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Racial and Ethnic Differences in the Relationship between Birth weight and Type 2 Diabetes Mellitus in Postmenopausal Women

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Abstract

Objective—To examine the relationship between self-reported birth weight and the adult occurrence of type 2 diabetes mellitus in a large multi-ethnic population of women.

Research Design and Methods—Baseline data from the Women's Health Initiative Observational Study [N= 75,993] was used to examine the association between participant birth weight category and prevalent type 2 diabetes. Models were adjusted for age and ethnicity. Adult BMI was investigated as a potential modifying variable. Sub-analyses were performed stratifying by race/ethnicity.

Results—Reporting a birth weight of <6 lbs. (OR=1.35, 95% CI=1.21-1.50) was significantly associated with self-reported type 2 diabetes compared to women who reported their birth weight between 7 and 8 lbs. 15 oz. Stratifying by race, birth weight of <6 lbs. was associated with type 2 diabetes in both White (OR=1.43, 95% CI=1.25-1.62) and Black (OR=1.31, 95% CI=1.04-1.64) women. A significant trend was observed in Hispanic women where increasing birth weight was

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associated with decreasing type 2 diabetes prevalence (P=0.04) whereas in Asian women increasing birth weight was associated with increasing type 2 diabetes prevalence (P=0.03). Adult socio-demographic covariates such as BMI appear to most significantly influence the direction of the association in White and Black women but not the other racial/ethnic groups.

Conclusions—The relationship between birth weight and risk for adult type 2 diabetes appears to be modified by race/ethnicity and to some extent BMI. To our knowledge this is the largest study of birth weight and type 2 diabetes in a multi-ethnic cohort of women to-date.

Type 2 diabetes mellitus is a serious global health problem, which has become more prevalent with each increasing year (1). According to national estimates from the Center for Disease Control, over 8% of the U.S. population in 2011 had type 2 diabetes with a higher prevalence in Hispanics (11.8%), Blacks (12.6%) and American Indians (16.1%) (2). type 2 diabetes has a complex etiology with multiple contributions from adult lifestyle, genetics and early development. There is strong, emerging evidence that low birth weight is a risk factor for type 2 diabetes in adulthood (3). These studies support the “fetal origins” or “Barker hypothesis” that postulates that adult chronic diseases arise due to developmental programming whereby fetal malnutrition and subsequent rapid weight gain in infancy and childhood lead to irrevocable changes in a person which in turn “programs” them for later life chronic disease (4). In addition to the epidemiologic evidence, studies have identified genes that independently increase the risk for low birth weight as well as type 2 diabetes(5). These findings support the “fetal insulin hypothesis”, which suggests that the same genetic factors that predispose to decreased fetal insulin secretion *in utero*, therefore resulting in low birth weight, may also affect insulin resistance in adulthood (6).

One of the current limitations on the study of birth weight and type 2 diabetes is a lack of generalizability; many studies focused on White males (3). The largest study on birth weight and type 2 diabetes in women is the Nurse's Health Study, which examined 1,199 women with diabetes and 67,197 without diabetes by six birth weight categories (7). There was a strong inverse relationship between birth weight and risk for type 2 diabetes adjusted for several demographic, early life and adulthood risk factors. Ethnicity was included in the adjusted model; however, this study did not have the capacity to examine the relationship between birth weight and type 2 diabetes in minority populations.

Another limitation of previous studies is how to statistically account for factors such as adult BMI and socioeconomic status that are likely in the causal pathway. Many studies observe a “U”-shaped distribution or positive association in that increasing birth weight is associated with increasing risk for type 2 diabetes; however, including adult BMI often reverses this association so that decreasing birth weight is associated with increasing risk for type 2 diabetes(3). This is known as the “reversal paradox” and has been well documented for the association between blood pressure and birth weight; however, the methodological principles apply to other adult chronic diseases as well (8). It is unclear if this pattern will be observed across different racial/ethnic groups.

We sought to address the challenges of previous studies by examining associations of birth weight and prevalent type 2 diabetes in a large multi-ethnic cohort from the Women's Health Initiative (WHI) Observational Study (OS). We evaluated the relationship of birth weight

with diabetes adjusted and unadjusted for adult BMI as well as stratified by racial/ethnic groups. To date, this is the largest study examining the association of birth weight with type 2 diabetes in a multi-ethnic cohort of postmenopausal women.

