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Childhood Obesity and Coronary Heart Disease

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Although there are several short-term complications of severe obesity among children [1–3], obese children also have an increased risk for coronary heart disease (CHD) in adulthood. The current chapter reviews the relation of childhood obesity to various CHD risk factors, atherosclerosis, and clinical disease in adulthood. Many of the presented data are from the Bogalusa Heart Study (Louisiana, USA), a long-term study of the early natural history of CHD [4]. This panel design of this study, which conducted seven examinations of children (ages 5–17 years) and four examinations of young adults (ages 18–37 years) between 1973 and 1995 [5], allows for both cross-sectional and longitudinal analyses.

Obesity and CHD Risk Factors in Childhood

Despite the inherent limitations of weight-height indices in quantifying adipose tissue, the body mass index (BMI, kg/m²) has been used as a surrogate measure of obesity among adults for many decades, and is now widely used among children. However, because BMI levels in early life vary substantially ($r \sim 0.5$) with age and height [1], it is necessary to represent BMI levels relative to a child's age and sex peers.

BMI levels among children can be classified by estimating levels at age 18 years from current BMI, and then applying the adult cutpoints of 25 kg/m² (overweight) and 30 kg/m² (obese) to these extrapolated values [6]. Sex-specific BMI-for-age centiles and Z-scores have also been developed from US data [7], and these values will be used throughout this chapter. It has been recommended that children with a BMI ≥ 95 th centile of these US data, which roughly corresponds to an expected BMI between 25 and 30 kg/m² at age 18 years [6], be

considered overweight. It should be realized, however, that because the relation of BMI to various diseases differs by ethnicity [8], a single classification scheme may not be appropriate for all children.

BMI levels among children show a non-linear relation to adverse levels of lipids, insulin, and blood pressure (fig. 1, upper panel), with the prevalence of adverse levels increasing markedly at very high BMI levels [9]. In these analyses of 5- to 17-year-olds ($n = 23,758$) from the Bogalusa Heart Study, risk-factor cutpoints were chosen so that prevalence of adverse levels of each characteristic was 5%. BMI was most strongly associated with levels of insulin ($r \sim 0.5$), and although the prevalence of adverse levels varied from $<1\%$ among the thinnest children to only 3% at the 85th centile of BMI, almost 40% of the children with a BMI >99 th centile had a high insulin level. Among these severely overweight children, the prevalence of other risk factors ranged from 15% (low HDL cholesterol) to 33% (high triglycerides).

Slightly stronger associations were observed with waist girth than for BMI. For example, whereas levels of HDL cholesterol showed a correlation of $r = -0.29$ with BMI, the correlation with waist girth was $r = -0.33$. Furthermore, HDL cholesterol levels were more strongly correlated with the subscapular skinfold thickness ($r = -0.28$) than with the triceps skinfold thickness ($r = -0.21$). Although the importance of visceral fat in these associations is uncertain [10], it is likely that these contrasting associations reflect some aspect of body fat distribution.

The relation of childhood obesity to the clustering of multiple risk factors has also been examined [11], and data from the Bogalusa Heart Study are summarized in the bottom panel of figure 1. Overall, about 20% of the examined children had adverse levels of at least one of the five risk factors considered, but this percentage varied from 10% among the thinnest children to 70% among the heaviest children. Similar to the findings for the individual risk factors, the associations were markedly non-linear. The increase was most striking for those with ≥ 3 risk factors, with the proportion increasing from 0% (thinnest children), to $\sim 1\%$ (85th BMI centile), and to $\sim 10\%$ (99th BMI centile). As the presence of multiple risk factors is strongly associated with the early stages of atherosclerosis [12], the recent secular increases in the prevalence of overweight (≥ 95 th centile) and severe overweight (≥ 99 th centile) among children [13, 14] are of particular concern.

Concurrent with these increases in childhood obesity, the prevalence of type 2 diabetes has also increased substantially among adolescents [15, 16]. Obesity is very common among these newly diagnosed cases, and it has been found that most of the increase in type 2 diabetes among Pima Indian children can be accounted for by changes in childhood obesity and intrauterine exposure to diabetes since 1970 [15].

