



Birth Weight and Risk of Type 2 Diabetes in the Black Women's Health Study: Does Adult BMI Play a Mediating Role?

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OBJECTIVE

To assess the association of birth weight with incident type 2 diabetes, and the possible mediating influence of obesity, in a large cohort of U.S. black women.

RESEARCH DESIGN AND METHODS

The Black Women's Health Study is an ongoing prospective study. We used Cox proportional hazards models to estimate incidence rate ratios (IRRs) and 95% CI for categories of birth weight (very low birth weight [$<1,500$ g], low birth weight [1,500–2,499 g], and high birth weight [$\geq 4,000$ g]) in reference to normal birth weight (2,500–3,999 g). Models were adjusted for age, questionnaire cycle, family history of diabetes, caloric intake, preterm birth, physical activity, years of education, and neighborhood socioeconomic status with and without inclusion of terms for adult BMI.

RESULTS

We followed 21,624 women over 16 years of follow-up. There were 2,388 cases of incident diabetes. Women with very low birth weight had a 40% higher risk of disease (IRR 1.40 [95% CI 1.08–1.82]) than women with normal birth weight; women with low birth weight had a 13% higher risk (IRR 1.13 [95% CI 1.02–1.25]). Adjustment for BMI did not appreciably change the estimates.

CONCLUSIONS

Very low birth weight and low birth weight appear to be associated with increased risk of type 2 diabetes in African American women, and the association does not seem to be mediated through BMI. The prevalence of low birth weight is especially high in African American populations, and this may explain in part the higher occurrence of type 2 diabetes.

Growing evidence has shown that early life experiences can have lasting effects on adult health (1–3). Low birth weight ($<2,500$ g), an indicator of a compromised fetal growth, has been associated with a higher risk of developing type 2 diabetes (4,5). However, to our knowledge, there are no studies assessing the relation of low birth weight to type 2 diabetes in African American women, a population disproportionately affected by low birth weight (6) and type 2 diabetes (7). In addition, few studies have examined very low birth weight ($<1,500$ g), which might confer an even higher risk of type 2 diabetes as adult (8).

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Two major hypotheses have been proposed to explain the observed association between low birth weight and type 2 diabetes: the thrifty phenotype, or fetal programming hypothesis (9,10), and the fetal insulin hypothesis (11). The thrifty phenotype hypothesis states that as a consequence of intrauterine malnutrition, the individual's metabolism is reprogrammed to become nutritionally thrifty. According to this hypothesis, the thrifty phenotype would confer a survival advantage under conditions of nutritional deprivation, but the individual would be more prone to developing diabetes and other metabolic defects as an adult under improved nutritional conditions (9,10). Children born small for gestational age tend to have high serum leptin concentrations during catch-up growth (12), which in turn has been associated with fat accumulation and higher insulin levels in adult life (13,14). The fetal insulin hypothesis states that low birth weight and diabetes are different phenotypes of the same genotype; genetic variants affecting fetal pancreas development would result in both reduced fetal growth, due to deficient insulin secretion, and higher risk of type 2 diabetes later in life because of the same underlying problem of compromised β -cell mass (11). Recent results provide support to the fetal insulin hypothesis, as three genetic loci associated with type 2 diabetes (*ADCY5*, *CDKAL1*, and *HHEX-IDE*) were also associated with low birth weight (15–17), and at least two of the shared loci (*CDKAL1* and *HHEX-IDE*) are involved in β -cell dysfunction (18,19). Because the underlying defect would be a deficiency in pancreas development, we would not expect, based on the fetal insulin hypothesis, that increased adiposity is a mediator between low birth weight and type 2 diabetes later in life.

In the current study, we assessed the relation of self-reported birth weight to adult risk of type 2 diabetes in the Black Women's Health Study (BWHS), a prospective cohort study. In particular, we evaluated whether extremes of the birth weight distribution are associated with an increased risk of incident type 2 diabetes. We also examined whether increased adiposity, as measured by higher prevalence of adult obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$), is a potential mediator of the relationship.

