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ORIGINAL PAPER

Joints effects of BMI and smoking on mortality of all-causes, CVD, and cancer

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Abstract

Obesity, underweight, and smoking are associated with an increased mortality. We investigated the joint effects of body mass index and smoking on all-cause and cause-specific mortality. Data of the Third National Health and Nutrition Examination Survey (1988–1994) including mortality follow-up until 2011 were used ($n = 17{,}483$). Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause, cardiovascular disease (CVD), and cancer mortality with BMI, smoking, and their combinations as exposure, stratified by sex. Normal weight never smokers were considered as reference group. Compared to normal weight never smokers, obese and underweight current smokers were the two combinations with the highest mortality from all-causes, CVD, and cancer. Among underweight current smokers, the HR of death from all-causes was 3.49 (95% CI 2.42–5.02) and for obese current smokers 2.76 (2.12–3.58). All-cause mortality was particularly high in women who were underweight and current smoker (3.88 [2.47–6.09]). CVD mortality risk was the highest among obese current smokers (3.33 [2.98–5.33]). Cancer mortality risk was the highest among underweight current smokers (5.28 [2.68–10.38]). Obese current smokers in the middle age group (between 40 and 59 years old) had the highest risk of all-cause mortality (4.48 [2.94–7.97]). No statistically significant interaction between BMI and smoking on all-cause and cause-specific mortality was found. The current study indicates that obesity and underweight in combination with smoking may emerge as a serious public health problem. Hence, public health messages should stress the increased mortality risk for smokers who are underweight or obese. Also, health messages regarding healthy lifestyle are aimed at maintaining a healthy body weight rather than just "losing weight" and at not starting smoking at all.

Keywords NHANES III · Obesity · Underweight · Smoking · Mortality

Introduction

Obesity and smoking are common and preventable causes of disease and mortality. They have both been linked to increased risk of mortality, in large part due to the cancers and cardiovascular diseases (CVD) [1]. Strong associations between obesity and all-cause and cause-specific mortality have been reported in several large systematic reviews and meta-analyses [2, 3]. Romero-Correl et al. [4] observed in their meta-analysis that mortality risk, after adjustments for age, sex, smoking, and hypertension, increased when the BMI was above 25 kg/m^2, and if the BMI was below 20 kg/m^2. Hence, the association is described as being either linear, U-shaped, or J-shaped [4–6].

Smoking is related to a high risk of all-cause and cause-specific mortality, such as cancer and cardiovascular diseases [7, 8]. Rate of death among current smokers is about three times higher compared to people who have never

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smoked [9, 10]. Despite the fact that smoking is a strong risk factor for several chronic disease and premature mortality, some issues have arisen regarding the effects of the joint association between body weight and smoking. Some studies examined the mortality associated with BMI and smoking combined and observed a strong correlation [1, 5, 11, 12]. Current smokers that were obese had a much higher mortality risk than never smokers who were normal weight. In particular, the risk of CVD mortality increased. Underweight current smokers also had a higher chance of premature death, for both cancer and CVD [1, 11]. Other studies showed inconsistent results with respect to the relationship between smoking and BMI on mortality [12–14]. In these studies, a significantly increased mortality among light and heavy smokers who were underweight or overweight was not seen. Studies that excluded smokers from their study population found a linear association between elevated BMI and mortality, suggesting that the increased risk of mortality among underweight people was due to smoking [6, 15].

As stated above, studies looking at the joint association between BMI and smoking on mortality have inconsistent results. In particular, the joint association between underweight and smoking on mortality is not clear. Therefore, the aim of this present study was to assess the joint association between different BMI categories in combination with smoking status with the risk of all-cause and cause-specific mortality in the National Health and Nutrition Examination Survey.

Materials and methods

Data collection and study population

Our analyses were based on the data of the Third National Health and Nutrition Examination Survey (NHANES III). NHANES III is a cross-sectional population-based study conducted by the National Center for Health Statistics, which is part of the Centers for Disease Control and Prevention (CDC). Participants are selected through a stratified multistage probability sample of 33,994 non-institutionalized persons. Data were collected in two phases (1988–1991 and 1991–1994). The aim of NHANES III was to gather information on the health and nutritional status of the population of the United States. Details on data collection of the NHANES III are published elsewhere [16].

