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Original Contribution

Body Mass Index in Adolescence in Relation to Cause-specific Mortality: A Follow-up of 230,000 Norwegian Adolescents

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The prevalence of obesity in childhood and adolescence has increased worldwide. Long-term effects of adolescent obesity on cause-specific mortality are not well specified. The authors studied 227,000 adolescents (aged 14–19 years) measured (height and weight) in Norwegian health surveys in 1963–1975. During follow-up (8 million person-years), 9,650 deaths were observed. Cox proportional hazards regression was used to compare cause-specific mortality among individuals whose baseline body mass index (BMI) was below the 25th percentile, between the 75th and 84th percentiles, and above the 85th percentile in a US reference population with that of individuals whose BMI was between the 25th and 75th percentiles. Risk of death from endocrine, nutritional, and metabolic diseases and from circulatory system diseases was increased in the two highest BMI categories for both sexes. Relative risks of ischemic heart disease death were 2.9 (95% confidence interval (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. There was also an increased risk of death from colon cancer (males: 2.1, 95% CI: 1.1, 4.1; females: 2.0, 95% CI: 1.2, 3.5), respiratory system diseases (males: 2.7, 95% CI: 1.4, 5.2; females: 2.5, 95% CI: 1.4, 4.8), and sudden death (males: 2.2, 95% CI: 1.2, 4.3; females: 2.7, 95% CI: 1.1, 6.6). Adolescent obesity was related to increased mortality in middle age from several important causes.

adolescent; body mass index; cause of death; follow-up studies; mortality; Norway; obesity

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk.

During the last decades, the prevalence of obesity has increased worldwide, and this phenomenon has generally been affecting all age groups (1). Adult obesity is usually associated with increased risk of several chronic diseases, including type 2 diabetes; hypertension; coronary heart disease; stroke; and colon, rectal, esophageal (adenocarcinoma), endometrial, and postmenopausal breast cancer (2–4). Of special concern is the increasing incidence of obesity among children and adolescents. However, the long-term effects of obesity in childhood and adolescence on morbidity and mortality are not well specified (5, 6).

Despite the wealth of evidence on the adverse consequences of obesity, controversy continues regarding the shape of the relation of body mass index (BMI) with mortality. Many studies show a U-shaped association of BMI with all-cause mortality (7), and, in some influential investigations, the point of inflection—with the lowest level of mortality—is above the cutpoint for overweight (8). Furthermore, some

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causes of death, particularly respiratory disease (9) and lung cancer (10), show inverse associations with BMI. It has been argued that the excess mortality among people whose BMI is lower than the optimal point may be generated by a mixture of reverse causation (early stages of disease lead to weight loss) and confounding, by cigarette smoking in particular (11). One approach to this issue is to investigate the predictive value of BMI measured at subadulthood ages, when smoking will be uncommon and weight loss due to developing chronic disease will not have occurred.

Previously, data from the national tuberculosis screening program in Norway were used to explore the association between body size in adolescence and total mortality (12). A higher risk of death with higher BMI was observed among both males and females. The aim of this study was to use the material from the tuberculosis screening program in Norway with extended follow-up and cause-of-death information to further investigate the associations between BMI and cause-specific mortality in a cohort comprising 227,000 males and females aged 14–19 years at measurement.

MATERIALS AND METHODS

Subjects

During 1963–1975, height and weight were measured as part of a screening program aimed at detecting tuberculosis in the general Norwegian population (13–15). The mass examination was compulsory for individuals aged 15 years or older, but height and weight were also measured in some individuals less than 15 years of age. Among those aged 15 years or older, the attendance rate was about 85 percent. This material (which included data on nearly 230,000 individuals aged 14–19 years) has been described previously, and the impact of height and weight on morbidity and mortality has been reported (12, 14, 15). In this study, extended follow-up of the individuals allowed for a considerably more detailed cause-of-death analysis than conducted previously.

