Perinatal Risk Factors for Diabetes in Later Life

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OBJECTIVE—Low birth weight is consistently associated with an increased risk of type 2 diabetes in adulthood, but the individual contributions from poor fetal growth and preterm birth are not known. We therefore investigated the significance of these two factors separately.

RESEARCH DESIGN AND METHODS—We identified a cohort of subjects born preterm or with low birth weight at term at four major delivery units in Sweden from 1925 through 1949. A comparison cohort of subjects was identified from the same source population. Of 6,425 subjects in all, 2,931 were born at <37 weeks of gestation and 2,176 had a birth weight <2,500 g. Disease occurrence among participants was assessed through nationwide hospital registers from 1987 through 2006.

RESULTS—During follow-up, there were 508 cases of diabetes. Low birth weight was strongly negatively associated with risk of diabetes (*P* for trend <0.0001). Both short gestational duration and poor fetal growth were associated with later diabetes (*P* for trend <0.0001 and <0.0004, respectively). Very preterm birth (≤32 weeks of gestation at birth) was associated with a hazard ratio (HR) of 1.67 (95% CI 1.33–2.11) compared with term birth. Birth weights below 2 SDs of mean birth weight for gestational age were associated with an HR of 1.76 (1.30–2.38) compared with birth weights between the mean weight and the weight at 1 SD above the mean.

CONCLUSIONS—Our results suggest that the association between low birth weight and diabetes is due to factors associated with both poor fetal growth and short gestational age. ***Diabetes* 58:523–526, 2009**

Type 2 diabetes affects hundreds of millions of people worldwide, and the prevalence is rising (1). Several studies have found an association between low birth weight and type 2 diabetes (2–12). The predominant explanation for this association has been the so-called fetal origins hypothesis, which suggests that fetal malnutrition induces adaptive changes in fetal glucose metabolism that become lasting, thereby contributing to an increased risk of type 2 diabetes and heart disease in adult life (2,13).

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The fetal origins hypothesis inherently assumes that low birth weight indicates fetal growth restriction rather than preterm birth. For ischemic heart disease and hypertension, this assumption has been found to be valid (14,15). In the case of type 2 diabetes, no study has assessed the hypothesis while distinguishing preterm birth from growth restriction. Therefore, the validity of the fetal origins hypothesis on risk of diabetes in adult life remains uncertain (16,17).

In this study, we followed a cohort of 6,425 subjects born between 1925 and 1949. We oversampled infants born before the 35th gestational week or with low birth weight to assess selective contributions from low birth weight and short gestational duration to risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS

The study cohort has been described in more detail previously (14). Within a well-defined source population, we manually examined ~250,000 births records from 1925 through 1949 and identified an exposed cohort by identifying all newborn infants with a gestational duration <35 weeks and/or a birth weight <2,000 g for girls and <2,100 g for boys. Subjects who emigrated or deceased before 1987 were excluded. For unexposed cohort members, we selected subjects who were not born preterm or with low birth weight. For convenience, we selected the first child born of the same sex and hospital of birth as each exposed subject.

Perinatal definitions and categorization. We used the date of the mother's last menstrual period to estimate gestational duration. Birth weight for gestational age was used as the measure of fetal growth. We used the Swedish reference curve for normal fetal growth (18) and categorized birth weights for gestational age into five groups according to their distance from the mean birth weight for gestational age (−2 SD or less, above −2 to −1 SD, above −1 to 0 SD, above 0 to 1 SD, and above 1 SD). Subjects whose birth weight was more than 4 SDs above or below the mean birth weight for gestational age were excluded.

The socioeconomic status of the family was assessed by the father's occupation, or by the mother's occupation in single-parent families, using three categories: high (college education), medium (white-collar workers and farm owners with no college education), and low (blue-collar workers and farmhands).

Follow-up and analysis. The follow-up started on 1 January 1987 and continued to 31 December 2006. We used the Swedish Register of Population and Population Changes to ascertain emigration and the Cause of Death Register to ascertain deaths. Diagnoses of diabetes were determined from the Hospital Discharge Register, which lists one main diagnosis and up to seven additional diagnoses. During the period 1987–1996, diagnoses were categorized according to the ICD-9 and thereafter according to the ICD-10. We considered cohort subjects as cases if they had a main or additional diagnosis of diabetes with diagnostic code 250 before 1997 and diagnostic code E11 after 1997.

