Published in final edited form as:
Arch Pediatr Adolesc Med. 2010 August ; 164(8): 732–738. doi:10.1001/archpediatrics.2010.115.

ENVIRONMENTAL FACTORS ASSOCIATED WITH CHILDHOOD-ONSET TYPE I DIABETES: AN EXPLORATION OF THE HYGIENE AND OVERLOAD HYPOTHESES

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Abstract

Objective—To assess the relationship between selected maternal and infant characteristics and risk of Type 1 diabetes, 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 1987–2005.

Participants—All children <19 years hospitalized for Type 1 diabetes (ICD-9 250.x1, 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 caesarian delivery. Infant factors included birthweight, 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, OR=0.56, 95% 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),

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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 BMI >30 (OR=1.29, 95% CI 1.01–1.64) was associated with increased risk of diabetes.

Conclusions—Environmental factors related to decreased antigenic stimulation in early life and maternal obesity may be associated with Type 1 diabetes.

INTRODUCTION

Type 1 diabetes mellitus (Type 1 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 upon young patients, their families, and society by increasing early complications such as blindness, kidney and cardiac disease, as well as medical costs. It is estimated that the direct costs of diabetes in the US in 2007 were $116 billion, accounting for 10% of US health care expenditures.(4) Some have estimated that 60–70% 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-, 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 of 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 infections, 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 make 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 which are potentially related to these hypotheses, include maternal age (19), caesarian section (20), birth order (21), birth weight (22), maternal gestational diabetes and pre-existing diabetes (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 1987–2005 from Washington State in order 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 1987–2005. The Comprehensive Hospital Abstract Reporting System (CHARS), created by the Washington State Department of Health, contains hospital discharge data for all non-federal hospitals in Washington State. All hospitalizations of children less than 19 years old during 1987–2005 with an ICD-9 code for diabetes mellitus (250.x1 and 250.x3) were identified in CHARS. Hospitalizations with ICD-9 codes indicating Type 2 diabetes (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, gender, and first initials of first and last name), and the name, gender 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 diabetes 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 (OR) and 95% confidence intervals (CI) for the associations of factors related to the hygiene hypothesis, including mothers' age (<18, 18–24, 25–34, >35 years), race (White, Black, Asian, Hispanic, and "Other non-white"), education (<12, 12, and 13+ years), marital status, caesarian-section delivery, prenatal smoking, number of prior births and pregnancies (0, 1, 2, 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, adequate plus) (27), and trimester prenatal care began (1^{st}, 2^{nd}, 3^{rd} or none). Additional information about the subject's insurance status (Medicaid or charity insurance at the birth hospitalization) was obtained from the linked CHARS record for the mother's delivery hospitalization (this linkage is routinely performed annually in Washington since 1987). Maternal factors potentially related to the overload hypothesis included age, diabetes status (established or gestational), BMI calculated from prepregnancy weight and height, and based on WHO classification (<18.5 undernourished, 18.5–24.99 normal, 25–29.99 overweight, ≥30 obese) (28) and pre-pregnancy weight (<100, 100–149, 150–199, 200+ lb.), caesarian-section, and prenatal smoking. Potentially related infant factors included gestational length (<37, 37–42, 42+ weeks), birth weight (<2500, 2500–3999, >= 4000 grams) and size for gestational age (small for gestational age (SGA), appropriate for gestational age (AGA), large for gestational age (LGA), with upper and lower 10^{th} 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 gender, 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, pre-pregnancy 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, pre-pregnancy 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 diabetics among the case group despite our exclusion of children with ICD-9 codes indicating the presence of this condition, sub-analyses were conducted restricting to cases who were younger than 10 years

of age at hospitalization. Sub-analyses were also conducted after exclusion of subjects with birth weights of 4000 grams 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; Stata Corporation, College Station, TX). 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 diabetes, 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 mothers with gestational diabetes (OR 1.19, 95%CI 0.83–1.70, both estimates adjusted for birth year only, data not shown). In order 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 "diabetes, type unknown" (2 cases, 5 controls), resulting in 1789 cases and 7252 controls for the remaining analyses.

