Prevalence of Cardiovascular Disease Risk Factors in U.S. Children and Adolescents With Diabetes

The SEARCH for Diabetes in Youth Study

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OBJECTIVE — The purpose of this study was to determine the prevalence and correlates of selected cardiovascular disease (CVD) risk factors among youth aged <20 years with diabetes.

RESEARCH DESIGN AND METHODS — The analysis included 1,083 girls and 1,013 boys examined as part of the SEARCH for Diabetes in Youth study, a multicenter, population-based study of youth 0–19 years of age with diabetes. Diabetes type was determined by a biochemical algorithm based on diabetes antibodies and fasting C-peptide level. CVD risk factors were defined as follows: HDL cholesterol <40 mg/dl; age- and sex-specific waist circumference >90th percentile; systolic or diastolic blood pressure >90th percentile for age, sex, and height or taking medication for high blood pressure; and triglycerides >110 mg/dl.

RESULTS — The prevalence of having at least two CVD risk factors was 21%. The prevalence was 7% among children aged 3–9 years and 25% in youth aged 10–19 years ($P < 0.0001$), 23% among girls and 19% in boys ($P = 0.04$), 68% in American Indians, 37% in Asian/Pacific Islanders, 32% in African Americans, 35% in Hispanics, and 16% in non-Hispanic whites ($P < 0.0001$). At least two CVD risk factors were present in 92% of youth with type 2 and 14% of those with type 1A diabetes ($P < 0.0001$). In multivariate analyses, age, race/ethnicity, and diabetes type were independently associated with the odds of having at least two CVD risk factors ($P < 0.0001$).

CONCLUSIONS — Many youth with diabetes have multiple CVD risk factors. Recommendations for weight, lipid, and blood pressure control in youth with diabetes need to be followed to prevent or delay the development of CVD as these youngsters mature.

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The metabolic syndrome is a clinical construct characterized by a clustering of cardiovascular disease (CVD) risk factors and is associated with an increased risk of type 2 diabetes (1), premature coronary heart disease incidence, and an increased risk of all-cause (2,3) and CVD mortality (2–4) in adults. It has been suggested that the metabolic syndrome should be addressed as a pragmatic approach leading to improved outcomes, rather than as a pathophysiologic construct (5), with a focus on treatment as appropriate for component CVD risk factors (6).

Using an age-modified definition of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria (7), the metabolic syndrome has also been described in adolescents (8). Specifically, data from the National Health and Nutrition Examination Survey (NHANES)1999–2000 showed that, with the recent increased prevalence of overweight and obesity and the severity of obesity in youths, the prevalence of the metabolic syndrome in adolescents aged 12–19 years has also increased from 4.2% in 1988–1994 (8,9) to 6.4% in 1999–2000, with >2 million adolescents estimated to have the metabolic syndrome (10,11). The prevalence of the metabolic syndrome reached 50% in severely obese (BMI 39.5–41.7 kg/m^2) youngsters (11). This increase in the prevalence of the metabolic syndrome could potentially be associated with an increase in risk of premature CVD. Results from the Cardiovascular Risk in Young Finns Study (12) showed a positive correlation between the number of risk factors at age

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Abbreviations: ATP III, Adult Treatment Panel III; CVD, cardiovascular disease; FCP, fasting C-peptide; NHANES, National Health and Nutrition Examination Survey; NCEP, National Cholesterol Education Program.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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12–18 years and carotid artery wall thickness at age 33–39 years.

In this analysis, we describe the prevalence of CVD risk factors included in the ATP III criteria for the metabolic syndrome, by age, sex, ethnicity, and diabetes type, in a multiracial population-based sample of children and adolescents with diabetes. This study is the most comprehensive multiethnic large-scale study of diabetes in youth that has been conducted to date.

