



Published in final edited form as:

Circulation. 2009 January 6; 119(1): 44–52. doi:10.1161/CIRCULATIONAHA.108.807289.

Body-mass Index and Vigorous Physical Activity and the Risk of Heart Failure among Men

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Abstract

Background—Elevated body-mass index (BMI, weight in kilograms/height in meters²), in the obese range (≥ 30) is associated with an excess risk of heart failure (HF). However, impact of overweight or preobese (BMI 25 to 29.9) status and physical activity to HF risk is unclear.

Methods and Results—In a prospective cohort of 21,094 men (mean age, 53 years) without known coronary heart disease at baseline in the Physicians' Health Study, we examined the individual and combined effects of BMI and vigorous physical activity (exercise to the point of breaking a sweat) to HF incidence from 1982 to 2007. We evaluated BMI as both a continuous (per 1 kg/m² increment) and a categorical (lean, <25, overweight, 25 to 29.9, and obese, ≥ 30) variable, and vigorous physical activity primarily as a dichotomous variable (inactive [rarely/never] vs. active [≥ 1 to 3 times a month]). During follow-up (mean 20.5 years), 1109 participants developed new-onset HF. In multivariable analyses, every 1 kg/m² increase in BMI was associated with an 11% (95% CI 9 to 13%) increase in HF risk. Compared with lean participants, overweight participants had a 49% (95% CI 32 to 69%) and obese participants had a 180% (95% CI 124 to 250%) increase in HF risk. Vigorous physical activity conferred an 18% (95% CI 4 to 30%) decrease in HF risk. No interaction was found between BMI and vigorous physical activity to HF risk ($p=0.96$). Lean-active men had the lowest and obese-inactive men had the highest risk of HF. Compared with lean-active men, the hazard ratios (95% CI) were 1.19 (0.94 to 1.51), 1.49 (1.30 to 1.71), 1.78 (1.43 to 2.23), 2.68 (2.08

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Conflict of Interest Disclosures:

None

to 3.45), and 3.93 (2.60 to 5.96) in lean-inactive, overweight-active, overweight-inactive, obese-active, and obese-inactive men respectively.

Conclusions—In this cohort of men, elevated BMI, even in preobese range, was associated with an increased risk of HF and vigorous physical activity was associated with a decreased risk. Public health measures to curtail excess weight, maintain optimal weight, and promote physical activity may limit the scourge of HF.

Keywords

Exercise; Heart Failure; Obesity; Overweight; Physical Activity

INTRODUCTION

Excess body weight, sedentary lifestyle, and heart failure (HF) are major public health problems in the United States and worldwide.^{1–6} In adult men and women living in the community, body-mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) is associated with the risk of HF^{7–13} in a positive,^{7–13} linear,^{10–12} and dose-response manner.¹¹ Although BMI in the obese range (≥ 30 kg/m²) is associated with an increased risk of HF,^{9,11,13} the risk conferred in the overweight or preobese (25 to 29.9 kg/m²) individuals is unclear.^{9,11} Consequently, the Heart Failure Society of America recommends a BMI of < 30 kg/m² as the target to prevent the development of HF.¹⁴

Physical activity is a key determinant of body weight and an important component for weight reduction and weight maintenance.^{1,2,15} Numerous health benefits of physical activity have been reported,¹⁵ but its influence on the risk of HF, especially in men, remains uncertain.⁸ Furthermore, the interaction of BMI and physical activity with the risk of HF is not known. Therefore, we investigated the relation of individual and combined effects of BMI and physical activity with the risk of HF in a large prospective cohort of men in the Physicians' Health Study (PHS).

METHODS

Study sample

The study design and methods of the PHS have been published previously.^{16,17} Briefly, the PHS was a randomized, double-blind, placebo-controlled trial that began in 1982 to evaluate the efficacy of low-dose aspirin and beta carotene according to a two-by-two factorial design among 22,071 US male physicians, 40 to 84 years of age, in the primary prevention of cardiovascular disease and cancer. At baseline, physicians with personal history of myocardial infarction, stroke, transient ischemic attack, cancer (except nonmelanoma skin cancer), liver or renal disease, peptic ulcer, gout, contraindications to aspirin consumption, and current use of aspirin, or other platelet active drugs, or nonsteroidal anti-inflammatory agents, or a vitamin A supplement were excluded. For the present investigation, we excluded 977 participants (4.4%) with missing baseline information on height, weight, or physical activity (248 participants), missing information on other covariates (712 participants), and HF prior to baseline examination (17 participants). After these exclusions, 21,094 participants comprised our baseline population. All participants provided written informed consent for enrollment in the Physicians' Health Study. The institutional review board at the Brigham and Women's Hospital (Boston, Mass), approved the research protocol for the present investigation.

Data collection

Baseline information on self-reported demographic, medical history, and lifestyle variables was collected using a mailed questionnaire in 1982. Every 6 months for the first year and

annually thereafter, participants provided information on compliance with randomized treatment assignments, various risk factors for chronic diseases, and newly diagnosed conditions in follow-up questionnaires. After the termination of the randomized aspirin¹⁶ and beta-carotene¹⁷ components of the trial, participants continued to provide information on risk factors and relevant outcomes in yearly mailed questionnaires.