Body weight was measured by using scales calibrated regularly and was noted to the nearest half kilogram. Body height was measured and noted to the nearest centimeter. Height was measured without shoes, and weight was measured with the subject wearing light clothing.

In this study, all individuals measured at ages 14–19 years were included, except those whose measurements were not performed according to the protocol, individuals who declined to be measured, individuals with disabilities, or women who claimed to be pregnant. Altogether, 226,682 individuals were eligible for the analysis. BMI was defined as (weight in kg)/(height in meters)^2. Information on covariates other than sex, age, time of measurement, and area of residence was not available.

All residents of Norway are assigned a unique 11-digit identification number. By linkage to the Cause of Death Registry at Statistics Norway, it was possible to follow the individuals in this study from date of measurement until emigration, cause-specific death, or January 1, 2005, whichever occurred first. Four individuals were lost to follow-up.

Causes of death (underlying causes) were coded according to the European short list for causes of death (16). For diabetes, however, subanalyses were performed in which we also included this diagnosis if it was recorded anywhere on the death certificate.

Statistical analysis

Multivariate Cox proportional hazards regression models, with time since measurement as the time variable, were fitted to obtain relative risk estimates of death from different causes (17). It was assumed that the hazard function for an individual with a covariate vector $\mathbf{x} = (x_1, x_2, \ldots, x_p)'$ could be expressed by $h(t;\mathbf{x}) = h_0(t) \times \exp(\mathbf{x}' \times \beta)$, where $h_0(t)$ represents the hazard function for an individual with covariate values all equal to 0, and $\beta = (\beta_1, \beta_2, \ldots, \beta_p)'$ is a vector of regression coefficients. The first measurement obtained at ages 14–19 years was used. In the analyses, the following three categorized variables were included:

1. Age at measurement: 14–16 years, 17–19 years.
2. Year of birth: 1943–1949, ≥1950.
3. BMI at baseline: Followed the guidelines of the Centers for Disease Control and Prevention/National Center for Health Statistics (18, 19) by using percentiles in a US reference population: <3rd, 3rd–4th, 5th–9th, 10th–24th, 25th–74th, 75th–84th, 85th–94th, ≥95th. In the results presented in the last two tables of this paper, the categories were combined into four: <25th, 25th–74th, 75th–84th, and ≥85th.

The proportionality assumption in the Cox model was assessed by inspecting log-minus-log plots. Analyses were performed separately for each sex. The statistical package SPSS (20) was used for estimating relative risks of death from specific causes, with 95 percent confidence intervals.

The hazard function of death (overall and from specific causes) by BMI in the Cox model was estimated by using penalized spline functions in S-plus, with 4 degrees of freedom (21). The four parts of figure 1 were derived from models including continuous variables for age at measurement and year of birth in addition to a variable for BMI corresponding to the percentiles in the reference population (18), assigned the values 1, 2, …, 8. The relative risk of a point a compared with a point b on the x-axis can be calculated by using the graphs to find the corresponding y values, y_a and y_b, and then calculate the relative risk by $e^{y_a - y_b}$.

RESULTS

A total of 226,678 individuals (114,977 males and 111,701 females; mean age, 17.0 years) were followed for on average 34.9 years (range, 0.0–41.5), comprising 7,900,414 person-years (table 1). Among these individuals, 9,650 deaths were observed. Mean age at death was 40 years for males and 43 years for females. For 63.4 percent of the males and 64.6 percent of the females, BMIs were between the 25th and 75th percentiles of the US reference population, whereas BMIs for 5.2 percent of the males and 8.0 percent of the females were above the 85th US reference percentile.

