A Clinical Tool to Relate Youth Risk Factors to Adult Cardiovascular Events and Type 2 Diabetes: The International Childhood Cardiovascular Cohort Consortium

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Objective To translate data relating childhood cardiovascular (CV) risk factors and adult CV disease and type 2 diabetes mellitus (T2DM) to clinically actionable values.

Study design This was a prospective observational study (n = 38 589) in the International Childhood Cardiovascular Cohort Consortium. Children at age 3 through 19 years were enrolled in the 1970s and 1980s and followed for more than 30 years. Five childhood CV risk factors (smoking, body mass index [BMI], systolic blood pressure, triglycerides, and total cholesterol) were related to adult CV events. Secondary analyses in a subset included low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, glucose, and insulin level. Age- and sex-specific z scores were calculated for each risk factor, and a combined-risk z score was calculated by averaging z scores for the 5 key CV risk factors. Risk factor z scores were back-transformed to natural units for clinical interpretation, with hazard ratios for adult CV events presented in color-coded tables (green: no increased risk; orange: 1.4 to <2.0-fold increased risk; red: at least doubling of risk). Risk levels for development of adult T2DM on the basis of BMI, glucose, and insulin were similarly calculated and presented.

Results Increased risk for CV events was observed at levels lower than currently defined abnormal clinical thresholds except for TC. Doubling of risk was observed at high normal levels just below the clinical cut point for abnormality. Risk for adult T2DM began at levels of BMI and glucose currently considered normal.

Conclusions On the basis of data showing significant relationships between childhood CV risk factors and adult CV events and T2DM, this study shows that risk in childhood begins below levels currently considered normal. *(J Pediatr 2025;276:114277)*.

Pediatric providers rely on cardiovascular (CV) risk factor guidelines developed by expert panels from national organizations (eg, American Academy of Pediatrics, American Heart Association, and the National Institutes of Health), for the assessment and management of CV risk factors in children. Unlike adult clinical thresholds, which are determined by observed epidemiologic relationships between risk factors and disease, pediatric guidelines typically have been based on the distribution of the risk factor in the childhood population by age and sex, or by adopting a single threshold that can be used for most ages and both sexes. Although these pediatric clinical thresholds, by necessity, were arbitrarily defined because of a lack of longitudinal studies assessing their relationship to adult CV disease and events, more

BMI	Body mass index
CV	Cardiovascular
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratios
I3c	International Childhood Cohort
IMT	Intima-media thickness
LDL-C	Low-density lipoprotein cholesterol
SBP	Systolic blood pressure
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglycerides

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recent studies show that CV risk factors in children are related to adult obesity,[1] hypertension,[2] dyslipidemia,[3] and diabetes.[4]

More importantly, recently analyses of longitudinal data from the International Childhood Cardiovascular Cohort (i3C) Consortium have shown that traditional childhood CV risk factors (smoking, body mass index [BMI], systolic blood pressure [SBP], triglycerides [TG], and total cholesterol [TC]) are associated with fatal and nonfatal CV events,[5] encouraging the development of clinical tools to improve risk assessment in childhood for adult CV disease.

This study presents a new set of CV risk factor thresholds to help identify children at risk for development of adult CV events. By translating the recently published i3C childhood risk factor z scores (i3C z-scores) into the natural units currently reported in clinical practice, a table and graphs are provided with new risk factor thresholds related to degree of risk, facilitating discussions and recommendations for children and their family. In addition, this work explores similar relationships for low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), glucose, and insulin, which were not included in the original article but frequently are measured in clinical practice. Finally, we provide clinical data to assess childhood BMI, glucose, and insulin in relation to increased risk of type 2 diabetes mellitus (T2DM) in adulthood.[6]

Methods

The i3C Consortium consists of 7 cohorts that enrolled a diverse sample of youth (urban, rural, Black, White) recruited at age 3-19 years in the 1970s and 1980s with longitudinal follow up to ages 32-65 years.[5,7,8] (**Supplemental Figure 1**, online; available at www.jpeds.com). A total of 38 589 participants were included (50% male, 15% Black).[5] The mean birth year was 1969 ± 6.3 years, with most childhood visits beginning in the early 1980s. The average age at childhood visits was 11.8 ± 3.1 years, with mean age at CV events occurring at 47.1 ± 7.4 years.

The data were merged into a single harmonized database.[5,8] National death indexes were accessed and living participants queried regarding CV events for which medical records were adjudicated by cardiologists and neurologists to confirm CV events. National registry data of medical diagnoses was used for Finland. Adult diabetes status was assessed by self-report (in Finland, medical diagnosis in the registry, fasting glucose, or Finnish national drug reimbursement was used).[9,6] Because a uniform protocol was not used by the individual cohorts during childhood, the number of measurements varied by cohort. Therefore, childhood smoking, BMI, SBP, TG, and TC were the primary focus of analysis, because these were available in most participants. For subsets, childhood levels of LDL-C, HDL-C, glucose, and insulin levels were available. Childhood smoking was defined as smoking enough during adolescence (generally more than a few puffs) that it was likely that adult smoking would ensue.[5,10]

