Original Investigation

Change in Body Mass Index Associated With Lowest Mortality in Denmark, 1976-2013

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IMPORTANCE Research has shown a U-shaped pattern in the association of body mass index (BMI) with mortality. Although average BMI has increased over time in most countries, the prevalence of cardiovascular risk factors may also be decreasing among obese individuals over time. Thus, the BMI associated with lowest all-cause mortality may have changed.

OBJECTIVE To determine whether the BMI value that is associated with the lowest all-cause mortality has increased in the general population over a period of 3 decades.

DESIGN, SETTING, AND PARTICIPANTS Three cohorts from the same general population enrolled at different times: the Copenhagen City Heart Study in 1976-1978 (n = 13 704) and 1991-1994 (n = 9482) and the Copenhagen General Population Study in 2003-2013 (n = 97 362). All participants were followed up from inclusion in the studies to November 2014, emigration, or death, whichever came first.

EXPOSURES For observational studies, BMI was modeled using splines and in categories defined by the World Health Organization. Body mass index was calculated as weight in kilograms divided by height in meters squared.

MAIN OUTCOMES AND MEASURES Main outcome was all-cause mortality and secondary outcomes were cause-specific mortality.

RESULTS The number of deaths during follow-up was 10 624 in the 1976-1978 cohort (78% cumulative mortality; mortality rate [MR], 30/1000 person-years [95% CI, 20-46]), 5025 in the 1991-1994 cohort (53%; MR, 16/1000 person-years [95% CI, 9-30]), and 5580 in the 2003-2013 cohort (6%; MR, 4/1000 person-years [95% CI, 1-10]). Except for cancer mortality, the association of BMI with all-cause, cardiovascular, and other mortality was curvilinear (U-shaped). The BMI associated with the lowest all-cause mortality increased by 3.3 from the 1976-1978 cohort compared with the 2003-2013 cohort.

	BMI Associated With Lowest Mortality by Type of Mortality (95% CI)		
Cohort	All-Cause	Cardiovascular	Other
1976-1978	23.7 (23.4-24.3)	23.2 (22.6-23.7)	24.1 (23.5-25.9)
1991-1994	24.6 (24.0-26.3)	24.0 (23.4-25.0)	26.8 (26.1-27.9)
2003-2013	27.0 (26.5-27.6)	26.4 (24.1-27.4)	27.8 (27.1-29.6)

The multivariable- adjusted hazard ratios for all-cause mortality for BMI of 30 or more vs BMI of 18.5 to 24.9 were 1.31 (95% CI, 1.23-1.39; MR, 46/1000 person-years [95% CI, 32-66] vs 28/1000 person-years [95% CI, 18-45]) in the 1976-1978 cohort, 1.13 (95% CI, 1.04-1.22; MR, 28/1000 person-years [95% CI, 17-47] vs 15/1000 person-years [95% CI, 7-31]) in the 1991-1994 cohort, and 0.99 (95% CI, 0.92-1.07; MR, 5/1000 person-years [95% CI, 2-12] vs 4/1000 person-years [95% CI, 1-11]) in the 2003-2013 cohort.

CONCLUSIONS AND RELEVANCE Among 3 Danish cohorts, the BMI associated with the lowest all-cause mortality increased by 3.3 from cohorts enrolled from 1976-1978 through 2003-2013. Further investigation is needed to understand the reason for this change and its implications.

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The controversy about determining the body mass index (BMI) that is associated with lowest all-cause mortality has been fuelled by differences in analytical approaches.[1-3] Depending on how the exposure is defined or which populations or subgroups are analyzed, it is possible to estimate different BMI values to be associated with lowest all-cause mortality.[4-11] The U-shaped pattern of the association of BMI with mortality has been a point of contention; the increased risk of mortality observed with BMI in the low normal range has been suggested to be caused by residual confounding due to concurrent disease or decline in BMI due to disease,[1] while others have suggested this is caused by a detrimental effect of low BMI.[2,3] However, whether the association has changed over time in the general population has not been addressed adequately. Previous findings indicate that while average BMI has increased over time in most countries, the prevalence of cardiovascular risk factors may be decreasing among obese individuals over time.[12] Thus, the BMI associated with lowest all-cause mortality may have changed over time. The few studies addressing this question have used subgroups from differently recruited cohorts with limited or incomplete follow-up, with conflicting results making firm conclusions difficult.[13,14]

In this study, the hypothesis that the BMI value associated with the lowest all-cause mortality has increased in the general population over a period of 3 decades was tested. If this was the case, a corresponding decrease in the risk of all-cause mortality among overweight and obese individuals should be observed during this period. For this purpose, 3 cohorts from the white Danish general population recruited in 1976-1978, 1991-1994, and 2003-2013 were analyzed.

