Birth Weight, Genetic Susceptibility, and Adulthood Risk of Type 2 Diabetes

Citation

Published Version
doi:10.2337/dc12-0168

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Accessibility
Birth Weight, Genetic Susceptibility, and Adulthood Risk of Type 2 Diabetes

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FRANK B. HU, PHD
LU QI, PHD

OBJECTIVE—Both stressful intrauterine milieu and genetic susceptibility have been linked to later-life diabetes risk. The current study aims to examine the interaction between low birth weight, a surrogate measure of stressful intrauterine milieu, and genetic susceptibility in relation to risk of type 2 diabetes in adulthood.

RESEARCH DESIGN AND METHODS—The analysis included two independent, nested case-control studies of 2,591 type 2 diabetic case subjects and 3,052 healthy control subjects. We developed two genotype scores: an obesity genotype score based on 32 BMI-predisposing variants and a diabetes genotype score based on 35 diabetes-predisposing variants.

RESULTS—Obesity genotype scores showed a stronger association with type 2 diabetes risk in individuals with low birth weight. In low–birth weight individuals, the multivariable-adjusted odds ratio (OR) was 2.55 (95% CI 1.34–4.84) by comparing extreme quartiles of the obesity genotype score, while the OR was 1.27 (1.04–1.55) among individuals with birth weight ≥2.5 kg (P for interaction = 0.017). We did not observe significant interaction between diabetes genotype scores and birth weight with regard to risk of type 2 diabetes. In a comparison of extreme quartiles of the diabetes gene score, the multivariable-adjusted OR was 3.80 (1.76–8.24) among individuals with low birth weight and 2.27 (1.82–2.83) among those with high birth weight (P for interaction = 0.16).

CONCLUSIONS—Our data suggest that low birth weight and genetic susceptibility to obesity may synergistically affect adulthood risk of type 2 diabetes.

Diabetes Care 35:2479–2484, 2012

Interestingly, only a few diabetes (13,14) or obesity (15) loci are directly related to birth weight and with quite complex effects: some type 2 diabetes risk alleles are associated with reduced (13) while some others with increased (14) birth weight. Those results suggest that the genetic variants and birth weight may affect the disease risk through different mechanisms. However, the pathways linking low birth weight or genetic variants to diabetes are intertwined. Therefore, we assume that these two types of risk factors may interact in determining risk of type 2 diabetes.

In this study, we assessed the potential interaction between birth weight and genetic susceptibility to type 2 diabetes and obesity on risk of type 2 diabetes in two independent prospective cohorts: the Nurses’ Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). The genetic susceptibility was evaluated by combining all the identified common variants from recent genome-wide association studies.
Birth weight, genes, and diabetes

Type 2 diabetes cases were defined as self-reported diabetes confirmed by a validated supplementary questionnaire (20,21). For cases before 1998, we used the National Diabetes Data Group criteria to define type 2 diabetes (22). We used the American Diabetes Association diagnostic criteria for type 2 diabetes diagnosis from 1998 onward (23). Control subjects were defined as those free of diabetes at the time of diagnosis for case subjects and remaining unaffected through follow-up (until 2006). We matched the case subjects to nondiabetic control subjects on age, month and year matched the case subjects to nondiabetic subjects and remaining unaffected diabetes at the time of diagnosis for case subjects were de

Assessment of covariates
Information about anthropometric data, smoking status, alcohol intake, menopausal status, postmenopausal hormone therapy (women only), and family history of diabetes was derived from the baseline questionnaires (16). We calculated BMI as weight in kilograms divided by the square of height in meters. Physical activity was expressed as METs per week using reported time spent on various activities—weighting each activity by its intensity level—in 1986 questionnaires for men and women. The validity of the self-reported body weight and physical activity data has previously been described (26–28).