For this study, data from the NHANES III exam file population 18 + years old were analyzed ($n = 17{,}752$). These data were linked to the National Death Index (NDI) mortality file with follow-up until December 2011. We excluded participants with missing data on mortality ($n = 14$), BMI and smoking ($n = 50$), and other covariates ($n = 205$). The final study population comprised 17,483 participants with a mean and maximum follow-up time of 16.6 years and 23.0 years, respectively.

Mortality

Ascertainment of end points was determined from the NHANES III prospective cohort mortality study. From the time of study enrolment (1988–1994) to 31 December 2011, participants were followed and their vital status determined. All-cause mortality, cancer mortality, and cardiovascular disease (CVD) mortality were used for this analysis. Deaths were classified by International Classification of diseases (Cancer: ICD-9 140–208, ICD-10 C00-C97; CVD: ICD-9 390–434, and 436–448, ICD-10 100–178).

Body mass index and smoking

Weight and height were measured by trained personnel, and body mass index (BMI) was calculated based on height and weight as the ratio of weight in kilograms and height in meters squared (kg/m^2). Underweight was defined as BMI < 18.5, normal weight as BMI ≥ 18.5 and < 25, overweight as BMI ≥ 25 and < 30, and obese as BMI ≥ 30. These categories correspond to those defined by the World Health Organization (WHO).

Information on cigarette smoking was based on self-reporting. The survey asked: Have you ever smoked 100 cigarettes or more in your life? Do you still smoke? If participants answered yes to both questions, they were defined as current smoker for the purpose of this study. If their answer was yes to the first and no to the second question they were defined as a former smoker. If they answered no to both questions, they were defined as never smoker. Normal weight and never smoker as well as the combination of the two variables were used as reference groups.

Covariates

Demographic variables were included as adjustment variables based on known or suspected confounders. The following covariates were included: age (in the Cox regression models, age was included as a continuous variables; when stratifying the analyses by age, we used a categorical variable with the three categories of 18–39 years [category 1], 40–59 years [category 2], 60–90 years [category 3]); sex as collected by NHANES III (male, female); race/ethnicity as self-reported from the participants (non-Hispanic whites, non-Hispanic blacks, Mexican Americans, and others). As a proxy of socio-economic status, educational level was used and classified as less than high school diploma, high school diploma, more than high school diploma. Alcohol consumption as self-reported by the survey's participants was defined as never to < 1 drink/week; ≥1 drink/week to

< 1 drink/day; ≥ 1 drink/day. Marital status was defined as married/living together, separated/widowed, and never married. Leisure time physical activity was defined by using the following questions: "In the past month, did you: Jog or run; ride bicycle/exercise bicycle; swim; do aerobics or aerobics dancing; other dancing; other exercises; do garden/yard work; lift weights; or any other sports?" The number of activities per week was classified as: inactive (0–1 activity/week), infrequently active (1- <5 activities/week), and active (≥ 5 activities/week).

Statistical analysis

Sample weights were used to obtain estimates representative for the population because participants did not have an equal probability of selection, oversampling of minority groups, and non-response. Sample weights were implemented through the survey function in STATA.

Descriptive analyses were conducted to estimate counts, means, and proportions of the participants' characteristics. Death rates for all-cause mortality and cancer- and CVD-specific mortality were calculated by dividing the number of deaths by the total number of person-years during the follow-up period. Cox proportional hazards models were conducted to estimate hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). All models were run for the total sample, men and women separately, and for the three age categories. Firstly, a Cox proportional hazards model was performed to investigate the risk of all-cause mortality, cancer, and CVD mortality for individuals with BMI and smoking status as separate variables. Hazard ratios were estimated for the total sample and men and women separately. Depending on the investigated model, the reference group was composed of participants with normal weight (BMI ≥ 18.5 and < 25 kg/m^2) or never smokers. Secondly, a Cox proportional hazards model was performed to investigate the risk of all-cause mortality, cancer, and CVD mortality for individuals with combined categories of BMI and smoking. The model was run for the total sample, by sex and by age categories. Normal weight never smokers were the reference group. Age, sex (in the model including all study participants), education, marital status, race/ethnicity, leisure activity level, and alcohol consumption were fitted in the Cox models. Sensitivity analyses were performed to assess whether the association of BMI, smoking, and their combinations with mortality varied according to the presence or absence of prevalent diseases (cancer, heart failure, heart attack). We also examined whether the associations changed when using smoking intensity (light/moderate/heavy; instead of one category for current smokers), waist-to-hip ratio or waist circumference (instead of BMI). We tested for a multiplicative interaction effect of smoking with BMI in the models. In order to calculate cumulative HRs for different risk combinations of BMI and smoking categories, we used linear combinations of the estimated HRs from the Cox models.

