Association of Parental History of Diabetes with Cardiovascular Disease Risk Factors in Children with Type 2 Diabetes

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Abstract

Aims—Determine if parental diabetes(DM) is associated with unhealthier cardiovascular disease(CVD) risk profiles in youth with type 2 diabetes(T2D), and whether associations differed by race/ethnicity.

Methods—Family history was available for 382 youth with T2D from 2001 prevalent and 2002–2005 incident SEARCH for Diabetes in Youth cohorts.

Parental DM was evaluated two ways—two-category— any parent vs. no parent DM (evaluated overall and stratified by race/ethnicity); four-category— both parents, mother only, father only, or no parent DM (evaluated overall only). Associations with hemoglobin
A1c(HbA1c), fasting lipids, blood pressure(BP), and urine albumin:creatinine ratio(ACR) were examined using regression models.

**Results**—Overall, sample characteristics included: 35.9% male, 19.1% non-Hispanic white(NHW), mean T2D duration 26.6 ± 22.2 months, mean HbA1c 7.9 ± 2.5% (62.6 ± 27.8mmol/mol). Unadjusted two-category comparisons showed youth with parental DM had higher HbA1c, higher DBP, and higher frequency of elevated ACR. Adjusted two-category comparisons showed associations remaining in non-stratified analysis for ACR [OR95%CI)=2.3(1.1, 5.0)] and in NHW youth for HbA1c [6.8% ± 0.4 v. 8.0 ± 0.4 (51.1±4.8mmol/mol v.63.9 ± 4.2), p=.015], DBP (67.7% ± 4.5 v. 76.9 ± 4.4 mmHg, p=.014) and lnTG (4.7±0.3 v. 5.3±0.3, p=.008). There were no significant findings in the adjusted four-category evaluation.

**Conclusions**—Parental history of diabetes may be associated with unhealthier CVD risk factors in youth with T2D.

**Keywords**
cardiovascular disease; type 2 diabetes; childhood; family history

1. **Introduction**

Cardiovascular disease (CVD) is an established macrovascular complication of type 2 diabetes (T2D), and individuals with T2D are known to be at an increased risk for early onset of CVD. Adults with any type of diabetes have death rates from CVD 1.7 times higher than adults who do not have diabetes (1). In adults aged 65 years and older with diabetes-related causes of death, 68% of death certificates also cite heart disease and 16% also cite stroke as causes of death (2). These problems are magnified in the population by the increasing incidence of T2D (3). Additionally, it is well-known that atherosclerosis emerges during childhood (4–5). Therefore, the estimated 5,100 youth who are diagnosed with T2D each year in the United States may be at a higher risk for cardiovascular morbidity and mortality because of the early onset and longer duration of T2D as they enter adulthood (6). The SEARCH for Diabetes in Youth Study (SEARCH) has shown that youth with T2D have more arterial stiffness than youth with type 1 diabetes (T1D), while the TODAY study has shown that over a 3 year period, the number of youth with T2D meeting recommended thresholds for treatment with lipid-lowering medication treatment tripled (7–8).

Familial clustering of cardiovascular disease risk factors such as T2D, hypertension, hypercholesterolemia, and hyperalbuminuria is well-known. Certainly, shared lifestyles are involved in the pathophysiology of the development of these disorders; however, family and twin studies also suggest underlying genetic and epigenetic influences (9–15). Additionally, CVD risk factors have been shown to differ by ethnicity (16). Considering the interplay of genetic background and epigenetic and lifestyle influences, it is plausible that the relationship between family history of diabetes and the risk for CVD in offspring may differ for individuals of varying racial or ethnic backgrounds.
Therefore, the goal of this study was to explore the association between parental diabetes and the CVD risk profiles of youth with T2D enrolled in the SEARCH study. The secondary goal of this study was to examine whether the association between parental history and CVD risk profile also differed by race or ethnicity. We hypothesized that unhealthier CVD risk factors [as assessed by higher levels of HbA1c, higher blood pressure (BP), higher fasting total cholesterol (TC), higher fasting low density lipoprotein (LDL), higher fasting triglycerides (TG), lower fasting high density lipoprotein (HDL), higher apolipoprotein B (apoB), and higher urine albumin to creatinine ratio (ACR)] would be most likely present in the offspring of two parents with diabetes and the most favorable profile would be seen in those without a parental history of diabetes. Among youth with T2D with at least one parent with diabetes, we hypothesized that those with a mother with diabetes would have a more adverse CVD risk profile than those with a father with diabetes due to the additional contribution of possible intrauterine exposure.

2. Subjects, Materials, and Methods

Data for these analyses were collected as part of the SEARCH study protocol. A detailed description of the SEARCH study methods has been published elsewhere(17). Briefly, SEARCH has been conducting population-based case ascertainment of youth < 20 years old with prevalent diabetes in 2001 and 2009 and newly diagnosed (incident) diabetes starting in 2002 and continuing through the present. SEARCH recruited participants from four geographically defined populations in Ohio, Colorado, South Carolina and Washington, as well as from Indian Health Service beneficiary roles of several American Indian populations, and among enrollees in a managed health care plan in California. Participants were invited to participate in a research visit, during which fasting blood samples were obtained if metabolically stable (defined as no episode of diabetic ketoacidosis during the previous month), physical measurements were taken, and questionnaires were administered. The study was reviewed and approved by the local Institutional Review Board(s) that had jurisdiction over the local study population and all participants provided informed consent and/or assent.