The mean age at the hospitalization which identified cases was 7.5 years (SE 4.2, 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 of age or younger; 49% of both cases and controls were females (data not shown).

Mothers of cases were slightly less likely than mothers of controls to be non-white, unmarried, to have smoked prenatally, to have used private insurance at the birth hospitalization or to have had prior live births (Table 1).

The OR for Type 1 DM increased with increasing maternal age (Table 1). Infants of mothers with BMI > 30 (OR=1.29, 95% CI 1.01–1.64), or with pre-pregnancy weight > 200 lbs also had increased ORs (1.62, 95% CI 1.22–2.14).

Infants of non-white mothers in all race categories had decreased ORs for Type 1 DM, ranging from 0.26 (95% CI 0.18–0.38) for Asians to 0.73 (95% CI 0.53–1.00) for African Americans.

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 one, 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 $p< 0.05$). Among all subjects as well as among first-born children, being born by caesarian-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 aged less than 10 years at hospitalization, our results did not change, except for 3 instances where 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 150–199 lbs (OR = 1.21, 95% CI 1.01–1.46), and C-section (OR = 1.17, 95% CI 1.01–1.35, data not shown). Results were unchanged when children with birth weights of 4000 grams or greater were excluded.

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

DISCUSSION

The incidence of childhood-onset Type 1 DM is increasing in most disease registries around the world at a rate of 3–5% 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 US 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 non-white race was also associated with a decreased risk for Type 1 DM; non-white 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 socioeconomic status and improved living conditions (factors for which we had little information) for children of older mothers compared to 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 caesarian-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 caesarian-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 BMI > 30 or whose pre-pregnancy weight was greater than 200 lb. 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 over-nutrition, whether pre- or post-natally, 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 post-natal 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 US 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, if they moved out of state before they were diagnosed, or if 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 out-migration by families with children is about 6% (47), and suggests that this would be a minor issue in our dataset. Our data only captures patients at non-federal 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 towards 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 were diabetic, 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 >4000 g (a possible marker of having a mother with undiagnosed diabetes), 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 diabetes may not be clear, particularly among adolescents, it is possible that some of our cases actually had Type 2 diabetes. 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 of age (where chance of Type 2 diabetes 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 non-genetic risk factors associated with Type 1 DM will help inform prevention programs and potentially reduce the burden of this devastating disease.

Acknowledgments

We would like to thank the Washington State Department of Health for data access, and Mr. William O'Brien for programming assistance.

Dr. D'Angeli received fellowship support from the Ruth L Kirschstein National Research Service Award (NIH), training grant number 2-T32-CA09168-31A1. Dr. Merzon received fellowship support from AAFMI (Advancing Academic Family Medicine in Israel). Drs. Valbuena, Paris, Tirschwell and Mueller, declare no financial conflict of interest. Drs. D'Angeli, Merzon, Valbuena and Mueller had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Dahlquist G, Mustonen L. Analysis of 20 years of prospective registration of childhood onset diabetes time trends and birth cohort effects. Swedish Childhood Diabetes Study Group. Acta Paediatr. 2000; 89(10):1231–1237. [PubMed: 11083381]
2. EURODIAB ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. Lancet. 2000; 355:873–876. [PubMed: 10752702]
3. Onkamo P, Vaananen S, Karvonen M, Tuomilehto J. Worldwide increase in incidence of Type I diabetes - the analysis of the data on published incidence trends. Diabetologia. 1999; 42(12):1395–1403. [PubMed: 10651256]
4. American Diabetes Association. Economic costs of diabetes in the U.S. in 2007. Diabetes Care. 2008; 31(3):3–20. [PubMed: 17959863]
5. Hirschhorn JN. Genetic epidemiology of type 1 diabetes. Pediatric Diabetes. 2003; 4:87–100. [PubMed: 14655265]
6. Karvonen M, Viik-Kajander M, Moltchanova E, Libman I, LaPorte R, Tuomilehto J. The Diabestes Mondiale (DiaMond) Project Group: Incidence of childhood type 1 diabetes worldwide. Diabetes Care. 2000; 23:1516–1526. [PubMed: 11023146]
7. Willis JA, Scott RS, Darlow BA, Nesbit JW, Anderson P, Moore MP, et al. Incidence of type 1 diabetes mellitus diagnosed before age 20 in Canterbury, New Zealand over the last 30 years. J Pediatr Endocrinol Metab. 2002; 15(5):637–643. [PubMed: 12014523]
8. Raymond NT, Jones JR, Swift PG, Davies MJ, Lawrence G, McNally PG, et al. Comparative incidence of Type 1 diabetes in children aged under 15 years from South Asian and White or other ethnic backgrounds in Leicestershire, UK 1989 to 1998. Diabetologia. 2001; 44 Suppl 3:B32–B36. [PubMed: 11724414]
9. Feltbower RG, Bodansky HJ, Mckinney PA, Houghton J, Stephenson CR, Haigh D. Trends in the incidence of childhood diabetes in south Asians and other children in Bradford, UK. Diabetic Medicine. 2002; 19:162–166. [PubMed: 11874434]
10. Weets I, De Leeuw IH, De Caju MVL, Rooman R, Keymeulen B, Mathieu C, et al. The incidence of type 1 diabetes in the age group 0–39 has not increased in Antwerp (Belgium) between 1989 and 2000. Diabetes Care. 2002; 25(5):840–846. [PubMed: 11978678]

