ARTICLE

Childhood Predictors of Adult Type 2 Diabetes at 9- and 26-Year Follow-ups

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Objective: To determine whether pediatric office measures (waist circumference, body mass index [BMI], systolic [SBP] and diastolic [DBP] blood pressure, and parental diabetes) and laboratory measures (glucose, triglyceride, high-density lipoprotein cholesterol, and insulin) predict risk of type 2 diabetes mellitus (T2DM) at ages 19 and 39 years.

Design: Nine- and 26-year prospective follow-ups of schoolchildren.

Setting: Urban and suburban schools.

Participants: One thousand sixty-seven girls starting at age 10 years in the National Growth and Health Study and 822 schoolchildren aged 6 to 18 years at entry from the Princeton Follow-up Study.

Outcome Measure: Development of T2DM.

Results: In the Princeton Follow-up Study, childhood SBP and BMI in the top fifth percentile and black race predicted T2DM at age 39 years (area under the receiver-operator curve [AUC] = 0.698). Adding a childhood glucose level of 100 mg/dL or higher, and high-density lipoprotein cholesterol in the bottom fifth percentile and triglyceride concentration in the top fifth percentile as explanatory variables increased AUC to 0.717 and 0.709, respectively. If childhood BMI, SBP, and DBP were all lower than the 75th percentile, likelihood of T2DM at age 39 years was 2%; the likelihood was 1% if the parents had no DM. In the National Growth and Heath Study, SBP in the top fifth percentile and parental diabetes predicted T2DM at age 19 years (AUC = 0.699). Adding insulin in the top fifth percentile increased AUC to 0.764, with insulin being a significant variable. If childhood BMI, SBP, and DBP were all lower than the 75th percentile, the likelihood of T2DM at age 19 years was 0.2%, 0.2% if the parents were also free of DM, and 0.3% if childhood insulin was also less than the 75th percentile.

Conclusions: Office-based childhood measures predict the presence and absence of future T2DM 9 and 26 years after baseline. Childhood insulin measurement improves prediction, facilitating approaches to primary prevention of T2DM.

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In the past 25 years, the prevalences of obesity and type 2 diabetes mellitus (T2DM) have increased concomitantly, and the age at onset of T2DM has dropped precipitously, especially in black females.[1,2] Models to identify children at increased and very low risk for young-adult T2DM could provide diagnostic and therapeutic insights into etiologic relationships of hyperinsulinemia, insulin resistance, and obesity with the development of T2DM[3,4] and could provide targeted avenues for prevention. It is not yet known whether the tripling of the rate of childhood obesity[5] will produce a tidal wave of T2DM in adulthood. In the SEARCH for Diabetes in Youth Study,[6] the incidence of DM (per 100 000 person-years) was 24.3 in 2002-2003. The authors of this study noted that "overall, type 2 DM was still relatively infrequent, but the highest rates (17.0 to 49.4 per 100 000 person-years) were documented among 15- to 19-year-old minority groups."[6]

Metabolic syndrome in childhood predicts development of premature cardiovascular events and T2DM 25 to 30 years later in young adulthood.[4,7] Nguyen et al[8] reported that the childhood homeostatic assessment model algorithm of insulin resistance, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), and high-density lipoprotein cholesterol (HDLC) were independent predictors of the development of T2DM in former schoolchildren in Bogalusa, Louisiana, as young adults. Cheung et al[9] reported that BMI at age 11 years could predict subjects' history of diabetes and hypertension as well as adult obesity at age 33 years. Franks et al[10] reported that obesity was a significant explanatory variable for T2DM in 5- to 19-year-old American Indians who did not have diabetes at entry.

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In the current study, we used longitudinal data from 2 studies: the National Growth and Health Study (NGHS), a 9-year cohort study of black and white girls enrolled at ages 9 and 10 years,[4] and the Princeton Follow-up Study (PFS), a 22- to 30-year follow-up of black and white former schoolchildren first studied in the National Heart, Lung and Blood Institute Lipid Research Clinics (NHLBI-LRC) Study from 1973 to 1976.[4] We hypothesized that abbreviated screening criteria based on common childhood office measures (BMI, systolic [SBP] and diastolic [DBP] blood pressure, waist circumference, and parental history of diabetes) would be an effective preliminary screen for future T2DM and that laboratory-based childhood measures (fasting serum insulin, glucose, triglycerides, and HDLC concentrations) would further improve the prediction of future T2DM.

