Diabetes Screening With Hemoglobin A_{1c} Versus Fasting Plasma Glucose in a Multiethnic Middle-School Cohort

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OBJECTIVE—To characterize middle-school students from the HEALTHY study with glycemic abnormalities, specifically high-risk hemoglobin A_{1c} (A1C) (hrA1C; A1C = 5.7–6.4%) and impaired fasting glucose (IFG; fasting plasma glucose [FPG] = 100–125 mg/dL).

RESEARCH DESIGN AND METHODS—History was collected by self-report, physical measurement was collected by trained study staff, and fasting blood was drawn by trained phlebotomists and analyzed centrally.

RESULTS—At baseline, among 3,980 sixth graders, 128 (3.2%) had hrA1C and 635 (16.0%) had IFG. Compared with A1C <5.7%, hrA1C was associated with non-Hispanic black race/ethnicity, family history of diabetes, and higher measurements of BMI, waist circumference, and fasting insulin. Compared with FPG <100 mg/dL, IFG was associated with Hispanic ethnicity; increased BMI, waist circumference, and fasting insulin; higher frequency of high blood pressure; and higher mean triglycerides. Two years later, children with hrA1C persisted as hrA1C in 59.4%, and one child (0.8%) developed A1C ≥6.5%; children with IFG persisted with IFG in 46.9%, and seven children (1.1%) developed FPG ≥126 mg/dL. Those with hrA1C compared with IFG had a higher BMI in sixth grade, which persisted to eighth grade.

CONCLUSIONS—In the HEALTHY study cohort, hrA1C and IFG define different groups of youth with differentially increased diabetes risk markers. IFG is approximately fivefold more common, but hrA1C is more persistent over time. Optimal screening strategies for diabetes in youth remain unresolved.

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The HEALTHY study was conducted to determine if a middle-school–based intervention program could reduce risk factors for type 2 diabetes in a multiethnic cohort of students (1,2). The primary outcome for the study was a change in the percent of students with a BMI ≥85th percentile (combined prevalence of overweight and obesity adjusted for sex and age), which decreased by ~4% in both intervention and control schools (P = NS) from sixth to eighth grades; however, among the sample of students who were overweight or obese (≥85th percentile) in sixth grade (50% of the sample), intervention schools showed greater reductions in the prevalence of obesity (BMI ≥95th percentile) than control schools, suggesting that the intervention had an effect on obesity rather than on overweight (3).

Among other risk factors for type 2 diabetes, hemoglobin A_{1c} (A1C) and fasting plasma glucose (FPG) were collected at baseline and the end of study. It has been suggested that A1C can identify adults with diabetes and prediabetes (4,5). There are few prospective data regarding glycemic risk markers in diverse populations of youth. HEALTHY data were used to determine the distribution, durability, and association of high-risk A1C (hrA1C) with other diabetes risk factors in comparison with impaired fasting glucose (IFG) to inform decision making regarding screening and prevention strategies in youth.

RESEARCH DESIGN AND METHODS

The protocol was approved by the institutional review boards of the sites in the HEALTHY Study Group, and parents and students provided appropriate signed informed consent and assent for data collection. Full details about the HEALTHY design and intervention are available elsewhere (1). Data were collected in a health screening held in 42 middle schools at baseline and study end. Participating students and their families received instructions and a phone call reminder to not eat or drink anything but water after midnight before the scheduled health screening. Students self-reported both race and ethnicity; Hispanic, non-Hispanic (NH) black, and NH white students (91.5% of the cohort) are included in this analysis. Family history (FH) of diabetes in first-degree blood relatives was provided by parents. Height and weight were measured without shoes using a stadiometer and Seca electronic scale. Waist circumference was measured to the nearest 0.1 cm using a Gulick tape on bare skin just above the iliac crest, this measurement was repeated until two values were ≤1 cm apart, and the average of these two measurements was used. Fasting blood samples were processed in the field and sent to a central facility (Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle, WA) for analysis. A1C = 5.7–6.4% and FPG = 100–125 mg/dL were defined as high risk for diabetes (5).

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*A complete list of the members of the HEALTHY Study Group can be found in the Supplementary Data online.