11. Feltbower RG, McKinney PA, Parslow RC, Stephenson CR, Bodansky HJ. Type 1 diabetes in Yorkshire, UK: time trends in 0–14 and 15–29 year-olds, age at onset and age-period-cohort modeling. Diabetic Medicine. 2003; 20:437–441. [PubMed: 12786676]
12. Bach JF. Six questions about the hygiene hypothesis. Cellular Immunology. 2005; 233:158–161. [PubMed: 15963966]
13. Gale EAM. A missing link in the hygiene hypothesis? Diabetologia. 2002; 45:588–594. [PubMed: 12032638]
14. Dahlquist G. Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. Diabetologia. 2006; 49:20–24. [PubMed: 16362279]
15. EURODIAB Substudy 2 Study Group. Rapid early growth is associated with increased risk of childhood type 1 diabetes in various European populations. Diabetes Care. 2002; 25:1755–1760. [PubMed: 12351473]
16. The EURODOAB Substudy 2 Study Group. Perinatal risk factors for childhood type 1 diabetes in Europe. Diabetes Care. 1999; 22:1698–1702. [PubMed: 10526738]
17. Vlajinac H, Sipetic S, Marinkovic J, Bjekic M, Kocev N, Sajic S. The Belgrade childhood diabetes study—comparison of children with type 1 diabetes with their siblings. Paediatr Perinat Epidemiol. 2006; 20:238–243. [PubMed: 16629698]
18. Hägglöf B, Blom L, Dahlquist G, Lönnberg G, Sahlin B. The Swedish childhood diabetes study: indications of severe psychological stress as a risk factor for type 1 (insulin-dependent) diabetes mellitus in childhood. Diabetologia. 1991 Aug; 34(8):579–583. [PubMed: 1936661]
19. Bingley PJ, Douek IF, Rogers CA, Gale EAM. Influence of maternal age at delivery and birth order on risk of type 1 diabetes in childhood: prospective population based family study. BMJ. 2000; 321:420–424. [PubMed: 10938050]
20. Patterson CC, Carson DJ, Hadden DR, Waugh NR, Cole SK. A case-control investigation of perinatal risk factors for childhood IDDM in Northern Ireland and Scotland. Diabetes Care. 1994; 17(5):376–381. [PubMed: 8062603]
21. Cardwell CR, Carson DJ, Patterson CC. Parental age at delivery, birth order, birth weight and gestational age are associated with the risk of childhood Type 1 diabetes: a UK regional retrospective cohort study. Diabetic Medicine. 2005; 22(2):200–206. [PubMed: 15660739]
22. Dahlquist G, Bennich SS, Kallen B. Intrauterine growth and risk of childhood onset insulin dependent (type 1) diabetes: population based case-control study. BMJ. 1996; 313(7066):1174–1177. [PubMed: 8916747]
23. Marshall AL, Chetwynd A, Morris JA, Placzek M, Smith C, Olabi A, et al. Type 1 diabetes mellitus in childhood: a matched case control study in Lancashire and Cumbris, UK. Diabet Medicine. 2004; 21(9):1035–1040.
24. Svensson J, Carstensen B, Mortensen HB, Borch-Johnsen K. Early childhood risk factors associated with type 1 diabetes- is gender important? European Journal of Epidemiology. 2005; 20:429–434. [PubMed: 16080591]
25. Patterson CC, Dahlquist G, Soltesz G, Green A. Is childhood-onset type 1 diabetes a wealth-related disease? An ecological analysis of European incidence rates. Diabetologia. 2001; 44 Suppl 3:B9–B16. [PubMed: 11724424]
26. Tedeschi A, Airaghi L. Is affluence a risk factor for bronchial asthma and type 1 diabetes? Pediatr Allergy Immunol. 2006; 17(7):533–537. [PubMed: 17014630]
27. Kotelchuck M. An Evaluation of the Kessner adequacy of Prenatal Care Index and a proposed Adequacy of Prenatal Care Utilization Index. Am J Public Health. 1994; 84(9):1414–1420. [PubMed: 8092364]
28. WHO technical report series 854. Physical status: The use and interpretation of anthropometry. 1995 [Accessed on January 30, 2009]. http://whqlibdoc.who.int\trs\WHO_TRS_854.pdf
29. Williams RL, Dreasy RK, Cunningham GC, Hawes WE, Norris FD, Tashiro M. Fetal growth and perinatal viability in California. Obstetrics & Gynecology. 1982; 59(5):624–632. [PubMed: 7070736]
30. Breslow, NE.; Day, NE. Statistical Methods in Cancer Research. Vol 1: The Analysis of Case-Control Studies. International Agency for Research on Cancer [IARC Scientific Publications No. 32]; Lyon: 1980. p. 223-226.

