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TITLE Childhood BMI and Fasting Glucose and Insulin Predict Adult Type 2 Diabetes: The International Childhood Cardiovascular Cohort (i3C) Consortium

YEAR Diabetes Care 2020 Nov; 43(11): 2821-2829.

DOI https://doi.org/10.2337/dc20-0822

VERSION Final Draft (AAM)

CITATION Childhood BMI and Fasting Glucose and Insulin Predict Adult Type 2 Diabetes: The International Childhood Cardiovascular Cohort (i3C) Consortium
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Diabetes Care Nov 2020, 43 (11) 2821-2829;
DOI: 10.2337/dc20-0822

Childhood Body Mass Index and Fasting Glucose and Insulin Predict Adult Type-2 Diabetes: The International Childhood Cardiovascular Cohort (i3C) Consortium

Short title: Child BMI,Glucose,Insulin Predict Adult T2DM

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The word count and number of tables and figures: 3,249 words, 3 tables, 1 figure

STRUCTURED ABSTRACT

Objective: To examine childhood body mass index (BMI), fasting glucose and insulin in relation to incident adult type-2 diabetes mellitus (T2DM).

Research Design and Methods: We used data from The International Childhood Cardiovascular Cohort Consortium. Data included childhood measurements (age 3-19) obtained during the 1970s-90s, a health questionnaire including self-report of adult T2DM (occurrence age, medication use) obtained at mean age 40 years, and a medical diagnosis registry (Finland).

Results: The sample included 6,738 participants. Of these, 436 (6.5%) reported onset of T2DM between ages 20-59 (mean 40.8) years, and 86% of them reported use of a confirmed anti-diabetic medication. BMI and glucose (age- and sex-standardized) were associated with incident T2DM after adjustment for cohort, country, sex, race, age and calendar year of measurement . Increasing levels of childhood BMI and glucose were related to incrementally increased risk of T2DM beginning at age 30, beginning at cutpointsbelow the 95th percentile for BMI and below 100 mg/dL for glucose. Insulin was positively associated with adult T2DM after adjustment for BMI and glucose and added to T2DM discrimination.

Conclusions: Childhood BMI and glucose are predictors of adult T2DM at levels previously considered to be within the normal range. These easy to apply measurements are appealing from a clinical perspective. Fasting insulin has the potential to be an additional predictor.

According to the most recent estimates from the World Health Organization (2014), diabetes (mostly type-2 diabetes mellitus [T2DM]) affects 8.5% (422 million) of the total world population aged 18 years and older(1). Although T2DM historically has been an adult disease, its precursors are found in childhood(2-4), and body composition and pathways of growth as early as in-utero have been associated with risk of developing T2DM(5). Thus, it is relevant to conduct studies in childhood in an attempt to identify factors associated with the risk for and development of T2DM.

Evidence from population-based studies has shown an association between childhood obesity and adult T2DM(5-11) and a few studies have suggested that childhood glucose levels are associated with the development of prediabetes and T2DM(7; 12-15). While childhood insulin has been reported to predict T2DM in young adulthood,(13) it has also been reported that adolescent insulin measurements were not related to adult T2DM(16). However, the levels of childhood body mass index (BMI) and glucose associated with adult T2DM have not been well defined(14), (17), and little information is available on whether childhood insulin might add to prediction of adult T2DM, beyond BMI and glucose. Using data from a collaboration of seven cohorts recruited in childhood and followed with repeated measures into adulthood, this study aims to develop a childhood risk profile for adult T2DM (18). We hypothesized that childhood BMI and glucose predict the risk of adult T2DM, and childhood insulin adds prediction to BMI and glucose.

RESEARCH DESIGN AND METHODS

The study sample

Participants for this study were drawn from the International Childhood Cardiovascular Cohort (i3C) Consortium, a collaboration of seven long-standing cohorts from three continents, including Young Finns Study, Finland; Childhood Determinants of Adult Health Study, Australia; Princeton Lipid Research Study and the National Heart, Lung, and Blood Institute Growth and Health Study, Cincinnati, OH, US; The Bogalusa Heart Study, Bogalusa, LA, US; The Minneapolis Children's Cohorts, Minneapolis, MN, US; and the Muscatine Study, Muscatine, IA, US. The children and adolescents in these cohorts were recruited during the 1970s to 1990s, with baseline assessment of cardiovascular risk factors. In 2015-2019, participants in Australia and the United States were re-contacted and completed a Heart Health Survey (HHS) questionnaire, including self-report of diabetes and a medication history, either on-line or by telephone interview. Participants in the Finnish cohort were followed up through 2011 but their data in the Finnish national medical registry were available through 2018.

The i3C consortium was established for general purposes of cardiovascular epidemiology. Because recruitment of participants and childhood data collection occurred prior to forming the consortium, each of the seven cohorts had individually designed protocols and the content and age of data collection by the cohorts was not uniform (18). The present study does not include data from the Childhood Determinants of Adult Health Study, Australia and the Muscatine Study, Muscatine, IA, US, because these studies do not have childhood measurements of blood glucose. Thus, the present study includes 4 US cohorts and 1 Finnish cohort: childhood BMI and blood glucose data from the Young Finns Study, Princeton Lipid

