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Gestational Diabetes Mellitus: The Real-World Evidence for Clinical Management and Adverse Health Outcomes in a Multi-racial/ethnic Population

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Gestational Diabetes Mellitus: The Real-World Evidence for Clinical Management and Adverse Health Outcomes in a Multi-racial/ethnic Population

A dissertation submitted in partial satisfaction

of the requirements for the degree Doctor of Philosophy

in Epidemiology

by

Xinyue Liu

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ABSTRACT OF THE DISSERTATION

Gestational Diabetes Mellitus: The Real-World Evidence for
Clinical Management and Adverse Health Outcomes
in a Multi-racial/ethnic Population

by

Xinyue Liu
Doctor of Philosophy in Epidemiology
University of California, Los Angeles, 2023
Professor Liwei Chen, Committee Chair

Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications, affecting of 6-9% pregnancies in the United States (US). It is linked to adverse health outcomes for both mothers and their offspring. There are well-known racial/ethnic differences in GDM prevalence and GDM-related adverse outcomes, but the reasons for the differences remain unknown. For example, Asians have the highest prevalence of GDM, which cannot be explained by the well-established risk factors, such as overweight/obesity and low socioeconomic status. In addition, there is no global consensus on GDM diagnostic methods and cut-offs. Given maternal glucose levels are progressively linked to adverse outcomes, maternal hyperglycemia can be divided into more granular categories than just GDM vs. non-GDM.

Regarding adverse health outcomes, it is still unclear whether GDM is associated with neurodevelopmental disorders (NDDs) in offspring and hypertension in mothers.

This thesis utilized real-world data from electronic medical records and published cohort studies to answer research questions related to GDM in order to bridge existing research gaps. We found that the more granular maternal hyperglycemic categories also had racial/ethnic differences and distinct health implications. We also found that GDM was associated with NDDs among young offspring born to non-Hispanic White mothers with GDM. Furthermore, GDM was associated with hypertension later in life among mothers.

These findings expand the current understanding of GDM diagnosis, GDM management, and GDM-related health implications.

The dissertation of Xinyue Liu is approved.

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2023

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

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Chen, L., Dai, J., Fei, Z., Liu, X., Zhu, Y., Rahman, M. L., Lu, R., Mitro, S.D, Yang, J., Hinkle, S.N., & Zhang, C. (2023). Metabolomic biomarkers of the Mediterranean diet in pregnant individuals: A prospective study. *Clinical Nutrition*, 42(3), 384-393.

Liu, X., Chen, L., Fei, Z., Zhao, S. K., Zhu, Y., Xia, T., Dai, J., Rahman, M.L., Wu, J., Weir, N.L., Tsai, M.Y., & Zhang, C. (2022). Physical activity and individual plasma phospholipid SFAs in pregnancy: a longitudinal study in a multiracial/multiethnic cohort in the United States. *The American Journal of Clinical Nutrition*, 116(6), 1729-1737.

Liu, X., Matthews, T. A., Chen, L., & Li, J. (2022). The associations of job strain and leisure-time physical activity with the risk of hypertension: the population-based Midlife in the United States cohort study. *Epidemiology and Health*, 44, e2022073.

Zhou, Z., Fan, Y., Thomason, D., Tang, W., Liu, X., et al. (2019). Economic Burden of Illness among Commercially Insured Patients with Systemic Sclerosis with Interstitial Lung Disease in the USA: a Claims Data Analysis. *Advances in Therapy*, 36(5), 1100-1113.

Goldsmith, J., Liu, X., Jacobson, J., & Rundle, A. (2016). New Insights into Activity Patterns in Children, Found using Functional Data Analyses. *Medicine and Science in Sports and Exercise*, 48(9), 1723.

1 CHAPTER ONE: INTRODUCTION

1.1 Background

Gestational diabetes mellitus (GDM), or glucose intolerance that is first recognized during pregnancy, is the most common medical complication during pregnancy[1], affecting 5-10% of pregnant women in the United States (US).[2-4] With the obesity epidemic, unhealthy lifestyles, and delayed age of motherhood, the incidence of GDM is growing rapidly in the US.[2, 5] GDM affects mothers from different racial/ethnic groups differently, with the highest incidence consistently observed among Asians and Hispanics[2, 6-9] In addition, a cost analysis in the US has found that the national costs of GDM in 2017 were $1.6 billion, with an average cost of $5,800 per case.[3] The rising prevalence and substantial costs make GDM a critical health concern in the US.

Universal screening of GDM at 24–28 gestational weeks (GW) is recommended for all pregnant women in the US. However, there is no consensus regarding the GDM screening methods. Although both one-step and two-step approaches are used, the two-step approach is still preferred in the US.[10-12] With different GDM diagnosis criteria, pregnant women may be classified as GDM or non-GDM despite having the same glucose levels, which has a profound impact on GDM prevalence, management, and its adverse health outcomes.[13, 14]

GDM management usually includes lifestyle interventions (first-line) and pharmacotherapies, including insulin and oral glucose-lowering medications. Around 15-30% of GDM women require pharmacotherapies (A2 GDM) to manage GDM, in addition to lifestyle interventions.[15] Although insulin is well accepted as the pharmacotherapy for GDM, due to the lack of long-term safety data, the use of oral glucose-lowering medications, such as metformin, is still controversial, despite their popularity in the US.[15-17]

GDM has been linked with increased risks of short-term and long-term adverse health outcomes for both mothers and their offspring.[18-20] Some evidence has shown that GDM affects health outcomes, such as type 2 diabetes and birth outcomes, differently by racial/ethnic groups.[21-23]

When examining the associations between GDM and adverse health outcomes, electronic health records have unique strengths due to their large sample sizes, real-world setting, and cost-efficiency. However, there may be missing data, unmeasured confounders, and misclassification of exposures and outcomes in electronic health records, as these data are not collected for research purposes.

In summary, GDM is a critical health concern in the US due to its high prevalence and its adverse health impacts on both mothers and their offspring. However, current guidelines in the US have inconsistent recommendations for both diagnostic criteria and pharmacologic management. In addition, racial/ethnic differences have been observed in GDM prevalence, management, and adverse health outcomes. It is critical to understand the GDM diagnosis, management, and adverse health outcomes in real-world settings in a multi-racial/ethnic population.

1.2 Conceptual Framework

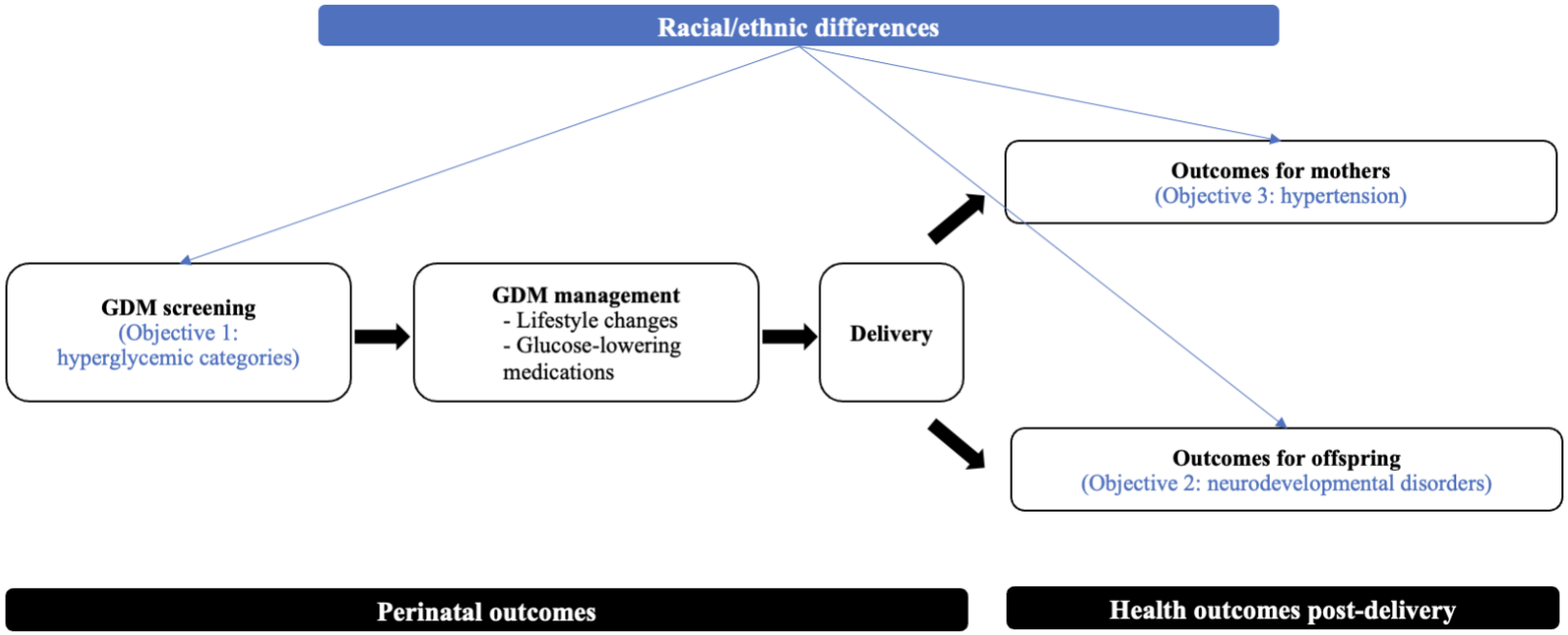


Figure 1.1. Conceptual framework of the thesis

2 CHAPTER TWO: BACKGROUND AND LITERATURE REVIEW

2.1 Gestational Diabetes Mellitus

2.1.1.1 Overview

GDM is one of the most common medical complications during pregnancy.[1, 24] The prevalence of GDM is increasing due to the obesity epidemic, unhealthy lifestyles, and delayed age of motherhood.[1, 24] From 2011 to 2019, the overall age-standardized GDM prevalence (aged 15-44 years with singleton first live births based on birth records) in the US raised from 4.76% to 6.35%.[25]

2.1.1.2 Racial/Ethnic Differences

GDM does not affect mothers from different racial/ethnic groups in the US equally, with the highest prevalence consistently observed among Asians.[2, 6-8, 26, 27] In addition, even among Asians, the prevalence of GDM varied a lot among subgroups, with the highest among Asian Indians and the lowest among Japanese.[7, 28] (Table 1)

Table 2.1. Prevalence of GDM by racial/ethnic groups in the US

	Shah, 2021, US[25]	Chen, 2019, US-CA[6]	Deputy, 2018, US[2]	Pu, 2015, US-CA[7]	Hedderson, 2012, US-CA[8]	Chu, 2009, US[28]	Lawrence, 2008, US-CA[26]	Ferrara, 2004, US-CA[27]
Non-Hispanic White	5.8%	7.9%	5.3%	7.0%	4.5%	-	5.3%	6.1%
Non-Hispanic Black	5.6%	9.0%	4.8%	4.9%	4.4%	-	8.5%	5.8%
Hispanic	6.7%	10.7%	6.6%	10.8%	6.8%	-	5.0%	7.6%
Asian/Pacific Islander	10.3%	-	-	-	-	-	11.8%	10.9%
Asian	-	15.5%	11.1%	-	10.2%	-	-	-
Asian Indian	12.9%	-	-	17.8%	-	8.0%	-	-
Chinese	9.1%	-	-	16.4%	-	6.4%	-	-
Filipino	10.3%	-	-	18.8%	-	6.9%	-	-
Japanese	5.4%	-	-	8.5%	-	3.5%	-	-
Korean	7.1%	-	-	12.1%	-	3.9%	-	-
Vietnamese	10.9%	-	-	18.7%	-	6.1%	-	-
American Indian	-	-	9.2%	-	-	-	-	-
Pacific Islander	-	-	8.4%	-	-	-	-	-
Other	-	-	5.8%	-	-	-	8.1%	-

2.1.2 GDM Screening and Diagnosis

Universal screening of GDM at 24–28 GW is recommended in the US, as randomized clinical trials (RCT) demonstrate that GDM treatments can improve maternal and perinatal outcomes.[10-12]

Given the association between hyperglycemia and adverse outcomes is continuous without a clear threshold, no diagnostic criteria for GDM have gained universal acceptance globally. In 2010, the International Association of Diabetes in Pregnancy Study Groups (IADPSG) published recommendations for the identification and classification of hyperglycemia in pregnancy, which define women who are first diagnosed with hyperglycemia during pregnancy as GDM (excluding the possibility of pre-existing diabetes). The IADPSG criteria have recommended a one-step method involving an oral glucose tolerance test (OGTT) at 24–28 GW.[29] In 2013, WHO has endorsed the IADPSG criteria.[30] The 2015 The International Federation of Gynecology and Obstetrics (FIGO) guideline has endorsed the IADPSG 2010 or

WHO 2013 criteria when possible as well as a more flexible approach that allows for differing diagnostic processes depending on resource constraints.[31] However, in the US, more than one approach has been adopted. The American College of Obstetricians and Gynecologists (ACOG) has recommended using the one-step Carpenter-Coustan criteria as the primary approach, and the one-step National Diabetes Data Group criteria as the alternative approach at 24–28 GW.[16] The American Diabetes Association (ADA) has recommended using either a one-step or a two-step approach at 24–28 GWs for all pregnant women not previously diagnosed with diabetes.[32] (Table 2) Although both one-step and two-step approaches are recommended in the US, according to a survey of 2,330 the Society for Maternal–Fetal Medicine (SMFM) members during 2014–2015, most clinicians (90.6%) preferred to use the two-step approach for the diagnosis of GDM.[33] As the one-step and two-step approaches are linked with different GDM prevalence and different rates for adverse health outcomes, knowing the specific GDM diagnosis criteria and actual maternal blood glucose levels is crucial when studying GDM in the US.

It is still controversial whether the one-step or two-step approach is better for health outcomes among women with GDM and their offspring. A recent large pragmatic RCT comparing one-step and two-step approach in the US has shown that one-step approach identified more GDM cases (RR: 1.94 [95% confidence interval 1.79, 2.11]), but no differences were found for large for gestational age (LGA), perinatal composite outcome, gestational hypertension or preeclampsia, and primary cesarean section.[34] However, several concerns about this RCT have been raised, including low compliance with GDM screening and treatment.[35]

Table 2.2. Diagnostic guidelines for GDM at 24–28 GW in the US

Organization	Thresholds
ACOG 2018[16] (two-step, Carpenter and Coustan)	Step 1: 50g glucose challenge test (GCT, non-fasting), step 2 if: - 1 h: 130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L) Step 2: 100g OGTT (fasting), GDM if ≥2 of following: - fasting: 95 mg/dL (5.3 mmol/L) - 1 h: 180 mg/dL (10.0 mmol/L) - 2 h: 155 mg/dL (8.6 mmol/L) - 3 h: 140 mg/dL (7.8 mmol/L)
ACOG 2018[16] (two-step, National Diabetes Data Group)	Step 1: 50g GCT (non-fasting), proceed to step 2 if: - 1 h: 130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L) Step 2: 100g OGTT (fasting), GDM if ≥2 of following: - fasting: 105 mg/dL (5.8 mmol/L) - 1 h: 190 mg/dL (10.6 mmol/L) - 2 h: 165 mg/dL (9.2 mmol/L) - 3 h: 145 mg/dL (8.0 mmol/L)
ADA 2020[32] (one-step, IADPSG)	75g OGTT (fasting), GDM if ≥1 of following: - fasting: 92 mg/dL (5.1 mmol/L) - 1 h: 180 mg/dL (10.0 mmol/L) - 2 h: 153 mg/dL (8.5 mmol/L)
ADA 2020[32] (two-step, Carpenter-Coustan)	Step 1: 50g GCT (non-fasting), proceed to step 2 if: - 1 h: 130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L) Step 2: 100g OGTT (fasting), GDM if ≥2 of following: - fasting: 95 mg/dL (5.3 mmol/L) - 1 h: 180 mg/dL (10.0 mmol/L) - 2 h: 155 mg/dL (8.6 mmol/L) - 3 h: 140 mg/dL (7.8 mmol/L)

2.1.3 GDM Management

The 2020 ADA guideline has recommended women with GDM self-monitor blood glucose and the glucose targets are: fasting glucose values <95 mg dl/L (5.3 mmol l/L), either 1-hour postprandial glucose <140 mg dl/L (7.8 mmol l/L) or 2-hour postprandial glucose <120 mg dl/L (6.7 mmol l/L), and HbA1c levels <6% (42 mmol/mol) or <7% (53 mmol/mol) if necessary.[15]

2.1.3.1 Guidelines for Pharmacological Management of GDM

After 1–2 weeks of lifestyle interventions, if glycemia remains elevated, pharmacological interventions should be initiated especially when excessive fetal growth is observed.[36] Recent

guidelines have provided conflicting recommendations regarding the pharmacological management of GDM. The 2020 ADA guideline has recommended using insulin for managing hyperglycemia in GDM when lifestyle behavior change is not sufficient.[15] ADA has also stated not to use metformin and glyburide as the first-line medications, because other glucose-lowering medications lack long-term safety data, and to discontinue metformin, when taking it to treat polycystic ovary syndrome and induce ovulation, before the end of the first trimester.[15] Among women who require to take glucose-lowering medications, the 2018 ACOG Practice Bulletin has recommended using insulin as the first-line treatment, and metformin as the second-line treatment, and ACOG has stated that glyburide is not preferred.[16] The 2018 SMFM statement on pharmacological treatment of GDM has stated that insulin and metformin are both reasonable first-line treatments when lifestyle interventions are not sufficient to control glucose.[17] (Table 3)

Table 2.3. Pharmacologic treatment guidelines for GDM not responding to lifestyle intervention

Organization	Year	Preferred agents	Alternative agents
ADA[15]	2020	Insulin	Metformin or glyburide
ACOG[16]	2018	Insulin	Metformin
SMFM[17]	2018	Insulin or metformin	Glyburide

2.1.3.2 Insulin, Metformin, and Glyburide Real-World Patterns

Insulin (i.e., human insulin, several insulin analogs, and insulin glargine) is effective, and it does not cross the placenta.[37, 38] However, insulin causes a burden for pregnant women, as it is time-consuming, inconvenient, and expensive.[1] Metformin (oral) suppresses hepatic glucose production, resulting in decreased fasting plasma glucose levels and HbA1c, and glyburide (oral) augments insulin secretion, leading to a reduction in fasting plasma glucose levels and HbA1c.[1] Although oral agents are cheap and convenient, they cross the placenta, which may affect the development of fetus.[1]

Glucose-lowering medications are widely used among women with GDM in the US. However, it is unclear whether the use of glucose-lowering medications is consistent with the current guideline recommendations in the US. Evidence has suggested that depending on the population, 15-30% of GDM women diagnosed by the two-step criteria in the US require other therapies including glucose-lowering medications to manage GDM in addition to lifestyle modifications.[15] Furthermore, although glyburide is not recommended as the preferred agent to treat women with GDM, a cohort study in the US has shown that 8.3% of GDM women were treated with glyburide/insulin.[39]

Glucose-lowering medications are also widely prescribed in other countries, including Canada and New Zealand. A large population-based cohort study in Canada found that from 2009 to 2014, the proportion of women with GDM treated with glycemic control therapies increased from 25.0% to 31.4% (insulin only: 23.6% to 28.3%; metformin ± insulin: 1.4% to 3.2%).[40] In a large population-based cohort study in New Zealand, 48.2% initiated a prescription for metformin or insulin.[41]

2.2 Gestational Diabetes Mellitus and Adverse Health Outcomes

2.2.1 Adverse Pregnancy Outcomes

Studies have found that GDM and maternal blood glucose levels are associated with adverse pregnancy outcomes such as preeclampsia, LGA, preterm birth, and cesarean section.

GDM and adverse pregnancy outcomes

GDM is associated with a higher risk of pregnancy outcomes. In a recent systematic literature review and meta-analysis, in studies with no insulin use, women with GDM had higher odds of macrosomia (OR 1.70 [95% confidence interval 1.23, 2.36]), LGA (1.57 [1.25, 1.97]), preterm delivery (1.51 [1.26, 1.80]), low 1 minute Apgar score (1.43 [1.01, 2.03]), and cesarean section (1.16 [1.03, 1.32]).[42] In studies with insulin use, the odds of admission to NICU (2.29 [1.59, 3.31]), LGA (1.61 [1.09, 2.37]), respiratory distress syndrome (1.57 [1.19, 2.08]), and neonatal jaundice (1.28 [1.02, 1.62]) were higher in women with GDM than in those without. [42]

Maternal blood glucose levels and adverse pregnancy outcomes

The large flagship multinational Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study has clearly shown that maternal glucose levels are strongly and continuously (with no obvious thresholds) associated with increased risks for birth weight >90th percentile, primary cesarean section, clinical neonatal hypoglycemia cord-blood serum C peptide >90th percentile, preterm delivery, shoulder dystocia or birth injury, NICU admission, hyperbilirubinemia, and preeclampsia.[43] In general, fasting plasma glucose levels were more strongly associated with these adverse outcomes compared with the 1-hour or 2-hour levels from the OGTT.[43]

2.2.1.1 Racial/ethnic Differences in Pregnancy Outcomes

In general, non-Hispanic Black women with GDM tend to have higher risks of adverse pregnancy outcomes than non-Hispanic White women, while Hispanics and Asians tend to have a lower risk. Among Asian subgroups, women from East Asians seem to have lower risks of adverse pregnancy outcomes than South Asians.

GDM and adverse pregnancy outcomes

Non-Hispanic Blacks with GDM are more likely to have preeclampsia[44], primary cesarean delivery[45], LGA[46], neonatal hypoglycemia[44], preterm deliveries[44], and intrauterine fetal demise[45] than non-Hispanic Whites. Furthermore, Hispanics with GDM are less likely to have preterm deliveries[21, 45], gestational hypertension[21], and large infants[21], while they are more likely to have shoulder dystocia[21] than non-Hispanic Whites. In addition, compared to non-Hispanic Whites with GDM, Asians are less likely to experience primary cesarean delivery[44, 45], macrosomia[45], and neonatal respiratory distress syndrome.[44] Among Asian subgroups, Native-Hawaiians/Pacific-Islanders and Filipinos with GDM are more likely to have macrosomia, while Chinese and Japanese with GDM have a similar risk of macrosomia, compared to non-Hispanic Whites.[23] In addition, compared to the general population in Canada, Chinese are less likely to have adverse maternal and neonatal outcomes, while South Asians are more likely to have adverse neonatal outcomes.[47]

Maternal blood glucose levels and adverse pregnancy outcomes

Limited studies have examined the associations between maternal blood glucose levels and pregnancy outcomes among racial/ethnic groups. For example, a large prospective study in the United Kingdom (UK) has found positive associations between fasting glucose and LGA, high infant adiposity, and cesarean section in both non-Hispanic Whites and South Asians.[48]

2.2.2 Long-term (i.e., Post-Delivery) Adverse Health Outcomes for Mothers

Studies have shown that GDM mothers have elevated risks for cardiometabolic diseases, such as diabetes, cardiovascular diseases (CVD), and metabolic syndrome post-delivery.

GDM recurrence

Although varying greatly across studies, GDM has a recurrence rate ranging from 30% to 84% in subsequent pregnancies.[49, 50]

GDM and diabetes in mothers

Several meta-analyses have found that women with GDM had a substantially (7-10 fold) higher risk of developing type 2 diabetes mellitus (T2DM) compared with non-GDM controls.[51-53] The flagship HAPO Follow-up Study (using the IADPSG criteria) with a median follow-up of 11.4 years has also found that the odds of mothers with GDM (52.2%) developing T2DM or prediabetes was 3.44 times (2.85, 4.14) higher than the odds of mothers without GDM (20.1%).[19]

GDM and CVD in mothers

Meta-analyses have revealed that GDM was associated with a higher risk (around 2-fold) of developing CVD among mothers.[54, 55] A 2018's review has reported the association between hyperglycemia in pregnancy and an elevated long-term risk of having CVD for women.[56] In addition, a dose-response relationship between glucose level regardless of GDM status during pregnancy and postpartum atherosclerotic morbidity has been reported.[57]

GDM and metabolic syndrome in mothers

Meta-analyses have demonstrated that GDM was associated with an elevated risk (3-4 fold) of metabolic syndrome in mothers.[58, 59] A study using the 1978–1996 Danish cohort has found that the odds of developing the WHO-defined metabolic syndrome were higher (OR 3.4 [2.5, 4.8]) in the GDM group than in the non-GDM group.[60]

2.2.2.1 Racial/ethnic Disparities of Long-term Adverse Health Outcomes for Mothers

Studies about the racial/ethnic differences in the association between GDM and subsequent cardiometabolic diseases are limited.

GDM and cardiometabolic diseases in mothers

Compared to non-Hispanic White mothers with GDM, non-Hispanic Blacks have a higher risk of subsequent diabetes[22, 61] and chronic conditions.[62] In addition, Hispanic mothers with GDM experience a higher risk of subsequent hypertension[63], and Asian mothers with GDM have a higher risk of diabetes than non-Hispanic White mothers[64].

2.2.3 Long-term Adverse Health Outcomes in Offspring

Studies have demonstrated that offspring born to GDM mothers have an increased risk of adverse cardiometabolic profiles. In addition, emerging evidence suggests that GDM is associated with an increased risk of autism spectrum disorder (ASD). However, other neurodevelopmental disorders such as communication disorders, although having higher prevalence, are rarely studied.

GDM and adverse cardiometabolic profiles in offspring

GDM is associated with a higher risk of overweight/obesity[65, 66], metabolic syndrome[65], insulin resistance[67], and prediabetes/diabetes[68] in offspring. Specifically, a recent systematic narrative literature review has found that GDM is positively associated with overweight/obesity and adverse metabolic profile in offspring.[66] In addition, the flagship HAPO Follow-up Study has shown that compared to their counterparts, offspring born to mothers with GDM had higher risks of being overweight/obese and elevated body fat percentage/waist circumference/skinfolds.[19]

GDM and neurodevelopmental disorders in offspring

Evidence has shown that GDM can induce changes in offspring's behaviors and gene transcription in the brain.[69] A recent meta-analysis has reported that GDM was associated with higher odds of ASD (1.42 [1.22, 1.65]), while not associated with attention-deficit/hyperactivity disorder (ADHD).[20] In addition, the timing of GDM diagnosis is important: ASD risks in offspring of mothers with GDM diagnosed ≤26 GW was 1.42 (1.16, 1.75), while offspring of mothers with GDM diagnosed >26 GW was not associated with an increased risk for ASD.[70] Furthermore, GDM with poor glucose control may be associated with ADHD: compared with controls, the risk of ADHD in offspring was higher (1.26 [1.14, 1.41]) for mothers with GDM needing antidiabetic medications, but was similar for mothers with GDM not needing antidiabetic medications.[71]

3 CHAPTER THREE: RESEARCH GAPS AND METHODOLOGICAL CHANLLENGES

3.1 Research Gaps

3.1.1 Diagnostic criteria and definitions

GDM refers to the onset or recognition of glucose intolerance during pregnancy. Initially, studies by O'Sullivan and Mahan indicated that GDM is primarily diagnosed in the second and third trimesters.[72] Currently, in the US, both the ACOG and the ADA accept the criteria using the two-step method, which involves a 50g GCT followed by a 100g 3-hour OGTT as established by Carpenter-Coustan[73]. However, ACOG also acknowledges the NDDG criteria[74]. The HAPO Study, which evaluated glucose tolerance in the late second and early third trimesters using a single-step approach with a 75g 2-hour OGTT, led to its adoption by the IADPSG and the WHO. There is still considerable debate surrounding the diagnostic criteria for GDM.

3.1.2 Race/ethnic differences in the GDM prevalence

Asians have the highest GDM prevalence, which cannot be explained by conventional risk factors, such as high pre-pregnancy BMI or low socioeconomic status (SES).[1, 24, 25, 28, 75, 76] Additionally, GDM prevalence varies substantially among Asian subgroups, with Japanese and Koreans consistently exhibiting a lower prevalence than other Asian subgroups, including Chinese, Vietnamese, Filipinos, and Asian Indians.[1, 24, 25, 28, 75, 76] In addition, non-Hispanic blacks have a relatively low prevalence of GDM, despite having more maternal smoking, high pre-pregnancy BMI, and low SES[1, 24, 25, 28, 75, 76]. The reasons for these racial/ethnic differences are still unclear.

3.1.3 GDM-related adverse health outcomes in mothers and offspring

<u>Neurodevelopmental disorders (NDD) in offspring</u>

NDD encompasses various impairments in cognitive or motor functions, including ASD, ADHD, speech/language disorder (SLD), developmental coordination disorder (DCD), learning disability, intellectual disability, and behavioral disorder.[77-79] Recent evidence indicates that offspring born to mothers with GDM may face an increased risk of adverse neurodevelopmental and cognitive outcomes.[1, 80] This heightened risk can be attributed to the direct impact of maternal hyperglycemia on fetal brain development[81-88] or indirectly through unfavorable neonatal outcomes like preterm birth.[1, 24, 89-92]

Previous studies have predominantly examined the association between GDM and the risk of ASD and ADHD in offspring, with limited research on other types of NDDs.[20, 71, 93, 94] In addition, no research has explored whether the association between GDM and NDDs varies by race/ethnicity.

Hypertension in mothers later in life

Hypertension, a condition that affects over 20% of adults globally, is considered a major risk factor for cardiovascular diseases, renal diseases, and dementia.[95-97] The association between GDM and hypertension can be attributed to direct metabolic and vascular damage[98] or indirect factors such as pregnancy-induced hypertension[90, 99] and type 2 diabetes.[52] Over the past decade, numerous studies have examined the relationship between GDM and hypertension in females, but the results have been contradictory. While several large studies conducted in North America, Europe, and Asia have reported a positive association between GDM and hypertension later in life[100-103], other large studies, including the multinational prospective Hyperglycemia and Adverse Pregnancy Outcome Follow-Up Study (HAPO-FUS), did not find a significant association.[104, 105] A comprehensive review of the association between GDM and hypertension later in life is lacking.

3.2 Methodological Challenges

3.2.1 Loss to Follow-up in Real-World Data

Real-world studies are convenient and useful sources to investigate health outcomes using longitudinal study designs. Real-world data is often driven by clinical and administrative encounters rather than research needs. Patients may be lost to follow-up in real-world databases due to several reasons including 1) patients not seeking medical care, 2) patients switching to another provider, or 3) death, which is not systematically captured by most real-world data systems.[106]

According to a study using electronic health records from 76 Community Health Centers across 20 States in the US, the attrition rate over a 3-year period was 33.5% for non-pregnant adults, and <25% for patients with diabetes or hypertension.[106] In addition, among Medicaid enrollees, 12% of community health center patients and 39% of single-provider practice patients changed providers after a 6-month gap between visits.[106]

Due to the frequent loss to follow-up, real-world data are often analyzed via a time-to-even framework. Selection bias due to loss to follow-up, or informative censoring, posts a threat to the internal validity of estimates.[107] Over the past years, techniques such as regression adjustment and inverse probability-of-censoring weighted estimation have been discussed to correct for loss to follow-up bias.[107, 108]

3.2.2 Uncontrolled Confounding in Real-World Data

Appropriate adjustment for confounding in epidemiologic studies is challenging, and the challenge becomes more pronounced in studies utilizing real-world data.[109] The crucial potential confounding factors, such as socioeconomic status, lifestyle factors, and family history, may be missing, leading to uncontrolled confounding.[109]

Researchers can conduct sensitivity analyses to assess the impacts of hypothetical unmeasured confounders.[109] In addition, propensity score calibration may be applied to adjust estimates if external data are available on multiple unmeasured confounders.[109] Furthermore, instrumental variable methods may also be useful to estimate treatment effects if there are unmeasured confounders.[109]

3.2.3 Misclassifications in Real-World Data

Medical coding and documentation in real-world databases can be influenced by factors outside of clinical care, which can introduce systematic bias and thus complicate their use for healthcare research. For example, electronic health records systems often have mandatory fields that must be completed for documentation purposes.[110] However, these fields may not always align perfectly with the clinical needs or research requirements, leading to incomplete or inaccurate data. In addition, coding practices and documentation may be influenced by the goal of optimizing insurance reimbursement.[110] Providers may prioritize certain codes over others to ensure proper payment, potentially affecting the accuracy and reliability of the data. Furthermore, when transitioning from paper-based systems to electronic databases, historical information may be automatically imported.[110] This process can introduce errors, inconsistencies, or outdated codes into the database, which can impact the quality and usefulness of the data.

It is important to validate the critical variables, such as exposure and outcome, against laboratory data, clinical charts, or sometimes self-report data.[110] Common statistics that measure misclassification include sensitivity, specificity, positive predictive value, negative predictive value, and the area under the receiver operating characteristic (ROC) curve.[110] In addition, misclassification bias can be corrected using various methods, such as quantitative bias analysis

with bias parameters of varying accuracy and disease status imputation using bootstrap methods and disease probability models.[111]

4 CHAPTER FOUR: METHODS

4.1 Data Source

Participants are from an academic health center in Los Angeles (i.e., Ronald Reagan UCLA Medical Center, Santa Monica UCLA Medical Center, and other UCLA-affiliated clinics and departments), which currently has data on 4.5 million unique patients. Data are assembled from an electronic health records system utilizing Epic software. Demographics, behaviors, diagnoses, procedures, laboratory tests, medications, visit details, vital signs, and vital status are available in the data.

4.1.1 Study Population

The study population includes mother-offspring pairs of all live deliveries in the UCLA hospitals between 2013/3/1 and 2021/8/31 (laboratory data are available starting from March 2013). In the dataset, 21,539 women delivered at least one baby, corresponding to a total number of 26,436 babies. Among 21,539 mothers, 8,741 (40.6%) were White, 5,052 (23.5%) were Hispanic, 3,692 (17.1%) were Asians, 2,486 (11.5%) were others and 461 (2.1%) were missing. The median follow-up time for mothers was 753 days (2.1 years), while the median follow-up time for offspring was 612 days (1.7 years).

4.1.2 Variables

Table 4.1. Available variables

Category	Variable
Patient Characteristics	Age (birth year)
	Sex
	Race/ethnicity and Asian subgroups
	Marital status
	Area deprivation index state level
	Area deprivation index national rank
	Religion
	Language
	Sexual orientation
	Sexual activity
	Tobacco use
	Alcohol use
Diagnoses	ICD-code and description
	Diagnosis date
	Primary diagnosis flag
Laboratory data	LOINC code and description
	Order date and time
	Specimen taken date and time
	Result date and time
	Result
	Reference unit
Medications	Medication ID and name
	Medication generic, class, and subclass names
	Order date
	Start date
	End date
	Quantity
	Refills
	Frequency
	Provider instructions
Procedures	Procedure type (ICD-code or CPT)
	Procedure code
	Procedure date
	Procedure description
Obstetrics and gynecology	Delivery method (C-section, vaginal)
	Delivery outcome (living, death)
	Apgar score
	Gestational age at delivery
	Birthweight

	Delivery date and time Mother estimated weight at start of pregnancy Mother weight at delivery
Vital signs	Vital sign type (blood pressure, pulse, temperature, height, weight, BMI, respiration, pulse oximetry) Vital sign take date and time
Encounter information	First encounter date Last encounter date

4.1.3 University of California, Los Angeles Glucose in Relation to Women and Babies' Health (UCLA GrownB)

Based on the UCLA electronic health records, we established a retrospective cohort, UCLA GrownB, which includes linked mother-offspring data delivered at UCLA medical center from March 1, 2013, to August 31, 2021. To be eligible for this cohort, mothers were between 18-49 years old at delivery, and offspring were born between 24-42 weeks of gestation.

4.2 Study Goals and Specific Objectives

4.2.1 Study Goals

The overall goals are to study the real-world distributions of maternal hyperglycemia, to investigate the associations of GDM with adverse health outcomes in both mothers and their offspring, and to study the racial/ethnic differences in maternal hyperglycemia and its adverse impacts.

4.2.2 Objective 1

To describe the real-world distributions of maternal hyperglycemic categories based on the two-step GDM screening approach, including the potential racial/ethnic differences, and their associations with adverse pregnancy outcomes.

- Aim 1: to examine if maternal hyperglycemic categories vary by racial/ethnic groups and Asian subgroups

- Aim 2: to explore the associations between maternal hyperglycemic categories and adverse pregnancy outcomes, including hypertensive disorders of pregnancy, cesarean delivery, LGA, and preterm birth

4.2.3 Objective 2

To examine whether GDM is associated with neurodevelopmental disorders in offspring, and whether race/ethnicity modifies the associations.

- Aim 1: to examine the associations of GDM with different types of neurodevelopmental disorders, autism spectrum disorder, attention deficit hyperactivity disorder, speech/language disorder, developmental coordination disorder, learning disability, intellectual disability, and behavioral disorder, and their combinations in offspring
- Aim 2: to investigate whether the associations varied by race/ethnicity

4.2.4 Objective 3

To examine whether GDM is associated with hypertension later in life and the impact of uncontrolled confounding due to psychological stress.

- Aim 2: to examine the association between GDM and hypertension later in life using a systematic literature review and meta-analysis of cohort studies
- Aim 3: to quantify the bias between GDM and hypertension later in life due to uncontrolled confounding of psychological stress

5 CHAPTER FIVE: RACIAL/ETHNIC DIFFERENCES IN MATERNAL HYPERGLYCEMIC CATEGORIES AND ASSOCIATED ADVERSE PREGNANCY OUTCOMES

5.1 Abstract

Objectives

In the United States (US), the two-step (50g glucose challenge test [GCT] and 3-hour 100g oral glucose tolerance test [OGTT]) gestational diabetes mellitus (GDM) screening is widely applied, which can be used to categorize pregnancies into various hyperglycemic groups. We aimed to investigate the racial/ethnic differences in hyperglycemic categories and to examine their associations with adverse pregnancy outcomes.