31. DIAMOND Project Group. Incidence and trends of childhood Type 1 diabetes worldwide 1990–1999. Diabet Med. 2006 Aug; 23(8):857–866. [PubMed: 16911623]
32. The Writing Group for the Search for Diabetes in Youth Study Group. The incidence of diabetes in youth in the United States. JAMA. 2007; 297(24):2716–2724. [PubMed: 17595272]
33. Knip M, Viojola R, Virtanen S, Hyoty H, Vaarala O, Akerblom H. Environmental triggers and determinants of type 1 diabetes. Diabetes. 2005; 54(2):S125–S136. [PubMed: 16306330]
34. Stipancic G, La Grasta Sabolic L, Malenica M, Radica A, Skrabic V, Tiljak MK. Incidence and trends of childhood Type 1 diabetes in Croatia from 1995 to 2003. Diabetes Res Clin Pract. 2008; 80(1):122–127. [PubMed: 18055059]
35. Haynes A, Bulsara MK, Bower C, Codde JP, Jones TW, Davis EA. Independent effects of socioeconomic status and place of residence on the incidence of childhood type 1 diabetes in Western Australia. Pediatr Diabetes. 2006; 7(2):94–100. [PubMed: 16629715]
36. Bodansky HJ, Staines A, Stephenson C, Haigh D, Cartwright R. Evidence for an environmental effect in the aetiology of insulin dependent diabetes in a transmigratory population. BMJ. 1992; 304(8633):1020–1022. [PubMed: 1586783]
37. Stene LC, Magnus P, Lie RT, Sovik O, Joner G. Maternal and paternal age at delivery, birth order, and risk of childhood onset type 1 diabetes: population based cohort study. BMJ. 2001; 323:1–4. [PubMed: 11440920]
38. Haynes A, Bower C, Bulsara MK, Finn J, Jones TW, Davis EA. Perinatal risk factors for childhood type 1 diabetes in western Australia—a population-based study (1980–2002). Diabet Med. 2007; 24:564–570. [PubMed: 17470192]
39. Patterson CC, Carson DJ, Hadden DR. Epidemiology of childhood IDDM in Northern Ireland 1989–1994: low incidence in areas with highest population density and most household crowding. Northern Ireland Diabetes Study Group. Diabetologia. 1996; 39(9):1063–1069. [PubMed: 8877290]
40. Staines A, Bodansky HJ, McKinney PA, Alexander FE, McNally RJQ, Law GR, et al. Small area variation in the incidence of childhood insulin-dependent diabetes mellitus in Yorkshire, UK: links with overcrowding and population density. Int J Epidem. 1997; 26:1307–1313.
41. Kaila B, Taback SP. The effect of day care exposure on the risk of developing type 1 diabetes: A meta-analysis of case-control studies. Diabetes Care. 2001; 24(8):1353–1358. [PubMed: 11473069]
42. Dalquist G, Kallen B. Maternal-child blood group incompatibility and other perinatal events increase the risk for early-onset type 1 (insulin dependent) diabetes. Diabetologia. 1992; 35(7): 671–675. [PubMed: 1644246]
43. Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ, et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. Diabetologia. 2008; 51(5):726–735. [PubMed: 18292986]
44. Stene LC, Magnus P, Lie TL, Sovik O, Joner G. No association between preeclampsia or caesarian section and incidence of type 1 diabetes among children: a large, population-based cohort study. Pediatric Research. 2003; 54(4):487–490. [PubMed: 12815116]
45. Wei JN, Li HY, Chang CH, Sung FC, Li CY, Lin CC, et al. Birth weight and type 1 diabetes among schoolchildren in Taiwan--A population-based case-controlled study. Diabetes Res Clin Pract. 2006; 74(3):309–315. [PubMed: 16814899]
46. Rewers A, Klingensmith G, Davis C, Petitti DB, Pihoker C, Rodriguez B, et al. Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: the Search for Diabetes in Youth Study. Pediatrics. 2008; 121(5):e1258–e1266. [PubMed: 18450868]
47. U.S. Department of Commerce. Economics and Statistics Administration, U.S. Census Bureau. Domestic Net Migration in the United States: 2000 to 2004.

