The work of McCarron et al has provided clear evidence that substantial changes in blood pressure levels can occur, and both these and other data suggest that such changes can occur in broad population groups. New epidemiological studies that provide reliable information about the most likely causes of these changes, and new large scale randomised trials that identify effective means of changing population levels of blood pressure, are needed. To have the greatest impact on the global burden of cardiovascular disease, however, the data from such studies must be directly applicable to the social, cultural, and economic circumstances of the less affluent sections of the global community.

Competing interests: None declared.

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Birth weight and childhood onset type 1 diabetes: population based cohort study

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Abstract

Objective To assess the associations between birth weight or gestational age and risk of type 1 diabetes.

Design Population based cohort study by record linkage of the medical birth registry and the National Childhood Diabetes Registry.

Setting Two national registries in Norway.

Participants All live births in Norway between 1974 and 1998 (1 382 602 individuals) contributed a maximum of 15 years of observation, a total of 8 184 994 person years of observation in the period 1989 to 1998. 1824 children with type 1 diabetes were diagnosed between 1989 and 1998.

Main outcome measures Estimates of rate ratios with 95% confidence intervals for type 1 diabetes from Poisson regression analyses.

Results The incidence rate of type 1 diabetes increased almost linearly with birth weight. The rate ratio for children with birth weights 4500 g or more compared with those with birth weights less than 2000 g was 2.21 (95% confidence interval 1.24 to 3.94), test for trend $P = 0.0001$. There was no significant association between gestational age and type 1 diabetes. The results persisted after adjustment for maternal diabetes and other potential confounders.

Conclusion There is a relatively weak but significant association between birth weight and increased risk of type 1 diabetes consistent over a wide range of birth weights.

Introduction

Type 1 diabetes mellitus results from an immune mediated destruction of the pancreatic β cells. The factors initiating the destructive process are largely unknown, but genetic and non-genetic factors are involved.¹ Putative environmental risk factors such as

viruses or nutritional factors may play a part early in life, possibly in utero.² An association between high birth weight or high birth weight for gestational age and increased risk of type 1 diabetes has been found in some relatively large case-control studies, even after exclusion of data from children whose mother had diabetes in pregnancy.³⁻⁵ On the other hand, several other case-control studies have not found any significant association.⁶⁻¹⁴ The magnitude of the association between birth weight and type 1 diabetes seems to be relatively small, and the lack of significant association in the latter studies may be explained by insufficient statistical power. We estimated the associations between birth weight and gestational age and the incidence rate of type 1 diabetes in a large population based cohort study that provided sufficient power to estimate these associations over a wide range of values.

Participants and methods

Participants

Since the beginning of 1989 all newly diagnosed cases of type 1 diabetes diagnosed in children aged up to 15 years in Norway have been prospectively registered with a high level of ascertainment in the National Childhood Diabetes Registry.¹⁵ We designed a cohort study by record linkage of the Medical Birth Registry of Norway and the childhood diabetes registry through the unique personal identification number assigned to all residents of Norway. Out of 1863 cases of type 1 diabetes diagnosed between 1 January 1989 and 31 December 1998, 1824 were linked. All live births in Norway between 1974 and 1998 contributed time under observation from birth to diagnosis of type 1 diabetes, age 15 years, or 31 December 1998, whichever occurred first. As registration of cases started in 1989, the time under observation was counted only from 1 January 1989 for those born before this date. Deaths in the first year of life were

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censored, but we did not have information on deaths between age 1 and 15 years of age. A total of 1 382 602 individuals contributed 8 184 994 person years of observation between 1989 and 1998. The mean (SD) time from birth to censoring was 10.2 (5.0) years, and the mean time under observation after 1 January 1989 was 5.9 (3.3) years. The mean age at diagnosis among the 1824 who developed type 1 diabetes was 8.6 (3.7) years. The study was approved by the regional ethics committee and the national data inspectorate.

Data analysis

From the entire cohort we excluded from analysis 2468 individuals (0.2%) with missing data on birth weight, including three who developed type 1 diabetes. Gestational age was calculated from the first day of bleeding in the last menstruation. Those with missing data on gestational age (6.9%) were included. We calculated the number of incident cases (D_j) and person time under observation (T_j) in each exposure category (j) using DATAB in the EPICURE package, version 1.8w.¹⁶ Incidence rates were calculated as D_j/T_j . To assess a “dose-response” relation we plotted incidence rates against median birth weight in seven categories and against median gestational age in six categories and a category for missing data. We calculated confidence intervals for the incidence rates based on the Poisson assumption and using a log transformation. We used the AMFIT program of EPICURE to fit Poisson regression models, providing estimated rate ratios with 95% confidence intervals. We use the likelihood ratio test for birth weight entered as a continuous variable to test for trend.