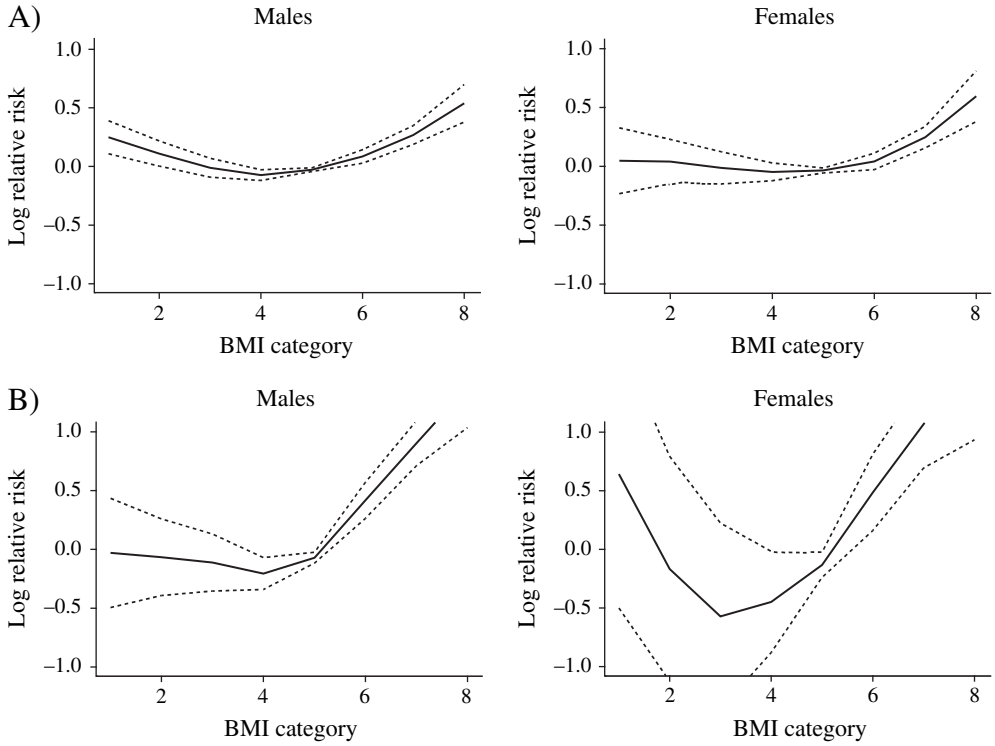

FIGURE 1. Logarithm of the hazard functions of death (solid line) with 95% confidence intervals (dashed lines), by body mass index (BMI) category (based on percentiles in a US reference population (18)—1: <3rd; 2: 3rd–4th; 3: 5th–9th; 4: 10th–24th; 5: 25th–74th; 6: 75th–84th; 7: 85th–94th; 8: ≥95th), from spline functions with 4 degrees of freedom, for persons in Norway measured in 1963–1975. Adjusted for age and birth year. A) total mortality, B) ischemic heart disease mortality.

Tables 2 and 3 show the relative risks of cause-specific mortality for males and females, respectively, according to different categories of baseline BMI. Compared with those for the reference group (BMI, 25th–74th percentiles in the reference population), the relative risks of death from endocrine, nutritional, and metabolic diseases and from diseases of the circulatory system were elevated in the two highest BMI groups of both males and females. The relative risks of death from diseases of the respiratory system and symptoms, signs, abnormal findings, and ill-defined causes were increased in the highest BMI group of both sexes.

For diseases of the circulatory system, ischemic heart disease was the dominant cause of death in males, whereas cerebrovascular disease was dominant in females. For both males and females, the risk of death from ischemic heart disease was increased in the two highest BMI categories (males: relative risk (RR) = 1.8, 95 percent confidence interval (CI): 1.5, 2.3 and RR = 2.9, 95 percent CI: 2.3, 3.6; females: RR = 2.1, 95 percent CI: 1.3, 3.4 and RR = 3.7, 95 percent CI: 2.3, 5.7). For males, the risk of death from other heart diseases and cerebrovascular diseases was increased in the highest BMI category as well. Furthermore, the risk of death from subarachnoid hemorrhage was increased in both the highest (RR = 1.9, 95 percent CI: 0.9, 3.8) and lowest (RR = 1.7, 95 percent CI: 1.1, 2.5) BMI categories. For females, there was an increased risk of death from cerebrovascular diseases in the lowest BMI category (RR = 1.7, 95 percent CI: 1.2, 2.5) and a moderately increased risk of death from subarachnoid hemorrhage in this BMI category (RR = 1.5, 95 percent CI: 0.9, 2.5). However, the risk of death from subarachnoid hemorrhage was not increased in the highest BMI category of females.