Genotyping and imputation
DNA was extracted from the buffy coat fraction of centrifuged blood using a commercially available kit (QIAmp Blood kit; Qiagen, Chatsworth, CA). We selected 32 established BMI-predisposing single nucleotide polymorphisms (SNPs) (Supplementary Table 1) and 35 established diabetes-predisposing SNPs (Supplementary Table 2). SNP genotyping and imputation have previously been described in detail (18,19). Briefly, samples were genotyped and analyzed using the Affymetrix Genome-Wide Human 6.0 array (Affymetrix; Santa Clara, CA) and the Birdseed calling algorithm. We used MACH (http://www.sph.umich.edu/csg/abecasis/MACH) to impute SNPs on chromosomes 1–22 with NCBI build 36 of Phase II HapMap CEU data (release 22) as the reference panel.

Genotype score computation
The obesity and diabetes genotype scores were calculated, respectively, on the basis of the 32 and 35 SNPs by using a previously described weighted method (19). We assumed that each SNP in the panel acts independently in an additive manner. Each SNP was weighted by $\beta$-coefficients obtained from published meta-analyses (9,11). (The original $\beta$ value can be found in the references listed in Supplementary Tables 1 and 2.) The genotype score was calculated by multiplying each $\beta$-coefficient by the number of corresponding risk alleles (best estimated number of alleles for imputed SNPs) and summing up the products. Because this produced a score out of 8.78 for obesity genotype score and 7.49 for diabetes genotype score (twice the sum of the $\beta$-coefficients), all values were divided by 8.78 (or 7.49) and multiplied by 32 (or 35) to make the genetic score easier to interpret. Most of the SNPs included in the genetic score were genotyped or had a high imputation quality score (MACH $r^2 \geq 0.8$) (Supplementary Tables 1 and 2).

Statistical analyses
$\chi^2$ tests and $t$ tests were used for comparison of proportions and means between case and control subjects for baseline characteristics. We used logistic regression to estimate the odds ratio (OR) for risk of type 2 diabetes, adjusting for age, smoking (never, past, or current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or $\geq 15.0$ g/day), menopausal status (pre- or postmenopausal [never, past, or current menopausal hormone use] [women only]), and physical activity (quintiles). Because the results were similar between men and women, similar analyses were repeated after pooling individual-level data from the two cohorts and further adjusting for sex. To examine the cumulative effects of the genotype scores, we compared the type 2 diabetes risk across the quartiles of the genotype scores according to their distribution in the study samples. To test for linear trends across quartiles of genotype score, we modeled the quartile medians as a continuous variable. We also performed the linear relation analysis between the genotype scores (as continuous variables) and risk of type 2 diabetes by using a restricted cubic spline regression model (29). We tested the interaction by comparing the log likelihood of the model including interaction term with the model that contained only the main effects.

To test the joint effect of the obesity genotype score and diabetes genotype score, we divided the sample into high and low genotype score based on the median value in control subjects and then classified participates into four subgroups according to the joint classification of obesity genotype score and diabetes genotype score: both low, only with high obesity genotype score, only with high diabetes genotype score, and both high. We then examined the association between the joint genotype score and type 2 diabetes stratified by birth weight.
We did a sensitivity analysis after excluding the individuals with birth weight >4.5 kg. Another sensitivity analysis only included the SNPs that were genotyped or had a high imputation quality score (MACH $r^2 \geq 0.8$). We considered two-sided $P$ values $<0.05$ to be statistically significant. Adjustments for multiple comparison tests were not performed because SNPs were selected on the basis of a priori hypothesis. Statistical analyses were performed in SAS 9.1 (SAS Institute, Cary, NC).

**RESULTS**—Baseline characteristics of case and control subjects in the NHS (women) and HPFS (men) are shown in Table 1. In both men and women, type 2 diabetic patients had significantly higher BMI, engaged in less physical activity, were more likely to smoke, and more likely had a family history of diabetes compared with control subjects. Women with type 2 diabetes consumed less alcohol and were more likely to be postmenopausal than their counterparts in the control group.