Methods

This retrospective cohort included pregnancies in an academic medical center between 3/1/2013-8/31/2021. Glycemic categories included: normal glucose tolerance (NGT, normal GCT), pregnancy-impaired glucose intolerance-0 (PIGT-0, abnormal GCT & 0 abnormal OGTT), PIGT-1 (abnormal GCT & 1 abnormal OGTT), GDM-0 (abnormal GCT, normal fasting & ≥2 abnormal postprandial OGTT), and GDM-1 (abnormal GCT, 1 abnormal fasting & ≥1 abnormal postprandial OGTT). Modified Poisson regressions with robust error variance were applied to estimate the age-adjusted prevalence ratio (PR) of hyperglycemic categories comparing each racial/ethnic group with non-Hispanic Whites and to estimate the multivariable-adjusted risk ratio (RR) of adverse pregnancy outcomes comparing hyperglycemic categories with NGT.

Results

Of the 11,405 pregnancies, 44.8% were non-Hispanic White, 19.9% were Asian, 17.5% were Hispanic, 3.9% were non-Hispanic Black, and 14.0% were other/unknown race/ethnicities. PIGT-0, PIGT-1, and GDM-0 had the highest prevalence in Asians, while GDM-1 had the highest prevalence in Hispanics. Compared to non-Hispanic Whites, the age-adjusted prevalence of all hyperglycemic groups was higher in Asians (PIGT-0: 1.51 [95% confidence interval, 1.35, 1.69]; PIGT-1: 2.18 [1.78, 2.68]; GDM-0: 2.55 [2.10, 3.10]; GDM-1: 1.55 [1.08, 2.21]) and Hispanics (PIGT-0: 1.32 [1.16, 1.50]; PIGT-1: 2.07 [1.67, 2.57]; GDM-0: 1.69 [1.35, 2.13]; GDM-1: 2.68 [1.93, 3.71]). Compared to NGT, PIGT-1 was independently associated with an increased risk of pregnancy-related hypertension (1.19 [95% CI 1.02, 1.38]), LGA (1.73 [1.37, 2.18]), and preterm birth (1.33 [1.05, 1.68]). PIGT-0 (1.23 [1.04, 1.45]) and GDM-0 (1.56 [0.87, 1.71]) were linked with a higher risk of preterm birth. GDM-1 tended to be associated with a higher risk of LGA (1.28 [0.87, 1.99]) and preterm birth (1.22 [0.87, 1.71]).

Conclusion

The hyperglycemic categories vary by race/ethnicity and have different implications for adverse pregnancy outcomes.

5.2 Introduction

Maternal hyperglycemia is a common pregnancy complication with intergenerational adverse health impacts and substantial economic burdens[1, 24, 25, 75, 76]. Screening for maternal hyperglycemia is universal in many countries, and pregnancies classified as gestational diabetes mellitus (GDM) are treated according to clinical guidelines[74, 112]. Over the past few decades, GDM prevalence has increased remarkably, with notable variations among racial/ethnic groups[1, 24, 25, 75, 76]. In the United States (US), Asians have the highest GDM prevalence, which cannot be explained by established risk factors, such as high pre-pregnancy body mass index (BMI) or low socioeconomic status (SES). Additionally, GDM prevalence varies among Asian subgroups, with Japanese and Koreans consistently exhibiting a lower prevalence than other Asian subgroups, particularly Asian Indians[1, 24, 25, 28, 75, 76]. There are also racial/ethnic differences in GDM-related pregnancy outcomes[113]. For example, Asians face a higher risk of small for gestational age (SGA) but a lower risk of pregnancy-related hypertension than non-Hispanic Whites[113]. Non-Hispanic Blacks experience the worst outcomes, including cesarean delivery, preterm birth, and maternal/neonatal intensive care unit admission[113].

Despite consensus on GDM treatment, there is a lack of global agreement regarding its diagnosis[1, 24, 75]. The long-lasting debates primarily stem from different opinions on which adverse outcomes to consider when choosing GDM screening methods and cut-offs[1, 24, 74, 112]. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommends the one-step approach utilizing a 2-hour 75g oral glucose tolerance test (OGTT) for GDM diagnosis[29]. However, most practices in the US still prefer the two-step approach, involving a 50g glucose challenge test (GCT) followed by a 3-hour OGTT using the Carpenter and Coustan criteria[74, 112]. The two-step approach results in an intermediate stage between

normal glucose tolerance (NGT) and GDM, known as pregnancy-impaired glucose tolerance (PIGT). It occurs when the GCT is failed but OGTT values do not meet the GDM diagnostic criteria. PIGT is also associated with adverse pregnancy outcomes, including gestational hypertension and large for gestational age (LGA)[114, 115]. Additionally, abnormal fasting OGTT may indicate hepatic insulin resistance, while abnormal postprandial OGTT may indicate muscle insulin resistance[116, 117]. The differential underlying causes may lead to distinct health implications[118, 119]. For example, abnormal fasting OGTT value is more related to LGA, while abnormal postprandial OGTT values are more associated with gestational hypertension and preterm birth[118, 119].

However, previous studies did not examine the racial/ethnic differences in maternal hyperglycemic categories, and often underrepresented or aggregated Asians into a single group. Thus, we aimed to examine if maternal hyperglycemic categories vary by racial/ethnic groups and Asian subgroups. Furthermore, as the consequences of maternal hyperglycemic categories, especially the untreated PIGT, remain unknown, we also aimed to investigate the associations between maternal hyperglycemic categories and adverse pregnancy outcomes.

5.3 Methods

Study population

We established a retrospective cohort (University of California, Los Angeles Glucose in Relation to Women and Babies' Health [UCLA GrownB]), which included 25,780 births (25,147 singletons and 633 multiple pregnancies; 21,544 mothers and 26,441 offspring) at UCLA medical center from March 1, 2013, to August 31, 2021. The medical center caters to patients from various socioeconomic backgrounds in the Los Angeles metropolitan area[32,33]. It includes four hospitals, 200+ clinics, serving 670,000+ unique patients, with 2.8 million outpatient visits

and 100,000 inpatient admissions annually. The UCLA Institutional Review Board approved this study for exemption. All data were extracted from electronic medical records.

The current study included 11,517 pregnancies from the UCLA GrownB cohort, with available laboratory data and maternal hyperglycemia screened via the two-step approach (>90% of pregnancies). Several reasons accounted for missing laboratory data, including inconsistent data collection in earlier years, lack of GDM screening, or screening performed at a different institution. We further excluded 112 (1.0%) pregnancies with diagnosed diabetes before pregnancy using International Classification of Diseases (ICD) codes (ICD-9: 250.x; ICD-10: E10.x, E11.x, and E13.x), resulting in a final analytical sample of 11,405 pregnancies. (Figure 1).

Pregnancies within the analytical sample tended to be slightly older age, non-Hispanic White/Asian ethnicity, married, singleton pregnancies, residence in more privileged neighborhoods, lower pre-pregnancy BMI, and fewer pre-existing chronic conditions, in contrast to the pregnancies that were excluded. (Supplementary Table 1)

Race/ethnicity and Asian subgroups

We considered self-identified race/ethnicity, including Hispanic, non-Hispanic Black, non-Hispanic White, and other/unknown race/ethnicities. We also considered self-identified Asian subgroups, including Asian Indian, Chinese, Filipino, Japanese, Korean, and other/unknown Asians.

Maternal glycemic categories

All pregnancies underwent GDM screening using the two-step approach, following the Carpenter & Coustan criteria (93.3% in 24-28 weeks of gestation, 2.7% <24 weeks of gestation, and 4.0% >28 weeks of gestation). A non-fasting 50g 1-hour GCT (abnormal cut-off, ≥140

mg/L) was applied first, and if the result was abnormal, a fasting 100g 3-hour OGTT (abnormal cut-offs, fasting: ≥95 mg/dL, 1-hour: ≥180 mg/dL; 2-hour: ≥155 mg/L; 3-hour: ≥140 mg/L) was followed[74, 112]. GDM was defined as having ≥2 abnormal OGTT values.

Based on glucose values from GCT and OGTT, maternal glycemic categories were classified into NGT (normal GCT value), PIGT (an intermediate stage: abnormal GCT and 0-1 abnormal OGTT value), and GDM (abnormal GCT and ≥2 abnormal OGTT values). The PIGT group was further split into two subtypes based on the number of abnormal OGTT values: PIGT-0 (0 abnormal OGTT value) or PIGT-1 (1 abnormal OGTT value). Similarly, the GDM group was further divided into two subtypes based on the number of abnormal fasting OGTT value: GDM-0 (0 abnormal fasting OGTT value [isolated postprandial]) or GDM-1 (1 abnormal fasting OGTT value [combined fasting and postprandial]). As only 95 pregnancies in the PIGT-1 group had an abnormal fasting OGTT value, we did not differentiate fasting vs. postprandial within this group. In summary, we classified the pregnancies into five mutually exclusive groups ordered by increasing glycemia severity: NGT, PIGT-0, PIGT-1, GDM-0, and GDM-1. (Figure 1)

Adverse pregnancy outcomes

We examined four adverse pregnancy outcomes with relatively high incidence: pregnancy-related hypertension, cesarean delivery, LGA, and preterm birth. Pregnancy-related hypertension was identified by ICD-codes (i.e., gestational hypertension [ICD-9: 642.3x, 642.9x; ICD-10: O13.x, O16.x] and pre-eclampsia/eclampsia [ICD-9: 642.4x, 642.5x, 642.6x; ICD-10: O14.x, O15.x]) using the diagnosis data. Cesarean delivery, LGA (>90 percentile of birthweight by gestational age and infant sex), and preterm birth (<37 completed weeks of gestation) were determined using the obstetrics and gynecology data.

Covariates

We extracted various covariates, including sociodemographic (i.e., age, race/ethnicity, marital status, and Area Deprivation Index [ADI]), behavioral (i.e., pre-pregnancy body mass index [BMI] and smoking during pregnancy), maternal (i.e., parity, singleton, and gestational weight gain), and clinical characteristics (i.e., Charlson Comorbidity Index [CCI]). Given the absence of socioeconomic information, we used the ADI to approximate socioeconomic status, factoring in elements like education, income, employment, and housing quality[120]. The ADI in California assigned rankings from 1 (least disadvantaged) to 10 (most disadvantaged) at the block group level[120]. We categorized ADI into four groups via quartiles, with missing data (~12%) treated as a distinct group. We used the CCI to assess pre-pregnancy chronic conditions, including cardiovascular diseases, liver diseases, and cancer[121, 122]. (Supplementary Table 2)

Statistical analyses

We described and compared maternal characteristics by maternal glycemic categories, racial/ethnic groups, and Asian subgroups using an Analysis of Variance (ANOVA) test for continuous variables or a chi-squared test for categorical variables. We also performed pairwise comparisons using a t-test for continuous variables or a chi-squared test for categorical variables. Additionally, we described the unadjusted prevalence of maternal glycemic categories in the overall sample and by racial/ethnic groups and Asian subgroups.

To achieve better model convergence, we applied modified Poisson regressions with a robust error variance[123], which is an alternative to log binomial regression, to compare the unadjusted and age-adjusted prevalence (prevalence ratio [PR] and 95% confidence interval [CI]) of maternal hyperglycemic categories comparing racial/ethnic groups and Asian subgroups with non-Hispanic Whites (reference). To account for correlation among siblings, a random effect for each pregnant individual was specified.

Several sensitivity analyses were performed to test the robustness of the results. First, we estimated the multivariable-adjusted PR of maternal hyperglycemic categories, controlling for known risk factors for maternal hyperglycemia, including maternal age, ADI, marital status, smoking during pregnancy, nulliparous, singleton pregnancy, CCI, and pre-pregnancy BMI. Second, we exclusively included the first pregnancy of each pregnant individual. Lastly, we eliminated pregnancies screened for GDM before 15 weeks of gestation due to potential presence of pre-pregnancy diabetes.

In addition, we utilized modified Poisson regressions with a robust error variance[123] to investigate the association between maternal glycemic categories and risk (risk ratio [RR] and 95% CI) for adverse pregnancy outcomes. NGT was the reference. We fitted both the unadjusted and adjusted models. Adjusted models controlled for pre-selected potential confounders: maternal age (continuous), race/ethnicity (Asian, Hispanic, non-Hispanic White, non-Hispanic Black, or other race/ethnicities), ADI (Q1, Q2, Q3, Q4, or unknown), marital status (yes/no), smoking during pregnancy (yes/no), nulliparous (yes/no), singleton pregnancy (yes/no), CCI (0, 1, or ≥2), and pre-pregnancy BMI (continuous).

The analyses were performed in R version 4.0.5. To address the issue of multiple comparisons and more specifically the false discovery rate, we employed the Benjamini-Hochberg method[124].

5.4 Results

Maternal characteristics

Of the 11,405 pregnancies, 44.8% were non-Hispanic White, 19.9% were Asian, 17.5% were Hispanic, 3.9% were non-Hispanic Black, and 14.0% were other/unknown race/ethnicities.

Among Asians, 23.2% were Chinese, 9.8% were Asian Indian, 8.0% were Filipino, 7.8% were Korean, 4.7% were Japanese, and 46.6% were other/unknown Asians.

In comparison to the NGT group, pregnancies in all other groups tended to be older and have a higher pre-pregnancy BMI. The PIGT-1, GDM-0, and GDM-1 were more likely to reside in disadvantaged neighborhoods than the NGT group. Both GDM-0 and GDM-1 were less likely to be nulliparous and have excessive weight gain compared to the NGT group. Additionally, glucose-lowering medications (A2 GDM, an indicator of insufficient glucose control using lifestyle changes only) were administered to 17.4% and 35.5% of pregnancies in the GDM-0 and GDM-1 groups, respectively. (Table 1)

In general, maternal characteristics varied across racial/ethnic groups and Asian subgroups. Asians tended to be married, have a lower pre-pregnancy BMI, experience singleton pregnancies, have fewer chronic conditions, and exhibit fewer excessive weight gain, but live in slightly more disadvantaged areas than non-Hispanic Whites. Hispanics and non-Hispanic blacks were more likely to be younger, unmarried, live in more disadvantaged areas, and have a higher pre-pregnancy BMI, compared to non-Hispanic Whites. Additionally, non-Hispanic Blacks also had a higher likelihood of excessive gestational weight gain than non-Hispanic Whites. (Supplementary Table 3) Among Asian subgroups, Filipinos and Koreans were more likely to reside in disadvantaged areas than non-Hispanic Whites. Chinese, Japanese, Koreans, and other/unknown Asians had a lower pre-pregnancy BMI than non-Hispanic Whites, while Filipinos had a higher pre-pregnancy BMI. Additionally, Chinese, Japanese, and Koreans were also less likely to experience excessive gestational weight gain compared to non-Hispanic Whites. (Supplementary Table 4)

Prevalence of maternal hyperglycemic categories by race/ethnicity and Asian subgroups

The distribution of glycemic categories varied among racial/ethnic groups and Asian subgroups. Among all pregnancies, 69.2% were classified as NGT, 16.7% as PIGT-0, 6.3% as PIGT-1, 5.6% as GDM-0, and 2.2% as GDM-1. Non-Hispanic Blacks had the highest prevalence of NGT (83.0%), followed by non-Hispanic Whites (75.9%), other/unknown race/ethnicities (68.0%), Hispanics (63.1%), and Asians (57.2%). Asians had the highest prevalence of PIGT-0, PIGT-1, and GDM-0, while Hispanics had the highest prevalence of GDM-1. Among Asian subgroups, Japanese had the highest prevalence of NGT (64.5%), followed by Chinese (59.6%), other/unknown Asians (56.9%), Asian Indians (55.9%), Koreans (55.2%), and Filipinos (50.6%). Hyperglycemic categories also varied across Asian subgroups, with Koreans having the highest prevalence of PIGT-0 (26.4%), Filipinos having the highest prevalence of GDM-0 (13.3%), and Asian Indians having the highest prevalence of both PIGT-1 (10.4%) and GDM-1 (5.4%). (Figure 2)

The age-adjusted prevalence of PIGT-0 and PIGT-1 was higher among Asians (PIGT-0, age-adjusted PR 1.51 [95% CI 1.35, 1.69]; PIGT-1, 2.18 [1.78, 2.68]), Hispanics (PIGT-0, 1.32 [1.16, 1.50]; PIGT-1, 2.07 [1.67, 2.57]), and other/unknown race/ethnicities (PIGT-0, 1.31 [1.14, 1.50]; PIGT-1, 1.49 [1.16, 1.92]) than among non-Hispanic Whites. Furthermore, GDM-0 and GDM-1 were also more prevalent among Asians (GDM-0, 2.55 [2.10, 3.10]; GDM-1, 1.55 [1.08, 2.21]) and Hispanics (GDM-0, 1.69 [1.35, 2.13]; GDM-1, 2.68 [1.93, 3.71]) than non-Hispanic Whites. In contrast, non-Hispanic Blacks were less likely to have PIGT-0 (0.63 [0.46, 0.87]) and GDM-0 (0.42 [0.20, 0.89]) compared to non-Hispanic Whites. (Table 2)

By Asian subgroups, the age-adjusted prevalence of PIGT-0 was higher among Koreans, Filipinos, Asian Indians, and other/unknown Asians than non-Hispanic Whites (Korean: age-adjusted RR 1.85 [95% CI 1.38, 2.50]; Filipino: 1.66 [1.22, 2.26]; Asian Indian: 1.41 [1.04,

1.91]; other/unknown Asian: 1.61 [1.39, 1.86]). Furthermore, PIGT-1 was more prevalent among all Asian subgroups than non-Hispanic Whites (Asian Indian: 2.57 [1.64, 4.03]; Filipino: 2.47 [1.51, 4.06]; Japanese: 2.40 [1.27, 4.54]; Chinese: 2.36 [1.71, 3.27]; Korean: 2.29 [1.35, 3.87]; other/unknown Asian: 1.92 [1.48, 2.51]). In addition, the age-adjusted prevalence of GDM-0 was higher in Filipinos, Chinese, Asian Indians, and other/unknown Asians than non-Hispanic Whites (Filipino: 3.22 [2.06, 5.04]; Chinese: 3.17 [2.36, 4.25]; Asian Indian: 2.24 [1.38, 3.63]; other/unknown Asian: 2.46 [1.93, 3.15]). Additionally, GDM-1 was more likely in Asian Indians than non-Hispanic Whites (3.68 [1.91, 7.09]), but not in other Asian subgroups. (Table 3)

In a sensitivity analysis, by additionally adjusting risk factors for maternal hyperglycemia, the adjusted prevalence stayed similar in general. It is noteworthy that although Hispanics had the highest unadjusted and age-adjusted prevalence of GDM-1, Asians had the highest multivariable adjusted (especially pre-pregnancy BMI) prevalence of GDM-1. (Supplementary Table 5 and Supplementary Table 6) In another sensitivity analysis, by including the first pregnancy of each pregnancy individual, the results were almost unchanged. (Supplementary Table 7 and Supplementary Table 8) Finally, when we excluded pregnancies screened before 15 weeks of gestation, the prevalence of GDM-1 decreased from 2.2% to 1.3%, and the PRs became not significant. (Supplementary Table 9 and Supplementary Table 10)

Maternal glycemic categories and risk of adverse pregnancy outcomes

After adjusting for potential confounders, the PIGT-1 group had an increased risk of pregnancy-related hypertension (adjusted RR 1.19 [95% CI 1.02, 1.38]), LGA (1.73 [1.37, 2.18]), and preterm birth (1.33 [1.05, 1.68]) than the NGT group. The PIGT-0 and GDM-0 groups also had a higher risk of preterm birth compared to the NGT group (PIGT-0: 1.23 [1.04, 1.45]; GDM-0: 1.56 [0.87, 1.71]). The GDM-1 group tended to have a higher risk of LGA (1.28

[0.87, 1.99]) and preterm birth (1.22 [0.87, 1.71]), although not statistically significant due to the limited sample size. (Table 4)

Discussion

In this retrospective cohort of 11,405 pregnancies, the prevalence of glycemic categories varied across racial/ethnic groups and Asian subgroups. The prevalence of PIGT-0, PIGT-1, and GDM-0 was the highest among Asians, while the prevalence of GDM-1 was the highest among Hispanics. Most Asian subgroups showed a greater prevalence of PIGT-0, PIGT-1, and GDM-0 compared to non-Hispanic Whites, while only Asian Indians displayed a higher prevalence of GDM-1. In addition, likely due to lacking GDM treatments, PIGT-1 had the poorest pregnancy outcomes, including a higher risk of pregnancy-related hypertension, LGA, and preterm birth than NGT. PIGT-0 was also associated with an elevated risk of preterm birth. GDM-0, primarily affecting Asians, was only associated with an increased risk of preterm birth than NGT, while GDM-1, mostly affecting Hispanics and Asian Indians, was associated with a higher risk of both LGA and preterm birth, although not significantly due to the limited sample size.

Previous studies did not investigate racial/ethnic differences in PIGT-0, PIGT-1, GDM-0, and GDM-1. Yet, our study revealed a higher prevalence of all hyperglycemic categories among Asians and Hispanics compared to non-Hispanic Whites, aligning with research indicating 2-3 times higher rates for these groups[1, 24, 75]. In our study, Asians were disproportionately affected by PIGT-0, PIGT-1, and GDM-0, while Hispanics were more susceptible to the most severe GDM-1. Kaiser Permanente Hawaii data also showed higher abnormal GCT proportions in Asians[125], resonating with our findings of elevated PIGT-0 and PIGT-1 prevalence among Asians. Though lacking data for pregnant individuals, a US population-based study discovered that Hispanics had the highest proportion of prediabetes using a fasting OGTT value (≥100

mg/dL)[126], and both Asians and Hispanics exhibited a high proportion of prediabetes using a 2-hour postprandial OGTT value (≥140 mg/dL)[126]. This is consistent with our findings that Hispanics are more likely to have GDM-1, while Asians are more likely to have GDM-0. For Asian subgroups, we observed that Koreans and Japanese had similar GDM prevalence than non-Hispanic Whites, consistent with previous literature[1, 24, 25, 28, 75, 76]. Our study also revealed that Koreans and Japanese had higher PIGT-0 and/or PIGT-1 prevalence than non-Hispanic Whites, and Asian Indians, unlike other Asian subgroups, were particularly impacted by GDM-1. However, a direct comparison with previous literature is not possible.

Potential explanations for the observed differences in maternal hyperglycemic categories by race/ethnicity and Asian subgroups may be complex. Abnormal postprandial OGTT values are primarily tied to muscle insulin resistance[116, 117], leading to high circulating glucose after a meal due to reduced glucose uptake by skeletal muscle. Physical activities, including aerobic and resistance exercises, could reduce muscle insulin resistance[127]. Conversely, abnormal fasting OGTT value is more linked to hepatic insulin resistance, resulting in high glucose due to failure to inhibit hepatic glucose production[116, 117]. Chronic inflammation due to obesity, especially visceral obesity, can contribute to hepatic insulin resistance[128]. In our study, Asians as a single group were more affected by PIGT-0, PIGT-1, and GMD-0 than non-Hispanic Whites, despite having low pre-pregnancy BMI and comparable SES. This could be attributed to fewer physical activities[129] and lean mass[130] in Asians. On the other hand, Hispanics tended to be more affected by GDM-1, probably due to the combination of low physical activity/muscle mass[129] and a high proportion of overweight/obesity (non-Hispanic White: 24.0 kg/m^2 vs. Hispanic: 27.2 kg/m^2). It is worth noting that after adjusting risk factors for glucose metabolism, especially pre-pregnancy BMI, Asians had the highest prevalence of GDM-1 as well, suggesting that pre-pregnancy BMI

was linked to a higher fasting glucose level in Hispanics. Although the prevalence of hyperglycemic categories consistently exceeded non-Hispanic Whites in most Asian subgroups, the prevalence varied across Asian subgroups, possibly due to the heterogeneity in GDM risk factor distributions across Asian subgroups[28]. In addition, genetic factors may also contribute to the differences by race/ethnicity and Asian subgroups[1].

According to the flagship Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, maternal hyperglycemia, including mild elevation, is progressively associated with adverse pregnancy outcomes, including pregnancy-related hypertension, cesarean delivery, LGA, and preterm birth[92]. Pregnancies classified as GDM are well-known to be associated with these adverse pregnancy outcomes[1, 24, 75]. In this study, we observed a positive association between GDM-0 and preterm birth and positive associations (although non-significant due to the limited sample size) between GDM-1 and LGA and preterm birth, which align with previous studies showing that abnormal postprandial OGTT values were associated preterm birth and abnormal fasting OGTT was associated with LGA[118, 119]. Furthermore, this study observed PIGT-1 was associated with a higher risk of pregnancy-related hypertension, LGA, and preterm birth, which is consistent with the results of a meta-analysis[115]. Interestingly, we found that PIGT-1 was associated with more adverse pregnancy outcomes compared to GDM-0 and GDM-1. This difference could be explained by GDM treatments, which may have attenuated the risk of adverse outcomes in pregnancies diagnosed with GDM. This is evident by observing a much higher proportion of excessive weight gain in NGT (28.5%), PIGT-0 (29.8%), and PIGT-1 (28.1%) than in GDM-0 (18.4%) and GDM-1 (17.7%).

This study has several strengths. First, this large study included a population with diverse racial/ethnic groups, especially Asian subgroups, allowing us to examine the racial/ethnic

differences in maternal hyperglycemic categories. Second, this study had detailed laboratory data, allowing us to classify maternal glycemia into five mutually exclusive categories: NGT, PIGT-0, PIGT-1, GDM-0, and GDM-1.

A few limitations of this study need to be considered. First, this study did not have data on certain risk factors for glucose metabolism, such as body composition, physical activity, and diet. Thus, we cannot directly explore how these factors contribute to the different distributions of hyperglycemic categories among racial/ethnic groups and Asian subgroups. Second, this study used data from an academic center in a large city in the US, limiting the generalizability of the study findings. Compared to the general population in LA county, there is a lower proportion of non-Hispanic White (59.2% vs. 70.2%) and a higher proportion of people with at least a high school degree (94.4% vs. 80.0%)[131, 132] in the UCLA medical center service area.

In conclusion, this racially/ethnically diverse retrospective cohort study found that the prevalence of hyperglycemic categories differed by race/ethnicity and Asian subgroups, with Asians more affected by PIGT-0, PIGT-1, and GDM-0, while Hispanics more impacted by the most severe GDM-1. In addition, Japanese and Koreans had a higher prevalence of PIGT-0 and PIGT-1 despite a similar prevalence of GDM than non-Hispanic Whites. Asian Indians had a particularly high prevalence of GDM-1. In addition, despite receiving GDM diagnosis and treatments, GDM-0 was associated with a higher risk of preterm birth, and GDM-1 was associated with an elevated risk of both LGA and preterm birth (not significant due to limited sample size). Furthermore, PIGT-1, affecting 6.3% of pregnancies, was associated with the poorest adverse pregnancy outcomes, suggesting that PIGT-1 may also need to be treated.

5.5 Tables and Figures

Table 5.1. Participant characteristics by maternal glycemic categories

	Overall (N = 11,405)	NGT (N = 7,893)	PIGT-0 (N = 1,907)	PIGT-1 (N = 720)	GDM-0 (N = 637)	GDM-1 (N = 248)	P-value
Maternal age, mean ± SD	34.3 ± 4.5	34.0 ± 4.5	34.8 ± 4.5*	35.1 ± 4.5*	34.9 ± 4.4*	35.4 ± 4.5*	<0.001*
Married, N (%)	9,690 (85.0)	6,712 (85.0)	1,650 (86.5)	598 (83.1)	537 (84.3)	193 (77.8)*	0.003*
Area Deprivation Index quartile, N (%)				*	*	*	<0.001*
Q1	2,492 (21.9)	1,807 (22.9)	410 (21.5)	135 (18.8)	115 (18.1)	25 (10.1)	
Q2	2,492 (21.9)	1,754 (22.2)	427 (22.4)	158 (21.9)	116 (18.2)	37 (14.9)	
Q3	2,491 (21.8)	1,669 (21.1)	435 (22.8)	170 (23.6)	151 (23.7)	66 (26.6)	
Q4	2,491 (21.8)	1,643 (20.8)	423 (22.2)	175 (24.3)	172 (27.0)	78 (31.5)	
Unknown	1,439 (12.6)	1,020 (12.9)	212 (11.1)	82 (11.4)	83 (13.0)	42 (16.9)	
Pre-pregnancy BMI, mean ± SD	24.5 ± 4.9	24.1 ± 4.6	24.8 ± 4.9*	26.1 ± 5.6*	25.3 ± 5.2*	30.1 ± 6.5*	<0.001*
Pre-pregnancy BMI category, N (%)			*	*	*	*	<0.001*
Underweight (<18.5 kg/m^2)	330 (2.9)	255 (3.2)	43 (2.3)	12 (1.7)	20 (3.1)	0 (0.0)	
Normal weight (18.5-24.9 kg/m^2)	7,045 (61.8)	5,165 (65.4)	1,122 (58.8)	356 (49.4)	343 (53.8)	59 (23.8)	
Overweight (25.0-29.9 kg/m^2)	2,597 (22.8)	1,699 (21.5)	456 (23.9)	203 (28.2)	163 (25.6)	76 (30.6)	
Obese (≥30.0 kg/m^2)	1,433 (12.6)	774 (9.8)	286 (15.0)	149 (20.7)	111 (17.4)	113 (45.6)	
Nulliparous (the first pregnancy), N (%)	8,216 (72.0)	5,703 (72.3)	1,342 (70.4)	507 (70.4)	497 (78.0)*	167 (67.3)	<0.001*
Singleton, N (%)	10,634 (93.2)	7,392 (93.7)	1,773 (93.0)	674 (93.6)	575 (90.3)*	220 (88.7)*	<0.001*
Smoking during pregnancy, N (%)	159 (1.4)	103 (1.3)	30 (1.6)	6 (0.8)	13 (2.0)	7 (2.8)	0.09
Charlson Comorbidity Index category, N (%)							0.06
0	9,264 (81.2)	6,387 (80.9)	1,544 (81.0)	594 (82.5)	541 (84.9)	198 (79.8)	
1	1,755 (15.4)	1,247 (15.8)	291 (15.3)	106 (14.7)	76 (11.9)	35 (14.1)	
≥2	386 (3.4)	259 (3.3)	72 (3.8)	20 (2.8)	20 (3.1)	15 (6.0)	
Infant male sex, N (%)	5,880 (51.6)	4,025 (51.0)	1,001 (52.5)	398 (55.3)	327 (51.3)	129 (52.0)	0.41
Total gestational weight gain (pound), mean ± SD	27.5 ± 12.0	28.8 ± 11.2	26.4 ± 12.3*	25.3 ± 13.4*	21.3 ± 12.8*	16.6 ± 14.3*	<0.001*
Excessive gestational weight gain, N (%)					*	*	<0.001*
Yes	3,248 (28.5)	2,351 (29.8)	535 (28.1)	201 (27.9)	117 (18.4)	44 (17.7)	
No	6,250 (54.8)	4,183 (53.0)	1,084 (56.8)	401 (55.7)	421 (66.1)	160 (66.1)	
Unknown	1,907 (16.7)	1,358 (17.2)	288 (15.1)	118 (16.4)	99 (15.5)	44 (17.7)	
50g GCT at GDM screening, mean ± SD	118 ± 28.8	106 ± 19.2	154 ± 14.6*	159 ± 17.3*	164 ± 18.5*	172 ± 25.6*	<0.001*
Glucose-lowering medication (A2 GDM), N (%)	199 (1.7)	-	-	-	111 (17.4)	88 (35.5)	<0.001*

Abbreviations: ANOVA, analysis of variance; EHR, electronic health record; GDM, gestational diabetes mellitus; GCT, glucose challenge test; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose tolerance; SD, standard deviation.

Notes: [1] The two step GDM screening approach involves a 1-hour 50g GCT and followed by a 3-hour 100g OGTT. NGT was defined as having a normal GCT value (<140 mg/L). PIGT-0 was defined as having an abnormal GCT value and normal OGTT values (fasting <95 mg/dL; 1-hour <180 mg/dL; 2-hour <155 mg/dL; 3-hour <140 mg/dL). PIGT-1 was defined as having an abnormal GCT value and 1 abnormal OGTT value. GDM-0 was defined as having an abnormal GCT value, a normal fasting OGTT value, and ≥2 abnormal postprandial OGTT values, while GDM-1 was defined as having an abnormal GCT, an abnormal fasting OGTT value, and ≥1 abnormal postprandial OGTT values. [2] Chi-squared or ANOVA test was used to calculate p-value cross groups; chi-squared or t-test was used to calculate p-values between each group and NGT. [3] Charlson comorbidity index was derived based on major chronic conditions, such as cardiovascular diseases, liver diseases, and cancer. (Supplementary Table 2) [4] Excessive gestational weight gain was defined according to the Institute of Medicine (IOM) guideline. [5] Glucose lowering medications included insulin, metformin, and glyburide.*Indicates statistically significant after controlling for multiple comparisons using the Benjamini-Hochberg method.

Table 5.2. Prevalence of maternal hyperglycemic categories by race/ethnicity

	%	Unadjusted PR (95% CI)	Age-Adjusted PR (95% CI)
Pregnancy impaired glucose tolerance-0 (PIGT-0, abnormal GCT & 0 abnormal OGTT)			
Non-Hispanic White (N = 5,108)	14.23%	1.00	1.00
Asian (N = 2,264)	21.42%	1.51 (1.34, 1.69)*	1.51 (1.35, 1.69)*
Non-Hispanic Black (N = 448)	8.71%	0.61 (0.44, 0.84)*	0.63 (0.46, 0.87)*
Hispanic (N = 1,991)	18.18%	1.28 (1.13, 1.45)*	1.32 (1.16, 1.50)*
Other/unknown (N = 1,594)	18.44%	1.30 (1.13, 1.48)*	1.31 (1.14, 1.50)*
Pregnancy impaired glucose tolerance-1 (PIGT-1, abnormal GCT & 1 abnormal OGTT)			
Non-Hispanic White (N = 5,108)	4.39%	1.00	1.00
Asian (N = 2,264)	9.14%	2.08 (1.72, 2.52)*	2.18 (1.78, 2.68)*
Non-Hispanic Black (N = 448)	3.57%	0.81 (0.49, 1.35)	0.80 (0.46, 1.41)
Hispanic (N = 1,991)	8.49%	1.93 (1.58, 2.36)*	2.07 (1.67, 2.57)*
Other/unknown (N = 1,594)	6.52%	1.49 (1.18, 1.88)*	1.49 (1.16, 1.92)*
Gestational diabetes mellitus (GDM-0, abnormal GCT & normal fasting & ≥2 abnormal postprandial OGTT)			
Non-Hispanic White (N = 5,108)	3.90%	1.00	1.00
Asian (N = 2,264)	9.94%	2.54 (2.09, 3.09)*	2.55 (2.10, 3.10)*
Non-Hispanic Black (N = 448)	1.56%	0.40 (0.19, 0.86)*	0.42 (0.20, 0.89)*
Hispanic (N = 1,991)	6.33%	1.62 (1.29, 2.04)*	1.69 (1.35, 2.13)*
Other/unknown (N = 1,594)	5.02%	1.29 (0.99, 1.68)	1.31 (1.01, 1.71)
Gestational diabetes mellitus (GDM-1, abnormal GCT & abnormal fasting & ≥1 abnormal postprandial OGTT)			
Non-Hispanic White (N = 5,108)	1.57%	1.00	1.00
Asian (N = 2,264)	2.34%	1.53 (1.07, 2.19)*	1.55 (1.08, 2.21)*
Non-Hispanic Black (N = 448)	1.34%	0.90 (0.39, 2.08)	0.95 (0.41, 2.20)
Hispanic (N = 1,991)	3.87%	2.47 (1.78, 3.41)*	2.68 (1.93, 3.71)*
Other/unknown (N = 1,594)	2.01%	1.32 (0.86, 2.00)	1.35 (0.89, 2.06)

Abbreviations: CI, confidence interval; GCT, glucose challenge test; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose intolerance; PR, prevalence ratio.

Notes: [1] The two step GDM screening approach involves a 1-hour 50g GCT and followed by a 3-hour 100g OGTT. NGT was defined as having a normal GCT value (<140 mg/L). PIGT-0 was defined as having an abnormal GCT value and normal OGTT values (fasting <95 mg/dL; 1-hour <180 mg/dL; 2-hour <155 mg/dL; 3-hour <140 mg/dL). PIGT-1 was defined as having an abnormal GCT value and 1 abnormal OGTT value. GDM-0 was defined as having an abnormal GCT value, a normal fasting OGTT value, and ≥2 abnormal postprandial OGTT values, while GDM-1 was defined as having an abnormal GCT, an abnormal fasting OGTT value, and ≥1 abnormal postprandial OGTT values.

[2] Poisson regressions with robust errors were applied to calculate RR. To account for correlation among siblings, a random effect for each pregnant individual was used.

*Indicates statistically significant after controlling for multiple comparisons using the Benjamini-Hochberg method.

