Published in final edited form as:
J Pediatr. 2012 May ; 160(5): 743–750. doi:10.1016/j.jpeds.2011.10.037.

Occurrence and Timing of Childhood Overweight and Mortality: Findings from the Third Harvard Growth Study

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Abstract

Objective—To assess the mortality experience of participants in the Third Harvard Growth Study (1922-1935) who provided ≥8 years of growth data.

Study design—A total of 1877 participants provided an average of 10.5 body mass index measurements between age 6 and 18 years. Based on these measurements, the participants were classified as ever overweight or ever >85th percentile for height in childhood. Age at peak height velocity was used to indicate timing of overweight relative to puberty. Relative risks of all-cause and cause-specific mortality according to measures of childhood growth were estimated using Cox proportional hazards survival analysis.

Results—For women, ever being overweight in childhood increased the risks of all-cause and breast cancer death; the risk of death from ischemic heart disease was increased in men. Men with a first incidence of overweight before puberty were significantly more likely to die from ischemic heart disease; women in the same category were more likely to die from all causes and from breast cancer.

Conclusion—We find evidence of long-term effects of having ever been overweight, with some evidence that incidence before puberty influences the pattern of risk.

Obesity in early life may represent a critical period for the initiation of disease processes, which affect chronic disease and longevity in adulthood. Given the tendency for obesity to track from childhood in adulthood,[1] the increasing prevalence of obesity in the United States and elsewhere is especially concerning.[2] The consequences of overweight in childhood are both immediate and long term.[3]

Although the relationship between adult obesity and mortality is well established, less is known about the long-term health effects of childhood obesity. A recent systematic review of the relationship between early body mass index (BMI) and risk of coronary heart disease (CHD) concluded that BMI measurement at any time between 7 and 30 years of age was positively related to CHD risk.[4] Another systematic review by Lloyd et al[5] concluded that the associations seen between childhood obesity and CHD risk are related to the tracking of BMI from childhood to adulthood. Cancer, the second-leading cause of death after CHD, also has been linked to body weight in adults at several specific sites.[6-8] Patterns of

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The authors declare no conflicts of interest.

childhood growth, especially those that affect final height, are associated with adult cancer risk.[9,10] In adult women, higher relative weight is associated with a reduced risk of premenopausal breast cancer, and higher BMI and greater adult weight gain are associated with an increased risk of post-menopausal breast cancer.[11] Previous studies in younger women have found inverse associations between fatness and the risk of premenopausal breast cancer independent of adult BMI,[12,13] suggesting a long-term protective effect. For ovarian cancer, the results are less consistent, with some, but not all, studies suggesting an association between BMI in early adulthood and increased risk of ovarian cancer.[14] An association between BMI earlier in life and risk of ovarian cancer has not yet been examined.

By necessity, much of the literature on long-term outcomes relies on historical cohort studies that typically have estimated disease endpoints in relation to a single measure of weight in childhood and thus are not suited to elucidating such measures as timing of first onset of overweight in childhood or timing of maturation. We investigated the association between growth during childhood and the risk of mortality from several causes in a historical cohort of 1877 men and women with available annual measurements of height and weight throughout childhood.

Methods

The Third Harvard Growth Study was a longitudinal study of the physical and mental growth of more than 3000 schoolchildren conducted between 1922 and 1935 by the Harvard School of Education.[15] The study subjects were first- and second-grade public school children from three middle-class cities north of Boston who were enrolled in 1922 and 1923. The subjects were measured annually until they graduated from or left high school. Subjects in the original growth study who had at least 8 years of growth data were considered in the present analysis (n = 1877). Two previous follow-ups of this cohort during adulthood provided additional information used for locating subjects and covariates for use in analysis. In 1968, when the cohort had a mean age 51.7 years, 45% of the original cohort was successfully contacted by mail for a midlife follow-up study.[16] A second follow-up conducted in 1988 studied 508 subjects selected from the original cohort based on adolescent BMI and traced 84% of those sampled.[17]

A total of 1877 subjects (1019 men and 858 women) were included in the present analysis. As of December 31, 1999, 1147 subjects (61.1%) were deceased and 469 (25.0%) were alive. For the remaining 261 (13.9%) subjects, partial follow-up information was established. For the entire cohort, the mean age on December 31, 1999, would have been 83.7 ± 1.0 years had all subjects still been alive.