Statistical Analysis

For all CV risk factors, i3C-derived age- and sex-specific z scores, and a combined-risk z score was calculated on the basis of a previously published method.[5] The i3C z scores were determined from data from all youth with risk factor data (total n = 42 196) and were calculated within 3-year age categories (eg, 3-<6 years, 6-<9 years, 9-<12 years, 12-<15 years, 15-<18 years, and 18-<20 years) by sex. Visit-specific measurements were centered at the i3C Consortium's age- and sex-specific mean and divided by the corresponding SD (TG and insulin were log transformed), resulting in z scores with mean 0 and SD 1 within sex and age category. Visit-level z scores for an individual were then averaged across childhood visits. Risk factors also were ranked within 0.5 z-score-width bins (≤−1.0 [lowest risk] to ≥+2.0 [highest risk]). Nonsmoking in youth was assigned i3C z score of 0, and smoking was assigned an i3C z score of +2. Hazard ratios (HRs) for CV events have been published previously.[5] Our new calculation of z scores for LDL-C, HDL-C, glucose, and insulin and their associations with adult CV events and BMI, glucose, and insulin and their association with adult T2DM were calculated with the same methods.[5]

Back transformations from the i3C z scores to natural units for clinical interpretation[8] were by either using published means and SDs by age group and sex (**Supplementary Table 4**, online; available at www.jpeds.com in Jacobs et al,[5] TC i3C z score translated to total cholesterol in mg/dL and mmol/L), or using natural units calculated for specified levels of the i3C z score for ease of presentation (eg, −1.0, −0.5, 0, 0.5 and 1.0). For example, **Supplementary Table 4**, online; available at www.jpeds.com[5] of the article in the *New England Journal of Medicine* shows that the mean and SD of TC for male subjects aged 9-11 years was 4.37 ± 0.82 mmol/L. The back-transformed z score of 0.5 is therefore computed to be 4.37 + 0.5*0.82 = 4.78 mmol/L.

When back-transforming i3C z scores into population-based percentiles (eg, the Centers for Disease Control and Prevention BMI percentiles and 2017 Clinical Practice Guidelines SBP percentiles), we used the mean observed BMI and SBP percentiles for participants within the specified levels of the i3C z-score (±0.02 z-score unit) for each age group and sex. For example, for BMI percentile 0.5 i3C BMI z score, individuals with an i3C BMI z score between 0.48 and 0.52 were identified within each age group and sex and their Centers for Disease Control and Prevention BMI percentile averaged. For some graphical presentations, sex-specific back-transformations were averaged to create a sex-averaged figure.

The degrees of risk associated in the tables and figures are color coded: no significantly increased risk (green, HR < 1.4); 1.4 to <2.0-fold significantly increased risk (orange); and ≥2-fold significantly increased risk (red). Clinical thresholds for CV risk factors (**Supplemental Table 1**, online; available at www.jpeds.com) are indicated by solid white lines on the figures.[11-14] Risk for the development of adult T2DM was calculated for BMI, glucose, and insulin using the same colors.[6]

Results

CV Risk Factor Levels and CV Events

Table I and Figure [5,11-14] (sex-specific figures: Supplemental Figure 2, online; available at www.jpeds.com) show the risk of adult CV events on the basis of the clinical CV risk factors back transformed from child i3C z-score categories with corresponding HRs. Significantly elevated risk (confidence not crossing 1) was observed at a z score of −0.5 for TG and LDL-C, 0 for BMI and SBP, and +0.5 for TC and insulin and any youth smoking. For HDL-C, the HR was not significant but there appeared to be a U-shaped relationship. The HR was greatest in the lowest HDL-C category (1.21, 95% CI 0.71-2.05) and in +1.5 <z< +2.0, the HR increased again (0.88, 95% CI 0.48-1.62, data not shown). Although the HR rises across z-score categories for glucose, no HRs were significant for prediction of CV events.

The clinical threshold for borderline (white line), demonstrates risk starting below the clinical cut-point. Increased risk for CV events begins at the high-normal range for all risk factors except for TC, where risk begins at borderline high. Female subjects aged 15-17 years with a BMI percentile of 66.7% (BMI of 22.5 kg/m^2) or with BP at the 43rd percentile (SBP 111 mm Hg), less than the definition for elevated blood pressure,[11] are at increased risk of a CV event in adulthood. Clinical levels for TG, TC, and LDL-C within current normal ranges also are associated with increased risk.[12] Risk factor levels in red represent more than doubling of risk for adult CV events (HR > 2), and are similar to currently defined borderline high-risk thresholds (eg, overweight, borderline lipids or elevated BP). Table I and Figure do not include smoking because it was assessed as either present (as a behavior likely to be sustained into adulthood) or absent, and smoking in childhood, particularly among adolescents, falls in the "red" category of high risk.

Relation of Risk Factor Levels to T2DM

Childhood glucose, insulin, and BMI levels all also predict T2DM.[4] Our previous work demonstrated that the risk for adult T2DM begins in i3C z-score categories that start at −0.5 for BMI, +0.5 for glucose, and 0 for insulin.[4] The childhood risk factor levels associated with increased risk for adult T2DM are presented in Table II. A 1.4 to <2 fold increased risk for T2DM in a 15- to 17-year-old female subjects starts at a BMI of 20.1 kg/m^2, glucose of 87.8 mg/dL, and insulin of 11.9 μM/L, all well below clinical borderline thresholds.

Use of the Combined Risk z Score for CV Events in Clinical Practice

In addition to the individual z scores and HRs, we calculated the combined risk factor z score for the 5 primary CV risk factors by taking the average of the z scores for the 5 primary CV risk factors (smoking, BMI, SBP, TG, and TC) and determining the HR according to Supplemental Table 2, online; available at www.jpeds.com.[5] An HR increase for CV events of 2.75 (95% CI 2.48-3.06) occurred for each increase by 1 in the risk score. Individuals with a combined CV risk score ≥1.5 above the median began to develop increased CV risk at approximately age 40 years.

