Gestational Diabetes Mellitus and Mental Illness in Alberta

by

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Abstract

Introduction: Research has shown a bidirectional relationship between type 2 diabetes and mental illness, and worse health outcomes for patients with both illnesses than those with either condition alone. However, there is limited research on the relationship between mental illness and gestational diabetes mellitus (GDM), and their impact on future health outcomes. This thesis investigated three questions: (1) the impact of GDM on the development of mental illness during pregnancy and post-partum; (2) the impact of mental illness prior to pregnancy on the development of GDM in pregnancy; and (3) the impact of GDM, mental illness, and both illnesses on the development of type 2 diabetes, hypertension and cardiovascular disease (CVD).

Methods: Administrative data from a population perinatal health registry was linked to physician claims, hospitalization records and outpatient visits to identify diagnosis of mental illness, diabetes, hypertension and cardiovascular disease among women who delivered in Alberta, Canada between April 1, 1999 and March 31, 2010. For the first study, generalized estimating equations (GEE) were used to determine the odds ratios of developing a mental illness during pregnancy and post-partum among women with GDM. GEE was also used for the second study, determining the odds ratio of GDM comparing women with and without a history of mental illness. The third study used cumulative incidence curves and cox proportional hazards to compare the development of diabetes, hypertension and cardiovascular disease among women with the following conditions during pregnancy: no GDM or mental illness, mental illness only, GDM only, or both GDM and mental illness.

Results: GDM in pregnancy was not associated with diagnosis of incident mental illness in pregnancy (OR=1.06, 95%CI=0.98,1.13) or post-partum (OR=1.03, 95%CI=0.97,1.10). The

odds of developing GDM was higher for women with a history of mental illness than without (OR=1.10, 95%CI=1.06,1.14). Women with both GDM and mental illness had the highest hazard rates for diabetes (22.4, 95%CI=19.2, 26.1), hypertension (2.0, 95%CI=1.7,2.3) and CVD (1.7, 95%CI=0.9,3.4). Women with GDM only had a significantly higher risk of diabetes (20.5, 95%CI=18.4, 22.9) and hypertension (1.7, 95%CI=1.6, 1.9) than women with mental illness (1.3, 95%CI=1.1, 1.5) and (1.1, 95%CI=1.1,1.2) respectfully. The risk for cardiovascular disease was higher for women with only mental illness (1.6, 95%CI=1.3, 1.9) than those with only GDM (1.5, 95%CI=1.0, 2.3).

Conclusion: GDM does not increase the risk of developing a mental illness in pregnancy or post-partum. However, women with a history of mental disorders prior to pregnancy have an increased risk of GDM. GDM and mental illness in pregnancy each result in increased rates of chronic disease and the highest risk is for women with both GDM and mental illness.

Preface

This thesis is an original work by Qendresa Beka. No part of this thesis has been previously published.

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1 Introduction

1.1 Statement of the Problem

1.1.1 Diabetes and mental illness

There is a greater prevalence of mental illness in patients with diabetes than in the general population [1–4]. However, there is limited research on whether this association exists during the perinatal (pregnancy and post-partum) period. Gestational diabetes mellitus (GDM) is a unique type of diabetes as the glucose metabolism disorder typically returns to normal following pregnancy [5]. GDM and mental illness in the perinatal period can each have negative consequences on maternal and child health. Having a better understanding of these illnesses may lead to more informed healthcare practices and fewer adverse health outcomes.

Mental illnesses during the perinatal period have been associated with numerous pregnancy, delivery and neonatal complications [6–9]. The most common mental illnesses in the perinatal period are anxiety and affective disorders.[8,10,11] Estimates for the prevalence of affective disorders range from 5 – 18% in the prenatal (pregnancy) period and from 10 – 20 % in the post-partum period [11–16]. Estimates for anxiety prevalence are lower, ranging from 6 – 8% in the prenatal period and 8 – 12% post-partum [11,13–15]. The wide ranges in prevalence are due to different diagnostic tools used to classify "anxiety" and "affective" disorders and variability in the exclusion/inclusion criteria used for each study population. Mental disorders can indirectly affect pregnancy outcomes by influencing the mother's behavior [6,17]. Mothers with a mental illness are less likely to maintain an active lifestyle and have a healthy diet [7,18–21]. Poor diet and low physical activity can lead to obesity, which increases the risk of congenital malformations and delivery complications [22]. Poor nutrition during pregnancy can also be detrimental to the baby's cognitive development [21]. Some evidence suggests that mental illness may also have direct effects on pregnancy outcomes through biological mechanisms [7,17,23]. Although the mechanisms remain uncertain, research has shown that having a mental illness in pregnancy increases the risk of complications such as placental abnormalities, antepartum hemorrhages, fetal distress, preterm birth, and low birth-weight infants [9,14,24–26]. Mental illness after delivery can also result in adverse outcomes. Mothers with mental illness in the post-partum period may

not provide sufficient care or adequate parenting for their infants [7]. This may result in developmental delays or behavioral disorders in childhood [7,27]. Without adequate intervention, these effects can cause long-lasting consequences for the child. Given these negative outcomes, it is necessary to learn more about mental illness in the perinatal period in order to develop strategies for intervention.

In Canada, there is no universal screening for mental illness during pregnancy or post-partum. A physician's awareness of mental health issues depends on the patient's willingness to report their symptoms and the physician's own attentiveness. This may result in physicians missing cases of mental illness and patients not receiving necessary treatment[28,29]. On the other hand, universal screening of GDM during pregnancy allows most cases to be captured and provided treatment[30,31]. If there is an association between GDM and mental illness in pregnancy, it may alert physicians to check for symptoms of mental illness in women with a GDM diagnosis. Although glucose intolerance typically returns to normal following delivery, the presence of GDM in pregnancy substantially increases the risk of future diabetes for both mother and child [32–34]. Untreated GDM increases the risk of complications during pregnancy and delivery[35]. Some of these complications include pre-eclampsia, hypertension and placental abnormalities[36,35,37,38]. To reduce these complications, women in Canada are screened for GDM at approximately 24 to 28 weeks of pregnancy[31]. There has been a worldwide increase in the prevalence of GDM in the last decade, resulting in increased research in this area [32,39]. However, there has been little focus on the association between GDM and maternal mental illness. Accordingly, the objective of this thesis is to investigate the relationship between GDM and mental illness in the perinatal period.

1.1.2 Gestational Diabetes and Perinatal Mental Illness

1.1.2.1 Mental illness and the development of GDM

Mental illness prior to pregnancy may directly or indirectly contribute to the development of gestational diabetes. In the general population, patients with mental illness have an increased risk of type 2 diabetes (T2DM)[2,3,40,41]. People with mental illness may engage in unhealthy lifestyles and behaviors, which can indirectly lead to T2DM [41,40,42]. However, some evidence has shown that even after controlling for lifestyle factors such as diet, physical activity, and smoking, those with mental illness have a greater likelihood of developing T2DM[40]. Although these mechanisms

may also apply to the perinatal period, there is less evidence on the relationship between mental illness and the development of gestational diabetes.

Only recently have researchers started looking into the mental history of women with GDM. Bowers et al[43] conducted a retrospective cohort study to determine whether a medical history of depression was associated with a diagnosis of GDM. They obtained medical chart and discharge records for over 120,000 women who gave birth across 19 hospitals in the United Sates. Depression and GDM were identified using ICD9 codes. They found that women with a previous history of depression had increased odds of developing GDM compared to those without a history of depression. Although this study had a large, multi-site sample size and adjusted for a number of key confounding variables, it also had some limitations. They did not have information on smoking status, and used insurance plan coverage as an indicator of socio-economic status (SES), which may not have been an accurate measure. They also did not specify the length of the time-period they referred to as "history" of depression. If women had different lengths of study "history," some women may have been misclassified in terms of their past diagnosis of mental illness.

A recent study using self-reported history of depression also showed a greater likelihood of having a history of mental illness amongst women with GDM compared to without GDM[44]. However, this study only studied 135 women and self-reported measures of mental illness history may not have been reliable. Another study compared depressive symptoms between women at high risk for GDM to those in the general population[45]. High risk was determined by either having a history of GDM or a pre-pregnancy BMI >= 30 kg/m^2. They did not find a difference in depressive symptoms between women at low or high risk for GDM. Further research is needed to better understand the association between mental illness prior to pregnancy and the development of GDM.

1.1.2.2 GDM diagnosis and mental Illness in pregnancy

Some women with no prior history of mental illness may develop a mental disorder during pregnancy. In the general population, it has been posited that the higher prevalence of mental illness in diabetic patients may be due to biological mechanisms related to diabetes, or due to the psycho-social impact of being diagnosed with a chronic disease [2,42,46]. A number of qualitative

studies have explored the effect a diagnosis of GDM has on women's emotions and experiences during pregnancy[47–51]. Initially following a GDM diagnosis, common reactions include feeling upset at the diagnosis, guilty about unhealthy lifestyle choices and concerned about pregnancy complications [49–51]. Learning to adapt to GDM and the requirements associated with it can be challenging during the pregnancy period. Monitoring glucose levels and following lifestyle recommendations may be overwhelming for women, and some may not feel capable of doing so [47,48]. In cases of low socio-economic status, women may not have the resources to make physical activity or dietary changes [49,51]. The individual or combined impact of these factors may contribute to the development of mental disorders following a GDM diagnosis.

A number of small studies have compared depression and anxiety between women with and without GDM. However, these studies vary widely in their definitions of depression and anxiety, and few have used clinical diagnoses as their outcome variable. Tools used to identify mental disorders have included questionnaires such as the Profile of Mood States-Bipolar Form, Edinburgh Postnatal Depression Scale (EPDS), Patient Health Questionnaire (PHQ-9), Center for Epidemiologic Studies Depression Scale (CES-D), and the Spielberger State-Trait Anxiety Inventory. Given the wide range of definitions and study samples used, results have been inconsistent regarding the association between GDM and the development of depression or anxiety. Some studies show no difference in the mental health of women diagnosed with GDM compared to those without GDM [44,52–57]. Others suggested that the initial diagnosis causes emotional distress, but women return to baseline later in the pregnancy [58–60]. Contrarily, a recent study using the EPDS found that women with GDM had greater elevated depressive symptoms than those without GDM.[61]

A larger study by Kozhimannil et al[62] used administrative data from New Jersey, US, to compare the prevalence of perinatal depression between women with and without diabetes. Prescription drug claims and ICD9 codes were used to identify diabetes and major depression, and the perinatal period was defined as the time frame from 6 months prior to pregnancy to one-year post-partum. They found that perinatal depression was nearly twice as prevalent among women with diabetes compared to women without diabetes. The odds ratios were similar between women with gestational diabetes and pre-gestational diabetes, albeit slightly higher for women with GDM and taking insulin compared to GDM without insulin. They did not explicitly

compare the odds ratio of depression between the pregnancy period and the post-partum period. However, once they restricted their analysis to only new cases of depression in the post-partum period, the postpartum odds ratio did not significantly differ from the odds ratio of the entire perinatal period. Katon et al[63] argued that the study by Kozhimannil was limited in that it only included low-income women and didn't adjust for the presence of other chronic medical conditions. In their study, Katon et al[63] used a large sample from an ongoing cohort of pregnant women to compare the prevalence of depression between women with and without GDM. After adjusting for chronic medical conditions, they found that women with GDM had similar odds of having depression during pregnancy as women without GDM. However, Katon et al[63] used the Patient Health Questionnaire (PHQ-9) rather than clinical diagnosis to identify depression.

Both studies were limited in that they did not distinguish between pre-existing and incident cases of depression, and did not adjust for maternal history of mental illness. Given that anxiety and depressive disorders are often recurrent, having a history of mental illness may confound the association between GDM and mental illness. Further research is needed to ascertain the association between GDM and the development of new-onset mental illness in pregnancy.

1.1.2.3 GDM diagnosis and mental illness post-partum

As with other chronic illnesses, when patients are diagnosed with diabetes it may have an impact on their psychological wellbeing. Adjusting to treatment regimens or lifestyle recommendations can be demanding, stressful and potentially isolating. Unlike type 2 or type 1 diabetes, gestational diabetes does not normally persist after delivery. If the psychosocial impact of managing diabetes contributes to mental disorders, then it is possible that symptoms of mental illness are also alleviated following delivery. By examining the incidence of mental illness prior to GDM, during the GDM period, and post-partum, we will gain insight into the impact of GDM diagnosis on mental illness. Furthermore, GDM increases the risk of developing type 2 diabetes for both the mother and child [33,64,65]. Having a post-partum mental illness may reduce a woman's ability to engage in healthier lifestyle choices, leading to an increased risk of developing type 2 diabetes [17,20,66]. Learning about the association between GDM and post-partum mental illness may broaden our understanding of the relationship between GDM and the development of type 2 diabetes.

