ORIGINAL ARTICLE

Childhood Adiposity, Adult Adiposity, and Cardiovascular Risk Factors

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ABSTRACT

BACKGROUND

Obesity in childhood is associated with increased cardiovascular risk. It is uncertain whether this risk is attenuated in persons who are overweight or obese as children but not obese as adults.

METHODS

We analyzed data from four prospective cohort studies that measured childhood and adult body-mass index (BMI, the weight in kilograms divided by the square of the height in meters). The mean length of follow-up was 23 years. To define high adiposity status, international age-specific and sex-specific BMI cutoff points for overweight and obesity were used for children, and a BMI cutoff point of 30 was used for adults.

RESULTS

Data were available for 6328 subjects. Subjects with consistently high adiposity status from childhood to adulthood, as compared with persons who had a normal BMI as children and were nonobese as adults, had an increased risk of type 2 diabetes (relative risk, 5.4; 95% confidence interval [CI], 3.4 to 8.5), hypertension (relative risk, 2.7; 95% CI, 2.2 to 3.3), elevated low-density lipoprotein cholesterol levels (relative risk, 1.8; 95% CI, 1.4 to 2.3), reduced high-density lipoprotein cholesterol levels (relative risk, 2.1; 95% CI, 1.8 to 2.5), elevated triglyceride levels (relative risk, 3.0; 95% CI, 2.4 to 3.8), and carotid-artery atherosclerosis (increased intima–media thickness of the carotid artery) (relative risk, 1.7; 95% CI, 1.4 to 2.2) ($P \leq 0.002$ for all comparisons). Persons who were overweight or obese during childhood but were nonobese as adults had risks of the outcomes that were similar to those of persons who had a normal BMI consistently from childhood to adulthood ($P > 0.20$ for all comparisons).

CONCLUSIONS

Overweight or obese children who were obese as adults had increased risks of type 2 diabetes, hypertension, dyslipidemia, and carotid-artery atherosclerosis. The risks of these outcomes among overweight or obese children who became nonobese by adulthood were similar to those among persons who were never obese. (Funded by the Academy of Finland and others.)

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N Engl J Med 2011;365:1876-85.

During the past three decades, the prevalences of overweight and obesity in the pediatric population have increased substantially.[1] Childhood obesity is a predictor of an increased rate of death, owing primarily to an increased risk of cardiovascular disease.[2-4] Forecasts suggest that the "obesity epidemic" may reverse the current trend of the declining rate of death from cardiovascular causes,[5] leading to a shorter lifespan for today's children.[6]

There is substantial evidence that the association between obesity and cardiovascular disease is explained by the adverse cardiovascular risk-factor profile that is frequently seen in obese adults. This profile includes increased rates of hypertension, dyslipidemia, and type 2 diabetes mellitus.[7,8] To date, the contribution of childhood body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) to long-term cardiovascular risk, independent of adult BMI, has not been clearly established. From a public health perspective, it would be important to determine whether becoming a nonobese adult can reverse the adverse effects of childhood overweight or obesity or whether childhood adiposity increases cardiovascular risk independently of adult BMI.

Four large studies of cardiovascular risk factors that initially involved children have followed participants into adulthood: the Bogalusa Heart Study (conducted in the United States),[9] the Muscatine Study (United States),[10] the Childhood Determinants of Adult Health (CDAH) study (Australia),[11] and the Cardiovascular Risk in Young Finns Study (YFS, Finland).[12] In the current study, we analyzed data from all four cohorts to determine whether a change from overweight or obesity during childhood to a nonobese BMI in adulthood, as compared with overweight or obesity during childhood that persists into adulthood, would be associated with a reduced risk of type 2 diabetes, hypertension, dyslipidemia, and carotid-artery atherosclerosis (as indicated by increased intima–media thickness of the carotid artery).

METHODS

STUDY COHORTS

Descriptions of the Bogalusa, Muscatine, CDAH, and YFS studies, including analyses of attrition to show the representativeness of the cohorts, have been published previously.[9-16] Each study was approved by the appropriate institutional review boards, and written informed consent was obtained from all the study participants or their parents.

The International Childhood Cardiovascular Cohort Consortium was created to perform an analysis of data from all four cohorts. Our analysis included participants from each of the four studies who had a baseline evaluation during childhood and underwent a follow-up evaluation as an adult. Details regarding the age range of the participants and the dates of evaluation in each study are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

All blood biochemical values were measured from fasting samples. Details of the methods used for the measurement of weight, height, blood pressure, lipid levels, glucose levels, carotid-artery intima–media thickness, and other covariates in each cohort study are provided in the Supplementary Appendix.