Because the i3C combined risk z score is a simple average of individual risk factor z scores, it is also possible to evaluate childhood risk in clinic on the basis of this combined risk score. To translate our i3C combined childhood risk factor z score into clinical use, one can use patient data to calculate estimated risk for adult CV disease (Table III provides some example vignettes). When a clinical value falls between 2 z-score risk categories, it may be convenient to use the lower end of the risk range, as this represents a more conservative risk approximation. Also, note that if a risk factor is missing, then the combined risk i3C z score may be approximated by taking the mean of the available risk factors. Because of the linear relationship between z score and HR, one can estimate the precise HR for an individual relative to the risk of a person with z score 0 with the equation, HR estimate = exp (z score*1.0116). For example, if the risk score is 0.5, then the HR relative to the risk for a person with z-score 0 is exp (0.5 * 1.0116) = exp(0.5058) = 1.66.

For example, consider a 9-year-old female subject who has never smoked (i3C risk z-score = 0). She has BMI of 16.6 kg/m^2 (45th percentile, normal BMI),[13] referring to Table I or Figure, this falls between i3C z score of −0.5 and 0 (i3C risk z-score = −0.5). Her SBP is 104 mm Hg (64th percentile, normotensive),[11] which falls between i3C z-score of 0 and + 0.5 (i3C risk z-score = 0). Her fasting TG level is 75 mg/dL (borderline high),[12] which falls between i3C z score of 0 and + 0.5 (i3C risk z score = 0), and her TC is 192 mg/dL (borderline high),[12] which falls between +0.5 and 1 (i3C risk z score = +0.5). Calculating the mean of the individual i3C z scores would yield a combined risk i3C z score of 0 (eg, [0 + −0.5 + 0 + 0 + 0.5]/5 = 0.0) (Table III). In this case, the i3C z score of 0 falls within the i3C z-score category of 0 to <0.5 which corresponds to an HR of 2.03 (95% CI 1.4-2.95) for CV event (Supplementary Table 2, online; available at www.jpeds.com), a more than doubling of risk compared with the lowest category.

Similarly, a 17 year-old male subject who is a regular tobacco user (eg, smokes 3 cigarettes a week and has friends who smoke: i3C risk z score = +2) with BMI of 26 kg/m^2 (90th percentile, overweight),[13] which falls between i3C z score of 1 and + 1.5 (i3C risk z-score = +1); SBP 133 mm Hg (stage 1 hypertension),[11] which corresponds to i3C z score >1 (i3C risk z score = +1); fasting TG level of 100 mg/dL (borderline high),[12] which falls between i3C z score of +0.5 and 1 (i3C risk z score = +0.5); and TC of 185 mg/dL (borderline high),[12] which falls between i3C z score +0.5 and 1 (i3C

Table I. Childhood CV risk factor levels associated with increased risk of adult CV events

