disease (COVID-19)

In the context of the current COVID-19 pandemic, anecdotal evidence indicates that both pregnant women and clinicians are increasingly unwilling to undergo or recommend the OGTT as the primary diagnostic tool for GDM [51]. These concerns are based on issues regarding the time spent exposed

when visiting clinics (up to two hours), potential need for multiple visits and time spent travelling. Furthermore, a diagnosis for GDM typically warrants the utilization of additional health care visits including diabetes mellitus education, sonogram imaging and routine glucose monitoring, all of which pose additional exposure risk for COVID-19. In response to these valid concerns, a joint consensus statement was released by DC and the SOGC [52], temporarily recommending that Canadian physicians: (a) continue to perform standard GDM screening if there are only minimal disruptions to lab testing and treatment capacity; (b) perform alternative GDM screening using HbA1C > 5.7% and random plasma glucose levels (RPG) > 11.1 mmol/L to warrant a diagnosis of GDM if the pandemic has caused severe disruptions.

These recommendations are temporary, given the unprecedented burden that the pandemic has inflicted on Canada's health care system as professional societies work towards producing comprehensive, patient-oriented and safety-motivated criteria. Generally, the revised Canadian recommendations prioritize specificity over sensitivity due to the shift of health care resources towards combatting COVID-19. These criteria are likely to underdiagnose women with GDM and detect only women with markedly elevated levels of plasma glucose [51]. While HbA1c testing poses the advantage of testing mean glucose levels over time and not requiring women to undergo fasting, several critical drawbacks limit its use as the standard of detection. The first main drawback is that HbA1c is less strongly associated with adverse maternal outcomes than mean OGTT glucose levels as demonstrated in the HAPO study. Secondly, the HbA1c test has reduced sensitivity, given that the proposed HbA1c > 5.7% approximates the 99th percentile of the HAPO cohort [8]. Testing using this approach alone would theoretically reduce the incidence of GDM in the HAPO cohort from 17.8% using the DC-recommended one-step approach to approximately 1% [51]. Controversy surrounding the need to reduce RPG diagnostic thresholds also exists among some Canadian physicians. This stems from HAPO study investigators choosing to unblind pre-diabetic women with a baseline RPG > 8.9 mmol/L as a safety precaution [8]. In terms of screening for overt diabetes mellitus, HbA1c and FPG are the standard screening tests implemented during the early stages of pregnancy (prior to 24 weeks). During the COVID-19 pandemic, Canadian guidelines have recommended that these tests remain unchanged for women with multiple clinical risk factors [52]. In addition, routine post-partum clinic follow ups are deferred until after the pandemic with antenatal care recommended to be administered via telemedicine approaches. Perhaps

administration of these alternative testing approaches during these times will provide policy makers additional knowledge and experience that may influence and/or re-establish national guideline recommendations in later years.

3.1.5. Voluntary Online Survey Responses

While many of the guideline recommendation disparities over the last thirty years between the national endocrine and obstetrical organizations of Canada have been resolved, individual variation among Canadian physicians may still exist. Given the absence of trials on the effectiveness of improving fetal-maternal outcomes using the proposed thresholds, physicians across Canada may still choose to base their diagnosis of GDM on different criteria (i.e., clinical expertise and opinion) which are typically subjective.

Overall, the survey was distributed to 105 physicians from the CanDIPS study group and elicited 13 responses (12.4% response rate). Respondents included a diverse pool of physicians in clinical practices across Canada (Montreal, Toronto, London, Saskatchewan and the North West territories), representing ongoing practices across different regions of Canada. 9 out of 13 respondents (69%) applied the two-step approach in their practice, indicating that more physicians were applying the preferred approach as endorsed by recent guidelines. All 9 respondents applied the appropriate 75 g OGTT thresholds recommended by the latest 2018 DC and 2019 SOGC guidelines (Table 1) and only required one abnormal value to diagnose GDM. Furthermore, 8 out of the 9 physicians using the two-step approach applied > 11.1 mmol/L as the criteria for an immediate diagnosis of GDM following a 50 g GCT; one respondent indicated the use of a lower threshold (10.3 mmol/L) as suggested by the earlier 1993/2003 DC CPGs. Four respondents (31%) indicated the use of one-step approach with values corresponding to the thresholds proposed in both the revised 2013/2018 DC and 2016/2019 SOGC guidelines.

A total of 9 out of 13 of physicians (70%) responded to the survey's question probing the use of early screening among pregnant women with multiple clinical risk factors. A total of 8 out of the 9 respondents who provided a response (89%) indicated early screening for overt diabetes mellitus prior to 24 weeks of gestation. Among these 8 respondents, 3 indicated the sole use of the typical criteria they practiced to screen at 24–28 weeks' gestation (one-step or two-step approach), 2

screened only using FPG values ranging between 5.1 and 6.9 mmol/L corresponding to GDM and 3 screened using A1C > 6.5% and FPG > 7.0 mmol/L to detect overt diabetes mellitus.

With regards to changes in clinical practice as a result of the COVID-19 pandemic, 4 out of 13 (31%) physicians provided a response during completion of the survey. One respondent had indicated no changes to their standard practice, two respondents indicated the use of A1C > 5.7 or random plasma glucose (RPG) > 11.1, and one respondent indicated the use of either A1C > 5.7, RPG > 11.1 or FPG > 5.3 to diagnose GDM. Although survey responses when queried on the "changes to screening and diagnosis of GDM during COVID-19" were low (n = 4), 75% of physician responses indicated change to their standard practice, consistent with recommendations advised from urgent update statement released by the CPG Steering Committees from DC and the SOGC [52].

Limitations of our survey include a low response rate and the potential for selection bias to influence the distribution of responses. The survey's contents were distributed solely to voluntary CanDIPS members (a subgroup task force of DC) due to accessibility (RB). Response rates and external validity may be improved in the future by distributing the surveys contents to health care providers that are members of the SOGC or other large-scale, family physician organizations.

Overall, our survey demonstrated consistent results among a voluntary pool of Can-DIPS members in clinical practices across Canada. Responses demonstrated widespread application of the latest national CPGs across our sample and it is possible that the disparities present over the last thirty years may be minimized in current, Canadian clinical practice.

4. Discussion

Historically, there has been debate concerning the optimal approach to screening GDM across Canada. As part of an overview of developments in GDM in the Canadian landscape, this scoping review highlights the history and evolution of national CPGs over the last three decades. We have reviewed the national CPGs published by the SOGC and DC, along with the ideological similarities and differences across each of their updated renditions. We have also reviewed the reported prevalence of GDM and attempted to capture the degree of variability in screening practices among physicians situated across Canada. Both the SOGC and DC have continuously updated their criteria

over time, with most physicians in Canada now adopting the latest, nationwide GDM recommendations in their clinical practice.

With revisions to the latest national CPGs now recommending the use of the one-step approach and only requiring one OGTT abnormal value to conclude a diagnosis, Canada has observed a rise in the estimated prevalence of GDM, as shown in Table 1. Disparities continue to exist, given that Canadian guidelines recommend two different screening approaches (one step vs. two step) for identifying GDM; the lack of consensus contributes to differing estimates of GDM prevalence in Canada. Though SOGC and DC recommendations are frequently guided by expert opinion and consensus, a number of key recommendations are now based on more recent large-scale, prospective cohort studies, such as the 2008 HAPO study [8]. With research aimed at highlighting the reason and level of disparity in Canada over the years, a step forward can be made towards reaching a consensus on a single, unified diagnostic approach to be recommended in future national guidelines.

Author Contributions: Both J.M. and K.D. contributed to the electronic search and assessment of eligible guidelines. J.M. reviewed the full-text articles of all relevant guidelines and performed data extraction, which underwent review by K.D. Voluntary, online surveys were distributed by R.B. All authors (J.M., S.M., R.B., N.G. and K.D.) contributed to the writing and editing of this article. All authors have read and agreed to the published version of the manuscript.
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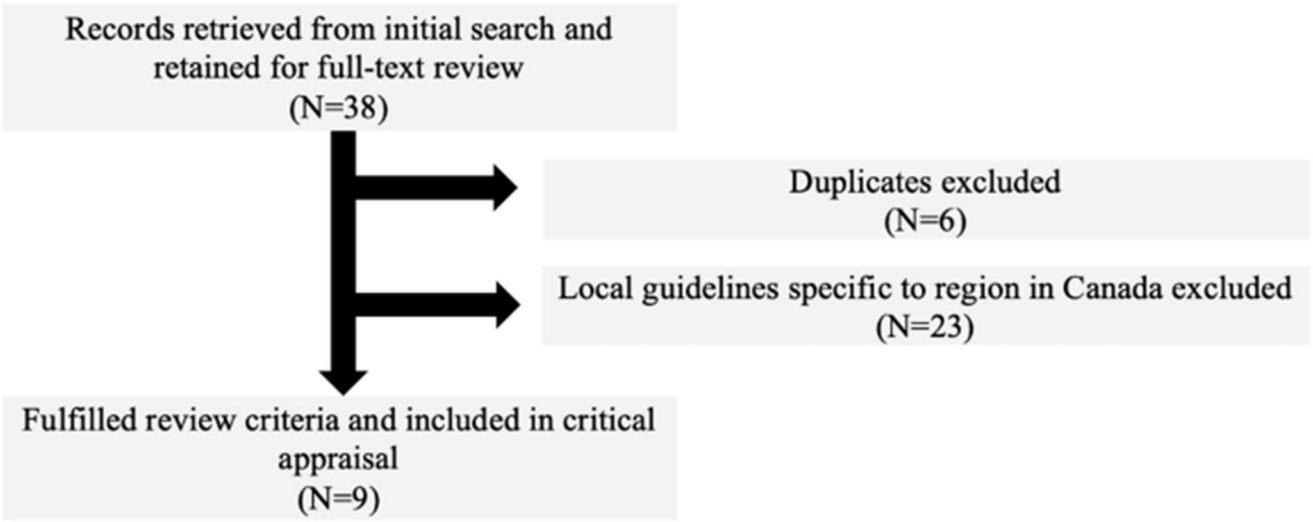
Informed Consent Statement: Not applicable.
Data Availability Statement: Not applicable.
Conflicts of Interest: The authors declare no conflict of interest.

Table 1. Screening and diagnostic criteria for gestational diabetes mellitus (GDM)

Professional Society, Year	Screening Population	Test	# of Abnormal Diagnostic Values	Fasting Glucose (mmol/L)	1 h Post Glucose Loading (mmol/L)	2 h Post Glucose Loading (mmol/L)	3 h Post Glucose Loading (mmol/L)	Estimated Prevalence of GDM in Canada [§]
Society of Obstetricians and Gynaecologists of Canada (SOGC)								
SOGC, 1992	Universal	2 step 3 h 100g *	2	5.3 or 5.8	10.0 or 10.6	8.6 or 9.2	7.8 or 8.0	3.8–6.5%
SOGC, 2002	Selective	2 step 2 h 75 g	2	5.3	10.0	8.6	–	3.8–6.5%
		2 step 3 h 100 g *	2	5.3 or 5.8	10.0 or 10.6	8.6 or 9.2	7.8 or 8.0	3.8–6.5%
SOGC, 2016	Universal	2 step 2 h 75 g †	1	5.3	10.6	9.0	–	7.0%
		1 step 2 h 75 g	1	5.1	10.0	8.5	–	16.1%
SOGC, 2019	Universal	2 step 2 h 75 g †	1	5.3	10.6	9.0	–	7.0%
		1 step 2 h 75 g	1	5.1	10.0	8.5	–	16.1%
Diabetes Canada (DC) ‡								
DC, 1998	Selective	2 step 2 h 75 g †	2	5.3	10.6	8.9	–	2.0–4.0%
		2 step 3 h 100 g	2	5.3	10.0	8.6	7.8	2.0–4.0%
DC, 2003	Universal	2 step 2 h 75 g	2	5.3	10.6	8.9	–	3.7%
DC, 2008	Universal	2 step 2 h 75 g	2	5.3	10.6	8.9	–	3.7%
DC, 2013	Universal	2 step 2 h 75 g †	1	5.3	10.6	9.0	–	7.0%
		1 step 2 h 75 g	1	5.1	10.0	8.5	–	16.1%
DC, 2018	Universal	2 step 2 h 75 g †	1	5.3	10.6	9.0	–	7.0%
		1 step 2 h 75 g	1	5.1	10.0	8.5	–	16.1%

