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# Intrauterine growth pattern and risk of childhood onset insulin dependent (type I) diabetes: population based case-control study

Gisela Dahlquist, Sara Sandberg Bennich, Bengt Källén

## Abstract

***Objective*—To investigate whether prenatal growth affects the risk of development of childhood onset insulin dependent (type I) diabetes mellitus.**

***Design*—Population based case-control study.**

***Setting*—Data from a nationwide childhood diabetes case register were linked with data from the nationwide Swedish Medical Birth Registry.**

***Subjects*—Data from a total of 4584 diabetic children born after 1973 and diagnosed with diabetes from 1978 to 1992 were studied. For each child with insulin dependent diabetes three control children were randomly selected from among all infants born in the same year and at the same hospital as the proband.**

***Main outcome measures*—Birth weight, gestation, maternal age and parity, number of previous spontaneous abortions, and sex specific birth weight by gestational week expressed as multiples of the standard deviation (SD).**

***Results*—There was a clear trend in the odds ratio for childhood onset diabetes according to SD of birth weight. The odds ratio (95% confidence interval) for small for gestational age after stratification for maternal age, parity, smoking habits, and maternal diabetes was 0.81 (0.65 to 0.99) and for large for gestational age after similar stratification was 1.20 (1.02 to 1.42).**

***Conclusions*—Intrauterine conditions that affect prenatal growth seem also to affect the risk of development of childhood diabetes in the way previously described for postnatal growth: a poor growth decreases and an excess growth increases the risk. The mechanism for this association is unclear.**

**Departments of Paediatrics and Epidemiology and Public Health, University of Umeå, S-901 85 Umeå, Sweden**
Gisela Dahlquist, *professor of paediatrics*

**Department of Internal Medicine, Uppsala University, Uppsala, Sweden**
Sara Sandberg Bennich, *MD student*

**Tornblad Institute, University of Lund, Lund, Sweden**
Bengt Källén, *professor*

Correspondence to:
Professor Dahlquist.

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## Introduction

There is evidence that both future immune reactivity[1] and carbohydrate metabolism[2] can be affected by the intrauterine environment of the fetus. Both types of associations may be relevant for the pathogenesis of insulin dependent (type I) childhood onset diabetes. In a previous study we reported on several perinatal risk determinants for insulin dependent diabetes[3] among which we found a significant effect of short gestation but no effect of birth weight or body length. We have now studied the importance of disturbances in intrauterine growth on the risk for childhood onset insulin dependent diabetes in greater detail, using extended material and the recently published normal growth chart for Swedish children.[4]

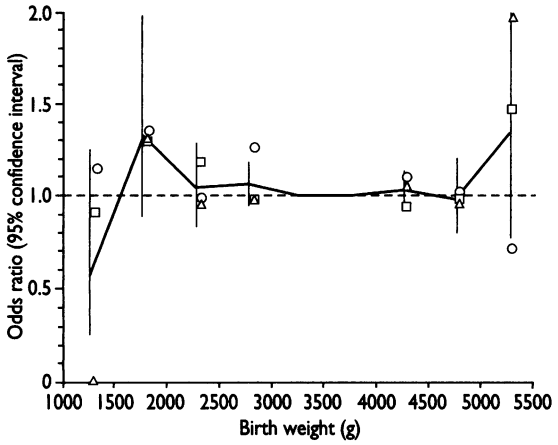


**Fig 1**—*Odds ratio for childhood insulin dependent diabetes according to birthweight class with birth weight 3000 g to 4000 g as reference (1.0). Vertical lines give 95% confidence intervals. Age at onset of diabetes: 0-4 years (○), 5-9 years (△), 10-14 years (□)*

## Subjects and methods

In Sweden all children younger than 15 years with diabetes are referred to paediatric departments. Since 1 July 1977 all incident cases of insulin dependent diabetes have been reported to the Swedish Childhood Diabetes Registry.[5] The level of ascertainment has been shown to vary between 96% and 99%.[6 7] From 1978 to 1992 a total of 4702 children born in 1973 or later were recorded in the diabetes registry.

The Swedish Medical Birth Registry began in 1973 and stores data on the pregnancy, delivery, and neonatal period for nearly all infants born in Sweden.[8] The two registries were linked with the unique personal identification number given to everyone living in Sweden. Linkage was obtained for 4584 children. Thus for 118 (2.5%) linkage failed; either the child was not born in Sweden or there was an error in the identification numbers used for linkage.

