JAMA Internal Medicine | Original Investigation

Association of Obesity or Weight Change With Coronary Heart Disease Among Young Adults in South Korea

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IMPORTANCE Previous studies have shown a U- or J-shaped association of body mass index (BMI) or change in BMI with coronary heart disease (CHD) among middle-aged and elderly adults. However, whether a similar association exists among young adults is unclear.

OBJECTIVE To determine whether an association exists between BMI or BMI change with CHD among young adults.

DESIGN, SETTING, AND PARTICIPANTS This population-based longitudinal study used data obtained by the Korean National Health Insurance Service from 2002 to 2015. The study population comprised 2 611 450 men and women aged between 20 and 39 years who underwent 2 health examinations, the first between 2002 and 2003 and the second between 2004 and 2005.

EXPOSURES World Health Organization Western Pacific Region guideline BMI categories of underweight, normal weight, overweight, obese grade 1, and obese grade 2 derived during the first health examination and change in BMI calculated during the second health examination.

MAIN OUTCOMES AND MEASURES Body mass index (calculated as weight in kilograms divided by height in meters squared). Absolute risks (ARs), adjusted hazard ratios (aHRs), and 95% CIs for acute myocardial infarction or CHD during follow-up from 2006 to 2015.

RESULTS Data from 1 802 408 men with a mean (SD) age of 35.1 (4.8) years and 809 042 women with a mean (SD) age of 32.5 (6.3) years were included. The mean (SD) BMI was 23.2 (3.2) for the total population, 24.0 (3.0) for men, and 21.4 (2.9) for women. Compared with normal weight men, overweight (AR, 1.38%; aHR, 1.18 [95% CI, 1.14-1.22]), obese grade 1 (AR, 1.86%; aHR, 1.45 [95% CI, 1.41-1.50]), and obese grade 2 (AR, 2.69%; aHR, 1.97 [95% CI, 1.86-2.08]) men had an increased risk of CHD ($P < .001$ for trend). Similarly, compared with normal weight women, overweight (AR, 0.77%; aHR, 1.34 [95% CI, 1.24-1.46]), obese grade 1 (AR, 0.95%; aHR, 1.52 [95% CI, 1.39-1.66]), and obese grade 2 (AR, 1.01%; aHR, 1.64 [95% CI, 1.34-2.01]) women had an increased risk of CHD ($P < .001$ for trend). Compared with participants who maintained their weight at normal levels, those who became obese had elevated CHD risk among men (0.35% increase in AR; aHR, 1.35 [95% CI, 1.17-1.55]) and women (0.13% increase in AR; aHR, 1.31 [95% CI, 0.95-1.82]). Weight loss to normal levels among obese participants was associated with reduced CHD risk for men (0.58% decrease in AR; aHR, 0.77 [95% CI, 0.64-0.94]) and women (0.57% decrease in AR; aHR, 0.66 [95% CI, 0.45-0.98]).

CONCLUSIONS AND RELEVANCE Obesity and weight gain were associated with elevated risk of CHD among young adults in this study. Studies that prospectively determine the association between weight change and CHD risk are needed to validate these findings.

JAMA Intern Med. doi:10.1001/jamainternmed.2018.2310
Published online June 18, 2018.

Supplemental content

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Coronary heart disease (CHD) is the leading cause of death globally, with 8.1 million deaths in 2013 being due to CHD.[1] Furthermore, CHD-associated mortality is expected to increase by 100% among men and 80% among women from 1990 to 2020,[2] highlighting the importance of identifying and controlling risk factors for CHD. Despite previous implications of obesity being a risk factor for CHD, the association between obesity and CHD has been controversial. Recent studies have shown that being overweight or obese is associated with lower risk of cardiovascular disease (CVD) or CVD-associated death, whereas being underweight is associated with increased risk of CVD, a phenomenon called the obesity paradox.[3,4] Moreover, numerous previous studies investigating the association between weight change and CVD and CVD-related mortality have shown a U- or J-shaped association, in which weight gain or loss leads to increased risk of CVD-related death.[5,6]

One plausible explanation for the obesity paradox may be that being slightly overweight or obese is associated with greater lean mass.[7] Older adults who lose weight lose mostly lean mass,[8] which could contribute to the increased risk of CVD events after weight loss. Because the body composition of fat and muscle mass is altered with age, the contributions of body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and change in BMI on CHD among middle-aged and elderly adults may differ from those among young adults. However, few studies have investigated the association between BMI or change in BMI with CHD among young adults.

In this large population-based longitudinal study, we used the Korean National Health Insurance Service (NHIS) database to assess whether an association exists between BMI or a change in BMI and the risk of developing acute myocardial infarction (AMI) or CHD among young adults.

Key Points

Question Does an association exist between body mass index or a change in body mass index and coronary heart disease among young adults?

Findings In this population-based longitudinal study of 2 611 450 men and women aged 20 to 39 years, high body mass index and body mass index gain were significantly associated with elevated risk of coronary heart disease, whereas body mass index loss was associated with reduced risk of coronary heart disease.

Meaning Obesity and weight gain were associated with increased risk of coronary heart disease among young adults although prospective studies are needed to validate these findings.

Methods

Study Population

The NHIS provides mandatory health insurance for all South Korean citizens, covering nearly all forms of health care, including health screening examinations for all employed and self-employed insured individuals aged 20 years or more as well as all dependents aged 40 years or older.[9] The NHIS database includes data on sociodemographic characteristics, hospital admissions, outpatient department visits, pharmaceutical visits, and health screening examinations. Health screening examinations include information on health behavior obtained from a questionnaire, physical examinations, and blood tests. In total, 74.8% of those who were eligible participated in the health screening examinations in 2014.[9] Several studies have used the NHIS database for epidemiologic studies, and its validity has been described in detail elsewhere.[9-11] The Seoul National University Hospital (Seoul, South Korea) institutional review board approved this study and waived the requirement for informed patient consent because data in the NHIS database are anonymized in adherence with strict confidentiality guidelines.