Research Study, the National Heart, Lung, and Blood Institute Growth and Health Study, The Bogalusa Heart Study, and The Minneapolis Insulin Study). Childhood insulin was not available in the Princeton Study and childhood glucose was available from half of the participants from the Young Finns Study. The base sample for studies of childhood anthropometric and laboratory measures predicting new onset T2DM at or after age 20 was all participants with followup age ≥20 years and with any childhood anthropometric or laboratory measure available, N = 18.626. Of the participants in these cohorts, we further excluded those in races other than black and white from our analytic samples relating to childhood BMI and glucose (N=6,738), childhood BMI, glucose and fasting insulin (N=5,196), and childhood BMI and fasting insulin (N=6,576),

Childhood measurements

BMI, fasting blood glucose and insulin were measured at least once during ages 3-19, with the laboratory analyses performed at each cohort site in nationally monitored facilities. These data were available in subsets of participants, depending on the study protocol in each cohort throughout childhood. Height was measured with a stadiometer and weight with a calibrated scale. BMI was calculated as kg/m^2. Information on cohort, country, age and calendar year of measurement, sex, and race was available for each cohort.

Adult T2DM ascertainment

Data on T2DM were based on a self-report Heart Health Survey conducted in the US and Australian cohorts in 2015-2019; data from Finland were obtained from a

national registry, and in a smaller group of Finnish individuals blood glucose and hemoglobin A1c were available through 2018. Historical and current medication information was also self-reported concurrently. We excluded participants who reported onset of diabetes before age 20 to separate child predictor data from adult outcome data. Most of the 7 participants who reported adolescent T2DM were severely obese in childhood, but the sample size was insufficient for meaningful analysis.

All previous examinations and the current HHS questionnaire were approved by each Institutional Review Board (IRB). Parental consent and signed participant assent were obtained for individuals less than age 18 years at the time of childhood examinations. For adults, the study was explained on-line in a preface to the HHS; completion of the questionnaire was taken to be implied consent. For the HHS completed by telephone interview, the questionnaire was administered by study coordinators who explained the study to the participants using standardized language, addressed participant questions, and verified the participant's willingness to participate prior to conducting the HHS.

Statistical Analysis

We computed the z-scores for BMI, fasting glucose level, and log transformed insulin (ln(insulin)), and then averaged across childhood visits (ages 3-19; median [interquartile range] numbers of child BMI, glucose and ln(insulin) 3 [2,4], 1 [1,3], and 2 [1,3], respectively) for each person. A z-score was based on age- and sex-specific mean and standard deviation values obtained from the i3C cohorts (Age categories

3-5, 6-8, 9-11, 12-14, 15-17, 18-19 years). This approach assumes that use of z-scores in variables centered at their group means equalizes across age and sex groups. **Supplemental Table S1** provides corresponding age-sex specific natural unit values of BMI, fasting glucose, and fasting insulin for z scores of -1, 0, 0.5, and 1.

We performed Cox regression analysis to predict the risk of adult T2DM with the z-scores of BMI and glucose, and ran a separate model including the risk score, defined as mean of childhood BMI and glucose z-scores. Adjustment was for individual mean age and calendar year across child visits, sex, race, country, and cohort. The time to event was computed as age at T2DM occurrence or censoring minus individual mean age across childhood visits. We calculated the unadjusted cumulative incidence for adult T2DM using the Kaplan-Meier method, stratified by childhood predictor categories which were equal interval and open-ended extreme. Given the perception that childhood obesity is a strong predictor of adult T2DM, we also examined the associations in subsets of participants with BMI below or above the age- and sex-specific average.

To examine whether childhood insulin predicts the risk of adult T2DM independent of childhood BMI and glucose, we examined the association between childhood ln(insulin) and risk of incident adult T2DM with adjustment for childhood BMI and glucose or adjustment for BMI only. If ln(insulin) was significantly associated with incident T2DM with adjustment, we stratified T2DM incidence according to categories of a risk score formed from childhood BMI, glucose and ln(insulin) by the category of the risk score formed from childhood BMI and glucose to calculate

absolute risks before and after reclassification by adding childhood ln(insulin). We examined the associations within each race group. We also examined childhood systolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and smoking and found no confounding. All analyses were conducted using SAS 9.4 (SAS institute, Cary, North Carolina, USA).

RESULTS

Sample description

There were 18,626 i3C participants with self-reported adult T2DM status in the Heart Health Survey or objectively diagnosed adult T2DM in the YFS, followed after age 19, and a measure of any of the anthropometric and laboratory data. As shown in Supplemental Table S2, T2DM prevalence was not different between the analytic sample (N= 6,738) and the larger i3C sample (N= 18,626) participants in this report (6.5% vs. 6.0%, P= 0.18). The analytic sample included more females and blacks, and had higher childhood BMI, lower childhood glucose and lower insulin z-scores; and the childhood measurements were obtained at a slightly younger age. Participants who were not included (N=11,888) in this report were mostly from two cohorts (Childhood Determinants of Adult Health Study, Australia and the Muscatine Study, Muscatine, IA, US) where childhood data on glucose and insulin were not obtained.

In the sample, 436 participants developed T2DM (2 also reported Type-1 diabetes). **Table 1** compares the 436 participants with T2DM to the 6,302 without

T2DM. Of the participants reporting T2DM, 86% also reported use of anti-diabetic medications. The onset of T2DM was between ages 20-59 (mean 40.8) years, and the participants with T2DM were slightly older than non-diabetic participants (48.0± 7.2 vs 43.8± 7.8 years; P< 0.001) years. After adjustment for age at adult follow-up, women had a higher risk of T2DM than men and blacks had a higher risk of T2DM than whites (P for both< 0.001). Risk of T2DM varied by cohort

Child BMI and glucose as predictors of adult T2DM

BMI showed weak correlation with glucose (r= 0.06). The z-scores of BMI and glucose were significantly associated with incident T2DM, with HR (95% CI) 1.55 (1.44, 1.67) and 1.24 (1.13, 1.35), respectively, per z-score unit after adjustment for cohort, country, sex, race, age and calendar year of measurement (**Table 2**). When BMI and glucose were combined into a risk score by using the mean of the two z-scores, the HR (95% CI) was 1.87 (1.72, 2.05) after adjustment for the aforementioned covariates. The positive associations of childhood BMI and glucose with the risk of adult T2DM were observed within each participating cohort (**Table 2**).