RESEARCH DESIGN AND METHODS

Study Population

The BWHS is an ongoing prospective follow-up study of African American women in the U.S. (20). The study began in 1995 when ~59,000 women aged 21–69 years enrolled through completing health questionnaires. Participants were approximately equally distributed in the Northeast, South, Midwest, and West. We collected information on demographics, medical and reproductive history, body weight, height, diet, smoking, physical activity, and other factors through the baseline questionnaire. Participants have been followed through biennial questionnaires to collect information on incident diseases and update information on risk factors. Follow-up rate through biennial questionnaires has been ~80% of the baseline cohort. The study protocol was approved by the Institutional Review Board of Boston University.

Questions about birth weight were asked on the 1997 questionnaire (see below), and thus the present analyses are based on follow-up beginning in 1997. Among the 24,085 women who provided adequate data on birth weight, we excluded those with diabetes, cancer, myocardial infarction, stroke, or coronary artery bypass graft surgery at baseline or incident diabetes diagnosed before age 30 years, which resulted in a final analytic sample of 21,624 women (Fig. 1). We followed women for a diagnosis of type 2 diabetes through 2013.

Birth Weight Assessment

On the 1997 follow-up questionnaire, women were asked their birth weight in categories (<4 lb; 4 lb to 5 lb, 8 oz; >5 lb, 8 oz; do not know) and their exact birth weight in pounds and ounces, if known. We used information from both questions to create four categories of birth weight (very low, <1,500 g; low, 1,500–2,499 g; normal, 2,500–3,999 g; and high, $\geq 4,000$ g). We carried out a validation study among 637 BWHS participants born in Massachusetts using birth registry data from the Massachusetts Department of Public Health to corroborate self-reported data on birth weight. The κ coefficient of agreement for the categorical data was 0.80, and there were no significant differences across categories of adult BMI at the time of reporting in 1997 ($P = 0.57$).

For exact self-reported birth weight, the Pearson correlation coefficient was 0.88, and there were no significant differences across BMI categories ($P = 0.38$). These results are in agreement with previous studies (21,22) that have shown the validity of retrospectively collected self-reported birth weight information. We also assessed reproducibility of self-reported birth weight in a subset of 776 BWHS participants who completed the 1997 questionnaire two times. The κ coefficient was 0.86 for categorical birth weight, and the Pearson correlation coefficient was 0.96 for exact birth weight.

Diabetes Assessment

On each of the biennial questionnaires, we asked about a diagnosis of diabetes in the previous 2 years. The accuracy of self-reported diabetes was assessed in a sample of 229 women who reported being diagnosed with diabetes, who consented to the release of medical records from their physicians, and whose providers replied to the request. We found the diagnosis of type 2 diabetes to be confirmed in 220 (96%) of the women. Of the nine remaining participants, two had type 1 diabetes, one had metabolic syndrome with no diabetes, one had steroid-induced diabetes, two had gestational diabetes mellitus, and three did not have diabetes.

Anthropometric Measures

Participants reported their height and weight in 1995. Weight information was updated on each biennial follow-up questionnaire, and it was used to calculate current BMI (weight in kilograms divided by the square of height in meters) using height in 1995. In validation studies of anthropometric measures conducted among 115 BWHS participants, Spearman correlations for self-reported versus technician-measured weight, as well as height, were 0.97, as well as 0.93, respectively (23,24).

Covariates

First-degree family history of diabetes was ascertained in 1995 and 1999. Information on whether the participant was born preterm was obtained from the 1997 questionnaire through the question, "Were you born 3 or more weeks early? (yes, no, don't know)." We observed high reproducibility ($\kappa = 0.86$) of self-reported preterm birth based

