Childhood Predictors of Young-Onset Type 2 Diabetes

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OBJECTIVE—Optimal prevention of young-onset type 2 diabetes requires identification of the early-life modifiable risk factors. We aimed to do this using longitudinal data in 1,604 5- to 19-year-old initially nondiabetic American Indians.

RESEARCH DESIGN AND METHODS—For type 2 diabetes prediction, we derived an optimally weighted, continuously distributed, standardized multivariate score (zMS) comprising commonly measured metabolic, anthropometric, and vascular traits (i.e., fasting and 2-h glucose, A1C, BMI, waist circumference, fasting insulin, HDL cholesterol, triglycerides, and blood pressures) and compared the predictive power for each feature against zMS.

RESULTS—In separate Cox proportional hazard models, adjusted for age, sex, and ethnicity, zMS and each of its component risk factors were associated with incident type 2 diabetes. Stepwise proportional hazards models selected fasting glucose, 2-h glucose, HDL cholesterol, and BMI as independent diabetes predictors; individually, these were weaker predictors than zMS ($P < 0.01$). However, a parsimonious summary score combining only these variables had predictive power similar to that of zMS ($P = 0.33$). Although intrauterine diabetes exposure or parental history of young-onset diabetes increased a child's absolute risk of developing diabetes, the magnitude of the diabetes-risk relationships for zMS and the parsimonious score were similar irrespective of familial risk factors.

CONCLUSIONS—We have determined the relative value of the features of the metabolic syndrome in childhood for the prediction of subsequent type 2 diabetes. Our findings suggest that strategies targeting obesity, dysregulated glucose homeostasis, and low HDL cholesterol during childhood and adolescence may have the most success in preventing diabetes. ***Diabetes* 56: 2964–2972, 2007**

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Received for publication 22 November 2006 and accepted in revised form 22 August 2007.

Published ahead of print at http://diabetes.diabetesjournals.org on 24 August 2007. DOI: 10.2337/db06-1639.

Additional information for this article can be found in an online appendix at http://dx.doi.org/10.2337/db06-1639.

DBP, diastolic blood pressure; IED, intrauterine exposure to diabetes; ODP, offspring of a diabetic parent; OGTT, oral glucose tolerance test; ONDP, offspring of nondiabetic parents; ROC, receiver operating characteristic; ROC AUC, area under the ROC curve; SBP, systolic blood pressure; zMS, standardized multivariate score.

Excess global mortality attributable to type 2 diabetes in the year 2000 is estimated at one million deaths in developing nations and 1.9 million deaths in developed nations, or 2–8% of all deaths globally (1). Although conventionally type 2 diabetes has been considered a disease of adulthood, its occurrence during youth is increasingly common (2–7). Children exposed to diabetes in utero are at much greater risk of becoming obese (8,9) and developing type 2 diabetes (9–11). Furthermore, individuals who develop type 2 diabetes in childhood and adolescence develop retinopathy and nephropathy at rates comparable with those of later-onset diabetes and by consequence have a substantial risk for microvascular complications at young ages (12). Thus, the prevention of young-onset type 2 diabetes presents a particularly important yet difficult challenge.

The optimal strategy for preventing any disease requires knowledge of its modifiable risk factors. In adult-onset diabetes, the risk factors include metabolic and anthropometric parameters such as hyperinsulinemia, impaired glucose regulation, obesity, and dyslipidemia (13), which when clustered together are often referred to as the metabolic syndrome. The strongest risk factors identified in adult Pima Indians are parental diabetes, BMI, insulin resistance, and impaired insulin secretion (10,14,15). Among Pima Indian children and adolescents free from diabetes, future type 2 diabetes is predicted by weight relative to height and concentrations of serum insulin and plasma glucose (16).

Few studies have explored the prospective relationships of risk factors related to the metabolic syndrome in childhood with subsequent type 2 diabetes, and little is known of the interdependence of these risk factors. Here, we explored the risk of young-onset type 2 diabetes associated with conventional anthropometric and metabolic traits in Pima Indian children and adolescents who had participated in a prospective cohort study. We also compared the ability of these risk factors, singly and in combination, to predict type 2 diabetes, and we examined the potential effect-modifying role of parental diabetes.

RESEARCH DESIGN AND METHODS

All residents of a geographic area of the Gila River Indian Community in Arizona ≥5 years old were invited to participate in a longitudinal study of diabetes. Participants selected for the present analysis consisted of 1,604 children and adolescents free from diabetes, the majority of whom are Pima or Tohono O'odham Indians (17,18), who had one or more research examination during childhood or adolescence (i.e., ≥5 and <20 years old) and one or more follow-up examination at which diabetes was assessed. During the time frame of the present study, 2,828 nondiabetic children and adolescents were examined: 300 of these were excluded from the present analyses because data were missing for one of the predictor variables, and 924 were excluded because they did not have a follow-up examination. Those without follow-up tended to have been seen later in the study period than those with follow-up; they were also older and more likely to be male, but, accounting for these factors, there were no significant differences in metabolic variables.

