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Childhood Obesity, Other Cardiovascular Risk Factors, and Premature Death

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ABSTRACT

BACKGROUND

The effect of childhood risk factors for cardiovascular disease on adult mortality is poorly understood.

METHODS

In a cohort of 4857 American Indian children without diabetes (mean age, 11.3 years; 12,659 examinations) who were born between 1945 and 1984, we assessed whether body-mass index (BMI), glucose tolerance, and blood pressure and cholesterol levels predicted premature death. Risk factors were standardized according to sex and age. Proportional-hazards models were used to assess whether each risk factor was associated with time to death occurring before 55 years of age. Models were adjusted for baseline age, sex, birth cohort, and Pima or Tohono O'odham Indian heritage.

RESULTS

There were 166 deaths from endogenous causes (3.4% of the cohort) during a median follow-up period of 23.9 years. Rates of death from endogenous causes among children in the highest quartile of BMI were more than double those among children in the lowest BMI quartile (incidence-rate ratio, 2.30; 95% confidence interval [CI], 1.46 to 3.62). Rates of death from endogenous causes among children in the highest quartile of glucose intolerance were 73% higher than those among children in the lowest quartile (incidence-rate ratio, 1.73; 95% CI, 1.09 to 2.74). No significant associations were seen between rates of death from endogenous or external causes and childhood cholesterol levels or systolic or diastolic blood-pressure levels on a continuous scale, although childhood hypertension was significantly associated with premature death from endogenous causes (incidence-rate ratio, 1.57; 95% CI, 1.10 to 2.24).

CONCLUSIONS

Obesity, glucose intolerance, and hypertension in childhood were strongly associated with increased rates of premature death from endogenous causes in this population. In contrast, childhood hypercholesterolemia was not a major predictor of premature death from endogenous causes.

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DESPITE RECENT INCREASES IN LIFE expectancy, the rising global prevalence of obesity may reverse this trend.¹ The rising rates and increasingly early onset of other chronic diseases such as type 2 diabetes may also affect mortality rates.²

Cardiovascular risk factors are common in children.^{3,4} Although early-onset diabetes has been shown to raise mortality rates,² and the relation between cardiovascular risk factors during adulthood and early death is well defined,⁵⁻⁷ little is known about the way in which cardiovascular risk factors that are present during childhood affect life span. Defining such relationships may help predict the long-term human and economic costs of cardiovascular risk factors in childhood and might justify interventions that are intended to improve health and reduce the rates of premature death.

In this study, we assessed the extent to which obesity, glucose intolerance, hypertension, and hypercholesterolemia in children without diabetes predicted premature death (defined as death before 55 years of age) in American Indians from Arizona.

METHODS

STUDY POPULATION

We invited residents in a well-defined geographic area of the Gila River Indian Community in Arizona, most of whom were Pima or Tohono O'odham Indians,^{8,9} to participate in a longitudinal study of diabetes and related disorders. Pima or Tohono O'odham Indian heritage was defined by the heritage of each of the child's parents, grandparents, and great-grandparents, as reported by the parents of the participating children. Included in the study were 4857 children and adolescents (5 to <20 years of age) who had at least 4/8 Pima or Tohono O'odham Indian heritage, did not have diabetes, and underwent one or more research examinations between February 1966 and December 2003. Participants were born between 1945 and 1984 and resided on the reservation during the study. Participants who were 18 years of age or older gave written informed consent; those younger than 18 years of age gave written assent and a parent or guardian gave written informed consent. The institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases approved the study.

STUDY EXAMINATIONS

We assessed the extent to which childhood body-mass index (BMI), 2-hour plasma glucose level during a 75-g oral glucose-tolerance test, and blood pressure and total cholesterol levels predicted premature death. The baseline examination was the first examination at which all these variables were measured. The analyses included data from the date of the baseline examination until the person's death, the person's 55th birthday, or the end of 2003, whichever came first. Vital status was ascertained as of December 31, 2003. Death records for community residents were maintained throughout the study period. Copies of death certificates were obtained. The underlying cause of death was classified as endogenous or external. We defined deaths due to endogenous causes as those in which the proximate cause was disease or self-inflicted injury, such as acute alcohol intoxication or drug use, and deaths due to external causes as those that resulted from such causes as accidents or homicide. These definitions are consistent with those used in previous mortality studies undertaken in this cohort.¹⁰ The cause of death was determined from a review of available clinical autopsy records and death certificates. (For a list of the specific causes of death and the corresponding *International Classification of Diseases, 9th Revision* [ICD-9] codes, see the Supplementary Appendix, available with the full text of this article at NEJM.org.)

