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Association of Obesity with cardiovascular disease mortality in the PLCO trial

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Abstract

Background—Obesity is a risk factor for cardiovascular disease (CVD) mortality, but the association between obesity and specific causes of CVD mortality are still under investigation.

Method—We prospectively examined body-mass index (BMI) in relation to CVD-specific causes of death in approximately 86,000 US men and women in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, followed for up to 13 years. BMI was calculated from self-reported weight and height at baseline. Hazard ratios (HRs) were calculated overall and stratified by sex, smoking status, and educational level.

Result—Overweight non-obese participants (BMI: 25.0–29.9) were not at excess risk for CVD mortality (HR and CIs are 1.02 [0.92–1.13], compared to participants of normal BMI (18.5–24.9). Excess CVD mortality was observed for participants of BMI 30.0–34.9 (HR and CIs: 1.29 [1.13–1.48], BMI 35.0–39.9 (HR and CIs: 1.87 [1.51–2.32]) and BMI 40.0+ (HR and CIs: 2.21 [1.57–3.21]) ($p<0.001$ for trend). BMI was unrelated to mortality due to stroke. The observed association of BMI with CVD was independent of gender, smoking status and educational level.

Conclusion—Obesity is associated with increased mortality due to CVD.

Introduction

Increased body-mass index (BMI), reflecting excess adiposity, is a well-documented risk factor for cardiovascular disease (Berrington de Gonzalez et al., 2010; Czernichow et al., 2011; de Koning et al., 2007; Larsson et al., 1984; Whitlock et al., 2009). Adiposity-associated risk may be explained by the relationship of elevated BMI with the risk-enhancing dyslipidemias, including elevated triglycerides, lower HDL-C, and increased small, dense LDL particles. Chronic inflammation in conjunction with dislipidemia, may also contribute to endothelial dysfunction and macrovascular changes, leading to the development of cardiovascular disease (Austin et al., 1998; Garber and Avins, 1994).

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The overall relationship of BMI with CVD mortality is established, however; there is uncertainty about the specific types of CVD most strongly related to excess weight (Kurth et al., 2005; Lenz et al., 2009; Mhurchu et al., 2004; Rexrode et al., 1997; Song et al., 2004), the gender-specificity of the relationships, and the potential effect modification of the BMI —CVD mortality relationship by smoking (Adams et al., 2006; Berrington de Gonzalez et al., 2010) or educational status (Wang et al., 2011; Winkleby et al., 1992).

In a large prospective study, we characterized BMI (calculated as weight in kilograms divided by height in meters squared) into six categories (including a morbidly obese group, BMI 40.0+) and examined BMI in relation to cardiovascular disease mortality overall and for specific causes of cardiovascular disease mortality. We also explored whether associations of obesity with cardiovascular disease differ according to gender, smoking status and educational levels.

Methods

Study Population

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, a large randomized controlled multicenter trial in the United States, was designed to evaluate selected methods for the early detection of these four cancers. The study enrolled approximately 155, 000 men and women from November 1993 to June 2001, ages 55 and 74, at sites in Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St Louis, MO; and Washington, DC. All participants were followed up to December 31, 2009. The institutional review boards of the U.S. National Cancer Institute and the 10 Study Centers approved the trial, and all participants provided written informed consent. Detailed information on the methods have been provided elsewhere (Ahn et al., 2009; Gohagan et al., 2000; Hayes et al., 2005; Prorok et al., 2000). For this investigation, participants were selected who completed a baseline questionnaire, who had no history of CVD (heart attack, hypertension or stroke), who had no personal history of cancer other than basal cell skin cancer prior to study entry, and who had a BMI between 15 kg/m^2 and 60 kg/m^2, resulting in a study population of 85,949 PLCO Trial participants. Participants with BMI < 15 kg/m^2 or >60kg/m^2 were excluded as outliers likely due to misreporting or miscoding of height or weight.