TABLE 1
Participant characteristics by age

Variable	5–9 years	10–14 years	15–19 years	5–19 years
n	529	936	653	1,604
Sex (% male)*	50	46	40	46
Age (years)	8.0 ± 1.3	12.2 ± 1.4	17 ± 1.4	12.1 ± 3.7
Height (cm)	130.9 ± 9.5	155.1 ± 9.7	165.8 ± 7.9	149.8 ± 16.7
Weight (kg)	36.2 ± 12.5	63.3 ± 20.8	84.8 ± 22.1	59.1 ± 26
BMI (kg/m^2)	20.7 ± 4.9	25.8 ± 6.5	30.7 ± 7.2	25.1 ± 7.2
% Overweight	22	26	32	28
% Obese	37	43	44	39
Waist (cm)	66.1 ± 13	82.6 ± 15.8	95.4 ± 16.6	80 ± 18.8
SBP (mmHg)	97.2 ± 12.1	109.4 ± 11.8	114.7 ± 12.3	106.6 ± 13.9
DBP (mmHg)	55 ± 9.4	59.6 ± 9.5	64.2 ± 9.8	59 ± 10
Fasting glucose (mmol/l)	4.7 ± 0.3	4.9 ± 0.4	4.9 ± 0.4	4.9 ± 0.4
2-h glucose (mmol/l)	5.3 ± 1.1	5.8 ± 1.3	5.7 ± 1.4	5.6 ± 1.3
A1C (%)	4.9 ± 0.4	5.1 ± 0.4	5.1 ± 0.4	5.1 ± 0.4
Cholesterol (mmol/l)	3.97 ± 0.69	3.95 ± 0.72	4.13 ± 0.76	4 ± 0.72
Triglycerides (mmol/l)†	0.69 (0.54–1.02)	0.89 (0.65–1.33)	1.06 (0.72–1.53)	0.87 (0.57–1.27)
HDL-C (mmol/l)	1.21 ± 0.29	1.11 ± 0.26	1.08 ± 0.26	1.13 ± 0.28
IED (%)‡	9	6	4	6
ODP (%)§	43	35	27	33

Data are means ± SD, percentages, or medians (25th–75th percentiles). The variables "% Overweight" and "% Obese" represent the proportion of individuals whose BMI is either >85th–97th percentiles (overweight) or >97th percentile (obese), based on Centers for Disease Control and Prevention 2000 U.S. population statistics (ref. 42) for age and sex. ‡IED data available for 509 of those aged 5–9 years, 875 of those aged 10–14 years, 601 of those aged 15–19 years, and 1,492 of those aged 5–19 years. §ODP data available for 275 of those aged 5–9 years, 466 of those aged 10–14 years, 332 of those aged 15–19 years, and 798 of those aged 5–19 years. HDL-C, HDL cholesterol.

Participants ≥18 years old gave written informed consent, whereas for participants <18 years old, written informed consent was given by a parent or guardian and written assent given by the participant. The Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases approved the study.

In the present analyses, the extent to which variables measured at an initial baseline examination predict the incidence of future diabetes was assessed. For analysis of the whole group (age 5–19 years), the first examination at which an individual was nondiabetic and at which all relevant predictor variables had been measured was taken as the baseline examination. The period of follow-up extended from this baseline examination until the diagnosis of diabetes or until the last examination, whichever came first. In addition to analysis for the whole group, analyses were conducted in 5-year age bands (5–9, 10–14, and 15–19 years) based on age at the baseline examination. In these analyses, an individual's first nondiabetic examination within the specified age range was taken as the baseline examination. Thus, individuals could appear in multiple age-groups if they had a nondiabetic examination when they were the relevant age and one or more subsequent examination. Parental diabetes was determined from examinations of both parents within the longitudinal study. For a child to be considered an offspring of a diabetic parent (ODP), one or more parent required a diagnosis of diabetes before age 30 years. For the children who were classified offspring of nondiabetic parents (ONDP), both parents required a nondiabetic examination at ≥30 years of age, irrespective of whether diabetes was diagnosed later in life. Individuals whose parents did not meet either set of criteria were considered of unknown status. Children were defined as having intrauterine exposure to diabetes (IED) if the mother had been diagnosed with diabetes before the child's birth, regardless of the mother's age at diagnosis. In eight individuals, IED occurred although the mother was >30 years old at onset of diabetes. Therefore, these children are classified as ONDP.

Measurements. Participants attended the clinic after an overnight fast. They underwent a 75-g oral glucose tolerance test (OGTT) for assessment according to World Health Organization diagnostic criteria (19). The participant was classified with type 2 diabetes if the fasting plasma glucose concentration was >7.0 mmol/l, the 2-h plasma glucose concentration was >11.1mmol/l, or there was an existing clinical diagnosis (as assessed by medical chart review). Standard anthropometric data were collected by trained observers with participants in lightweight clothing and no shoes as previously described in detail (10,12,16). No measures of puberty were available. Metabolic variables were measured according to previously described methods (10,12,16).

