Esther Zimmermann,[1] Michael Gamborg,[1] Thorkild I.A. Sørensen,[1,2,3] and Jennifer L. Baker[1,2]

Sex Differences in the Association Between Birth Weight and Adult Type 2 Diabetes

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PATHOPHYSIOLOGY

Low birth weight is a well-established risk factor for type 2 diabetes, but the risk at high birth weight levels remains uncertain. Potential sex differences in the associations are unexplored. We investigated whether sex influences the association of birth weight and adult type 2 diabetes, using a cohort of 113,801 men and 109,298 women, born 1936–1983, from the Copenhagen School Health Records Register, Denmark. During 5.6 million person-years of follow-up, 7,750 men and 4,736 women had a diagnosis of adult type 2 diabetes (30 years of age or older) obtained from national registers. When birth weights between 3.251 and 3.750 kg were used as the reference group for each sex separately, women with birth weights in the categories of 2.000 to 2.750 kg and 4.751 to 5.500 kg had hazard ratios [HRs] of type 2 diabetes of 1.46 (95% CI, 1.34–1.59) and 1.56 (1.20–2.04), respectively, whereas men had HRs of 1.20 (1.12–1.30) and 0.93 (0.76–1.15). Thus, sex modified the association, with stronger risk estimates of type 2 diabetes in women at both low and high birth weights compared with men (P = 0.001). In conclusion, birth weight is more strongly associated with type 2 diabetes in women than in men. Future search for sex-specific causal mechanisms may provide new insights into the early origins of type 2 diabetes.

Nearly 390 million people, or more than 8% of the world's population, are living with diabetes, which makes it one of the most challenging public health problems of today (1). Type 2 diabetes is a major risk factor for cardiovascular disease and is the seventh leading cause of death in the U.S. (2). Accumulating evidence supports the hypothesis that type 2 diabetes originates in early life (3). During the past decades, associations between low birth weight and an increased risk of type 2 diabetes in adult life have been consistently reported, and these findings were recently confirmed in two meta-analyses (4,5). There remains, however, uncertainty about whether high birth weights are associated with later type 2 diabetes, because increased risks (4) and reduced risks (5) have both been reported.

A lack of focus on sex-specific associations may explain some of the inconsistencies in the previous studies (4,5). The two largest single studies to date, the female-only Nurses' Health Study (6) and the male-only Health Professionals Follow-up Study (7), suggest that there are important sex differences in the relation between birth weight and later risk of type 2 diabetes (6,7). The birth weight–type 2 diabetes association was U-shaped in the study on nurses (6) but was inverse among the health professionals (7), although the confidence limits at the higher birth weight levels were wide and crossed unity in both studies. Both studies were retrospective, and their findings were based on birth weight information recalled over decades as well as recall of the physicians' diagnosis of type 2 diabetes (6,7), potentially resulting in selection and recall biases. Moreover, differences in study design, such as the age structure of the cohorts and length of follow-up, preclude a direct comparison of the results for men and women between these studies. Thus, whether the birth weight–type 2 diabetes association differs between men and women remains uncertain.

In the current study of a large population of Danish school children, we investigated the shape of the association between birth weight and adult type 2 diabetes and explored

[1]Institute of Preventive Medicine, Bispebjerg and Frederiksberg Hospitals, The Capital Region, Copenhagen, Denmark
[2]Novo Nordisk Foundation Center for Basic Metabolic Research, Section on Metabolic Genetics, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[3]Medical Research Council Integrative Epidemiology Unit, Bristol University, Bristol, U.K.

Corresponding author: Esther Zimmermann, esther.zimmermann@regionh.dk.

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the difference in the shape and strength of the association by sex.

