ARTICLE

Environmental Factors Associated With Childhood-Onset Type 1 Diabetes Mellitus

An Exploration of the Hygiene and Overload Hypotheses

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Objective: To assess the relationship between selected maternal and infant characteristics and risk of type 1 diabetes mellitus, specifically characteristics identified from birth records that may pertain to the hygiene or overload hypotheses.

Design: Population-based case-control study.

Setting: Washington State from 1987 to 2005.

Participants: All children younger than 19 years hospitalized for type 1 diabetes (*International Classification of Diseases, Ninth Revision* codes 250.x1 and 250.x3) identified (n=1852) from hospital discharge data and linked with their birth certificates. Controls (n=7408) were randomly selected from birth records, frequency matched on year of birth.

Main Exposures: Maternal factors included age, race, educational attainment, marital status, use of Medicaid insurance, body mass index, prepregnancy weight, prior births, timing and adequacy of prenatal care, and cesarean delivery. Infant factors included birth weight, size for gestational age, and gestational age.

Main Outcome Measure: The main outcome was first hospitalization for type 1 diabetes mellitus; adjusted odds ratios were estimated for the association of selected maternal and infant characteristics with type 1 diabetes.

Results: Consistent with the hygiene hypothesis, type 1 diabetes was negatively associated with having older siblings (for ≥3 siblings, odds ratio [OR], 0.56; 95% confidence interval [CI], 0.45-0.70) and with indicators of lower economic status or care access, such as an unmarried mother (OR, 0.79; 95% CI, 0.69-0.91), inadequate prenatal care (OR, 0.53; 95% CI, 0.40-0.71), or Medicaid insurance (OR, 0.67; 95% CI, 0.58-0.77). Related to the overload hypothesis, maternal body mass index of 30 or higher (OR, 1.29; 95% CI, 1.01-1.64) was associated with increased risk of diabetes.

Conclusion: Environmental factors related to decreased antigenic stimulation in early life and maternal obesity may be associated with type 1 diabetes.

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TYPE 1 DIABETES MELLITUS (DM) incidence is increasing, particularly in the youngest age groups,[1] a consistent finding in most pediatric disease registries in the world.[2,3] The rapid change in incidence cannot be explained by evolving genetic susceptibility. Increased incidence and earlier onset of type 1 DM increases the burden on young patients, their families, and society by increasing early complications, such as blindness and kidney and cardiac disease, as well as medical costs. It is estimated that the direct costs of DM in the United States in 2007 were $116 billion, accounting for 10% of US health care expenditures.[4] Some have estimated that 60% to 70% of the risk of type 1 DM may be due to genetic factors.[5] Though genetic factors are clearly important, they cannot explain the large international variation in the incidence rates of type 1 DM,[2,6] the recent rapid increase in incidence in genetically stable populations,[7] or the increased incidence in certain populations when they migrate from low-incidence to high-incidence areas.[8,9] Some reports also suggest that the incidence in young adults is not increasing despite increased incidence at younger ages, implying a shift to earlier age at onset rather than an overall increase in cases.[10,11]

Two major hypotheses pertain to environmental causes of the increasing incidence of type 1 DM in many populations around the world. The hygiene hypothesis suggests that improved hygiene and living conditions have decreased the frequency of childhood infec-

tions, leading to a modulation of the developing immune system and increasing risk for autoimmune and allergic diseases such as type 1 DM and asthma.[12,13] The overload or accelerator hypothesis suggests that overload of the pancreatic beta cells early in life makes them more prone to autoimmunity and cell death.[14] "Overload" may be caused by a high growth rate in fetal and early life[15] or by early-life stress, such as complicated pregnancy,[16] neonatal hospitalization, or even childhood psychological stress.[17,18] Factors previously examined for an association with type 1 DM, and that are potentially related to these hypotheses, include maternal age,[19] cesarean section,[20] birth order,[21] birth weight,[22] maternal gestational DM and preexisting DM,[23] parental education,[23] smoking,[23,24] and socioeconomic characteristics affecting care access and health status.[25,26]

We conducted a population-based case-control study using birth certificates linked with hospital discharge records for the years 1987 to 2005 from Washington State to examine potential factors associated with type 1 DM in children, particularly aspects relevant to the hygiene and overload hypotheses.