Data were modeled through conditional Cox regression, using the TPHREG procedure in SAS Statistical Software (version 9.1; SAS Institute, Cary, NC). Analyses were conditioned by calendar period of birth, socioeconomic status, and sex. Additional adjustments for gestational duration and fetal growth were also obtained by conditioning on these factors. Missing information on socioeconomic status was treated as a separate category when the analysis was stratified on this variable. The study was approved by the research ethics committee of the Karolinska Institutet.

RESULTS

At the start of follow-up, there were 6,425 subjects in the cohort. The distributions of birth weight, gestational du-

TABLE 1
Cohort subjects by gestational duration, birth weight, and fetal growth

	Gestational duration				
	≤32 weeks	33–36 weeks	37–42 weeks	≥43 weeks	Total
Birth weight (g)					
<1,500	132	19	0	0	151
1,500–1,999	403	392	39	1	835
2,000–2,499	307	716	161	6	1,190
2,500–2,999	144	454	377	25	1,000
3,000–3,499	0	252	1,045	70	1,367
3,500–3,999	0	110	1,105	94	1,309
≥4,000	0	2	494	77	573
Total	986	1,945	3,221	273	6,425
Fetal growth (SD)					
−2 or less	26	256	255	39	576
More than −2 to −1	94	240	522	86	942
More than −1 to 0	219	416	1,114	87	1,836
More than 0 to 1	208	400	902	50	1,560
More than 1	439	633	428	11	1,511
Total	986	1,945	3,221	273	6,425

Data are *n*.

ration, and fetal growth are presented in further detail in Table 1. During follow-up, 508 subjects were treated as inpatients with a main or an additional diagnosis of diabetes. Calendar period of birth, socioeconomic status, and sex were all associated with risk of diabetes (Table 2), and all further analyses were adjusted for these three variables.

Birth weight was strongly associated with risk of diabetes (Table 3). Furthermore, both fetal growth and gestational duration were independently associated with risk of diabetes (Table 3). To evaluate whether our choice of reference curves affected the association between fetal growth and risk of diabetes, we also analyzed the data with all growth category limits shifted 50 and 100 g downwards and upwards, but those alterations had no effect on the results (data not shown).

The association of fetal growth and gestational duration with risk of diabetes was not affected by calendar period of birth (Table 3). Likewise, none of the variables for maternal age, hypertensive diseases during pregnancy, twin status, or breast-feeding at time of hospital discharge were associated with risk when fetal growth or gestational duration were included in the model (data not shown).

Table 4 describes an analysis of interaction between fetal growth and gestational age on risk of diabetes. The association between poor fetal growth and diabetes was independent of gestational age, and likewise the association between low gestational age and diabetes was independent of fetal growth.

TABLE 2
HRs for diabetes by calendar period of birth, socioeconomic status, and fetal sex

	Diabetes according to ICD-9: 250 and ICD-10: E11			
	n	Cases (*n*)	Crude HR	CI
Calendar period of birth				
1925–1929	936	117	4.72	3.39–6.58
1930–1934	975	134	4.85	3.50–6.71
1935–1939	1,586	124	2.50	1.80–3.48
1940–1944	1,426	83	1.81	1.27–2.57
1945–1949	1,502	50	1	Ref.
Socioeconomic status				
High	309	13	0.45	0.26–0.79
Medium	912	47	0.57	0.42–0.77
Low	5,120	446	1	Ref.
Sex				
Male	3,819	360	1.78	1.47–2.15
Female	2,606	148	1	Ref.

DISCUSSION

This is the first study large enough to assess the individual contributions of fetal growth and length of gestation on risk of diabetes in adult life with appropriate statistical precision. Our data confirm the previously reported inverse association between birth weight and adult diabetes (2–12) and add the evidence that short gestational duration and fetal growth restriction are both independently associated with an increased risk of diabetes.

Our study is population based, information about birth characteristics was based on prospectively collected data, and follow-up was uniform across comparison groups through the use of register data. It is therefore unlikely, if not precluded, that measurement errors should vary between subjects with and without diabetes.