Exposures and covariates

On the baseline questionnaire, each physician reported his weight (in pounds) and height (in inches). The weight in kilograms was divided by the square of the height in meters to calculate BMI.^{1,2} The level of physical activity was ascertained at baseline using the single question: "How often do you exercise vigorously enough to work up a sweat?" Response options were rarely/never, 1 to 3 times a month, 1 time a week, 2 to 4 times a week, 5 to 6 times a week, and daily. Each physician also reported his age, parental history of myocardial infarction, cigarette smoking, frequency of alcohol consumption, and history of hypertension, diabetes mellitus, and hypercholesterolemia. On follow-up questionnaires, physicians reported the occurrence of myocardial infarction, which was confirmed on review of medical records by the PHS Endpoints Committee using the World Health Organization Criteria.¹⁸

Outcome ascertainment

A diagnosis of HF was self-reported by physician participants on the yearly follow-up questionnaires. To validate the diagnosis of HF using established epidemiologic criteria, we randomly selected 100 participants with a recent self-reported diagnosis of HF. Of these 100 participants, 8 had previously indicated that they not be contacted for additional information, and 4 had died. The remaining 88 participants were mailed a questionnaire to collect information on symptoms, signs, and laboratory investigations at the time of first diagnosis of HF and list of current medications for the treatment of HF. After two mailings followed by telephone contact, we collected and reviewed data from 76 of 88 (86%) to verify the diagnosis of HF. Among these 76 responders, 68 (89%) were on current treatment for HF and/or met the Framingham Heart Study criteria for HF at the time of first diagnosis.¹⁹ This extent of confirmation paralleled that reported by other investigators applying epidemiologic criteria to the validation of the physician-determined diagnosis of HF.^{20,21}

Statistical analysis

We performed all analyses using SAS software version 9.1.3 (SAS Institute, Cary, NC). We computed means (\pm standard deviations [SD]) for continuous variables and proportions (expressed as percentage) for categorical variables according to various categories of BMI and levels of vigorous physical activity. We constructed cumulative incidence curves for HF according to exposure categories using the Kaplan-Meier estimation method.

We used Cox-proportional hazards regression models to examine the effects of BMI and vigorous physical activity on the risk of HF. We expressed these results as hazard ratios, 95% confidence intervals (CIs), and p-values. We considered a two-sided p-value of <0.05 as statistically significant. To examine the individual effects of exposure variables on the risk of HF, we considered BMI as both a continuous variable (per increment of 1 kg/m^2) and a categorical variable (lean <25.0 [referent], overweight 25.0 to 29.9, and obese $\geq 30 \text{ kg/m}^2$);^{1, 2} and categorized vigorous physical activity as both a dichotomous variable (inactive [rarely or never active, referent], and active [any vigorous activity ≥ 1 to 3 times a month]) and a 4-category variable (rarely/never [referent], 1–3 times a month, 1–4 times a week, and 5–7 times a week). To evaluate the combined effects of BMI and vigorous physical activity on the risk of HF, we used the aforementioned three categories of BMI (lean, overweight, and obese) and two levels of vigorous physical activity (inactive and active) and constructed six groups: lean and active [referent], lean and inactive, overweight and active, overweight and inactive, obese

and active, and obese and inactive. Of note, because there were very few participants in the underweight category ($n=46$, BMI <18.5 kg/m²),^{1,2} we combined this category with normal group ($n=12,087$; body mass index 18.5 to <25.0 kg/m²)^{1,2} and classified them as lean group.

In multivariable analyses evaluating BMI and the risk of HF, we adjusted for (a) age only, (b) age, cigarette smoking (never [referent], past only, and current), alcohol consumption (rarely/never, monthly, weekly, and daily [referent]), parental history of myocardial infarction and random assignment to aspirin or beta-carotene (baseline variables not likely in the causal pathway), (c) the aforementioned baseline covariates and vigorous physical activity (rarely/never [referent] vs. ≥ 1 to 3 times a month), (d) all above covariates and presence or absence of history of hypertension, diabetes mellitus, and hypercholesterolemia (baseline variables likely on the causal pathway), and (e) all of the above baseline variables plus myocardial infarction (likely on the causal pathway) during follow-up as a time-dependent variable. We considered variables as likely or not likely in the causal pathway on the basis of prior epidemiologic evidence and biological plausibility.²² We used the same model-building approach in the evaluation of physical activity and the risk of HF (except that BMI was considered as a variable possibly in the causal pathway between vigorous physical activity and the risk of HF). We constructed trend models to assess for a gradient of risk across multicategory exposure variables for the risk of HF.

In multivariable models including all baseline covariates, we examined for effect modification between baseline covariates and BMI (per 1 kg/m² increment), and between baseline covariates and vigorous physical activity (inactive vs. any vigorous activity) on the risk of HF by introducing appropriate interaction terms. In the presence of statistically significant interactions (defined as p -value <0.05), we conducted stratified analyses according to various levels of the baseline covariate.

Of note, in statistical models adjusting for history of hypercholesterolemia, we introduced a dummy variable for missing information on this variable that made up about 12% of study participants. Finally, in secondary analyses, to account for the competing risk of death that may alter the probability of experiencing HF (the event of interest), we evaluated the individual effects of BMI and vigorous physical activity on the risk of composite of death or HF.