Table 5.3. Prevalence of maternal hyperglycemic categories by Asian subgroups

	%	Unadjusted PR (95% CI)	Age-Adjusted PR (95% CI)
Pregnancy impaired glucose tolerance-0 (PIGT-0, abnormal GCT & 0 abnormal OGTT)			
Non-Hispanic White (N = 5,108)	14.23%	1.00	1.00
Asian Indian (N = 222)	19.82%	1.39 (1.03, 1.89)*	1.41 (1.04, 1.91)*
Chinese (N = 525)	16.95%	1.19 (0.96, 1.48)	1.22 (0.98, 1.52)
Filipino (N = 180)	23.89%	1.68 (1.23, 2.28)*	1.66 (1.22, 2.26)*
Japanese (N = 107)	18.69%	1.31 (0.84, 2.05)	1.28 (0.82, 2.00)
Korean (N = 174)	26.44%	1.86 (1.38, 2.50)*	1.85 (1.38, 2.50)*
Other/unknown Asian (N = 1,056)	23.01%	1.62 (1.40, 1.87)*	1.61 (1.39, 1.86)*
Pregnancy impaired glucose tolerance-1 (PIGT-1, abnormal GCT & 1 abnormal OGTT)			
Non-Hispanic White (N = 5,108)	4.39%	1.00	1.00
Asian Indian (N = 222)	10.36%	2.36 (1.54, 3.63)*	2.57 (1.64, 4.03)*
Chinese (N = 525)	9.52%	2.17 (1.60, 2.95)*	2.36 (1.71, 3.27)*
Filipino (N = 180)	10.00%	2.28 (1.41, 3.69)*	2.47 (1.51, 4.06)*
Japanese (N = 107)	10.28%	2.34 (1.28, 4.29)*	2.40 (1.27, 4.54)*
Korean (N = 174)	10.34%	2.36 (1.46, 3.81)*	2.29 (1.35, 3.87)*
Other/unknown Asian (N = 1,056)	8.24%	1.88 (1.47, 2.41)*	1.92 (1.48, 2.51)*
Gestational diabetes mellitus (GDM-0, abnormal GCT & normal fasting & ≥2 abnormal postprandial OGTT)			
Non-Hispanic White (N = 5,108)	3.90%	1.00	1.00
Asian Indian (N = 222)	8.56%	2.20 (1.35, 3.57)*	2.24 (1.38, 3.63)*
Chinese (N = 525)	12.00%	3.08 (2.30, 4.13)*	3.17 (2.36, 4.25)*
Filipino (N = 180)	13.33%	3.24 (2.07, 5.08)*	3.22 (2.06, 5.04)*
Japanese (N = 107)	6.54%	1.67 (0.77, 3.62)	1.63 (0.75, 3.53)
Korean (N = 174)	5.75%	1.48 (0.77, 2.83)	1.48 (0.77, 2.82)
Other/unknown Asian (N = 1,056)	9.66%	2.48 (1.94, 3.17)*	2.46 (1.93, 3.15)*
Gestational diabetes mellitus (GDM-1, abnormal GCT & abnormal fasting & ≥1 abnormal postprandial OGTT)			
Non-Hispanic White (N = 5,108)	1.57%	1.00	1.00
Asian Indian (N = 222)	5.41%	3.40 (1.77, 6.54)*	3.68 (1.91, 7.09)*
Chinese (N = 525)	1.90%	1.28 (0.65, 2.52)	1.43 (0.73, 2.82)
Filipino (N = 180)	2.22%	1.48 (0.52, 4.18)	1.45 (0.51, 4.08)
Japanese (N = 107)	0.00%	-	-
Korean (N = 174)	2.30%	1.53 (0.54, 4.31)	1.55 (0.55, 4.38)
Other/unknown Asian (N = 1,056)	2.18%	1.43 (0.88, 2.31)	1.39 (0.86, 2.25)

Abbreviations: CI, confidence interval; GCT, glucose challenge test; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose intolerance; PR, prevalence ratio.

Notes: [1] The two step GDM screening approach involves a 1-hour 50g GCT and followed by a 3-hour 100g OGTT. NGT was defined as having a normal GCT value (<140 mg/L). PIGT-0 was defined as having an abnormal GCT value and normal OGTT values (fasting <95 mg/dL; 1-hour <180 mg/dL; 2-hour <155 mg/dL; 3-hour <140 mg/dL). PIGT-1 was defined as having an abnormal GCT value and 1 abnormal OGTT value. GDM-0 was defined as having an abnormal GCT value, a normal fasting OGTT value, and ≥2 abnormal postprandial OGTT values, while GDM-1 was defined as having an abnormal GCT, an abnormal fasting OGTT value, and ≥1 abnormal postprandial OGTT values.

[2] Poisson regressions with robust errors were applied to calculate RR. To account for correlation among siblings, a random effect for each pregnant individual was used.

*Indicates statistically significant after controlling for multiple comparisons using the Benjamini-Hochberg method.

Table 5.4. Association of PIGT and GDM subtypes with risk of adverse pregnancy outcomes

N = 11,405	%	Unadjusted RR (95% CI)	Fully Adjusted RR (95% CI)
Hypertensive disorders of pregnancy (gestational hypertension/pre-eclampsia/eclampsia)			
Normal glucose tolerance (NGT, N = 7,893)	19.75%	1.00	1.00
Pregnancy impaired glucose tolerance-0 (PIGT-0, N = 1,907)	20.98%	1.06 (0.95, 1.19)	1.03 (0.92, 1.15)
Pregnancy impaired glucose tolerance-1 (PIGT-1, N = 920)	26.11%	1.32 (1.14, 1.54)*	1.19 (1.02, 1.38)*
Gestational diabetes mellitus-0 (GDM-0, N = 637)	22.45%	1.14 (0.96, 1.35)	1.02 (0.86, 1.22)
Gestational diabetes mellitus-1 (GDM-1, N = 248)	31.85%	1.61 (1.29, 2.02)*	1.10 (0.87, 1.38)
Cesarean delivery			
Normal glucose tolerance (NGT, N = 7,893)	28.96%	1.00	1.00
Pregnancy impaired glucose tolerance-0 (PIGT-0, N = 1,907)	34.35%	1.19 (1.09, 1.29)*	1.10 (1.01, 1.20)
Pregnancy impaired glucose tolerance-1 (PIGT-1, N = 920)	36.39%	1.26 (1.11, 1.43)*	1.11 (0.97, 1.26)
Gestational diabetes mellitus-0 (GDM-0, N = 637)	36.11%	1.25 (1.09, 1.43)*	1.08 (0.94, 1.24)
Gestational diabetes mellitus-1 (GDM-1, N = 248)	43.95%	1.52 (1.25, 1.84)*	1.07 (0.88, 1.30)
Large for gestational age (>90 percentile)			
Normal glucose tolerance (NGT, N = 7,893)	6.70%	1.00	1.00
Pregnancy impaired glucose tolerance-0 (PIGT-0, N = 1,907)	7.87%	1.17 (0.98, 1.41)	1.17 (0.97, 1.41)
Pregnancy impaired glucose tolerance-1 (PIGT-1, N = 920)	12.22%	1.82 (1.45, 2.29)*	1.73 (1.37, 2.18)*
Gestational diabetes mellitus-0 (GDM-0, N = 637)	6.12%	0.91 (0.66, 1.27)	0.99 (0.71, 1.37)
Gestational diabetes mellitus-1 (GDM-1, N = 248)	11.69%	1.74 (1.20, 2.54)*	1.28 (0.87, 1.88)
Preterm birth (<37 weeks of gestation)			
Normal glucose tolerance (NGT, N = 7,893)	7.94%	1.00	1.00
Pregnancy impaired glucose tolerance-0 (PIGT-0, N = 1,907)	10.33%	1.26 (1.06, 1.50)*	1.23 (1.04, 1.45)*
Pregnancy impaired glucose tolerance-1 (PIGT-1, N = 920)	11.25%	1.43 (1.11, 1.83)*	1.33 (1.05, 1.68)*
Gestational diabetes mellitus-0 (GDM-0, N = 637)	15.70%	1.88 (1.48, 2.37)*	1.56 (1.26, 1.94)*
Gestational diabetes mellitus-1 (GDM-1, N = 248)	15.73%	1.90 (1.32, 2.72)*	1.22 (0.87, 1.71)

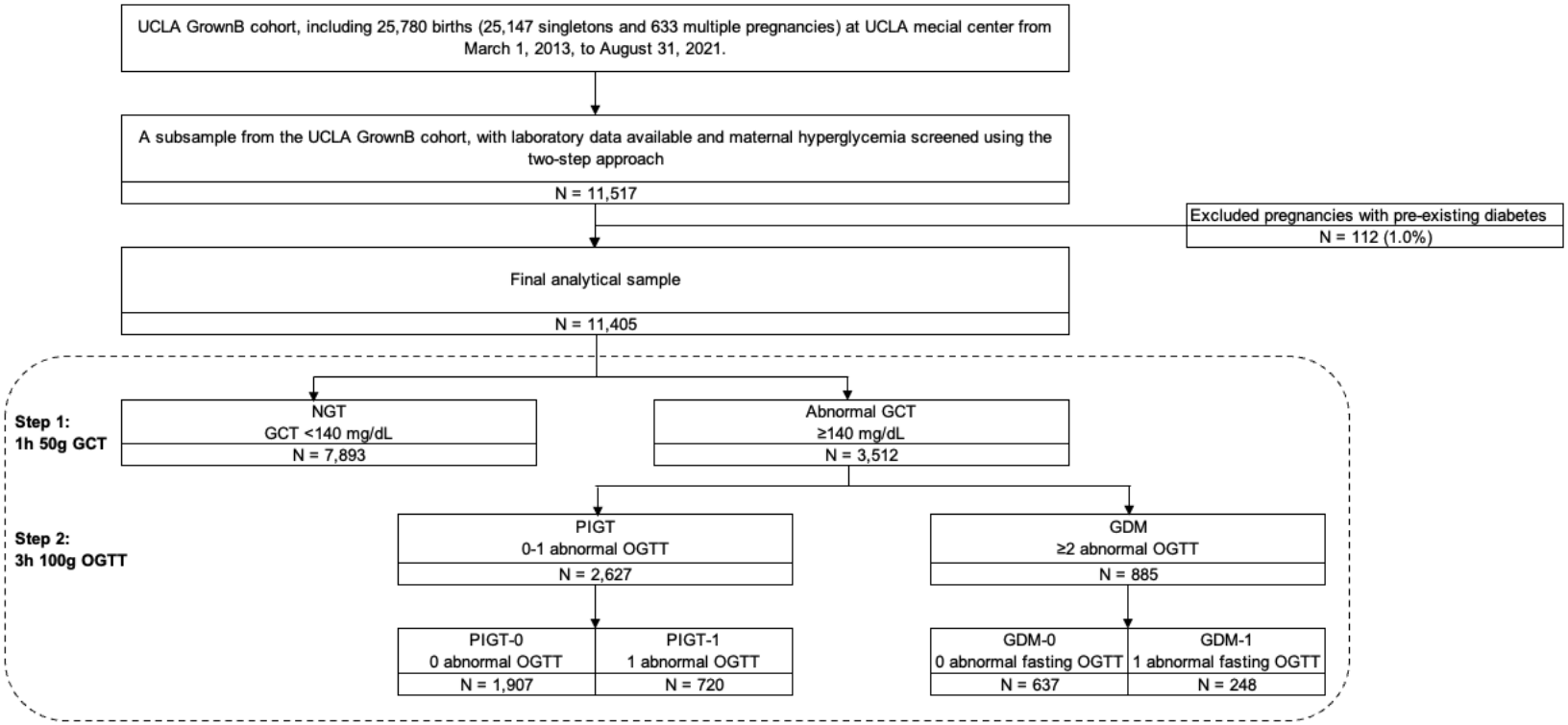
Abbreviations: ADI, area deprivation index; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; GCT, glucose challenge test; GDM, gestational diabetes mellitus; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose intolerance; RR, risk ratio.

Notes: [1] The two step GDM screening approach involves a 1-hour 50g GCT and followed by a 3-hour 100g OGTT. NGT was defined as having a normal GCT value (<140 mg/L). PIGT-0 was defined as having an abnormal GCT value and normal OGTT values (fasting <95 mg/dL; 1-hour <180 mg/dL; 2-hour <155 mg/dL; 3-hour <140 mg/dL). PIGT-1 was defined as having an abnormal GCT value and 1 abnormal OGTT value. GDM-0 was defined as having an abnormal GCT value, a normal fasting OGTT value, and ≥2 abnormal postprandial OGTT values, while GDM-1 was defined as having an abnormal GCT, an abnormal fasting OGTT value, and ≥1 abnormal postprandial OGTT values.

[2] Poisson regressions with robust errors were applied to calculate RR. To account for correlation among siblings, a random effect for each pregnant individual was used.

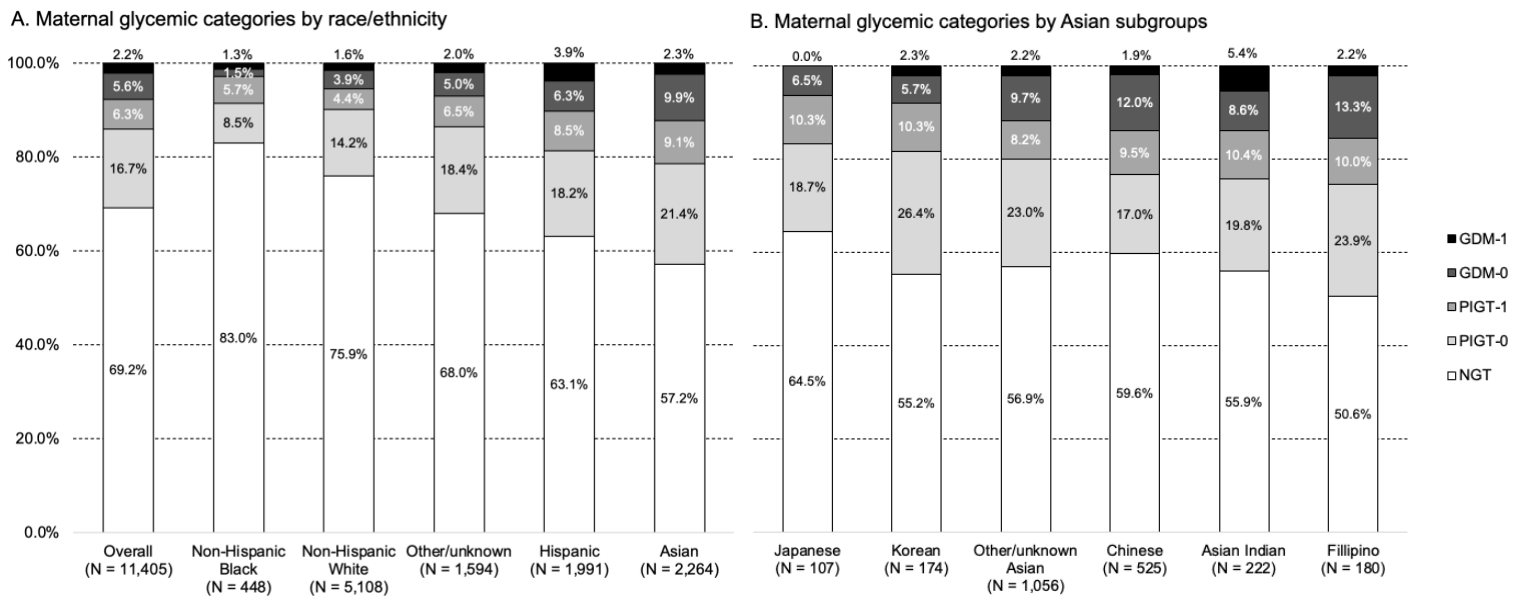
[3] Adjusted model controlled for maternal age, race/ethnicity, ADI, marital status, smoking during pregnancy, nulliparous, singleton pregnancy, CCI, and pre-pregnancy BMI.

*Indicates statistically significant after controlling for multiple comparisons using the Benjamini-Hochberg method.



Abbreviations: GCT, glucose challenge test; GDM, gestational diabetes mellitus; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose tolerance; UCLA, University of California, Los Angeles.

Figure 5.1. Sample selection flowchart and classification of glycemic categories. The two step GDM screening approach involves a 1-hour 50g GCT and followed by a 3-hour 100g OGTT. NGT was defined as having a normal GCT value (<140 mg/L). PIGT-0 was defined as having an abnormal GCT value and normal OGTT values (fasting <95 mg/dL; 1-hour <180 mg/dL; 2-hour <155 mg/dL; 3-hour <140 mg/dL). PIGT-1 was defined as having an abnormal GCT value and 1 abnormal OGTT value. GDM-0 was defined as having an abnormal GCT value, a normal fasting OGTT value, and ≥2 abnormal postprandial OGTT values, while GDM-1 was defined as having an abnormal GCT, an abnormal fasting OGTT value, and ≥1 abnormal postprandial OGTT values.



Abbreviations: GCT, glucose challenge test; GDM, gestational diabetes mellitus; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose tolerance.

Figure 5.2. Unadjusted maternal glycemic categories; A. maternal glycemic categories by race/ethnicity; B. maternal glycemic categories by Asian subgroups. The race/ethnicity or Asian subgroups were ordered by GDM prevalence from the lowest (left) to the highest (right). The two step GDM screening approach involves a 1-hour 50g GCT and followed by a 3-hour 100g OGTT. NGT was defined as having a normal GCT value (<140 mg/L). PIGT-0 was defined as having an abnormal GCT value and normal OGTT values (fasting <95 mg/dL; 1-hour <180 mg/dL; 2-hour <155 mg/dL; 3-hour <140 mg/dL). PIGT-1 was defined as having an abnormal GCT value and 1 abnormal OGTT value. GDM-0 was defined as having an abnormal GCT value, a normal fasting OGTT value, and ≥2 abnormal postprandial OGTT values, while GDM-1 was defined as having an abnormal GCT, an abnormal fasting OGTT value, and ≥1 abnormal postprandial OGTT values.

Supplementary Table 5.1. Participant characteristics by included vs. excluded in the subsample

	Overall (N = 26,541)	Included (N = 11,517)	Excluded (N = 15,024)	P-value
Maternal age, mean ± SD	33.6 ± 5.1	34.3 ± 4.5	33.1 ± 5.5	<0.001
Race/ethnicity, N (%)				<0.001
Non-Hispanic White	11,058 (41.7)	5,139 (44.6)	5,919 (39.4)	<0.001
Asian	4,487 (16.9)	2,290 (19.9)	2,197 (14.6)	
Asian Indian	454 (1.7)	223 (1.9)	231 (1.5)	
Chinese	874 (3.3)	533 (4.6)	341 (2.3)	
Filipino	336 (1.3)	183 (1.6)	153 (1.0)	
Japanese	187 (0.7)	110 (1.0)	77 (0.5)	
Korean	321 (1.2)	175 (1.5)	146 (1.0)	
Other/unknown Asians	2,315 (8.7)	1,066 (9.3)	1,249 (8.3)	
Hispanic	6,092 (23.0)	2.036 (17.7)	4,056 (27.0)	
Non-Hispanic Black	1,325 (5.0)	453 (3.9)	872 (5.8)	
Other/unknown	3,579 (13.5)	1,599 (13.9)	1,980 (13.2)	
Married, N (%)	20,728 (78.1)	9,975 (84.9)	10,953 (72.9)	<0.001
Area Deprivation Index (California) quartile, N (%)				<0.001
Q1	5,871 (22.1)	2,680 (23.3)	3,191 (21.2)	
Q2	5,870 (22.1)	2,702 (23.5)	3,168 (21.1)	
Q3	5,870 (22.1)	2,573 (22.3)	3,297 (25.0)	
Q4	5,870 (22.1)	2,109 (18.3)	3,761 (25.0)	
Unknown	3,060 (12.6)	1,453 (12.6)	1,607 (10.7)	
Pre-pregnancy BMI, mean ± SD	25.7 ± 5.5	24.6 ± 5.0	26.6 ± 5.7	<0.001
Pre-pregnancy BMI category, N (%)				<0.001
Underweight	634 (2.4)	332 (2.9)	302 (2.0)	
Normal weight	13,714 (51.7)	7,087 (61.5)	6,627 (44.1)	
Overweight	7,230 (27.2)	2,621 (22.8)	4,609 (30.7)	
Obese	4,963 (18.7)	1,477 (12.8)	3,486 (23.2)	
Nulliparous (the first pregnancy in the EHR), N (%)	19,203 (72.4)	8,284 (71.9)	10,919 (72.7)	0.18
Singleton, N (%)	24,619 (92.8)	10,734 (93.2)	13,885 (92.4)	0.01
Smoking during pregnancy, N (%)	367 (1.4)	159 (1.4)	208 (1.4)	0.98
Charlson Comorbidity Index category, N (%)				<0.001
0	21,649 (81.6)	9,269 (80.5)	10,919 (72.7)	
1	3,764 (14.2)	1,815 (15.8)	13,885 (92.4)	
≥2	1,128 (4.3)	433 (3.8)	695 (4.6)	
Infant male sex, N (%)	13,636 (51.4)	5,951 (51.7)	7,685 (51.2)	0.40

Abbreviations: BMI, body mass index; EHR, electronic health record; SD, standard deviation.

Notes: [1] Chi-squared or t-test was used to calculate p-values. [2] Other/unknown race/ethnicities included Pacific Islander, American Indian/Alaska Native, multiple races, other races, and unknown race/ethnicities. [3] Charlson comorbidity index was derived based on major chronic conditions, such as cardiovascular diseases, liver diseases, and cancer. (Supplementary Table 2)

Supplementary Table 5.2. Charlson Comorbidity Index diseases and weights

Comorbidity	ICD-9	ICD-10	Weight
Myocardial infarction	410.x, 412.x	I21.x, I22.x, 125.2	1
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0	1
Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 47.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, 177.1, 179.0, I179.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	1
Cerebrovascular disease	362.34, 430.x-438.x	G45.x, G46.x, H34.0, I60.x-I69.x	1
Dementia	290.x, 294.1, 331.2	F00.x-F03.x, F05.1, G30.x, G31.1	1
Chronic pulmonary disease	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3	1
Rheumatologic disease	446.5, 710.0-710.4, 714.0- 714.2, 714.8, 725.x	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0	1
Mild liver disease	531.x-534.x	K25.x-K28.x	1
Diabetes without chronic complications	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4	1
Diabetes with chronic complications	250.0-250.3, 250.8, 250.9	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	2
Hemiplegia or paraplegia	250.4-250.7	E10.2-E10.5, El0.7, E11.2-Ell11.5, E11.7, E12.2-E12.5, E12.7, E13.2- E13.5, E13.7, E14.2-E14.5, E14.7	2
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0-583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	I12.0, I113.1, N03.2-N03.7, N05.2- N05.7, N18.x, N19.x, N25.0, Z49.0- Z49.2, Z94.0, Z99.2	2
Any malignancy, including leukemia and lymphoma	140.x-172.x, 174.x-195.8, 200.x-208.x, 238.6	C00.x-C26.x, C30.x-C34.x, C37.x- C41.x, C43.x, C45.x-C58.x, C60.x- C76.x, C81.x-C85.x, C88.x, C90.x-C97.x	2
Moderate or severe liver disease	456.0-456.2, 572.2-572.8	I85.0, I185.9, I186.4, I198.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	3
Metastatic solid tumor	196.x-199.x	C77.x-C80.x	6
AIDS/HIV	042.x-044.x	B20.x-B22.x, B24.x	6

Abbreviations: AIDS/HIV, acquired immune deficiency syndrome/human immunodeficiency virus; ICD, International Classification of Diseases.

Supplementary Table 5.3. Participant characteristics by race/ethnicity

	Non-Hispanic White (N = 5,108)	Asian (N = 2,264)	Hispanic (N = 1,991)	Non-Hispanic Black (N = 448)	Other or unknown (N = 1,594)	P-value
Maternal age, mean ± SD	34.7 ± 4.2	34.6 ± 4.2	33.2 ± 5.2*	33.3 ± 5.7*	34.2 ± 4.5*	<0.001*
Married, N (%)	4,550 (89.1)	2,090 (92.3)*	1,375 (69.1)*	279 (62.3)*	1,396 (87.6)	<0.001*
Area Deprivation Index (California) quartile, N (%)		*	*	*	*	<0.001*
Q1	1,417 (27.7)	477 (21.1)	195 (9.8)	29 (6.5)	374 (23.5)	
Q2	1,216 (23.8)	567 (25.0)	299 (15.0)	65 (14.5)	345 (21.6)	
Q3	1,080 (21.1)	542 (23.9)	437 (21.9)	90 (20.1)	342 (21.5)	
Q4	787 (15.4)	378 (16.7)	791 (39.7)	196 (43.8)	339 (21.3)	
Unknown	608 (11.9)	300 (13.3)	269 (13.5)	68 (15.2)	194 (12.2)	
Pre-pregnancy BMI, mean ± SD	24.0 ± 4.6	23.0 ± 3.6*	27.2 ± 5.9*	27.5 ± 6.2*	24.2 ± 4.4	<0.001*
Pre-pregnancy BMI category, N (%)		*	*	*		<0.001*
Underweight	148 (2.9)	116 (5.1)	20 (1.0)	6 (1.3)	40 (2.5)	
Normal weight	3,393 (66.4)	1,631 (72.0)	825 (41.4)	176 (39.3)	1,020 (64.0)	
Overweight	1,089 (21.3)	404 (17.8)	588 (29.5)	141 (31.5)	375 (23.5)	
Obese	478 (9.4)	113 (5.0)	558 (28.0)	125 (27.9)	159 (10.0)	
Nulliparous (the first pregnancy), N (%)	3,640 (71.3)	1,691 (74.7)	1,350 (67.8)	339 (75.7)	1,196 (75.0)	<0.001*
Singleton pregnancy, N (%)	4,721 (92.4)	2,153 (95.1)*	1,864 (93.6)	420 (93.8)	1,476 (92.6)	<0.001*
Smoking during pregnancy, N (%)	78 (1.5)	17 (0.8)	34 (1.7)	13 (2.9)	17 (1.1)	0.002*
Charlson Comorbidity Index category, N (%)		*				<0.001*
0	4,130 (80.9)	1,911 (84.4)	1,566 (78.7)	349 (77.9)	1,308 (82.1)	
1	784 (15.3)	297 (13.1)	348 (17.5)	80 (17.9)	246 (15.4)	
≥2	194 (3.8)	56 (2.5)	77 (3.9)	19 (4.2)	40 (2.5)	
Infant male sex, N (%)	2,660 (52.1)	1,140 (50.4)	1,044 (52.4)	228 (50.9)	808 (50.7)	0.73
Total gestational weight gain (pound), mean ± SD	29.1 ± 11.5	26.5 ± 10.3*	24.3 ± 13.7*	27.2 ± 13.6*	27.5 ± 11.8*	<0.001*
Excessive gestational weight gain, N (%)		*		*		<0.001*
Yes	1,585 (31.0)	451 (19.9)	602 (30.2)	164 (36.6)	446 (28.0)	
No	2,681 (52.5)	1,423 (62.9)	1,091 (54.8)	194 (43.3)	861 (54.0)	
Unknown	842 (16.5)	390 (17.2)	298 (15.0)	90 (20.1)	287 (18.0)	
50g GCT at GDM screening, mean ± SD	114 ± 27.9	128 ± 29.2*	119 ± 28.4*	108 ± 24.9*	119 ± 29.5*	<0.001*

Abbreviations: ANOVA, analysis of variance; EHR, electronic health record; GCT, glucose challenge test; GDM, gestational diabetes mellitus; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose tolerance; SD, standard deviation.

Notes: [1] Chi-squared or ANOVA test was used to calculate p-value cross groups; chi-squared or t-test was used to calculate p-values between each group and non-Hispanic White. [2] Charlson comorbidity index was derived based on major chronic conditions, such as cardiovascular diseases, liver diseases, and cancer. (Supplementary Table 2) [3] 16.7% pregnancies had unknown total gestational weight gain. Excessive gestational weight gain was defined according to the Institute of Medicine (IOM) guideline. [4] Glucose lowering medications included insulin, metformin, and glyburide. *Indicates statistically significant after controlling for multiple comparisons using the Benjamini-Hochberg method.

Supplementary Table 5.4. Participant characteristics by Asian subgroups

	Non-Hispanic White (N = 5,108)	Asian Indian (N = 222)	Chinese (N = 525)	Filipino (N = 180)	Japanese (N = 107)	Korean (N = 174)	Other/unknown Asian (N = 1,056)	P-value
Maternal age, mean ± SD	34.7 ± 4.2	34.0 ± 3.8	33.4 ± 4.3*	35.2 ± 4.4	35.9 ± 4.0	34.8 ± 3.7	34.9 ± 4.1	<0.001*
Married, N (%)	4,550 (89.1)	213 (95.9)	495 (94.3)*	156 (86.7)	100 (93.5)	166 (95.4)	960 (90.9)	<0.001*
Area Deprivation Index (California) quartile, N (%)				*		*		<0.001*
Q1	1,417 (27.7)	42 (18.9)	101 (19.2)	17 (9.4)	30 (28.0)	29 (16.7)	258 (24.4)	
Q2	1,216 (23.8)	51 (23.0)	138 (26.3)	36 (20.0)	25 (23.4)	29 (16.7)	288 (27.3)	
Q3	1,080 (21.1)	58 (26.1)	113 (21.5)	48 (26.7)	24 (22.4)	53 (30.5)	246 (23.3)	
Q4	787 (15.4)	38 (17.1)	95 (18.1)	47 (26.1)	16 (15.0)	31 (17.8)	151 (14.3)	
Unknown	608 (11.9)	33 (14.9)	78 (14.9)	32 (17.8)	12 (11.2)	32 (18.4)	113 (10.7)	
Pre-pregnancy BMI, mean ± SD	24.0 ± 4.6	23.5 ± 3.7	22.2 ± 3.1*	25.5 ± 4.5*	22.8 ± 3.3*	22.5 ± 3.3*	23.0 ± 3.5*	<0.001*
Pre-pregnancy BMI category, N (%)			*	*		*	*	<0.001*
Underweight	148 (2.9)	13 (5.9)	30 (5.7)	3 (1.7)	5 (4.7)	10 (5.7)	44 (5.2)	
Normal weight	3,393 (66.4)	146 (65.8)	422 (80.4)	96 (53.3)	86 (80.4)	134 (77.0)	747 (70.7)	
Overweight	1,089 (21.3)	50 (22.5)	57 (10.9)	55 (30.6)	14 (13.1)	25 (14.4)	203 (19.2)	
Obese	478 (9.4)	13 (5.9)	16 (3.0)	26 (14.4)	2 (1.9)	5 (2.9)	51 (4.8)	
Nulliparous (the first pregnancy), N (%)	3,640 (71.3)	171 (77.0)	430 (81.9)*	132 (73.3)	77 (72.0)	133 (76.4)	748 (70.8)	<0.001*
Singleton pregnancy, N (%)	4,721 (92.4)	206 (92.8)	503 (95.8)	169 (93.9)	105 (98.1)	156 (89.7)	1,014 (96.0)	<0.001*
Smoking during pregnancy, N (%)	78 (1.5)	2 (0.9)	3 (0.6)	5 (2.8)	1 (0.9)	2 (1.1)	4 (0.4)	0.02*
Charlson Comorbidity Index category, N (%)			*					0.007*
0	4,130 (80.9)	188 (84.7)	463 (88.2)	144 (80.0)	89 (83.2)	149 (85.6)	878 (83.1)	
1	784 (15.3)	28 (12.6)	55 (10.5)	30 (16.7)	16 (15.0)	18 (10.3)	150 (14.2)	
≥2	194 (3.8)	6 (2.7)	7 (1.3)	6 (3.3)	2 (1.9)	7 (4.0)	28 (2.7)	
Infant male sex, N (%)	2,660 (52.1)	132 (59.5)	244 (46.5)	95 (52.8)	60 (56.1)	87 (50.0)	522 (49.4)	0.17
Total gestational weight gain (pound), mean ± SD	29.1 ± 11.5	27.4 ± 11.2	26.4 ± 9.3*	25.7 ± 9.9*	25.6 ± 9.4*	27.9 ± 8.9	26.5 ± 9.5*	<0.001*
Excessive gestational weight gain, N (%)			*		*	*	*	
Yes	1,585 (31.0)	54 (24.3)	92 (17.5)	52 (28.9)	13 (12.1)	36 (20.7)	214 (20.3)	<0.001*
No	2,681 (52.5)	123 (55.4)	351 (66.9)	106 (58.9)	66 (61.7)	110 (63.2)	667 (63.2)	
Unknown	842 (16.5)	45 (20.3)	92 (17.5)	22 (12.2)	28 (26.2)	28 (16.1)	175 (16.6)	
50g GCT at GDM screening, mean ± SD	114 ± 27.9	127 ± 30.8*	127 ± 27.9*	131 ± 31.6*	125 ± 26.1*	128 ± 28.5*	128 ± 29.5*	<0.001*

Abbreviations: ANOVA, analysis of variance; EHR, electronic health record; GCT, glucose challenge test; GDM, gestational diabetes mellitus; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose tolerance; SD, standard deviation.

Notes: [1] Chi-squared or ANOVA test was used to calculate p-value cross groups; chi-squared or t-test was used to calculate p-values between each group and non-Hispanic White. [2] Charlson comorbidity index was derived based on major chronic conditions, such as cardiovascular diseases, liver diseases, and cancer. (Supplementary Table 2) [3] 16.7% pregnancies had unknown total gestational weight gain. Excessive gestational weight gain was defined according to the Institute of Medicine (IOM) guideline. [4] Glucose lowering medications included insulin, metformin, and glyburide. *Indicates statistically significant after controlling for multiple comparisons using the Benjamini-Hochberg method.

Supplementary Table 5.5. Prevalence of maternal hyperglycemic categories by race/ethnicity

N = 11,405	%	Unadjusted PR (95% CI)	Age-Adjusted PR (95% CI)	Fully Adjusted PR (95% CI)
Pregnancy impaired glucose tolerance-0 (PIGT-0, abnormal GCT & 0 abnormal OGTT)				
Non-Hispanic White (N = 5,108)	14.23%	1.00	1.00	1.00
Asian (N = 2,264)	21.42%	1.51 (1.34, 1.69)*	1.51 (1.35, 1.69)*	1.54 (1.37, 1.73)*
Non-Hispanic Black (N = 448)	8.71%	0.61 (0.44, 0.84)*	0.63 (0.46, 0.87)*	0.61 (0.44, 0.84)*
Hispanic (N = 1,991)	18.18%	1.28 (1.13, 1.45)*	1.32 (1.16, 1.50)*	1.27 (1.11, 1.45)*
Other/unknown (N = 1,594)	18.44%	1.30 (1.13, 1.48)*	1.31 (1.14, 1.50)*	1.31 (1.14, 1.50)*
Pregnancy impaired glucose tolerance-1 (PIGT-1, abnormal GCT & 1 abnormal OGTT)				
Non-Hispanic White (N = 5,108)	4.39%	1.00	1.00	1.00
Asian (N = 2,264)	9.14%	2.08 (1.72, 2.52)*	2.18 (1.78, 2.68)*	2.23 (1.84, 2.70)*
Non-Hispanic Black (N = 448)	3.57%	0.81 (0.49, 1.35)	0.80 (0.46, 1.41)	0.66 (0.39, 1.10)
Hispanic (N = 1,991)	8.49%	1.93 (1.58, 2.36)*	2.07 (1.67, 2.57)*	1.64 (1.32, 2.04)*
Other/unknown (N = 1,594)	6.52%	1.49 (1.18, 1.88)*	1.49 (1.16, 1.92)*	1.49 (1.18, 1.89)*
Gestational diabetes mellitus (GDM-0, abnormal GCT & normal fasting & ≥2 abnormal postprandial OGTT)				
Non-Hispanic White (N = 5,108)	3.90%	1.00	1.00	1.00
Asian (N = 2,264)	9.94%	2.54 (2.09, 3.09)*	2.55 (2.10, 3.10)*	2.65 (2.17, 3.23)*
Non-Hispanic Black (N = 448)	1.56%	0.40 (0.19, 0.86)*	0.42 (0.20, 0.89)*	0.33 (0.15, 0.70)*
Hispanic (N = 1,991)	6.33%	1.62 (1.29, 2.04)*	1.69 (1.35, 2.13)*	1.40 (1.10, 1.79)*
Other/unknown (N = 1,594)	5.02%	1.29 (0.99, 1.68)	1.31 (1.01, 1.71)	1.27 (0.97, 1.65)
Gestational diabetes mellitus (GDM-1, abnormal GCT & abnormal fasting & ≥1 abnormal postprandial OGTT)				
Non-Hispanic White (N = 5,108)	1.57%	1.00	1.00	1.00
Asian (N = 2,264)	2.34%	1.53 (1.07, 2.19)*	1.55 (1.08, 2.21)*	2.09 (1.44, 3.01)*
Non-Hispanic Black (N = 448)	1.34%	0.90 (0.39, 2.08)	0.95 (0.41, 2.20)	0.45 (0.19, 1.07)
Hispanic (N = 1,991)	3.87%	2.47 (1.78, 3.41)*	2.68 (1.93, 3.71)*	1.48 (1.04, 2.11)*
Other/unknown (N = 1,594)	2.01%	1.32 (0.86, 2.00)	1.35 (0.89, 2.06)	1.41 (0.92, 2.17)

Abbreviations: ADI, area deprivation index; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; GCT, glucose challenge test; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose intolerance; PR, prevalence ratio.

Notes: [1] The two step GDM screening approach involves a 1-hour 50g GCT and followed by a 3-hour 100g OGTT. NGT was defined as having a normal GCT value (<140 mg/L). PIGT-0 was defined as having an abnormal GCT value and normal OGTT values (fasting <95 mg/dL; 1-hour <180 mg/dL; 2-hour <155 mg/dL; 3-hour <140 mg/dL). PIGT-1 was defined as having an abnormal GCT value and 1 abnormal OGTT value. GDM-0 was defined as having an abnormal GCT value, a normal fasting OGTT value, and ≥2 abnormal postprandial OGTT values, while GDM-1 was defined as having an abnormal GCT, an abnormal fasting OGTT value, and ≥1 abnormal postprandial OGTT values.

[2] Poisson regressions with robust errors were applied to calculate RR. To account for correlation among siblings, a random effect for each pregnant individual was used.

[3] Fully adjusted model controlled for maternal age, ADI, marital status, smoking during pregnancy, nulliparous, singleton pregnancy, CCI, and pre-pregnancy BMI.

*Indicates statistically significant after controlling for multiple comparisons using the Benjamini-Hochberg method.