Childhood Risk Factors and Risk of Adult CV Event													
	Male						Female						
i3C Z-score Category	3-5 years	6-8 years	9-11 years	12-14 years	15-17 years	18-19 years	3-5 years	6-8 years	9-11 years	12-14 years	15-17 years	18-19 years	HR (95% CI)
BMI	BMI (kg/m^2)												
z < -1.0	14.2	14.3	14.9	16.3	18.1	19.0	13.8	14.0	14.8	16.5	17.7	18.0	1.11 (0.82-1.49)
-1.0 < z < -0.5	15.1	15.5	16.5	18.2	20.1	21.1	14.9	15.3	16.6	18.7	20.1	20.8	1.21 (0.92-1.59)
-0.5 < z < 0.0	15.9	16.6	18.1	20.1	22.0	23.1	15.8	16.5	18.3	20.8	22.5	23.6	1.47 (1.10-1.95)
0.0 < z < 0.5	16.8	17.8	19.7	22.0	24.0	25.2	16.8	17.8	20.1	23.0	24.9	26.5	1.99 (1.46-2.71)
z ≥ 1.0	17.7	18.9	21.2	23.9	25.9	27.2	17.7	19.0	21.8	25.2	27.2	29.3	2.48 (1.74-3.52)
BMI	BMI Percentile (CDC)												
z < -1.0	8.9	14.5	16.9	18.8	18.9	10.6	8.8	14.1	15.2	20.7	16.6	8.0	1.11 (0.82-1.49)
-1.0 < z < -0.5	33.8	46.9	48.4	47.6	46.4	36.8	34.7	45.0	45.2	50.4	47.3	43.2	1.21 (0.92-1.59)
-0.5 < z < 0.0	59.6	72.7	72.3	70.9	69.3	63.8	63.1	70.1	70.0	74.1	66.7	73.2	1.47 (1.10-1.95)
0.0 < z < 0.5	84.2	87.2	85.3	85.0	83.8	81.1	82.1	84.1	84.4	86.8	86.0	87.3	1.99 (1.46-2.71)
z ≥ 1.0	92.8	93.2	92.5	92.3	91.9	90.7	92.4	91.3	92.4	93.2	92.6	93.4	2.48 (1.74-3.52)
SBP	SBP (mmHg)												
z < -1.0	86.0	90.0	94.0	98.7	104.7	107.1	84.7	88.5	93.3	98.5	100.9	100.7	1.01 (0.79-1.28)
-1.0 < z < -0.5	91.1	95.2	99.4	104.5	110.5	113.3	90.0	93.9	98.8	104.0	106.0	106.0	1.05 (0.81-1.36)
-0.5 < z < 0.0	96.1	100.4	104.7	110.0	116.3	119.3	95.0	99.4	104.3	109.3	111.0	111.0	1.39 (1.12-1.71)
0.0 < z < 0.5	101.3	105.5	110.0	116.0	122.3	125.5	100.3	104.7	109.7	114.7	116.3	116.3	1.69 (1.33-2.15)
z ≥ 1.0	106.3	110.7	115.3	121.4	128.0	131.7	105.3	110.0	115.0	120.0	121.3	121.3	2.00 (1.56-2.58)
SBP	SBP Percentile (2017 Clinical Practice Guideline)												
z < -1.0	24.8	26.3	25.2	23.3	20.7	13.2	21.8	26.0	26.1	22.0	20.2	11.9	1.01 (0.79-1.28)
-1.0 < z < -0.5	38.3	43.4	45.3	41.4	33.8	28.2	38.7	45.4	44.7	39.5	37.0	29.0	1.05 (0.81-1.36)
-0.5 < z < 0.0	59.1	65.0	65.3	58.4	52.0	51.6	57.1	67.2	63.6	60.1	43.0	49.0	1.39 (1.12-1.71)
0.0 < z < 0.5	76.8	81.0	83.2	76.8	70.4	71.5	78.7	82.5	78.0	78.4	75.2	69.2	1.69 (1.33-2.15)
z ≥ 1.0	90.5	91.9	92.7	87.5	86.5	89.0	88.7	91.0	90.6	88.3	86.5	83.4	2.00 (1.56-2.58)
TG	TG (mg/dL)												
z < -1.0	36.0	36.0	37.3	40.7	44.4	48.5	38.9	39.8	42.9	46.7	46.1	48.0	1.13 (0.80-1.61)
-1.0 < z < -0.5	44.0	44.2	46.7	51.4	56.2	60.9	47.2	48.6	53.5	57.3	56.5	59.7	1.50 (1.11-2.03)
-0.5 < z < 0.0	53.4	54.2	58.2	64.1	70.0	77.3	56.9	59.4	66.1	70.6	68.7	73.9	1.67 (1.24-2.26)
0.0 < z < 0.5	66.4	68.0	74.5	82.6	90.1	100.2	70.1	74.1	84.0	88.7	85.7	93.9	2.01 (1.47-2.76)
z ≥ 1.0	79.4	81.7	90.8	101.0	110.2	123.1	83.3	88.7	101.8	106.7	102.6	113.9	2.42 (1.66-3.53)
TG	TG (mmol/L)												
z < -1.0	0.41	0.41	0.42	0.46	0.50	0.55	0.44	0.45	0.48	0.53	0.52	0.54	1.13 (0.80-1.61)

(*continued*)