RESEARCH DESIGN AND METHODS

Study Population and Exposure Variables

The Copenhagen School Health Records Register (CSHRR) has been built in collaboration between the Institute of Preventive Medicine and the Copenhagen City Archives in Denmark. The CSHRR is a database of school health examination information on 372,636 children, born from 1930 to 1989, who ever attended school in the municipality of Copenhagen (8). Information on the name, sex, and date of birth was systematically recorded on individual health cards along with annual height and weight measurements (8). For children born in 1936 and onward, birth weight was reported by the parents (usually the mother) at the school entry health examination at 6–7 years of age and was noted on each child's health card. Maternal recall of offspring birth weight is generally very high (9). The CSHRR is the result of the retrieval and computerization of these school health examination data.

Data Linkage

The Danish Civil Registration System of vital statistics was established in 1968, and a unique government identification number was assigned to every citizen (10). The identification number for children who were in school in 1968 or later was recorded on their health card; otherwise, the identification numbers were retrieved using information on the name, date, and place of birth of the individual. The unique personal identification number was identified for 329,968 health records (89%) (8). The main reasons for nonidentification were death, emigration, or changes in women's surnames before 1968 (8).

Assessment of Type 2 Diabetes

Information on adult type 2 diabetes was obtained by linkage of the identification number to the Danish National Patient Register, which holds a complete hospital discharge history for every individual hospitalized in somatic hospitals in Denmark since 1977 (11). Data on outpatients and emergency patients have also been included since 1995 (11). The date of diagnosis was set to the date of the first discharge diagnosis with type 2 diabetes. We did not distinguish between whether the individuals were discharged with type 2 diabetes as a primary or an additional diagnosis. Type 2 diabetes was categorized according to the ICD 8th revision until 1994 (ICD-8 250) and ICD-10 thereafter (ICD-10 E11, E12, E13, and E14). On 1 January 1987, the ICD-8 code 249 (type 1 diabetes) was introduced in the Danish health care system, so from this point onward, distinguishing between type 1 diabetes and type 2 diabetes was possible. Before this time, the ICD-8 code 250 also could have contained type 1 diabetes. To reduce potential misclassification of type 2 diabetes, we restricted the lower bound for age at diagnosis to 30 years because most individuals with type 1 diabetes are diagnosed before this age.

Cohort for Analysis and Follow-up

The study population included 262,743 individuals, born between 1936 and 1983, who were alive on 1 January 1977 or 30 years of age, whichever came later. Among these individuals, 34,583 did not have birth weight information. To avoid recording errors at the extreme ends of the birth weight range, we excluded 4,383 individuals with birth weights below 2.0 kg or above 5.5 kg, leaving 113,801 men and 109,298 women for the analyses.

Follow-up started on 1 January 1977 or 30 years of age, whichever came later. Follow-up ended on the date of a type 2 diabetes diagnosis, death, emigration, or loss to follow-up, or on 31 December 2013, whichever came first. Information on vital status, emigration, or loss to follow-up was retrieved via the personal identification number from the Danish Civil Registration System (10).

Statistical Analyses

Mean and median values, SDs, and ranges were used to describe the characteristics for each sex. The risk of type 2 diabetes was modeled by Cox regression and presented as hazard ratios (HRs). Because age is strongly related to type 2 diabetes, we used age as the underlying time scale and entered the individuals from the age at which they could have been recorded as being diagnosed with type 2 diabetes. To take into account potential changes in the determinants of type 2 diabetes during the study period, all analyses were conducted with the baseline hazard estimated in 5-year strata of year of birth (1936–1939, 1940–1944, …, 1975–1979, 1980–1983). For all analyses, $P < 0.05$ was considered statistically significant.

Birth weight was divided into six categories (2.000–2.750; 2.751–3.250; 3.251–3.750; 3.751–4.250; 4.251–4.750; 4.751–5.500 kg). These categories were chosen to reduce the influence of digit preference. The birth weight category of 3.25–3.75 kg was used as the reference group for each sex. Furthermore, we performed a joint analysis in which women with birth weights between 3.25 and 3.75 kg were used as the reference. This approach estimates the HRs for the combinations of birth weight categories and sex with reference to a common baseline risk. To further investigate the shape and possible nonlinearity of the birth weight–type 2 diabetes association, we performed a piece-wise linear spline regression, with 3 knot points at 3.0, 3.5, and 4.0 kg, because the median and SD of birth weight are ~3.5 kg and 0.5 kg. A reference point of 3.5 kg was chosen for the graphical presentation. We investigated if the spline model differed by sex, and furthermore, compared the effect size within each spline between the sexes. The potential sex differences were tested on the multiplicative scale, based on likelihood ratio tests in nested models with and without cross-product terms.

