Sex differences in the association between birth weight and adult type 2 diabetes

Running title: birth weight and adult type 2 diabetes

Esther Zimmermann¹; Michael Gamborg¹; Thorkild IA Sørensen¹²³; Jennifer L Baker¹²

¹Institute of Preventive Medicine, Bispebjerg and Frederiksberg Hospitals, The Capital Region, Copenhagen, Denmark

²Novo Nordisk Foundation Center for Basic Metabolic Research, Section on Metabolic Genetics, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

³MRC Integrative Epidemiology Unit, Bristol University, Bristol, U.K.

E-mail addresses:

Esther Zimmermann: Esther.Zimmermann@regionh.dk

Michael Gamborg: Michael.Orland.Gamborg@regionh.dk

Thorkild I. A. Sørensen: Thorkild.Ingvor.Arrild.Soerensen@regionh.dk

Jennifer L. Baker: Jennifer.Lyn.Baker@regionh.dk

Corresponding author:

Esther Zimmermann, Institute of Preventive Medicine, Frederiksberg Hospital, Nordre Fasanvej 57, Hovedvejen, Indgang 5, stuen, 2000 Frederiksberg, Denmark.

Email: Esther.Zimmermann@regionh.dk, phone +45 3816 3051, fax +45 3816 3119

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Abstract

Low birth weight is a well-established risk factor for type 2 diabetes, but risk at high birth weight levels remains uncertain. Potential sex-differences in the associations are unexplored. We investigated if sex influences the birth weight-adult type 2 diabetes association, 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. Using birth weights between 3.251-3.750 kg as the reference group for each sex separately, women with birth weights in the categories of 2.000-2.750 kg and 4.751-5.500 kg, had hazard ratios [HRs] of type 2 diabetes of 1.46 (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-value=0.001). In conclusion, birth weight is more strongly associated with type 2 diabetes in women than 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 it is the seventh leading cause of death in the United States (2). Accumulating evidence supports the hypothesis that type 2 diabetes originates in early life (3). Over 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, as both increased (4) and reduced risks (5) have 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 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 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 on men and women between these studies. Thus, it remains uncertain whether the birth weight-type 2 diabetes association differs between men and women.
In the present study of a large population of Danish school children, we investigate the shape of the birth weight and adult type 2 diabetes association and explore the difference in 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 onwards birth weight was reported by the parents at the school entry health examination at 6-7 years of age and it was noted on each child’s health card. The validity of the birth weight values is very high with correlations exceeding 0.96 when validated against the Medical Birth Register (9). The CSHRR is the result of the retrieval and computerization of these school health examination data.

Data linkage

In 1968 the Danish Civil Registration System of vital statistics was established and a unique government identification number was assigned to every citizen (10). Children who were in school in 1968 or later had their identification number recorded on their health card; otherwise the identification numbers were retrieved using information on the name, date and place of birth of the individual. A total of 329,968 (89%) health records had the unique personal identification number identified (8). The main reasons for non-identification 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 via 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); since 1995 data on
outpatients and emergency patients have been included as well (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 International Classification of Disease
(ICD) 8$^{th}$ revision until 1994 (ICD-8 250) and the 10$^{th}$ revision thereafter (ICD-10 E11, E12, E13
and E14). On January 1, 1987 the ICD-8 code 249 (type 1 diabetes) was introduced in the Danish
healthcare system, so from this point onwards it was possible to distinguish between type 1 diabetes
and type 2 diabetes. Prior to 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, as the majority of 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 January 1, 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, standard deviations, 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). Since 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 potential changes in the determinants of type 2 diabetes during the study-period into account, all analyses were conducted with the baseline hazard estimated in 5-year strata of year of birth (1936-39, 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 reference group for each sex. Furthermore, we performed a joint analysis, in which women with birth weights between 3.25-3.75 kg were used as 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 non-linearity 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, since the median and standard deviation of birth weight are approximately 3.5 kg and 0.5 kg. For the graphical presentation, a reference point of 3.5 kg was chosen. 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 (1936-39, 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 pre-existing 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 of age, 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 3.25-3.75 kg, the risk estimates of type 2 diabetes were increased both for the birth weight categories below 3.25 kg as well as 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, while 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 3.25-3.75 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 weight values between 3.25-3.75 kg (Table 2). Women generally had lower risk estimates of adult type 2 diabetes in all the birth weight categories than men, though the risk estimates were of similar magnitude in the highest category of birth weight values between 4.75-5.50 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 for overall interaction < 0.001). Among women, there was an increased risk of adult type 2 diabetes at both lower and higher values of birth weight (Figure 1, panel A). Among men, the association was inverse through the normal range of birth weight up until 4.0 kg, and thereafter it levelled off (Figure 1, panel 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 kg of birth weight among women versus 0.87 (95% CI, 0.76-1.00) among men (P for interaction = 0.02). For the spline between 3.0 and 3.5 kg, women had a HR of 0.70 (95% CI, 0.59-0.84) and men a HR of 0.88 (95% CI, 0.76-1.01) (P for interaction = 0.06). From 3.5 kg to 4.0 kg, women had a HR of 0.93 (95% CI, 0.74-1.18) and men a HR of 0.72 (0.61-0.84) (P for interaction = 0.06). Above 4.0 kg, women had a HR of type 2 diabetes of 1.40 (95% CI, 1.11-1.77) and men a HR of 1.05 (95% CI, 0.89-1.24) per kg of birth weight (P for interaction = 0.05).
In this large prospective study including 12,486 cases of 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 levelled off at higher birth weight values. The association with adult type 2 diabetes at both the lower and upper birth weight values was stronger in women than men.