2.1. Measurements

Study visits occurred after an eight hour overnight fast. Participants did not take diabetes medications the morning of the visit. Participants on long-acting insulin took it the evening before the visit and then it was withheld. A brief physical examination was conducted including measurement of BP, weight, and height using standardized procedures. Body mass index was calculated (BMI [kg/m²]), and age- and sex-specific BMI z-scores were calculated using growth charts with a SAS program available from the Centers for Disease Control and Prevention(18). Waist circumference was measured using NHANES III protocol(19). Waist z-scores were calculated by age and gender from CDC growth reference year 2000. Race and ethnicity were self-reported using 2000 United States Census questions(20) and classified as Hispanic, non-Hispanic White(NHW), non-Hispanic Black(NHB), American Indian(AI), and Asian/Pacific Islander(API). For these analyses, race or ethnicity was categorized as NHB, Hispanic, NHW, and combined API/AI. API and AI were combined to create a category of comparable size to the other categories and also of
sufficient size for analysis. Family history of diabetes was collected by questionnaire; however, information on type of parental diabetes was not collected. History of parental diabetes at any time point (regardless of timing with offspring’s birth or diagnosis) was classified as a positive parental history in these analyses.

Fasting blood samples were used to analyze diabetes autoantibodies (DAA), HbA1c and lipids (TC, TG, HDL, LDL, and apoB). Spot urine samples were used to measure ACR. Assays were performed at the Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington. Glutamic acid decarboxylase-65 (GAD65) and insulinoma-associated-2 (IA-2A) autoantibodies were analyzed using a standardized protocol and a common serum calibrator developed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored standardization group(21). The cutoff values for positivity were 33 NIDDKU/ml for GAD65 and 5 NIDDKU/ml for IA-2A. HbA1c(%) was measured in whole blood with an automated nonporous ion-exchange high-performance liquid chromatography system(model G-7; Tosoh Bioscience, Montgomeryville, Pennsylvania).

2.2. Study Participants

Inclusion criteria for this report include all youth aged < 20 years whose diabetes was prevalent in 2001 or newly diagnosed in 2002–2005, with T2D as diagnosed by their health care provider and who had a SEARCH study visit (n=581). From the 581 individuals, we hierarchically excluded those with positive DAA (n=42), time from diagnosis to initial study visit was less than 3 months to allow for some stabilization of glycemic control which could otherwise negatively impact outcome measures (n=26), history of steroid use or diagnosis of other medical conditions frequently treated with steroids (n=9), missing information for race or ethnicity (n=4), missing information on all outcomes of interest (n=45), and those for whom we were unable to determine that at least 1 parent had diabetes or both parents did not have diabetes (n=73). For the four category exposure analysis, we excluded an additional 20 individuals for whom diabetes status could not be determined for both parents.

2.3. Statistical Analysis

Participant characteristics were described using means(SD) or proportions(%). Comparisons across parental diabetes groups were examined using chi square or Fisher’s exact test, as well as simple and multivariable logistic regression models (categorical outcomes), or simple and multivariable linear regression models (continuous outcomes). Natural log transformation was applied to the triglyceride variable before analysis due to skewed distribution.

Parental diabetes exposure groups were divided both into 2 categories [parental history of diabetes in either or both parents (parental DM) and no parental history of diabetes(no parental DM)] and 4 categories [both parents with history of diabetes(both parents DM), maternal history of diabetes only(maternal DM), paternal history of diabetes only(paternal DM), and no parental history of diabetes(no parental DM)]. The 2 category exposure definition was examined overall and stratified by the 4 race or ethnicity groups (NHB,
Hispanic, NHW, and API/AI), however the 4 category exposure definition was not stratified by race or ethnicity because of sample size limitations.

Modeling was conducted using sequential models with groups of covariates added to subsequent models culminating in the maximally adjusted model. Model covariates included: gender, clinic, highest parental education, smoking status, physical activity level, BMI z-score, waist z-score, time since diagnosis, age at diagnosis, insulin use, hypertensive medication use (blood pressure and ACR outcomes only), and lipid medication use (lipid outcomes only). In these descriptive analyses, we chose not to adjust for multiple comparisons, although by testing several variables in the present study, we may have increased the likelihood of uncovering spurious associations that would need verification in other populations.

All statistical comparisons were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA). Results were considered significant if $p < 0.05$.

3. Results

Overall, 382 participants were included in the two category analysis of parental diabetes, and 362 participants were included in the four category analysis of parental diabetes (Table 1). Participants in the two category analysis were diagnosed with T2D at a mean age of 13.8 ± 2.5 years, had been diagnosed for a mean of 26.6 ± 22.2 months at the time of their study visit, were predominantly of non-white racial or ethnic groups (38.2% NHB, 23.0% Hispanic, 19.6% API/AI), and had a mean BMI z-score at SEARCH visit of 2.1 ± 0.7. There were no differences between categories of parental diabetes for these participant characteristics in the two-category analysis. Participant characteristics were similar for those participants included in the four-category analysis with the exception of duration of diabetes at time of SEARCH visit. The duration of T2D in the four-category analysis varied significantly from 23.5 ± 20.8 months for those with no parental diabetes to 34.8 ± 25.5 for those with both parents having a diagnosis of diabetes ($p=0.009$).