There is reason to believe that GDM may influence the development of mental illness in the post-partum period. Qualitative research has suggested that many women remain concerned about the implications of GDM after delivery [47]. Along with the new roles and responsibilities a newborn brings, new mothers may find it challenging to maintain diet and activity recommendations.[17] For women that did not engage in healthy lifestyles prior to pregnancy, adopting new habits while also adjusting to new parental duties may cause increased levels of stress and negative affect [47–49]. The studies that have examined the relationship between GDM and postpartum mental illness have focused mainly on post-partum depression and have varied in their methods and results. A prospective cohort by Kim et al[54] showed that CES-D scores for post-partum depression did not differ between women with GDM in pregnancy compared to those without GDM. Four smaller studies, one using the Mental Health Inventory (MHI-5)[60], two using the Edinburgh Postnatal Depression Scale (EPDS)[61,59], and one using the Patient Health Questionnaire-9 (PHQ-9)[52] also showed no differences in depressive symptoms post-partum. One study found that GDM did not increase the risk of postpartum depression in white or Hispanic women, but decreased the risk for African women[67]. However, findings from a recent study showed that GDM did not affect the risk of postpartum depression and race did not modify the effect[68]. In contrast to these findings, the previously mentioned large population-based study by Kozhimannil et al[62] found that the women with GDM had a greater prevalence of clinically diagnosed post-partum depression than women without GDM. There is a need for further research into the association between GDM and post-partum mental illness.

1.1.3 Long-term consequences of GDM and maternal mental illness

Women with GDM in pregnancy have a greater risk of future chronic illnesses such as diabetes, hypertension, and cardiovascular disease [33,37,38,64]. However, there is less literature on the impact of perinatal mental illness on chronic disease development. Mental illness in pregnancy and post-partum may lead to unhealthy behaviors such as poor diet, inactive lifestyles and potential substance abuse.[9,17,18,20,69] These behaviors may consequently increase the risk of developing chronic disease. In the general population, patients with comorbid diabetes and mental illness have worse long-term health outcomes than patients with diabetes alone [42,70–72]. However, studies have not compared the individual and combined effects of GDM and perinatal mental illness on long-term outcomes. Chronic diseases carry a considerable burden on the Canadian healthcare

system. Learning about the effects of GDM and mental illness on chronic disease development will be useful for developing intervention strategies.

1.2 Summary

Although research supports a strong association between diabetes and mental illness, fewer studies have investigated this association in the perinatal period. Gestational diabetes mellitus (GDM) is a type of glucose intolerance that is identified in pregnancy but typically returns to normal after delivery. There is reason to suspect a bidirectional relationship between mental illness and GDM. Women with a history of mental illness may have an increased likelihood of developing GDM, and women with GDM may have an increased likelihood of developing a mental illness in pregnancy or post-partum. However, current research on this topic shows inconsistent findings. Both GDM and mental illness in the perinatal period can result in negative outcomes for the mother and child. For this thesis, we examine the nature of the association between GDM and perinatal mental illness, and determine whether the individual or combined effects of these disorders have an impact on future chronic disease development.

1.3 Thesis Objectives

1) Investigate the association between gestational diabetes mellitus (GDM) and perinatal mental illness. This will involve the following sub-objectives:
    a. Examine the effect of pre-pregnancy mental illness on the development of gestational diabetes.
    b. Examine the effect of GDM on the development of incident mental illness during pregnancy.
    c. Examine the effect of GDM on the development of incident mental illness in the one-year period post-partum.
2) Compare chronic disease development between women with one of the following conditions in pregnancy: gestational diabetes, mental illness, gestational diabetes and mental illness, neither gestational diabetes nor mental illness.

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2 Gestational diabetes mellitus and the development of perinatal mental illness: a population-cohort study

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2.1 Abstract

Background: Studies have shown an association between mental illness and type 2 diabetes, but there is limited research regarding gestational diabetes mellitus (GDM) and perinatal mental illness. This study examined the relationship between GDM and the development of mental illness during pregnancy and post-partum.

Methods: Administrative data from a perinatal health registry was linked to physician claims, hospitalization records and emergency room visits to identify diagnoses of mental illness in women with and without GDM. The population sample included all singleton deliveries in Alberta, Canada from April 1, 2000 to March 31, 2009. Generalized estimating equations were used to determine the association between GDM and mental illness in each period.

Results: Among 326,723 deliveries, 12,140 (3.7%) of mothers were diagnosed with GDM, 84,804 (26.0%) had a diagnosis of mental illness in the two years prior to pregnancy, 46,187 (14.1%) during pregnancy and 72,457 (22.2%) in the year post-partum. Women with GDM compared to no GDM had a greater prevalence of mental illness during pregnancy (16.1% vs 14.1%, p=<0.05) and post-partum (23.3% vs 22.1%, p=<0.05). However, after excluding those with a history of mental illness, GDM in pregnancy was not associated with diagnosis of incident mental illness in pregnancy (OR=1.06, 95%CI=0.98,1.13) or post-partum (OR=1.03, 95%CI=0.97,1.10).

Conclusions: In a large population cohort of Alberta women, 14% had at least one diagnosis of mental illness in pregnancy, and 22% in the post-partum period. Mental illness was more prevalent among women with GDM than without GDM, but GDM did not increase the risk of developing new-onset mental illness in pregnancy or post-partum.

Key Words:

Gestational diabetes mellitus, mental illness, perinatal, chronic disease

2.2 Introduction

Gestational diabetes mellitus (GDM) affects 4 – 10% of pregnancies and can result in pregnancy, delivery and long-term complications[1–5]. In the general population, the prevalence of mental disorders is higher among patients with type 2 diabetes[6–9]. However, there is less research regarding the association between gestational diabetes and mental illness in the perinatal (pregnancy and postpartum) period.

Mental illnesses, anxiety and affective disorders in particular, affect approximately 20% of women in the perinatal period and can have long-lasting impacts on maternal and child health[10–13]. Despite the high prevalence, there is limited research on the aetiology of these disorders and few women are screened for symptoms of mental illness during this time period. Given that GDM is routinely screened for in pregnancy, if a link exists between GDM and mental illness, it may provide opportunity for better recognition of mental disorders.

Available literature on this association shows differing results, partly due to the wide range of tools and criteria used to define mental disorders. Some studies have shown that women with GDM do not differ from those without GDM in terms of anxiety and depressive symptoms during pregnancy [14–16]. Others have suggested that diagnosis of GDM causes temporary rises in anxiety and depressive symptoms, but women return to baseline shortly after [17–19]. Studies on mental illness in the post-partum period have focused mainly on post-partum depression and generally show that women with and without GDM do not differ in terms of post-partum depressive symptoms [15,18,20,21]. However, one large population-based study found that women with GDM were nearly twice as likely to have a depression diagnosis in either pregnancy or post-partum[22].

To ascertain the impact of GDM on the clinical diagnosis of affective and anxiety disorders, we examined administrative data from women who delivered in Alberta, Canada from April 1, 2000 to March 31, 2009. We linked a population-based perinatal database with administrative health data and compared the development of mental disorders in women with and without GDM, after adjusting for clinical and demographic variables.

2.3 Methods

2.3.1 Data

This study used population-level administrative data from the province of Alberta, Canada. The Alberta Ministry of Health (Alberta Health) houses a number of databases with demographic information on registered residents and medical information on patients who use publicly funded health services.

The databases used in this study included the following:

1. Discharge abstract database, which contains information about diagnoses and services provided for patients discharged from an inpatient bed.
2. Ambulatory care database, which contains information on diagnoses and services provided for patients during ambulatory and emergency department visits.
3. Practitioner claims database, which contains information on fee for service claims made by physicians for insured health services.
4. Alberta Health Care Insurance Population (AHCIP) registry, which records demographic and geographic information on Albertans registered under the provincial health insurance plan.
5. Alberta Vital Statistics database, which contains death dates.
6. 2006 Census data, which contains neighbourhood-level measures of socio-economic status.

The Alberta Perinatal Health Program (APHP*)* is a clinical provincial database that collects maternal, obstetrical and neonatal clinical information during the perinatal period for all deliveries in Alberta[23]. Data was obtained from the APHP on all deliveries from April 2000 to March 2009. Records were de-identified and given scrambled identifiers to allow linking between databases. Each mother's records in the APHP were linked to all her Alberta Health records from April 1997 to March 2010.

2.3.2 Variable Definitions

Women were considered to have GDM if it was coded in the APHP database. In Alberta, screening for GDM occurs between 24 and 28 weeks of pregnancy, and diagnosis information is

routinely collected by the APHP[23]. The APHP database also contained information on pre-pregnancy weight (≤45 kg or ≥91 kg), smoking status during pregnancy, parity, pre-eclampsia or eclampsia, delivery information (multiple or singleton birth, c-section, induction), neonatal outcomes (birth weight, neonatal ICU stay, neonatal death) and self-reported pre-existing chronic medical conditions such as type 1 or 2 diabetes, retinopathy, heart disease, hypertension, chronic renal disease, epilepsy, severe asthma, lupus, or Crohn's disease. Women with a pre-pregnancy weight of ≤45 kg were considered underweight and ≥ 91 kg were considered overweight. A previously published algorithm was used to determine if infants were large for gestational age[24].

The AHCIP database provided information on Aboriginal band membership and patients' 3-digit residential postal codes, which were used to determine median household income (MHI) at the neighbourhood level from the 2006 Canadian census data. Quartiles of MHI were used as indicators of socio-economic status. Postal codes were also used to determine rural residence. Previously published algorithms were used to identify South Asian or Chinese ethnicity based on patients' surnames.[25–27] Patients who were not Aboriginal, Chinese or South Asian were considered Caucasian/Other for the purposes of this study.

Mental illness was defined as having at least one hospitalization, outpatient visit or physician claim for an affective or anxiety disorder. For hospitalizations and outpatient visits, ICD9 codes were used for diagnoses that occurred prior to 2002 and ICD10-CA codes for diagnoses thereafter. For physician claims, ICD9 codes were used for the duration of the study period. Box 2.1 provides detailed algorithms for the diagnosis codes included to define "affective" and "anxiety" disorders. These algorithms originated at the Manitoba Centre for Health Policy (MCHP), which used hospitalization information and physician claims to identify cases of mental disorders in women during the perinatal period[28]. We also considered an alternate algorithm to classify cases of anxiety if patients were diagnosed with anxiety at least twice within one year (Box 2.A1, Appendix).

2.3.3 Study Population

The study population consisted of singleton deliveries in Alberta from April 2000 to March 2009. Deliveries were excluded if mothers were not between the ages of 12 and 54, were not

Alberta residents, had pre-existing diabetes prior to the pregnancy, or were missing information on GDM diagnosis.

2.3.4 Statistical Analysis

Means and standard deviations of continuous variables were compared using two-tailed t-tests, and proportions were compared using chi-square tests. The entire cohort was used for prevalence and incidence measures, but women with a history of mental illness prior to pregnancy were excluded in the regression models. Logistic regression was used to estimate crude and adjusted odds ratios of mental illness during pregnancy and post-partum, with each delivery as the unit of analysis and GDM status as the exposure. Data was stratified into trimesters to compare differences in odds ratios during the pregnancy period. Generalized Estimating Equations (GEE) were used to account for correlation between deliveries of the same mother. The adjusted models included the following variables: age, overweight category, nulliparity, smoking status, ethnicity, median household income, urban residence, infant NICU stay, infant death, pre-or-eclampsia, prior chronic medical conditions and fiscal year. All analyses were conducted using SAS version 9.4.

2.4 Results

2.4.1 Baseline Characteristics

There were 349,718 deliveries in Alberta between April 2000 and March 2009 (Figure 2.1). After excluding mothers who were not Alberta residents (728), were less than 18 or greater than 54 years old (4,064), had non-singleton deliveries (11,893) or were missing GDM status (3,447) our study population consisted of 326,723 deliveries from 226,923 mothers. Among these deliveries, 12,140 (3.7%) of mothers were diagnosed with GDM.

Clinical and demographic characteristics are summarized on Table 2.1. Compared to those without GDM, women with GDM were older (32.1 ±5.3 years vs 29.1 ± 5.4 years), more likely to be overweight (18.4% vs 8.2%), less likely to live in a rural residence (12.3% vs 16.5%), less likely to be nulliparous (37.1% vs 42.8%) and less likely to be a smoker during pregnancy (16.3% vs 19.4%). The GDM group had greater proportions of Aboriginal (6.9% vs 5.9%), Chinese (6.9% vs 2.9%) and South Asian (15.5% vs 8.2%) and a smaller proportion of Caucasian (70.8% vs 83.0%) women compared to the non-GDM group. There were no large differences in categories of socioeconomic status between the two groups. Women with GDM were more likely to have pre-eclampsia or eclampsia (2.4% vs 1.2%), a c-section delivery (35.9% vs 24.3%), large for gestational age infants (17.8% vs 10.4%), and infants requiring neonatal ICU stay (17.8% vs 10.4%).