One limitation is the expanse of time between the subjects' dates of birth and the beginning of the follow-up. Study subjects were born between 1925 and 1949, but the follow-up did not start until 1987. The cohort therefore consists of subjects born >50 years ago who survived to 37–62 years of age. Another limitation was our inability to test whether the association between birth weight and diabetes might be explained by a common genetic etiology (19). A third limitation of our study is the lack of structured data on the neonatal care of these subjects, and so there can only be speculation as to what extent the knowledge derived from this cohort from the early 1900s applies to today's newborns.

In our cohort, ~70% of the subjects born at <33 weeks of gestation had a birth weight for gestational age that was above average. Selective survival favoring non–growth-restricted subjects among those born preterm may partly explain this skewness (20) and may have biased the obtained associations. However, childhood mortality declined steeply in Sweden from 1925 to 1949, whereas our risk estimates were fairly stable across birth cohorts. Thus, we think that selective survival is an unlikely explanation for our findings.

We used information on the mother's last menstrual period to estimate gestational age, which may lead to some misclassification. By excluding all subjects whose birth weight deviated more than 4 SDs from the mean birth weight for gestational age category, misclassification was reduced. Fetal growth was estimated through growth curves from ultrasonographically dated pregnancies from the 1990s. Reassuringly, our results remained unchanged when we altered the cutoff levels for the definition of fetal growth rate, indicating that the choice of reference curves does not affect the association.

Subjects in our cohort were registered as diabetic if they had required hospitalization, and because diabetes is frequently diagnosed in open clinics, we are likely to have underestimated the true incidence of diabetes. The absolute occurrence of diabetes in the study is therefore not

TABLE 3
HRs for diabetes by birth weight, fetal growth, and gestational duration

	All					Birth year 1925–1939				Birth year 1940–1949			
	n	Age at onset (years)	Cases (*n*)	HR	CI	*n*	Cases (*n*)	HR	CI	*n*	Cases (*n*)	HR	CI
Birth weight (g)													
<1,500	151	57.8 ± 9.6	17	1.97	1.17–3.31	74	8	1.27	0.61–2.66	77	9	3.82	1.79–8.18
1,500–1,999	835	62.2 ± 8.7	95	1.77	1.33–2.37	468	71	1.81	1.29–2.55	367	24	1.65	0.95–2.86
2,000–2,499	1,190	61.8 ± 8.6	120	1.45	1.10–1.90	680	90	1.48	1.08–2.04	510	30	1.36	0.81–2.29
2,500–2,999	1,000	61.8 ± 8.3	79	1.13	0.84–1.53	559	57	1.14	0.80–1.63	441	22	1.11	0.63–1.96
3,000–3,499	1,367	61.8 ± 9.3	94	1	Ref.	740	67	1	Ref.	627	27	1	Ref.
3,500–3,999	1,309	63.7 ± 8.2	71	0.78	0.57–1.07	686	57	0.88	0.62–1.25	623	14	0.55	0.29–1.04
≥4,000	573	62.9 ± 8.0	32	0.80	0.54–1.20	290	25	0.92	0.58–1.45	283	7	0.54	0.24–1.25
Total	6,425	62.0 ± 8.6	508			3,497	375			2,928	133		
P for trend					<0.0001				<0.0001				<0.0001
Fetal growth (SD)													
−2 or less	576	62.2 ± 8.9	70	1.76	1.30–2.38	329	56	1.72	1.22–2.41	247	14	1.88	0.96–3.67
More than −2 to −1	942	61.6 ± 9.8	93	1.43	1.08–1.89	498	58	1.13	0.81–1.58	444	35	2.58	1.51–4.41
More than −1 to 0	1,836	62.1 ± 8.4	121	0.94	0.73–1.23	985	91	0.89	0.66–1.19	851	30	1.16	0.67–2.02
More than 0 to 1	1,560	62.5 ± 8.1	107	1	Ref.	824	85	1	Ref.	736	22	1	Ref.
More than 1	1,511	61.6 ± 8.4	117	1.05	0.81–1.37	861	85	0.93	0.69–1.25	650	32	1.55	0.90–2.67
Total	6,425	62.0 ± 8.6	508			3,497	375			2,928	133		
P for trend					0.0004				0.003				0.04
Gestational duration (weeks)													
≤32	986	60.9 ± 8.2	109	1.67	1.33–2.11	555	74	1.47	1.11–1.95	431	35	2.82	1.77–4.48
33–36	1,945	62.1 ± 8.7	168	1.29	1.05–1.58	1,098	129	1.29	1.02–1.64	847	39	1.51	0.96–2.38
37–42	3,221	62.4 ± 8.9	216	1	Ref.	1,718	161	1	Ref.	1,503	55	1	Ref.
≥43	273	62.0 ± 7.0	15	0.92	0.55–1.56	126	11	1.03	0.56–1.90	147	4	0.76	0.23–2.44
Total	6,425	62.0 ± 8.6	508			3,497	375			2,928	133		
P for trend					<0.0001				0.004				<0.0001