CLASSIFICATION OF ADIPOSITY STATUS

For the definitions of childhood overweight and obesity, we used age-specific and sex-specific international BMI percentiles[17] to extrapolate cutoff points for subjects 3 to 18 years of age that correspond to adult BMIs of 25 (overweight) and 30 (obese) (see Table 1 in the Supplementary Appendix). With the use of these definitions, the prevalence of overweight or obesity among children was 12.2%, and the prevalence of obesity was 2.3%. Among adults, the prevalence of overweight or obesity was 54.9%, and the prevalence of obesity was 20.7%.

For the comparison of outcomes, the participants were categorized into four groups on the basis of adiposity status in childhood and adulthood. Group I included participants with normal BMI in childhood who were nonobese as adults; group II, those who were overweight or obese in childhood but nonobese as adults; group III, those who were overweight or obese in childhood and obese as adults; and group IV, those with normal BMI in childhood who were obese as adults.

DEFINITION OF STUDY OUTCOMES

Participants were classified as having type 2 diabetes mellitus if they had a fasting plasma glucose level of 7 mmol per liter (126 mg per deciliter) or higher, reported the use of oral glucose-lowering medication or insulin but had not reported having

type 1 diabetes, or had received a diagnosis of type 2 diabetes from a physician.[18] Participants were classified as having hypertension if they had a systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher or if they reported the use of blood-pressure–lowering medication. Dyslipidemia (referred to elsewhere in this article as high-risk lipid levels) was defined, according to National Cholesterol Education Program guidelines, as low-density lipoprotein (LDL) cholesterol levels of 160 mg per deciliter (4.14 mmol per liter) or higher, high-density lipoprotein (HDL) cholesterol levels of less than 40 mg per deciliter (1.03 mmol per liter), and triglyceride levels of 200 mg per deciliter (2.26 mmol per liter) or higher.[19] With respect to LDL cholesterol, subjects who were taking lipid-lowering medication were also classified as having dyslipidemia. We defined high-risk intima–media thickness in adulthood as an intima–media thickness equal to or greater than the 90th percentile for age-, sex-, race-, study-year–, and cohort-specific values.[20] In addition, a combined two-level outcome variable (with 0 indicating no high-risk outcomes and 1 indicating one to six high-risk outcomes) was constructed.

STATISTICAL ANALYSIS

We compared patient characteristics among the individual cohorts using chi-square tests or analyses of variance. Comparisons of the baseline characteristics of the study subjects among the adiposity groups were performed with the use of linear or logistic regression.

Relative risks and 95% confidence intervals were calculated with the use of Poisson regression to determine the associations between childhood adiposity status and adult outcomes and between adiposity groups and adult outcomes. Both data-pooling and meta-analysis[21,22] techniques were used. Effects of the interaction between cohort and adiposity group and between race and adiposity group were tested for all outcomes. To further determine the separate effects that adiposity status during childhood and adulthood had on the outcomes, we compared subjects in various adult BMI groups (<25, 25 to 30, and >30) according to childhood adiposity status (normal vs. overweight or obese).

We performed a series of sensitivity analyses to determine the influence on the results of age, length of follow-up, height, race, cohort, the use of an alternative definition (95th percentile of childhood BMI for childhood obesity) and measure (skinfold thickness) of adiposity, and the use of alternative definitions of diabetes and hypertension. In cohorts with available data, analyses were rerun after additional adjustments for socioeconomic status, stage of puberty, and smoking status. In the YFS, serial data from several follow-up assessments were used to determine the age at which adiposity normalized.

Statistical analyses were performed with the use of STATA software, version 10; SAS software, version 9.1.3; and the R statistical package. P values of less than 0.05 were considered to indicate statistical significance. All reported P values are two-tailed and have not been adjusted for multiple comparisons.

RESULTS

STUDY COHORT

The study cohort consisted of 6328 subjects (2961 male and 3367 female subjects) with a mean (±SD) age of 11.4±4.0 years at baseline. The mean length of follow-up was 23.1±3.3 years. Among 5554 subjects who had had normal weight as children, 812 (14.6%) were obese as adults. Among 774 subjects who had been overweight or obese as children, 500 (64.6%) were obese as adults, and among 147 subjects who had been obese as children, 121 (82.3%) were obese as adults. With respect to the individual adiposity groups defined above, there were 4742 subjects in group I, 274 in group II, 500 in group III, and 812 in group IV. Characteristics of the participants according to cohort are shown in Table 1; baseline (childhood) characteristics according to adiposity group are shown in Table 2 in the Supplementary Appendix.