We considered sex, maternal age at delivery (<25, 25-30, and ≥ 30 years), maternal parity (0, ≥ 1), caesarean section, maternal pre-eclampsia, attained age (0-4.9, 5-9.9, and 10-14.9 years), and calendar period of birth (1974-83, 1984-90, and 1991-8) as potential confounders. We did stratified analyses and included potential confounders in the regression models, both one by one and all covariates together to assess confounding. The effect of excluding multiple births and maternal diabetes mellitus (any type) diagnosed before or during the index pregnancy was also investigated. To test whether the association of birth weight and type 1 diabetes was homogenous in different age groups and in different categories of gestational age, we tested the significance of the respective interaction terms. We regarded a two sided P value less than 0.05 or a 95% confidence interval excluding the value 1.0 for the rate ratio as significant.

Results

Figure 1 shows that the incidence rate of type 1 diabetes increased almost linearly with birth weight. The rate ratio for the highest category of birth weight (≥ 4500 g) compared with the lowest (<2000 g) was 2.21, and the trend was highly significant (table). The estimates were virtually unchanged after stratification by gestational age or exclusion of children whose mother had diabetes in pregnancy and multiple births or after adjustment for other potential confounders. The simple Poisson regression model predicted a 1.7% increase in incidence rate per 100 g increase in birth weight (95% confidence interval 0.9% to 2.6%).

Fig 1 Birth weight and incidence rate of type 1 diabetes with 95% confidence intervals. Birth weight values are medians in categories <2000 g, 2000-2499 g, 2500-2999 g, 3000-3499 g, 3500-3999 g, 4000-4499 g, and ≥ 4500 g

Rate ratios for type 1 diabetes by birth weight in Norwegian children*

Birth weight (g)	Incident cases	Person years	Rate ratio (95% CI)
<2000	14	129 522	1.00 (reference)
2000-2499	41	214 995	1.76 (0.96 to 3.24)
2500-2999	174	884 884	1.82 (1.06 to 3.14)
3000-3499	561	2 566 646	2.02 (1.19 to 3.44)
3500-3999	648	2 846 744	2.11 (1.24 to 3.58)
4000-4499	316	1 229 034	2.38 (1.39 to 4.06)
≥ 4500	67	279 978	2.21 (1.24 to 3.94)

*P=0.0001 for test for trend over all birth weights.

Figure 2 shows the dose-response relation between gestational age and the incidence rate of type 1 diabetes. In Poisson regression analyses there was no significant association between gestational age and type 1 diabetes, neither crude nor after adjustment for potential confounders or exclusion of extreme values (data not shown).

The contribution to the person time from children who died in the first year of life was counted only until their death because of the known increased infant mortality in low birthweight infants. Low birth weight has also been associated with deaths in children between the ages of 1 and 15 years, which would potentially overestimate our observed rate ratio.¹⁷

Fig 2 Gestational age and incidence rate of type 1 diabetes with 95% confidence intervals. Gestational age values are medians in categories <34, 34-36.9, 37-39.9, 40-40.9, 41-42.9, and ≥ 43 weeks (missing category is arbitrarily placed at 45.5 weeks)

However, the cumulative mortality between 1 and 15 years is small. Using the data from Samuelsen et al,¹⁷ we calculated that the expected bias in our estimated rate ratio would be less than 1% (data not shown).

Discussion

Our most important finding was a linear increase in the incidence of type 1 diabetes with increasing birth weight over a wide range of birth weights, independent of gestational age, maternal diabetes, and other potential confounders.

The advantage of this study is the large sample size and the fact that the data are based on computerised registries with nearly complete coverage. Furthermore, we were able to take into account other potential confounders, such as maternal diabetes, sex, gestational age, maternal age at delivery, maternal parity, caesarean section, and pre-eclampsia. As the incidence rate of childhood onset type 1 diabetes in Norway remained stable in the study period^{15 18} and the association between birth weight and type 1 diabetes persisted after adjustment for calendar period of birth, it is unlikely that time trends have resulted in a spurious association between birth weight and type 1 diabetes. As in all non-experimental research, we cannot exclude the possibility that unmeasured factors were confounders. We did not have information on socioeconomic status of the children's families, such as maternal education or on maternal smoking during pregnancy. However, maternal education is unlikely to explain our results as high maternal education is associated with increased birth weight and has been weakly associated with a decreased risk of type 1 diabetes.^{6 19}

