

# Insulin and BMI as Predictors of Adult Type 2 Diabetes Mellitus

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## abstract

**BACKGROUND AND OBJECTIVES:** Fasting insulin concentrations are increasingly being used as a surrogate for insulin resistance and risk for type 2 diabetes (T2DM), although associations with adult outcomes are unclear. Our objective was to determine whether fasting insulin concentrations in childhood associate with later T2DM.

**METHODS:** Fasting insulin values were available from 2478 participants in the longitudinal Cardiovascular Risk in Young Finns Study at baseline age 3 to 18 years, along with data on adult T2DM ( $N = 84$ , mean age = 39.6 years).

**RESULTS:** Among 3- to 6-year-olds, a 1-SD increase in fasting insulin was associated with a relative risk (RR) of 2.04 (95% confidence interval [CI], 1.54–2.70) for later T2DM, which remained significant after we adjusted for BMI and parental history of T2DM. For those aged 9 to 18 years, a 1-SD increase in insulin was associated with an RR of 1.32 (95% CI, 1.06–1.65) for T2DM, but this became nonsignificant after we adjusted for BMI and parental history of T2DM. In the latter age group, a 1-SD increase in BMI was associated with an RR of 1.45 (95% CI, 1.21–1.73) for T2DM, with adjustment for insulin and parental history of T2DM not improving this association. BMI in younger children was not associated with later T2DM. In life course analyses, those with T2DM had higher fasting insulin levels in early childhood and later adulthood but not in peripubertal years.

**CONCLUSIONS:** Elevated fasting insulin concentrations in early childhood, but not adolescence, are independently associated with an elevated risk of T2DM in adulthood.

**WHAT'S KNOWN ON THIS SUBJECT:** Fasting insulin levels in childhood are increasingly being used as a surrogate for insulin resistance and risk of later type 2 diabetes, despite only a moderate correlation with whole-body insulin sensitivity and few data related to adult outcomes.

**WHAT THIS STUDY ADDS:** Elevated insulin values between the ages of 3 and 6 years are associated with an elevated risk for later type 2 diabetes. In 9- to 18-year-olds, elevated BMI (but not insulin values) is associated with later type 2 diabetes.

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Childhood obesity is associated with elevated risk for later type 2 diabetes mellitus (T2DM) and cardiovascular disease.<sup>1</sup> Approximately 3% of the world's population has diabetes, with this figure expected to increase to 4.4% (366 million) by 2030.<sup>2</sup> Longitudinal studies have shown that childhood obesity increases risk for later T2DM predominantly through tracking of obesity over many years and into adult life.<sup>3-5</sup> During childhood, greater BMIs are associated with concomitant increases in risk factors for later disease,<sup>6</sup> and youth with greater adiposity are more likely to develop insulin resistance and prediabetes.<sup>7</sup> T2DM develops in those who continue to gain weight<sup>8</sup> and in those with a genetic susceptibility for reduced compensatory insulin secretion in response to peripheral insulin resistance.<sup>9,10</sup> T2DM in the pediatric population has also emerged as a significant health care problem,<sup>11</sup> necessitating the development of new guidelines for its management.<sup>12</sup>

With the high prevalence of childhood obesity, pediatricians are routinely encountering obese patients in clinical practice, and yet, despite guidelines,<sup>13-16</sup> few report feeling competent in managing comorbidities.<sup>17</sup> In assessing T2DM risk it has become routine to recommend measurement of a fasting insulin concentration, as a surrogate marker of insulin resistance, alongside measures of glucose metabolism.<sup>15</sup> However, current consensus from all major guidelines states that "there is no justification for screening children for insulin resistance, even those who are obese."<sup>18</sup> The reasons for this guideline include a lack of normative data, a variety of methods used to measure insulin resistance, and, importantly, a lack of adequate longitudinal studies to relate insulin resistance in childhood to long-term outcomes.<sup>18</sup> Furthermore, it has been shown that fasting insulin only

moderately correlates with insulin sensitivity (as determined by hyperinsulinemic-euglycemic clamp studies) in adolescence,<sup>19</sup> and because puberty induces a significant reduction in insulin sensitivity,<sup>20</sup> agreed cutoff points for fasting insulin concentrations throughout childhood and adolescence have not been established.

