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

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OBJECTIVE
To examine childhood 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 (age 3–19 years) measurements obtained during the 1970s-1990s; 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 and 59 (mean 40.8) years, and 86% of them reported use of a confirmed antidiabetic 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 an incrementally increased risk of T2DM beginning at age 30 years, beginning at cut points <95th percentile for BMI and <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 (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 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 the Young Finns Study, Finland; the Childhood Determinants of Adult Health Study, Australia; the Princeton Lipid Research Study and the National Heart, Lung, and Blood Institute Growth and Health Study, Bogalusa, LA; the Minneapolis Children’s Cohorts, Minneapolis, MN; and the Muscatine Study, Muscatine, IA. The children and adolescents in these cohorts were recruited during the 1970s–1990s, with baseline assessment of cardiovascular risk factors. In 2015–2019, participants in Australia and the U.S. were recontacted and completed the Heart Health Survey (HHS) questionnaire, including self-report of diabetes and a medication history, either online 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 before 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 current study does not include data from the Childhood Determinants of Adult Health Study and the Muscatine Study because these studies do not have childhood measurements of blood glucose. Thus, the current study includes four U.S. cohorts and one Finnish cohort (childhood BMI and blood glucose data from the Young Finns Study, the 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 one-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 years was all participants with follow-up age ≥20 years and with any childhood anthropometric or laboratory measure available (N = 18,626). In the analytic sample (n = 6,738), we included only white and black participants with childhood BMI and glucose measurements. Fasting insulin was also available in a subset (n = 5,196 of 6,738). In secondary analysis of BMI and insulin, not requiring glucose measurement, 6,576 participants were available.

Childhood Measurements

BMI, fasting blood glucose, and insulin were measured at least once during ages 3–19 years, 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/m². 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 the self-report HHS conducted in the U.S. 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 years to separate child predictor data from adult outcome data. Most of the seven 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. Parental consent and signed participant assent were obtained for individuals age <18 years at the time of childhood examinations. For adults, the study was explained online 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 before 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 years), with median (interquartile range) numbers of childhood BMI, glucose, and ln (insulin) of 3 (2, 4), 1 (1, 3), and 2 (1, 3), respectively, for each participant. A z-score was based on age- and sex-specific mean and SD values obtained from the i3C cohorts (age categories 3–5, 6–8, 9–11, 12–14, 15–17, and 18–19 years). This approach assumes that use of z-scores in variables centered at their group means equalizes across age- and sex groups. Supplementary Table 1 provides corresponding age- and sex-specific natural unit values of BMI, fasting glucose, and fasting insulin for z scores of −1, 0, 0.5, and 1. The average of the z-scores is the most statistically comprehensive method for using repeated measures. We separately analyzed the first measure or last measure as the childhood predictor of T2DM; the estimated mean z-score led to an as large or larger regression coefficient as any individual measure (data not shown). We also analyzed separately by age 3–11 and 12–19 years. Substantial differences in findings do not appear.
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 childhood 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, LDL cholesterol, HDL cholesterol, triglycerides, and smoking and found no confounding. All analyses were conducted using SAS 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS
Sample Description
There were 18,626 i3C participants with self-reported adult T2DM status in the HHS or objectively diagnosed adult T2DM in the Young Finns Study, followed after age 19 years, and a measure of any of the anthropometric and laboratory data. As shown in Supplementary Table 2, T2DM prevalence was not different between the analytic sample (n = 6,738) and the larger i3C sample (N = 18,626) in this report (6.5% vs. 6.0%, P = 0.18). Nevertheless, there were differences between those who had or did not have the requisite measurements. 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 and Muscatine Study), where childhood data on glucose and insulin were not obtained.