ASSOCIATIONS OF CHILDHOOD OVERWEIGHT OR OBESITY WITH OUTCOMES IN ADULTHOOD

Childhood overweight or obesity was a predictor of type 2 diabetes and high-risk HDL cholesterol levels in the Bogalusa, Muscatine, and YFS cohorts (Table 2). In the Bogalusa and CDAH cohorts, there was an association between childhood overweight or obesity and the prevalence of high-risk LDL cholesterol levels. In all the cohorts, there was a significant association with hypertension and high-risk triglyceride levels. In the Bogalusa and YFS

Table 1. Characteristics of Subjects in the Four Cohorts, in Childhood and Adulthood.*

Variable	Bogalusa (N=635)	Muscatine (N=722)	CDAH (N=2331)	YFS (N=2640)	P Value†
Sex — no. (%)					<0.001
Male	261 (41.1)	345 (47.8)	1147 (49.2)	1208 (45.8)	
Female	374 (58.9)	377 (52.2)	1184 (50.8)	1432 (54.2)	
Black race — no. (%)‡	227 (35.7)				
Characteristics of participants as children					
Age — yr					
Mean	12.6±3.5	14.6±1.9	11.1±2.5	10.6±5.0	<0.001
Range	4–18	8–19	7–15	3–18	
Height — cm	153.0±17.8	163.4±10.2	146.9±15.4	141.7±25.9	<0.001
Body-mass index¶	20.0±4.3	21.4±3.4	18.1±2.7	17.9±3.1	<0.001
Overweight or obese — no. (%)	147 (23.1)	148 (20.5)	261 (11.2)	218 (8.3)	<0.001
Obese — no. (%)	48 (7.6)	27 (3.7)	39 (1.7)	33 (1.2)	<0.001
Regular smoking — no. (%)§	127 (20.0)	not available	201 (8.6)	204 (7.7)	<0.001
Characteristic of participants as adults					
Age — yr					
Mean	33.9±3.5	38.6±2.9	31.0±2.6	36.6±5.6	<0.001
Range	23–43	33–46	26–36	24–45	
Body-mass index¶	30.2±7.9	28.2±5.8	25.7±4.8	25.9±4.8	<0.001
Intima–media thickness — mm	0.74±0.16	0.71±0.15	0.60±0.10	0.66±0.10	<0.001
Length of follow-up — yr	21.3±1.6	24.0±2.1	19.9±0.6	26.0±2.3	<0.001
Overweight or obese — no. (%)	447 (70.4)	486 (67.3)	1166 (50.0)	1373 (52.0)	<0.001
Obese — no. (%)	274 (43.1)	241 (33.4)	357 (15.3)	440 (16.7)	<0.001
Type 2 diabetes mellitus — no. (%)‖	48 (7.6)	26 (3.6)	18 (0.8)	37 (1.4)	<0.001
Hypertension — no./total no. (%)**	86/635 (13.5)	43/722 (6.0)	183/2331 (7.9)	389/2637 (14.8)	<0.001
High-risk LDL cholesterol — no./total no. (%)††	102/635 (16.1)	53/722 (7.3)	176/2252 (7.8)	315/2605 (12.1)	<0.001
High-risk HDL cholesterol — no./total no. (%)‡‡	190/635(29.9)	281/722 (38.9)	263/2272 (11.6)	507/2631 (19.3)	<0.001
High-risk triglycerides — no./total no. (%)§§	81/635 (12.8)	109/722 (15.1)	145/2272 (6.4)	340/2640 (12.9)	<0.001
Daily smoking — no./total no. (%)	186/635 (29.3)	212/722 (29.4)	347/2217 (15.7)	676/2614 (25.9)	<0.001

* Plus–minus values are means ±SD. The four study cohorts were the Bogalusa Heart Study,[9] the Muscatine Study,[10] the Childhood Determinants of Adult Health (CDAH) study,[11] and the Cardiovascular Risk in Young Finns Study (YFS).[12]
† P values are for the comparisons across cohorts, with the use of analysis of variance and chi-square tests.
‡ Race was self-reported.
§ Regular smoking was defined as smoking at least once a week.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.
‖ Participants were classified as having type 2 diabetes mellitus if they had a fasting plasma glucose level of 7 mmol per liter (126 mg per deciliter) or higher, reported the use of oral glucose-lowering medication or insulin but had not reported having type 1 diabetes, or had received a diagnosis of type 2 diabetes from a physician.
** Participants were classified as having hypertension if they had a systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher or if they reported the use of blood-pressure–lowering medication.
†† Participants were classified as having high-risk low-density lipoprotein (LDL) cholesterol levels if they had LDL cholesterol levels of 160 mg per deciliter (4.14 mmol per liter) or higher or were taking cholesterol-lowering medications.
‡‡ High-risk high-density lipoprotein (HDL) cholesterol levels were defined as levels of less than 40 mg per deciliter (1.03 mmol per liter).
§§ High-risk triglyceride levels were defined as levels of 200 mg per deciliter (2.26 mmol per liter) or higher.