Methods

Participants

The Copenhagen City Heart Study (CCHS) was initiated in 1976-1978 and was also sampled 15 years later in 1991-1994. Individuals aged 20 to 100 years were randomly invited from the national Danish Civil Registration System to reflect the Danish general population.[15,16]

The Copenhagen General Population Study (CGPS) was sampled in 2003-2013, and participants were recruited as for the CCHS. Individuals aged 20 to 100 years were randomly invited from the national Danish Civil Registration System to reflect the Danish general population.[15,16] None of the individuals had attended the CCHS.

The studies were approved by institutional review boards and Danish ethical committees, and participants provided written informed consent. All individuals were white of Danish descent as determined by the Danish Civil Registration System; that is, the participants and both parents were Danish citizens and were born in Denmark.[17]

BMI, Waist Circumference, and Waist-Hip Ratio

Measurements were completed by trained staff at 1 clinic center. Weight was measured without shoes and in light clothing to the nearest 0.1 kg on professional scales. Height was measured to the nearest 0.1 cm with a stadiometer.

Waist circumference was measured midway between the lowest edge of the ribcage and the highest edge of the iliac crest, whereas hip circumference was measured at the widest point between the iliac crest and symphysis pubis. Waist-hip ratio was calculated as waist circumference divided by hip circumference. Waist-hip ratio was only available in the CCHS 1991-1994 and CGPS 2003-2013 examinations.

Potential Confounders

Confounders were chosen based on the World Health Organization (WHO) global health status report evaluating the most common risk factors for all-cause mortality and their possible association with BMI.[18] Diabetes, hypertension, and history of cardiovascular disease were deliberately excluded as potential confounders as they would act in the causal pathway between obesity and mortality.[15,19-22] That is, potential confounders were selected a priori based on what has been shown to be associated with mortality and obesity, but variables thought to lie in the causal pathway between obesity and mortality were excluded. Participants filled in a questionnaire on smoking status (never, former, or current), tobacco consumption (number of cigarettes per day), alcohol consumption (type and amount per week), intensity of leisure-time physical activity during a week (<2 hours, 2-4 hours of light physical activity, >4 hours of activity or 2-4 hours of intense activity, and >4 hours of intense activity), and level of income (high, medium, and low using cohort-specific categories), reviewed together with an investigator on the day of attendance. Cumulative tobacco consumption was calculated for former and current smokers in pack-years; a pack-year was defined as 20 cigarettes or equivalent per day for a year. Standard hospital assays were used to measure plasma cholesterol. History of cardiovascular disease or cancer was used in stratified analyses and was defined as history of ischemic heart disease, stroke, and any cancer except for nonmelanoma skin cancer according to national registries, as done previously.[16,23]

End Points

The 100% complete Danish Civil Registration System records the date of death for all persons living in Denmark, while the national Danish Causes of Death Registry records ranked main causes of death as well as contributing causes of death, as reported by the attending physician in general practice, by the attending physician at a hospital, or by a physician in a forensic or pathology department. Analyzing the accuracy of the Danish Causes of Death Registry for individual end points has only been performed for selected diagnoses; for example, for fatal myocardial infarction, the positive predictive value is 70% and the sensitivity is 89%,[24] and for neoplastic diseases, the positive predictive value is 92% and the sensitivity is 85%.[25] Causes of death were classified according to the *International Classification of Diseases, Eighth Revision* or *Tenth Revision* (*ICD-8* or *ICD-10*), as done previously[26]: cancer death was considered present if 1 of the top 3 ranked causes of death was a cancer diagnosis (*ICD-8* codes 140-209, *ICD-10* codes C00-C97); remaining deaths were classified as cardiovascular death if 1 of the top 3 ranked causes of death had a

cardiovascular disease diagnosis (*ICD-8* codes 390-458, *ICD-10* codes I00-I99); and all other deaths were classified as other death. Alternative analyses using the underlying cause of death only showed similar results; thus, for simplicity only 1 end point definition was included. The national Danish Causes of Death Registry (end of follow-up, December 2012) lags the Danish Civil Registration System (end of follow-up, November 2014) by almost 2 years, so some deaths could not be classified by cause (1976-1978: 404 deaths, 1991-1994: 377, 2003-2013: 1870).

Statistical Analyses

Analyses were carried out using Stata/SE version 13.1, and 2-sided *P* values <.05 were considered statistically significant. In the cohorts, the data were 99.6% complete in relation to potential confounders; the missing data were imputed using multivariable chained imputation (mi impute chained) with fully conditional specification. However, without the imputations, results were similar to those presented.