For each child with insulin dependent diabetes for whom linkage was successful, three control children were selected randomly from among all infants born that year at the same hospital as the proband child. Only living children were accepted as controls; routinely, dates of death are linked to the birth registry for all children dying within Sweden.

We analysed the following variables from the birth registry: birth weight, gestation, maternal age and parity, maternal diagnosis of diabetes during pregnancy, and maternal smoking in early pregnancy. By using a published graph of sex specific normal birth weight for each gestational week in the Swedish population and based on data from the birth registry[4] for each case and control, we calculated the difference from the expected weight and expressed it in standard deviations (estimated as 12% of expected weight). Among all records birth weight was known in 4538 (99%), gestation in 4492 (98%), and maternal age and parity in all. Maternal smoking was known only after 1983 and was then stated in 93% (1238 (27%) of all). Deviation in intrauterine growth could be determined in 4447 (97%). There was no difference between cases and controls in the completeness of the records.

Analyses of birth weight, gestation, and intrauterine growth were restricted to singleton pregnancies. The diagnosis of maternal diabetes before 1987 (ICD-8, (international classification of diseases, eighth revision) did not differentiate between insulin dependent diabetes and gestational diabetes, but from 1987 onwards the two conditions got separate codes. This means that before 1987 there was a slight dilution of maternal insulin dependent diabetes with gestational diabetes.

*Statistical methods*—Relative risks were calculated by using Mantel-Haenszel[9] estimates of odds ratios after various stratifications. We estimated 95% confidence intervals with a test based method. Tests for homogeneity between strata were made with the Breslow and Day test.[10] To study trends in a frequency table we used exact trend statistics (version 2.1, CYTEL Software Corporation, Cambridge, MA, USA).

## Results

Among the mothers of children with diabetes 73 had a diagnosis of diabetes during pregnancy; among the controls 56 mothers had such a diagnosis. The rate of recorded diabetes in control children was thus 1:246 or 4.1 per 1000.

### BIRTH WEIGHT AND GESTATION

Determinants of birth weight and gestation comprised maternal age and parity, maternal smoking, and maternal diabetes.

Figure 1 shows the crude odds ratio for the development of childhood onset insulin dependent diabetes for each birthweight class with 3000 g to 4000 g as reference (1.0); no obvious relation was seen. A dichotomised analysis with stratification for maternal age, parity, smoking habits, and maternal diabetes of the risk associated with a birth weight <2500 g gave an odds

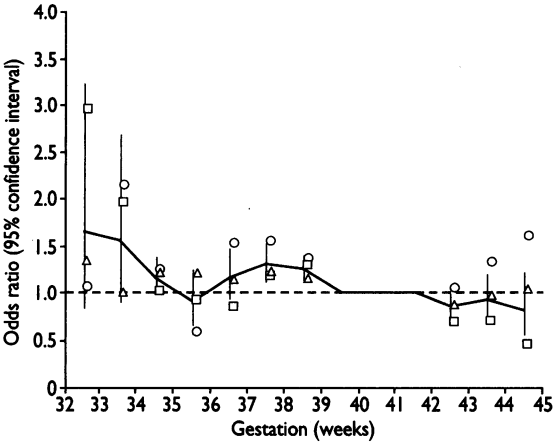


**Fig 2**—*Odds ratio for childhood insulin dependent diabetes according to gestation with weeks 39-41 as reference (1.0). Vertical lines give 95% confidence intervals. Age at onset of diabetes: 0-4 years (○), 5-9 years (△), 10-14 years (□)*

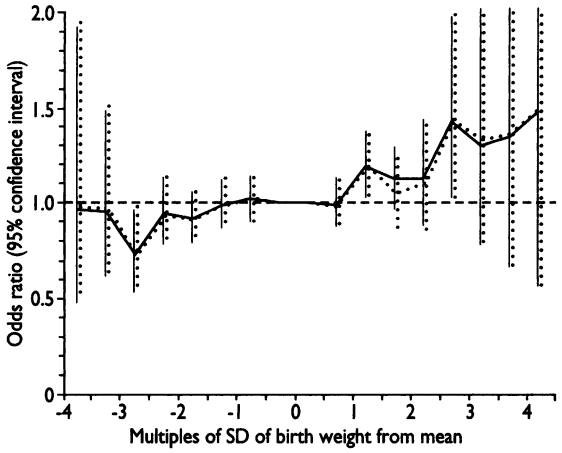


**Fig 3**—*Odds ratio for childhood insulin dependent diabetes according to multiples of SD in birth weight with −0.5 to +0.5 SD as reference (1.0). Vertical lines give 95% confidence intervals. Dotted line represents odds ratio (95% confidence interval) after removal of data from infants whose mothers had diabetes*

ratio (95% confidence interval) of 1.03 (0.86 to 1.24), which was not significantly different when age of onset of diabetes (0-4, 5-9, or 10-14 years) was considered.