Table 2. Relative Risks of High-Risk Outcomes in Adulthood among Participants in Four Cohort Studies Who Were Overweight or Obese in Childhood.*

Outcome	Bogalusa	Muscatine	CDAH	YFS	Male Subjects†	Female Subjects†	All Subjects†
Type 2 diabetes							
Relative risk (95% CI)	2.2 (1.3–3.8)	3.4 (1.6–7.1)	0.5 (0.1–3.5)	2.6 (1.2–5.8)	3.8 (2.1–6.9)	1.8 (1.1–3.0)	2.4 (1.6–3.6)
P value	0.006	0.002	0.46	0.02	<0.001	0.02	<0.001
Hypertension							
Relative risk (95% CI)	2.0 (1.3–2.8)	2.3 (1.4–3.9)	1.5 (1.0–2.2)	1.8 (1.4–2.3)	1.8 (1.5–2.2)	1.7 (1.3–2.4)	1.8 (1.5–2.1)
P value	<0.001	0.001	0.03	<0.001	<0.001	<0.001	<0.001
High-risk LDL cholesterol							
Relative risk (95% CI)	1.8 (1.3–2.6)	1.3 (0.7–2.4)	1.6 (1.1–2.3)	1.2 (0.8–1.7)	1.2 (0.9–1.6)	2.0 (1.4–2.7)	1.4 (1.2–1.8)
P value	0.001	0.39	0.02	0.31	0.18	<0.001	<0.001
High-risk HDL cholesterol							
Relative risk (95% CI)	1.5 (1.2–1.9)	1.3 (1.1–1.6)	1.4 (1.0–1.9)	1.6 (1.2–2.0)	1.2 (1.0–1.5)	1.8 (1.4–2.3)	1.4 (1.2–1.6)
P value	0.001	0.004	0.06	0.001	0.03	<0.001	<0.001
High-risk triglycerides							
Relative risk (95% CI)	1.8 (1.2–2.7)	1.8 (1.2–2.5)	1.8 (1.2–2.6)	1.5 (1.1–2.0)	1.6 (1.3–2.1)	1.6 (1.1–2.3)	1.6 (1.3–1.9)
P value	0.009	0.002	0.007	0.01	<0.001	0.02	<0.001
High-risk carotid-artery intima–media thickness‡							
Relative risk (95% CI)	2.5 (1.5–4.1)	1.4 (0.9–2.2)	1.0 (0.7–1.3)	1.5 (1.1–2.1)	1.3 (1.0–1.7)	1.3 (1.0–1.7)	1.3 (1.1–1.6)
P value	0.001	0.14	0.98	0.007	0.05	0.06	0.007

* Childhood overweight and obesity were defined according to the international cutoff points[17] (see Table 1 in the Supplementary Appendix). CI denotes confidence interval, HDL high-density lipoprotein, and LDL low-density lipoprotein.
† These analyses included pooled data from all four cohorts, adjusted for age, height, cohort, and length of follow-up. The pooled analysis of all subjects was also adjusted for sex.
‡ High-risk intima–media thickness was defined as an intima–media thickness equal to or greater than the 90th percentile for age-, sex-, race-, study-year–, and cohort-specific values.

cohorts, childhood overweight or obesity was associated with high-risk intima–media thickness.

In pooled analyses of the four cohorts, significant associations were observed between childhood overweight or obesity and all the outcomes we assessed. Similar risk estimates were seen in a meta-analysis (Table 3 in the Supplementary Appendix). When the 95th percentile of childhood BMI was used to define childhood obesity, the associations were significant with respect to all the outcomes except high-risk LDL cholesterol levels (relative risk, 1.2; 95% confidence interval [CI], 0.8 to 1.6; P=0.49). Among female subjects in the four cohorts, childhood overweight or obesity was associated with all the outcomes except high-risk intima–media thickness, and among male subjects with all the outcomes except high-risk LDL cholesterol levels (Table 2).

INFLUENCE OF ADIPOSITY IN CHILDHOOD AND ADULTHOOD

Pooled Analyses

In pooled analyses, the risks among subjects who were overweight or obese in childhood but nonobese as adults (group II) were similar to the risks among subjects who had a consistently normal BMI (group I), with respect to all the outcomes we assessed (Table 3). In contrast, subjects who were obese as adults, irrespective of their childhood adiposity status (i.e., groups III and IV), had a significantly increased risk with respect to all the outcomes. Similar estimates were shown in a meta-analysis (Table 4 in the Supplementary Appendix) and in analyses in which the 95th percentile of childhood BMI was used to define childhood obesity (data not shown). In a pooled analysis (Table 3), the relative risks were significantly lower among

Table 3. Relative Risks of High-Risk Outcomes in Adulthood According to Adiposity Group in Childhood and Adulthood.*