Supplementary Table 5.6. Prevalence of maternal hyperglycemic categories by Asian subgroups

N = 11,405	%	Unadjusted PR (95% CI)	Age-Adjusted PR (95% CI)	Fully Adjusted PR (95% CI)
Pregnancy impaired glucose tolerance-0 (PIGT-0, abnormal GCT & 0 abnormal OGTT)				
Non-Hispanic White (N = 5,108)	14.23%	1.00	1.00	1.00
Asian Indian (N = 222)	19.82%	1.39 (1.03, 1.89)*	1.41 (1.04, 1.91)*	1.40 (1.03, 1.90)*
Chinese (N = 525)	16.95%	1.19 (0.96, 1.48)	1.22 (0.98, 1.52)	1.24 (1.00, 1.56)
Filipino (N = 180)	23.89%	1.68 (1.23, 2.28)*	1.66 (1.22, 2.26)*	1.64 (1.20, 2.23)*
Japanese (N = 107)	18.69%	1.31 (0.84, 2.05)	1.28 (0.82, 2.00)	1.30 (0.83, 2.03)
Korean (N = 174)	26.44%	1.86 (1.38, 2.50)*	1.85 (1.38, 2.50)*	1.88 (1.39, 2.53)*
Other/unknown Asian (N = 1,056)	23.01%	1.62 (1.40, 1.87)*	1.61 (1.39, 1.86)*	1.62 (1.40, 1.88)*
Pregnancy impaired glucose tolerance-1 (PIGT-1, abnormal GCT & 1 abnormal OGTT)				
Non-Hispanic White (N = 5,108)	4.39%	1.00	1.00	1.00
Asian Indian (N = 222)	10.36%	2.36 (1.54, 3.63)*	2.57 (1.64, 4.03)*	2.52 (1.64, 3.88)*
Chinese (N = 525)	9.52%	2.17 (1.60, 2.95)*	2.36 (1.71, 3.27)*	2.50 (1.83, 3.42)*
Filipino (N = 180)	10.00%	2.28 (1.41, 3.69)*	2.47 (1.51, 4.06)*	2.04 (1.26, 3.30)*
Japanese (N = 107)	10.28%	2.34 (1.28, 4.29)*	2.40 (1.27, 4.54)*	2.45 (1.33, 4.49)*
Korean (N = 174)	10.34%	2.36 (1.46, 3.81)*	2.29 (1.35, 3.87)*	2.63 (1.62, 4.27)*
Other/unknown Asian (N = 1,056)	8.24%	1.88 (1.47, 2.41)*	1.92 (1.48, 2.51)*	1.98 (1.54, 2.54)*
Gestational diabetes mellitus (GDM-0, abnormal GCT & normal fasting & ≥2 abnormal postprandial OGTT)				
Non-Hispanic White (N = 5,108)	3.90%	1.00	1.00	1.00
Asian Indian (N = 222)	8.56%	2.20 (1.35, 3.57)*	2.24 (1.38, 3.63)*	2.20 (1.36, 3.58)*
Chinese (N = 525)	12.00%	3.08 (2.30, 4.13)*	3.17 (2.36, 4.25)*	3.20 (2.37, 4.32)*
Filipino (N = 180)	13.33%	3.24 (2.07, 5.08)*	3.22 (2.06, 5.04)*	3.00 (1.92, 4.70)*
Japanese (N = 107)	6.54%	1.67 (0.77, 3.62)	1.63 (0.75, 3.53)	1.71 (0.79, 3.71)
Korean (N = 174)	5.75%	1.48 (0.77, 2.83)	1.48 (0.77, 2.82)	1.41 (0.74, 2.71)
Other/unknown Asian (N = 1,056)	9.66%	2.48 (1.94, 3.17)*	2.46 (1.93, 3.15)*	2.62 (2.04, 3.35)*
Gestational diabetes mellitus (GDM-1, abnormal GCT & abnormal fasting & ≥1 abnormal postprandial OGTT)				
Non-Hispanic White (N = 5,108)	1.57%	1.00	1.00	1.00
Asian Indian (N = 222)	5.41%	3.40 (1.77, 6.54)*	3.68 (1.91, 7.09)*	4.98 (2.58, 9.61)*
Chinese (N = 525)	1.90%	1.28 (0.65, 2.52)	1.43 (0.73, 2.82)	2.30 (1.15, 4.61)*
Filipino (N = 180)	2.22%	1.48 (0.52, 4.18)	1.45 (0.51, 4.08)	1.28 (0.45, 3.61)
Japanese (N = 107)	0.00%	-	-	-
Korean (N = 174)	2.30%	1.53 (0.54, 4.31)	1.55 (0.55, 4.38)	2.17 (0.77, 6.15)
Other/unknown Asian (N = 1,056)	2.18%	1.43 (0.88, 2.31)	1.39 (0.86, 2.25)	2.06 (1.25, 3.38)*

Abbreviations: ADI, area deprivation index; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; GCT, glucose challenge test; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose intolerance; PR, prevalence ratio.

Notes: [1] The two step GDM screening approach involves a 1-hour 50g GCT and followed by a 3-hour 100g OGTT. NGT was defined as having a normal GCT value (<140 mg/L). PIGT-0 was defined as having an abnormal GCT value and normal OGTT values (fasting <95 mg/dL; 1-hour <180 mg/dL; 2-hour <155 mg/dL; 3-hour <140 mg/dL). PIGT-1 was defined as having an abnormal GCT value and 1 abnormal OGTT value. GDM-0 was defined as having an abnormal GCT value, a normal fasting OGTT value, and ≥2 abnormal postprandial OGTT values, while GDM-1 was defined as having an abnormal GCT, an abnormal fasting OGTT value, and ≥1 abnormal postprandial OGTT values. [2] Poisson regressions with robust errors were applied to calculate RR. To account for correlation among siblings, a random effect for each pregnant individual was used. [3] Fully adjusted model controlled for maternal age, ADI, marital status,

smoking during pregnancy, nulliparous, singleton pregnancy, CCI, and pre-pregnancy BMI. *Indicates statistically significant after controlling for multiple comparisons using the Benjamini-Hochberg method.

Supplementary Table 5.7. Prevalence of maternal hyperglycemic categories by race/ethnicity (the first pregnancy in EHR)

N = 8,216	%	Unadjusted PR (95% CI)	Age-Adjusted PR (95% CI)
Pregnancy impaired glucose tolerance-0 (PIGT-0, abnormal GCT & 0 abnormal OGTT)			
Non-Hispanic White (N = 3,640)	13.98%	1.00	1.00
Asian (N = 1,691)	21.47%	1.54 (1.34, 1.76)*	1.55 (1.35, 1.77)*
Non-Hispanic Black (N = 339)	9.73%	0.70 (0.49, 0.99)	0.72 (0.51, 1.03)
Hispanic (N = 1,350)	16.22%	1.16 (0.99, 1.39)	1.21 (1.03, 1.42)*
Other/unknown (N = 1,196)	18.23%	1.30 (1.11, 1.53)*	1.32 (1.13, 1.55)*
Pregnancy impaired glucose tolerance-1 (PIGT-1, abnormal GCT & 1 abnormal OGTT)			
Non-Hispanic White (N = 3,640)	4.64%	1.00	1.00
Asian (N = 1,691)	8.75%	1.89 (1.51, 2.35)*	1.91 (1.54, 2.39)*
Non-Hispanic Black (N = 339)	3.83%	0.83 (0.47, 1.45)	0.87 (0.50, 1.54)
Hispanic (N = 1,350)	7.93%	1.71 (1.34, 2.17)*	1.83 (1.43, 2.33)*
Other/unknown (N = 1,196)	5.85%	1.26 (0.95, 1.67)	1.28 (0.97, 1.70)
Gestational diabetes mellitus (GDM-0, abnormal GCT & normal fasting & ≥2 abnormal postprandial OGTT)			
Non-Hispanic White (N = 3,640)	4.31%	1.00	1.00
Asian (N = 1,691)	11.12%	2.58 (2.09, 3.19)*	2.61 (2.11, 3.23)*
Non-Hispanic Black (N = 339)	1.47%	0.34 (0.14, 0.83)*	0.36 (0.15, 0.88)*
Hispanic (N = 1,350)	6.07%	1.41 (1.08, 1.84)*	1.50 (1.15, 1.96)*
Other/unknown (N = 1,196)	5.43%	1.26 (0.94, 1.68)	1.28 (0.96, 1.71)
Gestational diabetes mellitus (GDM-1, abnormal GCT & abnormal fasting & ≥1 abnormal postprandial OGTT)			
Non-Hispanic White (N = 3,640)	1.40%	1.00	1.00
Asian (N = 1,691)	2.42%	1.73 (1.15, 2.61)*	1.78 (1.18, 2.68)*
Non-Hispanic Black (N = 339)	1.47%	1.05 (0.42, 2.64)	1.13 (0.45, 2.84)
Hispanic (N = 1,350)	3.26%	2.33 (1.55, 3.48)*	2.57 (1.71, 3.85)*
Other/unknown (N = 1,196)	2.17%	1.55 (0.79, 2.49)	1.59 (0.99, 2.56)

Abbreviations: ADI, area deprivation index; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; GCT, glucose challenge test; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose intolerance; PR, prevalence ratio.

Notes: [1] The two step GDM screening approach involves a 1-hour 50g GCT and followed by a 3-hour 100g OGTT. NGT was defined as having a normal GCT value (<140 mg/L). PIGT-0 was defined as having an abnormal GCT value and normal OGTT values (fasting <95 mg/dL; 1-hour <180 mg/dL; 2-hour <155 mg/dL; 3-hour <140 mg/dL). PIGT-1 was defined as having an abnormal GCT value and 1 abnormal OGTT value. GDM-0 was defined as having an abnormal GCT value, a normal fasting OGTT value, and ≥2 abnormal postprandial OGTT values, while GDM-1 was defined as having an abnormal GCT, an abnormal fasting OGTT value, and ≥1 abnormal postprandial OGTT values. [2] Poisson regressions with robust errors were applied to calculate RR. *Indicates statistically significant after controlling for multiple comparisons using the Benjamini-Hochberg method.

Supplementary Table 5.8. Prevalence of maternal hyperglycemic categories by Asian subgroups (the first pregnancy in EHR)

N = 8,216	%	Unadjusted PR (95% CI)	Age-Adjusted PR (95% CI)
Pregnancy impaired glucose tolerance-0 (PIGT-0, abnormal GCT & 0 abnormal OGTT)			
Non-Hispanic White (N = 3,640)	13.98%	1.00	1.00
Asian Indian (N = 171)	18.71%	1.34 (0.94, 1.91)	1.36 (0.95, 1.95)
Chinese (N = 430)	16.28%	1.16 (0.91, 1.49)	1.20 (0.93, 1.54)
Filipino (N = 132)	23.48%	1.68 (1.17, 2.41)*	1.66 (1.15, 2.38)*
Japanese (N = 77)	19.48%	1.39 (0.83, 2.33)	1.37 (0.82, 2.28)
Korean (N = 133)	24.81%	1.77 (1.25, 2.52)*	1.78 (1.25, 2.53)*
Other/unknown Asian (N = 748)	24.22%	1.74 (1.47, 2.06)*	1.74 (1.47, 2.06)*
Pregnancy impaired glucose tolerance-1 (PIGT-1, abnormal GCT & 1 abnormal OGTT)			
Non-Hispanic White (N = 3,640)	4.64%	1.00	1.00
Asian Indian (N = 171)	8.19%	1.76 (1.02 3.04)	1.81 (1.05, 3.13)
Chinese (N = 430)	8.60%	1.85 (1.30, 2.65)*	1.94 (1.36, 2.77)*
Filipino (N = 132)	6.82%	1.47 (0.75, 2.87)	1.44 (0.74, 2.81)
Japanese (N = 77)	11.69%	2.52 (1.29, 4.92)*	2.44 (1.25, 4.78)*
Korean (N = 133)	10.53%	2.27 (1.31, 3.91)*	2.28 (1.32, 3.94)*
Other/unknown Asian (N = 748)	8.69%	1.87 (1.41, 2.49)*	1.87 (1.40, 2.49)*
Gestational diabetes mellitus (GDM-0, abnormal GCT & normal fasting & ≥2 abnormal postprandial OGTT)			
Non-Hispanic White (N = 3,640)	4.31%	1.00	1.00
Asian Indian (N = 171)	10.53%	2.44 (1.50, 3.97)*	2.51 (1.54, 4.09)*
Chinese (N = 430)	13.26%	3.07 (2.27, 4.16)*	3.21 (2.37, 4.36)*
Filipino (N = 132)	15.15%	3.51 (2.21, 5.59)*	3.44 (2.16, 5.49)*
Japanese (N = 77)	7.79%	1.81 (0.80, 4.08)	1.76 (0.78, 3.97)
Korean (N = 133)	6.02%	1.39 (0.69, 2.84)	1.40 (0.69, 2.85)
Other/unknown Asian (N = 748)	10.56%	2.45 (1.87, 3.21)*	2.44 (1.86, 3.20)*
Gestational diabetes mellitus (GDM-1, abnormal GCT & abnormal fasting & ≥1 abnormal postprandial OGTT)			
Non-Hispanic White (N = 3,640)	1.40%	1.00	1.00
Asian Indian (N = 171)	7.02%	5.01 (2.67, 9.39)*	5.66 (3.01, 10.64)*
Chinese (N = 430)	1.86%	1.33 (0.63, 2.80)	1.55 (0.73, 3.27)
Filipino (N = 132)	2.27%	1.62 (0.51, 5.20)	1.50 (0.47, 4.81)
Japanese (N = 77)	0.00%	-	-
Korean (N = 133)	1.50%	1.07 (0.26, 4.41)	1.14 (0.28, 4.69)
Other/unknown Asian (N = 748)	2.14%	1.53 (0.87, 2.68)	1.54 (0.88, 2.70)

Abbreviations: ADI, area deprivation index; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; GCT, glucose challenge test; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose intolerance; PR, prevalence ratio.
Notes: [1] The two step GDM screening approach involves a 1-hour 50g GCT and followed by a 3-hour 100g OGTT. NGT was defined as having a normal GCT value (<140 mg/L). PIGT-0 was defined as having an abnormal GCT value and normal OGTT values (fasting <95 mg/dL; 1-hour <180 mg/dL; 2-hour <155 mg/dL; 3-hour <140 mg/dL). PIGT-1 was defined as having an abnormal GCT value and 1 abnormal OGTT value. GDM-0 was defined as having an abnormal GCT value, a normal fasting OGTT value, and ≥2 abnormal postprandial OGTT values, while GDM-1 was defined as having an abnormal GCT, an abnormal fasting OGTT value, and ≥1 abnormal postprandial OGTT values. [2] Poisson regressions with robust errors were applied to calculate RR. *Indicates statistically significant after controlling for multiple comparisons using the Benjamini-Hochberg method.

Supplementary Table 5.9. Prevalence of maternal hyperglycemic categories by race/ethnicity (excluding pregnancies screened <15 weeks of gestation)

N = 11,212	%	Unadjusted PR (95% CI)	Age-Adjusted PR (95% CI)
Pregnancy impaired glucose tolerance-0 (PIGT-0, abnormal GCT & 0 abnormal OGTT)			
Non-Hispanic White (N = 4,710)	11.08%	1.00	1.00
Asian (N = 1,900)	16.35%	1.49 (1.30, 1.72)*	1.50 (1.30, 1.73)*
Non-Hispanic Black (N = 414)	5.31%	0.48 (0.31, 0.73)*	0.50 (0.32, 0.76)*
Hispanic (N = 1,615)	11.85%	1.08 (0.91, 1.27)	1.13 (0.96, 1.34)
Other/unknown (N = 1,397)	14.10%	1.27 (1.08, 1.50)*	1.29 (1.10, 1.52)*
Pregnancy impaired glucose tolerance-1 (PIGT-1, abnormal GCT & 1 abnormal OGTT)			
Non-Hispanic White (N = 4,710)	3.04%	1.00	1.00
Asian (N = 1,900)	7.47%	2.45 (1.94, 3.10)*	2.48 (1.96, 3.14)*
Non-Hispanic Black (N = 414)	2.66%	0.88 (0.47, 1.62)	0.92 (0.50, 1.72)
Hispanic (N = 1,615)	5.33%	1.74 (1.33, 2.29)*	1.87 (1.43, 2.46)*
Other/unknown (N = 1,397)	4.44%	1.46 (1.08, 1.98)	1.49 (1.11, 2.02)*
Gestational diabetes mellitus (GDM-0, abnormal GCT & normal fasting & ≥2 abnormal postprandial OGTT)			
Non-Hispanic White (N = 4,710)	2.85%	1.00	1.00
Asian (N = 1,900)	7.63%	2.65 (2.08, 3.38)*	2.68 (2.10, 3.42)*
Non-Hispanic Black (N = 414)	1.69%	0.60 (0.28, 1.30)	0.64 (0.29, 1.37)
Hispanic (N = 1,615)	4.15%	1.44 (1.06, 1.94)*	1.54 (1.14, 2.09)*
Other/unknown (N = 1,397)	3.51%	1.24 (0.89, 1.74)	1.27 (0.91, 1.77)
Gestational diabetes mellitus (GDM-1, abnormal GCT & abnormal fasting & ≥1 abnormal postprandial OGTT)			
Non-Hispanic White (N = 4,710)	1.23%	1.00	1.00
Asian (N = 1,900)	1.47%	1.26 (0.79, 2.00)	1.28 (0.80, 2.04)
Non-Hispanic Black (N = 414)	0.48%	0.43 (0.10, 1.79)	0.46 (0.11, 1.91)
Hispanic (N = 1,615)	1.55%	1.30 (0.80, 2.12)	1.43 (0.88, 2.34)
Other/unknown (N = 1,397)	1.29%	1.10 (0.64, 1.90)	1.12 (0.65, 1.94)

Abbreviations: ADI, area deprivation index; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; GCT, glucose challenge test; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose intolerance; PR, prevalence ratio.
Notes: [1] The two step GDM screening approach involves a 1-hour 50g GCT and followed by a 3-hour 100g OGTT. NGT was defined as having a normal GCT value (<140 mg/L). PIGT-0 was defined as having an abnormal GCT value and normal OGTT values (fasting <95 mg/dL; 1-hour <180 mg/dL; 2-hour <155 mg/dL; 3-hour <140 mg/dL). PIGT-1 was defined as having an abnormal GCT value and 1 abnormal OGTT value. GDM-0 was defined as having an abnormal GCT value, a normal fasting OGTT value, and ≥2 abnormal postprandial OGTT values, while GDM-1 was defined as having an abnormal GCT, an abnormal fasting OGTT value, and ≥1 abnormal postprandial OGTT values. [2] Poisson regressions with robust errors were applied to calculate RR. *Indicates statistically significant after controlling for multiple comparisons using the Benjamini-Hochberg method.

Supplementary Table 5.10. Prevalence of maternal hyperglycemic categories by Asian subgroups (excluding pregnancies screened <15 weeks of gestation)

N = 11,212	%	Unadjusted PR (95% CI)	Age-Adjusted PR (95% CI)
Pregnancy impaired glucose tolerance-0 (PIGT-0, abnormal GCT & 0 abnormal OGTT)			
Non-Hispanic White (N = 4,710)	11.08%	1.00	1.00
Asian Indian (N = 180)	16.11%	1.45 (1.00, 2.11)	1.48 (1.02, 2.15)
Chinese (N = 455)	13.63%	1.23 (0.94, 1.60)	1.26 (0.97, 1.65)
Filipino (N = 150)	19.33%	1.74 (1.20, 2.54)*	1.73 (1.19, 2.52)*
Japanese (N = 93)	11.83%	1.07 (0.59, 1.94)	1.04 (0.57, 1.89)
Korean (N = 145)	20.00%	1.80 (1.24, 2.62)*	1.81 (1.24, 2.62)*
Other/unknown Asian (N = 877)	17.56%	1.58 (1.32, 1.90)*	1.58 (1.32, 1.89)*
Pregnancy impaired glucose tolerance-1 (PIGT-1, abnormal GCT & 1 abnormal OGTT)			
Non-Hispanic White (N = 4,710)	3.04%	1.00	1.00
Asian Indian (N = 180)	8.89%	2.92 (1.74, 4.92)*	3.01 (1.79, 5.07)*
Chinese (N = 455)	6.81%	2.24 (1.52, 3.31)*	2.36 (1.59, 3.49)*
Filipino (N = 150)	7.33%	2.42 (1.31, 4.49)*	2.39 (1.29, 4.43)*
Japanese (N = 93)	8.60%	2.82 (1.38, 5.79)*	2.69 (1.31, 5.53)*
Korean (N = 145)	8.97%	2.95 (1.66, 5.23)*	2.96 (1.67, 5.25)*
Other/unknown Asian (N = 877)	7.18%	2.37 (1.76, 3.19)*	2.35 (1.75, 3.17)*
Gestational diabetes mellitus (GDM-0, abnormal GCT & normal fasting & ≥2 abnormal postprandial OGTT)			
Non-Hispanic White (N = 4,710)	2.85%	1.00	1.00
Asian Indian (N = 180)	6.11%	2.17 (1.15, 4.08)*	2.23 (1.18, 4.21)*
Chinese (N = 455)	10.11%	3.53 (2.49, 5.00)*	3.68 (2.59, 5.24)*
Filipino (N = 150)	11.33%	3.62 (2.09, 6.26)*	3.60 (2.09, 6.22)*
Japanese (N = 93)	5.38%	1.84 (0.73, 4.64)	1.78 (0.71, 4.49)
Korean (N = 145)	3.45%	1.20 (0.48, 2.99)	1.20 (0.48, 2.99)
Other/unknown Asian (N = 877)	6.96%	2.45 (1.79, 3.35)*	2.44 (1.78, 3.33)*
Gestational diabetes mellitus (GDM-1, abnormal GCT & abnormal fasting & ≥1 abnormal postprandial OGTT)			
Non-Hispanic White (N = 4,710)	1.23%	1.00	1.00
Asian Indian (N = 180)	2.22%	1.69 (0.57, 5.06)	1.88 (0.64, 5.57)
Chinese (N = 455)	1.54%	1.33 (0.59, 2.99)	1.48 (0.65, 3.33)
Filipino (N = 150)	2.00%	1.60 (0.50, 5.66)	1.72 (0.52, 5.71)
Japanese (N = 93)	0.00%	-	-
Korean (N = 145)	1.38%	1.21 (0.29, 5.14)	1.25 (0.29, 5.29)
Other/unknown Asian (N = 877)	1.37%	1.19 (0.87, 2.26)	1.16 (0.61, 2.21)

Abbreviations: ADI, area deprivation index; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; GCT, glucose challenge test; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PIGT, pregnancy impaired glucose intolerance; PR, prevalence ratio.

Notes: [1] The two step GDM screening approach involves a 1-hour 50g GCT and followed by a 3-hour 100g OGTT. NGT was defined as having a normal GCT value (<140 mg/L). PIGT-0 was defined as having an abnormal GCT value and normal OGTT values (fasting <95 mg/dL; 1-hour <180 mg/dL; 2-hour <155 mg/dL; 3-hour <140 mg/dL). PIGT-1 was defined as having an abnormal GCT value and 1 abnormal OGTT value. GDM-0 was defined as having an abnormal GCT value, a normal fasting OGTT value, and ≥2 abnormal

postprandial OGTT values, while GDM-1 was defined as having an abnormal GCT, an abnormal fasting OGTT value, and ≥1 abnormal postprandial OGTT values. [2] Poisson regressions with robust errors were applied to calculate RR. *Indicates statistically significant after controlling for multiple comparisons using the Benjamini-Hochberg method.

6 CHAPTER SIX: GESTATIONAL DIABETES MELLITUS AND RISK OF NEURODEVELOPMENTAL DISORDERS IN YOUNG OFFSPRING

6.1 Abstract

Background

Previous studies examined the associations of gestational diabetes mellitus (GDM) with autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). However, the associations between GDM and other neurodevelopmental disorders (NDDs), such as the common speech/language disorder (SLD) and developmental coordination disorder (DCD), are rarely studied and whether the associations vary by race/ethnicity remains unknown.

Objectives

To examine the associations of GDM with individual NDDs in young offspring and investigate whether the associations varied by race/ethnicity.

Study Design

This retrospective cohort study (Glucose in Relation to Women and Babies' Health [GrownB]) included 14,480 mother-offspring pairs in a large medical center in the United States (US) from 3/1/2013 to 8/31/2021. We ascertained GDM using the validated International Classification of Disease (ICD) codes (ICD-9: 648.8x; ICD-10: O24.4x), and identified NDDs (SLD, DCD, ASD, and other NDDs [ADHD, behavioral disorder, intellectual disability, and learning difficulty]) and their combinations using validated algorithms. We compared the hazard of NDDs during the entire follow-up period between offspring born to mothers with and without GDM using multivariable Cox regression models.

Results

Among all mothers, 19.9% were Asians, 21.8% were Hispanics, 41.0% were non-Hispanic Whites, and 17.3% were other/unknown race/ethnicity. During the median follow-up of 3.5 years (range: 1.0-6.3 years) after birth, 8.7% of offspring developed at least one NDD. GDM was associated with a higher risk of SLD (adjusted hazard ratio: 1.59 [95% confidence interval, 1.07, 2.35]), DCD (2.36 [1.37, 4.04]), ASD (3.16 [1.36, 7.37]), other NDDs (3.12 [1.51, 6.47]), any NDD (1.86 [1.36, 2.53]), combination of SLD and ASD (3.79 [1.35, 10.61]), and combination of SLD and DCD (4.22 [1.69, 10.51]) among offspring born to non-Hispanic White mothers. No associations between GDM and any NDDs or their combinations were observed among offspring born to mothers of other racial/ethnic groups.

Conclusions

We observed an elevated risk of NDDs in young offspring born to non-Hispanic White mothers with GDM, but not among other racial/ethnic groups.

6.2 Introduction

Gestational diabetes mellitus (GDM) affects around 4-9% of pregnancies in the United States (US) with a rising prevalence in the past decades[1, 4, 5, 24, 25, 133, 134]. GDM is linked with a higher risk of adverse neonatal outcomes (e.g., large for gestational age [LGA] and preterm birth[1, 24, 89, 91, 92]) and cardiometabolic disorders later in life (e.g., type 2 diabetes mellitus, obesity, and hypertension[1, 24, 68, 135-137]). Recent epidemiologic studies reported an association between GDM and an elevated risk of neurodevelopmental disorders (NDDs)[70, 71, 93, 94, 138-140]. NDDs are heterogeneous conditions caused by complex interactions between genes and the environment[77, 141]. Commonly diagnosed NDDs in the US include autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), speech/language disorder (SLD), developmental coordination disorder (DCD), learning disability, intellectual disability, and

behavioral disorders[78, 79, 141, 142]. Although each condition is diagnosed separately, NDDs often co-occur[78]. In the US, the typical diagnostic age varies across NDDs, with ASD, SLD, and DCD usually diagnosed between 3-6 years, while ADHD, learning disability, intellectual disability, and behavioral disorders usually diagnosed between 7-9 years[78]. Most previous studies, however, focused on associations between GDM and the risk of ASD and ADHD[70, 71, 93, 94, 138-140]. A few studies also investigated the association between GDM and intellectual disability[93, 94, 138, 140], but none studied the prevalent SLD and DCD.

There are well-known racial/ethnic differences in GDM prevalence, with Asians and Hispanics having 2-3 times greater prevalence than non-Hispanic Whites[1, 24, 25]. Studies also reported racial/ethnic differences in GDM-related adverse neonatal outcomes[113]. For example, offspring born to non-Hispanic Whites with GDM had a lower risk of preterm birth, small for gestational age (SGA), and admission to neonatal intensive care unit (NICU) but a higher risk of LGA and macrosomia, compared to offspring born to Asians, Hispanics, and non-Hispanic Blacks with GDM[113]. However, no research explored whether the association between GDM and NDDs varies by race/ethnicity. Therefore, we aimed to examine the associations of GDM with individual and combinations of NDDs in offspring and to evaluate whether these associations vary across race/ethnicity.

6.3 Methods

Study population

The retrospective cohort, University of California, Los Angeles Glucose in Relation to Women and Babies' Health (UCLA GrownB), included 25,780 births (25,147 singletons and 633 multiple pregnancies; 21,544 mothers and 26,441 offspring) at UCLA medical center (electronic medical records) from March 1, 2013, to August 31, 2021. UCLA medical center has 4 hospitals

and >200 clinics, serving patients from socioeconomically diverse backgrounds. It has over 670,000 unique patients, 2.8 million outpatient visits, and 100,000 inpatient admissions annually. The study was approved for exemption by the UCLA Institutional Review Board.

The eligibility criteria for this study were singleton live births between 24-44 weeks of gestation and followed-up ≥1 year of age (N=15,179). We excluded 27 pairs where mothers were <16 or >49 years old at delivery, 337 pairs where mothers did not receive prenatal care at UCLA, and 335 pairs where mothers had pre-pregnancy diabetes (International Classification of Diseases [ICD]-9: 250.x; ICD-10: E10.x, E11.x, and E13.x). The final analytical sample included 14,480 mother-offspring pairs. (Figure 1)

Ascertainment of GDM

UCLA medical center has applied universal GDM testing between 24-28 weeks of gestation via a two-step approach, recommended by the American College of Obstetricians and Gynecologists since 2001[143] and throughout the entire study period, including the COVID-19 pandemic[74]. We ascertained GDM using the ICD codes (ICD-9: 648.8x [abnormal glucose tolerance of mother]; ICD-10: O24.4x [GDM])[144]. Around 70% and 30% of GDM diagnoses were identified using ICD-10 and ICD-9 codes, respectively. Among 53% of mothers with GDM testing laboratory data, the accuracy of all ICD-codes was 97.2% (sensitivity: 96.2%; specificity: 97.3%; positive predictive value [PPV]: 72.5%; negative predictive value: 99.7%), and the accuracy of ICD-9 and ICD-10 codes was 93.2% and 97.7%, respectively.

Ascertainment of NDDs

UCLA medical center has implemented universal developmental surveillance and screening during well-child visits at 9, 18, and 30 months of age, following the American Academy of Pediatrics guideline since 2006 and throughout the entire study period[145, 146].

Universal ASD-specific screening was also performed at 18 and 24 months of age[147]. Specific screening for other NDDs, such as ADHD[148] and SLD[149], was applied whenever necessary. The NDDs were identified via validated algorithms designed for real-world data[78, 150, 151]. (Supplementary Table 1, Supplementary Table 2)

Covariates

We extracted participant characteristics, including sociodemographic (e.g., age, race/ethnicity, and Area Deprivation Index [ADI]), behavioral (e.g., pre-pregnancy BMI and smoking during pregnancy), maternal (e.g., parity and excessive gestational weight gain), and clinical characteristics (e.g., mental disorders and Charlson Comorbidity Index [CCI]). (Supplementary Table 2) We used ADI to approximate socioeconomic status (e.g., income, education, and housing), which provides rankings at the block group level in California from 1 (least disadvantaged) to 10 (most disadvantaged)[120]. We used CCI to assess pre-pregnancy chronic disorders, such as cardiovascular diseases and cancer[121, 122]. (Supplementary Table 3)

We also extracted antidiabetic medication use (i.e., insulin, metformin, and glyburide) using prescription data, and pregnancy outcomes (e.g., pre-eclampsia/eclampsia, preterm birth, and LGA [>90 percentile birth weight by gestational age and offspring sex][152]) using diagnosis, procedure, or obstetrics and gynecology data. (Supplementary Table 2)

In addition, we obtained well-child visits using ICD-codes (ICD-9: V20.2x, V20.3x; ICD-10: Z00.11x, Z00.12x) and Current Procedural Terminology codes (99381, 99382, 99383, 99391, 99392, 99393) from the diagnosis and procedure data.

Statistical analyses

We described characteristics of all participants and by GDM status. Missing values were observed for race/ethnicity (3.0%), ADI (11.7%), and total excessive gestational weight gain (15.7%). Missing values were classified as unknown.

The primary outcomes were SLD, DCD, ASD, and other NDDs. Due to a small number of events, we combined ADHD, learning disability, intellectual disability, and behavioral disorder into the other NDDs category. The secondary outcomes included a composite outcome of any NDD and the most frequent three combinations of NDDs, because of the frequent co-occurrence and the potential shared biological mechanisms across NDDs[77, 78]. We first obtained the unadjusted cumulative incidence of any NDD among offspring born to mothers with vs. without GDM in all participants and by race/ethnicity (non-Hispanic White vs. other race/ethnicities). Then, we estimated unadjusted and adjusted hazard ratios (HR) and 95% confidence interval (CI) of NDDs comparing offspring born to mothers with vs. without GDM using Cox models. We defined the event date as the first NDD diagnosis date and censored offspring who were lost to follow-up at the last encounter day[153]. To account for the correlation among siblings, a random effect on each pregnant individual was specified. The proportional hazard assumption was verified using scaled Schoenfeld residuals. The adjusted models controlled for pre-selected potential confounders: maternal age (continuous), race/ethnicity (non-Hispanic White, other race/ethnicities), marital status (yes, no), ADI quartiles (Q1, Q2, Q3, Q4, or unknown), pre-pregnancy body mass index (BMI, underweight [<18.5 kg/m^2], normal weight [18.5-24.9 kg/m^2], overweight [25.0-29.9 kg/m^2], or obese [≥30.0 kg/m^2]), smoking during pregnancy (yes, no), CCI (0, 1, or ≥2), depression (yes, no), substance (alcohol, cannabis, and cocaine) use (yes, no), polycystic ovarian syndrome (PCOS, yes, no), birth year (categorical, 2013-2020), and offspring sex (male, female).

In addition, we examined racial/ethnic differences by adding an interaction term for GDM status and race/ethnicity to the models. Offspring born to mothers with and without GDM had similar incidence rates of NDDs among Asians, Hispanics, and other race/ethnicities. To ensure sufficient power, we combined them into the other race/ethnicities group. Supplementary Figure 1 displays the directed acyclic graph showing the hypothesized relationship between GDM, NDDs, confounders, and the effect measure modifier (i.e., race/ethnicity).

We performed several sensitivity analyses. First, we examined the association between GDM and any NDD among four racial/ethnic groups (i.e., Asian, Hispanic, non-Hispanic White, and other/unknown). Second, we stratified GDM ascertainment by ICD-9 and ICD-10 codes to evaluate potential exposure misclassification, as the accuracy of ICD-10 codes was higher than ICD-9 codes for GDM. Third, we stratified the association by GDM severity (i.e., A1 GDM [lifestyle interventions only] and A2 GDM [additional antidiabetic medications]) to evaluate the influence of glycemic control. Finally, we additionally adjusted for pregnancy complications (gestational hypertension; pre-eclampsia/eclampsia) and adverse birth outcomes (preterm birth; LGA) to evaluate their impacts on the association.

We conducted analyses in R version 4.0.5. To account for multiple comparisons, we used the Benjamini-Hochberg method[124], setting the overall false discovery rate (FDR) threshold to <0.05.

6.4 Results

Study participant characteristics

Among mothers, 19.9% were Asians, 21.8% were Hispanics, 41.0% were non-Hispanic Whites, and 17.3% were other/unknown race/ethnicities. Among offspring, 9.8% were exposed

to GDM. Offspring born to mothers with GDM were more likely to have preterm birth and LGA than those born to mothers without GDM.

Compared to mothers without GDM, mothers with GDM were less likely to be non-Hispanic White and married, while more likely to be older, with overweight/obese pre-pregnancy BMI, live in a disadvantaged neighborhood, smoke during pregnancy, have pre-pregnancy mental and chronic disorders, and experience more adverse maternal outcomes (e.g., gestational hypertension, excessive gestational weight gain, and Cesarean delivery). Among the 1417 mothers with GDM, 18.3% received antidiabetic medications (i.e., A2 GDM). (Table 1)

Incidence rates of NDDs

During the median follow-up of 3.5 years (range: 1.0-6.3 years) after birth, there were 990 (6.8%) offspring with SLD, 295 (2.0%) with DCD, 158 (1.1%) with ASD, 99 (0.7%) with other NDDs (ADHD: 62 [0.4%]; behavioral disorder: 27 [0.2%], intellectual disability: 10 [0.1%], and learning difficulty: 10 [0.1%]), 1253 (8.7%) with any NDD, 127 (0.9%) with SLD and ASD, 115 (0.8%) with SDL and DCD, and 40 (0.3%) with ASD and DCD. The unadjusted incidence rate for individual NDDs was the highest for SLD (19.01 [95% CI: 17.84, 20.18] per 1000 person-years), followed by DCD (5.47 [4.85, 6.09]), ASD (2.90 [2.45, 3.35]), and other NDDs (1.80 [1.44, 2.16]) (ADHD: 1.13 [0.85, 1.41]; behavioral disorder: 0.49 [0.31, 0.68], intellectual disability: 0.18 [0.07, 0.30]; learning difficulty: 0.18 [0.07, 0.30]). The unadjusted incidence rate of any NDD was 24.36 (95% CI: 23.02, 25.69) per 1000 person-years. For the most frequent three combinations of NDDs, the unadjusted incidence rate of SLD and ASD (2.44 [2.02, 2.87]) was the highest, followed by SLD and DCD (2.23 [1.82, 2.64]), and ASD and DCD (0.75 [0.51, 0.98]). (Table 2)

Associations between GDM and NDDs in all participants and by race/ethnicity

In all participants, the unadjusted cumulative incidence of any NDD tended to be higher among offspring born to mothers with GDM than without GDM. Stratified by race/ethnicity, the unadjusted cumulative incidence of any NDD was only higher among offspring born to non-Hispanic Whites with GDM. (Figure 2)

In all participants, GDM tended to be associated with a higher risk of DCD (adjusted HR: DCD 1.42 [95% CI: 1.01, 2.00]), ASD (1.22 [0.76, 1.96]), other NDDs (1.42 [0.79, 2.57]), any NDD (1.13 [0.94, 1.35]), combination of SLD and ASD (1.28 [0.77, 2.14]), and combination of SLD and DCD (1.43 [0.84, 2.42]), although not statistically significant. However, GDM was not associated with SLD (1.03 [0.84, 1.26]). (Table 2) The association between GDM and combination of ASD and DCD was not evaluated due to small number of events.