Table 1—*Clinical and metabolic characteristics of sixth-grade subjects (baseline) by normal and at-risk categories*

	A1C			FPG		
	<5.7 (*n* = 3,852)	5.7–6.4 (*n* = 128)	*P* value	<100 (*n* = 3,345)	100–125 (*n* = 635)	*P* value
Age, years; mean (SD) min–max	11.3 (0.6) 10–14	11.5 (0.7) 10–14	0.0012	11.3 (0.5) 10–14	11.4 (0.6) 10–14	0.0024
Sex, %						
Male	47.3	51.6	0.3320	45.5	57.2	<0.0001
Female	52.7	48.4		54.5	42.8	
Race/ethnicity, %						
Hispanic	60.1	50.0	NC	57.9	69.5	0.0001
NH black	18.1	50.0		20.6	11.6	
NH white	21.8	0.0		21.5	18.9	
FH of diabetes, %						
Yes	16.9	33.3	<0.0001	16.8	20.6	0.0629
No	83.1	66.7		83.2	79.4	
BMI, mm/kg^2; mean (SD)	22.2 (5.3)	25.6 (7.3)	<0.0001	22.1 (5.3)	23.2 (5.6)	<0.0001
BMI *z* score; mean (SD)	0.9 (1.1)	1.4 (1.0)	<0.0001	0.9 (1.1)	1.1 (1.0)	<0.0001
BMI percentile, %						
<85	50.7	36.7	0.0001	51.6	43.0	<0.0001
85–94	19.5	17.2		19.6	18.9	
≥95	29.8	46.1		28.8	38.1	
Waist circumference, cm; mean (SD)	75.7 (14.4)	82.9 (18.7)	<0.0001	75.4 (14.4)	78.8 (15.0)	<0.0001
Waist circumference percentile, %						
<90	71.1	59.4	0.0044	71.9	64.5	0.0003
≥90	28.9	40.6		28.1	35.5	
Fasting insulin, μU/dL; mean (SD)	13.0 (11.2)	19.7 (18.3)	<0.0001†	12.2 (10.0)	18.6 (16.6)	<0.0001†
Fasting insulin, %						
<30	93.7	82.0	<0.0001	94.9	85.0	<0.0001
≥30	6.3	18.0		5.1	15.0	
A1C, %; mean (SD)				5.12 (0.29)	5.23 (0.30)	<0.0001
A1C, %						
<5.7				97.6	92.6	<0.0001
5.7–6.4				2.4	7.4	
Fasting glucose, mg/dL; mean (SD)	93.4 (6.3)	97.2 (8.3)	<0.0001			
Fasting glucose, %						
<100	84.7	63.3	<0.0001			
100–125	15.3	36.7				
BP, %						
Not high	96.7	94.5	0.1192	97.1	94.3	0.0003
High‡	3.3	5.5		2.9	5.7	
TGs, mg/dL; mean (SD)	89.4 (53.1)	90.6 (53.4)	0.4885†	88.7 (52.0)	93.3 (58.5)	0.0281†
TGs, %						
<150	90.1	92.2	0.4824	90.3	89.3	0.5175
≥150	9.9	7.8		9.7	10.7	
HDL, mg/dL; mean (SD)	52.4 (12.2)	53.1 (13.7)	0.7335	52.6 (12.3)	51.6 (12.1)	0.2249
HDL, %						
<40	13.4	13.3	0.8345	13.3	13.9	0.9736
≥40	86.6	86.7		86.7	86.1	

NC, model does not converge due to cell with zero frequency. †Tests performed on insulin and TGs log transformed to normal distribution. ‡High BP defined as systolic BP ≥130 or diastolic BP ≥85.

Analyses were performed on the cohort of students with fasting glucose and A1C values at both baseline (start of sixth grade) and the end of the study (end of eighth grade). Four students were excluded based on baseline values suggestive of diabetes (three with FPG ≥126 mg/dL and one with A1C ≥6.5%), leaving a sample size of 3,980. Descriptive statistics are presented as mean (SD) or percent. General linear mixed models were used to analyze the differences between intervention and control schools (6,7), with the covariance structure appropriately adjusting for variability both between cluster (school) and within cluster (students within the same school) (8,9). Comparisons between intervention versus control schools were not significant for either A1C ($P = 0.9066$) or IFG ($P = 0.6980$); therefore, data are presented without regard to treatment group. P values <0.05 are considered statistically significant without adjustment for multiple comparisons.