2.4.2 Prevalence of mental health disorders

Among 326,723 records, 138,835 (42.5%) of mothers had at least one diagnosis of mental illness during the study time-period. The period prevalence of these disorders was 26.0% in the two years prior to pregnancy, 14.1% during pregnancy and 22.2% in the year post-partum. A greater proportion of mental illness diagnoses were for anxiety disorders than for depressive disorders (Table 2). The prevalence of mental illness was higher among women with GDM than without GDM in all three periods: prior to pregnancy (28.4% vs 25.8%), during pregnancy (16.1% vs 14.1%) and post-partum (23.3% vs 22.1%). The impact of an alternative algorithm, based on 2 anxiety claims in one year, decreased the prevalence of mental health to 16.0% prior to pregnancy, 7.5% during pregnancy and 15.5% post-partum. These results are provided in Table 2.A1 of the Appendix.

The incidence of new cases of mental illness was 6.8% during pregnancy and 9.7% in the post-partum period. There were no statistically significant differences in incidence between women with GDM and without GDM during pregnancy or post-partum (Table 2.2).

2.4.3 Perinatal mental illness

For overall mental illness in the perinatal (pregnancy and post-partum) period, the unadjusted, adjusted and GEE models each showed no statistically significant difference between the GDM and non-GDM pregnancies (Table 2.3). When restricting it to only the pregnancy period, the unadjusted model had an odds ratio of 1.11 (95%CI=1.02, 1.18) but this was attenuated to a non-significant value in the adjusted (1.06, 95% CI=0.99, 1.14) and GEE (1.06, 95% CI=0.98,1.13) models. Similarly, trimesters 1 and 2 showed significant odds ratios in the unadjusted models (1.12, 95% CI=1.02, 1.23 and 1.13, 95%CI=1.00, 1.29, respectively) but were not significant in the adjusted models. None of the three models showed significant odds ratios for trimester 3 or the year post-partum.

2.5 Discussion

In our population-based cohort of 326,723 deliveries, 3.7% were diagnosed with GDM. These women were older, more likely to be overweight and more likely to be of Aboriginal, Chinese or South Asian ethnicity. They were also more likely to have pregnancy or delivery complications, such as pre-eclampsia or eclampsia, c-section delivery, large for gestational age infants or infants requiring neonatal ICU.

In our cohort, 42% of women had at least one diagnosis of mental illness during the study period. Most diagnoses (26%) were found in the two years prior to pregnancy. Many of these cases were recurrent, as the prevalence during pregnancy and post-partum was nearly double the incidence of new cases. There was a greater prevalence of mental illness among women with GDM than without GDM prior to pregnancy, during pregnancy and post-partum. This suggested an association between mental illness and GDM. However, when we restricted to incident mental illness in pregnancy and post-partum there were no differences between women with and without GDM. Therefore, there wasn't any evidence of a temporal relationship between GDM and the development of mental illness in pregnancy or post-partum.

Our results are consistent with those reported previously. A number of small studies, using depression scales such as the Edinburgh Postnatal Depression Scale (EPDS), the Center for Epidemiologic Studies-Depression Scale (CES-D), and the Patient Health Questionnaire-9 (PHQ-9) found no differences in depressive symptoms between women with and without GDM, in pregnancy or postpartum.[15,18,20,29,30] A larger study, using the Patient Health Questionnaire-9 as well as records of antidepressant use, also found no difference between women with and without GDM.[16] Contrastingly, a recent study found that women with GDM were more likely to have elevated prenatal depressive symptoms using the EPDS than women without GDM.[20]

A recent study by Walmer et al used ICD-9 criteria to identify cases of depression, anxiety and other mental health disorders in the post-partum period for a prospective cohort of women visiting the Massachusetts General Hospital for prenatal care.[31] Similar to our study, they found no significant difference in incidence of mental illness after adjusting for clinical and demographic variables. Kozhimannil et al used administrative health records and prescription data to compare the diagnosis of perinatal depression in a cohort of women with and without

diabetes in pregnancy.[22] They found that depression in the perinatal period was nearly twice as prevalent among women with diabetes. However, they did not consider anxiety and didn't distinguish between pre-existing and incident cases of depression. Our study focused on the impact of GDM on the development of new-onset mental illness, and thus excluded women with a prior history of mental illness.

The use of administrative data posed some limitations for the study. Women were classified as having a mental illness if they had at least one physician claim, hospitalization, or outpatient visit for a mood or anxiety disorder. This may not have captured all patients experiencing a mental disorder, as symptoms of mental illness may be undetected by physicians or under-reported by patients[32,33]. Studies are currently exploring algorithms to capture mental illness using administrative data, but case definitions vary and few focus on the perinatal period[34]. When we considered another algorithm for classification of mental disorders, prevalence estimates decreased but there were still differences between women with and without GDM in each time period. Another limitation was that during pregnancy, it may be difficult to distinguish between mental illness and pregnancy-related stress or anxiety[33,35–37]. Further research combining self-reported measures with clinical diagnoses may result in more accurate classification on women with mental illness.

Using administrative data also limited the confounding variables we could adjust for in our models. Other than one variable indicating whether a woman weighed ≥91kg, there was no other measure of a woman's BMI. An algorithm based on surnames was used to identify ethnicity, which may have misclassified some patients. Patients may have also been misclassified in terms of socioeconomic status or the smoking indicator. There was no reason to suspect differential misclassification between the exposure groups, but misclassification of these variables may have resulted in residual confounding. Furthermore, we lacked information on physical activity, dietary habits, and social support, which may confound the relationship between GDM and development of mental illness.

2.6 Conclusion

Mental illness was more prevalent among women with GDM than without GDM, but the two groups were similar in incidence of new cases during pregnancy and post-partum. Therefore, this

study did not find a temporal relationship between GDM and development of mental illness. Nevertheless, 14-22% of women were diagnosed with a mental illness during the perinatal period, which signifies the need for monitoring and health care services to address these disorders. Given the negative consequences of mental illness during pregnancy and post-partum, identifying risk factors and reducing the risk for these diseases may lead to better outcomes for mothers and infants.

2.7 Figure Legends

Box 2.1 Classification of mental illness in the perinatal period

Figure 2.1 Study sample selection

Table 2.1 Comparison of maternal characteristics for deliveries in Alberta between April 1, 2000 and March 31, 2009 (N = 326,723)

Table 2.2 Diagnosis of depressive and anxiety disorders in the perinatal period among mothers of deliveries in Alberta from April 1, 2000 to March 31, 2009 (N = 326,723)

Table 2.3 Relationship between GDM and incident mental illness in the perinatal period excluding women with a history of mental illness prior to pregnancy (N = 241,919)

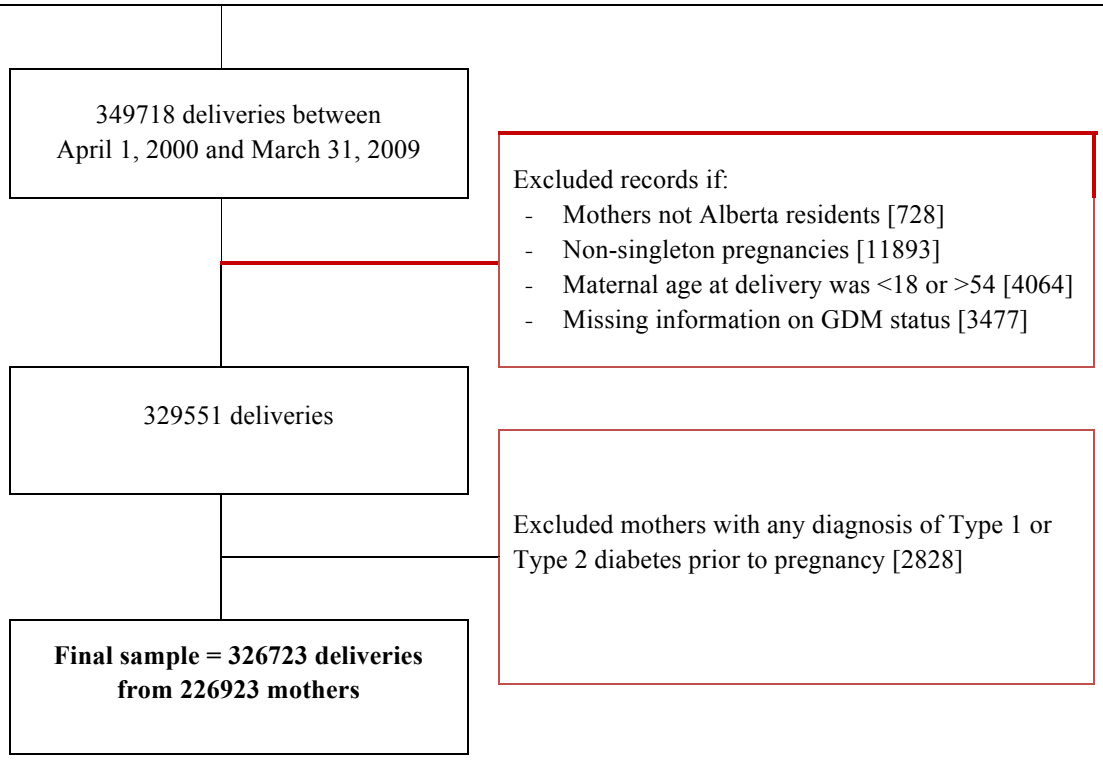
2.8 Figures

Box 2.1 Classification of mental illness in the perinatal period

A woman was classified as having a diagnosis of mental illness if she had:

- One or more hospitalizations with diagnosis for depressive disorder, affective psychoses, neurotic depression or adjustment reaction
  - ICD9 – 296.2-296.8, 300.4, 309, 311
  - ICD10 – F31, F32, F33, F34.1, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8, F53.0, F93.0
- One or more physician visits with diagnosis for depressive disorder, affective psychoses or adjustment reaction
  - ICD9 – 296, 309, 311
- One or more hospitalizations with a diagnosis for anxiety disorders
  - ICD9 – 300 (exclude 300.13, 300.14, 300.15)
  - ICD10 - F32.0, F34.1, F40, F41, F44, F45.0, F45.1, F45.2, F48, F68.0, F99
- One or more physician visits with a diagnosis for anxiety disorders
  - ICD-9 – 300

Figure 2.1 Study sample selection



2.9 Tables

Table 2.1 Comparison of maternal characteristics for deliveries in Alberta between April 1, 2000 and March 31, 2009 (N=326,723)[a]

	Mothers without GDM **N=314,583 (96.3%)**	Mothers with GDM **N=12,140 (3.7%)**	P-value
Age			
Mean, years (SD)	29.1 (5.4)	32.1 (5.3)	< 0.001
≥35 years	53126 (16.9)	4082 (33.6)	< 0.001
Underweight (Weight ≤ 45 kg)	1718 (0.6)	93 (0.8)	< 0.001
Overweight (Weight ≥ 91 kg)	25811 (8.2)	2232 (18.4)	< 0.001
Smoker at any point during pregnancy	61140 (19.4)	1983 (16.3)	< 0.001
Rural residence	51953 (16.5)	1493 (12.3)	< 0.001
Ethnicity			< 0.001
Aboriginal	18588 (5.9)	836 (6.9)	
Caucasian/Other	261237 (83.0)	8593 (70.8)	
Chinese	8989 (2.9)	831 (6.9)	
South Asian[b]	25769 (8.2)	1880 (15.5)	
Median household income ($CAD)			< 0.001
<50 101	75475 (24.0)	2909 (24.0)	
50 101 - 64 677	81179 (25.8)	3070 (25.3)	
64 678 - 83 503	74936 (23.8)	3095 (25.5)	
> 83 503	82979 (26.4)	3066 (25.3)	
Nulliparity	134507 (42.8)	4509 (37.1)	< 0.001
Pregnancy complications			
Pre/eclampsia	3713 (1.2)	289 (2.4)	< 0.001
C-section	76388 (24.3)	4356 (35.9)	< 0.001
Neonatal death	2136 (0.7)	69 (0.6)	< 0.001
Neonatal ICU stay	30944 (10.5)	2014 (17.5)	< 0.001
Large for gestational age	32569 (10.4)	2153 (17.8)	< 0.001

[a]Data presented as total number (n) and proportion (%) of group, unless stated otherwise
[b]Not including Chinese

Table 2.2 Diagnosis of depressive and anxiety disorders in the perinatal period among mothers of deliveries in Alberta from April 1, 2000 to March 31, 2009 (N = 326,723)