RESEARCH DESIGN AND METHODS

We performed a post hoc analysis using data from the Women's Health Initiative Observational Study (WHI-OS) described in detail elsewhere (9). Women were recruited from 40 WHI clinical centers across the United States between 1993 and 1998 (9). The WHI-OS recruited 93,676 postmenopausal women between the ages of 50 and 79. The purpose of the WHI-OS was to study clinical, behavioral and socio-demographic risk factors for a wide range of specific disease outcomes that are of particular importance to women including cardiovascular disease, breast cancer, obesity and type 2 diabetes. Women reported their birth weight as belonging to one of the following categories: unknown, less than 6 pounds (lbs.), 6 lbs. to 7 lbs. 15 ounces (oz.), 8 lbs. to 9 lbs. 15 oz., and 10 or more lbs. Women also reported if they were born 4 or more weeks premature and if they were a twin or triplet.

For our analysis, we excluded women who reported being a twin or triplet (N=1,615), women with missing birth weight or preterm birth status (N=13,888), women who reported being born 4 or more weeks premature (N=1,991), women missing information on self-reported type 2 diabetes status (N=94) and women who reported receiving a diagnosis of “sugar diabetes” when they were less than 21 years old (N=95) as they might actually be reporting type 1 diabetes. There were 75,993 women included in the final sample.

We defined prevalent type 2 diabetes at baseline as a self-report of a physician diagnosis of ‘sugar diabetes when not pregnant’ or women who were taking pills for diabetes or receiving insulin shots. This definition had been validated in the WHI study and is consistent with medication inventories and fasting glucose measurements with a concordance of 77% (10).

The baseline characteristics of the cohort were compared according to type 2 diabetes with chi square tests. Logistic regression was used to assess the association between birth weight category and type 2 diabetes at baseline adjusting for baseline age [<50-59, 60-69 and 70-79+] and race/ethnicity [White, Black, Asian/Pacific Islander, Hispanic and Other/Unknown]. We evaluated the effects of the birth weight-type 2 diabetes association with the addition neighborhood socioeconomic status (NSES), defined elsewhere (11) and body mass index at enrollment [≤25, 25-<30 and ≥30]. Our third model included other well-established risk factors for type 2 diabetes including family history of adult diabetes, physical activity [No activity, some activity of limited duration, 2-<4 episodes/week of moderate to strenuous activity, 4 episodes/week of moderate to strenuous activity], smoking [never, past and current], alcohol use [never, past and current], hypertension [none, untreated and treated], history of cardiovascular disease, hysterectomy, prior postmenopausal hormone therapy [never used, past user and current user], and having been breastfed. Analyses were performed in Stata version 12.1 (Stata Corporation, College Station, TX).

RESULTS

Baseline characteristics

Of the 75,993 women in this analysis, 4,002 (5.3%) reported prevalent diabetes. At baseline women with type 2 diabetes were older, Black, Hispanic or Asian, less educated and had lower income than those without type 2 diabetes (**Table 1**). Women with type 2 diabetes were more likely to have a higher BMI, a family history of type 2 diabetes, were less physically active, more likely to be current smokers, more likely to be past but not current alcohol users, more likely to have a history of hypertension or cardiovascular disease, more likely to have had a hysterectomy, were more likely to never have used hormone therapy and reported with greater frequency having been breastfed.

Birth weight and type 2 diabetes

Women with type 2 diabetes reported lower birth weight (**Table 1**). In the model adjusting for baseline age and ethnicity, there was a "U"-shaped distribution; the lower (<6 lbs.) birth weight category, as compared to the reference birth weight of 6 to 7 lbs. 15 oz., was associated with an increased risk for type 2 diabetes (OR=1.35, 95% CI=1.21-1.50). The higher (≥10 lbs.) birth weight category trended toward a higher prevalence of type 2 diabetes, although this was not significant (OR=1.13, 95% CI=0.95-1.34) (**Table 2**). Including BMI and NSES as covariates resulted in an inverse relationship between birth weight and type 2 diabetes (P<0.001). Compared to the reference birth weight category, lower birth weight (<6 lbs.) remained associated with an increased risk for type 2 diabetes (OR=1.30, 95% CI=1.16-1.46); however, the larger birth weight categories (8-9 lbs. 15 oz. and ≥10 lbs.) were now associated with a decreased risk for type 2 diabetes, although this association was not significant for the ≥10 lbs. birth weight category (P=0.03 and P=0.17, respectively). Including additional diabetes risk factors strengthened the inverse relationship between birth weight and type 2 diabetes risk, the association between the lower birth weight category and type 2 diabetes was less significant (P=0.04) compared to the model adjusted for age and ethnicity only; however, the higher birth weight categories both became significantly associated with a decreased risk for type 2 diabetes (**Table 2**).

