All cause mortality and body mass index in a young Asian occupational cohort without baseline metabolic syndrome components

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Abbreviated title: underweight, overweight, obesity and mortality rates.

Grant support: The work was support by the MRC-KHIDI UK-KOREA PARTNERING AWARD to CDB, KS, and SW (Medical Research Council MC_PC_16016)
CDB is supported in part by the Southampton National Institute for Health Research Biomedical Research Centre.

Keywords: underweight, obesity, metabolic syndrome, mortality rates, smoking, all cause mortality

KS takes full responsibility for the data collection and integrity of the analyses. CDB, SHW, KS have written the manuscript and all authors have read and agree the manuscript as written.

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Abbreviations list: MetS, metabolic syndrome; ALT, alanine aminotransaminases; AST, aspartate transaminase; hsCRP, high sensitivity C Reactive Protein; gGT, gamma-glutamyl transpeptidase; HDLc, high density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; BMI, body mass index; cardiovascular disease (CVD), IR (insulin resistant/resistance)

Word count: 3372

Abstract

Background. The aim was to investigate associations between underweight, overweight and obesity and all cause, cancer and cardiovascular disease (CVD) mortality, excluding subjects with known CVD), diabetes, hypertension and components of the metabolic syndrome (MetS) at baseline.

Methods. The study population consisted of examinees participating in a health screening in Korea from 2002 to 2013. Data were analyzed in 162,194 subjects (in a retrospective cohort study design-median (interquartile range (IQR) follow up 4.9 (1.8- 8.5 years))). The outcomes were all cause mortality, cancer and CVD.

Results. The mean (age range) and median age (IQR) at baseline were 36.9(20.0-85.3) and 35.2 (30.8-40.6) years. There were 436 deaths during follow up. For men and women together, the fully adjusted HR for underweight and all cause mortality, cancer and CVD was 1.53 (95% CIs 1.06-2.20), 1.21 (95% CIs 0.68-2.14) and 1.34 (95% CIs 0.40-4.49) respectively. In contrast, the fully adjusted HR for overweight/obesity combined and all cause mortality was 0.77 (95%CIs 0.63-0.95) and there were non significant trends towards decreased cancer and CVD mortality. The association between overweight/obesity and all cause mortality was similar for men and women considered separately and for overweight and obesity as separate BMI categories. Smoking did not seem to explain the increased HR in the underweight BMI category.

Conclusions. In a young metabolically healthy adult cohort, underweight was associated with increased all cause mortality and overweight/obesity was associated with decreased all cause mortality if CVD, diabetes, hypertension and components of the metabolic syndrome (MetS) are excluded.

Introduction

Some population based studies that have investigated relationships between body mass index (BMI) and all cause mortality have shown lower all-cause mortality in people who are overweight (BMI) compared with normal weight subjects [1-5], whereas others have shown increased mortality.[6,7] Associations between BMI and all cause mortality vary by age and the effects of increasing BMI on mortality are less pronounced in the elderly than in young or middle-aged adults.[8] Recently, a U-shaped relationship between BMI and mortality has been shown in the elderly[9] and there may be a curvilinear relationship between BMI and mortality with the lowest mortality being found at BMIs towards the upper end of the normal weight category in younger age groups.[10] Thus there may be different associations between BMI and all cause mortality in younger versus older age groups.

BMI is a proxy measure for adiposity in population-based studies and it is well established that increasing body fat is strongly associated with components of the metabolic syndrome (MetS). Whether the components of the MetS, such as type 2 diabetes, hypertension or dyslipidemia are responsible for a relationship between body fatness and all cause mortality is uncertain, but we have recently shown in a large Korean cohort that co-existing CVD, diabetes or hypertension explained much of the increased risk of CVD mortality in obese individuals. [11]

Studies utilizing measurements of BMI are often criticized because BMI also reflects the amount of muscle mass, and a BMI measurement is not able to assess amounts of harmful ectopic, or visceral fat.[12] However, interesting recent data from a relatively small (n=1000) observational study of 6 year follow up in an elderly Korean population has questioned the harmful effects of visceral fat in the elderly population.[13] In this study, higher amounts of visceral fat, assessed by abdominal computed tomography, were associated with decreased all-cause mortality and specifically a 1 standard deviation (SD) increase in visceral fat mass was associated with a 36% decrease in all cause mortality.