Statement of Responsibility

Dr. Kenchaiah had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and agree to the manuscript as written.

RESULTS

Baseline characteristics

About 40% of physicians in our sample were overweight and approximately 5% were obese at baseline. As anticipated, a greater proportion of obese individuals exercised less and had a history of hypertension and diabetes mellitus (Table 1). However, a marginally greater proportion of obese were current smokers. Physicians who rarely or never exercised vigorously were older, had higher BMI, smoked cigarettes more often, and had a greater prevalence of hypertension and diabetes mellitus. By design, randomized aspirin and beta-carotene treatment was similar across all categories of BMI and physical activity.

BMI and the risk of heart failure

During a mean \pm SD follow-up of 20.5 ± 5.4 years (maximum, 24.8 years; 431,654 total person-years), 1109 men developed new-onset HF. The cumulative incidence of HF increased with increasing categories of BMI (Figure 1A).

In models adjusting for variables not likely in the causal pathway between BMI and HF (age, smoking, alcohol consumption, parental history of myocardial infarction), each 1 kg/m^2 increase in BMI was associated with a 13% increase in the risk of HF (Table 2). Compared with lean men, overweight men showed a 62%-increased risk of HF and obese men a 240%-increased risk. Increasing categories of BMI were associated with a stepwise increase in the risk of HF (p for trend <0.0001). Including vigorous physical activity as a covariate in multivariable analyses did not materially alter the excess risk of HF associated with elevated BMI. Additional adjustment for baseline variables possibly in the causal pathway between elevated BMI and HF (hypertension, diabetes mellitus, and hypercholesterolemia) resulted in decline of the hazard ratio from 1.62 to 1.49 in overweight men and from 3.38 to 2.80 in obese men, thus explaining approximately 21.0% and 24.4% of the excess risk of HF in overweight and obese men respectively.

During follow-up, 764 (6.3%) in the lean, 702 (8.7%) in the overweight, and 117 (12.6%) in the obese group developed myocardial infarction. Interim myocardial infarction preceded the onset of HF in 77 (15.9%), 87 (16.5%), and 14 (14.4%) of lean, overweight, and obese participants with HF, respectively. The association between BMI and HF remained robust after adjustment for all baseline covariates and interim myocardial infarction as a time-dependent variable. In these models, every 1 kg/m^2 increment in BMI was associated with a hazard ratio of 1.11 (95% CI 1.09 to 1.12). Compared with lean participants, the hazard ratios were 1.46 (95% CI 1.29 to 1.66) and 2.65 (95% CI 2.12 to 3.31) in overweight and obese participants, respectively.

Vigorous physical activity and the risk of heart failure

Compared with participants in the inactive group, those in the active group had a lower cumulative incidence of HF (Figure 1, Panel B). The divergence of these curves was apparent within 5 years of follow-up.

In models adjusting for lifestyle and other variables not likely in the causal pathway, vigorous physical activity of at least 1 to 3 times a month was associated with a significant 26% reduction in the risk of HF (Table 2). Compared with men who rarely or never vigorously exercised, there was a 23%, 20%, and 36% reduction in the risk of HF among men who vigorously exercised for 1 to 3 times a month, 1 to 4 times a week, and 5 to 7 times a week respectively (P for trend across categories, <0.001). Inclusion of BMI as an additional covariate in multivariable analyses resulted in a minor change in the effect of vigorous physical activity on the risk of HF. After adjustment for known baseline variables presumably in the causal pathway (BMI, hypertension, diabetes mellitus, and hypercholesterolemia), the risk reduction of HF conferred by vigorous physical activity changed from 24% to 18%, thereby accounting for about 25% of the decreased risk. In these analyses, a statistically significant trend toward decreasing HF risk was found with increasing levels of vigorous physical activity (p for trend 0.016).

During follow-up, interim myocardial infarction occurred in a greater proportion of inactive (278 events, 9.8%) compared with active (1305 events, 7.2%) participants. Myocardial infarction preceded the onset of HF among similar proportion of inactive (47 events, 22.8%) and active (206 events, 22.8%) participants who developed HF. In models adjusting for all covariates at baseline and myocardial infarction during follow-up as a time-dependent variable,

the association between vigorous physical activity and HF remained significant. As compared with inactive participants, the hazard ratio for incident HF among active participants was 0.85 (95% CI 0.73 to 0.99).

Combined effect of BMI and vigorous physical activity on the risk of heart failure

In models evaluating BMI as a continuous variable (per increment of 1 kg/m²) and vigorous physical activity as a dichotomous variable (inactive vs. active), no significant interaction ($p=0.96$) between BMI and vigorous physical activity with the risk of HF. After adjustment for all baseline covariates, compared with participants who were lean and active, the risk of HF was found increased progressively by 19% (albeit statistical nonsignificant) in the lean and inactive, 49% in the overweight and active, 78% in the overweight and inactive, 168% in the obese and active, and 293% in the obese and inactive groups (Figure 2).

Effect modification by other baseline covariates

Elevated BMI was associated with a relatively greater risk of HF among younger compared with older participants (p for interaction =0.020) and among nondiabetic as compared with diabetic participants (p for interaction <0.0001) (Table 3). Other baseline covariates inclusive of parental history of myocardial infarction, cigarette smoking, alcohol consumption, history of hypertension, history of hypercholesterolemia, or aspirin intake did not alter the effect of BMI to the risk of HF (all p for interaction >0.40).

