June 2022

Preterm Birth and Subsequent Risk of Type 2 Diabetes Among Postmenopausal Women in the Women's Health Initiative

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A Thesis Presented

By

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Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

MASTER OF SCIENCE

May 2022

Master of Science in Epidemiology

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ACKNOWLEDGEMENTS

First off, I would like to greatly thank Dr. Spracklen for her enormous attention and assistance she has provided me with throughout the years I've known her. From sparking my interest in epidemiology to working with me through much of my graduate program, her efforts to aid my success are grand and greatly appreciated.

Secondly, I would like to thank Dr. Lisa Chasan-Taber for serving on my committee and helping me create a foundation for my research. She was essential to getting the ball rolling, and showed me how far I could roll it.

Finally, I would like to thank my family and peers. Their consistent support through difficult times ensured that I could prevail. I would not have been able to continue pursuing this achievement without the lasting support of those dear to me.

ABSTRACT

PRETERM BIRTH AND SUBSEQUENT RISK OF TYPE 2 DIABETES AMONG POSTMENOPAUSAL WOMEN IN THE WOMEN'S HEALTH INITIATIVE

MAY 2022

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Type 2 diabetes (T2D) is increasing in the United States, currently affecting 11.3% of the nation. The Developmental Origins of Health and Disease Hypothesis suggests that environmental stresses *in utero* and in early stages of life, such as preterm birth (<37 weeks gestational age), can lead to development of adulthood diseases, including T2D. However, research on the association between preterm birth and T2D is sparse and predominantly based on European ancestry populations. We examined this association in postmenopausal women (N = 85,356) from the Women's Health Initiative, a nationwide prospective cohort. Logistic regression models were used to examine the association between self-reported preterm birth and T2D status, adjusting for demographic and lifestyle covariates. Preterm birth was significantly and positively associated with odds of T2D at baseline (unadjusted: OR=1.51, 95% CI 1.24, 1.83; P<0.0001). The association remained significant and strengthened after adjustment for demographic (OR=1.78, 95% CI 1.40-2.27; P<0.0001) and lifestyle factors (OR=1.78, 95% CI 1.38-2.30; P<0.0001). Sensitivity analyses restricted to women born in the lowest birth weight category (<6 pounds), confirmed the significant, positive association between preterm birth and T2D. Logistic regression models stratified by race/ethnicity suggested the positive associations were consistent across race/ethnic groups, but most of the analyses were underpowered. Examining the relationship between preterm birth and T2D will further our understanding of T2D development, and contribute to the prevention of the disease and its complications.

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CHAPTER 1

INTRODUCTION

1.1 Overview and Public Health Significance of Type 2 Diabetes

T2D is a chronic health condition that affects the body's ability to utilize insulin. Insulin is a hormone secreted by the pancreas that allows cells to intake glucose and generate energy for the body.[1] Cells in the body of a person with T2D become insulin resistant, meaning they do not properly intake glucose from the bloodstream, resulting in high blood glucose.[1]

A diagnosis of diabetes can result from various tests that examine blood glucose. A fasting blood glucose test can be conducted with a simple blood test following an overnight (≥8 hours) fast, and a resulting blood glucose of greater than 126 mg/dL indicates diabetes.[1] A glucose tolerance test also measures fasting blood glucose; patients are to drink a liquid with high glucose content, and then blood draws are performed at one, two, and sometimes three hours after drinking the liquid to measure the glucose response. A blood glucose of over 200 mg/dL at the two hour mark indicates diabetes.[1] Additionally, an hemoglobin A1C (HbA1c) test can measure a person's average blood glucose over the past two or three months; an HbA1c level of 6.5% or higher indicates diabetes.[1] All of these tests indicate *any* diabetes; to diagnose diabetes as type 2, the patient must not be pregnant, and tests to identify indicators of type 1 diabetes, such as blood tests for autoantibodies or urine tests for ketones, must result negative.