Table I. Continued

-1.0 < z < -0.5	0.50	0.50	0.53	0.58	0.63	0.69	0.53	0.55	0.60	0.65	0.64	0.67	1.50 (1.11-2.03)
-0.5 < z < 0.0	0.60	0.61	0.66	0.72	0.79	0.87	0.64	0.67	0.75	0.80	0.78	0.83	1.67 (1.24-2.26)
0.0 < z < 0.5	0.75	0.77	0.84	0.93	1.02	1.13	0.79	0.84	0.95	1.00	0.97	1.06	2.01 (1.47-2.76)
z ≥ 1.0	0.90	0.92	1.03	1.14	1.24	1.39	0.94	1.00	1.15	1.20	1.16	1.29	2.42 (1.66-3.53)
TC	TC (mg/dL)												
z < -1.0	134.1	132.1	137.2	128.8	124.0	131.2	136.8	134.6	138.4	132.5	132.3	137.5	1.13 (0.89-1.44)
-1.0 < z < -0.5	150.6	147.3	153.1	145.6	139.6	149.5	153.1	150.6	154.7	147.9	148.7	157.0	1.20 (0.95-1.51)
-0.5 < z < 0.0	166.3	162.2	168.9	161.7	154.8	167.1	169.1	166.4	170.8	164.1	165.0	176.0	1.29 (0.98-1.7)
0.0 < z < 0.5	182.5	177.3	184.8	178.1	170.2	185.0	185.3	182.4	187.0	179.9	181.4	195.0	1.78 (1.36-2.35)
z ≥ 1.0	198.6	192.3	200.6	194.5	185.6	202.9	201.5	198.3	203.2	195.6	197.8	214.5	1.93 (1.42-2.63)
TC	TC (mmol/L)												
z < -1.0	3.47	3.42	3.55	3.33	3.21	3.39	3.54	3.48	3.58	3.43	3.42	3.56	1.13 (0.89-1.44)
-1.0 < z < -0.5	3.89	3.81	3.96	3.77	3.61	3.87	3.96	3.89	4.00	3.82	3.85	4.06	1.20 (0.95-1.51)
-0.5 < z < 0.0	4.30	4.19	4.37	4.18	4.00	4.32	4.37	4.30	4.42	4.24	4.27	4.55	1.29 (0.98-1.7)
0.0 < z < 0.5	4.72	4.58	4.78	4.61	4.40	4.78	4.79	4.72	4.84	4.65	4.69	5.04	1.78 (1.36-2.35)
z ≥ 1.0	5.14	4.97	5.19	5.03	4.80	5.25	5.21	5.13	5.25	5.06	5.12	5.55	1.93 (1.42-2.63)
LDL-C	LDL-C (mg/dl)												
z < -1.0	52.3	69.6	71.2	66.2	65.2	71.5	73.9	73.3	74.9	68.6	69.0	74.1	1.11 (0.88-1.41)
-1.0 < z < -0.5	86.3	83.7	86.0	81.0	79.0	87.6	89.1	88.7	90.1	83.1	84.0	91.1	1.28 (1.04-1.57)
-0.5 < z < 0.0	101.4	97.9	100.7	95.8	92.8	103.7	104.4	104.1	105.3	97.5	99.1	108.0	1.55 (1.22-1.96)
0.0 < z < 0.5	116.6	112.0	115.5	110.6	106.7	119.8	119.6	119.5	120.4	111.9	114.1	125.0	1.69 (1.24-2.30)
z ≥ 1.0	131.7	126.1	130.2	125.3	120.5	135.9	134.9	134.9	135.6	126.4	129.2	142.0	2.06 (1.56-2.72)
LDL-C	LDL-C (mmol/L)												
z < -1.0	1.35	1.80	1.84	1.71	1.69	1.85	1.91	1.90	1.94	1.77	1.78	1.92	1.11 (0.88-1.41)
-1.0 < z < -0.5	2.23	2.17	2.22	2.09	2.04	2.26	2.30	2.29	2.33	2.15	2.17	2.35	1.28 (1.04-1.57)
-0.5 < z < 0.0	2.62	2.53	2.60	2.48	2.40	2.68	2.70	2.69	2.72	2.52	2.56	2.79	1.55 (1.22-1.96)
0.0 < z < 0.5	3.01	2.90	2.99	2.86	2.76	3.10	3.09	3.09	3.11	2.89	2.95	3.23	1.69 (1.24-2.30)
z ≥ 1.0	3.41	3.26	3.37	3.24	3.12	3.51	3.49	3.49	3.51	3.27	3.34	3.67	2.06 (1.56-2.72)
HDL-C	HDL (mg/dL)*												
z < -1.0	45.0	45.1	46.1	40.3	36.6	35.5	43.5	43.2	42.2	41.4	41.9	41.2	1.21 (0.71-2.05)
-1.0 < z < -0.5	52.9	53.7	54.8	48.9	44.1	42.9	51.8	51.8	50.5	49.2	49.2	48.9	1.12 (0.70-1.81)
-0.5 < z < 0.0	60.9	62.3	63.4	57.5	51.7	50.3	60.1	60.4	58.8	57.0	56.6	56.6	1.03 (0.64-1.65)
0.0 < z < 0.5	68.9	70.9	72.0	66.1	59.2	57.7	68.4	69.1	67.1	64.8	63.9	64.3	0.92 (0.55-1.55)
z ≥ 1.0	76.8	79.6	80.6	74.7	66.8	65.1	76.6	77.7	75.4	72.5	71.2	71.9	0.83 (0.5-1.39)
HDL-C	HDL (mmol/L)*												
z < -1.0	1.16	1.17	1.19	1.04	0.95	0.92	1.13	1.12	1.09	1.07	1.08	1.07	1.21 (0.71-2.05)
-1.0 < z < -0.5	1.37	1.39	1.42	1.26	1.14	1.11	1.34	1.34	1.31	1.27	1.27	1.26	1.12 (0.70-1.81)

(*continued*)

Table I. Continued

-0.5 < z < 0.0	1.57	1.61	1.64	1.49	1.34	1.30	1.55	1.56	1.52	1.47	1.46	1.46	1.03 (0.64-1.65)
0.0 < z < 0.5	1.78	1.83	1.86	1.71	1.53	1.49	1.77	1.79	1.73	1.67	1.65	1.66	0.92 (0.55-1.55)
z ≥ 1.0	1.99	2.06	2.08	1.93	1.73	1.68	1.98	2.01	1.95	1.88	1.84	1.86	0.83 (0.5-1.39)
Glucose	**Glucose mg/dl**												
z < -1.0	70.8	71.7	75.1	78.4	76.8	74.8	69.5	71.5	74.1	75.7	67.3	67.7	0.97 (0.71-1.31)
-1.0 < z < -0.5	75.8	77.0	79.8	82.8	81.4	80.4	74.2	75.9	79.5	80.4	74.1	75.6	1.01 (0.78-1.30)
-0.5 < z < 0.0	80.9	82.3	84.5	87.3	86.0	86.1	78.9	80.4	84.9	85.1	80.9	83.6	1.1 (0.84-1.44)
0.0 < z < 0.5	86.0	87.6	89.2	91.7	90.6	91.7	83.7	84.8	90.4	89.8	87.8	91.5	1.13 (0.80-1.61)
z ≥ 1.0	91.1	92.9	93.9	96.1	95.2	97.3	88.4	89.2	95.8	94.6	94.6	99.4	1.22 (0.81-1.84)
Insulin	**Insulin (microM/L)**												
z < -1.0	2.1	3.3	4.3	5.5	5.9	5.7	2.4	3.8	4.9	7.1	7.0	5.5	0.98 (0.71-1.35)
-1.0 < z < -0.5	3.1	4.5	5.6	7.3	7.9	7.6	3.5	5.1	6.8	9.2	9.1	7.4	1.09 (0.79-1.50)
-0.5 < z < 0.0	4.6	6.2	7.4	9.7	10.5	10.2	5.1	7.0	9.3	12.1	11.9	10.0	1.18 (0.82-1.70)
0.0 < z < 0.5	6.9	8.5	9.8	12.8	14.1	13.7	7.5	9.4	12.8	15.8	15.6	13.5	1.46 (1.09-1.94)
z ≥ 1.0	10.3	11.6	12.9	16.9	18.8	18.3	11.0	12.7	17.6	20.6	20.5	18.1	1.6 (1.17-2.20)

CDC, Centers for Disease Control and Prevention.
Back-transformed risk factor levels were computed at the lower limit of each indicated category. Data for BMI, SBP, TC, TG adapted from supplemental Table 5 from Jacobs et al[5] (reprinted with permission) and from unpublished data (LDL-C, HDL-C, glucose, insulin).
*Reference category for HDL-C was z ≥ +2.0.