RESEARCH DESIGN AND METHODS

— Data for this analysis derive from the SEARCH for Diabetes in Youth Study. A detailed description of SEARCH study methods has been published elsewhere (11). In brief, the SEARCH study is a multicenter study that began conducting population-based ascertainment of nongestational cases of diagnosed diabetes in youth <20 years of age (non-Hispanic white, African-American, Hispanic, Asian/Pacific Islander, and American Indian children and adolescents) in 2001 for prevalent cases and continuing with case ascertainment for incident cases through the present. SEARCH has six centers that are located in Ohio, Colorado, Washington, South Carolina, Hawaii, and Southern California. Diabetes cases were identified in geographically defined populations in Ohio (eight counties encompassing and surrounding Cincinnati), Washington (five counties encompassing and surrounding Seattle), and South Carolina and Colorado (selected counties in these states for 2001 prevalent cases and statewide in subsequent years for incident cases). The diabetes cases were identified among health plan enrollees in Hawaii (Hawaii Medical Services Association, MedQuest, and Kaiser Permanente Hawaii) and similarly in Southern California (Kaiser Permanente Southern California). Coordinated by the Colorado center, diabetes cases were also identified among three American Indian populations in Arizona and Colorado and among members of the Gila River Pima Indian community participating in the National Institute of Diabetes and Digestive and Kidney Diseases Pima Indian Diabetes Study.

The diabetes cases were considered to be valid if they were diagnosed by a health care provider. To identify 2001 prevalent cases, centers used databases and data sources that were sometimes common to all of the centers (e.g., hospital discharge records) and sometimes unique to a specific center (e.g., laboratory data on performance of HbA_{1c} [A1C] tests) as well as networks of reporting providers, as described previously (13). Reporting providers were the primary source of identification of newly diagnosed diabetes cases in 2002.

Before implementation of the protocol, the study was reviewed and approved by the local institutional review boards that had jurisdiction over the local study population. Using Health Insurance Portability and Accountability Act–compliant procedures, youths with diabetes identified by the SEARCH recruiting network were asked to complete a survey that collected information on age, sex, age at diagnosis, diabetes treatment history, and race/ethnicity. Youths, excluding those with secondary diabetes, who replied to the survey were then invited to a study visit. Before the study visit, written informed consent was obtained according to the guidelines established by the local institutional review board from subjects who were ≥18 years of age or from the parent or guardian if the subject was <18 years of age. Written assent was also obtained from the subjects who were <18 years of age as governed by local institutional review board instructions.

Physical examinations were conducted on the children who were aged ≥3 years. The physical examination measures included height, weight, waist circumference, blood pressure, and an examination to determine the presence or absence of acanthosis nigricans. A staff member from each site was trained and certified using a standard protocol. The site primary trainer then trained and certified the study personnel locally. Recertification of the staff was conducted annually.

Height was measured in centimeters using a stadiometer. Weight was measured in kilograms using an electronic scale. Waist circumference was measured just above the uppermost lateral border of the right ilium using the NHANES protocol (14). A fiberglass tape was used for the patients with a waist circumference up to 150 cm and, for larger patients, a flexible steel tape was used. Height, weight, and waist circumference were measured and recorded twice. A third measurement was done if the first and second measures differed by >0.5 cm for height, >0.3 kg for weight, and >1.0 cm for waist circumference. Height and weight measurements were used to calculate BMI.

Three blood pressure measurements were obtained using a portable mercury manometer, and cuffs of five different sizes were available for use, depending on the size of the arm of the participants. The blood pressure measurement was conducted after the patient had been sitting for at least 5 min. A detailed protocol was followed (15).

Blood was drawn after fasting for at least 8 h for measurement of diabetes autoantibodies (GAD65, insulinoma-associated protein 2, A1C, fasting glucose, C-peptide, and lipids [total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and VLDL cholesterol]). Laboratory samples were obtained only if there was no episode of diabetic ketoacidosis within the prior month. Specimens were processed at the site and shipped within 24 h to the Northwest Lipid Metabolism and Diabetes Research Laboratories in Seattle, Washington, which serves as the study central laboratory, for analyses. Details on lipid, diabetes autoantibodies, and C-peptide measurements have been published previously (13).