RESULTS—Among the 3,980 students in sixth grade, a small proportion (3.2%) had hrA1C and a fivefold larger group (16.0%) had IFG. Table 1 shows the association of demographic and baseline physical and metabolic characteristics for normal and high-risk categories of A1C and FPG. hrA1C was associated with a higher prevalence of NH black ethnicity/race, FH of diabetes, BMI, waist circumference, and fasting insulin. Of those with hrA1C, 36.7% had IFG, compared with 15.3% of those with A1C <5.7%. There was no association between A1C and sex, high blood pressure (BP), triglycerides (TGs), or HDL cholesterol.

Table 1 also shows that IFG was associated with male sex, Hispanic ethnicity, BMI, waist circumference, fasting insulin, high BP, and mean TGs, but not FH of diabetes, TGs ≥150 mg/dL, or HDL cholesterol. Among those with IFG, only 7.4% also exhibited hrA1C in comparison with only 2.4% among those with FPG <100 mg/dL.

Table 2 demonstrates the relationship of sixth-grade baseline and eighth-grade end-of-study (EOS) results. Of the 128 students with hrA1C at baseline, 76 (59.4%) had hrA1C and 1 (0.8%) had A1C ≥6.5% at EOS. Of the 635 with IFG in sixth grade, 298 (46.9%) had IFG in eighth grade and 7 (1.1%) had FPG ≥126 mg/dL. Of the 12 youth with evidence of diabetes by A1C or FPG in eighth grade, 4 (33.3%) had A1C ≥6.5% and 11 (91.7%) had FPG ≥126 mg/dL; in sixth grade, among these 12 youth, 1 (8.3%) had hrA1C and 7 (58.3%) had IFG.

Table 3 explores the baseline characteristics of those with persistent (from sixth to eighth grade) abnormalities of A1C and FPG. The sample size becomes small for those with hrA1C at baseline, but in general, there are trends to greater prevalence of baseline risk markers for diabetes in those with persistent elevated A1C as compared with those that revert to A1C <5.7% in eighth grade. The same trends are present for IFG, where the increased sample size contributes to more statistically significant comparisons between those with persistent elevated glucose compared with those who reverted to normal in eighth grade, specifically male sex, BMI, waist circumference, fasting insulin, A1C, and prevalence of high BP, TGs, and HDL, but not prevalence of high-risk race/ethnicity or FH of diabetes.

Table 4 examines the baseline characteristics of the four subgroups defined by both A1C and FPG baseline values: normal for A1C (nA1C) and FPG (NFG), hrA1C with NFG, IFG with nA1C, and hrA1C with IFG. In general the 3,264 sixth graders with nA1C and NFG had the least high-risk characteristics in both sixth and eighth grades. Likewise, the 47 youth with both hrA1C and IFG had the highest rates of FH for diabetes, indices of obesity, waist circumference, and fasting insulin and high BP in sixth grade, and these differences largely persisted in eighth grade. Sixth graders with hrA1C but NFG (n = 81) as compared with those with IFG but nA1C (n = 588) had similar risk markers, although there were significantly greater abnormalities in BMI and obesity (defined by BMI percentile ≥95) but lower fasting insulin. By eighth grade, those with hrA1C but NFG compared with those with IFG but nA1C had statistically significantly greater abnormalities in BMI, BMI z score, obesity, waist circumference, and fasting insulin. Change or persistence in BMI percentile over the study did not have a major effect on the durability of glycemic abnormalities (data not shown).

