

Fasting Plasma Glucose Levels Within the Normoglycemic Range in Childhood as a Predictor of Prediabetes and Type 2 Diabetes in Adulthood

The Bogalusa Heart Study

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Objectives: To determine whether childhood elevated fasting plasma glucose (FPG) levels within the normoglycemic range predict diabetes in adulthood.

Design: Retrospective cohort study.

Setting: Community of Bogalusa, Louisiana.

Participants: Normoglycemic (n=1723), prediabetic (n=79), and type 2 diabetic (n=47) adults aged 19 to 44 years followed up serially for an average of 21 years since childhood.

Main Exposures: Association of elevated baseline childhood FPG levels with the prediabetic or diabetic status at the last survey in adulthood.

Main Outcome Measures: Receiver operating characteristic analysis and longitudinal logistic regression odds ratios.

Results: The prevalent rate of adult diabetes status by quartiles of baseline childhood FPG levels showed an ad-

verse trend for prediabetes ($P < .001$) and diabetes ($P = .03$), with an apparent threshold occurring at or above the 50th percentile (86 mg/dL). Regarding the predictive value of the above threshold, the area under the receiver operating curve analysis yielded a C value of 0.855 for prediabetes and 0.789 for diabetes models, with sensitivity and specificity, respectively, of 76.9% and 85.2% for prediabetes and 75.0% and 76.0% for diabetes. In a multivariate analysis that included anthropometric, hemodynamic, and metabolic variables from childhood to adulthood and baseline childhood FPG status (\geq vs $<$ 50th percentile), individuals with elevated childhood FPG levels were 3.40 times more likely to develop prediabetes ($P < .001$) and 2.06 times more likely to develop diabetes ($P = .05$) as adults.

Conclusion: The fact that elevated FPG level in childhood, even within the normoglycemic range, is a predictor of type 2 diabetes in younger adulthood has implications for health care policy.

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WHILE 19 MILLION people have type 2 diabetes mellitus, 54 million individuals show impaired fasting glucose as adults, which may represent a prediabetic state.¹ This carbohydrate-insulin imbalance becomes one of the most common causes of death in the United States.² It is also recognized that cardiovascular morbidity and mortality risks are elevated in individuals with relatively increased fasting plasma glucose (FPG) levels within the reference range.³⁻⁵

The American Diabetes Association (ADA) has lowered the diagnostic cutoff point for impaired fasting glucose from 110 mg/dL to 100 mg/dL (to convert to millimoles per liter, multiply by 0.0555) to improve prediction of type 2 diabetes.⁶ How-

ever, the current criteria for diagnosis of type 2 diabetes set by the ADA are not age specific.⁷ Studies have recently demonstrated that higher plasma glucose levels within the normoglycemic range might be a predictor of diabetes,⁸⁻¹⁰ although it raises

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controversy regarding the implications for health care policy.^{11,12} Further, FPG and the prevalence of impaired carbohydrate metabolism are known to increase with age.^{13,14} Also, glycated hemoglobin, an indicator of long-term glucose homeostasis, is positively correlated with age in nondiabetic populations, even after eliminating individuals with impaired FPG and/or impaired glucose tolerance.¹⁵ Although the

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association between fasting glucose levels in the reference range and type 2 diabetes mellitus has been described on single baseline measurements for younger adults^{8,9} and older age groups,¹⁰ such data on long-term, longitudinal, and progressive changes in the cardiometabolic risk variables from childhood to younger adulthood are scant. This study examined the prediction of normal FPG levels for the development of type 2 diabetes for a 21-year period beginning in childhood.

METHODS

STUDY POPULATION

The Bogalusa Heart Study is being conducted in the semirural, biracial (65% white and 35% black) community of Bogalusa, Louisiana. Between 1978 and 1994, 6 cross-sectional studies of school-aged children were conducted. In addition, 8 cross-sectional surveys were conducted between 1978 and 2002 with young adults who have been examined previously as children. The details of the study design, participation, and protocols were described elsewhere.¹⁶ It consists of multiple cross-sectional studies that resulted in serial observations from childhood to young adulthood, allowing longitudinal analyses.