Therefore, it is important to determine the association between fasting insulin levels in childhood and later risk of T2DM, through appropriately designed longitudinal studies. We have previously shown in the Cardiovascular Risk in Young Finns Study (YFS) that high insulin levels in youth predict metabolic syndrome in young adulthood.<sup>21</sup> The present analyses take advantage of the latest extended follow-up of this cohort, with the primary aim to assess the association between fasting insulin measurements in childhood and the development of T2DM in early and mid-adult life.

## METHODS

### Participants

The study population consisted of participants of the YFS, a population-based follow-up study on cardiovascular risk factors in Finland.<sup>22</sup> The first cross-sectional study was conducted in 1980. Altogether 4320 children and adolescents aged 3, 6, 9, 12, 15, and 18 years were randomly chosen from the population register of these areas to produce a representative sample of Finnish children. Of these children, 3596 (83%) participated in the original study. Since then, regular follow-ups have been performed. In the present analyses, data were included from 2478 participants enrolled in the YFS who were aged 3 to 18 years in 1980 and had follow-up for T2DM on either the 2001, 2007, or 2011 adult survey (then aged 24-49 years). More detailed

methods from the YFS have been previously published.<sup>23</sup> The study received ethical approval, and written informed consent was obtained from the study subjects, or their parents, for each of the examinations.

### Measures

We measured height to the nearest 0.5 cm by using a wall-mounted stadiometer (Seca, Chino, CA), and we measured weight to the nearest 0.1 kg with a digital Seca scale. Healthy weight, overweight, or obesity status in childhood was defined according to age- and gender-specific BMI cutoff points developed by Cole et al.<sup>24</sup> We measured serum insulin concentration in 1 laboratory by using a modification of the immunoassay method of Herbert et al.<sup>25</sup> in childhood (1980, 1983, and 1986) and by microparticle enzyme immunoassay kit (Abbott Laboratories, Chicago, IL) in adulthood (2001, 2007, and 2011). Corrections for interassay changes in insulin values in the 1980s were undertaken at that time.<sup>26</sup> We used an equation to correct results between 2001 and 2007 because of changes in the standardization of the method performed by the reagent manufacturer. This change was purely technical and did not change the performance of the method. According to the manufacturer, the expected change would be -24%, and in-house testing showed an average change of -19%. A second equation was then used to correct for changes between insulin assay results in 2007 and 2011 because a different assay and instrument was used in 2011. However, both assays and instruments were from the same manufacturer, with the same standardization, and so no differences in specificity or accuracy were expected. On testing, we found that the average change in analytical level was 2%.

We determined pubertal stage (prepubertal, peripubertal, or postpubertal) at baseline by using Tanner chart stages. Formal

orchidometric measurements were not performed. Prepubertal children were those with no evidence of pubic hair growth and either absent breast development in girls or prepubertal genital appearances in boys. Peripubertal adolescents were those who showed evidence of pubic hair or breast development and genital development. This definition therefore included those with pubarche as being peripubertal (in the absence of true puberty), because adrenarche is associated with increased insulin levels.<sup>27</sup> Those with completed puberty were classified as postpubertal. Information related to a parental history of T2DM was available from questionnaire data collected from the parents, and those classified as having a parental history of T2DM had an affected mother or father.

### Definition of T2DM in Adulthood

T2DM was defined at follow-up as a fasting plasma glucose  $\geq 7$  mmol/L (in the absence of type 1 diabetes mellitus), in accordance with American Diabetes Association criteria.<sup>28</sup> A participant was also classified as having T2DM if he or she had a hemoglobin A1c  $\geq 6.5\%$  (48 mmol/mmol), reported in questionnaires such a diagnosis made by a physician, or was taking an oral glucose-lowering medication.

