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Eight-year change in body mass index and subsequent risk of cardiovascular disease among healthy non-smoking men

Thomas S. Bowman, MD, MPH, **Tobias Kurth, MD, ScD**, **Howard D. Sesso, ScD, MPH**, **JoAnn E. Manson, MD, DrPH**, and **J. Michael Gaziano, MD, MPH**
From the Veterans Affairs Boston Healthcare System - Massachusetts Veterans Affairs Epidemiology, Research, and Information Center (TSB, JMG); Divisions of Aging (TSB, TK, HDS, JMG) and Preventive Medicine (TK, HDS, JEM, JMG), Department of Medicine, Brigham and Women's Hospital; and the Department of Epidemiology (TK, HDS, JEM), Harvard School of Public Health - all in Boston, MA.

Abstract

Objective—To determine how change in BMI over 8 years is associated with risk of subsequent cardiovascular disease (CVD) among middle aged men.

Method—Prospective cohort study among 13,230 healthy men (aged 51.6±8.7 years) in the Physicians' Health Study. BMI was collected at baseline in 1982 and after 8 years, at which time follow-up began. Subsequent CVD events were collected and confirmed through March 31, 2005. Cox proportional hazards models evaluated BMI at 8 years and risk of CVD, 8 year change in BMI and risk of CVD, and whether change in BMI added prognostic information after the consideration of BMI at 8 years.

Results—1,308 major CVD events occurred over 13.5 years. A higher BMI at year 8 was associated with an increased risk of CVD. Compared to a stable BMI (±0.5 kg/m^2), a 0.5–2.0 kg/m^2 increase had a multivariable-adjusted RR of 1.00 (0.86–1.16). A ≥2.0 kg/m^2 increase had a multivariable-adjusted RR of 1.39 (1.16–1.68), however further adjustment for BMI reduced the RR to 1.00 (0.81–1.23). A decrease in BMI had a multivariable RR of 1.23 (1.07–1.42) which was unaffected by adjustment for BMI at 8 years.

Conclusion—A higher BMI and a rising BMI were both associated with an increased risk of CVD, however an increasing BMI did not add prognostic information once current BMI was considered. In contrast, a declining BMI was associated with an increased risk of CVD independent of current BMI.

MESH headings

Cardiovascular disease; Body mass index; Prospective studies; Risk factors

Corresponding author and requests for reprints: Thomas S. Bowman, MD MPH, VA Boston Healthcare System, Division of Aging; Brigham and Women's Hospital, 1620 Tremont Street, Boston, MA 02120, Phone: 617-525-7811; Fax: 617-525-7739, Email: tsbowman@partners.org.

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Introduction

As rates of overweight and obesity continue to increase in the United States (Ogden et al., 2006) and worldwide, (Joint WHO/FAO expert consultation, 2003) the burden of disease from excess weight is becoming substantial (Allison et al., 1999) and may soon reduce life expectancy (Olshansky et al., 2005, Ezzati et al., 2002). While obesity has been consistently associated with an increased risk of cardiovascular disease (CVD), (McGee, 2004, Joint WHO/FAO expert consultation, 2003) few studies have evaluated whether the consideration of long-term change in BMI may provide additional information in the prediction of CVD.

Prior observational studies have supported the idea that the lowest risk of CVD may be among those with a stable weight (Harris et al., 1997, Diaz et al., 2005, Wannamethee et al., 2005) while both weight loss and gain have been associated with a poorer health status (Harris et al., 1997) and increased CVD mortality (Breeze et al., 2005, Lee and Paffenbarger, 1993). In assessing change in BMI, observational studies must be careful to minimize confounding by factors such as smoking status, physical activity, (Rosengren et al., 1999) and potential underlying malignancy (Wannamethee et al., 2002).

The objective of this study was to use prospective data from a large cohort with long-term follow-up to better understand how change in BMI is associated with risk of CVD and whether the consideration of BMI trajectory could add prognostic information beyond knowledge of current BMI. Therefore, we evaluated how change in BMI over the prior 8 years was associated with risk of major CVD events among 13,230 healthy men followed for a median of 13.5 years.