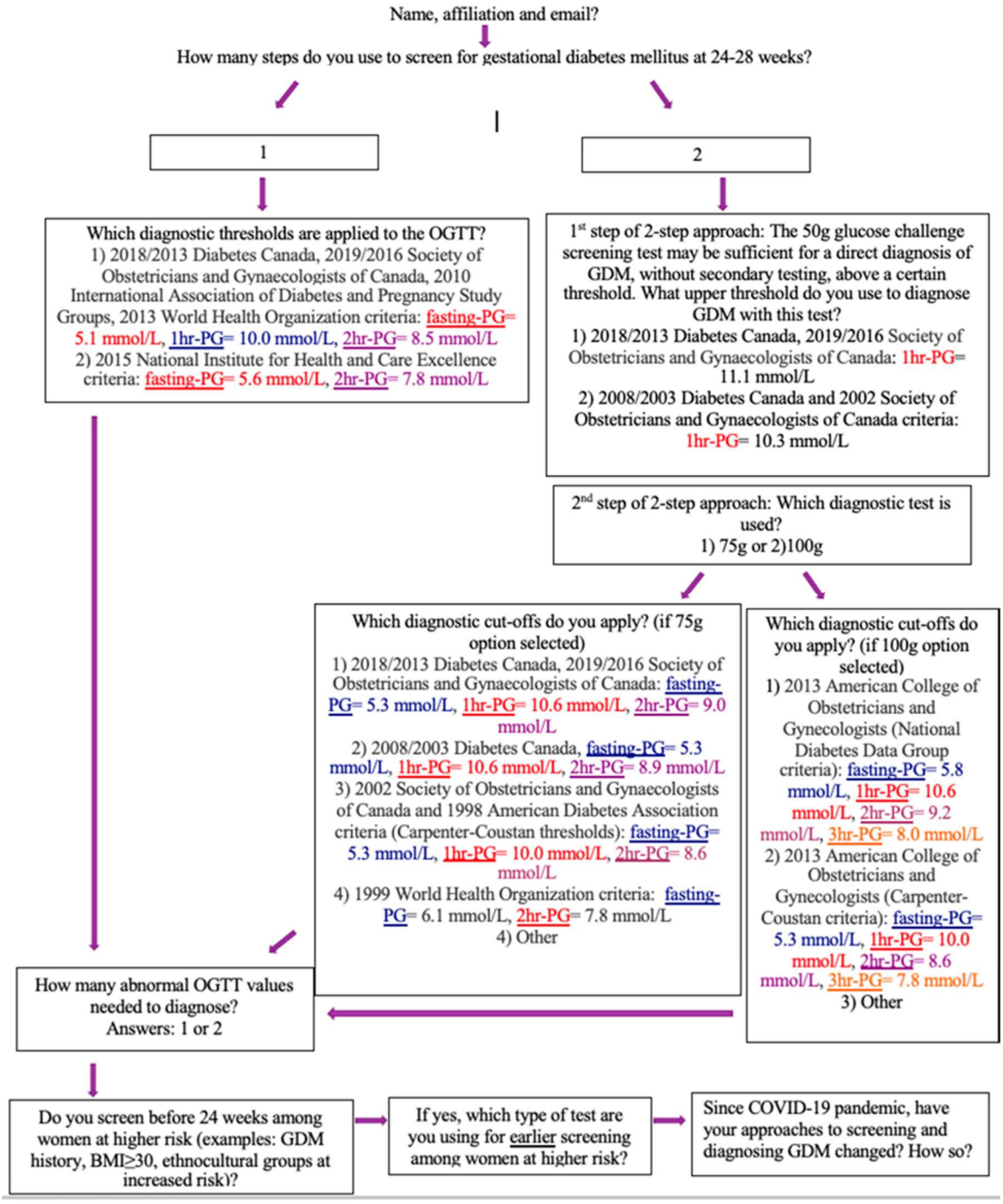
* Includes both Carpenter–Coustan and National Diabetes Data Group (NDDG) criteria. The Carpenter–Coustan criteria are the lower, more inclusive thresholds illustrated in this row.
†Preferred approach.
‡Formerly known as the Canadian Diabetes Association.
§ Estimates of GDM prevalence as reported in each CPG; derived from observational cohort studies described in the respective guidelines.

Figure 1. Flow diagram of selection strategy and article reviews



6.3 Supplementary Materials, Manuscript 4

Figure A1. Contents of voluntary, online survey distributed to CanDIPS members.



CanDIPS = Canadian Diabetes in Pregnancy Study Group

Chapter 7: Summary and Discussion

Among multiparous women, it was unclear in the literature whether the frequency of GDM and/or GHTN occurrences, as well as their sequence, influence the degree of risk for developing diabetes, hypertension, and CVD. The goal of my thesis was to elucidate whether risk assessment for their development should move beyond 'ever/never' GDM and GHTN dichotomies, and harness information on the history of these risk indicators that extend beyond one pregnancy. My findings throughout this thesis consistently demonstrate that consideration of both the number and ordinal pregnancy of any GDM/GHTN occurrence offers greater nuances in estimating the risk for each of the aforementioned outcomes. Women average two offspring, making the findings of this thesis relevant to many women.

I focused on a particular subset of women with at least two deliveries. I did not examine women without pregnancies or women with a single pregnancy. Both these groups of women have different baseline risks for future CMD,[284,285] compared to women with two deliveries. I did not include women with my outcomes of interest (diabetes, hypertension, or CVD) before their first pregnancy. Women with GDM and/or GHTN/preeclampsia in their first pregnancy would be more likely to develop my outcomes of interest between pregnancies than women without first pregnancy GDM and/or GHTN/preeclampsia. Thus, I also excluded this group of women, in which the outcomes of interest manifested before a second pregnancy even occurred. My dissertation focuses on women with at least two singleton consecutive livebirth deliveries without diabetes, hypertension or CVD before the first pregnancy, between pregnancies, or before 12 weeks' postpartum of the second delivery (index date; **Figure 8**). By focusing on a particular subset of women, I was able to apply a precision medicine orientation to a group that represents a large cross section of women.

7.1 Patterns of gestational diabetes across two pregnancies serving as a risk indicator for future diabetes

In Chapter 3 (Manuscript 1), I investigated associations between GDM and incident diabetes among nearly half a million women with two consecutive singleton deliveries in Quebec, Canada. These women were free of diabetes at baseline and had not developed diabetes between pregnancies. Using data from the provincial health administrative and vital statistics databases of Quebec, I was able to estimate associations between patterns of GDM absence, occurrence, and recurrence across two

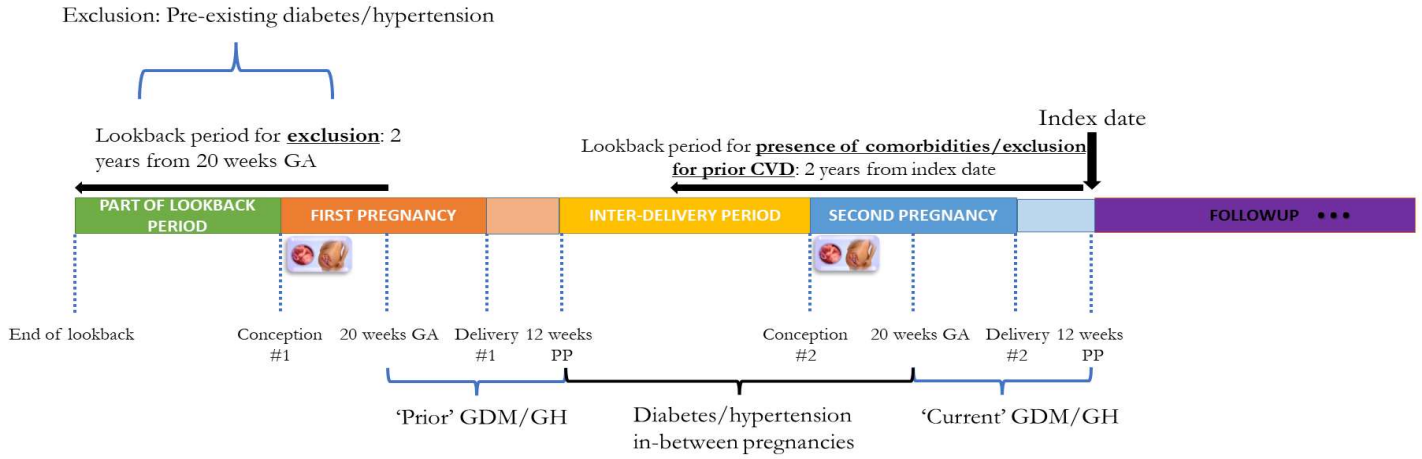
pregnancies and their associations with the risk of developing diabetes later in life. I captured the outcome of interest by applying the validated CCDSS definition of diabetes,[257,258] requiring two outpatient codes within two years or one hospitalization diagnostic code. I used Cox PH models to evaluate associations between GDM status and incident diabetes. I accounted for GHTN and other adverse pregnancy occurrences (SGA, LGA and preterm birth), in which interactions ($p<0.05$ for interaction terms) between each of these risk indicators were considered and tested. I demonstrated that GDM occurring only in a single pregnancy was associated with higher hazards of diabetes when it occurred in a second pregnancy than when it occurred in a first. GDM in both pregnancies was associated with the highest hazards, compared to absence of GDM. Direct comparisons between GDM groups were also conclusive; for example, when GDM only in the first pregnancy was set as the reference group, those with GDM only in the second pregnancy demonstrated conclusively higher hazards for future development of diabetes.

The key novel discovery of this manuscript was that a single GDM occurrence in a first pregnancy was associated with lower hazards for diabetes than a single GDM occurrence in a second pregnancy. Thus, not all women with a single occurrence of GDM are on the same risk trajectory of developing diabetes later in life. Given the impact of dietary and physical activity changes on diabetes risk, as demonstrated in previous studies among women with a GDM history,[138,139] such changes motivated by a first GDM pregnancy could account for absence of GDM in a second pregnancy and lower hazards of diabetes development thereafter. Conversely, women without GDM in the first pregnancy who later developed GDM in the second pregnancy may have gained excess weight in the first pregnancy and had difficulty losing such weight[286] or gained weight during the period between their pregnancies, thus entering a higher risk trajectory.[166,243] Previous studies have shown that increasing levels of weight gain in the inter-delivery period are associated with stepwise increased risks for new occurrence of GDM in second pregnancy.[166] For many, the additional responsibilities of parenthood[287] may challenge efforts to consistently engage in healthful behaviors, such as healthful eating and exercising. Additionally, in some women, pregnancy itself may impair a woman's beta cell function,[288] increasing her susceptibility towards developing GDM in the second pregnancy, and diabetes later in life. Given these findings, women and their health care providers should consider the number and order of GDM occurrences in estimating future risks for type 2 diabetes and the urgency of preventive action.

7.1.1 Defining gestational diabetes

I defined GDM using a validated algorithm proposed by Shah *et al.*,[45] which applied general diabetes codes along with and GDM diagnostic codes to a pregnancy-specific period (20 weeks' gestation to 12 weeks' postpartum). Their algorithm approximates the relevant pregnancy period with a 120-day lookback period, which would approximate 24 to 40 weeks of a 40-week pregnancy. Because I had information on actual gestational age at birth, I used this information to capture the appropriate pregnancy-specific period more accurately (**Figure 8**). Instead of considering the period at or after 24 weeks' gestation, I considered the period at or after 20 weeks' gestation, as this aligns with clinical GDM definitions; diabetes prior to this pregnancy time point is considered to be pre-existing diabetes.[237,289] Most health administrative databases in Canada do not record gestational age in their databases, but this was made possible for the purposes of my study through data linkage to the Quebec Birth Registry. The importance of using general diabetes as well as GDM-specific codes lies in the possibility that some physicians may use more general codes, even in pregnancy (as described in **Chapter 7.5.1**). Consistent with the Shah approach, I excluded pre-existing diabetes, removing women with any recorded diabetes code up to 20 weeks gestation (two-year lookback). CCDSS definitions apply a two-year time frame to define prior chronic diseases.[290] We were not permitted to request all prior data for all persons in our cohort (Quebec government's data privacy and confidentiality requirements); instead, we were permitted three years prior to the first delivery. As discussed, I also excluded women who developed diabetes in between pregnancies because my focus was on patterns of GDM across two pregnancies.