Statistical analysis. Analyses were performed using SAS software (V8.02; SAS Institute, Cary, NC). Participant characteristics are presented as the arithmetic mean ± SD or as the median (25th–75th) percentiles if the variable was not of Gaussian distribution. If necessary to reduce skewness, data were approximately normalized via logarithmic transformation. Proportional hazards models were used to test the association between each childhood metabolic trait and development of young-onset diabetes (i.e., age of diagnosis <30 years of age), with control for age at baseline examination, sex, and fraction of Pima heritage. The validity of the proportionality assumption was tested for each variable by including a time-dependent interaction term (20). To facilitate comparisons among variables, the hazard rate ratio (HRR) was calculated for a 1-SD difference for each of the variables. To compare each of the variables with an optimal prediction score (standardized multivariate score [zMS]), we fit a proportional hazards model that included all of the predictor variables (i.e., fasting and 2-h glucose, A1C, BMI, waist circumference, fasting insulin, HDL cholesterol, triglycerides, systolic blood pressure [SBP], and diastolic blood pressure [DBP]) in addition to age, sex, and heritage. The ability of zMS to predict diabetes was then compared with that for each of the individual variables by the likelihood ratio test that compares the full model with that containing only the individual variable, age, sex, and heritage. The HRR associated with zMS was computed for a standardized sum of the individual variables weighted by their regression coefficients in the zMS model. Parsimoniously predictive subsets of the variables were identified by a backward stepwise procedure. All potential predictor variables were included in the initial model, and the weakest predictor was sequentially eliminated until all remaining variables were retained at $P < 0.05$; (age, sex, and heritage were not made available to the stepwise procedure and are, thus, forcibly included in all models). To assess the extent that this submodel captured the information contained in the fully optimized model containing all variables, these two models were compared by the likelihood ratio test. These procedures were undertaken in each age stratum and in the entire dataset containing all children (i.e., 5–19 years of age). For children with data for parental diabetes status, we calculated HRRs for each variable stratified by parental diabetes and tested for interactions between parental diabetes status and each variable.

Although the likelihood ratio test can compare models in which one is a subset of the other, it does not compare models that are not subsets. The comparison of pairs of variables in their ability to predict diabetes was, therefore, conducted by analysis of receiver operating characteristic (ROC) curves. To adjust for potentially confounding variables and to account for variable follow-up time, ROC curves were calculated by a modification of the method of Le, which makes use of the probability of an event, as predicted by the model, for each individual (21). The predicted probability that an individual would develop diabetes, given his or her follow-up time, was calculated on the basis of a proportional hazards model that included age, sex, fraction of Pima heritage, and the relevant predictor variable(s). This prediction score is based on the regression coefficients derived from the model, an individual's values for the predictor values, follow-up time for the individual,

TABLE 2
Correlation coefficients for each of the component features of the zMS in children aged 5–19 years

	BMI	Waist	Fasting glucose	2-h glucose	SBP	DBP	Triglycerides	HDL-C	A1C
Waist	0.94*								
Fasting glucose	0.21*	0.24*							
2-h glucose	0.35*	0.36*	0.42*						
SBP	0.29*	0.32*	0.18*	0.18*					
DBP	0.19*	0.18*	0.03	0.04	0.30*				
Triglycerides	0.36*	0.38*	0.21*	0.35*	0.20*	0.11*			
HDL-C	−0.37*	−0.39*	−0.11*	−0.17*	−0.13*	−0.05†	−0.37*		
A1C	0.24*	0.26*	0.18*	0.19*	0.14*	0.04	0.10*	−0.12*	
Fasting insulin	0.51*	0.52*	0.34*	0.44*	0.22*	0.13*	0.36*	−0.29*	0.20*

Data are Pearson correlation coefficients; $n = 1{,}604$. Level of statistical significance: *$P < 0.0001$; †$P < 0.05$. HDL-C, HDL cholesterol.

and the baseline survival function (22). The methods of DeLong et al. (23) were used to calculate area under the ROC curve (ROC AUC) associated with each prediction score along with its SE and to assess the statistical significance of the difference in the ROC AUCs for pairs of variables. Simulation studies suggest that this method is appropriate for the present data (supplementary Table 1 of the online appendix [available at http://dx.doi.org/10.2337/db06-1639]). However, the calculation of the AUC in survival analysis setting is complicated and can depend on how follow-up time is incorporated in the model (24,25); furthermore, the ROC AUC is nonparametric and may not be the most sensitive measure of model fit (26). Therefore, we also compared models with Akaike's information criterion (27) and used a permutation procedure to test the statistical significance of differences in Akaike's information criterion for pairs of variables. This analysis produced similar conclusions to the ROC analysis (as shown in supplementary Table 2, which is detailed in the online appendix).

RESULTS

Participant characteristics and correlations among variables. Table 1 shows characteristics for children (5–9 years old), young adolescents (10–14 years old), and older adolescents (15–19 years old). Analyses were conducted by age-group and in all groups combined (i.e., 5–19 years old). Correlations among the metabolic variables, partialled for age and sex, are shown in Table 2. The correlations for most pairs of variables were statistically significantly different from 0. The highest correlation was between BMI and waist, whereas correlations of DBP with the other variables tended to be modest.

Prediction of young-onset type 2 diabetes

Age-stratified analyses of diabetes incidence. Data on 529 children, 936 young adolescents, and 653 older adolescents without diabetes were available for analyses. During follow-up, there were 22 incident cases of diabetes in children (median 5.2 years follow-up; incidence of 7.5/1,000 person-years), 45 incident cases in young adolescents (median 4.8 years follow-up; incidence of 9.2/1,000 person-years), and 53 incident cases in older adolescents (median 4.4 years follow-up; incidence of 16.4/1,000 person-years).

In separate Cox proportional hazard models, all of the variables predicted diabetes except fasting glucose in children, SBP and DBP in young adolescents, and SBP in older adolescents (Table 3). In children, the highest HRR for an individual predictor trait was for waist circumference, whereas fasting glucose was the weakest predictor of diabetes. In young adolescents, the highest HRR was observed for 2-h glucose, and DBP was the weakest predictor. In older adolescents the strongest predictors of diabetes were waist circumference, BMI, 2-h glucose, fasting glucose, and A1C, whereas the weakest predictors were SBP and DBP. The HRR for zMS in all age-groups was higher than that for any individual variable, as expected, because it is derived to optimize its predictive ability.

