Preterm birth – a risk factor for type 2 diabetes?
- The Helsinki Birth Cohort Study

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Objective: The association between low birth weight and type 2 diabetes is well established. We studied whether preterm birth carries a similar risk.

Research Design and Methods: The Helsinki Birth Cohort includes 13345 men and women born between 1934 and 1944. Of them, 12813 had adequate data on length of gestation, which we linked with data on special reimbursement for diabetes medication.

Results: 5.1% of the subjects had received special reimbursement after age 40. In subjects born before 35 weeks of gestation, the odds ratio for diabetes was 1.68 (95% confidence interval 1.06 to 2.65) as compared with those born at term. After adjustment for birth weight relative to length of gestation, it was 1.59 (1.00 to 2.52).

Conclusions: Preterm birth before 35 weeks of gestation is associated with an increased risk of type 2 diabetes in adult life. The risk is independent of that associated with slow fetal growth.
Because preliminary analyses suggested a non-linear relationship between gestational age and risk of diabetes (p for quadratic trend=0.009), we illustrate this relationship by presenting gestational age in categories. The study was accepted by Ethics Committee. Data were linked by permission from the Ministry of Social and Health Affairs.

RESULTS
Clinical characteristics are shown in Supplemental Table 1 in the online appendix available at http://care.diabetesjournals.org. More men (6.5%) than women (3.6%) had diabetes. As there was no interaction between the effects of sex and gestational age (p=0.3), we present the results pooled for both sexes. Subjects with diabetes had a lower birth weight: For each SD unit lower birth weight adjusted for the length of gestation, the odds ratio for diabetes was 1.20 (95% CI 1.11 to 1.30). There was no quadratic relationship between birth weight SD score and diabetes and no interaction between the effects of preterm birth and birth weight SD score (p’s ≥ 0.5).

The odds ratios for diabetes in subjects born before 35 completed weeks of gestation was 1.69 as compared with subjects born at term. When further adjusted for childhood socio-economic status, whether firstborn, and birth weight SD score, it was 1.59 (Figure 1); with further adjustment for maternal BMI in late pregnancy, it was 1.72 (95% confidence interval 1.03 to 1.69). The odds of diabetes were also increased in subjects born after 42 weeks of gestation, which attenuated to non-significance after adjustment for birth weight SD score.

DISCUSSION
Our main finding was that preterm birth before 35 weeks of gestation is associated with an increased risk of type 2 diabetes in adult life. The risk is independent of that associated with slow fetal growth. We found also evidence for a moderately increased risk in people born post term, which remains to be confirmed. We have previously discussed the limitations of the Helsinki Birth Cohort Study (8,9). While the diagnosis of diabetes was confirmed by a physician at the National Social Insurance Institution (11), this was limited to subjects who use medication for diabetes.

Two previous studies have reported an increased risk of type 2 diabetes in middle-aged or older people born preterm. These studies and our study each assess a different subset of people who develop diabetes. A study in the Aberdeen 1950 to 1956 cohort assessed diabetes by self-report at age 46-50 years (7), thus limited to early-onset cases. In a Swedish cohort born between 1925 and 1949, diabetes was assessed from Hospital Discharge Register for 1987 to 2006 (6), which may be biased towards cases with complications requiring hospitalization. Our study was based on medication reimbursement and thus includes also non-hospitalized cases. That the findings are consistent in these studies is a strong argument for an increased risk of diabetes conferred by preterm birth.

Several putative mechanisms could underlie an association between preterm birth and type 2 diabetes. Studies in children (5) and young adults (4) born preterm at very low birth weight (<1500 g) show increased indices of impaired glucose regulation already from an early age onwards. The study in children used intravenous glucose tolerance test and suggested that this is attributable to low insulin sensitivity. This finding was however not confirmed in a study in young adults which however included also term small-for-gestational age subjects and was focused on a lesser degree of prematurity (3). Impaired glucose regulation can be in part contributed to by the lower amount of muscle mass (4) and lower rates of physical activity (13).
These may originate from the immediate postnatal period in preterm infants, which corresponds to late gestation in infants born at term, but is characterised by highly different environmental conditions than those in utero. Among infants born at term, this period is important in determining the risk of type 2 diabetes (2,12).

In conclusion, our results reinforce previous suggestions that preterm birth is a risk factor of type 2 diabetes later in life.

**Author contributions.** EK conceived the hypothesis, collected, cleaned and analyzed data, wrote the first draft of the paper and contributed to redrafts. CO contributed to data collection, analyzed data and contributed to redrafts of the paper. DJPB contributed to data collection and to redrafts of the paper. JGE conceived the Helsinki Birth Cohort Study, collected and cleaned data, and contributed to redrafts of the paper. All authors have approved the final version of the paper.

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**FIGURE LEGEND**

**Figure 1.** Odds ratios (OR; 95% confidence intervals) for diabetes according to gestational age at birth. Thick bars (*): adjusted for sex and year of birth; thin bars (†): adjusted for sex, year of birth, whether firstborn, socio-economic status in childhood and birth weight relative to length of gestation.