METHODS

We conducted a population-based case-control study of pediatric cases of type 1 DM identified in hospital discharge records linked to birth certificate data from 1987 to 2005. The Comprehensive Hospital Abstract Reporting System, created by the Washington State Department of Health, contains hospital discharge data for all nonfederal hospitals in Washington state. All hospitalizations of children younger than 19 years during 1987 to 2005 with an *International Classification of Diseases, Ninth Revision* code for DM (250.x1 and 250.x3) were identified in the Comprehensive Hospital Abstract Reporting System. Hospitalizations with *International Classification of Diseases, Ninth Revision* codes indicating type 2 DM (250.x0 and 250.x2) were excluded. These records were unduplicated, using the unique identifier contained in all records, to identify the earliest hospitalization for each individual with a type 1 DM diagnosis within the database born during the study years (n=2752). These records were then linked, using an identifier code in the hospital discharge record (birth date, sex, and first initials of first and last name) and the name, sex, and birth date information in the vital records, to Washington state birth records of all singleton infants born during these years to identify potential cases for study (n=1852). For comparison, controls in a ratio of 4:1 (n=7408) were randomly selected from birth certificates of singletons without DM hospitalizations, frequency matched on year of birth.

Exposure information for the study was obtained from each subject's birth record. Preliminary evaluation of risk estimates was conducted by stratified analyses. Subsequently, we used multivariable logistic regression to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of factors related to the hygiene hypothesis, including mothers' age (<18, 18-24, 25-34, and ≥35 years), race (white, black, Asian, Hispanic, and "other nonwhite"), education (<12, 12, and ≥13 years), marital status, cesarean section delivery, prenatal smoking, number of prior births and pregnancies (0, 1, 2, and ≥3), number of older siblings (estimated by number of prior births now living), use of prenatal care based on the Kotelchuck index of adequacy of prenatal care (inadequate, intermediate, adequate, and adequate plus),[27] and trimester prenatal care began (first, second, and third or none). Additional information about the subject's insurance status (Medicaid or charity insurance at the birth hospitalization) was obtained from the linked Comprehensive Hospital Abstract Reporting System record for the mother's delivery hospitalization (this linkage has been routinely performed annually in Washington since 1987). Maternal factors potentially related to the overload hypothesis included age; DM status (established or gestational); body mass index (BMI) calculated from prepregnancy weight and height (calculated as weight in kilograms divided by height in meters squared) and based on World Health Organization classification (<18.5, undernourished; 18.5-24.99, normal; 25-29.99, overweight; and ≥30, obese)[28]; and prepregnancy weight (<100, 100-149, 150-199, and ≥200 lb); cesarean section; and prenatal smoking. Potentially related infant factors included gestational length (<37, 37-42, and >42 weeks), birth weight (<2500, 2500-3999, and ≥4000 g), and size for gestational age (small for gestational age, appropriate for gestational age, and large for gestational age, with upper and lower 10th percentiles calculated[29] using Washington State data 1989-2002 as a standard). Factors evaluated for their potential effects on the relationships of interest included maternal age, race, educational level, marital status, medical insurance at the birth hospitalization, BMI, prenatal smoking, number of prior live births, and infant sex and birth weight. Subanalyses were also conducted to determine if results varied by birth year categories; they did not. Levels of missing data were generally similar for cases and controls; missing data for all infant variables, maternal age, race, and marital status were less than 5%. For 3 variables (maternal education, prepregnancy weight, and BMI), information was available only for birth records from 1992 or later. The greatest level of missing data was for BMI (33% of cases, 38% of controls). Among subjects with missing data for BMI, prepregnancy weight, and maternal education, maternal and infant characteristics were distributed similarly to these distributions in the overall study population. Analyses were restricted to subjects with known relevant information for each risk estimate.