Among the youths who had the SEARCH study examination, diabetes was classified by pathophysiologic type based on a biochemical algorithm designed by the SEARCH for Diabetes Study Group using GAD65 and insulinoma-associated protein 2 autoantibodies (diabetes antibodies) and fasting C-peptide (FCP) as follows: type 1A = positive for diabetes antibodies and FCP <0.8 ng/ml; possible type 1A = positive for diabetes antibodies and FCP 0.8 to <2.9 ng/ml; possible type 1 = negative for diabetes antibodies and FCP <0.8 ng/ml; type 2 = negative for diabetes antibodies and FCP ≥2.9 ng/ml; possible type 2 = negative for diabetes antibodies and FCP 0.8 to <2.9 ng/ml; hybrid diabetes = positive for diabetes antibodies and FCP ≥2.9 ng/ml. This classification has been revised from that published previously (13).

A total of 1,013 boys and 1,083 girls aged 3–19 years at the time of the examination who were prevalent cases in 2001 or had newly diagnosed diabetes (incident) in 2002 and who had participated in the study visit and had complete data as of 1 November 2004 are included in this analysis. The mean age was 12.7 years. Based on the total number of validated cases in the SEARCH registry, the overall response rate to in-person visits was 58% for children aged 3–9 years and 46% for youth aged 10–19 years.

For this study, CVD risk factors were defined according to the NCEP ATP III

Table 1—*Presence of selected CVD risk factors and of at least two CVD risk factors by age, sex, ethnicity, diabetes type, and duration of diabetes*

	Total (*n*)	↑ BP	↑ TGs	↓ HDL	↑ Waist	At least two CVD risk factors	χ^2 *P* value*
Age at examination							
3–9 years	466	76 (16)	17 (4)	31 (7)	61 (13)	34 (7)	<0.0001
10–19 years	1,630	497 (30)	374 (23)	254 (16)	381 (23)	402 (25)	
Sex							
Female	1,083	282 (26)	219 (20)	131 (12)	280 (26)	244 (23)	0.0438
Male	1,013	291 (29)	172 (17)	154 (15)	162 (16)	192 (19)	
Race/ethnicity							
Native American	41	25 (61)	27 (66)	17 (41)	23 (56)	28 (68)	
Asian/Pacific Islander	46	18 (39)	14 (30)	11 (24)	15 (33)	17 (37)	
African American	173	68 (39)	35 (20)	25 (14)	63 (36)	55 (32)	
Multiple race	82	25 (30)	10 (12)	11 (13)	27 (33)	19 (23)	
Hispanic	225	79 (35)	67 (30)	39 (17)	68 (30)	79 (35)	
Non-Hispanic white	1,529	358 (23)	238 (16)	182 (12)	246 (16)	238 (16)	<0.0001
Diabetes type							
Type 1A	1,376	305 (22)	198 (14)	126 (9)	208 (15)	198 (14)	
Possible type 1A	142	54 (38)	36 (25)	32 (23)	56 (39)	60 (42)	
Hybrid	29	19 (66)	16 (55)	15 (52)	27 (93)	23 (79)	
Possible type 1	389	107 (28)	60 (15)	45 (12)	42 (11)	48 (12)	
Possible type 2	97	42 (43)	40 (41)	29 (30)	49 (51)	49 (51)	
Type 2	63	46 (73)	41 (65)	38 (60)	60 (95)	58 (92)	<0.0001
Duration of diabetes							
<1 year	169	43 (25)	22 (13)	36 (21)	54 (32)	43 (25)	
1 year	1,927	530 (28)	369 (19)	249 (13)	388 (20)	393 (20)	0.121

Data are *n* (%) unless otherwise indicated. *Test for at least two CVD risk factors versus less than two CVD risk factors. ↑ BP, systolic or diastolic blood pressure ≥90th percentile for age, sex, and height or taking blood pressure medication; ↓ HDL, HDL cholesterol ≤40 mg/dl; ↑ TG, triglycerides ≥110 mg/dl; ↑ Waist, waist circumference ≥90th percentile for age and sex.

definition modified for age (9). CVD risk factors were defined as follows: HDL cholesterol ≤40 mg/dl; waist circumference ≥90th percentile for age and sex (S. Cook, NHANES III, personal communication); systolic or diastolic blood pressure ≥90th percentile for age, sex, and height (16) or taking medication for high blood pressure; and triglycerides ≥110 mg/dl.