### Statistical Analyses

We performed all statistical analyses by using Stata 10 or 12 (Stata Corp, College Station, TX). Statistical significance was inferred at a 2-tailed  $P < .05$ .

### Participant Characteristics

Participant characteristics are presented as mean (SD) or median (interquartile range) for normal or skewed continuous variables, respectively, and percentages for dichotomous variables. Where statistical comparison of participants' characteristics were deemed important,  $t$  tests and  $\chi^2$  analyses were used for continuous and dichotomous variables.

### Fasting Insulin Levels and BMI in Childhood as Measures of Risk for Adult T2DM

We initially assessed fasting insulin in childhood as both continuous (gender- and pubertal stage-specific Z score) and dichotomous (gender- and pubertal stage-determined 95th percentile in the present cohort) variables. The 95th percentile limits for prepubertal, peripubertal, and postpubertal male participants were 13.0 IU/L, 19.0 IU/L, and 21.5 IU/L, whereas values for female participants were 13.5 IU/L, 25.5 IU/L, and 23.5 IU/L, respectively. We estimated relative risks (RRs) and 95% confidence intervals (CIs) by using Poisson regression with robust standard errors to examine the association between childhood insulin levels (continuous and dichotomous) and the dichotomous outcome of adult T2DM. Because there was a significant interaction between childhood insulin and age ( $P = .01$ ), whereby the effect was stronger among the youngest 2 age cohorts, analyses were stratified into 2 groups according to child age (3–6 years and 9–18 years). The association between each child insulin variable and later T2DM was examined with the use of the following 4 models. Model 1 adjusted for age, gender, and duration of follow-up. Model 2 adjusted for these variables and child BMI. Model 3 adjusted for variables in Model 2 and parental history of T2DM.

We undertook similar analyses, replacing BMI for insulin and adjusting for child insulin values and parental history of T2DM, in Models 2 and 3. The dichotomous approach for the predictor variable BMI compared “normal weight” with “overweight/obese” children, using cutoff points defined by Cole et al.<sup>24</sup>

### Life-Course Analysis of Fasting Insulin Levels and BMI on Adult T2DM

Using multilevel mixed modeling with maximum likelihood estimation, we

then compared risk factor trajectories of fasting insulin and BMI as a function of age for 2 groups: those with T2DM in adulthood and those without. This approach allows for missing data (assuming they are missing at random) and takes into account correlations between repeated measures on the same individual. All analyses were adjusted for gender and time (a categorical age variable), and the models for fasting insulin and BMI were mutually adjusted for the other factor. The resulting  $\beta$  coefficient represents the cumulative burden of both fasting insulin and BMI on T2DM. Subsequently, we fitted interaction terms between diabetes group and time that compares the trajectory of the risk factor (insulin or BMI) between diabetes groups. These analyses indicate the age at which differences in risk factors between the groups can be identified. In all models, an unstructured covariance matrix was used.

## RESULTS

### Participant Characteristics

Participant characteristics are shown in Table 1. The mean (SD) time between baseline and follow-up was 29.1 (3.3) years and ranged from 21 to 31 years. There were 84 cases of T2DM in adult life. As expected, those with T2DM had a significantly greater BMI (mean adult BMI 31.3 vs 25.6 [ $P < .001$ ] and youth BMI 20.0 vs 17.8 [ $P < .001$ ]) than those without. The percentage of overweight or obese children at age 3 to 6 years was 1.5% (12/795) and 4.3% at age 9 to 18 years (72/1683). Furthermore, there was a higher proportion of adults with T2DM who were overweight or obese as children, when compared with those of healthy weight status (8.9% vs 2.9% respectively;  $\chi^2 P < .001$ ). Those with a parental history of T2DM were also more likely to develop T2DM in adult life (12.1% vs 3.2%;  $\chi^2 P < .001$ ).