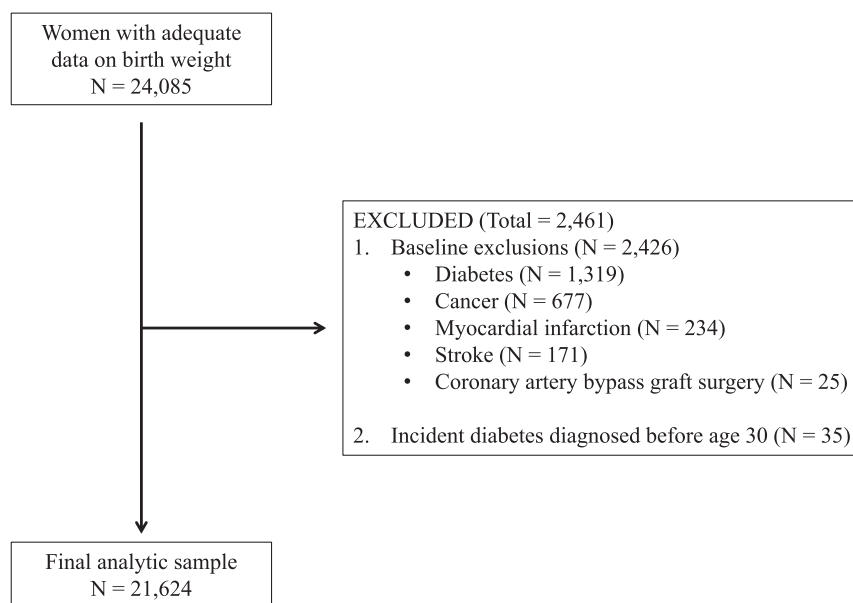


Figure 1—Final analytic sample after exclusions. Among the 24,085 women who provided adequate data on birth weight, we excluded those with diabetes ($N = 1,319$), cancer ($N = 677$), myocardial infarction ($N = 234$), stroke ($N = 171$), or coronary artery bypass graft surgery ($N = 25$) at baseline or incident diabetes diagnosed before 30 years of age ($N = 35$), which resulted in a final analytic sample of 21,624 women.

on data from 776 BWHS participants who returned duplicate questionnaires in 1997. Data on vigorous physical activity (hours/week) were obtained from the 1995 questionnaire and updated in follow-up questionnaires. Information on energy intake (calories per day) was estimated from 1995 and 2001 food frequency questionnaires (25,26) using the Diet*Calc software, version 1.4.1, from the National Cancer Institute (27). For assessment of individual socioeconomic status (SES), years of education were ascertained in 1995 and 2003. Neighborhood SES was measured as previously described (28,29). Briefly, participants' current addresses were linked through geocoding (Mapping Analytics, Rochester, NY) to 2000 U.S. Census block groups. Factor analysis of block group census variables identified six variables (median household income; median housing value; percentage of households receiving interest, dividend, or net rental income; percentage of adults aged 25 years or older who have completed college; percentage of employed persons age 16 years or older who are in occupations classified as managerial, executive, or professional; and percentage of families with children that are not headed by a single female) that were used to calculate an index of neighborhood SES.

Statistical Analysis

We compared age-adjusted baseline characteristics across birth weight categories by computing means of continuous risk factors and proportions of categorical variables in each group.

We calculated incidence rate ratios (IRRs) and 95% CIs using age- and period-stratified Cox proportional hazards models. We calculated person-years of follow-up as the number of years from 1997 (i.e., baseline of the current study) to first diagnosis of diabetes, death, loss of follow-up, or end of follow-up (2013)—whichever came first. We used the Andersen-Gill approach to update time-varying covariates. Multivariable models included terms for first-degree family history of diabetes (yes or no), preterm birth (yes, no, or do not know), dietary caloric intake (quintiles of kilocalories per day), vigorous physical activity (none, <1 h/week, 1–4 h/week, or ≥ 5 h/week), years of education (≤ 12 , 13–15, 16, or ≥ 17 years), and quintiles of the index of neighborhood SES. In secondary analysis, we restricted our models to women not born preterm to make sure any observed association between very low and low birth weight and diabetes is due to fetal growth restriction rather than being born preterm. We used several approaches to assess whether birth

weight affects risk of type 2 diabetes through an effect on BMI. First, we compared analyses without and with adjustment for BMI (<25, 25–29, 30–34, 35–39, or ≥ 40 kg/m²). Second, we performed mediation analysis to estimate the proportion of the association between birth weight and type 2 diabetes that is explained by BMI. We estimated mediation proportion, defined as $1 - \frac{\text{birth weight effect with BMI}}{\text{birth weight effect without BMI}}$, and 95% CI using the partial likelihood function (30) of Cox models with and without BMI as implemented in the SAS MEDiate macro (31). Birth weight effects are in logarithmic scale. Third, we conducted BMI-stratified analyses (nonobese women, BMI <30 kg/m², and obese women, BMI ≥ 30 kg/m²). Finally, we assessed the association of birth weight with incident obesity (BMI ≥ 30 kg/m²) by estimating IRRs adjusted for age, questionnaire cycle, being born preterm, energy intake, vigorous physical activity, years of education (≤ 12 , 13–15, 16, or ≥ 17 years), and quintiles of the index of neighborhood SES.