All analyses were carried out using Stata™ (Stata Statistical Software: Release 13.1. College Station, TX: StataCorp LP). Final analyses were conducted in 2016.

Results

The study population ($n = 17,483$) consisted of 8,150 men and 9,333 women. During follow-up, a total of 5,351 deaths occurred, of which 1,150 were caused by cancer and 1,318 by CVD.

Baseline characteristics of the study population by BMI categories and smoking are shown in Table 1. 46% of women had a normal BMI and 55% were never smokers. Most men indicated normal weight (41%) or were overweight (39%), and smoking status was equally distributed over all three categories. Distribution of racial/ethnic groups differed by BMI group and smoking status, with non-Hispanic Blacks and Mexican Americans having more unfavorable profiles. Participants who were never married or had high school education were less likely to be overweight or obese than married or divorced or less educated participants, respectively.

BMI and smoking on all-cause mortality, CVD mortality, and cancer mortality

Table 2 shows the HR with a 95% confidence interval (CI) for BMI and smoking, including their combinations, on all-cause mortality, CVD mortality, and cancer mortality for the fully adjusted model. Obesity, but not overweight was associated with increased all-cause and cause-specific mortality in the total sample; this association was statistically significant in the total sample and in women separately. Also, former and current smokers were more likely to die prematurely, which was seen for the total sample and men and women only.

In the total sample, underweight participants had a significantly higher all-cause mortality risk independent of smoking status than normal weight never smoking participants (Table 3). Underweight men only had a significantly higher mortality risk when they were current smokers (HR 2.71 [95% CI 1.72–4.27]; Table 3). Underweight women had a significantly higher risk than normal weight women in all smoking categories. Among overweight participants, current smokers had a particularly increased risk of dying from all-causes, CVD, and cancer. The association between overweight and mortality of non-smoking men was inverse compared to normal weight men who never smoked (HR 0.66 [95% CI 0.52–0.86]). The mortality risk increased significantly for overweight or obese men who were current

Table 1 Baseline characteristics (% unless otherwise indicated)[a] of participants of NHANES III (1988–1994)

	BMI (kg/m^2)				Smoking status		
	< 18.5	≥ 18.5–<25	≥ 25–<30	≥ 30	Never	Former	Current
	n = 507	*n* = 7,675	*n* = 5,560	*n* = 3,741	*n* = 8,147	*n* = 4,388	*n* = 4,948
Prevalence (%)	2.9	43.9	31.8	21.4	46.6	25.1	28.3
Sex: mean age (SD)							
Male: 47.2 (0.3) *n* = 8,150	1.3	41.2	38.7	18.8	37.3	30.9	31.8
Female: 44 (0.2) *n* = 9,333	4.3	46.4	25.5	23.8	55.2	19.7	25.1
Age categories							
18–39	3.8	52.3	27	16.9	51.6	14.2	34.2
40–59	1.8	36.2	34.4	27.6	39.7	31.6	28.7
60–90	2.3	36.1	38.7	22.9	45.2	40	14.8
Ethnicity							
Non-Hispanic white	2.8	44.9	31.8	20.5	43.5	27.8	28.7
Non-Hispanic black	2.7	37.8	31.6	27.9	52.3	15.3	32.4
Mexican American	1.5	36.3	37.2	25	58	19.6	22.4
Others	4.2	48.6	28.6	18.6	62.3	16	21.7
Marital status							
Married	2	41	34.4	22.6	43.2	28.8	28
Divorced/widowed	2.9	42	30	25.1	43.2	26.3	30.5
Never married	6	55.7	24.4	13.9	61.4	11.4	27.2
Leisure time physical activity							
Inactive	2.8	38.7	32.6	25.9	45.3	25.2	29.5
Infrequently active	2.7	46.3	32.4	18.6	45.5	24.1	30.4
Active	3.3	51.9	29.4	15.4	50.9	25.9	23.2
Alcohol intake							
Never	3.2	39.2	31.5	26.1	54.1	24.1	21.8
≤ 1 drink/week	2.5	45.3	31	21.2	46.8	24.1	29.1
> 1 drink/week to < 1 drink/day	2.5	50.5	32.2	14.8	38.5	24	37.5
≥ 1 drink/day	3.4	47.6	35.4	13.6	25.2	38	36.8
Education							
< High school	1.4	36.3	37	25.3	54.2	23.7	22.1
High school	2.7	41.2	32	24.1	40.4	23.7	35.9
> High school	3.3	48.6	30.9	17.2	54	27	19