**TABLE 1** Baseline and Follow-up Characteristics of Participants, Stratified According to Baseline Age

Time Point	Characteristic	Child Age (1980)	
		3–6 y	9–18 y
Baseline	Number of participants	795	1683
	Male (%)	45.0	44.4
	Age (y)	4.6 (1.5)	13.4 (3.3)
	BMI	15.6 (1.5)	18.9 (3.0)
	BMI status (% normal wt/overweight/obese <sup>a</sup> )	92.5/5.8/1.8	91.5/7.7/0.8
	Pubertal status (% prepubertal/peripubertal/postpubertal)	100/0/0	26.8/34.4/38.8
	Proportion with a parental history of T2DM (%)	1.5	2.7
Follow-up	Insulin measurement (IU/L)	5.0 (3.0,7.5)	10.5 (7.5,14.5)
	Age (y)	33.4 (3.9)	42.6 (4.7)
	Proportion with T2DM (%)	1.5	4.3

Data are mean (SD) or median (interquartile range) for continuous variables and percentages for dichotomous variables. Percentages may not add to 100% because of rounding.

<sup>a</sup> According to the definition of Cole et al.<sup>24</sup>

### Fasting Insulin Levels in Childhood and Adolescence and Risk of T2DM in Adult Life

Fasting insulin values in those who did, and did not, develop T2DM in adult life are shown in Fig 1. A significant association was seen between fasting insulin values in early childhood (age 3–6 years) and T2DM in adult life, which remained significant after we adjusted for age, gender, duration of follow-up, child BMI, and parental history of T2DM (Table 2). In older children and adolescents (aged 9–18 years) a significant association between fasting insulin values and later T2DM was seen after adjustment for gender, age, and duration of follow-up, but this association became insignificant after we adjusted for child BMI (Table 2). Similar results were seen when fasting insulin measures were dichotomized into normal or high groups (based on 95th percentiles for gender and pubertal status; Table 2).

### BMI in Childhood and Adolescence and Risk of T2DM in Adult Life

Similar analyses to those described earlier, but for BMI, showed opposite results for the age groups. Here, a significant association was observed for BMI in later childhood and adolescence (age 9–18 years) with T2DM in adult life, which remained significant after we adjusted for age, gender, duration of follow-up, child

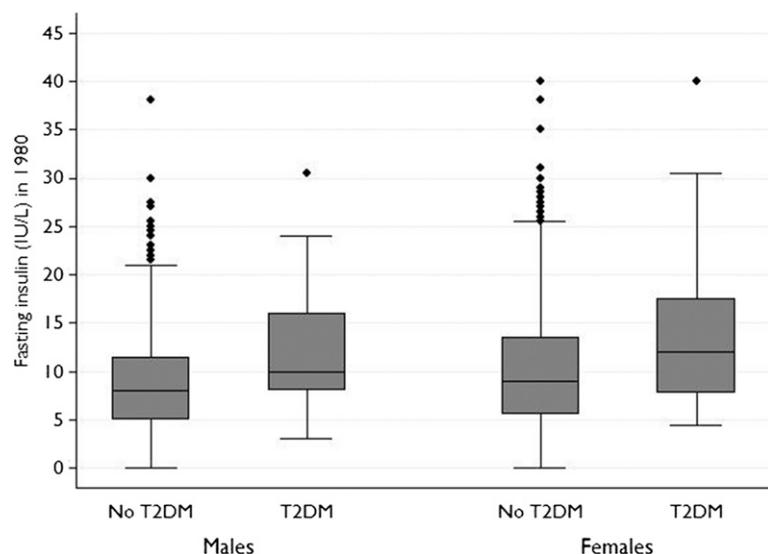
insulin level, and parental history of T2DM (Table 3). In younger children, however, no significant associations were seen between BMI and later risk of T2DM. Results were similar when BMI was dichotomized into “normal weight” or “overweight/obese” categories, as defined by Cole et al.<sup>24</sup> (Table 3).