Outcome and Adiposity Group	Male Subjects			Female Subjects			All Subjects		
	%	Relative Risk (95% CI)	P Value†	%	Relative Risk (95% CI)	P Value†	%	Relative Risk (95% CI)	P Value†
Type 2 diabetes									
Group I	0.5	Reference		1.3	Reference		1.0	Reference	
Group II	1.8	3.6 (0.8–16.3)	0.10	0.7	0.5 (0.1–4.0)	0.54	1.1	1.3 (0.4–4.1)	0.69
Group III	6.9	10.3 (4.7–22.7)	<0.001	7.9	3.8 (2.1–6.8)	<0.001	7.4	5.4 (3.4–8.5)	<0.001
Group IV	4.6	7.5 (3.5–16.1)	<0.001	6.9	3.5 (2.1–5.9)	<0.001	5.8	4.5 (2.9–6.8)	<0.001
Hypertension									
Group I	15.3	Reference		6.9	Reference		10.8	Reference	
Group II	16.0	1.1 (0.7–1.8)	0.61	3.2	0.6 (0.2–1.4)	0.25	8.8	0.9 (0.6–1.4)	0.80
Group III	37.0	2.5 (2.0–3.2)	<0.001	19.6	3.2 (2.3–4.4)	<0.001	28.5	2.7 (2.2–3.3)	<0.001
Group IV	30.0	1.8 (1.4–2.2)	<0.001	19.6	2.6 (2.0–3.4)	<0.001	23.6	2.1 (1.7–2.4)	<0.001
High-risk LDL cholesterol									
Group I	12.7	Reference		5.9	Reference		9.1	Reference	
Group II	13.6	1.1 (0.7–1.9)	0.61	4.6	0.9 (0.4–1.9)	0.79	8.5	1.1 (0.7–1.6)	0.81
Group III	19.0	1.5 (1.1–2.0)	0.02	16.5	2.7 (1.8–3.9)	<0.001	17.8	1.8 (1.4–2.3)	<0.001
Group IV	22.3	1.7 (1.3–2.2)	<0.001	8.2	1.3 (0.9–1.8)	0.25	14.7	1.5 (1.2–1.9)	<0.001
High-risk HDL cholesterol									
Group I	23.9	Reference		7.2	Reference		15.0	Reference	
Group II	21.9	0.9 (0.6–1.3)	0.58	8.5	1.1 (0.6–2.0)	0.64	14.3	1.0 (0.7–1.3)	0.77
Group III	47.2	1.7 (1.4–2.1)	<0.001	30.5	3.3 (2.4–4.3)	<0.001	39.1	2.1 (1.8–2.5)	<0.001
Group IV	51.7	2.0 (1.7–2.3)	<0.001	25.7	3.0 (2.3–3.8)	<0.001	38.1	2.2 (1.9–2.6)	<0.001
High-risk triglycerides									
Group I	11.0	Reference		4.2	Reference		7.4	Reference	
Group II	5.9	0.6 (0.3–1.2)	0.13	3.9	1.0 (0.4–2.3)	0.99	4.8	0.7 (0.4–1.2)	0.21
Group III	34.0	3.0 (2.4–3.9)	<0.001	12.4	2.9 (1.9–4.4)	<0.001	23.4	3.0 (2.4–3.8)	<0.001
Group IV	35.7	3.2 (2.6–3.9)	<0.001	15.0	3.2 (2.3–4.4)	<0.001	25.0	3.2 (2.7–3.8)	<0.001
High-risk carotid-artery intima–media thickness									
Group I	12.5	Reference		12.7	Reference		12.6	Reference	
Group II	15.2	1.2 (0.7–1.9)	0.49	8.8	0.7 (0.4–1.2)	0.16	11.7	0.9 (0.6–1.3)	0.54
Group III	18.1	1.5 (1.1–2.2)	0.01	22.5	1.9 (1.4–2.6)	<0.001	20.2	1.7 (1.4–2.2)	0.002
Group IV	17.5	1.5 (1.1–1.9)	0.007	17.9	1.6 (1.2–2.0)	<0.001	17.7	1.5 (1.3–1.8)	0.009

* Data are pooled from four large studies of cardiovascular risk factors — the Bogalusa Heart Study, the Muscatine Study, the Childhood Determinants of Adult Health study, and the Cardiovascular Risk in Young Finns Study. The analyses were adjusted for age, sex, height, length of follow-up, and cohort. The adiposity groups were as follows: group I (4742 subjects) included subjects with a normal BMI in childhood who were nonobese as adults; group II (274 subjects), those who were overweight or obese in childhood but nonobese as adults; group III (500 subjects), those who were overweight or obese in childhood and obese as adults; and group IV (812 subjects), those with a normal BMI in childhood who were obese as adults.