The risk of death from diabetes mellitus was also increased for males with both low and high BMIs. When diabetes was analyzed both as underlying cause and mentioned on the death certificate, the relative risks of death were 1.8 (95 percent CI: 1.1, 2.8) and 3.6 (95 percent CI: 2.4, 5.5) for males and 2.6 (95 percent CI: 1.4, 4.7) and 5.6 (95 percent CI: 3.3, 9.6) for females in the two highest BMI categories. The total number of deaths for which diabetes was the underlying cause and was mentioned on the death certificate was 196 for males and 76 for females.

There was an increased risk of sudden death for both sexes (males: RR = 2.2, 95 percent CI: 1.2, 4.3; females: RR = 2.7, 95 percent CI: 1.1, 6.6) and of death from chronic lower respiratory diseases for males (RR = 4.1, 95 percent CI: 1.8, 9.0) in the highest BMI category. Respiratory mortality was also elevated among both men and women whose BMI was low. There was no association between BMI and mortality resulting from mental and behavioral disorders.

TABLE 1. Numbers of deaths and individuals in different categories and overall sex-specific death rates for males and females measured in 1963–1975, Norway

Variable	Males				Females			
	No. of deaths	No. of individuals	Proportion of individuals	Death rate*	No. of deaths	No. of individuals	Proportion of individuals	Death rate*
No. of years since measurement								
0–4	605	114,977	100	106	151	111,701	100	27
5–9	541	114,210	99	95	142	110,826	99	26
10–14	513	113,417	99	91	216	110,047	99	39
15–19	614	112,639	98	109	279	109,438	98	51
20–24	851	111,781	97	153	475	108,861	97	88
25–29	1,165	110,679	96	212	654	108,160	97	122
30–34	1,377	107,698	94	297	894	105,639	95	196
≥35	687	66,138	58	432	486	65,818	59	300
Age (years) at measurement								
14–16	3,111	59,316	52	150	1,561	57,480	51	77
17–19	3,242	55,661	48	169	1,736	54,221	49	92
Year of birth								
1940–1949	1,753	24,679	21	190	1,024	25,149	23	108
≥1950	4,600	90,298	79	150	2,273	86,552	77	77
Body mass index category†								
<3rd	167	2,373	2	206	37	1,296	1	83
3rd–4th	104	1,690	1	178	35	953	1	107
5th–9th	268	4,824	4	161	81	2,912	3	80
10th–24th	927	18,367	16	146	358	12,856	12	80
25th–74th	3,915	72,922	63	154	2,044	72,211	65	81
75th–84th	528	8,802	8	172	390	12,591	11	88
85th–94th	330	4,803	4	198	290	7,797	7	106
≥95th	114	1,196	1	278	62	1,085	1	163
Total	6,353	114,977	100	159	3,297	111,701	100	84

* No. of deaths per 100,000 person-years.
† Percentiles in a US reference population (18).

The relative risk of overall cancer death was moderately increased in the highest BMI group (males: RR = 1.2, 95 percent CI: 0.9, 1.5; females: RR = 1.2, 95 percent CI: 1.1, 1.5). Both males and females in the highest BMI category had an increased risk of death from colon cancer (RR = 2.1, 95 percent CI: 1.1, 4.1 and RR = 2.0, 95 percent CI: 1.2, 3.5, respectively). The risk of breast cancer did not differ across BMI categories, and this finding was not altered when the risks of death at less than 50 years of age and at age 50 years or older were examined separately. For females, there was also an increased risk of death from cervical cancer in the highest BMI category.

Analyses of total mortality omitting the first 15 years of follow-up gave results similar to those presented in tables 2 and 3. Likewise, examining participants measured at ages 14–16 and 17–19 years separately revealed findings similar to those for the whole cohort.