Several methods were used to confirm the vital status of each subject, including searches of the Social Security Death Index, the Massachusetts Registry of Vital Records and Statistics, and the National Death Index Plus system were conducted. For all probable and exact matches, the underlying cause of death code provided by the National Death Index Plus was used in our analyses. For any questionable match where the death occurred outside the state of Massachusetts, a copy of the death certificate was obtained for review. For deaths not covered by the National Death Index Plus system (before 1979), we submitted the multiple cause of death data obtained from the vital records office to National Center for Health Statistics staff, who provided us with a code for the underlying cause of death.

Information from previous follow-ups of this cohort, credit bureau searches, school reunion committees, and town resident books (Massachusetts only) were used to establish vital status and the last date known alive. If the vital status of a subject was verified as of December 31,

1999, then the subject was considered to be alive. If a subject was verified to be alive at a previous date, then that date was considered the date last known living. Subjects with a confirmed cause of death occurring after December 31, 1999, were assumed to be alive for this analysis. Study procedures were approved by the Institutional Review Board at Tufts University.

International Classification of Diseases, 9th Revision (ICD-9) codes were used to define deaths from ischemic heart disease (IHD) and breast and ovarian cancers. Mortality from IHD was defined as an ICD-9 code of 410-414.9 as the underlying cause of death; mortality from breast cancer, as an ICD-9 code of 174.0-174.9 (malignant neoplasm of the breast) as the underlying cause of death; and mortality from ovarian cancer, as an ICD-9 code of 183.0-183.9 (malignant neoplasm of the ovaries) as the underlying cause of death.

The average number of childhood height and weight measurements per subject was 10.5 (range, 8-12), and there were a total of 129 686 person-years of follow-up overall. BMI was calculated as weight in kilograms divided by height in meters squared from annual measurements of height and weight. BMI-for-age and height-for-age *z*-scores were calculated based on the least mean squares method as implemented in the Centers for Disease Control and Prevention growth reference standards.[18] Whether or not each subject was ever above the 85th percentile for BMI for age at any point during the study period was determined. In addition, height for age was used to determine whether each subject was ever above the 85th percentile of height for age. These indicator variables were used as predictors in survival analyses.

The Preece-Baines model I was fitted to annual height and weight measurements to estimate age at peak height velocity (PHV) for each subject.[19] Age at PHV was used as a measure of maturational timing. A variable representing the timing of the first incidence of overweight was constructed from BMI for age and age at PHV. Age at PHV minus 1 year was calculated to represent the onset of puberty.[20] If this age was less than or equal to age at first incidence of overweight, then the subject was considered to have had his or her first incidence of overweight after puberty. If this age was greater than the age at first incidence of overweight, then the subject was considered to have had the first incidence of overweight before puberty. Subjects who were never overweight during childhood served as the reference category.

Statistical Analysis

The Student t test was used to compare differences in age at PHV by sex, and to compare differences in age at death between those with and without midlife weight information. ORs (an estimate of relative risk) of all-cause and cause-specific mortality according to integrated measures of growth in childhood were estimated from Cox proportional hazards survival analyses. Survival time was calculated from the date of birth and either date of death or the date last known to be alive. Using data from the 1968 follow-up of this cohort, for the subset of female subjects with fertility data from 1968 (n = 557), the analyses of breast and ovarian cancer mortality outcomes were adjusted for gravidity status (ever pregnant, yes/no). Using BMI data from both the 1968 (self-reported BMI) and 1988 (recalled BMI at age 50 years) follow-ups of this cohort, analyses that included midlife BMI as a covariate for all-cause and IHD-related outcomes were conducted.

Results

Mean age at death was 69.2 years for women and 67.6 years for men ($P = .05$). As expected, subjects without midlife weight data were significantly younger at death than those subjects with midlife weight data. The mean age at death for subjects with information on midlife

weight status was 72.3 years, compared with 64.7 years for subjects without midlife weight data ($P < .001$, Student t test). A total of 287 subjects (217 men and 70 women) died from IHD, at a mean age of 68.8 ± 10.3 years. Men died from IHD at a significantly younger age than women IHD ($P < .001$) (Table I).