To take follow up age into account, we plotted Kaplan-Meier curves (**Figures 1A-1C**) to present the probability for developing T2DM over adult ages (beginning at age 20) for BMI z-score, glucose z-score and the risk z-score (based on BMI and glucose). We categorized each child risk variable by an interval of 0.5-unit z-scores with open-ended extremes, and assessed the levels of childhood risk factors associating with cumulative incidence of adult T2DM. Participants in the four lowest z-score categories (z-scores < +0.5 in aggregate) of childhood BMI showed similar

risk of T2DM, while those with BMI z-scores +0.5 - < +1 and scores ≥ +1 had incrementally increased risk of T2DM beginning at age 30 (Figure 1A). Similar patterns were observed for childhood glucose category, though risk difference is minimal between the childhood glucose z-score +0.5 - < +1 and ≥ +1 categories. Participants with the risk score (BMI and glucose) > +1 had 15% and 28% risk of T2DM at ages 40 and 50, compared to 12.5% and 18% in those with the risk score +0.5 - < +1 and to 6% and 3.5% in those with the risk score < +0.5 at ages 40 and 50, respectively.

The z-scores from -1 to +1 for BMI and glucose are back-transformed to natural units in **Supplemental Table S1**. Focusing on the higher z-scores, which are significantly associated with development of adult T2DM, for each age and sex subgroup the mean absolute glucose level of z-score of +0.5 ranged from 83.8 to 91.8 mg/dL, and the mean absolute glucose level of a z-score of +1 ranged from 88.4 to 99.4 mg/dL. Each of these levels is lower than the historically defined cut point for impaired fasting glucose of 100 mg/dL. Mean BMI cut points at a z-score of +0.5 ranged between the 75th and 90th percentiles and mean BMI cut points at a BMI z-score of +1 ranged between the 85th and 95th percentiles, all below the CDC defined percentiles for obesity (19).

Insulin as an additional predictor

Childhood fasting insulin was assessed in 5,196 participants in whom childhood BMI and glucose were also assessed. The correlation coefficient was 0.39 between childhood ln(insulin) and BMI z-scores and was 0.18 between childhood

ln(insulin) and glucose z-scores. After adjustment for BMI or BMI and glucose in childhood, childhood ln(insulin) was positively associated with risk of adult T2DM overall and in each participating study (**Table 2**). Kaplan-Meier curves show risk of adult T2DM increased at ln(insulin) z-score levels of at least 0.5 (**Figure 1D**). Similar Kaplan-Meier patterns were observed for the BMI, glucose and ln(insulin) risk score (**Figure 1E**). Findings were similar in **Supplemental Table S3** in analyses of all available childhood fasting insulin values (6,576 participants; childhood BMI measured, but glucose assessment not required).

To examine whether childhood insulin adds to the prediction of the risk of adult T2DM beyond that of childhood BMI and glucose, **Table 3** shows observed T2DM risk for reclassified individuals with the addition of childhood ln(insulin), based on childhood BMI and glucose (mean of BMI, glucose and ln(insulin) z-scores vs. mean of BMI and glucose z-scores). Increasing risk within a column is indicative of improved discrimination by using the mean BMI, glucose, and ln(insulin) z scores rather than the mean BMI and glucose z-scores. For each expected risk category of the mean BMI and glucose z-score, observed risk was higher, the higher the expected risk category of mean BMI, glucose, and fasting insulin z-score. The one exception was for the 51 people whose expected risk was +0.5 - < +1 according to the mean BMI and glucose z-score and expected risk was ≥ +1 according to the the mean BMI, glucose, and fasting insulin z-score.

Prediction in participants with lower BMI

The relation of childhood glucose to incident adult T2DM was further assessed by level of BMI (z-scores <0 vs. ≥0). Glucose distribution was similar between the two BMI subgroups. For example, the glucose difference between participants with T2DM and without T2DM was similar for the two BMI groups (glucose mean ± SD in BMI z-score <0: 0.24 ± 0.73; in BMI z-score >0: 0.28 ± 0.81), and the range of glucose (75^{th}, 90^{th}, and 95^{th} percentiles) was also similar (0.59, 1.04, and 1.35 in the BMI z-score <0 and 0.68, 1.22 and 1.36 in the BMI z-score ≥0 groups).

Multivariable analysis among participants with BMI z-scores <0 shows that glucose z-score was positively associated with T2DM occurrence, with a HR (95% CI) of 1.21 (1.07, 1.36) after adjustment for BMI z-score as well as cohort, country, sex, race, age and calendar year of measurement as covariates (**Supplemental Table S4**). ln(insulin) z-score was also positively associated with T2DM occurrence among participants with BMI z-scores <0, with a HR (95% CI) of 1.15 (0.92, 1.44) after adjustment for BMI and glucose z-scores as well as the aforementioned covariates.(**Supplemental Table S4**).