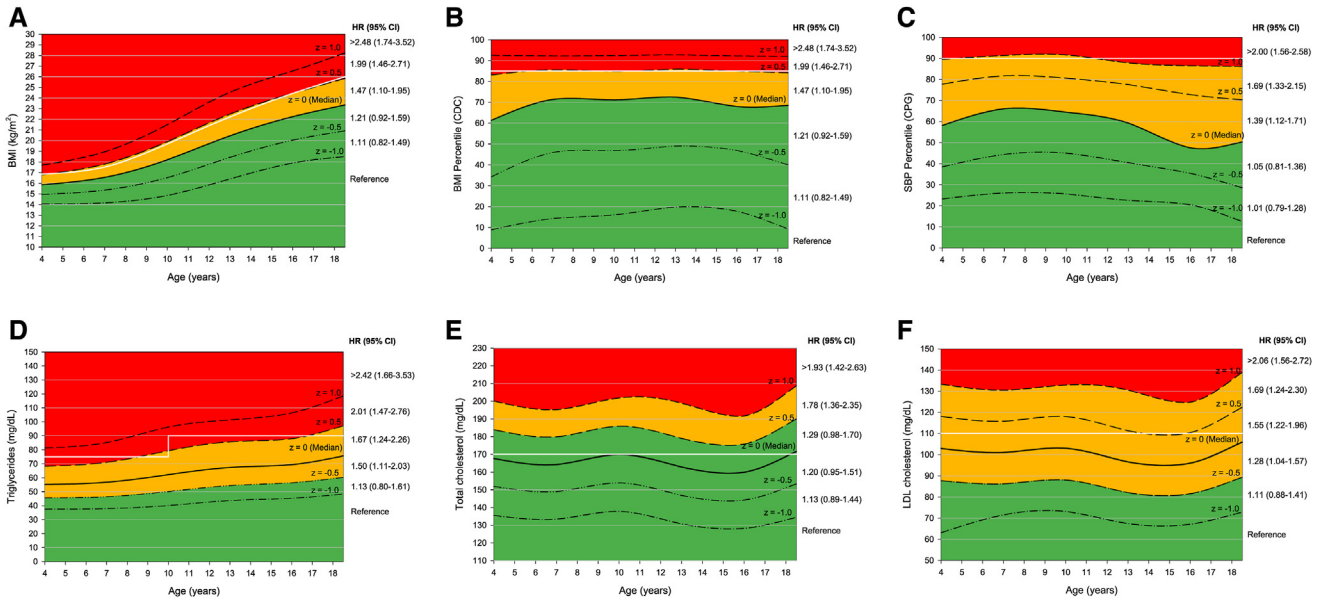

Figure. Categories of risk for adult CV events by childhood CV risk factor levels across pediatric ages. Sex-averaged values of CV risk factors presented by i3C z-score category. **A,** BMI (kg/m^2); **B,** BMI Centers for Disease Control and Prevention percentile; **C,** TC (mg/dL); **D,** TG (mg/dL); **E,** SBP clinical practice guideline percentile; and **F,** LDL-C (mg/dL). Risk for adult CV events is indicated by *green* (low risk), *orange* (significant HR 1.4 to <2), and *red* (significant HR ≥2). *Dotted lines* on the graph are category separators, and *solid white lines* are the currently accepted clinical cut-points (**Supplemental Table 1**, online; available at www.jpeds.com).[11-14] HR for categories so defined is indicated to the *right* of each graph. Data adapted from Jacobs et al.[5]

Table II. Childhood risk factor levels associated with increased risk of adult T2DM