Table 2—*Cross tabulations of A1C and FPG in sixth- and eighth-grade students for sample* **n** = *3,980*

	Sixth grade			
	A1C		FPG	
Eighth grade	<5.7 (n = 3,852)	5.7–6.4 (n = 128)	<100 (n = 3,345)	100–125 (n = 635)
A1C, n (%)				
<5.7 mg/dL	3,761 (97.6)	51 (39.8)	3,231 (96.6)	581 (91.5)
5.7–6.4 mg/dL	88 (2.3)	76 (59.4)	112 (3.3)	52 (8.2)
≥6.5 mg/dL	3 (0.1)	1 (0.8)*	2 (0.1)	2 (0.3)†
FPG, n (%)				
<100 mg/dL	3,031 (78.7)	73 (57.0)	2,774 (82.9)	330 (52.0)
100–125 mg/dL	811 (21.0)	54 (42.2)	567 (17.0)	298 (46.9)
≥126 mg/dL	10 (0.3)	1 (0.8)*	4 (0.1)	7 (1.1)†

*This is the same child. †The two youth with eighth-grade A1C ≥6.5% are among the seven with eighth-grade FPG ≥126 mg/dL.

CONCLUSIONS—In 2009, an international expert committee of the American Diabetes Association, the International Diabetes Federation, and the European Association for the Study of Diabetes recommended that A1C ≥6.5% be used to diagnose diabetes (4). Although prediabetes was not originally discussed in this report, it was subsequently suggested that A1C values of 5.7–6.4% identified high risk for diabetes along with IFG and impaired glucose tolerance (5). In the data analyzed to establish A1C as a diagnostic test, pediatric subjects were not well represented.

The HEALTHY Study provides one of the largest population-based datasets of nondiabetic children with A1C measures. In the sixth-grade cohort, hrA1C was a relatively uncommon finding (3.2%) compared with IFG (16.0%). In the sixth grade, compared with those with A1C <5.7%, hrA1C was associated with known risk factors for diabetes, including NH black race/ethnicity, FH of diabetes, BMI, waist circumference, and fasting insulin, as well as a more than twofold increased risk of having IFG. hrA1C was not associated with sex or traditional cardiovascular disease risk factors (BP, HDL, and TGs). In contrast, IFG was associated with male sex, Hispanic ethnicity, indices of obesity, waist circumference, fasting insulin, high BP, and mean TGs, but not FH of diabetes, high TGs, or HDL cholesterol. Although there were fewer students with hrA1C compared with those with IFG, they had an elevated high-risk profile with regard to FH, BMI, and waist circumference. Finally, hrA1C was relatively more likely to persist from sixth to eighth grade than IFG. There were very few children who developed FPG or A1C consistent with the diagnosis of diabetes in HEALTHY; more were identified in eighth grade by FPG than by A1C, and more often they had IFG rather than hrA1C in sixth grade.

There has been great controversy about the utility of the A1C test versus glucose measurements for screening and diagnosis of diabetes (10). One issue often raised is that there may be higher A1C at a given level of glycemia in people of African descent. However, there is controversy regarding the significance of these

Table 3—*Demographics and metabolic characteristics of eighth-grade subjects in the sample "at risk" at baseline divided into eighth-grade category "normal" or "not normal"*