A total of 1849 fasting adult subjects (68% white; 42% male) were selected from the last 3 surveys (1995 to 2002) of adults for this retrospective cohort study. At the baseline examination, the children with a history of treatment of diabetes mellitus or who had a fasting glucose level of 100 mg/dL or higher were excluded. At the initial screening, the mean (SD) age was 10.8 (4.0) years (range, 4 to 18 years). At the most recent screening, the mean (SD) age was 31.9 (6.5) years (range, 19 to 44 years). The mean follow-up interval was 21 years. The number of screenings and follow-up visits between childhood and adulthood ranged from 2 to 9 times. In all, 91% of subjects were screened 3 or more times and 63%, 4 to 6 times, with a total of 9202 observations.

Based on the data at the last survey, adult subjects were classified as normoglycemic, prediabetic, or diabetic according to the ADA criteria.⁷ Individuals were considered normoglycemic ($n=1723$) if they had a fasting glucose level of 99 mg/dL or lower; prediabetic ($n=79$), between 100 and 125 mg/dL; or diabetic ($n=47$), they (1) had a fasting glucose level of 126 mg/dL or higher or (2) had a history of treatment for the condition. The institutional review board of the Tulane University Health Sciences Center approved the study and consent forms used for these surveys; informed consent was obtained from the study participants in adulthood and from parents or guardians in childhood.

GENERAL EXAMINATION

Identical protocols were used by trained examiners, nurses, and technicians across all surveys; procedures for general examination were described previously.¹⁷ Briefly, subjects were instructed to fast for 12 hours before the screening, with compliance ascertained by interview on the day of examination. Information on personal health and medication history were obtained by questionnaires. Anthropometric and blood pressure measurements were collected in replicate and mean values were used. In the longitudinal analysis, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) was used as a measure of overall adiposity and subscapular skinfold for truncal fatness. Blood pressure measurements were obtained using the right arm of the subjects in a relaxed, sitting position. Systolic and diastolic blood pressures were

recorded at the first and fourth Korotkoff phases using a mercury sphygmomanometer. Mean arterial pressure was calculated as diastolic blood pressure plus one-third pulse pressure.

LABORATORY ANALYSES

Cholesterol and triglycerides levels were initially measured using chemical procedures on a Technicon Autoanalyzer II (Technicon Instrument Corporation, Tarrytown, New York) according to the laboratory manual of the Lipid Research Clinics Program. Later, these variables were determined by enzymatic procedures on the Abbott VP instrument (Abbott Laboratories, North Chicago, Illinois) and on the Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, Indiana) afterward. Both chemical and enzymatic procedures met the performance requirements of the Lipid Standardization Program of the Centers for Disease Control and Prevention, which has routinely monitored the precision and accuracy of cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol measurements since the beginning of this study. Serum lipoprotein cholesterol levels were analyzed using a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures.¹⁸ The intraclass correlation coefficients between the blind duplicate (10% random sample) values ranged from 0.86 to 0.98 for HDL cholesterol, 0.86 to 0.98 for low-density lipoprotein (LDL) cholesterol, and 0.88 to 0.99 for triglycerides.

Plasma glucose was measured initially by a glucose oxidase method using a Beckman Instant Glucose Analyzer (Beckman Instruments, Palo Alto, California). After 1991, glucose was measured in adults using a multichemistry (SMA20) profile by enzymatic procedures using the multichannel Olympus Au-5000 Analyzer (Olympus, Lake Success, New York). Plasma immunoreactive insulin levels were measured by a commercial radioimmunoassay kit (Phadebas; Pharmacia Diagnostics, Piscataway, New Jersey). The intraclass correlation coefficients between blind duplicate values ranged from 0.94 to 0.98 for insulin and 0.86 to 0.98 for glucose. In addition, an index of insulin resistance was calculated according to the homeostasis model assessment of insulin resistance (HOMA-IR) formula¹⁹: $HOMA-IR = [\text{insulin (microunits per milliliter)} \times \text{glucose (millimoles per liter)}] / 22.5$. This model was considered useful in assessing insulin resistance in epidemiological studies.²⁰

STATISTICAL ANALYSIS

All statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, North Carolina). In the analyses, the race and sex groups were combined to increase statistical power and to simplify the presentation. Continuous variables were tested for normality using a Kolmogorov-Smirnov test. Values of triglycerides, glucose, insulin, and HOMA-IR were log transformed to improve normality, as applicable. General linear models were used to examine the cardiometabolic risk factor variables by status of adult diabetes, adjusted for age, race, and sex. The distribution of childhood fasting glucose was split by the median (86 mg/dL) to define high and low values. The trends of adult diabetes status by children FPG quartile levels were examined using the Cochran-Armitage trend test.