Potential interactions between birth weight (linear splines), year of birth (1936–1939, 1940–1944, …, 1975–1979, 1980–1983), and year of type 2 diabetes diagnosis (<1999, 1999–2005, 2005–2010, >2010) were also tested using likelihood ratio tests, as described above. No

interactions between birth weight and year of birth (all $P > 0.21$) or year of diagnosis (all $P > 0.25$) were observed. The proportional hazard assumptions were assessed by a test based on Schoenfeld residuals (12), and no deviations were detected (all $P > 0.06$).

Ethics

The study was approved by the Danish Data Protection Agency (Datatilsynet). All analyses were conducted on anonymous data. According to the Danish Act of Processing of Personal Data (Persondataloven), informed consent is not required for register-based research of preexisting personal data.

RESULTS

The mean birth weight was 3.3 kg among women and 3.4 kg among men (Table 1). During 5,618,720 person-years of follow-up, covering the age range from 30 to 78 years, fewer women (n = 4,736) than men (n = 7,750) had a discharge diagnosis of type 2 diabetes (Table 1).

Sex and Birth Weight in Categories

In women, compared with the reference category of birth weight between 3.25 and 3.75 kg, the risk estimates of type 2 diabetes were increased for the birth weight categories below 3.25 kg and in the category above 4.75 kg (Table 2). Among men, the risk estimates of type 2 diabetes were increased in the birth weight categories below 3.25 kg and were slightly decreased in the birth weight categories between 3.75 and 4.75 kg compared with the sex-specific reference category of birth weight between 3.25 and 3.75 kg (Table 2). To examine the combined effects of sex and birth weight on type 2 diabetes, we used a joint reference group of women with birth weights between 3.25 and 3.75 kg (Table 2). Women generally had lower risk estimates of adult type 2 diabetes in all of the birth weight categories than men, although the risk estimates were of similar magnitude in the highest category of birth weights between 4.75 and 5.50 kg (Table 2).

Effect of Sex on the Shape and Strength of the Association Between Type 2 Diabetes and Birth Weight

The birth weight–type 2 diabetes association was also assessed using linear splines with three knot points, which is a more flexible alternative to the categorical approach where the association is estimated as a step-function. Overall, the shape of the association differed between the sexes ($P < 0.001$ for overall interaction). Among women, the risk of adult type 2 diabetes was increased at both lower and higher values of birth weight (Fig. 1*A*). Among men, the association was inverse through the normal range of birth weight up to 4.0 kg, and leveled off thereafter (Fig. 1*B*). In this spline model, the HRs of type 2 diabetes for birth weights between 2.0 and 3.0 kg were 0.68 (95% CI, 0.59–0.79) per kilogram of birth weight among women versus 0.87 (95% CI, 0.76–1.00) among men (P = 0.02 for interaction). For the spline between 3.0 and 3.5 kg, women had an HR of 0.70 (95% CI, 0.59–0.84), and men had an HR of 0.88 (95% CI, 0.76–1.01; P = 0.06 for interaction). From 3.5 to 4.0 kg, women had an HR of 0.93 (95% CI, 0.74–1.18), and men had an HR of 0.72 (95% CI, 0.61–0.84; P = 0.06 for interaction). Above 4.0 kg, the HR of type 2 diabetes per kilogram of birth weight was 1.40 (95% CI, 1.11–1.77) for women and was 1.05 (95% CI, 0.89–1.24) for men (P = 0.05 for interaction).