METHODS

INFORMED CONSENT

In PFS, data were collected following a protocol approved by the Children's Hospital Institutional Review Board, with signed informed consent.[11,12] In NGHS, procedures followed were in accordance with ethical standards of the institutional review boards of the centers that approved the study. Signed informed consent was obtained from the girls' parents or guardians and assent from the girls. Moreover, there is an active human subjects approval under which analyses for this study were conducted.

NATIONAL GROWTH AND HEALTH STUDY

The NGHS has been described previously.[12] It was a 9-year, multicenter cohort study conducted under contract with NHLBI to explicate the origins of black-white disparities in both obesity and its effects on cardiovascular disease risk factors in women. Race was self-declared[12] and enrollment was restricted to racially concordant households, ie, to girls who said they were black or white and whose parents or guardians said that they were black or white, respectively. Office-based predictors for T2DM (BMI, SBP, and DBP) were measured at age 10 years, and waist circumference was added at age 11 years. The NGHS clinical centers in Cincinnati, Ohio, and Washington, DC, measured fasting insulin and glucose concentrations at baseline (age 10 years),[13] ages 15 to 16 years, and age 19 years, as previously described.[14] The first insulin and glucose measurements at age 10 and 15 to 16 years were used as predictors of T2DM. Fasting lipid profiles were measured at age 10 years, and triglyceride and HDLC concentrations were also used as laboratory-based predictors of T2DM. Screening tests were offered to parents, but participation was limited, so parental lipids were not used as predictors.

PRINCETON FOLLOW-UP STUDY

The PFS was a 26-year follow-up (1998-2003)[15] of former schoolchildren from the Cincinnati Clinic of the National Institutes of Health–NHLBI-LRC Prevalence Program (1973-1978). The LRC[11,16] and PFS[15] have both been described previously. Briefly, the NHLBI-LRC was a multistage survey of lipids and other cardiovascular risk factors.[11,16] The LRC studied students in grades 1 through 12 and subsets of their parents. The student population in LRC was 72% white and 28% black, with a mean age of 12.4 years (SD, 3.3 years). Eighty-four percent of eligible students participated at the initial LRC study visit and 91% participated at subsequent visits; participation rates did not differ significantly between races. The PFS was conducted to assess changes in the family fasting lipoprotein cholesterol correlations from the period of shared households to that of separate households.[15] In 1998, eligible former schoolchildren with a mean age of 38.6 years (SD, 3.6 years) were invited by mail and in follow-up telephone calls to participate in the PFS, 22 to 30 (median 26) years after their initial LRC sampling. There was no contact with the former schoolchildren during intervals in these studies. In the LRC, data were collected according to the collaborative National Institutes of Health–NHLBI protocol.[17] Office measures (age, race, sex, BMI, SBP, DBP, and parental history of diabetes) and laboratory tests (triglyceride, HDLC, and fasting glucose) were collected. However, waist circumference and insulin were only measured in PFS, not in LRC.

DIAGNOSIS OF DIABETES

Diagnosis of diabetes was based on World Organization of Health criteria, fasting glucose of 126 mg/dL (to convert to micromoles per liter, multiply by 0.0555) or higher, and self-reported diabetes with treatment by a physician.[18] The LRC and NGHS subjects whose first measured fasting blood glucose was 126 mg/dL[18] or higher were excluded from this article.

In the LRC, participants eligible for PFS (students and their parents) were asked, "Was any of the medication you took during the past 2 weeks for diabetes? (yes, no, unknown)." If the answer was yes or unknown, then they were asked, "Have you taken Orinase, Diabinese, phenformin, insulin, other medicine for diabetes?" In the PFS (22-30 years later), all participants (former students and their parents) were asked, "Please indicate whether or not you are taking any medications prescribed by your physician (oral diabetes medication, insulin by injection, blood pressure medication)." In addition, participants were asked if their biological mother (or father) had ever been told by a medical physician that she (or he) had diabetes.