While T2DM risk was higher in blacks, the associations were not modified by race. P values for interaction by race in the analysis of BMI, glucose and insulin were all greater than 0.15. We compared the black with the white groups in terms of the BMI, glucose and insulin analyses (**Supplemental Table S5**). Overall, there is little difference in risk relationships between black and white participants regarding the above variables. Childhood BMI, glucose and ln(insulin) were positively associated with the risk of adult T2DM in both the black and white groups.

CONCLUSIONS

This population-based study shows that childhood BMI and blood glucose levels, both individually and in combination, were positively associated with the risk of adult T2DM. From age 30, the incidence of T2DM started to increase when BMI and glucose z-scores were at least +0.5 and more obviously when they were at least +1, suggesting that potential cut points could be selected within the range of z-scores from +0.5 to +1 for childhood BMI and glucose. While the natural units at these z-scores vary by age and sex, these values are lower than the currently used cut points for childhood obesity (BMI ≥ 95th percentile) and impaired fasting glucose (≥100 mg/dL). Childhood insulin was positively associated with the risk of adult T2DM and adding insulin further increased the separation between the predictions of T2DM and non-T2DM, namely improved discrimination. Therefore, the prospective nature of this study with longitudinal follow-up into adulthood and adult ascertainment of T2DM shows not only child risk factors for adult T2DM, but also shows that the risk begins at lower levels of the risk factors than currently appreciated.

The positive relation between childhood BMI and adult T2DM risk has been previously reported(7; 10; 13; 20). Data from the present study suggest that childhood BMI cut points corresponding to 75th-90th percentile BMI based on CDC growth charts are at heightened risk for adult T2DM. This finding contrasts with the BMI criteria for high-risk T2DM put forth by the American Diabetes Association and American Academy of Pediatrics (greater than 85th percentile), by including children who were traditionally normal weight(2; 3). Our data show little correlation between BMI and glucose in childhood and suggest that children with low BMI (BMI z-scores

<0) can develop adult T2DM by having elevated childhood glucose levels. It is known that children who are normal weight by traditional weight criteria may have insulin resistance(21-24), or increased percentage of body fat(25). Physiologically, adiposity may be associated with insulin resistance through elevated leptin levels(22) and/or levels of free fatty acids(26). It is reasonable to suggest that overweight/obesity leads to insulin resistance beginning in late adolescence and subsequent T2DM, a pathway also suggested by data from the Bogalusa Heart Study showing that elevated BMI during ages 5-7 precedes impaired glucose metabolism during ages 12-14(27). Our findings, advocate for T2DM prevention efforts even in children whose BMI is in the "high normal" range.

Previous studies have shown that elevated childhood glucose levels beyond 100 mg/dL predict T2DM risk(3; 12; 15). In contrast, our findings show childhood glucose levels above 84-90 mg/dL for children aged 3-11 and 88-92 mg/dL for adolescents aged 12-19 (z-scores ≥ +0.5) were associated with increased risk of adult T2DM. As the survival curve shows small difference in T2DM risk between the category of a z-score +0.5 - < +1 and the categories of glucose z-scores < +0.5, it would be more conservative to select cut points of high glucose at a value above a z-score of +0.5. The cut point lower than 100 mg/dL is in agreement with a report from the Bogalusa Heart Study among 1,849 participants (n T2DM=47) showing a threshold of childhood fasting glucose ≥86 mg/dL, predicting a 2.1 times higher risk for adult T2DM than those with a lower childhood glucose level(14). Another report using data from the Bogalusa Heart Study and Young Finns Study applied the cut point of 75th percentile glucose (approximately 86-93 mg/dL across ages 12-18,

modified National Cholesterol Education Program definition for metabolic syndrome) showing high glucose level is associated with 1.5 times risk of T2DM (95 CI 0.8, 2.9; n T2DM=37)(28). There are some differences between the Bogalusa Study analysis and our analysis, in that Bogalusa participants were selected differently and evaluated at mean age 35 (vs. mean age 45 in our study), the Bogalusa Study did not account for follow-up periods in statistical models and did not explore cut points by age and sex due to the small number of T2DM events(14). In any case, the present data extend T2DM follow up in both Bogalusa and Young Finn participants. It has been reported that childhood glucose levels of 90-100 mg/dL were associated with a lower β-cell function, thus lower insulin sensitivity(29). Therefore, the findings from the literature and our study support a role of "high normal" glucose as a predictor of adult T2DM.

Childhood insulin was associated with the risk of T2DM in adulthood and it has added value in prediction of adult T2DM risk. However, insulin is not routinely measured in most pediatric practices and values have historically been difficult to standardize and interpret due to wide variability in assays between laboratories and over time, as well as fluctuations related to the insulin resistance of puberty(16). While lower childhood insulin may have some degree of predictive value, future studies are needed to further assess its utility as a screening tool for risk of adult T2DM.

Strengths and Limitations:

This study has several strengths. First, as a part of the i3C Consortium, well-established quality control procedures were used for data collection and followed within each participating cohort. Second, a large proportion of i3C had repeated measurements of cardiometabolic risk variables in childhood, which enabled us to reduce individual variability of measurements. Third, this study was conducted in a large sample and participants were followed over 30 years.