Data were obtained from the NHIS database between 2002 and 2015 for all individuals aged between 20 and 39 years in 2002. Among the 2 692 643 participants who underwent health examinations during the first (2002 and 2003) and second (2004 and 2005) health screening periods, 1721 individuals with missing BMI values were excluded. In addition, 90 individuals who died as well as 6168 individuals who had received a diagnosis of CHD before the index date of January 1, 2006, were excluded. The 73 214 individuals with missing covariate values were also excluded. The final study population consisted of 2 611 450 men and women.

Key Variables

The BMI was determined during each health examination period. When evaluating the association of BMI with AMI or CHD, BMI values from the second (2004 and 2005) health screening period were used. Participants were categorized by BMI using the World Health Organization Western Pacific Region guideline strata of underweight (<18.5), normal weight (18.5-22.9), overweight (23.0-24.9), obese grade 1 (25.0-29.9), or obese grade 2 (≥30.0).[12] The change in BMI was calculated by subtracting BMI values obtained during the second health examination from those of the first health examination, and the resulting change was categorized as normal (<23.0), overweight (23.0-24.9), or obese (≥25.0).

Hospital admission records and death certificates were used to identify AMI and CHD events. All diagnoses on hospital discharge or death are recorded in the NHIS database using *International Classification of Diseases, 10th Revision* (*ICD-10*) codes from the World Health Organization. Causes of death were determined by physicians at the time of death. Because hospital admission records must be submitted to the NHIS for hospitals to receive payment, the follow-up for CHD events is likely to be complete. Consistent with the American Heart Association, the *ICD-10* codes for AMI of I21 and for CHD of I20 to I25 were used.[13] We defined an event of CHD as 2 or more days of hospital admission or death with causes listed as *ICD-10* codes for AMI or CHD. Multiple previous studies have used hospital admission records and death certificates to identify cardiovascular events using the NHIS data.[14,15]

Statistical Analysis

All participants were followed up starting January 1, 2006, and ending at a CHD event, date of death, or December 31, 2015,

whichever came first. The following were considered covariates: age (continuous variable; years), household income (categorical variable; first, second, third, or fourth quartiles), physical activity (categorical variable; none, 1-2, 3-4, 5-6, or 7 times per week), alcohol consumption (categorical variable; none, 0-1, 1-2, 3-4, or 5 or more times per week), tobacco consumption (categorical variable; never, past, quit, light, moderate, or heavy), systolic blood pressure (continuous variable), fasting serum glucose level (continuous variable), total cholesterol (continuous variable), or Charlson comorbidity index (CCI; continuous variable).

Individuals who quit were defined as those who reported having smoked tobacco during the first health examination but having quit during the second health examination, whereas past tobacco smokers were those who reported having quit in both the first and second health examinations. Light, moderate, and heavy smokers were those who reported having smoked 1 to 9, 10 to 19, or 20 or more cigarettes per day, respectively. Household income was derived from each patient's insurance premium, and the CCI was calculated using the *ICD-10* codes for major comorbidities between 2002 and 2005. The algorithm for the calculation of CCI using *ICD-10* codes was adapted from another study.[16]

Absolute risk (AR) was calculated by determining the percentage of events per number of people based on BMI or BMI change. Cox proportional hazards regression analysis was conducted to obtain the adjusted hazard ratios (aHRs) and 95% CIs of AMI and CHD based on BMI and change in BMI. The risk of AMI and CHD were calculated after adjustments for all covariates. Restricted cubic splines[17] of BMI or BMI change were used to graphically assess the association between BMI or a change in BMI with AMI or CHD. The lowest value of the Akaike information criteria was used to determine the number of knots, using a range of 3 to 7 knots. Stratified subgroup analyses were conducted by dividing the participants into subgroups for age, physical activity, smoking, and CCI. The aHRs of CHD for the covariates as well as per unit of BMI or change in BMI were determined. The aHRs of CHD were determined based on BMI after adjustments for metabolic mediators.

Statistical significance was defined as 2-sided *P* values <.05. All analyses were conducted with SAS, version 9.4 (SAS Institute Inc) and Stata, version 14 (Stata Corp).

Results

In total, 30 372 CHD events were detected during 25 868 244 person-years of follow-up. The mean (SD) BMI was 23.2 (3.2) for the total population, 24.0 (3.0) for men, and 21.4 (2.9) for women (**Table 1**). The aHRs of the covariates for CHD are provided in eTable 1 in the Supplement. Older age, lower household income, and tobacco or alcohol consumption as well as higher blood pressure, fasting serum glucose level, total cholesterol level, and CCI were associated with increased risk of CHD.

Higher BMI was associated with increased risk of AMI and CHD among both men and women (**Figure 1**). A BMI gain was associated with greater risk of AMI and CHD among men and women, whereas a BMI loss was associated with decreased risk of AMI and CHD for both sexes (**Figure 2**). Compared with normal weight individuals, men who were in the overweight (AR, 1.38%; aHR, 1.18 [95% CI, 1.14-1.22]), obese grade 1 (AR, 1.86%; aHR, 1.45 [95% CI, 1.41-1.50]), or obese grade 2 (AR, 2.69%; aHR, 1.97 [95% CI, 1.86-2.08]) strata and women who were in the overweight (AR, 0.77%; aHR, 1.34 [95% CI, 1.24-1.46]), obese grade 1 (AR, 0.95%; aHR, 1.52 [95% CI, 1.39-1.66]), or obese grade 2 (AR, 1.01%; aHR, 1.64 [95% CI, 1.34-2.01]) strata had increased risk of CHD (*P* < .001 for trend for each sex) (**Table 2**). The risks of AMI and CHD were significantly elevated for every unit increase in BMI and change in BMI for both sexes (eTable 2 in the Supplement). The increased risks of CHD for overweight and obese participants were preserved when the study population was grouped by age, physical activity, smoking status, or CCI (eTable 3 in the Supplement). The association of high BMI with CHD appeared to be stronger among women with a history of smoking compared with that for men who had ever smoked.

