Higher Maternal Body Mass Index Is Associated with an Increased Risk for Later Type 2 Diabetes in Offspring

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Objectives To investigate whether the body mass index (BMI) of a child's mother is associated with an increased future risk of type 2 diabetes, independent of genetic risk or childhood metabolic, behavioral, and environmental factors.

Study design The analyses were based on the Cardiovascular Risk in Young Finns Study including 1835 individuals aged 3-18 years at baseline with data on maternal BMI, childhood metabolic factors, as well as 34 newly identified type 2 diabetes susceptibility alleles. These subjects were then followed-up over 21-27 years.

Results Maternal BMI (OR for 1-SD increase 1.54 [95% CI 1.12-2.11], $P = .008$) and child's systolic blood pressure (1.54 [1.01-2.35], $P = .04$) were significantly associated with increased odds for later type 2 diabetes, in a multivariable analysis adjusted for age, sex, type 2 diabetes genetic risk score, childhood BMI, insulin, lipids, dietary factors, socioeconomic status, and mother's age, and history of type 2 diabetes. A risk prediction model, which included maternal BMI status outperformed one which utilized only child's BMI data (area under the receiver operating characteristic curve 0.720 vs 0.623, $P = .02$). The inclusion of genetic risk score and other baseline risk variables did not additionally improve prediction (area under the receiver operating characteristic curve 0.720 vs 0.745, $P = .40$).

Conclusions Maternal BMI is a useful variable in determining offspring risk of developing type 2 diabetes. *(J Pediatr 2013;162:918-23)*.

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Recently estimated global prevalence figures suggest that approximately 1 in 15 adults have type 2 diabetes.[1] This condition is associated with significant morbidity and mortality, including blindness, lower-limb amputations, end-stage renal failure, and fatal cardiovascular disease.[1] Childhood obesity and pediatric metabolic syndrome are both associated with an increased risk of later type 2 diabetes and cardiovascular disease, with recent data indicating that the majority of this increased risk is attributable to the strong tracking of obesity, which occurs across the life-course.[2,3] However, approximately 1 in 5 obese adults appear metabolically healthy,[4] highlighting that many factors other than adiposity influence long-term risk of weight-related disease.

A systematic review that evaluated 94 risk models for type 2 diabetes found that of the 85 models with available data, only 4 omitted any measure of adiposity emphasizing its importance.[5] The majority included some assessment of a family history of diabetes, a factor known to be important in modifying risk, despite the intriguing finding that the incorporation of actual genetic data to prediction models do not appear to improve prediction over clinical and sociodemographic data.[5] No prediction models to date, however, have included any measure of maternal body mass index (BMI) despite evidence of a link between maternal obesity and reduced insulin sensitivity and secretion in the offspring.[6] In addition, maternal BMI has been shown to predict subsequent risk of obesity among children.[7,8]

AUC	Area under the receiver operating characteristic curve
BMI	Body mass index
BP	Blood pressure
IFG	Impaired fasting glucose
NRI	Net reclassification improvement
SNP	Single nucleotide polymorphism

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In the present study, we tested the hypothesis that the BMI of a child's mother is associated with an increased future risk of type 2 diabetes, independent of other childhood metabolic, behavioral, and environmental factors, as well as 34 newly identified type 2 diabetes susceptibility alleles.[9-12] Analyses of data from 1835 participants aged 3-18 years at baseline, and subsequently followed-up 21-27 years, were undertaken within the Cardiovascular Risk in Young Finns Study.

Methods

The Cardiovascular Risk in Young Finns Study is an on-going multicenter follow-up study of atherosclerosis risk factors. The first cross-sectional survey was conducted in 1980, when 3596 individuals aged 3-18 years participated.[13] These participants were randomly chosen from the national register of the study areas. Since 1980, several follow-up studies have been conducted. The latest 21- and 27-year follow-up surveys were performed in 2001 and 2007, when 2283 (ages 24-39 years) and 2204 (ages 30-45 years) of the original participants attended. For this study, the sample comprised of those participants who had complete risk factor data available from baseline, adult data on type 2 diabetes available from the 2001 or 2007 surveys (follow-up time 21-27 years, mean 23.8 years), and genome-wide analyses performed. Those subjects whose mother was pregnant during the baseline study (in 1980) were excluded. Altogether, the study sample was 1835 individuals. Among those who participated in both follow-up waves, data were used only from the 2007 wave. Participants gave written informed consent, and the study was approved by local ethics committees.