Birth weight and type 2 diabetes by race/ethnicity

When adjusting for age and stratifying by race, a "U"-shaped distribution between birth weight and type 2 diabetes prevalence was observed in White women (p<0.01). Including NSES and BMI as covariates resulted in a significant inverse distribution (p<0.001), where lower birth weight was associated with higher type 2 diabetes prevalence (OR=1.35, 95% CI=1.17-1.55) and higher birth weight categories were associated with a lower type 2 diabetes prevalence, although these were not individually significant (**Table 3**). In Black women a "U-shaped" distribution was observed for both the age-adjusted and the adult BMI and NSES adjusted models, but the trends were not significant. The lower birth weight category (<6 lbs.), as compared to the referent, was associated with a higher risk for type 2 diabetes in the model adjusted for age only (OR=1.31, 95% CI=1.04-1.64). Including adjustments for adult BMI and NSES attenuated the association between the low birth weight category and type 2 diabetes (OR=1.24 95% CI=0.95-1.61), as compared to the referent, in Black women (**Table 3**). In Asian women, higher birth weight was associated

with a significant trend toward higher type 2 diabetes prevalence (P=0.03). This trend persisted, but was no longer significant (P=0.22) after adjusting for adult BMI and NSES. None of the individual birth weight categories were significant, as compared to the referent, for either model in Asian women. In Hispanic women, higher birth weight was significantly associated with a lower risk for type 2 diabetes in in the age adjusted model (OR=0.43 95% CI=0.13-1.38) and when including NSES and BMI as covariates (OR=0.25, 95% CI=0.06-1.05) (**Table 3**).

CONCLUSIONS

Type 2 diabetes is a complex disease with multiple contributions from genetics, socio-demographic and lifestyle risk factors. There is strong evidence from human and animal studies that early nutrition and growth *in utero* contributes to the development of type 2 diabetes in adulthood (4, 12). However, few studies have had the ability to examine the relationship between birth weight and type 2 diabetes in multiple racial and ethnic groups as well as assess the impact of potential mediators such as adult BMI. We found the relationship between birth weight and type 2 diabetes was different among racial/ethnic groups. We also found that including adult BMI and neighborhood socio-economic status only changed the relationship between birth weight and type 2 diabetes in White women.

Our results were similar to the NHS and other studies. We observed a strong inverse relationship between birth weight and type 2 diabetes when including adult BMI (3, 7). The validity of including adult lifestyle risk factors in models examining birth weight and adult chronic disease is controversial because adult BMI is likely on the causal pathway for type 2 diabetes(8). There have been several studies reporting this “reversal paradox” when including adult BMI and socioeconomic status as covariates in the assessment of birth weight and risk for type 2 diabetes(3). These studies suggest that potential over-fitting could be influencing the associations in a different direction. Indeed, we also observed that the effects were strengthened after adjusting for many type 2 diabetes risk factors. However, we observed that this “reversal paradox” was only apparent in White women and not in the other racial/ethnic groups. In addition, the lower birth weight category (<6 lbs.) was significantly associated with an increased risk for type 2 diabetes in the entire cohort, White women and to some extent Black women, as compared to birth weight of 6 to 7 lbs. 15 oz., regardless of the adjustment for adult BMI and socio-economic status.

The underlying reason for the observed differences in the relationship between birth weight and prevalent type 2 diabetes among different racial/ethnic groups is unclear. The “U-shaped” distribution that was observed in Black women regardless of adjustment for adult BMI may be due to the higher rates of maternal diabetes, maternal obesity and lack of prenatal care compared to other racial/ethnic groups (13-15). In the United States the prevalence of delivering a low birth weight infant is much higher among Black women with a prevalence of ~12% compared to White (7%), Hispanic (6%) and Asian (8%) women (15). It remains unclear as to why lower birth weight is protective for type 2 diabetes in Asian women but not the other racial/ethnic groups. It may be that maternal nutrition plays a large role in these observed differences, as it has been shown that maternal nutrition is not only important for fetal growth but also impacts the child's risk for adult chronic disease (16, 17).

Several studies support that the associations between fetal growth and later-life illness may be attributed, in part, to genetic and epigenetic mechanisms (18-20).