Figure 8: Timeline of applied exclusions and exposure ascertainment windows



7.1.2 Categorizing the primary exposure

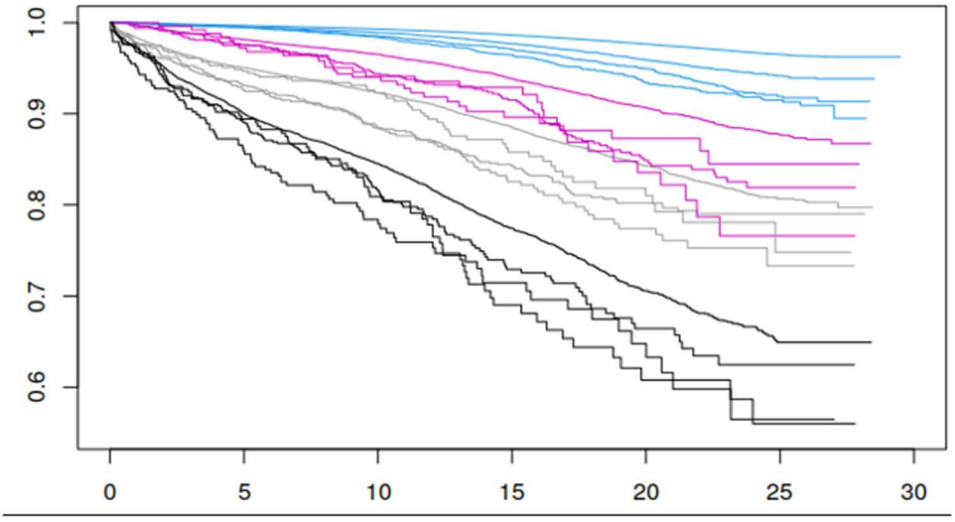
Initially, I had considered modelling occurrences of GDM and GHTN as a single variable with 16 categories (similar to Manuscript 3's secondary analysis). I created 16 exposure categories, labelled as $GDM_{XY}GHTN_{XY}$ where a 1 in the subscript indicated condition present, 0 indicated absence, and the order of the digits corresponded to first (X) or second (Y) pregnancy: $GDM_{00}GHTN_{00}$ (reference), $GDM_{00}GHTN_{10}$, $GDM_{00}GHTN_{01}$, $GDM_{00}GHTN_{11}$, $GDM_{01}GHTN_{00}$, $GDM_{01}GHTN_{10}$, $GDM_{01}GHTN_{01}$, $GDM_{01}GHTN_{11,}$ $GDM_{10}GHTN_{00}$, $GDM_{10}GHTN_{10}$, $GDM_{10}GHTN_{01}$, $GDM_{10}GHTN_{11,}$ $GDM_{11}GHTN_{00}$, $GDM_{11}GHTN_{10}$, $GDM_{11}GHTN_{01}$, $GDM_{11}GHTN_{11}$. However, upon review of log-minus-log survival plots (**Figure 9**) and Schoenfeld's residuals, this variable did not meet the proportional hazards assumption when diabetes was the outcome. For example, after roughly 10 years of follow-up, I observed survival curves crossing in those with $GDM_{00}GHTN_{10}$ and $GDM_{00}GHTN_{01}$. These curves demonstrated similar survival probabilities in the first ten years, crossed at 10 years and continued to remain similar until about 22 years of the follow-up, which at this point the curves crossed over again. This reflects that in earlier years of follow-up and during later years of the follow up until after about 22 years, the survival probabilities (and baseline risks) were similar, irrespective of whether GHTN occurred in the first or second pregnancy. Subsequently, at certain time points, the survival experience of one group became better or worse relative to the other. The same patterns were observed when comparing survival probabilities between $GDM_{11}GHTN_{10}$ and $GDM_{11}GHTN_{11}$, with the survival probabilities overlapping as early as two years into the follow-up. Thus, truncation of the follow-up time as early as ten years into the follow-up did not solve the issue with crossing survival trajectories.

The overall association of incident diabetes with patterns of GHTN are anticipated to be of lower magnitude than GDM status, likely accounting for similarity of GHTN in first or second pregnancy in relationship to diabetes hazards. Explanatory power in a Cox regression model refers to the model's ability to explain or predict the variation in survival times based on the independent variables or covariates included in the model. Upon entering GDM and GHTN as separate variables in the model, as expected, GDM was shown to have significantly higher explanatory power in the model, reflected with lower Bayesian Information Criteria values and stronger associations with incident diabetes (as depicted by the magnitude of the HR; e.g., HR=4.35, 95%CI 4.06-4.67 for those with GDM in first pregnancy, compared to absence of GDM in either pregnancy) versus a binary indicator of GHTN

occurrence (collapsed as present in either or both pregnancies; HR=1.65, 95% CI 1.57-1.73, compared to absence of GHTN in either pregnancy).

Notably, the PH assumption was satisfied when GDM was categorized as four levels (GDM_{00}, GDM_{10}, GDM_{01}, GDM_{11}) as shown in Figure 2 of Manuscript 1; however, when GHTN was categorized similarly (four categories), I again noticed departures from the PH assumption. Again, I speculate that this is due to the fact that GHTN operated as a weaker independent variable in the adjusted model and may not have effectively differentiated between groups in terms of diabetes risk (due to its limited explanatory power and marginal impact on diabetes hazards). As a result, when this variable was examined individually in survival plots, substantial variability in survival curves may have been observed due to inherent baseline risks that differ due to other stronger predictors, such as GDM status, that are not accounted for in crude survival plots, leading to crossing curves. Because I speculated that this GHTN grouping did not significantly contribute to explaining the variation in survival times or predicting survival outcomes, I opted to collapse GHTN into a binary variable (absence or presence, irrespective of number of occurrences or ordinal number of pregnancy with a single occurrence). By collapsing this variable, I was successful in mitigating the noise and variability of the crude diabetes survival probability, allowing the survival curves to better reflect the true differences in survival probabilities between groups based on other more relevant predictors; this resulted in stable and more interpretable survival curves that no longer exhibited crossing patterns. Thus, in relationship to the diabetes outcome, it appeared reasonable to consider GHTN as an "ever/never" binary variable in the adjusted model, but GDM as a four-level categorical variable depicting the particular order of its occurrences (absence of GDM, present in first, second, or both pregnancies).

Figure 9: Kaplan Meier curves depicting diabetes-free survival across 16 categories of GDM/GHTN



The blue curves represent those with no GDM (held constant), but four various levels of GHTN ($GHTN_{00}$, $GHTN_{10}$, $GHTN_{01}$, $GHTN_{11}$). The pink curves represent those with GDM in first (held constant), but various levels of GHTN. The gray curves represent those with GDM in second (held constant), but various levels of GHTN. Lastly, the black curves represent those with GDM in both (held constant), but various levels of GHTN. Although GDM status is held constant across each colored strata, notice the substantial levels of noise and crossing survival curves when GHTN status varies.

7.1.3 Age as a spline variable

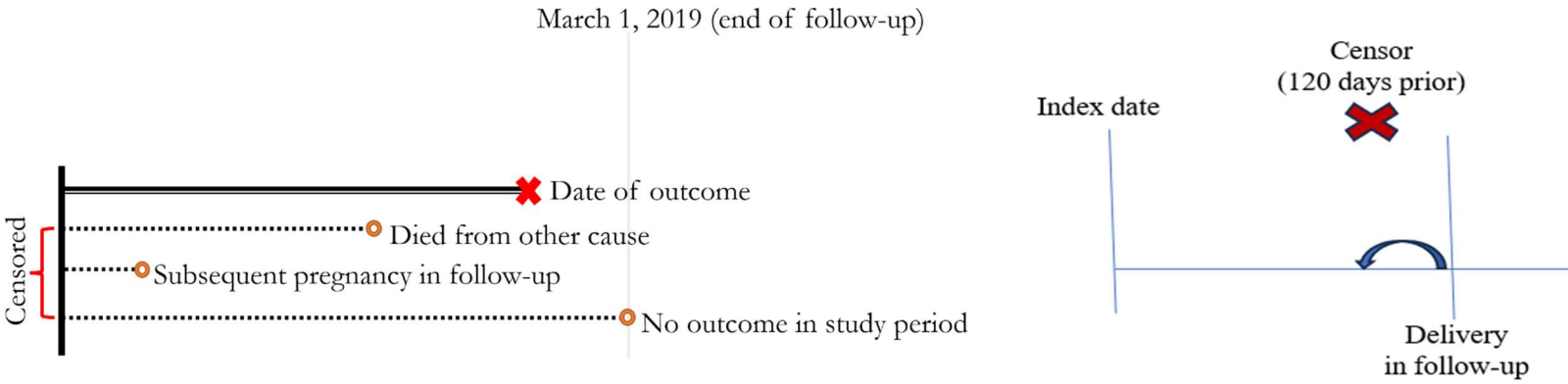
The linearity assumption was not met when I modelled maternal age as a continuous variable. The PH assumption was also violated when I attempted to categorize baseline maternal age into four categories that aligned with the distribution of my study population of reproductive aged women (<25, 25-30, 30-35, >35). I thus opted to model age as a spline using the default knot selection procedure in SAS, which automatically selects the knot position based on the distribution of age values and the density observations across intervals; this approach generated a piecewise polynomial function with six knots and four degrees of freedom. Modelling maternal age with this approach allowed for flexible non-linear modeling of the relationship between the maternal age and the log-hazard function over time, without imposing restrictive assumptions on the underlying relationship.

7.1.4 Censoring subsequent pregnancies in the follow-up

My study cohort included women with at least two singleton deliveries during the cohort inception period (1990-2012). The majority of women in my cohort only had two deliveries throughout the entire duration of the follow-up (71%, N=306,144). One third (29%, N=125,836) had one or more pregnancies after their second delivery. In these women, I censored the follow-up 120 days before the

third delivery date. Furthermore, studies have demonstrated that the lowest risk of developing diabetes are observed among women with a single pregnancy, and rise both in women without pregnancy history, and women with higher numbers of pregnancies.[284] Because I did not have data on gestational age for pregnancies beyond the second (which allows us to ascertain the date of conception), I censored at 120-days prior to the subsequent delivery (**Figure 10**; delivery date ascertained with the utilization of delivery-specific codes). This pregnancy-specific lookback period was used in the Shah *et al.* validation study[246] that sought to identify optimal algorithms for identifying GDM within health administrative databases but did not have gestational age information.[246]

Figure 10. Censoring for additional, subsequent pregnancies after the index date



7.1.5 Exclusion of prior CVD

CVD is the most common complication of diabetes. I excluded individuals with CVD prior to the second delivery, as women may develop CVD between pregnancies, and may alter their lifestyle/management to prevent a recurrent event. Diabetes prevention/management is a key aspect of preventing a recurrent CVD event. Our study aims to evaluate GDM as a predictor of diabetes, for early action during the years after delivery to prevent diabetes and its complications. My index date was 12 weeks after the delivery of the second-born. I aimed to exclude CVD prior to the index date and applied a two-year time window prior to this date; this approach was also applied to Manuscripts 1, 2 and 3. Because I included both outpatient diagnostic data as well as hospitalization diagnoses, this captured both recent CVD and history of CVD. Women with an even earlier CVD history would have related outpatient clinic follow-ups, as confirmed by review of my dataset. Many definitions of

chronic disease in Canadian health administrative datasets use such a two-year period, including those from the CCDSS.[290,291]

7.1.6 Sensitivity analysis accounting for gravidity

In a sensitivity analysis, I redefined my cohort to retain women with a first or second pregnancy that resulted in a stillbirth (N=3,705 stillbirths; see **Supplemental Table 3, Manuscript 1**). Within this cohort (total N=435,685; 12,415 diabetes events), I also adjusted for miscarriages in between pregnancies (N=51,360 miscarriages). I removed prior history of paternal diabetes and hypertension from the model, as this information is unavailable for stillbirths. I captured between-pregnancy miscarriage by requiring one outpatient or hospitalization diagnostic code for miscarriage/abortion (ICD-9: 630-638, ICD-10: O03-O05) occurring from 12 weeks postpartum of the first pregnancy and the derived conception date of the second pregnancy. Accounting for stillbirth pregnancies and miscarriages between pregnancies did not importantly impact my HRs evaluating associations between GDM and diabetes. The association between miscarriages between pregnancies and diabetes was inconclusive (HR=1.03, 95%CI 0.97-1.09), while stillbirths in the first or second pregnancy were conclusively associated with a 19% increase in hazards (HR=1.19, 95%CI 1.04-1.38) for the development of diabetes.

7.1.7 Simple sensitivity bias analysis

I performed indirect adjustments (simple sensitivity bias analysis) for obesity and smoking. GDM may lie on a causal pathway between obesity and diabetes (e.g., obesity to GDM to diabetes), and so whether we should account for it is debatable. Nonetheless, I opted to do so, in order to understand GDM's independent association with diabetes. My hazard ratios were somewhat attenuated with the adjustment for obesity, but still high in magnitude, with between-group differences preserved. Smoking is a potential confounder for associations between GDM and diabetes, as it may contribute to the development of both, but is unlikely to be on the causal pathway between these two conditions. Indirect adjustment for smoking did not importantly alter my HRs for diabetes. I derived the prevalence of obesity and smoking from a comparable external cohort. Briefly, I leveraged my access (used for the purposes of another one of my published studies)[292] to a random sample of Canadian citizens who completed the 2004 CCHS (Cycle 2.2) and consented to probabilistic record linkage, conducted by Statistics Canada, to the 2004-2017 Discharge Abstract Database (to ascertain underlying causes of hospitalization) and Canadian Mortality Database (to determine cause of death,

as applicable). I applied specific inclusion criteria (e.g., limited to women aged 12-50 years with at least two deliveries recorded; without prior diabetes, hypertension, or CVD at baseline) to mimic the inclusion criteria applied to my primary cohort. I did this to maximize subject comparability between both datasets. I classified the 1,231 women who met these inclusion criteria by GDM status, and computed proportions smoking (occasional smoker/daily smoker versus non-smoker) and/or with obesity at baseline. I then adjusted the HRs and CIs corresponding to the primary GDM exposures in the present study, with these proportions along with reported associations of these factors with incident diabetes in the literature. Adjusting for unmeasured confounders using this method requires the model to adjust for one unmeasured variable at a time and for the unmeasured variable to be dichotomous.