Body Mass Index

Body-mass index (BMI), a measure of adiposity was calculated from self-reported weight and height at baseline and categorized in six groups (i.e.<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–40.0, > 40.0), that incorporated the definitions of underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), and obesity (>30.0) proposed by the World Health Organization(1995). In all analysis, the BMI category of 18.5–24.9 was considered the reference group.

Mortality end point

The end points in our analysis were deaths from all cardiovascular disease (codes 390 to 459 of International Classification of Diseases, Ninth Revision [ICD-9]) and selected specific cardiovascular disease. Follow-up was censored at study withdrawal, last annual questionnaire, the 13th year of follow-up, or end of study through December 31, 2009, whichever came first. Specific cardiovascular diseases were ascertained from death certificates or medical records and was coded according to the ICD-9, including ischemic heart disease (ICD-9 codes 410-414); acute myocardial infarction (AMI) (ICD-9 codes 410); heart failure (ICD-9 code 428); heart rhythm disturbance (ICD-9 codes 426,427);

hypertensive disease (ICD-9 code 401-404) and stroke (cerebrovascular accident) (ICD-9 code 430-438).

Statistical analysis

Multivariable-adjusted mortality was calculated for each category of BMI. Cox proportional-hazard models, with attained age as the underlying time variable, were adjusted for sex, age (<65,65+), race (white, black, hispanic, others), study arm, study centre, educational level (12 years or less of education, post high school or some college, college graduate or postgraduate), smoking status (never, ever), history of diabetes, physical activity (none, less than 1 hour/week, 1 hour/week, 2 hours/week, 3 hours/week, 4^+ hours/week). In addition, we also carried out stratified analyses for sex (male, female), smoking status (never /ever),and educational level (12 years or less or completed high school, post high school or some college, college graduate or postgraduate). We carried out trend tests to investigate the relationship of overweight (BMI of 25.0–29.9) and obesity (BMI ≥ 30.0) to CVD mortality, in comparison to normal subjects (BMI of 18.5–24.9), with the score for each category based on the median level of BMI in the category. The likelihood ratio test χ^2 was used to test for interaction of sex, smoking and educational level with BMI in relation to death from cardiovascular disease. In a sensitivity analysis, we evaluated the BMI—CVD mortality relationship after exclusion of mortality experience in the first two years of follow-up. All analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, North Carolina). All statistical tests were 2 sided and the tests were considered statistically significant at the p <.05 level.

Result

Characteristics of the study cohort

Among 85,949 people in this study, 51.6% were women. The median age at baseline of subjects was 61.00 years old, the median BMI was 25.90 kg/m^2, 43.7% reported that they had never smoked and 11.1% reported that they were current smokers. A total of 2,065 CVD deaths were reported during up to 13-years of follow-up (median: 12.3 years). The prevalence of current smoking decreased with increasing BMI and obese individuals tended to be younger, female, and have less education (Table 1).

BMI and cardiovascular diseases mortality

The multivariate HRs for cardiovascular disease mortality increased with increasing BMI, compared to the reference normal body size of BMI 18.5–24.9 (p<0.001 for trend) (Table 2), although risks were also elevated in subjects below normal body size (BMI<18.5), compared to the referent. Overweight (BMI 25.0–29.9) was not associated with an increased risk in our study ((HR 1.02, CIs: 0.92–1.13). Compared to referent normal participants (BMI: 18.5–24.9), our study showed increasing risks with increasing BMI for specific causes of cardiovascular disease, except for stroke (p for trend 0.56). Risks among those with the greatest BMI (40.0+) were particularly strong for heart failure (HR 7.29, CI: 2.41–22.10) and hypertensive disease (HR 4.91, CI: 1.38–17.52). Sensitivity analyses carried out by excluding person-time and deaths that occurred within the first 2 years of follow-up showed similar results (data not show).