† P values are for the comparison with group I (reference).

subjects who were overweight or obese during childhood but nonobese as adults (group II) than among subjects who were consistently obese or who became obese as adults (groups III and IV). The only exception was the relative risk of high-risk LDL cholesterol levels, which was lower — but not significantly lower — in group II than in group IV (relative risk, 1.1; 95% CI, 0.7 to 1.6; vs. relative

risk, 1.5; 95% CI, 1.2 to 1.9; P=0.10). The association between the normalization of BMI and low risk was similar in male and female subjects (Table 3). The risk estimates for hypertension and high-risk HDL cholesterol levels among obese women, irrespective of their childhood adiposity status, were higher than those among obese men.

Meta-Analysis

As shown in Figure 1, the two larger studies (CDAH and YFS) had a greater influence on the results of the meta-analysis than did the two smaller studies (Bogalusa and Muscatine); however, the overall effect was similar in each cohort. The risk of one or more high-risk outcomes among subjects who were overweight or obese in childhood but nonobese as adults (group II) was similar to the risk among those who had a consistently normal BMI (group I). Subjects who were obese as adults (groups III and IV) had a significantly increased risk of having one or more high-risk outcomes.

Additional Analyses

The observation that the risk of high-risk outcomes among subjects who were overweight or obese as children but nonobese as adults was similar to the risk among subjects who had a favorable BMI in both childhood and adulthood was seen consistently in a series of sensitivity analyses (see Tables 5 to 15 and Fig. 1 in the Supplementary Appendix). No significant interactions between cohort and adiposity group or between race and adiposity group were identified. The influence on risk estimates of various levels of adult overweight and obesity can be seen in Figure 2 in the Supplementary Appendix. This figure shows the relative risks among subjects who had normal weight in childhood, as compared with those who were overweight or obese in childhood, in subgroups according to the BMI as adults (<25, 25 to 30, and >30). The increase in risk was seen predominantly in adult subjects who had a BMI greater than 30, regardless of their childhood BMI.

To determine the effect of childhood adiposity status on the risk of high-risk outcomes among obese adults, we compared the relative risks of high-risk outcomes between the subjects who were overweight or obese in childhood and obese in adulthood (group III) and those who had normal weight in childhood but were obese as adults (group IV). The relative risk of hypertension was significantly higher in group III than in group IV (relative risk, 2.7; 95% CI, 2.2 to 3.3; vs. relative risk, 2.1; 95% CI, 1.7 to 2.4; P=0.01). No significant differences were seen with respect to the other outcomes.

We also constructed multivariable models for predicting each outcome, with adult obesity, childhood adiposity, or both included in the model. The associations between childhood adiposity and adult outcomes were attenuated and became nonsignificant after adjustment for adult obesity, except for the association between childhood obesity and hypertension in adulthood (Tables 16 and 17 in the Supplementary Appendix). Childhood obesity was significantly associated with hypertension even after adjustment for adult obesity (relative risk, 1.5; 95% CI, 1.1 to 2.1; P=0.009).

Data collected in the YFS allowed us to determine the timing of BMI normalization. The age range in which the BMI decreased to normal levels in the greatest number of previously overweight or obese children was the 12-to-15-year age range, but the risk of adult outcomes was similar regardless of the average age at which BMI normalized (Tables 18 and 19 in the Supplementary Appendix).

DISCUSSION

Childhood overweight or obesity is associated with adverse long-term outcomes. Previous studies have shown that obesity in childhood predicts the development of type 2 diabetes mellitus and cardiovascular disease.[2-4,23-25] In addition, a high BMI in childhood is known to be associated with a high risk of obesity in adulthood.[26] Our data confirm both the increase in cardiovascular risk associated with childhood overweight or obesity and the tracking of adiposity between childhood and adulthood.

However, it has not been clear whether the association between childhood adiposity and cardiovascular risk persists when overweight or obese children become nonobese as adults. In our study, we found that a decrease in adiposity between childhood and adulthood was associated with marked reductions in the risks of type 2 diabetes, hypertension, and dyslipidemia. The risk of type 2 diabetes among obese adults (regardless of whether they were obese in childhood), as compared with the risk among nonobese adults who were overweight or obese as children, was increased by a factor of 4. In line with our findings, a recent retrospective report showed that obese girls who became lean as adults did not have an increased risk of type 2 diabetes.[27] We also observed that obese adults, irrespective of their