The increased risk of type 2 diabetes associated with low birth weight in both sexes in the present study fits with previous findings from two large meta-analyses based on 6,901 (4) and 6,090 (5) cases of type 2 diabetes. For birth weight values above 4.0 kg, we found increased risk estimates of adult type 2 diabetes among women, but no association among men. However, based on the categorical analysis, 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., who reported increased risk of type 2 diabetes for birth weights above 4.0 kg compared with the reference category of 2.5-4.0 kg (4), but their sub-analysis suggested that the association was mainly driven by birth weights above 4.5 kg (4). 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., who reported inconclusive results for birth weights above 4.0 kg in relation to type 2 diabetes (5), though it should be noted that the shape of the association was investigated in a reduced sample of less than 900 cases. A major limitation is that neither of the meta-analyses reported sex-specific results. The present 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 men. Therefore, we 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 have previously
shown 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 low birth weight individuals are at an increased
risk of both 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, as these conditions share some of the same
characteristics, such as increased insulin resistance and hyperglycaemia (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 present study. However, as maternal obesity has
a prevalence of 12% (25), undiagnosed maternal hyperglycaemia, 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, as 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 men. Regardless of the exact mechanism, high birth
weight serves as an indicator of risk in women, 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 present study. It has been shown that
testosterone is 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 be partly explained by an increased
susceptibility to gestational overnutrition and maternal glucose values in female versus male
foetuses (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 approximately 100 g, and therefore
unlikely to fully explain the different associations with type 2 diabetes for birth weights above 4.0
kg.
From a public health perspective, a key challenge is to understand the underlying mechanisms of the association between birth weight and adult type 2 diabetes in order 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 body mass index of the mothers (40), and the risk associated with a high birth weight among women may therefore have an even larger impact in future generations. Due to the U-shaped association among women, birth weight is not an obvious target to intervene on, and population increases in birth weight may actually be harmful.

Major advantages of the present study are the large sample size, the substantial number of type 2 diabetes cases 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 less women than men had type 2 diabetes after 30 years of age. This is in accordance with previous reports from both Denmark (41) and the USA (42), and support the validity of the case ascertainment of type 2 diabetes in the present study. Selection bias cannot explain our findings, as the attrition in sample size was due to missing birth weight data which is independent of a later ascertainment of type 2 diabetes. Moreover, in Denmark access to health care is free 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 based on discharge diagnoses in hospital records. Since 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 the relatively more severe type 2 diabetes cases, misclassification of the observed type 2 diabetes cases is minimal. Moreover, we did not have data on weight or diabetes in the mothers as this information was not recorded on the child’s school health card. Finally, we were unable to take other potential explanatory factors into account such as socioeconomic status. The meta-analyses by Whincup et al adjusted for socioeconomic status and found that it did not influence the association between birth weight and type 2 diabetes (5). Thus, had we been able to take this factor into account, it is not likely to have changed our findings.