Longitudinal multivariate logistic regression analyses (generalized equation estimation method) were used to determine which longitudinal changes in risk variables since childhood predicted adult diabetes status. Model 1 included the 50th percentile or higher vs lower than the 50th percentile (reference) of baseline childhood glucose levels as categorical variables, adjusted for age, age squared, race, sex, and sex \times race interaction, as applicable. Model 2 added BMI and triglycerides to assess their potential roles as confounding fac-

Table 1. Baseline Cardiometabolic Characteristics of Children Within the Fasting Normoglycemic Range by Diabetes Status in Adulthood

Childhood Variable	Mean (SD)		
	Normoglycemia (n=1723)	Prediabetes (n=79)	Diabetes (n=47)
Age, y ^a	10.7 (4.0)	12.4 (3.9) ^b	12.4 (4.2) ^c
BMI	18.2 (3.8)	19.2 (3.3)	22.0 (6.0) ^b
Subscapular skin fold, mm	12.5 (6.6)	13.8 (6.3)	17.0 (8.2) ^b
Systolic BP, mm Hg	100.5 (10.9)	104.4 (11.6)	106.4 (12.6) ^d
Diastolic BP, mm Hg	61.6 (9.6)	64.2 (11.1)	64.8 (9.6)
MAP, mm Hg	74.6 (9.3)	77.6 (10.4)	78.6 (9.4)
HDL cholesterol, mg/dL	61.7 (17.6)	63.8 (22.0)	52.3 (18.5) ^b
LDL cholesterol, mg/dL	87.8 (24.9)	89.5 (26.0)	92.1 (30.7)
Triglycerides, mg/dL	64.5 (31.6)	67.1 (29.5)	79.2 (32.1) ^c
Triglycerides to HDL cholesterol ratio	1.43 (5.05)	1.38 (1.70)	2.31 (3.48)
Glucose, mg/dL	84.6 (7.9)	88.4 (7.8) ^c	87.2 (6.7)
Insulin, μ U/mL	7.72 (5.62)	10.68 (10.62)	11.68 (8.54)
HOMA-IR	1.8 (1.4)	2.6 (2.8)	3.0 (2.3)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; MAP, mean arterial pressure.

SI conversion factors: To convert HDL and LDL cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, by 0.0113; glucose to millimoles per liter, by 0.0555; insulin to picomoles per liter, by 6.945.

^a P values for age were adjusted for race and sex; all others adjusted for age, race, and sex.

^b Statistically significant difference from normoglycemia; $P < .001$.

^c Statistically significant difference from normoglycemia; $P < .01$.

^d Statistically significant difference from normoglycemia; $P < .05$.

tors of the tested relationship between fasting plasma glucose levels and diabetic status. The final multivariate model included 50th percentile or higher vs lower than the 50th percentile of childhood glucose levels observed at childhood baseline as categorical variables and BMI, mean arterial pressure, HDL cholesterol, LDL cholesterol, triglycerides, and HOMA index as longitudinal continuous variables, adjusted for age, age squared, race, sex, and sex \times race interaction, as applicable. Nonsignificant terms ($P > .05$) were removed from the model by backward stepwise procedure. To evaluate the discriminatory capability of the models using the area under the receiver operating characteristic (ROC) curve (C statistic), the multivariate logistic regressions were sequentially performed on the association of high level of fasting glucose observed at baseline in childhood (single measurements per subject) (top quintile, quartile, tertile, or 50th percentile vs the rest) with prediabetic or diabetic status at the last survey in adulthood adjusted for age, age squared, race, sex, and other variables retained in the longitudinal multivariate logistic regression models. Between-model comparisons were assessed by ranking participant risk by decile and performing a χ^2 analysis of the estimates. Further, the ROC curve was plotted for identifying the diagnostic properties of specific cutoff points of glucose levels in predicting diabetic status, based on the maximum combination of sensitivity and specificity, and their area under the ROC curve.