Cox proportional hazards regression was used to estimate hazard ratios with 95% confidence intervals for the association between BMI and mortality end points, and age was used as time scale with delayed entry (left truncation). Thus, age differences were automatically adjusted for, and analyses are referred to in text, tables, and figures as age adjusted. Multivariable Cox regression was adjusted for age, year of birth, sex, smoking status, cumulative tobacco consumption, alcohol consumption, leisure-time physical activity, income, and plasma cholesterol. The proportional hazards assumption was assessed in Cox regression models graphically by plotting −ln[−ln(survival)] vs ln(analysis time) and evaluation of scaled residuals with no major violations observed. The relationships were evaluated with the use of restricted cubic splines.[27] The number of knots, between 3 and 7, was chosen according to 2 criteria to balance best fit and overfitting: (1) best fit: lowest value of Akaike information criteria[28] and (2) parsimony: if Akaike information criteria were within 2 of each other for different knots, the lowest number of knots was chosen. Follow-up time for each participant began at the day of examination and ended at death, emigration (1976-1978: 53, 1991-1994: 80, 2003-2013: 380), or November 2014, whichever occurred first. Age-adjusted mortality rates were calculated using Poisson regression models stratified by 10-year age groups from 20 to 80 years, and individuals older than 80 years were combined into 1 group. To derive an aggregated estimate of mortality rate, estimates were combined using a meta-analytic approach with random effects as each age group was expected to have a different underlying mortality rate.[29]

The BMI that was associated with lowest mortality was the BMI with the lowest hazard ratio in each cohort; 95% confidence intervals for these estimates were derived using nonparametric bootstrap estimation with 5000 replications.[30] Additional analyses were conducted using WHO categories, with BMI less than 18.5 as underweight, BMI of 18.5 to 24.9 as normal weight, BMI of 25.0 to 29.9 as overweight, and BMI of 30 or more as obese.

Note that due to overlap of participants between CCHS 1976-1978 and 1991-1994, standard techniques for comparing the estimates could not be used directly. Thus, estimates were compared from each CCHS cohort with CGPS 2003-2013 separately.

Results

The cohorts consisted of 13 704 individuals with BMI measurements from the 1976-1978 cohort (participation rate, 74%; 6329 men and 7375 women), 9482 with BMI from the 1991-1994 cohort (participation rate, 61%; 4164 men and 5318 women), and 97 362 individuals with BMI measurements from the 2003-2013 cohort (participation rate, 43%; 43 783 men and 53 579 women). Of these, 6793 attended both the 1976-1978 cohort and the 1991-1994 cohort. Across the 3 cohorts, tobacco consumption decreased, whereas alcohol consumption, physical activity, and income increased from 1976-1978 to 2003-2013 (**Table**). The number of deaths during follow-up was 10 624 (78% cumulative mortality; mortality rate [MR], 30/1000 person-years [95% CI, 20-46]) in the 1976-1978 cohort, 5025 (53%; MR, 16/1000 person-years [95% CI, 9-30]) in 1991-1994, and 5580 (6%; MR, 4/1000 person-years [95% CI, 1-10]) in 2003-2013. With follow-up restricted to 9 years, the MR was 13/1000 person-years (95% CI, 6-28) in 1976-1978, 13/1000 person-years (95% CI, 6-25) in 1991-1994, and 4/1000 person-years (95% CI, 1-10) in 2003-2013. Among those who died, the median age at death was 77 years in the 1976-1978 cohort, 81 years in the 1991-1994 cohort, and 79 years in the 2003-2013 cohort, whereas median follow-up was 19.8 years, 11.0 years, and 4.6 years, respectively.

BMI and the Lowest Mortality

There was a nonlinear association of BMI with all-cause mortality in all 3 cohorts as both high and low BMI were associated with high all-cause mortality. However, the BMI associated with the lowest mortality increased over 3 decades (**Figure 1**). The association of BMI with cardiovascular mortality and other mortality showed a similar pattern (**Figure 2**); however, the association with cancer mortality was not U-shaped, and the BMI associated with the lowest mortality could not be determined.

The BMI associated with the lowest all-cause mortality was 23.7 (95% CI, 23.4-24.3) in 1976-1978, 24.6 (95% CI, 24.0-26.3) in 1991-1994, and 27.0 (95% CI, 26.5-27.6) in 2003-2013 (Figure 1). The corresponding BMI estimates for cardiovascular mortality were 23.2 (95% CI, 22.6-23.7), 24.0 (95% CI, 23.4-25.0), and 26.4 (95% CI, 24.1-27.4), respectively, and for other mortality, 24.1 (95% CI, 23.5-25.9), 26.8 (95% CI, 26.1-27.9), and 27.8 (95% CI, 27.1-29.6), respectively (Figure 2).