Methods

Study Population

Study subjects are from the Physicians' Health Study (PHS). In 1982-3, letters were sent to 261,248 U.S. male physicians aged 40 to 84 years on the American Medical Association mailing list that included an invitation to participate in a randomized, double-blind, placebo-controlled trial testing aspirin and beta-carotene in the primary prevention of CVD and cancer. The letters contained informed consent forms and an initial questionnaire to provide baseline information. By the end of 1983, 104,353 completed enrollment questionnaires had been returned with participants indicating whether they would willing to participate in a long-term clinical study. After exclusions due to existing comorbidities, 22,071 apparently healthy male physicians without prior history of CVD, cancer (except non-melanoma skin cancer) or other major illnesses were enrolled in the study. (Steering Committee of the Physicians' Health Study Research Group, 1989). For the trial participants, more detailed baseline information was collected by self-report through mailed questionnaires for demographic, lifestyle and medical history information, including systolic blood pressure (SBP). The PHS has been approved by the Institutional Review Board of the Brigham and Women's Hospital in Boston, MA.

Every six months for the first year and annually thereafter, participants reported demographic and lifestyle factors including newly diagnosed medical conditions, such as CVD and cancer. Height and weight were collected on the baseline questionnaire and weight was next collected on the 8 year questionnaire. Deaths were usually reported by family members and were verified by medical records and death certificates.

From the Physicians' Health Study cohort, we excluded men with missing height or weight information on the 0 year questionnaire (n=3) or missing weight information on the 8 year questionnaire (n=527). We excluded those with a history of diabetes (n=482), current smoking (n=2,108) or a BMI <18.5 kg/m^2 (n=42). We excluded participants with a nonfatal myocardial infarction (MI), nonfatal stroke, transient ischemic attack (TIA), revascularization or angina

between 0 and 8 years (n=1,179). To reduce confounding due to weight loss from underlying malignancy, we furthermore excluded participants diagnosed with cancer from 0 to 8 years (n=854) and through 13.5 years of study follow-up (n=3,382). As a result of these exclusions, our study population consisted of 13,230 participants evaluated for the development of incident CVD, with follow-up beginning at return of the 8 year questionnaire. We included former smokers since it is likely that most had remote smoking histories and were unlikely to re-start smoking in middle age.

Ascertainment of BMI, change in BMI and WHO categories

BMI was calculated as (weight in kilograms) divided by (height in meters)^2. We assumed that among these middle-aged men, height remained constant from baseline to 8 years. Change in BMI was calculated as (BMI at 8 years) – (BMI at 0 years). In addition, using World Health Organization (WHO) criteria (Joint WHO/FAO expert consultation, 2003), participants were categorized into normal (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2) or obese (≥30 kg/m^2) at baseline and at 8 years.

Evaluation of incident CVD

All participants who reported a CVD event on a questionnaire were asked permission to review their medical records. The Endpoints Committee confirmed diagnoses after review of the medical records and results of diagnostic tests. Deaths were classified by trained nosologists using the first revision of the *Ninth International Classification of Diseases* in conjunction with the *Automated Classification of Medical Entities Decision Tables* to manually select underlying cause of death. In the PHS, there is a 99% follow-up rate.

The main outcome measure was a major CVD event consisting of nonfatal MI, nonfatal stroke or CVD death. The occurrence of nonfatal myocardial infarction was confirmed by physician review using WHO criteria (World Health Organization, 1971). For nonfatal stroke, a neurologist evaluated medical records and brain imaging to confirm a focal neurological deficit of sudden onset and vascular mechanism that lasted >24 hours (Walker et al., 1981). CVD death consisted of ICD codes 390–459 which included an etiology of ischemic heart disease, MI, cerebrovascular disease or other CVD cause.

Statistical analysis

Means or proportions of variables were computed for the study cohort. We examined the distributions of BMI at baseline and at 8 years and calculated the change in BMI. We then determined the number of participants with a BMI in the normal (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2) or obese (>30 kg/m^2) category at baseline and 8 years. Follow-up time was calculated in person-years from return of the 8 year questionnaire.