This method of indirect adjustment was reported by another group of investigators, who also used CCHS as their external data source.[293] I thus fulfilled the key requirements for indirect adjustments, which are: a) access to a large external data source that is representative of the original study population, b) inclusion of personal risk factors that are recorded or can be derived within the external dataset, though not available in the original study population (e.g., anthropometric measures, cigarette smoking), c) ability to delineate proportions with these personal risk factors (e.g., obesity, smoking) within the external data set that are stratified by the exposure categories of interest in the main study. I then fulfilled the final requirement d) estimates of the associations between the unmeasured potential confounder (e.g., obesity, smoking) and the outcome of interest in the literature (e.g., diabetes) among a sample that reflects the study population, which reported an HR of 1.13 for smokers versus non smokers,[294] and an HR of 3.90 for obesity (BMI $\geq$ 30 kg/ m^2) versus normal weight (BMI 18.5–24.9 kg/m^2).[295] The indirectly-adjusted confidence intervals can be derived by applying the same bias factor (denominator of the equation) to the lower and upper limits of the confidence interval generated from my analyses.

Below, I also include a demonstration of the calculation being applied to the HR among women with GDM in the first pregnancy only, indirectly adjusting for smoking (**Figure 11**). I note the following:

- the denominator of the equation is the bias factor that is applied to the numerator (HR from our analysis).
- P_e, P_s, and P_{se} are extracted from the secondary 2004-2005 CCHS Cycle 2.2 cohort.

- HR (related to smoking) was obtained from the following study,[294] which examined the association of diabetes with smoking among women, and demonstrated a HR of 1.13.
- The indirectly-adjusted CIs can be derived by applying the same bias factor (denominator of the equation) to the lower and upper limits of the CI generated from our analyses.

Figure 11. Simple sensitivity bias analysis equation applied to our primary estimates

$$HR_{(\text{corrected for smoking})} = \frac{HR_{(\text{from our analysis})}}{HR_{(\text{related to smoking, from literature})}^{P_{se}-P_eP_s}}$$

Notation

P_{se} = proportion within specific exposure category who smoke

P_e = proportion of those corresponding to specific exposure category among all women with two consecutive singleton pregnancies

P_s = proportion who smoke among all women with two consecutive singleton pregnancies

$$HR_{(\text{corrected for smoking})} = 4.35 \,/\, 1.13^{\,(8/32 - [32/1231]*[300/1231])} = 4.23$$

7.2 Patterns of gestational hypertension (with or without preeclampsia) across two pregnancies serving as a risk indicator for future hypertension

In Chapter 4 (Manuscript 2), I sought to build on my key findings among multiparous women and examined whether the sequence of a GHTN occurrence (i.e., affecting first or second pregnancy), in addition to the total number of occurrences, impacted the magnitude of risk for hypertension later in life. I therefore examined all possible patterns of GHTN (with or without preeclampsia) absence, occurrence, and recurrence across two pregnancies in a Cox PH model that also accounted for the presence of other adverse pregnancy outcomes, along with other covariates. As for GDM and diabetes, I identified progressively escalating hazards for hypertension across GHTN occurrence categories, moving from absence of GHTN in either pregnancy, GHTN in the first but not in the

second, GHTN in the second but not in the first, and GHTN in both. Again, a single occurrence of GHTN demonstrated importantly different risks, based on whether the first or second pregnancy was affected. Similarly, my initial hypothesis that speculated those with GHTN occurring in a second pregnancy were in a higher-risk trajectory than first-pregnancy GHTN was confirmed. As described, this ranking of risk was based on the idea that between pregnancies, women may adopt healthier lifestyle habits that reduce rates of GHTN recurrence in a subsequent pregnancy, and ultimately overall hypertension risk. Similar to Manuscript 1, I applied simple sensitivity bias analyses to indirectly adjust for obesity and smoking, along with censoring additional, subsequent pregnancies detected after the index date (**see Chapter 7.2.1**). My model estimates remained robust even after I applied indirect adjustments for obesity and smoking (see **Manuscript 2, results**). Given these findings, healthcare providers should inquire not only about the presence of a previous GHTN history in women, with or without preeclampsia, but also about the number of previous affected pregnancies and their sequence in those pregnancies.

7.2.1 Defining gestational hypertension

I applied diagnostic codes for GHTN, in addition to more general hypertension codes. Both GHTN-specific and general hypertension codes were applied to a specific pregnancy period (20 weeks' gestation to 12 weeks' postpartum; **Figure 8**), in attempt to reduce misclassification bias. I utilized derived data on gestational age of the pregnancy to define this exposure window. As described earlier, some women were assigned hypertension codes from 20 weeks' gestation or onwards during their pregnancy window. To mitigate the potential reduction in specificity arising from this approach, I excluded all instances of pre-existing hypertension thereby ensuring that women with any form of hypertension coded during pregnancy, whether designated as pregnancy-specific or essential, were identified as having new-onset GHTN in my study, provided the hypertension diagnosis was absent up to 20 weeks gestation. To perform this exclusion, I similarly applied a two-year lookback period respective to the first pregnancy based on the rationale described in **Chapter 7.1.1**.

7.2.2 Categorizing the primary exposure

In these analyses, GHTN with or without preeclampsia (collapsed) categorized into the neither, first only, second only, and both pregnancies categories fulfilled PH assumptions in relationship to hypertension development. The methodological challenge was that the assumptions were not met when I attempted to model the association of hypertension with separate patterns of GHTN (without

preeclampsia) and preeclampsia as a single variable. Grouping the exposure with this approach led to nine categories (GHTNa here indicating GHTN alone [without preeclampsia], PE indicating preeclampsia): $GHTNa_{00}PE_{00}$ (reference), $GHTNa_{10}$, $GHTNa_{01}$, $GHTNa_{11}$, PE_{10}, PE_{01}, PE_{11}, $GHTN_{10}PE_{01}$, $GHTNa_{01}PE_{10}$. Upon reviewing the crude survival versus log-time plot, I observed that for the individual categories of GHTN without preeclampsia compared to preeclampsia (e.g., GHTN in first without preeclampsia compared to preeclampsia in first), survival probabilities were often very similar when the affected pregnancy was held constant, resulting in numerous incidents of crossing survival curves. Aligned with this, if the affected pregnancy was held constant, those with GHTN alone (e.g., GHTN alone only in first pregnancy, HR=2.89, 95%CI 2.73-3.05) demonstrated similar HRs of developing hypertension to those with GHTN with preeclampsia (e.g., preeclampsia only in first pregnancy, HR=2.45, 95%CI 2.32-2.57) when derived as a single variable in the model (model not shown). Based on previous studies that have demonstrated that the presence of preeclampsia is associated with heightened perinatal morbidity and mortality compared to GHTN alone, my aim was to examine if this increase in risk persists for a long-term outcome, such as maternal hypertension. In this instance, the influence of preeclampsia on crude survival probabilities may not have been substantial enough to consistently differentiate from groups of women without preeclampsia when the affected pregnancy was held constant.

In order to allow us to mitigate violations to the PH assumption and delineate differences in hazards associated with GHTN alone versus preeclampsia, compared to absence of these conditions, I conducted separate analyses among two different subgroups of women. One included women without any form of GHTN and also those with preeclampsia, but excluded those who had GHTN without preeclampsia. The other subcohort included those without any form of GHTN and those with GHTN without preeclampsia, but excluded those with preeclampsia. Contrary to nine levels of the exposure failing to meet the PH assumption, these four levels of each exposure group satisfied the assumption in each of their respective analyses. I note that although direct comparisons were not made between GHTN alone and preeclampsia, the risks of hypertension appeared similar when comparing across two separate subcohorts. Similarly, the key finding that the difference in risks associated with a single occurrence in a first pregnancy, compared to single occurrence in a second, applied to both GHTN with preeclampsia and GHTN without preeclampsia.

7.2.3 Inclusion of GDM as a covariate

Interestingly, GDM was also found to be conclusively associated with hypertension, with similar risks whether GDM affected the first or second pregnancy, likely due to the lessened magnitude of its association with hypertension compared to GHTN or preeclampsia. Those with recurrent GDM were among those at the highest risk of developing hypertension, compared to those without GDM. Given these findings, it may be important for health care providers to inquire about other adverse pregnancy outcomes, specifically GDM, in order to adopt a precision medicine-focused approach towards hypertension prevention efforts.

7.3 Patterns of gestational diabetes and gestational hypertension across two pregnancies serving as risk indicators for future cardiovascular disease

In Chapter 5 (Manuscript 3), I aimed to quantify CVD risk in relationship to the number of GDM/GHTN occurrences, given my earlier findings that demonstrated their patterns to be signals of increasing diabetes and hypertension risk. Moreover, both diabetes and hypertension themselves are independently associated with later CVD in life. Among my cohort of women with two deliveries, in the Manuscript 3, I examined the cumulative numbers of GDM and GHTN occurrences across two consecutive singleton pregnancies (none, one, two, and three or more), in addition to all of their possible joint combinations (secondary analysis), in relationship to CVD development. In the primary analysis, I demonstrated a stepwise increase in CVD hazards moving from absence of GDM or GHTN in either pregnancy, to one occurrence of GDM or GHTN, two occurrences of GDM and/or GHTN, and three or more occurrences. In a secondary analysis, which explored the particular sequence of these conditions, GDM and GHTN occurrences were associated with similar hazards of CVD, irrespective of the pregnancy in which they occur. For example, having both GDM and GHTN in a single pregnancy was associated with similar hazards as having GDM in one and GHTN in the other. Similarly, having GDM and/or GHTN in the first pregnancy was associated with a similar magnitude of CVD hazards as having both GDM and/or GHTN in the second pregnancy. These findings differed from findings in Manuscripts 1 and 2 and my initial hypotheses, which speculated that single occurrences in subsequent pregnancies signaled shift to a higher risk-trajectory than those with a single occurrence in their first pregnancy; instead, I observed similar levels of CVD hazards across both groups.

7.3.1 Categorizing the primary exposure

Contrary to Manuscript 1 and 2, I was able to model joint co-occurrences of GDM and GHTN as a single variable with 16 categories (presented in a secondary analysis) without violating the PH assumption. I created 16 exposure categories, labelled as $GDM_{XY}GHTN_{XY}$ where a 1 in the subscript indicated condition present, 0 indicated absence, and the order of the digits corresponded to first (X) or second (Y) pregnancy: $GDM_{00}GHTN_{00}$ (reference), $GDM_{00}GHTN_{10}$, $GDM_{00}GHTN_{01}$, $GDM_{00}GHTN_{11}$, $GDM_{01}GHTN_{00}$, $GDM_{01}GHTN_{10}$, $GDM_{01}GHTN_{01}$, $GDM_{01}GHTN_{11,}$ $GDM_{10}GHTN_{00}$, $GDM_{10}GHTN_{10}$, $GDM_{10}GHTN_{01}$, $GDM_{10}GHTN_{11,}$ $GDM_{11}GHTN_{00}$, $GDM_{11}GHTN_{10}$, $GDM_{11}GHTN_{01}$, $GDM_{11}GHTN_{11}$. I speculate the PH assumption was met given that both GDM and GHTN are recognized risk indicators of future CVD with similar magnitudes of risk, as reviewed in the contents of this manuscript. Assessing both the crude survival plots and Schoenfeld residuals generated from the adjusted model, both GDM and GHTN patterns of occurrence were shown to substantially contribute and adequately influence CVD survival probabilities that consistently differentiate between various levels of the exposure. For ease of interpretability for readers of this published manuscript, as recommended by reviewers, I opted to present the HRs from these 16 exposure groups as a secondary analysis. In my primary analysis, I chose to collapse GDM/GHTN by total occurrences (1, 2, ≥3) across the span of both pregnancies; these analyses demonstrated escalating increase in CVD hazards as total occurrences rose. From a knowledge translation standpoint, the act of defining my exposure groups according to the cumulative total number of GDM/GHTN occurrences may enhance the clarity of my research findings, in contrast to discussing hazards across 16 groups of the exposure. Presenting the primary analysis exposure with four categories simplified my otherwise complex findings, highlighting the most salient differences, and enabling more straightforward identification of associations that the general public can interpret with ease. My approach effectively allows researchers to streamline the presentation of data, making it easier for stakeholders, policymakers, and the general public to understand and apply the results to real-world contexts.

7.3.2 Defining cardiovascular disease

I applied validated codes for myocardial infarction, stroke and angina (hospitalization or cause of death; requiring at least one code) as specified by Tu *et al.*[296], in addition to: a) validated procedural codes for angioplasty, endarterectomy or coronary artery bypass surgery[297] and b) several additional ICD-codes for CVD that are Quebec-specific and were manually reviewed by my supervisors. I did

not identify CVD from outpatient data given that my definition of CVD encompasses acute or severe conditions that typically require hospitalization or emergency care. Moreover, I did not rely on outpatient CVD codes given increased variability in coding practices in outpatient settings, potential incompleteness of documentation, and complexity of the disease presentation. I did include outpatient codes when excluding people with prior CVD, to help ensure that individuals with potential pre-existing CVD were removed.

