

# Maternal BMI Before Pregnancy, Maternal Weight Gain During Pregnancy, and Risk of Persistent Positivity for Multiple Diabetes-Associated Autoantibodies in Children With the High-Risk HLA Genotype

The MIDIA study

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## RESEARCH DESIGN AND METHODS

— From July 2001 to December 2007, the MIDIA (Norwegian acronym for “Environmental Triggers of Type 1 Diabetes”) study recruited newborns from the general population of Norway with an HLA genotype DR4-DQ8/DR3-DQ2 (DRB1\*0401-DQA1\*03-DQB1\*0302/DRB1\*03-DQA1\*05-DQB1\*02) conferring high risk of type 1 diabetes. Of the 46,939 newborns genotyped, 1,003 (2.14%) carried the high-risk genotype. From that group, 885 children were followed longitudinally with questionnaires and gave blood samples for autoantibody testing at age 3, 6, 9, and 12 months and then annually (8). Children who tested positive for autoantibodies at the age of 12 months or older were scheduled for retesting more frequently than every 12 months. If positive for a single autoantibody, the children were scheduled for retesting every 6th month; if positive for two or three autoantibodies, they were scheduled for retesting every 3rd month. Autoantibodies to insulin, GAD, and insulinoma-associated protein 2 (IA2) were measured using radiobinding assays at the Hormone Laboratory at Aker University Hospital (8), which has participated in the Antibody Standardization Program (DASP) since 2003 (9). In 2007, the disease specificity was 91% for anti-GAD, 95% for anti-IA2, and 96% for insulin autoantibody (IAA), while the disease sensitivity was 50% for anti-GAD, 64% for anti-IA2, and 22% for IAA. Positivity for two or more islet autoantibodies is a strong predictor for type 1 diabetes in young children (10). The end point in this analysis was defined as repeated positivity for two or more of the above-mentioned islet autoantibodies (on at least two consecutive occasions) or the onset of type 1 diabetes (islet autoimmunity). All cases of islet autoimmunity were negative for autoantibodies at age 3 months, and islet autoantibodies potentially

**OBJECTIVE** — To assess whether maternal BMI before pregnancy and weight gain during pregnancy predicted the risk of islet autoimmunity in genetically susceptible children.

**RESEARCH DESIGN AND METHODS** — Of 46,939 newborns screened for the high-risk HLA genotype DR4-DQ8/DR3-DQ2, 1,003 were positive and 885 were followed with serial blood samples tested for autoantibodies to insulin, GAD, and insulinoma-associated protein 2 (IA2). The end point was defined as repeated positivity for two or three autoantibodies or the onset of type 1 diabetes (islet autoimmunity).

**RESULTS** — Thirty-six children developed islet autoimmunity, of whom 10 developed type 1 diabetes. Both maternal BMI  $\geq 30$  kg/m<sup>2</sup> before pregnancy and maternal weight gain  $\geq 15$  kg predicted the increased risk of islet autoimmunity (hazard ratio [HR] 2.5,  $P = 0.023$ , and HR 2.5,  $P = 0.015$ , respectively), independent of maternal diabetes.

**CONCLUSIONS** — Maternal weight may predict risk of islet autoimmunity in offspring with a high genetic susceptibility for type 1 diabetes.

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Type 1 diabetes is caused by specific autoimmunity against pancreatic  $\beta$ -cells. The incidence of type 1 diabetes is increasing worldwide, and Norway currently has one of the world's highest incidence rates (1,2). The etiology is multifactorial, determined by a combination of genetic and nongenetic factors. In Norway, 2.1% of newborns carry the HLA genotype DR4-DQ8/DR3-DQ2, which confers a relative risk for type 1 diabetes in excess of 20 and an estimated

absolute risk of 7% by age 15 years (3,4). Nongenetic factors have been difficult to identify. Islet autoimmunity may start as early as in the 1st year of life before clinical type 1 diabetes with variable duration or even in utero (5). Studies have suggested that growth and obesity in childhood are associated with risk of type 1 diabetes and islet autoimmunity (6,7), but we are not aware of previous studies investigating the role of maternal BMI or weight gain in pregnancy.

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**Table 1—Association of maternal BMI before pregnancy, weight gain during pregnancy, and other characteristics with risk of persistent positivity for multiple islet autoantibodies in children in the MIDIA study**