We used Cox proportional hazard models to calculate hazard ratios as the measure for relative risks (RRs) and 95% confidence intervals (CIs) of CVD. We first evaluated the relationship between BMI (in kg/m^2) at 8 years (BMI at start of follow-up) and risk of CVD, adjusting for age only. We then adjusted for these potential confounders that were measured at year 0: frequency of exercise to sweat (rarely/never, once a month to once a week, ≥2 times a week), alcohol use (rarely/never, monthly, weekly or daily) (Camargo et al., 1997), and past cigarette smoking (never, past). Our exposure variable satisfied the proportional hazards assumption by the Wald test evaluating the interaction of time and change in BMI. Using a normal BMI at 8 years as the reference group, we then evaluated the risk of CVD among the overweight and obese participants using the same modeling strategy.

We then evaluated change in BMI over the prior 8 years and risk of subsequent CVD. The reference group consisted of participants with a stable BMI (±0.5 kg/m^2) from baseline to the

8 year questionnaire. We then compared the reference group to participants who lost more than 0.5 kg/m^2, gained 0.5 to <2.0 kg/m^2, or gained ≥2.0 kg/m^2. We first adjusted for age only and then included exercise, alcohol use and past cigarette smoking in the multivariable model. To assess the effect of considering current BMI in assessing risk of CVD, we then further adjusted for BMI at start of follow-up (e.g. return of the 8 year questionnaire). We evaluated the relationship between current BMI and change in BMI using an interaction term. In subgroup analyses, we assessed change in BMI stratified by WHO category at 96 months, using a stable normal BMI as the reference category.

To determine if change in BMI has differential effects based upon age, we decided a priori to stratify the cohort at age 60 years to examine the effect of age on change in BMI and risk of CVD (Sesso et al., 2000). The test for interaction used ordinal variables to assess change in BMI (4 categories) and age (2 categories). All RRs are presented with 95% confidence intervals (CIs), and all reported P values are two-sided. Analyses were performed using SAS version 9.1 (Cary, NC).

Results

The study cohort of 13,230 participants had a baseline mean (SD) age of 51.6 (8.7) years and average BMI of 24.6 (2.7) kg/m^2 (Table 1). Based upon WHO criteria, 60 percent were in the normal weight category while 36 percent were overweight and four percent were obese. Among these male physicians, 42 percent were former smokers, 15 percent drank alcohol at least daily, and 57 percent exercised at least twice a week. A history of hypertension was reported by 19 percent, and the average SBP was 124.6 (11.1) mm Hg.

At return of the 8 year questionnaire, the average BMI had increased to 25.3 (3.3) kg/m^2, an increase of 0.6 (2.0) kg/m^2. BMI remained stable in 4,005 (30.3%) men while 4,639 (35.1%) men gained a modest 0.5 to 2.0 kg/m^2, and 1,833 (13.9%) men gained ≥2.0 kg/m^2. Among participants who gained ≥2.0 kg/m^2, the average increase was 3.9 kg/m^2, and 34.2% were now classified as obese. A decrease in BMI of more than 0.5 kg/m^2 occurred among 2,753 (20.8%) participants; these men were older, exercised less, and were more likely to have hyperlipidemia, hypertension and a higher SBP (all $p<0.01$).

During follow-up for this study that began at return of the 8 year questionnaire and lasted a subsequent 13.5 years, there were 1,308 CVD events (nonfatal MI, nonfatal stroke or CVD death). BMI at start of follow-up was linearly related (per one unit increase in kg/m^2) to an increased risk of CVD in the age-adjusted model (RR=1.06; 95% CI: 1.04, 1.07) that was unchanged after adjustment for exercise, alcohol and past smoking. Compared to men with a normal BMI at start of follow-up, those in the overweight category had an increased risk of CVD in the age-adjusted model (RR=1.29; 95% CI: 1.15, 1.45) which was unchanged by multivariable adjustment (Table 2). Men who were obese had an even higher risk of CVD in the age-adjusted model (RR=1.95; 95% CI: 1.61, 2.36) which was minimally attenuated by multivariable adjustment (RR=1.90; 95% CI: 1.56, 2.30).