Table 3 and eTable 4 in the Supplement indicate the association of change in the BMI strata with AMI or CHD. Weight gain among normal weight individuals to obese levels was associated with greater risk of CHD among men (0.35% increase in AR; aHR, 1.35 [95% CI, 1.17-1.55]) and women (0.13% increase in AR; aHR, 1.31 [95% CI, 0.95-1.82]). Compared with obese individuals who maintained their weight, those who reduced their weight to normal levels had reduced risk of CHD for men (0.58% decrease in AR; aHR, 0.77 [95% CI, 0.64-0.94]) and women (0.57% decrease in AR; aHR, 0.66 [95% CI, 0.45-0.98]). Compared with those who maintained normal weight, those who were overweight at baseline but became normal weight had elevated risk of CHD among both men (aHR, 1.13 [95% CI, 1.05-1.21]) and women (aHR, 1.24 [95% CI, 1.07-1.42]).

The contribution of metabolic mediators to the risk of BMI on CHD are given in eTable 5 in the Supplement. Before adjustments for the metabolic mediators, the aHRs (95% CI) for individuals in the obese grade 2 stratum were 2.51 (2.38-2.65) for men and 1.95 (1.59-2.37) for women. After adjustments for all 3 metabolic mediators, the aHRs (95% CI) for individuals in the obese grade 2 stratum were 1.97 (1.86-2.08) for men and 1.64 (1.34-2.01) for women, corresponding to an excess risk of obesity to CHD of 35.8% (34.5%-37.7%) for men and 32.6% (26.3%-42.4%) for women.

Discussion

In this large-scale, population-based, longitudinal study, we showed that high BMI was associated with increased risk of AMI and CHD among young adults. Furthermore, BMI gain was associated with increased risk, whereas BMI loss was associated with reduced risk of AMI and CHD. To our knowledge, this is the first study to show that losing weight and maintaining normal BMI is associated with decreased risk of CHD among young adults.

The results from previous prospective studies with similar age groups are in accordance with the increased risk of CHD