Among offspring born to non-Hispanic Whites with GDM, the risk of SLD (adjusted HR: 1.59 [1.07, 2.35]), DCD (2.36 [1.37, 4.04]), ASD (3.16 [1.36, 7.37]), other NDDs (3.12 [1.51, 6.47]), any NDD (1.86 [1.36, 2.53]), combination of SLD and ASD (3.79 [1.35, 10.61]), and combination of SLD and DCD (4.22 [1.69, 10.51]) was elevated than offspring born to non-Hispanic Whites without GDM. In contrast, no statistically significant association between GDM and NDDs was observed among other race/ethnicities. (Table 3)

In a sensitivity analysis, stratifying the association between GDM and any NDD by four racial/ethnic groups showed similar results. In addition, stratifying the GDM ascertainment by ICD-9 and ICD-10 codes, the results remained unchanged overall, but the association was higher when using ICD-10 than ICD-9 codes. Furthermore, compared to A1 GDM, the association was higher between A2 GDM and any NDD, suggesting that poorer glycemic control had a stronger link to NDDs. Lastly, additionally adjusting for pregnancy complications and adverse outcomes attenuated the association slightly. (Supplementary Table 4)

6.5 Discussion

This retrospective cohort study found that young offspring born to mothers with GDM had elevated risks of common NDDs and their combinations than those born to mothers without GDM, but only among non-Hispanic Whites.

We are unaware of any previous studies examining the association of GDM with SLD, DCD, or their combinations. In a recent meta-analysis, GDM was associated with a 1.42 times higher ASD risk[20]. However, this meta-analysis only included studies in the US, Canada, or Israel that did not report the association by race/ethnicity[20]. In a large study of Kaiser Permanente in Southern California, which also included racially diverse participants, GDM diagnosed ≤26 weeks of gestation was associated with a 1.42 times higher risk of ASD in offspring[70]. Our study observed a similar but non-significant GDM-ASD association (adjusted HR: 1.22 [95% CI: 0.76, 1.96]) in all participants, although we had younger offspring (median 3.5 vs. 5.5 years) than the Kaiser population. Additionally, we found the risk of ASD was 3.16 times higher comparing offspring born to GDM vs. non-GDM mothers among non-Hispanic Whites. This result is comparable to a population-based study in Israel with predominantly non-Hispanic Whites, which reported a 4.44 higher risk of ASD in offspring born to GDM vs. non-GDM mothers[140]. Furthermore, the meta-analysis did not find a GDM-ADHD association[20]. Although ADHD is a common NDD, it is often diagnosed in children 4-18 years (mean age between 7-8 years)[78, 148]. Our study mostly included young offspring (median 3.5 years, range 1.0-6.3 years), leading to only 62 ADHD cases (unadjusted HR:1.42 [95% CI: 0.68, 3.00], adjusted HR: non-converged). For intellectual disability, two studies in Sweden and the US reported a positive association between GDM and intellectual disability[93, 94], while a study in

Taiwan found a negative association[138]. In our study, only 10 offspring had intellectual disability, and none were born to mothers with GDM, making estimation impossible.

Potential mechanisms underlying the association between GDM and NDDs may involve multiple pathways, and uncontrolled hyperglycemia likely plays a major role. A US study found that HbA1c >6.5% in early pregnancy was associated with a higher risk of ASD[154]. Uncontrolled hyperglycemia during pregnancy may directly interfere with fetal brain development through epigenetic modifications[81-83], chronic inflammation[84, 85], oxidative stress[86, 87], or hypoxia[88]. In our study, compared to A1 GDM, there was a greater association between A2 GDM and any NDD (adjusted HR: 1.06 vs. 1.39), supporting that uncontrolled hyperglycemia may have a direct impact on fetal brain development. It is also likely that the associations between GDM and NDDs are mediated by GDM-related pregnancy complications (e.g., hypertensive disorders of pregnancy) or adverse birth outcomes (e.g., preterm birth and LGA) [89-92, 155-157]. In our study, however, additional adjustment for gestational hypertensive disorders, preterm birth, and LGA only attenuated the association between GDM and any NDD slightly (adjusted HR: 1.13 to 1.10), suggesting that the pathway through adverse outcomes may only contribute to a small part of the observed association. (Supplementary Table 4)

One explanation for the observed racial/ethnic differences may be differential glycemic control. Although non-Hispanic Whites have a lower GDM prevalence than Asians and Hispanics[1, 24, 25], we found non-Hispanic Whites with GDM had more A2 GDM (19.7% vs. 17.7%) than other race/ethnicities. (Supplementary Table 5) Nevertheless, both A1 and A2 GDM were associated with a higher risk of NDD (adjusted HR: A1 GDM, 1.91; A2 GDM, 2.03) among non-Hispanic Whites in our study. (Supplementary Table 6) Unfortunately, self-monitoring of glucose levels among mothers with GDM were not available in our data. It is also

possible that offspring born to mothers of other racial/ethnic groups receive NDD diagnosis later than offspring born to non-Hispanic White mothers[158]. For example, a study reported a significant delay in ASD diagnosis in non-Hispanic Blacks than non-Hispanic Whites[159]. In our study, we observed that non-Hispanic White offspring had more well-child visits than Hispanic and non-Hispanic Black offspring (non-Hispanic White: 2.6 annually vs. Hispanic: 2.3, non-Hispanic Black: 2.4). (Supplementary Table 6)

Future studies, particularly those with a longer follow-up, diverse geographical regions, and a larger sample size, are warranted to confirm our findings. Specifically, understanding the biological mechanism between GDM and NDDs and causes of racial/ethnic differences are essential to inform preventive strategies.

Strength and limitations

This study has several strengths. First, this study included 41.0% non-Hispanic White mothers and 59.0% mothers of other race/ethnicities, allowing us to examine racial/ethnic differences. Second, this study examined the associations of GDM with SLD, DCD, and their combinations, which have not been reported in previous studies. In addition, the ascertainments of GDM and NDDs were using approaches with high validity (GDM: accuracy 97.2%, PPV 72.5%; NDDs: PPV generally 82%-98%[150]). Furthermore, the incidence of any NDD (8.7%) in this study aligned with incidence estimated using US national insurance claim data (5-10% by 5 years old[78]) and the National Health Interview Survey (10.6% between 3-5 years old[79]). Also, SLD is the most prevalent NDD in both our study (6.8%) and the US national statistics (4-6% by 5 years old)[78]. Finally, we carefully controlled for potential confounders, including demographic, socioeconomic, clinical, and lifestyle factors.

A few limitations need be considered. First, the participants were from an academic center in a large US city, limiting the generalizability of the study findings to other settings. Compared to the general population in Los Angeles, the population in the service area include more non-Hispanic White (59.2% vs. 25.3%) and people with a high school degree or higher (94.4% vs. 80.0%)[131, 132]. Second, given the relatively short follow-up time (median 3.5 years), our study lacked power to evaluate NDDs with low incidence among young offspring, including ADHD and intellectual disability. Finally, we do not have measures of physical activity, diet, and environmental factors, such as air population, thus residual confounding may exist. These uncontrolled confounders were usually not available in previous studies[20], and their influence need to be assessed in future studies.

In conclusion, this study found that offspring born to non-Hispanic Whites with GDM had an increased risk of common NDDs and their combinations. This study is the first to describe the racial and ethnic differences in the association between GDM and NDDs, as well as the association between GDM and SLD, DCD, and their combinations.

6.6 Tables and Figures

Table 6.1. Participant characteristics and maternal/birth outcomes by gestational diabetes mellitus

	Overall N = 14,480	Non-GDM N = 13,063	GDM N = 1417
Maternal characteristics			
Maternal age at delivery, mean (SD)	33.7 (4.9)	33.5 (4.9)	34.8 (4.8)
Race/ethnicity, N (%)			
Asian	2882 (19.9)	2487 (19.0)	395 (27.9)
Hispanic	3154 (21.8)	2738 (21.0)	416 (29.4)
Non-Hispanic White	5934 (41.0)	5544 (42.4)	390 (27.5)
Other/unknown[1]	2510 (17.3)	2294 (17.6)	216 (15.2)
Area Deprivation Index (California) quartiles, N (%)			
Quartile 1	3198 (22.1)	2979 (22.8)	219 (15.5)
Quartile 2	3198 (22.1)	2908 (22.3)	290 (20.5)
Quartile 3	3198 (22.1)	2864 (21.9)	334 (23.6)
Quartile 4	3197 (22.1)	2794 (21.4)	403 (28.4)
Unknown	1689 (11.7)	1518 (11.6)	171 (12.1)
Married, N (%)	11,764 (81.2)	10,647 (81.5)	1117 (78.8)
Pre-pregnancy BMI (kg/m^2), mean (SD)	25.1 (5.2)	24.9 (5.0)	27.0 (6.0)
Pre-pregnancy BMI category, N (%)			
Underweight (<18.5 kg/m^2)	415 (2.9)	384 (2.9)	31 (2.2)
Normal weight (18.5-24.9 kg/m^2)	8099 (55.9)	7502 (57.4)	597 (42.1)
Overweight (25.0-29.9 kg/m^2)	3714 (25.6)	3303 (25.3)	411 (29.0)
Obese (≥30.0 kg/m^2)	2252 (15.6)	1874 (14.3)	378 (26.7)
The first pregnancy in the EHR, N (%)	10,375 (71.7)	9374 (71.8)	1001 (70.6)
Smoking during pregnancy, N (%)	178 (1.2)	151 (1.2)	27 (1.9)
Polycystic ovarian syndrome, N (%)	559 (3.9)	463 (3.5)	96 (6.8)
Mental disorders, N (%)			
Anxiety disorder	1732 (12.0)	1572 (12.0)	160 (11.3)
Bipolar disorder	61 (0.4)	54 (0.4)	7 (0.5)
Depression	1183 (8.2)	1044 (8.0)	139 (9.8)
Sleep disorder	599 (4.1)	547 (4.2)	52 (3.7)
Schizophrenia	97 (0.7)	84 (0.6)	13 (0.9)
Substance use (e.g., alcohol, cannabis, and cocaine)	332 (2.3)	287 (2.2)	45 (3.2)
Charlson Comorbidity Index[2], mean (SD)	0.2 (0.7)	0.2 (0.6)	0.3 (0.8)
Charlson Comorbidity Index category[2], N (%)			
0	11,953 (82.5)	10,675 (81.7)	1131 (79.8)

1	2019 (13.9)	1930 (14.8)	206 (14.5)
≥2	508 (3.5)	458 (3.5)	80 (5.6)
Maternal outcomes			
Gestational hypertension, N (%)	1486 (10.3)	1272 (9.7)	214 (15.1)
Pre-eclampsia/eclampsia, N (%)	1026 (7.1)	903 (6.9)	123 (8.7)
Total gestational weight gain (pounds)[3], mean (SD)	23.1 (14.2)	23.6 (14.2)	18.8 (13.3)
Excessive gestational weight gain[4], N (%)			
Yes	3359 (23.2)	239 (16.9)	3120 (23.9)
No	8841 (61.1)	967 (68.2)	7874 (60.3)
Unknown	2280 (15.7)	211 (14.9)	2069 (15.8)
Cesarean delivery, N (%)	4247 (29.5)	3755 (28.7)	519 (36.6)
Induced labor, N (%)	3226 (22.3)	2872 (22.0)	354 (25.0)
Birth outcomes			
Gestational age at delivery (weeks), mean (SD)	39.2 (1.8)	39.3 (1.8)	38.7 (1.8)
Preterm birth (<37 weeks of gestation), N (%)	995 (6.9)	839 (6.4)	156 (11.0)
Induced preterm birth, N (%)	153 (1.1)	132 (1.0)	21 (1.5)
Spontaneous (non-induced) preterm birth, N (%)	842 (5.8)	707 (5.4)	135 (9.5)
Birth weight (gram)[5], mean (SD)	3301.3 (530.3)	3307.5 (528.3)	3244.1 (545.4)
Large for gestational age[6], N (%)	1130 (7.8)	1001 (7.7)	129 (9.1)
Congenital malformation, N (%)	785 (5.4)	702 (5.4)	83 (5.9)
Shoulder dystocia, N (%)	141 (1.0)	125 (1.0)	16 (1.1)
Offspring characteristics			
Offspring male sex, N (%)	7542 (52.1)	6817 (52.2)	725 (51.2)
Offspring follow-up years, median (min-max)	3.5 (1.0-6.3)	3.5 (1.0-6.3)	3.5 (1.0-6.3)
Total number of routine offspring health visits[7], mean (SD)	8.3 (4.8)	8.3 (4.8)	8.1 (4.9)
Annual number of routine offspring health visits[7], mean (SD)	2.6 (1.8)	2.6 (1.8)	2.5 (1.8)

Abbreviations: BMI, body mass index; EHR: electronic health records; GDM, gestational diabetes mellitus; SD, standard deviation.

Notes:

[1] Other/unknown included non-Hispanic Black, Pacific Islander, American Indian/Alaska Native, multiple races, other, and unknown (~3.0%).

[2] Charlson Comorbidity Index was derived based on major chronic conditions, such as cardiovascular diseases, liver diseases, and cancer.

[3] ~15.7% pregnant individuals had unknown gestational weight gain.

[4] Excessive gestational weight gain was defined according to the Institute of Medicine (IOM) guideline.

[5] After adjusting for gestational age at delivery, birth weight was 27.4g higher in the GDM group than in the non-GDM group.

[6] Large for gestational age was defined as >90 percentile of birth weight by gestational age and sex.

[7] Routine newborn, infant, or child health visits on distinct days.

Table 6.2. Associations of gestational diabetes mellitus with neurodevelopmental disorders in all participants

	Unadjusted incidence rate (95% CI) per 1000 PY			HR (95% CI)	
N = 14,480	All participants	Non-GDM (reference)	GDM	Unadjusted	Adjusted
Speech/language disorder (SLD)	19.01 (17.84, 20.18)	18.64 (17.42, 19.87)	22.42 (18.35, 26.49)	1.20 (0.98, 1.46)	1.03 (0.84, 1.26)
Developmental coordination disorder (DCD)	5.47 (4.85, 6.09)	5.12 (4.50, 5.75)	7.76 (5.39, 10.13)	1.50 (1.07, 2.09)*	1.42 (1.01, 2.00)
Autism spectrum disorder (ASD)	2.90 (2.45, 3.35)	2.77 (2.31, 3.24)	4.10 (2.39, 5.82)	1.49 (0.94, 2.35)	1.22 (0.76, 1.96)
Other neurodevelopmental disorder (NDD)	1.81 (1.45, 2.17)	1.75 (1.38, 2.11)	2.41 (1.10, 3.71)	1.42 (0.79, 2.54)	1.42 (0.79, 2.57)
Any NDD	24.36 (23.02, 25.69)	23.77 (22.38, 25.15)	29.81 (25.10, 34.53)	1.26 (1.07, 1.47)*	1.13 (0.94, 1.35)
Combination of SLD and ASD	2.44 (2.02, 2.87)	2.30 (1.87, 2.73)	3.74 (2.06, 5.42)	1.62 (0.80, 3.29)	1.28 (0.77, 2.14)
Combination of SLD and DCD	2.23 (1.82, 2.64)	2.11 (1.69, 2.52)	3.39 (1.78, 5.01)	1.61 (0.96, 2.69)	1.43 (0.84, 2.42)

Abbreviations: ASD, autism spectrum disorder; BMI, body mass index; CI, confidence interval; DCD, developmental coordination disorder; GDM, gestational diabetes mellitus; HR, hazard ratio; NDD, neurodevelopmental disorder; PY, person-year; SLD, speech/language disorder.

Notes:

[1] HR and 95% CI was estimated using Cox regression models with a random effect for each pregnant individual to account for the correlation among siblings.

[2] Adjusted models controlled for maternal age, marital status, race/ethnicity (all participants only), Area Deprivation Index, pre-pregnancy BMI, smoking during pregnancy, Charlson Comorbidity Index, polycystic ovarian syndrome, depression, substance use, birth year, and offspring sex.

[3] Other NDDs included attention-deficit/hyperactivity disorder (unadjusted incidence rate 1.13 [95% CI 0.85, 1.41] per 1000 PY), behavioral disorder (0.49 [0.31, 0.68]), intellectual difficulty (0.18 [0.07, 0.30]), and learning disability (0.18 [0.07, 0.30]). They were combined into one group due to small number of events.

[4] The association between GDM and combination of ASD and DCD was not evaluated due to small number of events: unadjusted incidence rate 0.75 (95% CI 0.51, 0.98) per 1000 PY.

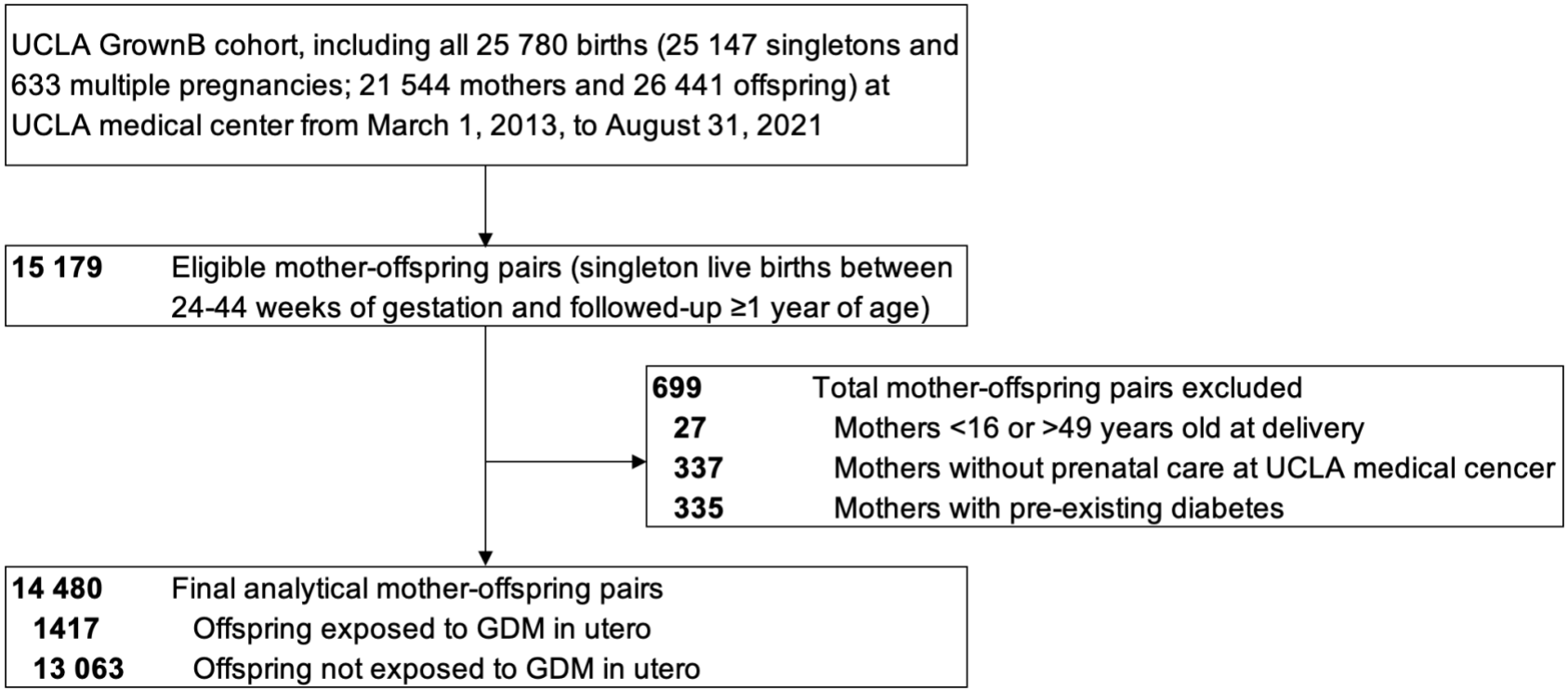
*Indicates statistically significant after correction of multiple comparisons using the Benjamini-Hochberg method.

Table 6.3. Associations of gestational diabetes mellitus with neurodevelopmental disorders by race/ethnicity

	Unadjusted incidence rate (95% CI) per 1000 PY		HR (95% CI)	
N = 14,480	Non-GDM (reference)	GDM	Unadjusted	Adjusted
Speech/language disorder (SLD)				
Non-Hispanic White (N = 5934)	13.03 (11.47, 14.60)	20.64 (13.21, 28.08)	1.62 (1.10, 2.40)*	1.59 (1.07, 2.35)*
Other race/ethnicities (N = 8456)	22.87 (21.08, 24.66)	23.10 (18.24, 27.95)	0.99 (0.79, 1.25)	0.91 (0.72, 1.15)
P-value for interaction by race/ethnicity			0.03	0.02
Developmental coordination disorder (DCD)				
Non-Hispanic White (N = 5934)	4.80 (3.86, 5.74)	11.18 (5.73, 16.63)	2.35 (1.38, 4.02)*	2.36 (1.37, 4.04)*
Other race/ethnicities (N = 8456)	5.35 (4.51, 6.19)	6.49 (3.95, 9.02)	1.18 (0.77, 1.80)	1.11 (0.72, 1.71)
P-value for interaction by race/ethnicity			0.05	0.03
Autism spectrum disorder (ASD)				
Non-Hispanic White (N = 5934)	1.49 (0.97, 2.01)	4.77 (1.24, 8.29)	3.28 (1.42, 7.58)*	3.16 (1.36, 7.37)*
Other race/ethnicities (N = 8456)	3.72 (3.01, 4.43)	3.85 (1.91, 5.80)	1.03 (0.59, 1.79)	0.92 (0.52, 1.61)
P-value for interaction by race/ethnicity			0.02*	0.02*
Other neurodevelopmental disorder (NDD)				
Non-Hispanic White (N = 5934)	1.92 (1.10, 3.71)	6.09 (2.12, 10.05)	3.20 (0.79, 2.54)*	3.12 (1.51, 6.47)*
Other race/ethnicities (N = 8456)	1.62 (1.15, 2.09)	1.02 (0.02, 2.02)	0.66 (0.24, 1.83)	0.61 (0.22, 1.70)
P-value for interaction by race/ethnicity			0.01*	0.01*
Any NDD				
Non-Hispanic White (N = 5934)	18.74 (16.86, 20.62)	35.16 (25.39, 44.94)	1.92 (1.41, 2.60)*	1.86 (1.36, 2.53)*
Other race/ethnicities (N = 8456)	27.55 (25.58, 29.52)	27.80 (22.45, 33.15)	1.00 (0.81, 1.24)	0.92 (0.74, 1.14)
P-value for interaction by race/ethnicity			<0.001*	<0.001*
Combination of SLD and ASD				
Non-Hispanic White (N = 5934)	1.04 (0.60, 1.49)	3.57 (0.45, 6.69)	3.49 (1.28, 9.50)*	3.79 (1.35, 10.61)*
Other race/ethnicities (N = 8456)	3.25 (2.57, 3.93)	3.81 (1.82, 5.79)	1.15 (0.65, 2.04)	1.01 (0.56, 1.81)
P-value for interaction by race/ethnicity			0.05	0.04
Combination of SLD and DCD				
Non-Hispanic White (N = 5934)	1.20 (0.72, 1.68)	4.38 (0.88, 7.87)	3.64 (1.49, 8.92)*	4.22 (1.69, 10.51)*
Other race/ethnicities (N = 8456)	2.79 (2.15, 3.42)	3.02 (1.24, 4.81)	1.08 (0.57, 2.03)	1.00 (0.53, 1.91)
P-value for interaction by race/ethnicity			0.03	0.03

Abbreviations: ASD, autism spectrum disorder; BMI, body mass index; CI, confidence interval; DCD, developmental coordination disorder; GDM, gestational diabetes mellitus; HR, hazard ratio; NDD, neurodevelopmental disorder; PY, person-year; SLD, speech/language disorder.

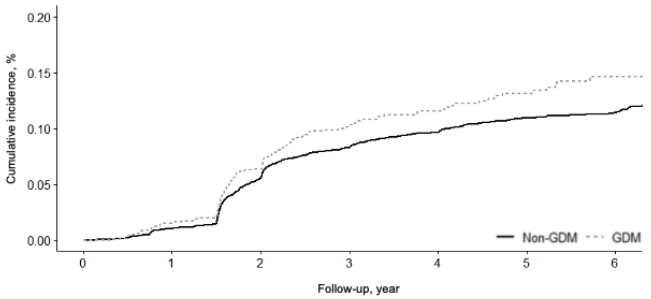
Notes: [1] HR and 95% CI was estimated using Cox regression models with a random effect for each pregnant individual to account for the correlation among siblings. [2] Adjusted models controlled for maternal age, marital status, Area Deprivation Index, pre-pregnancy BMI, smoking during pregnancy, Charlson Comorbidity Index, polycystic ovarian syndrome, depression, substance use, birth year, and offspring sex. [3] Other NDDs included attention-deficit/hyperactivity disorder (unadjusted incidence rate 1.13 [95% CI 0.85, 1.41] per 1000 PY), behavioral disorder (0.49 [0.31, 0.68]), intellectual difficulty (0.18 [0.07, 0.30]), and learning disability (0.18 [0.07, 0.30]). They were combined into one group due to small number of events. [4] The association between GDM and combination of ASD and DCD was not evaluated due to small number of events: unadjusted incidence rate 0.75 (95% CI 0.51, 0.98) per 1000 PY. *Indicates statistically significant after correction of multiple comparisons using the Benjamini-Hochberg method.



Abbreviations: GDM, gestational diabetes mellitus; ICD, International Statistical Classification of Diseases; UCLA, University of California, Los Angeles.
Note: Pre-pregnancy diabetes were identified using ICD-9 codes: 250.x and ICD-10 codes: E10.x, E11.x, E13.x.

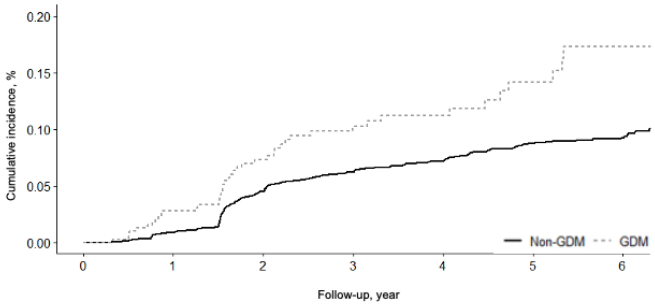
Figure 6.1. Sample selection flow diagram. This graph describes the steps for sample selection from the Grown B cohort; the eligibility criteria of the study were singleton live births between 24-44 weeks of gestation and followed-up ≥1 year of age.

A. All participants (N = 14 480)



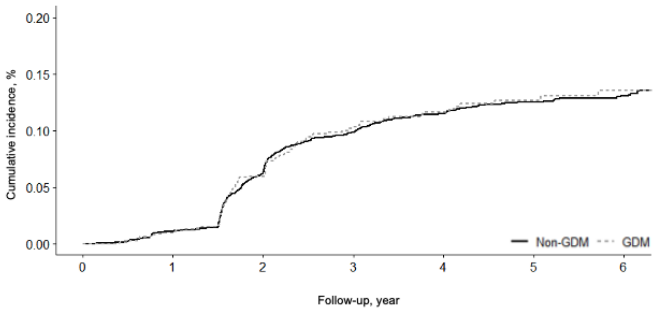
No. at risk							
Non-GDM	13063	12932	9728	7175	5019	3205	1777
GDM	1417	1396	1054	764	526	345	206

B. Non-Hispanic White (N = 5934)



No. at risk							
Non-GDM	5544	5496	4196	3118	2194	1400	769
GDM	390	379	272	207	149	101	59

C. Other race/ethnicity (N = 8546)



No. at risk							
Non-GDM	7519	7436	5532	4057	2825	1805	1008
GDM	1027	1017	782	557	377	244	147

Abbreviations: GDM, gestational diabetes mellitus; NDD, neurodevelopmental disorder.

Figure 6.2. Cumulative unadjusted incidences of any neurodevelopmental disorder by gestational diabetes mellitus in all participants and by race/ethnicity. A to C, cumulative unadjusted incidences of any neurodevelopmental disorder by gestational diabetes mellitus (GDM vs. non-GDM): (A) all participants, (B) non-Hispanic White, (C) other race/ethnicities.

Supplementary Table 6.1. Algorithms for ascertaining neurodevelopmental disorders

	Algorithms
Autism spectrum disorder (ASD)	At ≥1 year old with ≥2 dates with diagnosis
Attention-deficit/hyperactivity disorder (ADHD)	At ≥2 years old, with any of the following: 1. ≥2 dates with diagnosis; 2. ≥2 dispensing of atomoxetine, clonidine, guanfacine, (dextro/lisdex) amphetamine, (dex)methylphenidate; 3. ≥1 dx, and ≥1 dispensing
Learning difficulty	At ≥2 years old with ≥1 diagnosis
Speech/language disorder (SLD)	At ≥1.5 years old with ≥2 dates with diagnosis
Intellectual disability	At ≥2 years old with ≥2 dates with diagnosis
developmental coordination disorder (DCD)	Any age with ≥2 dates with diagnosis
Behavioral disorder	At ≥2 years old with ≥2 dates with diagnosis

Supplementary Table 6.2. Diagnosis codes

	ICD-9	ICD-10
Maternal outcomes		
Gestational diabetes mellitus	648.8x	O24.4x
Pre-eclampsia/eclampsia	642.4x, 642.5x, 642.6x	O14.x, O15.x
Gestational hypertension	642.3x, 642.9x	O13.x, O16.x
Induction of labor	73.01x, 73.1x, 73.4x	3E003VJ, 3E0P7GC, 3E0P7VZ, 0U7C7ZZ, 0U7C7DZ
Birth outcomes		
Neonatal hypoglycemia	775.6x	P70.3, P70.4
Shoulder dystocia	660.4	O66.0
Congenital malformation	740.x-759.x	Q00.x-Q99.x
Chronic disorders		
Pre-existing diabetes	250.x	E10.x, E11.x, E13.x
Polycystic ovary syndrome (PCOS)	256.4x	E28.2x
Mental disorders		
Depression	296.2x, 296.3x, 296.8x, 300.4x, 311.x	F32.x, F33.x
Bipolar disorder	296.4x, 296.5x, 296.6x, 296.7x	F25.x, F31.x
Schizophrenia/psychosis	295.x, 296.89x, 296.9x, 298.x	F06.x, F20.x, F22.x, F23.x, F28.x F29.x
Anxiety disorder	300.0x, 300.2x, 308.x, 309.x	F41.x, F40.8x, F40.9x, F43.2x
Sleep disorder	307.4, 327.x, 780.5x, 347.x	F51x, G47.x
Substance use (e.g., alcohol, cannabis, and cocaine)	303.x, 304.x, 305.x	F10.x-F19.x
Neurodevelopmental disorders (NDD)		
Autism spectrum disorder (ASD)	299.x except 299.1x	F84.x except F84.2x, F84.3x
Attention-deficit/hyperactivity disorder (ADHD)	314.x	F90.x
Learning difficulty	315.0x, 315.1x, 315.2x	F81.0x, F81.2x, F81.9x, R48.0
Speech/language disorder (SLD)	315.3x except 315.34	F80.x except F80.4x, H93.25
Intellectual disability	317.x, 318.x, 319.x	F70.x-F79.x
developmental coordination disorder (DCD)	315.4x	F82.x
Behavioral disorder	312.x, 313.x	F63.x, F91.x, F93.8x, F93.9x, F94.x, F98.8x, F98.9x

Abbreviation: ICD, International Classification of Diseases.

Supplementary Table 6.3. Diagnosis codes and weights for calculating the Charlson Comorbidity Index

Comorbidity	ICD-9	ICD-10	Weight
Myocardial infarction	410.x, 412.x	I21.x, I22.x, 125.2	1
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0	1
Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 47.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, 177.1, 179.0, I179.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	1
Cerebrovascular disease	362.34, 430.x-438.x	G45.x, G46.x, H34.0, I60.x-I69.x	1
Dementia	290.x, 294.1, 331.2	F00.x-F03.x, F05.1, G30.x, G31.1	1
Chronic pulmonary disease	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3	1
Rheumatologic disease	446.5, 710.0-710.4, 714.0- 714.2, 714.8, 725.x	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0	1
Mild liver disease	531.x-534.x	K25.x-K28.x	1
Diabetes without chronic complications	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4	1
Diabetes with chronic complications	250.0-250.3, 250.8, 250.9	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	2
Hemiplegia or paraplegia	250.4-250.7	E10.2-E10.5, El0.7, E11.2-Ell11.5, E11.7, E12.2-E12.5, E12.7, E13.2- E13.5, E13.7, E14.2-E14.5, E14.7	2
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0-583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	I12.0, I113.1, N03.2-N03.7, N05.2- N05.7, N18.x, N19.x, N25.0, Z49.0- Z49.2, Z94.0, Z99.2	2
Any malignancy, including leukemia and lymphoma	140.x-172.x, 174.x-195.8, 200.x-208.x, 238.6	C00.x-C26.x, C30.x-C34.x, C37.x- C41.x, C43.x, C45.x-C58.x, C60.x- C76.x, C81.x-C85.x, C88.x, C90.x-C97.x	2
Moderate or severe liver disease	456.0-456.2, 572.2-572.8	I85.0, I185.9, I186.4, I198.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	3
Metastatic solid tumor	196.x-199.x	C77.x-C80.x	6
AIDS/HIV	042.x-044.x	B20.x-B22.x, B24.x	6

Abbreviations: AIDS/HIV, acquired immune deficiency syndrome/human immunodeficiency virus; ICD, International Classification of Diseases.

Supplementary Table 6.4. Sensitivity analyses for the association between gestational diabetes mellitus and any neurodevelopmental disorder

	HR (95% CI)	
N = 14 480 (GDM vs. non-GDM [reference])	Unadjusted	Adjusted
Sensitivity analysis 1: stratified by four racial/ethnic groups		
Any NDD	1.26 (1.07, 1.47)*	1.13 (0.94, 1.35)
Non-Hispanic White	1.92 (1.41, 2.60)*	1.86 (1.36, 2.53)*
Asian	1.04 (0.72, 1.51)	0.96 (0.66, 1.40)
Hispanic	1.05 (0.77, 1.42)	1.00 (0.73, 1.38)
Other race/ethnicities	0.79 (0.47, 1.31)	0.74 (0.44, 1.23)
P-value for interaction by race/ethnicity	<0.001*	<0.001*
Sensitivity analysis 2: stratified by ICD-9 (N = 4441) and ICD-10 (N = 10 039) codes		
Any NDD (GDM diagnosed prior to 2015/10/01, ICD-9 codes)	1.49 (0.94, 2.35)	1.22 (0.76, 1.96)
Non-Hispanic White	1.62 (0.99, 2.65)	1.55 (0.95, 2.54)
Other race/ethnicities	0.97 (0.69, 1.37)	0.89 (0.63, 1.26)
P-value for interaction by race/ethnicity	0.10	0.07
Any NDD (GDM diagnosed post 2015/10/01, ICD-10 codes)	1.32 (1.06, 1.64)*	1.18 (0.94, 1.47)
Non-Hispanic White	2.15 (1.47, 3.16)*	2.07 (1.41, 3.04)*
Other race/ethnicities	1.03 (0.79, 1.34)	0.96 (0.74, 1.26)
P-value for interaction by race/ethnicity	0.002*	0.001*
Sensitivity analysis 3: stratified by A1 GDM A1 (N = 1158) and A2 GDM (N = 259)		
Any NDD, GDM A1	1.18 (0.97, 1.44)	1.06 (0.87, 1.29)
Non-Hispanic White	1.87 (1.32, 2.66)*	1.91 (1.34, 2.72)*
Other race/ethnicities	0.93 (0.74, 1.18)	0.86 (0.68, 1.09)
P-value for interaction by race/ethnicity	0.001*	<0.001*
Any NDD, GDM A2	1.60 (1.13, 2.27)*	1.39 (0.98, 1.98)
Non-Hispanic White	2.09 (1.15, 3.81)*	2.03 (1.11, 3.73)*
Other race/ethnicities	1.35 (0.88, 2.06)	1.20 (0.78, 1.85)
P-value for interaction by race/ethnicity	0.27	0.21
Sensitivity analysis 4: additionally adjusting for hypertensive disorders of pregnancy, LGA, and preterm birth		
Any NDD	1.26 (1.07, 1.47)*	1.10 (0.92, 1.32)
Non-Hispanic White	1.92 (1.41, 2.60)*	1.86 (1.36, 2.56)*
Other race/ethnicities	1.00 (0.81, 1.24)	0.90 (0.73, 1.12)
P-value for interaction by race/ethnicity	<0.001*	<0.001*

Abbreviations: BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; HR, hazard ratio; LGA, large for gestational age; ICD, International Classification of Diseases; NDD, neurodevelopmental disorder.
Notes: [1] HR and 95% CI was estimated using Cox regression models with a random effect for each pregnant individual to account for the correlation among siblings. [2] Adjusted models controlled for maternal age, marital status, race/ethnicity (all participants only), Area Deprivation Index (California), pre-pregnancy BMI, smoking during pregnancy, Charlson Comorbidity Index, polycystic ovarian syndrome, depression, substance use, birth year, and offspring sex. Sensitivity analysis 4 additionally adjusted for hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia/eclampsia), LGA, and preterm birth. *Indicates statistically significant after correction of multiple comparisons using the Benjamini-Hochberg method.