Data are means ± SD unless otherwise indicated. Analyses are adjusted for calendar period of birth, socioeconomic status, and sex.

interpretable. The relative risks of diabetes, however, could not be inflated but, rather, could be biased toward unity by such underestimation.

In this study, follow-up did not cover the entire life span of the subjects. For subjects born in 1925, follow-up started at the age of 61 years, whereas for subjects born in 1949, it stopped at the age of 57 years. Because risk estimates were similar regardless of birth period, we find it unlikely that this truncated follow-up has had more than a marginal influence on our results.

The fetal origins hypothesis suggests that fetal undernutrition during middle and late gestation triggers lasting hormonal and metabolic adaptations that ultimately lead to insulin resistance and diabetes (13,19,21). Our finding that not only fetal growth restriction but also short gestational duration contribute to the risk of diabetes is not entirely compatible with that hypothesis. It suggests, rather, that the association between low birth weight and diabetes has two components: one component mediated through poor fetal growth and the other through preterm birth. It cannot be ruled out that the effect on glucose metabolism of preterm birth and fetal growth share a common mechanistic pathway. It could, for example, be speculated that the association between low birth weight and diabetes could be due to postnatal nutritional exposures, both in those born small for gestational age and those born preterm. Unfortunately, we were unable to assess postnatal diet and infant growth in the present data.

Previous studies have found results consistent with ours. In a study on insulin resistance, Hofman et al. (16) found that infants born preterm and with appropriate weight for gestational age faced the same increase in risk of insulin resistance as did infants born small for gestational age at term. In a recent study of Hovi at al. (17), the authors found that preterm infants with very low birth weight (<1,500 g) showed similar patterns of glucose

TABLE 4
HRs for the joint effect of fetal growth and gestational duration on risk of diabetes

	Gestational duration			
	<32 weeks	33–36 weeks	37–42 weeks	>43 weeks
Fetal growth (SD)				
−2 or less	0.82 (0.11–5.98)	2.24 (1.42–3.53)	2.24 (1.45–3.45)	1.93 (0.69–5.36)
More than −2 to −1	3.43 (1.94–6.05)	1.87 (1.16–3.03)	1.52 (1.02–2.28)	1.24 (0.53–2.90)
More than −1 to 0	2.21 (1.37–3.56)	1.31 (0.84–2.05)	0.95 (0.66–1.39)	0.45 (0.11–1.87)
More than 0 to 1	2.05 (1.26–3.32)	1.35 (0.86–2.12)	1 (ref)	0.46 (0.06–3.33)
More than 1	1.58 (1.04–2.39)	1.31 (0.88–1.94)	0.91 (0.56–1.49)	4.30 (1.04–17.9)

Data are HR (95% CI). Analyses are adjusted for calendar period of birth, socioeconomic status, and sex.

intolerance and insulin resistance regardless of whether they were born small or appropriately sized for gestational age.

In a recent meta-analysis on the association between birth weight and diabetes, Harder et al. (22) reported an additional association between high birth weight and risk of diabetes. We did not find such an association in our data, but our study was designed to study the risks in the lower end of the birth-weight spectrum, and consequently we lacked the power to assess the association between high birth weight and risk of diabetes with precision.

Consistent with the fetal origins hypothesis, we have previously found that the association between low birth weight and risk of both ischemic heart disease and hypertension was entirely mediated through poor fetal growth (14,15). The risk patterns in the present analysis are, however, distinct from our findings on heart disease and hypertension, suggesting that different mechanisms are involved in the perinatal origins of these diseases.

In conclusion, we have found that the association between low birth weight and risk for diabetes seems to be mediated through both poor fetal growth and preterm birth. The underlying programming mechanisms seem to involve not only prenatal but also postnatal factors.

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