NHANES National Health and Nutrition Examination Survey, *SD* standard deviation, *BMI* body mass index

[a]Percentages were obtained using sampling weights

smokers. Obese women had a higher risk of mortality in all smoking categories. Obese current smokers in the middle age group (40–59 years old) had the highest risk of all-cause mortality (4.48 [2.94–7.97]). But there was no statistically significant interaction between smoking and BMI.

Obesity and smoking were independent risk factors for dying from CVD and cancer (Table 2). Overweight or obesity combined with current smoking were linked to CVD and cancer mortality in both men and women (Table 3). In the total sample, individuals with obesity had an increased mortality risk for all-causes, CVD, and cancer, independent of smoking status. The mortality risk of CVD of obese current and former smoking men increased significantly. Obese women who were current smokers also had a significantly increased mortality risk for CVD. The mortality risk for cancer increased significantly for obese current and former smoking men and women. Underweight smokers had an increased risk of dying from cancer, but due to the small numbers confidence intervals are wide.

Table 2 Hazard ratios (HR) of death from all-causes, CVD, and cancer, according to BMI and smoking; NHANES III 1988–1994

	Men			Women			All participants		
	All-causes	CVD	Cancer	All-causes	CVD	Cancer	All-causes	CVD	Cancer
Number of deaths	2,825	734	645	2,526	584	505	5,351	1,318	1,150
Number of participants per group	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Underweight[a] $n=507$	1.51 (1.06–2.17)	1 (0.55–1.82)	1.46 (0.70–3.07)	1.78 (1.29–2.46)	1.42 (0.60–3.35)	1.52 (0.73–3.18)	1.67 (1.29–2.16)	1.26 (0.67–2.39)	1.55 (0.88–2.75)
Normal weight[a] $n=7,675$	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Overweight[a] $n=5,560$	0.81 (0.71–0.91)	0.93 (0.72–1.19)	0.78 (0.59–1.01)	1.07 (0.94–1.22)	0.98 (0.75–1.29)	1.17 (0.85–1.61)	0.92 (0.84–1.01)	0.96 (0.80–1.16)	0.92 (0.75–1.13)
Obese[a] $n=3,741$	1.1 (0.93–1.30)	1.31 (0.96–1.80)	1.12 (0.80–1.55)	1.33 (1.14–1.54)	1.45 (1.07–1.95)	1.59 (1.16–2.17)	1.2 (1.08–1.34)	1.37 (1.12–1.70)	1.31 (1.05–1.66)
Never smoker $n=8,147$	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Former smoker $n=4,338$	1.3 (1.10–1.50)	1.35 (1.04–1.74)	1.57 (1.15–2.16)	1.36 (1.99–1.55)	1.15 (0.87–1.52)	1.77 (1.29–2.44)	1.33 (1.21–1.46)	1.25 (1.04–1.49)	1.82 (1.46–2.28)
Current smoker $n=4,948$	1.9 (1.60–2.30)	2.06 (1.49–2.86)	2.8 (1.90–4.05)	2.33 (1.96–2.77)	2.33 (1.67–3.27)	3.41 (2.50–4.64)	2.17 (1.92–2.46)	2.14 (1.69–2.71)	3.3 (2.60–4.20)

NHANES National Health and Nutrition Examination Survey, *CVD* cardiovascular disease, *BMI* body mass index, *HR* hazard ratio, *CI* confidence interval

Adjusted for age, alcohol, race, marital status, education, activity

[a]Underweight (BMI: < 18.5 kg/m^2); normal weight (BMI: ≥ 18.5–<25 kg/m^2); overweight (BMI: ≥ 25.0–<30 kg/m^2); obese (BMI: ≥ 30 kg/m^2)

Sensitivity analyses

We performed sensitivity analyses with the exclusion of participants with cancer, heart failure, and heart attack at baseline, for all performed analyses (results not shown). A major change in the results was not observed. Only when we excluded prevalent diseases, we observed a statistically significant interaction between smoking and BMI on CVD mortality; the risk estimates, however, did not change appreciably ($P=0.031$; details not shown). Other sensitivity analyses with inclusion of smoking intensity, waist-to-hip ratio, and waist circumference led to similar results as the original analyses (results not shown).