The OR for type 2 diabetes associated with a one-point increase of the obesity genotype score, corresponding to one BMI-increasing allele and was 1.03 (95% genotype score, corresponding to one with a one-point increase of the obesity risk. Further adjustment for BMI at-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men</th>
<th>Women</th>
<th>Case subjects</th>
<th>Control subjects</th>
<th>$P$</th>
<th>Case subjects</th>
<th>Control subjects</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1,124</td>
<td>1,298</td>
<td>1,467</td>
<td>1,754</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.1 ± 8.6</td>
<td>55.0 ± 8.4</td>
<td>43.5 ± 6.7</td>
<td>43.1 ± 6.8</td>
<td>0.05</td>
<td>27.4 ± 5.0</td>
<td>23.5 ± 3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>27.7 ± 4.0</td>
<td>25.0 ± 2.7</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>27.4 ± 5.0</td>
<td>23.5 ± 3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>36.8</td>
<td>15.9</td>
<td>&lt;0.001</td>
<td>49.6</td>
<td>22.1</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>11.8</td>
<td>7.3</td>
<td>&lt;0.001</td>
<td>29.5</td>
<td>20.8</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol intake (g/day)</td>
<td>11.2 ± 16.2</td>
<td>12.1 ± 15.3</td>
<td>0.18</td>
<td>4.4 ± 9.1</td>
<td>6.6 ± 10.0</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity (MET h/week)</td>
<td>14.6 ± 19.0</td>
<td>21.1 ± 25.2</td>
<td>&lt;0.001</td>
<td>11.7 ± 15.3</td>
<td>14.3 ± 18.7</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal hormone use</td>
<td>35.0</td>
<td>31.3</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low birth weight (≤2.5 kg)</td>
<td>6.8</td>
<td>5.7</td>
<td>0.39</td>
<td>12.1</td>
<td>9.7</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are age-adjusted means ± SD or % unless otherwise indicated.

We also performed birth weight–stratified analysis for the combined genotype score of obesity and diabetes (Table 4). Among individuals with low birth weight, the multivariate-adjusted OR of type 2 diabetes were 3.32 (95% CI 1.17–6.61) for those only with high obesity genotype score, 3.16 (1.58–6.33) for those only with high diabetes genotype score, and 4.7 (2.34–9.45) for those with both high scores compared with those with both low scores. Among the individuals with high birth weight, the corresponding ORs were 1.15 (0.94–1.42), 1.42 (1.17–1.74), and 1.72 (1.41–2.1), respectively ($P$ for interaction = 0.05).

We did sensitivity analyses by excluding individuals whose birth weight was >4.5 kg or by excluding SNPs with a low imputation quality score (MACH $r^2 < 0.8$). The results were not materially changed.

**CONCLUSIONS**—In two nested case-control studies from prospective cohorts of men and women, we observed consistent associations of obesity genotype score and diabetes genotype score with risk of type 2 diabetes. We observed significant interaction between birth weight and obesity genotype score in predicting diabetes, and the genetic effects were more pronounced in low–birth weight individuals than in those with high birth weight.

The association between genetic susceptibility and risk of type 2 diabetes presented in our study was in line with the...
Birth weight, genes, and diabetes

Table 2—Association between genotype scores and risk for type 2 diabetes in men and women