Table 1. Descriptive Characteristics of Study Participants

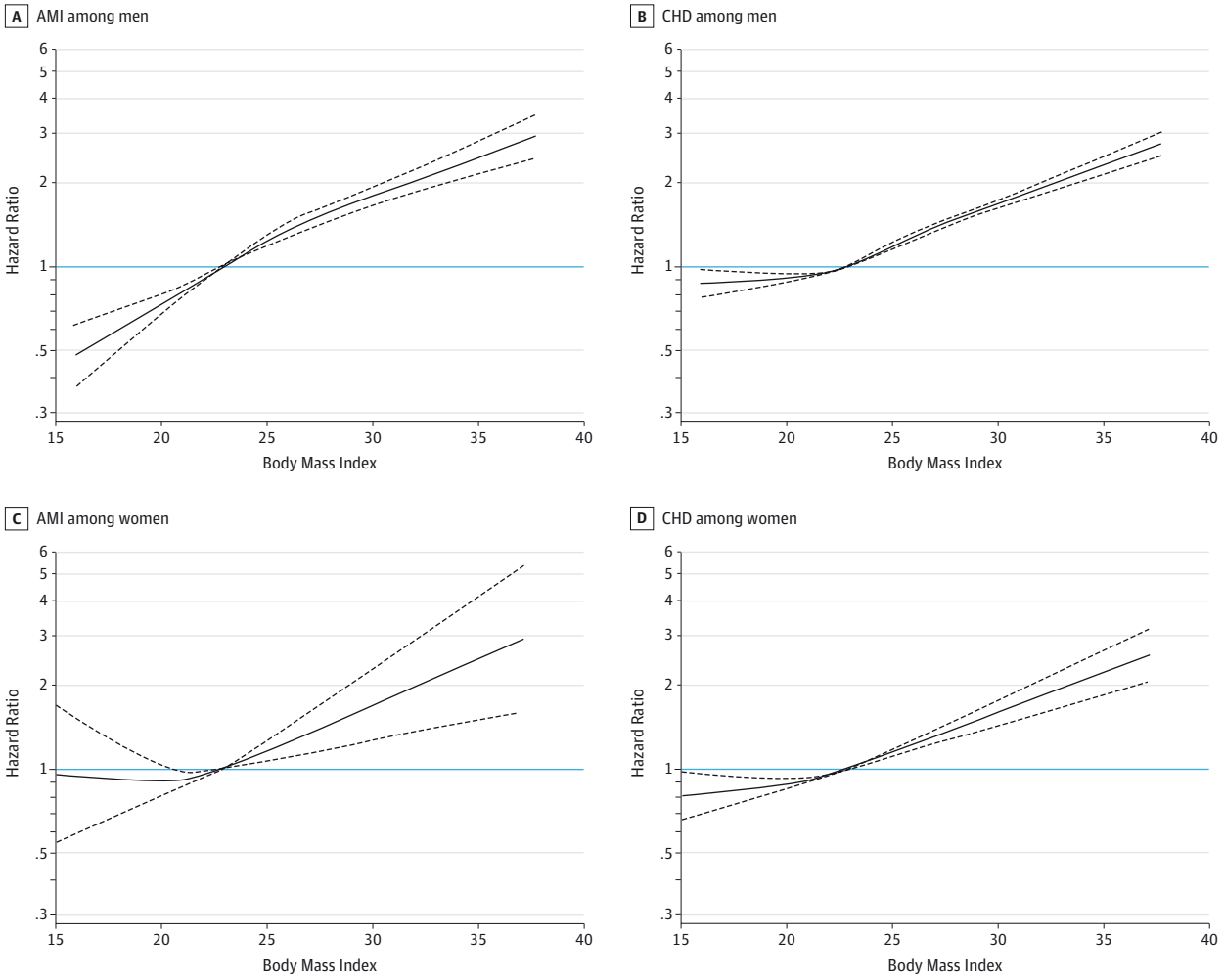
Characteristic	Participants, No. (%)		
	Total	Men	Women
Total No.	2 611 450	1 802 408	809 042
Age, mean (SD), y	34.3 (5.5)	35.1 (4.8)	32.5 (6.3)
20-24	104 416 (4.0)	30 126 (1.7)	74 290 (9.2)
25-29	458 525 (17.6)	211 055 (11.7)	247 470 (30.6)
30-34	751 357 (28.8)	569 014 (31.6)	182 343 (22.5)
≥35	1 297 152 (49.7)	992 213 (55.1)	304 939 (37.7)
BMI, mean (SD)	23.2 (3.2)	24.0 (3.0)	21.4 (2.9)
<18.5	139 029 (5.3)	37 717 (2.1)	101 312 (12.5)
18.5-22.9	1 150 812 (44.1)	637 079 (35.4)	513 733 (63.5)
23.0-24.9	590 128 (22.6)	480 852 (26.7)	109 276 (13.5)
25.0-29.9	660 134 (25.3)	585 534 (32.5)	74 600 (9.2)
≥30.0	71 347 (2.7)	61 226 (3.4)	10 121 (1.3)
Household income, quartile			
First (lowest)	310 440 (11.9)	164 583 (9.1)	145 857 (18.0)
Second	570 296 (21.8)	328 567 (18.2)	241 729 (29.9)
Third	943 564 (36.1)	676 666 (37.5)	266 898 (33.0)
Fourth (highest)	787 150 (30.1)	632 592 (35.1)	154 558 (19.1)
Physical activity, sessions per week			
0	1 309 836 (50.2)	776 031 (43.1)	533 805 (66.0)
1-2	877 972 (33.6)	699 264 (38.8)	178 708 (22.1)
3-4	298 420 (11.4)	229 953 (12.8)	68 467 (8.5)
5-6	56 510 (2.2)	43 143 (2.4)	13 367 (1.7)
7	68 712 (2.6)	54 017 (3.0)	14 695 (1.8)
Alcohol consumption, drinks per week			
0	980 413 (37.5)	485 045 (26.9)	495 368 (61.2)
<1	730 575 (28.0)	518 142 (28.8)	212 433 (26.3)
1-2	708 256 (27.1)	618 401 (34.3)	89 855 (11.1)
3-4	163 284 (6.3)	153 768 (8.5)	9516 (1.2)
≥5	28 922 (1.1)	27 052 (1.5)	1870 (0.2)
Tobacco consumption			
Never	1 420 679 (54.4)	641 885 (35.6)	778 794 (96.3)
Past	172 870 (6.6)	161 517 (9.0)	11 353 (1.4)
Quit	108 717 (4.2)	106 151 (5.9)	2566 (0.3)
Light (1-9 cigarettes per day)	174 210 (6.7)	162 849 (9.0)	11 361 (1.4)
Moderate (10-19 cigarettes per day)	541 060 (20.7)	536 526 (29.8)	4534 (0.6)
Heavy (≥20 cigarettes per day)	193 914 (7.4)	193 480 (10.7)	434 (0.1)
Systolic blood pressure, mean (SD), mm Hg	119.7 (13.8)	122.9 (13.2)	112.4 (12.2)
Fasting serum glucose, mean (SD), mg/dL	90.4 (18.9)	92.0 (20.3)	87.0 (14.9)
Total cholesterol, mean (SD), mg/dL	187.0 (38.7)	191.2 (39.5)	177.5 (35.2)
Charlson comorbidity index			
0	1 326 181 (50.8)	947 982 (52.6)	378 199 (46.8)
1	896 511 (34.3)	597 197 (33.1)	299 314 (37.0)
≥2	388 758 (14.9)	257 229 (14.3)	131 529 (16.3)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

SI conversion factors: To convert serum glucose and total cholesterol to millimoles per liter, multiply by 0.0555 and 0.0259, respectively.

with high BMI observed in our study. For example, in a study investigating the association of BMI with CVD-related mortality, Selmer and Tverdal[18] found that the risk of dying of CHD increased for every 5-unit BMI increase among persons aged between 30 and 59 years (HR, 1.30; 95% CI, 1.21-1.39). Similarly, Seidell and colleagues[19] showed that the risk of dying of CHD increased among overweight and obese individuals aged between 30 and 54 years. In a large cohort study investigating weight gain from early to middle adulthood among US women in the Nurses' Health Study and US men in the Health Professionals Follow-Up Study cohorts, Zheng and colleagues[20] showed that weight gain from age 18 or 21 to 55 years was associated with elevated risk of CVD. Another previous study[21] investigating weight change and CHD using the Honolulu Heart Program cohort revealed that gaining 2.5 kg or more was associated with increased risk of CHD.