Recently, the concept of metabolically healthy obesity (MHO) has been used to define a state where obesity is associated with better health (i.e. the ‘obesity paradox’[14]). Additionally, whether any association between underweight and increased all cause mortality is due to the presence of pre-existing cardiovascular and metabolic disease states (or risk factors) is not fully understood. Therefore, in a large, relatively young and healthy occupational cohort

(with low levels of pre-existing disease), our aim was to investigate associations between BMI and all cause mortality, cancer and CVD mortality, having excluded subjects from the analyses who had pre-existing diabetes, hypertension, CVD and components of the MetS at baseline. Specifically, we tested whether BMI was associated with mortality outcomes after subjects with established risk factors and diseases such as diabetes, CVD, hypertension and features of the MetS had been excluded.

Materials and Methods

The study population consisted of examinees who participated in a comprehensive health screening program at Kangbuk Samsung Hospital, Seoul, Korea from 2002 to 2012 (N=396,951). The purpose of the screening program is to promote health through early detection of chronic diseases and their risk factors. Additionally, in Korea, the Industrial Safety and Health Law requires employees to participate in annual or biennial health examinations. About 80% of the participants were employees of various companies and local governmental organizations and their spouses with the remaining participants registering individually for the program.

This analysis was performed in 2015. For this analysis, 234,757 people were excluded for one or more of the following reasons: 25 subjects with missing data on body mass index at baseline; two subjects were missing pulse and blood pressure; 86,649 subjects with a history of malignancy, CVD, hypertension or diabetes (**Figure 1**). Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, self-report history of hypertension, or current use of antihypertensive medication. Diabetes mellitus was defined as a fasting serum glucose level ≥126 mg/dl, a self-reported history of diabetes, or current use of diabetic medication. We then excluded participants who had any of the following metabolic abnormalities: 1)fasting blood glucose≥100 mg/dl or current use of blood glucose–lowering agents (n=94451); 2) blood pressure≥130/85 mm Hg or current use of blood pressure–lowering agents(n=92526); 3) triglyceride levels≥150 mg/dl or current use of lipid-lowering agents(n=100658); 4) high-density lipoprotein cholesterol (HDL-C)<40 mg/dl in men or<50 mg/dl in women(n=61114) [15]. After exclusion of these subjects, the total number of metabolically-healthy individuals included in the study was 162,194 [median (IQR) follow up=4.94 (1.77-8.49) years]. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, which exempted the requirement for informed consent as de-identified data were used for the analysis.

Data on medical history, medication use, and health-related behaviors were collected through a self-administered questionnaire while the physical measurements and serum biochemical parameters were measured by trained staff, all collected during the health examinations. Details regarding alcohol use included the frequency of intake per week and the average intake on each occasion. Current smokers were identified and the weekly frequency of

moderate- or vigorous-intensity physical activity assessed. Trained nurses measured sitting blood pressure with standard mercury sphygmomanometers. Blood specimens were sampled from the antecubital vein after more than 12 hours of fasting. Serum levels of glucose, total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol were measured using Bayer Reagent Packs (Bayer Diagnostics, Leverkusen, Germany) on an automated chemistry analyzer (Advia 1650™ Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). Regular calibration and quality control measurements were performed throughout the study period using a validated calibrator and quality control materials. The clinical laboratory has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BMI was classified according to Asian-specific criteria (underweight, BMI <18.5 kg/m^2; normal weight, BMI of 18.5 to 23 kg/m^2; overweight, BMI of 23 to 25 kg/m^2; and obese, BMI≥25 kg/m^2).