Statistical analyses

For each CVD risk factor, we created a binary variable for the presence/absence of that characteristic (i.e., increased waist circumference, yes/no). Next, we calculated the frequencies (and percentages) of each binary variable, both overall and by age, sex, ethnicity, diabetes type, and duration of diabetes. χ^2 tests were used to determine whether there were significant differences in the proportions between the groups. Logistic regression models were fit in which the outcome was the presence of selected risk factors and the presence of at least two risk factors. Age (3–9 and 10–19 years), sex, ethnicity, and diabetes type as defined by SEARCH were entered as potential predictors. All of the analyses were performed using SAS statistical software (version 8.2; SAS Institute, Cary, NC).

RESULTS — Table 1 shows the prevalence of individual CVD risk factors (high blood pressure, high triglyceride levels, low HDL cholesterol, and high waist circumference) and the prevalence of at least two of the CVD risk factors by age, sex, ethnicity, diabetes type, and duration of diabetes. The prevalence of selected CVD risk factors for children aged 3–9 and 10–19 years, respectively, was 16 and 30% for high blood pressure, 4 and 23% for high triglyceride levels, 7 and 16% for low HDL levels, and 13 and 23% for increased waist circumference. The prevalence of at least two CVD risk factors was 7 and 25%, respectively. Of interest, metabolic syndrome–associated risk factors were observed in an age-group in which the majority of children are prepubescent, although they were significantly more common among youth aged 10–19 years than in those aged 3–9 years ($P < 0.0001$). Girls had a higher prevalence of increased waist circumference, whereas boys had a higher prevalence of low HDL ($P < 0.05$). No significant sex differences were observed for blood pressure and triglyceride levels. The prevalence of two or more CVD risk factors in addition to diabetes was 23% among girls and 19% among boys ($P = 0.044$).

The prevalence of at least two CVD risk factors and of the individual risk factors was higher in all of the racial/ethnic minority groups compared with non-Hispanic whites. Native Americans had the highest prevalence followed by the Asian/Pacific Islanders, Hispanics, and African Americans.

Youth with type 2 diabetes had the highest prevalence of each of the selected CVD risk factors (≥60%), especially high waist circumference (95%), as well as having at least two of the CVD risk factors (92%), followed by youths with hybrid and "possible type 2" diabetes. The rates were lower among youth with "possible type 1" or type 1A diabetes (12 and 14%, respectively, with at least two of the CVD risk factors; *P* for diabetes type < 0.0001). Among all the youth with duration of diabetes of <1 year and ≥1 year, the prevalence of at least two CVD risk factors was 25 and 20%, respectively ($P = 0.12$).

Table 2—*Odds ratios of selected CVD risk factors and of at least two CVD risk factors in relation to age, sex, ethnicity, and diabetes type (2001 prevalent and 2002 incident cases)*