Figure 2 shows the crude odds ratio for the development of childhood onset insulin dependent diabetes according to gestation, with weeks 39-41 as reference (1.0). There was an indicated increased risk with short gestation. A comparison of preterm (<37 completed weeks) and term infants, with stratification for maternal age, parity, smoking habits, and maternal diabetes, gave an odds ratio of 1.25 (0.99 to 1.33). There is thus a suggested but not significant excess risk with preterm births.

### INTRAUTERINE GROWTH

To compare intrauterine growth in cases and controls, each child's birth weight was expressed as multiples of SD from the sex specific "normal" weight as defined from the medical birth registry.[4] Figure 3 shows crude odds ratios at different scores (in 0.5 SD units) with the interval –0.5 to +0.5 SD as a reference (1.0). There is a clear cut trend in this graph with a reduced risk at low multiples of SD and an increased risk at high multiples. A summary of the exact distribution of trend statistics gave trend = 4.1; P<0.001. Exclusion of data from children whose mothers had a diagnosis of diabetes in pregnancy did not change the association.

The odds ratio for small for gestational age, defined as <2 SD after stratification for maternal age, parity, smoking habits, and maternal diabetes, was 0.81 (0.65 to 0.99). Exclusion of data from children whose mothers had a diagnosis of diabetes in pregnancy did not change the odds ratio, and there was no clear cut difference according to age at onset in the child, even though only the group aged 5-9 years gave a significantly deviating odds ratio (0.62; 0.44 to 0.89).

The odds ratio for large for gestational age, defined as >2 SD after similar stratifications, was 1.20 (1.02 to 1.42), again similar according to age at onset. Exclusion of data from children whose mothers had a diagnosis of diabetes in pregnancy hardly changed the odds ratio (1.19; 1.00 to 1.40).

## Discussion

In the present study we have shown that disturbances of intrauterine growth affect the risk of the child developing childhood onset insulin dependent diabetes. Small for gestational age tends to diminish the risk, large for gestational age increases it. Epidemiological studies from different parts of the world consistently show a peak in incidence occurring during the rapid pubertal growth spurt.[11,12] Case-control studies have also shown that an increased growth rate before puberty[13] and even in infancy[14] is associated with an increased risk for childhood onset insulin dependent diabetes. That the opposite may be true—that is, that starvation leading to a reduced growth rate is protective—is indicated by the findings of a very low prevalence of insulin dependent diabetes mellitus in men born during the war and the immediate postwar period in Germany.[15] Our data indicate that even prenatal growth can have an effect on the risk of the development of childhood onset insulin dependent diabetes; low birth weight for gestational age reducing the risk and a high birth weight increasing it. This also explains the finding previously reported by us, that maternal smoking during pregnancy is a protective factor for childhood onset insulin dependent diabetes.[3]

Routinely recorded register data may be incomplete, but as data are recorded long before the child develops diabetes, no systematic bias can be introduced. One problem is that the information on maternal diabetes may be incomplete, which may to some extent question the conclusions drawn after exclusion of data from children whose mothers had diabetes during pregnancy.

### Key messages

- The intrauterine environment of the fetus may affect the risk of development of both insulin dependent (type I) and non-insulin dependent (type II) diabetes
- By linking two nationwide population based registers the effect of intrauterine growth on the risk for childhood onset insulin dependent diabetes is estimated
- There was a clear trend in the risk for childhood onset diabetes according to differences in birth weight by gestational age expressed as multiples of SD from population means
- The adjusted odds ratio for babies who were small for gestational age was significantly decreased and for large for gestational age babies was significantly increased
- A poor intrauterine growth decreases and an excess growth increases the risk of development of childhood insulin dependent diabetes

The important factor that might confound our results is maternal insulin dependent diabetes. Such diagnosis in the mother is, however, less likely to be underreported. Non-insulin dependent (type II) diabetes probably accounts for only a minority of those with a diagnosis of maternal diabetes, but before 1987 some might have been gestational diabetes. The mean prevalence of insulin dependent diabetes in Swedish women of all ages, 1977-87, was reported to be 3.6 per 1000,[16] indicating that our findings of maternal diabetes of 4.1 per 1000 among the control mothers is not an underestimate.