Several limitations of this study should be noted. First, this is an observational study; thus, the possibility of residual confounding cannot be eliminated, and we cannot infer any causal effect. It is conceivable that genetic or in utero factors would contribute to both the childhood measurements and the adult disease. Second, puberty has been suggested to increase insulin resistance(30; 31), and with insufficient data of sexual development and insulin resistance, it was not possible to evaluate this association. However, we used age-specific cut points in order to reduce the influence of age-related pubertal (and growth) changes. Third, the i3C included black and white participants from the US and Finland, and it is unclear whether the conclusions are generalizable to other races and/or low-income countries. *Fourth, self-report was used in 6 of the i3C cohorts. Although self-report underestimates T2DM occurrence, most self-reports of T2DM are probably correct. This concept is supported by the use of anti-diabetic medications, as it is commonly known that only a small proportion of people with adult T2DM are not treated with medications.* Previous reports on the quality of information obtained from self-report on diabetes in middle age populations have shown moderate-to-high sensitivity (66%-84%), high specificity (97%-99.7%), and high reliability (92-97%)(32-34). The

Finnish cohort used their biochemical test at their clinic vists and their national medical database to ascertain T2DM.

In conclusion, childhood BMI and glucose, individually and in combination, are predictors of adult T2DM risk at levels currently considered to be mostly within the normal range. Insulin has the potential to be an additional predictor, and its clinical utility could be improved by developing a more standardized approach to the measurement in the future. The provisionally suggested cut points, which are lower than currently defined as abnormal, suggest revisiting the criteria of childhood BMI and glucose as predictors of adult T2DM risk and initiating lifestyle interventions at lower BMI and glucose thresholds.

ACKNOWLEDGMENTS

T.H. wrote the manuscript and analyzed data. D.R.J. provided oversight for data analysis. A.R.S. contributed to the discussion and reviewed/edited the manuscript. L.A.B., T.L.B., S.R.D., T.D., M.J., R.J.P., O.T.R., E.M.U., A.V., J.G.W, N.K, and K.A.M. reviewed/edited the manuscript, J.S. contributed to study design and data collection, designed/reviewed/edited the manuscript, and took responsibility for the contents of the article.

This work was supported by the US National Institutes of Health (NIH; grant number R01 HL121230). Harmonization and other data work prior to obtaining NIH funding was supported by the Australian National Health and Medical Research Council Project (grant number APP1098369, APP211316), the Academy of Finland (grant numbers: 126925, 121584, 124282, 129378, 117787 and 41071), the Social

Insurance Institution of Finland; Kuopio, Tampere, and Turku University Hospital Medical Funds, Juho Vainio Foundation, Paavo Nurmi Foundation, Finnish Foundation of Cardiovascular Research, Finnish Cultural Foundation, Sigrid Juselius Foundation, and Yrjö Jahnsson Foundation.

The authors have no conflict of interest.

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Table 1. Descriptive characteristics of childhood risk factors for adult self-reported T2DM (N=6,738)

	T2DM	Not T2DM	P diff
Overall, n (row %)	436 (6.5%)	6,302 (93.5%)	
Age at adult follow-up			
Mean (SD)	48.0 (7.2)	43.8 (7.8)	<0.001
Range	27 - 62	20 - 62	
Age at T2DM occurrence			
Mean (SD)	40.8 (8.7)	N/A	N/A
Range	20 - 59	N/A	
Sex, n (row % *)			0.011
Male	153 (4.8%)	2,569 (95.2%)	
Female	283 (6.2%)	3,733 (93.8%)	
Race, n (row % *)			<0.001
White	292 (5.0%)	4,520 (95.0%)	
Black	144 (7.4%)	1,782 (92.6%)	
Cohort			<0.001
Bogalusa Heart Study	265 (7.4%)	2,961 (92.6%)	
Minneapolis Children's Cohort (Insulin Study)	13 (4.6%)	477 (95.4%)	
National Heart, Lung, and Blood Institute Growth and Health Study	9 (3.0%)	428 (97.0%)	
Princeton Lipid Research Study	79 (5.4%)	709 (94.6%)	
Young Finns Study	70 (3.8%)	1,727 (96.2%)	

T2DM: type-2 diabetes mellitus

* T2DM prevalence adjusted for age at adult follow-up

Table 2. Multivariable analysis for the association of childhood BMI, glucose, and ln(insulin) z-scores with adult T2DM *

Model		Overall	BHS	Princeton	YFS	NHGS+MN Insulin
			BMI and glucose			
	n T2DM/N	436/6,738	265/3,226	79/788	70/1,797	22/927
Multivariable model						
BMI	HR (95% CI)	1.55 (1.44, 1.67)	1.52 (1.39, 1.66)	1.40 (1.15, 1.69)	2.02 (1.57, 2.62)	1.84 (1.40, 2.42)
	P	<0.001	<0.001	<0.001	<0.001	<0.001
Glucose	HR (95% CI)	1.24 (1.13, 1.35)	1.32 (1.16, 1.52)	1.08 (0.82, 1.42)	1.22 (1.04, 1.42)	1.46 (0.89, 2.40)
	P	<0.001	<0.001	0.590	0.012	0.134
Risk score model						
Mean BMI and glucose	HR (95% CI)	1.87 (1.72, 2.05)	2.08 (1.81, 2.40)	1.60 (1.22, 2.10)	1.64 (1.36, 1.97)	2.97 (1.93, 4.58)
	P	<0.001	<0.001	<0.001	<0.001	<0.001
			BMI, glucose and ln(insulin)			
	n T2DM/N	284/5,196	198/2,605	0/0	70/1,797	15/789
Multivariable model						
BMI	HR (95% CI)	1.44 (1.31, 1.59)	1.39 (1.24, 1.55)		1.82 (1.34, 2.48)	1.62 (1.12, 2.36)
	P	<0.001	<0.001		<0.001	0.011
Glucose	HR (95% CI)	1.23 (1.10, 1.37)	1.34 (1.08, 1.68)		1.20 (1.02, 1.41)	2.36 (0.99, 5.65)
	P	<0.001	0.010		0.031	0.055
ln(insulin)	HR (95% CI)	1.34 (1.16, 1.56)	1.26 (1.07, 1.50)		1.33 (0.87, 2.02)	1.93 (1.09, 3.41)
	P	<0.001	0.008		0.189	0.025
Risk score model						
Mean BMI, glucose, and ln(insulin)	HR (95% CI)	2.38 (2.08, 2.73)	2.40 (1.99, 2.90)		2.11 (1.64, 2.72)	5.80 (2.98, 11.3)
	P	<0.001	<0.001		<0.001	<0.001