In the sample, 436 participants developed T2DM (92 self-reported having type 1 diabetes in the U.S. [2 reported T2DM also] and 20 biochemically diagnosed in Finland were included as not having T2DM; exclusion of these participants did not affect the conclusions). Table 1 compares the 436 participants with T2DM with the 6,302 without T2DM. Of the participants reporting T2DM, 86% also reported use of antidiabetic medications. The onset of T2DM was between ages 20 and 59 years (mean 40.8 years), and the participants with T2DM were slightly older than the participants without diabetes (48.0 ± 7.2 years 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.

Childhood 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 hazard ratios (HRs) (95% CIs) of 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 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 (Fig. 1A–C) to present the probability for developing T2DM over adult ages (beginning at age 20 years) for BMI, glucose, and risk z-scores (on the basis of 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 associated 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 of 0.5 to < 1 and scores ≥ 1 had incrementally increased risk of T2DM beginning at age 30 years (Fig. 1A). Similar patterns were observed for childhood glucose category, although risk difference is minimal between the childhood glucose z-score 0.5 to < 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 years compared with 12.5% and 18% in those with the risk score 0.5 to < 1 and with 6% and 3.5% in those with the risk score < 0.5 at ages 40 and 50 years, respectively.

The z-scores from − 1 to 1 for BMI and glucose are back-transformed to natural units in Supplementary Table 1. 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 Centers for Disease Control and Prevention–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 that risk of adult T2DM increased at ln(insulin) z-score levels of at least 0.5 (Fig. 1D). Similar Kaplan-Meier patterns were observed for the BMI, glucose, and ln(insulin) risk

<table>
<thead>
<tr>
<th>Table 2—Multivariable analysis for the association of childhood BMI, glucose, and ln(insulin) z-scores with adult T2DM</th>
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<tbody>
<tr>
<td>Model</td>
</tr>
<tr>
<td>BMI and glucose</td>
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<tr>
<td>n T2DM/N</td>
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<tr>
<td>Multivariable model</td>
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<tr>
<td>BMI</td>
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<tr>
<td>HR (95% CI)</td>
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<td>P value</td>
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<td>Glucose</td>
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<tr>
<td>HR (95% CI)</td>
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<td>P value</td>
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<tr>
<td>Risk score model</td>
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<tr>
<td>Mean BMI and glucose</td>
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<td>HR (95% CI)</td>
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<td>P value</td>
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<td>BMI, glucose and ln(insulin)</td>
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<td>n T2DM/N</td>
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<td>HR (95% CI)</td>
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<td>ln(insulin)</td>
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<tr>
<td>Risk score model</td>
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<tr>
<td>Mean BMI, glucose, and ln(insulin)</td>
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<td>HR (95% CI)</td>
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<td>P value</td>
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</table>

Cox regression analysis with childhood variable z-scores. The z-scores are age- and sex-standardized deviates on the basis of the i3C distribution. Adjustment is for individual mean age and calendar year across childhood 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. BHS, Bogalusa Heart Study; MN Insulin, Minneapolis Children’s Cohort (Insulin Study); NHGS, National Heart, Lung, and Blood Institute Growth and Health Study; Princeton, Princeton Lipid Research Study; YFS, Young Finns Study.
Findings were similar 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) on the natural scale, corresponding to cut points of 0.5 and 1, are shown in Supplementary Table 1.

Figure 1—Kaplan-Meier figures of T2DM over time, stratified by childhood risk factors: BMI z-score (A), glucose z-score (B), mean BMI and glucose z-scores (C), ln(insulin) z-score (D), and mean BMI, glucose, and ln(insulin) z-scores (E). The z-scores on the natural scale, corresponding to cut points of 0.5 and 1, are shown in Supplementary Table 1.
basis of 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 participants whose expected risk was 0.5 to ±1 according to the mean BMI and glucose z-score, and expected risk was ≥1 according to 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.