	Depressive		Anxiety		Depressive or Anxiety	
	No GDM n (%)	GDM n (%)	No GDM n (%)	GDM n (%)	No GDM n (%)	GDM n (%)
First diagnosis of mental illness						
2 years prior to pregnancy	31252 (9.9)	1295 (10.7)*	50805 (16.2)	2191 (18.1)*	81351 (25.9)*	3453 (28.4)*
Pregnancy	4752 (1.5)	149 (1.2)*	16667 (5.3)	730 (6.0)*	21322 (6.8)	876 (7.2)
Trimester 1	2282 (0.7)	80 (0.7)	8673 (2.8)	373 (3.1)*	10912 (3.5)	452 (3.7)
Trimester 2	1320 (0.4)	35 (0.3)*	4821 (1.5)	224 (1.9)*	6111 (1.9)	258 (2.1)
Trimester 3	1150 (0.4)	34 (0.3)	3173 (1.0)	133 (1.1)	4299 (1.4)	166 (1.4)
1 year post-partum	13638 (4.3)	490 (4.0)	17276 (5.5)	654 (5.4)	30683 (9.8)	1135 (9.4)
At least one diagnosis of mental illness during time period						
2 years prior to pregnancy	40019 (12.7)	1678 (13.8)*	58968 (18.7)	2571 (21.2)*	81351 (25.9)	3453 (28.4)*
Pregnancy	15540 (4.9)	673 (5.5)*	33087 (10.5)	1477 (12.2)*	44235 (14.1)	1952 (16.1)*
Trimester 1	8954 (2.9)	404 (3.3)*	18530 (5.9)	828 (6.8)*	25798 (8.2)	1161 (9.6)*
Trimester 2	5810 (1.9)	247 (2.0)	11670 (3.7)	584 (4.8)*	16441 (5.2)	784 (6.5)*
Trimester 3	5323 (1.7)	243 (2.0)*	8563 (2.7)	362 (3.0)	13034 (4.1)	575 (4.7)*
1 year post-partum	39405 (12.5)	1595 (13.1)*	43001 (13.7)	1772 (14.6)*	69623 (22.1)	2834 (23.3)*
* = $p < 0.05$ comparing GDM vs. no GDM						

Table 2.3 Relationship between GDM and mental illness in the perinatal period, excluding women with a history of mental illness within two years prior to pregnancy (N= 241,919)

	Unadjusted		Adjusted[a]		GEE[a]	
	OR	95% CI	OR	95%CI	OR	95% CI
Pregnancy and Post-partum	1.05	1.00, 1.11	1.05	0.99, 1.10	1.05	0.99, 1.10
Pregnancy	1.11	1.04, 1.20	1.06	0.99, 1.14	1.06	0.98, 1.13
Trimester 1	1.12	1.02, 1.23	1.08	0.97, 1.19	1.05	0.96, 1.17
Trimester 2	1.13	1.00, 1.29	1.05	0.92, 1.20	1.06	0.94, 1.20
Trimester 3	1.04	0.89, 1.21	1.03	0.87, 1.20	1.02	0.87, 1.19
1 year post-partum	0.99	0.93, 1.06	1.03	0.97, 1.10	1.03	0.97, 1.10
[a]Adjusted for: age, overweight category, nulliparity, smoking status, ethnicity, median household income, urban residence, prior chronic medical conditions, infant NICU stay, infant death, pre-or-eclampsia and fiscal year.						

2.10 References

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Appendix

Box 2.A1: Classification of mental illness in the perinatal period

A woman was classified as having a diagnosis of mental illness if she had:

- One or more hospitalizations with diagnosis for depressive disorder, affective psychoses, neurotic depression or adjustment reaction
  - ICD9 – 296.2-296.8, 300.4, 309, 311
  - ICD10 – F31, F32, F33, F34.1, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8, F53.0, F93.0
- One or more physician visits with diagnosis for depressive disorder, affective psychoses or adjustment reaction
  - ICD9 – 296, 309, 311
- One or more hospitalizations with a diagnosis for anxiety disorders
  - ICD9 – 300 (exclude 300.13, 300.14, 300.15)
  - ICD10 - F32.0, F34.1, F40, F41, F44, F45.0, F45.1, F45.2, F48, F68.0, F99
- **At least two physician visits with a diagnosis for anxiety disorders**
  - ICD-9 – 300

Table 2.A1 Diagnosis of depressive and anxiety disorders in the perinatal period among mothers of deliveries in Alberta from April 1, 2000 to March 31, 2009 (N = 326,723) using a second algorithm

	Depressive		Anxiety		Depressive or Anxiety	
	No GDM n (%)	GDM n (%)	No GDM n (%)	GDM n (%)	No GDM n (%)	GDM n (%)
At least one diagnosis of mental illness during time period						
2 years prior to pregnancy	40019 (12.7)	1678 (13.8)*	15139 (4.8)	632 (5.2)*	50111 (15.9)	2093 (17.2)*
Pregnancy	15540 (4.9)	673 (5.5)*	9375 (3.0)	441 (3.6)*	23470 (7.5)	1058 (8.7)*
Trimester 1	8954 (2.9)	404 (3.3)*	4817 (1.5)	233 (1.9)*	13184 (4.2)	620 (5.1)*
Trimester 2	5810 (1.9)	247 (2.0)	3610 (1.2)	198 (1.6)*	9024 (2.9)	427 (3.5)*
Trimester 3	5323 (1.7)	243 (2.0)*	3056 (1.0)	134 (1.1)	8013 (2.6)	364 (3.0)*
1 year post-partum	39405 (12.5)	1595 (13.1)	13134 (4.2)	567 (4.7)*	48677 (15.5)	1996 (16.4)*
* = $p < 0.05$ comparing GDM vs. no GDM						

3 Mental illness and the development of gestational diabetes mellitus (GDM)

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3.1 Abstract

Background: Patients with mental illness have an increased risk of developing type 2 diabetes but there is limited research on mental illness and gestational diabetes mellitus (GDM). We conducted a retrospective population-level cohort to examine the association between mental illness and the development of GDM

Methods: The study population included all singleton deliveries in Alberta, Canada from April 1, 2000 to March 31, 2010. Administrative data from a perinatal health registry were linked to physician claims, hospitalization records and outpatient visits to identify any diagnoses of affective or anxiety disorders within two years prior to pregnancy and GDM diagnosis during pregnancy. Generalized estimating equations were used to determine the odd ratio of GDM comparing women with and without a history of mental illness.

Results: Among 373,674 deliveries of 253,911 mothers, 25.7% had a history of mental illness and 3.8% developed GDM. The multivariate-adjusted odds of developing GDM was higher for women with a history of mental illness than without (OR=1.10, 95%CI=1.06,1.14).

Conclusions: Women with a history of mental illness have a greater risk of developing gestational diabetes. Improved recognition and treatment of mental illness may reduce incidence of GDM.

Key Words:

Gestational diabetes mellitus, mental illness, pregnancy, affective disorder, anxiety disorder

3.2 Introduction

Gestational diabetes mellitus (GDM) increases the risk of pregnancy and delivery complications, as well as future chronic disease development[1–4]. Identifying risk factors for GDM will aid in intervention efforts to reduce its incidence and consequent complications. Although studies have shown an increased risk of type 2 diabetes (T2DM) in patients with a history of mental illness, few have investigated this relationship in the perinatal period[5–10]

Mental illness may directly or indirectly contribute to the development of diabetes. Patients with recurrent mental disorders are less likely to meet diet and physical activity recommendations, which may then lead to obesity and diabetes[11–16]. Although the biological mechanisms are not well-established, there is evidence to suggest that depression may increase inflammation and cause hormonal changes through the hypothalamic-pituitary-axis, leading to elevated blood glucose levels and the development of diabetes[12,17–19].

There is some evidence of an association between depression history and GDM diagnosis. A large, population-based retrospective cohort compared clinical diagnosis of depression between women with and without GDM[20]. The women with GDM were more likely to have a medical history of depression than women without GDM. A smaller study found similar results using self-reported history of depression[21]. In this study we considered both affective and anxiety disorders to determine the effect of common mental illnesses on the development of GDM. Using a retrospective, population-level cohort, we compared the development of GDM among women with and without a history of mental disorders within two years prior to pregnancy.

3.3 Methods

3.3.1 Data

This study used population-level administrative data from the province of Alberta, Canada. The Alberta Ministry of Health (Alberta Health) houses a number of databases with demographic information on registered residents and medical information on patients who use publicly funded health services.

The databases used in this study included the following:

7. Discharge abstract database, which contains information about diagnoses and services provided for patients discharged from an inpatient bed.
8. Ambulatory care database, which contains information on diagnoses and services provided for patients during ambulatory and emergency department visits.
9. Practitioner claims database, which contains information on fee for service claims made by physicians for insured health services.
10. Alberta Health Care Insurance Population (AHCIP) registry, which records demographic and geographic information on Albertans registered under the provincial health insurance plan.
11. Alberta Vital Statistics database, which contains death dates.
12. 2006 Census data, which contains neighbourhood-level measures of socio-economic status.

The Alberta Perinatal Health Program (APHP*)* is clinical provincial database that collects maternal, obstetrical and neonatal clinical information during the perinatal period for all deliveries in Alberta[22]. Data was obtained from the APHP on all deliveries from April 2000 to March 2009. Records were de-identified and given scrambled identifiers to allow linking between databases. Each mother's records in the APHP were linked to all her Alberta Health records from April 1997 to March 2010.

3.3.2 Variable Definitions

Women were considered to have GDM if it was coded in the APHP database. In Alberta, screening for GDM occurs between 24 and 28 weeks of pregnancy, and diagnosis information is routinely collected by the APHP[22]. The APHP database also contained information on pre-

pregnancy weight (≤45 kg or ≥91 kg), smoking status during pregnancy, parity, pre-eclampsia or eclampsia, delivery information (multiple or singleton birth, c-section, induction), neonatal outcomes (birth weight, neonatal ICU stay, neonatal death) and self-reported pre-existing chronic medical conditions such as type 1 or 2 diabetes, retinopathy, heart disease, hypertension, chronic renal disease, epilepsy, severe asthma, lupus, or Crohn's disease. Women with a pre-pregnancy weight of ≤45 kg were considered underweight and ≥ 91 kg were considered overweight. A previously published algorithm was used to determine if infants were large for gestational age[23].

The AHCIP database provided information on Aboriginal band membership and patients' 3-digit residential postal codes, which were used to determine median household income (MHI) at the neighborhood level from the 2006 Canadian census data. Quartiles of MHI were used as indicators of socio-economic status. Postal codes were also used to determine rural residence. Previously published algorithms were used to identify South Asian or Chinese ethnicity based on patients' surnames.[24–26] Patients who were not Aboriginal, Chinese or South Asian were considered Caucasian/Other for the purposes of this study.

Mental illness was defined as having at least one hospitalization, outpatient visit or physician claim for an affective or anxiety disorder. For hospitalizations and outpatient visits, ICD9 codes were used for diagnoses that occurred prior to 2002 and ICD10-CA codes for diagnoses thereafter. For physician claims, ICD9 codes were used for the duration of the study period. Box 3.1 provides detailed algorithms for the diagnosis codes included to define "affective" and "anxiety" disorders. These algorithms originated at the Manitoba Centre for Health Policy (MCHP), which used hospitalization information and physician claims to identify cases of mental disorders in women during the perinatal period[27].

3.3.3 Study Population

The study population consisted of all singleton deliveries in Alberta from April 1999 to March 2010. Mothers were excluded if they were not between the ages of 18 and 54, were not Alberta residents or were not insured with the AHCIP at the time of delivery, had pre-existing diabetes prior to the pregnancy, or were missing information on parity, age, smoking status or median household income (Figure 3.1).

3.3.4 Statistical Analysis

Means and standard deviations of continuous baseline characteristics were compared using two-tailed t-tests, and proportions were compared using chi-square tests. Logistic regression was used to estimate crude and adjusted odds ratios of GDM, with each delivery as the unit of analysis and mental illness history as the exposure. Generalized Estimating Equations (GEE) were used to account for correlation between deliveries of the same mother. The adjusted models included the following variables: age, overweight category, nulliparity, smoking status, ethnicity, median household income, urban residence, infant NICU stay, infant death, pre-or-eclampsia, prior medical conditions and fiscal year. All analyses were conducted using SAS version 9.4.

3.4 Results

Among 373,674 deliveries of 253,911 mothers, 95,867 (25.7%) had at least one diagnosis of a mental illness within two years prior to pregnancy. Comparison of women with and without a history of mental illness (Table 3.1) showed that women with mental illness were slightly older, heavier, more likely to be a smoker in pregnancy, and less likely to be nulliparious. In terms of ethnicity, women with GDM were more likely to be Aboriginal and less likely to be Chinese or South Asian. The women with mental illness also had greater proportions of pre-eclampsia, c-section delivery, neonatal ICY stay and large for gestational age babies.

Crude estimates showed that women with a history of mental illness had a greater likelihood of developing GDM (OR=1.13, 95%CI=1.09, 1.17; Table 3.2). The odds ratio was slightly lower once adjusted for covariates (OR=1.11, 95%CI=1.06, 1.15) and further attenuated with the GEE model (OR=1.10, 95%CI=1.06,1.14).

3.5 Discussion

Women with a medical history of mental illness were more likely to develop gestational diabetes mellitus (GDM) than women with no history of mental illness. This is consistent with research from the general population, which has shown that patients with mental disorders are more likely to develop type 2 diabetes[5,6,10,11,28,29]. Although there is limited research on prenatal mental illness and GDM, these results are consistent with findings from two prior studies, which showed that women with GDM were more likely to have a history of depression[20,21]. In particular, a large population-based study, using administrative data, found that women with GDM had 1.42 times the odds of having a history of depression compared to women without GDM[20]. However, this study did not specify the period of time defined as "history" of depression, and did not include any other mental disorders aside from depression.