Mortality follow-up between January 1, 2002 and December 31, 2012 was based on the nationwide death certificate data of the Korea National Statistical Office. Deaths among subjects were confirmed by matching the information to death records. Death certificates from the National Statistical Office were identified with the use of identification numbers assigned to subjects at birth. Abstractors coded the causes of death according to the International Classification of Diseases, 10^{th} revision. Since all deaths in Korea are required by law to be reported to this office, the data on death from any cause used in this study can be regarded as accurate and others have used a similar approach to describe associations with all cause mortality in Korean subjects. [16]

Statistical analyses.

The $\chi 2$-test and student t-tests were used to compare the characteristics of the study participants at baseline according to whether subjects were alive or dead at follow up. The distribution of continuous variables was evaluated, and right-skewed variables (triglycerides, ALT, AST, GGT, hsCRP and HOMA-IR) were log-transformed for one-way analysis of variance (ANOVA) testing of between group differences. Descriptive statistics were used to summarize the characteristics of participants by BMI categories. Cox proportional hazards models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CIs),

for all-cause mortality, comparing the BMI categories with the normal weight BMI category as the reference group. The Fine and Gray proportional sub-distribution hazards regression analysis was also used to model CVD- and cancer- mortality while treating any other cause of death as a competing risk. [17] We initially adjusted for age and sex, and further adjusted for alcohol intake and exercise, educational attainment (college graduation or higher), center, year of screening exam). The proportional hazards assumption was checked by examining graphs of estimated log (-log) survival. We also performed stratified analysis in pre-specified subgroups defined by age (<50 vs. ≥50), sex (women vs. men), smoking (non-smoker vs. current smoker), alcohol intake (<20 vs. ≥20g of alcohol per day), vigorous exercise (<3 vs. ≥ 3 times a week), education level (<college graduation vs. ≥ college graduation), CRP (<1.0 vs. ≥1.0 mg/l) and fatty liver (no vs. yes); interactions between subgroups were tested using likelihood ratio tests comparing models with and without multiplicative interaction terms. The statistical analysis was performed using STATA version 14.0 (StataCorp LP, College Station, TX, USA). All reported p values are two tailed, and <0.05 were considered statistically significant.

Results

The mean (age range) and median age (IQR) at baseline were 36.9(20.0-85.3) and 35.2 (30.8-40.6) years. **Table 1** shows the baseline characteristics of the cohort according to whether subjects were alive or dead at follow up. The median (IQR) follow up was [4.94 (1.77-8.49)] years. Recognized cardiovascular risk factors were all adversely affected or influenced in those subjects who died during follow up. These risk factors included higher blood pressure, higher LDL-C concentration, lower HDL-C concentration, the percentage of people smoking, and educational attainment level.

Tables 2 and 3 show the baseline characteristics of the cohort by BMI categories (underweight, normal weight, overweight and obese) in men **(Table 2)** and in women **(Table 3)**. For men and for women, blood pressure and LDL-C concentration increased, with increasing BMI categories. In contrast, the percentage of men who were smokers was higher in the underweight BMI category and the percentage of people who were smokers was lower in the overweight and obese BMI categories, compared with the normal weight BMI category. Additionally, the proportion of people taking regular exercise increased with BMI category.

Table 4 shows the hazard ratios for associations between each BMI category and all cause mortality adjusted for age, and adjusted for multiple potential confounders with the normal weight BMI category as the reference group. Overweight and obesity were combined to increase the number of deaths in a single overweight/obesity group. The association between overweight/obesity and all cause mortality was similar for men and women considered separately. We modelled the shape of the association between BMI and all-cause mortality in men and women combined and these data are shown in **Figure 2**.

Table 5 shows the hazard ratios for associations between each BMI category and cancer mortality adjusted for age, and adjusted for multiple potential confounders with the normal weight BMI category as the reference group.

Additionally, despite the increase in CVD risk factors in the overweight/obese BMI category compared with other BMI categories, there was no increase in CVD deaths in the overweight/obese category. Although the number of CVD deaths was small in this young cohort, we investigated HRs for CVD mortality in each BMI category, adjusting for the same potential confounders that are shown in **Table 4**. In this analysis, although the 95%CIs were

wide, there was a similar pattern of the point estimates of HRs across BMI categories, to the pattern we had observed across BMI categories for all cause mortality, (**Table 6**).