BMI: Body mass index; T2DM: type-2 diabetes mellitus
* Cox regression analysis with childhood variable z-scores. Z-scores are age-sex standardized deviates based on the i3C distribution. Adjustment is for individual mean age and calendar year across child visits, sex, race, country, and cohort. The time to event was computed as age at T2DM occurrence or censoring minus individual mean age across child visits.

Table 3. Risk (probability) table for reclassified individuals with the addition of childhood ln(insulin), based on childhood BMI and glucose. (n T2DM/N=244/5,196=0.055)

Mean BMI, glucose and ln(insulin) z-scores	Mean BMI and glucose z-scores †					
	< +0.5		+0.5 - < +1		≥ +1	
	N	Risk (SE)	N	Risk (SE)	N	Risk (SE)
< +0.5	4,213	0.040 (0.003)	162	0.056 (0.018)	2	*
+0.5 - < +1	144	0.097 (0.025)	289	0.125 (0.019)	88	0.136 (0.037)
≥ +1	4	*	51	0.118 (0.046)	243	0.156 (0.023)
All (BMI/glucose marginal risk)	4,361	0.042 (0.003)	502	0.102 (0.013)	333	0.150 (0.020)

BMI: body mass index, T2DM: type-2 diabetes; SE: standard error

* Risk value ignored in cells with N < 5

† Increasing risk within a column is indicative of improved discrimination by using the mean BMI, glucose, and ln(insulin) z scores rather than the mean BMI and glucose z-scores

FIGURE LEGEND

Figure 1. Kaplan-Meier figures of type-2 diabetes mellitus (T2DM) over time, stratified childhood risk factors: A) body mass index (BMI) z-score, B) glucose z-score, C) mean BMI and glucose z-scores, D) ln(insulin) z-score, and E) mean BMI, glucose and ln(insulin) z-scores. Z-score categories: black diamond: < -1; white square: -1, < -0.5; black triangle: -0.5, < 0; white diamond: 0, < +0.5; cross: +0.5, < +1; black circle: ≥ +1. Z-scores on the natural scale, corresponding to cut points of +0.5 and +1 were shown in Supplemental Table S1.

Supplemental Table S1. Back transformed value for BMI, glucose, and insulin for z-scores of -1, 0, 0.5, and 1

Variable	Sex	z-score	Age 3-5	Age 6-8	Age 9-11	Age 12-14	Age 15-17	Age 18-19
BMI (kg/m2)	Male	-1	14.2	14.3	14.9	16.3	18.1	19.0
		0	15.9	16.6	18.1	20.1	22.0	23.1
		0.5	16.8	17.8	19.7	22.0	24.0	25.2
		1	17.7	18.9	21.2	23.9	25.9	27.2
	Female	-1	13.8	14.0	14.8	16.5	17.7	18.0

		0	15.8	16.5	18.3	20.8	22.5	23.6
		0.5	16.8	17.8	20.1	23.0	24.9	26.5
		1	17.7	19	21.8	25.2	27.2	29.3
Glucose	Male	-1	70.8	71.7	75.1	78.4	76.8	74.8
(mg/dl)		0	81.0	82.3	84.5	87.3	86.1	86.1
		0.5	86.1	87.6	89.2	91.7	90.7	91.7
		1	91.1	92.9	93.9	96.1	95.2	97.3
	Female	-1	69.5	71.5	74.1	75.7	67.3	67.7
		0	78.9	80.4	84.9	85.1	80.9	83.6
		0.5	83.8	84.8	90.4	89.9	87.8	91.5
		1	88.4	89.2	95.8	94.6	94.6	99.4
Insulin	male	-1	2.1	3.3	4.3	5.5	5.9	5.7
(microM/L)		0	4.6	6.2	7.4	9.7	10.5	10.2
		0.5	7.5	8.9	10.2	13.3	14.7	14.3

	1	10.3	11.6	12.9	16.9	18.8	18.3
female	-1	2.4	3.8	4.9	7.1	7.0	5.5
	0	5.1	7.0	9.3	12.1	11.9	10.0
	0.5	8.1	9.9	13.5	16.4	16.2	14.1
	1	11.0	12.7	17.6	20.6	20.5	18.1

BMI: Body mass index

Supplemental Table S2. Descriptive characteristics in participants included in the analytic sample (black and white participants with childhood BMI and glucose measures both available) vs. not included (all others with followup age ≥20 years and with any childhood anthropometric or laboratory measure available), Total N = 18.626.