In childhood and adulthood, height and weight were measured, and BMI calculated as weight, kg/(height, m)^2. In childhood, overweight and obesity were defined using age- and sex-stratified 85th and 95th percentile cut-points, respectively.[14] Other baseline variables were obtained as follows. Blood pressure (BP) was measured using a standard mercury sphygmomanometer. For the determination of serum lipid levels, venous blood samples were drawn after an overnight fast.[13] Serum insulin was measured with an immunoassay method.[15] Questionnaires were used to obtain data on diet and birth weight. Information on diet was obtained with a short 19-item non-quantitative food frequency questionnaire.[16] In 12- to 18 year-olds, information on smoking habits was collected during a medical examination in a solitary room where the participants could respond confidentially and undisturbed. Regular cigarette smoking on a weekly basis or more often was defined as smoking. Glucose concentrations in adulthood were determined by the enzymatic hexokinase method (glucose reagent; Olympus, County Clare, Ireland).

Questionnaires during the baseline study were used to obtain data on mother's age (range 21-66 years), height, weight, education (number of school years), and history of type 2 diabetes at baseline in 1980. BMI was calculated as weight, kg/(height, m)^2. Overweight was defined as BMI $\geq$ 25 kg/m^2, and obesity was defined as BMI $\geq$ 30 kg/m^2. Data on father's BMI was available for 1611 individuals.

Genetic Analyses

Genotyping of 34 single nucleotide polymorphisms (SNPs) (*PPARG* rs1801282, *KCNJ11* rs5219, *TCF7L2* rs7903146, *SLC30A8* rs13266634, *HHEX* rs1111875, *LOC387761* rs7480010, *CDKN2B* rs10811661, *IGF2BP2* rs4402960, *CDKAL1* rs7754840, *FTO* rs9939609, *HNF1B* rs7501939, *WFS1* rs10010131, *JAZF1* rs864745, *CDC123* rs12779790, *TSPAN8* rs7961581, *THADA* rs7578597, *ADAMTS9* rs4607103, *NOTCH2* rs10923931, *KCNQ1* rs2283228, *MTNR1B* rs10830963, *ADRA2A* rs10885122, *FAM148A* rs11071657, *CRY2* rs11605924, *ADCY5* rs11708067, *SLC2A2* rs11920090, *FADS1* rs174550, *DGKB* rs2191349, *PROX1* rs340874, *GCK* rs4607517, *G6PC2* rs560887, *GLIS3* rs7034200, *GCKR* rs780094, *MADD* rs7944584, *GIPR* rs10423928),[9-12] comprising 20 risk SNPs for type 2 diabetes and 14 risk SNPs for fasting and 2-hour glucose in an oral glucose tolerance test, was performed using Illumina Bead Chips (Human 670K; Illumina, San Diego, California). A genotype risk score was calculated as an arithmetic sum variable of risk alleles in these 34 SNPs.

Classification of Outcomes

To determine the presence of type 2 diabetes, data from adult follow-ups in 2001 and 2007 were used. Participants were classified as having type 2 diabetes mellitus if they had a fasting plasma glucose of 7 mmol/L (126 mg/dL) or greater, reported use of oral glucose-lowering medication or insulin but had not reported having type 1 diabetes, or reported receiving a diagnosis of type 2 diabetes by a practicing physician.[17] Of those 10 subjects reporting use of oral glucose-lowering medications, all but 1 also had glucose levels 7 mmol/L (126 mg/dL) or greater or diabetes diagnosis by physician. In additional analyses after exclusion of that subject, the main results were essentially similar to those reported. Impaired fasting glucose (IFG) was defined using a cut-point of 5.6 mmol/L (100 mg/dL).[18]

Statistical Analyses

Group comparisons were performed using *t* test for continuous variables and χ^2 test for categorical variables. To study the associations of baseline risk variables and genetic risk score with the offspring's risk of type 2 diabetes in adulthood, age- and sex-aOR were calculated using logistic regression analysis. Next, a multivariable logistic regression analysis was constructed to determine the independent predictors of type 2 diabetes. We also examined the effect of mother's BMI using a categorized variable [normal (<25 kg/m^2)/overweight (25-30 kg/m^2)/obese (>30 kg/m^2)]. Several interaction analyses were performed to examine whether the effects of mother's BMI on type 2 diabetes risk are similar in respect to age, sex, and mother's age. These generalized linear models included the following terms: mother's BMI, studied variable, and mother's BMI*studied variable interaction term.

The incremental value of adding risk variables to predict type 2 diabetes was examined based on multivariate logistic regression models. The ability of several models to predict disease risk was estimated using C statistics by calculating