ORIGINAL ARTICLE

Body-Mass Index in 2.3 Million Adolescents and Cardiovascular Death in Adulthood

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ABSTRACT

BACKGROUND

In light of the worldwide increase in childhood obesity, we examined the association between body-mass index (BMI) in late adolescence and death from cardiovascular causes in adulthood.

METHODS

We grouped data on BMI, as measured from 1967 through 2010 in 2.3 million Israeli adolescents (mean age, 17.3±0.4 years), according to age- and sex-specific percentiles from the U.S. Centers for Disease Control and Prevention. Primary outcomes were the number of deaths attributed to coronary heart disease, stroke, sudden death from an unknown cause, or a combination of all three categories (total cardiovascular causes) by mid-2011. Cox proportional-hazards models were used.

RESULTS

During 42,297,007 person-years of follow-up, 2918 of 32,127 deaths (9.1%) were from cardiovascular causes, including 1497 from coronary heart disease, 528 from stroke, and 893 from sudden death. On multivariable analysis, there was a graded increase in the risk of death from cardiovascular causes and all causes that started among participants in the group that was in the 50th to 74th percentiles of BMI (i.e., within the accepted normal range). Hazard ratios in the obese group (≥95th percentile for BMI), as compared with the reference group in the 5th to 24th percentiles, were 4.9 (95% confidence interval [CI], 3.9 to 6.1) for death from coronary heart disease, 2.6 (95% CI, 1.7 to 4.1) for death from stroke, 2.1 (95% CI, 1.5 to 2.9) for sudden death, and 3.5 (95% CI, 2.9 to 4.1) for death from total cardiovascular causes, after adjustment for sex, age, birth year, sociodemographic characteristics, and height. Hazard ratios for death from cardiovascular causes in the same percentile groups increased from 2.0 (95% CI, 1.1 to 3.9) during follow-up for 0 to 10 years to 4.1 (95% CI, 3.1 to 5.4) during follow-up for 30 to 40 years; during both periods, hazard ratios were consistently high for death from coronary heart disease. Findings persisted in extensive sensitivity analyses.

CONCLUSIONS

A BMI in the 50th to 74th percentiles, within the accepted normal range, during adolescence was associated with increased cardiovascular and all-cause mortality during 40 years of follow-up. Overweight and obesity were strongly associated with increased cardiovascular mortality in adulthood. (Funded by the Environment and Health Fund.)

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Overweight and obesity in adolescents have increased substantially in recent decades and affect a third of the adolescent population in some developed countries.[1] Obesity early in life is considered to be a risk factor for death from cardiovascular disease and from all causes in adulthood,[2-5] although not all investigators concur[6]; such obesity may limit the increase in life expectancy that otherwise would be achieved.[7,8] Despite progress in prevention and treatment of cardiovascular disease, cardiovascular mortality among young adults either has not declined or the decline has slowed over recent decades in several developed countries coincident with the obesity epidemic.[9,10] Some,[2,3,11] although not all,[12] studies suggest that a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) that falls within the upper-normal range in adolescence is associated with an increased risk of death from cardiovascular causes, although a determination of the BMI threshold that is associated with such an increased risk of remains uncertain. Thus, our main objective was to assess the risk of fatal cardiovascular events in adulthood according to the BMI range during adolescence. We also estimated the predicted proportion of cardiovascular deaths that could be attributed to the increasing prevalence of overweight and obesity among adolescents.

Our study was based on a national database of 2.3 million Israeli adolescents in whom height and weight were measured between 1967 and 2010. We assessed the association between the BMI in late adolescence and death from coronary heart disease, stroke, and sudden death in adulthood.

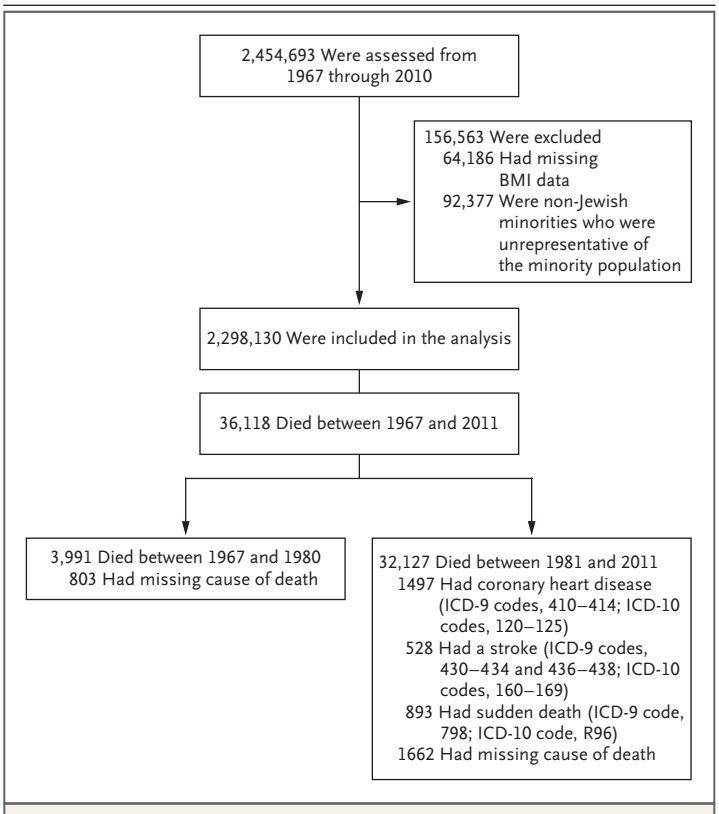


Figure 1. Study Design and Mortality Outcomes.