DISCUSSION

In this large prospective study of 12,486 individuals with type 2 diabetes, we found that the shape and strength of the birth weight–type 2 diabetes association differed by sex. Among women, the association between birth weight and type 2 diabetes was U-shaped. In men, birth weight was inversely associated with adult type 2 diabetes but leveled off at higher birth weights. The association with adult type 2 diabetes at both the lower and upper birth weights was stronger in women than in men.

The increased risk of type 2 diabetes associated with low birth weight in both sexes in the current study fits with previous findings from two large meta-analyses based on 6,901 (4) and 6,090 (5) individuals with type 2 diabetes. For birth weights above 4.0 kg, we found increased risk estimates of adult type 2 diabetes among women but no association among men. However, the categorical analysis showed that the association among women appeared to be driven by birth weights above 4.75 kg. The finding for women is in support of Harder et al. (4), who reported an increased risk of type 2

Table 1—Characteristics of the 223,099 children born between 1936 and 1983 included in this study

	Women		Men	
	n		*n*	
Birth weight (kg), mean ± SD	109,298	3.3 ± 0.5	113,801	3.4 ± 0.6
Type 2 diabetes diagnoses, *n*	109,298	4,736	113,801	7,750
Age at entry (years), median (range)	109,298	30.0 (30.0–41.0)	113,801	30.0 (30.0–41.0)
Age at exit (years), median (range)	109,298	59.3 (30.0–77.9)	113,801	57.9 (30.0–77.9)
Age at type 2 diabetes (years), median (range)	4,736	57.9 (30.0–77.7)	7,750	57.4 (30.0–77.8)

The age at entry is 30 years or the individual's age on 1 January 1977 when follow-up started, whichever came last. The age at exit is the individual's age at the first type 2 diabetes diagnosis, death, emigration, or loss to follow-up. The age at type 2 diabetes is the individual's age when first discharged from the hospital with a type 2 diabetes diagnosis.

Table 2—HRs and 95% CIs of adult type 2 diabetes by sex and birth weight

	Women			Men			
Birth weight (kg)	*n*	% (*n*) of cases	HR (95% CI)	*n*	% (*n*) of cases	HR (95% CI)*	HR (95% CI)†
2.000–2.750	15,796	3.7 (856)	1.46 (1.35–1.59)	12,387	7.7 (958)	1.20 (1.12–1.30)	2.28 (2.10–2.47)
2.751–3.250	37,078	4.5 (1,650)	1.17 (1.09–1.26)	31,414	7.1 (2,235)	1.07 (1.01–1.13)	2.02 (1.90–2.16)
3.251–3.750	38,221	3.4 (1,481)	1 (Reference)	41,976	6.8 (2,840)	1 (Reference)	1.90 (1.78–2.02)
3.751–4.250	14,438	3.9 (571)	1.01 (0.92–1.12)	21,127	6.1 (1,279)	0.88 (0.83–0.94)	1.67 (1.55–1.80)
4.251–4.750	2,938	4.1 (121)	1.00 (0.83–1.20)	5,548	6.2 (343)	0.85 (0.76–0.95)	1.61 (1.43–1.81)
4.751–5.500	827	6.9 (57)	1.56 (1.19–2.03)	1,349	7.0 (95)	0.93 (0.76–1.15)	1.77 (1.44–2.18)

The analysis was stratified by birth cohort. $P = 0.001$ for interaction between sex and birth weight in six categories in relation to adult type 2 diabetes. *HR of adult type 2 diabetes in men, using men with a birth weight between 3.251 and 2.750 kg as reference. †HR of adult type 2 diabetes in men, using women with a birth weight between 3.251 and 2.750 kg as reference.

diabetes for birth weights above 4.0 kg compared with the reference category of 2.5–4.0 kg, but their subanalysis suggested that the association was mainly driven by birth weights above 4.5 kg. This suggests that female babies with macrosomia face an increased risk of type 2 diabetes in adulthood. The association for men is in accordance with the study by Whincup et al. (5), who reported inconclusive results for birth weights above 4.0 kg in relation to type 2 diabetes, although it should be noted that the shape of the association was investigated in a reduced sample of less than 900 individuals. A major limitation is that neither meta-analysis reported sex-specific results.