	Eighth grade					
Baseline category→	hrA1C (5.7–6.4) at baseline (*n* = 128)			High-risk FPG (100–125) at baseline (*n* = 635)		
EOS category→	A1C <5.7 (*n* = 51)	A1C ≥5.7 (*n* = 77)	*P* value	FPG <100 (*n* = 330)	FPG ≥100 (*n* = 305)	*P* value
Age at baseline, years; mean (SD) min–max	11.4 (0.8) 10–14	11.5 (0.6) 11–14	0.4566	11.3 (0.6) 10–14	11.4 (0.6) 10–14	0.3902
Sex, %						
Male	41.2	58.4	0.0590	47.3	67.9	<0.0001
Female	58.8	41.6		52.7	32.1	
Race/ethnicity, %						
Hispanic	58.8	44.2	0.7540	70.0	68.9	0.8667
NH black	41.2	55.8		11.5	11.8	
NH white	0.0	0.0		18.5	19.3	
FH of diabetes, %						
Yes	29.4	64.4	0.3739	18.0	23.1	0.1684
No	70.6	35.6		82.0	76.9	
BMI, mm/kg^2; mean (SD)	27.0 (6.9)	28.3 (8.6)	0.3950	23.6 (5.3)	25.9 (6.7)	<0.0001
BMI *z* score; mean (SD)	1.4 (0.9)	1.4 (1.0)	0.8347	0.8 (1.0)	1.2 (1.0)	<0.0001
BMI percentile, %						
<85	37.2	40.3	0.8043	57.6	43.6	<0.0001
85–94	21.6	10.4		18.8	15.7	
≥95	41.2	49.3		23.6	40.7	
Waist circumference, cm; mean (SD)	86.6 (16.5)	89.4 (21.3)	0.3402	80.0 (13.4)	86.4 (17.0)	<0.0001
Waist circumference percentile, %						
<90	64.7	61.0	0.6759	81.5	65.9	<0.0001
≥90	35.3	39.0		18.5	34.1	
Fasting insulin, μU/dL; mean (SD)	20.3 (14.6)	26.7 (21.4)	0.1046*	15.9 (11.1)	23.1 (17.6)	<0.0001*
Fasting insulin, %						
<30	86.3	71.4	0.0573	91.2	80.0	<0.0001
≥30	13.7	28.6		8.8	20.0	
A1C, %; mean (SD)				5.14 (0.31)	5.30 (0.42)	<0.0001
A1C, %						
<5.7				96.1	86.6	<0.0001
5.7–6.4				3.9	12.8	
≥6.5				0.0	0.7	
Fasting glucose, mg/dL; mean (SD)	95.7 (7.4)	100.2 (11.3)	0.0054			
Fasting glucose, %						
<100	68.6	49.3	0.0196			
100–125	31.4	49.4				
≥126	0.0	1.3				
BP, %						
Not high	90.2	94.8	0.3282	94.2	89.5	0.0315
High†	9.8	5.2		5.8	10.5	
TGs, mg/dL; mean (SD)	76.6 (41.5)	81.9 (38.6)	0.4948*	79.6 (41.5)	89.8 (42.4)	0.0002*
TGs, %						
<150	98.0	92.2	0.1784	94.8	91.1	0.0710
≥150	2.0	7.8		5.2	8.9	
HDL, mg/dL; mean (SD)	52.2 (13.1)	51.6 (14.5)	0.7440	52.1 (11.8)	48.6 (12.4)	0.0003
HDL, %						
<40	17.6	18.2	0.9300	13.6	21.6	0.0076
≥40	82.4	81.8		86.4	78.4	

*Tests performed on insulin and TGs log transformed to normal distribution. †High BP defined as systolic BP ≥130 or diastolic BP ≥85.

Table 4—*Clinical and metabolic characteristics of sixth- and eighth-grade subjects by normal and at-risk baseline categories*