Figure 1. Association of Body Mass Index With Acute Myocardial Infarction (AMI) or Coronary Heart Disease (CHD) Among Young Adults



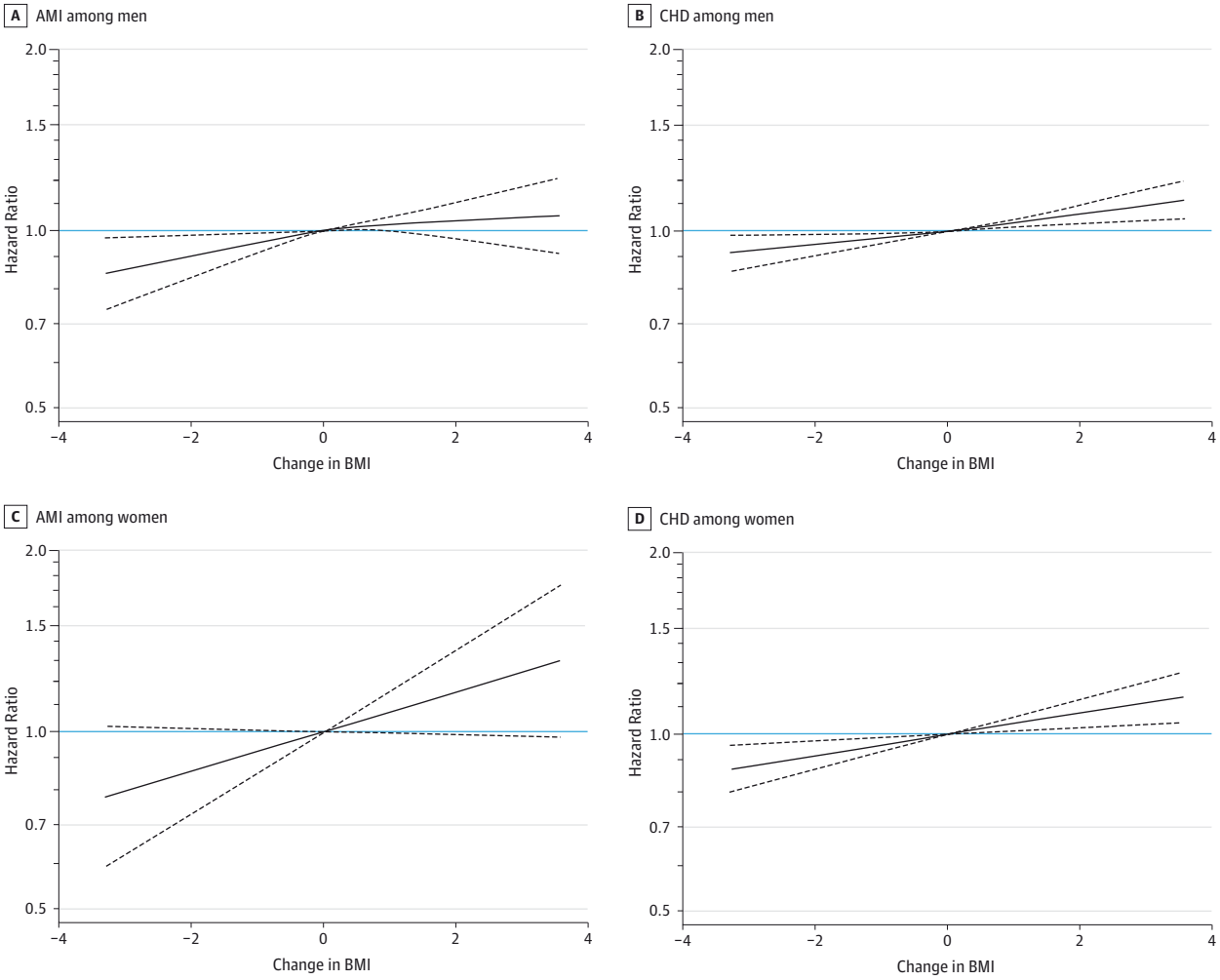
Solid lines indicate hazard ratios; dashed lines, 95% CIs from restricted cubic spline regression. Restricted cubic splines were constructed with knots chosen according to Akaike information criteria. Hazard ratios were calculated using Cox proportional hazards regression analysis after adjustments for age, household income, physical activity, alcohol and tobacco consumption, systolic blood pressure, fasting serum glucose level, total cholesterol level, and Charlson comorbidity index. Body mass index, calculated as weight in kilograms divided by height in meters squared, was measured during the second health examination (2004-2005).

Overweight and obesity increases the risk of CHD by elevating the risk of other cardiovascular risk factors, such as hypertension, dyslipidemia, and type 2 diabetes.[22,23] Obesity is associated with higher sympathetic nervous system activity, leptin concentrations, and angiotensin-aldosterone activity, which may lead to greater salt retention and higher blood pressure.[24] Obesity may also contribute to the development of type 2 diabetes and dyslipidemia by elevating C-reactive protein levels, thereby promoting a systemic inflammatory state.[25] We showed in the present study that blood pressure, total cholesterol levels, and fasting serum glucose levels may contribute to approximately one-third of the excess risk of CHD associated with obesity among young adults. These results are consistent with those of the BMI Mediated Effects study,[26] which found that blood pressure, cholesterol levels, and blood glucose levels accounted for 46% (95% CI, 42%-50%) of the excess risk of CHD with elevated BMI.

Unlike our results, previous studies have indicated a significantly increased risk of CHD among underweight individuals (HR, 1.70; 95% CI, 1.42-2.05) compared with those with normal BMI.[27,28] In addition, other studies[21,29] have failed to show that weight loss is associated with reduced risk of CHD, and a study investigating weight loss strategies and the risk of CHD using the Nurses' Health Study cohort[30] found that compared with no intervention, for individuals with BMIs greater than 25 and without chronic diseases, a 5% loss in BMI was associated with increased risk of CHD.