	Included in analytic sample	Not included in analytic sample	P difference
N (otherwise noted)	6,738	11,888	
Adult T2DM, n (%)	436 (6.5%)	713 (6.0%)	0.20
Male, n (%)	2,722 (40.4%)	5,517 (46.4%)	<0.001
Race, n (%)			<0.001
US Black	1,926 (28.6%)	257 (2.2%)	
Others	0 (0.0%)	363 (3.1%)	
Cohort, n (%)			<0.001
Bogalusa Heart Study	3,326 (47.9%)	205 (1.7%)	
Childhood Determinants of Adult Health Study	0 (0.0%)	3,036 (25.5%)	
Minneapolis Children's Cohort	490 (7.3%)	686 (5.8%)	

Muscatine Study	0 (0.0%)	6,039 (50.8%)	
National Heart, Lung, and Blood Institute Growth and Health Study	437 (6.5%)	62 (0.5%)	
Princeton Lipid Research Study	788 (11.7%)	71 (0.6%)	
Young Finns Study	1,797 (26.7%)	1,789 (15.1%)	
Child BMI z-score	-0.06 (0.99)	-0.12 (0.80)*	<0.001
Child Glucose z-score	0.01 (0.82)	1.10 (3.77)†	0.020
Child ln(insulin) z-score	-0.02 (0.82)	0.09 (0.83)‡	<0.001
Age of first child measurement, year	12.1 (3.1)	12.5 (3.1)*	<0.001

BMI: body mass index; T2DM: type-2 diabetes mellitus

*N=11,882 (not included due to missing glucose)

†N=68 (not included due to participant being of other race, missing BMI, or being a Young Finns Study participant with biochemically diagnosed Type 1 diabetes)

‡N=5,196 (included) and 1,818 (not included due to missing glucose or being a Young Finns Study participant with biochemically diagnosed Type 1 diabetes)

Supplemental Table S3. Multivariable analysis for the association of childhood BMI and ln(Insulin) z-scores with adult T2DM *

Model		Overall	BHS	YFS	NHGS+MN Insulin
	n T2DM/N	388/6,576	199/2,610	174/3,560	15/794
Multivariable model					
BMI	HR (95% CI)	1.50 (1.37, 1.65)	1.41 (1.26, 1.57)	1.79 (1.47, 2.17)	1.61 (1.09, 2.35)
	P	<0.001	<0.001	<0.001	0.016
ln(insulin)	HR (95% CI)	1.31 (1.14, 1.49)	1.31 (1.11, 1.55)	1.15 (0.92, 1.45)	2.30 (1.30, 4.08)
	P	<0.001	0.001	0.222	0.004
Risk score model					
Mean of BMI and ln(insulin)	HR (95% CI)	2.03 (1.81, 2.28)	1.89 (1.63, 2.18)	2.17 (1.70, 2.76)	3.33 (2.06, 5.38)
	P	<0.001	<0.001	<0.001	<0.001

BMI: Body mass index; T2DM: type-2 diabetes mellitus

* Cox regression analysis with childhood BMI and ln(Insulin) z-scores. Z-scores are age-sex standard deviates based on the i3C distribution. Adjustment is for individual mean age and calendar year across child visits, sex, race, country, and cohort. The time to event was computed as age at T2DM occurrence or censoring minus individual mean age across childhood visits. Princeton has no childhood insulin data.

Supplemental Table S4. Multivariable analysis for the association of childhood BMI and glucose z-scores with adult T2DM, according to childhood BMI levels *

Risk factor models	BMI below age- and sex-average		BMI at or above age- and sex-average	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
	BMI and glucose			
n T2DM/N	215/4,400		221/2,338	
Multivariable model				
BMI z-score	1.35 (0.92, 1.97)	0.123	1.46 (1.30, 1.63)	<0.001
Glucose z-score	1.21 (1.07, 1.36)	0.002	1.33 (1.12, 1.59)	0.001
Risk score model:				
Mean of BMI and glucose z-scores	1.49 (1.19, 1.86)	<0.001	2.00 (1.69, 2.36)	<0.001
	BMI, glucose, and ln(insulin)			

n T2DM/N	133/3,363		151/1,833	
Multivariable model				
BMI z-score	1.30 (0.79, 2.12)	0.302	1.31 (1.14, 1.50)	<0.001
Glucose z-score	1.21 (1.05, 1.39)	0.008	1.31 (1.03, 1.68)	0.029
ln(insulin) z-score	1.15 (0.92, 1.44)	0.227	1.47 (1.20, 1.79)	<0.001
Risk score model:				
Mean of BMI, glucose, and ln(insulin) z-scores	1.70 (1.22, 2.38)	0.002	2.50 (1.99, 3.14)	<0.001

BMI: Body mass index; T2DM: type-2 diabetes mellitus

* Cox regression analysis with childhood BMI and glucose z-scores. Z-scores are age-sex standard deviates based on the i3C distribution. Adjustment is for individual mean age and calendar year across child visits, sex, race, country, and cohort. The time to event was computed as age at T2DM occurrence or censoring minus individual mean age across childhood visits. P for interaction >0.10 except for comparison of mean of BMI and glucose z-scores, p interaction = 0.03.