T2D is a rising issue across the nation as approximately one in ten Americans is diagnosed with diabetes, the majority of which are T2D.[1] By 2030, it is predicted that the prevalence of T2D will reach 54.9 million Americans.[2] As of 2017, the global prevalence of T2D was 6.8%, equaling roughly 462 million individuals.[3] The prevalence of T2D is rising even more rapidly in low- to middle-income countries.[4] T2D prevalence is higher among men (14%) as compared to women (12%) in the United States.[5] However, women have more severe complications of diabetes, and have a higher risk of developing comorbidities such as cardiovascular disease when compared to men.[6,7] Descriptive epidemiology studies of T2D have

also indicated differences in T2D prevalence by self-reported racial/ethnic category in the United States. In 2017, T2D prevalence was estimated to be 9.0% in Asians, 13.2% in African-Americans, 12.8% in Hispanics, 7.6% in Non-Hispanic Whites, 6.0% in Alaskan Natives, and 24.1% in southern Arizona Native Americans.[8] Insulin resistance has also been found to be higher in all racial/ethnic groups when compared to Non-Hispanic Whites.[9]

There is no cure for T2D and treatment of T2D is largely centered around self-management. Self-management of T2D includes healthy eating, exercising, maintaining a healthy weight, and monitoring your own blood glucose. Healthy eating involves eating on a regular schedule, increasing fiber intake, reducing refined grains, and eating moderate amounts of low-fat diary, meats and fish.[10] Exercise for adults with T2D should include at least 150 minutes of aerobic exercise a week, such as walking, running, or swimming, in addition to two or three sessions of resistance exercise, such as sports, weight lifting, or yoga.[10] People with T2D can monitor their own blood glucose using a glucometer, and may need to do so multiple times daily in order to detect periods of high blood glucose. In addition to self-management, a healthcare provider may prescribe diabetes medication to help regulate blood glucose such as Metformin, which works to increase insulin sensitivity and results in improving the body's ability to utilize insulin.[10] Additionally, insulin therapy may be a form of treatment for T2D, which involves injecting long-lasting and fast-acting insulin for sleeping overnight and eating meals during the day, respectively.

T2D has the potential to significantly reduce quality of life and lead to diagnosis of other serious health conditions or comorbidities. Adults with diabetes are twice as likely to have heart disease than adults without diabetes and at a younger age.[1] Compared to people without diabetes, people with diabetes are also more likely to have symptoms of heart disease as well, such as high blood pressure and high LDL cholesterol. Heart disease can result in hospitalization or death. Similarly, adults with diabetes are more likely to be diagnosed with chronic kidney disease (CKD), affecting as many as one in three adults with diabetes.[1] Advanced CKD requires dialysis

or a kidney transplant for survival. High blood glucose from diabetes also increases sugar content in saliva, making it easier for the bacteria in plaque to survive, which will contribute to tooth damage and potential tooth loss.[1]

Diabetes also causes nerve damage over time. Diabetic neuropathy is a possible result of chronic high blood glucose, and can result in a range of outcomes: numbness or weakness; bladder and bowel problems; severe pain in the hip, thigh, buttock, and stomach; and aches behind the eyes. Diabetic neuropathy, in combination with blood vessels in the retina being damaged due to high blood glucose, can also cause blurry vision.[1] In addition, the nerve signals that travel between the inner ear and brain can be damaged, resulting in hearing loss.[1] When combined with nerve damage in the feet, poor blood flow can cause ulcers, which can become infected. However, patients often fail to notice their foot ulcers due to reduced feeling from nerve damage, and, if left unchecked, may result in amputation. Lastly, the consequences of having diabetes can become overwhelming and can very easily reduce quality of life and negatively impact mental health.[1]

1.2 Epidemiology of Type 2 Diabetes

T2D has multiple modifiable and non-modifiable risk factors. Modifiable risk factors include being overweight, physically active less than three times a week, and having a diagnosis of prediabetes.[10] Non-modifiable risk factors include age, fat distribution, family history of T2D/genetic predisposition, race and ethnicity (more common in individuals who identify as Black, Hispanic, Native American, and Asian), blood lipid levels, and having gestational diabetes in the past.[1,10]

Obesity is a major contributor to the onset of diabetes. Being overweight or obese increases the number of bodily substances that induce insulin resistance, including nonesterified fatty acids (NEFAs), glycerol, hormones, cytokines, and proinflammatory markers.[11] It is also hypothesized that the NEFAs secreted by excessive adipose tissue in obese people contribute to