Childhood Risk Factor Levels and Risk of Adult T2DM													
	Male						Female						
i3C Z-score Category	3-5 years	6-8 years	9-11 years	12-14 years	15-17 years	18-19 years	3-5 years	6-8 years	9-11 years	12-14 years	15-17 years	18-19 years	HR (CI)
BMI	BMI (kg/m^2)												
z < -1.0	14.2	14.3	14.9	16.3	18.1	19.0	13.8	14.0	14.8	16.5	17.7	18.0	1.12 (0.83-1.52)
-1.0 < z < -0.5	15.1	15.5	16.5	18.2	20.1	21.1	14.9	15.3	16.6	18.7	20.1	20.8	1.45 (1.08-1.95)
-0.5 < z < 0.0	15.9	16.6	18.1	20.1	22.0	23.1	15.8	16.5	18.3	20.8	22.5	23.6	1.91 (1.40-2.59)
0.0 < z < 0.5	16.8	17.8	19.7	22.0	24.0	25.2	16.8	17.8	20.1	23.0	24.9	26.5	2.83 (2.06-3.90)
z ≥ 1.0	17.7	18.9	21.2	23.9	25.9	27.2	17.7	19.0	21.8	25.2	27.2	29.3	4.17 (2.95-5.84)
BMI	BMI Percentile (CDC)												
z < -1.0	8.9	14.5	16.9	18.8	18.9	10.6	8.8	14.1	15.2	20.7	16.6	8.0	1.12 (0.83-1.52)
-1.0 < z < -0.5	33.8	46.9	48.4	47.6	46.4	36.8	34.7	45.0	45.2	50.4	47.3	43.2	1.45 (1.08-1.95)
-0.5 < z < 0.0	59.6	72.7	72.3	70.9	69.3	63.8	63.1	70.1	70.0	74.1	66.7	73.2	1.91 (1.40-2.59)
0.0 < z < 0.5	84.2	87.2	85.3	85.0	83.8	81.1	82.1	84.1	84.4	86.8	86.0	87.3	2.83 (2.06-3.90)
z ≥ 1.0	92.8	93.2	92.5	92.3	91.9	90.7	92.4	91.3	92.4	93.2	92.6	93.4	4.17 (2.95-5.84)
Glucose	Glucose mg/dl												
z < -1.0	70.8	71.7	75.1	78.4	76.8	74.8	69.5	71.5	74.1	75.7	67.3	67.7	1.06 (0.61-1.85)
-1.0 < z < -0.5	75.8	77.0	79.8	82.8	81.4	80.4	74.2	75.9	79.5	80.4	74.1	75.6	1.07 (0.65-1.77)
-0.5 < z < 0.0	80.9	82.3	84.5	87.3	86.0	86.1	78.9	80.4	84.9	85.1	80.9	83.6	1.37 (0.83-2.26)
0.0 < z < 0.5	86.0	87.6	89.2	91.7	90.6	91.7	83.7	84.8	90.4	89.8	87.8	91.5	1.68 (1.00-2.82)
z ≥ 1.0	91.1	92.9	93.9	96.1	95.2	97.3	88.4	89.2	95.8	94.6	94.6	99.4	2.59 (1.47-4.57)
Insulin	Insulin (microM/L)												
z < -1.0	2.1	3.3	4.3	5.5	5.9	5.7	2.4	3.8	4.9	7.1	7.0	5.5	1.12 (0.59-2.12)
-1.0 < z < -0.5	3.1	4.5	5.6	7.3	7.9	7.6	3.5	5.1	6.8	9.2	9.1	7.4	1.29 (0.72-2.33)
-0.5 < z < 0.0	4.6	6.2	7.4	9.7	10.5	10.2	5.1	7.0	9.3	12.1	11.9	10.0	2.14 (1.22-3.76)
0.0 < z < 0.5	6.9	8.5	9.8	12.8	14.1	13.7	7.5	9.4	12.8	15.8	15.6	13.5	3.57 (2.03-6.27)
z ≥ 1.0	10.3	11.6	12.9	16.9	18.8	18.3	11.0	12.7	17.6	20.6	20.5	18.1	3.76 (2.04-6.91)

Green indicates no increased risk, *yellow* indicates 1.4 to < 2.0-fold increased risk, and *red* indicates over 2-fold increased risk of adult event.
Data adapted from Hu et al.[6]

risk z score = +0.5). This averages to a combined i3C risk z score of +1.0 (eg, [2 + 1 + 1 + 0.5 + 0.5]/5 = 1), corresponding to an HR of 6.11 (3.67-9.65) (**Supplementary Table 2**, online; available at www.jpeds.com and **Table III**), a 6-fold increased risk for having a CV event as an adult.

Discussion

It is known that childhood CV risk factors are related to adult obesity,[1] hypertension,[2] dyslipidemia,[3] and diabetes[4,6] and to noninvasive measures of atherosclerosis, including coronary artery calcium,[15] and carotid intima-media thickness.[1,16] With the recent prospective analyses from the i3C Consortium, we now have clear evidence that a relationship exists between childhood CV risk factors and development of adult CV events.[5] The implication is that it is possible to develop diagnostic strategies not presently available to identify children at risk for future adult CV disease.

The present study provides a revised approach to early identification of children at risk for adult CV events. By back transforming i3C z-score risk factor data into traditionally used risk factor measurement units, this study shows that risk for adult CV events begins at risk factor levels lower than threshold levels currently used clinically and suggests that clinical care of

Table III. Examples of clinical cases with clinical vs i3C z-score risks

Age and Sex		Smoking (yes or no)	BMI, kg/m² (%ile)	SBP, mmHg (%ile)	TG, mg/dL	TC, mg/dL	Combined risk z-score calculation	HR lookup from Supp. Table 2	Potential Clinical Impression
9yo F	Clinical values	No	16.6 (45%ile)	104 (64%ile)	75	192			**Low to moderate risk**
	Clinical risk level	Average risk	Normal BMI	Normal SBP	Borderline high TG	Borderline high TC			
	I3C z-score/ i3C risk level	0	-0.5	0	0	0.5	(0 + -0.5 + 0 + 0 + 0.5)/5= **0**	**2.03 (1.40-2.95)**	**Moderate to high risk**
15yo F	Clinical values	Yes	22.5 (67%ile)	116 (43%ile)	69	165			**Low risk** except smoking
	Clinical risk level	Smoking risk	Normal BMI	Normal SBP	Normal TG	Normal TC			
	I3C z-score/ risk level	2	0	0	0	0	(2+0 + 0 + 0 + 0)/5=**0.5**	**2.03 (1.40-2.95)**	**Moderate to high risk**
9yo M	Clinical values	No	20 (85%ile)	115 (92.7%)	75	185			**Moderate risk**
	Clinical risk level	Average risk	Overweigh t BMI	Pre-HTN	Borderline high TG	Borderline high TC			
	I3C z-score/ risk level	0	0.5	1	0.5	0.5	(0 + 0.5 + 1 +0.5 + 0.5)/5= **0.50**	**3.36 (2.31-4.89)**	**High risk**
17yo M	Clinical values	Yes	26 (90%ile)	133 (90%ile)	100	185			**Moderate to high risk**
	Clinical risk level	Smoking risk	Overweigh t BMI	Pre-HTN	Borderline high TG	Borderline high TC			
	I3C z-score/ risk level	2	1	1	0.5	0.5	(2+ 1 + 1 + 0.5+0.5) /5=**0.60**	**6.11 (3.67-9.65)**	**Very high risk**