BMI and cardiovascular disease in stratified analysis

Risks for cardiovascular disease mortality were similar in smokers and nonsmokers ($P_{interaction}$=0.71) (Table 3 and Figure 1). No clear differentials were observed between BMI and cardiovascular disease mortality by sex ($P_{interaction}$=0.56) or educational level ($P_{interaction}$=0.47), although BMI—CVD mortality relationships tended to be stronger in subjects with more education (Table 3).

Discussion

In this prospective study, obesity was strongly associated with risk of death from cardiovascular disease, as also reported in a large pooling study, including participants in the PLCO Trial (Berrington de Gonzalez et al., 2010). Our study showed that these excesses are observed for several specific causes of cardiovascular mortality, including heart failure and hypertensive disease in morbidly obese study participants (BMI 40.0+). We found, however, no evidence of a BMI association with stroke mortality. Excess risks for cardiovascular disease overall or for specific types were not identified in non-obese, overweight participants (BMI 25.0–29.9). Our study also indicated that BMI—cardiovascular disease relationships tended to be non-significantly stronger in people with higher educational level, while no evidence of effect modification was found with respect to gender or smoking.

We did not identify excess risks for cardiovascular mortality in the non-obese, overweight. There is some uncertainty about the relationship of overweight (BMI 25.0–29.9) with cardiovascular disease mortality (Adams et al., 2006; Flegal et al., 2007; McGee, 2005), although several large studies have reported significant, if modest, effects (Adams et al., 2006; Berrington de Gonzalez et al., 2010 Zheng, 2011 #60; Flegal et al., 2007; McGee, 2005; Sasazuki et al., 2011; Whitlock et al., 2009; Batty et al., 2006). Overall, it appears that the non-obese, overweight experience modest excesses in CVD mortality, compared to subjects of normal weight.

Several studies indicate that obesity is related to excess mortality from stroke, particularly for ischaemic rather than hemorrhagic stroke (Kurth et al., 2005; Manson et al., 1990; Park et al., 2008; Rexrode et al., 1997; Whitlock et al., 2009; Zheng et al., 2011). Our study showed no BMI-associated differential in stroke mortality, possibly because we could not evaluate risk for ischaemic and hemorrhagic stroke separately, due to small numbers. Other studies have reported BMI-associated excess risks for heart failure and hypertensive disease (Kenchaiah et al., 2002; Whitlock et al., 2009), consistent with our findings.

National patterns of increasing obesity are largely a consequence of technological changes in food preparation practices and greater availability of cheaper, high caloric food (Swinburn et al., 2011), resulting in chronic energy excess in relation to increasingly limited physical activity (Gortmaker et al., 2011). Diet, physical activity and patterns of weight gain are influenced by complex life styles factors which could also play a role in relation to obesity and CVD (Buttar et al., 2005). Smoking could also modify the relationship between BMI and risk of death from cardiovascular disease (Lahti-Koski et al., 2002; Yusuf et al., 2004). Educational level, an indicator of socioeconomic status, could also distort the relation between BMI and cardiovascular disease mortality (Wang et al., 2011; Winkleby et al., 1992). Our stratified analyses address these potential effect modifiers, showing no overall impact, although noting modest differentials in risk by educational status.

Our study has limitations. BMI was calculated from self-reported height and weight and could be affected by imprecise measurements and misclassification (Chiolero et al., 2007; Connor Gorber et al., 2007), although correlations between self-reported and measured weight and height are generally high (Spencer et al., 2002; Stewart, 1982). Additionally, waist-to-hip ratio and other anthropometric measures unavailable for our study may provide additional insight about adiposity-related cardiovascular disease mortality (Kizer et al., 2010; Wormser et al., 2011). Our study had strengths in that we reported on all and specific causes of cardiovascular disease mortality in a large cohort and evaluated the potential effect-modifying impact of gender, smoking and educational level.

In summary, our findings indicate that obesity is associated with elevated risk of death from all cardiovascular disease and from major specific causes of cardiovascular disease.

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Important potential effect modifiers of the observed BMI—CVD mortality relationship did not explain the observed associations in our study.