The hazard functions of the risk of death by BMI were estimated by using spline functions (figure 1). The association between the relative risk of death and BMI was almost U-shaped for all-cause mortality and for ischemic heart diseases. However, the proportion of persons in the left part of the U was small, as shown in table 1.

DISCUSSION

Analyses of the associations between BMI in adolescence and cause-specific mortality in a large Norwegian cohort revealed an increased risk of death from diseases of the circulatory system, most strongly from ischemic heart disease, and from endocrine, nutritional, and metabolic diseases in those whose BMI was high. There was also an increased risk of death from diseases of the respiratory system, colon cancer, and sudden death for adolescents whose BMI was

TABLE 2. For males measured in 1963–1975, relative risks of death (cause-specific and overall mortality) with 95% confidence intervals, adjusted for age and birth year, by body mass index in adolescence, Norway

Cause of death	Body mass index category ((weight in kg)/(height in meters)^2) in adolescence*											p value†
	<25th (942,467 person-years)			25th–74th (2,539,557 person-years)‡		75th–84th (307,375 person-years)			≥85th (207,816 person-years)			
	No. of deaths	RR§	95% CI§	No. of deaths	RR	No. of deaths	RR	95% CI	No. of deaths	RR	95% CI	
Malignant neoplasms	285	0.9	0.8, 1.0	836	1.0	101	1.0	0.8, 1.2	77	1.2	0.9, 1.5	0.2
Colon	21	1.0	0.6, 1.6	59	1.0	7	1.0	0.4, 2.2	10	2.1	1.1, 4.1	0.1
Larynx and trachea/bronchus/lung	57	1.1	0.8, 1.5	144	1.0	16	0.9	0.6, 1.5	13	1.2	0.7, 2.0	0.5
Lymphatic/hematopoietic tissue	57	1.1	0.8, 1.5	139	1.0	15	0.9	0.5, 1.5	13	1.2	0.7, 2.1	0.3
Endocrine, nutritional, and metabolic diseases	38	1.4	1.0, 2.1	68	1.0	19	2.4	1.4, 4.0	13	2.5	1.4, 4.5	0.5
Diabetes mellitus	32	1.7	1.1, 2.6	49	1.0	12	2.1	1.1, 4.0	7	1.9	0.8, 4.1	0.1
Mental and behavioral disorders	87	1.2	0.9, 1.6	197	1.0	17	0.7	0.4, 1.2	12	0.7	0.4, 1.3	0.05
Diseases of the circulatory system	240	1.0	0.8, 1.1	660	1.0	139	1.8	1.5, 2.1	129	2.5	2.1, 3.0	<0.001
Ischemic heart diseases	149	1.0	0.8, 1.2	411	1.0	89	1.8	1.5, 2.3	93	2.9	2.3, 3.6	<0.001
Other heart diseases	24	0.8	0.5, 1.2	82	1.0	14	1.4	0.8, 2.5	12	1.8	1.0, 3.4	0.2
Cerebrovascular diseases	52	1.2	0.9, 1.7	115	1.0	17	1.2	0.7, 2.0	18	1.9	1.2, 3.2	1.0
Diseases of the respiratory system	30	1.5	1.0, 2.4	52	1.0	7	1.1	0.5, 2.5	11	2.7	1.4, 5.2	0.1
Chronic lower respiratory diseases	13	1.4	0.7, 2.8	25	1.0	4	1.3	0.5, 3.8	8	4.1	1.8, 9.0	0.6
Digestive system diseases	64	1.2	0.9, 1.6	144	1.0	16	0.9	0.5, 1.5	16	1.4	0.8, 2.3	0.1
Chronic liver disease	46	1.3	0.9, 1.8	99	1.0	13	1.1	0.6, 1.9	10	1.3	0.7, 2.4	0.3
Symptoms, signs, abnormal findings, ill-defined causes	41	0.7	0.5, 1.1	147	1.0	24	1.4	0.9, 2.1	20	1.7	1.1, 2.7	0.02
Sudden death	16	0.7	0.4, 1.2	62	1.0	8	1.1	0.5, 2.3	11	2.2	1.2, 4.3	0.003
External causes of injury and poisoning	574	1.0	0.9, 1.1	1,526	1.0	172	0.9	0.8, 1.1	137	1.1	0.9, 1.3	0.9
Suicide and intentional self-harm	186	1.1	0.9, 1.3	454	1.0	62	1.1	0.9, 1.5	37	1.0	0.7, 1.4	0.7
Other	107	1.0	0.8, 1.3	285	1.0	33	1.0	0.7, 1.4	29	1.3	0.9, 1.9	0.6
Total	1,466	1.0	0.9, 1.1	3,915	1.0	528	1.1	1.0, 1.2	444	1.4	1.3, 1.6	0.006