This discrepancy regarding the association between being underweight or losing weight and CHD may be due to the younger age of our study population compared with that in previous studies. Because the prevalence of sarcopenia, the reduction of lean mass, increases with age,[31] young adults tend to have greater lean mass and lower fat mass than their middle-aged and elderly counterparts with similar BMI. Several pre-

Figure 2. Association of the Change in Body Mass Index (BMI) With Acute Myocardial Infarction (AMI) or Coronary Heart Disease (CHD) Among Young Adults



Solid lines indicate hazard ratios, and dashed lines indicate 95% CIs from restricted cubic spline regression. Restricted cubic splines were constructed and hazard ratios were calculated as indicated in the legend to Figure 1 with the additional adjustment for baseline BMI, calculated as weight in kilograms divided by height in meters squared, measured during the first health examination (2002-2003).

vious studies using computed tomography,[32] dual-energy x-ray absorptiometry,[33] or other measures of body composition, such as calf muscle area,[31] have shown that young adults tend to have a higher muscle to fat mass ratio than older adults. Greater muscle mass is associated with better exercise capacity and cardiorespiratory fitness, which may in turn lead to decreased risk of CHD.[34,35] Because increased levels of leptin, a hormone released by adipocytes, have been associated with increased risk of CVD,[36] the greater proportion of fat mass among elderly adults who lose weight may elevate the risk of CHD.[22]

Greater frequencies of comorbidities and chronic diseases observed among middle-aged and elderly adults, in whom weight loss may act as a surrogate marker for worsening health, compared with younger adults might also have contributed to the increased risk of CHD among underweight individuals or to the lack of CHD risk-reducing benefit with weight loss in previous studies. Despite our study population consisting of young adults, a population generally associated with low rates of chronic diseases, we attempted to account for the possibility of serious illnesses contributing to weight loss. We conducted a sensitivity analysis by excluding patients who had received a diagnosis of CHD within the first 4 years of follow-up as well as by analyzing subgroups of individuals who had never smoked tobacco and had no chronic conditions (CCI of 0). Although we do not present a figure of this analysis, our results continued to indicate a reduced risk of CHD with weight loss.

Strengths and Limitations

There are several limitations to consider when interpreting the results of our study. First, owing to the observational nature of our study and because the reasons for the weight changes were unknown, we could not establish a cause-effect relationship between obesity or weight change and CHD. Thus, fu-

Table 2. Hazard Ratios for Acute Myocardial Infarction and Coronary Heart Disease by BMI Strata Among Young Adults

Outcome	Underweight (BMI < 18.5)	Normal (BMI = 18.5-22.9)	Overweight (BMI = 23.0-24.9)	Obesity Grade 1 (BMI = 25.0-29.9)	Obesity Grade 2 (BMI ≥ 30.0)
Male participants					
Total No.	37 717	637 079	480 852	585 534	61 226
AMI events, No.	52	1498	1676	2955	479
Person-years	374 420	6 334 620	4 782 171	5 818 395	607 076
Absolute risk, %[a]	0.14	0.24	0.35	0.50	0.78
aHR (95% CI)[b]	0.65 (0.50-0.86)	1 [Reference]	1.32 (1.23-1.42)	1.70 (1.59-1.81)	2.31 (2.08-2.57)
CHD events, No.	339	6606	6634	10 898	1644
Person-years	373 009	6 308 469	4 756 846	5 778 032	600 990
Absolute risk, %[a]	0.90	1.04	1.38	1.86	2.69
aHR (95% CI)[b]	0.99 (0.89-1.10)	1 [Reference]	1.18 (1.14-1.22)	1.45 (1.41-1.50)	1.97 (1.86-2.08)
Female participants					
Total No.	101 312	513 733	109 276	74 600	10 121
AMI events, No.	41	240	102	79	12
Person-years	1 010 725	5 124 987	1 089 714	743 274	100 863
Absolute risk, %[a]	0.04	0.05	0.09	0.11	0.12
aHR (95% CI)[b]	1.15 (0.82-1.61)	1 [Reference]	1.54 (1.21-1.95)	1.55 (1.19-2.02)	1.64 (0.91-2.96)
CHD events, No.	321	2225	840	711	102
Person-years	1 009 243	5 114 407	1 086 905	739 993	100 350
Absolute risk, %[a]	0.32	0.43	0.77	0.95	1.01
aHR (95% CI)[b]	1.02 (0.91-1.15)	1 [Reference]	1.34 (1.24-1.46)	1.52 (1.39-1.66)	1.64 (1.34-2.01)

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared and measured during the second health examination [2004-2005]).

[a] Calculated by the rate of events in percentage (number events per number of participants) during 10 y' follow-up.

[b] Calculated by Cox proportional hazards regression analysis adjusted for age, household income, physical activity, tobacco and alcohol consumption, systolic blood pressure, fasting serum glucose level, total cholesterol level, and Charlson comorbidity index.

ture prospective studies comparing intentional and unintentional weight loss are needed. Although we attempted to account for this by adjusting for and conducting subgroup analyses for physical activity according to the number of times per week (as determined in a self-reported questionnaire), this measure may be insufficiently sensitive to accurately determine the contribution of physical activity to the association between obesity and CHD. Therefore, studies investigating the association of BMI with CHD using a more detailed measure of physical activity, for example, with metabolic equivalent values, are needed.

Second, because waist circumference was not available, obesity was defined solely by BMI, which may not adequately reflect certain aspects of body composition, such as fat distribution, particularly because young adults have a higher proportion of muscle mass for the same BMI than do middle-aged and elderly adults.[31-33] Thus, future studies are needed that use other measures of adiposity, such as waist circumference, waist to hip ratio, and waist to height ratio. Third, the present study population comprised young adults who had health insurance through their employers or were self-insured, a group that may have certain sociodemographic tendencies, such as high income and healthy lifestyle behaviors. Although we attempted to take this into account by adjusting for household income, physical activity, and tobacco and alcohol consumption, future studies with a broader study population are needed to validate the findings of our study. Finally, the results on whether becoming normal weight among overweight or obese individuals eliminates the risk associated with having been overweight or obese are mixed. Although the reasons for this are unclear, the duration of obesity may play an important role, as longer duration obesity may lead to longer exposure to the CHD risk-increasing contributions of obesity. Therefore, future studies investigating the association between duration of obesity and CHD are also needed.