Possible explanations for the association between mental illness on GDM development include both biological and behavioral mechanisms. Depression and anxiety can cause immune-inflammatory dysregulation and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which may lead to abdominal adiposity and the development of diabetes[17–19,30]. Mental disorders may also lead to unhealthy behaviors, such as poor dietary intake and low physical activity levels, which increase the risk of diabetes[13,15,31–34]. Treatment of anxiety and affective disorders may also contribute to the development of diabetes, as medication side-effects may potentially act as mediators in this relationship[31,35]. Considering these factors in future research will provide greater insight into the relationship between mental illness and GDM.

The use of population-based administrative data posed some limitations for the study. Physician claims, hospitalizations and outpatient visits were used to identify women with a history of mental illness. This may have resulted in a selection bias, as only patients who had interacted with the healthcare system for their mental disorders were included in the case definition. Physician attentiveness, social stigma, and cultural values may each influence whether a patient seeks medical attention for symptoms of mental illness. The population databases also had limited information on some key variables. Overweight status was determined by a binary variable indicating whether the mother was greater than 91 Kg during pregnancy. Overweight

and obesity are associated with both mental illness and diabetes, and thus may have an affect the relationship between mental illness and GDM.

Socio-economic status was disseminated from maternal postal code and neighborhood-level income provided by census data. Aboriginal status was determined through band membership, as indicated in the population registry. Otherwise, ethnicity was derived from previously validated algorithms based on patients' surnames[24–26]. Systematically collected measures of BMI, socio-economic status and ethnicity may have provided more accurate estimates of the effect of mental illness on the development of GDM. Furthermore, the databases did not contain information on relationship status, social support, physical activity, or diet. Each of these may affect the impact mental illness has on the development of adverse health outcomes such as GDM. These limitations on key variables may have resulted in residual confounding in the study.

3.6 Conclusion

Having a history of mental illness prior to pregnancy increased the risk of GDM. GDM has been associated with a number of pregnancy, neonatal and long-term complications[3]. Better identification and treatment of mental illness may result in fewer cases of GDM. Moreover, women with a history of mental illness are likely to have recurrent episodes triggered by pregnancy, increasing the risk of adverse outcomes for the mother and child. Investing in better diagnosis and treatment of mental disorders prior to pregnancy may lead to both short and long-term benefits for women and children.

3.7 Figure Legends

Box 3.1 Algorithm for definition of mental illness

Figure 3.1 Study sample selection

Table 3.1 Comparison of maternal characteristics for deliveries in Alberta between April 1 2000 and March 31 2010, overall and by history of mental illness prior to pregnancy

Table 3.2 Unadjusted and multivariate-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between history of mental illness and development of GDM

3.8 Figures

Box 3.1: Algorithm for definition of mental illness

A woman was classified as having a diagnosis of mental illness if she had:

- One or more hospitalizations with diagnosis for depressive disorder, affective psychoses, neurotic depression or adjustment reaction
  - ICD9 – 296.2-296.8, 300.4, 309, 311
  - ICD10 – F31, F32, F33, F34.1, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8, F53.0, F93.0
- One or more physician visits with diagnosis for depressive disorder, affective psychoses or adjustment reaction
  - ICD9 – 296, 309, 311
- One or more hospitalizations with a diagnosis for anxiety disorders
  - ICD9 – 300 (exclude 300.13, 300.14, 300.15)
  - ICD10 - F32.0, F34.1, F40, F41, F44, F45.0, F45.1, F45.2, F48, F68.0, F99
- One or more physician visits with a diagnosis for anxiety disorders
  - ICD-9 – 300

Figure 3.1: Study sample selection

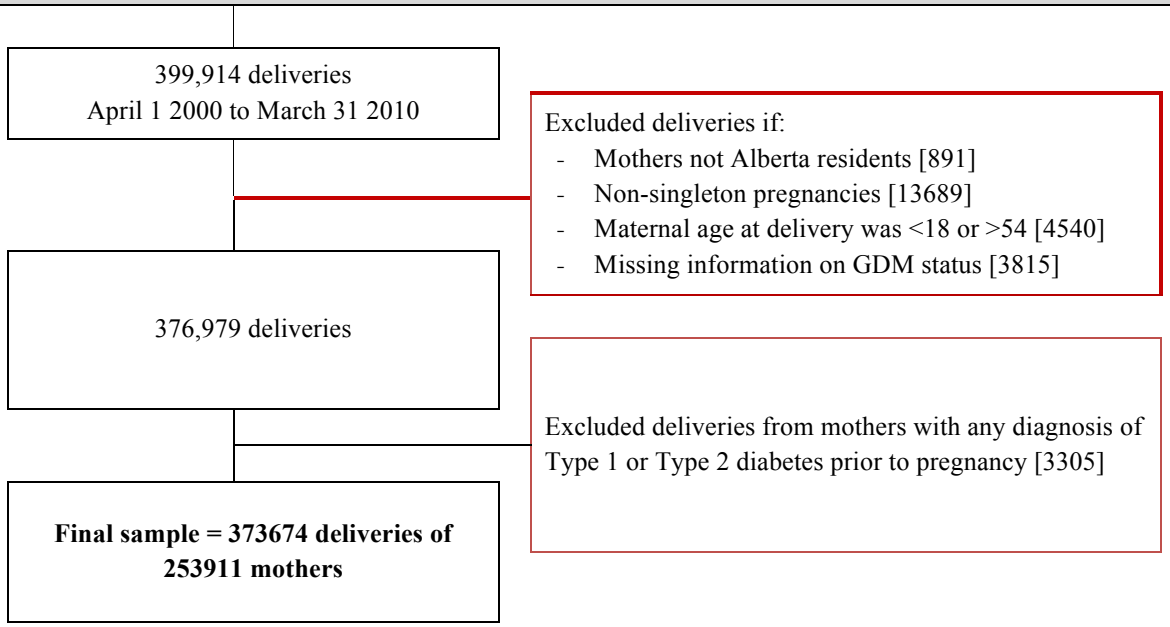

Table 3.1 Comparison of maternal characteristics for deliveries in Alberta between April 1 2000 and March 31 2010, overall and by history of mental illness prior to pregnancy[a]

	Full cohort **N=373,674**	Women with no history of mental illness **N=277,807 (74.3%)**	Women with history of mental illness **N=95,867 (25.7%)**	P-value
Age (years)				
Mean (±SD)	29.3 (5.4)	29.2 (5.4)	29.4 (5.6)	< 0.001
Median (IQR)	29 (25, 33)	29 (25, 33)	29 (25, 33)	<0.001
≥35 years	65867 (17.6)	47750 (17.2)	18117 (18.9)	< 0.001
Underweight (≤ 45 kg)	2065 (0.6)	1584 (0.6)	481 (0.5)	< 0.001
Overweight (≥ 91 kg)	32303 (8.6)	22521 (8.1)	9782 (10.2)	< 0.001
Ethnicity				< 0.001
Aboriginal	21988 (5.9)	14568 (5.2)	7420 (7.7)	
Caucasian/Other	307975 (82.4)	228480 (82.2)	79495 (82.9)	
Chinese	11290 (3.0)	9507 (3.4)	1783 (1.9)	
South Asian[b]	32421 (8.7)	25252 (9.1)	7169 (7.5)	
Median Household Income (CAD)				< 0.001
<50 101	89612 (24.0)	65860 (23.7)	23752 (24.8)	
50 101 - 64 677	97014 (26.0)	72679 (26.2)	24335 (25.4)	
64 678 - 83 503	87712 (23.5)	65291 (23.5)	22421 (23.4)	
> 83 503	99312 (26.6)	73958 (26.6)	25354 (26.5)	
Rural residence	61248 (16.4)	45841 (16.5)	15407 (16.1)	0.0019
Nulliparity	159043 (42.6)	123957 (44.6)	35086 (36.6)	< 0.001
Smoked during pregnancy	70587 (18.9)	47077 (17.0)	23510 (24.5)	< 0.001
Pregnancy or Neonatal Complications				
Pre/eclampsia	4559 (1.2)	3320 (1.2)	1239 (1.3)	0.0179
C-section	93153 (24.9)	68579 (24.7)	24574 (25.6)	< 0.001
Neonatal death	2483 (0.7)	1801 (0.7)	682 (0.7)	< 0.001
Neonatal ICU stay	37137 (10.6)	26616 (10.2)	10521 (11.7)	< 0.001
Large for gestational age	39197 (10.6)	28560 (10.4)	10637 (11.2)	< 0.001
GDM	14353 (3.8)	10339 (3.7)	4014 (4.2)	<0.001

[a]Data is presented as number of individuals (n) and proportion of group (%), unless otherwise specified
[b]Not including Chinese

Table 3.2 Unadjusted and multivariate-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between history of mental illness and development of GDM

	Unadjusted		Adjusted[a]		GEE[a]	
	OR	95% CI	OR	95%CI	OR	95% CI
GDM	1.13	1.09, 1.17	1.11	1.06, 1.15	1.10	1.06, 1.14

[a]Adjusted for: age, overweight category, nulliparity, smoking status, ethnicity, median household income, urban residence, pre-or-eclampsia, prior chronic medical conditions and fiscal year

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4 Examining the impact of gestational diabetes mellitus and perinatal mental illness on chronic disease development

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4.1 Abstract

Background: Gestational diabetes mellitus (GDM) and perinatal mental illness increase the risk of pregnancy and neonatal complications, but less is known about their impact on future chronic disease development. This study examined the individual and combined effects of GDM and perinatal mental illness on the mother's development of Type 2 diabetes, hypertension and cardiovascular disease (CVD).

Methods: Administrative data from a population perinatal health registry was linked to physician claims, hospitalization records and outpatient visits to identify diagnosis of diabetes, hypertension and cardiovascular disease among women with the following conditions during pregnancy: no GDM or mental illness, mental illness only, GDM only, both GDM and mental illness. The study population included deliveries by each mother who delivered in Alberta, Canada from April 1, 1999 to March 31, 2010. Cumulative incidence curves and cox proportional hazards were used to examine the effect of GDM and perinatal mental illness on the development of each chronic disease.

Results: Among 242,743 mothers, 1971 (0.8%) were diagnosed with both GDM and mental illness, 6866 (2.8%) with GDM only, 48,484 (20.0%) with mental illness only and 185,422 (76.4%) with neither GDM nor mental illness, with a mean follow-up time of 5.5 years. The women with both GDM and mental illness had a hazard ratio of 22.4 (95%CI=19.2, 26.1) for diabetes, 2.0 (95%CI=1.7,2.3) for hypertension and 1.7 (95%CI=0.9,3.4) for CVD compared to women with neither GDM nor mental illness. Women with only GDM had a hazard ratio of 20.5 (95%CI=18.4, 22.9) for diabetes, 1.7 (95%CI=1.6, 1.9) for hypertension and 1.5 (95%CI=1.0, 2.3) for CVD. Women with only mental illness had a hazard ratio of 1.3 (95%CI=1.1, 1.5) for diabetes, 1.1 (95%CI=1.1,1.2) for hypertension and 1.6 (95%CI=1.3, 1.9) for CVD.

Conclusions: GDM and mental illness each increase the mother's risk of developing type 2 diabetes, hypertension or cardiovascular disease. Having both conditions results in the highest risk for chronic disease development.

Key Words: Gestational diabetes mellitus, mental illness, perinatal, chronic disease, diabetes, hypertension, cardiovascular disease

4.2 Introduction

The burden of chronic disease is a significant public health issue and understanding pathways to its development will strengthen efforts for prevention. Perinatal mental illness and gestational diabetes mellitus (GDM) are two conditions that affect many pregnancies and can result in adverse pregnancy, delivery and neonatal outcomes[1–4]. Women with GDM have an increased risk of future chronic disease development but less is known about the long-term consequences of perinatal mental illness.[5–8]

Mental illness in the perinatal period affects approximately 15 – 20 % of women[1,9–11]. In pregnancy, it increases the risk of placental abnormalities, developmental delays and premature deliveries.[4,12–17] In the post-partum period, mothers with a mental illness may engage in unhealthy behaviors, such as poor dietary choices, physical inactivity, or substance abuse.[9,18–22] Mental illness may also reduce quality of parenting, which can lead to problems in the child's cognitive, behavioral and psychological development.[1,4,12,16]

GDM affects 4 – 10% of pregnancies and is increasing in prevalence[3,23]. In pregnancy, it increases the risk of congenital anomalies, pre-eclampsia, high birth weight, cesarean deliveries and preterm birth.[3,24–28] Mothers with GDM have a significantly increased risk of developing T2DM subsequent to the pregnancy, and also have a higher risk of developing hypertension and cardiovascular disease.[5,7,8,29,30]

In the general population, patients with comorbid diabetes and mental illness show worse adherence to medical recommendations and have worse health outcomes than those without mental illness[31–34]. However, there is a lack of research on the combined effect of gestational diabetes and perinatal mental illness. In this study, we used population-level databases to examine the long-term impact of GDM, mental illness, and GDM with mental illness on the development of diabetes, hypertension and cardiovascular disease among women who delivered in Alberta, Canada from April 1, 1999 to March 31, 2010.