Officially coded underlying causes of death were available starting in 1981, whereas data regarding service-related deaths were available from the Israel Defense Forces throughout the full study period (1967 through 2011). The body-mass index (BMI) among adolescents between the ages of 16 and 19 years was determined from measurements of weight and height during medical examinations as part of their evaluation for service in the Israeli military. Codes in the *International Classification of Diseases* (ICD) referring to the primary cardiovascular outcomes are indicated in parentheses. The underlying cause of death was coded from death notifications by the Israel Central Bureau of Statistics, according to the ICD 9th revision (ICD-9) from 1981 through 1997 and 10th revision (ICD-10) from 1998 through 2011.

METHODS

STUDY POPULATION

One year before mandatory military service, Israeli adolescents who are 17 years of age are required to undergo a medical evaluation (Fig. 1). Of the 2,454,693 adolescents between the ages of 16 and 19 years who were examined from January 1, 1967, to December 31, 2010, we excluded 64,186 with missing weight and height measurements and 92,377 who were from non-Jewish populations, since these adolescents were not representative of the overall minority population, in which residents are mostly exempt from military service and therefore are not routinely called up for an obligatory health examination. These exclusions resulted in a study sample of 2,298,130 participants, which included a nationally representative group of Jewish men but not of Jewish women, since Orthodox women are also exempt from military service.

MORTALITY OUTCOMES AND DOCUMENTATION OF CAUSE OF DEATH

The primary outcomes of the study were deaths that had occurred by June 30, 2011, and that were attributed to coronary heart disease, stroke, sudden death from an unknown cause, or a combination of the three categories (total car-

diovascular causes). Codes for causes of death from the *International Classification of Diseases* (ICD) are provided in Fig. 1. We also evaluated deaths from noncardiovascular causes and all causes. We linked the underlying cause of death, as officially coded from death notifications by the Israel Central Bureau of Statistics according to the ICD ninth revision (ICD-9) (1981–1997) and tenth revision (ICD-10) (1998–2011), to the military health-examination database; the official cause of death was unavailable before 1981. Deaths among Israel Defense Forces personnel have been recorded since 1967 with a notation as to whether the death was service-related.

DATA COLLECTION AND STUDY VARIABLES

We calculated the BMI from weight and height measured by means of a beam balance and stadiometer with each participant barefoot and wearing underwear. Physicians reviewed medical records, performed the health examinations, and provided standardized diagnostic codes where applicable. Data regarding education, socioeconomic status, and country of origin were recorded.

The age at the time of examination, year of birth, and height were treated as continuous variables. Education was grouped according to whether the participant attended formal schooling for less than 9 years, 10 years, 11 years, or 12 years. Socioeconomic status was estimated according to residential locality,[13] with participants grouped into low, medium, and high categories. The place of origin was defined as the birthplace of the father or grandfather (if the father was born in Israel) and categorized according to country or region. BMI values were grouped according to percentiles for age and sex established by the U.S. Centers for Disease Control and Prevention (CDC)[14] as follows: less than 5th percentile (underweight), 5th to 24th percentile (reference group), 25th to 49th percentile, 50th to 74th percentile, 75th to 84th percentile, 85th to 94th percentile (overweight), and 95th percentile or higher (obese) (Table 1). We also analyzed absolute BMI values.

STUDY OVERSIGHT AND CONDUCT

The study was funded by a research grant from the Environment and Health Fund in Jerusalem. The first and last authors designed the study, wrote the first draft of the manuscript, incorporated revisions from the coauthors, and made the decision to submit the manuscript for publication. The institutional review board of the Israel Defense Forces Medical Corps approved the study and waived the requirement for written informed consent.

STATISTICAL ANALYSIS

We calculated unadjusted rates of death per person-year and Kaplan–Meier survival curves for the BMI percentile categories. We used Cox proportional-hazards models to estimate the hazard ratios and 95% confidence intervals for the cardiovascular-specific outcomes. In these analyses, we compared the CDC percentile categories with the reference group, which included BMI values in the 5th through 24th percentiles. Time to event was modeled. Follow-up began at the time of the original medical examination and concluded on the date of death from any cause or June 30, 2011, whichever came first.

Included in multivariable models as potential confounders were all available variables that were known to be associated with cardiovascular outcomes and with BMI and that were confirmed in our study (age, birth year, sex, education, socioeconomic status, and country of origin) as well as height, which was not confirmed as an association in our study (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). We included age, birth year, and sex in model 1 and all the variables in model 2. We imputed missing values for country of origin, education, and socioeconomic status (1.4% of the cohort) using multiple imputation algorithms (SAS Miner, version 13.1). The assumption of proportionality of the hazards was confirmed for all variables.

We applied the PHREG procedure to account for competing risks using the Cox proportional-hazards model (PROC PHREG, SAS software, version 9.4). In tests for trend, we applied linear and quadratic terms using the midpoint of each BMI percentile group or the median of each absolute BMI group. Spline models (SmoothHR and survival packages, R software, version 3.2.2) were fit to estimate the BMI value associated with minimum cardiovascular mortality and the lowest BMI associated with significantly increased mortality. Details regarding extensive sensitivity analyses are provided in the Supplementary Appendix.