All participants underwent a 75-g oral glucose-tolerance test; results were interpreted according to World Health Organization diagnostic criteria.¹¹ We considered diabetes to be present if the fasting plasma glucose concentration was more than 7.0 mmol per liter (126 mg per deciliter), if the 2-hour plasma glucose concentration was 11.1 mmol per liter (200 mg per deciliter) or more, or if a previous clinical diagnosis was documented. Blood pressure was measured and standard anthropometric data were obtained while participants were wearing lightweight clothing and no shoes; the data were collected by trained study personnel.^{8,9,12} No measures of puberty were available. Blood assays were performed as described previously.^{8,9,12} Alcohol dependence in adulthood (for which data were available from 2672 of the participants) was estimated with the use of the CAGE questionnaire.¹³

STATISTICAL ANALYSIS

Analyses were performed with the use of SAS software, version 9.1 (SAS Institute). The characteristics of the participants are presented as arithmetic means (\pm SD) or, in the case of characteristics with skewed distributions, as medians and ranges. The z scores, which were standardized within sex and 1-year age strata, were computed for use in regression analyses. Age-standardized and sex-standardized incidence was calculated by the direct method with the use of the total study population as the reference group. Incidence-rate ratios were calculated from the incidence data with the use of Poisson regression controlled for age, sex, and Pima or Tohono O'odham Indian heritage. For incidence analyses, follow-up was truncated at 55 years of age, since there were few person-years beyond that point. Cox proportional-hazards models were used to test for associations between the baseline childhood risk factors and time to death, with adjustment for baseline age, sex, Pima or Tohono O'odham Indian heritage, and birth year, since birth year was correlated with many variables of interest (e.g., $r=0.36$ for the correlation between BMI and birth year). We tested the validity of the proportionality assumption for each variable by including a time-dependent interaction term in the baseline models.¹⁴ When this assumption was violated, stratified proportional-hazards models were fitted and a summarized incidence-rate ratio was calculated across strata; no material differences in death rates were observed across sex and baseline-age strata (data not shown).

RESULTS

PREMATURE DEATH AMONG STUDY PARTICIPANTS

Table 1 shows the baseline characteristics of the participants. During the follow-up period, 559 of the 4857 participants (11.5%) died before they reached 55 years of age. A total of 166 deaths were from endogenous causes: 59 were attributed to alcoholic liver disease, 22 to cardiovascular disease, 21 to infections, 12 to cancer, 10 to diabetes or diabetic nephropathy, 9 to acute alcoholic poisoning or drug overdose, and 33 to other causes (see the Supplementary Appendix for a list of ICD-9 codes). Table 2 shows the rates of premature death by 10-year age strata.

CHILDHOOD OBESITY AND PREMATURE DEATH

BMI was positively associated with the risk of premature death from endogenous causes (incidence-

Table 1. Baseline Characteristics of the Participants and Prevalence of Death before 55 Years of Age.*

Variable	Value
Sex — no. (%)	
Male	2397 (49.4)
Female	2460 (50.6)
Age — yr	
Mean	11.3 \pm 3.7
Range	5–19
Age group — no. (%)	
5–9	2075 (42.7)
10–14	1913 (39.4)
15–19	869 (17.9)
Body-mass index [†]	
Mean	21.9 \pm 6.1
Range	12.4–55.3
Obesity — no. (%) [‡]	1394 (28.7)
2-hr glucose — mmol/liter	
Mean	5.5 \pm 1.2
Range	1.3–11.0
Impaired glucose tolerance — no. (%)	198 (4.1)
Blood pressure — mm Hg	
Systolic	
Mean	106 \pm 16
Range	58–196
Diastolic	
Mean	59 \pm 11
Range	6–110
Hypertension — no. (%) [§]	607 (12.5)
Total cholesterol — mmol/liter	
Mean	3.8 \pm 0.7
Range	1.6–11.2
Hypercholesterolemia — no. (%) [¶]	182 (3.7)
Follow-up period — yr	
Median	23.9
Range	0.04–37.9
Death — no. (%)	
From all causes	559 (11.5)
From endogenous causes	166 (3.4)
From external causes	393 (8.1)

* Plus-minus values are means \pm SD. To convert values for glucose to milligrams per deciliter, multiply by 18.01. To convert values for cholesterol to milligrams per deciliter, multiply by 38.67.