* Categorized according to percentiles in a US reference population (18).

† *p* value for test of linear trend using body mass index in eight categories (<3rd, 3rd–4th, 5th–9th, 10th–24th, 25th–74th, 75th–84th, 85th–94th, ≥95th) as a continuous variable.

‡ Reference category.

§ RR, relative risk; CI, confidence interval.

very high (above the 85th percentile in the US reference population) at baseline.

Strengths and limitations

One of the major strengths of this study is the large number of individuals included, being recruited from a compulsory national tuberculosis screening program in Norway in the 1960s and 1970s and followed up for more than 30 years. Furthermore, the measurements were performed in a standardized way. Follow-up of the study subjects was almost complete by using national population-based registries; of the 226,682 individuals eligible for the study, 97.9 percent were registered as either being alive by the end of follow-up or having died. Altogether, 2.1 percent had emigrated, and only four individuals were lost to follow-up.

A weakness of our study is the lack of information on potential confounders other than age, sex, and year of birth. Potential confounders include social class/socioeconomic position, physical activity, diet, weight changes during follow-up, prevalent diseases at the time of measurement, and smoking. The socioeconomic confounding of adolescent BMI during this time period is likely to be small but cannot be excluded, particularly among the females (22). However, our finding that the BMI–mortality relation appears to be specific (BMI is associated with some outcomes but not others) provides some evidence against a general effect generated by confounding by socioeconomic position. To investigate the possibility that weight was influenced by persistent diseases at the time of measurement, we conducted analyses for total mortality omitting the first 15 years of follow-up. Similar results were found.

Lifetime smoking habits of Norwegian men and women born between 1890 and 1974 have been described previously (23). The proportion of ever smokers was 40–50 percent among males and 30–40 percent among females in the

TABLE 3. For females measured in 1963–1975, relative risks of death (cause-specific and overall mortality) with 95% confidence intervals, adjusted for age and birth year, by body mass index in adolescence, Norway