Variables that changed ORs by more than 10% were adjusted for in the analyses. Unless otherwise indicated, all ORs are adjusted for maternal age, marital status, and the frequency matching variable, birth year. Potential effect modifiers were evaluated by inspection of stratum-specific risk estimates for important differences and the Breslow-Day test for homogeneity. The likelihood ratio test[30] was used to evaluate possible trends. Because of concern that there may be residual misclassification of type 2 DM among the case group despite our exclusion of children with *International Classification of Diseases, Ninth Revision* codes indicating the presence of this condition, subanalyses were conducted restricting to cases who were younger than 10 years at hospitalization. Subanalyses were also conducted after exclusion of subjects with birth weights of 4000 g or greater, in an effort to exclude offspring of diabetic mothers who had not yet been diagnosed. Analyses were conducted using Stata software (version 9; StataCorp, College Station, Texas). Institutional review board approvals were granted by the Washington State Department of Health and the University of Washington prior to conduct of this study.

RESULTS

Although few mothers (21 among cases; 14 among controls) reportedly had established DM, having a mother with this characteristic was associated with an increased risk of type 1 DM (OR, 6.13; 95% CI, 3.11-12.08); approximately 2% of both cases and controls had

Table. Maternal and Infant Characteristics of Cases With Type 1 Diabetes Mellitus and Their Controls, Washington State 1987-2005[a]

	No. (%)		
	Cases (n = 1789)[b]	Controls (n = 7252)[b]	OR
Maternal characteristics			
Age, y[c]			
<18	49 (3)	288 (4)	0.94 (0.68-1.30)
18-24	490 (27)	2430 (34)	1 [Reference]
25-34	1023 (57)	3734 (51)	1.28 (1.13-1.45)
≥35	226 (13)	797 (11)	1.32 (1.10-1.58)
Race[d]			
White	1550 (87)	5632 (78)	1 [Reference]
Black	48 (3)	266 (4)	0.73 (0.53-1.00)
Asian	29 (2)	396 (5)	0.26 (0.18-0.38)
Hispanic	77 (4)	578 (8)	0.52 (0.41-0.67)
Other nonwhite	30 (2)	198 (3)	0.62 (0.42-0.92)
Educational level, y[d,e]			
<12	94 (5)	688 (10)	0.57 (0.43-0.75)
12	299 (17)	1195 (16)	1 [Reference]
≥13	506 (28)	1678 (23)	1.09 (0.92-1.29)
Unmarried[f]	360 (20)	1891 (26)	0.79 (0.69-0.91)
Medicaid or Medicare insurance[d]	420 (23)	2232 (31)	0.67 (0.58-0.77)
Prenatal smoker[d]	258 (14)	1283 (18)	0.87 (0.75-1.01)
BMI[d,e]			
<18.5	22 (1)	132 (2)	0.67 (0.42-1.06)
18.5-24.9	382 (21)	1457 (20)	1 [Reference]
25-29.9	140 (8)	515 (7)	1.03 (0.83-1.28)
≥30	111 (6)	327 (5)	1.29 (1.01-1.64)
Prepregnancy weight, lb[d,e]			
<100	10 (<1)	56 (<1)	0.86 (0.44-1.71)
100-149	426 (24)	1910 (26)	1 [Reference]
150-199	227 (13)	843 (12)	1.18 (0.99-1.42)
≥200	78 (4)	213 (3)	1.62 (1.22-2.14)
Live births now living[d]			
0	786 (44)	2998 (41)	1 [Reference]
1	587 (33)	2340 (32)	0.87 (0.77-0.98)
2	265 (15)	1116 (15)	0.79 (0.67-0.93)
≥3	122 (7)	683 (9)	0.56 (0.45-0.70)

(continued)

mothers with gestational DM (OR, 1.19; 95% CI, 0.83-1.70, both estimates adjusted for birth year only, data not shown). To focus more specifically on the environmental hypotheses regarding type 1 DM, all subsequent analyses excluded subjects with established maternal DM (21 cases, 14 controls), gestational DM (40 cases, 137 controls), and DM, type unknown (2 cases, 5 controls), resulting in 1789 cases and 7252 controls for the remaining analyses.