The results may be affected by confounders which were not taken into consideration in the analysis. One such possible confounder is socioeconomic class, which is associated with retardation in intrauterine growth, but previous studies in Sweden have shown that low socioeconomic class is associated with an increased risk of childhood onset insulin dependent diabetes[17] and would therefore tend to bias the odds ratio towards 1.0.

In conclusion, this study indicates that disturbances in intrauterine growth may affect the risk of a child developing insulin dependent diabetes. If this association is a direct one further studies on the underlying cause are needed.

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Conflict of interest: None.

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# Do socioeconomic differences in mortality persist after retirement? 25 Year follow up of civil servants from the first Whitehall study

M G Marmot, Martin J Shipley

**Abstract**

***Objective*—To assess the risk of death associated with work based and non-work based measures of socioeconomic status before and after retirement age.**

***Design*—Follow up study of mortality in relation to employment grade and car ownership over 25 years.**

***Setting*—The first Whitehall study.**

***Subjects*—18 133 male civil servants aged 40-69 years who attended a screening examination between 1967 and 1970.**

***Main outcome measure*—Death.**

***Results*—Grade of employment was a strong predictor of mortality before retirement. For men dying at ages 40-64 the lowest employment grade had 3.12 times the mortality of the highest grade (95% confidence interval 2.4 to 4.1). After retirement the ability of grade to predict mortality declined (rate ratio 1.86; 1.6 to 2.2). A non-work based measure of socioeconomic status (car ownership) predicted mortality less well than employment grade before retirement but its ability to predict mortality declined less after retirement. Using a relative index of inequality that was sensitive to the distribution among socioeconomic groups showed employment grade and car ownership to have independent associations with mortality that were of equal magnitude after retirement. The absolute difference in death rates between the lowest and highest employment grades increased with age from 12.9 per 1000 person years at ages 40-64 to 38.3 per 1000 at ages 70-89.**

***Conclusions*—Socioeconomic differences in mortality persist beyond retirement age and in magnitude increase with age. Social differentials in mortality based on an occupational status measure seem to decrease to a greater degree after retirement than those based on a non-work measure. This suggests that alongside other socioeconomic factors work itself may play an important part in generating social inequalities in health in men of working age.**

**Department of Epidemiology and Public Health, University College London Medical School, London WC1E 6BT**
M G Marmot, *professor*
Martin J Shipley, *senior lecturer in medical statistics*

Correspondence to:
Professor Marmot.

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## Introduction

Do social inequalities in death rates that are apparent at younger ages persist into old age? It might be imagined that as the cumulative probability of death for each person approaches 100% social and other predictors of differences in death rates would discriminate less well. In Britain much of the analysis of social class differences in adults has used the registrar general's classification based on occupation and has therefore been confined to people of working age. Other social classifications show differentials in mortality continuing beyond age 65, but differences are reduced.[1-3] In the United States the shorter life expectancy of people with less education continues but the black-white differential in mortality (largely social in origin) is reversed after age 75.[4]

A major question with occupation based social class differentials in mortality is the extent to which resulting mortality differences are due to occupation itself or to broader social differentials.[5] If due to work, social differences in mortality should narrow after retirement; if due to other factors associated with socioeconomic position, the narrowing may be less. We examined this in data from the 25 year follow up of British civil servants in the first Whitehall study. By using a work based measure of status (employment grade) the Whitehall study showed an inverse social gradient in mortality that was steeper than that observed nationally with the registrar general's classification of social class.[6] A non-work based measure (car ownership) added to the predictive power.[7] By using both work based and non-work based socioeconomic measures and analysing mortality differentials before and after usual retirement age we can examine the persistence of social gradients in mortality into older ages and the specific contribution of a work-based measure.

## Subjects and methods

In the Whitehall study 19 019 men aged 40-69 years attended the initial screening between September 1967 and January 1970. Men were classified into four employment grades: administrative, professional and executive, clerical, and other. "Other" included messengers and other unskilled manual workers. For some analyses we grouped the four employment grades as high (administrative and professional and executive) and low (clerical and other). For 886 men from the diplomatic service and the British Council employment grading was different. These men were excluded from analysis.

Data regarding car ownership were available from answers to the question, "Do you own a car?" The questionnaires used in the study were modified during the study, and data on car ownership were collected only from the 70% of men seen during the middle period of the survey. Other studies have used access to a car rather than ownership of a car as a classification of social class. We expect there to be almost perfect agreement between these two definitions, as the Whitehall study men were middle aged and most likely the head of household.

Records from 99.3% of the remaining 18 133 men were identified and flagged at the National Health Service Central Registry, which notified us of all deaths up to the end of January 1995. A total of 18 001 men were therefore fol-