Despite these limitations, our study has a number of strengths. To our knowledge, this is the first study to investigate the association of BMI and change in BMI with CHD among young adults. Unlike the results from previous studies with study populations of middle-aged and elderly adults, our results show that weight reduction was associated with reduced risk of CHD among young adults. Furthermore, our large study population enhances the generalizability of our results. We were also able to adjust for key metabolic media-

Table 3. Hazard Ratios of AMI and CHD by Change in BMI Strata Among Young Adults[a]

Strata	Baseline BMI < 23.0			Baseline BMI = 23.0-24.9			Baseline BMI ≥ 25.0		
	Follow-up BMI < 23.0	Follow-up BMI = 23.0-24.9	Follow-up BMI ≥ 25.0	Follow-up BMI < 23.0	Follow-up BMI = 23.0-24.9	Follow-up BMI ≥ 25.0	Follow-up BMI < 23.0	Follow-up BMI = 23.0-24.9	Follow-up BMI ≥ 25.0
Male participants									
Total No.	597 890	135 002	15 208	69 859	271 660	122 776	7047	74 190	508 776
AMI events, No.	1301	355	56	225	999	438	24	322	2940
Person-years	5 945 096	1 343 371	151 254	694 148	2 701 914	1 221 136	69 797	736 887	5 053 081
Absolute risk, %[b]	0.22	0.26	0.37	0.32	0.37	0.36	0.34	0.43	0.58
Change in AR, %[b]	[Reference]	0.04	0.15	−0.05	1 [Reference]	−0.01	−0.24	−0.15	1 [Reference]
aHR[c,d] (95% CI)	1 [Reference]	1.18 (1.05-1.32)	1.67 (1.28-2.19)	0.87 (0.76-1.01)	1 [Reference]	1.02 (0.91-1.14)	0.66 (0.44-0.99)	0.80 (0.71-0.89)	1 [Reference]
CHD events, No.	5913	1510	204	926	3883	1758	106	1241	10 580
Person-years	5 921 487	1 337 221	150 448	690 601	2 687 355	1 214 367	69 390	732 269	5 014 207
Absolute risk, %[b]	0.99	1.12	1.34	1.33	1.43	1.43	1.50	1.67	2.08
Change in AR, %[b]	[Reference]	0.13	0.35	−0.10	1 [Reference]	0.00	−0.58	−0.41	1 [Reference]
aHR[c,d] (95% CI)	1 [Reference]	1.10 (1.03-1.16)	1.35 (1.17-1.55)	0.94 (0.87-1.01)	1 [Reference]	1.07 (1.01-1.13)	0.77 (0.64-0.94)	0.83 (0.78-0.88)	1 [Reference]
Female participants									
Total No.	574 648	41 961	6987	34 466	50 843	18 888	5931	16 482	58 846
AMI events, No.	258	35	2	21	45	20	2	22	69
Person-years	5 732 880	418 523	69 725	343 741	507 082	188 283	59 091	164 109	586 129
Absolute risk, %[b]	0.04	0.08	0.03	0.06	0.09	0.11	0.03	0.13	0.12
Change in AR, %[b]	[Reference]	0.04	−0.01	−0.03	1 [Reference]	0.02	−0.09	−0.01	1 [Reference]
aHR (95% CI)[c,d]	1 [Reference]	1.49 (1.04-2.12)	ND	0.79 (0.47-1.33)	1 [Reference]	1.23 (0.72-2.08)	ND	1.21 (0.75-1.98)	1 [Reference]
CHD events, No.	2306	272	37	213	402	168	27	166	608
Person-years	5 722 026	417 290	69 565	342 699	505 193	187 503	58 924	163 422	583 275
Absolute risk, %[b]	0.40	0.65	0.53	0.62	0.79	0.89	0.46	1.01	1.03
Change in AR, %[b]	[Reference]	0.25	0.13	−0.17	1 [Reference]	0.10	−0.57	−0.02	1 [Reference]
aHR (95% CI)[c,d]	1 [Reference]	1.31 (1.15-1.48)	1.31 (0.95-1.82)	0.95 (0.80-1.13)	1 [Reference]	1.22 (1.02-1.46)	0.66 (0.45-0.98)	1.08 (0.91-1.29)	1 [Reference]

Abbreviations: AMI, acute myocardial infarction; AR, absolute risk; aHR, adjusted hazard ratio; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; ND, not determined, owing to insufficient events.

[a] Baseline BMI was measured during the first health examination (2002-2003), and follow-up BMI was measured during the second health examination (2004-2005).

[b] Absolute risk calculated by the rate of events in percentage (events per number of people) during 10 years of follow-up.

[c] Hazard ratio calculated by Cox proportional hazards regression analysis adjusted for age, household income, physical activity, tobacco and alcohol consumption, systolic blood pressure, fasting serum glucose level, total cholesterol level, and Charlson comorbidity index.

[d] Risk compared among those within the same baseline BMI strata (eg, baseline BMI < 23.0).

tors, including blood glucose levels, blood pressure, and total cholesterol levels. Finally, we attempted to take into account the possibility of reverse causality by extensive subgroup and sensitivity analyses, which enhanced the reliability of our findings.

Conclusions

Obesity and weight gain were associated with greater CHD risk among young adults. The loss of weight for obese individuals was associated with reduced risk of CHD. Future prospective studies that investigate the association of intentional and unintentional weight change with CHD are needed to clarify the interpretations of our findings.

ARTICLE INFORMATION

Accepted for Publication: April 11, 2018.

Published Online: June 18, 2018. doi:10.1001/jamainternmed.2018.2310

Author Contributions: Dr S. M. Park 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.
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Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by a grant (20170322652-00) from the Ministry of Health and Welfare of South Korea.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Additional Information: This study used NHIS data (NHIS-2017-1-143) from the Korean NHIS.