	Both nA1C and FPG (*n* = 3,264)	At-risk A1C (5.7–6.4) but not FPG (*n* = 81)	At-risk FPG (100–125) but not A1C (*n* = 588)	At-risk both A1C and FPG (*n* = 47)	*P* value for at-risk A1C but not FPG vs. at-risk FPG but not A1C
Sixth grade					
Age, years; mean (SD) min–max	11.3 (0.5) 10–14	11.4 (0.7) 10–14	11.3 (0.6) 10–14	11.5 (0.7) 10–14	0.2703
Sex, %					
Male	45.4	49.4	57.3	55.3	0.7936
Female	54.6	50.6	42.7	44.7	
Race/ethnicity, %					
Hispanic	58.3	43.2	70.1	61.7	NC
NH black	19.6	56.8	9.5	38.3	
NH white	22.1	0.0	20.4	0.0	
FH of diabetes, %					
Yes	16.6	28.8	18.9	41.2	0.0805
No	83.4	71.2	81.1	58.8	
BMI, mm/kg^2; mean (SD)	22.1 (5.3)	24.9 (7.2)	22.9 (5.3)	26.9 (7.4)	0.0019
BMI *z* score; mean (SD)	0.9 (1.1)	1.3 (1.0)	1.0 (1.0)	1.6 (0.9)	0.0864
BMI percentile, %					
<85	51.9	40.7	44.1	29.8	0.0189
85–94	19.6	18.5	19.2	14.9	
≥95	28.5	40.8	36.7	55.3	
Waist circumference, cm; mean (SD)	75.3 (14.3)	80.6 (18.4)	78.2 (14.5)	86.9 (18.7)	0.0980
Waist circumference percentile, %					
<90	72.1	62.9	65.4	53.2	0.6307
≥90	27.9	37.1	34.6	46.8	
Fasting insulin, μU/dL; mean (SD)	12.2 (9.7)	15.9 (16.9)	18.0 (16.3)	26.2 (19.1)	0.0125†
Fasting insulin, %					
<30	95.1	88.9	86.2	70.2	0.5253
≥30	4.9	11.1	13.8	29.8	
BP, %					
Not high	97.0	98.8	94.9	87.2	0.1751
High‡	3.0	1.2	5.1	12.8	
TGs, mg/dL; mean (SD)	88.7 (52.1)	89.2 (52.0)	93.3 (58.8)	93.1 (56.2)	0.8838†
TGs, %					
<150	90.3	92.6	89.1	91.5	0.3997
≥150	9.7	7.4	10.9	8.5	
HDL, mg/dL; mean (SD)	52.5 (12.3)	53.1 (11.7)	51.5 (11.7)	53.0 (16.7)	0.6299
HDL, %					
<40	13.3	12.3	13.8	14.9	0.9049
≥40	86.7	87.7	86.2	85.1	
Eighth grade					
BMI, mm/kg^2; mean (SD)	23.8 (5.6)	27.2 (7.9)	24.4 (5.8)	28.7 (8.0)	<0.0001
BMI *z* score; mean (SD)	0.8 (1.0)	1.3 (1.0)	1.0 (1.0)	1.5 (0.9)	0.0044
BMI percentile, %					
<85	55.5	40.7	52.0	36.2	0.0007
85–94	20.7	17.3	17.9	10.6	
≥95	23.8	42.0	30.1	53.2	
Waist circumference, cm; mean (SD)	80.3 (14.3)	86.8 (18.9)	82.5 (14.9)	90.8 (20.4)	0.0066
Waist circumference percentile, %					
<90	78.8	65.4	75.3	57.5	0.0536
≥90	21.2	34.6	24.7	42.5	

Continued on p. 434

Table 4—*Continued*

	Both nA1C and FPG (n = 3,264)	At-risk A1C (5.7–6.4) but not FPG (n = 81)	At-risk FPG (100–125) but not A1C (n = 588)	At-risk both A1C and FPG (n = 47)	P value for at-risk A1C but not FPG vs. at-risk FPG but not A1C
Fasting insulin, μU/dL; mean (SD)	16.7 (14.2)	22.0 (17.8)	18.7 (14.3)	27.9 (20.9)	0.0368†
Fasting insulin, %					
<30	90.0	81.5	87.1	70.2	0.1629
≥30	10.0	18.5	12.9	29.8	
BP, %					
Not high	97.0	93.8	92.0	91.5	0.5597
High‡	3.0	6.2	8.0	8.5	
TGs, mg/dL; mean (SD)	82.8 (48.1)	78.7 (42.2)	84.8 (42.7)	81.7 (35.5)	0.8745†
TGs, %					
<150	93.1	95.1	93.0	93.6	0.5587
≥150	6.9	4.9	7.0	6.4	
HDL, mg/dL; mean (SD)	51.5 (12.3)	51.9 (12.2)	50.3 (11.8)	51.7 (16.5)	0.4416
HDL, %					
<40	15.6	14.8	17.0	23.4	0.8239
≥40	84.4	85.2	83.0	76.6	

NC, model does not converge due to cell with zero frequency. †Tests performed on insulin and TGs log transformed to normal distribution. ‡High BP defined as systolic BP ≥130 or diastolic BP ≥85.

differences and whether they are of genetic or socioeconomic origin (11). There is an evolving consensus that, at least in selected adult populations where the A1C measurement is appropriate (e.g., no clinical conditions associated with reduced erythrocyte survival) and when the assay is appropriately performed, A1C identifies a population with diabetes that is smaller than that defined by FPG or oral glucose tolerance test (OGTT) but with similar or higher risk of microvascular and macrovascular complications.