Comparison with previous studies

Our data support the results of some relatively large studies,^{3-5 20} as well as a study in experimental animals.²¹ In a large population based study from Sweden, however, Dahlquist et al found an association between birth weight relative to the average for any particular gestational age and type 1 diabetes but no significant association with birth weight per se.³ This apparent discrepancy is difficult to explain. Dahlquist et al adjusted for maternal smoking during pregnancy in a subset of their data, indicating that maternal smoking did not influence their result.³ Consistent with our observation, an increase in both mean birth weight and the incidence of type 1 diabetes has been observed in many Western countries in the past two to three decades.^{22 23} However, the magnitude of the association between birth weight and type 1 diabetes was estimated as a 1.7% increase in incidence rate per 100 g increase in birth weight, which is probably not sufficient to explain these secular trends in type 1 diabetes. Detection of such a relatively weak association requires a large sample size. For instance, 2500 cases and 2500 controls are needed to attain 80% power to detect a significant association between birth weights of 2500 g and more versus less than 2500 g and type 1 diabetes in a case-control study if the true odds ratio is 1.5 and 5% of the population have birth weights less than 2500 g. This indicates that most of the published case-control studies may have had far too little power to detect such an association.

What is already known on this topic

Results of case-control studies of birth weight and risk of type 1 diabetes have been inconsistent

It is possible that a relatively weak association exists, and large studies are needed to find out if this is the case

What this study adds

This is the largest study of birth weight and type 1 diabetes published to date, and the first one to use a cohort design

The incidence of type 1 diabetes increased almost linearly with increasing birth weight over a wide range of birth weights, independent of gestational age, maternal diabetes, and other potential confounders

The trend was highly significant, but the increment in risk with increasing birth weight was still relatively low

Possible explanations

Both birth weight and gestational age are influenced by several factors, such as maternal diabetes during pregnancy, nutrition, and parity, and may be viewed as markers of the combined effect of many factors. Potential factors explaining the present results would have to be associated with both increased birth weight and increased risk of type 1 diabetes over a wide range of birth weights. Maternal diabetes is one such candidate but is not likely to explain the observed association as the association persisted after exclusion of data from children whose mother had diabetes in pregnancy. As only a very small proportion of the children had a mother with diabetes diagnosed before or during pregnancy (0.5%), even a hypothetical underreporting of maternal diabetes is unlikely to explain the observed association. This indicates that other rare conditions probably do not explain the observed relation either. We cannot exclude the possibility that some genetic factors predispose to both higher birth weight and type 1 diabetes. A common genetic variant of the insulin gene region has been associated with lower birth weight in one study, but the effect was weak and significant only in a subgroup.²⁴ The same variant is associated with an increased risk of type 1 diabetes.²⁵ Allelic variation in the insulin gene region is therefore likely to diminish the association between birth weight and type 1 diabetes.

We can only speculate about biological mechanisms that could explain a hypothetical causal effect of birth weight on risk of type 1 diabetes. Insulin is the most important fetal growth factor late in pregnancy.²⁶ In vitro studies have shown that pancreatic β cells actively secreting insulin express more antigens associated with diabetes²⁷ and are more susceptible to insults by interleukin 1²⁸ compared with less active β cells. Increased growth in utero may therefore lead to an increased risk of later immune mediated destruction of the pancreatic β cells. Low birth weight has been associated with impaired cellular immune competence up

to 5 years of age²⁹ and with increased mortality from infectious diseases in the age group 1-15 years.^{17, 30} Perhaps an impaired cellular immune response makes children less prone to immune mediated destruction of the β cells? It has been speculated that the decrease in pancreatic β cell mass associated with reduced birth weight is relevant in the association between reduced birth weight and increased risk of type 2 diabetes.³¹ Our findings indicate that a possible reduction in pancreatic β cell mass associated with reduced birth weight is not relevant for type 1 diabetes.

Conclusion

We found a relatively weak but significant association between birth weight and increased risk of childhood onset type 1 diabetes consistent over a wide range of birth weights. It is possible that perinatal factors influence the risk type 1 diabetes, but the mechanisms are unknown.

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Contributors: OS and GJ had the original idea for the study, and GJ was the principal investigator. RTL and PM provided advice in presentation and interpretation of the results. LCS was responsible for the data analysis and wrote the paper. All authors commented on the earlier drafts and helped interpret the findings. LCS and GJ are guarantors.

Competing interests: None declared.

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