Discussion

In this large population-based study, we examined the joint associations of BMI and smoking status on mortality. The coexistence of obesity or underweight with current smoking was associated with a higher risk of mortality compared to normal weight never smokers. In line with other studies, there was an increased mortality risk at both extremes of the BMI range [2, 3, 6, 17]. The association of obesity or underweight in combination with smoking on mortality suggested a U- or J-shaped association. We only found a statistically significant interaction effect between smoking and BMI on CVD mortality when we excluded prevalent diseases from our analyses.

Consistent with our findings, both smoking and obesity are independent risk factors for premature death, and the combination of obesity and smoking results in an exponentially increased mortality risk [1, 18, 19]. The study of Freedman et al. (2006) [1] was one of the first reports which provided an association between the combination of obesity and current smoking on mortality risk. They came to the conclusion that combining smoking with obesity poses high mortality risks. Another study showed that a coexistence of current smoking with obesity was associated with an especially high risk of death [11]. Meyer et al. (2015) [10] recommended for persons with obesity to quit smoking, because the combination of smoking with

Table 3 Hazard ratios (HR) of death from all-causes, CVD, and cancer, according to smoking and BMI categories; NHANES III 1988–1994

BMI category	Men				Women				All participants			
	Underweight[b]	Normal[b]	Overweight[b]	Obese[b]	Underweight[b]	Normal[b]	Overweight[b]	Obese[b]	Underweight[b]	Normal[b]	Overweight[b]	Obese[b]
Smoking status	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
All-causes												
Never	2.31 (0.96–5.59)	1 (ref.)	0.66 (0.52–0.86)	0.93 (0.68–1.27)	1.59 (1.06–2.34)	1 (ref.)	1.03 (0.87–1.22)	1.34 (1.12–1.61)	1.65 (1.15–2.37)	1 (ref.)	0.9 (0.78–1.03)	1.19 (1.02–1.39)
Former	1.1 (0.59–2.04)	1.13 (0.89–1.43)	0.94 (0.75–1.17)	1.22 (0.95–1.58)	3.67 (1.14–11.82)	1.36 (1.1–1.7)	1.51 (1.22–1.87)	1.62 (1.29–2.04)	2.39 (1.10–5.16)	1.35 (1.15–1.59)	1.22 (1.05–1.41)	1.51 (1.28–1.78)
Current	2.71 (1.72–4.27)	1.65 (1.28–2.14)	1.48 (1.11–1.93)	2.05 (1.43–2.93)	3.88 (2.47–6.09)	2.2 (1.74–2.77)	2.5 (1.89–3.30)	3.27 (2.23–4.80)	3.5 (2.43–5.02)	2.06 (1.74–2.44)	2 (1.66–2.43)	2.76 (2.11–3.59)
p interaction[a]	0.12				0.78				0.7			
CVD												
Never	0.58 (0.12–2.90)	1 (ref.)	0.91 (0.56–1.47)	0.88 (0.47–1.64)	1.9 (0.76–4.77)	1 (ref.)	0.83 (0.59–1.16)	1.42 (0.10–2.02)	1.7 (0.73–3.88)	1 (ref.)	0.87 (0.66–1.15)	1.22 (0.90–1.65)
Former	2.35 (1.16–4.78)	1.31 (0.82–2.05)	1.05 (0.69–1.61)	1.62 (1.01–2.61)	Undetermined	1.23 (0.79–1.90)	1.16 (0.72–1.88)	1.37 (0.84–2.24)	1.38 (0.68–2.8)	1.29 (0.95–1.72)	1.1 (0.82–1.45)	1.54 (1.11–2.13)
Current	1.07 (0.27–4.28)	1.56 (0.92–2.63)	1.85 (1.09–3.13)	3.12 (1.63–5.96)	2.82 (0.63–12.58)	1.65 (0.91–2.99)	2.84 (1.67–4.83)	3.59 (1.83–7.05)	2 (0.59–6.81)	1.61 (1.11–2.34)	2.21 (1.53–3.18)	3.33 (2.08–5.33)
p interaction[a]	0.06				0.35				0.06			
Cancer												
Never	0.79 (0.15–4.00)	1 (ref.)	0.78 (0.42–1.42)	1.27 (0.58–2.79)	0.67 (0.20–1.86)	1 (ref.)	1.15 (0.73–1.8)	1.71 (1.10–2.66)	0.67 (0.25–1.76)	1 (ref.)	0.99 (0.7–1.43)	1.52 (1.03–2.23)
Former	0.79 (0.15–4.00)	1.53 (0.85–2.76)	1.32 (0.77–2.72)	1.84 (1.01–3.35)	9.94 (2.35–42.07)	2.04 (1.17–3.56)	1.94 (1.14–3.39)	2.32 (1.36–3.94)	6 (1.53–23.7)	2.03 (1.38–3)	1.8 (1.27–2.55)	2.33 (1.59–3.40)
Current	6.05 (2.34–15.68)	3.07 (1.72–5.49)	2.12 (1.10–4.07)	2.9 (1.36–6.17)	4.29 (1.74–10.55)	3.08 (1.92–4.94)	4.38 (2.6–7.41)	5.95 (3.49–10.14)	5.27 (2.68–10.38)	3.5 (2.45–5)	3.15 (2.10–4.74)	4.8 (3.08–7.48)
p interaction[a]	0.37				0.81				0.6			