Of the 36,118 deaths that were recorded be-

Table 1. Characteristics of the Participants at Baseline, According to Percentile of Body-Mass Index (BMI).*

Variable	BMI Percentile							
	<5th (N=150,488)	5th to 24th (N=472,226)	25th to 49th (N=600,966)	50th to 74th (N=577,331)	75th to 84th (N=216,086)	85th to 94th (N=194,972)	≥95th (N=86,061)	All Percentiles (N=2,298,130)
Age — yr	17.4±0.5	17.4±0.5	17.3±0.4	17.3±0.4	17.3±0.4	17.3±0.4	17.3±0.4	17.3±0.4
Male sex — no. (%)	109,138 (73)	302,527 (64)	353,265 (59)	320,517 (56)	116,233 (54)	108,820 (56)	59,520 (69)	1,370,020 (60)
Median BMI (IQR)								
Men	17.2 (16.7–17.6)	18.9 (18.5–19.4)	20.6 (20.2–21.0)	22.4 (21.9–23.0)	24.3 (23.9–24.7)	26.4 (25.7–27.3)	30.8 (29.4–32.9)	21.1 (19.4–23.1)
Women	16.8 (16.3–17.1)	18.4 (18.0–18.9)	20.1 (19.7–20.6)	22.1 (21.5–22.8)	24.2 (23.9–24.8)	26.8 (26.0–27.9)	32.0 (30.8–34.1)	21.1 (19.4–23.2)
BMI range†								
Men	12.11–17.84	17.85–19.71	19.72–21.41	21.42–23.62	23.63–25.12	25.13–28.43	28.44–47.54	12.11–47.54
Women	12.55–17.31	17.32–19.20	19.21–21.00	21.01–23.51	23.52–25.33	25.34–29.81	29.82–47.32	12.55–47.32
Height — cm								
Men	173.1±7.1	173.3±6.8	173.4±6.7	173.6±6.8	173.8±6.8	174.0±6.9	174.1±7.3	173.5±6.9
Women	163.2±6.5	162.5±6.1	162.1±6.0	161.8±6.0	161.8±6.1	161.8±6.2	162.3±6.4	162.1±6.1
Completed high school — %	75	78	80	82	83	82	81	80
Low socioeconomic status — %	26	25	24	24	24	25	27	24
Country or region of origin — %								
Israel	5	6	6	6	6	6	7	6
Former USSR	12	12	12	13	14	14	16	13
Asia	32	28	25	23	22	22	21	25
North Africa	22	24	25	25	25	25	26	24
Europe	25	28	31	32	33	32	30	31
Ethiopia	4	2	1	<1	<1	<1	<1	1

* Plus–minus values are means ±SD. The BMI is the weight in kilograms divided by the square of the height in meters. IQR denotes interquartile range, and USSR Union of Soviet Socialist Republics.

† Listed are the BMI ranges of the participants at a mean age of 17.3 years. For each of the 48 months between the ages of 16.0 years and 19.99 years, there is a different age- and sex-specific BMI range that determines the percentile of BMI, as measured by the U.S. Centers for Disease Control and Prevention (a total of 96 in this study).

Table 2. Duration of Follow-up and Cause of Death, According to Percentile of BMI during Adolescence.*

Variable	BMI Percentile during Adolescence							
	<5th (N=150,488)	5th to 24th (N=472,226)	25th to 49th (N=600,966)	50th to 74th (N=577,331)	75th to 84th (N=216,086)	85th to 94th (N=194,972)	≥95th (N=86,061)	All Percentiles (N=2,298,130)
Study follow-up								
Median duration (IQR) — yr	18.4 (10.4–28.5)	19.2 (10.7–29.8)	19.5 (10.6–30.5)	18.9 (10.0–29.9)	17.7 (9.1–28.3)	15.8 (8.0–25.5)	12.0 (6.0–20.5)	18.4 (9.9–29.3)
Cumulative duration — person-yr	2,778,207	8,967,197	11,494,064	10,782,122	3,848,492	3,229,523	1,197,403	42,297,007
Cause of death								
Coronary heart disease								
No. of deaths	72	238	324	373	176	199	115	1,497
Male sex — no. (%)	68 (94)	232 (97)	304 (94)	341 (91)	161 (91)	187 (94)	108 (94)	1,401 (94)
Mean age at death — yr	47.0±8.9	47.5±8.2	47.5±7.8	47.8±8.2	46.8±8.7	47.3±8.0	46.7±8.7	47.4±8.2
Incidence rate per 10,000 person-yr	0.259	0.265	0.282	0.346	0.457	0.616	0.960	0.354
Stroke								
No. of deaths	31	107	114	140	55	55	26	528
Male sex — no. (%)	30 (97)	87 (81)	85 (75)	111 (79)	34 (62)	46 (84)	25 (96)	418 (79)
Mean age at death — yr	44.2±11.9	45.4±11.2	45.0±11.2	46.8±9.4	46.6±9.6	46.4±10.0	49.3±8.6	46.0±10.4
Incidence rate per 10,000 person-yr	0.112	0.119	0.099	0.130	0.143	0.170	0.217	0.125
Sudden death								
No. of deaths	74	185	214	215	86	75	44	893
Male sex — no. (%)	70 (95)	177 (96)	197 (92)	187 (87)	75 (87)	67 (89)	41 (93)	814 (91)
Mean age at death — yr	41.4±10.4	40.4±10.5	41.4±10.9	42.9±10.7	41.0±10.6	40.0±11.7	39.0±10.2	41.3±10.8
Incidence rate per 10,000 person-yr	0.266	0.206	0.186	0.199	0.223	0.232	0.367	0.211
Total cardiovascular causes								
No. of deaths	177	530	652	728	317	329	185	2,918
Male sex — no. (%)	168 (95)	496 (94)	586 (90)	639 (88)	270 (85)	300 (91)	174 (94)	2,633 (90)
Mean age at death — yr	44.2±10.4	44.6±10.2	45.1±9.9	46.2±9.5	45.2±9.7	45.5±9.8	45.2±9.7	45.3±9.8
Incidence rate per 10,000 person-yr	0.637	0.591	0.567	0.675	0.824	1.019	1.545	0.690
Noncardiovascular causes†								
No. of deaths	2059	6147	7574	7193	2725	2397	1114	29,209