We next evaluated change in BMI from baseline to 8 years and risk of subsequent CVD, using those with a stable BMI (± 0.5 kg/m^2) as the reference group (Table 3). Participants who lost more than 0.5 kg/m^2 had a modestly elevated risk of CVD in the age-adjusted model (RR=1.27; 95% CI: 1.11, 1.47) which was slightly reduced by multivariable adjustment (RR=1.23; 95% CI: 1.07, 1.42). Those with a modest increase in BMI from 0.5–2.0 kg/m^2 did not have an increased risk of CVD in the age-adjusted (RR=1.02; 95% CI: 0.88, 1.18) or multivariable model (RR=1.00; 95% CI: 0.86, 1.16). An increase of ≥2.0 kg/m^2 was associated with an increased risk of CVD in the age-adjusted (RR=1.44; 95% CI: 1.20, 1.73) and multivariable model (RR=1.39; 95% CI: 1.16, 1.68). There was not a significant interaction between change in BMI and current BMI (p, interaction=0.57). When we stratified by WHO category at start

of follow-up, the lowest RRs were among men with a normal BMI who had either a stable or slight increase (0.5–2.0 kg/m^2) in BMI over the prior 8 years.

We next examined the effect of including BMI at 8 years in the multivariable models. For men who gained ≥2.0 kg/m^2, further adjustment for BMI eliminated any increased risk associated with weight gain over the prior 8 years (multivariable RR=1.00; 95% CI: 0.81, 1.23), indicating that BMI alone was sufficient to assess risk of CVD and the increase in BMI over the prior 8 years did not add prognostic information. In contrast, among men who lost more than 0.5 kg/m^2, the consideration of current BMI did not change the increased risk associated with a decrease in BMI (multivariable RR=1.28; 95% CI: 1.11, 1.48), indicating that a downward BMI trajectory provided prognostic information beyond the consideration of current BMI.

We next stratified our cohort by age 60 years at baseline and evaluated 8 year change in BMI and risk of subsequent CVD (Table 4). In age-adjusted and multivariable models, the highest RRs were among younger men who gained weight and older men who lost weight (p, interaction=0.01).

Discussion

In this large prospective study of healthy men, a BMI increase of ≥2.0 kg/m^2 over the prior 8 years was associated with an increased risk of CVD, however this did not add prognostic information when current BMI was considered. A decline in BMI of more than 0.5 kg/m^2 was associated with an increased risk of CVD regardless of current BMI, particularly among older men. The consideration of a long-term decrease in BMI may be useful in assessing risk of subsequent CVD.

The characteristics of our study population were similar to those of the community-based Framingham Heart Study where average BMI levels, along with rates of overweight and obesity, increased with advancing age (Vasan et al., 2005). In our cohort of healthy men, higher levels of initial BMI were associated with an increased risk of CVD, results consistent with the PHS enrollment cohort (Adjani et al., 2004), a cohort of individuals without traditional CVD risk factors (Yan et al., 2006), middle-aged British men (Wannamethee et al., 2005) and prior meta-analyses evaluating baseline BMI and risk of CVD (McGee, 2004, Asia Pacific Cohort Studies Collaboration, 2004).

With regard to weight change, several cross-sectional and prospective studies have shown that maintaining a normal BMI throughout middle and older adulthood is associated with the lowest risk of CVD. In the National Health and Nutrition Examination Survey (NHANES), a stable non-obese weight was associated with the lowest risk of CVD mortality (Diaz et al., 2005). In the Cardiovascular Health Study, a heavier baseline weight was associated with increased risk of CVD and weight gain was associated with an increased risk of CVD (Harris et al., 1997). In an older cohort, higher mortality rates were observed among overweight and obese participants as well as among those with long-term weight loss, regardless of initial BMI (Corrada et al., 2006). While it is difficult to compare studies of weight change due to differences in cohort characteristics, timing of measurements and length of follow-up, our finding that an increase in BMI was associated with an increased risk of CVD was consistent with other cohorts. The increased risk of CVD due to an increase in BMI may be due to the accumulation of CVD risk factors, including type 2 diabetes (American Diabetes Association, 2006).