Supplementary Table 6.5. Participant characteristics among mothers with gestational diabetes mellitus by race/ethnicity

	Non-Hispanic White (N = 390)	Other race/ethnicities				
		Combined (N = 1027)	Asian (N = 395)	Hispanic (N = 416)	Non-Hispanic Black (N = 42)	Other/unknown (N = 174)
Glucose lowering medication use, N (%)	77 (19.7)	182 (17.7)	75 (19.0)	66 (15.9)	6 (14.3)	35 (20.1)
Insulin only, N (%)	43 (11.0)	94 (9.2)	38 (9.6)	33 (7.9)	1 (2.4)	22 (12.6)
Metformin/glyburide/combinations, N (%)	34 (8.7)	88 (8.6)	37 (9.4)	33 (7.9)	5 (11.9)	13 (7.5)
Maternal outcomes						
Gestational hypertension, N (%)	68 (17.4)	146 (14.2)	49 (12.4)	61 (14.7)	12 (28.6)	24 (13.8)
Pre-eclampsia/eclampsia, N (%)	32 (8.2)	91 (8.9)	28 (7.1)	47 (11.3)	4 (9.5)	12 (6.9)
Total gestational weight gain (pounds)[1], mean (SD)	21.2 (13.6)	17.9 (13.0)	19.5 (12.0)	15.6 (13.9)	17.6 (14.4)	19.7 (12.3)
Excessive gestational weight gain[2], N (%)						
Yes	85 (21.8)	154 (15.0)	46 (11.6)	71 (17.1)	8 (19.0)	29 (16.7)
No	257 (65.9)	710 (69.1)	299 (75.7)	275 (66.1)	19 (45.2)	117 (67.2)
Unknown	48 (12.3)	163 (15.9)	50 (12.7)	70 (16.8)	15 (35.7)	28 (16.1)
Cesarean delivery, N (%)	145 (37.2)	374 (36.4)	132 (33.4)	149 (35.8)	19 (45.2)	74 (42.5)
Induced labor, N (%)	115 (29.5)	239 (23.3)	89 (22.5)	106 (25.5)	8 (19.0)	36 (20.7)
Birth outcomes						
Gestational age at delivery (weeks), mean (SD)	38.8 (1.7)	38.7 (1.8)	38.9 (1.5)	38.5 (2.1)	38.5 (1.7)	38.7 (1.8)
Preterm birth (<37 weeks of gestation), N (%)	36 (9.2)	120 (11.7)	35 (8.9)	57 (13.7)	6 (14.3)	22 (12.6)
Induced preterm birth, N (%)	8 (2.1)	13 (1.3)	4 (1.0)	5 (1.2)	2 (4.8)	2 (1.1)
Spontaneous (non-induced) preterm birth, N (%)	28 (7.2)	107 (10.4)	31 (7.8)	52 (12.5)	4 (9.5)	20 (11.5)
Birth weight (gram), mean (SD)	3300 (530)	3220 (550)	3200 (494)	3260 (494)	3130 (519)	3230 (587)
Large for gestational age[3], N (%)	35 (9.0)	94 (9.2)	26 (6.6)	44 (10.6)	2 (4.8)	22 (12.6)
Congenital malformation, N (%)	26 (6.7)	57 (5.6)	16 (4.1)	26 (6.3)	0 (0.0)	15 (8.6)
Shoulder dystocia, N (%)	2 (0.5)	14 (1.4)	3 (0.8)	6 (1.4)	0 (0.0)	5 (2.9)
Offspring male sex, N (%)	190 (48.7)	535 (52.1)	206 (52.2)	213 (51.2)	24 (57.1)	92 (52.9)
Laboratory results at GDM diagnosis	N = 257	N = 685	N = 294	N = 257	N = 22	N = 112
Gestational age (weeks) at GDM diagnosis, mean (SD)	26.6 (4.2)	26.1 (4.7)	25.8 (4.5)	26.3 (4.8)	28.4 (4.5)	26.2 (4.8)
Fasting glucose level (mg/dL) at GDM diagnosis, mean (SD)	86.4 (11.2)	86.4 (10.1)	84.6 (9.8)	88.7 (10.8)	86.2 (8.3)	86.1 (8.6)
Fasting glucose level ≥95 mg/dL at GDM diagnosis, N (%)	58 (22.6)	143 (20.9)	48 (16.3)	70 (27.2)	4 (18.2)	21 (18.8)

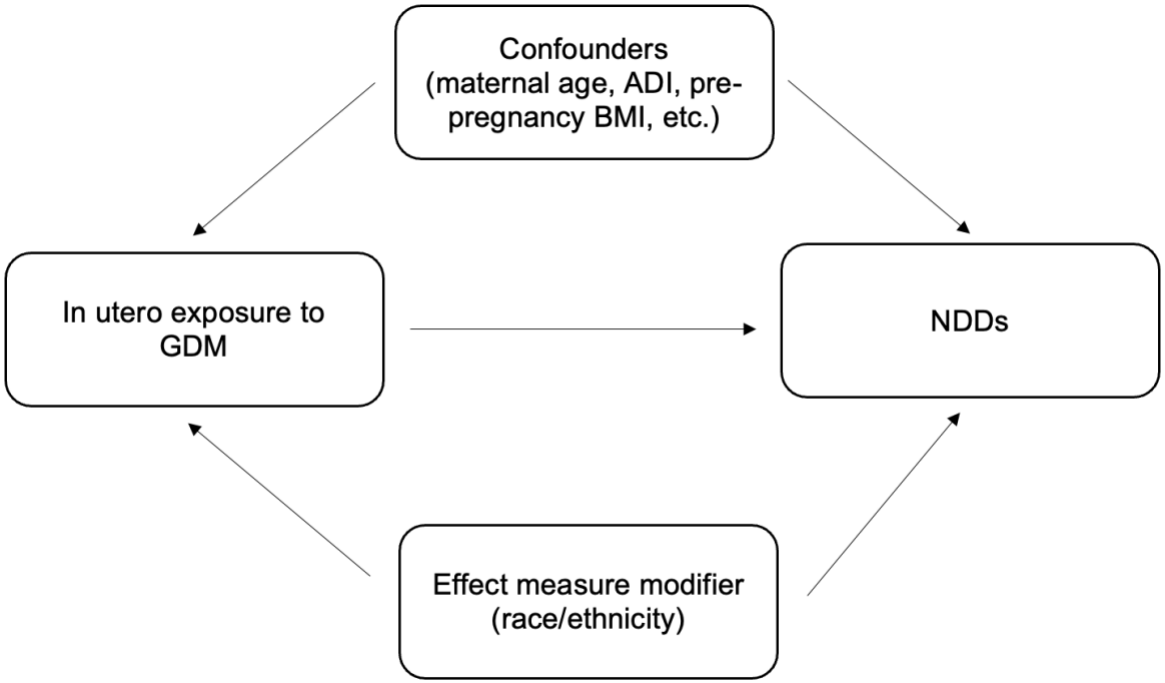
Abbreviations: GDM, gestational diabetes mellitus; SD, standard deviation.

Notes: [1] ~14.9% pregnant individuals had unknown gestational weight gain. [2] Excessive gestational weight gain was defined according to the Institute of Medicine (IOM) guideline. [3] Large for gestational age was defined as >90 percentile of birth weight by gestational age and sex.

Supplementary Table 6.6. Offspring characteristics by race/ethnicity

	Non-Hispanic White (N = 5934)	Other races/ethnicities				
		Combined (N = 8546)	Asian (N = 2882)	Hispanic (N = 3154)	Non-Hispanic Black (N = 682)	Other/unknown (N = 1828)
Offspring follow-up years, median (min-max)	3.5 (1.0-6.3)	3.5 (1.0-6.3)	3.5 (1.0-6.3)	3.7 (1.0-6.3)	3.7 (1.0-6.3)	3.3 (1.0-6.3)
Total number of routine offspring health visits[1], mean (SD)	8.2 (5.0)	8.3 (4.7)	9.3 (4.3)	7.5 (5.0)	7.8 (4.6)	8.1 (4.7)
Annual number of routine offspring health visits[1], mean (SD)	2.6 (1.9)	2.6 (1.8)	2.9 (1.7)	2.3 (1.8)	2.4 (1.6)	2.7 (1.9)

Abbreviation: SD, standard deviation.
Note: [1] Routine newborn, infant, or child health visits on distinct days.



Abbreviations: ADI, Area Deprivation Index; BMI, body mass index; CCI, Charlson Comorbidity Index; GDM, gestational diabetes mellitus; NDD, neurodevelopmental disorder.

Supplementary Figure 6.1. Directed acyclic graph for the total effect of associations between gestational diabetes mellitus and neurodevelopmental disorders. Exposure was GDM; outcome was NDDs; confounders included maternal age, ADI, pre-pregnancy BMI, etc.; race/ethnicity was considered an effect measure modifier.

7 CHAPTER SEVEN: GESTATIONAL DIABETES MELLITUS AND RISK OF HYPERTENSION LATER IN LIFE

7.1 Abstract

Objectives

Gestational diabetes mellitus (GDM) is associated with a substantially increased risk of type 2 diabetes, but the association between GDM and hypertension later in life remains unclear. We conducted a systematic literature review and meta-analysis to examine the association of GDM and hypertension among mothers. We also performed a quantitative bias analysis to quantify the impact of uncontrolled confounding due to antenatal psychological stress.

Methods

We searched electronic databases (PUBMED, EMBASE, and Web of Science) through November 2022. Eligible studies were cohort studies that reported the association of GDM with hypertension among mothers. We calculated and pooled unadjusted risk ratio (RR) with 95% confidence interval (CI) for each study using a random effects model. We performed the quantitative bias analysis using the bias formula approach.

Results

The 15 cohort studies included a total of 3,959,520 participants and 106,560 cases of hypertension. The median/mean duration of follow-up were 2 to 20 years. GDM was associated with an elevated rate (pooled RR: 1.78 [95% CI: 1.47, 2.17]) of hypertension later in life. The RR was lower among cohorts assessing incident hypertension (1.58 [95% CI: 1.29, 1.95]) than those assessing prevalent hypertension (2.60 [95% CI: 2.40, 2.83]). The quantitative bias analysis revealed that if the uncontrolled confounder of antenatal psychological stress was

additionally adjusted, the positive association between GDM and hypertension later in life would attenuate slightly but remain positive.

Conclusion

The results suggest that GDM is positively associated with hypertension later in life.

7.2 Introduction

Gestational diabetes mellitus (GDM), or glucose intolerance first recognized during pregnancy, is one of the most common pregnancy complications[1, 24]. GDM affects around 6-15% of pregnancies globally, with a rising prevalence during the past decades[1, 24]. It is well-recognized that GDM is associated with a substantially higher (almost 10-fold) risk of subsequent type 2 diabetes[52], and thus clinical guidelines[160, 161] recommend a universal screening program for type 2 diabetes mellitus among individuals with GDM. Nevertheless, there is no systematic literature review on the association between GDM and hypertension later in life.

Hypertension, which affects more than 20% of adults globally, is one of the most critical risk factors for cardiovascular diseases, renal diseases, and dementia[95-97]. GDM may be associated with hypertension directly through metabolic and vascular damage[98], or indirectly through pregnancy-induced hypertension[90, 99] and type 2 diabetes[52]. In the past decade, several studies have investigated the association between GDM and hypertension later in life, but the findings have been conflicting. Specifically, although multiple studies in North America, Europe, and Asia have observed a positive association between GDM and hypertension later in life[100-103], other large studies, including the multinational prospective Hyperglycemia and Adverse Pregnancy Outcome Follow-Up Study (HAPO-FUS), did not find a significant association[104, 105].

Furthermore, GDM and hypertension share many common risk factors, including demographics (e.g., advanced age and race/ethnicity), socioeconomic status (e.g., income and

education), lifestyle factors (e.g., smoking, unhealthy diet, sedentary lifestyle, and overweight/obesity), and psychological stress (an umbrella term for a range of phenomena, including stress, depression, and anxiety[162])[1, 24, 163]. While data for demographics, socioeconomic status, and lifestyle factors are often available for confounding control, psychological stress has not been controlled for in previous studies. Given that antenatal psychological stress is independently associated with a higher risk for both GDM[1, 24, 164-167] and hypertension[163, 168-171], there may be uncontrolled confounding for the association between GDM and hypertension later in life due to psychological stress.

To our knowledge, a comprehensive review of the association between GDM and hypertension later in life is lacking. As such, the aim of this study was to conduct a systematic literature review and meta-analysis of cohort studies to investigate the rate of hypertension in individuals with GDM. In addition, we performed a bias analysis to account for potential uncontrolled confounding caused by antenatal psychological stress.

7.3 Methods

This systematic literature review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[172] guideline.

Search Strategy

We performed literature searches without language restriction in electronic databases PubMed, EMBASE, and Web of Science from inception to 11/16/2022. We also performed a manual search for the references of the included studies. (Supplementary Table 1)

Study Selection

The inclusion criteria were: 1) the study population was pregnant individuals (biological females) of any age; 2) study exposure included GDM (i.e., GDM lab results, self-report, report

from medical professionals, medical records, or birth certificates); 3) study outcome included hypertension (i.e., measured blood pressures, self-report, report from medical professionals, or medical records) subsequent to the index pregnancy and post the 12-week postpartum period; 4) measure of association and variability (i.e., risk ratio [RR], hazard ratio [HR], odds ratio [OR], or incidence rate ratio [IRR]) between GDM and hypertension were reported or could be calculated; 5) cohort studies (including nested case-control studies). We only included cohort studies to assure the temporal relationship between GDM and hypertension later in life[173].

The exclusion criteria were 1) studies without original data or comparison groups (e.g., case studies, editorials, and reviews) and conference abstracts; 2) non-cohort studies (e.g., ecological studies, cross-sectional studies, and case-control studies); 3) the measure of association or variability between GDM and hypertension was not reported or could not be calculated; 4) only joint association of GDM and another condition (e.g., gestational hypertension, preeclampsia, and obesity) with hypertension was reported and independent association between GDM and hypertension could not be extracted/calculated; 5) no reference group; and 6) duplicate publication/population. For publications with duplicate populations, we included the studies with the largest sample size.

Two investigators independently screened titles and abstracts (X. Liu and X. Li) first, and then full texts (X. Liu and R. Wen) for eligibility. Disagreements were resolved through group discussions. (Figure 1)

Data extraction

We extracted the following information from the included studies: study characteristics (i.e., first author name, publication year, study country, study design, cohort name/data source, sample size, and length of follow-up), participant characteristics (i.e., maternal age at baseline

and race/ethnicity), exposure ascertainment, exposure prevalence, outcome ascertainment, outcome rate (prevalence or incidence), multivariable-adjusted measures of association and variability, statistical model, and adjusted and/or matched covariates. We requested data from investigators to obtain missing information. For studies that reported multiple estimates of association, we extracted the estimate with the greatest level of adjustment for potential confounders.

Two investigators independently extracted data (X. Liu and R. Wen), and discrepancies were resolved through group discussions.

Data synthesis and analysis

We chose RR as the measure of effect estimates. As the rate of hypertension was relatively low (≤20%) in most studies, we used HR, IRR, and OR to approximate RR. In two studies (Tam 2012[174] and Heida 2015[105]), where the rate of hypertension was >20% and OR was used as the measure of association, we converted OR to RR using an established method previously described (i.e., $RR = OR/(1-p_0+p_0*OR)$, p_0 = proportion of outcome in the reference group)[175, 176]. We estimated the standard errors (SE) of studies on the logarithm scale from 95% CI (i.e., SE = (ln(upper limit)-ln(lower limit))/3.92).

Due to the high heterogeneity, we summarized the effect estimates using a random effects model[177]. We assessed the heterogeneity across studies using Cochran's Q test[178] and I^2 statistics[179] (level of heterogeneity: low ≤ 25%; moderate: 25-75%; high: >75%). We also assessed publication bias using funnel plots, Begg's test[180] and Egger's test[181]. We additionally performed stratified analyses by measure of outcome (incident vs. prevalent cases), measure of association (RR, HR, vs. OR), study design (prospective vs. retrospective cohort), length of follow-up (<5, 5-15, vs. ≥15 years), study quality (poor vs. fair/good), study location (Asia

[China and Singapore] vs. North America [United States and Canada], vs. Europe [Finland, Netherlands, Ireland, France, Sweden, United Kingdom, and Denmark]), and adjustment of potential mediators (yes vs. no). To examine the influence of each study, we conducted sensitivity analyses by excluding studies one by one from the meta-analyses.

Qualitative bias assessment

We assessed the risk of bias for the included studies using the Newcastle-Ottawa Scale (NOS) for Cohort Studies[182]. The NOS contains three domains: selection (4 items, maximum one star per item), comparability (1 item, maximum 2 stars), and outcome (3 items, maximum one star per item). We rated the quality of the studies by awarding stars in each domain following the guidelines of the NOS ("good": 3/4 stars in selection, 1/2 stars in comparability, and 2/3 stars in outcomes; "fair": 2 stars in selection, 1/2 stars in comparability, and 2/3 stars in outcomes; "poor": 0/1 star in selection, or 0 stars in comparability, or 0/1 star in outcomes). Two investigators independently assessed risk of bias (X. Liu and R. Wen), and discrepancies were resolved through group discussions.

Quantitative bias analysis

We performed a quantitative bias analysis[183-185] to explore the potential impact of uncontrolled confounding due to antenatal psychological stress, as it is an independent risk factor for both GDM[1, 24, 164-167] and hypertension[163, 168-171], but it was unadjusted in most studies. The hypothesized directed acyclic diagram (DAG) is shown in Supplementary Figure 1. First, we assigned a wide range of values for the prevalence of antenatal psychological stress among mothers without GDM (p_0: 15%) and with GDM (p_1: 15% to 40% by increments of 5% [≥30% was unlikely])[16-19], and the RR between antenatal psychological stress and hypertension (RR_{UD}:

1.0 to 5.0 by increments of 0.5 [≥3.0 was unlikely]) [20-23]. Second, we obtain a range of bias factors using the formula[186]:

$$\text{Bias factor} = \frac{RR_{UD} \times p_1 + 1 - p_1}{RR_{UD} \times p_0 + 1 - p_0}$$

Lastly, we divided the observed RR of each study by a bias factor and pooled the bias-adjusted RR using a random effects model. We repeated the last step for each bias factor to get a range of pooled bias-adjusted RR. The detailed steps of quantitative bias analysis were described in previous publications[183, 185] and Supplementary Table 2.

All statistical analysis was performed using R version 4.1.2 (R package "Metafor"[187]). P-value < 0.05 was considered statistically significant.

7.4 Results

Search results and study characteristics

In the 1,301 records identified from the initial search, we excluded 1,275 records based on title and abstract, leaving 26 studies for further evaluation. We subsequently excluded 13 studies after full-text assessment: 8 did not report an independent measure of association/variability, 3 were duplicate populations, 1 was not a cohort study, and 1 did not have a reference group. We additionally identified 7 records based on citation search and excluded 5 studies: 3 did not report the outcome, 1 was duplicate population, and 1 was not a cohort study. (Figure 1) 15 cohort studies met the inclusion criteria, with a total of 3,959,520 participants and 106,560 cases of hypertension. The 15 studies were published between 2010 and 2022, with 8 prospective and 7 retrospective cohorts. The studies varied in sample size, ranging from 139 to 1,518,990. The median/mean duration of follow-up ranged from >2 to 20 years, and the mean maternal age at baseline ranged from 24 to 34 years old. Of the 15 studies, 7 were in Europe, 4

were in North America, 3 were in Asia, and 1 was multinational. The prevalence of GDM ranged from 1.8% to 14.2%.

GDM was self-reported, extracted from medical databases, or ascertained using OGTT tests. There was also heterogeneity of the GDM screening methods across studies. Hypertension was self-reported, extracted from medical databases, or ascertained based on measured blood pressure or medication use. Studies reported OR, HR, or RR, and controlled for potential confounders including maternal age, BMI, race/ethnicity, parity, socioeconomic status, and smoking. Other potential confounders (e.g., physical activity and diet) were not consistently controlled for, and potential mediators (e.g., pre-eclampsia/gestational hypertension or subsequent GDM/diabetes) were controlled for in some studies. 4 studies were rated as poor quality, mainly due to lacking confounding control or controlling for covariates that were measured at follow-up (e.g., smoking or income at follow-up). (Table 1, Table 2, and Supplementary Table 3)

Gestational diabetes mellitus and hypertension later in life

Of the 15 cohort studies, 11 found that GDM was significantly associated with hypertension later in life, while 4 did not observe a significant association. The random effects meta-analysis indicated that GDM was associated with a higher rate of hypertension (pooled RR,1.78 [95% CI: 1.47, 2.17]), however, with a high heterogeneity for the effect estimate (I^2, 98.0%; $p<0.001$ for heterogeneity). (Figure 2) In the sensitivity analyses, the results did not change substantially after excluding studies one by one, with pooled RRs ranging from 1.72 to 1.89 and I^2 ranging from 97.1%-98.2%. (Supplementary Table 4)

We found that the pooled RR for the association between GDM and hypertension later in life was 1.58 (95% CI: 1.29, 1.95) among studies assessing incident hypertension, lower than

2.60 (95% CI: 2.40, 2.83) among studies assessing prevalent hypertension. We did not find evidence of heterogeneity in the stratified analyses by measure of association (RR, HR, vs. OR), study design (prospective vs. retrospective cohort), length of follow-up (<5 vs. 5-15, ≥15 years), study location (Asia, North America, vs. Europe), study quality (poor vs. fair/good), and adjustment of potential mediators (yes vs. no). (Table 3)

Publication bias

In addition, the funnel plot was generally symmetrical. (Supplementary Figure 2) The p-values for Egger's test and Begg's test were 0.93 and 0.83, respectively, indicating no evidence of publication bias.

Quantitative bias analysis of uncontrolled confounding of psychological stress

The quantitative bias analysis indicated that additionally adjusting for the uncontrolled antenatal psychological stress would attenuate the positive association between GDM and hypertension later in life. However, based on plausible values of the prevalence of antenatal psychological stress among mothers with and without GDM and the RR between antenatal psychological stress and hypertension, the uncontrolled confounding is unlikely to fully explain the observed positive association. To attenuate the RR between GDM and hypertension later in life to close to 1 (null association), antenatal psychological stress would need to have a much higher prevalence in mothers with GDM (>40%) than those without GDM (15%) and have a strong positive association with hypertension risk (RR>5). (Figure 3)

7.5 Discussion

In this meta-analysis of 15 cohort studies, including 3,959,520 participants and 106,560 cases of hypertension, GDM was positively associated with hypertension later in life (pooled RR: 1.78 [95% CI: 1.47, 2.17]). The RR was lower among studies assessing incident

hypertension (1.58 [95% CI: 1.29, 1.95]) than those assessing prevalent hypertension (2.60 [95% CI: 2.40, 2.83]). The quantitative bias analysis indicated that the observed positively association was unlikely to be attenuated to null by additionally adjusting for the uncontrolled confounder of antenatal psychological stress.

Our findings advance the current state of knowledge about the association between GDM and adverse cardiometabolic outcomes among mothers. A previous meta-analysis has revealed that GDM was associated with a substantially elevated risk (RR: 9.51 [95% CI: 7.14, 12.67]) of subsequent type 2 diabetes[52]. In addition, two recent meta-analyses have found that GDM is associated with a higher risk of subsequent cardiovascular diseases (CVD) (Kramer 2019[54] [cohort and case-control]: 1.98 [95% CI: 1.57, 2.50] and Li 2018[55] [cohort]: 1.74 [95% CI: 1.28-2.35]). Although these two meta-analyses did not specify whether hypertension was considered a CVD, most of the included studies in the meta-analyses defined CVD as coronary heart disease (ischemic heart disease), myocardial infarction, cerebrovascular disease (stroke or transient ischemic attack), or peripheral vascular disease[54, 55]. Furthermore, these two meta-analyses used the counts of CVD cases in the mothers with GDM and non-GDM to estimate unadjusted RRs[54, 55], which did not account for potential confounders and may lead to an overestimation of the association. In contrast, our study pooled adjusted RRs controlling for potential confounders. Another meta-analysis on the association between GDM and CVD risk factors, including blood pressure, has found that mothers with GDM had higher systolic blood pressure (2.47 mmHg [95% CI: 1.74, 3.40]) and diastolic blood pressure (1.89 mmHg [95% CI: 1.32, 2.46]) than those without GDM[188]. This study aligns with our results, but it included cohort, case-control, and cross-sectional studies[188], so the temporal relationship between GDM and blood pressure was unclear. On the other hand, the multinational HAPO FUS did not find a significant association

between GDM and subsequent hypertension (OR: 1.16 [95% CI: 0.87, 1.52]) after controlling for field center, maternal age, gestational age, height, and BMI at pregnancy OGTT, parity, maternal smoking during pregnancy, maternal drinking during pregnancy, family history of diabetes, and family history of hypertension[104]. Additionally controlling for mean arterial blood pressure during pregnancy further attenuated the association (OR: 1.04 [95% CI: 0.78, 1.38])[104]. The inconsistency between the HAPO FUS and our results may be that HAPO FUS included a less severe GDM population, by excluding unblinded patients who had extreme plasma glucose (i.e., fasting plasma glucose ≥5.8 mmol/l, 2-hour OGTT plasma glucose ≥11.1 mmol/l, random plasma glucose ≥8.9 mmol/l, or any plasma glucose value <2.5 mmol/l) and those who experienced preterm birth for the pregnancy with GDM[104]. We also observed a weaker association between GDM and hypertension later in life in publications measuring incident hypertension (1.58 [95% CI: 1.29, 1.95]) than those measuring prevalent hypertension (2.60 [95% CI: 2.40, 2.83]). Although we could not compare this result with previous studies directly, it is consistent with the previous literature that pre-existing hypertension is a risk factor for GDM[91].

The precise underlying mechanisms for the association between GDM and hypertension among mothers remain unclear. It is plausible that the observed association reflects pre-existing insulin resistance, as insulin resistance is linked with both GDM[189] and hypertension[190]. In addition, the higher risk of hypertension among mothers with GDM may be mediated through the development of pregnancy-induced hypertension (e.g., gestational hypertension[90] and pre-eclampsia[99]) or subsequent type 2 diabetes[52]. It is also biologically possible that our finding reflects a causal association between GDM and subsequent hypertension, where the metabolic and vascular damage caused by GDM increases the risk of hypertension later in life.

Nevertheless, future studies are needed to further elucidate the underlying mechanisms for the association between GDM and hypertension later in life.

Given that GDM and hypertension share many common risk factors[1, 24, 163], uncontrolled confounding is one of the critical issues that prevents us from inferring a causal relationship. Although antenatal psychological stress is one of the major risk factors for both GDM[1, 24, 164-167] and hypertension[163, 168-171], none of the included cohort studies controlled for it. Our quantitative bias analysis indicated that additionally control for antenatal psychological stress was unlikely to attenuate the observed positive association between GDM and hypertension later in life to null.

This study has several strengths. First, we performed a quantitative bias analysis to quantify the impact of potential uncontrolled confounding due to antenatal psychological stress. Second, most included studies used appropriate study designs and had fair or good quality. Third, the included cohort studies covered a wide range of countries/regions and racial/ethnic groups, increasing the generalizability of the study findings. Lastly, most included studies carefully controlled for potential confounders, including maternal age, BMI, race/ethnicity, parity, socioeconomic status, and smoking.

Some limitations of this study are worth mentioning. First, the included cohort studies were observational in nature, and thus residual confounding cannot be completely ruled out. Nevertheless, we performed a quantitative bias analysis of uncontrolled confounding due to antenatal psychological stress. Second, there was high heterogeneity in GDM and hypertension ascertainments. GDM ascertainment not only varied across studies (i.e., self-report, OGTT tests, or clinical codes), but also differed by countries/regions, due to a lack of global consensus[1]. Hypertension ascertainment also differed across studies (i.e., self-report, clinical codes, or measured blood pressures) and two studies[102, 191] only utilized medical claims/records during

hospitalizations, which may lead to underdiagnosis of hypertension, as participants without hospitalizations would be classified as no hypertension.

Conclusion

In summary, in this meta-analysis of 15 cohort studies, we found that GDM was positively associated with hypertension later in life. The association between GDM and incident hypertension was weaker than the association between GDM and prevalent hypertension. Furthermore, by additionally adjusting for the uncontrolled confounder of antenatal psychological stress, the positive association between GDM and hypertension later in life would attenuate slightly but remain positive.

7.6 Tables and Figures

Table 7.1. Characteristics of the included studies

Study	Country	Study design	Cohort name/Data source	Sample size	Median length of follow-up, years	Mean (SD) age at baseline, years	Race/ethnicity
Pirkola, 2010[192]	Finland	Prospective cohort	Northern Finland Birth Cohort 1986	6,484	20.0	GDM: 29.1[3] (NA) Non-GDM: 26.7[3] (NA)	Non-Hispanic White
Tobias, 2011[100]	United States	Prospective cohort	Nurses' Health Study II	25,305	12.6[1]	GDM: 32.7 (3.6) non-GDM: 32.7 (3.5)	Mixed (non-Hispanic White [92.6%], Black [0.9%], Hispanic [1.1%], Asian [1.9%], other [1.9%], and unknown [1.7%])
Tam, 2012[174]	Hong Kong, China	Prospective cohort	Antenatal clinic of tertiary referral hospital	139	15.0	GDM: 28.8 (4.3) non-GDM: 28.2 (4.6)	Asian (Chinese)
Bentley-Lewis, 2014[63]	United States	Retrospective cohort	Massachusetts General Hospital Obstetrical Department	4,010	3.8	GDM: 32.2 (5.4) non-GDM: 30.3 (6.1)	Mixed (non-Hispanic White [51.3%], Black [6.0%], Hispanic [26.1%], Asian [7.2%], other [5.5%], and unknown [4.0%])
Heida, 2015[105]	Netherlands	Retrospective cohort	European Prospective Investigation into Cancer and Nutrition (EPIC)-NL cohort	22,265	29.1[1,2]	GDM: 31.9 (5.5) non-GDM: 28.6 (5.6)	Mixed (non-Hispanic White [82.6%], Chinese [3.7%], South Asian [9.2%], and Aboriginal [4.5%])
Kaul, 2015[193]	Canada	Retrospective cohort	Alberta Perinatal Health Program (clinical database for deliveries) linked with Alberta Ministry of Health (administrative claims data)	240,083	5.3	GDM: 23.9[4] (NA) non-GDM: 24.3[4] (NA)	NA (general population of Alberta, Canada)
Noctor, 2015[194]	Ireland	Prospective cohort	ATLANTIC-DIP (four Irish antenatal centers)	643	2.6-3.3[1]	GDM: 34.1[3] (5.0) Non-GDM: 34.3[3] (5.1)	Non-Hispanic White
Goueslard, 2016[102]	France	Retrospective cohort	French medico-administrative database (hospitalizations only)	1,518,990	7.0	GDM: 31.8 (NA) non-GDM: 29.4 (NA)	NA (general population of France)
Parikh, 2017[195]	Sweden	Retrospective cohort	Swedish Medical Birth Register and other nationwide registers combined with the Västerbotten Intervention Program cohort	15,896	14.4[1,2]	25.6[4] (4.4)	NA (general population of Västerbotten, Sweden)
Daly, 2018[101]	United Kingdom	Retrospective cohort	The Health Improvement Network (electronic medical records in primary care)	45,736[5]	2.9	GDM: 33.0 (5.4) non-GDM: 33.0 (5.4)	Mixed (non-Hispanic White [38.2%], South Asian [4.1%], Afro-Caribbean [2.3%], other [2.6%], and unknown [52.8%])
McKenzie-Sampson, 2018[191]	Canada	Retrospective cohort	Discharge abstracts in Quebec's Maintenance and Use of Data for the Study of Hospital Clientele registry (hospitalizations only)	1,070,667	14.5[1]	27.6[3] (NA)	NA (general population of Quebec, Canada)
Li, 2018[196]	Singapore	Prospective cohort	Growing Up in Singapore Towards Healthy Outcomes birth cohort	276	5.0	30.1[3] (NA)	Asian (Chinese [55.1%], Malay [21.7%], and Asian Indian [23.2%])

Shen, 2019[103]	China	Prospective cohort	Tianjin Women's and Children's Health Center	1,968	3.5[1]	GDM: 30.1 (3.5) non-GDM: 29.7 (2.8)	Asian (Chinese)
Maresh, 2022[104]	Multinational	Prospective cohort	Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Follow-up Study	4,572	10.0-14.0	GDM: 31.7 (5.3) non-GDM: 29.7 (5.6)	Mixed (non-Hispanic White [47.0%], Black [15.5%], Hispanic [10.4%], Asian [25.2%], and other [1.8%])
Yu, 2022[197]	Denmark	Prospective cohort	National registries linked through a unique central personal register number; all adult females who had their first pregnancy during 1978-2016	1,002,486	16.2	27.0[6] (NA)	NA (general population of Denmark)

Abbreviation: GDM, gestational diabetes mellitus; IQR, interquartile range; NA, not available.
Notes: [1] Mean length of follow-up was reported/estimated. [2] Mean length of follow-up from the first pregnancy was reported. [3] Mean age at baseline was estimated/calculated. [4] Mean age at the first pregnancy was reported. [5] Sample size of the association between GDM and hypertension was reported. [6] Median age at the first pregnancy was reported.

Table 7.2. Exposure/outcome ascertainments, measure/variability of association, and quality rating of the included studies

Study	GDM ascertainment	GDM prevalence	HTN ascertainment	HTN rate	HTN incidence/ prevalence	Statistical model	Adjusted/matched variables	Quality rating[4]
Pirkola, 2010[192]	2h 75g OGTT (fasting≥5.5; 1h≥11.0; 2h≥8.0 mmol/L) among females at risk for GDM	1.9%	ICD-8: 400-404 ICD-9: 401-405 ICD-10: I10, I11, I15 (hospitalizations) or on hypertensive medication	7.5%	Incidence	Direct calculation[1] (RR)	-	Poor
Tobias, 2011[100]	Self-reported physician diagnosis	5.6%	Self-reported physician diagnosis	12.4%	Incidence	Cox regression (HR)	Adjusted: age, BMI, history of toxemia/preeclampsia/gestational hypertension, family history of hypertension/type 2 diabetes, parity, DASH score, alcohol, total physical activity, smoking status, race/ethnicity, analgesic use, oral contraceptive use, birth weight, BMI at age 18 years	Good
Tam, 2012[174]	2h 75g OGTT (fasting≥7.0; 2h≥7.8 mmol/L, WHO 1999)	14.2% before matching 32.3% after matching	SBP ≥140, DBP ≥90 mmHg, or on hypertensive medication	22.3%	Prevalence	Logistic regression[2] (OR)	Adjusted: age, overweight in early pregnancy, and family history of diabetes, and subsequent diabetes Matched: age	Fair
Bentley-Lewis, 2014[63]	1st step: 1h 75g GLT (>7.8 mmol/L) 2nd step: 2 abnormal 3h 100g OGTT (fasting≥5.3; 1h≥10.0; 2h≥8.6; 3h≥7.8 mmol/L, Carpenter-Coustan)	4.6% before matching 20.0% after matching	ICD-9: 401	6.0%	Incidence	Cox regression (HR)	Adjusted: age, BMI, parity, race, gestational weight gain, baseline systolic blood pressure, and preeclampsia Matched: gravidity	Good
Heida, 2015[105]	Self-reported	4.9%	SBP ≥140 mmHg, DBP ≥90 mmHg, on hypertensive medication, or self-report	34.4%	Incidence	Logistic regression[2] (OR)	Adjusted: age, BMI, cohort, hypertensive disorder of pregnancy, smoking and alcohol consumption at hypertension ascertainment, history of myocardial infarction and stroke, prevalent diabetes mellitus, and total cholesterol/HDL ratio	Poor
Kaul, 2015[193]	Diagnosed based on Canadian Diabetes Association guidelines and routinely captured in the database	3.6%	ICD-9: 401-405 ICD-10: I10-I15	3.1%	Incidence	Cox regression (HR)[3]	Adjusted: age, parity, ethnicity, socioeconomic status, smoking status during pregnancy, preeclampsia, and subsequent GDM	Good
Noctor, 2015[194]	2h 75g OGTT (≥1: fasting≥5.1; 1h ≥10; 2h≥8.5 mmol/L, IADPSG) for all pregnant	NA	SBP ≥130, DBP ≥85 mmHg	25.2%	Prevalence	Direct calculation (RR)	-	Poor

	females) or among females at risk							
Goueslard, 2016[102]	ICD-10 (hospitalizations)	4.1%	ICD-10 (hospitalizations)	0.8%	Prevalence	Logistic regression (OR)	Adjusted: age, obesity, hypertensive disorders during pregnancy, and subsequent diabetes	Fair
Parikh, 2017[195]	ICD-9: 648W ICD-10: O24.4	1.8%	SBP ≥140, DBP ≥90 mmHg, or on hypertensive medication	9.6%	Incidence	Logistic regression (OR)	Adjusted: age at first birth, total parity, lowest gestational age, birth of a small-for-gestational age infant, stillbirth, placental abruption, preeclampsia, current smoking, alcohol consumption, body mass index, education, and income at 40 years of age	Poor
Daly, 2018[101]	Clinical codes	12.2% before matching 19.7% after matching	Clinical codes	1.7%	Incidence	Poisson regression (IRR)	Adjusted: age, BMI, Townsend quintile, and smoking Matched: age and timing of pregnancy	Good
McKenzie-Sampson, 2018[191]	ICD-9: 648.8, V12.21 ICD-10: O24.8 (hospitalizations)	6.3%	ICD-10: I10-I15 (hospitalizations)	1.8%	Incidence	Cox regression (HR)	Adjusted: age, parity, time period, socioeconomic deprivation, and preeclampsia	Good
Li, 2018[196]	2h 75g OGTT (fasting≥7.0; 2h≥7.8 mmol/L, WHO 1999)	NA before matching 56.9% after matching	SBP ≥140, DBP ≥90 mmHg, or on hypertensive medication	9.1%	Incidence	Modified Poisson regression (RR)	Adjusted: age, ethnicity, education, pre-pregnancy BMI, and parity Matched: age, ethnicity, and pre-pregnancy BMI	Good
Shen, 2019[103]	2h 75g OGTT (fasting≥7.0; 2h≥7.8 mmol/L, WHO 1999)	6.1% before matching 64.2% after matching	SBP ≥130, DBP ≥85 mmHg, or on hypertensive medication	9.3%	Prevalence	Logistic regression (OR)	Adjusted age, postpartum years, weight gain during pregnancy, education, family income, family history of diabetes, current smoking, passive smoking, current alcohol drinking, leisure time physical activity, sleeping time, energy consumption, fiber, fat, protein and carbohydrate consumption, and sweetened beverage drinking Matched: delivery date and child sex	Fair
Maresh, 2022[104]	2h 75g OGTT (≥1: fasting≥5.1; 1h ≥10; 2h≥8.5 mmol/L, IADPSG)	14.0%	SBP ≥140, DBP ≥90 mmHg, or on hypertensive medication	9.0%	Incidence	Logistic regression (OR)	Adjusted: field center, age, gestational age, height, BMI at pregnancy OGTT, parity, maternal smoking during pregnancy, maternal drinking during pregnancy, family history of diabetes, and family history of hypertension, and mean arterial blood pressure	Good

Yu, 2022[197]	ICD-8: 634.74, Y6449 ICD-10: O24.4, O24.9	2.1%	ICD-8: 400-404 ICD-10: I10-I15	5.3%	Incidence	Cos regression (HR)	Adjusted: time period of first delivery, age at first delivery, pre-pregnancy obesity, education, parity, smoking during pregnancy, cohabitation, residence, country of origin, maternal CVD history, and paternal CVD history	Good

Abbreviations: BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; HTN, hypertension; HDL, high density lipoprotein; GLT, glucose tolerance test; GDM, gestational diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; OR, odds ratio; HR, hazard ratio; IRR, incidence rate ratio; OGTT, oral glucose tolerance test; ICD, International Classification of Diseases; PCOS, polycystic ovary syndrome; WHO, World Health Organization; IADPSG, International Association of Diabetes and Pregnancy Study Groups.
Notes: [1] Unadjusted RR was calculated directly using number of events and participants in the GDM and non-GDM groups. Unadjusted HRs were reported in 5 groups in the original paper: no risk factors for GDM (no OGTT test): 1.00, GDM and normal weight: 1.52 (0.72-3.21), GDM and overweight: 9.16 (6.06-13.85), OGTT normal and normal weight: 0.94 (0.70-1.27), OGTT normal and overweight: 2.86 (2.10-3.90). [2] Due to a high proportion of the outcome, adjusted ORs were converted to RR. [3] Values for GDM only vs. no GDM no overweight were extracted and compared. [4] Details for quality rating is in supplementary Table 2.