The underlying cause of death was breast cancer in 29 female subjects and ovarian cancer in 15 female subjects. Mean age at death from breast cancer was 63.2 ± 13.5 years, and mean age at death from ovarian cancer was 67.9 ± 13.5 years. Women who died of breast cancer died 6.4 years earlier than those who died from other causes ($P = .02$). Mean age at menarche in the 230 female subjects with data on age at menarche was 12.8 ± 0.95 years.

Ever Overweight during Childhood

Overall, 23% of subjects were overweight at one or more measurements in childhood (classified as ever overweight), with approximately one-third of them overweight only once. The subjects who were overweight were overweight an average of 3.9 ± 3.1 times. In childhood, women were overweight significantly more times than men (mean difference equal to 0.8 times; $P < .01$). In addition, the percentage of subjects ever overweight in childhood was similar in the 3 vital status groups: 24% of subjects who were dead were ever overweight, 22% of those who were alive were ever over-weight, and 23% of those with partial follow-up were ever overweight. The relative risks of all-cause mortality and cause-specific mortality associated with ever overweight in childhood are shown in Table II. In men, the relative risk of death from IHD was approximately 1.4 times higher (95% CI, 1.04-1.9) in the subjects who were ever overweight in childhood. In women, the relative risk of death from all causes was 1.4 times higher (95% CI, 1.1-1.8) in those who were ever overweight in childhood. The relative risk of death from breast cancer was approximately 2 times higher in those who were ever overweight in childhood compared with those who never overweight in childhood (relative risk [RR], 2.1; 95% CI, 0.99-4.5; $P = .05$). The risk of ovarian cancer was not associated with being ever overweight in childhood.

Height for Age *z*-Score Ever >85th Percentile

In 7% of subjects, height-for-age z-score was >85th percentile on one or more measurements in childhood. Age at PHV did not differ between women who died from breast cancer and those who did not ($P = .29$, Student t test), or between women who died from ovarian cancer and those who did not ($P = .46$, Student t test). No significant relationship was found between death from all causes, death from IHD, or death from ovarian cancer and ever having a height-for-age z-score >85th percentile. For death from breast cancer, subjects who ever had a height-for-age z-score above the 85th percentile were 2.8 times more likely to die from this disease than women whose height-for-age z-score never exceeded the 85th percentile (95% CI, 1.1-7.4) (Table II).

Timing of Overweight in Relation to Maturational Timing

PHV estimates were available in 74% of the males and 94% of the females. Sixteen percent of subjects had their first incidence of overweight before puberty. The first incidence of overweight occurred before puberty in 17% of the subjects classified as dead, 14% of subjects classified as alive, and 15% of subjects with only partial follow-up. The relative risks of mortality from all causes and cause-specific mortality associated with the timing of the first incidence of overweight before puberty are presented in Table III. In men, the relative risk of death from all causes was not associated with the timing of overweight in relation to maturational status. Women who experienced their first incidence of overweight before puberty had a significantly increased risk of death from all causes compared with women who were never overweight in childhood (RR, 1.5; 95% CI, 1.1-1.9). The risk of death from IHD was 1.4 times higher in men with a first incidence of overweight before

puberty compared with men who were never overweight during childhood (95% CI, 1.02-2.0). Women with a first incidence of overweight before puberty were at increased risk of death from IHD (RR, 2.0; 95% CI, 1.1-3.5). The risk of death from breast cancer was increased by ~2-fold (95% CI, 1.0-5.3; $P = .05$) in women with a first incidence of overweight before puberty compared with women who were never overweight. The risk of death from ovarian cancer was significantly elevated (~4-fold; 95% CI, 1.1-15.5) in women with a first incidence of overweight after puberty compared with women who were never overweight.

Consideration of Adult Weight Status and Gravidity Status

Results from analysis of the impact of adult BMI and of pregnancy status on the associations between measures of childhood growth and mortality are shown in Table IV. The unadjusted risks presented in these secondary analyses are restricted only to those subjects who had data available on these covariates. Sample sizes of the restricted samples are specified in Table IV.