REFERENCES

1. Roth GA, Huffman MD, Moran AE, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation*. 2015;132(17):1667-1678.

2. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases, part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation*. 2001;104(22):2746-2753.

3. Chen Y, Copeland WK, Vedanthan R, et al. Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium. *BMJ*. 2013;347:f5446.

4. Whitlock G, Lewington S, Sherliker P, et al; Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373(9669):1083-1096.

5. Nanri A, Mizoue T, Takahashi Y, Noda M, Inoue M, Tsugane S; Japan Public Health Center- based Prospective Study Group. Weight change and all-cause, cancer and cardiovascular disease mortality in Japanese men and women: the Japan Public Health Center-Based Prospective Study. *Int J Obes (Lond)*. 2010;34(2):348-356.

6. Bowman TS, Kurth T, Sesso HD, Manson JE, Gaziano JM. Eight-year change in body mass index and subsequent risk of cardiovascular disease among healthy non-smoking men. *Prev Med*. 2007;45(6):436-441.

7. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet*. 2006;368(9536):666-678.

8. Miller SL, Wolfe RR. The danger of weight loss in the elderly. *J Nutr Health Aging*. 2008;12(7):487-491.

9. Cheol Seong S, Kim YY, Khang YH, et al. Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea. *Int J Epidemiol*. 2017;46(3):799-800.

10. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: the National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol*. 2017;46(2):e15.

11. Seong SC, Kim YY, Park SK, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. *BMJ Open*. 2017;7(9):e016640.

12. Consultation WHOE; WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363(9403):157-163.

13. Mozaffarian D, Benjamin EJ, Go AS, et al; Writing Group Members; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation*. 2016;133(4):e38-e360.

14. Kim K, Park SM, Lee K. Weight gain after smoking cessation does not modify its protective effect on myocardial infarction and stroke: evidence from a cohort study of men. *Eur Heart J*. doi:10.1093/eurheartj/ehx761

15. Song YM, Cho HJ. Risk of stroke and myocardial infarction after reduction or cessation of cigarette smoking: a cohort study in Korean men. *Stroke*. 2008;39(9):2432-2438.

16. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139.

17. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med*. 1989;8(5):551-561.

18. Selmer R, Tverdal A. Body mass index and cardiovascular mortality at different levels of blood pressure: a prospective study of Norwegian men and women. *J Epidemiol Community Health*. 1995;49(3):265-270.

19. Seidell JC, Verschuren WM, van Leer EM, Kromhout D. Overweight, underweight, and mortality: a prospective study of 48,287 men and women. *Arch Intern Med*. 1996;156(9):958-963.

20. Zheng Y, Manson JE, Yuan C, et al. Associations of weight gain from early to middle adulthood with major health outcomes later in life. *JAMA*. 2017;318(3):255-269.

21. Galanis DJ, Harris T, Sharp DS, Petrovitch H. Relative weight, weight change, and risk of coronary heart disease in the Honolulu Heart Program. *Am J Epidemiol*. 1998;147(4):379-386.

22. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol*. 2009;53(21):1925-1932.

23. Messerli FH, Ventura HO, Reisin E, et al. Borderline hypertension and obesity: two prehypertensive states with elevated cardiac output. *Circulation*. 1982;66(1):55-60.

24. Poirier P, Giles TD, Bray GA, et al; American Heart Association; Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2006;113(6):898-918.

25. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006;444(7121):875-880.

26. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G; Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects). Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants. *Lancet*. 2014;383(9921):970-983.

27. Wormser D, Kaptoge S, Di Angelantonio E, et al; Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease:

collaborative analysis of 58 prospective studies. *Lancet*. 2011;377(9771):1085-1095.

28. Mongraw-Chaffin ML, Peters SAE, Huxley RR, Woodward M. The sex-specific association between BMI and coronary heart disease: a systematic review and meta-analysis of 95 cohorts with 1·2 million participants. *Lancet Diabetes Endocrinol*. 2015;3(6):437-449.

29. Willett WC, Manson JE, Stampfer MJ, et al. Weight, weight change, and coronary heart disease in women: risk within the 'normal' weight range. *JAMA*. 1995;273(6):461-465.

30. Danaei G, Robins JM, Young JG, Hu FB, Manson JE, Hernán MA. Weight loss and coronary heart disease: sensitivity analysis for unmeasured confounding by undiagnosed disease. *Epidemiology*. 2016;27(2):302-310.

31. Lauretani F, Russo CR, Bandinelli S, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol (1985)*. 2003;95(5):1851-1860.

32. Ohkawa S, Odamaki M, Ikegaya N, Hibi I, Miyaji K, Kumagai H. Association of age with muscle mass, fat mass and fat distribution in non-diabetic haemodialysis patients. *Nephrol Dial Transplant*. 2005;20(5):945-951.

33. Kyle UG, Genton L, Hans D, Karsegard L, Slosman DO, Pichard C. Age-related differences in fat-free mass, skeletal muscle, body cell mass and fat mass between 18 and 94 years. *Eur J Clin Nutr*. 2001;55(8):663-672.

34. O'Donovan G, Owen A, Kearney EM, et al. Cardiovascular disease risk factors in habitual exercisers, lean sedentary men and abdominally obese sedentary men. *Int J Obes (Lond)*. 2005;29(9):1063-1069.

35. Lee DC, Sui X, Artero EG, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. *Circulation*. 2011;124(23):2483-2490.

36. Romero-Corral A, Sierra-Johnson J, Lopez-Jimenez F, et al. Relationships between leptin and C-reactive protein with cardiovascular disease in the adult general population. *Nat Clin Pract Cardiovasc Med*. 2008;5(7):418-425.