The major causes of death by BMI category are shown in **(Table 7)** and these data show that was no increase in deaths from lung cancer or other key cancers in the underweight BMI category.

We investigated whether there were differences in the associations between BMI and all cause mortality in clinically relevant subgroups for each BMI category **(Table 8)**. In order to determine whether there were any differences between the overweight and obese groups, these two BMI groups were kept separate for this analysis. These data showed that smoking status was not associated with any increase in HR for all cause mortality in each BMI category, compared with the comparable HR for all cause mortality in non smokers in each BMI category. Interestingly, in the underweight group there was an increased risk of all cause mortality in the non smokers, whereas there was not any increase in mortality in current smokers.

Discussion

The novel results of our study show that in a young metabolically healthy adult cohort without diabetes, hypertension, CVD, or components of MetS, underweight was associated with increased all cause mortality and in the overweight and obesity groups there was a strong (non significant) trend towards decreased all cause mortality. Combining overweight and obesity, to increase the number of deaths into a single overweight/obesity group, the fully adjusted HR for overweight/obesity and all cause mortality showed a significant decrease in mortality . Despite there being a worse profile for established CVD risk factors such as increased blood pressure and LDL-C concentration, in the overweight and obese group, there was a significant decrease in the HR for all cause mortality in this BMI group.

Previously it has been shown that smoking accounted for the increase in HR for all cause mortality in the underweight BMI group. [16] In the underweight BMI group in our relatively young cohort, the percentage of both men and women who were smokers in this BMI category was higher than for any other BMI category. However, there was no increase in lung cancers detected in this BMI group and furthermore the sub group analyses showed that the HR for all cause mortality was not increased for smokers versus non smokers in any of the BMI groups. Thus our data does not seem to support the notion that smoking accounts for the increased HR for all cause mortality in underweight young metabolically healthy subjects.

A recent systematic review and meta-analysis of 97 studies provided a sample size of more than 2.88 million individuals and more than 270,000 deaths in which to study relationships between BMI and all cause mortality but there were few studies in Asian cohorts and in this ethnic group the influence of underweight and overweight/obesity is unclear. [1] Although we have studied ~162,000 young adults over an 11 year period of follow up, there were only 436 deaths, reflecting both the young age of the cohort and the exclusion of subjects with preexisting metabolic and CVD disease at baseline. However, our aim was to study associations between BMI and all cause mortality in these young adults and the size of our cohort and the 11 years of follow up at the beginning of the 21st century will help inform the size and necessary duration of follow up of other studies of this type in the future. Most studies to date that have investigated associations between BMI and all cause mortality have included older people who are often metabolically unhealthy, and who may have sarcopenia and frailty. Additional factors such as diabetes, hypertension and MetS in older subjects may

confound associations between BMI and all cause mortality in overweight and obese subjects, and sarcopenia and frailty may confound associations between BMI and all cause mortality, particularly in underweight individuals.