RESULTS

Table 1 shows baseline characteristics of participants by birth weight categories. At baseline, of the 21,624 women included in the study, 2.3% had a very low birth weight, 23.9% had low birth

Table 1—Age-adjusted baseline (1997) characteristics by birth weight categories

Characteristic	Birth weight categories			
	Very low ($<1,500$ g)	Low ($1,500$ – $2,499$ g)	Normal ($2,500$ – $3,999$ g)	High ($\geq 4,000$ g)
Number of women	489	5,166	14,290	1,679
Age, years, mean	37.8	39.6	37.7	41.2
BMI, kg/m^2 , mean	28.8	27.8	28.1	29.4
Energy intake in 1995, kcal/day, mean	1,493	1,468	1,483	1,516
Family history of diabetes, %	30	34	35	42
Born 3 or more weeks early, %				
Yes	79	24	3	1
No	9	47	77	78
Do not know	12	29	20	21
Vigorous exercise, %				
None	45	43	40	43
<1 h/week	15	17	17	16
1 – 4 h/week	30	30	33	30
≥ 5 h/week	10	9	10	10
Neighborhood SES, %				
1st quintile (poorest neighborhood)	24	18	18	19
5th quintile (wealthiest neighborhood)	13	18	19	18
Education (years)				
≤ 12	26	16	15	16
13 – 15	38	37	37	37
16	20	26	26	25
≥ 17	17	22	22	22

weight, 66.0% had normal birth weight, and 7.8% had high birth weight.

Over 16 years of follow-up and a total of 263,980 person-years, there were 2,388 incident diabetes cases (Table 2). In the multivariate model, very low and low birth weight were associated with an increased risk of type 2 diabetes relative to normal birth weight. IRRs were 1.40 (95% CI 1.08–1.82) for very low birth weight and 1.13 (1.02–1.25) for low birth weight. Estimates were essentially unchanged with additional control for BMI. Mediation analysis showed that BMI was not a significant mediator of the association of birth weight with type 2 diabetes. In an analysis restricted to women who were not born preterm, an association of low birth weight with risk of type 2 diabetes was observed similar to that in the overall sample: IRR 1.19 (1.04–1.35). However, there was almost complete overlap between being born preterm and having a very low birth weight, preventing analysis of very low birth weight among women born full term. High birth weight was not associated with risk of type 2 diabetes.

The same patterns of risk were found within strata of BMI (BMI <30 vs. ≥ 30 kg/m^2 ; P for interaction = 0.25). In addition, no significant differences on risk

were observed across the five BMI categories (<25 , 25–39, 30–34, 35–39, and ≥ 40 kg/m^2 ; P for interaction = 0.33) (data not shown). To further explore the hypothesis that very low and low birth weight may affect risk of type 2 diabetes through a higher risk of obesity, we assessed the relation of birth weight with incident obesity (BMI ≥ 30 kg/m^2) in a multivariate model adjusting for age, questionnaire cycle, being born preterm, energy intake, vigorous physical activity, years of education, and neighborhood SES. Relative to women with normal birth weight, neither women with very low birth weight, IRR 1.01 (95% CI 0.81–1.26), nor women with low birth weight, 0.91 (0.84–0.99), had an increased risk of incident obesity; women with high birth weight had a borderline higher risk of incident obesity, 1.12 (1.00–1.26) (data not shown).