RESULTS

Mean levels of anthropometric, hemodynamic, and metabolic variables at baseline (childhood) are presented in

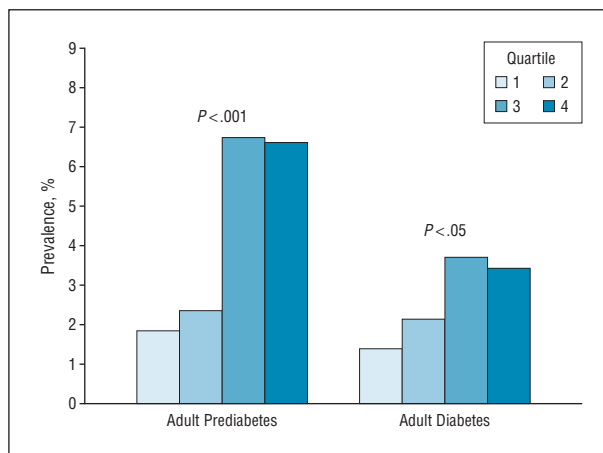


Figure 1. Prevalence of adult diabetes status by quartiles of childhood fasting plasma glucose levels within the normoglycemic range in the Bogalusa Heart Study. Levels of fasting plasma glucose according to the quartiles were less than 80 mg/dL (to convert to millimoles per liter, multiply by 0.0555) for quartile 1; 80 to 85 mg/dL, quartile 2; 86 to 90 mg/dL, quartile 3; and 91 to 99 mg/dL, quartile 4.

Table 1 by diabetes status in adulthood. The prediabetic group vs normoglycemic groups displayed significantly higher age; the diabetic group, higher age, BMI, subscapular skin fold, systolic blood pressure, and triglycerides, and lower HDL cholesterol.

The prevalence rate of adult diabetes status by quartiles of childhood FPG within the reference range is shown in **Figure 1**. Significant adverse trends were noted for both prediabetic ($P < .001$) and diabetic ($P = .03$) groups. The threshold for the association between the prevalent rates of both adult prediabetes and diabetes and childhood FPG quartiles appeared to occur at or above the median level (86 mg/dL).

On the basis of sensitivity and specificity data, the ROC curve analyses yielded an optimal cutoff glucose level of 86 mg/dL for both prediabetes and diabetes. In terms of predictive value, the C statistics or the area under the ROC curve at or above 50th percentile of FPG vs the rest were 0.855 (95% confidence interval [CI], 0.730-0.978) and 0.789 (95% CI, 0.666-0.915) in prediabetic and diabetic models, respectively. Thus, the level of FPG observed in childhood for predicting both prediabetes and diabetes in adulthood supported the median value of 86 mg/dL as a reasonable threshold. The sensitivity and specificity of this cutoff value for adult prediabetic and diabetic groups were 76.9% (95% CI, 60.7-88.9) and 85.2% (95% CI, 83.2-87.1) and 75.0% (95% CI, 57.8-87.9) and 76.0% (95% CI, 74.5-78.5), respectively.

Table 2 shows the results of a multivariable adjusted longitudinal logistic regression model that included BMI, mean arterial pressure, HDL cholesterol, LDL cholesterol, triglycerides, and HOMA-IR since childhood as a continuous variable, and childhood baseline FPG at or above vs below the 50th percentile as categorical variable. The adverse levels of the following variables emerged as independent correlates with significant odds ratios: childhood FPG, LDL cholesterol, and HOMA-IR for prediabetes and childhood FPG, BMI, and HOMA-IR for diabetes. Alternate multivariate analyses using subscapular skin fold instead of BMI gave essentially identical results (data not shown).

Table 2. Multivariate Prediction of Adult Diabetes Status by Baseline Childhood FPG Levels and Other Cardiometabolic Risk Variables Since Childhood

Independent Variable ^a	Prediabetes vs Normoglycemia		Diabetes vs Normoglycemia	
	OR ^b (95% CI)	P Value	OR ^b (95% CI)	P Value
Model 1				
Childhood FPG level				
<50th percentile	1 [Reference]		1 [Reference]	
≥50th percentile	3.53 (2.01-6.18)	<.001	1.90 (1.01-3.59)	.05
Model 2				
BMI	1.04 (1.01-1.07)	.009	1.13 (1.10-1.17)	<.001
Triglycerides	1.17 (1.03-1.33)	.01	1.28 (1.08-1.51)	.004
Childhood FPG level				
<50th percentile	1 [Reference]		1 [Reference]	
≥50th percentile	3.50 (2.00-6.13)	<.001	1.88 (1.01-3.66)	.04
Model 3				
BMI	...		1.09 (1.04-1.13)	<.001
LDL cholesterol	1.40 (1.12-1.74)	.003	...	
HOMA-IR	1.23 (1.13-1.35)	<.001	1.27 (1.16-1.39)	<.001
Childhood FPG level				
<50th percentile	1 [Reference]		1 [Reference]	
≥50th percentile	3.40 (1.87-6.18)	<.001	2.06 (1.01-4.23)	.05

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; ellipses, did not retain in the model; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; OR, odds ratio.