4.3 Methods

4.3.1 Data

This study used population-level administrative data from the province of Alberta, Canada. The Alberta Ministry of Health (Alberta Health) houses a number of databases with demographic information on residents and medical information on patients who use publicly funded health services.

The databases used in this study included the following:

13. Discharge abstract database, which contains information about diagnoses and services provided for patients discharged from an inpatient bed.
14. Ambulatory care database, which contains information on diagnoses and services provided for patients during ambulatory and emergency department visits.
15. Practitioner claims database, which contains information on fee for service claims made by physicians for insured health services.
16. Alberta Health Care Insurance Population (AHCIP) registry, which records demographic and geographic information on Albertans registered under the provincial health insurance plan.
17. Alberta Vital Statistics database, which contains death dates.
18. 2006 Census data, which contains neighborhood-level measures of socio-economic status.

The Alberta Perinatal Health Program (APHP*)* is a clinical provincial database that collects maternal, obstetrical and neonatal clinical information during the perinatal period for all deliveries in Alberta[35]. Data was obtained from the APHP on all deliveries from April 1999 to March 2010. Records were de-identified and given scrambled identifiers to allow linking between databases. Each mother's records in the APHP were linked to all her Alberta Health records from April 1997 to March 2010.

4.3.2 Variable Definitions

Women were considered to have GDM if it was coded in the APHP database. In Alberta, screening for GDM occurs between 24 and 28 weeks of pregnancy, and diagnosis information is routinely collected by the APHP[35]. The APHP database also contained information on pre-

pregnancy weight (≤45 kg or ≥91 kg), smoking status during pregnancy, parity, pre-eclampsia or eclampsia, delivery information (multiple or singleton birth, c-section, induction), neonatal outcomes (birth weight, neonatal ICU stay, neonatal death) and self-reported pre-existing chronic medical conditions such as type 1 or 2 diabetes, retinopathy, heart disease, hypertension, chronic renal disease, epilepsy, severe asthma, lupus, or Crohn's disease. Women with a pre-pregnancy weight of ≤45 kg were considered underweight and ≥ 91 kg were considered overweight. A previously published algorithm was used to determine if infants were large for gestational age[36].

The AHCIP database provided information on Aboriginal band membership and patients' 3-digit residential postal codes, which were used to determine median household income (MHI) at the neighborhood level from the 2006 Canadian census data. Quartiles of MHI were used as indicators of socio-economic status. Postal codes were also used to determine rural residence. Previously published algorithms were used to identify South Asian or Chinese ethnicity based on patients' surnames.[37–39] Patients who were not Aboriginal, Chinese or South Asian were considered Caucasian/Other for the purposes of this study.

Mental illness was defined as having at least one hospitalization, outpatient visit or physician claim for an affective or anxiety disorder during pregnancy or in the three months following delivery. For hospitalizations and outpatient visits, ICD9CM codes were used for diagnoses that occurred prior to 2002 and ICD10-CA codes for diagnoses thereafter. For physician claims, ICD9 codes were used for the duration of the study period. Box 4.1 provides detailed algorithms for the diagnosis codes included to define "affective" and "anxiety" disorders. These algorithm originated at the Manitoba Centre for Health Policy (MCHP), which used hospitalization information and physician claims to identify cases of mental disorders in women during the perinatal period[40].

Hospitalization data and physician claims were also used to identify diagnoses of type 2 diabetes, hypertension and cardiovascular disease. Diabetes was identified using the National Diabetes Surveillance System (NDSS) case definition of one hospitalization or two outpatient visits in two years[41]. For consistency, the same algorithm was used for hypertension and cardiovascular disease. Box 4.2 specifies the ICD9CM and ICD10-CA codes used to identify each disorder.

4.3.3 Study Population

The study population consisted of all Albertan women who delivered from April 1 1999 to March 31 2010. For mothers with multiple deliveries during the study time period, only the first singleton delivery was included in the study. Mothers were also excluded if they were not between the ages of 18 and 54, had low pre-pregnancy weight (≤45 kg), were missing information on age, weight, gestational age at delivery or GDM status, or had pre-existing medical conditions such as diabetes, cardiovascular disease, hypertension, retinopathy, chronic renal disease, epilepsy, severe asthma, lupus, or Crohn's disease.

4.3.4 Statistical analysis

Descriptive and inferential statistics were used to compare women with the following diagnostic conditions: no GDM or mental illness, only GDM, only mental illness or both GDM and mental illness. F-tests and Kruskal-Wallis tests were used to compare the mean and medians, respectively, of continuous baseline characteristics and chi-square tests for percentages of categorical variables. The Kaplan-Meier method and long-rank tests were used to visualize and compare the cumulative incidence diabetes, hypertension and cardio-vascular disease across the four groups. Cox proportional hazard models were used to determine the relative hazard of developing each outcome between the four groups. The models were adjusted for the following variables: age, height, overweight category, nulliparity, pre-or-eclampsia, smoking status, ethnicity, median household income, urban residence and fiscal year. All analyses were conducted using SAS version 9.4.

4.4 Results

4.4.1 Baseline Characteristics

Among 242,743 women who delivered between April 1999 and March 2010, 1,971 (0.8%) were diagnosed with both GDM and mental illness during pregnancy, 6866 (2.8%) with GDM only, 48,484 (20.0%) with mental illness only, and185, 422 (76.4%) with neither GDM nor mental illness. Comparison of maternal characteristics (Table 4.1) showed that the four groups differed in a number of variables.

The differences were greater between women with and without GDM than women with and without mental illness. Women with GDM were older, heavier, shorter, less likely to live in a rural residence, less likely to be nulliparious, less likely to be of Caucasian ethnicity and more likely to be Aboriginal, Chinese or South Asian. There were no notable differences in median household income across the four groups. Smoking habits varied across the four groups, the largest proportion of smokers were those with a mental illness, followed by those with no GDM or mental illness and those with both GDM and mental illness. Those with only GDM were the least likely to be smokers in pregnancy.

4.4.2 Obstetrical and neonatal complications

Women with both GDM and mental illness were most likely to have pre-eclampsia or eclampsia (2.9%), followed by women with only GDM (2.3%). Women with only mental illness had the same prevalence of pre-eclampsia (1.4%) as women with no GDM or mental illness (1.4%; Table 4.2). Similarly, the rates for c-section delivery and labour induction were higher for women with GDM than those with mental illness, and highest for women with both GDM and mental illness. Average birth weight was similar across the four groups, but women with GDM were more likely to have large for gestational age infants. The rates of neonatal death were highest for women with only mental illness (1.5%), followed by women with both GDM and mental illness (1.2%), but similar between women with GDM and those with no GDM or mental illness. Women with both GDM and mental illness had highest proportions of neonatal ICU stay (20.6%), followed by women with only GDM (17.0%), and women with only mental illness (12.4%), compared to women with no GDM or mental illness (10.7%).

4.4.3 Cumulative Incidence

Women with GDM had a higher cumulative incidence of diabetes than those with no GDM (Figure 4.2). The cumulative incidence of diabetes did not differ significantly between women with both GDM and mental illness (20.1%) and women with only GDM (18.9%; p=0.13). Women with only mental illness had a significantly higher cumulative incidence of diabetes (1.4%) than women with no GDM or mental illness (1.1%; p<0.001).

The four groups differed significantly in cumulative incidence of hypertension (p<0.05). Women with both GDM and mental illness had the highest incidence of hypertension (17.1%), followed by women with only GDM (14.1%), only mental illness (6.3%) and no GDM or mental illness (5.4%).

The cumulative incidence of cardiovascular disease did not differ significantly between women with both GDM and mental illness (1.2%) compared to women with only GDM (1.2%; p=0.68). The incidence was lower for women with only mental illness (0.8%) but was significantly higher than for women with no GDM or mental illness (0.5%; p<0.001).

4.4.4 Hazard Ratios

Compared to women with no GDM or mental illness, women with both GDM and mental illness had a higher hazard of developing diabetes (HR=22.4, 95% CI=19.2, 26.1; Table 4.3) than women with only GDM (HR=20.5, 95% CI=18.4, 22.9), and both were higher than women with only mental illness (HR=1.3, 95% CI=1.1, 1.5).

The hazard ratio for hypertension was highest in women with both GDM and mental illness (HR=2.0, 95% CI=1.7, 2.3), followed by women with only GDM (HR=1.7, 95% CI=1.6, 1.9) then women with only mental illness (HR=1.1, 95% CI=1.1, 1.2).

The hazard ratio for cardiovascular disease (CVD) was highest in women with both GDM and mental illness but was not statistically significant (HR=1.7, 95% CI=0.9, 3.4). Women with mental illness had a higher hazard rate of CVD (HR=1.6, 95% CI=1.3, 1.9) than women with GDM (HR=1.5, 95% CI=1.0, 2.3).

4.5 Discussion

GDM and perinatal mental illness each increased the risk of chronic disease development subsequent to pregnancy. The hazard ratio for diabetes was slightly higher for women with both mental illness and GDM than for women with only GDM, and both were significantly higher than women with only mental illness. Women with mental illness had a 30% increased hazard rate of developing diabetes compared to women with no mental illness or GDM. The effect of GDM on the future development of diabetes, hypertension and cardiovascular disease has been previously investigated by Kaul et. al.[5], who examined the individual and combined impacts of GDM and high maternal weight gain on chronic disease development. Our results are consistent with findings from this study, as well as others indicating a significantly increased risk of diabetes subsequent to GDM[5,7,30,42] To our knowledge, no prior studies have examined the long-term effect of perinatal mental illness on the development of diabetes. However, research on general population supports an increased risk of diabetes in patients with mental illness.[34,43,44]

Compared to women with neither condition, the hazard rate for hypertension was 10% greater for women with mental illness and 70% greater for women with GDM. Women with both GDM and mental illness had double the hazard rate of developing hypertension as those with neither condition. The incidence of cardiovascular disease was lower than hypertension or diabetes, but women with mental illness had a greater risk than women with GDM. The increased risk of hypertension and cardiovascular disease among women with GDM has been shown in previous studies.[5,29,45] Although studies have not directly examined the risk of these diseases following perinatal mental illness, in the general population there is a greater prevalence of hypertension and cardiovascular disease among patients with depression or anxiety[46,47]

The use of administrative data posed some limitations for the study. Physician claims, hospitalizations and outpatient visits were used to identify women with a history of mental illness. This may have resulted in a selection bias, as only patients who had interacted with the healthcare system for their mental disorders were included in the case definition. Physician attentiveness, social stigma, and cultural values may each influence whether a patient seeks medical attention for symptoms of mental illness. Patients were classified as having mental illness if they had at least one diagnosis of an affective or anxiety disorder during pregnancy or

post-partum, as based on an algorithm used by the Manitoba Centre for Health Policy[40]. To our knowledge, there is no validated algorithm to determine cases of perinatal mental illness using administrative data. Therefore, the specificity of this method to determine cases of mental illness is unknown.

The population databases also had limited information on some key variables. Overweight status was determined by a binary variable indicating whether the mother was greater than 91 Kg during pregnancy. Socio-economic status was represented by median household income, as disseminated from maternal postal code and neighborhood-level income data from the 2006 Census. Ethnicity was determined by aboriginal band membership information from the population registry and previously validated algorithms based on patients' surnames[37–39]. Systematically collected measures of BMI, socio-economic status and ethnicity may have provided more accurate estimates of the effect of mental illness on the development of GDM. Furthermore, the databases did not contain information on relationship status, social support, physical activity, or diet. Each of these may affect the impact mental illness and GDM have on the development of chronic disease.

4.6 Conclusion

GDM and perinatal mental illness each increase the risk of chronic disease development, and the risk is highest for women with both GDM and mental illness. The perinatal period is a crucial time for both mother and infant. Developing policies for better identification and treatment of mental illness may be an investment to better health outcomes in the future. Chronic disease is a significant public health issue. Although further research is needed to better understand the progress from pregnancy to chronic disease, recognizing mental illness and GDM as factors for chronic disease development will result in more effective intervention strategies.

4.7 Figure Legends

Box 4.1 Algorithm for definition of mental illness

Box 4.2 Algorithm for definition of each chronic disease

Figure 4.1 Study sample selection

Figure 4.2 Cumulative incidence of diabetes, hypertension and cardiovascular disease for women with: no GDM or mental illness, GDM only, mental illness only, and both GDM and mental illness.