[†] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[‡] Obesity was defined as a body-mass index in the 95th percentile or higher of the U.S. population according to the 2000 database of the Centers for Disease Control and Prevention.¹⁵

[§] Hypertension was defined according to the criteria of the National High Blood Pressure Education Program.¹⁶

[¶] Hypercholesterolemia was defined as a cholesterol level higher than the cutoff point designated by the American Heart Association (total cholesterol, 5.18 mmol per liter [200 mg per deciliter]).¹⁷

Table 2. Premature Death among Study Participants, According to Age at Study Entry.*

Age	Person-Years of Follow-up	Premature Death						
		All Causes		External Causes		Endogenous Causes		
		no.	no./1000 person-yr	no.	no./1000 person-yr	no.	no./1000 person-yr	% of all deaths
5–14 yr	20,066	6	0.30	6	0.30	0	0	0
15–24 yr	43,081	190	4.41	181	4.20	9	0.21	4.7
25–34 yr	31,163	190	6.10	144	4.62	46	1.48	24.2
35–44 yr	17,154	108	6.30	47	2.74	61	3.56	56.5
45–54 yr	4,646	65	13.99	15	3.23	50	10.76	76.9

* Participants were 5 to 19 years of age when they entered the study. Person-years of follow-up were partitioned according to age over the course of the follow-up period. The incidence analysis was stratified according to decade of age and truncated at the age of 55 years.

rate ratio per 1 unit of BMI z score, 1.40; 95% confidence interval [CI], 1.20 to 1.63). BMI was positively, but not significantly, associated with death from external causes (incidence-rate ratio per 1 SD of standardized BMI, 1.19; 95% CI, 1.00 to 1.42).

Children in the highest quartile of age-standardized and sex-standardized BMI had significantly higher rates of death than did children in the lowest quartile (Fig. 1 and Table 3). The rates of death from endogenous causes among children in the highest quartile of BMI were more than double those among children in the lowest quartile (incidence-rate ratio, 2.30; 95% CI, 1.46 to 3.62) (Table 3). This finding could not be explained just by the presence of extremely obese children in the highest quartile, however, since none of the 51 extremely obese children (BMI z score >3) died during the follow-up period, possibly because these participants were younger and from more recent birth cohorts (median follow-up, 21.4 years) than participants who were less obese. The association between BMI and premature death from endogenous causes was attenuated but remained significant after adjustment for baseline glucose level, cholesterol level, and blood pressure (incidence-rate ratio for the highest BMI quartile vs. the lowest quartile, 1.41; 95% CI, 1.19 to 1.67) (Table 3).

A total of 1394 of the children (28.7%) were obese, which was defined as a BMI in the 95th percentile or higher on the Centers for Disease Control and Prevention (CDC) growth charts.¹⁵ Among the obese children as compared with the nonobese children, the incidence-rate ratios were

1.31 (95% CI, 1.10 to 1.57) for premature death from all causes, 1.90 (95% CI, 1.37 to 2.65) for death from endogenous causes, and 1.14 (95% CI, 0.92 to 1.41) for death from external causes.

CHILDHOOD GLUCOSE, CHOLESTEROL, AND BLOOD-PRESSURE LEVELS AND PREMATURE DEATH

The 2-hour plasma glucose level during a 75-g oral glucose-tolerance test, expressed in age-standardized and sex-standardized units, was not associated with premature death from either endogenous or external causes. However, children in the highest quartile of glucose level had a 73% higher risk of premature death from endogenous causes than children in the lowest quartile (Table 3). Adjustment for childhood BMI reduced the magnitude of the association (incidence-rate ratio, 1.24; 95% CI, 0.79 to 1.96).