Unadjusted comparison of CVD risk profile outcomes by the two categories of parental history of diabetes revealed that participants with a parental history of diabetes overall had significantly higher HbA1c [8.1% ± 2.5 v. 7.4 ± 2.6 (65.4mmol/mol ± 27.3 v. 57.2 ± 28.2), $p=0.008$], higher DBP (74.3 mmHg ± 10.4 v. 71.7 ± 10.8, $p=0.025$), and higher percentage with elevated ACR [25.9% v. 15.5, OR95% CI) 1.9(1.02, 3.52), $p=0.043$] than those in the no parental diabetes group (Table 1). However, none of these relationships except elevated ACR were significant after initial adjustments for confounders (Table 2). In the models stratified by race or ethnicity, significantly higher HbA1c, DBP, and lnTG remained after adjustment in the NHW group with parental diabetes compared to the NHW group without parental diabetes [HbA1c 8.0% ± 0.4 v. 6.8 ± 0.4 (63.9 mmol/mol ± 4.2 v. 51.1 ± 4.8), $p=0.015$; DBP 76.9 mmHg ± 4.4 v. 67.7 ± 4.5, $p=0.014$; and lnTG 5.3 ± 0.3 v. 4.7 ±0.3, $p=0.008$]. However, none of the other race or ethnic group-related models demonstrated significant associations between CVD risk factors and parental history of diabetes (data not shown). Interaction of race or ethnicity groups with the two-category exposure on CVD risk factors was only statistically significant for DBP ($p=0.048$).
Unadjusted four category comparison of CVD risk profile outcomes (Table 1) revealed significant differences in HbA1c levels (p=0.047) such that the highest HbA1c was in the group with both parents with diabetes (8.5% ± 2.5, 68.9 mmol/mol ± 27.7) followed by those with a father with diabetes (8.1% ± 2.6, 65.0 mmol/mol ± 28.5), a mother with diabetes (8.0% ± 2.5, 63.9 mmol/mol ± 27.3), and no parent with diabetes (7.4% ± 2.6, 57.2 mmol/mol ± 28.2) [p=0.01 for both parents v. no parent with diabetes]. Differences were no longer significant when controlled for demographic and health behavior variables (data not shown).

4. Discussion

Our unadjusted findings suggest that among the total sample of youth with T2D, a parental history of diabetes is associated with higher HbA1c, higher DBP, and higher odds of elevated ACR, and the association with ACR remained after adjustment. Among the NHW youth, all models showed HbA1c and DBP to be significantly associated with parental diabetes, and lnTG emerged as significantly associated. No significant associations were observed among the other three race or ethnic groups studied.

Our study furthers previous work in SEARCH examining the influence of parental diabetes on characteristics of youth with T2D, including the finding that youth with T2D who are exposed to diabetes in utero are diagnosed at a younger age and that history of maternal diabetes and obesity during pregnancy accounts for 47.2% of T2D in youth (22–23). SEARCH has also previously shown that children with T2D who have a family history of diabetes onset after age 25 had more atherogenic lipid profiles, higher blood pressures, larger waist circumferences, and higher BMI z-scores (24). However, in this earlier SEARCH phase, siblings and grandparents were included along with the parents and not differentiated from the parents in the analysis.

Previous studies report from various populations that both support and contradict our findings. The Bogalusa Heart Study showed that young adults without diabetes who are offspring of parents with diabetes are more likely to be hypertensive and have higher TG levels, lower HDL, and higher LDL levels, and longitudinal changes in risk markers did not differ by race (25). Altinli et al. reported increased SBP in offspring of parents with diabetes but no difference in DBP or lipid levels in a Turkish population (26). A systematic review and meta-analysis examining blood pressure in offspring of mothers with diabetes also found only increased SBP (27). However, several other studies from the Netherlands, Germany, India, and the United States have not found associations over time between parental history of diabetes, metabolic syndrome, or gestational diabetes with offspring lipid, blood pressure, or HbA1c measurements (28–31). Pima Indian adults with T2D who are offspring of mothers with T2D have been shown to have higher odds of microalbuminuria, though family history of diabetes was not shown to be associated with microalbuminuria in Swedish youth with insulindependent diabetes (32, 10). The finding of a larger proportion with microalbuminuria and higher DBP among offspring of parents with T2D is alarming considering that these markers independently increase the risk of mortality in people with young-onset T2D (33).

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The present study did not directly compare the CVD risk profiles between race or ethnic groups, and prior studies conflict regarding whether NHW individuals are more likely to have CVD risk factors compared to individuals of other race or ethnic groups. For example, SEARCH has previously shown that hypertension disproportionately affects minority race or ethnic youth with either T1D or T2D compared to NHW youth (34), while the TODAY study has reported a higher prevalence of hypertension in NHW youth with T2D than NHB and Hispanic youth (35), and a systematic review showed NHW adults with either T1D or T2D have a higher risk for CVD complications than NHB, Hispanic Americans, and Asian Americans (36). Therefore, it is possible that the higher HbA1c, DBP, and lnTG that the present study found in the NHW group with a parental history of diabetes may compound an underlying higher risk for CVD in NHW youth with T2D.