Of the 84 participants who developed T2DM in adult life, 61 had a normal BMI and insulin value in childhood. However, only 8.2% of the cohort was overweight or obese at baseline, and this precluded additional analyses

relating to the additional value of fasting insulin levels with later T2DM risk in this group. Across the whole cohort, however, there was no significant interaction between insulin and BMI in either the continuous or categorical models (all  $P > .21$ ).

### Life-Course Analysis of Fasting Insulin Levels and BMI on Adult T2DM

Participants with T2DM in adulthood had, on average, greater mean levels of fasting insulin (1.55 IU/L; 95% CI, 1.42–1.69;  $P < .001$ ) and BMI (1.28; 95% CI, 0.62–1.95;  $P < .001$ ) across the life course. Although these coefficients were reduced by ~20% when both fasting insulin and BMI were included in the same model, significant independent differences between those with and those without T2DM remained (Table 4). A visual representation of differences in fasting insulin and BMI as a function of age for those with and without T2DM is shown in Fig 2. Independent of BMI, those with T2DM in adulthood had elevated fasting insulin levels in early childhood and adulthood but not in the peripubertal years (Fig 2A). However, the differences in BMI tended to emerge



**FIGURE 1**

Vertical box plots of youth fasting insulin levels according to gender and T2DM status at follow-up. For each plot, the line within the box represents the median. The lower and upper lines of the box represent the 25th and 75th percentiles and the lower and upper adjacent lines (whiskers) the 10th and 90th percentiles, respectively. Closed circles indicate outliers.

**TABLE 2** RRs and 95% CIs of Adult T2DM According to Insulin Levels in Childhood, Stratified by Age

Child predictor	Child Age	n/N	Model 1		Model 2		Model 3	
			RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Fasting insulin (continuous) <sup>a</sup>	3–6 y	12/795	2.04 (1.54–2.70)	<.001	2.05 (1.49–2.84)	<.001	2.05 (1.49–2.83)	<.001
	9–18 y	72/1683	1.32 (1.06–1.65)	.01	1.17 (0.92–1.49)	.19	1.16 (0.93–1.46)	.20
Fasting insulin (dichotomous) <sup>b</sup>	3–6 y	12/795	6.40 (1.35–30.25)	.02	7.12 (1.19–42.51)	.03	7.00 (1.17–41.9)	.03
	9–18 y	72/1683	2.72 (1.39–5.30)	.003	1.72 (0.85–3.49)	.13	1.56 (0.76–3.19)	.22

Model 1: adjusted for gender, age, and duration of follow-up. Model 2: adjusted for all covariates in Model 1 and additionally adjusted for child BMI. Model 3: as for Model 2 with parental history of T2DM.

<sup>a</sup> Expressed for a 1-SD increase in insulin.

<sup>b</sup> Defined as fasting insulin >95th percentile, standardized for gender and pubertal status. N = 795 for all age 3- to 6-y models; N = 1683 for all age 9- to 18-y models. Note: Interaction term between fasting insulin and age group (3- to 6-y-olds vs 9- to 18-y-olds), P = .01.

during adolescence, becoming significant from the age of 15 years (Fig 2B). Again, in these analyses we noted no significant interaction between fasting insulin and BMI.