In models of impaired glucose tolerance (i.e., 2-hour glucose level of 7.8 to 11.0 mmol per liter [140 to 199 mg per deciliter])¹⁸ as compared with normal glucose tolerance as the predictor variable, the incidence-rate ratios were 0.90 (95% CI, 0.63 to 1.30) for all-cause premature death, 0.81 (95% CI, 0.39 to 1.65) for death from endogenous causes, and 0.94 (95% CI, 0.62 to 1.43) for death from external causes. Children with impaired glucose tolerance accounted for 15% of the children in the highest quartile of plasma glucose levels and were all in the top decile of the standardized 2-hour glucose distribution.

No significant associations were observed between death rates and childhood cholesterol levels or blood pressure (Table 3). In models in which hypercholesterolemia, as defined by the

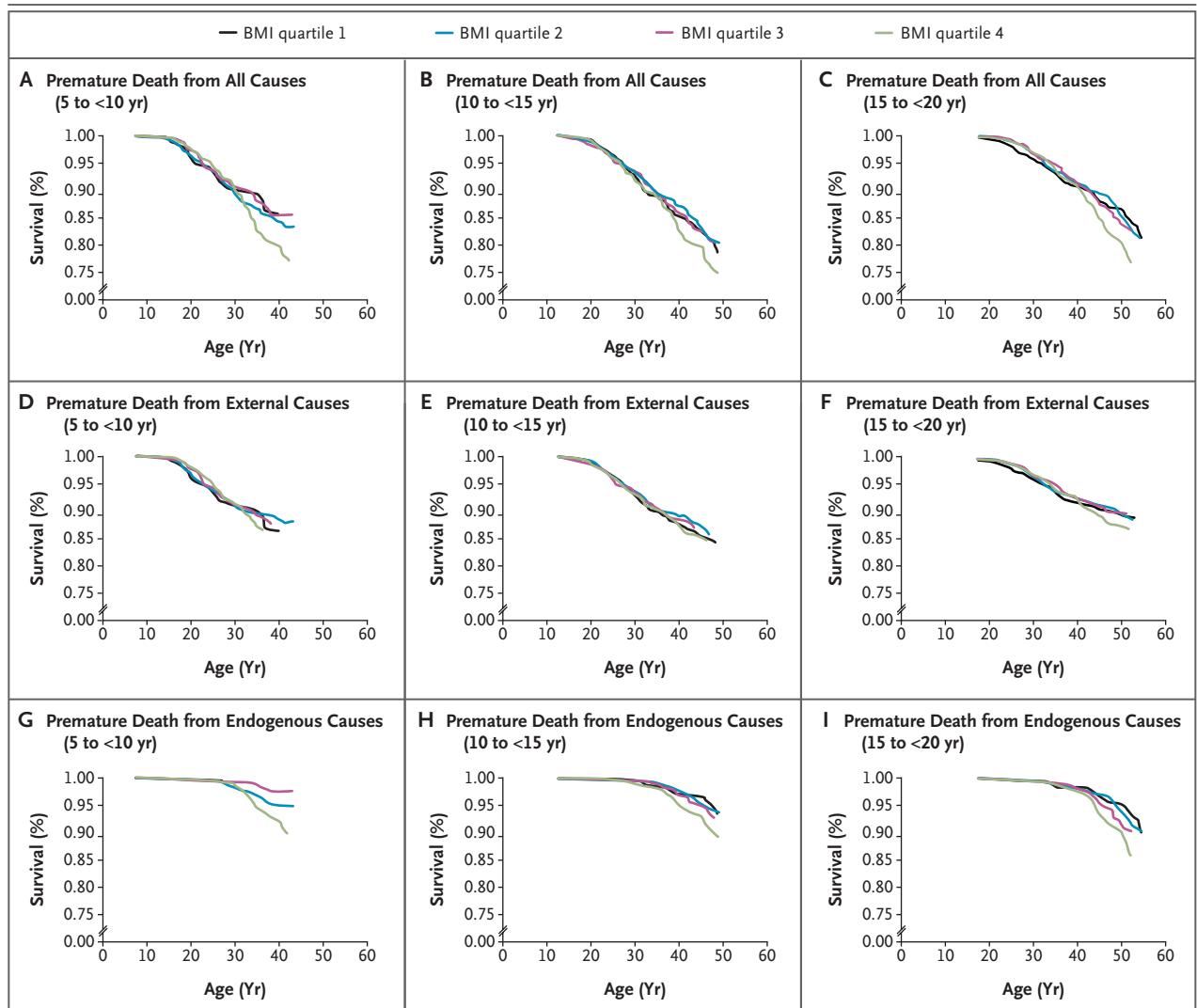


Figure 1. Kaplan–Meier Curves for Premature Death.