Male sex — no. (%)	1815 (88)	5079 (83)	5910 (78)	5289 (74)	1995 (73)	1778 (74)	942 (85)	22,808 (78)
Mean age at death — yr	37.2±12.0	37.4±12.3	37.9±12.5	38.5±12.4	39.2±12.6	39.6±12.5	38.7±12.3	38.2±12.4
Incidence rate per 10,000 person-yr)	7.411	6.855	6.589	6.671	7.081	7.422	9.303	6.906
Death from all causes†								
No. of deaths	2236	6677	8226	7921	3042	2726	1299	32,127
Male sex — no. (%)	1983 (89)	5575 (83)	6496 (79)	5928 (75)	2265 (74)	2078 (76)	1116 (86)	25,441 (79)
Age at death — yr	37.8±12.1	38.0±12.3	38.5±12.4	39.2±12.4	39.8±12.5	40.3±12.3	39.6±12.1	38.9±12.4
Incidence rate per 10,000 person-yr	8.048	7.446	7.157	7.346	7.904	8.441	10.848	7.596

* Plus–minus values are means ±SD. Person-years of follow-up were calculated from 1981 through 2011.
† Included in this category are 1662 deaths for which the cause was missing. Excluded are 3991 deaths from 1967 through 1980 for which the official underlying cause of death was not available. Such exclusion was designed to be consistent with the numbers of deaths from cardiovascular causes that were determined from 1981 through 2011.

tween 1967 and 2011, a total of 3991 occurred between 1967 and 1980. Of these deaths, 3188 were attributed to causes related to military service, and 803 had a missing underlying cause. The cause of death was also missing for 1662 of the 32,127 deaths (5.2%) that occurred from 1981 through 2011, predominantly among young adults (of whom 48% were <35 years of age and 24% were 35 to 44 years of age). We conducted simulations of the potential effect of the 2465 missing causes of death (6.8% of all deaths) on the associations. We calculated population-attributable fractions (or population-attributable risk percentages, the proportion by which cardiovascular mortality in the population would be reduced if the exposure were eliminated) under an unverifiable causal assumption (Table S2 in the Supplementary Appendix). The main analyses were performed with the use of SPSS software, version 21.0 (IBM).

RESULTS

PARTICIPANTS

Baseline characteristics of the study participants are shown in Table 1. The mean age at the time of the medical evaluation was 17.3±0.4 years. A total of 85% of the cohort were Israeli born, although their families came from multiple countries. More than 75% had completed high school, with the lowest percentage in the underweight group. Low socioeconomic status was more prevalent among both underweight and obese participants.

BMI IN ADOLESCENCE AND CARDIOVASCULAR MORTALITY

During 25,959,547 and 16,337,460 person-years of follow-up in men and women, respectively, there were 2918 deaths from cardiovascular causes (2633 in men and 285 in women), including 1497 deaths from coronary heart disease, 528 from stroke, and 893 from sudden death from an unknown cause. The mean ages at the time of death were 47.4 years for coronary heart disease, 46.0 years for stroke, and 41.3 years for sudden death (Table 2). The low proportional mortality attributed to cardiovascular deaths (9.1%) reflects the relatively young ages in our cohort at the end of follow-up (Fig. S1 in the Supplementary Appendix). The shorter median follow-up in the overweight and obese groups

probably reflects the more recent increase in obesity (Table 2). From 1981 through 2011, there were 29,209 deaths from noncardiovascular causes and 32,127 deaths from all causes. A list of the main causes of death in our cohort and a comparison with the officially coded major causes of death among persons of similar ages in the general Israeli population are provided in Table S3 in the Supplementary Appendix.

The rates of death per person-year were generally lowest in the group that had BMI values during adolescence in the 25th to 49th percentiles, with higher rates observed among those below the 5th percentile. There was a graded increase in crude rates of cardiovascular death starting in the group of participants who had BMI values in the 50th to 74th percentiles (Table 2), a finding that was confirmed by the Kaplan–Meier survival curves for total cardiovascular mortality (Fig. S1 in the Supplementary Appendix). In unadjusted Cox models, starting in the 50th to 74th percentiles for BMI, participants had increased rates of death from coronary heart disease, stroke, and total cardiovascular causes; starting in the 75th to 84th percentiles, participants had an increased risk of sudden death (Table S4 in the Supplementary Appendix).