β-cell dysfunction,[11] which results in reduced insulin production. Physical inactivity is a risk factor largely through its interaction with obesity. Physical inactivity will accelerate the pathogenesis of T2D by allowing adipose tissue to accumulate.[12] Being physically active, on the other hand, will increase insulin sensitivity in the presence of weight loss,[12] making physical inactivity and physical activity expected opposites as a risk factor and protective factor, respectively. Often seen in conjunction with obesity and physical inactivity, prediabetes is a condition where blood glucose levels are elevated, but not enough to cause a T2D diagnosis.[1] 15-30% of individuals with prediabetes progress to T2D.[1]

Additional risk factors of T2D have been studied. An increase in systolic blood pressure is associated with increased risk of T2D, but the biological mechanism explaining the association is not clear.[13,14,15] Smoking is another significant risk factor[13] as it promotes adverse fat distribution in the body via nicotine signaling,[16] which contributes to obesity. Additionally, the effects of smoking reduce insulin sensitivity and impair β-cell function, resulting in both ineffective use and production of insulin.[16] Similarly, repeated awakenings during the night, insufficient sleep, excessive sleep, and irregular sleep lead to reduced insulin sensitivity, even in otherwise healthy individuals that lack other common risk factors of T2D.[17] When total cholesterol varies greatly within an individual over time, the risk of developing T2D increases.[18] Further, low HDL cholesterol increases the risk of T2D,[19] and a large cholesterol ratio (total cholesterol divided by HDL cholesterol) increases the risk of T2D.[20] Also, low levels of testosterone[21] and sex hormone binding globulin[22] are both associated with increased risk of T2D.

1.3 Preterm Birth and the Risk for Type 2 Diabetes

The Developmental Origins of Health and Disease Hypothesis (DOHaD) hypothesis (also known as the Fetal Origins Hypothesis or Barker Hypothesis) states that environmental stresses *in utero* and in early stages of life influence one's risk for developing non-communicable diseases across the lifecourse.[23] Developmental plasticity refers to a human being's ability to adapt to their

environment *in utero*, and it is during the critical periods of developmental plasticity that changes to growth occur which can contribute to the development of adulthood diseases.[23] For example, Barker describes how a mother that is malnourished will send 'signals' to the baby to essential warn it that there will be a lack of nutrients after birth. As a result of the maternal signals, the baby will adapt its developmental processes, essentially 'reprogramming' the infant to reduce its body size and alter its metabolism.[23] The adaptations performed *in utero* can have lasting effects on the human being, which connect to non-communicable disease throughout childhood and adulthood.

Preterm birth, or being born at or before 37 weeks gestation, is one event that might trigger changes in a baby's growth that are described in the DOHaD.[23] Babies born prematurely do not finish the entire growth process during pregnancy, which is detrimental to their health as the brain, lungs, and liver fully develop during the last few weeks of pregnancy.[1] Without the completion of crucial organ development, it is possible that lasting issues throughout childhood and adulthood could be set in motion at infancy.[23]

Worldwide, nearly 11% of births occur preterm,[24] but this rate is not equal across racial/ethnic groups as, for example, preterm birth rates in African-Americans (14.4%) are much higher than preterm birth rates in Non-Hispanic Whites or Hispanics (9.1% and 9.8%, respectively).[1] Previous work has suggested preterm birth may contribute to T2D.[24,25,26,27,28] However, the prior work has focused on White, non-Hispanic populations, which may not be generalizable to other populations, especially those individuals who are at higher risk for T2D.

1.4 Physiologic Mechanisms of the Relationship between Preterm Birth and Type 2 Diabetes

A physiological mechanism for the association between preterm birth and T2D is not clearly established, but the DOHaD may provide a reasonable theory. Following this assumption, it is believed that fetal malnutrition negatively modifies fetal glucose metabolism. Lasting hormonal and metabolic adaptations resulting from fetal malnutrition lead to insulin resistance,[27]

which causes chronic high blood glucose, and, in turn, T2D. While the standard cause effect in the DOHaD is low birthweight,[27] there is reason to believe preterm birth can be substituted in this hypothesis as fetal malnutrition can also lead to preterm birth.

1.5 Study Objectives, Significance, and Innovation

This study proposes to evaluate the relationship between being born preterm and risk for T2D. Specifically, the aims of the study are:

Aim 1A: To assess the relationship between preterm birth and risk for T2D among postmenopausal women from the Women's Health Initiative

Hypothesis 1A: Among postmenopausal women from the Women's Health Initiative, those born preterm will be at increased risk of developing T2D as compared to those born full term.