## DISCUSSION

The high prevalence of childhood obesity, alongside its recognized links with insulin resistance and T2DM,<sup>1</sup> has led to increased awareness that fasting insulin levels may be a useful indicator of long-term risk for T2DM, even among nonobese youth.<sup>29–31</sup> This is despite a lack of longitudinal data linking childhood insulin levels with later T2DM.<sup>18</sup> In this study we investigated the association between fasting insulin levels in childhood and later T2DM, alongside measures of BMI in childhood, in a longitudinal cohort of Finnish individuals. Because puberty is known to reduce insulin sensitivity,<sup>20</sup> we chose to examine the associations between insulin and BMI with later T2DM in 2 distinct age categories: 3- to 6-year-olds and 9- to 18-year-olds. Clear associations were seen between raised insulin levels in early childhood and later T2DM risk,

which were independent of effects of BMI, whereas insulin values between the ages of 9 to 18 years were not associated with later risk of T2DM. Instead, in this group BMI appeared to better associate with later T2DM, consistent with a previous report that examined associations between pediatric metabolic syndrome and later cardiovascular risk factors and T2DM.<sup>32</sup>

Three major studies have previously examined the association between insulin levels in childhood and later T2DM. Nguyen et al<sup>33</sup> showed that children in the top decile for insulin were >5 times more likely to develop T2DM than those with a lower insulin value in 1120 participants of the Bogalusa Heart Study, whereas Morrison et al<sup>34</sup> demonstrated among 556 North American schoolgirls that fasting insulin concentrations at age 10 predicted T2DM at a mean age of 24 years. However, both studies were biracial and had few participants with T2DM in adult life (n = 25 and 11, respectively). A third study, in Pima Indians, demonstrated that elevated fasting insulin concentrations in

childhood and adolescence were also associated with an elevated risk of developing T2DM but only over a short follow-up period of 8 years.<sup>35</sup> No studies to date have examined these associations in whites, in the absence of an ethnically derived increased risk for T2DM.

The finding that insulin levels in older children and adolescents are not associated with long-term T2DM may be simply related to the general increase in fasting insulin levels seen in peripubertal adolescents,<sup>20</sup> which may potentially mask pathologic increases in insulin levels that would otherwise indicate pancreatic strain. Interestingly, however, these associations remained when insulin levels were dichotomized into normal or high levels, using the 95th percentile for gender and pubertal stage. Furthermore, we undertook separate life course analyses, which evaluated the association between fasting insulin concentrations at different ages in childhood in those with and without adult T2DM, and these analyses showed that raised fasting insulin concentrations at 3

**TABLE 3** RRs and 95% CIs of Adult T2DM According to BMI Levels in Childhood, Stratified by Age

Child Predictor	Child Age	Model 1		Model 2		Model 3	
		RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
BMI (continuous) <sup>a</sup>	3–6 y	1.16 (0.60–2.21)	.66	0.97 (0.47–1.98)	.92	0.97 (0.47–1.99)	.93
	9–18 y	1.45 (1.21–1.73)	<.001	1.38 (1.12–1.69)	.002	1.38 (1.12–1.69)	.002
BMI (dichotomous) <sup>b</sup>	3–6 y	1.11 (0.12–10.33)	.93	0.65 (0.04–10.37)	.76	0.66 (0.04–10.58)	.77
	9–18 y	3.48 (2.09–5.81)	<.001	3.05 (1.76–5.30)	<.001	3.17 (1.84–5.47)	<.001

Model 1: adjusted for gender, age, and duration of follow-up. Model 2: adjusted for all covariates in Model 1 and additionally adjusted for child insulin. Model 3: as for Model 2 with parental history of T2DM.

<sup>a</sup> Expressed for a 1-SD increase in BMI.