	↑ BP	↑ TGs	↓ HDL	↑ Waist	At least two CVD risk factors
Age at examination					
3–9 years	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
10–19 years	1.83 (1.39–2.41)	6.12 (3.70–10.13)	1.87 (1.25–2.79)	1.32 (0.96–1.80)	2.76 (1.89–4.03)
Sex					
Male	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Female	0.79 (0.65–0.97)	1.16 (0.91–1.47)	0.67 (0.51–0.88)	1.77 (1.39–2.26)	1.10 (0.86–1.40)
Race/ethnicity					
Non-Hispanic white	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Asian/Pacific Islander	1.61 (0.84–3.05)	1.43 (0.70–2.93)	1.56 (0.62–2.97)	1.09 (0.50–2.38)	1.68 (0.81–3.48)
African American	1.48 (1.04–2.11)	0.70 (0.45–1.10)	0.58 (0.34–0.97)	1.30 (0.85–1.98)	1.06 (0.69–1.63)
Hispanic	1.52 (1.11–2.07)	1.79 (1.27–2.51)	1.13 (0.75–1.71)	1.63 (1.14–2.33)	2.25 (1.60–3.16)
Multiple race	1.28 (0.77–2.13)	0.55 (0.27–1.14)	0.83 (0.41–1.70)	2.08 (1.20–3.59)	1.24 (0.67–2.30)
Native American	2.22 (1.10–4.48)	3.58 (1.73–7.42)	1.36 (0.64–2.91)	1.05 (0.43–2.56)	2.0.79 (1.24–6.31)
Diabetes type					
Type 1A	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Possible type 1A	1.80 (1.24–2.61)	1.63 (1.07–2.50)	2.81 (1.80–4.38)	3.39 (2.31–4.97)	3.66 (2.50–5.35)
Hybrid	5.04 (2.26–11.25)	5.85 (2.59–13.21)	11.49 (5.18–25.48)	63.99 (14.81–276.48)	17.64 (6.86–45.39)
Possible type 1	1.34 (1.03–1.74)	1.14 (0.83–1.58)	1.30 (0.90–1.87)	0.69 (0.48–0.98)	0.86 (0.61–1.21)
Possible type 2	2.12 (1.37–3.29)	3.39 (2.13–5.38)	4.30 (2.62–7.07)	4.83 (3.09–7.55)	4.74 (3.02–7.42)
Type 2	6.56 (3.63–11.86)	7.33 (4.11–13.08)	14.38 (8.01–25.81)	100.93 (30.66–332.32)	46.77 (18.23–120.00)

Data are odds ratio (95% CI). From logistic regression models, each result adjusted for all other variables shown. ↑ BP, systolic or diastolic blood pressure ≥90th percentile for age, sex, and height or taking blood pressure medication; ↓ HDL, HDL cholesterol ≤40 mg/dl; ↑ TGs, triglycerides ≥110 mg/dl; ↑ Waist, waist circumference ≥90th percentile for age and sex.

Table 2 shows the odds ratios for having individual CVD risk factors and at least two of the CVD risk factors, including age, sex, ethnicity, and diabetes type as covariates. Age, race/ethnicity, and diabetes type were independently associated with having at least two additional CVD risk factors ($P < 0.0001$). Older youth, ethnic minorities, and youth with type 2 and hybrid diabetes (compared with those with type 1A diabetes) had significantly greater odds of having at least two additional CVD risk factors ($P < 0.0001$). Sex was not independently associated with the presence of at least two CVD risk factors, after adjusting for covariates.

CONCLUSIONS — The SEARCH findings reported here suggest that the prevalence of multiple CVD risk factors is high among children and adolescents with diabetes, including children <10 years of age. The study also showed that youth from minority groups with diabetes have a higher prevalence of having at least two additional metabolic syndrome–associated CVD risk factors compared with non-Hispanic white youth ($P < 0.0001$). Girls also had a greater prevalence of two or more CVD risk factors compared with boys; however, after adjusting for age, sex, race/ethnicity, and diabetes type, sex was not independently associated with having two or more additional CVD risk factors.

It is especially interesting to note that two or more additional CVD risk factors were not only present frequently among youth with type 2 and hybrid diabetes but also that a nontrivial proportion of youth with type 1A and type 1 diabetes also presented metabolic abnormalities, especially among ethnic minorities. The observed lower prevalence of CVD risk factors in possible type 2 compared with type 2 diabetes and for type 1A compared with possible type 1A diabetes may reflect an underlying degree of insulin resistance as reflected in the FCP measurement used to create these categories, with higher FCP values in the type 2 and possible type 1A diabetic groups.