After multivariable adjustment, the risk of death from coronary heart disease was already significantly higher among those with adolescent BMI values in the 50th to 74th percentiles than among those with BMI values in the 5th to 24th percentiles (hazard ratio, 1.5; 95% confidence interval [CI], 1.3 to 1.8), as were the risks of death from total cardiovascular causes (hazard ratio, 1.3; 95% CI, 1.2 to 1.5), and from noncardiovascular causes and all causes, and there were graded increases in the risk of death from all cardiovascular-specific causes as BMI percentile levels increased above the 50th to 74th percentiles (Table 3 and Fig. 2, and Table S4 and Fig. S2 in the Supplementary Appendix). After multivariable adjustment, obesity was associated with hazard ratios of 4.9 (95% CI, 3.9 to 6.1) for death from coronary heart disease, 2.6 (95% CI, 1.7 to 4.1) for death from stroke, 2.1 (95% CI, 1.5 to 2.9) for sudden death from unknown causes, 3.5 (95% CI, 2.9 to 4.1) for death from total cardiovascular causes, 1.5 (95% CI, 1.4 to 1.6) for death from noncardiovascular causes, and 1.7 (95% CI, 1.6 to 1.8) for death from all causes (Table 3, and Table S4 in the Supplementary Appendix). Participants in the BMI group categorized as overweight (85th to 94th percentiles) had hazard ratios of 3.0 (95% CI, 2.5 to 3.7) for death from coronary heart disease, 1.8 (95% CI, 1.3 to 2.5) for death from stroke, 1.5 (95% CI, 1.1 to 1.9) for sudden death, and 2.2 (95% CI, 1.9 to 2.6) for death from total cardiovascular causes. The hazard ratios were generally lowest for all categories of death among participants in the BMI groups that were in the 25th to 49th or the 5th to 24th BMI percentiles.

In calculations of the risk of death from total cardiovascular causes at different follow-up times and 10-year intervals, the association between cardiovascular mortality and increased BMI was evident by 10 years of follow-up (hazard ratio, 2.0; 95% CI, 1.1 to 3.9) and was more pronounced during the follow-up period from 30 to 40 years (hazard ratio, 4.1; 95% CI, 3.1 to 5.4) (Table S5 and Fig. S3 in the Supplementary Appendix). The risk was persistently high for death from coronary heart disease across the entire period of follow-up.

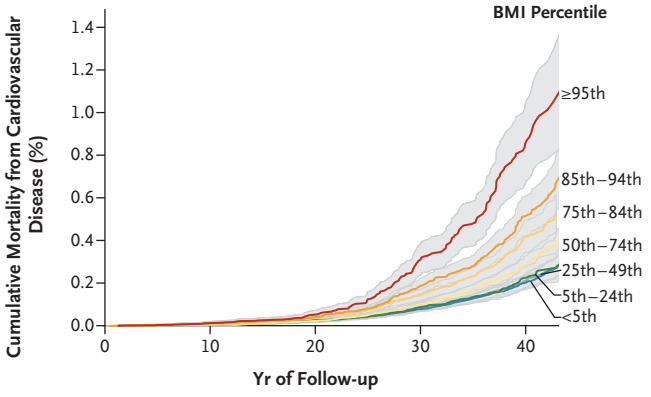
In the analysis of absolute values of BMI, participants with a BMI ranging from 20.0 to 22.4 had a higher risk of death from coronary heart disease than did those with a BMI ranging from 17.5 to 19.9 (hazard ratio, 1.2; 95% CI, 1.1 to 1.4) (Table S6 in the Supplementary Appendix). The risks of death from stroke, sudden death, and total cardiovascular causes (along with noncardiovascular causes and all causes) were also elevated starting with a BMI of 22.5 and increased more steeply among the extremely obese for cardiovascular-specific death. We used multivariable-adjusted spline models to estimate that the minimum risks of death from stroke, sudden death, and cardiovascular causes were among participants who had BMI values of 19.8, 19.3, and 18.3, respectively, whereas the association with death from coronary artery disease was graded across the full range of BMI-percentile groups. Participants had a significantly elevated risk of death from total cardiovascular causes starting at BMI values above 20.3 (Fig. S4 in the Supplementary Appendix). To compare our data with previous observations,[2] we computed z scores of BMI for the 1,854,522 participants who were 17 or 18 years of age when they were evaluated. After multivariable adjustment, the hazard ratios for death from coronary heart disease were 1.54 (95% CI, 1.46 to 1.62) for men

Table 3. Hazard Ratios for Cause of Death, According to Percentile of BMI during Adolescence.*