In the NGHS follow-up at age 19 years, subjects were asked, "Do you have a health condition, if yes, what is it, and do you regularly see a doctor for it?" For subjects responding yes to any of these 3 questions, they were then asked, "Do you take any pills or insulin?"

At follow-up at age 39 years in PFS or age 19 years in NGHS (**Table 1**), we did not have a measurement of C-peptides or diabetes autoantibody levels, the gold standard methods[6] of distinguishing type 1 from type 2 diabetes. The PFS (8 of 48) and NGHS (1 of 9) subjects with follow-up fasting blood glucose of 126 mg/dL or higher at ages 39 and 19 years, respectively, who were taking insulin were excluded from the data set to allow the analyses to focus on subjects with T2DM. Parental DM was diagnosed in NGHS by interviewing the parents as part of enrolling their daughter.

STATISTICAL ANALYSIS

Black-white racial differences in the incidence of T2DM were assessed by χ^2 or Fisher exact tests. In each analysis sample, age-, sex-, and race-specific 95th (and for HDLC, fifth) percentiles were calculated (**Tables 2**, **3**, **4**, and **5**). χ^2 or Fisher exact tests were used to compare associations between the top fifth (or HDLC, bottom fifth) percentiles and T2DM (Table 2 and Table 4). Sensitivity, specificity, and positive and negative predictive values for office- and laboratory-based screening for later T2DM were calculated overall and by race. These values did not differ by sex or race, so we present only overall results for each study (Table 2 and Table 4).

To identify children who were unlikely to develop T2DM at age 19 years in NGHS and at age 39 years in PFS, children

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Table 1. Summary Data for the PFS and NGHS Populations at Baseline and Follow-up

	Median							
	PFS Participants (n=822)				NGHS Participants (n=1067)			
	Baseline[a]		Follow-up[b]		Baseline[c]		Follow-up[d]	
Characteristic	Black[e]	White[f]	Black[g]	White[h]	Black[i]	White[j]	Black[k]	White[l]
No. of participants	226	596	226	596	563	504	563	504
Age, y	12.4	12.6	37.9	38.8	10.1	9.9	19.2	19.0
Sex, M/F, No.	95/141	294/302			0/563	0/504		
BMI	19.4	19.4	28.9	26.8	18.2	16.7	24.9	22.1
Waist circumference, cm			96.4	94.7	64.3	60.4	75.5	71.0
SBP, mm Hg	100	104	120	118	101	100	110	107
DBP, mm Hg	62	62	80	78	69	67	71	70
Glucose, mg/dL	85	86	87	89	94	93	87	86
Triglyceride, mg/dL	62	70	83	111	64	71	64	86
HDLC, mg/dL	58	52	46	42	54	53	52	50
Insulin, μU/mL			7.8	6.1	12.7	8.1	10.0	7.0
Follow-up duration, mean (SD), median (range), y			26.2 (1.4), 26.2 (22.3-30.0)				9.1 (0.3), 9.0 (8.4-10.7)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DBP, diastolic blood pressure; HDLC, high-density lipoprotein cholesterol; NGHS, National Growth and Heath Study; PFS, Princeton Follow-up Study; SBP, systolic blood pressure.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; HDLC to millimoles per liter, multiply by 0.0259; and triglycerides to millimoles per liter, multiply by 1.8.

[a] Mean (SD) age: 12.4 (3.3) years.
[b] Mean (SD) age: 38.6 (3.6) years.
[c] Mean (SD) age: 10.0 (0.5) years.
[d] Mean (SD) age: 19.1 (0.7) years.
[e] Mean (SD) age: 12.1 (3.2) years.
[f] Mean (SD) age: 12.5 (3.3) years.
[g] Mean (SD) age: 38.0 (3.4) years.
[h] Mean (SD) age: 38.9 (3.6) years.
[i] Mean (SD) age: 10.1 (0.5) years.
[j] Mean (SD) age: 10.0 (0.6) years.
[k] Mean (SD) age: 19.2 (0.7) years.
[l] Mean (SD) age: 19.0 (0.7) years.

were categorized as having BMI, SBP, and DBP lower than the 75th percentile,[19,20] parents free of DM (Table 2 and Table 4), and (NGHS only) fasting serum insulin lower than the 75th percentile (Table 4).[21] The likelihood of having late-teenage (NGHS) or young-adult (PFS) T2DM was then assessed.