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Highlights

- We prospectively examined body-mass index (BMI) in relation to cardiovascular disease (CVD)-specific causes of death in approximately 86,000 US men and women, followed for up to 13 years.
- Obesity is associated with increased mortality due to CVD.
- The observed association of BMI with CVD was independent of gender, smoking status and educational level.

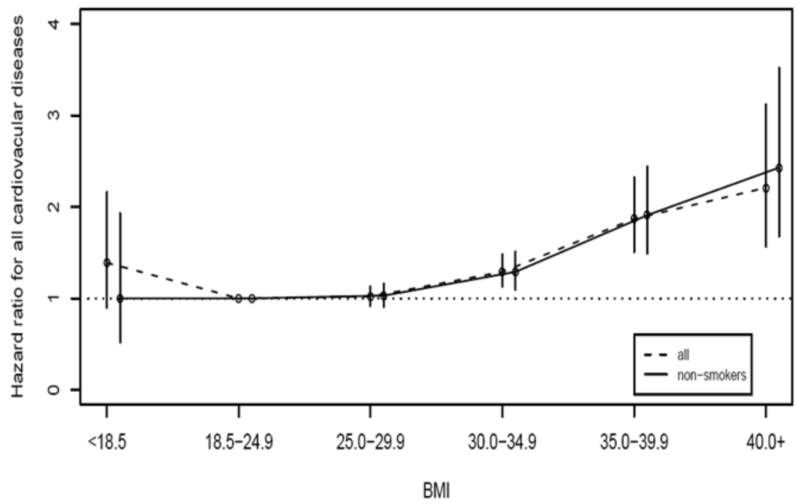

Figure 1. Hazard Ratios for Deaths from Cardiovascular Disease, according to Body-Mass Index, for All Study Participants and for Healthy Subjects Who Never Smoked

Hazard ratio and 95% confidence intervals were shown for all participants and non-smokers. The hazard ratios were stratified by smoking status and adjusted by sex, age (<65, 65+), race (white, black, hispanic, others), study arm, study center, educational level (<=high school, some college, above college), history of diabetes, and physical activity (None, less than 1 hour/week, 1 hour/week, 2 hours/week, 3 hours/week, 4+ hours/week).