7.3.3 Differences in findings related to the sequence of GDM/GHTN occurrences for CVD outcome, in contrast to diabetes and hypertension

In our analyses, we determined that the number of GDM occurrences and their sequence (higher hazards with second pregnancy GDM than first pregnancy GDM) were associated with increases in diabetes hazards (**Manuscript 1**). Similarly, both the number and sequence of GHTN and of preeclampsia occurrences were associated with hypertension risk (**Manuscript 2**). For CVD, the number of GDM and GHTN/preeclampsia occurrences were associated with increasingly greater CVD hazards (**Manuscript 3**). However, in those with a single GDM or GHTN/preeclampsia occurrence, whether this occurred in the first or the second pregnancy did not appear to make a difference to CVD hazards.

One likely explanation for this lies in the fact that this analysis involved more exposure categories with fewer outcomes overall (4228 events) and within each exposure category (16 categories), compared to our previous models examining diabetes (4 exposure categories; 12,205 events) and hypertension (4 exposure categories; 27,755 events) as outcomes, potentially reducing the power of our model. This reduction in power arises because the precision of the estimated HRs decreases as the number of events becomes sparser across exposure groups. Consequently, the model may not have sufficient statistical power to detect significant associations or differences between GDM/GHTN occurring in a first versus second pregnancy.

Alternatively, compared to diabetes or hypertension hazards, the difference in CVD hazards between the ordinal pregnancy of any GDM/GHTN occurrence may be due to the longer median follow-up time until this event of interest (16.5 years between the index date and CVD versus 11-11.5 years for diabetes and hypertension). This longer time period may have obscured differences, as other factors

such as behavioral changes, environmental factors, or aging may have influenced these observed associations.

7.3.4 Secondary analyses: Retaining women with diabetes and/or hypertension development between pregnancies and examining associations with individual components of the composite CVD outcome

In one secondary analysis, I modified my study inclusion criteria to retain women who had developed diabetes and/or hypertension between pregnancies, and collapsed diabetes between pregnancies with GDM in second pregnancy and hypertension between pregnancies with GHTN in second pregnancy. I collapsed these categories because separating these categories would have led to an excessive number of exposure groups (25 to 36 exposure categories); this would have reduced my statistical power and complicated the interpretability of my findings. Furthermore, when I had expanded the exposure groups to include women with diabetes and/or hypertension between pregnancies as a separate level of the exposure, associations with CVD were similar in magnitude to the GDM/GHTN in second pregnancy categories, but were not conclusive. I therefore deemed it reasonable to collapse these groups in a secondary analysis and believe this provided a more complete portrait of my study population and the associations I delineated. In another secondary analysis, I opted to individual components of the primary composite CVD outcome (myocardial infarction, stroke, and hospitalized angina, separately) to allow for a more nuanced understanding of each outcome's individual effects, avoiding the potential loss of information or misinterpretation associated with combining diverse events into a single composite measure.

7.4 Variations in the screening and diagnosis of GDM

Lastly, in Chapter 6 (Manuscript 4), I summarized the criteria and order of GDM screening algorithms suggested by the Canadian diabetes and obstetrics societies throughout the last three decades, indicating the intervals of different guideline recommendations. Although not presented in the published manuscript itself, for the purposes of my thesis dissertation and given the findings from my scoping review, I also attempted to account for these temporal trends by assessing how adjusting for the calendar years of each pregnancy influenced estimates between GDM and each of the aforementioned outcomes in my models. I focused on physician-diagnosed GDM, as captured through the health administrative databases. Universal screening for GDM was first recommended by

the Society of Obstetricians and Gynecologists of Canada in 1992, and subsequently by Diabetes Canada in 2003. Although it varied across physicians, universal screening was likely operating in practice for many years prior to these guidelines. However, for the period between 1990 and 2003, it is possible that I classified some women with GDM, as not having GDM due to the various screening recommendations during this time. Adjusting for calendar year may help to mitigate misclassification errors caused by inter-physician variability as a result of temporal trends in guideline recommendations over the years. Including calendar year as a covariate allowed me to isolate the association of GDM while controlling for any underlying changes in the outcome variables associated with time, helping ensure that the estimated association of GDM was not confounded by temporal trends or other time-varying factors. Upon comparing models with their inclusion and exclusion, these variables did not importantly impact my effect estimates. I acknowledge that accounting for calendar years may not fully capture all relevant temporal variations in my outcome variables. While incorporating calendar years in my models can help capture temporal trends over time, it may not adequately account for other important temporal trends. For example, diabetes development is influenced by a multitude of factors beyond calendar years, such as changes in lifestyle behaviors, advancements in medical technology, shifts in diagnostic criteria, and evolving socioeconomic conditions. I acknowledge that calendar years cannot account for all of these temporal trends, with the potential for residual confounding to influence the association between calendar years and each of these outcomes. Therefore, while accounting for calendar years can provide valuable insights into long-term trends, a comprehensive analysis of temporal patterns in diabetes, hypertension and CVD occurrence requires careful consideration of multiple temporal factors to ensure accurate inference and interpretation.

The following tables (**Tables 2-5**) were created for the purpose of this thesis to demonstrate that inclusion of calendar years of each woman's pregnancy did not importantly alter the HRs.

Table 2. Comparing effect estimates of the diabetes outcome, with and without inclusion of years of pregnancy to account for temporal trends in the diagnosis of gestational diabetes

Exposure	Excluding years of pregnancy in model	Including years of pregnancy in model	Absolute Δ HR
No GDM	Reference	Reference	
GDM in first pregnancy	4.35 (4.06-4.67)	4.36 (4.07-4.68)	+0.01
GDM in second pregnancy	7.68 (7.31-8.07)	7.64 (7.28-8.03)	-0.04

GDM in both pregnancies	15.8 (15.0-16.6)	15.8 (15.1-16.7)	0
GDM in first pregnancy	Reference	Reference	
GDM in second pregnancy	1.76 (1.63-1.91)	1.75 (1.62-1.90)	-0.01
GDM in both pregnancies	3.63 (3.36-3.93)	3.63 (3.36-3.93)	0
GDM in second pregnancy	Reference	Reference	
GDM in both pregnancies	2.06 (1.94-2.19)	2.07 (1.95-2.20)	+0.01

Table 3. Comparing effect estimates of the hypertension outcome, with and without inclusion of years of pregnancy to account for temporal trends in the diagnosis of gestational diabetes

Exposure	Excluding years of pregnancy in model	Including years of pregnancy in model	Absolute Δ HR
GDM variable in primary model			
No GDM	Reference	Reference	
GDM in first pregnancy	1.40 (1.31-1.49)	1.39 (1.31-1.48)	-0.01
GDM in second pregnancy	1.44 (1.37-1.52)	1.44 (1.37-1.51)	0
GDM in both pregnancies	1.76 (1.65-1.88)	1.78 (1.67-1.89)	+0.02
GDM variable in model examining association of hypertension with preeclampsia			
No GDM	Reference	Reference	
GDM in first pregnancy	1.44 (1.34-1.54)	1.43 (1.33-1.53)	-0.01
GDM in second pregnancy	1.50 (1.42-1.59)	1.50 (1.42-1.58)	0
GDM in both pregnancies	1.84 (1.71-1.97)	1.85 (1.73-1.99)	+0.01
GDM variable in model examining association of hypertension with GHTN (without preeclampsia)			
No GDM	Reference	Reference	
GDM in first pregnancy	1.41 (1.32-1.51)	1.40 (1.31-1.49)	-0.01
GDM in second pregnancy	1.50 (1.42-1.58)	1.49 (1.41-1.57)	-0.01
GDM in both pregnancies	1.83 (1.71-1.96)	1.85 (1.73-1.98)	+0.02

Footnote: I also observed stable effect estimates for the primary GHTN variable, which demonstrated minimal change in hazard ratios when pregnancy years were included in the final models. Although not the primary focus of Manuscript 2, I show effect estimates from the GDM variable above due to the possibility of temporal trends that influenced their diagnostic criteria over the years, as discussed in Manuscript 4.

Table 4. Comparing effect estimates of the composite cardiovascular disease outcome, with and without inclusion of years of pregnancy to account for secular trends in the diagnosis of gestational diabetes

Exposure	Excluding years of pregnancy in model	Including years of pregnancy in model	Absolute Δ HR
No GDM or GHTN	Reference	Reference	
1 GDM or GHTN occurrence	1.47 (1.35-1.61)	1.47 (1.35-1.61)	0
2 GDM and or GHTN occurrences	1.91 (1.68-2.17)	1.90 (1.67-2.17)	-0.01

≥3 GDM or GHTN occurrences	2.93 (2.20-3.90)	2.92 (2.19-3.88)	-0.01
1 GDM or GHTN occurrence	Reference	Reference	
2 GDM and or GHTN occurrences	1.30 (1.12-1.50)	1.29 (1.12-1.50)	-0.01
≥3 GDM or GHTN occurrences	1.99 (1.48-2.67)	1.98 (1.48-2.65)	-0.01
2 GDM and or GHTN occurrences	Reference	Reference	
≥3 GDM or GHTN occurrences	1.54 (1.13-2.09)	1.53 (1.13-2.09)	-0.01

Table 5. Comparing effect estimates of the composite cardiovascular disease outcome (across 16 exposure categories), with and without inclusion of years of pregnancy to account for secular trends in the diagnosis of gestational diabetes

Exposure	**Excluding years of pregnancy in model**	**Including years of pregnancy in model**	**Absolute Δ HR**
No GDM or GHTN	Reference	Reference	
Only GHTN (No GDM)			
GHTN in first pregnancy	1.53 (1.35-1.74)	1.53 (1.34-1.74)	0
GHTN in second pregnancy	1.60 (1.30-1.98)	1.60 (1.30-1.97)	0
GHTN in both pregnancies	2.19 (1.79-2.68)	2.18 (1.78-2.67)	-0.01
Only GDM (No GHTN)			
GDM in first pregnancy	1.38 (1.15-1.65)	1.39 (1.16-1.66)	+0.01
GDM in second pregnancy	1.41 (1.21-1.65)	1.41 (1.21-1.65)	0
GDM in both pregnancies	1.69 (1.39-2.06)	1.68 (1.38-2.05)	-0.01
Combinations of GHTN + GDM			
GHTN in first pregnancy + GDM in first pregnancy	2.00 (1.20-3.32)	2.01 (1.21-3.33)	+0.01
GHTN in second pregnancy + GDM in second pregnancy	2.42 (1.34-4.39)	2.43 (1.34-4.39)	+0.01
GHTN + GDM in both pregnancies	4.73 (2.68-8.35)	4.71 (2.67-8.31)	-0.02
GHTN in first pregnancy + GDM in in second pregnancy	1.82 (1.17-2.83)	1.82 (1.17-2.82)	0
GDM in first pregnancy + GHTN in second pregnancy	1.51 (0.57-4.02)	1.51 (0.57-4.03)	0
GHTN in first pregnancy + GDM in both pregnancies	2.71 (1.63-4.50)	2.70 (1.62-4.48)	-0.01
GHTN in second pregnancy + GDM in both pregnancies	2.43 (1.09-5.43)	2.43 (1.09-5.41)	0
GDM in first pregnancy + GHTN in both pregnancies	2.49 (1.04-6.00)	2.48 (1.03-5.96)	-0.01
GDM in second pregnancy + GHTN in both pregnancies	2.60 (1.40-4.85)	2.58 (1.39-4.81)	-0.02

7.5 Broad study design considerations

7.5.1 Strengths and limitations

My study has certain limitations that need to be acknowledged. Administrative datasets serve as powerful tools for clinical investigators; however, their utilization must be coupled with caution of their inherent constraints. Healthcare databases primarily gather information for physician reimbursement and administrative oversight purposes, rather than explicitly for research objectives. Consequently, the data accuracy may be a concern for some variables, particularly diagnostic codes. The accuracy of using diagnostic codes depends largely on the correct documentation of the diagnosis by physicians, availability of records, and accurate interpretation and review by the medical coder/physician throughout the evaluation procedure. I applied validated diagnostic codes for each exposure and outcome of interest to mitigate potential misclassification.