Variable	BMI Percentile during Adolescence						
	<5th	5th to 24th	25th to 49th	50th to 74th	75th to 84th	85th to 94th	≥95th
Cause of death							
Coronary heart disease							
Hazard ratio (95% CI)†	0.95 (0.73–1.24)	1.00 (reference)	1.11 (0.94–1.31)	1.49 (1.27–1.76)	2.17 (1.78–2.64)	3.02 (2.50–3.65)	4.89 (3.91–6.12)
P value	0.72		0.23	<0.001	<0.001	<0.001	<0.001
Stroke							
Hazard ratio (95% CI)†	0.94 (0.63–1.41)	1.00 (reference)	0.84 (0.65–1.10)	1.18 (0.92–1.53)	1.42 (1.03–1.97)	1.81 (1.30–2.51)	2.64 (1.72–4.08)
P value	0.77		0.21	0.19	0.034	<0.001	<0.001
Sudden death							
Hazard ratio (95% CI)†	1.15 (0.88–1.50)	1.00 (reference)	0.99 (0.81–1.20)	1.17 (0.96–1.42)	1.41 (1.09–1.82)	1.46 (1.11–1.91)	2.09 (1.50–2.91)
P value	0.33		0.91	0.12	0.009	0.006	<0.001
Total cardiovascular causes							
Hazard ratio (95% CI)†	1.02 (0.86–1.21)	1.00 (reference)	1.01 (0.90–1.14)	1.32 (1.18–1.48)	1.76 (1.53–2.03)	2.25 (1.96–2.58)	3.46 (2.93–4.10)
P value	0.79		0.81	<0.001	<0.001	<0.001	<0.001
Noncardiovascular causes							
Hazard ratio (95% CI)	1.05 (1.00–1.11)	1.00 (reference)	0.99 (0.95–1.02)	1.04 (1.01–1.08)	1.16 (1.11–1.21)	1.23 (1.17–1.29)	1.54 (1.44–1.64)
P value	0.04		0.37	0.019	<0.001	<0.001	<0.001
All causes							
Hazard ratio (95% CI)	1.05 (1.00–1.11)	1.00 (reference)	0.99 (0.96–1.02)	1.06 (1.03–1.10)	1.20 (1.15–1.26)	1.30 (1.24–1.36)	1.68 (1.58–1.78)
P value	0.039		0.45	<0.001	<0.001	<0.001	<0.001

* A total of 2918 participants died from cardiovascular causes (including 1497 from coronary heart disease, 528 from stroke, and 893 from sudden death of unknown cause), 29,209 died from noncardiovascular causes, and 32,127 died from all causes. Hazard ratios were calculated with the use of the Cox proportional-hazards method among 2,298,130 participants between the ages of 16 and 19 years at the time of examination with 42,297,007 person-years of follow-up; the hazard ratios were adjusted for age, birth year, sex, socioeconomic status, country of origin, educational level, and height. In these analyses, we accounted for competing risk (deaths from other causes). In tests for trend for all comparisons, $P<0.001$ for linear terms and $P\leq0.004$ for quadratic terms.

† The hazard ratio in this category was essentially unchanged when socioeconomic status and height were excluded from the seven-covariate model.



No. at Risk

Participants at risk	1,712,018	1,042,018	540,636	160,145
Cumulative person-yr	17,201,301	30,718,320	38,472,521	41,926,636
Cumulative cardiovascular deaths	185	609	1,577	2,676

Figure 2. Body-Mass Index (BMI) during Adolescence and Subsequent Cardiovascular Mortality.

Shown are rates of death from cardiovascular causes during up to 44 years of follow-up according to the percentile of BMI during adolescence, among 2,298,130 participants who were assessed between the ages of 16 and 19 years. Included in the 2918 deaths from cardiovascular causes were deaths from coronary artery disease and stroke and sudden deaths of unknown cause. Gray shading denotes 95% confidence intervals. The model was adjusted for sex, age at examination, birth year, education, residential socioeconomic status, country of origin, and height. Also shown are the numbers of participants at risk, cumulative person-years, and the cumulative numbers of deaths from cardiovascular causes through 40 years of follow-up. An additional 242 deaths from cardiovascular causes occurred between 40 years and the study cutoff of 44 years.

and 1.58 (95% CI, 1.31 to 1.91) for women per 1-unit increment in the z score.

The findings persisted in a series of sensitivity analyses, including a sex-specific analysis (which showed overall consistency between the sexes), an analysis restricted to adolescents with unimpaired health status, an analysis modeling the association without competing risks that used the group with BMI values in the 25th to 49th percentiles as the reference category, analyses that were restricted to participants who were evaluated after 1981 and to those who were evaluated from 1967 through 1980, an analysis comparing deaths that occurred before the age of 45 years with those that occurred at the age of 45 years or older, analyses according to calendar periods of follow-up and country of origin, and an analysis that included all cardiovascular diseases defined according to ICD coding (9.9% of all deaths) (Table S4 and Tables S7 through S13 in the Supplementary Appendix). Simulation of deaths with an unknown underlying cause with varying assignment as cardiovascular deaths was shown to have a minor effect on the association between BMI and the study outcomes (Tables S14 and S15 in the Supplementary Appendix). In an analysis of population-attributable fractions, among participants with a BMI higher than the 50th percentile in 2013, the projected population-attributable fractions were 28% for death from total cardiovascular causes and 36% for death from coronary heart disease (Table S2 in the Supplementary Appendix).