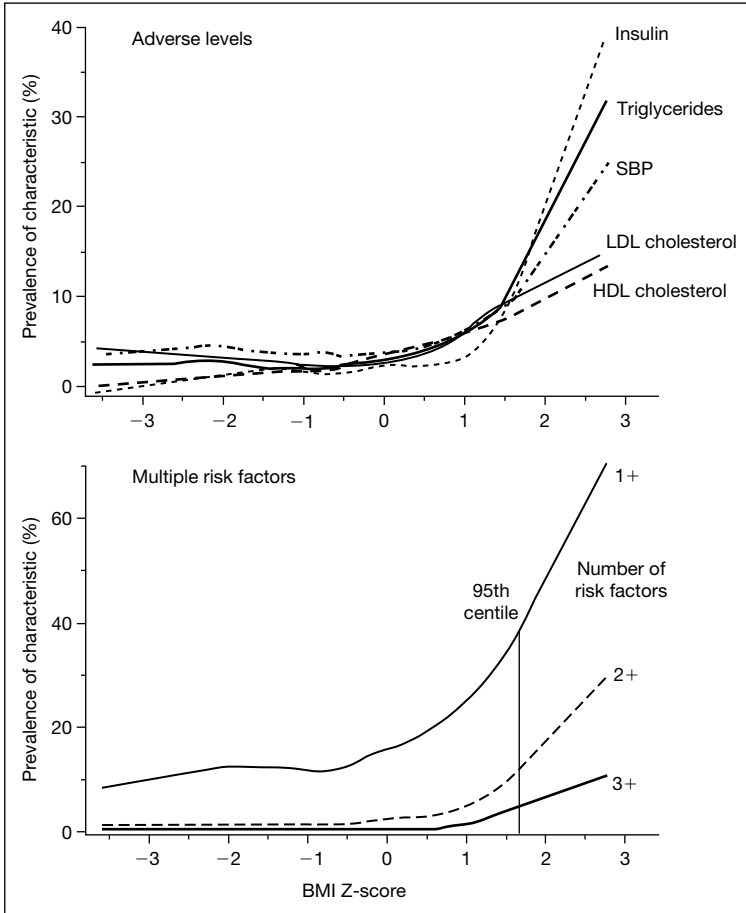


Fig. 1. The top panel shows the relation of BMI (Z-Scores) to the proportion of 5- to 17-year-olds in the Bogalusa Heart Study having adverse levels of insulin, triglycerides, LDL cholesterol, HDL cholesterol, and systolic blood pressure. Adverse levels were defined as those >95th centile (race, sex, and age specific); adverse levels of HDL cholesterol were <5th centile. BMI Z-scores were calculated from national US data, and Z-scores of 1.04, 1.64 and 2.33 correspond to the 85th, 95th and 99th centiles of BMI, respectively. The bottom panel shows the relation of BMI Z-scores to the prevalence of children having one or more, two or more, or three or more of the five risk factors considered.

In addition to these associations, childhood obesity is associated other CHD risk factors, such as left ventricular hypertrophy, elevated levels of C-reactive protein, homocysteine and lipoprotein(a), and various pro-coagulant factors [17, 18]. Furthermore, whereas childhood BMI is inversely associated with levels

of HDL cholesterol and large HDL, it is positively associated with levels of small HDL [19]. These contrasting associations with HDL subclasses may also increase the progression of atherosclerosis [20].

Longitudinal Associations with Adult Complications

Risk Factors

It has been estimated that ~40% of overweight children will be obese in adulthood (positive predictive value), while 15 to 20% of obese adults had been overweight as children (sensitivity) [21, 22]. Although these estimates are greatly influenced by the cutpoints used to define overweight and obesity [23], correlational analyses also indicate a moderate degree of tracking for BMI. For example, over a (mean) 17-year follow-up of 2- to 17-year-olds, the correlation between childhood and adult levels of BMI was 0.61 [24].

Although adults who had been overweight children have adverse risk factor levels [25], the persistence of obesity throughout life suggests that these associations may reflect the importance of adult, rather than childhood, weight status. This possibility was examined in a cohort study of 2609 children (ages 2–17 years) who were followed for an average of 17 years (table 1) [24]. As compared with adults who had been relatively thin (BMI <50th centile) children, those who had been overweight in childhood had a 12.4 kg/m² higher BMI, a 7 mg/dl lower HDL cholesterol level, and adverse levels of other risk factors (first two columns).