Table 1

Baseline Characteristics of Participants and levels of BMI

	Body Mass Index					
	<18.5 (N=737)	**18.5–24.9 (N=33025)**	**25.0–29.9 (N=36484)**	**30.0–34.9 (N=11899)**	**35.0–39.9 (N=2851)**	**>=40.0 (N=953)**
Age, years	63.5	62.3	62.0	61.4	60.8	60.4
Gender, %						
Female	578 (78.4)	20394 (61.8)	15260 (41.8)	5674 (47.7)	1755 (61.6)	712 (74.7)
Male	159 (21.6)	12631 (38.3)	21224 (58.2)	6225 (52.3)	1096 (38.4)	241 (25.3)
Smoking status, %						
Never	357 (48.4)	15615 (47.3)	15073 (41.3)	4842 (40.7)	1187 (41.6)	449 (47.1)
Current	172 (23.3)	4373 (13.2)	3672 (10.1)	1050 (8.8)	239 (8.4)	65 (6.8)
Past	197 (26.7)	12137 (36.8)	16030 (43.9)	5536 (46.3)	1326 (46.5)	442 (44.3)
Cigar/Pipe only	11 (1.5)	893 (2.7)	1703 (4.7)	468 (3.9)	97 (3.4)	17 (1.8)
Race, %						
White, Non-Hispanic	619 (84.0)	29701 (89.9)	33294 (91.3)	10857 (91.2)	2557 (89.7)	839 (88.0)
Black, Non-Hispanic	19 (2.6)	758 (2.3)	1179 (3.2)	555 (4.7)	182 (6.4)	79 (8.3)
Hispanic	8 (1.1)	537 (1.6)	731 (2.0)	248 (2.1)	65 (2.3)	20 (2.1)
Other	91 (12.4)	2029 (6.1)	1280 (3.5)	239 (2.0)	47 (1.7)	15 (1.6)
Educational level, %						
12 years or less	193 (26.2)	8339 (25.3)	10525 (28.4)	3896 (32.8)	966 (33.9)	337 (34.4)
Post high school	252 (34.2)	10750 (32.6)	12342 (33.8)	4225 (35.5)	1069 (37.5)	363 (38.1)
College graduate or postgraduate	288 (39.1)	13877 (42.0)	13551 (37.1)	3760 (31.6)	808 (28.3)	251 (26.3)
Study centre of origin, %						
Colorado	72 (9.8)	3342 (9.9)	3302 (8.8)	842 (7.0)	157 (5.5)	51 (4.9)
Georgetown	33 (4.5)	1910 (5.8)	1661 (4.6)	402 (3.4)	61 (2.3)	21 (1.9)
Hawaii	125 (17.0)	3103 (9.8)	2102 (6.1)	448 (4.1)	98 (3.4)	34 (2.8)
Henry Ford Health System	126 (17.1)	4723 (15.1)	5134 (15.1)	1959 (18.0)	552 (21.5)	230 (26.1)
Minnesota	102 (13.8)	5501 (16.2)	7262 (19.1)	2433 (18.5)	492 (16.1)	158 (13.3)
Washington	75 (10.2)	3430 (10.2)	3682 (9.9)	1214 (9.9)	313 (10.2)	89 (9.9)
Pittsburgh	65 (8.2)	3616 (10.6)	4400 (11.8)	1470 (12.1)	353 (12.2)	116 (12.8)
Utah	75 (10.2)	3368 (10.2)	3513 (9.5)	1084 (9.2)	271 (9.0)	76 (8.2)
Marshfield	44 (6.0)	2907 (8.7)	4200 (11.4)	1567 (12.9)	421 (13.6)	139 (13.0)

	Body Mass Index					
	<18.5 (N=737)	**18.5–24.9 (N=33025)**	**25.0–29.9 (N=36484)**	**30.0–34.9 (N=11899)**	**35.0–39.9 (N=2851)**	**>=40.0 (N=953)**
Alabama	20 (2.7)	1125 (3.7)	1228 (3.8)	480 (5.0)	133 (2.1)	39 (7.2)

*Number of each BMI categories may not sum up to total N due to missing values.

Table 2

Hazard Ratios for Deaths from CVD and Cause-specific CVD, according to Body-Mass Index

Categories	Body-Mass Index						P for Trend
	<18.5 (N=737)	18.5–24.9 (N=33025)	25.0–29.9 (N=36484)	30.0–34.9 (N=11899)	35.0–39.9 (N=2851)	40.0+ (N=953)	
All CVD							
No. of deaths	21	698	877	331	101	37	<0.001
Hazard ratio (95% CI)	1.39 (0.90–2.16)	1.00	1.02 (0.92–1.13)	1.29 (1.13–1.48)	1.87 (1.51–2.32)	2.21 (1.57–3.12)	
All Ichemic Heart Disease							
No. of deaths	10	285	392	157	47	13	0.080
Hazard ratio (95% CI)	0.85 (0.42–1.71)	1.00	0.99 (0.89–1.09)	1.00 (0.80–1.25)	0.93 (0.65–1.32)	1.08 (0.56–2.09)	
AMI							
No. of deaths	5	182	221	85	28	8	0.025
Hazard ratio (95% CI)	1.29 (0.53–3.16)	1.00	0.92 (0.75–1.12)	1.16 (0.89–1.52)	1.74 (1.14–2.65)	1.77 (0.86–3.65)	
Heart failure							
No. of deaths	0	30	31	14	3	4	0.009
Hazard ratio (95% CI)	0	1.00	0.87 (0.52–1.45)	1.37 (1.00–2.02)	1.67 (0.71–2.65)	7.29 (2.41–22.10)	
Heart Rhythm Disturbance							
No. of deaths	2	53	64	26	5	3	0.024
Hazard ratio (95% CI)	1.90 (0.45–7.96)	1.00	1.07 (0.73–1.55)	1.58 (0.97–2.57)	1.52 (0.60–3.88)	3.20 (0.98–10.52)	
Hypertensive Disease							
No. of deaths	1	20	27	19	6	3	0.002
Hazard ratio (95% CI)	2.27 (0.30–17.14)	1.00	0.98 (0.54–1.77)	2.12 (1.10–4.06)	2.22 (0.81–6.11)	4.91 (1.38–17.52)	
Stroke							
No. of deaths	2	145	149	35	16	3	0.563
Hazard ratio (95% CI)	0.55 (0.14–2.22)	1.00	0.94 (0.74–1.19)	0.74 (0.51–1.08)	1.54 (0.91–2.61)	0.60 (0.15–2.43)	