Adjusted for age, alcohol, race, marital status, education, activity

NHANES National Health and Nutrition Examination Survey, *CVD* cardiovascular disease, *BMI* body mass index, *HR* hazard ratio, *CI* confidence interval

[a]*P* for interaction between BMI, smoking, and mortality was performed by Wald test

[b]Underweight (BMI: <18.5 kg/m^2); normal weight (BMI: ≥18.5– <25 kg/m^2); overweight (BMI: ≥ 25.0– <30 kg/m^2); obese (BMI: ≥ 30 kg/m^2)

obesity lead to a higher risk for cancer. A possible explanation for this association between smoking and obesity on mortality could be that smokers are more likely to have unhealthy lifestyle habits. They tend to have low leisure time physical activity and a lower consumption of fruit and vegetables [20]. These unhealthy behaviors favor weight gain. Obese heavy smokers in particular tend to have a poor general lifestyle [21]. Smoking and obesity are both associated with insulin resistance, higher blood pressure, and an increased level of stress hormones [22]. This may result in higher risk of CVD and various types of cancer [15]. Several studies have reported obesity as a risk factor for various cancers [3, 23, 24]. This may be due to insulin resistance and a chronic, subclinical inflammation in the visceral fat [24, 25]. As our study showed, the mortality risk of cancer is especially elevated in obesity when it occurs combined with current smoking.

As reflected in our results, the relationship between underweight and a higher mortality risk is mostly explained by the confounding effect of smoking [15, 26]. In this study, we observed significantly higher mortality for current smokers and former smokers with underweight. In line with our study, Pednekar et al. (2007) [5] showed in their study from India, that tobacco use and underweight had multiplicative joint effects on mortality. Ma et al. (2013) [11] came to the conclusion that current smokers with underweight were at high risk of death. Smokers tend to be leaner compared to never smokers. On average, male smokers tend to be 1 BMI unit and female smokers 1.5 BMI units lighter than non-smokers [15]. Smoking is a risk factor for respiratory disease, smoking-related cancers, and impaired kidney function [3, 27]. We also found a moderately increased all-cause mortality risk in participants with underweight who never smoked. Other studies also showed that after excluding smoking from the analysis, underweight participants still had an increased risk of all-cause mortality [5, 13, 26, 28]. An explanation for these findings may be pre-existing diseases at baseline. When studies excluded underweight participants with underlying diseases, current smokers, and those who died within the first 5 years of follow-up, they found no significant associations between underweight and all-cause mortality [26, 29]. In our study, we observed an elevated all-cause mortality for older participants (60 to 90 years old) with underweight who never smoked. Older participants are more likely to carry chronic diseases and comorbidities, leading to low BMI, which may have biased the results.

A statistically significant interaction effect between smoking and BMI on mortality was not observed in this study. Several other studies have also been unable to see an interaction effect [12, 30, 31]. It is possible that smoking potentiates the effects of cardiovascular risk factors, like dyslipidemia, hypertension, or insulin resistance [23]. This could explain the interaction effect we found between smoking and BMI on CVD mortality in the sensitivity analyses.