The current study had a prospective design and a substantial number of individuals with type 2 diabetes to investigate the association between birth weight and adult type 2 diabetes separately in men and women from the same population. A key finding is that the relative risk of type 2 diabetes below 3.0 kg and above 4.0 kg was greater in women than in men, which suggests that birth weight exerts a greater adverse effect on type 2 diabetes in women than in men. We therefore propose that future studies should explicitly investigate potential sex differences in the association between birth weight and later type 2 diabetes rather than just adjusting for sex in the model. We previously showed a similar sex-dependent pattern for the association between birth weight and adult blood pressure, with a U-shaped association in women but an inverse and less strong association in men (13), suggesting that the sex-specificity of the traits is a more general phenomenon than hitherto recognized.

The association between low birth weight and later type 2 diabetes may originate in utero, when the fetus is exposed to adverse environmental factors (14,15). Placental insufficiency and inadequate nutrition could, in addition to a low birth weight, also cause permanent changes in the body's structure and physiology (14,15). Such alterations may be beneficial in the short-term but appear to be detrimental to health in later stages of life, where individuals with a low birth weight are at an increased risk of insulin resistance and pancreatic dysfunction essentially leading to type 2 diabetes (14–16). Alternative pathways involving epigenetic and genetic factors have been proposed as well (17–20). The association between low birth weight and adult type 2 diabetes was consistent across birth cohorts that spanned 48 years in our study, which makes it plausible that biologic mechanisms rather than changing social or environmental factors contribute to the association.

For high birth weights, studies have suggested that potential mechanisms leading to type 2 diabetes are via gestational diabetes and maternal obesity because these conditions share some of the same characteristics, such as

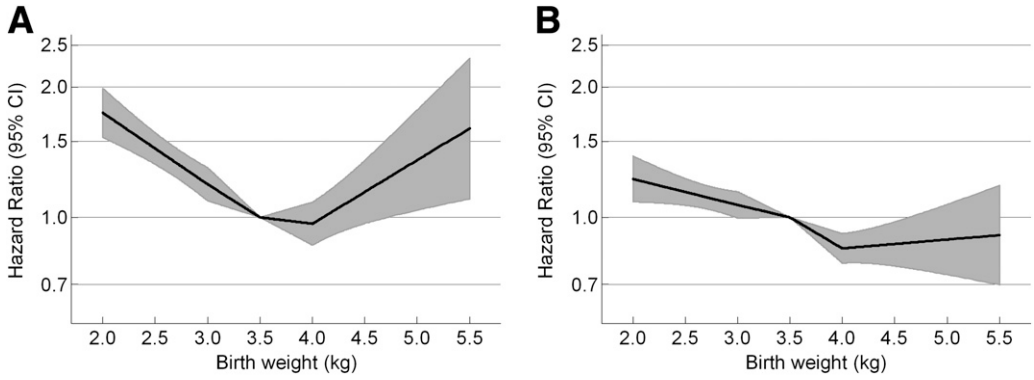

Figure 1—HRs and 95% CIs of adult type 2 diabetes according to birth weight for women (*A*) and men (*B*). The analysis was stratified by birth cohort.

increased insulin resistance and hyperglycemia (21–23). The prevalence of gestational diabetes is below 3% in Denmark (24) and is therefore unlikely to explain all of the association with high birth weight in women in the current study. However, because maternal obesity has a prevalence of 12% (25), undiagnosed maternal hyperglycemia, leading to both high birth weight and increased fetal insulin levels, could also be part of the explanation. Other etiologies may be related to later life influences because a high birth weight is associated with an increased risk of both child (26) and adult obesity (27,28), which again are risk factors for type 2 diabetes (29–31). However, none of these relationships can plausibly explain the stronger association with type 2 diabetes for high birth weight in women than in men. Regardless of the exact mechanism, high birth weight serves as an indicator of risk in women that is not entirely attributable to high birth weight per se.