Table 4.1 Characteristics of study population from mothers who delivered in Alberta from April 1 1999 to March 31, 2010, overall and grouped by diagnosis of GDM or mental illness in pregnancy

Table 4.2 Proportions of obstetrical and neonatal complications of mothers who delivered in Alberta between April 1 1999 and March 31 2010, overall and grouped by diagnosis of GDM or mental illness in pregnancy

Table 4.3 Cox proportional hazard ratios (HR) for the development of diabetes, hypertension and cardiovascular disease comparing women with no GDM or mental illness, mental illness only, GDM only and both GDM and mental illness

4.8 Figures

Box 4.1 Algorithm for definition of mental illness

A woman was classified as having a diagnosis of mental illness if she had:

- One or more hospitalizations with diagnosis for depressive disorder, affective psychoses, neurotic depression or adjustment reaction
    - ICD9 – 296.2-296.8, 300.4, 309, 311
    - ICD10 – F31, F32, F33, F34.1, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8, F53.0, F93.0
- One or more physician visits with diagnosis for depressive disorder, affective psychoses or adjustment reaction
    - ICD9 – 296, 309, 311
- One or more hospitalizations with a diagnosis for anxiety disorders
    - ICD9 – 300 (exclude 300.13, 300.14, 300.15)
    - ICD10 - F32.0, F34.1, F40, F41, F44, F45.0, F45.1, F45.2, F48, F68.0, F99
- One or more physician visits with a diagnosis for anxiety disorders
    - ICD-9 – 300

Box 4.2 Algorithm for definition of each chronic disease

	ICD9CM	**ICD10CA**
Diabetes	250	E10, E11, E12, E13, E14
Hypertension	401, 402, 403, 404, 405	I10, I11, I12, I13, I14, I15
Cardiovascular disease	430, 431, 432, 433, 434, 435, 436, 437, 438, 36234	G45, G46, H340, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69
One hospitalization or two outpatient visits within 2 years, as per National Diabetes Surveillance System (NDSS) case definition. [41]		

Figure 4.1 Study sample selection

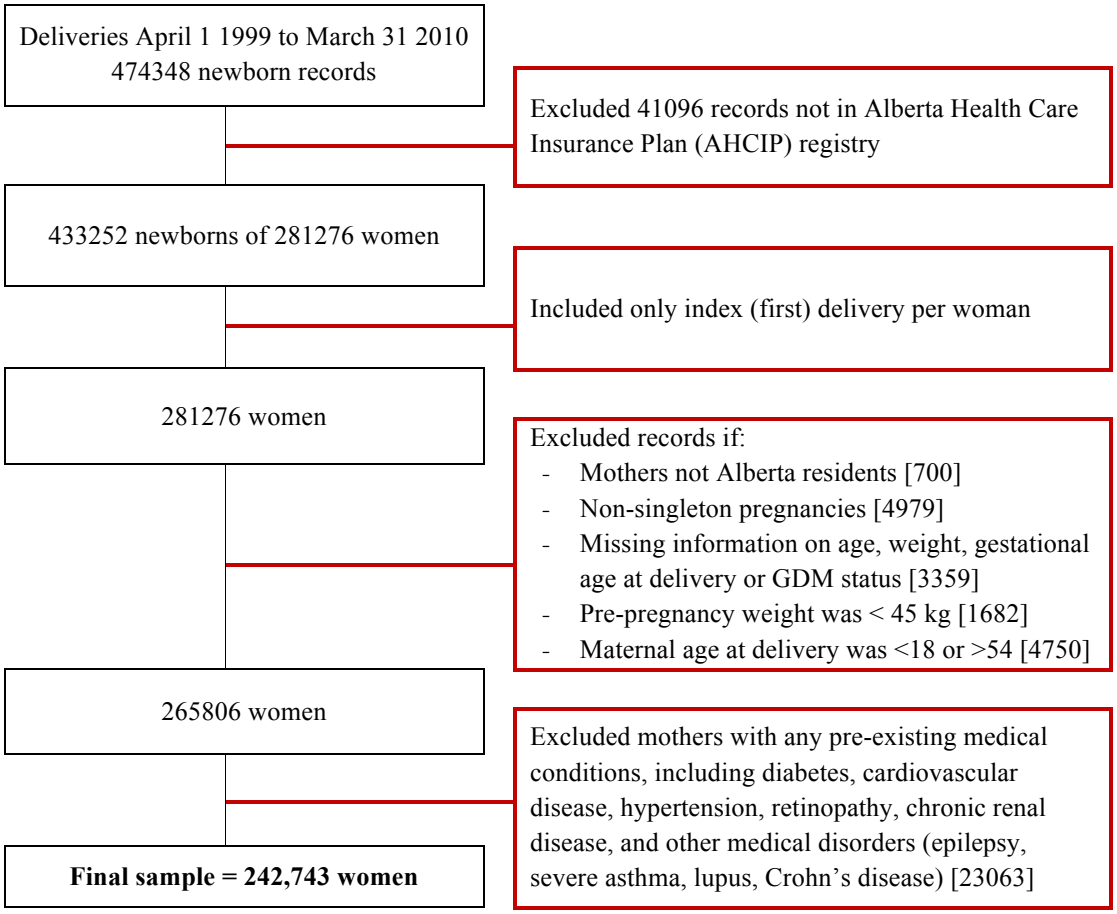


Figure 4.2 Cumulative incidence of (A) Diabetes, (B) Hypertension and (C) Cardiovascular Disease for women with: no GDM or mental illness, GDM only, mental illness only, and both GDM and mental illness.

A.

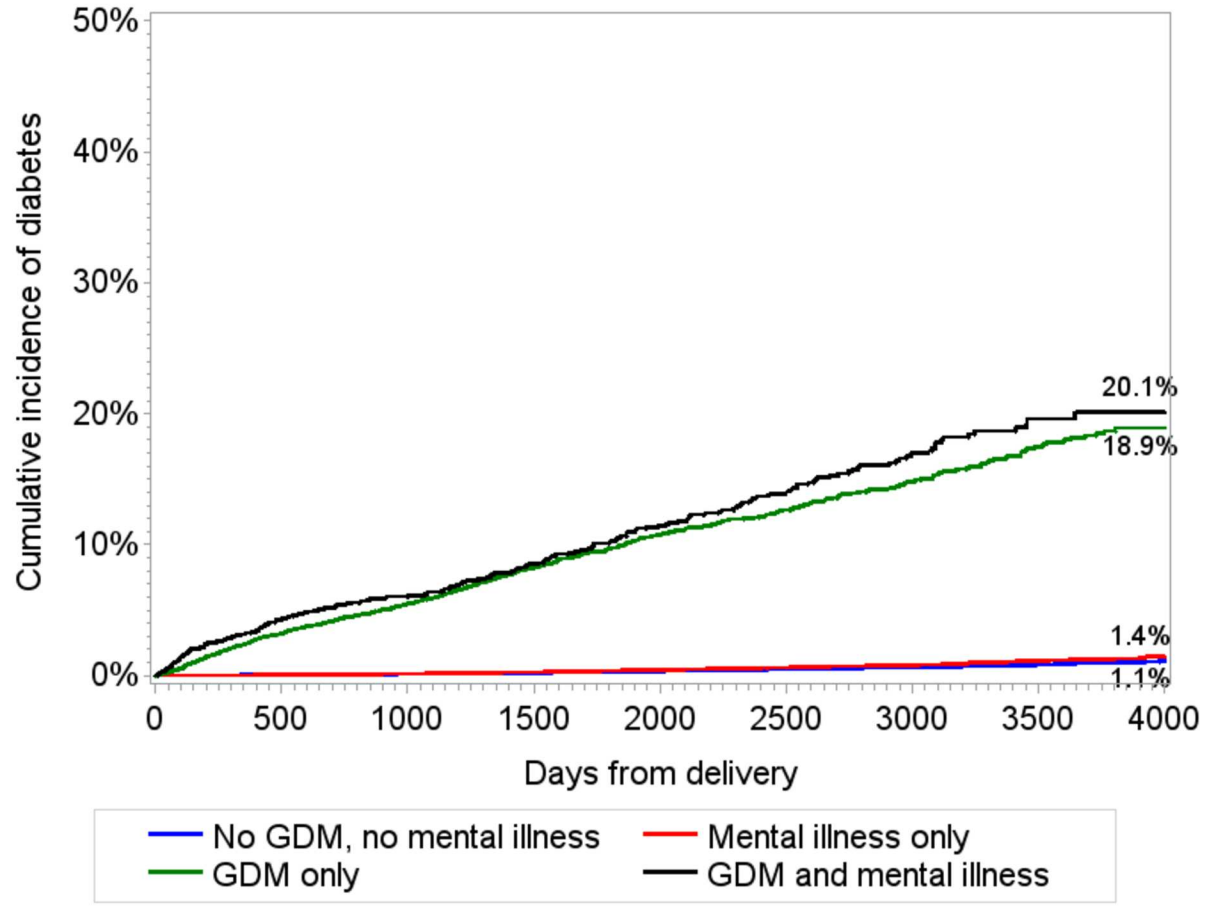


Figure 4.2 Cumulative incidence of (A) Diabetes, (B) Hypertension and (C) Cardiovascular Disease for women with: no GDM or mental illness, GDM only, mental illness only, and both GDM and mental illness.

B.

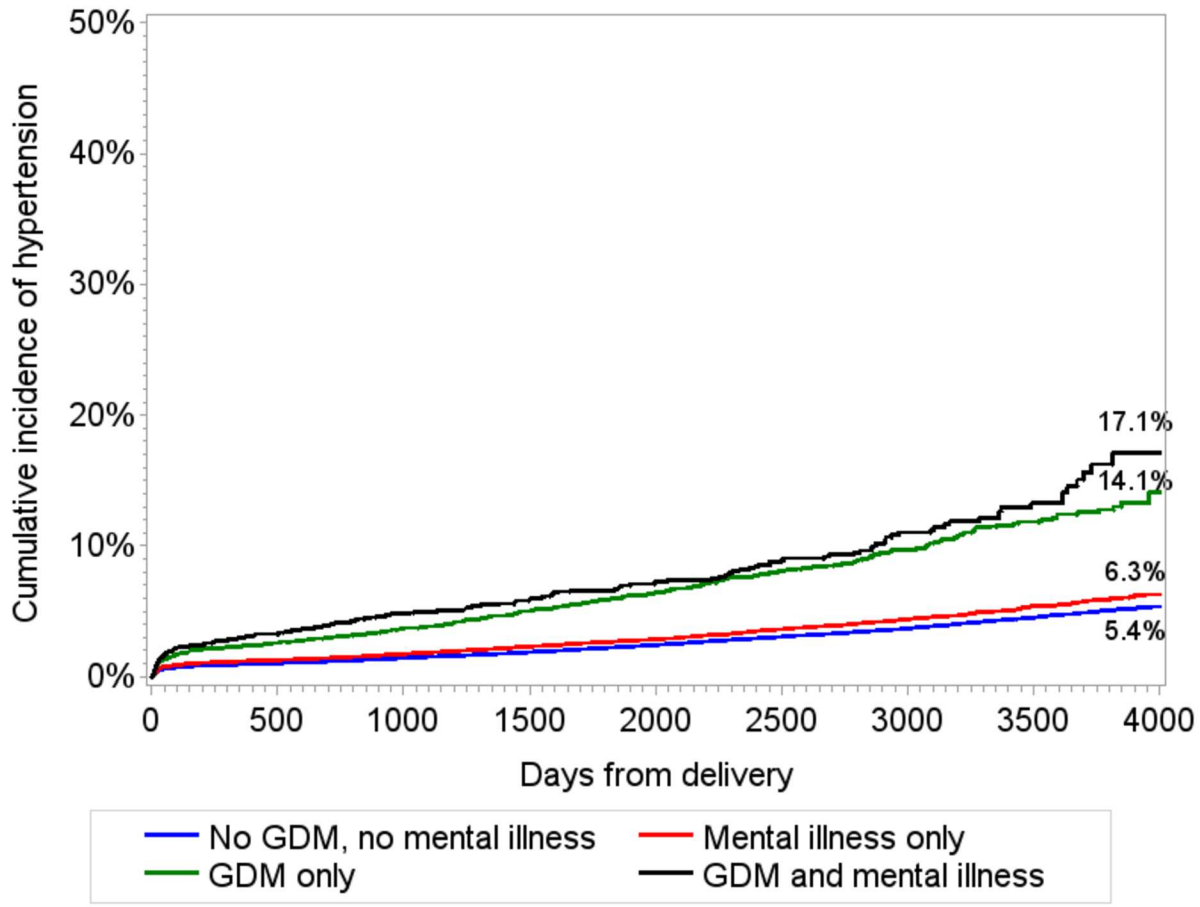
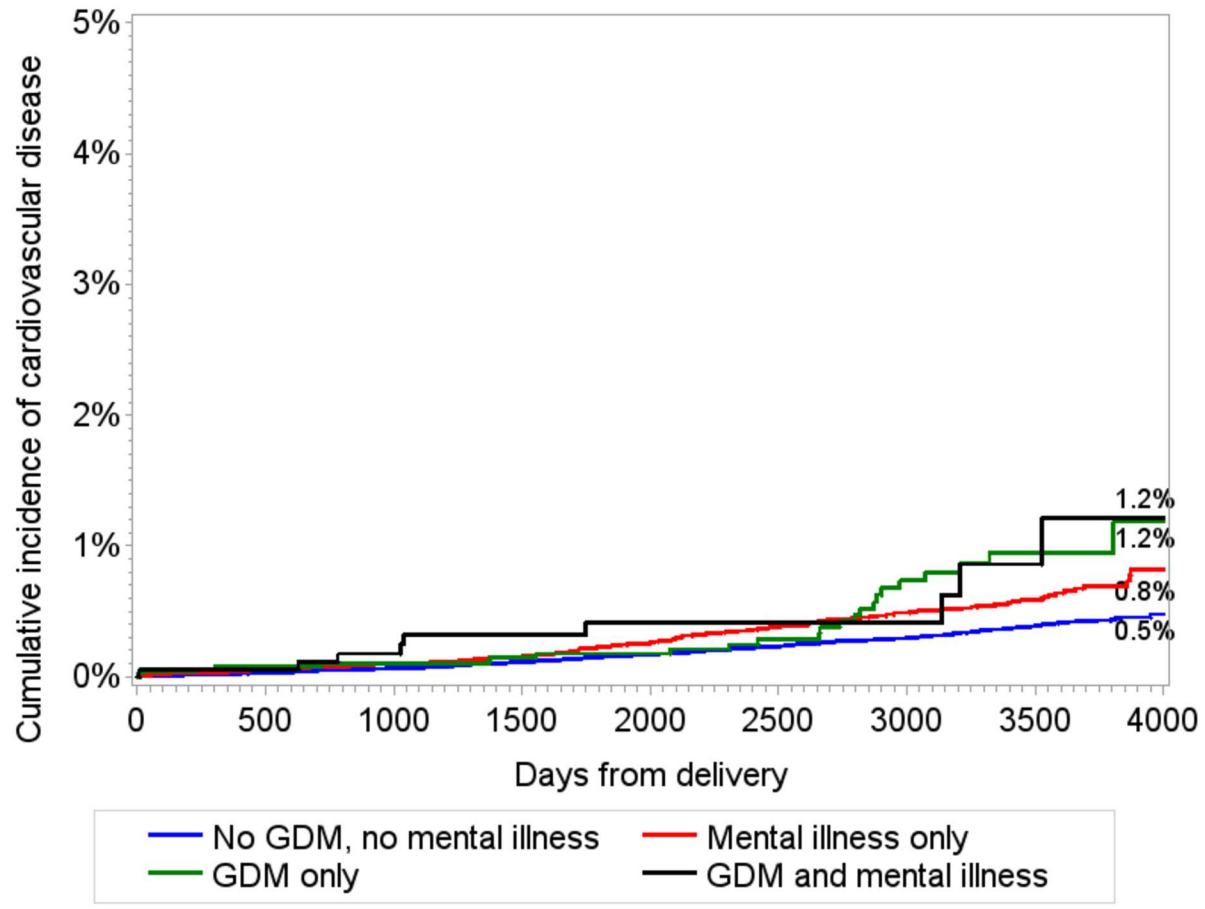