Table 4 shows, in children, the ROC AUC for each predictor trait and P values for pairwise comparisons between them. The strongest individual predictors of diabetes were waist circumference and BMI, which did not differ significantly in predictive power from zMS. Other predictor variables were significantly weaker predictors of diabetes than zMS, waist circumference, or BMI. In children, a stepwise proportional hazards model selected

TABLE 3
HRRs for risk of young-onset type 2 diabetes associated with a 1-SD difference in the predictor variable

	5–9 years ($n = 529$)			10–14 years ($n = 936$)			15–19 years ($n = 620$)			5–19 years ($n = 1{,}604$)		
	HRR	95% CI	P	HRR	95% CI	P	HRR	95% CI	P	HRR	95% CI	P
zMS	6.8	(3.9–12.1)	<0.01	3.7	(2.8–4.9)	<0.01	3.1	(2.3–4.1)	<0.01	3.4	(2.7–4.1)	<0.01
Waist	4.4	(2.7–7.1)	<0.01	2.1	(1.6–2.7)	<0.01	1.9	(1.5–2.4)	<0.01	2.2	(1.8–2.7)	<0.01
BMI	4.1	(2.6–6.3)	<0.01	2.1	(1.6–2.6)	<0.01	2.0	(1.5–2.5)	<0.01	2.2	(1.6–2.2)	<0.01
Fasting glucose	1.4	(0.9–2.2)	0.13	2.2	(1.6–2.8)	<0.01	2.0	(1.5–2.5)	<0.01	2.0	(1.7–2.5)	<0.01
2-h glucose	2.3	(1.6–3.2)	<0.01	2.6	(2.1–3.2)	<0.01	2.1	(1.7–2.8)	<0.01	2.4	(2–2.8)	<0.01
A1C	1.8	(1.1–2.8)	0.01	2.5	(1.8–3.5)	<0.01	1.9*	(1.4–2.6)	<0.01	1.9	(1.5–2.3)	<0.01
Fasting insulin	1.5	(1.2–1.9)	<0.01	1.6	(1.4–1.9)	<0.01	1.4	(1.2–1.6)	<0.01	1.5	(1.4–1.7)	<0.01
Triglycerides	2.1	(1.5–2.9)	<0.01	1.4	(1.2–1.8)	<0.01	1.6	(1.3–1.9)	<0.01	1.5	(1.3–1.8)	<0.01
HDL-C	0.3	(0.1–0.5)	<0.01	0.5	(0.3–0.7)	<0.01	0.5	(0.4–0.8)	<0.01	0.5	(0.4–0.6)	<0.01
SBP	1.8	(1.2–2.7)	<0.01	1.3	(0.9–1.8)	0.12	1.2	(0.9–1.6)	0.18	1.3	(1.1–1.6)	<0.01
DBP	1.7	(1.1–2.5)	<0.01	1.0	(0.8–1.4)	0.86	1.4	(1.1–1.8)	0.01	1.4	(1.1–1.7)	<0.01

Data are stratified by age. *In this model A1C violated the assumption of proportionality. Because the model is intended for prediction of disease onset and not to optimize the point estimate, we present the untruncated HRR. If follow-up time is truncated to 8 years, which is where the model no longer violates the proportionality assumption, the HRR is 2.4 (95% CI 1.7–3.2). Predictor variables were standardized (z score) within 1-year age strata. HDL-C, HDL cholesterol.