	Affected	Unaffected	Unadjusted HR (95% CI)	P
<i>n</i>	36	797		
Follow-up from birth (months)	14.0 (4.5–31)*	28.6 (3.2–86)*	NA	NA
Sex (female)	21 (58)	411 (48)	1.40 (0.72–2.7)	0.32
Maternal BMI (kg/m <sup>2</sup> )				
<25	21 (58)	540 (66)	1.0 ref.	
25–29.9	6 (17)	186 (23)	0.83 (0.33–2.05)	0.68
≥30	9 (25)	92 (11)	2.48 (1.14–5.4)	0.023
Mean (interquartile range)	26.2 (21.8–29.4)	24.4 (21.3–26.2)	1.07 (1.01–1.13)	0.021
Maternal weight gain (kg)				
<15	10 (28)	414 (50)	1.0 ref.	
≥15	26 (72)	405 (50)	2.47 (1.19–5.1)	0.015
Mean (interquartile range)	16.1 (13.5–19.0)	14.6 (11.0–18.0)	1.04 (0.99–1.10)	0.14
Child's weight gain 3–12 months (kg)	3.82 (3.3–4.2)	3.63 (3.1–4.1)	1.33 (0.94–1.89)	0.11
Child's length gain 3–12 months (cm)	14.75 (14–15)	14.67 (13–16)	1.03 (0.89–1.20)	0.66
Age at weaning (months)	10.25 (8–12)	9.50 (6–12)	1.00 (0.94–1.06)	0.99
Duration exclusive breastfeeding (months)	3.52 (2.25–4.5)	3.29 (1.25–4.5)	1.05 (0.89–1.24)	0.56
First-degree type 1 diabetic relative	11 (31)	52 (6.1)	5.92 (2.91–12.0)	<0.001
Maternal pregestational type 1 diabetes	3 (8.3)	19 (2.2)	3.67 (1.12–12.0)	0.031
Maternal gestational diabetes†	0 (0)	12 (1.4)	NA	NA
Maternal age at birth (years)	31.1 (28.0–33.5)	30.7 (28.0–34.0)	1.01 (0.94–1.09)	0.71
Smoking in pregnancy	3 (8.3)	160 (19)	0.41 (0.12–1.32)	0.14
Maternal education				
≤3 years high school	13 (36)	329 (39)	1.0 ref.	Global
≥4 years university	16 (44)	343 (41)	1.20 (0.58–2.5)	0.89
>4 years university	7 (19)	171 (20)	1.00 (0.40–2.5)	
Child is first born vs. later born	8 (22)	300 (35)	0.54 (0.25–1.18)	0.12

Data are *n* (%) for categorical variables, mean (interquartile range) for continuous variables, and \*mean (range) where indicated. All HRs for continuous variables are per unit increment (1 kg/m<sup>2</sup> or 1 kg wt gain). Maternal BMI before pregnancy was missing for 31 children, maternal weight gain was missing for 30 children, gestational diabetes was missing for 47 children, maternal age at birth was missing for 11 children, smoking in pregnancy was missing for 5 children, maternal education was missing for 6 children, duration of exclusive breast feeding was missing for 16 children, weight of the child at 3 months was missing for 69 children, length of the child at 3 months was missing for 74 children, weight of the child at 12 months was missing for 144 children, and length of the child at 12 months was missing for 149 children. †None of the mothers reported type 2 diabetes. The variables used in the regression model for the case group had none missing. NA, not applicable.

originating from the mother were excluded from the end point definition (8). Mother's weight, height, and other demographic data (Table 1) were collected using mailed structured questionnaires when each child was 3 months old, with follow-up information at age 6, 9, and 12 months. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% CIs for islet autoimmunity using Stata (version 10; College Station, TX). Follow-up time was counted from birth to the date of the last blood sample (noncases) or to the midpoint between the date of the last negative blood sample for islet autoantibodies and the date of the first positive sample for islet autoantibodies (cases with islet autoimmunity).

**RESULTS**— The descriptive characteristics are shown in Table 1. Both maternal BMI ≥30 kg/m<sup>2</sup> before pregnancy (relative to <25 kg/m<sup>2</sup>) and weight gain of ≥15 kg

during pregnancy (relative to <15 kg) predicted an approximate two- to threefold increase in the risk of islet autoimmunity shown in Table 1. The estimated HRs were only marginally influenced by mutual adjustment or by adjustment for other potential confounding factors listed in Table 1. For instance, in a regression model simultaneously including maternal BMI ≥30 kg/m<sup>2</sup> before pregnancy, maternal weight gain ≥15 kg during pregnancy, presence of first-degree relatives with type 1 diabetes, child's weight gain at 3–12 months of age, duration of total breastfeeding, duration of exclusive breastfeeding, birth order, and smoking in pregnancy, the HR (95% CI) for BMI ≥30 kg/m<sup>2</sup> was 2.27 (1.004–5.15) and for maternal weight gain ≥15 kg was 2.60 (1.25–5.41).

**CONCLUSIONS**— Maternal obesity before pregnancy and weight gain (≥15

kg) during pregnancy significantly predicted increased risk of persistent multiple positivity for islet autoantibodies in offspring with high genetic susceptibility for type 1 diabetes.

Many factors are associated with women's BMI and pregnancy weight gain, such as diet, physical activity, and socioeconomic status (11), but few such factors are known to influence their children's risk of developing islet autoimmunity or type 1 diabetes (12), making confounding by such factors less likely. Maternal diabetes is among the most obvious potential confounders, but controlling for this in the regression analyses had little influence on our main result. Consistent results after adjustment for the child's weight gain, age at weaning, or duration of exclusive breastfeeding, and also after restricting the analyses to cases seroconverting before 12 months of age (data not shown),

suggests that a potential role of postnatal factors is less likely to explain our observations. A potential weakness in our study is that maternal height and weight were self-reported. In the event that self-reporting leads to some measurement error, the fact that height and weight were reported before the mothers had any information of islet autoantibody positivity makes it most likely that any bias would have been nondifferential with respect to the end point in our study and thus attenuated the observed relation with islet autoimmunity. Unfortunately, we did not have any measure of insulin sensitivity of the mothers, but this could perhaps be included in future studies.

In conclusion, the current study adds to the evidence that factors operating early in life may influence the risk of advanced islet autoimmunity, which in itself strongly predicts type 1 diabetes. As with any novel result, independent replication will be needed and further research is warranted to unravel the potential mechanisms.

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