One of the great strengths of SEARCH is that its cohort derives from a diverse racial and ethnic population. A limitation for the present study is that current SEARCH data do not differentiate between types of parental diabetes (eg, T1D, T2D, gestational, or MODY). Therefore, further associations between the particular type of parental diabetes and the offspring’s CVD risk factors may be found if this information were available. An additional limitation of the present study is the use of a single random urine specimen. Intraindividual variation in ACR and orthostatic proteinuria are common in adolescents (37, 38). However, both situations would bias the results toward the null hypothesis due to nondifferential misclassification.

Exploring the association between parental diabetes and the CVD risk factors of offspring is difficult due to the insidious nature of T2D onset in many people. However, this work and many of the studies cited herein support a contribution of parental diabetes to adverse CVD risk factors in offspring. Given the known risk of premature CVD morbidity and mortality in adults with T2D and the rising incidence of T2D in youth, further work is required in youth with T2D to define both the contribution of parental diabetes to CVD risk in offspring and interventions to limit CVD risk.

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References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014.

2. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.

3. Centers for Disease Control and Prevention. National Diabetes Surveillance System. Available online at: http://www.cdc.gov/diabetes/statistics. Retrieved 1/27/2014

4. Berenson GS, Wattigney WA, Tracy RE, et al. Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (the Bogalusa Heart Study). Am.J.Cardiol. 1992; 70:851–858. [PubMed: 1529936]

5. Strong JP, Malcom GT, McMahan CA, et al. Prevalence and extent of atherosclerosis in adolescents and young adults. JAMA. 1999; 281:727–735. [PubMed: 10052443]

6. Lawrence JM, Imperatore G, Pettitt DJ, Dabelea D, Linder B, Mayer-Davis EJ, Isom S, Pihoker C, Stendiford DA, Marcovina SM, D’Agostino RB Jr, Saydah SH. for the SEARCH for Diabetes in Youth Study Group. Incidence of diabetes in U.S. youth by type, race/ethnicity and age, 2008 – 2009. Diabetes. 2014; 63(Suppl1):A407.

7. Wadwa RP, Urbina EM, Anderson AM, et al. Measures of Arterial Stiffness in Youth with Type 1 and Type 2 Diabetes: The SEARCH for Diabetes in Youth Study. Diabetes Care. 2010 Apr; 33(4):881–886. [PubMed: 20067960]

8. TODAY Study Group. Lipid and inflammatory cardiovascular risk worsens over 3 years in youth with type 2 diabetes: the TODAY clinical trial. Diabetes Care. 2013 Jun; 36(6):1758–1764. [PubMed: 23704675]

9. Bunt JC, Tataranni PA, Salbe AD. Intrauterine exposure to diabetes is a determinant of hemoglobin A(1)c and systolic blood pressure in pima Indian children. J Clin Endocrinol Metab. 2005 Jun; 90(6):3225–3229. [PubMed: 15797952]

10. Nelson RG, Morgenstern H, Bennett PH. Intrauterine diabetes exposure and the risk of renal disease in diabetic Pima Indians. Diabetes. 1998 Sep; 47(9):1489–1493. [PubMed: 9726239]

11. Lascaux-Lefebvre V, Ruidavets JB, Arveiler D, et al. Influence of parental histories of cardiovascular risk factors on risk factor clusters in the offspring. Diabetes Metab. 2001 Sep. 27:503–509. [PubMed: 11547225]

12. Shear CL, Webber LS, Freedman DS, Srinivasan SR, Berenson GS. The relationship between parental history of vascular disease and cardiovascular disease risk factors in children: the Bogalusa Heart Study. Am J Epidemiol. 1985 Nov; 122(5):762–771. [PubMed: 3876762]

13. Carmelli D1, Cardon LR, Fabsitz R. Clustering of hypertension, diabetes, and obesity in adult male twins: same genes or same environments? Am J Hum Genet. 1994 Sep; 55(3):566–573. [PubMed: 8079995]

14. Hong Y1, Pedersen NL, Brismar K, de Faire U. Genetic and environmental architecture of the features of the insulin-resistance syndrome. Am J Hum Genet. 1997 Jan; 60(1):143–152. [PubMed: 8981957]

15. Mayer EJ, Newman B, Austin MA, Zhang D, Quesenberry CP Jr, Edwards K, Selby JV. Genetic and environmental influences on insulin levels and the insulin resistance syndrome: an analysis of women twins. Am J Epidemiol. 1996 Feb 15; 143(4):323–332. [PubMed: 8633616]