Stepwise logistic regression was used to first assess childhood office-based measures as explanatory variables for future T2DM, and then laboratory-based measures were added (Table 3 and Table 5). For both NGHS and PFS, office-based predictors included race (white=1, black=2); parental history of DM (no=0, yes=1); and BMI, SBP, and DBP at or above the 95 percentile (all scored no=0, yes=1). In NGHS, waist circumference at or above the 95th percentile, and in PFS, sex (male=1, female=2) were added as explanatory variables (Table 3 and Table 5). Laboratory-based measures included triglyceride concentration above the 95th percentile, HDLC concentration below the fifth percentile, and glucose concentration of at least 100 mg/dL. In NGHS, insulin above the 95th percentile was added as an explanatory variable (scored no=0, yes=1).

RESULTS

The 9-year follow-up of NGHS girls included 80.2% of eligible girls, and the 22- to 30-year PFS follow-up included 53% of eligible former schoolchildren. In NGHS, participants did not differ at age 10 years ($P>.05$) from participants lost to follow-up for race, age, BMI, glucose, or waist circumference. After covariance adjusting for age and race, NGHS participants did not differ ($P>.05$) from nonparticipants by childhood fasting serum insulin. Hence, the NGHS cohort did not reflect a selection bias at the time of follow-up. In PFS, comparisons of LRC summary data on participants retained and lost to follow-up showed higher childhood BMI in retained subjects (19.4 vs 18.7, $P<.001$). After adjustment for age, sex, race, and BMI, there were no differences ($P>.2$) between PFS participants and nonparticipants for childhood LRC total cholesterol, HDLC, low-density lipoprotein cholesterol, and triglyceride; lipid values were similar in nonparticipants and participants.

Table 1 presents summary data for the NGHS and PFS populations at study entry at ages 10 and 12 years, respectively, and on follow-up 9 years later in the NGHS and 22 to 30 years later in the PFS. After exclusions of diabetes cases at childhood entry (mean age, 10 years in NGHS; 12 years in PFS), of 48 PFS subjects with glucose concentrations of at least 126 mg/dL at follow-up at age 39 years, 8 were taking insulin. Because we did not measure C-peptide or diabetes autoantibody levels at entry or follow-up,[6] we could not determine whether these 8 subjects had type 1 diabetes or T2DM treated with insulin, and data from these 8 subjects were excluded from analysis, leaving 40 PFS subjects with T2DM at a mean age of 39 years. In the PFS cohort, the incidence of T2DM

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Table 2. Sensitivity, Specificity, and Positive and Negative Predictive Values for Type 2 DM in PFS

Characteristic	No. of Participants	No. (%)		%				*P* Value
		Type 2 DM	No Type 2 DM	Sensitivity	Specificity	Predictive Value: Positive	Predictive Value: Negative	
BMI								
>95th percentile	41	8 (20)	33 (80)	21		20		<.001
≤95th percentile	744	30 (4)	714 (96)		96		96	
SBP								
>95th percentile	24	5 (21)	19 (79)	19		21		.003
≤95th percentile	582	2 (4)	560 (96)		97		96	
DBP								
>95th percentile	17	1 (6)	16 (94)	4		6		
≤95th percentile	589	26 (4)	563 (96)		97		96	
Glucose								
≥100 mg/dL	30	6 (20)	24 (80)	15		20		<.001
<100 mg/dL	792	34 (4)	758 (96)		97		96	
Parental DM								
Yes	277	26 (9)	251 (91)	67		9		<.001
No	501	13 (3)	488 (97)		66		97	
Triglyceride								
>95th percentile	43	7 (16)	36 (84)	18		16		.003
≤95th percentile	779	33 (4)	746 (96)		95		96	
HDLC								
<Fifth percentile	34	4 (12)	30 (88)	10		12		
≥Fifth percentile	780	36 (5)	744 (95)		96		95	
BMI, SBP, and DBP <75th percentile	336	6 (2)	330 (98)					
BMI, SBP, and DBP <75th percentile and no parental DM	221	3 (1)	218 (99)					

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DBP, diastolic blood pressure; DM, diabetes mellitus; HDLC, high-density lipoprotein cholesterol; PFS, Princeton Follow-up Study; SBP, systolic blood pressure.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; HDLC to millimoles per liter, multiply by 0.0259; and triglycerides to millimoles per liter, multiply by 1.8.