Vigorous physical activity conferred a reduction in the risk of HF among non-diabetic but not among diabetic participants (p for interaction <0.001) (Table 3). None of the other baseline covariates influenced the relation between vigorous physical activity and incident HF (all p for interaction ≥ 0.10).

Secondary analyses

During follow-up, 3159 (26.0%) in the lean group, 2473 (30.8%) in the overweight group, and 399 (42.9%) in the obese group died or developed HF. In analyses adjusting for all baseline covariates, each increment of 1 kg/m² in BMI was associated with a hazard ratio of 1.06 (95% CI 1.05 to 1.06) to the risk of death or HF. Compared with participants in the lean group, hazard ratios were 1.12 (95% CI 1.06 to 1.18) for overweight participants and 1.97 (95% CI 1.77 to 2.19) for obese participants (p for trend <0.0001).

The composite outcome of death or HF occurred in a lesser proportion of active men (4897 events, 26.8%) as compared with inactive men (1134 events, 39.9%). In multivariable analyses adjusting for all baseline covariates, vigorous physical activity was associated with a lower risk of death or HF (hazard ratio 0.81, 95% CI 0.76 to 0.87). In analyses of vigorous physical activity as a 4-level categorical variable, the hazard ratios were 0.80 (95% CI 0.73–0.88) for 1 to 3 times a month, 0.81 (95% CI 0.76 to 0.87) for 1 to 4 times a week, and 0.84 (95% CI 0.77 to 0.91) for 5 to 7 times a week of vigorous physical activity (p for trend <0.0001).

DISCUSSION

Principal findings

In men, we found that higher BMI was associated with a greater risk of HF. This increased risk occurred in a linear fashion without evidence of a threshold and was evident not only in obese (BMI ≥ 30 kg/m²) but also in overweight or preobese (BMI 25 to 29.9 kg/m²) men. Vigorous physical activity was associated with a reduced risk of HF, and increasing levels of vigorous physical activity were associated with a graded reduction in the risk of HF. BMI and vigorous physical activity did not modify each other's individual effect on HF risk. Lean and active individuals had the lowest risk of HF; obese and inactive individuals had the highest risk. The

statistically significant association of elevated BMI with an increased risk of the composite of death or HF and vigorous physical activity with a decreased risk of this combined outcome suggests that death as a competing event is an unlikely reason for the observed association between BMI and vigorous physical activity with the risk of HF.

Elevated BMI was associated with a greater risk of HF in all subgroups, although its effect was stronger in younger as compared with older participants and in non-diabetic as compared with diabetic participants. The beneficial impact of vigorous physical activity was evident in all categories of baseline covariates except among diabetics, where no association was noted, likely because of the small sample size of this subgroup.

Comparison with previous studies

The increased risk of HF among obese individuals noted in our investigation is consistent with that found in previously published studies.^{7–11,13} However, statistically non-significant association between overweight but not obese (preobese) status and the risk of HF has been reported among men in a nested case-control analyses from United Kingdom-based General Practice Research Database (589 cases vs. about 2500 age-matched controls, relative risk 0.9, and 95% CI 0.7 to 1.3)⁹ and a prospective cohort analyses from the Framingham Heart Study (2704 men, 252 events, mean follow-up 14 years, hazard ratio 1.20, and 95% CI 0.87 to 1.64).¹¹ The observed non-significant association may have been due to the smaller number of men and HF endpoints evaluated in these studies. In the present investigation, we noted a statistically significant 49% increase in the risk of HF among overweight men, suggesting a continuous gradient of HF risk across increasing categories of BMI (lean to overweight to obese).

In multivariable analyses of 5545 men in the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study, compared with low levels of recreational physical activity (determined using the question: “Do you get much exercise in things you do for recreation [sports, or hiking, or anything like that], or hardly any exercise, or in between?”), medium to high levels of recreational physical activity were associated with a statistically nonsignificant 12% (95% CI –6 to 28%) decline in the risk of HF.⁸ In contrast, in our cohort of 21,094 men, vigorous physical activity (defined as exercise to the point of breaking a sweat) for at least 1 to 3 times a month conferred a significant 18% reduction in the risk of HF. The larger sample size of men investigated in our study and difference in the definition of physical activity may partially explain the reason for demonstrating a significant association between vigorous physical activity and the reduced risk of HF in our investigation.

Mechanisms

Several mechanisms by which elevated BMI increases the risk of HF have been proposed. These include promotion of atherogenic risk factors such as hypertension,^{23,24} insulin resistance,^{25,26} diabetes mellitus,^{27–29} and dyslipidemia,¹ that enhance the risk of myocardial infarction.^{30,31} These factors may mediate or independently increase the risk of HF.^{7,8,10,12,30,32} Excess weight may alter cardiac structure and function,^{33–35} activate neuroendocrine pathways,^{36–38} predispose to sleep-disordered breathing,^{39–41} and promote chronic kidney disease^{42–45} that may subsequently manifest as overt HF.³² Increased BMI is an anthropometric surrogate of surplus total body fat,⁴⁶ and evidence from animal models suggest direct myocardial lipotoxicity in the pathogenesis of cardiomyopathy.^{47–49}

Greater levels of physical activity promote weight loss,⁵⁰ improve lipoprotein profile,⁵¹ and reduce the risk of hypertension,⁵² diabetes mellitus,^{53,54} and coronary artery disease.^{55,56} These favorable influences on cardiovascular risk profile may, in turn, reduce the likelihood of HF.