Figure 4.2 Cumulative incidence of (A) Diabetes, (B) Hypertension and (C) Cardiovascular Disease for women with: no GDM or mental illness, GDM only, mental illness only, and both GDM and mental illness.

C.



TABLES

Table 4.1 Characteristics of study population from mothers who delivered in Alberta between April 1 1999 and March 31 2010, overall and grouped by diagnosis of GDM or mental illness in pregnancy[a]

	Full cohort n (%)	No GDM, no mental illness n (%)	Mental illness only n (%)	GDM only n (%)	Both GDM and mental illness n (%)	P-value
Total	242743 (100)	185422 (76.4)	48484 (20.0)	6866 (2.8)	1971 (0.8)	
Age (years)						
Mean (±SD)	28.7 (5.5)	28.5 (5.5)	28.9 (5.7)	31.8 (5.4)	31.9 (5.5)	<0.01
Median (IQR)	29 (25, 33)	28 (24, 32)	29 (25, 33)	32 (28, 36)	32 (28, 36)	<0.01
≥35 years	38265 (15.8)	27030 (14.6)	8373 (17.3)	2220 (32.3)	642 (32.6)	<0.01
Pre-pregnancy weight (kg)						
45 – 90	223253 (92.1)	171503 (92.6)	44377 (91.6)	5761 (84.5)	1612 (82.3)	<0.01
≥ 91	19226 (7.9)	13752(7.4)	4060 (8.4)	1066 (15.5)	348 (17.7)	<0.01
Height < 152 cm	4501 (1.9)	3304 (1.8)	820 (1.7)	296 (4.3)	81 (4.1)	<0.01
Ethnicity						<0.01
Aboriginal	11427 (4.7)	8516 (4.6)	2432 (5.0)	355 (5.2)	124 (6.3)	
Caucasian	201452 (83.0)	154560 (83.4)	40672 (83.9)	4791 (69.8)	1429 (72.5)	
Chinese	8342 (3.4)	6203 (3.4)	1403 (2.9)	621 (9.0)	115 (5.8)	
South Asian[b]	21522 (8.9)	16143 (8.7)	3977 (8.2)	1099 (16.0)	303 (15.4)	
Median Household Income (CAD)						<0.01
<50 101	59401 (24.7)	45513 (24.8)	11826 (24.7)	1591 (23.4)	471 (24.2)	
50 101 - 64 677	61395 (25.5)	47516 (25.8)	11678 (24.4)	1722 (25.3)	479 (24.6)	
64 678 - 83 503	58850 (24.5)	45141 (24.6)	11444 (23.9)	1762 (25.9)	503 (25.8)	
> 83 503	60806 (25.3)	45690 (24.9)	12899 (27.0)	1722 (25.3)	495 (25.4)	
Rural residence	36849 (15.2)	29824 (16.1)	6084 (12.6)	752 (11.0)	189 (9.6)	<0.01
Nulliparity	155853 (64.2)	118977 (64.2)	31868 (65.7)	3867 (56.3)	1141 (57.9)	<0.01
Smoked during pregnancy	47983 (19.8)	35378 (19.1)	11145 (23.0)	1086 (15.8)	374 (19.0)	<0.01

[a]Data is presented as number of individuals (n) and proportion of group (%), unless otherwise specified
[b]Not including Chinese

Table 4.2 Proportion of obstetrical and neonatal complications of mothers who delivered in Alberta between April 1 1999 and March 31 2010, overall and grouped by diagnosis of GDM or mental illness in pregnancy[a]

	Full cohort n (%)	No GDM, no mental illness n (%)	Mental illness only n (%)	GDM only n (%)	Both GDM and mental illness n (%)	P-value
Obstetrical						
Pre-eclampsia or eclampsia	3438 (1.4)	2516 (1.4)	704 (1.5)	161 (2.3)	57 (2.9)	<0.01
C-section	60036 (24.7)	44576 (24.0)	12331 (25.4)	2420 (35.3)	709 (36.0)	<0.01
Labor induction	73303 (30.2)	54383 (29.3)	14969 (30.9)	3060 (44.6)	891 (45.2)	<0.01
Birth-weight (Kg)						
Mean +/- SD	3.4 (0.6)	3.4 (0.6)	3.3 (0.7)	3.4 (0.6)	3.3 (0.6)	<0.01
Median (IQR)	3.4 (3.1, 3.7)	3.4 (3.1, 3.7)	3.4 (3.0, 3.7)	3.4 (3.0, 3.7)	3.4 (3.0, 3.7)	<0.01
Large for gestational age	22713 (9.4)	17125 (9.3)	4275 (8.9)	1003 (14.6)	310 (15.8)	<0.01
Neonatal death	1575 (0.7)	819 (0.4)	706 (1.5)	27 (0.4)	23 (1.2)	<0.01
Neonatal ICU stay	25044 (11.3)	18047 (10.7)	5529 (12.4)	1087 (17.0)	381 (20.6)	<0.01

[a]Data is presented as number of individuals (n) and proportion of group (%), unless otherwise specified
[b]Not including Chinese

Table 4.3 Cox proportional hazard ratios (HR) for the development of diabetes, hypertension and cardiovascular disease comparing women with no GDM or mental illness, mental illness only, GDM only and both GDM and mental illness

	Adjusted Hazard Ratios (95% CI)		
	Diabetes	Hypertension	Cardiovascular disease
No GDM, no mental illness	1.00	1.00	1.00
Mental illness only	1.3 (1.1, 1.5)	1.1 (1.1,1.2)	1.6 (1.3, 1.9)
GDM only	20.5 (18.4, 22.9)	1.7 (1.6, 1.9)	1.5 (1.0, 2.3)
Both GDM and mental illness	22.4 (19.2, 26.1)	2.0 (1.7, 2.3)	1.7 (0.9, 3.4)

Adjusted for: age, overweight, height, ethnicity, median household income, urban residence, smoking status, nulliparity, pre-eclampsia or eclampsia, fiscal year

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5 Conclusion

5.1 Summary of Research

Conditions in pregnancy and post-partum can have long-lasting impacts on the health of the mother and infant. Gestational diabetes and mental illness can each result in pregnancy, delivery and long-term complications[1–6]. In the general population, patients with diabetes have a higher prevalence of mental disorders, with evidence suggesting a bidirectional relationship[7,8]. Our objective was to investigate the presence of this association in the perinatal period. We found that women with a history of mental disorders within two years prior to pregnancy had a 10% increased risk of developing GDM. However, excluding these women with a history of mental illness, GDM did not significantly increase the risk of developing mental illness in pregnancy or post-partum.

Prior research has shown an increased risk of diabetes, hypertension and cardiovascular disease among women with GDM[1,9,10]. However, few have studied the impact of mental illness on chronic disease development. In the general population, patients with comorbid diabetes and mental illness are less likely to follow medical recommendations and have a higher mortality rate[11–13]. We were interested in examining the development of chronic disease among women with mental illness, and comparing it to women with only GDM, women with both GDM and mental illness, and women with no GDM or mental illness.

Our study showed that women with GDM and mental illness had the highest risk of developing diabetes and hypertension. Women with only GDM had a significantly greater risk of developing type two diabetes than those with mental illness only, but women with mental illness still had a 30% increased risk. In terms of hypertension, women with both GDM and mental illness had double the hazard rate as those with neither condition. Women with only GDM had a greater hazard rate than those with only mental illness. For cardiovascular disease, overall incidence was low but women with mental illness had a greater risk than women with only GDM.

In summary, pre-pregnancy mental illness contributes to GDM development, but GDM development does not increase the risk of incident mental illness in pregnancy or post-partum.

Having either GDM or mental illness increases the risk of chronic disease development and the risk is greatest for women with both GDM and mental illness.

5.2 Implications for Future Research

Through this research we found that mental illness contributes to the development of GDM, but did not explore mechanisms involved in the pathway. Studies on the etiology of type 2 diabetes suggest that mental illness may lead to diabetes through both biological and behavioral processes. Having a mental disorder may affect a person's diet choices, activity levels and harmful substance use, which may consequently lead to diabetes[14–18]. Mental illness can also cause disturbances in the regulation of hormones through the hypothalamic-pituitary-adrenal axis, which may lead to visceral adiposity and eventual diabetes[17,19,20]. Although these mechanisms are beyond the scope of our investigation, further research into these pathways may allow us to develop intervention methods to prevent the onset of diabetes.

Similarly, although we found that mental illness and GDM each lead to the development of type 2 diabetes, hypertension and cardiovascular disease, future research is needed to understand the pathways leading to their development. Furthermore, our research focused on health outcomes for mothers affected by GDM and mental illness. There is limited research on how these conditions affect the long-term health of the infant. The perinatal period is a crucial time for the infant's development, and gaining insight into the risk factors and consequences of these conditions may lead to interventions that reduce adverse health outcomes.

5.3 Implications for Future Policy

The prevalence and public health burden of mental illness is increasing worldwide [21]. Finding effective ways to recognize, treat and manage mental illnesses will improve health outcomes for a large number of people. In our research, we found that having a history of mental illness prior to pregnancy increased the risk of developing GDM. Effective treatment of mental illness prior to delivery may prevent cases of GDM. Furthermore, many women with a history of mental illness have recurrent episodes in pregnancy and post-partum, which increases the likelihood of complications.

Approximately one in four women have a mental illness in the perinatal period[22,23]. Our study showed that among all deliveries in Alberta from April 1 2000 to March 31 2009, 26% of women were diagnosed with a mental disorder prior to pregnancy, 14% during pregnancy and 22% post-partum. Despite this high prevalence, few countries have implemented policies to screen for mental illness[23]. The Canadian Task Force on Preventative Health Care does not recommend routinely screening for depression for adults even if they are considered to be of high risk for depression[24]. Barriers such as social stigma or cultural perceptions of mental illness may prevent women from discussing symptoms of mental illness with physicians. Therefore many cases may be undetected and untreated.

Screening for mental illness in pregnancy and post-partum will reduce the number of undetected cases and may reduce pregnancy complications and adverse child outcomes, such as sub-optimal mental health and development. Our study showed that perinatal mental illness also contributes to the future development of diabetes, hypertension and cardiovascular disease. Chronic disease is a significant burden to the Canadian healthcare system. Recognizing and treating mental illness will be beneficial for both short-term consequences and long-term outcomes.

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