^aModel 1 indicates FPG level (≥50th percentile vs <50th percentile) in childhood at baseline; model 2, model 1 + BMI and triglycerides since childhood, as continuous variables; model 3, model 2 + mean arterial pressure, high-density lipoprotein cholesterol, LDL cholesterol, and HOMA-IR since childhood, as continuous variables.

^bLongitudinal logistic regression model with generalized equation estimation method, adjusted for age, age squared, race, and sex, and the race × sex interaction, as applicable.

COMMENT

The study explores the natural history of impaired glucose regulation and related diabetes status in a community-based population of children free from a selection bias, monitored longitudinally for a period of 21 years. The data linked the conditions of prediabetes and type 2 diabetes mellitus in young adults to childhood FPG at baseline and concurrent longitudinal changes in other cardiometabolic risk variables from childhood to young adulthood. The results show a significantly increased risk (>2-fold) for developing adult prediabetes and type 2 diabetes in children in the 86 to 99 mg/dL FPG group compared with those in the less than 86 mg/dL group, even after controlling for other traditional cardiometabolic risk factors. This observation suggests that elevated FPG within the currently accepted reference range in childhood may portend a diabetic condition (prediabetes or diabetes) in young adulthood.

Whether the risk of developing type 2 diabetes mellitus is best determined by fasting or postchallenge glucose testing remains unclear. Recent studies have indicated that FPG level is a strong and consistent predictor of diabetes risk.^{8-10,21,22} The FPG level has been proven to have high reproducibility, small variability, and a favorable application to clinical practice.²³ The ADA recommends using fasting glucose tests for the diagnosis of diabetes because it is not practical to implement a 75-g oral glucose tolerance test in a routine manner, especially in a large population study.^{7,24}

The definition of the reference range of fasting plasma glucose level was recently revised by the ADA to be less

than 100 mg/dL^{6,7} instead of less than 110 mg/dL. This cutoff value is applied without distinction of age group, even in youth.²⁴ The increase in sequential changes in FPG level, even within the reference range, was correlated with the higher risk of developing diabetes.⁹ Further, previous findings have shown that a fasting plasma glucose level of more than 94 mg/dL elevates the risk of diabetes.²⁵ Other articles have even suggested a lower threshold.^{8,10,21} In the current study, a fasting plasma glucose level of 86 to 99 mg/dL vs less than 86 mg/dL observed in childhood significantly increased (>2-fold) the risk of developing prediabetes and diabetes in adulthood, regardless of other traditional cardiometabolic risk factors; this is consistent with earlier studies in childhood²¹ and young adulthood.⁸

The observed FPG cutoff level for predicting type 2 diabetes mellitus in the study cohort, although within the reference range, was slightly lower than found previously (87 mg/dL in healthy young men from the Metabolic, Lifestyle, and Nutrition Assessment in Young Adults [MELANY] cohort study⁸ and 90 mg/dL in older age in the Kaiser Permanente Northwest retrospective cohort study¹⁰). This difference can be explained by the lower average age at baseline of our cohort. Indeed, a progressively increasing FPG¹³ and glycosylated hemoglobin¹⁵ level with age in nondiabetic subjects has been noted earlier.

It has been reported that inclusion of obesity status and triglyceride levels enhances the predictability of a high reference FPG level with respect to type 2 diabetes mellitus.⁸ The present study supports this and an earlier observation that a high reference FPG level, as well as insulin resistance index and BMI, is independently related

to adult diabetes.^{8,10} Further, obesity and insulin resistance are well-known interrelated risk factors for type 2 diabetes.^{22,26,27}

As a limitation, this study lacks data on postchallenge glucose, in vivo insulin action and secretion, and glycosylated hemoglobin in childhood to determine the status of glucose homeostasis. Instead, an established simple surrogate measure of insulin resistance (HOMA-IR) applicable to population studies was used. Further, information on adipocytokines might have provided additional insight into childhood glucose homeostasis.

In summary, these findings indicate that excess FPG observed in childhood, albeit within the currently accepted reference range, may predict diabetic status (pre-diabetes and type 2 diabetes mellitus) in young adulthood, independent of other traditional cardiometabolic risk factors. Additional population-based studies are needed to develop consensus regarding FPG cutoff values to define the risk of type 2 diabetes mellitus in this age group.

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