Aim 1 B: To assess for an interaction of race/ethnicity on the relationship between preterm birth and risk for T2D among postmenopausal women from the Women's Health Initiative

Hypothesis 1B: Among postmenopausal women from the Women's Health Initiative, the association between preterm birth and T2D will differ between race/ethnicity groups.

This proposal is **innovative** because it will be the first, to our knowledge, to study preterm birth as a risk factor for T2D stratified by race/ethnicity. This proposal is **significant** because T2D is a global problem, leading to a tremendous loss of quality of life, and contributes to overall mortality. Understanding preterm birth as a risk factor for T2D could aid our efforts, as a society, to intervene early among those at risk for T2D.

CHAPTER 2

METHODS

2.1 Women's Health Initiative

The Women's Health Initiative (WHI) is an ongoing national health study that focuses on evaluating cardiovascular disease, cancers, and osteoporotic fractures in postmenopausal women. Briefly, the WHI is a prospective cohort study that recruited postmenopausal women aged 50-79 from 1993-1998 into either the clinical trials (WHI-CT; n = 67,932) or the observational study (WHI-OS; n = 93,676).[29] Details on the WHI's study design, recruitment, and implementation have been described elsewhere.[30,31] All study protocols were approved by the Institutional Review Board of each participating clinical center, and all participants provided written informed consent at study initiation.

2.2 Baseline Measures

When women enrolled into the WHI-OS, they completed structured, self-administered questionnaires that aimed to collect information on demographics, medical history, reproductive history, family history, personal habits such as drinking and smoking, diet, physical activity, and psychosocial factors. Women were asked to report if they were born full term or four or more weeks premature ("preterm"). They were also asked to report if they were born as a twin or triplet and reported their birth weight as one of the following categories: less than 6 pounds (lbs), 6 lbs to 7 lbs 15 ounces (oz), 8 lbs to 9 lbs 15 oz, or 10 or more lbs. A physical assessment was performed at baseline by trained study staff to collect physical measurements, such as height, weight, and blood pressure. Participants were also asked to bring their medications with them to the physical assessment to be recorded by the trained study staff.

2.3 Outcome Definitions and Measurement

Data on prevalent diabetes status were obtained at baseline through the self-reported questionnaires. Women were asked to report if "a doctor had ever told them they had sugar diabetes or high blood sugar when they were not pregnant" (yes/no), their age when they were first told they had sugar diabetes, by category (<21, 21-29, 30-39, 40-49, 50-59, 60-69, or 70 or older), and if they ever took insulin shots or diabetes pills (yes/no). To limit the diabetes cases to only those with type 2 diabetes, we used the following criteria: 1) self-reported physician diagnosis of 'sugar diabetes or high blood sugar when they were not pregnant'; 2) ≥30 years of age at first diagnosis; and 3) self-reported using insulin or diabetes pills as a treatment for their diabetes. While it is possible that women with type 1 diabetes could still be included in our analyses, this definition has been validated in WHI and is consistent with medication inventories and fasting glucose measurements with a concordance of 77%.[32]

2.4 Study Exclusion Criteria

For our analyses, women were excluded if they reported being a twin or triplet (n = 1,418), were <30 years of age at the time of their diabetes diagnosis (n = 215), or reported being hospitalized for a diabetic coma (n = 72). In analyses stratified by birth weight and race/ethnicity, women were excluded if they were missing data on their birth weight or race/ethnicity, respectively.

2.5 Statistical Analysis

Descriptive statistics for participants included in the analyses were generated using t-tests for continuous variables and chi-square tests for categorical variables. Logistic regression models estimated odds ratios (OR) and 95% confidence intervals (95% CI) for the association between preterm birth and prevalent T2D with and without adjustments for demographic and lifestyle factors. In all models, we used "full term birth" as the referent category. Covariates selected for

inclusion in our models are well-known risk factors for T2D and include baseline measures for age, Normalized Socio-Economic Status (NSES), geographic region, educational level, race/ethnicity, family history of diabetes, BMI, smoking status, and alcohol use. Because of the prior association between birth weight and T2D,[26] we also present models with and without adjustment for birth weight category. However, because birth weight and gestational age (including preterm birth) are strongly correlated, adjustment for birth weight category can adjust away part or all of an association between preterm birth and T2D; as such, we also present results stratified by birth weight category. Additional logistic regression models were used to examine possible effect modification by race/ethnicity. Statistical tests were two-sided, and p-values <0.05 were considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