DISCUSSION

In this nationwide population-based study, we found an association between the BMI in late adolescence and subsequent cardiovascular mortality, predominantly in midlife, since the cohort did not include participants who had reached the older ages at which cardiovascular disease is a dominant cause of death. BMI, including measurements in the currently accepted mid-normal range, was associated with a graded increase in the risk of death from cardiovascular causes. Obesity during adolescence was associated with a substantially increased risk of cardiovascular outcomes in middle age, particularly death from coronary heart disease. The associations, which were similarly evident in both sexes, persisted strongly for cardiovascular deaths occurring during four decades after the measurement of BMI in adolescence. The association withstood a series of sensitivity analyses. The population-attributable fractions in our study are projected to rise with the secular shift in the BMI distribution and indicate that overweight and obesity in adolescence may account for a fifth of cardiovascular deaths and a quarter of deaths from coronary heart disease by the time the participants reach midlife. Modeled predictions for the United States point to a marked increase in the incidence of coronary heart disease and in the rate of death in young and middle adulthood.[15]

Several studies[2-4,11,16] (although not all[6]) have shown an association between obesity during adolescence and a future risk of death from coronary heart disease, with conflicting evidence regarding death from cerebrovascular causes.[5,6] In the study by Baker et al.,[2] in which investigators evaluated the association between childhood BMI and coronary events in adulthood, the BMI at the age of 7 years was associated with adult mortality from coronary heart

disease (hazard ratio, 1.10 per 1-unit increment in the z score in boys); the strength of the association increased up to the age of 13 years (hazard ratio, 1.24). In our study, in similar analyses restricted to adolescents who were 17 or 18 years of age, we estimated hazard ratios for death from coronary heart disease of 1.54 and 1.58 for boys and girls, respectively, findings that appear to be consistent with a stronger association in adolescence than earlier in childhood.

The large size of our study, which incorporated more than 42 million person-years of follow-up, provided adequate statistical power to assess the associations within the currently accepted normal range of BMI values. Excess all-cause mortality (including cardiovascular mortality) starting at the 50th percentile of adolescent BMI values confirmed the findings of an earlier study on a portion of this cohort.[17] Thus, the classification of BMI according to the accepted normal range (i.e., the 5th to 84th percentiles and a BMI ranging from 18.5 to 25.0) may underestimate the risk associated with being overweight in adolescence. This inference is supported by our findings that there is a graded increase in the risk of death starting at the mid-normal range of adolescent BMI (50th to 74th percentiles) and that the high-normal BMI range (75th to 84th percentiles) was associated with hazard ratios of 2.2 for coronary heart disease and 1.8 for total cardiovascular causes.

Our findings appear to provide a link between the secular trends in adolescent overweight and coronary mortality during the past decades. In contrast to the steep decline in the rate of death from cardiovascular causes among older age groups, cardiovascular mortality among young adults has not decreased or the decline has slowed in several developed countries.[9,10]

How might adolescent BMI affect adult cardiovascular mortality? In our study, we could not control for important risk factors (e.g., smoking, exercise, and physical fitness)[18] or for adult BMI. We have considered two pathways by which adolescent BMI might influence cardiovascular outcomes in adulthood. First, obesity may be deleterious during adolescence, since it has been associated with unfavorable metabolic abnormalities (suggesting an indirect pathway mediated through risk factors such as unfavorable plasma lipid or lipoprotein levels, increased blood pressure, impaired glucose metabolism, and insulin resistance[15,19]), cardiac remodeling,[20] lengthening of the QT interval,[21] and formation of coronary and aortic atherosclerotic plaques.[22] Furthermore, a mendelian randomization study showed a strong association between BMI and several cardiometabolic risk markers in the young (even within the nonobese weight range), which effectively ruled out uncontrolled confounding and reverse causation as explanations for their findings.[23] Increased coronary risk associated with adolescent obesity persisted in a subgroup in our cohort,[24] even after adjustment for BMI in young adulthood, which suggests the importance of the timing of exposure to obesity during a lifetime.[12,25] However, other studies[26,27] have not shown an independent association between BMI during adolescence and adult cardiovascular disease after adjustment for adult BMI. Second, as BMI tracks over time[25,26] (and more strongly starting at the age of 18 years[28]), adult BMI may mediate the risk association. The association between adult BMI and cardiovascular disease is supported by a mendelian randomization study.[29] Such a pathway might explain the association between seemingly normal levels of BMI (50th to 74th percentiles) and death from total cardiovascular causes and between a BMI of more than 20.0 and death from coronary artery disease. In the absence of adult measures of BMI, we were unable to address this question.

Our study has certain limitations. First, as noted, in the absence of adult measures of BMI, we could not assess an independent effect of adolescent BMI on death from cardiovascular disease in adulthood. Second, cause-specific data were unavailable to us for 6.8% of all deaths. However, simulations indicated only minor effects of missing data on our risk estimates. Third, we were unable to account for important cardiovascular lifestyle risk factors that may confound the BMI association, although adjustment for smoking had no effect in other studies,[3,25] and a mendelian randomization study showed effects for BMI that were independent of confounding.[23] Fourth, since our follow-up included participants in early and mid-adulthood but not in the older age groups in which cardiovascular death predominates, fewer than 10% of our study participants died from cardiovascular causes. Fifth, although the study sample was highly representative of the Israeli adolescent male Jewish population, it was less representative of Israeli women, and our findings need to be confirmed in a racially and ethnically diverse

population. Finally, since we were analyzing only death outcomes, we cannot determine whether BMI was associated with the incidence of cardiovascular disease, death from cardiovascular disease, or both. The strengths of the study include the use of standardized measurements of weight and height rather than recalled values,[30] the large sample size, and the extended follow-up, which provided adequate power to examine narrow subgroups of BMI percentiles.

In conclusion, an increased BMI in late adolescence, even within the currently accepted normal range, was strongly associated with cardiovascular mortality in young adulthood or midlife. We could not determine whether an increased BMI in adolescence is an independent risk factor, is mediated by adult obesity, or both. The secular shift to the right in the distribution of adolescent BMI and the rising prevalence of overweight and obesity among adolescents may account for a substantial and increasing future burden of cardiovascular disease, particularly coronary heart disease.