The mean age at the hospitalization that identified cases was 7.5 years (SE, 4.2 years; range, 0-18 years, similar to the mean age of 7.6 years for all children <19 years hospitalized with type 1 DM in Washington), with 75% of cases hospitalized at 10 years or younger; 49% of both cases and controls were female (data not shown).

Mothers of cases were slightly less likely than mothers of controls to be nonwhite and unmarried and to have smoked prenatally, used private insurance at the birth hospitalization, or had prior live births (**Table**).

The OR for type 1 DM increased with increasing maternal age (Table). Infants of mothers with a BMI of 30 or higher (OR, 1.29; 95% CI, 1.01-1.64) or with a prepregnancy weight of 200 lb or higher (OR, 1.62; 95% CI, 1.22-2.14) also had increased ORs.

Infants of nonwhite mothers in all race categories had decreased ORs for type 1 DM, ranging from 0.26 (95% CI, 0.18-0.38) for infants of Asian mothers to 0.73 (95% CI, 0.53-1.00) for infants of African American mothers.

Infants of a mother with less than a high school education had a decreased OR for type 1 DM, as did those with an unmarried mother or whose mother smoked prenatally, used Medicaid insurance, or had inadequate or late prenatal care. Relative to having no prior live births, infants of women with 1 or more prior births (total and now living) had ORs for the association with type 1 DM that were all less than 1, and there is evidence of a decreasing OR with increasing number of prior live births (for 3 or more live births, OR, 0.56; 95% CI, 0.45-0.70, test for trend $P<.05$). Among all subjects as well as among first-born children, being born by cesarean section delivery was associated with a modestly, but not statistically significant, increased OR for type 1 DM. When analyses were restricted to the 1305 cases younger than 10 years at hospitalization, our results did not change, except for 3 instances where

Table. Maternal and Infant Characteristics of Cases With Type 1 Diabetes Mellitus and Their Controls, Washington State 1987-2005[a] (continued)

	No. (%)		
	Cases (n = 1829)[b]	Controls (n = 7389)[b]	OR
Trimester prenatal care began[d]			
First	1451 (81)	5477 (76)	1 [Reference]
Second	211 (12)	1123 (15)	0.78 (0.66-0.91)
Third or none	32 (2)	224 (3)	0.59 (0.41-0.86)
Adequacy of prenatal care[d]			
Inadequate	60 (3)	441 (6)	0.53 (0.40-0.71)
Intermediate	158 (9)	677 (9)	0.84 (0.69-1.03)
Adequate	486 (27)	1712 (24)	1 [Reference]
Adequate plus	168 (9)	656 (9)	0.93 (0.76-1.14)
Cesarean section delivery[g]	387 (22)	1433 (20)	1.12 (0.98-1.27)
Primary cesarean section delivery[g]	172 (22)	579 (19)	1.16 (0.95-1.40)
Infant characteristics			
Birth weight, g[h]			
<2500	74 (4)	324 (4)	0.93 (0.72-1.21)
2500-3999	1448 (81)	5911 (82)	1 [Reference]
≥4000	261 (15)	998 (14)	1.07 (0.92-1.24)
Size for gestational age[h]			
SGA	80 (4)	372 (5)	0.86 (0.66-1.11)
AGA	787 (44)	3144 (43)	1 [Reference]
LGA	95 (5)	354 (5)	1.07 (0.84-1.36)
Gestational age, wk[h]			
<37	114 (6)	438 (6)	1.05 (0.85-1.30)
37-42	1539 (86)	6208 (86)	1 [Reference]
>42	92 (5)	438 (6)	0.85 (0.67-1.08)