<table>
<thead>
<tr>
<th></th>
<th>Continuous score</th>
<th>Quartile 1 (lowest)</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4 (highest)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obesity genotype score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>491</td>
<td>551</td>
<td>634</td>
<td>746</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>32.6 (22.6–34.3)</td>
<td>35.8 (34.3–37.0)</td>
<td>38.3 (37.1–39.6)</td>
<td>41.8 (39.7–52.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>1.10 (1.08–1.12)</td>
<td>1.00</td>
<td>1.37 (1.07–1.77)</td>
<td>1.88 (1.47–2.39)</td>
<td>2.54 (2.00–3.21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariate adjusted*</td>
<td>1.11 (1.08–1.13)</td>
<td>1.00</td>
<td>1.43 (1.07–1.91)</td>
<td>1.88 (1.42–2.49)</td>
<td>2.76 (2.10–3.62)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>682</td>
<td>799</td>
<td>841</td>
<td>899</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>32.5 (23.9–34.3)</td>
<td>35.9 (34.3–37.0)</td>
<td>38.5 (37.1–39.9)</td>
<td>41.8 (39.9–51.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>1.06 (1.04–1.08)</td>
<td>1.00</td>
<td>1.50 (1.22–1.85)</td>
<td>1.66 (1.35–2.04)</td>
<td>1.91 (1.56–2.34)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariate adjusted*</td>
<td>1.08 (1.05–1.10)</td>
<td>1.00</td>
<td>1.47 (1.15–1.88)</td>
<td>1.76 (1.38–2.25)</td>
<td>2.13 (1.67–2.70)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are OR (95% CI) unless otherwise indicated. *Adjusted for sex, age, family history of diabetes (yes or no), smoking (never, past, or current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥15.0 g/day), physical activity (quintiles), menopausal status (women only), and BMI (for diabetes gene scores only).

findings of other studies (12,19). A genetic score based on 12 obesity-predisposing common genetic variants was associated with risk of incidence of type 2 diabetes (12). In the current study, we updated the obesity genotype score to included 32 SNPs and found similar results. Our previous study reported the joint effect of 10 diabetes-associated common genetic variants on the development of type 2 diabetes (19). In the current study, the computation of the diabetes genotype scores was expanded by inclusion of 25 newly identified loci. The updated genotype scores represent broader characteristics of genetic risk profile and account for more variation in disease risk. Each additional BMI-increasing allele in the obesity genotype score was associated with a 3–4% (95% CI 1–6%) increased odds of developing type 2 diabetes, while each additional diabetes genotype score, corresponding to one risk allele, was associated with an 8–11% (4–13%) increased odds of developing type 2 diabetes.

Intriguingly, we observed that the overall genetic susceptibility to obesity showed stronger associations with diabetes risk among participants with low birth weight than among those with high birth weight. Two previous studies investigated the interaction between birth weight and genetic factors with regard to BMI. One

Table 3—Association between BMI and diabetes genotype scores and risk for type 2 diabetes according to birth weight in pooled analysis of men and women

<table>
<thead>
<tr>
<th>Birth weight (kg)</th>
<th>n (case/control subjects)</th>
<th>Quartile 1 (lowest)</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4 (highest)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese genotype score*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.5</td>
<td>174/169</td>
<td>1.00</td>
<td>1.23 (0.63–2.40)</td>
<td>2.06 (1.07–3.97)</td>
<td>2.55 (1.34–4.84)</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>1,540/1,878</td>
<td>1.00</td>
<td>1.12 (0.91–1.37)</td>
<td>1.22 (1.00–1.48)</td>
<td>1.27 (1.04–1.55)</td>
<td>0.01</td>
</tr>
<tr>
<td>P for interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.017</td>
</tr>
<tr>
<td>Diabetic genotype score*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.5</td>
<td>174/169</td>
<td>1.00</td>
<td>2.01 (0.93–4.32)</td>
<td>3.26 (1.47–7.22)</td>
<td>3.80 (1.76–8.24)</td>
<td>0.0006</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>1,540/1,878</td>
<td>1.00</td>
<td>1.40 (1.11–1.76)</td>
<td>1.51 (1.20–1.89)</td>
<td>2.27 (1.82–2.83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P for interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
</tbody>
</table>