Table 3. Stepwise Logistic Regression Models for Type 2 DM in PFS[a]

Candidate Explanatory Variable	Significant Explanatory Variable	Sign	*P* Value	OR (95% CI)	AUC
Office measures at baseline: race, sex, BMI, SBP, DBP, parents' DM, 70 observations, 26 cases of type 2 DM	SBP in top fifth percentile	+	.003	5.78 (1.81-18.4)	0.698
	Black race	+	.008	3.05 (1.34-6.93)	
	BMI in top fifth percentile	+	.02	4.00 (1.28-12.5)	
Office measures plus glucose at baseline, 570 observations, 26 cases of type 2 DM	SBP in top fifth percentile	+	.002	6.15 (1.92-19.8)	0.717
	Black race	+	.009	3.04 (1.33-6.94)	
	BMI in top fifth percentile	+	.02	4.13 (1.30-13.2)	
	Glucose ≥100 mg/dL	+	.01	4.68 (1.40-15.6)	
Office measures plus lipids at baseline, 565 observations, 26 cases of type 2 DM	SBP in top fifth percentile	+	.002	5.96 (1.91-18.6)	0.709
	Triglyceride in top fifth percentile	+	.004	4.58 (1.63-12.9)	
	Black race	+	.006	3.19 (1.40-7.27)	
Office measures, glucose, and lipids at baseline, 565 observations, 26 cases of type 2 DM	SBP in top fifth percentile	+	.002	5.96 (1.91-18.6)	0.709
	Triglyceride in top fifth percentile	+	.004	4.58 (1.63-12.9)	
	Black race	+	.006	3.19 (1.40-7.27)	

Abbreviations: AUC, area under the receiver-operator curve; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; DBP, diastolic blood pressure; DM, diabetes mellitus; OR, odds ratio; PFS, Princeton Follow-up Study; SBP, systolic blood pressure.

[a]Candidate explanatory variables included race, sex, parents' diabetes, and categorical variables (race-, sex-, and age-specific percentile, top 5th vs ≤95th percentile) of baseline BMI, SBP, DBP, and triglyceride; glucose (≥100 vs <100 mg/dL [to converet to millimoles per liter, multiply by 0.0555]); and high-density lipoprotein cholesterol (race-, sex-, and age-specific percentile, bottom fifth vs ≥fifth percentile).

in young adulthood (at a mean age of 39 years) was 40 of 822 (4.9%); incidence was higher in black women (9.9%) than in white women (4%) ($P = .02$), and 4.7% in black men vs 3.4% in white men. In NGHS, having excluded cases of diabetes at entry and with further exclusions by insulin use at age 19 years, 8 girls at age 19 years were judged to have T2DM. At 9-year follow-up in NGHS, at median ages of 19.2 years in black women and 19 years in white women, T2DM was present in 7 in 563 black women (1.2%) and 1 in 504 white women (0.2%).

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Table 4. Sensitivity, Specificity, and Positive and Negative Predictive Values for Type 2 DM in NGHS