Cause of death	Body mass index category ((weight in kg)/(height in meters)^2) in adolescence*											*p* value†
	<25th (625,238 person-years)			25th–74th (2,522,523 person-years)‡		75th–84th (443,257 person-years)			≥85th (312,180 person-years)			
	No. of deaths	RR§	95% CI§	No. of deaths	RR	No. of deaths	RR	95% CI	No. of deaths	RR	95% CI	
Malignant neoplasms	235	0.9	0.8, 1.0	1,075	1.0	193	1.0	0.9, 1.2	166	1.2	1.1, 1.5	0.004
Colon	13	0.8	0.5, 1.5	63	1.0	16	1.4	0.8, 2.5	16	2.0	1.2, 3.5	0.02
Larynx and trachea/bronchus/lung	34	1.1	0.7, 1.6	130	1.0	16	0.7	0.4, 1.2	18	1.1	0.7, 1.8	0.5
Breast	61	0.8	0.6, 1.1	290	1.0	55	1.1	0.8, 1.4	31	0.9	0.6, 1.2	0.6
Cervix uteri	12	0.7	0.4, 1.2	72	1.0	12	0.9	0.5, 1.7	17	1.9	1.1, 3.2	0.007
Ovary	24	1.1	0.7, 1.7	88	1.0	16	1.0	0.6, 1.7	7	0.6	0.3, 1.4	0.2
Lymphatic/hematopoietic tissue	18	0.7	0.4, 1.1	107	1.0	21	1.1	0.7, 1.8	14	1.1	0.6, 1.8	0.3
Endocrine, nutritional, and metabolic diseases	5	0.9	0.3, 2.3	23	1.0	14	3.5	1.8, 6.8	16	5.7	3.0, 11	<0.001
Diabetes mellitus	0			16		13			14			
Mental and behavioral disorders	13	1.2	0.6, 2.2	44	1.0	4	0.5	0.2, 1.4	8	1.5	0.7, 3.1	0.8
Diseases of the circulatory system	65	1.3	1.0, 1.8	194	1.0	52	1.5	1.1, 2.1	57	2.4	1.8, 3.2	0.001
Ischemic heart diseases	15	1.0	0.5, 1.7	62	1.0	23	2.1	1.3, 3.4	28	3.7	2.3, 5.7	<0.001
Other heart diseases	8			18		7			3			
Cerebrovascular diseases	36	1.7	1.2, 2.5	86	1.0	16	1.1	0.6, 1.8	16	1.5	0.9, 2.6	0.2
Diseases of the respiratory system	18	1.9	1.1, 3.2	40	1.0	11	1.5	0.8, 3.0	13	2.5	1.4, 4.8	0.4
Chronic lower respiratory diseases	14	1.8	1.0, 3.4	32	1.0	8	1.4	0.6, 3.0	8	1.9	0.9, 4.2	1.0
Digestive system diseases	13	0.9	0.5, 1.6	60	1.0	14	1.3	0.7, 2.3	9	1.2	0.6, 2.4	0.6
Chronic liver disease	11	1.1	0.5, 2.1	42	1.0	9	1.2	0.6, 2.5	3	0.6	0.2, 1.8	0.4
Symptoms, signs, abnormal findings, ill-defined causes	9	0.8	0.4, 1.7	42	1.0	8	1.1	0.5, 2.3	12	2.4	1.2, 4.5	0.01
Sudden death	1	0.2	0.0, 1.5	19	1.0	3	0.9	0.3, 3.1	6	2.7	1.1, 6.6	0.001
External causes of injury and poisoning	107	1.1	0.9, 1.4	394	1.0	67	1.0	0.7, 1.2	39	0.8	0.6, 1.1	0.2
Suicide and intentional self-harm	55	1.4	1.0, 1.8	166	1.0	25	0.8	0.6, 1.3	12	0.6	0.3, 1.0	0.01
Other	46	1.1	0.8, 1.5	172	1.0	27	0.9	0.6, 1.3	32	1.5	1.0, 2.2	0.8
Total	511	1.0	0.9, 1.1	2,044	1.0	390	1.1	1.0, 1.2	352	1.4	1.2, 1.5	<0.001

* Categorized according to percentiles in a US reference population (18).

† *p* value for test of linear trend using body mass index in eight categories (<3rd, 3rd–4th, 5th–9th, 10th–24th, 25th–74th, 75th–84th, 85th–94th, ≥95th) as a continuous variable.

‡ Reference category.

§ RR, relative risk; CI, confidence interval.

birth cohorts included in our study. However, BMI was unrelated to death from lung cancer in our study, the cause of death most strongly associated with smoking, despite several other studies showing an inverse association of BMI with risk of lung cancer mortality. Our study may have not shown this finding because BMI was assessed either before people had begun smoking or before they had been smoking for many years. However, we did find elevated respiratory disease mortality among those whose BMI was low. This finding is in agreement with studies of older adults (9). The fact that lung cancer risk was not elevated in this group suggests that confounding by smoking is not the explanation.