Table 7.3. Random effects meta-analysis of the adjusted risk ratios between gestational diabetes mellitus and hypertension later in life: stratified analysis by subgroups

	N of studies	RR (95% CI)	I^2	P for heterogeneity	P for stratification
Total	15	1.78 (1.47, 2.17)	98.0%	<0.001	-
Measure of outcome					
Incidence	11	1.58 (1.29, 1.95)	97.1%	<0.001	<0.001
Prevalence	4	2.60 (2.40, 2.83)	52.8%	0.11	
Measure of association[1]					
RR	3	1.96 (1.37, 2.80)	95.2%	<0.001	0.34
HR	5	1.91 (1.50, 2.45)	97.6%	<0.001	
OR	6	1.63 (1.04, 2.54)	96.0%	<0.001	
Study design					
Prospective cohort	8	1.84 (1.38, 2.46)	97.5%	<0.001	0.76
Retrospective cohort	7	1.73 (1.31, 2.29)	98.1%	<0.001	
Median/mean follow-up duration					
<5 years	5	2.15 (1.72, 2.70)	80.7%	0.005	0.31
5-15 years	7	1.68 (1.27, 2.22)	97.8%	<0.001	
≥15 years	3	1.81 (1.37, 2.39)	96.4%	<0.001	
Study location[2]					
Asia	3	2.36 (1.51, 3.70)	12.5%	0.32	0.59
North America	4	1.76 (1.38, 2.24)	94.9%	<0.001	
Europe	7	1.82 (1.33, 2.48)	98.9%	<0.001	
Study quality					
Poor	4	1.48 (0.95, 2.29)	98.1%	<0.001	0.28
Fair/good	11	1.93 (1.57, 2.36)	97.2%	<0.001	
Adjusted for potential mediators[3]					
Yes	8	1.63 (1.23, 2.17)	98.0%	<0.001	0.32
No	7	1.98 (1.54, 2.55)	97.1%	<0.001	

Abbreviations: CI, confidence interval; RR, risk ratio; IRR, incidence rate ratio.
Notes: [1] One study (Daly, 2018[101]) that reported IRR was excluded. [2] One multinational study (Maresh, 2022[104]) was excluded. Asia included China and Singapore; North America included United States and Canada; Europe included Finland, Netherlands, Ireland, France, Sweden, United Kingdom, and Denmark. [3] Potential mediators included gestational hypertension/preeclampsia and subsequent gestational diabetes mellitus/diabetes.

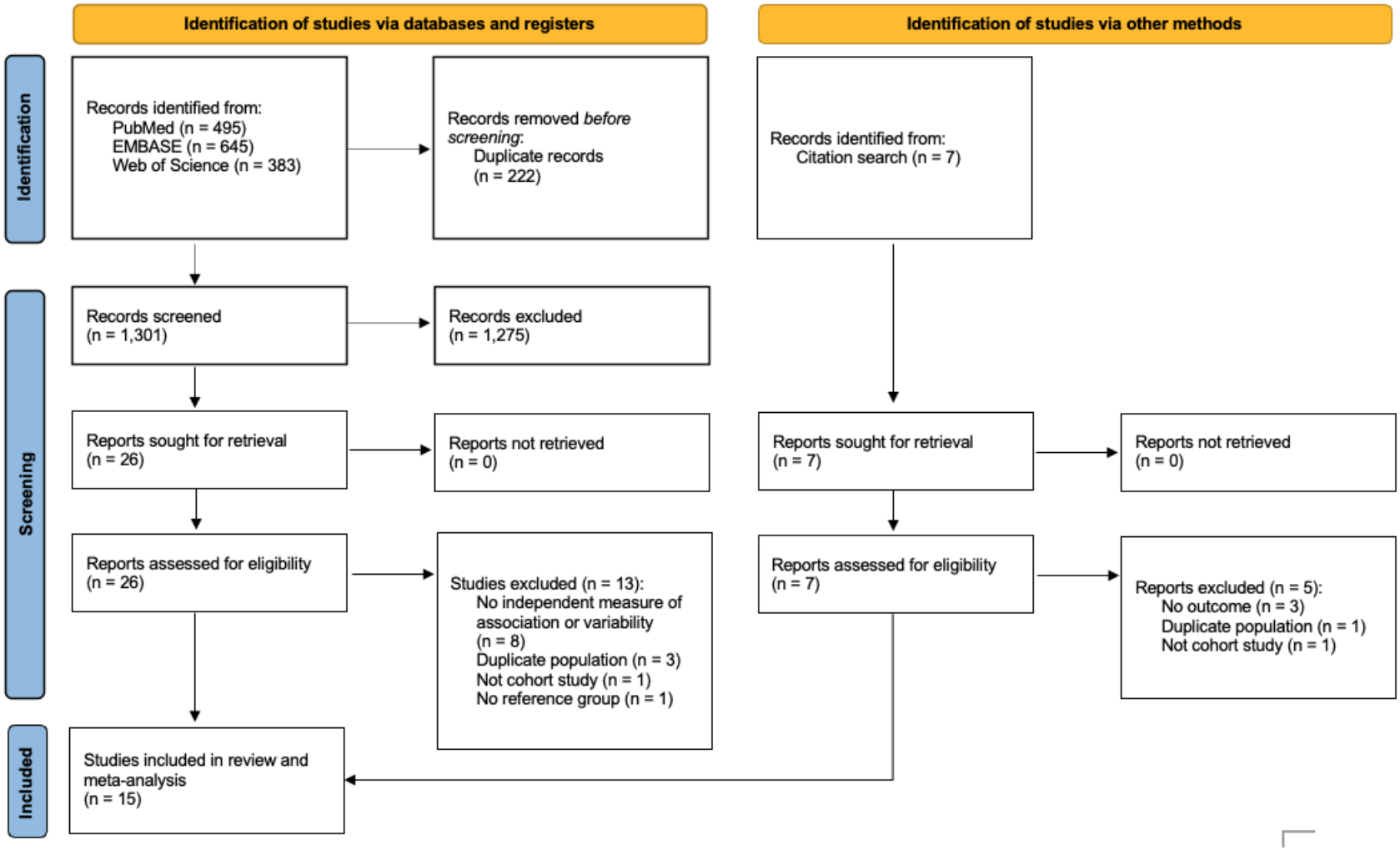
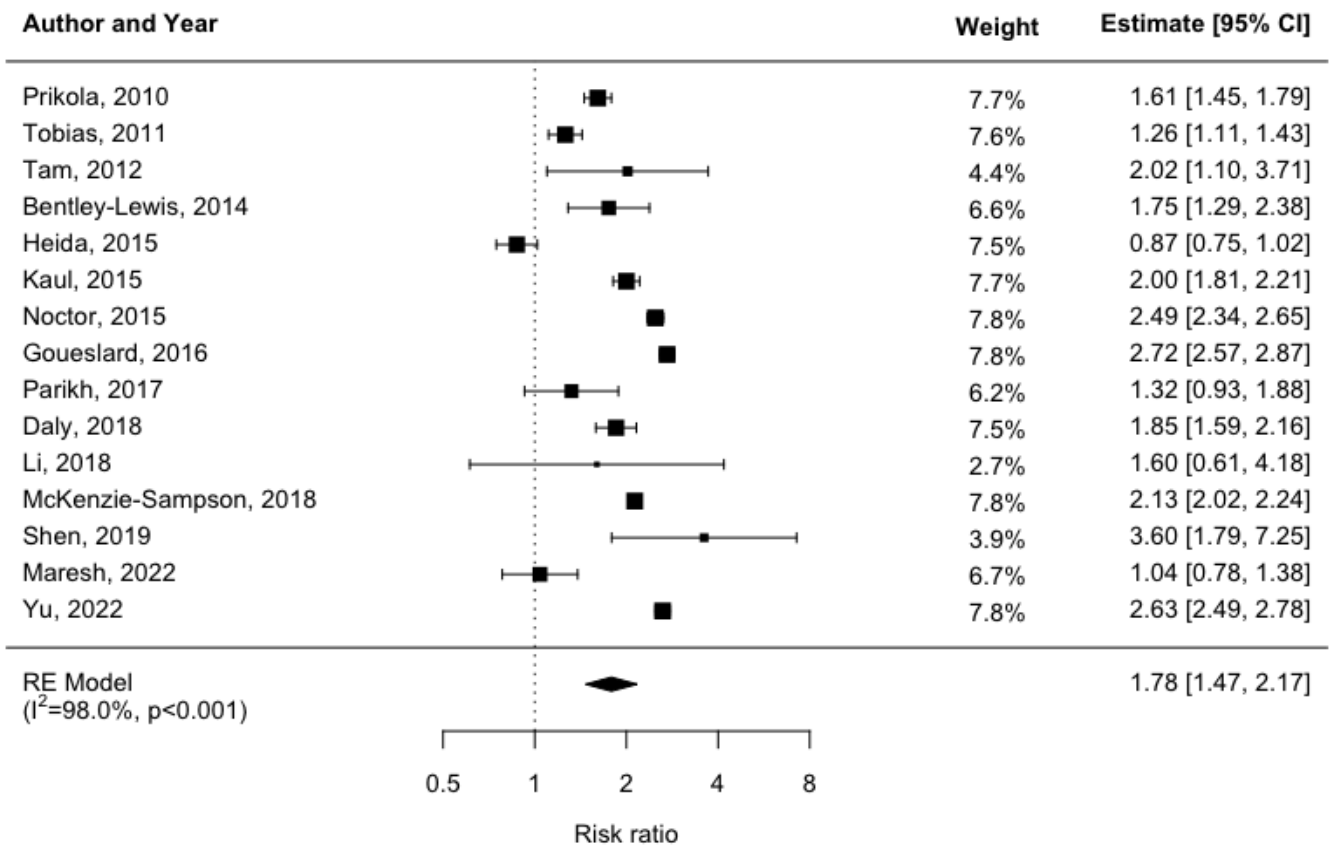
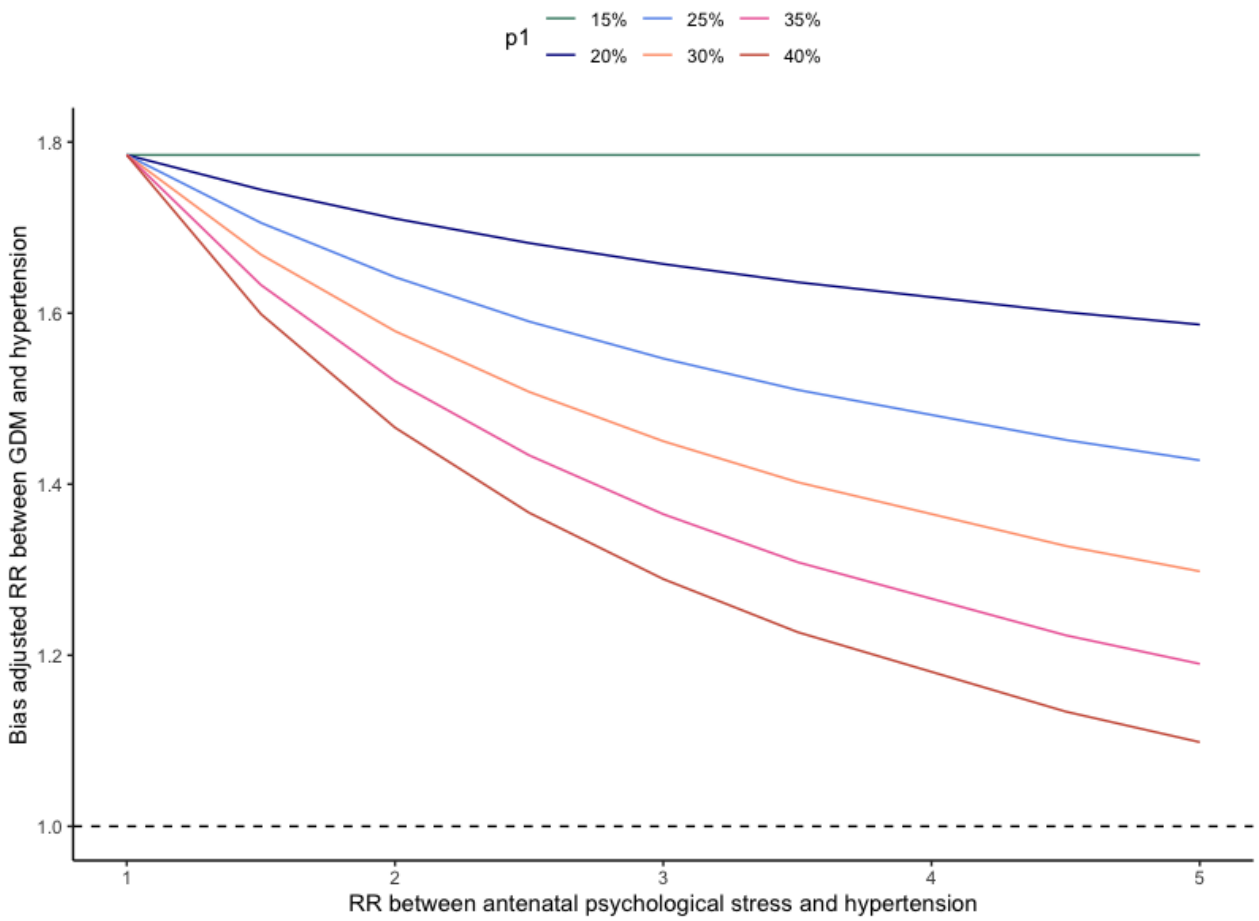


Figure 7.1. Flow diagram of systematic literature search. For publications with duplicate population, we included the publication with the largest sample size



Abbreviations: CI, confidence interval; RE, random effects.

Figure 7.2. Random effects meta-analysis of the adjusted risk ratios between gestational diabetes mellitus and hypertension later in life. Weights are from random effects analysis.



Abbreviations: GDM, gestational diabetes mellitus; RR, risk ratio.

Figure 7.3. Random effects meta-analysis with quantitative bias analysis of uncontrolled confounding due to psychological stress. X-axis: RR between psychological stress and hypertension (1.0-5.0 by increments of 0.5); Y-axis: bias adjusted RR between GDM and hypertension; the prevalence of psychological stress in females without GDM (p_0): 15%; the prevalence of psychological stress in females with GDM (p_1): 15%-40% by increments of 5%.

Supplementary Table 7.1. Search strategy of the systematic literature review

PubMed
((("Hypertension"[Mesh] OR "high blood pressure" OR "elevated blood pressure" OR "hypertensive disease" OR "hypertensive disorder")) AND (("Diabetes, Gestational"[Mesh] OR "gestational diabetes" OR (("hyperglycemia" OR "Hyperglycemia"[Mesh]) AND ("pregnancy" OR "Pregnancy"[Mesh])) OR "diabetic pregnancy"))) AND ("Cohort Studies"[Mesh] OR "cohort" OR "longitudinal" OR "follow-up") AND "Adult"[Mesh]
EMBASE
('pregnancy diabetes mellitus'/de OR 'gestational diabetes':ti,ab,kw OR ('hyperglycemia'/exp AND 'pregnancy'/exp) OR 'diabetic pregnancy':ti,ab,kw) AND ('hypertension'/de OR 'high blood pressure':ti,ab,kw OR 'elevated blood pressure':ti,ab,kw OR 'hypertensive disease':ti,ab,kw OR 'hypertensive disorder':ti,ab,kw) AND ('cohort analysis'/exp OR 'cohort':ti,ab,kw OR 'longitudinal':ti,ab,kw OR 'follow-up':ti,ab,kw) AND ('article'/it OR 'article in press'/it OR 'review'/it) AND ([adult]/lim OR [middle aged]/lim OR [young adult]/lim)
Web of Science
("gestational diabetes" OR (“hyperglycemia” AND “pregnancy”) OR “diabetic pregnancy”) AND ("hypertension” OR "high blood pressure" OR "elevated blood pressure" OR "hypertensive disease" OR "hypertensive disorder") AND ("cohort studies" OR "longitudinal" OR “follow-up”)

Supplementary Table 7.2. Steps of quantitative bias analysis for uncontrolled confounding

Step 1. Assign a range of plausible p_0, p_1, and RR_{UD} p_1 is the prevalence of antenatal psychological stress in GDM p_0 is the prevalence of antenatal psychological stress in non-GDM RR_{UD} is the risk ratio relating antenatal psychological stress and hypertension, given GDM
Step 2. Obtain a range of bias factors Bias factor = $(RR_{UD}*p_1+1-p_1)/(RR_{UD}*p_0+1-p_0)$
Step 3. Obtain $RR_{adjusted}$ for each study $RR_{adjusted} = RR_{unadjusted}$/bias factor where $RR_{pre\text{-}adjusted}$ is the observed risk ratio; and $RR_{adjusted}$ is the bias-adjusted risk ratio

Abbreviations: RR, risk ratio.
Note:
[1] We assumed that the standard errors of the $RR_{adjusted}$ were not affected by unmeasured confounding.

Supplementary Table 7.3. Risk of bias of the included studies

	Selection				Comparability	Outcome			
Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	No outcome at start of study	Comparability based on design or analysis	Assessment of outcome	Follow-up long enough	Adequacy of follow-up	Quality rating
Pirkola, 2010[192]	*	*	- (screening only among females at risk)	*	- (not accounted for any potential confounders)	*	*	*	Poor
Tobias, 2011[100]	*	*	- (self-report)	*	**	- (self-report)	*	*	Good
Tam, 2012[174]	- (single center)	*	*	-	* (not accounted for socioeconomic status)	*	*	- (loss to follow-up >20%)	Fair
Bentley-Lewis, 2014[63]	- (single center)	*	*	*	* (adjusted for potential mediator: preeclampsia)	*	*	*	Good
Heida, 2015[105]	*	*	- (self-report)	*	- (adjusted covariates that were measured after exposure)	*	*	*	Poor
Kaul, 2015[193]	*	*	*	*	* (not accounted for BMI at baseline; adjusted for potential mediators: preeclampsia and subsequent GDM)	*	*	*	Good
Noctor, 2015[194]	*	*	*	-	- (not account for any potential confounders)	*	*	- (loss to follow-up unknown)	Poor
Goueslard, 2016[102]	*	*	*	-	* (not accounted for socioeconomic status; adjusted for potential	- (hospitalizations)	*	*	Fair

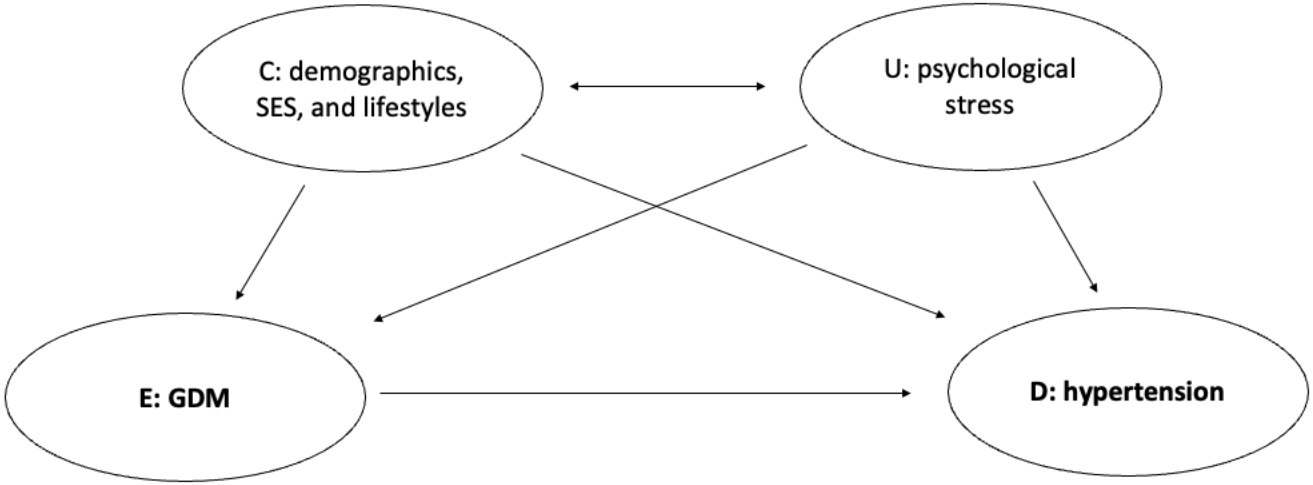
					mediators: hypertensive disorders in pregnancy and subsequent diabetes)				
Parikh, 2017[195]	*	*	*	*	- (adjusted covariates that were measured after exposure)	*	*	*	Poor
Daly, 2018[101]	*	*	*	*	**	*	*	*	Good
McKenzie-Sampson, 2018[191]	*	*	*	*	* (not accounted for BMI at baseline)	- (hospitalizations)	*	*	Good
Li, 2018[196]	*	*	*	*	**	*	*	- (loss to follow-up >20%)	Good
Shen, 2019[103]	- (single center)	*	*	-	* (not accounted for BMI at baseline)	*	*	- (loss to follow-up >20%)	Fair
Maresh, 2022[104]	*	*	*	*	* (not accounted for socioeconomic status)	*	*	*	Good
Yu, 2022[197]	*	*	*	*	**	*	*	*	Good

Abbreviations: BMI, body mass index; NOS, Newcastle Ottawa Scale.
Notes: [1] We used the NOS for Cohort Studies to assess risk of bias. [2] We rated the quality of the studies by awarding stars in each domain following the guidelines of the NOS ("good": 3/4 stars in selection, 1/2 stars in comparability, and 2/3 stars in outcomes; "fair": 2 stars in selection, 1/2 stars in comparability, and 2/3 stars in outcomes; "poor": 0/1 star in selection, or 0 stars in comparability, or 0/1 star in outcomes).

Supplementary Table 7.4. Random effects meta-analysis of the adjusted risk ratios between gestational diabetes mellitus and hypertension later in life: excluding the included study one by one

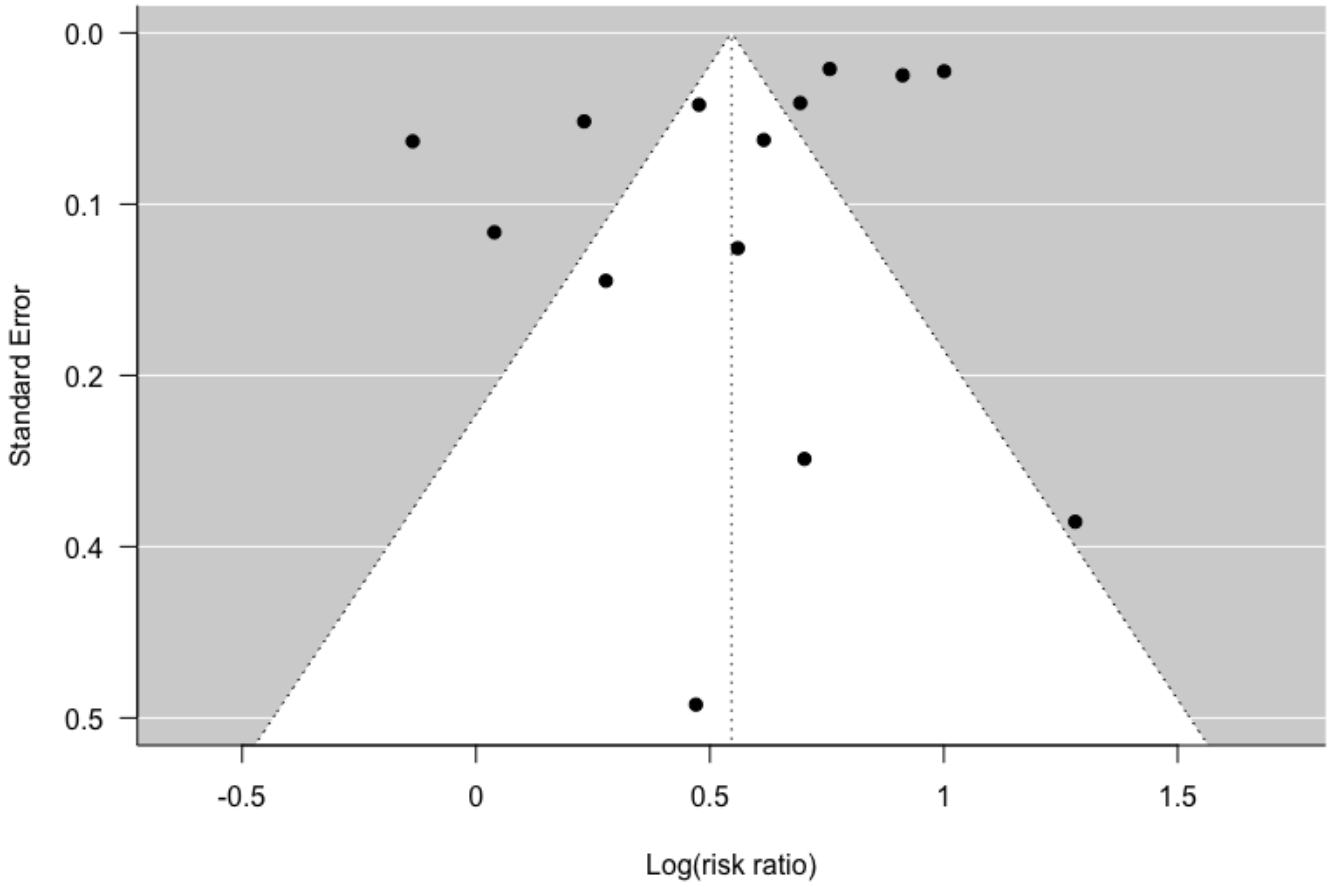
One by one excluded studies	Pooled RR (95% CI)	I^2	P for heterogeneity
Pirkola, 2010[192]	1.80 (1.46, 2.22)	98.1%	<0.001
Tobias, 2011[100]	1.84 (1.50, 2.25)	98.0%	<0.001
Tam, 2012[174]	1.77 (1.45, 2.17)	98.2%	<0.001
Bentley-Lewis, 2014[63]	1.79 (1.45, 2.20)	98.2%	<0.001
Heida, 2015[105]	1.89 (1.60, 2.24)	97.1%	<0.001
Kaul, 2015[193]	1.77 (1.43, 2.18)	98.1%	<0.001
Noctor, 2015[194]	1.74 (1.42, 2.12)	97.7%	<0.001
Goueslard, 2016[102]	1.72 (1.41, 2.09)	97.4%	<0.001
Parikh, 2017[195]	1.82 (1.49, 2.23)	98.1%	<0.001
Daly, 2018[101]	1.78 (1.44, 2.20)	98.2%	<0.001
McKenzie-Sampson, 2018[191]	1.79 (1.47, 2.19)	98.2%	<0.001
Li, 2018[196]	1.76 (1.43, 2.17)	97.7%	<0.001
Shen, 2019[103]	1.74 (1.43, 2.11)	98.0%	<0.001
Maresh, 2022[104]	1.86 (1.53, 2.25)	97.9%	<0.001
Yu, 2022[197]	1.73 (1.42, 2.11)	97.5%	<0.001

Abbreviations: CI, confidence interval; RR, risk ratio.



Abbreviations: C, confounders; D, disease; E, exposure; GDM, gestational diabetes mellitus; SES, socioeconomic status; U, uncontrolled confounder. Note: [1] We assumed that confounders were measured prior to the assessment of GDM.

Supplementary Figure 7.1. Directed acyclic diagram for the total effect of the association between gestational diabetes mellitus and hypertension later in life



Note: Egger's test: p = 0.93; Begg's test: p = 0.83

Supplementary Figure 7.2. Funnel plot to assess publication bias of included studies

8 CHAPTER EIGHT: DISCUSSION

8.1 Objectives

The objectives of the studies within this dissertation were to use real-world data to better understand the racial/ethnic differences and implications of applying the current GDM diagnostic methods and criteria in the US, and to improve our understanding of GDM and long-term adverse health outcomes among mothers and their offspring. Critical gaps in the literature were identified, including the racial/ethnic differences in maternal hyperglycemia and their implications for pregnancy outcomes, and the association between GDM and neurodevelopmental disorders in offspring as well as hypertension in mothers.

This dissertation focused on three main objectives:

1) To investigate the real-world distributions of maternal hyperglycemic categories based on the two-step GDM screening approach, including the potential racial/ethnic differences, and their associations with adverse pregnancy outcomes.
2) To examine whether GDM is associated with neurodevelopmental disorders in offspring and whether race/ethnicity modifies the associations.
3) To examine whether GDM is associated with hypertension later in life and the impact of uncontrolled confounding due to psychological stress.

To address these objectives, this dissertation used data from UCLA's electronic health records to establish a retrospective cohort, called UCLA GrownB. This cohort includes linked mother-offspring pairs (21,544 mothers and 26,437 offspring) delivered at UCLA medical center from March 1, 2013, to August 31, 2021. A wealth of data is available on demographics, SES, GDM screening laboratory results, use of glucose-lowering medications, medical procedures, disease diagnosis, and birth outcomes.

8.2 Main Findings

Racial/ethnic differences in maternal hyperglycemic categories and their associations with adverse pregnancy outcomes

Maternal glucose levels, including a mild elevation, are progressively associated with adverse health outcomes for mothers and their offspring. In the US, the two-step approach (50g GCT and 3-hour 100g OGTT) is widely applied to screen GDM, leading to a lower prevalence of GDM, compared to the one-step approach recommended by international organizations. As a result, a large proportion of pregnancies with hyperglycemia are not diagnosed and treated in the US. Based on the laboratory results during GDM screening, pregnancies could be classified into more granular hyperglycemic categories than GDM vs. non-GDM. We classified the pregnancies into five mutually exclusive glycemic categories ordered by severity: NGT (normal GCT), PIGT-0 (abnormal GCT & normal OGTT), PIGT-1 (abnormal GCT & 1 abnormal OGTT), GDM-0 (abnormal GCT, 0 abnormal fasting & ≥2 abnormal postprandial OGTT), and GDM-1 (abnormal GCT, 1 abnormal fasting & ≥1 abnormal postprandial OGTT). In addition, GDM has well-known racial/ethnic differences, with Asians and Hispanics having a higher prevalence than non-Hispanic Whites. It is important to understand if racial/ethnic differences persist in these more granular hyperglycemic categories.

We found that the glycemic categories varied by racial/ethnic groups and Asian subgroups. The prevalence of the most severe category, GDM-1, was the highest among Hispanics and the prevalence of all other hyperglycemic categories was the highest among Asians. In Asian subgroups, only Asian Indians had a higher prevalence of GDM-1 than non-Hispanic Whites. Although the GDM prevalence in Japanese and Koreans is comparable to non-Hispanic Whites, they still had a higher prevalence of the intermediate stages between NGT and

GDM, (i.e., PIGT-0 and PIGT-1) than non-Hispanic Whites. Although we cannot compare our results with previous literature directly, these results align with previous evidence that Asians and Hispanics have a higher prevalence of GDM than non-Hispanic Whites[1, 24, 75]. Potential explanations for the observed differences in maternal glycemic categories by race/ethnicity and Asian subgroups may be related to differences in genetics, physical activity, diet, and body mass composition[116, 117, 129, 130, 198, 199].

Furthermore, PIGT-1 had the worst pregnancy outcomes, including a higher risk of pregnancy-related hypertension, LGA, and preterm birth than NGT. PIGT-0 was also associated with an elevated risk of preterm birth. Among pregnancies diagnosed with GDM, GDM-0 was only associated with an increased risk of preterm birth than NGT, while GMD-1 was associated with both LGA and preterm birth, although not significant due to the limited sample size. These results are in line with previous literature that maternal hyperglycemia, including mild levels, is progressively associated with adverse pregnancy outcomes[92]. In addition, lack of treatment among pregnancies classified as PIGT-0 and PIGT-1 may explain why they had the poorest pregnancy outcomes.

In summary, our results suggest that the intermediate stages between NGT and GDM affect certain racial/ethnic groups (e.g., Asians and Hispanics) and Asian subgroups (e.g., Koreans, Asian Indians, and Filipinos) disproportionally. Because these pregnancies are not treated for hyperglycemia, their pregnancy outcomes may be worse. In addition, although Asians had the highest prevalence of GDM, they were more likely to be affected by the lesser severe type, GDM-0, while Hispanics were more likely to be affected by the more severe type, GDM-1. In conclusion, pregnancies with PIGT, especially PIGT-1, may also be treated. GDM subtypes may receive tailored treatments to better manage blood glucose during pregnancy.

Association between GDM and risk of NDDs among young offspring

According to our real-world data, during the median follow-up of 3.5 years, 8.7% of offspring developed NDD. We found that offspring born to mothers with GDM had elevated risks of NDDs (i.e., any NDD, SLD, DCD, ASD, other NDDs, combination of SLD and ASD, and combination of SLD and DCD) than their counterparts born to mothers without GDM, but only among non-Hispanic Whites. No association between GDM and NDDs was observed among offspring born to mothers of other race/ethnicities.

Our results align with previous literature that GDM is associated with a higher risk of ASD[20], while due to a small number of events of ADHD in our sample of young offspring, we cannot directly compare our results with previous studies about ADHD. There are no previous studies on other individual NDDs and the potential racial/ethnic differences. Potential biological mechanisms for the association between GDM and NDDs may involve uncontrolled hyperglycemia during pregnancy interfering with fetal brain development directly through epigenetic modifications[81-83], chronic inflammation[84, 85], oxidative stress[86, 87], or hypoxia[88]. It is also likely that the associations between GDM and NDDs are mediated by poor pregnancy outcomes related to GDM[89-92, 155-157]. Furthermore, the observed racial/ethnic differences in the association of GDM with NDDs may be related to differences in glucose control. Even though non-Hispanic White mothers had a lower prevalence of GDM than Asian and Hispanic mothers[1, 24, 25], they may experience a higher proportion of uncontrolled glucose (i.e., aggressive progression of A2 GDM) than other race/ethnicities. It is also possible that non-Hispanic White offspring are more likely to be diagnosed with NDDs at a younger age than those of other race/ethnicities due to differential ascertainment[158, 159].

Our findings suggest that young offspring born to mothers with GDM may need to be monitored for their cognitive development to start interventions early.

Association between GDM and risk of hypertension later in life

Individuals affected by GDM are at a substantially increased risk of type 2 diabetes, but the results are still conflicting about the association between GDM and hypertension later in life. Our study found that GDM was associated with a 78% higher rate of hypertension later in life, including 1.58 times higher rate among studies assessing incident hypertension and 2.60 times higher rate among studies assessing prevalence hypertension.

Psychological stress is a well-known risk factor for both GDM and hypertension. Because none of these cohort studies controlled for psychological stress for the association between GDM and hypertension later in life, we conducted a quantitative bias analysis to quantify the impact of the uncontrolled confounder, psychological stress, on the observed association between GDM and hypertension. Our results revealed that even though additionally adjusting for psychological stress would attenuate the association, it is unlikely to result in a null association (i.e., attenuate the 78% higher rate to 0%).

Our findings are consistent with previous evidence about the positive associations between GDM and type 2 diabetes[52] and cardiovascular diseases (i.e., coronary heart disease, myocardial infarction, cerebrovascular disease, or peripheral vascular disease)[54, 55] later in life. The observed weaker association between GDM and hypertension later in life in publications measuring incident hypertension than those measuring prevalent hypertension is in line with the existing literature that pre-existing hypertension is a risk factor for GDM[91].

The observed association may be related to pre-existing insulin resistance[189, 190], mediated through gestational hypertension[90]/pre-eclampsia[99]/subsequent type 2 diabetes[52], or reflect a causal association between GDM and subsequent hypertension.

The results suggest that mothers with GDM may also need to be followed up on their blood pressure to prevent future cardiovascular diseases and other diseases such as cognitive decline related to hypertension.