The graphs show the rates of premature death from all causes, external causes, and endogenous causes according to quartiles of age-standardized and sex-standardized body-mass index at different baseline ages during childhood and adolescence. Plots were computed with the use of baseline data. Age at baseline for each age group was taken as the midpoint of the age range.

American Heart Association cutoff point (total cholesterol level, 5.18 mmol per liter [200 mg per deciliter]), was used as the predictor variable,¹⁷ the incidence-rate ratios were 1.33 (95% CI, 0.95 to 1.88) for all-cause premature death, 1.70 (95% CI, 0.96 to 3.01) for death from endogenous causes, and 1.18 (95% CI, 0.77 to 1.80) for death from external causes.

With hypertension defined according to the criteria of the National High Blood Pressure Education Program¹⁶ in the case of children and as 140/90 mm Hg or higher in the case of participants 18 years of age or older, there was no sig-

nificant association with rates of death from all causes (incidence-rate ratio, 1.15; 95% CI, 0.93 to 1.43) or from external causes (incidence-rate ratio, 0.98; 95% CI, 0.75 to 1.29). However, childhood hypertension was strongly associated with the rate of death from endogenous causes (incidence-rate ratio, 1.57; 95% CI, 1.10 to 2.24).

POTENTIAL MEDIATORS OF THE ASSOCIATION BETWEEN OBESITY AND DEATH

Most deaths occurred in study participants who were not known to have diabetes. Of the 559 participants in whom diabetes developed, 79 died:

Table 3. Incidence-Rate Ratios for Premature Death, According to Quartile of Variables.*

Variable	Premature Death from All Causes		Premature Death from External Causes		Premature Death from Endogenous Causes	
	IRR (95% CI)	P value	IRR (95% CI)	P value	IRR (95% CI)	P value
Body-mass index		0.02		0.35		<0.01
Q2 vs. Q1	0.91 (0.72–1.16)		0.82 (0.62–1.09)		1.24 (0.77–2.00)	
Q3 vs. Q1	1.01 (0.80–1.24)		0.94 (0.71–1.23)		1.28 (0.78–2.09)	
Q4 vs. Q1	1.31 (1.04–1.66)		1.06 (0.80–1.40)		2.30 (1.46–3.62)	
2-Hour glucose		0.37		0.78		0.12
Q2 vs. Q1	1.10 (0.86–1.40)		1.00 (0.76–1.32)		1.43 (0.88–2.30)	
Q3 vs. Q1	0.97 (0.75–1.24)		0.88 (0.66–1.18)		1.24 (0.75–2.04)	
Q4 vs. Q1	1.17 (0.93–1.48)		1.02 (0.77–1.39)		1.73 (1.09–2.74)	
Systolic blood pressure		0.19		0.80		0.09
Q2 vs. Q1	0.92 (0.71–1.21)		0.98 (0.73–1.33)		0.75 (0.43–1.30)	
Q3 vs. Q1	1.15 (0.90–1.48)		1.11 (0.83–1.49)		1.26 (0.77–2.07)	
Q4 vs. Q1	1.16 (0.91–1.48)		1.08 (0.81–1.45)		1.34 (0.83–2.15)	
Diastolic blood pressure		0.72		0.96		0.35
Q2 vs. Q1	1.08 (0.84–1.38)		1.07 (0.80–1.42)		1.09 (0.66–1.82)	
Q3 vs. Q1	0.99 (0.78–1.27)		0.99 (0.75–1.32)		1.00 (0.61–1.64)	
Q4 vs. Q1	1.11 (0.88–1.41)		1.01 (0.76–1.34)		1.40 (0.89–2.19)	
Total cholesterol		0.14		0.21		0.77
Q2 vs. Q1	1.08 (0.85–1.37)		1.07 (0.81–1.42)		1.11 (0.71–1.75)	
Q3 vs. Q1	1.04 (0.81–1.32)		1.01 (0.76–1.34)		1.11 (0.71–1.75)	
Q4 vs. Q1	1.30 (1.02–1.65)		1.30 (0.99–1.72)		1.28 (0.81–2.02)	

* Incidence-rate ratios (IRRs) were calculated by means of Poisson regression according to quartiles of variables standardized by age and sex. P values are for linear trends across quartiles. Q denotes quartile.