The health administrative definition used in my study was not able to accurately distinguish between type 1 and type 2 diabetes. However, it is important to note that over 95% of all diabetes cases in adults are type 2 diabetes.[11,12] It is worth mentioning that women diagnosed with GDM and/or GHTN may have more interactions with the healthcare system compared to those without such a medical history. This increased interaction may lead to more testing and diagnoses of diabetes, hypertension, and CVD, which could potentially introduce a detection bias towards overestimating the risk of these diseases in mothers. Nevertheless, it is important to highlight that the observed increase in risk in my study was substantial and unlikely to be explained solely by detection bias. Another limitation is the potential misclassification of individuals with non-European ancestry who were born in North America, Europe, or Australia but reported a European first language. These individuals were classified in the reference ethnocultural category; this approach would misclassify second generation immigrants and later generations. However, it is worth noting that individuals who report a European language as their first language are likely to share some behaviors with the reference group due to the process of acculturation.[298]

Unfortunately, I did not have access to data on health behaviors, which could have helped confirm the mechanisms behind the higher risks observed in women with a single occurrence of GDM and/or GHTN in a second pregnancy compared to occurrences in a first pregnancy, with diabetes and hypertension. Having information of health behaviors may also have helped us confirm the mechanisms behind the highest risks observed among those with recurrent occurrences in all of my

analyses, or the increase in risk when partners of women had a history of diabetes, hypertension and/or CVD. However, previous studies have indicated that there is often concordance of health behaviors within couples,[299-301] which suggests that this could be a contributing factor. Additionally, it is important to mention that I did not have data on GDM/GHTN management strategies, laboratory values to corroborate ICD-coded diagnoses, prepartum weight status, gestational weight gain, and smoking status. As described in **Chapter 7.1.7**, the appropriateness of accounting for obesity in the analysis of the association between GDM/GHTN and future CMD risk can be debated if obesity is considered to be on the causal pathway. To address this, I conducted sensitivity analyses that indirectly adjusted for obesity while modelling the hazards for each outcome of interest, in addition to my primary analyses that did not, allowing me to compare effect estimates from both of these analyses. Similarly, I applied identical methods of simple sensitivity bias analysis to indirectly account for the effects of smoking through indirect adjustment, but acknowledge that residual confounding may exist. Adjusting for unmeasured confounders using this method requires the model to adjust for one unmeasured variable at a time and for the unmeasured variable to be dichotomous.

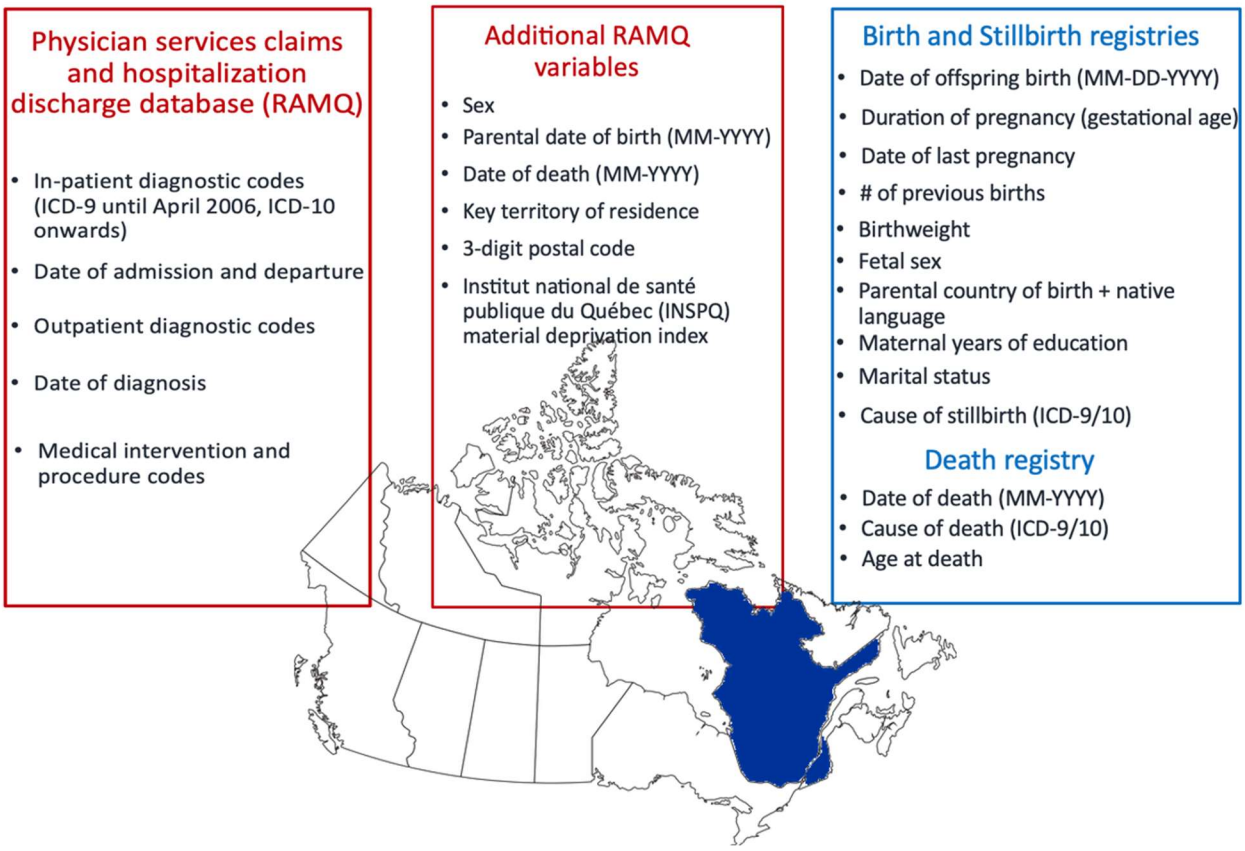
In summary, my analyses build upon the scarce literature on the topic of cumulative and sequential occurrences of GDM/GHTN, and highlight the importance of refining diabetes, hypertension and CVD risk among women with such comprehensive available when formulating prevention strategies. The strengths of my study include its cohort design, large sample size, the incorporation of validated definitions for my exposures and outcomes, and the inclusion of indicators of ethnocultural background, deprivation level, and co-occurring adverse pregnancy outcomes (preterm birth, SGA and LGA; GHTN when assessing diabetes risk, GDM in hypertension risk assessment), utilizing information on offspring size and gestational length of the pregnancy. These are factors that are not typically available in health administrative database studies.

7.5.2 Utilization of health administrative databases

My dataset was created by merging health administrative, birth registry, and death registry databases for the purpose of my studies. The health administrative database used are maintained by the RAMQ, a government agency that administers universal coverage for physician services in Quebec, Canada. This program covers 99% of Quebec residents, and approximately 85-95% of medical visits billed to RAMQ are on a fee-for-service basis. In order to create a comprehensive database linking mother-father-offspring demographics (family tetrads) and outcomes, the Institut de la statistique du Québec

performed probabilistic data linkage between the Régie de l'assurance maladie du Québec databases and vital statistics data (Quebec's Birth, Stillbirth and Death Registries; **Figure 12**) based on multiple identifiers using specialized software (G-Link, designed by Statistics Canada). Briefly, this probabilistic matching method helps to find matching records between two different source files. This strategy works by calculating the likelihood that two records from separate files belong to the same individual, incorporating comparison rules/algorithms that consider various factors to make accurate matches between records. By using this method, the Institut de la statistique du Québec can make the most of the available information when linking data to files from the Régie de l'assurance maladie du Québec, even if there are missing data or errors. The G-link software can handle a wide range of matches, allowing it to accommodate for missing data (across source files) or mismatch errors. Using this information, the software adjusts the importance given to different values and generates the probability that two records make a concordant pair.

Figure 12. Linkage of the Régie de l'assurance maladie du Québec and Institut de la statistique du Québec datasets



7.5.3 Consideration of follow-up time and alternative models for survival analysis

My primary objective was to evaluate the association between patterns of my pregnancy-specific exposure(s) and the development of CMD over time. With regards to the time considerations, I conducted survival analyses to accommodate variations in follow-up duration, which was crucial in my investigation. I generated Kaplan Meier plots and developed adjusted Cox PH models. I did not adjust for other events occurring between the exposure and outcome that I deemed part of the causal pathway (e.g., I did not adjust for diabetes or hypertension developed during the follow-up when evaluating associations between GDM/GHTN and CVD). I did not identify any key time-dependent covariates in my analyses that were important to consider. I ensured that all variables met my PH criteria assumption, validated through survival plots and Schoenfeld residuals.

While Cox models do not assume a baseline hazard, Weibull models account for specified baseline hazards that vary monotonically (in one direction) as a function of survival time over the years of follow-up. I considered that this could have been relevant in our cohort of young- to middle- aged women, given that CMD baseline hazards increase monotonically with age, rising substantially after 50 years of age, and follow-up is up to 29 years. Employing a Weibull regression model offers a valuable analytical approach due to its flexibility in modeling time-to-event data and its ability to accommodate varying baseline hazards. While exploring various parametric regression models, including the Weibull model, I found that the estimates obtained were comparable to those derived from the Cox proportional hazards model (**Table 6**). Ultimately, I opted for the Cox model due to its widespread familiarity to clinical audiences.

Table 6. Weibull regression estimates compared to Cox proportional hazards estimates of the association of GDM with incident diabetes

	Variable	**Hazard ratio (95% CI) from Weibull regression**	**Hazard ratio (95% CI) from primary analysis**
Exposure	**Gestational diabetes occurrences**		
	No GDM	*Reference*	*Reference*
	GDM in first pregnancy	3.68 (3.45-3.93)	4.35 (4.06-4.67)
	GDM in second pregnancy	6.03 (5.73-6.35)	7.68 (7.31-8.07)
	GDM in both pregnancies	11.3 (10.7-12.0)	15.8 (15.0-16.6)

7.5.4 Consideration of alternative study designs

To explore the connections between GDM and/or GHTN and the cardiometabolic well-being of the mother, various observational study designs can be considered. One potential design is a longitudinal prospective study, in which expectant mothers are regularly evaluated for diabetes, hypertension, and CVD throughout pregnancy and postpartum. This type of study would offer valuable and high-quality data. However, it is important to note that prospective cohort studies require a significant amount of time to complete, especially when the outcome of interest may take decades to manifest. Moreover, the need for regular reassessments adds to the expenses and resources required; performing a prospective cohort study for this type of research question would drastically reduce my sample size, ultimately leading to reduced statistical power and the inability to detect differences in first- versus second-affected pregnancies. It is also worth mentioning that selection bias may come into play, as individuals who volunteer to participate may differ from the general population. Additionally, the Hawthorne effect, characterized by altered behavior due to awareness of being observed, could potentially impact the study's outcomes. Given these important limitations, prospective follow-up of study participants may be considered less relevant to addressing specific research questions, especially when provincial health administrative databases with universal coverage are available.

Alternatively, a retrospective design offers the advantage of using data from a broad population over an extended duration and at reduced expense. In particular, my research studies employ population-based health administrative data, which can mitigate selection bias since participation does not rely on volunteers, but rather data accrues as part of routine healthcare practices. Furthermore, I leveraged health administrative data to identify diagnostic codes at the time of their record, mitigating the potential issue of recall bias that is typical in studies that instead rely on participant survey responses to ascertain the exposure or outcome of interest. However, the utilization of population-based health administrative data introduces potential issues such as detection bias and the misclassification of both disease exposures and outcomes (as discussed in **Chapter 7.5.1**). Notably, since health administrative databases primarily capture interactions with the healthcare system, asymptomatic disease outcomes are more likely to be identified among frequent healthcare users compared to infrequent or non-users. Individuals who seldom or never consult a physician may erroneously be categorized as free of disease, despite potentially having an undiagnosed condition. I leveraged long follow-up periods (up to 29 years of follow-up), made possible using these data sources, allowing me to accommodate for delays in symptom presentation and/or patient visits.

Lastly, I designed my studies to warrant that all women had at least two livebirth pregnancies during the exposure window, and subsequently censored additional pregnancies detected after the index date. I performed this approach to ensure that the number of pregnancies was kept as uniform as possible among my study cohort, given that parity itself is linked with future CMD risk.[284,285] Furthermore, in a simulation study conducted by Grandi *et al.*,[302] the investigators assessed the association between several similar important predictors (including GHTN, GDM, SGA, preterm birth, among other covariates) with CVD-free survival using Cox PH models, and compared effect estimates from four different cohort approaches: those with first deliveries only, a random sample of one delivery per woman, all eligible deliveries per woman, and all eligible deliveries with censoring at subsequent pregnancies. Aligned with my methodological approach described above (ensuring uniform parity), findings from this simulation study concluded that models developed using only first deliveries were less generalizable to multiparous women, and likely underestimate the hazards if the outcome is associated with parity. For example, while a GHTN-affected pregnancy was shown to be associated with 30% reduced hazards (HR=0.70, 95%CI 0.66-0.75) in CVD-free survival among women with only a first delivery, GHTN was associated with a 45% decrease (HR=0.55, 95%CI 0.51-0.59) in CVD-free survival hazards among the cohort of women with a random sample of deliveries. Similar discrepancies in HRs were demonstrated for GDM when comparisons were drawn across the aforementioned cohorts (HR=0.32 [95%CI 0.30-0.35]) versus HR=0.41 [95%CI 0.37-0.45], respectively). Differences in the effect estimates were even more pronounced for SGA and preterm birth covariates when altering the cohort design. Thus, to increase transportability and applicability, the authors suggest that separate study cohorts are carefully derived based on the woman's parity during the exposure window, to allow the study findings to accurately reflect the target population intended for assessment in real-world practice.