However, within categories of adults who were normal-weight (adult BMI <25 kg/m²) or obese (≥30 kg/m²), risk factor levels varied only slightly according to childhood weight status (final four columns). For example, there was a 1 mg/dl difference (<25 kg/m²) or no difference (≥30 kg/m²) in HDL cholesterol levels according to childhood weight status within categories of adult BMI. Furthermore, normal-weight adults who had been overweight children had a *lower* (−23 mg/dl, $p < 0.05$) mean triglyceride level than did other normal-weight adults, likely resulting from a relative decrease in BMI levels [26] in this group of overweight children who became normal-weight adults. Overall, these findings indicate that the relation of childhood obesity to adult risk factors is indirect, resulting from the persistence of childhood obesity into adulthood.

Atherosclerosis

The initial stages of atherosclerosis are associated with maternal hypercholesterolemia among neonates [27]. Based on pathology studies of children and young adults, childhood obesity also appears to be important in the

Table 1. Mean risk factor levels in adulthood by categories of adult BMI and childhood BMI centile; the Bogalusa Heart Study

	Childhood BMI centile		Adult BMI, kg/m ²			
			<25 kg/m ²		≥30 kg/m ²	
			Childhood BMI centile		Childhood BMI centile	
	<50	≥95	<50	≥95	<50	≥95
n	1,317	186	950	12	96	144
Childhood BMI centile	24	97	22	96	28	98
<i>Adult levels</i>						
Age, years	27	0	27	-2	29	-2
BMI, kg/m ²	22.5	+12.4*	21.1	+2.5*	33.2*	+4.9*
Triglycerides, mg/dl ^a	82	+16*	76	-23*	130	-6
LDL cholesterol, mg/dl	112	+9*	107	0	130	-4
HDL cholesterol, mg/dl	52	-7*	54	+1	42	0
Insulin, mU/l ^a	8	+6*	7	0	17	0
SBP, mm Hg	112	+5*	111	-6	117	2
DBP, mm Hg	72	+4*	71	-3	77	+1

^aGeometric means are shown for levels of triglycerides and insulin.

*p < 0.05 for difference in adult levels between persons whose childhood BMI was <50 centile or ≥95 centile.

development of these early lesions. For example, among subjects who died (ages 2–39 years) from external causes, previously measured BMI was associated ($r = 0.24\text{--}0.41$) with the extent of fatty streaks and fibrous plaques [12]. Furthermore, although some correlations were not statistically significant, raised lesions in the coronary artery also appear to be associated with subcutaneous fat (as assessed by the thickness of the panniculus adiposus) and BMI measured at death among 15- to 34-year-olds [28].

The relation of childhood obesity to atherosclerosis has also been studied using B-mode ultrasonography, a non-invasive technique that can quantify the intima-media thickness (IMT) of the carotid artery [29]. Despite various limitations [30] carotid IMT is thought to be a marker of generalized atherosclerosis, and IMT among adults is associated with obesity and other CHD risk

factors [31], arteriographically documented coronary artery disease [32], and subsequent CHD [33]. Furthermore, weight loss decreases the rate of IMT progression [34].

Although there have been fewer studies of children, hypercholesterolemia is associated with carotid IMT by age 6 years [35]. Several cross-sectional studies have also found that obesity in childhood and adolescence is associated with carotid IMT [36–38], and in most studies the predictive ability of BMI is similar to that for lipid and lipoprotein levels. Although childhood obesity was not associated with carotid IMT in some studies [39, 40], it was found to be associated with other characteristics of the carotid artery, such as wall stiffness or endothelial dysfunction.

The most interesting use of B-mode ultrasonography, however, is in longitudinal studies can examine the relation of childhood obesity to carotid IMT in adulthood. For example, levels of BMI and triceps skinfold thickness among 8- to 18-year-olds were predictive of the adult carotid IMT (ages 33 to 42 years) in the Muscatine Heart Study [41]. Although the longitudinal associations with carotid IMT were statistically significant only among women ($r = 0.18$ for childhood BMI), these relationships over an approximately 25-year follow-up period are noteworthy. These findings also extend an earlier report from the same group [42] showing that childhood weight is related to coronary artery calcification (assessed by electron beam computed tomography) in adulthood. In this earlier study, the observed associations between childhood weight and the presence of adult calcification were slightly stronger among men (odds ratio = 2.9) than among women (odds ratio = 2.1).