16. Forouhi NG, Sattar N. CVD risk factors and ethnicity--a homogeneous relationship? Atheroscler Suppl. 2006 Apr; 7(1):11–19. [PubMed: 16500156]
17. SEARCH Study Group. SEARCH for Diabetes in Youth: a multicenter study of the prevalence, incidence and classification of diabetes mellitus in youth. Control Clinical Trials. 2004; 25:458–471.
18. Centers for Disease Control and Prevention (CDC). A SAS program for the CDC growth charts [article online]. 2011 Jun.
19. Fernandez JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. J Pediatr. 2004 Oct; 145(4):439–444. [PubMed: 15480363]
20. Ingram DD, Parker JD, Schenker N, et al. United States Census 2000 population with bridged race categories. Vital Health Stat 2. 2003 Sep.(135):1–55. [PubMed: 14556588]
21. Bonifacio E, Yu L, Williams AK, et al. Harmonization of glutamic acid decarboxylase and islet antigen-2 autoantibody assays for national institute of diabetes and digestive and kidney diseases consortia. J Clin Endocrinol Metab. 2010 Jul; 95(7):3360–3367. [PubMed: 20444913]
22. Pettitt DJ, Lawrence JM, Beyer J, et al. Association between maternal diabetes in utero and age at offspring's diagnosis of type 2 diabetes. Diabetes Care. 2008 Nov; 31(11):2126–2130. [PubMed: 18694977]
23. Dabelea D, Mayer-Davis EJ, Lamichhane AP, et al. Association of intrauterine exposure to maternal diabetes and obesity with type 2 diabetes in youth: the SEARCH Case-Control Study. Diabetes Care. 2008 Jul; 31(7):1422–1426. [PubMed: 18375420]
24. Gilliam LK, Liese AD, Bloch CA, et al. Family History of Diabetes, Autoimmunity, and Risk Factors for Cardiovascular Disease Among Children with Diabetes in The SEARCH for Diabetes in Youth Study. Pediatric Diabetes. 2007; 8:354–361. [PubMed: 18036060]
25. Srinivasan SR, Frontini MG, Berenson GS. Bogalusa Heart Study. Longitudinal changes in risk variables of insulin resistance syndrome from childhood to young adulthood in offspring of parents with type 2 diabetes: the Bogalusa Heart Study. Metabolism. 2003 Apr; 52(4):443–450. [PubMed: 12701056]
26. Altiņš S, Elevī M, Ozkul AA, Kara PG, Karsidag K, Dogru M. Insulin resistance and metabolic syndrome in children of parents with diabetes mellitus. J Pediatr Endocrinol Metab. 2007 Mar; 20(3):431–436. [PubMed: 17451082]
27. Aceti A, Sathakumaran S, Logan KM, et al. The diabetic pregnancy and offspring blood pressure in childhood: a systematic review and meta-analysis. Diabetologia. 2012 Nov; 55(11):3114–3127. [PubMed: 22948491]
28. Abbasi A, Corpeleijn E, van der Schouw YT, et al. Parental history of type 2 diabetes and cardiometabolic biomarkers in offspring. Eur J Clin Invest. 2012 Sep; 42(9):974–982. [PubMed: 22568410]
29. Beyerlein A, Nehring I, Rosario AS, von Kries R. Gestational diabetes and cardiovascular risk factors in the offspring: results from a cross-sectional study. Diabet Med. 2012 Mar; 29(3):378–384. [PubMed: 21916975]
30. Krishnaveni GV, Veena SR, Hill JC, Kehoe S, Karat SC, Fall CH. Intrauterine exposure to maternal diabetes is associated with higher adiposity and insulin resistance and clustering of cardiovascular risk markers in Indian children. Diabetes Care. 2010 Feb; 33(2):402–404. [PubMed: 19918007]
31. Pankow JS, Jacobs DR Jr, Steinberger J, Moran A, Sinaiko AR. Insulin resistance and cardiovascular disease risk factors in children of parents with the insulin resistance (metabolic) syndrome. Diabetes Care. 2004 Mar; 27(3):775–780. [PubMed: 14988301]
32. Rudberg S, Statin EL, Dahlquist G. Familial and perinatal risk factors for micro- and macroalbuminuria in young IDDM patients. Diabetes. 1998 Jul; 47(7):1121–1126. [PubMed: 9648837]
33. Constantinou MI, Molynexaux L, Limacher-Gisler F, et al. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes Care. 2013 Dec; 36(12):3863–3869. [PubMed: 23846814]
34. Rodriguez BL, Dabelea D, Liese AD, et al. SEARCH Study Group. Prevalence and correlates of elevated blood pressure in youth with diabetes mellitus: the SEARCH for diabetes in youth study. J Pediatr. 2010 Aug; 157(2):245–251. [PubMed: 20394942]
35. TODAY Study Group. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. Diabetes Care. 2013 Jun; 36(6):1735–1741. [PubMed: 23704672]

36. Lanting LC, Joung IM, Mackenbach JP, Lamberts SW, Bootsma AH. Ethnic differences in mortality, end-stage complications, and quality of care among diabetic patients: a review. Diabetes Care. 2005; 28(9):2250–2258.

37. Brandt JR, Jacobs A, Raissy HH, et al. Orthostatic proteinuria and the spectrum of diurnal variability of urinary protein excretion in healthy children. Pediatr Nephrol. 2010; 25:1131–1137. [PubMed: 20165888]

38. McHardy KC, Gann ME, Ross IS, Pearson DW. A simple approach to screening for microalbuminuria in a type 1 (insulin-dependent) diabetic population. Ann Clin Biochem. 1991; 28:450–455. [PubMed: 1958047]
Table 1
Characteristics of Youth with Type 2 Diabetes by Parental History of Diabetes, mean (SD) or percent