8.3 Strength and Limitations

Overall, this large real-world study using electronic health records from UCLA provides us with an opportunity to investigate the racial/ethnic differences in hyperglycemic categories and the between GDM and NDDs in offspring. First, this cohort has rich data on both mothers and their offspring, including demographics, socioeconomics, behavior, diagnosis, procedure, medication, and lab results. In addition, this cohort has a multiracial/multiethnic population: 40.6% White, 23.5% Hispanic, 17.1% Asian, 11.5% other, and 2.1% unknown. Furthermore, compared to using ICD codes and other algorithms to identify pregnancies (subject to errors), this study captures all pregnancies consistently with detailed data on pregnancy and birth outcomes and reliable linkage to offspring. Finally, this cohort has a median follow-up of 3.5 years among offspring, allowing us to capture several NDDs.

In addition to the strengths of the data itself, several analytical strengths of this dissertation are noteworthy. First, we carefully controlled for a broad range of potential confounders, including sociodemographic, socioeconomic, and lifestyle factors. In addition, we carefully considered and addressed missing data. Additionally, we used validated codes or algorithms to define our exposures and outcomes to minimize biases due to misclassifications. Furthermore, we ruled out the possibility of differential loss to follow-up in our cohort. Finally, we applied a

quantitative bias analysis to examine the impact of uncontrolled confounding of psychological stress on the association between GDM and subsequent hypertension.

A few limitations need to be acknowledged. First, this study did not have data on certain potential confounders, such as body composition, physical activity, diet, and air pollution. In addition, this study used electronic health records from an academic center in a large city, limiting the generalizability of the study findings. Compared to the general population in LA county, there is a lower proportion of non-Hispanic White (59.2% vs. 70.2%) and a higher proportion of people with at least a high school degree (94.4% vs. 80.0%)[131, 132] in the service area.

8.4 Conclusions and Future Research Directors

The findings from the dissertation using real-world data bridge the gaps and expand the understanding of the diagnosis of GDM, the adverse health implications for both mothers and their offspring, and the racial/ethnic differences in GDM prevalence and health impacts. Specifically, we observed racial/ethnic differences in more granular hyperglycemic categories vs. dichotomized categories (GDM vs. non-GDM). We also found that these hyperglycemic categories were all linked to adverse pregnancy outcomes. Furthermore, we found that GDM was associated with various NDDs in young offspring born to non-Hispanic White mothers and GDM was associated with hypertension later in life among mothers.

Although the findings of the thesis contribute to a growing body of literature on our comprehensive understanding of the diagnosis and management of GDM and its health implications, further research is needed. Specifically, studies examining the underlying reasons for the racial/ethnic differences in the prevalence of maternal hyperglycemic categories are needed in order to better identify strategies to close the racial/ethnic disparities. In addition,

studies with a longer follow-up for offspring are needed to improve our understanding of the long-term impact of GDM on NDDs, especially those diagnosed among older kids, such as ADHD. Studies revealing the biological mechanisms of the association between GDM and NDDs are also needed. Furthermore, studies measuring the potential mediating effect of type 2 diabetes and pregnancy-related hypertension are needed to further elucidate how GDM and hypertension later in life are linked.

9 CHAPTER NINE: REFERENCES

1. McIntyre HD, Catalano P, Zhang C, et al. Gestational diabetes mellitus. Nature reviews Disease primers. 2019;5(1):1-19.

2. Deputy NP, Kim SY, Conrey EJ, et al. Prevalence and changes in preexisting diabetes and gestational diabetes among women who had a live birth—United States, 2012–2016. Morbidity and Mortality Weekly Report. 2018;67(43):1201.

3. Dall TM, Yang W, Gillespie K, et al. The economic burden of elevated blood glucose levels in 2017: diagnosed and undiagnosed diabetes, gestational diabetes mellitus, and prediabetes. Diabetes care. 2019;42(9):1661-1668.

4. DeSisto CL, Kim SY, Sharma AJ. Peer reviewed: Prevalence estimates of gestational diabetes mellitus in the United States, pregnancy risk assessment monitoring system (prams), 2007–2010. Preventing chronic disease. 2014;11.

5. Bardenheier BH, Imperatore G, Gilboa SM, et al. Trends in gestational diabetes among hospital deliveries in 19 US States, 2000–2010. American journal of preventive medicine. 2015;49(1):12-19.

6. Chen L, Shi L, Zhang D, et al. Peer Reviewed: Influence of Acculturation on Risk for Gestational Diabetes Among Asian Women. Preventing chronic disease. 2019;16.

7. Pu J, Zhao B, Wang EJ, et al. Racial/ethnic differences in gestational diabetes prevalence and contribution of common risk factors. Paediatric and perinatal epidemiology. 2015;29(5):436-443.

8. Hedderson M, Ehrlich S, Sridhar S, et al. Racial/ethnic disparities in the prevalence of gestational diabetes mellitus by BMI. Diabetes care. 2012;35(7):1492-1498.

9. Singh GK, DiBari JN. Marked disparities in pre-pregnancy obesity and overweight prevalence among US women by race/ethnicity, nativity/immigrant status, and sociodemographic characteristics, 2012–2014. Journal of obesity. 2019;2019.

10. Force UPST. Gestational diabetes mellitus, screening. 2014.

11. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. New England Journal of Medicine. 2009;361(14):1339-1348.

12. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. New England Journal of Medicine. 2005;352(24):2477-2486.

13. Behboudi-Gandevani S, Amiri M, Yarandi RB, et al. The impact of diagnostic criteria for gestational diabetes on its prevalence: a systematic review and meta-analysis. Diabetology & metabolic syndrome. 2019;11(1):1-18.

14. Brown FM, Wyckoff J. Application of one-step IADPSG versus two-step diagnostic criteria for gestational diabetes in the real world: impact on health services, clinical care, and outcomes. Current diabetes reports. 2017;17(10):1-13.

15. Association AD. 14. Management of diabetes in pregnancy: Standards of Medical Care in Diabetes—2020. Diabetes Care. 2020;43(Supplement 1):S183-S192.

16. Mellitus GD. ACOG Practice Bulletin No. 190. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2018;131(2):e49-e64.

17. Committee SP. SMFM Statement: Pharmacological treatment of gestational diabetes. Am J Obstet Gynecol. 2018;218(5):1.

18. Ethridge Jr JK, Catalano PM, Waters TP. Perinatal outcomes associated with the diagnosis of gestational diabetes made by the international association of the diabetes and pregnancy study groups criteria. Obstetrics and gynecology. 2014;124(3):571.

19. Lowe WL, Scholtens DM, Lowe LP, et al. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. Jama. 2018;320(10):1005-1016.

20. Rowland J, Wilson CA. The association between gestational diabetes and ASD and ADHD: a systematic review and meta-analysis. Scientific reports. 2021;11(1):1-16.

21. Berggren EK, Boggess KA, Funk MJ, et al. Racial disparities in perinatal outcomes among women with gestational diabetes. Journal of women's health. 2012;21(5):521-527.

22. Xiang A, Li B, Black M, et al. Racial and ethnic disparities in diabetes risk after gestational diabetes mellitus. Diabetologia. 2011;54(12):3016-3021.

23. Hunsberger M, Rosenberg KD, Donatelle RJ. Racial/ethnic disparities in gestational diabetes mellitus: findings from a population-based survey. Women's Health Issues. 2010;20(5):323-328.

24. Chen L, Mayo R, Chatry A, et al. Gestational diabetes mellitus: its epidemiology and implication beyond pregnancy. Current Epidemiology Reports. 2016;3(1):1-11.

25. Shah NS, Wang MC, Freaney PM, et al. Trends in gestational diabetes at first live birth by race and ethnicity in the US, 2011-2019. Jama. 2021;326(7):660-669.

26. Lawrence JM, Contreras R, Chen W, et al. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999–2005. Diabetes care. 2008;31(5):899-904.

27. Ferrara A, Kahn HS, Quesenberry CP, et al. An increase in the incidence of gestational diabetes mellitus: Northern California, 1991–2000. Obstetrics & Gynecology. 2004;103(3):526-533.

28. Chu SY, Abe K, Hall LR, et al. Gestational diabetes mellitus: all Asians are not alike. Preventive medicine. 2009;49(2-3):265-268.

29. Diabetes IAo, Panel PSGC. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes care. 2010;33(3):676-682.

30. Organization WH. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. World Health Organization 2013.

31. Hod M, Kapur A, Sacks DA, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care#. International Journal of Gynecology & Obstetrics. 2015;131:S173-S211.

32. Association AD. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2020. Diabetes care. 2020;43(Supplement 1):S14-S31.

33. Bimson BE, Rosenn BM, Morris SA, et al. Current trends in the diagnosis and management of gestational diabetes mellitus in the United States. The Journal Of Maternal-Fetal & Neonatal Medicine. 2017;30(21):2607-2612.

34. Hillier TA, Pedula KL, Ogasawara KK, et al. A pragmatic, randomized clinical trial of gestational diabetes screening. New England Journal of Medicine. 2021;384(10):895-904.

35. Coustan DR, Dyer AR, Metzger BE. One-step or 2-step testing for gestational diabetes: which is better? American journal of obstetrics and gynecology. 2021;225(6):634-644.

36. Kjos SL, Schaefer-Graf UM. Modified therapy for gestational diabetes using high-risk and low-risk fetal abdominal circumference growth to select strict versus relaxed maternal glycemic targets. Diabetes care. 2007;30(Supplement 2):S200-S205.

37. Charlton RA, Klungsøyr K, Neville AJ, et al. Prescribing of antidiabetic medicines before, during and after pregnancy: a study in seven European regions. PLoS One. 2016;11(5):e0155737.

38. Lepercq J, Lin J, Hall GC, et al. Meta-analysis of maternal and neonatal outcomes associated with the use of insulin glargine versus NPH insulin during pregnancy. Obstetrics and gynecology international. 2012;2012.

39. Castillo WC, Boggess K, Stürmer T, et al. Association of adverse pregnancy outcomes with glyburide vs insulin in women with gestational diabetes. JAMA pediatrics. 2015;169(5):452-458.

40. Bowker S, Savu A, Yeung R, et al. Patterns of glucose-lowering therapies and neonatal outcomes in the treatment of gestational diabetes in Canada, 2009–2014. Diabetic Medicine. 2017;34(9):1296-1302.

41. Landi SN, Radke S, Engel SM, et al. Association of long-term child growth and developmental outcomes with metformin vs insulin treatment for gestational diabetes. JAMA pediatrics. 2019;173(2):160-168.

42. Ye W, Luo C, Huang J, et al. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. bmj. 2022;377.

43. Metzger BE, Contreras M, Sacks D, et al. Hyperglycemia and adverse pregnancy outcomes. New England journal of medicine. 2008;358(19):1991-2002.

44. Nguyen BT, Cheng YW, Snowden JM, et al. The effect of race/ethnicity on adverse perinatal outcomes among patients with gestational diabetes mellitus. American journal of obstetrics and gynecology. 2012;207(4):322. e321-322. e326.

45. Esakoff TF, Caughey AB, Block-Kurbisch I, et al. Perinatal outcomes in patients with gestational diabetes mellitus by race/ethnicity. The Journal of Maternal-Fetal & Neonatal Medicine. 2011;24(3):422-426.

46. Sridhar SB, Ferrara A, Ehrlich SF, et al. Risk of large-for-gestational-age newborns in women with gestational diabetes by race and ethnicity and body mass index categories. Obstetrics and gynecology. 2013;121(6):1255.

47. Mukerji G, Chiu M, Shah BR. Gestational diabetes mellitus and pregnancy outcomes among Chinese and South Asian women in Canada. The Journal of Maternal-Fetal & Neonatal Medicine. 2013;26(3):279-284.

48. Farrar D, Fairley L, Santorelli G, et al. Association between hyperglycaemia and adverse perinatal outcomes in south Asian and white British women: analysis of data from the Born in Bradford cohort. The lancet Diabetes & endocrinology. 2015;3(10):795-804.

49. England L, Kotelchuck M, Wilson HG, et al. Estimating the recurrence rate of gestational diabetes mellitus (GDM) in Massachusetts 1998–2007: Methods and findings. Maternal and child health journal. 2015;19(10):2303-2313.

50. Nohira T, Kim S, Nakai H, et al. Recurrence of gestational diabetes mellitus: rates and risk factors from initial GDM and one abnormal GTT value. Diabetes research and clinical practice. 2006;71(1):75-81.

51. Bellamy L, Casas J-P, Hingorani AD, et al. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet. 2009;373(9677):1773-1779.

52. Vounzoulaki E, Khunti K, Abner SC, et al. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. Bmj. 2020;369.

53. Dennison RA, Chen ES, Green ME, et al. The absolute and relative risk of type 2 diabetes after gestational diabetes: a systematic review and meta-analysis of 129 studies. Diabetes research and clinical practice. 2021;171:108625.

54. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia. 2019;62(6):905-914.

55. Li J, Song C, Li C, et al. Increased risk of cardiovascular disease in women with prior gestational diabetes: a systematic review and meta-analysis. Diabetes research and clinical practice. 2018;140:324-338.

56. Retnakaran R. Hyperglycemia in pregnancy and its implications for a woman's future risk of cardiovascular disease. Diabetes research and clinical practice. 2018;145:193-199.

57. Charach R, Wolak T, Shoham-Vardi I, et al. Can slight glucose intolerance during pregnancy predict future maternal atherosclerotic morbidity? Diabetic Medicine. 2016;33(7):920-925.

58. Xu Y, Shen S, Sun L, et al. Metabolic syndrome risk after gestational diabetes: a systematic review and meta-analysis. PloS one. 2014;9(1):e87863.

59. Tranidou A, Dagklis T, Tsakiridis I, et al. Risk of developing metabolic syndrome after gestational diabetes mellitus-a systematic review and meta-analysis. Journal of Endocrinological Investigation. 2021;44:1139-1149.

60. Lauenborg J, Mathiesen E, Hansen T, et al. The prevalence of the metabolic syndrome in a Danish population of women with previous gestational diabetes mellitus is three-fold higher than in the general population. The Journal of Clinical Endocrinology & Metabolism. 2005;90(7):4004-4010.

61. Wang Y, Chen L, Horswell R, et al. Racial differences in the association between gestational diabetes mellitus and risk of type 2 diabetes. Journal of women's health. 2012;21(6):628-633.

62. Bazargan-Hejazi S, Ruiz M, Ullah S, et al. Racial and ethnic disparities in chronic health conditions among women with a history of gestational diabetes mellitus. Health Promotion Perspectives. 2021;11(1):54.

63. Bentley-Lewis R, Powe C, Ankers E, et al. Effect of race/ethnicity on hypertension risk subsequent to gestational diabetes mellitus. The American journal of cardiology. 2014;113(8):1364-1370.

64. Lee AJ, Hiscock RJ, Wein P, et al. Gestational diabetes mellitus: clinical predictors and long-term risk of developing type 2 diabetes: a retrospective cohort study using survival analysis. Diabetes care. 2007;30(4):878-883.

65. Clausen TD, Mathiesen ER, Hansen T, et al. Overweight and the metabolic syndrome in adult offspring of women with diet-treated gestational diabetes mellitus or type 1 diabetes. The Journal of Clinical Endocrinology & Metabolism. 2009;94(7):2464-2470.

66. Nijs H, Benhalima K. Gestational diabetes mellitus and the long-term risk for glucose intolerance and overweight in the offspring: A narrative review. Journal of clinical medicine. 2020;9(2):599.

67. Grunnet LG, Hansen S, Hjort L, et al. Adiposity, dysmetabolic traits, and earlier onset of female puberty in adolescent offspring of women with gestational diabetes mellitus: a clinical study within the Danish National Birth Cohort. Diabetes Care. 2017;40(12):1746-1755.

68. Clausen TD, Mathiesen ER, Hansen T, et al. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. Diabetes care. 2008;31(2):340-346.

69. Aviel-Shekler K, Hamshawi Y, Sirhan W, et al. Gestational diabetes induces behavioral and brain gene transcription dysregulation in adult offspring. Translational psychiatry. 2020;10(1):1-11.

70. Xiang AH, Wang X, Martinez MP, et al. Association of maternal diabetes with autism in offspring. Jama. 2015;313(14):1425-1434.

71. Xiang AH, Wang X, Martinez MP, et al. Maternal gestational diabetes mellitus, type 1 diabetes, and type 2 diabetes during pregnancy and risk of ADHD in offspring. Diabetes Care. 2018;41(12):2502-2508.

72. O'Sullivan J, Mahan C. Criteria for the oral glucose tolerance test in pregnancy. Diabetes 1964; 13: 278-285. Analytical Methods for Atomic Absorption Spectrophotometry Perkin-Elmer, Norwalk, Connecticut USA. 1971.

73. Coustan DR, Carpenter MW. Detection and treatment of gestational diabetes. Clinical obstetrics and gynecology. 1985;28(3):507-515.

74. Caughey AB, Turrentine M. ACOG PRACTICE BULLETIN: Gestational Diabetes Mellitus. Obstetrics and Gynecology. 2018;131(2):E49-E64.

75. Farrar D. Hyperglycemia in pregnancy: prevalence, impact, and management challenges. International journal of women's health. 2016:519-527.

76. Martin B, Sacks DA. The global burden of hyperglycemia in pregnancy–Trends from studies in the last decade. Diabetes research and clinical practice. 2018;145:17-19.

77. Thapar A, Rutter M. Neurodevelopmental disorders. Rutter's child and adolescent psychiatry. 2015:31-40.

78. Straub L, Bateman BT, Hernandez-Diaz S, et al. Neurodevelopmental disorders among publicly or privately insured children in the United States. JAMA psychiatry. 2022;79(3):232-242.

79. Zablotsky B, Black LI, Maenner MJ, et al. Prevalence and trends of developmental disabilities among children in the United States: 2009–2017. Pediatrics. 2019;144(4).

80. Chu AH, Godfrey KM. Gestational diabetes mellitus and developmental programming. Annals of Nutrition and Metabolism. 2020;76(3):4-15.

81. Chandna A, Kuhlmann N, Bryce C, et al. Chronic maternal hyperglycemia induced during mid-pregnancy in rats increases RAGE expression, augments hippocampal excitability, and alters behavior of the offspring. Neuroscience. 2015;303:241-260.

82. Vrachnis N, Antonakopoulos N, Iliodromiti Z, et al. Impact of maternal diabetes on epigenetic modifications leading to diseases in the offspring. Experimental diabetes research. 2012;2012.

83. Deth R, Muratore C, Benzecry J, et al. How environmental and genetic factors combine to cause autism: A redox/methylation hypothesis. Neurotoxicology. 2008;29(1):190-201.

84. Corrêa-Silva S, Alencar AP, Moreli JB, et al. Hyperglycemia induces inflammatory mediators in the human chorionic villous. Cytokine. 2018;111:41-48.

85. Buehler M. A proposed mechanism for autism: an aberrant neuroimmune response manifested as a psychiatric disorder. Medical hypotheses. 2011;76(6):863-870.

86. King GL, Loeken MR. Hyperglycemia-induced oxidative stress in diabetic complications. Histochemistry and cell biology. 2004;122(4):333-338.

87. Wells PG, McCallum GP, Chen CS, et al. Oxidative stress in developmental origins of disease: teratogenesis, neurodevelopmental deficits, and cancer. Toxicological sciences. 2009;108(1):4-18.

88. Teramo K, Klemetti M, Tikkanen M, et al. Maternal diabetes and fetal hypoxia. Duodecim; Laaketieteellinen Aikakauskirja. 2013;129(3):228-234.

89. Group HSCR. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. Diabetes. 2009;58(2):453-459.

90. Bryson CL, Ioannou GN, Rulyak SJ, et al. Association between gestational diabetes and pregnancy-induced hypertension. American journal of epidemiology. 2003;158(12):1148-1153.

91. Hedderson MM, Ferrara A, Sacks DA. Gestational diabetes mellitus and lesser degrees of pregnancy hyperglycemia: association with increased risk of spontaneous preterm birth. Obstetrics & Gynecology. 2003;102(4):850-856.

92. Coustan DR, Lowe LP, Metzger BE, et al. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus. American journal of obstetrics and gynecology. 2010;202(6):654. e651-654. e656.

93. Chen S, Zhao S, Dalman C, et al. Association of maternal diabetes with neurodevelopmental disorders: autism spectrum disorders, attention-deficit/hyperactivity disorder and intellectual disability. International journal of epidemiology. 2021;50(2):459-474.

94. Li M, Fallin MD, Riley A, et al. The association of maternal obesity and diabetes with autism and other developmental disabilities. Pediatrics. 2016;137(2).

95. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. The Lancet. 2016;387(10017):435-443.

96. Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and dementia—a comprehensive review. Therapeutic advances in neurological disorders. 2009;2(4):241-260.

97. Zhou B, Perel P, Mensah GA, et al. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. Nature Reviews Cardiology. 2021;18(11):785-802.

98. Sullivan SD, Umans JG, Ratner R. Gestational diabetes: implications for cardiovascular health. Current diabetes reports. 2012;12:43-52.

99. Wendland EM, Duncan BB, Belizán JM, et al. Gestational diabetes and pre-eclampsia: common antecedents? Arquivos Brasileiros de Endocrinologia & Metabologia. 2008;52:975-984.

100. Tobias DK, Hu FB, Forman JP, et al. Increased risk of hypertension after gestational diabetes mellitus: findings from a large prospective cohort study. Diabetes care. 2011;34(7):1582-1584.

101. Daly B, Toulis KA, Thomas N, et al. Increased risk of ischemic heart disease, hypertension, and type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: a population-based cohort study. PLoS medicine. 2018;15(1):e1002488.

102. Goueslard K, Cottenet J, Mariet A-S, et al. Early cardiovascular events in women with a history of gestational diabetes mellitus. Cardiovascular diabetology. 2016;15(1):1-7.

103. Shen Y, Li W, Leng J, et al. High risk of metabolic syndrome after delivery in pregnancies complicated by gestational diabetes. Diabetes research and clinical practice. 2019;150:219-226.

104. Maresh M, Lawrence J, Scholtens D, et al. Association of glucose metabolism and blood pressure during pregnancy with subsequent maternal blood pressure. Journal of human hypertension. 2022;36(1):61-68.

105. Heida KY, Franx A, Van Rijn BB, et al. Earlier age of onset of chronic hypertension and type 2 diabetes mellitus after a hypertensive disorder of pregnancy or gestational diabetes mellitus. Hypertension. 2015;66(6):1116-1122.

106. Huguet N, Kaufmann J, O'Malley J, et al. Using electronic health records in longitudinal studies: estimating patient attrition. Medical care. 2020;58:S46-S52.

107. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology. 2004:615-625.

108. Howe CJ, Cole SR, Chmiel JS, et al. Limitation of inverse probability-of-censoring weights in estimating survival in the presence of strong selection bias. American journal of epidemiology. 2011;173(5):569-577.

109. Brookhart MA, Stürmer T, Glynn RJ, et al. Confounding control in healthcare database research: challenges and potential approaches. Medical care. 2010;48(6 0):S114.

110. Young JC, Conover MM, Jonsson Funk M. Measurement error and misclassification in electronic medical records: methods to mitigate bias. Current epidemiology reports. 2018;5:343-356.

111. Walraven Cv. A comparison of methods to correct for misclassification bias from administrative database diagnostic codes. International Journal of Epidemiology. 2018;47(2):605-616.

112. Committee ADAPP, Committee: ADAPP. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2022. Diabetes Care. 2022;45(Supplement_1):S17-S38.

113. Venkatesh KK, Lynch CD, Powe CE, et al. Risk of Adverse Pregnancy Outcomes Among Pregnant Individuals With Gestational Diabetes by Race and Ethnicity in the United States, 2014-2020. JAMA. 2022;327(14):1356-1367.

114. Selen DJ, Thaweethai T, Schulte CC, et al. Gestational Glucose Intolerance and Risk of Future Diabetes. Diabetes Care. 2023;46(1):83-91.

115. Roeckner JT, Sanchez-Ramos L, Jijon-Knupp R, et al. Single abnormal value on 3-hour oral glucose tolerance test during pregnancy is associated with adverse maternal and neonatal outcomes: a systematic review and metaanalysis. American Journal of Obstetrics and Gynecology. 2016;215(3):287-297.

116. Basu R, Barosa C, Jones J, et al. Pathogenesis of prediabetes: role of the liver in isolated fasting hyperglycemia and combined fasting and postprandial hyperglycemia. The Journal of Clinical Endocrinology & Metabolism. 2013;98(3):E409-E417.

117. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of β-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes care. 2006;29(5):1130-1139.

118. Papachatzopoulou E, Chatzakis C, Lambrinoudaki I, et al. Abnormal fasting, post-load or combined glucose values on oral glucose tolerance test and pregnancy outcomes in women with gestational diabetes mellitus. Diabetes Research and Clinical Practice. 2020;161:108048.

119. Black MH, Sacks DA, Xiang AH, et al. Clinical outcomes of pregnancies complicated by mild gestational diabetes mellitus differ by combinations of abnormal oral glucose tolerance test values. Diabetes Care. 2010;33(12):2524-2530.

120. Kind AJ, Buckingham WR. Making neighborhood-disadvantage metrics accessible—the neighborhood atlas. The New England journal of medicine. 2018;378(26):2456.

121. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical care. 2005:1130-1139.

122. Charlson ME, Carrozzino D, Guidi J, et al. Charlson comorbidity index: a critical review of clinimetric properties. Psychotherapy and Psychosomatics. 2022;91(1):8-35.

123. Zou G. A modified poisson regression approach to prospective studies with binary data. American journal of epidemiology. 2004;159(7):702-706.

124. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal statistical society: series B (Methodological). 1995;57(1):289-300.

125. Pedula KL, Hillier TA, Schmidt MM, et al. Ethnic differences in gestational oral glucose screening in a large US population. Ethnicity & Disease. 2009;19(4):414-419.

126. Menke A, Casagrande S, Cowie CC. Contributions of A1c, fasting plasma glucose, and 2-hour plasma glucose to prediabetes prevalence: NHANES 2011–2014. Annals of epidemiology. 2018;28(10):681-685. e682.

127. Turcotte LP, Fisher JS. Skeletal muscle insulin resistance: roles of fatty acid metabolism and exercise. Physical therapy. 2008;88(11):1279-1296.

128. Meshkani R, Adeli K. Hepatic insulin resistance, metabolic syndrome and cardiovascular disease. Clinical biochemistry. 2009;42(13-14):1331-1346.

129. Katzmarzyk PT, Lee I-M, Martin CK, et al. Epidemiology of physical activity and exercise training in the United States. Progress in cardiovascular diseases. 2017;60(1):3-10.

130. Hong S, Chang Y, Jung H-S, et al. Relative muscle mass and the risk of incident type 2 diabetes: A cohort study. PloS one. 2017;12(11):e0188650.

131. US Census Bureau, Population Estimates. 2022.

132. Ronald Reagan UCLA Medical Center Community Health Needs Assessment. 2019.

133. Lavery J, Friedman A, Keyes K, et al. Gestational diabetes in the United States: temporal changes in prevalence rates between 1979 and 2010. BJOG: An International Journal of Obstetrics & Gynaecology. 2017;124(5):804-813.

134. Baraban E, McCoy L, Simon P. Peer Reviewed: Increasing Prevalence of Gestational Diabetes and Pregnancy-Related Hypertension in Los Angeles County, California, 1991–2003. Preventing chronic disease. 2008;5(3).

135. Lowe Jr WL, Scholtens DM, Kuang A, et al. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal gestational diabetes mellitus and childhood glucose metabolism. Diabetes care. 2019;42(3):372-380.

136. Lowe WL, Lowe LP, Kuang A, et al. Maternal glucose levels during pregnancy and childhood adiposity in the Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study. Diabetologia. 2019;62(4):598-610.

137. Lu J, Zhang S, Li W, et al. Maternal gestational diabetes is associated with offspring's hypertension. American journal of hypertension. 2019;32(4):335-342.

138. Chen KR, Yu T, Lien YJ, et al. Childhood neurodevelopmental disorders and maternal diabetes: A population-based cohort study. Developmental Medicine & Child Neurology. 2023;65(7):933-941.

139. Connolly N, Anixt J, Manning P, et al. Maternal metabolic risk factors for autism spectrum disorder—an analysis of electronic medical records and linked birth data. Autism research. 2016;9(8):829-837.

140. Sacks KN, Friger M, Shoham-Vardi I, et al. Prenatal exposure to gestational diabetes mellitus as an independent risk factor for long-term neuropsychiatric morbidity of the offspring. American journal of obstetrics and gynecology. 2016;215(3):380. e381-380. e387.

141. American Psychiatric Association D, Association AP. Diagnostic and statistical manual of mental disorders: DSM-5: American psychiatric association Washington, DC 2013.

142. Avenevoli S, Baio J, Bitsko RH, et al. Mental health surveillance among children--United States, 2005-2011. 2013.

143. ACOG. American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Obstetrics. Clinical management guidelines for obstetrician-gynecologists. Number 30, September 2001 (replaces Technical Bulletin Number 200, December 1994). Gestational diabetes. Obstetrics and Gynecology. 2001;98:525-538.

144. Hsu S, Selen DJ, James K, et al. Assessment of the Validity of Administrative Data for Gestational Diabetes Ascertainment. American Journal of Obstetrics & Gynecology MFM. 2023;5(2):100814.

145. Disabilities CoCW, Pediatrics SoDB, Committee BFS, et al. Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening. Pediatrics. 2006;118(1):405-420.

146. Lipkin PH, Macias MM, Norwood KW, et al. Promoting optimal development: identifying infants and young children with developmental disorders through developmental surveillance and screening. Pediatrics. 2020;145(1).

147. Hyman SL, Levy SE, Myers SM, et al. Identification, evaluation, and management of children with autism spectrum disorder. Pediatrics. 2020;145(1).

148. Wolraich ML, Hagan JF, Allan C, et al. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2019;144(4).

149. Siu AL. Screening for speech and language delay and disorders in children aged 5 years or younger: US Preventive Services Task Force recommendation statement. Pediatrics. 2015;136(2):e474-e481.

150. Straub L, Bateman BT, Hernandez-Diaz S, et al. Validity of claims-based algorithms to identify neurodevelopmental disorders in children. Pharmacoepidemiology and Drug Safety. 2021;30(12):1635-1642.

151. Straub L, Hernández-Díaz S, Bateman BT, et al. Association of antipsychotic drug exposure in pregnancy with risk of neurodevelopmental disorders: a national birth cohort study. JAMA internal medicine. 2022;182(5):522-533.

152. Aris IM, Kleinman KP, Belfort MB, et al. A 2017 US reference for singleton birth weight percentiles using obstetric estimates of gestation. Pediatrics. 2019;144(1).

153. Lesko CR, Edwards JK, Cole SR, et al. When to censor? American journal of epidemiology. 2018;187(3):623-632.

154. Xiang AH, Chow T, Martinez MP, et al. Hemoglobin A1c levels during pregnancy and risk of autism spectrum disorders in offspring. JAMA. 2019;322(5):460-461.

155. Zhang M, Gazimbi MM, Chen Z, et al. Association between birth weight and neurodevelopment at age 1–6 months: results from the Wuhan Healthy Baby Cohort. BMJ open. 2020;10(1):e031916.

156. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. Child's nervous system. 2010;26(9):1139-1149.

157. Gumusoglu SB, Chilukuri AS, Santillan DA, et al. Neurodevelopmental outcomes of prenatal preeclampsia exposure. Trends in neurosciences. 2020;43(4):253-268.

158. Alegria M, Vallas M, Pumariega AJ. Racial and ethnic disparities in pediatric mental health. Child and Adolescent Psychiatric Clinics. 2010;19(4):759-774.

159. Mandell DS, Listerud J, Levy SE, et al. Race differences in the age at diagnosis among Medicaid-eligible children with autism. Journal of the American Academy of Child & Adolescent Psychiatry. 2002;41(12):1447-1453.

160. Association AD. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2021. Diabetes care. 2021;44(Supplement 1):S15-S33.

161. Webber J, Charlton M, Johns N. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period (NG3). British Journal of Diabetes. 2015;15(3):107-111.

162. Drapeau A, Marchand A, Beaulieu-Prevost D. Epidemiology of psychological distress. Mental illnesses-understanding, prediction and control. 2012;69(2):105-106.

163. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nature Reviews Nephrology. 2020;16(4):223-237.

164. Arafa A, Dong J-Y. Depression and risk of gestational diabetes: A meta-analysis of cohort studies. Diabetes research and clinical practice. 2019;156:107826.

165. Minschart C, De Weerdt K, Elegeert A, et al. Antenatal depression and risk of gestational diabetes, adverse pregnancy outcomes, and postpartum quality of life. The Journal of Clinical Endocrinology & Metabolism. 2021;106(8):e3110-e3124.

166. Beka Q, Bowker S, Savu A, et al. History of mood or anxiety disorders and risk of gestational diabetes mellitus in a population-based cohort. Diabetic Medicine. 2018;35(1):147-151.

167. Hinkle SN, Buck Louis GM, Rawal S, et al. A longitudinal study of depression and gestational diabetes in pregnancy and the postpartum period. Diabetologia. 2016;59(12):2594-2602.

168. Liu M-Y, Li N, Li WA, et al. Association between psychosocial stress and hypertension: a systematic review and meta-analysis. Neurological research. 2017;39(6):573-580.

169. Babu GR, Jotheeswaran A, Mahapatra T, et al. Republished: is hypertension associated with job strain? A meta-analysis of observational studies. Postgraduate medical journal. 2014;90(1065):402-409.

170. Meng L, Chen D, Yang Y, et al. Depression increases the risk of hypertension incidence: a meta-analysis of prospective cohort studies. Journal of hypertension. 2012;30(5):842-851.

171. Pan Y, Cai W, Cheng Q, et al. Association between anxiety and hypertension: a systematic review and meta-analysis of epidemiological studies. Neuropsychiatric disease and treatment. 2015:1121-1130.

172. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):264-269.

173. Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. The Lancet. 2002;359(9303):341-345.

174. Tam W-H, Ma RC-W, Yang X, et al. Cardiometabolic risk in Chinese women with prior gestational diabetes: a 15-year follow-up study. Gynecologic and obstetric investigation. 2012;73(2):168-176.

175. Zhang J, Kai FY. What's the relative risk?: A method of correcting the odds ratio in cohort studies of common outcomes. Jama. 1998;280(19):1690-1691.

176. Gidwani R, Russell LB. Estimating transition probabilities from published evidence: a tutorial for decision modelers. Pharmacoeconomics. 2020;38(11):1153-1164.

177. Borenstein M, Hedges LV, Higgins JP, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. Research synthesis methods. 2010;1(2):97-111.

178. Cochran WG. The combination of estimates from different experiments. Biometrics. 1954;10(1):101-129.

179. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002;21(11):1539-1558.

180. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994:1088-1101.

181. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315(7109):629-634.

182. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European journal of epidemiology. 2010;25:603-605.

183. Inoue K, Beekley J, Goto A, et al. Depression and cardiovascular disease events among patients with type 2 diabetes: A systematic review and meta-analysis with bias analysis. Journal of Diabetes and its Complications. 2020;34(12):107710.

184. Arah OA. Bias analysis for uncontrolled confounding in the health sciences. Annual review of public health. 2017;38:23-38.

185. Goto A, Arah OA, Goto M, et al. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. Bmj. 2013;347.

186. Arah OA, Chiba Y, Greenland S. Bias formulas for external adjustment and sensitivity analysis of unmeasured confounders. Annals of epidemiology. 2008;18(8):637-646.

187. Viechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of statistical software. 2010;36(3):1-48.

188. Pathirana MM, Lassi Z, Ali A, et al. Cardiovascular risk factors in women with previous gestational diabetes mellitus: a systematic review and meta-analysis. Reviews in Endocrine and Metabolic Disorders. 2021;22(4):729-761.

189. Catalano PM, Kirwan JP, Haugel-de Mouzon S, et al. Gestational diabetes and insulin resistance: role in short-and long-term implications for mother and fetus. The Journal of nutrition. 2003;133(5):1674S-1683S.

190. Mancusi C, Izzo R, di Gioia G, et al. Insulin resistance the hinge between hypertension and type 2 diabetes. High Blood Pressure & Cardiovascular Prevention. 2020;27:515-526.

191. McKenzie-Sampson S, Paradis G, Healy-Profitós J, et al. Gestational diabetes and risk of cardiovascular disease up to 25 years after pregnancy: a retrospective cohort study. Acta diabetologica. 2018;55:315-322.

192. Pirkola J, Pouta A, Bloigu A, et al. Prepregnancy overweight and gestational diabetes as determinants of subsequent diabetes and hypertension after 20-year follow-up. The Journal of Clinical Endocrinology & Metabolism. 2010;95(2):772-778.

193. Kaul P, Savu A, Nerenberg K, et al. Impact of gestational diabetes mellitus and high maternal weight on the development of diabetes, hypertension and cardiovascular disease: a population-level analysis. Diabetic Medicine. 2015;32(2):164-173.

194. Noctor E, Crowe C, Carmody LA, et al. ATLANTIC-DIP: prevalence of metabolic syndrome and insulin resistance in women with previous gestational diabetes mellitus by International Association of Diabetes in Pregnancy Study Groups criteria. Acta Diabetologica. 2015;52:153-160.

195. Parikh NI, Norberg M, Ingelsson E, et al. Association of pregnancy complications and characteristics with future risk of elevated blood pressure: the Västerbotten Intervention Program. Hypertension. 2017;69(3):475-483.

196. Li L-J, Aris IM, Su LL, et al. Effect of gestational diabetes and hypertensive disorders of pregnancy on postpartum cardiometabolic risk. Endocrine connections. 2018;7(3):433.

197. Yu Y, Soohoo M, Sørensen HT, et al. Gestational diabetes mellitus and the risks of overall and type-specific cardiovascular diseases: a population-and sibling-matched cohort study. Diabetes Care. 2022;45(1):151-159.

198. Wulan S, Westerterp K, Plasqui G. Ethnic differences in body composition and the associated metabolic profile: a comparative study between Asians and Caucasians. Maturitas. 2010;65(4):315-319.

199. Wang J, Thornton JC, Russell M, et al. Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. The American journal of clinical nutrition. 1994;60(1):23-28.