Supplemental Table S5. Multivariable analysis for comparison of the association of childhood BMI, glucose, and ln(insulin) z-scores with adult T2DM in Black and White participants

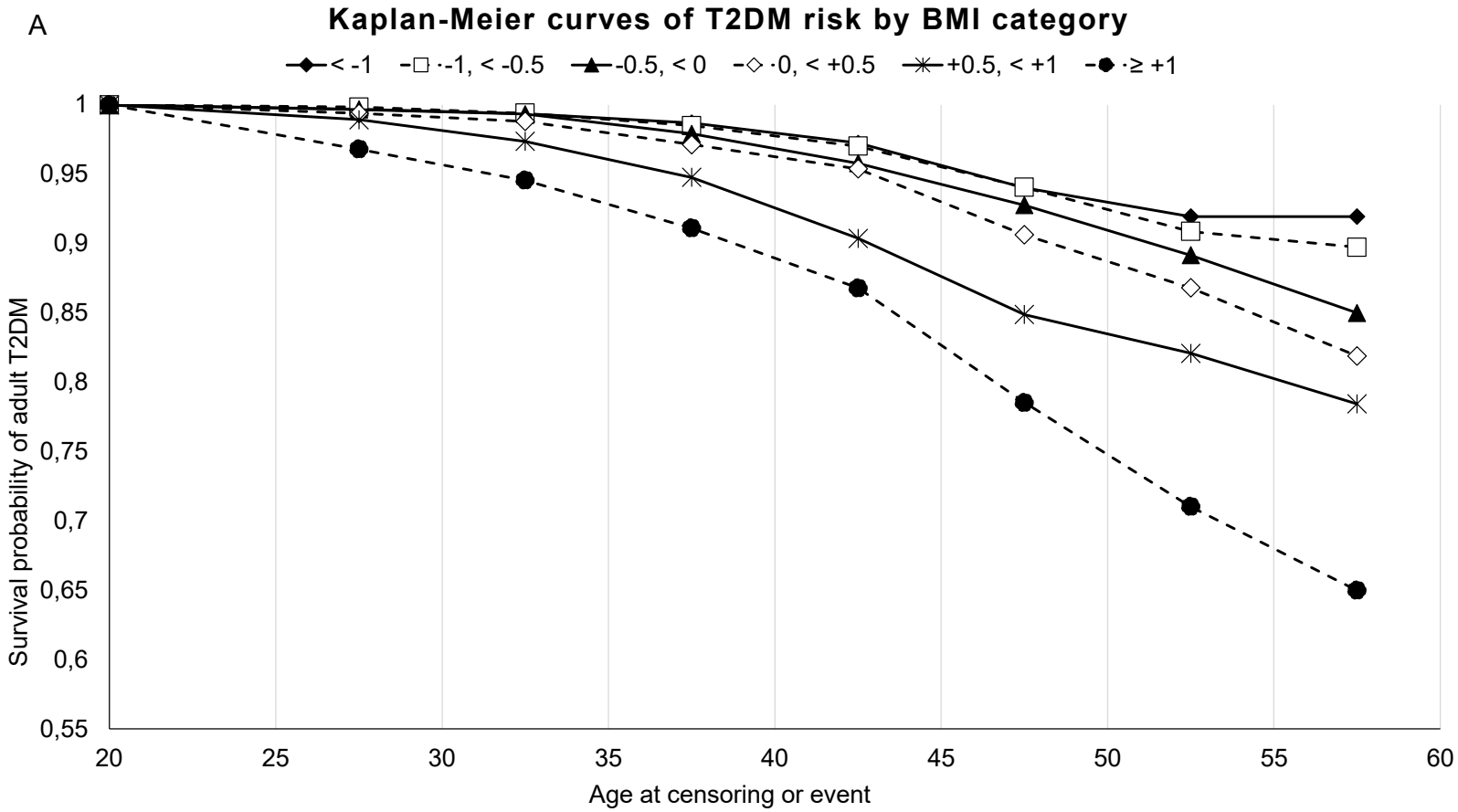
Model		Overall	Black	White
	N T2DM/N	436/6,738	144/1,926	292/4,812
Multivariable model				
BMI	HR (95% CI)	1.55 (1.44, 1.67)	1.40 (1.24, 1.57)	1.66 (1.51, 1.83)
	P	<0.001	<0.001	<0.001
Glucose	HR (95% CI)	1.24 (1.13, 1.35)	1.20 (0.98, 1.48)	1.26 (1.14, 1.39)
	P	<0.001	0.080	<0.001
	N T2DM/N	284/5,196	98/1,529	186/3,667
Multivariable model				
BMI	HR (95% CI)	1.44 (1.31, 1.59)	1.31 (1.12, 1.53)	1.54 (1.36, 1.74)
	P	<0.001	<0.001	<0.001
Glucose	HR (95% CI)	1.23 (1.10, 1.37)	1.20 (0.90, 1.61)	1.24 (1.10, 1.39)

	P	<0.001	0.212	<0.001
ln(insulin)	HR (95% CI)	1.34 (1.16, 1.56)	1.35 (1.07, 1.71)	1.31 (1.08, 1.60)
	P	<0.001	0.011	0.007

BMI: Body mass index; T2DM: type-2 diabetes mellitus

* Cox regression analysis with childhood variable z-scores. Z-scores are age-sex standardized deviates based on the i3C distribution. Adjustment is for individual mean age and calendar year across child visits, sex, race, country, and cohort. The time to event was computed as age at T2DM occurrence or censoring minus individual mean age across child visits. P values for interaction by race in the analysis of BMI, glucose and insulin were all greater than 0.15.

A


Kaplan-Meier curves of T2DM risk by BMI category
< -1
-1, < -0.5
-0.5, < 0
0, < +0.5
+0.5, < +1
≥ +1
Survival probability of adult T2DM
1
0,95
0,9
0,85
0,8
0,75
0,7
0,65
0,6
0,55
20
25
30
35
40
45
50
55
60
Age at censoring or event