In men, no significant relationship was found between being ever overweight and all-cause mortality. For women, both the unadjusted and adjusted risk for death from all causes was ~1.5-fold higher in those who were ever overweight in childhood than in those who were never overweight in childhood. This finding is similar to the result for analysis of the complete cohort (Table II). In men, after adjusting for midlife BMI, the relationship between being ever overweight and death from IHD was no longer statistically significant. In women, the relationship between being ever overweight and death from IHD was significant in the subset of women with adult BMI data and after adjusting for midlife BMI (RR, 2.8; 95% CI, 1.3-6.0). This is in contrast to results for the entire cohort, which demonstrated no association between being ever overweight in childhood and death from IHD. In terms of the timing of overweight in relation to maturational status, women with a first incidence of overweight before puberty were ~4 times more likely to die from IHD than those who were never overweight in childhood (both unadjusted and adjusted for adult BMI).

The risk of death from breast cancer was ~2.6 times greater in women who were ever overweight in childhood compared with those not ever overweight in childhood, both in the subset of women with data on pregnancy status and when pregnancy status was included in the survival model (Table IV). The significant relationship between the timing of the first incidence of overweight and death from breast cancer remained significant after adjusting for whether or not a subject had ever been pregnant (RR, 2.7; 95% CI, 1.1-6.7). In addition, the risk of death from ovarian cancer remained elevated in women whose first incidence of overweight occurred after puberty after adjusting for pregnancy status (Table IV). After adjusting for pregnancy status, the relationship between height status and death from breast cancer was no longer significant (data not shown).

Discussion

The “critical periods” hypothesis posits the existence of developmental periods during which the effect of environmental exposures, broadly defined, are amplified. Dietz et al[21] first suggested that adolescence was one of 3 critical periods in the development of obesity. Our findings in our largely white historical cohort support the idea that childhood weight status has an effect on disease outcome, but do not suggest that the adolescent period is of particular importance. Overweight occurring before puberty increased the risk of IHD mortality in males and the risks of all-cause and breast cancer mortality among females. Adolescence, especially in the current obesogenic environment, may represent a period of heightened risk for obesity or risk for persistent obesity with earlier onset given the myriad psychosocial changes that accompany emerging independence.[22] Our lack of longitudinal

data after the childhood period precludes an evaluation of the duration of obesity and disease outcomes. Everhart et al[23] reported that number of years in the obese state was the best predictor of type 2 diabetes in a Pima cohort.

Our previous analysis conducted in a subset of this cohort found an association between being overweight in adolescence and increased risks of all-cause mortality and CHD mortality in men, but not in women.[17] Owen et al[4] examined 15 studies (including the 1988 follow-up of our cohort[17]) relating BMI between age 2 and 30 years to later CHD risk and found a positive correlation between BMI between age 7 and <18 years and later CHD risk (RR, 1.09; 95% CI, 1.00-1.20), and that sex and year of birth had little effect on the results. In a large population-based cohort study of 276 835 children born between 1930 and 1976, each 1-unit increase in BMI *z*-score at every age from 7 to 13 years in boys and from 10 to 13 years in girls was associated with a significant increase in risk of any CHD event.[24] In a cohort of Native Americans born between 1945 and 1984, rates of death from endogenous causes were more than twice as great in children in the highest BMI quartile compared with those in the lowest BMI quartile.[25] In a large study of 227 000 Norwegian adolescents aged 14-19 years, the relative risk of death due to IHD was 2.9 (95% CI, 2.3-3.6) for males and 3.7 (95% CI, 2.3-5.7) for females in the highest BMI category compared with the reference group.[26]

Several lifestyle and environmental risk factors have been associated with the occurrence of breast cancer[27]; their relationship to survival from the disease is less clear. Current BMI has been reported as a risk factor for death from breast cancer, but few studies have examined BMI in childhood in relation to breast cancer mortality. One study found no associations between BMI at age 18 and weight change and breast cancer mortality independent of other factors; weight and height were self-reported.[28] Analyses of data from the Nurses' Health Study found an independent inverse relationship between body fatness at a young age and breast cancer risk throughout life.[12,13] In the aforementioned Norwegian cohort, the risk of death from breast cancer did not differ across BMI categories captured during adolescence only.[26] This is in contrast to results from our analysis, in which women who were overweight at some time in childhood (ever overweight) had an increased risk of death from breast cancer, with some suggestion that first incidence before puberty increased the risk even further. The lack of consistency with the literature may be related to differences in the measures used to define overweight, ages in childhood studied, or disease outcome (mortality vs morbidity), or may reflect the historical nature of this cohort of women, whose reproductive history and/or exposure to environmental factors might differ from subsequent cohorts.