* The hazard ratios were calculated using age as the underlying time scale, adjusted for sex, age (<65, 65+), race (white, black, hispanic, others), educational level (<=high school, some college, above college), smoking status (never, ever), study arm, study center, history of diabetes and physical activity (None, less than 1 hour/week, 1 hour/week, 2 hours/week, 3 hours/week, 4+ hours/week).

Table 3

Hazard Ratios for Deaths from CVD, according to Body-Mass Index, Stratified by Smoking status, Gender and Educational Levels

Categories	Body-Mass Index						P for Trend	P for interaction
	<18.5	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	40.0+		
Non-smokers only								
No. of deaths	9	488	650	249	79	32	<0.001	0.71
Hazard ratio (95% CI)	1.00 (0.52–1.93)	1.00	1.03 (0.91–1.16)	1.29 (1.10–1.51)	1.91 (1.49–2.44)	2.43 (1.68–3.52)		
Males								
No. of deaths	10	412	644	226	65	10	<0.001	0.56
Hazard ratio (95% CI)	2.23 (1.19–4.18)	1.00	1.00 (0.88–1.14)	1.31 (1.10–1.55)	2.13 (1.62–2.79)	1.65 (0.87–3.10)		
Females								
No. of deaths	11	286	233	105	36	27	<0.001	
Hazard ratio (95% CI)	1.05 (0.57–1.93)	1.00	1.04 (0.87–1.24)	1.23 (0.98–1.55)	1.45 (1.01–2.08)	2.31 (1.51–3.52)		
Education level 1 ⋇								
No. of deaths	12	237	304	116	39	11	0.129	0.47
Hazard ratio (95% CI)	2.42 (1.34–4.35)	1.00	0.93 (0.78–1.11)	1.05 (0.83–1.32)	1.52 (1.07–2.17)	1.27 (0.68–2.37)		
Education level 2 ⋇								
No. of deaths	9	246	312	124	40	193.46	<0.001	
Hazard ratio (95% CI)	1.60 (0.82–3.14)	1.00	1.03 (0.87–1.23)	1.40 (1.12–1.76)	1.96 (1.38–2.79)	(2.11–5.67)		
Education level 3 ⋇								
No. of deaths	0	211	259	91	22	7	<0.001	
Hazard ratio (95% CI)	/	1.00	1.14 (0.94–1.37)	1.60 (1.24–2.07)	2.30 (1.47–3.61)	2.79 (1.30–5.99)		

⋇ Education level 1 indicated person who has 12 years or less education or completed school; education level 2 indicated person who has post high school other than college, or some college; education level 3 indicated person who is a college graduate or postgraduate.

* The hazard ratios were calculated using age as the underlying time scale, adjusted for sex, age (<65, 65+), race (white, black, hispanic, others), educational level (<=high school, some college, above college), smoking status (never, ever), study arm, study center, history of diabetes and physical activity (None, less than 1 hour/week, 1 hour/week, 2 hours/week, 3 hours/week, 4+ hours/week), except where the variable was treated as a stratifying variable.