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REFERENCES

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA 2014;311:806-14.
2. Baker JL, Olsen LW, Sørensen TIA. Childhood body-mass index and the risk of coronary heart disease in adulthood. N Engl J Med 2007;357:2329-37.
3. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents — a follow-up of the Harvard Growth Study of 1922 to 1935. N Engl J Med 1992;327:1350-5.
4. Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker HC. Childhood obesity, other cardiovascular risk factors, and premature death. N Engl J Med 2010;362:485-93.
5. Engeland A, Bjørge T, Søgaard AJ, Tverdal A. Body mass index in adolescence in relation to total mortality: 32-year follow-up of 227,000 Norwegian boys and girls. Am J Epidemiol 2003;157:517-23.
6. Lawlor DA, Martin RM, Gunnell D, et al. Association of body mass index measured in childhood, adolescence, and young adulthood with risk of ischemic heart disease and stroke: findings from 3 historical cohort studies. Am J Clin Nutr 2006;83:767-73.
7. Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med 2005;352:1138-45.
8. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. JAMA 2003;289:187-93.
9. O'Flaherty M, Allender S, Taylor R, Stevenson C, Peeters A, Capewell S. The decline in coronary heart disease mortality is slowing in young adults (Australia 1976-2006): a time trend analysis. Int J Cardiol 2012;158:193-8.
10. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. J Am Coll Cardiol 2007;50:2128-32.
11. Bjørge T, Engeland A, Tverdal A, Smith GD. Body mass index in adolescence in relation to cause-specific mortality: a follow-up of 230,000 Norwegian adolescents. Am J Epidemiol 2008;168:30-7.
12. van Dam RM, Willett WC, Manson JE, Hu FB. The relationship between overweight in adolescence and premature death in women. Ann Intern Med 2006;145:91-7.
13. Israel Central Bureau of Statistics. Characterization and classification of local authorities by the socio-economic level of the population. Jerusalem: Israel Central Bureau of Statistics, 2006.
14. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: methods and development. Vital Health Stat 11 2002;2002(246):1-190.
15. Bibbins-Domingo K, Coxson P, Pletcher MJ, Lightwood J, Goldman L. Adolescent overweight and future adult coronary heart disease. N Engl J Med 2007;357:2371-9.
16. DiPietro L, Mossberg HO, Stunkard AJ. A 40-year history of overweight children in Stockholm: life-time overweight, morbidity, and mortality. Int J Obes Relat Metab Disord 1994;18:585-90.
17. Twig G, Afek A, Shamiss A, et al. Adolescence BMI and trends in adulthood mortality: a study of 2.16 million adolescents. J Clin Endocrinol Metab 2014;99:2095-103.
18. Shah RV, Murthy VL, Colangelo LA, et al. Association of fitness in young adulthood with survival and cardiovascular risk: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. JAMA Intern Med 2016;176:87-95.
19. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. N Engl J Med 2015;373:1307-17.
20. Mangner N, Scheuermann K, Winzer E, et al. Childhood obesity: impact on cardiac geometry and function. JACC Cardiovasc Imaging 2014;7:1198-205.
21. Güven A, Özgen T, Güngör O, Aydın M, Baysal K. Association between the corrected QT interval and carotid artery intima-media thickness in obese children. J Clin Res Pediatr Endocrinol 2010;2:21-7.
22. McGill HC Jr, McMahan CA, Herderick EE, Malcom GT, Tracy RE, Strong JP. Origin of atherosclerosis in childhood and adolescence. Am J Clin Nutr 2000;72:Suppl:1307S-1315S.
23. Würtz P, Wang Q, Kangas AJ, et al. Metabolic signatures of adiposity in young adults: Mendelian randomization analysis and effects of weight change. PLoS Med 2014;11(12):e1001765.
24. Tirosh A, Shai I, Afek A, et al. Adolescent BMI trajectory and risk of diabetes versus coronary disease. N Engl J Med 2011;364:1315-25.
25. Jeffreys M, McCarron P, Gunnell D, McEwen J, Smith GD. Body mass index in early and mid-adulthood, and subsequent mortality: a historical cohort study. Int J Obes Relat Metab Disord 2003;27:1391-7.
26. Gray L, Lee IM, Sesso HD, Batty GD. Body weight in early and mid-adulthood in relation to subsequent coronary heart disease mortality: 80-year follow-up in the Harvard Alumni Study. Arch Intern Med 2011;171:1768-70.
27. Juonala M, Magnussen CG, Berenson GS, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med 2011;365:1876-85.
28. Kvaavik E, Tell GS, Klepp KI. Predictors and tracking of body mass index from adolescence into adulthood: follow-up of 18 to 20 years in the Oslo Youth Study. Arch Pediatr Adolesc Med 2003;157:1212-8.
29. Hägg S, Fall T, Ploner A, et al. Adiposity as a cause of cardiovascular disease: a Mendelian randomization study. Int J Epidemiol 2015;44:578-86.
30. Keith SW, Fontaine KR, Pajewski NM, Mehta T, Allison DB. Use of self-reported height and weight biases the body mass index-mortality association. Int J Obes (Lond) 2011;35:401-8.