7.6 Implications for clinical practice and public health policy

To mitigate the impact of CMD, it is essential to pinpoint populations at heightened risk for timely evaluation and intervention concerning modifiable risk elements. Pregnancy constitutes a crucial juncture in a woman's life, marked by significant physiological alterations aimed at facilitating fetal growth and development. This period offers a distinct opportunity for early assessment of cardiometabolic well-being. The intricate interplay between maternal physiology, fetal advancement, and subsequent maternal health outcomes emphasizes the necessity of comprehending cardiometabolic risk factors during this critical phase. Specifically, GDM and GHTN stand out as

modifiable pregnancy-associated indicators of diabetes, hypertension, and CVD risk in women spanning from young adulthood to middle age.

My findings underscore a departure from the conventional understanding prevalent in prior studies that collapse GDM/GHTN history as an 'ever/never' dichotomy without considering the number of occurrences or its sequence, information that is often readily available through review of a woman's medical charts. As described in Manuscripts 1 and 2, not all women with a single of GDM or GHTN occurrence are on the same trajectory of risk for developing diabetes or hypertension, respectively. This insight holds significant implications for both the research community and clinicians. For example, my findings imply that women with a GDM occurrence in a first pregnancy, who do not develop either diabetes between pregnancies or GDM in the second pregnancy, may have implemented effective preventive measures against diabetes. Similar findings were demonstrated when assessing the magnitude of the association between patterns of GHTN and hypertension development. If validated, it is advisable to encourage these women to maintain these measures. Conversely, the emergence of new-onset GDM or the recurrence of GDM/GHTN in a subsequent pregnancy should prompt action for prevention or adjustments to ongoing interventions. Although, this pattern was not observed for CVD, I demonstrated that cumulative occurrences of GDM/GHTN are associated with escalating risk, and women should be encouraged to implement healthful behaviors, as early as the first occurrence, in order to mitigate climbing risks associated with increased occurrences. Furthermore, for an outcome as multifactorial as CVD, I provide evidence to shift that paradigm that GDM and GHTN have independent effects as considered in most studies, but that both conditions may be operating synergistically. I could not consider modelling GDM/GHTN conjointly for the diabetes and hypertension outcome given departures from the PH assumption, as described in **Chapters 7.1.2 and 7.2.2**.

In a clinical context, my work underscores the early stage at which GDM and GHTN provide an opportune moment for health monitoring and lifestyle modifications. Specifically, these findings emphasize pregnancy as an early opportunity to initiate health monitoring and lifestyle adjustments, with GDM and GHTN serving as important risk signals for future CMD risk. Such interventions hold promise in mitigating the burden associated with diabetes, hypertension, and CVD, particularly in cases where the woman experiences an occurrence in a later pregnancy or for the case of CVD, when she experiences both conditions concurrently. Overall, my findings reinforce the notion of a

personalized risk estimation towards estimating diabetes, hypertension, and CVD risk in women, along with necessitating tailored prevention strategies and fair referral pathways to alleviate the burden of CMD.

7.7 Major future research directions

Scarce previous studies have examined the risks of CMD in relationship to the cumulative number of complicated pregnancies or only among women with recurrent these indicators occurring both in the first and second pregnancy. My team and I are among the first investigators to quantify the magnitude of risk associated with of GDM or GHTN and these long-term outcomes among women with an initial occurrence in a second pregnancy. My supervisor is also one of the first investigators to assess co-occurring patterns of GDM and GHTN occurrences in a single pregnancy, in relation to diabetes, hypertension and CVD risk. Manuscript 3 built on these findings and I was able to evaluate co-occurrence across two pregnancies and associated risks with future CVD in a secondary analysis. Future studies should build on the limited evidence and aim to comprehensively assess both the sequence and cumulative history of GDM and GHTN onset, along with their co-occurrence. As described, CVD risk calculators often do not incorporate pregnancy-specific risk factors in their assessment; consideration of such may further refine risk estimation for maternal diabetes, hypertension and CVD, among young reproductive-aged women. Thus, a natural extension of this may also aim to test, replicate, and validate if risk engines can be enhanced with potential consideration of these indicators among other cohorts of young multiparous women. Following the refinement of the models, it is imperative to prioritize external validation within comparable patient cohorts to evaluate the model's capacity for precise risk stratification.

In addition, incorporation of data on GDM management, lifestyle behaviors and changes (e.g., exercise and diet), and the assessment of weight in the pre- and post-partum period would be ideal to confirm my hypotheses that speculate that the increased risk of GDM/GHTN occurrence in a second pregnancy, compared to a first-affected pregnancy, can be attributed to these important factors. I did not have information on medication use, diet, or other lifestyle changes (e.g. exercise). Diet and levels of exercise are not recorded in these administrative healthcare databases. All women in Quebec require insurance for medication, but this is through private insurance plans by employers for most; the remainder have coverage through the public health plan. All residents at or above 65 years of age are covered by the public plan, but this does not apply to my cohort, as my cohort primarily includes

younger women of reproductive age (average age at baseline: 30.1 years). Accounting for such risk indicators would enhance the generalizability and applicability of future studies conducted on this important topic. Lastly, early intervention trials focusing on lifestyle modifications such as exercise and diet are of paramount importance in mitigating CMD. These trials play a crucial role in identifying effective strategies for preventing or delaying the onset of CMD among high-risk women whose pregnancies are affected by GDM/GHTN. By intervening at an early stage, when individuals may exhibit a better cardiometabolic risk profile, there is a greater opportunity to instill long-term behavior changes that can positively impact health outcomes. Lifestyle interventions targeting exercise and diet not only address modifiable risk factors but also empower individuals to take proactive steps towards better health. Moreover, such trials provide valuable insights into the efficacy and feasibility of implementing lifestyle interventions on a larger scale, ultimately contributing to the development of evidence-based public health strategies that can target GDM and GHTN as important risk signals for CMD later in life.

7.8 Closing remarks

This dissertation offers significant methodological and substantive contributions to refining and enhancing risk assessment during the perinatal period and women's long-term cardiometabolic health. In my doctoral work, I examined the association between two serious pregnancy complications, GDM and GHTN, and their association with subsequent diabetes, hypertension and CVD, as well as reviewing the evolution of GDM recommendations over time, constitutes the primary focus of this doctoral thesis. Additionally, thorough discussion is provided regarding methodological hurdles and considerations inherent in modeling the association between each of these cardiometabolic disorders across two successive pregnancies. The study's findings underscore the importance of recognizing pregnancy complications when evaluating CMD risk among women of reproductive age, emphasizing the need for a tailored risk prediction tool to facilitate early identification of individuals who would benefit from both short- and long-term monitoring and targeted treatment of important cardiometabolic risk factors. These findings lay the groundwork for the development of personalized medicine approaches to CMD risk prediction in women, offering valuable guidance for healthcare professionals in treatment decisions and policymakers in formulating recommendations for managing this high-risk population.

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Appendix A. Studies in the literature examining associations of diabetes with gestational diabetes occurrences beyond one pregnancy

A. Cohort of women with unrestricted # of deliveries

Study investigators	Study population (total number of pregnancies allowed in cohort)	Exposure definition (order considered or total number of episodes?)	Outcome definition	Other confounders accounted for (GHTN, LGA, paternal diabetes)	Comparison group / effect estimates for type 2 diabetes
Diaz *et al.*[271] Prospective cohort study (US)	47,000 women (aged 35-74 [mean age=55]; free of diabetes/breast cancer at baseline; sister with a history of breast cancer; no limit to # of pregnancies [or may not have had any pregnancy]). Enrolled: 2003-2009. Follow-up: Until 2018.	Self-assessed history of # of previous pregnancies affected by GDM (1414 women with at least 1 previous GDM. Follow-up pregnancies (514) and subsequent GDM not considered in follow-up.	Annual self-assessment of recent diagnoses/ medications (90% follow-up; 3300 events).	• BMI at baseline • Race • Education • Time since last GDM diagnosis (time-dependent covariate)	Any history versus absence of GDM (reference group; may include women who did not even have pregnancy) HR= 2.50 (2.15-2.91). HR= 5.07 (3.36-7.65) when including time_since_GDMdiag interaction. Cumulative number of GDM pregnancies (did not consider total number of past pregnancies or ordinal pregnancy number; reference group includes women who may have had no pregnancy) – no subsequent pregnancy required Absence of GDM (reference group) 1 occurrence of GDM, HR= 2.26 (1.90-2.69) 2 occurrences of GDM, HR=3.24 (2.32-4.52) ≥3 occurrences of GDM, HR= 4.78 (2.77-8.25)

					Absence of GDM (reference group) including time since GDM diagnosis interaction. 1 occurrence of GDM, HR = 4.48 (2.93-6.87) 2 occurrences of GDM, HR = 6.22 (3.79-10.2) ≥3 occurrences of GDM, HR= = 9.35 (4.84-18.1)
Retnakaran *et al.*[267] Retrospective cohort study (Ontario)	16800 women with previous GDM diagnosed (1st pregnancy) Capture period: 2000-2007 Follow-up: Until 2008.	Medical records (ICD)	Medical records (ICD; 2731 events)	• age, • income • region of residence • Number of pregnancies (time-dependent covariate)	Two occurrences (irrespective of ordinal pregnancy number) versus one occurrence of GDM (reference group; no subsequent pregnancy) Two GDM occurrences, HR= 1.16 (1.01-1.34) GDM in first pregnancy but absence in subsequent pregnancy, HR= 0.34 (0.24-0.41)
Russell *et al.*[268] Retrospective cohort study (Ontario)	1401 Women with previous GDM (1st pregnancy) Capture period: 1989-2002	Medical records	Medical records (251 events)	• age • weight at pre pregnancy and delivery • endocrine disease/chronic HT • drug therapy	Recurrence versus one occurrence of GDM (reference group; no subsequent pregnancy) Recurrence, HR= 2.3 (1.6-3.4)

	Follow-up: Until 2002.			• GHTN at 1st pregnancy not significant • Infant weight (macrosomia?) at 1st pregnancy not significant • Preterm delivery at 1st pregnancy not significant • GDM status at subsequent pregnancy • Neonatal hypoglycemia • Apgar score (offspring health)	GDM in first pregnancy but absence in subsequent pregnancy, HR= 0.8 (0.5-1.2)
Pallardo *et al.*[273] Prospective cohort (Madrid)	788 women with previous GDM Enrollment/follow-up: 1987-1997	OGTT test (selective screening)	OGTT test (43 events)	Macrosomia/LGA – frequency tables (not in multivariable model)	Recurrence versus one occurrence of GDM (reference group; no subsequent pregnancy required) Recurrence, OR =2.40 (1.11-5.19) – estimate derived from frequency tables, multivariable showed non-conclusive association
Steinhart *et al.*[272] Retrospective cohort study (Navajo Natives-New Mexico)	111 Navajo native women with previous GDM diagnosed Capture period: 1983-1987 Follow-up: Until 1994.	Medical records	Medical records + offered GTT testing (if records showed no type 2 diabetes)	BMI at baseline Infant weight	Recurrence versus one occurrence of GDM (no subsequent pregnancy required) Recurrence, OR= 24.8 (3.0-1132.2)

Winhofer *et al.*[303] Prospective cohort (Austria)	Prior GDM, recurrent GDM, non-recurrent GDM (GDM+ no subsequent pregnancy), healthy controls matched for BMI and age.	OGTT	Glucose metabolism (OGTT)		No difference at 5 year follow-up between rec-GDM and non-recGDM regarding: glucose tolerance, insulin secretion/sensitivity.
B. Cohort of women with ≥ 2 deliveries					
Yefet *et al.*[269] Retrospective cohort study (Israel)	788 women with previous GDM diagnosed (with consecutive deliveries at the hospital; free of diabetes at baseline and between deliveries Capture period: 1991-2012 Follow-up: Until 2014.	Medical records (ICD)	Medical records (ICD; 178 events)	• Macrosomia at 1st GDM pregnancy = HR = 1.7 (1.0-2.8) • Prepregnancy BMI and GWG • Interdelivery period not significant • Miscarriage/ectopic pregnancy in past • Apgar score • OGTT • Age • Race + other demographics • Parity • Family history	<u>Recurrence versus one occurrence of GDM (subsequent pregnancy required)</u> Recurrence, HR =2.4 (1.6-2.7)
Bernstein *et al.*[270] Retrospective cohort study	1091 women with previous GDM diagnosed (and consecutive delivery within 3 years) Capture period: 2006-2012	Medical records (ICD)	Medical records (ICD)	• GWG • Inter-delivery period • Age • Race • Education • Medication (GDM severity)	<u>Recurrence versus one occurrence of GDM (subsequent pregnancy required)</u> Recurrence, HR =2.36 (131-4.27)

	Follow-up: Up to 2012, required the maximum follow-up for diabetes to be within three years after the second delivery.				