Characteristic	No. of Participants	No. (%)		%				P Value
		Type 2 DM	No Type 2 DM	Sensitivity	Specificity	Predictive Value		
						Positive	Negative	
BMI								
>95th percentile	43	1 (2)	42 (98)	13		2		
≤95th percentile	1015	7 (1)	1008 (99)		96		99	
Waist circumference								
>95th percentile	40	1 (3)	77 (93)	13		3		
≤95th percentile	1006	7 (1)	999 (99)		96		99	
SBP								
>95th percentile	48	2 (4)	46 (96)	25		4		.048
≤95th percentile	1009	6 (1)	1003 (99)		96		99	
DBP								
>95th percentile	28	1 (4)	27 (96)	13		4		
≤95th percentile	987	7 (1)	980 (99)		97		99	
Parental DM								
Yes	57	2 (4)	55 (96)	25		4		
No	809	6 (1)	803 (99)		94		99	
Glucose								
≥100 mg/dL	138	3 (2)	135 (98)	38		2		
<100 mg/dL	929	5 (1)	924 (99)		87		99	
Insulin								
>95th percentile	48	3 (6)	45 (94)	38		6		.004
≤95th percentile	1013	5 (0.5)	1008 (99.5)		96		99.5	
Triglycerides								
>95th percentile	37	1 (3)	36 (97)	13		3		
≤95th percentile	847	7 (1)	840 (99)		96		99	
HDLC								
<Fifth percentile	36	2 (6)	34 (94)	25		6		.04
≥Fifth percentile	835	6 (1)	829 (99)		96		99	
BMI, SBP, and DBP <75th percentile	545	1 (0.2)	544 (99.8)					
BMI, SBP, and DBP <75th percentile and no parental DM	425	1 (0.2)	424 (99.8)					
BMI, SBP, DBP, and insulin <75th percentile	465	1 (0.2)	397 (99.8)					
BMI, SBP, DBP, and insulin <75th percentile and no parental DM	359	1 (0.3)	358 (99.7)					

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DBP, diastolic blood pressure; DM, diabetes mellitus; HDLC, high-density lipoprotein cholesterol; NGHS, National Growth and Heath Study; SBP, systolic blood pressure.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

Table 5. Stepwise Logistic Regression Models for Type 2 DM in NGHS[a]

Candidate Explanatory Variable	Significant Explanatory Variable	Sign	P Value	OR (95% CI)	AUC
Office measures at baseline: age, race, BMI, waist circumference, SBP, DBP, parents' DM, 802 observations, 8 cases of type 2 DM	SBP in top fifth percentile	+	.02	7.72 (1.47-40.55)	.699
	Parents had DM	+	.05	5.22 (1.002-27.23)	
Office measures at baseline plus first available insulin measurement, 799 observations, 8 cases of type 2 DM	Insulin in top fifth percentile	+	<.001	15.4 (3.30-72.0)	.764
	Parents had DM	+	.03	7.09 (1.26-39.8)	
Office measures plus lipids at baseline, 665 observations, 8 cases of type 2 DM	SBP in top fifth percentile	+	.03	6.38 (1.15-35.5)	.695
	HDLC in bottom fifth percentile	+	.04	6.18 (1.11-34.4)	
	Parents had DM	+	.047	5.48 (1.03-29.3)	
Office measures plus glucose at baseline, 802 observations, 8 cases of type 2 DM	SBP in top fifth percentile	+	.02	7.72 (1.47-40.55)	.699
	Parents had DM	+	.05	5.22 (1.002-27.23)	

Abbreviations: AUC, area under the receiver-operator curve; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; DBP, diastolic blood pressure; DM, diabetes mellitus; HDLC, high-density lipoprotein cholesterol; NGHS, National Growth and Heath Study; OR, odds ratio; SBP, systolic blood pressure.

[a] Candidate explanatory variables included race, parents' diabetes, and categorical variables (top 5th percentile vs ≤95th) of baseline age, BMI, waist circumference, SBP, DBP, triglyceride, and insulin; glucose (≥100 vs <100 mg/dL [to convert to millimoles per liter, multiply by 0.0555]); and HDLC (bottom fifth percent vs ≥fifth percentile).

Table 2 presents sensitivity, specificity, and positive and negative predictive values for T2DM based on office- and laboratory-based measures in univariate analyses for PFS subjects. Except for parental diabetes, specificity was higher than sensitivity for all factors, and negative predictive values were greater than positive pre-

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dictive values. Specificity and negative predictive values were greater than 90%. Sensitivity was generally low, except for parental diabetes, which was 67%. In the PFS, childhood predictors significantly associated with young-adult T2DM were parents' DM history ($P<.001$), glucose of at least 100 mg/dL ($P<.001$), BMI in the top fifth percentile ($P<.001$), SBP in the top fifth percentile ($P=.003$), and triglyceride concentration in the top fifth percentile ($P=.003$).

In PFS, if childhood BMI, SBP, and DBP were lower than the 75th percentile, the likelihood of young-adult T2DM 22 to 30 years later was low (6 of 336 [2%]). If the parents were also free of DM, the likelihood of young-adult T2DM was lower (3 of 221 [1.4%]).