TABLE 4
Pairwise comparisons for ROC AUCs by age-groups

	zMS	BMI	Waist	Fasting glucose	2-h glucose	Fasting insulin	A1C	HDL-C	Triglycerides	SBP	DBP
5–9 years											
AUC (SE)	0.90 (0.03)	0.85 (0.04)	0.88 (0.03)	0.63 (0.05)	0.77 (0.05)	0.70 (0.06)	0.68 (0.05)	0.75 (0.05)	0.71 (0.05)	0.66 (0.06)	0.65 (0.06)
zMS		0.09	0.13	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
BMI			0.12	<0.01	0.04	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Waist				<0.01	0.02	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Fasting glucose					<0.01	0.02	0.14	<0.01	0.03	0.41	0.58
2-h glucose						0.02	0.03	0.47	0.09	0.01	<0.01
Fasting insulin							0.63	0.09	0.66	0.25	0.17
A1C								0.11	0.48	0.57	0.38
HDL									0.18	<0.01	<0.01
Triglycerides										0.17	0.19
SBP											0.76
10–14 years											
AUC (SE)	0.82 (0.03)	0.63 (0.05)	0.64 (0.04)	0.64 (0.05)	0.74 (0.04)	0.63 (0.05)	0.68 (0.04)	0.62 (0.05)	0.55 (0.05)	0.54 (0.05)	0.53 (0.05)
zMS		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
BMI			0.24	0.90	0.02	0.87	0.11	0.58	<0.01	<0.01	<0.01
Waist				0.93	0.02	0.60	0.18	0.32	<0.01	<0.01	<0.01
Fasting glucose					<0.01	0.75	0.24	0.60	0.01	<0.01	<0.01
2-h glucose						<0.01	0.14	<0.01	<0.01	<0.01	<0.01
Fasting insulin							0.11	0.73	<0.01	<0.01	<0.01
A1C								0.06	<0.01	<0.01	<0.01
HDL									<0.01	<0.01	<0.01
Triglycerides										0.36	0.05
SBP											0.34
15–19 years											
AUC (SE)	0.76 (0.03)	0.64 (0.04)	0.65 (0.04)	0.66 (0.04)	0.68 (0.04)	0.61 (0.04)	0.66 (0.04)	0.63 (0.04)	0.63 (0.04)	0.58 (0.04)	0.59 (0.04)
zMS		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
BMI			0.45	0.47	0.22	0.10	0.34	0.61	0.54	<0.01	0.02
Waist				0.62	0.30	0.04	0.50	0.44	0.37	<0.01	<0.01
Fasting glucose					0.46	0.02	0.83	0.18	0.22	<0.01	<0.01
2-h glucose						0.01	0.55	0.04	0.04	<0.01	<0.01
Fasting insulin							0.03	0.23	0.36	0.01	0.18
A1C								0.13	0.17	<0.01	<0.01
HDL									0.83	<0.01	0.02
Triglycerides										<0.01	0.02
SBP											0.17
5–19 years											
AUC (SE)	0.78 (0.02)	0.68 (0.03)	0.68 (0.03)	0.66 (0.03)	0.72 (0.03)	0.64 (0.03)	0.65 (0.03)	0.64 (0.01)	0.61 (0.03)	0.58 (0.03)	0.58 (0.03)
zMS		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
BMI			0.23	0.35	0.08	0.03	0.10	0.04	<0.01	<0.01	<0.01
Waist				0.21	0.14	0.01	0.06	0.01	<0.01	<0.01	<0.01
Fasting glucose					<0.01	0.43	0.63	0.51	0.02	<0.01	<0.01
2-h glucose						<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Fasting insulin							0.80	0.91	0.03	<0.01	<0.01
A1C								0.86	0.07	<0.01	<0.01
HDL									0.02	<0.01	<0.01
Triglycerides										<0.01	0.02
SBP											0.32

Data are n (SE) or P values for the tests comparing the models. Comparisons between zMS and individual variables were conducted by the likelihood ratio test, whereas comparisons between individual variables were conducted by comparison of the ROC AUCs. Predictor variables were standardized (z score) within 1-year age strata. HDL-C, HDL cholesterol.

TABLE 5
Pairwise comparisons of the full model with each partial model derived from a stepwise regression procedure

	Model	AUC (SE)	χ^2 (d.f.)	*P*
5–9 year olds	Full model (zMS)	0.90 (0.02)	0	—
	Waist	0.88 (0.03)	13.91 (9)	0.13
10–14 year olds	Full model (zMS)	0.82 (0.03)	0	—
	BMI, A1C, 2-h glucose	0.79 (0.03)	8.81 (7)	0.27
15–19 year olds	Full model (zMS)	0.76 (0.03)	0	—
	Waist, A1C, 2-h glucose	0.74 (0.03)	9.24 (7)	0.24
5–19 year olds	Full model (zMS)	0.78 (0.02)	0	—
	Fasting glucose, 2-h glucose, BMI, HDL-C	0.77 (0.02)	6.95 (6)	0.33

Data are stratified by age-group. *P* value is for pairwise comparison of full model with partial model. All models include terms for age, sex, and heritage. Predictor variables were standardized (*z* score) within 1-year age strata. The value of the likelihood ratio test for comparison with the full model is given by χ^2 with d.f. in parentheses. *P* values are calculated by this likelihood ratio test. HDL-C, HDL cholesterol.

waist circumference as the sole predictor of incident diabetes with age, sex, and heritage forced into the model.

Table 4 shows, in young adolescents, the ROC AUC for each trait and *P* values for pairwise comparisons between them. The strongest individual predictor of diabetes was 2-h plasma glucose. However, 2-h plasma glucose was a significantly weaker predictor of incident diabetes than zMS, as were all other predictor variables. BMI and waist circumference did not differ significantly in ability to predict diabetes; 2-h plasma glucose was a significantly better predictor than was fasting plasma glucose. The stepwise proportional hazards model selected 2-h plasma glucose, A1C, and BMI as significant independent predictors of incident diabetes. The predictive properties for this partial model and for zMS are shown in Table 5. This model, which contains all three independent predictors, predicted incident diabetes with precision similar to that of zMS.

Table 4 shows, in older adolescents, the ROC AUC for each trait and *P* values for pairwise comparisons between them. The strongest individual predictor of diabetes was 2-h plasma glucose. However, 2-h plasma glucose was a significantly weaker predictor of incident diabetes than zMS, as were all other predictor variables. Two-hour plasma glucose, fasting plasma glucose, and A1C were all similar in their ability to predict diabetes. BMI and waist circumference were also similar, as were HDL cholesterol and triglycerides. The stepwise proportional hazards model selected 2-h plasma glucose, A1C, and waist circumference as the predictors of incident diabetes. This partial summary score, which contains all three individual predictors, was not a significantly weaker predictor of incident diabetes than zMS (Table 5).

All subjects (aged 5–19 years old). The entire dataset included data on 1,604 children and adolescents without diabetes, with 92 incident cases of diabetes during follow-up (median 5.5 years' follow-up; incidence of 10.2/1,000 person-years). In separate Cox proportional hazard models, significant associations with incident diabetes were observed for all predictor traits. The strongest single predictors of diabetes in 5- to 19-year-old subjects were 2-h glucose, waist circumference, and BMI, whereas the weakest were DBP and SBP (Table 3).