| Variable                      | Two Categories Parental Diabetes Exposure | Four Categories Parental Diabetes Exposure (n=362)* | p-value |
|-------------------------------|------------------------------------------|-----------------------------------------------|---------|
|                               | N | Total Sample (n=382) | Parental DM (n=254) | No Parental DM (n=128) | Both Parents DM (n=54) | Maternal DM (n=128) | Paternal DM (n=52) | No Parental DM (n=128) | p-value |
| Male %                        | 382 | 35.9 | 32.7 | 42.2 | .067 | 31.5 | 34.4 | 28.9 | 42.2 | .271 |
| Race/Ethnicity                | 382 | 38.2 | 39.4 | 35.9 | 35.2 | 39.8 | 36.5 | 35.9 | 24.1 | 24.2 | 25.0 | 22.7 | .597 |
| Non-Hispanic Black            | 38.2 | 23.0 | 23.2 | 22.7 | .322 | 24.1 | 24.2 | 25.0 | 22.7 | .597 |
| Hispanic                      | 23.0 | 20.9 | 17.2 | 29.6 | 18.0 | 19.2 | 17.2 | .597 |
| Asian/Pacific Islander or American Indian | 19.6 | 16.5 | 24.2 | 11.1 | 18.0 | 19.2 | 24.2 | .597 |
| Non-Hispanic White            | 19.1 | 18.0 | 19.2 | 24.2 | .597 |
| BMI z-score                   | 370 | 2.1(0.7) | 2.1(0.6) | 2.0(0.9) | .438 | 2.0(0.6) | 2.1(0.6) | 2.0(0.7) | 2.0(0.9) | .556 |
| Waist z-score                 | 358 | 1.7(1.0) | 1.7(0.9) | 1.7(1.1) | .546 | 1.6(0.8) | 1.7(0.9) | 1.8(0.9) | 1.7(1.1) | .635 |
| Age at Diagnosis (years)      | 382 | 13.8(2.5) | 13.6(2.5) | 14.1(2.5) | .061 | 13.6(2.8) | 13.5(2.3) | 14.1(2.5) | 14.1(2.5) | .106 |
| Duration of Type 2 Diabetes (months) | 382 | 26.6(22.2) | 28.2(22.8) | 23.5(20.8) | .054 | 34.8(25.5) | 24.6(21.2) | 28.8(22.1) | 23.5(20.8) | .009 |
| Highest Parent Education      | 374 | 16.8 | 17.7 | 15.1 | 19.2 | 22.2 | 7.8 | 15.1 | .100 |
| < High School                 | 16.8 | 32.7 | 40.5 | .502 | 26.9 | 32.5 | 33.3 | 40.5 | .100 |
| High School Grad              | 35.3 | 32.7 | 40.5 | .502 | 26.9 | 32.5 | 33.3 | 40.5 | .100 |
| Some Coll/Assoc. Degree       | 31.6 | 33.1 | 28.6 | 26.9 | 33.3 | 41.2 | 28.6 | .100 |
| Bachelor +                    | 31.6 | 33.1 | 28.6 | 26.9 | 33.3 | 41.2 | 28.6 | .100 |
| Smoking                       | 372 | 13.4 | 15.4 | 9.6 | 11.5 | 16.8 | 18.0 | 9.6 | .110 |
| Current                       | 13.4 | 15.4 | 9.6 | 11.5 | 16.8 | 18.0 | 9.6 | .110 |
| Former                        | 25.0 | 22.7 | 29.6 | .159 | 25.0 | 16.0 | 30.0 | 29.6 | .110 |
| Never                         | 61.6 | 61.9 | 60.8 | 63.5 | 67.2 | 52.0 | 60.8 | .110 |
| % Activity < 3 Days/Week      | 372 | 47.3 | 49.0 | 44.0 | .363 | 40.4 | 50.4 | 46.0 | 44.0 | .607 |
| Variable                      | N  | Two Categories Parental Diabetes Exposure | Four Categories Parental Diabetes Exposure (n=362)* |
|-------------------------------|----|------------------------------------------|--------------------------------------------------|
|                               |    | Total Sample (n=382)                     | Both Parents DM (n=54)                          |
|                               |    | Parental DM (n=254)                      | Maternal DM (n=128)                            |
|                               |    | No Parental DM (n=128)                   | Paternal DM (n=52)                             |
|                               |    |                                          | No Parental DM (n=128)                         |
|                               |    | p-value                                  | p-value†                                      |
| % 2+ Hours TV/Day             | 343| 71.8                                     | 73.1                                           |
|                               |    | 69.6                                     | 68.0                                           |
|                               |    | 76.0                                     | 70.0                                           |
| % on Hypertension Meds        | 343| 14.0                                     | 17.8                                           |
|                               |    | 14.9                                     | 14.7                                           |
|                               |    | 12.2                                     | 8.5                                            |
| % on Lipid-Lowering Meds      | 343| 3.8                                      | 2.2                                            |
|                               |    | 4.0                                      | 2.6                                            |
|                               |    | 3.5                                      | 8.5                                            |
| % on Insulin                  | 343| 37.6                                     | 40.0                                           |
|                               |    | 37.7                                     | 34.5                                           |
|                               |    | 37.4                                     | 42.6                                           |
|                               |    |                                          | 37.4                                           |
| HbA1c %                       | 361| 7.9(2.5)                                 | 8.5(2.5)                                      |
|                               |    | 8.1(2.5)                                 | 8.0(2.5)                                      |
|                               |    | 7.4(2.6)                                 | 8.1(2.6)                                      |
|                               |    |                                          | 7.4(2.6)                                      |
|                               |    | **.008**                                 | **.047**                                      |
| HbA1c (mmol/mol)              | 361| 62.6(27.8)                               | 68.9(27.7)                                    |
|                               |    | 65.4(27.3)                               | 63.9(27.3)                                    |
|                               |    | 57.2(28.2)                               | 65.0(28.5)                                    |