To assess follow-up–dependent changes in the BMI associated with the lowest mortality, the estimates from 2 years of follow-up to maximum follow-up were plotted for the 1976-1978 and 2003-2013 cohorts (**Figure 3**). Graphically, there was no evidence of convergence or a follow-up–dependent influence on the estimates, indicating that the BMI associated with the lowest mortality was consistently different between the 2 cohorts.

Table. Baseline Characteristics of Individuals in the 3 Cohorts From the Danish General Population

	1976-1978 (n = 13 704)	1991-1993 (n = 9482)	2003-2013 (n = 97 362)	*P* Values[a]
Age, median (IQR), y	54 (45-61)	61 (49-71)	58 (48-67)	<.001
Men, No. (%)	6329 (46)	4165 (44)	43 783 (45)	<.05
Current smoker, No. (%)	8769 (64)	4644 (49)	17 242 (18)	<.001
Cumulative tobacco consumption, median (IQR), pack-years[b]	20 (10-32)	26 (14-40)	15 (6-30)	<.001
Alcohol consumption, median (IQR), g/wk	48 (0-168)	60 (12-156)	96 (36-180)	<.001
Leisure-time physical activity <2 h/wk, No. (%)	2703 (20)	1200 (13)	6191 (6)	<.001
Low income, No. (%)[c]	3757 (27)	2094 (22)	12 769 (13)	<.001
Total cholesterol, median (IQR), mg/dL	232 (205-263)	235 (205-271)	217 (189-244)	<.001
Body mass index, median (IQR)[d]	24.7 (22.3-27.5)	25.0 (22.6-28.1)	25.6 (23.2-28.5)	<.001
Follow-up time, person-years	324 157	150 802	583 073	
No. of deaths	10 624	5025	5580	

Abbreviation: IQR, interquartile range.

SI conversion factor: To convert total cholesterol to mmol/L, multiply by 0.0259.

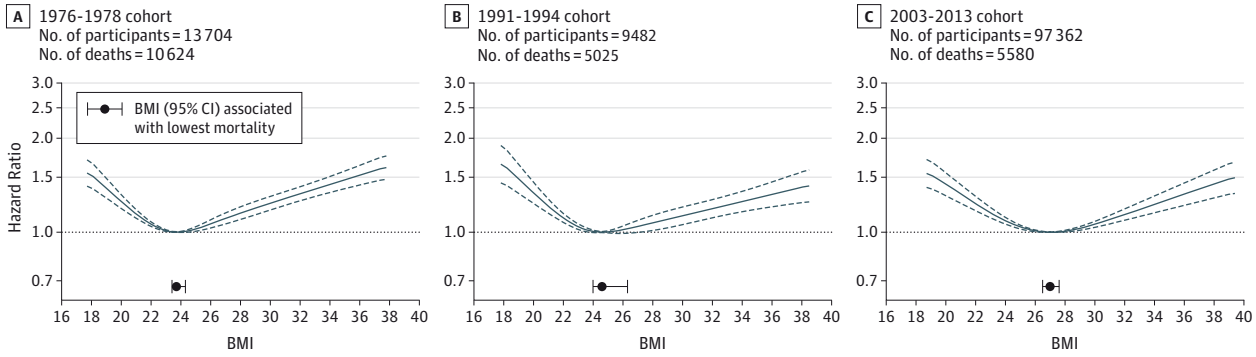
[a] *P* values were calculated using the Kruskal-Wallis test for both comparisons, ie, the 1976-1978 cohort vs the 2003-2013 cohort and the 1991-1994 cohort vs the 2003-2013 cohort.

[b] In current and former smokers only.

[c] Income was classified differently in the 3 cohorts: 3 groups in 1976-1978 and 4 groups in the other cohorts.

[d] Calculated as weight in kilograms divided by height in meters squared.