Strengths and limitations

NHANES III is a large, representative, well-standardized, and controlled survey that follows up to 23 years on vital status. Results can be generalized to the US population. Though the sample size was large, there was high variability. Due to the small sample size of the underweight participants, and particularly former smokers with underweight, the estimates were imprecise. In this study, different known confounders were included. Mortality risks in never smokers with obesity and underweight might be explained by socio-economic status (SES). A higher SES may have a positive impact on diet, exercise, and coping with daily stressors, which can prolong life [32–34]. We are confident that we have taken the most important confounders into account. Nevertheless, confounding due to unknown or unmeasured factors cannot be excluded. For example, we only included the absence of cancer, heart attack, and heart failure into the sensitivity analyses, but other pre-existing diseases, such as diabetes or chronic obstructive pulmonary disease at baseline could have biased the results. Especially, in participants with underweight, pre-existing diseases could have played an important role in the increased mortality risk. On the other hand, it is not known if these diseases induced weight loss before baseline and whether such weight loss biased the results. Dividing smokers into light, moderate, and heavy categories in the sensitivity analyses gave us in-depth information about the dose–response effect of smoking on mortality in the different BMI categories. Heavy smoking is associated with bad lifestyle habits and can lead to a lower BMI or higher BMI [22, 35]. Some studies showed an increased body weight to obesity level among heavy smokers [36, 37]. Although the results did not change when we included smoking intensity into the analyses, misclassification could have occurred. Information about smoking intensity in the NHANES III data was based on self-reporting, and people mostly underreport their smoking habits, which could have led to an over- or underestimation in the results.

A strength of this study was that information about BMI was based on height and weight measured in a standardized way. Thereby, measurement bias and misclassification of subjects in the wrong BMI category was minimized. Still, most of the information in this study, like smoking status, was given by self-reporting, which induced measurement and recall error. In general, there is a growing debate about possible needs for different BMI cut-off points. The BMI categories are defined independently of age, sex, and ethnicity. There is growing evidence that due to different body proportions, BMI may not correspond to the same percentage of body fat and body fat distributions

in all ethnic groups [38, 39]. For example, the proportion of overweight and obesity is lower in Asian Americans, but their mortality risk is increased [40]. Some degree of misclassification in this study is therefore inevitable. Although BMI is correlated with more direct measurements of body fat, it does not directly measure adiposity or lean body mass. Elderly people tend to have an increase in waist-to-hip ratio, because body fat shifts from peripheral to central sites without an increase in BMI [39, 41]. Therefore, we took waist-to-hip ratio and waist circumference into account in the sensitivity analyses. Finally, there is no information about changes over time as measurements were taken at baseline. Changes in weight and smoking during follow-up may have had an impact on the mortality risk. There were no data available on the duration of quitting for former smokers at baseline and no data on current smokers who had quit during the follow-up period. Thus, we could not examine the effects of the duration of quitting and compare smokers who quit with those who did not during follow-up. Also, in these data, we had no information about passive smoking. This could have led to over- or underestimation of the risk of mortality. Last, but not least, we conducted a larger number of statistical analyses and cannot exclude chance as an alternative explanation for some of the significant associations we observed; additionally, the number of underweight participants is small, leading to wide confidence intervals.

Conclusion

The combination of underweight and obesity with current and former smoking was related to a particularly high mortality from all-causes, CVD, and cancer. The often suggested U-shaped or J-shaped association between body weight/BMI and mortality, however, was seen among all groups of smoking behavior. Even when we excluded prevalent diseases from our analyses, a higher mortality risk for smokers with underweight still existed, especially for cancer. Although all smokers should be better informed about cessation programs, the results of our analysis point out that smokers with high or low BMI should be particularly targeted for smoking cessation programs. Public health messages should better inform smokers with low or high BMI about their increased mortality risk.

Author contributions EL collected, analyzed, and interpreted study data. EL wrote the first draft of the manuscript. SR, TL, and DF critically revised and improved the content of the manuscript. All authors read and improved the final manuscript.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

Informed consent Informed consent was obtained from all participants when participating in NHANES III.

Ethical approval The protocols for the conduct of NHANES III were approved by the institutional review board of the National Center for Health Statistics, US Centers for Disease Control and Prevention.

Data sharing statement No additional unpublished data from the study are available. However, NHANES data are publically available.

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