Abbreviations: AGA, appropriate for gestational age; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); LGA, large for gestational age; OR, odds ratio; SGA, small for gestational age.
[a] Excludes those whose mothers had "established diabetes," "diabetes, type unknown," or "gestational diabetes."
[b] Numbers may not sum to total because of missing data.
[c] Adjusted for birth year and marital status.
[d] Adjusted for birth year, maternal age, and marital status.
[e] Among 973 cases and 3932 controls born in 1992 or later when data were available on birth record.
[f] Adjusted for birth year and maternal age.
[g] Odds ratio for cesarean section adjusted for birth year, birth weight, and parity. Odds ratio for primary caesarian section adjusted for birth year and birth weight.
[h] Adjusted for birth year.

the previous ORs that were of borderline statistical significance became statistically significant. This included the ORs for the associations of type 1 DM with prenatal smoking (OR, 0.83; 95% CI, 0.70-0.99), prepregnancy weight of 150 to 199 lbs (OR, 1.21; 95% CI, 1.01-1.46), and cesarean section (OR, 1.17; 95% CI, 1.01-1.35), (data not shown). Results were unchanged when children with birth weights of 4000 g or greater were excluded.

None of the infant characteristics examined were associated with significantly increased or decreased ORs for type 1 DM.

COMMENT

The incidence of childhood-onset type 1 DM is increasing in most disease registries around the world at a rate of 3% to 5% annually,[1-3,31] an increase thought to be due to environmental causes. Recent results from a multicenter US study that included a portion of our study population[32] suggest that incidence is increasing in the United States as well. It has been reported that only 10% of those who are genetically predisposed to type 1 DM actually develop the disease[33]; however, that percentage appears to be changing and environmental factors may play an increasingly important role in determining risk. Earlier onset of type 1 DM increases the suffering and costs associated with this disease. The hygiene and overload hypotheses attempt to explain the environmental causes of the increasing incidence of type 1 DM.

We found that maternal factors, but not infant characteristics examined, were more strongly associated with type 1 DM in children. Many results were supportive of the hygiene hypothesis. Several maternal factors associated with a decreased OR (low educational level, unmarried status, Medicaid insurance, inadequate prenatal care) are associated with lower socioeconomic status (SES). Having a mother of nonwhite race was also associated with a decreased risk for type 1 DM; nonwhite race likely has a genetic basis for altered risk but is also associated with lower SES. Lower SES has been reported in other studies to be consistently associated with decreased risk for type 1 DM. For example, a correlation between higher gross domestic product and lower infant mortality with increased incidence of type 1 DM has been observed,[25,26] countries with rapid development have increased incidence of type 1 DM,[34] and within a single country, a greater incidence of type 1

DM was noted in groups with higher SES.[35] Finally, migration studies show an increased type 1 DM incidence in population groups who move from an area of low incidence to one of high incidence.[8,9,36]

We found an inverse association between increasing number of siblings and risk of type 1 DM, as have multiple prior studies.[19-21,24,37,38] This is consistent with the hygiene hypothesis as more siblings could lead to earlier and more antigenic exposure in life. Similarly, there have been reports of decreased risk of type 1 DM associated with sharing a room with a sibling,[23] more crowded living conditions,[39,40] and day care exposure[41]; all are factors potentially related to antigenic simulation.

We observed an increased OR for type 1 DM in children of mothers older than 25 years. Other studies have observed an association with older maternal age[19-21,24,37,38] but have also reported a complex interaction between maternal age and number of prior siblings, an interaction we did not observe. The increased OR associated with older maternal age may be related to higher SES and improved living conditions (factors for which we had little information) for children of older mothers compared with children of the youngest mothers. The increased OR for type 1 DM in children of older mothers might also be attributed to more complicated deliveries, causing "stress"-induced pancreatic dysfunction as suggested by the overload hypothesis; however, our data do not strongly support this speculation since there was no striking dose response noted in the odds of type 1 DM associated with maternal age.