Appendix B. Studies in the literature examining associations of hypertension with gestational hypertension occurrences beyond one pregnancy

Study investigators	**Exposure groups compared** **(requiring women with at least two pregnancies)**	**Effect estimates**
GHTN (without preeclampsia)		
No studies found	N/A	N/A
GHTN (with preeclampsia)		
Brouwers *et al.*[278]	Preeclampsia in first pregnancy versus both pregnancies	Pooled RR = 2.33 (95% CI 1.86-1.92)
Lykke *et al.*[21]	Absence of preeclampsia (reference group) versus a) first-affected pregnancy, b) second-affected pregnancy, and c) recurring preeclampsia Note: this is the only study that examined preeclampsia exposure groups similar to ours; however, they did not simultaneously account for GHTN, nor did the investigators examine associations of hypertension with GHTN alone.	Absence of preeclampsia (reference group) First-affected pregnancy, HR= 2.70 (95%CI 2.51-2.90) Second-affected pregnancy, HR= 4.34 (95%CI 3.98-4.74) Recurring preeclampsia, HR= 6.00 (95%CI 5.40-6.67)
Magnussen *et al.*[279]	Absence of preeclampsia (reference group) versus a) one-affected pregnancy (irrespective of ordinal pregnancy number) and b) two pregnancies affected (irrespective of ordinal pregnancy number)	Absence of preeclampsia (reference group) One affected pregnancy, HR=3.1 (2.2-4.3) Two affected pregnancies, HR=
Spaan *et al.*[280]	First-affected pregnancy versus recurring preeclampsia	First-affected pregnancy (reference group) Recurrent preeclampsia, HR= 4.3 (95%CI 1.60-11.5)
Engeland *et al.*[281]	Absence of preeclampsia (reference group) versus a) one-affected pregnancy, and b) two-affected pregnancies	Absence of preeclampsia (reference group) One-affected pregnancy, HR= 2.0 (95%CI 2.0-2.0) Two-affected pregnancies, HR= 2.8 (95%CI 2.7-3.0)
GHTN (with or without preeclampsia)		
Van Oostwaard *et al.*[217]	First-affected pregnancy (reference group) versus recurring GHTN Note: the investigators exposure definition includes those with preeclampsia superimposed on hypertension (methodological flaw given that hypertension is their outcome of interest)	First-affected pregnancy (reference group) Recurring GHTN, HR= 3.7 (95%CI 2.3-6.1)
Van Oostwaard *et al.*[274]	First-affected pregnancy (reference group; occurring in the term period of pregnancy) versus recurring GHTN	First-affected pregnancy (reference group) Recurring GHTN, HR= 2.8 (95%CI 1.5-2.3)

Van Oostwaard *et al.*[276]	First-affected pregnancy (reference group; occurring in the preterm period of pregnancy) versus recurring GHTN	First-affected pregnancy (reference group) Recurring GHTN, HR= 8.7 (95%CI 3.30-23.0)
Auger *et al.*[275]	Absence of GHTN (reference group) versus a) first-affected pregnancy, and b) recurring GHTN Note: the investigators exposure definition includes those with preeclampsia superimposed on hypertension (methodological flaw given that hypertension is their outcome of interest)	Absence of GHTN (reference group) First-affected pregnancy, HR= 3.7 (95%CI 3.5-3.9) Recurring GHTN, HR= 7.2 (95%CI 6.6-7.8)
Stuart *et al.*[277]	Absence of GHTN (reference group) versus a) first-affected pregnancy, b) second-affected pregnancy, and c) recurring GHTN Note: this is the only study that examined GHTN (with or without preeclampsia) exposure groups similar to ours; however, they did not simultaneously account for GDM, nor did the investigators examine associations of hypertension with GHTN alone or preeclampsia, separately (exposure definition collapses them both together).	Absence of preeclampsia (reference group) First-affected pregnancy, HR= 1.85 (95%CI 1.73-1.98) Second-affected pregnancy, HR= 2.40 (95%CI 2.18-2.64) Recurring preeclampsia, HR= 3.53 (95%CI 3.17-3.93)

Appendix C. Studies in the literature examining associations of cardiovascular disease with gestational diabetes/gestational hypertension occurrences beyond one pregnancy

A. Defined cohort of women with ≥2 deliveries

i) Follow up after the second delivery

Study investigators	Exposure Definition			Other APOs accounted for	Effect Estimates
	Preeclampsia superimposed on pre-existing hypertension	*GHTN with preeclampsia*	*GHTN without preeclampsia*		
Wikstrom *et al.*[304]		☑	☑	None[a]	<u>Ischaemic heart disease</u> Reference group: Women with no GHTN (with or without preeclampsia) in first or second pregnancy First-affected pregnancy, incidence rate ratio (IRR) = 1.9 (95%CI 1.5-2.4) Second-affected pregnancy, IRR= 2.4 (95%CI 1.8-3.2) Recurring GHTN, IRR= 2.8 (95%CI 2.0-3.9)
Lykke *et al.*[21]		☑		SGA, preterm delivery, placental abruption and stillbirth	Reference group: Women with GHTN (without preeclampsia) or women with no GHTN in first or second pregnancy <u>Ischaemic heart disease</u> First-affected pregnancy, HR= 1.4 (95%CI 1.2-1.6)

					Second-affected pregnancy, HR= 2.2 (95%CI 1.9-2.6) Recurring GHTN, HR= 3.3 (95%CI 2.7-4.1) <u>Stroke</u> First-affected pregnancy , HR= 1.3 (95%CI 1.1-1.5) Second-affected pregnancy HR= 1.7 (95%CI 1.5-2.0) Recurring GHTN, HR= 1.6 (95%CI 1.2-2.0) <u>Heart failure</u> First-affected pregnancy, HR= 1.4 (95%CI 1.1-1.8) Second-affected pregnancy , HR= 1.9 (95%CI 1.4-2.7) Recurring GHTN, HR= 2.9 (95%CI 2.0-4.2)
Riise *et al.*[305]			☑	SGA, preterm delivery[b]	<u>CVD</u> Reference group: Women with no GHTN (with or without preeclampsia), SGA, or preterm delivery in first or second pregnancy First-affected pregnancy, HR= 1.7 (95%CI 1.5-2.0) Second-affected pregnancy, HR= 2.4 (95%CI 2.1-2.8) Recurring GHTN, HR= 1.9 (95%CI 1.3-2.6)

					First-affected pregnancy + SGA/preterm, HR= 2.0 (95%CI 1.6-2.5) Second-affected pregnancy + SGA/preterm, HR= 3.0 (95%CI 2.2-4.1) Recurring GHTN + SGA/preterm, HR= 3.6 (95%CI 2.4-5.2)
ii) Follow-up initiated from first delivery					
Auger *et al.*[275]	☑	☑	☑	GDM	Reference group: Women with no GHTN (with or without preeclampsia) in first or second pregnancy <u>CVD</u> First-affected pregnancy, HR= 2.3 (95%CI 2.2-2.4) Recurring GHTN, HR= 3.9 (95%CI 6.6-4.2) <u>Ischaemic heart disease</u> First-affected pregnancy, HR= 1.9 (95%CI 1.7-2.2) Recurring GHTN, HR= 3.3 (95%CI 2.6-4.2) <u>Myocardial infarction</u> First-affected pregnancy, HR= 2.0 (95%CI 1.6-2.4) Recurring GHTN, HR=3.0 (95%CI 2.1-4.3) <u>Angina</u> First-affected pregnancy, HR= 1.9 (95%CI 1.5-2.4)

					Recurring GHTN, HR= 3.3 (95%CI 2.1-5.2) <u>Stroke</u> First-affected pregnancy, HR= 1.6 (95%CI 1.4-1.9) Recurring GHTN, HR= 3.0 (95%CI 2.3-4.1)
B. Women with ≥1 delivery					
i) Follow-up initiated from first delivery					
Skjaerven *et al.*[306]	☑	☑		None[c]	<u>CVD</u> Reference group: Women with GHTN (without preeclampsia) or women with no GHTN in first or subsequent pregnancies First-affected pregnancy + no recurrence in second, third or fourth pregnancy, HR= 1.5 (95%CI 1.2-1.9) Absence of GHTN in first pregnancy + recurrence in second, third or fourth pregnancy, HR= 2.0 (95%CI 1.5-2.6) First-affected pregnancy + recurrence in second, third or fourth pregnancy, HR= 2.0 (95%CI 1.2-3.3) Absence of GHTN in first pregnancy + ≥2 occurrences in second, third or fourth pregnancy, HR= 3.8 (95%CI 1.6-9.1) GHTN in first pregnancy + ≥2 occurrences in second, third or fourth pregnancy, HR= 5.0 (95%CI 1.9-13.3)

Haßdenteufel *et al.*[307]		☑		GDM	<u>CVD</u> Reference group: Women with GHTN (without preeclampsia) or women with no GHTN in first pregnancy or subsequent pregnancies 1 occurrence, HR=1.3 (95%CI 1.2-1.4) ≥2 occurrences, HR=1.5 (95%CI 1.2-1.9)
Kessous *et al.*[308]		☑		None[d]	<u>Total cardiovascular hospitalizations (proportions reported)</u> Absence of GHTN= 2.7% 1 occurrence= 4.4% ≥2 occurrences= 6.0% <u>Simple cardiovascular events</u> Absence of GHTN= 1.2% 1 occurrence= 1.6% ≥2 occurrences= 2.2% <u>Complex cardiovascular events</u> Absence of GHTN= 1.3% 1 occurrence= 2.7%

					≥2 occurrences= 4.6%
ii) Follow-up initiated from last delivery					
Honigberg et al.[309]		☑	☑	SGA, preterm delivery	<u>Heart failure</u> Reference group: Women with no GHTN (with or without preeclampsia) in first or subsequent pregnancies GHTN without preeclampsia in first pregnancy only, HR= 1.3 (95%CI 0.6-2.8) GHTN with preeclampsia in first pregnancy only, HR= 1.5 (95%CI 0.9-2.4) Absence of GHTN in first+ GHTN (without preeclampsia) in subsequent pregnancies, HR= 3.2 (95%CI 1.8-5.6) No GHTN in first pregnancy + GHTN with preeclampsia in subsequent pregnancies, HR= 2.9 (95%CI 1.9-4.5) GHTN without preeclampsia in first pregnancy + GHTN (with or without preeclampsia) in subsequent pregnancies, HR= 1.7 (95%CI 0.5-5.2) GHTN with preeclampsia in first pregnancy + GHTN (with or without preeclampsia) in subsequent pregnancies, HR=3.5 (95%CI 2.1-5.8)

ii) Follow-up initiated from first delivery affected by GHTN					
Chen et al.[310]		☑	☑	Preterm delivery	<u>Heart failure</u> Reference group: Women with GHTN (without preeclampsia) affecting only one pregnancy ≥2 occurrences, HR= 2.7 (95%CI 1.6-4.7)
ii) Follow-up initiated from delivery most-severely affected by GHTN[e]					
Theilen et al.[311]		☑	☑	Preterm delivery	<u>Ischaemic heart disease</u> Reference group: Women with no GHTN (with or without preeclampsia) in first or subsequent pregnancies 1 occurrence, HR=2.1 (data non-conclusive and not shown) ≥2 occurrences, HR=3.3 (95%CI 2.0-5.4)

Note: I conducted a thorough literature search on PubMed/MEDLINE, Embase, Web of Science, Scopus, Cochrane Library and CINAHL for studies examining CVD risk associated with at various patterns of GDM occurrences. To the best of my knowledge, no previous studies in the literature have examined patterns of GDM beyond one pregnancy and its association with future CVD risk. Below, I present the findings from the literature related to CVD risk associated with patterns of GHTN occurrences.

[a]The authors attempt to account for preterm delivery and SGA in other analyses mentioned in the paper, but not in analyses examining patterns of recurrence across pregnancies (data not shown). Additionally, although the eligibility criteria required women in cohort 2 with two deliveries between 1973-1982, the follow-up was staggered by 4-14 years due to the limited coverage of the Hospital Discharge Register before 1987; therefore, the follow-up time was restricted from 1987-2001.

[b]Instead of adjusting for SGA and preterm delivery, the authors stratified the exposure by including combinations of GHTN (without preeclampsia) with SGA/preterm delivery affecting the respective pregnancy.

[b']The authors attempt to account for preterm delivery and gestational diabetes in other analyses mentioned in the paper, but not in analyses examining patterns of recurrence across pregnancies (data not shown).

[d]The authors did not present an adjusted model examining associations between CVD and GHTN recurrence. Only percentages are displayed here.

[e]The index exposed pregnancy was defined as the most severely affected pregnancy, with diagnoses ranked from least to most severe as follows: gestational hypertension, preeclampsia, HELLP syndrome, eclampsia. If two pregnancies were affected equally, then the earliest pregnancy was used.