Data are multivariate-adjusted OR (95% CI) unless otherwise indicated. *Adjusted for sex, age, smoking (never, past, or current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥15.0 g/day), physical activity (quintiles), menopausal status (women only), and BMI (for diabetes gene scores only).
found that the effect of risk alleles of SNPs in the FTO gene was more evident among individuals with low birth weight than among those with high birth weight (30). The other study did not find a significant interaction between birth weight (low, medium, or high) and obesity genotype score (based on 24 SNPs) in prediction of adult BMI in Danish subjects (P for interaction = 0.07) (31). The birth weight–gene interaction in relation to type 2 diabetes was tested in one study based on nine diabetes risk alleles, which showed that the individuals with the lowest birth weight and the most high-risk genotypes had the greatest risk of type 2 diabetes (32). These observations, including ours, suggest that low birth weight may strengthen the deleterious effects of genetic variants on the development of obesity or type 2 diabetes in later life. As shown in the present study, high obesity genetic susceptibility and high diabetes genetic susceptibility were jointly associated with a 72% increase in the odds of developing type 2 diabetes in individuals with high birth weight, while among low–birth weight individuals, the increase in the odds of developing type 2 diabetes was 370%.

The potential mechanisms underlying the birth weight–gene interactions remain unclear. The fetal programming hypothesis postulates that early life events play a powerful role in influencing later susceptibility to chronic diseases including type 2 diabetes (1,2). Low birth weight reflects intrauterine growth restriction, which may induce poor development of pancreatic β-cell mass and function (3), retarded skeletal muscle development (33), changed set point of the hypothalamic-pituitary-adrenal axis (34), or epigenetic alterations such as DNA methylation (35). These alterations may subsequently affect insulin secretion or insulin resistance. Of note, all these changes may overlap with pathways linking the genetic variations to the development of type 2 diabetes (2), making the interactions between low birth weight and genetic factors possible. Our data indicate that the obesity-associated genetic variants, which are more closely related to insulin resistance (9), are more likely modulated by birth weight status than the type 2 diabetes–associated genetic variants, which are more tightly related to insulin secretion (β-cell function).

A major strength of the current study is our consistent findings from two well-established large prospective cohorts. The minimal population stratification in our study samples reduces the potential bias due to heterogeneous genetic structure (18). Several limitations deserve comments. First, the genetic variants only account for a small fraction of interindividual variation in BMI and diabetes risk. Second, birth weight was not available for one-third of participants in NHS and HPFS. This may reduce our power to detect the moderate interaction. Since characteristics of the individuals with missing birth weight were comparable to those who reported birth weight, the missing data are unlikely to artificially affect the associations (36). In conclusion, our data suggest that low birth weight and genetic susceptibility to obesity may synergistically affect risk of type 2 diabetes in adulthood. Our findings highlight the importance of more extensive intervention in the low–birth weight population, especially in those with a high-risk genetic profile, to reduce diabetes risk in later life. Future studies are warranted to investigate the potential mechanisms and verify our findings, especially in other ethnicities.

### Acknowledgments
This study was supported by Grant HL-71981 from the National Institutes of Health and Grant DK46200 from the Boston Obesity Nutrition Research Center. L.Q. was a recipient of the American Heart Association Scientist Development Award (0730094N). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

No potential conflicts of interest relevant to this article were reported.

Y.L. and Q.Q designed the study, contributed to the data analysis and interpretation of data, reviewed the manuscript, and wrote the first draft of the manuscript. T.W. contributed to the data analysis and reviewed the manuscript. F.B.H. and L.Q designed the study, contributed to the data collection and analysis and interpretation of data, reviewed the manuscript, and supervised the study. L.Q. 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.

The authors thank all the participants of the NHS and the HPFS for their continued cooperation.

### References

Table 4—Association between joint genotype scores and risk for type 2 diabetes according to birth weight in pooled analysis of men and women

<table>
<thead>
<tr>
<th>BMI genotype score</th>
<th>Joint genotype score</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes genotype score</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Birth weight (kg)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.5</td>
<td>1.00</td>
<td>3.32 (1.17–6.61)</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>1.00</td>
<td>1.15 (0.94–1.42)</td>
</tr>
<tr>
<td>P for interaction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are OR (95% CI) unless otherwise indicated. *Adjusted for sex, age, smoking (never, past, or current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥15.0 g/day), menopausal status (women only), and physical activity (quintiles).

*Li and Associates*
Birth weight, genes, and diabetes