40 from endogenous causes and 39 from external causes. Adjusting the BMI prediction models for incident diabetes did not significantly alter the risk estimates (incidence-rate ratio for the highest BMI quartile vs. the lowest quartile, 2.70; 95% CI, 1.70 to 4.31). In contrast, inclusion of diabetes in the 2-hour glucose model reduced the risk estimate for the highest quartile of 2-hour glucose levels, and the association between the highest and lowest quartiles was not significant (incidence-rate ratio, 1.10; 95% CI, 0.72 to 1.68). In Cox proportional-hazards models that included 2672 participants, there were no significant associations between childhood BMI and alcohol dependency in adulthood (incidence-rate ratio per unit of BMI z score, 1.01; 95% CI, 0.96 to 1.07).

DISCUSSION

It is well known that obesity, glucose intolerance, hypertension, and hypercholesterolemia in adult-

hood increase mortality rates. We conducted the present study to determine whether the presence of these risk factors in childhood predicts premature death. The rate of death from endogenous causes in the highest quartile of childhood BMI was more than double that in the lowest quartile, and the rate in the highest quartile of childhood two-hour plasma glucose levels during a 75-g oral glucose-tolerance test was 73% higher than that in the lowest quartile. Although neither blood pressure nor cholesterol level in childhood, when included as a continuous variable, significantly predicted premature death, childhood hypertension increased the risk of premature death from endogenous causes by 57%.

The absence of an association between premature death and cholesterol levels may be due partly to the low proportion of deaths due to cardiovascular disease in this cohort (13.3%). Treatment for any of the predictor traits during childhood or during adulthood did not appear to

explain the pattern of association (data not shown). No childhood risk factor that was examined significantly predicted rates of premature death from external causes.

Childhood obesity predicted premature death from endogenous, but not external, causes. The study was not powered to analyze effects on more specific categories of cause of death. Including only liver-related causes of death in the analysis reduced the magnitude of the association of premature death with childhood BMI and with the 2-hour glucose level, but the direction and pattern of associations were similar to those observed when all endogenous causes of death were included.

We considered whether the relationship between childhood BMI and premature death reflects associations with adiposity or some other component of body mass. Our study began before the availability of modern adiposity measures such as dual-energy x-ray absorptiometry. However, we previously reported relationships between BMI and adipose mass and between adipose mass and the cardiovascular risk factors in this population¹⁹; in that study, BMI and adiposity were strongly correlated ($r > 0.96$), varying little with age and sex, and BMI and adipose mass were similarly correlated with the cardiovascular risk factors. Thus, the observations for childhood BMI reported here are likely to reflect a positive association between adiposity and rates of premature death.

In a study involving 508 U.S. adolescents (13 to 18 years of age) who were born between 1922 and 1935, overweight (>75th percentile of the sample distribution) was associated with increased rates of death due to coronary heart disease.²⁰ Two studies have assessed the relationship between body weight and mortality in European birth cohorts from the early 20th century.^{21,22} In a study of 2299 Welsh children born between 1937 and 1939, there was no association between childhood BMI and death from cardiovascular causes.²¹ However, there was an association between childhood BMI and death from all causes; the lowest rate of death was seen in the next-to-lowest BMI quartile and the highest rate of death in the highest quartile, suggesting that, as in the case of adult Pima Indians,²³ a U-shaped relationship exists between obesity and mortality. In the second European study, involving 504 overweight children and adolescents admitted to hospitals in