While weight loss has been shown to improve CVD risk factors (Stampfer, 2005), the effect of weight loss on CVD events in observational studies has been inconsistent. Weight loss was associated with an increased risk of CVD both in NHANES (Diaz et al., 2005) and the Cardiovascular Health Study (Harris et al., 1997). Among nearly 50,000 overweight middle-

aged men in the U.S., intentional weight loss was not associated with risk of CVD mortality (Williamson et al., 1999), and observed weight loss did not decrease risk of CVD among overweight and obese men in Britain (Wannamethee et al., 2005). In a prospective study of overweight men and women in Finland, successful intentional weight loss was associated with an increased risk of total mortality (Sorenson et al., 2005) which was similar to an Israeli study where a loss of more than 5 kg over 5 years was associated with a higher risk of subsequent mortality (Yaari and Goldbourt, 1998). In our cohort of healthy middle-aged non-smoking men, the observation that a decline in BMI over 8 years was associated with an increased risk of CVD may have been due to the possibility of subclinical disease leading to weight loss and an increased risk of CVD. We attempted to minimize this effect by selecting a healthy cohort of middle-aged men without any evidence of malignancy over the entire study period.

Study limitations and strengths

Participant information was collected by mailed questionnaire, however self-reported medical information by physicians is highly correlated with measured values, particularly for BMI (r=0.96) (Klag et al., 1993). BMI was assessed at only two time points and unmeasured interval fluctuations in BMI may have occurred that could affect general health status (Diaz et al., 2005). We included former smokers but did not have information on amount of smoking exposure or time since quitting. We did not have information about intention to lose weight, a process that may lead to lifestyle changes that influence risk of CVD. Our study cohort consisted of white men of similar socioeconomic status, and this may affect the generalizability to other populations. While we controlled for many potential confounders using available information, as with any observational study, residual and unmeasured confounding may exist (e.g. due to dietary or other lifestyle factors).

Strengths include the large number of participants with a large number of confirmed CVD events and nearly complete follow-up over an extended time period. To minimize confounding by smoking, diabetes, or underlying malignancy (Wannamethee et al., 2002), our cohort consisted of only nonsmoking, apparently healthy men without known malignancy throughout the entire length of follow-up. In addition, our prospective study was not subject to recall bias regarding recalled weight (Corrada et al., 2006), prior alcohol use or physical activity (Rosengren et al., 1999).

Conclusions

In this prospective cohort study of healthy middle-aged non-smoking men, higher levels of baseline BMI were associated with an increased risk of CVD and knowledge of an increasing BMI over the prior 8 years did not improve the ability to predict risk of CVD. Men with a decline of more than 0.5 kg/m^2 were at an increased risk of CVD independent of current BMI, and the consideration of a long-term decline in BMI may be useful in evaluating risk of CVD, particularly among older men.

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TABLE 1

Characteristics of 13,230 men in the Physicians' Health Study (1982–2005), categorized by 8 year change in BMI prior to follow-up for a major CVD event (nonfatal MI, nonfatal stroke or CVD death)*

Characteristic	Change in BMI (kg/m^2) < −0.5	> −0.5 to <0.5	≥0.5 to <2.0	≥2.0	Total
No.	2,753	4,005	4,639	1,833	13,230
Average change in BMI	−1.4 (1.2)	0.03 (0.25)	1.10 (0.40)	3.9 (2.8)	0.6 (2.0)
Baseline age (years)†	55.3 (10.2)	52.4 (8.7)	49.9 (7.5)	48.7 (7.0)	51.6 (8.7)
BMI at baseline (kg/m^2)†	25.3 (3.0)	24.2 (2.3)	24.4 (2.4)	25.2 (3.1)	24.6 (2.7)
WHO category at baseline†					
Normal	51.5	66.3	63.4	50.6	60.0
Overweight	42.2	32.2	34.3	42.0	36.4
Obese	6.4	1.5	2.2	7.4	3.6
Past cigarette smoking, % †	45.1	40.3	40.8	44.5	42.1
Alcohol use, %†					
Rarely/Never	23.9	22.9	21.1	19.2	22.0
Monthly	49.5	50.5	52.8	53.6	51.5
Weekly	10.8	11.5	11.7	12.3	11.5
Daily	15.8	15.1	14.5	14.9	15.0
Physical activity†					
rarely/never	13.8	10.4	10.1	12.9	11.3
1/month to 1/week	32.9	31.7	31.3	33.3	32.0
≥2/week	53.3	57.9	58.7	53.9	56.6
History of hypertension, % †	24.7	18.0	17.2	20.1	19.4
SBP, mm Hg†	126.8 (11.9)	124.3 (10.8)	123.8 (10.7)	124.2 (11.2)	124.6 (11.1)
Hyperlipidemia % †	12.0	11.8	10.4	9.1	11.0
After 8 years					
BMI (kg/m^2)	23.8 (2.9)	24.2 (2.3)	25.5 (2.5)	29.2 (4.1)	25.3 (3.3)
Weight change (pounds)	9.9 (7.8)	0.2 (1.8)	7.7 (2.9)	19.2 (10.1)	
WHO category†					
Normal	67.8	66.2	44.1	11.0	51.1
Overweight	27.7	32.2	51.7	54.9	41.2
Obese	3.2	1.6	4.3	34.2	7.4