|                               |    |                                          | 57.2(28.2)                                    |
|                               |    | **.008**                                 | **.047**                                      |
| SBP mmHg                      | 376| 117.5(12.8)                              | 118.3(10.5)                                   |
|                               |    | 117.6(13.0)                              | 118.3(14.0)                                   |
|                               |    | 117.2(12.3)                              | 114.7(14.1)                                   |
|                               |    |                                          | 117.2(12.3)                                   |
|                               |    | **.743**                                 | **.381**                                      |
| DBP mmHg                      | 376| 73.4(10.6)                               | 75.0(9.3)                                     |
|                               |    | 74.3(10.4)                               | 74.1(10.6)                                    |
|                               |    | 71.7(10.8)                               | 74.8(10.4)                                    |
|                               |    |                                          | 71.7(10.8)                                    |
|                               |    | **.025**                                 | **.111**                                      |
| Total Cholesterol mg/dL       | 324| 178.7(41.5)                              | 182.5(42.4)                                   |
|                               |    | 180.0(41.5)                              | 177.5(40.8)                                   |
|                               |    | 176.3(41.7)                              | 184.0(40.7)                                   |
|                               |    |                                          | 176.3(41.7)                                   |
|                               |    | **.440**                                 | **.658**                                      |
| HDL mg/dL                     | 324| 41.6(10.2)                               | 41.7(10.4)                                    |
|                               |    | 41.7(10.5)                               | 42.0(11.0)                                    |
|                               |    | 41.3(9.8)                                | 40.6(9.8)                                     |
|                               |    |                                          | 41.3(9.8)                                     |
|                               |    | **.759**                                 | **.884**                                      |
| LDL mg/dL                     | 324| 106.7(32.6)                              | 108.6(32.9)                                   |
|                               |    | 107.9(32.7)                              | 109.3(34.1)                                   |
|                               |    | 104.5(32.4)                              | 109.1(30.6)                                   |
|                               |    |                                          | 104.5(32.4)                                   |
|                               |    | **.374**                                 | **.707**                                      |
| TG mg/dL                      | 324| 169.1(172.5)                             | 185.1(166.3)                                  |
|                               |    | 173.9(186.0)                             | 142.8(100.3)                                  |
|                               |    | 160.1(143.6)                             | 213.5(301.5)                                  |
|                               |    | -                                       | 160.1(143.6)                                  |
|                               |    | **.043**                                 | **.282**                                      |
| lnTG                          | 324| 4.9(7)                                   | 4.9(7)                                        |
|                               |    | 4.8(7)                                   | 4.8(6)                                        |
|                               |    |                                          | 5.0(7)                                        |
|                               |    |                                          | 4.8(6)                                        |
|                               |    |                                          | 5.0(8)                                        |
|                               |    |                                          | 4.8(7)                                        |
|                               |    | **.282**                                 | **.146**                                      |
| ApoB mg/dL                    | 237| 93.6(28.3)                               | 94.8(26.5)                                    |
|                               |    | 95.0(27.9)                               | 92.0(27.5)                                    |
|                               |    | 90.9(29.1)                               | 106.9(26.9)                                   |
|                               |    |                                          | 90.9(29.1)                                    |
|                               |    | **.043**                                 | **.061**                                      |
| % with Elevated ACR           | 308| 22.4                                     | 32.6                                          |
|                               |    | 25.9                                     | 23.3                                          |
|                               |    | 15.5                                     | 24.4                                          |
|                               |    |                                          | 15.5                                          |
|                               |    | **.043**                                 | **.146**                                      |