CHAPTER 3

Results

Baseline characteristics were compared between preterm and full term participants (Table 1). Women born preterm were more likely to be younger at baseline and have a higher level of education than women born full term. Women born preterm also had a slightly higher mean BMI at baseline than women born full term. At baseline, women born preterm and those born at term were similar with respect to other characteristics, including family history of T2D, geographic location, self-reported race/ethnicity, smoking status, and alcohol consumption.

We then calculated the unadjusted and adjusted odds ratios for the association between preterm birth status and T2D (Table 2). Preterm birth was significantly and positively associated with odds of T2D at baseline (unadjusted: OR=1.51, 95% CI 1.24, 1.83; P<0.0001). The association remained significant and strengthened after adjustment for demographic (OR=1.78, 95% CI 1.40-2.27; P<0.0001) and lifestyle factors (OR=1.78, 95% CI 1.38-2.30; P<0.0001).

As expected, models that included adjustment for birth weight category demonstrated an attenuated association between preterm birth status and T2D (Table 2). To consider the potential relationships of birth weight and preterm birth status with T2D separately, we calculated unadjusted and adjusted odds of T2D stratified by preterm birth status (Table 3). Even when limiting our analyses to women born in the lowest birth weight category (<6 lbs), a significant, positive association between preterm birth and T2D was observed in both the demographic- (adjOR=1.49, 95% CI 1.11-2.00) and demographic and lifestyle-adjusted models (adjOR=1.48, 95% CI 1.09-2.01).

Results from stratification by race/ethnicity are presented in Table 4. Similar to the overall results, we observed a positive association between preterm birth and T2D in women who identified as White in both the unadjusted (OR=1.79, 95% CI 1.43-2.23) and adjusted models (adjOR=1.94, 95% CI 1.46-2.60). We did not have sufficient power within the other race/ethnicity categories to identify significant associations. However, the results still suggest a

positive association between preterm birth and T2D among women who identified as African American, Asian or Pacific Islander, Hispanic/Latino, and Other.

Table 1: Baseline characteristics of 85,356 WHI participants by birth status			
	Born Preterm	**Born Full term**	**Pa**
	N = 1,999	**N = 83,357**	
Age at baseline (mean, STD)	62.0 (7.3)	63.5 (7.4)	<.0001
Family History of type 2 diabetes (N, %)			0.29
No	1,316 (68.8)	53,939 (67.6)	
Yes	598 (31.2)	25,832 (32.4)	
NSES (mean, STD)	75.3 (8.6)	75.3 (8.7)	0.82
BMI (mean, STD)	27.7 (6.0)	27.2 (5.8)	0.0003
Geographic Region (N, %)			0.20
Northeast	415 (20.8)	19,001 (22.8)	
South	533 (26.7)	21,567 (25.9)	
Midwest	457 (22.9)	18,494 (22.2)	
West	594 (29.7)	24,295 (29.1)	
Education (N, %)			0.0003
<High school diploma/GED	352 (17.8)	17,312 (20.9)	
School after high school	949 (47.9)	39,701 (48.0)	
College degree or higher	681 (34.4)	25,692 (31.1)	
Race/Ethnicity (N, %)			0.25
White	1,690 (85.4)	70,003 (84.5)	
Black	162 (8.2)	6,538 (7.9)	
Asian/Pacific Islander	41 (2.1)	2,275 (2.8)	
Hispanic	62 (3.1)	3,076 (3.7)	
Other	23 (1.2)	920 (1.1)	
Smoking Status (N, %)			0.10
Never	1,018 (51.7)	41,650 (50.6)	
Past	812 (41.2)	35,489 (43.1)	
Current	141 (7.2)	5,137 (6.3)	
Alcohol Consumption (N, %)			0.41
Never	215 (10.9)	9,475 (11.5)	
Past	447 (22.5)	17,718 (21.5)	
Current	1,321 (66.6)	55,417 (67.1)	

Note. P-values are from t-tests and chi-square statistics and compare women born preterm to women born full term.