Study strengths and limitations

The large sample size, prospective nature of analyses, long duration of follow-up, adequate adjustment for confounding variables (including interim myocardial infarction), and evaluation of composite of HF and all-cause death as an endpoint to account for competing risk of death are particular strengths of our study. Several limitations are also relevant. First, although the mean age of PHS participants were similar to other published cohorts from the general population,^{7–11} the incidence rate of HF was lower in the PHS. This is likely explained by the fact that the PHS is made up of physicians who were generally healthier in terms of coronary risk factors, presumably had better access to healthcare, and as a group belonged to a higher socioeconomic status. Second, measures of weight and height and frequency of vigorous physical activity were self-reported. This is likely to result in modest nondifferential misclassification that may underestimate the true hazard ratios of HF. Third, the small sample size (n=46) precluded evaluation of the impact of underweight status (BMI <18.5 kg/m²) on the risk of HF. Fourth, our study assessed the impact of vigorous physical activity, and its frequency was ascertained at one point in time. The intensity and frequency of activity may change over time, which conceivably underestimates the magnitude of the true association between vigorous physical activity and HF. Fifth, data on left ventricular function at the time of onset of HF were not available to assess the influence of excess weight and vigorous physical activity to the risk of HF with preserved versus impaired left ventricular ejection fraction. Finally, our study population consisted of men, and the results of our investigation cannot be generalized to women.

Future Implications

It is intriguing to note that exercise to the point of breaking a sweat even at frequency as low as 1 to 3 times a month was associated with a reduced risk of HF. This finding may imply that any vigorous physical activity is an indicator of healthier lifestyle in men at risk of developing HF. Whether specific domains (at work, for transport, in domestic duties, or in leisure time),³ modes (aerobic vs. muscle-strengthening, and intentional vs. usual activities), types (e.g., walking, jogging, swimming, bicycling, or stair-climbing), duration (short vs. long bouts of activity), or amount (total energy expenditure)¹⁵ of physical activity have different degrees of beneficial impact on the risk of HF needs further evaluation.

Our findings indicate that both overweight (preobese) and obese men have an increased risk of HF, and men with higher levels of vigorous physical activity have a reduced risk. Additional research is warranted to ascertain whether intentional weight reduction to optimal levels in overweight and obese individuals, together with improved physical activity would lessen the probability of HF. Meanwhile, on the basis of published evidence^{7–11} inclusive of prospective cohort data from the Framingham Heart study¹¹ and the present investigation from the PHS that demonstrate significantly increased risk of HF in overweight (preobese) women and men respectively, perhaps a BMI of <25 kg/m² represents an optimal goal for the primary prevention of HF. Clinical trials targeting improvements in BMI and physical activity levels will be critically important in determining whether our observational data bear clinical relevance.

In the United States, approximately 37% are overweight (preobese), 25% are obese, 38% do not achieve the recommended amount of physical activity, and 14% are inactive.⁴ Recent global estimates also reveal comparable high prevalence of excess weight and physical inactivity.⁵ Concurrently, HF continues to impose substantial morbidity, mortality, and financial costs.⁶ Hence, public health approaches to curtail excess weight, to maintain optimal weight, and to promote regular physical activity have the potential to limit the scourge of HF.

Acknowledgements

We thank the staff at the Physicians' Health Study for data management.

Funding/Support:

The study was supported in part by grants HL-26490 and HL-34595 from the National Heart, Lung and Blood Institute, Bethesda, Md; and grants CA-34944, CA-40360, and CA-097193 from the National Cancer Institute, Bethesda, Maryland.

Role of Sponsor:

The sponsoring organizations played no role in the design and conduct of the study; in the collection, management, analyses, and interpretation of data; or in the preparation, review, and approval of the manuscript.