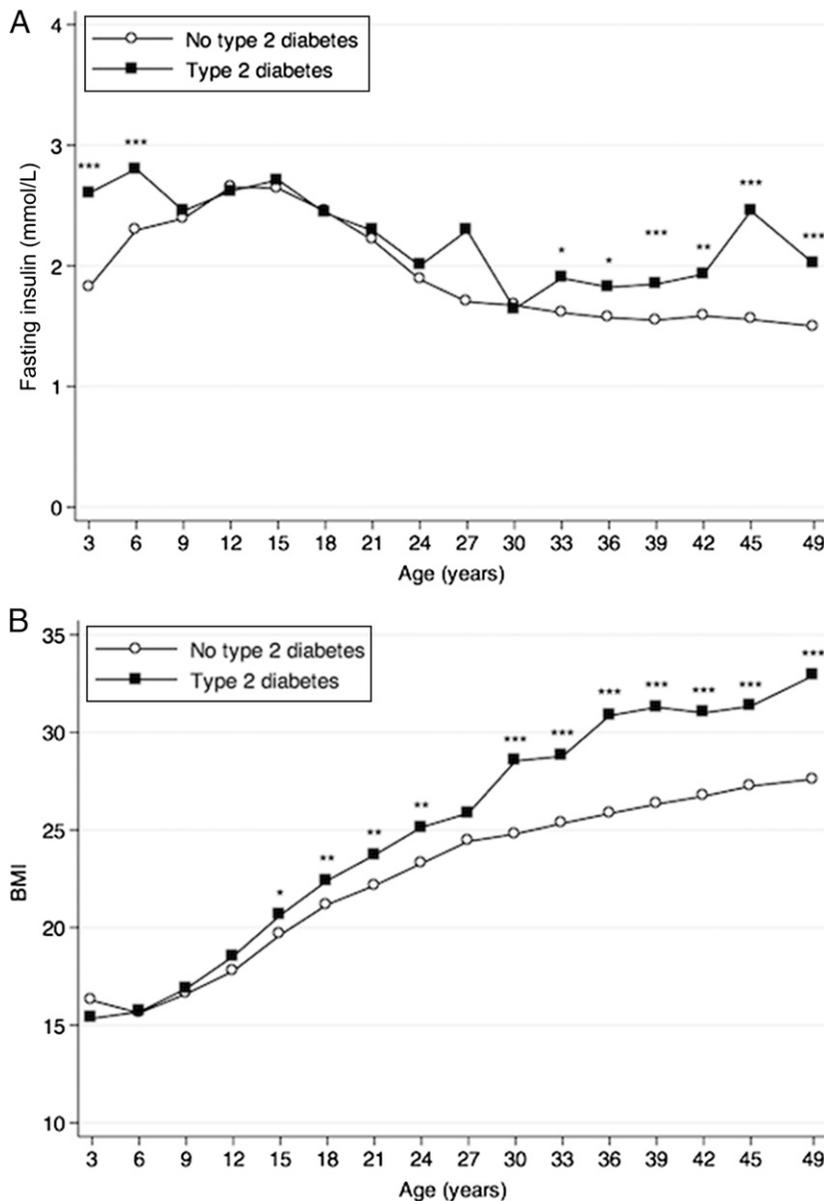
<sup>b</sup> Defined as a 2-level categorical variable (normal wt vs overweight or obese) according to Cole's cutoff points. N = 795 for all age 3- to 6-y models; N = 1683 for all age 9- to 18-y models.

**TABLE 4** Mean Difference in Insulin and BMI Throughout the 31-y Follow-up Between Those With and Without T2DM

Model	Adjustments	Insulin (mmol/L) <sup>a</sup>			BMI		
		$\beta$	95% CI	<i>P</i>	$\beta$	95% CI	<i>P</i>
1	Gender and time (age)	1.55	1.42–1.68	<.001	1.27	0.61–1.93	<.001
2A	Model 1 and BMI	1.28	1.19–1.39	<.001	—	—	—
2B	Model 1 and insulin	—	—	—	1.00	0.36–1.65	.002

Regression coefficients ( $\beta$ ) indicate mean differences in insulin and BMI over time between participants with and without type 2 diabetes. Each row indicates mean differences after adjustment for the longitudinal variables specified in each model.

<sup>a</sup> Values are geometric means.