Table 4 shows the ROC AUC for each predictor trait and *P* values for pairwise comparisons between them. The strongest predictors of diabetes in all subjects were waist circumference, BMI, and 2-h glucose. However, these traits were significantly weaker predictors of incident diabetes than zMS, as were all other predictor variables. Two-hour glucose was a significantly better predictor than fasting glucose or A1C. The weakest predictors of diabetes in the combined data were DBP and SBP.

The stepwise proportional hazards model selected fasting glucose, 2-h glucose, HDL cholesterol, and BMI as the significant predictors of incident diabetes. Table 5 shows the comparison of predictive properties for the partial summary score comprising these variables versus those for zMS. By comparison with zMS, the partial model predicted incident diabetes with comparable precision to the full model. A reduced model, comprising only 2-h glucose, BMI, and HDL cholesterol, was also of comparable precision to zMS ($P = 0.11$).

Influence of parental history of young-onset diabetes (aged 5–19 years). Parental history of young-onset (age <30 years) diabetes was available for a subsample of 798 of the total population of children and adolescents. In total, 267 (33%) offspring had one or more parent who developed diabetes before the age of 30 years (ODP), whereas the parents of 531 offspring had not developed diabetes at this age (ONDP). The overall incidence of diabetes for the ODP group was 24.2/1,000 person-years and 8.9/1,000 person-years for the ONDP group. The median ages of diabetes onset for the parents in this study were 35.1 years for the mothers and 37.0 years for the fathers. Among the parents who had not developed diabetes by the age of 30 years, the incidence after 30 years of age was 42.6 cases/1,000 person-years.

Having a parent with diabetes before the age of 30 is in itself a major risk factor for diabetes in offspring; the HRR for parental diabetes (yes/no) in the model adjusted for age, sex, and heritage was 3.6 (95% CI 2.2–6.0, $P < 0.0001$) for the whole cohort. The full model containing zMS plus parental diabetes fit significantly better than a model including only age, sex, heritage, and parental diabetes ($P < 0.01$). The full model including parental diabetes fit significantly better than the full model without parental diabetes ($P < 0.01$).

We tested for interactions between parental history of diabetes and predictor variables on the risk of diabetes in the offspring (Fig. 1). In the interaction models, parental history modified the diabetes risk relationships for DBP, where the magnitude of the effect (per SD unit of predictor variable) was stronger in ONDP than in ODP. Figure 1 also shows the incidence of diabetes by tertiles of each risk factor in the ODP and ONDP groups. For all risk factors, the incidence of diabetes was greatest in the ODP group. With the exception of HDL cholesterol, the incidence of