Stockholm between 1921 and 1947, weight gain between puberty and young adulthood was associated with cardiovascular disease, diabetes, and death from all causes.²² A limitation of these studies is that obesity was uncommon during the study period. For example, of the 2299 children in the Welsh study,²¹ only 92 (4.0%) had a BMI above the 90th percentile for the age-specific and sex-specific distributions of the 1990 British population, and British children in 1990 were leaner than their contemporary counterparts.²⁴

In the Arizona Pima Indians, unlike most other ethnic groups, childhood obesity has been common for decades.²⁵ It has been estimated that at the turn of the 21st century, approximately 15% of U.S. children between the ages of 6 and 19 years (11 million children) were overweight or obese,²⁶ a prevalence that is unlikely to decline in the near future²⁷ and that is triple the prevalence among children of the same age in the 1960s.^{28,29} In the present study, 1394 children (28.7%) were obese (BMI, ≥ 95 th percentile on the 2000 CDC growth charts). This prevalence is similar to that observed in contemporary Hispanic and African-American children.²⁷ Thus, although we studied a population with high rates of obesity and diabetes, our findings may reflect the future burden of premature death among contemporary children from other ethnic groups and may be more generalizable than the findings in previous studies.

In this study, we compared mortality rates with several clinical risk factors as variables. Adjusting the obesity models for the development of diabetes in adulthood did not significantly alter the risk estimates, whereas adjusting the glucose models for subsequent diabetes did attenuate the association between childhood glucose levels and premature death. Hence, dysregulated glucose metabolism in childhood may be a mediator of the effects of childhood obesity on mortality rates, but it does not appear to be the sole or dominant factor; however, the association between childhood glucose intolerance and premature death does appear to be mediated by the development of subsequent diabetes.

The pattern of the relationships between the risk factors and observed mortality supports the view that childhood obesity is an early metabolic derangement, whereas most of the other risk factors evolve later. In fact, the predictive power of a risk score for type 2 diabetes (including

measures of obesity and insulin, blood-pressure, glucose, and lipid levels) in children is almost entirely dependent on abdominal obesity, whereas in adolescents, the risk profile has evolved to include obesity, hyperglycemia, and dyslipidemia.³⁰ Our findings complement those in our previous study, which showed that type 2 diabetes, when it occurs during adolescence in this population, strongly predicts subsequent renal failure and death.²

Although there was no significant association between childhood hypercholesterolemia and death before 55 years of age in this young cohort, an elevated cholesterol level in childhood may emerge as a significant risk factor and other causes of death may predominate if the cohort is followed to older ages. Cholesterol levels, however, are lower in American Indians than they are in most other ethnic groups,³¹ a finding that may partially explain the absence of association for this trait. The relationship between BMI and high-density lipoprotein (HDL) cholesterol is relatively strong in Pima children ($r = -0.3$ to -0.6), but the relationship between BMI and total cholesterol is weaker ($r = 0.1$).¹⁹ The effect of BMI on premature death might be attributable in part to low HDL-cholesterol concentrations, which were not measured in most of the study participants. Nevertheless, we speculate that low HDL-cholesterol levels are likely to mediate rather than confound this relationship.

It is possible that the relationship between childhood BMI and mortality is confounded by unmeasured lifestyle factors. Nevertheless, obesity can be both the cause and the consequence of adverse lifestyle factors such as physical inactivity, excessive caloric intake, and specific nutrient preferences. Thus, such factors may be important components of the causal pathway between obesity and death. It is also possible that

genetic factors have pleiotropic effects on BMI and mortality.

Childhood obesity is predictive of excess mortality in several divergent settings,²⁰⁻²² indicating that obesity itself is causally related to either death or other commonly related factors. Even if preventing childhood obesity does not affect the risk of death, increased physical activity and modification of diet are likely to have long-term benefits. The lack of specific data on such factors is a limitation of this study.

In summary, obesity in children who do not have diabetes is associated with an increased rate of death from endogenous causes during early adulthood, an association that may be partially mediated by the development of glucose intolerance and hypertension in childhood. In contrast, the cholesterol level in childhood is not a major determinant of premature death in this population. Childhood obesity is becoming increasingly prevalent around the globe. Our observations, combined with those of other investigators, suggest that failure to reverse this trend may have wide-reaching consequences for the quality of life and longevity. Such evidence underscores the importance of preventing obesity starting in the early years of life.

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