**FIGURE 2** Comparison of the life course trajectory between participants with and without T2DM in adulthood: A, fasting insulin; B, BMI. Data are adjusted for gender and BMI in part A and adjusted for gender and insulin in part B. Black squares indicate those with T2DM in adulthood; white circles indicate those without T2DM in adulthood. \**P* < .05, \*\**P* < .01, \*\*\**P* < .001.

and 6 years of age, but not beyond this age, were clearly associated with later T2DM (Fig 1). Fasting insulin became discriminatory again only in adults aged  $\geq 33$  years. These findings, alongside the fact that three-quarters of those who developed T2DM in adult life in our cohort were of normal weight and had normal insulin levels in childhood, suggest that fasting insulin values are not useful in older children and adolescents in determining risk for later T2DM. This novel finding therefore supports current assumption that, at a population level, “there is no justification for screening children for insulin resistance, even those who are obese.”<sup>18</sup>

The main strength of this study is the large cohort size, with baseline measures in childhood and a sufficient period of follow-up during which a significant number developed T2DM. The cohort is well described and of uniform ethnicity and has made important discoveries.<sup>36</sup> Access to well-defined data on important variables that affect insulin sensitivity and diabetes risk, such as pubertal stage and parental history of T2DM, allowed analyses to be undertaken with due consideration to important confounders. We were also able to undertake life course analyses, which meant that findings were not inferred from a single measure of fasting insulin in childhood. We restricted our analyses to fasting insulin rather than also taking into account changes in glucose metabolism, because hemoglobin A1c values were not available from early time points within the study, and the homeostasis model assessment of insulin resistance (accounting for variations in insulin and glucose) has not been shown to be more reflective of insulin sensitivity in normal populations of children than fasting insulin alone.<sup>37</sup>

However, there are several limitations to this study, of which we highlight the most important. First, data from

large longitudinal cohorts may not be translatable to individual assessments in clinical practice. Second, the overweight and obesity prevalence rate at baseline in the study cohort was low, compared with current rates, and we have therefore kept our analyses to assessing the association between fasting insulin levels in childhood with later T2DM to the whole cohort, given that many researchers are beginning to use fasting insulin levels in normal-weight children as an indicator of long-term T2DM risk. Third, the number of T2DM cases in adulthood in our cohort is just at a level that is sufficient for it to be assessed as an outcome variable. Over time, more cases are expected, and repeat analyses of the type undertaken in this article will be needed. Fourth, we acknowledge that BMI may not be the best measure of adiposity. Although a more appropriate measure, such as waist circumference, would have been useful, this was not available in childhood in the YFS. However, results from sensitivity analyses that adjusted for sum of triceps and

subscapular skinfolds collected at baseline were essentially similar to those shown (data not shown). In terms of variability in insulin measures over time, corrections were applied in the 1980s and 2000s for consistency, but because of differences between assays in the 1980s and 2000s, it is impossible to provide a correction factor to allow absolute consistency between the decades. We have not been able to undertake comparison studies, and there is nothing in the literature comparing the 2 assay techniques. Generally, however, as new methods are developed they become more sensitive, specific, and accurate than older methods. We observed significant differences in insulin values in the 1980s between those who did, and did not, later develop T2DM, and this finding suggests that the accuracy of insulin values measured in the 1980s was sufficient to limit noise and allow these effects to be seen. Conversely, if no differences had been found in childhood, then it could be argued that this may have resulted from

inaccuracies in the insulin assays at that time. However, this was not the case. Finally, although visual inspection of pubertal status by a trained physician is more reliable than self-reported measures, testicular volumes were not measured, and this may have affected the pubertal staging used in the analyses.

In conclusion, we report that elevated fasting insulin concentrations in young children may be useful in determining who is at greatest risk of developing T2DM in adult life. However, in older children and adolescents there was no clear association between insulin levels and later T2DM; instead, associations were seen with BMI. Taken together, these data suggest that caution is warranted in interpreting elevated fasting insulin levels in older childhood and adolescence as an indicator of risk for the development of later T2DM.

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