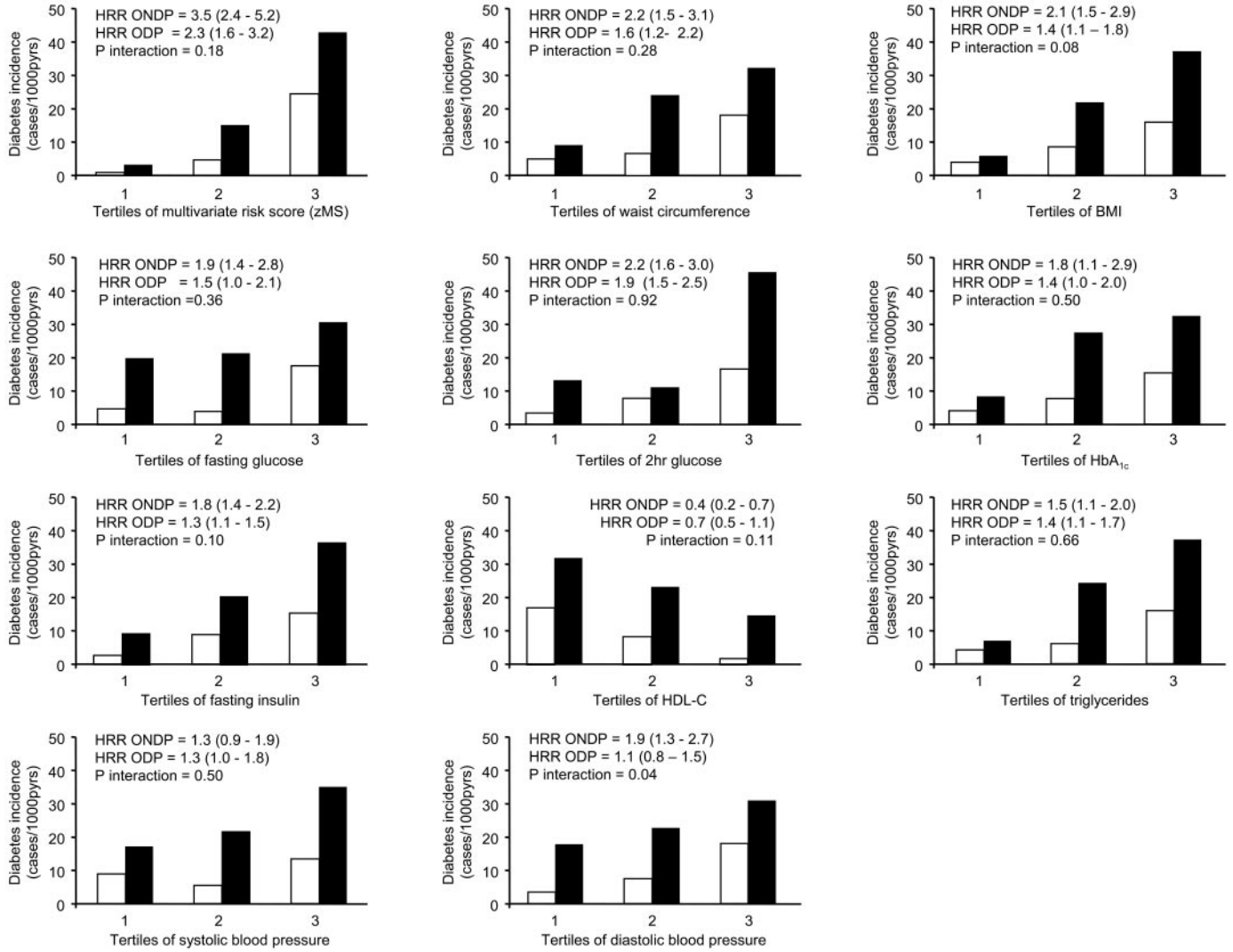

FIG. 1. Interaction between parental history of young-onset (<30 years of age) type 2 diabetes and offspring metabolic, anthropometric, and vascular traits on risk of young-onset type 2 diabetes in the offspring. Data are for offspring aged 5.0–19.9 years (n = 267 ODP and n = 531 ONDP). HRR is per standardized unit with 95% CI. P interaction, P value for interaction term of variable by parental diabetes status. Data are adjusted for age, sex, and fraction of Indian heritage and divided into tertiles for each variable. Incidence of diabetes was then calculated for each tertile stratified by diabetes status of the parents. □, offspring of parents free from type 2 diabetes at 30 years of age (ONDP); ■, offspring of at least one parent who developed type 2 diabetes by 30 years of age (ODP).

diabetes was greatest in the highest tertile of each predictor variable.

Influence of IED (5–19 years). There were 92 children in the IED group, of whom 19 developed diabetes over a median follow-up of 4.9 years (incidence 39.9/1,000 person-years), and 1,399 children in the non-IED group, of whom 68 developed diabetes during a median follow-up of 5.6 years (incidence 8.5/1,000 person-years). The HRR for IED was 5.9 (95% CI 3.3–10.4) compared with that for no IED. There were statistically significant interactions between IED and fasting glucose ($P < 0.01$) and A1C ($P = 0.02$) as predictors for diabetes such that the relationships were stronger in non-IED children.

DISCUSSION

Although type 2 diabetes has conventionally been considered a disease with an age of onset >40 years, it is now becoming increasingly prevalent at earlier ages (2–7). In high-risk populations, such as American Indians and those exposed to diabetes in utero, the prevalence of type 2 diabetes during youth exceeds the rates during adulthood in low-risk populations (28). Here, we sought to determine the independent modifiable risk factors in childhood that predict the development of young-onset type 2 diabetes (i.e., onset <30 years of age).

In 5- to 9-year-old subjects, waist circumference was the strongest and single significant modifiable predictor of diabetes in multivariate analyses, with almost the same predictive power as all metabolic, anthropometric, and vascular predictors combined. In 10- to 14-year-old subjects, the strongest independent modifiable predictors were 2-h glucose, BMI, and A1C, whereas in the 15- to 19-year-old subjects, the strongest predictors were 2-h glucose, waist circumference, and A1C. As with waist circumference in 5- to 9-year-old subjects, in combination, these variables predicted diabetes almost as well as the

model in which all variables were used. When age-groups were combined (i.e., 5–19 years), the independent modifiable predictors were BMI, fasting glucose, 2-h glucose, and HDL cholesterol. The implications are that whereas obesity alone is adequate to assess risk for future diabetes in young children, it may be necessary to measure both obesity and glycemia to accurately ascertain risk in adolescents, and HDL cholesterol was important when considering all age-groups. Although blood pressure and serum insulin were individually predictive of diabetes, they did not provide additional information once obesity, glycemia, and lipids were accounted for. Similar conclusions were obtained by a factor analysis in adult Pimas that showed that factors representing glucose and lipid metabolism and body size were each independently associated with incident diabetes, whereas a blood pressure factor was not (29).

We purposefully do not define thresholds for each predictor trait above and below which children can be considered to be at risk or not at risk of diabetes because our data indicated that the risk relationships are continuous. However, because we recognize that the absence of thresholds makes it difficult to apply the findings of this study to the clinical setting, we provide a risk-score calculator, in which a child's risk of type 2 diabetes can be estimated relative to the average child in this study (http://intramural.niddk.nih.gov/research/T2Diabetescalc/startPage.shtml and the online appendix).

Although parental history of young-onset diabetes certainly increased a child's risk for future diabetes, there was little in the way of effect modification, with DBP being the only trait to show significant interaction. When IED was considered, there were significant interactions with fasting glucose and A1C, which were both poor predictors of diabetes in children exposed to diabetes in utero. In addition, conclusions of the present analysis were not different when parental diabetes or IED were included in the models (data not shown). There are a number of explanations for why fasting glucose is a somewhat weaker predictor of diabetes than 2-h glucose in these data. For example, it is possible that not all children were truly fasted when the examination took place, which would reduce the predictive power of the measure. It is also possible that in children, defects in glucose homeostasis are only evident when the β-cells are challenged; under fasting (less stressful) conditions, the mechanisms for glucose regulation may be able to cope adequately. This is likely particularly true in the youngest prepubertal children, who have low demands on β-cell function. During puberty, insulin action worsens and fasting glucose, fasting insulin, and insulin secretion increase (30). In young and old adolescents, milder degrees of β-cell failure may only emerge during and after puberty, making glucose concentrations more predictive of diabetes risk.