Multiple logistic regression analysis was used to identify independent office- and laboratory-based predictors of future T2DM in PFS (Table 3). Childhood SBP and BMI in the top fifth percentile as well as black race were associated with T2DM in young adulthood, with an area under the receiver-operator curve (AUC) of 0.698. Adding childhood glucose improved the model fit, with childhood glucose of 100 mg/dL or higher being an additional significant explanatory variable (AUC=0.717). When childhood lipids were added as explanatory variables, significant variables included SBP and triglyceride concentration in the top fifth percentile and black race (AUC=0.709). Adding childhood glucose as an explanatory variable along with lipids did not change the model.

Table 4 presents sensitivity, specificity, and positive and negative predictive values for T2DM based on office- and laboratory-based measures in univariate analyses for NGHS subjects. As in the PFS analyses (Table 2), specificity was greater than sensitivity, and negative predictive values were greater than positive predictive values. Specificity values were greater than 90% except for glucose, which was 87%. Sensitivity was generally low, except for insulin in the top fifth percentile (38%). The childhood variable with the highest positive predictive value was insulin in the top fifth percentile, followed by HDLC in the bottom fifth percentile. In NGHS, the childhood laboratory predictor most significantly associated with late-teenage T2DM was insulin in the top fifth percentile; development of late-teenage T2DM was 12 times more likely for childhood insulin in the top fifth percentile (6% vs 0.5%; Fisher exact, $P=.004$).

In NGHS, if childhood BMI, SBP, and DBP were lower than the 75th percentile, the likelihood of T2DM at age 19 years was 1 in 545 (0.2%), and if parents were also free of DM, the likelihood of T2DM was 1 in 425 (0.2%). If insulin was also lower than the 75th percentile, the likelihood of T2DM was 1 in 465 (0.2%).

In multivariate analyses of NGHS data, among office-based variables, childhood SBP in the top fifth percentile and parental diabetes predicted T2DM 9 years later (AUC=0.699) (Table 5). When insulin in the top fifth percentile at age 10 years was an added explanatory variable, the AUC of the model rose to 0.764, with insulin in the top fifth percentile and parental diabetes as significant explanatory variables. With childhood lipids added to the office measures as explanatory variables, HDLC in the bottom fifth percentile was a significant explanatory variable (AUC=0.695). Adding childhood glucose to office measures gave the same model as office measures alone.

COMMENT

In univariate analyses in PFS, childhood office-based predictors most significantly associated with young-adult T2DM were BMI and SBP in the top fifth percentile and parents' DM history. The most significant laboratory measures included glucose of at least 100 mg/dL and triglyceride level in the top fifth percentile. When BMI, SBP, and DBP were all lower than the 75th percentile and there was no parental DM, the likelihood of children developing T2DM 22 to 30 years later was only 1%. The simple office childhood measures independently associated with young-adult T2DM were SBP and BMI in the top fifth percentile along with black race. The association of childhood SBP in the top fifth percentile with young-adult T2DM may, speculatively, reflect the broader association of childhood obesity with young-adult metabolic syndrome.[22] Similarly, Nguyen et al[8] have concluded that "adverse levels of risk variables of metabolic syndrome, adiposity, and measures of glucose homeostasis accelerating since childhood characterize the early natural history of type 2 diabetes and underscore the importance of early prevention and intervention on risk factors beginning in childhood." In our study, the ability to identify the likelihood of T2DM was improved by adding childhood glucose (AUC=0.717) and triglyceride concentration (AUC=0.709). Hence, simple office and laboratory measurements and knowledge of parental diabetes usefully predicted development of T2DM 22 to 30 years later.

In univariate analysis in NGHS, the childhood laboratory predictor most significantly associated with late-teenage T2DM was insulin concentration in the top fifth percentile; development of late-teenage T2DM was 12 times more likely for childhood insulin in the top fifth percentile (6% vs 0.5% $P=.004$). Moreover, high insulin in NGHS had good sensitivity (38%) as a screening test for young-adult T2DM. When childhood BMI, SBP, and DBP were all lower than the 75th percentile and there was no parental diabetes, the likelihood of developing T2DM at age 19 years was 0.2%, and if insulin was also lower than 75th percentile, the likelihood of developing T2DM was 0.3%. Hence, simple office measurements, knowledge of parental diabetes, and childhood insulin predicted near absence of T2DM 9 years later.