Low birth weight reflects a poor intrauterine environment and can be a product of several maternal complications of pregnancy including preterm birth, preeclampsia and intrauterine growth restriction. This insufficient environment can cause lasting changes through epigenetic, structural and physiological mechanisms that result in altered β-cell mass and function, which in turn leads to inadequate insulin secretion (12). This is supported by recent large genome-wide association (GWA) studies that have identified several genes that have a shared association with low or high birth weight and adult type 2 diabetes(5). Our study was limited in the ability to account for *in utero* and childhood exposures because these variables were not collected in WHI. Additionally, a significant number of women (N=13,888) were excluded from analyses due to missing information on birth weight and preterm birth and these women tended to be older, Black, Hispanic or Asian and more likely to have type 2 diabetes compared to our study population.

Our other study limitations were similar to those of the NHS. We were limited to evaluating self-reported categories of birth weight rather than continuous values derived from vital or medical records (21-23). Yet, validity has been demonstrated for the correlation of categories of self-reported birth weight to medical record information, particularly for low birth weight (24). Higher birth weight categories (≥10 lbs.) have been shown to be less reliable (24), thus, lower precision among the higher birth weight categories may explain why the association between higher birth weight category and type 2 diabetes was more affected by the adjustment of covariates such as adult BMI and neighborhood socioeconomic status.

We did not have glucose levels measured on all participants in our study. Therefore, we relied on self-reported prevalent type 2 diabetes, which may be vulnerable to reporting bias and thus affect our results. However, the validity of self-report has previously been demonstrated in the WHI cohort, with high concordance to medication inventories (77%) (10). As our women were between 50-70 years of age at enrollment our study may be subject to survivor bias for the association with type 2 diabetes; however, most other studies (7, 17, 25) have studied participants similar in age to those of the women in WHI.

In conclusion we demonstrate that lower birth weight was associated with higher risk for type 2 diabetes in Whites and Blacks in the largest study to-date of postmenopausal women. This study overcomes a major limitation of previous studies, in that we were able to examine the association of birth weight and type 2 diabetes in several ethnic and racial groups including Blacks, Hispanics and Asians. This study suggests and is supported by others that individuals born low birth weight should be closely followed for the development of later life chronic disease as they are at an increased risk to develop conditions such as type 2 diabetes in adulthood. Additionally, our research supports the role of early life development in later-life chronic disease and thus interventions targeted during pre-conception to reduce the incidence of infants born low birth weight may reduce the burden of later-life chronic disease (26).

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Table 1

Baseline characteristics of study participants by prevalent type 2 diabetes

	No diabetes N=71,991	Type 2 Diabetes N=4,002	P
Age at baseline (years)			<0.001
<50-59	24,167 (33.6)	1,004 (25.1)	
60-69	31,375 (43.6)	1,915 (47.9)	
70-79+	16,449 (22.9)	1,083 (27.1)	
Ethnicity			<0.001
White	61,989 (86.1)	2,720 (68.0)	
Black	4,801 (6.7)	778 (19.4)	
Asian or Pacific Islander	1,699 (2.4)	141 (3.5)	
Hispanic	2,334 (3.2)	252 (6.3)	
Other/Unknown	1,168 (1.6)	111 (2.8)	
Education			<0.001
<= High school diploma/GED	13,983 (19.6)	1,197 (30.2)	
School after high school	26,117 (36.6)	1,590 (40.1)	
College degree or higher	31,349 (43.9)	1,174 (29.6)	
Family income			<0.001
<$20,000	9,437 (13.1)	1,135 (28.4)	
$20,000-$49,999	28,965 (40.2)	1,652 (41.3)	
$50,000-$74,999	14,067 (19.5)	558 (13.9)	
$75,000+	14,670 (20.4)	371 (9.3)	
Unknown/missing	4,852 (6.7)	286 (7.2)	
BMI at baseline			<0.001
<=25	30,254 (42.5)	626 (15.8)	
25-<30	24,309 (34.2)	1,152 (29.2)	
>=30	16,599 (23.3)	2,173 (55.0)	
Family history of adult diabetes			<0.001
No	48,039 (69.3)	1,329 (35.8)	
Yes	21,264 (30.7)	2,389 (64.3)	
Physical activity			<0.001
No activity	9,100 (12.8)	796 (20.2)	
Some activity of limited duration	26,864 (37.7)	1,744 (44.2)	
2-<4 episodes/week of moderate to strenuous activity (>=20 min/episode)	13,415 (18.8)	640 (16.2)	
4 episodes/week of moderate to strenuous activity (>=20 min/episode)	21,880 (30.7)	767 (19.4)	
Smoking Status			0.02
Never	35,713 (50.3)	2,007 (51.1)	
Past	30,918 (43.5)	1,638 (41.7)	
Current	4,444 (6.3)	282 (7.2)	
Alcohol use			<0.001
Never drinker	7,225 (10.1)	736 (18.6)	
Past drinker	12,306 (17.2)	1,544 (39.0)	