Figure 1. Multivariable-Adjusted Hazard Ratios for All-Cause Mortality in the 1976-1978, 1991-1994, and 2003-2013 Cohorts According to Body Mass Index



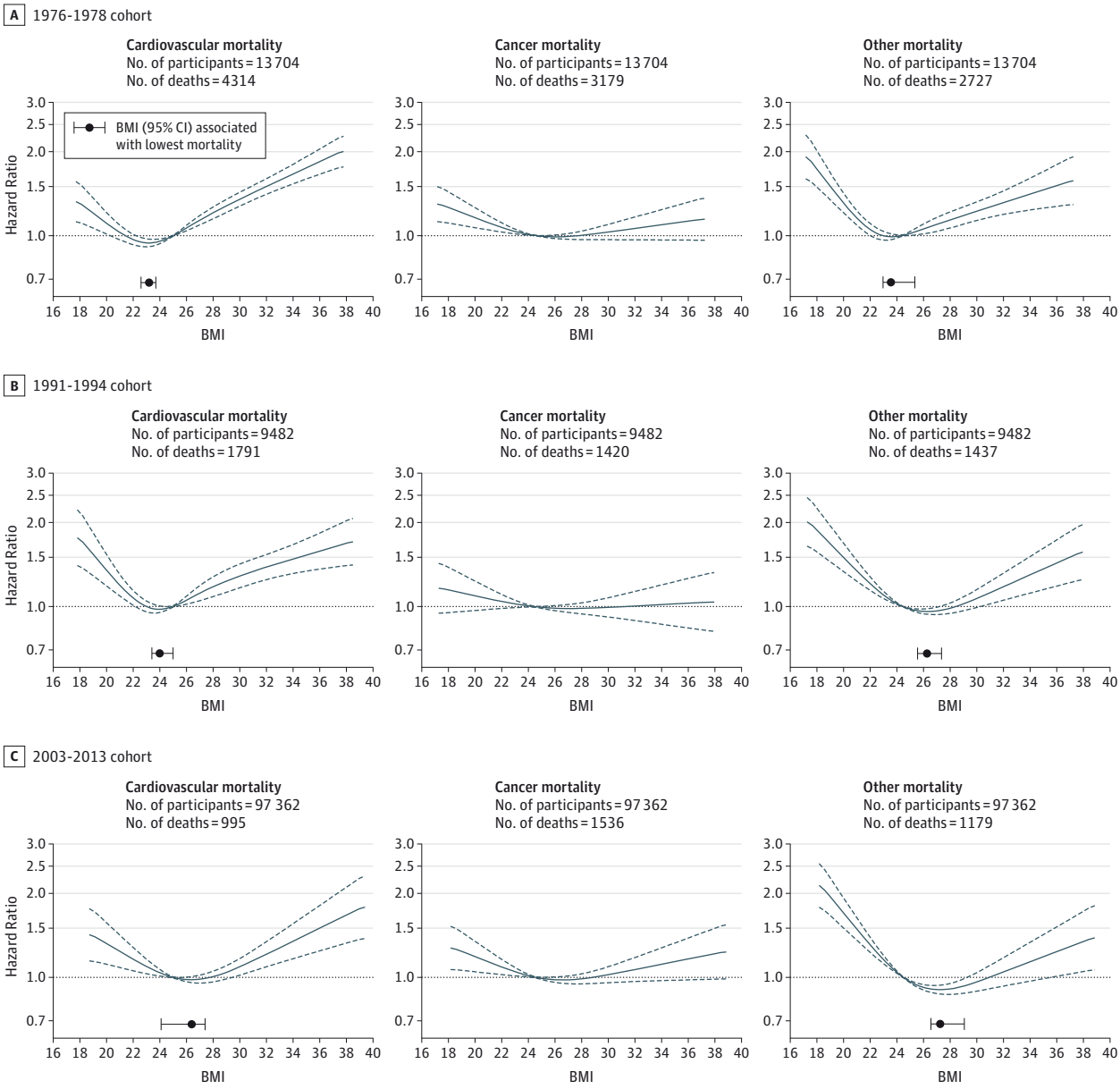
Solid lines are multivariable-adjusted hazard ratios, and dashed lines indicate 95% confidence intervals derived from restricted cubic spline regression with knots chosen by Akaike information criterion as described in Methods. The graphs are truncated at the 1st and 99th percentiles. The Cox regression was adjusted for age, sex, smoking status, cumulative tobacco consumption, alcohol consumption, leisure-time physical activity, income, and plasma cholesterol level. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