We observed a borderline increased OR for type 1 DM associated with cesarean section delivery. Though it is biologically plausible that vaginal delivery may be an important source of exposure to antigen, as per the hygiene hypothesis, prior studies have given inconsistent results regarding this association. Some researchers have reported an increased risk for type 1 DM after cesarean section[20,42,43]; others find no association.[16,44]

Findings from our study that support the overload hypothesis are the increased ORs for type 1 DM associated with having a mother with a BMI of 30 or higher or whose prepregnancy weight was of 200 lb or higher. To our knowledge, ours is the first study to use BMI data to assess the risk associated with type 1 DM. The results are consistent with the overload hypothesis that suggests that overnutrition, whether prenatally or postnatally, may cause overload or stress to the developing pancreas, which subsequently predisposes to type 1 DM. Other studies have reported associations between birth weight,[15,16,38,45] being born large for gestational age, and rapid postnatal growth with an increased risk for type 1 DM[15]; however, we did not find statistically significant associations between infant characteristics and type 1 DM. The reasons for this are unclear, but one possibility is that our exclusion of subjects with diabetic mothers may have excluded the relevant pathway for these associations.

Several other studies have reported decreased risk for type 1 DM in children of prenatal smokers.[23,24] Our estimate suggested a slightly decreased risk in children of smokers; however, this result was not statistically significant. A decreased OR would support the overload hypothesis as smokers tend to have smaller infants and other studies have found a decreased risk for type 1 DM among children who are born small[15,16,38,45]; thus, a decreased risk for type 1 DM among children of smokers may act through this pathway.

Strengths of our study include that it is population based and one of the largest studies in the United States to examine prenatal and perinatal factors associated with type 1 DM and provides new information related to maternal BMI. Another strength is that the exposure information was recorded prior to disease onset and is not subject to recall bias that may affect case-control studies based on interview. Limitations include data misclassification inherent in any vital records database. Underestimation of smoking and BMI information is plausible as these are undesirable traits. Some cases of type 1 DM may have been included among our controls if they were not hospitalized at diagnosis, they moved out of state before they were diagnosed, or they were hospitalized at a federal hospital. We believe that these numbers would be quite small; most children are admitted to the hospital when first diagnosed with type 1 DM for glucose stabilization and intensive education. Those who are diagnosed early, before onset of diabetic ketoacidosis, likely have better access to medical care and, therefore, have higher SES[46]; the result of capturing these higher SES cases would likely be to increase the risk estimates associated with factors relating to the hygiene hypothesis, a potential ascertainment bias. Census data indicate that outmigration by families with children is about 6%[47] and suggest that this would be a minor issue in our data set. Our data only capture patients at nonfederal facilities; however, we believe the number of diabetic children treated at military hospitals in Washington State represents a small proportion of the total cases. Overall, the effect of these various types of misclassification would tend to drive the risk estimates toward the null. We also had no information about genetic predisposition to type 1 DM or other possible risk factors, such as infant feeding history. We attempted to address genetic predisposition to some extent by excluding subjects whose mothers had DM; however, the possible impact of residual confounding by this, or other risk factors, is difficult to ascertain. That we observed no association of type 1 DM with infant birth weight greater than 4000 g (a possible marker of having a mother with undiagnosed DM), and that our results also were unchanged when these large infants were excluded, is some indication that our results are unlikely to be biased by unmeasured genetic predisposition. Finally, because the actual diagnosis of type 1 vs type 2 DM may not be clear, particularly among adolescents, it is possible that some of our cases actually had type 2 DM. Although we lacked further information that would allow us to confirm diagnoses, when we restricted our analyses to only children hospitalized at younger than 10 years (where chance of type 2 DM is rarer), the results did not change, indicating that any bias due to such misclassification is likely to be small.

Our data support findings from other studies that have examined the association between maternal factors and type 1 DM in children. We did not find important associations between infant characteristics and risk for type 1 DM. Our data suggest that type 1 DM may be related

to maternal obesity and to environmental factors that are associated with decreased antigenic exposure in early life; these results support both the hygiene and overload hypotheses. These results add to our current understanding of possible environmental etiologies of type 1 DM. Our results support other research that suggests that pregnant women should achieve and maintain a healthy weight. A better understanding of the nongenetic risk factors associated with type 1 DM will help inform prevention programs and potentially reduce the burden of this devastating disease.

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