Table 2: Relationship between Preterm Birth and Type 2 Diabetes among postmenopausal women in the WHI			
	Birth Status		Pa
	Preterm OR (95% CI)	Full term OR (95% CI)	
N	1,999	83,357	
Type 2 Diabetes			
Unadjusted (cases = 3,326)	1.51 [1.24 , 1.83]	1.00 [Ref]	<.0001
Unadjusted & Birthweight (cases = 2,916)	1.13 [0.91 , 1.34]	1.00 [Ref]	0.27
Adj for Demographics (cases=2,132)	1.78 [1.40 , 2.27]	1.00 [Ref]	<.0001
Adj for Demographics & Birthweight (cases=1,899)	1.43 [1.09 , 1.87]	1.00 [Ref]	0.0102
Adj for Demographic & Lifestyle Factors (cases=2,063)	1.78 [1.38 , 2.30]	1.00 [Ref]	<.0001
Adj for Demographic & Lifestyle Factors & Birthweight (cases=1,839)	1.44 [1.08 , 1.90]	1.00 [Ref]	0.0125

Table 3: Relationship between Preterm Birth and Type 2 Diabetes among postmenopausal women in the WHI stratified by Birthweight				
	Birthweight Category			
	< 6 lbs OR (95% CI)	**6-7.9 lbs OR (95% CI)**	**8-9.9 lbs OR (95% CI)**	**≥ 10 lbs OR (95% CI)**
N (T2D Cases)	7876 (435 cases)	51107 (1,851 cases)	15171 (524 cases)	2595 (106 cases)
Type 2 Diabetes				
Unadjusted (cases=2,916)	1.18 [0.94 , 1.48]	0.60 [0.27 , 1.35]	**3.37 [1.01 , 11.19]**	---
Adj for Demographics (cases=1,899)	**1.49 [1.11 , 2.00]**	0.96 [0.42 , 2.19]	1.32 [0.17 , 10.51]	---
Adj for Demographics & Lifestye Factors (1,839)	**1.48 [1.09 , 2.01]**	1.06 [0.46 , 2.44]	1.58 [0.19 , 13.18]	---

Note. Referent group is full term births. OR, 95% CI: 1.00, [Ref]

Table 4: Relationship between Preterm Birth and Type 2 Diabetes among postmenopausal women in the WHI stratified by Race/Ethnicity					
	Race/Ethnicity				
	White OR (95% CI)	**Black or African American OR (95% CI)**	**Asian or Pacific Islander OR (95% CI)**	**Hispanic/Latino OR (95% CI)**	**Other OR (95% CI)**
N (T2D cases)	71,693 (2,100 cases)	6700 (783 cases)	2316 (116 cases)	3138 (220 cases)	943 (47 cases)
Type 2 Diabetes					
Unadjusted (cases=3,266)	**1.79 [1.43 , 2.23]**	0.94 [0.58 , 1.55]	0.97 [0.23 , 4.08]	1.71 [0.77 , 3.80]	0.86 [0.11 , 6.55]
Unadjusted & Birthweight (cases = 2,871)	**1.32 [1.03 , 1.70]**	0.87 [0.51 , 1.48]	1.04 [0.24 , 4.57]	1.21 [0.51 , 2.87]	0.76 [0.08 , 7.05]
Adj for Demographics (cases = 2,132)	**1.99 [1.51 , 2.64]**	1.29 [0.73 , 2.27]	1.41 [0.31 , 6.35]	1.34 [0.39 , 4.58]	2.04 [0.24 , 17.47]
Adj for Demographics & Birthweight (cases=1,899)	**1.52 [1.11 , 2.09]**	1.22 [0.65 , 2.28]	1.43 [0.28 , 7.18]	0.88 [0.24 , 3.20]	1.22 [0.11 , 13.69]
Adj for Demographics & Lifestye Factors (cases = 2,063)	**1.94 [1.46 , 2.60]**	1.41 [0.78 , 2.56]	1.06 [0.20 , 5.72]	1.32 [0.38 , 4.65]	3.81 [0.44 , 33.01]
Adj for Demographics & Lifestye Factors & Birthweight (cases = 1,839)	**1.49 [1.07 , 2.07]**	1.23 [0.64 , 2.37]	0.87 [0.14 , 5.51]	0.94 [0.25 , 3.57]	1.87 [0.16 , 21.82]

Note. Referent group is full term births. OR, 95% CI: 1.00, [Ref]

CHAPTER 4

DISCUSSION

In the well-established Women's Health Initiative cohort of postmenopausal women, we found that women born prematurely were at increased odds of developing T2D compared to women born full term. Adjustment for demographic and lifestyle factors weakened, but did not eliminate, this relationship.