Having excluded metabolically unhealthy individuals at baseline from our analyses, why was underweight associated with an increased HR for all cause mortality in our young adult cohort? Recent work has shown that grip strength, as a proxy for sarcopenia, is a stronger predictor of all cause and cardiovascular mortality than systolic blood pressure. [17] Since grip strength is a measure of muscle strength, and because muscle strength declines with older age, and is also lower in underweight subjects, [18] we can speculate that the increased risk of all cause mortality that we have observed in the underweight group may reflect muscle dysfunction or decreased muscle mass in this BMI group. The factors associated with low skeletal muscle mass (SMM), sarcopenia, and sarcopenic obesity has recently been investigated using nationally representative samples of 18, 363 people aged ≥65 years from diverse geographical regions of the world [19]. High percentage body fat was associated with low skeletal muscle mass and low levels of physical activity were associated with sarcopenia and sarcopenic obesity. Thus, it is plausible to speculate that low muscle mass and decreased oxidative capacity with decreased numbers of muscle mitochondria could be an important factor mediating a link between underweight and increased mortality Whether the effect of sarcopenia on mortality outcomes is the same in men and women is uncertain and this question has recently been addressed in a population-based cohort study among 4425 older adults from the Third National Health and Nutrition Survey (1988-1994) [20]. Sarcopenia was associated with increased all cause mortality in both men and women, but sarcopenia was only associated with increased CVD mortality in women and not in men. Sarcopenia was not associated with cancer-specific mortality in men or women. Interestingly, in this study obesity, defined using body mass index or waist circumference, did not modify the relationship between sarcopenia and all-cause mortality suggesting that a metabolical phenotype could be linked to decreased mortality (as we showed previously in this cohort [11] because such individuals have greater muscle mass.

Although in the overweight and obese BMI category there was a decreased HR for all cause mortality, for men, mean age was very similar across BMI groups and for women, mean age increased across increasing BMI categories. Additionally and surprisingly, given the decreased HR for all cause mortality in the overweight/obesity group for both men and

women, blood pressure and LDL-C concentration increased, liver enzyme concentrations (alanine and aspartate transaminases and gamma glutamyl transferase) increased, and glucose concentrations and HOMA-IR increased across increasing BMI categories. It is plausible given the relatively young age of our cohort that there is still low lifetime exposure to these recognized risk factors and as the overweight and obese group grows older these risk factors have a deleterious effect to increase the numbers of subjects developing diabetes, hypertension and CVD. The percentage of people taking regular exercise was increased in men and women in the overweight and obesity groups and it is possible that there was a benefit of this physical activity that contributed to the decreased HR for all cause mortality in the overweight/obese group.

There are strengths and limitations to our study that need to be considered. We studied ~162,000 metabolically healthy, relatively young adult men and women at baseline. Although the period of follow up was 11 years for many subjects, the median period of follow up was approximately five years. As we have stated previously for this cohort [11] with the relatively small numbers of deaths, there was insufficient power to exclude subjects who died during the first few years of the study in order to exclude the possible effects of reverse causality. However, it is likely that in this cohort, the effect of reverse causality is small, since the study included relatively young subjects, a large proportion of whom were in employment, and who are therefore predominantly healthy. Additionally, it is possible that the use of medication to decrease risk of CVD (e.g. antihypertensives or statins) taken during the study period could have influenced the data for CVD and all cause mortality. However, it is important to note that the numbers of individuals taking such medications is likely to be small. Waist circumference was not used to exclude subjects at baseline as this measurement was only available in approximately 50% of the cohort at baseline, although it should be noted that virtually all the metabolically unhealthy subjects in our cohort will have been excluded by virtue of having excluded subjects with other features of the MetS, diabetes, hypertension and existing hypertension. Additionally, as we have described previously for this cohort [11], a measure of socio-economic status was not obtained, and the estimates of alcohol intake and exercise are likely to be imprecise. People identified as abstinent of any alcohol consumption at the time of the questionnaire (at the time of the occupational health check) may previously have consumed alcohol. Also, the lifetime exposure to smoking may still be too small in this young cohort to see the deleterious impact of smoking. Furthermore,

although our cohort is relatively young it is not possible to determine whether having lower BMI affected mortality in patients with cancer. It is also not possible to determine whether underweight as part of an anorexia/cachexia syndrome contributes to increased mortality in this patient group (with underweight being part of the natural course of progression of the disease state).