In NGHS, the best simple office measures independently associated with late-teenage T2DM included SBP in the top fifth percentile and parental diabetes. Adding childhood insulin improved discriminations of T2DM, with significant explanatory variables including insulin in the top fifth percentile and parental diabetes. Similar to our findings, childhood homeostatic assessment model algorithm of insulin resistance, BMI, and HDLC were independent predictors of development of T2DM in former Louisiana schoolchildren as young adults.[8] Body mass index at age 11 years predicts individuals' history of diabetes and hypertension as well as adult obesity at age 33 years.[9] Obesity was a significant explanatory variable for T2DM in 5- to 19-year-old American Indians without diabetes at entry.[10] In 12- to 19-year-old participants in the National Health and Nutrition Examination Survey 2005-2006, adolescents with hyperinsulinemia had a 4-fold higher preva-

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lence of impaired fasting glucose and/or impaired glucose tolerance than those without.[23] Obesity and parental diabetes are associated with an increased risk of T2DM in adolescence, irrespective of ethnic background.[24,25]

In the PFS cohort, with 22- to 30-year follow-up from age 12 to 39 years, the 26-year incidence of T2DM was 4.9%, comparable with the report by the International Diabetes Federation (5.9%).[26] In PFS, the incidence of T2DM was higher in black women (9.9%) than in white women (3.4%) ($P < .05$).

Our data have practical clinical value in assessment of preteenaged and teenaged children, since children with SBP, triglyceride, BMI, and insulin in the top fifth percentile, a glucose concentration of at least 100 mg/dL, and a parent with diabetes could be targeted for primary prevention of T2DM through diet, exercise, and possibly insulin-sensitizing drug intervention, with special focus on overweight children with a positive family history of DM. The insulin-sensitizing drug metformin has been shown to decrease BMI and reduce hyperinsulinemia in overweight adolescents with[27,28] and without[29] polycystic ovary syndrome.

The close association of BMI with insulin makes it difficult to know which comes first in the pathophysiology of obesity and T2DM. We have reported that preteenage insulin resistance predicts subsequent weight gain, impaired fasting glucose, and T2DM.[14] Mosca et al[30] reported that insulin resistance in adults appears to interact with high-fat diets to increase weight gain. Kahn and Flier[31] proposed that insulin resistance–hyperinsulinemia can be caused by obesity and can contribute to development of obesity via an interaction with total and fat calories, an interaction we have reported in NGHS.[14] Lustig[32] theorized that the genesis of obesity may lie in hyperinsulinemia.

In NGHS, when fasting serum insulin was added as an explanatory variable, development of T2DM at age 19 years was best explained by high insulin and parental diabetes. In PFS, childhood SBP and BMI in the top fifth percentile, black race, and a glucose concentration of at least 100 mg/dL and less than 126 mg/dL were associated with T2DM 22 to 30 years later. This information should have practical clinical value in assessment of children with a goal of preventing T2DM (particularly in black individuals).

Our study had several limitations. Childhood insulin was measured only in NGHS and not PFS. Length of follow-up was 22 to 30 years in PFS and 9 years in NGHS. Although we excluded cases of DM with fasting blood glucose concentration of 126 mg/dL or higher and/or insulin use at childhood entry, though we recorded insulin use at follow-up, we could not differentiate type 1 from type 2 DM in insulin users at follow-up. We did not obtain blood samples for measurement of glutamic acid decarboxylase antibodies and fasting C-peptide levels, used to characterize clinically assigned DM type.[6] Although participating parents' DM was diagnosed by interview and fasting blood glucose of 126 mg/dL or higher, DM in nonparticipating parents was obtained by interview of their offspring. Our study was also limited by absence of data for postchallenge glucose and insulin. Fasting serum insulin was measured rather than determined through the euglycemic-hyperinsulinemic clamp, which is the gold standard.[33] However, as noted by Schwartz et al,[33] owing to the clamp procedure's time-consuming, invasive nature, it is difficult to use in large epidemiological studies or routine clinical practice, especially in children.

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Announcement

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