Our findings expand on previous studies of Pima Indian children. In 1,258 Pima Indian children aged 5–19 years, some of whom are included in the present analyses, McCance et al. (16) reported associations between incident type 2 diabetes during an average of 8.4 years' follow-up and glucose intolerance, fasting insulin, relative weight, and parental diabetes. Of these, 1,120 children had one or more parent who developed diabetes at some stage during follow-up, and 101 of these children were themselves diagnosed with diabetes at follow-up. Of the 138 children who had no parental history of diabetes, only one was diagnosed with diabetes at follow-up. The current study focuses on a more recent birth cohort but has fewer incident cases of diabetes and a shorter mean follow-up time than the study by McCance et al. (16) because the subjects here were restricted to those with HDL cholesterol and triglycerides, the measurement of which only began in 1993. We also defined parental diabetes differently by using diabetes before the age of 30 years in a parent and requiring a nondiabetic examination in both parents after the age of 30 years for an individual to be classified as offspring of parents without diabetes.

Data elsewhere relating metabolic risk clustering in childhood with incident diabetes are scarce. However, several studies have investigated the prevalence of the metabolic syndrome (16,31–39) and the cross-sectional relations between obesity (34,39), insulin sensitivity (35), and the metabolic syndrome in children. Using factor analysis in data on 4,522 children and adults (5–38 years old) from the Bogalusa Heart Study, Srinivasan et al. (38) identified two metabolic syndrome clusters, the first comprising fasting insulin, HDL cholesterol, triglycerides, and ponderal index and the second comprising fasting insulin and blood pressures. These data were subsequently used to assess the relationships between metabolic syndrome clusters and cardiovascular disease risk in adulthood; the strongest associations with heart disease were for insulin resistance and obesity (32,33).

Many of the existing studies of metabolic syndrome in children have used adaptations of adult criteria. Because these definitions are not supported by etiological data in children, they are of uncertain relevance and may lack sensitivity. An additional consideration, common to all studies of metabolic syndrome, is the need to consider the colinearity of predictor variables, which may give rise to uninterpretable effect estimates when highly correlated predictors are included in the same model. Finally, most published data on metabolic syndrome in children are cross-sectional and therefore inadequate for determining the temporal relationships between predictors and outcome variables. In the present study, we compared an optimally fit model with either individual or combinations of predictor variables to determine which variable, or combination, is most predictive of diabetes. This analysis uses global predictive properties of the models, which unlike the parameter estimates, are not sensitive to multicolinearity. This approach also permits the use of continuously distributed data rather than categorical scores of uncertain pathophysiological relevance and reduced statistical power. In addition, one can test whether individual variables that appear to measure the same general phenomenon have statistically significant differences in predictive properties. For example, the most parsimonious model in all of the age-groups included either waist circumference or BMI, but because there were no significant differences between the ROC AUCs for these particular variables, the choice of which obesity measure to perform could be based on convenience. On the other hand, 2-h glucose was a significantly stronger predictor than other measures of glycemia in young adolescents and in all age-groups combined, indicating that an OGTT may be required for optimal prediction in these groups.

Longitudinal data concerning the childhood risk factors for type 2 diabetes are sparse in part because young-onset type 2 diabetes remains relatively uncommon even in high-risk populations. The present study is limited by the small number of incident cases, particularly among the youngest children, and it is possible that some models are

overfitted because of this. The population studied is also more susceptible to type 2 diabetes than most, with a high prevalence of parental diabetes and IED, and thus does not reflect the general U.S. population. Nonetheless, the risk relationships identified here are generally stronger in children whose parents were free from diabetes at a young age. Furthermore, in the past, observations within American Indian cohorts have subsequently been replicated in lower-risk populations (6,40,41). Thus, the evidence presented here provides data on target risk factors needed for the design of interventions aimed at preventing young-onset type 2 diabetes. Whether such strategies are specific to American Indian children or can be generalized to other populations in the future remains to be determined.

As reported previously, IED and family history of diabetes are major risk factors for diabetes in offspring (9–11). Thus, although our data suggest that strategies designed to lower lipids, glucose, and adiposity in childhood may help prevent diabetes, it is likely that optimal prevention will require parallel strategies that focus on reducing the inherited risk factors, such as hyperglycemia during pregnancy. For either purpose, intensive lifestyle intervention is likely to be among the most effective of the available preventive therapies.

In summary, in young children it may be possible to predict young-onset type 2 diabetes using simple and noninvasive measures of obesity, whereas in adolescents, an OGTT and measures of HDL cholesterol and A1C may be necessary. Our findings may prove informative for prevention strategies targeting the early-life risk factors for type 2 diabetes. They also point to the features of a childhood-specific metabolic syndrome score that are relevant for type 2 diabetes prediction.

ACKNOWLEDGMENTS

This research was supported by the National Institute of Diabetes and Digestive and Kidney Diseases intramural research program.

We thank members of the Gila River Indian Community and other volunteers for participating in this study, the staff of the Diabetes Epidemiology and Clinical Research Section for conducting the examinations, and Dr. David J. Pettitt for advice.

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