*Overall variable sample sizes for two category exposure comparison (n=382) are similar to four category exposure comparison (n=362)

†p-value for overall test of differences among all 4 groups

‡p = .01
| Variable          | Overall | Non-Hispanic White |
|-------------------|---------|--------------------|
|                   | N | Parental DM | No Parental DM | p-value | N | Parental DM | No Parental DM | p-value |
| HbA1c (%)         |   |              |                |         |   |              |                |         |
| Model 1*          | 343| 8.4(0.2)    | 7.8(0.3)       | 0.037   | 67| 8.1(0.4)    | 6.8(0.4)       | 0.003   |
| Model 2*          | 317| 8.4(0.2)    | 7.8(0.3)       | 0.034   | 63| 8.0(0.4)    | 6.6(0.4)       | 0.004   |
| Model 3*          | 287| 8.5(0.2)    | 8.1(0.3)       | 0.085   | 58| 8.0(0.4)    | 6.8(0.4)       | 0.015   |
| HbA1c (mmol/mol)  |   |              |                |         |   |              |                |         |
| Model 1*          | 343| 68.5(2.4)   | 62.0(3.0)      | 0.037   | 67| 65.2(4.0)   | 50.5(4.4)      | 0.003   |
| Model 2*          | 317| 68.4(2.4)   | 61.6(3.0)      | 0.034   | 63| 64.1(4.1)   | 49.1(4.8)      | 0.004   |
| Model 3*          | 287| 69.8(2.3)   | 64.7(2.8)      | 0.085   | 58| 63.9(4.2)   | 51.1(4.8)      | 0.015   |
| SBP (mmHg)        |   |              |                |         |   |              |                |         |
| Model 1*          | 359| 120.3(1.1)  | 119.6(1.4)     | 0.585   | 68| 119.6(2.6)  | 115.2(2.9)     | 0.160   |
| Model 2*          | 331| 119.6(1.1)  | 119.1(1.3)     | 0.711   | 64| 120.2(2.5)  | 115.2(3.0)     | 0.108   |
| Model 3*          | 299| 120.0(1.3)  | 119.8(1.6)     | 0.923   | 59| 120.1(4.0)  | 115.0(4.1)     | 0.134   |
| DBP (mmHg)        |   |              |                |         |   |              |                |         |
| Model 1*          | 359| 73.9(0.9)   | 71.9(1.1)      | 0.084   | 68| 72.9(2.8)   | 65.6(3.1)      | 0.029   |
| Model 2*          | 331| 74.1(0.9)   | 71.7(1.2)      | 0.051   | 64| 73.2(2.7)   | 64.5(3.1)      | 0.009   |
| Model 3*          | 299| 74.9(1.2)   | 72.3(1.4)      | 0.043   | 59| 76.9(4.4)   | 67.7(4.5)      | 0.014   |
| TC (mg/dL)        |   |              |                |         |   |              |                |         |
| Model 1*          | 307| 184.3(4.0)  | 180.7(4.9)     | 0.483   | 63| 178.5(10.5) | 167.4(11.5)    | 0.357   |
| Model 2*          | 288| 184.2(4.2)  | 180.1(5.1)     | 0.450   | 60| 177.3(11.7) | 164.3(14.1)    | 0.330   |
| Model 3*          | 260| 198.9(7.2)  | 194.8(8.0)     | 0.466   | 55| 199.3(17.9) | 184.2(18.9)    | 0.271   |
| HDL (mg/dL)       |   |              |                |         |   |              |                |         |
| Model 1*          | 307| 40.4(0.9)   | 41.0(1.2)      | 0.613   | 63| 35.9(2.0)   | 38.3(2.2)      | 0.288   |
| Variable          | Overall                      | Non-Hispanic White                       |
|-------------------|------------------------------|-----------------------------------------|
|                   | N               | Parental DM | No Parental DM | p-value | N               | Parental DM | No Parental DM | p-value |
| **LDL (mg/dL)**   |                 |             |               |         |                 |             |               |         |
| Model 1†          | 307             | 110.5(3.2) | 108.1(3.9)    | 0.556   | 63              | 109.2(7.7) | 100.5(8.4)    | 0.323   |
| Model 2†          | 288             | 110.2(3.3) | 108.5(4.0)    | 0.693   | 60              | 108.0(8.5) | 98.4(10.3)    | 0.323   |
| Model 3‡          | 260             | 120.9(5.8) | 119.9(6.4)    | 0.824   | 55              | 128.6(12.4)| 113.6(13.0)   | 0.118   |
| **lnTG**          |                 |             |               |         |                 |             |               |         |
| Model 1*          | 307             | 5.0(0.1)   | 4.9(0.1)      | 0.099   | 63              | 5.2(0.2)   | 4.7(0.2)      | 0.011   |
| Model 2†          | 288             | 5.0(0.1)   | 4.9(0.1)      | 0.063   | 60              | 5.2(0.2)   | 4.6(0.2)      | 0.004   |
| Model 3‡          | 260             | 5.2(0.1)   | 5.0(0.1)      | 0.018   | 55              | 5.3(0.3)   | 4.7(0.3)      | 0.008   |
| **ApoB (mg/dL)**  |                 |             |               |         |                 |             |               |         |
| Model 1*          | 224             | 98.9(3.2)  | 93.0(3.9)     | 0.178   | 47              | 102.3(9.5) | 88.8(9.5)     | 0.244   |
| Model 2†          | 207             | 98.9(3.2)  | 92.0(4.0)     | 0.123   | 45              | 103.7(10.2)| 85.9(11.1)    | 0.191   |
| Model 3‡          | 192             | 108.6(5.3) | 101.3(5.9)    | 0.119   | 42              | 149.0(20.1)| 127.8(19.1)   | 0.089   |
| **% Elevated ACR**|                 |             |               |         |                 |             |               |         |
| Model 1*          | 295             | 2.3(1.2, 4.5)| reference     | 0.018   | 60              | 7.4(0.8, 67.6)| reference   | 0.075   |
| Model 2†          | 276             | 2.4(1.2, 4.9)| reference     | 0.017   | 58              | 7.4(0.7, 79.0)| reference   | 0.099   |
| Model 3‡          | 251             | 2.3(1.1, 5.0)| reference     | 0.033   | 54              | 10.9(0.5, 233.0)| reference  | 0.126   |

*Model 1 adjusts for gender, race or ethnicity (overall only), clinic, highest parental education, smoking status, and activity level.
†Model 2 includes all variables in Model 1, and additionally adjusts for BMI z-score, and waist z-score.
‡Model 3 includes all variables in Model 2, and additionally adjusts for: time since diagnosis, age at diagnosis, and insulin use, plus anti-hypertensive medication use (SBP, DBP, and ACR outcomes only), and lipid-lowering medication use (lipid outcomes only).
§Hosmer and Lemeshow Goodness-of-Fit test shows significant lack-of-fit.