BMI in Categories and Mortality

Using WHO categories of BMI, with BMI of 18.5 to 24.9 as the reference, showed corresponding results: the risk of all-cause mortality was reduced from 1976-1978 through 1991-1994 to 2003-2013 for both BMI of 25 to 29.9 and BMI of 30 or greater (**Figure 4**). However, the multivariable-adjusted hazard ratios for BMI less than 18.5 vs BMI of 18.5 to 24.9 were similar across all 3 time periods. The multivariable-adjusted hazard ratios for all-cause mortality for BMI of 25 to 29.9 vs BMI of 18.5 to 24.9 were 1.04 (95% CI, 0.99-1.08; MR, 35/1000 person-years [95% CI, 24-51] vs 28/1000 person-years [95% CI, 18-45]) in the 1976-1978 cohort, 0.97 (95% CI, 0.91-1.04; MR, 22/1000 person-years [95% CI, 12-39] vs 15/1000 person-years [95% CI, 7-31]) in the 1991-1994 cohort, and 0.86 (95% CI, 0.82-0.92; MR, 4/1000 person-years [95% CI, 1-10] vs 4/1000 person-years [95% CI, 1-11]) in the 2003-2013 cohort. The corresponding hazard ratios for BMI of 30 or greater vs BMI of 18.5 to 24.9 were 1.31 (95% CI, 1.23-1.39; MR, 46/1000 person-years [95% CI, 32-66] vs 28/1000 person-years [95% CI, 18-45]) in the 1976-1978 cohort, 1.13 (95% CI, 1.04-1.22; MR, 28/1000 person-years [95% CI, 17-47] vs 15/1000 person-years [95% CI, 7-31]) in the 1991-1994 cohort, and 0.99 (95% CI, 0.92-1.07; MR, 5/1000 person-years [95% CI, 2-12] vs 4/1000 person-years [95% CI, 1-11]) in the 2003-2013 cohort.

The association between BMI and mortality is susceptible to confounding by age, sex, smoking, and presence of cardiovascular disease or cancer, and therefore the analyses were repeated stratified by these variables. Stratified analyses showed a similar pattern as in the main analyses; that is, the risk of all-cause mortality was reduced from 1976-1978 through 1991-1994 to 2003-2013 for BMI of 25 to 29.9 and BMI of 30 or greater (eFigure 1 in the Supplement).

Figure 2. Multivariable-Adjusted Hazard Ratios for Cause-Specific Mortality in the 1976-1978, 1991-1994, and 2003-2013 Cohorts According to Body Mass Index



Solid lines are multivariable-adjusted hazard ratios, and dashed lines indicate 95% confidence intervals derived from restricted cubic spline regression with knots chosen by Akaike information criterion as described in Methods. A body mass index (BMI) of 25 was used as the reference (calculated as weight in kilograms divided by height in meters squared). There is no BMI data marker and error bar for cancer mortality because the 95% confidence intervals for the hazard ratios overlap almost the entire upper range of BMI in all 3 cohorts. The graphs are truncated at the 1st and 99th percentiles. The Cox regression was adjusted for age, sex, smoking status, cumulative tobacco consumption, alcohol consumption, leisure-time physical activity, income, and plasma cholesterol level.

Sensitivity Analyses

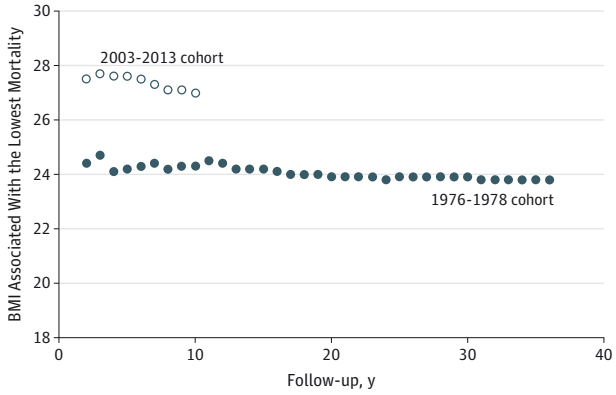
Analyses restricted to never-smokers without a history of cardiovascular disease or cancer showed different patterns in the 3 time periods, from an almost linearly increasing risk of all-cause mortality with increasing BMI in the 1976-1978 cohort to a U-shaped pattern in the 2003-2013 cohort (BMI associated with the lowest mortality, 26.1), with an intermediate pattern in the 1991-1994 cohort (eFigure 2 in the Supplement). The BMI associated with the lowest mortality in the 1976-1978 cohort was the lowest BMI value on the plot, that is, approximately 18, as the association was linear, while in the 1991-1994 cohort the 95% confidence intervals for hazard ratios overlapped 1 in almost the entire range of BMI values. In analyses stratified by age, ie, 60 years and younger and older than 60 years, the BMI associated with the lowest mortality was higher in the 2003-2013 cohort (≤60 years: 26.7, >60 years: 27.3)

compared with the 1976-1978 cohort (≤60 years: 23.5, >60 years: 24.4) (eFigure 3 in the Supplement).