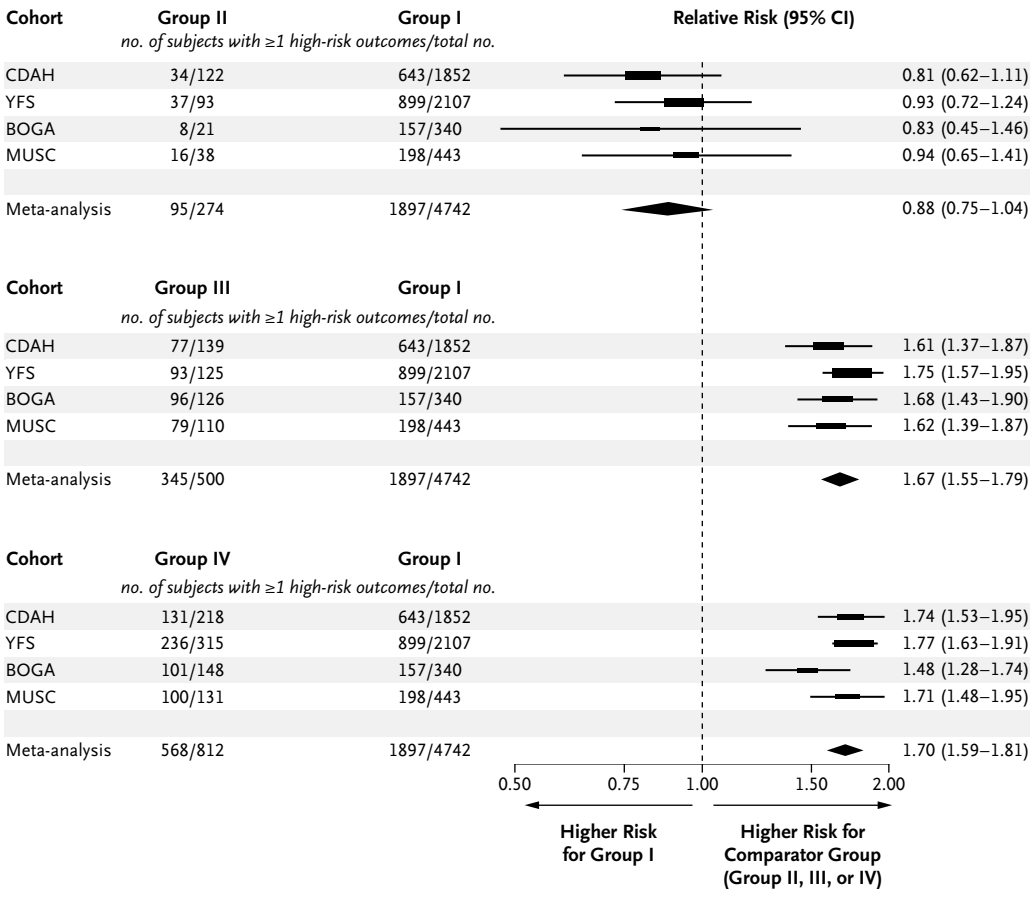

Figure 1. Forest Plots Showing Relative Risks of High-Risk Outcomes in Four Cohorts.

Data were analyzed from four large studies of cardiovascular risk factors — the Bogalusa Heart Study (BOGA) the Muscatine Study (MUSC), the Childhood Determinants of Adult Health (CDAH) study, and the Cardiovascular Risk in Young Finns Study (YFS). In each individual study cohort and in a meta-analysis of all four cohorts, the risk of one or more of the following high-risk outcomes is shown: type 2 diabetes, hypertension, high-risk low-density lipoprotein cholesterol levels (≥160 mg per deciliter [4.14 mmol per liter]), high-risk high-density lipoprotein cholesterol levels (<40 mg per deciliter [1.03 mmol per liter]), high-risk triglyceride levels (≥200 mg per deciliter [2.26 mmol per liter]), and high-risk carotid-artery intima–media thickness (≥90th percentile for age-, sex-, race-, study-year–, and cohort-specific values). Subjects who had a normal body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) in childhood and were nonobese as adults (group I) were compared with subjects who were overweight or obese in childhood but nonobese as adults (group II), subjects who were overweight or obese in childhood and obese as adults (group III), and subjects with a normal BMI in childhood who were obese as adults (group IV). The size of each box is proportional to the weight of the cohort in the meta-analysis. The diamonds represent the relative risks estimated from the meta-analysis, with the lateral points indicating the 95% confidence intervals. The P values for heterogeneity were 0.86 for the comparison of group II with group I, 0.77 for the comparison of group III with group I, and 0.30 for the comparison of group IV with group I, suggesting that there was no dissimilarity between cohorts.

childhood BMI, had risks of hypertension and dyslipidemias that were higher by a factor of approximately 2 to 3 than the risks among persons who were overweight or obese in childhood but nonobese as adults.