We speculate that sex hormones in utero may play a role in developing the sexual dimorphism between birth weight and type 2 diabetes observed in the current study. Testosterone has been shown to be a sex-dependent factor in the etiology of type 2 diabetes among adults, whereas estradiol showed no difference between the sexes (32). Type 2 diabetes is associated with low testosterone levels in men but high levels of testosterone in women (32). High maternal testosterone levels during pregnancy are associated with low birth weight in the offspring (33). Moreover, maternal testosterone levels correlate positively with fetal testosterone levels (34), providing a link to the higher relative risk among the low birth weight females. The difference between the sexes at the higher birth weight levels may also be partly explained by an increased susceptibility to gestational overnutrition and maternal glucose values in female versus male fetuses (35,36). Another factor to consider is that girls are born lighter than boys (37). Thus, a heavy girl is more extreme in the birth weight distribution than a heavy boy. However, the difference in mean birth weight between females and males is ~100 g, and therefore unlikely to fully explain the different associations with type 2 diabetes for birth weights above 4.0 kg.

A key challenge from a public health perspective is to understand the underlying mechanisms of the association between birth weight and adult type 2 diabetes to identify targets for possible intervention. Low birth weight could be a marker of prematurity. We did not have information on gestational age and were therefore not able to account for this factor in the analyses. However, studies have shown that the association between a low birth weight and type 2 diabetes persisted after adjustment for gestational age (14,30). Another study showed that preterm birth and poor fetal growth were independent risk factors for the association between a low birth weight and type 2 diabetes (38). Hence, prematurity is not likely to explain all of the association between low birth weight and later type 2 diabetes. In Denmark, the proportion of infants with low birth weights has been stable during the last decades, whereas there has been an increase in infants with high birth weights (39). The latter has primarily been attributed to increases in the BMI of the mothers (40), and the risk associated with a high birth weight among women may therefore have an even larger effect in future generations. The U-shaped association among women indicates that birth weight is not an obvious target to intervene on, and population increases in birth weight may actually be harmful.

Major advantages of the current study are the large sample size, the substantial number of subjects with type 2 diabetes, and the prospective design, which allowed us to explicitly investigate the association between birth weight and adult type 2 diabetes separately in women and men from the same population. We found that fewer women than men had type 2 diabetes after 30 years of age. This is in accordance with previous reports from Denmark (41) and the U.S. (42) and supports the validity of the case ascertainment of type 2 diabetes in the current study. Selection bias cannot explain our findings because the attrition in sample size was due to missing birth weight data, which is independent of a later ascertainment of type 2 diabetes. Moreover, access to health care is free in Denmark, and we had minimal loss to follow-up; hence, the follow-up procedure does not induce selection bias.

There are also limitations. The case ascertainment of individuals with type 2 diabetes was determined from discharge diagnoses in hospital records. Because type 2 diabetes is frequently diagnosed by general practitioners and in outpatient clinics, we have likely underestimated the true incidence of type 2 diabetes, which possibly could bias the reported HRs. Conversely, since we likely included individuals with more severe type 2 diabetes, misclassification of the observed subjects with type 2 diabetes is minimal. Moreover, we did not have data on weight or diabetes in the mothers because this information was not recorded on the child's school health card. Finally, we were unable to take into account other potential explanatory factors such as socioeconomic status. The meta-analyses by Whincup et al. (5) adjusted for socioeconomic status and found that it did not influence the association between birth weight and type 2 diabetes; thus, this factor would not likely have changed our findings had we been able to take it into account.

We conclude that when compared with the risk at birth weights around the median, women had a higher relative risk of type 2 diabetes at both low and high birth weights than men. We propose that future epidemiologic and mechanistic studies should explicitly investigate this sex difference as this may provide new insights into the early origins of type 2 diabetes.

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