Inconsistency of results also characterizes previous studies of weight and ovarian cancer risk. An analysis of data from the Nurses' Health Study found a weak inverse association between body fatness at ages 5 and 10 years and ovarian cancer risk in the original cohort (Nurses' Health Study Cohort) and a nonsignificant positive association in the Nurses' Health Study Cohort II.[29] In the Norwegian cohort, the risk of death from ovarian cancer did not differ across BMI categories.[26] To the best of our knowledge, the present analysis is the first to examine repeated measures of BMI in childhood in relation to ovarian cancer mortality. We found a statistically significant relationship between death from ovarian cancer and a first incidence of overweight after puberty; however, our findings are based on only 15 ovarian cancer deaths. Further investigation of the timing of overweight and ovarian cancer is needed.

Because maturational timing and overweight are linked, it is not possible to tease out their relative contribution.[30] Early age at menarche is a well-established risk factor for breast cancer, whereas previous studies of the association between age at menarche and ovarian

cancer risk have provided conflicting results.[27] There is little available information on the relationship between the timing of puberty and cardiovascular risk in adulthood. Children in the Fels Longitudinal Study who matured early tended to have greater BMI, waist circumference, and body fat percentage and were more likely to have an adverse cardiovascular risk profile compared with children who matured late.[31] The differences in these risk factors between early and late maturers were significant for body fat percentage and fasting plasma triglycerides and plasma insulin levels. In the Fels Longitudinal Study, the mean age at PHV was 13.7 ± 1.0 years for boys and 11.6 ± 0.9 years for girls. In our historical cohort, age at PHV was slightly later in both boys (14.1 ± 0.92) and girls (12.1 ± 0.96).

The issue of whether overweight in childhood has an independent effect on adult cardiovascular health has important implications. The appropriateness of statistically adjusting for midlife weight status is controversial from both statistical and practical standpoints. Statisticians caution against adjustment for a variable that lies in the so-called "causal pathway" between exposure and disease, because this can induce artifactual associations—the "reversal paradox."[32] From a practical perspective, guidance for the individual child or for child policy cannot usefully account for subsequent life events, because the future adult state is unknown and unknowable during childhood. These issues have spawned lively debate.[33-36] In our secondary analyses, controlling for adult weight status in the 60% of the cohort studied at midlife, adjustment for adult weight status had little or no effect on the association between childhood obesity and mortality. It should be emphasized, however, that the relative risks estimated in this subset differed from those estimated in the whole cohort, which was not unexpected, given that this subgroup excluded any subject who died before age 53 years or was too ill to respond from possible follow-up.

The lack of a relationship between height and mortality other than breast cancer in our study is in contrast to the results of several previous studies. Analyses from the Helsinki birth cohort showed that slow growth in height between birth and early childhood (age 2-4 years) followed by rapid "catch-up" growth increases the risks of hypertension, stroke, and CHD later in life.[37-39] Of note, this pattern of height and weight growth has been linked to overweight in adulthood.[40] A longitudinal analysis from a large Danish cohort with more than 3000 cases of breast cancer found that tallness at age 14 years, low BMI at age 14 years, and peak growth at an early age were associated with breast cancer risk.[41] We were not able to address early growth because we had no information on growth before age 6 years. Height has been positively associated with breast cancer in many epidemiologic studies.[27,42-44] In a pooled analysis of primary data from 12 prospective cohort studies, Schouten et al[45] found that height was associated with ovarian cancer risk, especially in premenopausal women.