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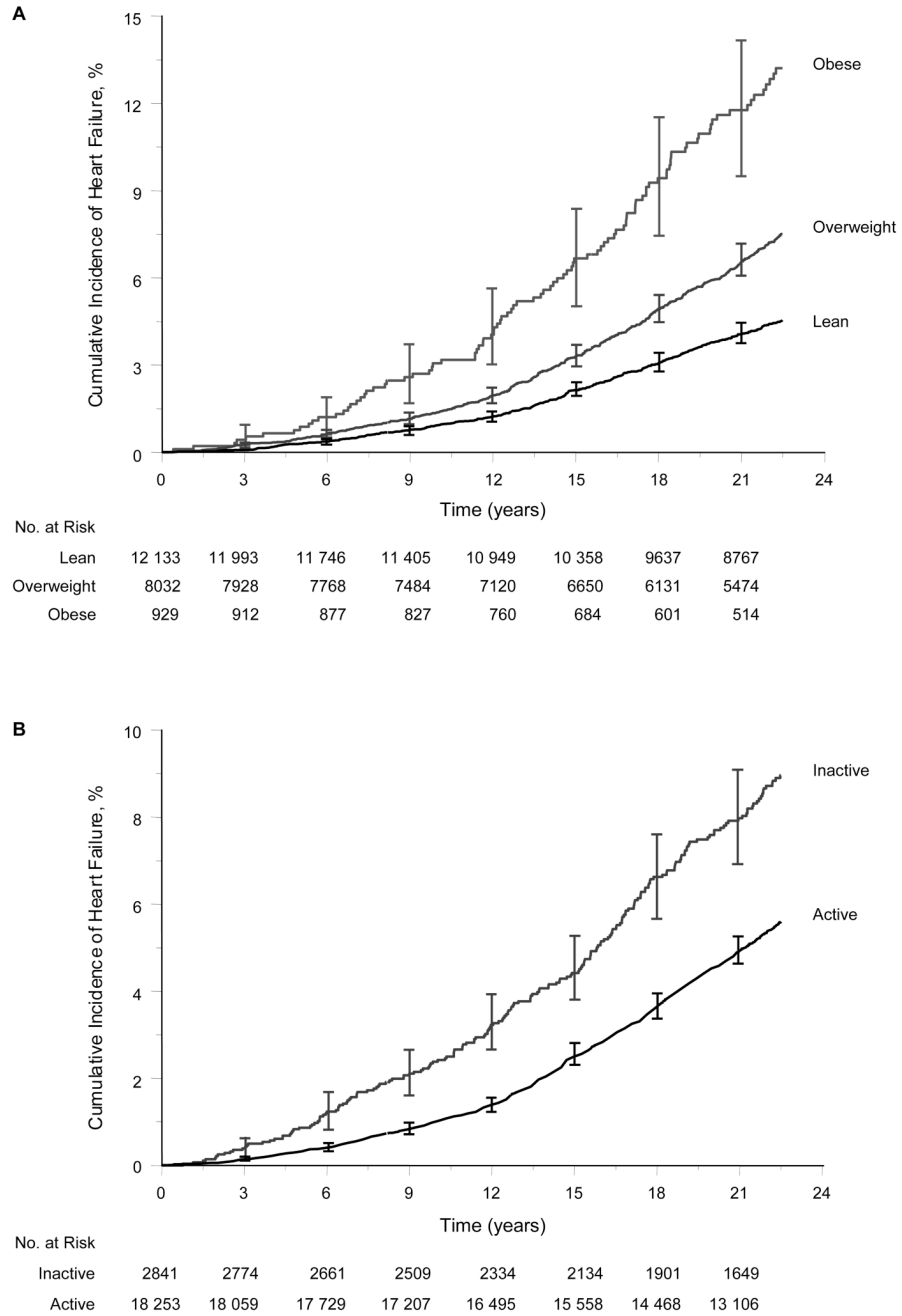
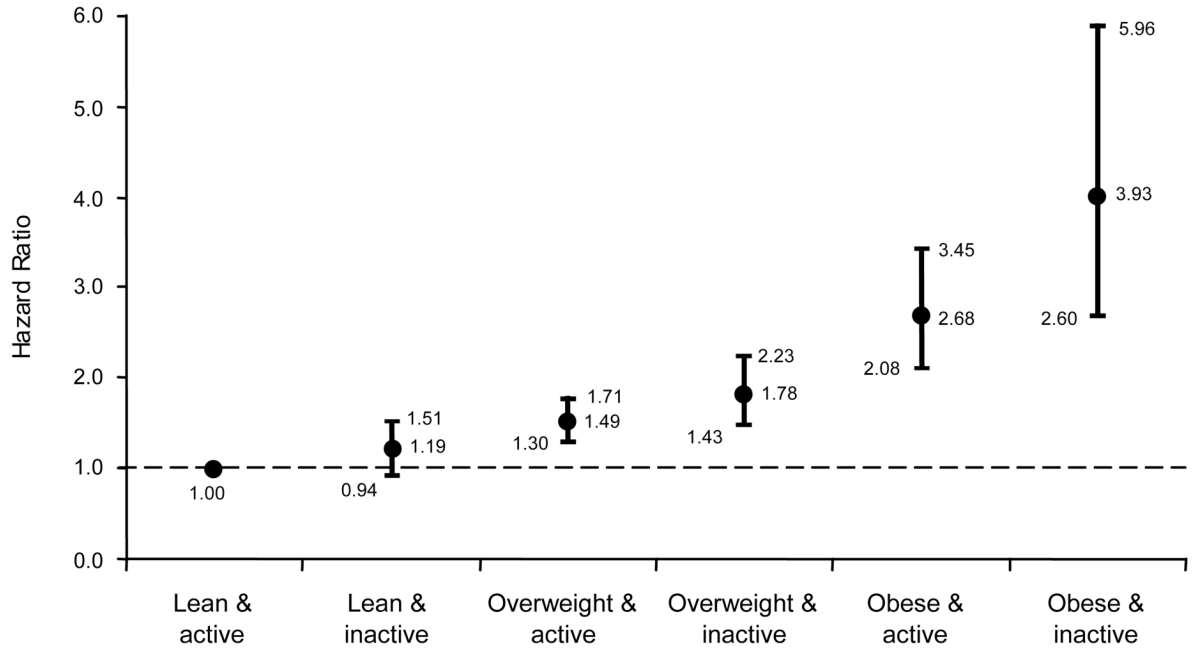


Figure 1. Cumulative Incidence of Heart Failure According to Categories of Body-mass Index (Panel A) and Vigorous Physical Activity (Panel B) at the Base-line Examination
 Body mass index is weight in kilograms (kg) divided by the square of the height in meters (m²). The body mass index was <25 kg/m² in lean participants, 25 to 29.9 kg/m² in overweight participants, and ≥30 kg/m² in obese participants. Active participants vigorously exercised for at least 1 to 3 times a month and inactive participants rarely/never exercised vigorously. Vertical bars represent 95% confidence intervals for the cumulative incidence.