Conclusions

We conclude that when compared to 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.
Acknowledgements

Author contributions:

Data Access and Responsibility: EZ and JLB are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors

Statistical analysis: EZ, MG

Interpretation of data: All authors

Drafting of the manuscript: EZ

Critical revision of the manuscript for important intellectual content: All authors

Conflicts of interest disclosure:

None reported

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Role of the Funder:

The funders had no influence on the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication
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Table 1. Characteristics of the 223,099 children born between 1936 and 1983 included in this study

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No.</td>
</tr>
<tr>
<td>Birth weight (kg), mean ±SD</td>
<td>109,298 3.3 ±0.5</td>
<td>113,801 3.4 ±0.6</td>
</tr>
<tr>
<td>Type 2 diabetes diagnoses,</td>
<td>109,298 4,736</td>
<td>113,801 7,750</td>
</tr>
<tr>
<td>number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at entry (y), median (range)</td>
<td>109,298 30.0 (30.0-41.0)</td>
<td>113,801 30.0 (30.0-41.0)</td>
</tr>
<tr>
<td>Age at exit (y), median (range)</td>
<td>109,298 59.3 (30.0-77.9)</td>
<td>113,801 57.9 (30.0-77.9)</td>
</tr>
<tr>
<td>Age at type 2 diabetes,</td>
<td>4,736 57.9 (30.0-77.7)</td>
<td>7,750 57.4 (30.0-77.8)</td>
</tr>
<tr>
<td>median (range)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: kg, kilogram; No, Number; SD, Standard Deviation; y, years

The age at entry, is either 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 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 hospital with a type 2 diabetes diagnosis.
Table 2. Hazard ratios and 95% confidence intervals of adult type 2 diabetes by sex and birth weight

<table>
<thead>
<tr>
<th>Birth weight kg</th>
<th>No.</th>
<th>% (No.) of cases</th>
<th>HR (95% CI)</th>
<th>No.</th>
<th>% (No.) of cases</th>
<th>HR (95% CI)*</th>
<th>HR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.000-2.750</td>
<td>15,796</td>
<td>3.7 (856)</td>
<td>1.46 (1.35-1.59)</td>
<td>12,387</td>
<td>7.7 (958)</td>
<td>1.20 (1.12-1.30)</td>
<td>2.28 (2.10-2.47)</td>
</tr>
<tr>
<td>2.751-3.250</td>
<td>37,078</td>
<td>4.5 (1,650)</td>
<td>1.17 (1.09-1.26)</td>
<td>31,414</td>
<td>7.1 (2,235)</td>
<td>1.07 (1.01-1.13)</td>
<td>2.02 (1.90-2.16)</td>
</tr>
<tr>
<td>3.251-3.750</td>
<td>38,221</td>
<td>3.4 (1,481)</td>
<td>1 [reference]</td>
<td>41,976</td>
<td>6.8 (2,840)</td>
<td>1 [reference]</td>
<td>1.90 (1.78-2.02)</td>
</tr>
<tr>
<td>3.751-4.250</td>
<td>14,438</td>
<td>3.9 (571)</td>
<td>1.01 (0.92-1.12)</td>
<td>21,127</td>
<td>6.1 (1,279)</td>
<td>0.88 (0.83-0.94)</td>
<td>1.67 (1.55-1.80)</td>
</tr>
<tr>
<td>4.251-4.750</td>
<td>2,938</td>
<td>4.1 (121)</td>
<td>1.00 (0.83-1.20)</td>
<td>5,548</td>
<td>6.2 (343)</td>
<td>0.85 (0.76-0.95)</td>
<td>1.61 (1.43-1.81)</td>
</tr>
<tr>
<td>4.751-5.500</td>
<td>827</td>
<td>6.9 (57)</td>
<td>1.56 (1.19-2.03)</td>
<td>1,349</td>
<td>7.0 (95)</td>
<td>0.93 (0.76-1.15)</td>
<td>1.77 (1.44-2.18)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; kg, kilogram; No, Number

*HR of adult type 2 diabetes in men, using men with a birth weight between 3.251-2750 kg as reference

†HR of adult type 2 diabetes in men, using women with a birth weight between 3.251-2750 kg as reference

The analysis was stratified by birth cohort

P-value for interaction between sex and birth weight in six categories in relation to adult type 2 diabetes: 0.001
Figure 1. Hazard ratios and 95% confidence intervals of adult type 2 diabetes according to birth weight for (A) women and (B) men

(A)  

(B)  

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; kg, kilogram; N, Number
The analysis was stratified by birth cohort