These findings were supported by multivariable models that showed that with respect to type 2 diabetes, dyslipidemias, and high-risk intima–media thickness, the effect of childhood adiposity (regardless of the definition) was reduced and became nonsignificant when adult obesity was taken into account. Only the association between childhood obesity and the risk of hypertension remained significant (although the association was

attenuated) after accounting for adult obesity. The finding with respect to hypertension was also seen in comparisons among adiposity groups; obese adults who were overweight or obese as children had a higher risk of hypertension than did obese adults who had normal weight as children. This result suggests that childhood adiposity has a residual effect on the risk of hypertension. Nevertheless, a reduction in adiposity status was associated with a reduced risk for hypertension, as for the other outcomes.

Childhood BMI is a predictor of adult BMI, and obesity is very hard to treat once it is established.[28] As shown here, although BMI does track over time, some children and adolescents with a high BMI become nonobese as adults, and this change is associated with a reduction in cardiovascular risk. Although the observational nature of our study precludes making clinical recommendations, we hypothesize that reducing BMI in children and adolescents who are overweight or obese could reduce their cardiovascular risk. If this hypothesis is correct, primary care physicians should not take the pessimistic view that once childhood obesity is established, cardiovascular risk is also determined but should recognize that cardiovascular risk may be substantially reduced if childhood obesity is successfully treated.

Some limitations of our study should be considered. First, differences among the cohorts in the acquisition of data did not allow complete comparisons to be made across cohorts with respect to some variables, such as puberty stage and socioeconomic status. Second, since the cohorts comprised young adults, we were not able to study the associations of adiposity status with cardiovascular events. Instead, we used cardiovascular risk factors and carotid intima–media thickness as the outcomes. Third, with respect to the establishment of causality, observational studies are prone to bias; therefore, we cannot make definitive statements regarding causality. Fourth, owing to a lack of comprehensive serial data, we were unable to examine in detail the timing of BMI normalization. Analyses restricted to YFS suggested that normalization most frequently occurs around the time of puberty, but the numbers in these analyses were very small. Fifth, the association between adult obesity and cardiovascular outcomes may be influenced by differential acquisition of muscle and adipose tissue in childhood.[29,30] Therefore, high BMI is not an ideal marker of adiposity in children, since it may reflect either adiposity or muscularity. However, similar results were seen when childhood skinfold thickness was used as the measure of adiposity (see Table 12 in the Supplementary Appendix). Finally, since the study participants were predominantly white, the results cannot be generalized to other races or ethnic groups. Although the exclusion of blacks did not affect the results, we caution against generalizing the findings to different races or ethnic groups.

In summary, our analysis of data from four longitudinal cohort studies showed that childhood overweight or obesity was predictive of type 2 diabetes, hypertension, dyslipidemia, and high-risk carotid intima–media thickness in adulthood. The data also showed that persons who had normal BMI in childhood but who became obese as adults had adverse risk-factor profiles, whereas those who were overweight or obese as children but who became nonobese as adults had a cardiovascular-risk profile that was similar to that of persons who were never obese.

These analyses were supported by funding from the individual studies. The Cardiovascular Risk in Young Finns Study was supported by grants from the Academy of Finland (121584, 126925, 124282, 129378), the Social Insurance Institution of Finland, the Turku University Foundation, Special Federal Grants for University Hospitals, the Juho Vainio Foundation, Paavo Nurmi Foundation, the Finnish Foundation of Cardiovascular Research, Orion-Farmos Research Foundation, and the Finnish Cultural Foundation. The Childhood Determinants of Adult Health study was supported at baseline by the Commonwealth Departments of Sport, Recreation and Tourism, and Health; the National Heart Foundation; and the Commonwealth Schools Commission and at follow-up by the National Health and Medical Research Council, the Heart Foundation, the Tasmanian Community Fund, and Veolia Environmental Services; authors from the Murdoch Children's Research Institute are supported by the Victorian Government Operational Infrastructure Support Program; Dr. Sabin is supported through a National Health and Medical Research Council Health Professional Training Fellowship (APP1012201). The Bogalusa Heart Study was supported by grants from the National Institute on Aging (AG-16592) and the National Heart, Lung, and Blood Institute (HL-38844) of the National Institutes of Health (NIH) and from the American Heart Association. The Muscatine Study was supported by grants from the National Heart, Lung, and Blood Institute (HL-14230 and HL-54730), and the General Clinical Research Centers Program (RR-00059) of the NIH.

Dr. Sabin reports receiving lecture fees from Pfizer; Dr. Daniels, receiving consulting fees from Merck; and Dr. Viikari, receiving lecture fees from Merck, AstraZeneca, and Pfizer. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the teams that collected data at all measurement time points across all study centers; the persons who participated as both children and adults in these longitudinal studies; and biostatisticians Ville Aalto, Irina Lisinen, Hans Helenius, and Russell Thomson for statistical advice.

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