The prevalence of at least two additional CVD risk factors in youth with diabetes was substantially higher than that reported previously in the general population (9,10). An increasing prevalence of the metabolic syndrome has been reported previously both in nondiabetic boys and girls and among non-Hispanic white, African-American, and Hispanic adolescents. No comparative data are available for nondiabetic American Indians and Asian/Pacific Islanders. The syndrome is particularly prevalent among overweight (BMI ≥95th percentile) adolescents, who have a prevalence of >30% (10). The prevalence reached 50% in severely obese youths (11). Duncan et al. (10) reported that 12% of the adolescents aged 12–19 years have increased waist circumference, 8% have fasting glucose levels ≥100 mg/dl, 23% have high triglyceride levels, 23% have low HDL levels, and 8% have elevated blood pressure. Interestingly, in the present sample of youth with diabetes aged 10–19 years, prevalence of having high triglyceride or low HDL levels was not higher than that reported among nondiabetic youth; however (without adjusting for race/ethnic differences between studies), SEARCH participants did have a comparatively higher prevalence of high blood pressure and high waist circumference (Table 1).

In contrast, among the SEARCH participants, 25% of youth aged 12–19 years have at least two additional metabolic syndrome–associated CVD risk factors compared with 6.4% of the adolescents aged 12–19 years in the general population in 1999–2000 (10). There are no previously reported data on the metabolic syndrome in children aged <12 years, and there are no widely accepted criteria

for the metabolic syndrome in children. Nonetheless, these findings suggest that children and adolescents with diabetes may be at significant increased risk of premature CVD and emphasize the importance of prevention, recognition, treatment, and control of these adverse metabolic syndrome components for the prevention of CVD.

One of the limitations of this study was the lower response rates for in-person visits among older youth, as well as among minority groups (46%) versus non-Hispanic white youth (49%) ($P < 0.05$). Because older youth and minority groups have a higher prevalence of multiple CVD risk factors, our overall estimates may be conservative. However, comparisons conducted between the respondents and the nonrespondents at the two study sites where this was possible showed no difference in lipid levels (data not shown), suggesting that the SEARCH sample is representative.

There are no data examining the impact of the metabolic syndrome in children and adolescents on subsequent CVD morbidity and mortality. However, in adults, the presence of multiple CVD risk factors and the metabolic syndrome has been shown to be associated with CVD mortality (3,4) as well as all-cause mortality (3,17). The metabolic syndrome appears to be especially harmful to women who have diabetes (17).

The NCEP ATP III recognizes the metabolic syndrome as a secondary target of risk reduction therapy after the primary target of LDL cholesterol reduction for the prevention of CVD. For the management of the metabolic syndrome, the NCEP ATP III recommends treatment of the underlying causes of the syndrome such as obesity and physical inactivity as well as treatment of associated lipid and nonlipid risk factors (6). Individuals with diabetes are considered to be at very high risk for CVD (18). In a recent joint statement, the American Diabetes Association and the European Association for the Study of Diabetes recommended the evaluation and treatment of each CVD risk factor, without regard to the number of factors present (6). Also recently, the American Heart Association and the National Heart, Lung, and Blood Institute reiterated the clinical value of the concept of the metabolic syndrome (19). All of these organizations agree that it is essential to evaluate and treat each of the risk factors, independently of whether the criteria for the metabolic syndrome are met. Further research is needed in children and adolescents with diabetes to explore the potential to reduce the risk of these adverse CVD risk factors and the metabolic syndrome. Recommendations for weight control and lipid and blood pressure therapy in children with diabetes have been developed (20). Considering that many youth with diabetes, including type 1 and type 1A diabetes, have multiple CVD risk factors, these findings emphasize the importance of these recommendations if we are to decrease the risk of macrovascular disease in youth with diabetes.

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