	Lean & active	Lean & inactive	Overweight & active	Overweight & inactive	Obese & active	Obese & inactive
No. of Events	402	82	428	100	73	24
No. at Risk	10 667	1466	6836	1196	750	179
Percent Events	3.8	5.6	6.3	8.4	9.7	13.4
Person-y of Follow-Up	223 308	28 164	140 321	22 452	14 313	3098
Rate per 10 000 Person-y	18.0	29.1	30.5	44.5	51.0	77.5

Figure 2. Risk of Heart Failure According to Combined Categories of Body-mass Index and Vigorous Physical Activity at the Base-Line Examination

Vertical bars represent the 95 percent confidence intervals for the hazard ratios. The referent group includes men with a BMI lower than 25 and who vigorously exercised at least 1 to 3 times a month. Hazard ratios were adjusted for age, cigarette smoking (never [referent], past only, current), alcohol consumption (rarely/never, monthly, weekly, daily [referent]), and presence or absence of parental history of myocardial infarction, history of hypertension, diabetes mellitus, and hypercholesterolemia, and random assignment to aspirin or beta-carotene at base-line.

Table 1
 Baseline Characteristics According to Body Mass Index and Vigorous Physical Activity Categories in the Physicians' Health Study*

Characteristic	Body-mass index categories			Vigorous physical activity categories			
	Lean (n=12133)	Overweight (n=8032)	Obese (n=929)	p-value	Inactive (n=2841)	Active (n=18253)	p-value
Age (years)	52.9 ± 9.7	53.6 ± 9.1	52.8 ± 8.8	<0.001	55.7 ± 10.0	52.7 ± 9.3	<0.0001
Body mass index (kg/m ²)	23.0 ± 1.3	26.6 ± 1.3	32.4 ± 2.8	<0.0001	25.2 ± 3.2	24.7 ± 2.7	<0.0001
Lean (%)	100	—	—		51.6	58.4	
Overweight (%)	—	100	—		42.1	37.4	
Obese (%)	—	—	100		6.3	4.1	
Vigorous physical activity (%)				<0.0001			
Inactive (rarely/never)	12.1	14.9	19.3		100	—	
Low active (1-3/month)	12.6	16.1	18.3		—	16.4	
Medium active (1-4/week)	56.0	56.3	53.0		—	64.7	
High active (5-7/week)	19.3	12.7	9.5		—	18.9	
Parental history of myocardial infarction	9.0	9.6	10.5	0.12	8.2	9.4	0.025
Cigarette smokers (%)				<0.0001			
No	51.7	47.1	42.8		45.1	50.2	<0.0001
Past	38.1	41.0	43.5		39.7	39.4	
Current	10.2	11.9	13.7		15.1	10.4	
Alcohol consumption (%)				<0.0001			
Rarely	14.4	15.2	19.5		19.8	14.1	<0.0001
Monthly	10.7	11.2	15.8		14.1	10.7	
Weekly	49.1	49.5	46.6		40.1	50.5	
Daily	25.8	24.1	18.1		26.1	24.6	
History of hypertension (%)	18.9	28.8	42.4	<0.0001	29.8	22.8	<0.0001
Blood pressure (mm Hg)							
Systolic	124.3 ± 11.4	128.1 ± 11.7	132.4 ± 12.8	<0.0001	127.8 ± 12.5	125.8 ± 11.7	<0.0001
Diastolic	77.7 ± 7.4	80.0 ± 7.3	82.7 ± 7.9	<0.0001	79.7 ± 7.6	78.7 ± 7.5	<0.0001
History of diabetes mellitus (%)	2.2	3.2	6.7	<0.0001	5.8	2.3	<0.0001
History of hypercholesterolemia (%)							

Characteristic	Body-mass index categories			Vigorous physical activity categories		
	Lean (n=12133)	Overweight (n=8032)	Obese (n=929)	Inactive (n=2841)	Active (n=18253)	p-value
Present	9.8	11.6	10.9	11.5	10.4	0.066
Missing	11.4	12.2	14.7	11.0	12.0	
Study medications						
Aspirin (%)	50.3	49.5	49.7	49.5	50.0	0.57
Beta-carotene	49.9	50.0	51.9	49.2	50.2	0.39

* Body mass index is weight in kilograms (kg) divided by the square of the height in meters (m²). The body mass index was <25 kg/m² in lean participants, 25 to 29.9 kg/m² overweight participants, and ≥30 kg/m² in obese participants. Data on blood pressure were available for 10755 participants in the lean group, 7124 participants in the overweight group, 818 participants in the obese group, 2457 participants in the inactive group, and 16240 participants in the active group. Plus – minus values are means ± standard deviation.