	No diabetes N=71,991	Type 2 Diabetes N=4,002	P
Current drinker	52,042 (72.7)	1,679 (42.4)	
Hypertension at baseline			<0.001
No	48,955 (69.2)	1,394 (35.7)	
Untreated	5,396 (7.6)	436 (11.2)	
Treated	16,423 (23.2)	2,071 (53.1)	
History of cardiovascular disease			<0.001
No	57,821 (82.0)	2,571 (65.9)	
Yes	12,681 (18.0)	1,330 (34.1)	
Hysterectomy			<0.001
No	42,435 (59.0)	1,974 (49.4)	
Yes	29,500 (41.0)	2,026 (50.7)	
Prior postmenopausal hormone therapy (HT)			<0.001
Never used	28,029 (39.0)	2,093 (52.4)	
Past user	10,663 (14.8)	645 (16.1)	
Current user	33,238 (46.2)	1,258 (31.5)	
Birth weight			<0.001
<6 lbs	5,891 (8.2)	458 (11.4)	
6-7.99 lbs	48,991 (68.1)	2,639 (65.9)	
8-9.99 lbs	14,622 (20.3)	756 (18.9)	
>=10 lbs	2,487 (3.5)	149 (3.7)	
Breastfed			<0.001
No	15,764 (26.9)	716 (21.6)	
Yes	43,119 (73.2)	2,598 (78.4)	

Table 2

Relationship of birth weight to prevalent type 2 diabetes among postmenopausal women in the Women's Health Initiative

	Birth Weight Category				
	<6 lbs.	**6-7.9 lbs.**	**8-9.9 lbs.**	**>=10 lbs.**	**P***
N	6,349	51,630	15,378	2,636	
+age and ethnicity (N=75,993)	1.35 (1.21-1.50)	Reference	1.01 (0.93-1.10)	1.13 (0.95-1.34)	0.02
+NSES and BMI (N=67,210)	1.30 (1.16-1.46)	Reference	0.90 (0.82-0.99)	0.88 (0.73-1.06)	<0.001
+other diabetes risk factors† (N=51,030)	1.16 (1.01-1.33)	Reference	0.88 (0.79-0.98)	0.72 (0.57-0.92)	<0.001

Data are odds ratio (95% CI).

*P for linear trend across all four birth weight categories.

†Adjusted for age, ethnicity, neighborhood socioeconomic status (NSES), body mass index (BMI), family history of diabetes, physical activity, smoking, alcohol, hypertension, history of cardiovascular disease, hysterectomy, prior postmenopausal hormone therapy, breastfed.

Table 3

Relationship of birth weight to prevalent type 2 diabetes by race/ethnicity

	Birth Weight Category				
	<6 lbs.	**6-7.9 lbs.**	**8-9.9 lbs.**	**>=10 lbs.**	**P***
+age					
White (N=64,709)	1.43 (1.25-1.62)	Reference	0.99 (0.90-1.10)	1.07 (0.88-1.31)	0.007
Black (N=5,579)	1.31 (1.04-1.64)	Reference	1.12 (0.91-1.38)	1.44 (0.95-2.19)	0.98
Asian (N=1,840)	0.87 (0.53-1.42)	Reference	1.56 (0.92-2.66)	2.77 (0.91-8.43)	0.03
Hispanic (N=2,586)	1.39 (0.96-2.02)	Reference	0.95 (0.66-1.37)	0.43 (0.13-1.38)	0.04
+NSES and BMI					
White (N=57,547)	1.35 (1.17-1.55)	Reference	0.88 (0.79-0.97)	0.86 (0.69-1.07)	<0.001
Black (N=4,526)	1.24 (0.95-1.61)	Reference	1.06 (0.84-1.35)	1.07 (0.64-1.77)	0.55
Asian (N=1,660)	0.87 (0.52-1.47)	Reference	1.16 (0.64-2.10)	2.02 (0.62-6.56)	0.22
Hispanic (N=2,373)	1.30 (0.88-1.94)	Reference	0.84 (0.57-1.24)	0.25 (0.06-1.05)	0.01

Data are odds ratio (95% CI).

*P for linear trend across birth weight categories.