F, female; *M*, male.

children should focus on early CV prevention. This finding is attributable, in part, to the i3C data being related to actual adult CV events, as opposed to current thresholds developed from population-based distributions of risk factor levels in children.

Within each risk factor, increased risk for adult CV events began with z scores between −0.5 and + 0.5. Although identifying elevated risk factor levels is important, for every independent risk factor we also found that a combined risk z score was stronger in identifying adult CV risk, and 55% of children have a combined CV risk z score around 0 to 1 SD above the median. This translates to a large number of potentially at-risk children whose risk factor levels are not considered clinically actionable by current pediatric CV disease-prevention guidelines. The data from this study highlight the importance of maintaining ideal CV health from a young age to decrease the risk of adult CV disease, and that prophylactic interventions should begin before levels increase to currently accepted levels of risk.

Knowing that childhood risk factor levels track into adulthood, as shown by previous i3C studies,[1,2,4,10,17,18] it is reasonable to conclude that recognizing the risk of adult CV disease at lower childhood risk factor levels has the potential to reduce or delay development of adult CV disease. For instance, our previous work on childhood obesity found that 56% of children with obesity developed severe class II/III obesity (BMI >35 kg/m^2) as adults, especially in Black children, although only 6% of children of normal weight later developed severe obesity as adults.[1] A greater trajectory of BP increase from childhood to adolescence has been shown to predict adult hypertension.[2] Similarly, lipoprotein levels

have been shown to track from pediatric levels into adulthood and elevated pediatric levels predict adult dyslipidemia.[18] With regards to smoking, our previous work found that subjects who were regular smokers or frequent experimenters at a younger age were more likely to be regular adult smokers and those that were infrequent smokers who nevertheless smoked during adulthood were more likely to quit by age 40 years. These findings support efforts to limit access to cigarettes at a young age.[10] Metabolic derangements have also been shown to track across the early lifespan. Even modestly elevated levels of glucose (>84-90 mg/dL for 3-11 year olds and >88-92 mg/dL for 12-19 year olds), BMI (75-90%), and insulin in youth predict adult T2DM.[4]

Childhood CV risk also has been related to noninvasive measures of atherosclerosis in adults, including coronary artery calcium in the Muscatine Heart Study[19,20] and carotid intima-media thickness (IMT) in i3C cohorts, with increased carotid IMT found in adult subjects who had worse CV risk factor profile at age 9 years.[16] Fortunately, improvement in risk factors before middle age has been associated with a reduction in the prevalence of adult metabolic syndrome and intermediate measures of atherosclerosis (carotid IMT).[21,22] This underscores the utility of using the i3C childhood risk score in the clinical setting to alter the trajectory of risk for development of adult CV disease.

This study benefits from a large sample of youth from urban and rural areas in the US, Finland, and Australia followed prospectively for nearly 40 years, representing a unique opportunity to evaluate long-term risk from childhood CV risk factor measurements. However, the data are not nationally representative of the US geographically or ethnically, with a lack of Hispanic and Asian representation. Despite differing event rates in White and Black participants in the i3C consortium, the previous analysis did not detect differing relationships between childhood CV risk factors and adult CV events by race, reducing this concern. A recent study also developed "Clinical CVH Charts."[23] Our approach has the advantage of presenting a combined CV risk score on the basis of direct observation of both childhood risk factors and CV events rather than pooling of childhood cohorts (with risk factor data) and then extrapolating to adult cohorts (with event data).

Recently published i3C data, which show the significant relationship between childhood CV risk factors and adult CV events,[5] reinforce general public health recommendations that primordial prevention of premature CV disease and events should begin in childhood. The present study, using i3C data, expands on that study by showing that introduction of strategies aimed at lowering adult CV disease risk should begin at childhood risk factor levels below the currently recommended pediatric thresholds. Using the i3C childhood risk score may prompt a practitioner to reinforce lifestyle changes, increase the frequency of monitoring of CV risk factors, or recommend cardiac evaluation. Furthermore, attention of pediatricians to these risk evaluations in support of broad-based public health interventions. In summary, this research provides new pediatric thresholds to identify pediatric patients at increased risk of adult CV events up to 40 years later. ■

CRediT authorship contribution statement

Jessica Haley: Writing – original draft, Formal analysis. **Jessica G. Woo:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **David R. Jacobs:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lydia Bazzano:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Stephen Daniels:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Terry Dwyer:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Markus Juonala:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Olli Raitakari:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alan Sinaiko:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Julia Steinberger:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alison Venn:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kara M. Whitaker:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Elaine M. Urbina:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

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