Table 1

Maternal and infant characteristics of cases with Type 1 Diabetes Mellitus and their controls, Washington State 1987–2005 [a]

	Cases(N =1789)[b]		Controls(N=7252)[b]		
	n	%	n	%	OR
Maternal characteristics					
Age (years)[c]					
<18	49	3	288	4	0.94 (0.68, 1.30)
18–24	490	27	2430	34	1.00 (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	1.00 (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)
Others	30	2	198	3	0.62 (0.42, 0.92)
Educational level (years)[d,e]					
<12	94	5	688	10	0.57 (0.43, 0.75)
12	299	17	1195	16	1.00 (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	1.00 (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)
Pre-pregnancy weight (lbs)[d,e]					
<100	10	<1	56	<1	0.86 (0.44, 1.71)

	Cases(N =1789)[b]		Controls(N=7252)[b]		
	n	**%**	**n**	**%**	**OR**
100–149	426	24	1910	26	1.00 (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	1.00 (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)
	Cases(N =1829)[b]		Controls(N=7389)[b]		
Trimester prenatal care began[d]					
1st	1451	81	5477	76	1.00 (reference)
2nd	211	12	1123	15	0.78 (0.66, 0.91)
3rd/ 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	1.00 (reference)
Adequate+	168	9	656	9	0.93 (0.76, 1.14)
Caesarian section delivery[g]	387	22	1433	20	1.12 (0.98, 1.27)
Primary Caesarian section delivery [g]	172	22	579	19	1.16 (0.95, 1.40)
Infant Characteristics					
Birthweight (grams)[h]					
<2500	74	4	324	4	0.93 (0.72, 1.21)
2500–3999	1448	81	5911	82	1.00 (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	1.00 (reference)

	Cases(N =1789)[b]		Controls(N=7252)[b]		
	n	%	n	%	OR
LGA	95	5	354	5	1.07 (0.84, 1.36)
Gestational Age (weeks)[h]					
<37	114	6	438	6	1.05 (0.85, 1.30)
37–42	1539	86	6208	86	1.00 (reference)
>42	92	5	438	6	0.85 (0.67, 1.08)

[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 1992 or later when data available on birth record.

[f] Adjusted for birth year, and maternal age.

[g] OR for Caesarian section adjusted for birth year, birth weight, and parity. OR for Primary Caesarian section adjusted for birth year, and birth weight.

[h] Adjusted for birth year.