CONCLUSIONS

In this large prospective study of U.S. black women, we found that very low and low birth weights were associated with higher risk of incident type 2 diabetes. Although the association with low birth weight was independent of being born preterm, we could not distinguish

between very low birth weight and being born preterm, since virtually all with very low birth weight were also born preterm. The association of very low and low birth weight with incidence of type 2 diabetes was not mediated by BMI, as the association remained almost unchanged after adjustment for BMI, mediation analysis did not show significant mediation by BMI, and an association was also present among nonobese women. The observed association also was not explained by variation in SES. With regard to high birth weight, we did not observe an increased risk of incident type 2 diabetes, despite the fact that women with high birth weight tended to have a higher risk of incident obesity relative to women with normal birth weight. Although the relation of birth weight to risk of type 2 diabetes has been assessed in several previous studies (32–36), to our knowledge ours is the first report on this relation in African American women, a population with high frequency of low birth weight (6) and high incidence of type 2 diabetes (7). A meta-analysis of 14 studies reported a U-shaped relation of birth weight with risk of type 2 diabetes, with both low birth weight and high birth weight associated with higher risk of type 2 diabetes relative to normal birth

Table 2—IRR (95% CI) for diabetes according to birth weight categories in the BWHS: 1997–2013

Models	Birth weight categories			
	Very low ($<1,500$ g)	Low ($1,500$ – $2,499$ g)	Normal ($2,500$ – $3,999$ g)	High ($\geq 4,000$ g)
All women				
Cases/person-years, <i>n/n</i>	72/5,486	655/62,269	1,479/175,958	182/20,267
IRR: multivariate*	1.40 (1.08–1.82)	1.13 (1.02–1.25)	1.00 (reference)	0.87 (0.74–1.01)
IRR: multivariate + BMI†	1.47 (1.13–1.91)	1.20 (1.08–1.32)	1.00 (reference)	0.78 (0.67–0.91)
Mediation proportion, % (95% CI)	–13.8 (–40.4 to 12.8), <i>P</i> = 0.31	–47.2 (–175.2 to 80.7), <i>P</i> = 0.47	—	–72.2 (–222.6 to 78.2), <i>P</i> = 0.35
Among women not born preterm				
Cases/person-years, <i>n/n</i>	2/521	297/28,946	1,115/136,229	138/15,594
IRR: multivariate + BMI‡	—	1.19 (1.04–1.35)	1.00 (reference)	0.80 (0.67–0.96)
Among nonobese women (BMI <30 kg/m²)				
Cases/person-years, <i>n/n</i>	26/3,361	208/38,991	415/109,202	43/11,105
IRR: multivariate + BMI§	1.68 (1.07–2.62)	1.16 (0.97–1.39)	1.00 (reference)	0.72 (0.53–1.00)
Among obese women (BMI ≥ 30 kg/m²)				
Cases/person-years, <i>n/n</i>	46/2,087	439/21,910	1,054/65,664	139/9,088
IRR: multivariate + BMI§	1.33 (0.96–1.85)	1.20 (1.06–1.35)	1.00 (reference)	0.82 (0.68–0.98)

*Multivariate model: adjusted for age, questionnaire cycle, first-degree family history of diabetes, being born preterm (yes, no, or do not know), activity levels (none, <1 h/week, 1–4 h/week, or ≥ 5 h/week), energy intake (quintiles of kcal/day), neighborhood SES quintiles, and education level (≤ 12 , 13–15, 16, or ≥ 17 years). †BMI (<25 , 25–29, 30–34, 35–39, or 40 kg/m²). ‡Adjusted for age, questionnaire cycle, first-degree family history of diabetes, activity levels, energy intake, neighborhood SES, subject's education level, and BMI (categories). §Adjusted for age, questionnaire cycle, first-degree family history of diabetes, being born preterm, activity levels, energy intake, neighborhood SES, subject's education level, and BMI (continuous).

weight (4). A more recent and bigger meta-analysis of 31 studies reported an overall inverse relation of birth weight with risk of type 2 diabetes (5), and exclusion of macrosomic infants ($>4,000$ g birth weight) had little effect on the overall inverse association (5). However, there was substantial heterogeneity between populations, with few groups, particularly Native Americans, showing a U-shaped relation of birth weight and risk of type 2 diabetes (5). Our results are consistent with both meta-analyses in showing that low birth weight is associated with higher risk of type 2 diabetes, and we show that this increased risk extends to very low birth weight. However, because of the almost complete overlap between very low birth weight and being born preterm, we could not assess an independent effect of very low birth weight, and it is unclear how much of the observed association is due to being born preterm. We did not find an increased risk of type 2 diabetes for women who had a high birth weight even though they had a higher risk of incident obesity relative to women who had normal birth weight. To date, the relation of high birth weight to type 2 diabetes is unclear, as two meta-analyses provide conflicting findings (4,5). Our results are also consistent with a recent report using data from the National