The present study has several noteworthy weaknesses. Because our disease endpoint was mortality, we were unable to assess the impact of childhood growth on disease incidence, the fundamental measure of disease risk. An examination of age-standardized mortality rates for breast cancer in 20 countries for 1950-1992 found that breast cancer mortality rates generally increased in the earlier decades, but more recently have reached a plateau or begun to decline in most countries.[46] A birth cohort effect was suggestive of a decline in breast cancer rates among women born after about 1920, especially in Canada, The Netherlands, the United Kingdom, and the United States. The distribution of age at death from breast cancer suggests that the majority of these deaths likely occurred after menopause (range of age at death, 31.8-81.6 years), with 9 of the 29 deaths occurring before age 55, but does not provide direct information on whether the cancer was premenopausal or postmenopausal. Our lack of information on whether the cancer was incident before or after menopause precluded analysis by menopausal status for breast and ovarian cancer deaths. Before the

late 1970s when screening mammography for breast cancer became more routine, death from breast cancer could have resulted from a cancer that was present for many years. Our analysis of the timing of overweight relative to puberty was restricted to the 94% of females and 74% of males for whom growth models could be fit; the limited observations after puberty, especially in males, hindered our ability to fit growth curves to all study subjects. If the mortality experience in relation to overweight in these subjects differed from those whose curves were fitted, then our findings would be subject to bias. In addition, information on other potential confounders, such as smoking, physical activity, and diet, was unavailable. Analysis of data from a historical cohort that predates the current high levels of pediatric obesity raises uncertainty as to the extent to which these observations are relevant to current patterns of childhood growth in BMI. However, this concern is offset by the desire to gain insight into such long-term consequences.

A major strength of this study is the availability of multiple, standardized measurements of height and weight on each subject. The density of childhood measures support evaluation of timing of overweight as well as estimation of a marker of pubertal status. In addition, the lengthy follow-up period accumulated a total of 129 686 person-years of follow-up, giving the study substantial statistical power. Middle-class cities and towns were chosen for study, limiting the impact of the Great Depression of 1929, which occurred during the original growth study. Other strengths include restriction of the cohort based on socioeconomic status, as well as availability of midlife measures of height, weight, and gravid status. Finally, the availability of cause-specific death information on a cohort with nearly complete survival outcomes enhances the value of this life-course study.

Acknowledgments

We thank Dr William Rand for his assistance with the Preece-Baines growth modeling and its interpretation.

Glossary

BMI	Body mass index
CHD	Coronary heart disease
ICD-9	International Classification of Diseases, 9th Revision
IHD	Ischemic heart disease
PHV	Peak height velocity
RR	Relative risk

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Table I

Summary statistics for subjects with at least 8 years of childhood data

	Men (n = 1019)			Women (n = 858)		
	n	**Mean (SD)**	**%**	**n**	**Mean (SD)**	**%**
Childhood anthropometry						
Number of childhood measurements	10749	10.6 (1.3)		9014	10.5 (1.3)	
Mean BMI *z*-score	1019	–0.05(0.71)		858	–0.07 (0.78)	
Mean height-for-age *z*-score	1019	–0.82 (0.92)		858	–0.79 (0.95)	
Age at first incidence of overweight	232	8.5 (2.8)		206	9.3 (3.2)	
Age at PHV	755	14.1 (0.92)		804	12.1 (0.96)	
Age at menarche				230	12.8 (0.95)	
BMI-for-age ever >85th percentile	232	-	23	206	-	24
BMI-for-age ever >95th percentile	47	-	5	63	-	7
Height-for-age ever >85th percentile	72	-	7	59	-	7
First incidence of overweight before puberty	166	-	16	135	-	16
First incidence of overweight after puberty	19	-	2	53	-	6
Follow-up						
Midlife BMI	481	25.6 (3.1)		477	24.4 (3.8)	
Ever pregnant (total, n = 557)	-	-	-	404	-	73
Vital status						
Age at death	716	67.6 (13.5)		431	69.2 (14.4)	
Age at death from IHD	217	67.4 (10.6)		70	73.2 (8.0)	
Age at death from breast cancer	-	-		29	63.2 (13.5)	
Age at death from ovarian cancer	-	-		15	67.9 (13.6)	

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Table II

RR of mortality associated with ever overweight or ever >85th percentile for height in childhood

Outcome	Deaths	Ever overweight, RR (95% CI) *	Ever >85th percentile height, RR (95% CI) †
All-cause mortality			
Men	716	0.98(0.82-1.2)	1.2(0.88-1.5)
Women	431	1.4 (1.1-1.8) ‡	1.1 (0.73-1.5)
IHD			
Men	217	1.4 (1.04-1.9) §	0.81 (0.45-1.5)
Women	70	1.6(0.95-2.6)	0.65 (0.20-2.0)
Breast cancer			
Men	-	-	-
Women	29	2.1 (0.99-4.5)	2.8 (1.1-7.4) §
Ovarian cancer			
Men	-	-	-
Women	15	1.8(0.61-5.2)	2.0 (0.46-9.1)

* Reference category is never overweight.