*Values are mean ± one standard deviation

†P<0.01

BMI=Body mass index; WHO=World Health Organization; SBP=Systolic blood pressure

TABLE 2

RRs (95% CIs) from Cox proportional hazards models of a major CVD event (nonfatal MI, nonfatal stroke or CVD death) among men in the Physicians' Health Study (1982–2005), according to World Health Organization (WHO) category at 8 year questionnaire

WHO category	Cases	Person-years	Age-adjusted	Multivariable*
Normal (18.5–<25.0 kg/m^2) (n=6,765)	610	84,267	1.00 (ref)	1.00 (ref)
Overweight (25.0–<30.0 kg/m^2) (n=5,453)	561	67,482	1.29 (1.15–1.45)	1.29 (1.15–1.45)
Obese (≥30 kg/m^2) (n=973)	129	11,863	1.95 (1.61–2.36)	1.90 (1.56–2.30)

* adjusted for age, level of physical activity, alcohol use, and history of past cigarette smoking

Note: 39 participants (8 cases) were excluded due to a body mass index <18.5

TABLE 3

RRs (95% CIs) from Cox proportional hazards models of a major CVD event (nonfatal MI, nonfatal stroke or CVD death) among men in the Physicians' Health Study (1982–2005), according to change in BMI over prior 8 years

Change in BMI	Cases	Person-years	Age-adjusted	Multivariable*	Multivariable + BMI†
<−0.5 (n=2,753)	405	32,223	1.27 (1.11–1.47)	1.23 (1.07–1.42)	1.28 (1.11–1.48)
−0.5 to <0.5 (n=4,005)	385	50,042	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.5 to <2.0 (n=4,639)	348	58,738	1.02 (0.88–1.18)	1.00 (0.86–1.16)	0.92 (0.79–1.07)
≥2.0 (n=1,833)	170	22,963	1.44 (1.20–1.73)	1.39 (1.16–1.68)	1.00 (0.81–1.23)

*adjusted for age, level of physical activity, alcohol use, and history of past cigarette smoking

†further adjusted for BMI (kg/m^2) on 8 year questionnaire

TABLE 4

RRs (95% CIs) from Cox proportional hazards models of a major CVD event (nonfatal MI, nonfatal stroke or CVD death) among men in the Physicians' Health Study (1982–2005), according to change in BMI over prior 8 years, stratified by baseline age

	Age-adjusted	Multivariable*	Multivariable + BMI†
Change in BMI			
< 60 years			
<−0.5 (n=1,868)	1.18 (0.95–1.47)	1.15 (0.92–1.43)	1.18 (0.95–1.46)
−0.5 to <0.5 (n=3,210)	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.5 to <2.0 (n=4,155)	1.06 (0.88–1.27)	1.05 (0.87–1.26)	0.94 (0.78–1.14)
≥2.0 (n=1,693)	1.55 (1.24–1.93)	1.51 (1.21–1.88)	0.97 (0.75–1.25)
≥60 years			
<−0.5 (n=885)	1.33 (1.10–1.61)	1.30 (1.07–1.57)	1.33 (1.09–1.61)
−0.5 to <0.5 (n=795)	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.5 to <2.0 (n=484)	0.94 (0.74–1.21)	0.91 (0.71–1.17)	0.88 (0.68–1.13)
≥2.0 (n=140)	1.12 (0.77–1.63)	1.09 (0.75–1.59)	0.93 (0.61–1.42)

BMI=body mass index

*adjusted for age, level of physical activity, alcohol use, and history of past cigarette smoking

†further adjusted for BMI (kg/m^2) at 8 years

P, interaction=0.01