Table 2
Results of Cox Proportional Hazards Regression Models Evaluating the Association of Body Mass Index and Vigorous Physical Activity to the Risk of Heart Failure

	No. of events/ No. at risk (%)	Follow-Up, Person-y (Rate per 10 000 Person-y)	Hazard ratio (95% confidence interval)		
			Age-adjusted	Multivariable-adjusted*	Multivariable-adjusted [†]
I. Body mass index (kg/m²)					
A. As continuous variable					
Per unit increment	1109/21094 (5.3)	431,654 (25.7)	1.14 (1.12–1.16)	1.13 (1.11–1.15)	1.11 (1.09–1.13)
B. As categorical variable					
Lean (<25)	484/12133 (4.0)	251,471 (19.2)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Overweight (25 to 29.9)	528/8032 (6.6)	162,773 (32.4)	1.65 (1.46–1.87)	1.62 (1.43–1.83)	1.49 (1.32–1.69)
Obese (≥30)	97/929 (10.4)	17,411 (55.7)	3.54 (2.85–4.41)	3.38 (2.71–4.21)	2.80 (2.24–3.50)
P for trend			<0.0001	<0.0001	<0.0001
II. Vigorous Physical Activity					
A. As dichotomous variable					
Inactive (rarely/never)	206/2841 (7.3)	53,713 (38.4)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Active (≥1 to 3 times a month)	903/18253 (4.9)	377,941 (23.9)	0.74 (0.63–0.86)	0.76 (0.66–0.89)	0.82 (0.70–0.96)
B. As 4-category variable					
Rarely/never	206/2841 (7.3)	53,713 (38.4)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1 to 3 times a month	145/2991 (4.8)	62,190 (23.3)	0.76 (0.61–0.94)	0.77 (0.62–0.96)	0.78 (0.63–0.97)
1 to 4 times a week	610/11813 (5.2)	245,208 (24.9)	0.78 (0.66–0.91)	0.80 (0.68–0.94)	0.86 (0.73–1.01)
5 to 7 times a week	148/3449 (4.3)	70,543 (21.0)	0.60 (0.49–0.74)	0.64 (0.52–0.79)	0.73 (0.59–0.90)
P for trend			<0.0001	<0.001	0.016

* Adjusted for age, cigarette smoking (never [referent], past only, and current), alcohol consumption (rarely/never, monthly, weekly, and daily [referent]), parental history of myocardial infarction, and random assignment to aspirin or beta-carotene in all models (baseline covariates not likely in the causal pathway).

[†] Adjusted for aforementioned baseline covariates and vigorous physical activity (rarely/never [referent], and ≥1–3 times a month) in models IA and IB and body-mass index (lean [referent], overweight, and obese) in models IIA and IIB.

‡ Adjusted for all above baseline covariates and presence or absence of history of hypertension, diabetes mellitus, and hypercholesterolemia (baseline covariates likely in the causal pathway)

Table 3

Results of Cox Proportional Hazards Regression Models Evaluating the Association of Body Mass Index and Vigorous Physical Activity to the Risk of Heart Failure Stratified According to Various Levels of Baseline Covariates

	No. of events/No. at risk (%)	Follow-Up, Person-y (Rate per 10000 Person-y)	Multivariable Hazardratio* (95% CI)	P for Interaction	
I. Body mass index as a continuous variable (per 1 kg/m² increment)					
A. Age					
<50 years	126/8704 (1.4)	194,427 (6.5)	1.15 (1.10–1.20)	0.020	
50–59.9 years	405/7147 (5.7)	150,136 (27.0)	1.09 (1.06–1.12)		
≥60 years	578/5243 (11.0)	87,271 (66.2)	1.09 (1.06–1.12)		
B. Diabetes mellitus					
No	1012/20,505 (4.9)	422,477 (24.0)	1.11 (1.09–1.13)	<0.0001	
Yes	97/589 (16.5)	9178 (105.7)	1.07 (1.02–1.12)		
II. Vigorous physical activity as a dichotomous variable					
A. Diabetes Mellitus					
No					
Inactive (rarely/never)	183/2675 (6.8)	51,334 (35.6)	1.00 (referent)	<0.001	
Active (≥1 to 3 times a month)	829/17,830 (4.6)	371,143 (22.3)	0.80 (0.68–0.94)		
Yes					
Inactive (rarely/never)	23/166 (13.9)	2380 (96.6)	1.00 (referent)		
Active (≥1 to 3 times a month)	74/423 (17.5)	6798 (108.9)	1.02 (0.63–1.64)		

* Adjusted for cigarette smoking (never [referent], past only, and current), alcohol consumption (rarely/never, monthly, weekly, and daily [referent]), parental history of myocardial infarction, random assignment to aspirin or beta-carotene, and presence or absence of history of hypertension, and hypercholesterolemia in all models, and additionally for diabetes mellitus and vigorous physical activity (rarely/never [referent], and ≥1–3 times a month) in model IA, age (per year increment) and vigorous physical activity in model IB, and age and body-mass index (per 1 kg/m²) in model IIA.