† Reference category is never >85th percentile for height.

‡ $P \leq .01$.

§ $P < .05$.

Table III

RR of mortality associated with timing of overweight [*]

	Men (n = 755)		Women (n = 804)	
Outcome	**Deaths**	**RR (95% CI)**	**Deaths**	**RR (95% CI)**
All-cause mortality	541		394	
Never overweight in childhood		-		-
First incidence before puberty		1.03 (0.83-1.3)		1.5 (1.1-1.9)[†]
First incidence after puberty		0.84 (0.45-1.6)		1.3 (0.89-1.9)
IHD	169		60	
Never overweight in childhood		-		-
First incidence before puberty		1.4 (1.02-2.0)[‡]		2.0 (1.1-3.5)[‡]
First incidence after puberty		1.8(0.78-4.0)		0.95 (0.29-3.1)
Breast cancer			28	
Never overweight in childhood	-	-		-
First incidence before puberty	-	-		2.3 (1.0-5.3)
First incidence after puberty	-	-		1.4(0.31-5.9)
Ovarian cancer			14	
Never overweight in childhood	-	-		-
First incidence before puberty	-	-		1.1 (0.25-5.4)
First incidence after puberty	-	-		4.2 (1.1-15.5)[‡]

[*] Reference category is never overweight in childhood.

[†] $P \leq .01$.

[‡] $P < .05$.

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Table IV

Unadjusted and adjusted RRs of mortality associated with ever overweight in childhood and timing of overweight in childhood among subset of subjects with data on midlife BMI or pregnancy

	Men			Women		
	n	Unadjusted	Adjusted*	n	Unadjusted	Adjusted*
All cause						
Ever overweight (overall)†	322	1.2 (0.92-1.5)	1.1 (0.86-1.5)	231	1.5 (1.1-2.0)†	1.5 (1.1-2.0)‡
Never overweight in childhood	262	-	-	210	-	-
First incidence before puberty		1.2 (0.92-1.6)	1.2 (0.87-1.6)		1.5 (1.1-2.2)§	1.5 (1.04-2.2)§
First incidence after puberty		0.95 (0.39-2.3)	0.80 (0.32-2.0)		1.4 (0.88-2.3)	1.4 (0.86-2.3)
IHD						
Ever overweight (overall)†	95	1.6 (1.1-2.5)§	1.4 (0.90-2.3)	29	2.9 (1.4-6.1)‡	2.8 (1.3-6.0)‡
Never overweight in childhood	80	-	-	23	-	-
First incidence before puberty		1.6 (0.97-2.6)	1.4 (0.81-2.3)		4.3 (1.8-10.1)‡	4.5 (1.9-11.1)‡
First incidence after puberty		1.4 (0.34-5.7)	0.88 (0.20-3.8)		1.9 (0.42-8.5)	2.0 (0.44-9.1)
Breast cancer	-					
Ever overweight (overall)†		-	-	24	2.6 (1.1-5.8)§	2.6 (1.1-5.9)§
Never overweight in childhood		-	-	23	-	-
First incidence before puberty					2.7 (1.1-6.7)§	2.7 (1.1-6.7)§
First incidence after puberty					1.9(0.43-8.3)	1.9(0.44-8.5)
Ovarian cancer	-					
Ever overweight (overall)†		-	-	11	2.1 (0.63-7.4)	2.2 (0.64-7.6)
Never overweight in childhood		-	-	11	-	-
First incidence before puberty		-	-		0.80 (0.10-6.5)	0.81 (0.10-6.6)
First incidence after puberty		-	-		6.1 (1.6-23.5)‡	6.3 (1.6-24.3)‡

*All-cause and ischemic outcomes are adjusted for midlife BMI; breast and ovarian cancer adjusted for ever pregnant.

†Reference group for each model is never overweight.

‡$P \leq .01$.

§$P < .05$.