In analyses where estimates were plotted according to follow-up, the estimates for the 1976-1978 cohort were parallel to the estimates for the 2003-2013 cohort for the same length of follow-up for BMI of 25 to 29.9 vs BMI of 18.5 to 24.9 and BMI 30 or greater vs BMI of 18.5 to 24.9 (eFigure 4 in the Supplement). However, for BMI of 30 or greater vs BMI of 18.5 to 24.9, estimates increased with increasing length of follow-up.

The distribution of BMI, waist-hip ratio, and waist circumference was different between the cohorts with higher BMI and waist circumference in 2003-2013, but lower waist-hip ratio for men (eFigure 5 in the Supplement). Mean height increased across the 3 cohorts; therefore, height-adjusted analyses were carried out; the results were similar to height-unadjusted analyses (eFigure 6 in the Supplement vs Figure 4). Also, analyses adjusted for hypertension, diabetes, and history of cardiovascular disease were carried out; however, the results were similar to the unadjusted analyses (Figure 1 vs eFigure 7 in the Supplement).

Figure 3. Body Mass Index Associated With Lowest All-Cause Mortality According to Follow-up Time in the 1976-1978 and 2003-2013 Cohorts



The 1991-1994 cohort was not included because it is not independent of the 1976-1978 cohort due to overlap of participants. Follow-up was consecutively restricted to the number of years indicated. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

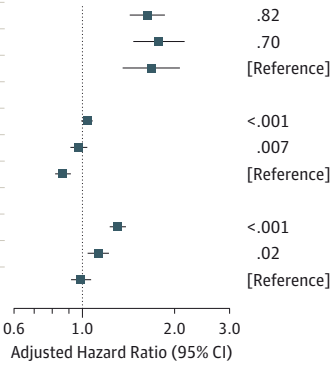
Discussion

The BMI value associated with the lowest all-cause mortality has increased by 3.3 over 3 decades from 1976-1978 to 2003-2013. Furthermore, the hazard ratio for all-cause mortality that was associated with BMI of 30 or greater vs BMI of 18.5 to 24.9 decreased from 1.3 to 1.0 over this 30-year period. These latter findings were robust in analyses stratified by age, sex, smoking status, and history of cardiovascular disease or cancer.

Usually, the controversy over the different observed associations between BMI and mortality has been ascribed to how studies handle confounding by age, sex, smoking status, and baseline disease.[1-11] However, analyses stratified for these variables did not explain the observed secular trend. Although, the pattern changed from linear to U shaped among never-smokers, this finding is compatible with the interpretation that the BMI associated with the lowest mortality has increased as the BMI associated with lowest mortality increased from approximately 18 in the 1976-1978 cohort to approximately 26 in the 2003-2013 cohort. A potential explanation for the secular trend may be that while improved treatment for cardiovascular risk factors or complicating diseases has reduced mortality in all weight classes, the effects may have been greater at higher BMI levels than at lower BMI levels.[12] Because obesity is a causal risk factor for hypertension, diabetes, cardiovascular disease, and dyslipidemia,[15,19-22] obese individuals

Figure 4. Association of Body Mass Index in Categories With All-Cause Mortality in the 1976-1978, 1991-1994, and 2003-2013 Cohorts

Cohort	No. of Participants	No. of Deaths	Mortality Rate per 1000 Person-Years (95% CI)	No. of Participants	No. of Deaths	Mortality Rate per 1000 Person-Years (95% CI)	Adjusted Hazard Ratio for All-Cause Mortality (95% CI) (Reference, BMI 18.5-24.9)	*P* Values
	BMI 18.5-24.9			BMI <18.5				
1976-1978	7044	4995	28 (18-45)	296	238	43 (24-75)	1.63 (1.43-1.86)	.82
1991-1994	4505	2018	15 (7-31)	189	119	26 (11-60)	1.78 (1.47-2.15)	.70
2003-2013	41736	2150	4 (1-11)	820	89	7 (2-28)	1.68 (1.35-2.08)	[Reference]
	BMI 18.5-24.9			BMI 25-29.9				
1976-1978	7044	4995	28 (18-45)	4761	3975	35 (24-51)	1.04 (0.99-1.08)	<.001
1991-1994	4505	2018	15 (7-31)	3391	1974	22 (12-39)	0.97 (0.91-1.04)	.007
2003-2013	41736	2150	4 (1-11)	39036	2277	4 (1-10)	0.86 (0.82-0.92)	[Reference]
	BMI 18.5-24.9			BMI ≥30				
1976-1978	7044	4995	28 (18-45)	1603	1416	46 (32-66)	1.31 (1.23-1.39)	<.001
1991-1994	4505	2018	15 (7-31)	1397	914	28 (17-47)	1.13 (1.04-1.22)	.02
2003-2013	41736	2150	4 (1-11)	15770	1064	5 (2-12)	0.99 (0.92-1.07)	[Reference]



Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and categorized using World Health Organization criteria. Estimates were derived using Cox regression adjusted for age, sex, smoking status, cumulative tobacco consumption, alcohol consumption, leisure-time physical activity, income, and plasma cholesterol level. *P* values are for comparison of the 1976-1978 and 1991-1994 estimates with the 2003-2013 estimate.

may have had a higher selective decrease in mortality.[18] Indirect evidence of this effect is seen in the findings as the deaths occur at similar time periods in the 3 cohorts, but cohorts recruited at later periods have an increase in the BMI associated with the lowest mortality, possibly suggesting a period effect related to changes in clinical practice, such as improved treatments, or general public health status, such as decreased smoking or increased physical activity. Treatment effects and public health changes could not be tested directly in these cohorts, but a similar secular trend has been noted in other cohorts.[13,31,32] As the standard WHO categories were used across all 3 cohorts to better compare the cohorts both within this study and with other studies, the differences cannot be attributed to different categorizations of BMI.[6,33] Furthermore, a lower mortality rate with a higher percentage surviving to older age could change the BMI associated with the lowest mortality as suggested in a recent meta-analysis.[10] In the present data, the difference is 1 unit or less in BMI associated with the lowest mortality for age older than 60 years vs 60 years or younger in all 3 cohorts, indicating that this is only a partial explanation.

Another interesting finding in this study is that the optimal BMI in relation to mortality is placed in the overweight category in the most recent 2003-2013 cohort. This finding was consistent in both the whole population sample (optimal BMI, 27) and in a subgroup of never-smokers without history of cardiovascular disease or cancer (optimal BMI, 26.1). If this finding is confirmed in other studies, it would indicate a need to revise the WHO categories presently used to define overweight, which are based on data from before the 1990s.[34]

This study has several strengths. First, the 3 samples from the Danish general population were drawn from the same population in Copenhagen, varying only with regard to time of recruitment. Second, the assessment and registration of covariates was almost identical in the 3 cohorts. Third, there was complete follow-up; that is, every single individual could be followed up to end of follow-up, death, or emigration. Fourth, relevant confounders had been registered, allowing for sensitivity analyses to explore the secular trends in the association of BMI with all-cause mortality in detail, to exclude that the differences were due to obvious confounders.

Potential limitations of this study include that there was different follow-up time in the 3 cohorts. Sensitivity analyses indicated that the differences between the 1976-1978 and 2003-2013 cohorts could not be explained by different follow-up time. Another limitation is that the 1976-1978 and 1991-1994 cohorts overlapped, which could raise concern regarding survivor selection bias in the latter cohort beyond that normally observed in studies of the general population. However, comparison of the 1976-1978 and 2003-2013 cohorts alone would give similar conclusions. Furthermore, the 1991-1994 cohort was supplemented with younger participants at recruitment to counter this bias. In addition, only white Danes were included, possibly restricting generalizability of the results to other ethnicities and countries with other health care settings. However, we are not aware of data to suggest that the present findings would not be applicable to most ethnicities in developed countries. The participation rate was lower in the 2003-2013 cohort compared with the older cohorts, which could indicate a greater risk of healthy participant bias compared with the older cohorts. However, for this to be a viable source of bias, a selective participation of healthier individuals in the overweight and obese groups compared with the normal weight group should be observed. Nevertheless, overall mortality statistics indicate that the 2003-2013 cohort is comparable with the overall Danish population: the crude mortality rate in Denmark was 9 per 1000 person-years (51 340 deaths; population, 5.6 million) in 2014, and the causes of death were cardiovascular in 23% and cancer in 30% of cases.[35] In the 2003-2013 cohort, the crude mortality rate was 9 per 1000 person-years, and causes of death were cardiovascular in 26% and cancer in 41% of cases. Using self-reported data, the Danish Health Authority has estimated that 47% of the population has a BMI of 25 or greater; the corresponding proportion was 56% in the 2003-2013 cohort.[36] Also, a limitation is that the question of causality cannot be addressed in an observational study, ie, whether the causal association between BMI and all-cause mortality has changed over time.

Conclusions

Among 3 Danish cohorts, the BMI associated with the lowest all-cause mortality increased by 3.3 from 1976-1978 through 2003-2013. Further investigation is needed to understand the reason for this change and its implications.

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