Similarly, a recent study in obese youth demonstrated that the A1C cut point of ≥6.5% was relatively insensitive for detecting diabetes compared with FPG or OGTT; however, A1C did perform similarly in defining youth at high risk of diabetes with prospective follow-up (12). A second study in youth demonstrated lower sensitivity of A1C measurements to define diabetes and especially prediabetes as defined by FPG or OGTT (13). This raises the issue of whether lower A1C thresholds should be used to define glycemic abnormalities in youth, as has been suggested elsewhere (14). Setting a cut point to define diabetes risk categorically as low or high in screening is inherently controversial as there is a continuously increasing risk for the future development of diabetes as the level of any glycemic marker approaches the diagnostic cut point. If the rationale for defining diabetes risk is to intervene to prevent disease, the choice of the cut point to define high risk must take into account how many individuals would need to be treated at what cost in order to prevent diabetes. These issues are even more complex in youth, as glycemic measures are in flux related to pubertal development. Furthermore, the prospective studies that would be required to define the cardiovascular and microvascular consequences of subclinical glycemic abnormalities in youth and the potential mitigating effect of interventions would be extremely large and prolonged. Inherently, the evidence base for the cut points for high risk for diabetes in youth is even more arbitrary than in adults.

In the HEALTHY cohort, the FPG and A1C tests identify two different high-risk populations. The IFG population is five times as large and less likely to persist with glycemic abnormalities but more hypertensive and more dyslipidemic. Arguably, these features suggest a population where there may be a benefit of intervention and follow-up to prevent cardiovascular risk. The hrA1C population is a relatively small minority of those with glycemic abnormalities, but they are substantially more obese and exhibit the other most powerful risk factors for diabetes in youth (FH and ethnicity) more frequently. These features may be more amenable for diabetes prevention and follow-up strategies. However, only 58% of those with diabetes at the end of the study had either hrA1C or IFG at the beginning, and the vast majority of those with hrA1C or IFG at the beginning of the study did not develop diabetes over 2 years, suggesting modest screening value of either measure. Further study is required to establish the optimal screening and intervention strategy to reduce cardiometabolic risk in youth.

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intervention materials are available for download at http://www.healthystudy.org/.

References

1. HEALTHY Study Group. HEALTHY study rationale, design and methods: moderating risk of type 2 diabetes in multi-ethnic middle school students. Int J Obes (Lond) 2009;33(Suppl. 4):S4–S20
2. Kaufman FR, Hirst K, Linder B, et al.; HEALTHY Study Group. Risk factors for type 2 diabetes in a sixth- grade multiracial cohort: the HEALTHY study. Diabetes Care 2009;32:953–955
3. Foster GD, Linder B, Baranowski T, et al.; HEALTHY Study Group. A school-based intervention for diabetes risk reduction. N Engl J Med 2010;363:443–453
4. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–1334
5. American Diabetes Association. Standards of medical care in diabetes – 2011. Diabetes Care 2011;34(Suppl. 1):S11–S61
6. Diggle P, Heagerty P, Liang KY, Zeger SL. *Analysis of Longitudinal Data*. Oxford, Oxford University Press, 2002
7. Molenberghs G, Verbeke G. *Models for Discrete Longitudinal Data*. New York, Springer, 2005
8. Murray DM. *Design and Analysis of Group-Randomized Trials*. New York, Oxford University Press, 1998
9. Donner A, Klar N. *Design and Analysis of Cluster Randomization Trials in Health Research*. London, Arnold Publishers, 2000
10. Sacks DB. A1C versus glucose testing: a comparison. Diabetes Care 2011;34:518–523
11. Maruthur NM, Kao WH, Clark JM, et al. Does genetic ancestry explain higher values of glycated hemoglobin in African Americans? Diabetes 2011;60:2434–2438
12. Nowicka P, Santoro N, Liu H, et al. Utility of hemoglobin A(1c) for diagnosing prediabetes and diabetes in obese children and adolescents. Diabetes Care 2011;34:1306–1311
13. Lee JM, Wu E-L, Tarini B, Herman WH, Yoon E. Diagnosis of diabetes using hemoglobin A1c: should recommendations in adults be extrapolated to adolescents? J Pediatr 2011;158:947–952, e1–e3
14. Tsay J, Pomeranz C, Hassoun A, et al. Screening markers of impaired glucose tolerance in the obese pediatric population. Horm Res Paediatr 2010;73:102–107