Comparison with other studies

Low BMI is an adverse prognostic factor once chronic obstructive pulmonary disease has developed (24). It has been suggested that chronic pulmonary disease reflects a process of abnormal inflammatory response to inhaled agents—a process that may begin early and that leads to a systemic inflammatory response, weight loss, and skeletal muscle atrophy (25). This hypothesis that the early stages of lung disease lead to weight loss or inhibited weight gain, rather than higher BMI being protective against poor respiratory health, could be tested by using the Mendelian randomization approach (26) through relating *FTO*, a common

genetic variant associated with higher BMI, to respiratory health outcome measures. If there were indeed a protective effect of higher BMI, then individuals carrying genetic variants associated with higher BMI should be at lower risk of indices of poor respiratory health.

In addition to raised respiratory mortality among those with low BMI, elevated mortality is seen at high BMI. Studies have suggested that obesity is a risk factor for adult asthma. In a Norwegian prospective study exploring the relation between body weight and asthma, the risk of asthma increased steadily with BMI in both males and females (27). Epidemiologic studies have also suggested an association between obesity and asthma in children, and longitudinal studies have produced convincing evidence for an overall relation of asthma incidence to baseline obesity (28). In our study, there was an increased risk of death from diseases of the respiratory system for individuals (males and females) in the highest BMI category and an increased risk of death from chronic lower respiratory diseases for males.

There is much concern that the rise in childhood and adolescent obesity will result in increased risk of cardiovascular diseases in the future. However, the evidence in support of this concern is somewhat uncertain (5, 29–31). A recent Danish study showed that higher BMI during childhood (ages 7–13 years) was associated with an increased risk of coronary heart disease in adulthood (32). In a Dutch nested case-control study, the adjusted coronary heart disease mortality risk ratio was 2.5 for men whose BMI was $\geq$25 at age 18 years (30). The results from three historical cohort studies in Great Britain did not, however, provide strong evidence that being overweight or obese in childhood, adolescence, and young adulthood was associated with future risk of cardiovascular disease (5). In our study, there was a large increase in risk of death from ischemic heart disease for both males and females whose BMI was above the 75th percentile at baseline compared with the reference category.

Our findings of an increased risk of mortality below the age of 60 years from heart disease and other causes associated with high BMI are supported by a recent US study by Flegal et al. (33). However, in that study, age and weight were measured after age 25 years. We previously explored the persistence of obesity from adolescence into adulthood (34). Whether the excess mortality among obese adolescents can be ascribed to obesity in adolescence or to later obesity, however, is difficult to determine. Although some of the reverse causation in the association between adult BMI and mortality will be removed by using adolescent BMI, we still observed a U-shaped relation between BMI and mortality in middle age.

Both cohort and case-control studies have shown positive associations between adult BMI and risk of colorectal cancer, especially colon cancer. The relation has generally been more consistent and stronger for men than for women (35). A follow-up of the Harvard Growth Study of 1922–1935 showed an increased risk of colorectal cancer mortality for men who were overweight in adolescence. However, the number of cases was small (6). In addition, results from the Harvard Alumni Health Study demonstrated that overweight during young adulthood was associated with higher risk of colon cancer, although less important than overweight during middle age (36). We found an increased risk of mortality from colon cancer for both males and females in the highest BMI category (above the 85th percentile), most pronounced for individuals being measured at ages 17–19 years.

BMI as a measure of adiposity in adolescents is not ideal. However, a workshop on childhood obesity convened by the International Obesity Task Force in 1997 concluded that BMI offers a reasonable measure of fatness in children and adolescents (37).

Although follow-up in the present study was up to 42 years, the oldest persons were aged 61 years (mean, 52) when exiting the study. Consequently, the study relates to excess mortality in early adulthood through to middle age, which is also reflected in the relative frequency of the different causes of death.

Conclusion

In this study, obesity in adolescence was related to increased mortality from several important causes of death in middle age. Increasing levels of obesity in adolescence could presage adverse trends in these causes of death in future decades. The causal nature of the few causes of death we found to be associated with low BMI in adolescence needs to be investigated by using innovative research methods.

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