It would be very interesting to determine if the longitudinal relations of childhood obesity to carotid IMT and coronary artery calcification in adulthood were mediated by the persistence of childhood obesity into adulthood, or if the effects of childhood obesity were independent of adult weight status.

Coronary Heart Disease

There are reports of pathologic changes in the conduction system of obese children [43], and several cohort studies [44–48] have examined the relation of childhood obesity to CHD in adulthood. Whereas some children have been followed prospectively [47, 48], other investigators have identified cohorts in adulthood who had baseline (historical) data previously collected by schools [44, 45] or in preparation for military service [46]. In addition, the relation of BMI at age 18 years, based on the recalled weight of middle-aged adults, to subsequent CHD has been examined [49, 50].

These long-term studies, many of which span over 50 years, are very difficult to conduct, and some investigators have been able to re-examine (or trace) only about one half of eligible subjects [45]. Furthermore, there are many

differences in the design and analysis of these studies, including (1) the classification of overweight (typically the upper fourth or fifth of the BMI distribution); (2) sample sizes that range from 508 [47] to >78,000 [46], and (3) mean, baseline ages that ranged from ~8 years [48] to 19 years [44]. In addition, few studies have data on BMI levels in both childhood and adulthood [45, 47, 49, 50], and in all cases, one of the two estimates is based on self-reported weight, increasing the possibility of misclassification.

Despite these differences, the results of these studies suggest that overweight children are at increased risk for CHD in adulthood, with relative risks (RRs) generally ranging from 1.7 to 2.6. These consistent findings, which can be contrasted with those of studies of adult obesity, may be due to the long follow-up periods, as well as to the lack of confounding by preclinical disease and cigarette smoking. In addition, the strength of the relation of obesity to CHD decreases with age among adults [51], and it is possible that this interaction with age extends to adolescents and children. However, it is unclear if the relation of childhood obesity to adult complications varies by the length of follow-up, or if there is a J-shaped relation, with the optimal BMI level being slightly below the median [46, 48]. Although it has been suggested that childhood obesity is more strongly related to adult CHD among boys than girls [47], associations with adult carotid IMT are stronger among girls [41].

As is the case adult risk factor levels [24], it is also possible that the increased risk among overweight children for CHD may be due to adult (rather than childhood) weight status. The results of the Harvard Growth Study [47] provide the strongest evidence supporting an independent effect of childhood obesity, in which adjustment for adult BMI only slightly reduced the relation of childhood overweight (BMI >75th centile) to CHD morbidity (RRs of 2.8 vs. 2.5) over a 55-year follow-up period among men. These investigators, however, found that childhood overweight was not related to CHD morbidity or total mortality among women.

In contrast, other results have emphasized the greater importance of adult weight status. For example, overweight (>20% above average weight) children in Washington County had relatively high rates of vascular disease in adulthood [45], but the highest rates were seen among thin children who became overweight in adulthood. Somewhat similar results were reported by the Nurses Health Study [49], in which the relation of (self-reported) BMI at age 18 years to subsequent CHD was entirely attributable to the persistence of obesity throughout life; controlling for adult BMI reduced the RR among those with a BMI >23.3 kg/m² at age 18 years from 2.0 to 1.0. It is possible that weight gain after the cessation of growth, which would largely reflect accumulated fat mass, may be more pathological than weight gain during growth and development [1].

Conclusions

Overweight children are at increased risk for adverse levels of CHD risk factors, atherosclerosis, and CHD in adulthood. Although it is possible that the adult complications are due to the persistence of obesity throughout life, these consequences will become increasingly evident due to the recent secular increases in childhood obesity. In addition, the risks associated with the high BMI levels currently seen among children may be substantially greater than those associated with the less severe levels of childhood overweight seen before 1970.

Because of the long follow-up periods needed to study the relation of childhood obesity to CHD, non-invasive techniques such as B-mode ultrasonography and electron beam tomography, will likely provide the most useful information on the relation of childhood obesity to atherosclerosis. The difficulties in preventing and reversing obesity, along with the frequent nonadherence of adolescents to lifestyle changes and medical treatment, will complicate treatment and prevention efforts.

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