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

<table>
<thead>
<tr>
<th>Mean BMI and glucose z-scores†</th>
<th>&lt;0.5</th>
<th>0.5 to &lt;1</th>
<th>≥1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BMI, glucose, and ln(insulin) z-scores</td>
<td>n</td>
<td>Risk (SE)</td>
<td>n</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>4,213</td>
<td>0.040 (0.003)</td>
<td>162</td>
</tr>
<tr>
<td>0.5 to &lt;1</td>
<td>144</td>
<td>0.097 (0.025)</td>
<td>289</td>
</tr>
<tr>
<td>≥1</td>
<td>4</td>
<td>*</td>
<td>51</td>
</tr>
<tr>
<td>All (BMI/glucose marginal risk)</td>
<td>4,361</td>
<td>0.042 (0.003)</td>
<td>502</td>
</tr>
</tbody>
</table>

*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.
for the two BMI groups (glucose mean ± SD in BMI z-score < 0: 0.24 ± 0.73; in BMI
z-score ≥ 0.28 ± 0.81), and the range of glucose (75th, 90th, and 95th percentiles) was also similar
(0.59, 1.04, and 1.35, respectively, in the BMI z-score < 0 and 0.68, 1.22 and 1.36, respectively, in
the BMI z-score ≥0 groups).

Multivariable analysis among participants with BMI z-scores < 0 shows that
percentage and glucose z-score positively associated with T2DM occurrence, with an 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 mea-
measurement as covariates (Supplementary Table 4). The ln(insulin) z-score was also
positively associated with T2DM occurrence among participants with BMI z-
scores < 0, with an HR of 1.15 (0.92, 1.44) after adjustment for BMI and glucose
z-scores as well as the aforementioned covariates (Supplementary Table 4).

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 > 0.15. We compared the black with the white groups in terms of the BMI, glucose, and insulin analyses (Supple-
mentary Table 5). 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 the 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 years, 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 child-
hood 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 im-
paired fasting glucose (≥ 100 mg/dL). Childhood insulin was positively associated
with the risk of adult T2DM, and adding insulin further increased the separa-
tion between the predictions of T2DM
and non-T2DM, namely improved discrimina-
tion. Therefore, the prospective nature of this study with longitudinal follow-up into adulthood and adult as-
certainment of T2DM not only shows 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 child-
hood BMI and adult T2DM risk has been previously reported (7,10,13,20). Data
from the current study suggest that childhood BMI cut points corresponding to
the BMI z-score to 0.5, it would be
more conservative to select cut points of
high glucose at a z-score value of > 0.5. The cut point < 100 mg/dL is in agree-
ment 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, predict-
ing 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 (≥ 86–93 mg/dL
across ages 12–18 years [modified Na-	ional Cholesterol Education Program
definition for metabolic syndrome]), show-
ing that higher 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 a mean age of 35 years
(vs. a mean age of 45 years in our study)
and that the Bogalusa study did not
account for follow-up periods in statis-
tical models and did not explore cut points by age and sex because of the small number of T2DM events (14). In any
case, the present data extend T2DM follow-up in both Bogalusa and Young
Finns participants. It has been reported
that childhood glucose levels of 90–100
mg/dL were associated with a lower β-cell function and 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 because of wide variability in assays between labo-
atories and over time as well as fluctua-
tions related to the insulin resistance of
puberty (16). While lower childhood in-
sulin may have some degree of predictive value, future studies are needed to fur-
ter assess its utility as a screening tool
for risk of adult T2DM.

This study has several strengths. First, as a part of the i3C Consortium, well-
"established quality control procedures were used for data collection and fol-
lowed 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 >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 on sexual development and insulin resistance, it was not possible to evaluate this association. However, we used age-specific cut points to reduce the influence of age-related pubertal (and growth) changes. Third, the i3C included black and white participants from the U.S. 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 six 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 antidiabetic medications because 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-aged 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 its biochemical test at clinic visits and its 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.

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**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** 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/editied the manuscript. L.A.B., T.L.B., S.R.D., T.D., N.H.-K., M.J., K.A.M. R.J.P., 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/editied the manuscript. J.S. contributed to study design and data collection and designed, reviewed, and edited the manuscript. J.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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