Health and Nutrition Examination Survey (NHANES) cycles 2001–2010, which found that low birth weight but not high birth weight was associated with type 2 diabetes risk factors such as fasting glucose, fasting insulin, and HOMA in 10,758 U.S. children and adolescents aged 6–15 years (37). Although the evidence is still limited, it may be that higher adult BMI in persons who had a high birth weight reflects more lean tissue than fat mass (38,39), explaining the apparently paradoxical observation that individuals who had high birth weight had higher BMI as an adult but not higher risk of type 2 diabetes relative to persons who had normal birth weight.

Mediation analysis in our study suggested that adult BMI did not play a major role as a mediator of the relation between very low and low birth weight and development of type 2 diabetes in adulthood. This conclusion is supported by other results such as the following: 1) adjustment for BMI did not attenuate the association of very low and low birth weight with risk of type 2 diabetes, 2) very low and low birth weight were associated with increased risk of type 2 diabetes even among nonobese women, and 3) women who had very low and low birth weight did not have an increased risk of incident obesity relative to

women who had a normal birth weight. Results from animal models and human studies suggest a multifactorial etiology that includes neuroendocrine alterations (40–42), deregulation of lipid metabolism (43–45), and pancreatic dysfunction (46–48) among others. Recent evidence suggests that low birth weight and type 2 diabetes may share a genetic basis (15–17), and at least two of the shared loci (*CDKAL1* and *HHEX-IDE*) have been implicated in β -cell dysfunction (18,19). These observations lend support to the fetal insulin hypothesis (49), which states that low birth weight and type 2 diabetes later in life are manifestations of the same genotype, and they are due to impairment of β -cell development that is genetically programmed (15). It is noteworthy that regardless of the potential mechanisms, the impact of low birth weight on the risk of type 2 diabetes may be stronger among African Americans, as a recent study found a more substantial association between low birth weight and components of the insulin resistance syndrome among African American children than among white children (45).

The current study has several strengths including its large size, high rate of follow-up, and ability to control

for important confounding variables. It also has some limitations. Information on birth weight was self-reported many years after the fact, raising the possibility of exposure misclassification. However, our validation study showed high correlations between self-reported birth weight and birth registry data, and there were no differences across BMI categories. Thus, although we cannot exclude a certain degree of misclassification, this was most likely at random and generally would result in attenuation of our findings. While information about type 2 diabetes was also self-reported, a validation study found self-report to have high sensitivity (96%) for diabetes diagnosis. In addition, because the prevalence of undiagnosed diabetes among African American women is ~4% (7) we do not expect a major effect of undiagnosed diabetes on our estimates of risk. With respect to anthropometric measurements, our validation study showed very high correlations between self-reported and technician-measured weight and height. We cannot rule out the presence of residual confounding due to unmeasured variables such as maternal metabolic status during pregnancy. For example, we had no information about maternal gestational diabetes mellitus, which is a risk factor for development of type 2 diabetes in the offspring later in life (50). The current prevalence of gestational diabetes mellitus among African American women is ~4% (51), but based on temporal trends this prevalence was most likely <2% during the time most of the study's participants were born (51). It is unlikely that unmeasured gestational diabetes mellitus, given its low prevalence, had a major impact on our results. Finally, although we cannot establish a causal link between low birth weight and type 2 diabetes in adulthood, taken together our results, most previous observational studies, and results from animal models do suggest a causal role of compromised fetal growth in the development of type 2 diabetes.

In summary, this large prospective study of African American women suggests that both very low and low birth weight are associated with a higher risk of incident type 2 diabetes. This relation was not mediated by BMI, suggesting that mechanisms independent of BMI are responsible for the observed

association. The prevalence of low birth weight is especially high in African American populations, and this may explain in part the higher occurrence of type 2 diabetes.

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Author Contributions. E.A.R.-N. analyzed data and wrote the manuscript. J.R.P. and L.R. were responsible for the concept, design, and data collection in the BWHS; contributed to discussion; and reviewed and edited the manuscript. H.G. analyzed data. L.A.W., V.G.V., and J.L.R. contributed to the discussion and reviewed and edited the manuscript. E.A.R.-N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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