4.1 Comparison with Prior Literature

To our knowledge, five epidemiologic studies have evaluated the relationship between preterm birth and risk of T2D, including two prospective cohort studies[24,26] and three cross-sectional studies.[25,27,28] Three studies adjusted for birth weight in analyses assessing this relationship.[25,26,28] Consistent with our cross-sectional results, all five studies identified statistically significant associations between preterm birth and T2D (HR/OR range: 1.26-2.45). The range in effect size is most likely explained by methodological differences in study design. Two studies excluded participants with birth weights greater than 2 SDs[25] or 4 SDs[27] above or below the mean birth weight relative to gestational age. While our study relied on self-report of preterm birth, prior studies used medical records to obtain the exposure status.[24,25,26,27,28] Outcome status was frequently obtained from medical records,[24,27] national registry,[25] or following oral glucose tolerance test upon study enrollment,[26] but two studies, including ours, relied on self-report.[28] All of the prior studies were conducted in predominantly Non-Hispanic White populations, potentially limiting their external validity. These studies may not be generalizable to populations of other races/ethnicities as this association may be diminished or strengthened in these groups due to potential biological differences in how preterm birth affects the development of T2D. With our diverse cohort, we attempted to stratify our results by race/ethnicity and also considered race/ethnicity as an effect modifier. Among individuals identifying as White, we still observed a significant association between preterm birth and T2D that was stronger than in the

race/ethnicity-combined analyses. Unfortunately, we lacked power in the other race/ethnicity groups to observe a significant association, although most of the results still suggested preterm birth to be a risk factor.

4.2 Strengths and Limitations

Our study has multiple strengths to support the findings. Since the WHI is a large-scale national study, our study analyzed a sample size of over 85,000 diverse participants with extensive phenotypic data collection. We were also able to consider numerous covariates in our analyses, as the WHI included self-reported data on many potential confounders. Additionally, we performed sensitivity analyses stratified by birth weight category and race/ethnicity.

However, our study faced several limitations. We relied on self-reported data for assessing both the outcome and the exposure. WHI evaluated the validity of the self-reported T2D in a subset of participants by using medical records to confirm diabetes status and found a PPV of 91.8% for self-reported prevalent diabetes, a PPV of 82.2% for self-reported incident diabetes, and a NPV of 94.5% for no report of diabetes.[33] While not perfect, these validity statistics suggest self-reporting diabetes status in the WHI is mostly accurate, and any misclassification that did occur is likely non-differential. Unfortunately, the validity of the preterm birth variable is unknown, and we are unaware of studies outside of WHI that conducted any validity studies; therefore, the extent of exposure misclassification for our study is unknown. However, if the preterm birth exposure was misclassified, we would expect it to have occurred non-differentially in both cases and controls, biasing the results toward the null.

Our study had additional limitations as well. Despite our large sample size, we had a limited number of preterm births (n=1,999) and T2D cases (n=3,326). As a result, some of our models were likely underpowered, especially in our sensitivity analyses. Additionally, it is possible that our study is limited by survivor bias. Both being born preterm and being diagnosed with T2D can cause adverse health effects and may have prevented women from enrolling in the

WHI because of illness or early death. Therefore, we are prevented from enrolling a sample of women that fully represents the population at risk, which will bias the results towards the null. Finally, we did not have data on other *in utero* pregnancy exposures or conditions (e.g., *in utero* tobacco smoke exposure, gestational diabetes) that may explain the observed relationship, as this data was not collected as a part of the WHI.

4.3 Conclusion and Future Directions

In conclusion, we found that being born preterm is significantly associated with T2D in postmenopausal women. Our research further supports the role of early life exposures and later-life conditions, and, therefore, interventions targeted during preconception and prenatal care to reduce the incidence of preterm birth may reduce the incidence of T2D. However, further research examining the association between preterm birth and subsequent risk of T2D is needed in diverse populations to further our understanding of the generalizability and persistence of the association in other populations.

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