In conclusion, in a large, predominantly single ethnicity, young adult cohort in whom we excluded all subjects with CVD, diabetes, hypertension and components of the MetS at baseline, we show that underweight was associated with increased all cause mortality and in a combined overweight/obesity group there was decreased all cause mortality (compared with the normal weight BMI reference group). We suggest that further research is needed to understand the mechanisms by which underweight young adults who are metabolically healthy are at increased risk of all cause mortality. Underweight middle aged adults are often ignored in clinical practice as they are perceived to be at low risk. We suggest that there should be a focus on providing lifestyle advice in this patient group, stressing the importance of physical activity, good nutrition, smoking cessation and limited alcohol consumption for good health. Such an approach in this 'at risk' group of patients should limit any further adverse impact on health of low levels of physical activity, poor diet, smoking and high alcohol consumption on mortality. Additionally, a focus on treating conditions associated with overweight and obesity as they develop, such as type 2 diabetes and hypertension, (rather than focussing on tackling obesity per se), is likely to have a greater impact on all cause mortality in middle aged obese populations.

Figure 1 legend.
Flow chart showing criteria for inclusion of subjects in the study.

Figure 2 legend.
Model of the shape of the association (hazard ratios) between BMI and all cause mortality for men and women combined. The proportion of the cohort by each 2kg/m^2 increment is also shown

Acknowledgments

We acknowledge the efforts of the health screening group at Kangbuk Samsung Hospital, Korea. The work was support by the MRC-KHIDI UK-KOREA PARTNERING AWARD to CDB, KS, and SW (Medical Research Council MC_PC_16016). CDB is supported in part by the Southampton National Institute for Health Research Biomedical Research Centre.

All authors have no conflicts of interest.

All authors declare that: 1) the paper is not under consideration elsewhere; 2) none of the paper's contents have been previously published; 3) all authors have read and approved the manuscript; 4) the full disclosure of any relationship with industry; and 5) All authors have no relevant conflicts of interest. K.S contributed to the hypothesis, wrote methods and contributed to discussion, S.R analyzed data, S.W and C.B. wrote introduction, results and discussion, K.S, J.L, E.C, J.K, S.L reviewed/edited the manuscript and contributed to discussion. K.S. is the guarantor for the article

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Table 1. Baseline characteristics of the whole cohort according to whether subjects were alive or dead at follow up

Characteristics	Alive	Dead	*P* value
Number = 162,194	161,758	436	
Age (years)*	36.9(7.9)	46.3(13.1)	<0.001
Male	43.2	62.6	<0.001
Systolic BP (mmHg)*	106.7(10.0)	109.6(9.2)	<0.001
Diastolic BP (mmHg)*	68.5(7.7)	70.9(8.2)	<0.001
Glucose (mg/dl)*	88.5(6.3)	88.2(6.6)	0.4096
Total cholesterol (mg/dl)*	187.7(30.8)	192.8(34.8)	0.0005
LDL-C (mg/dl)*	108.2(28.2)	110.6(29.4)	0.0739
HDL-C (mg/dl)*	62.0(12.3)	60.6(13.3)	0.0156
Triglycerides (mg/dl)†	76(58-100)	86.5(66.5-111)	<0.001
ALT†	17(13-23)	21(15-30)	<0.001
AST†	20(17-24)	24(20-30)	<0.001
GGT†	15(11-23)	19(12-32)	<0.001
hsCRP†(mg/l)†	0.3 (0.1-0.7)	0.5 (0.1-1.3)	<0.001
HOMA-IR†	1.32(0.88-1.73)	1.46(1.12-1.79)	<0.001
Current smoker (%)	21.9	37.6	<0.001
Alcohol intake, 20g/day (%)	11.3	17.4	<0.001
Regular exercise (%)§	15.1	18.7	0.040
High education level (%)	77.3	51.7	<0.001
Seoul center (%)	32.1	26.2	0.007
BMI (kg/m2)			

Data are *mean (standard deviation), †median (interquartile range), or percentage.

Abbreviations: BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; hs CRP , high-sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment -Insulin resistance. § ≥ 1 time per week

Student's unpaired t tests and Mann Whitney U tests were used to test for differences in normally and non normally distributed data.

Table 2 Baseline characteristics according to group (men)

Characteristics	Overall	BMI categories (kg/m^2)				*P*
		Underweight (< 18.5)	**Normal weight (18.5 – 22.9)**	**Overweight (23.0 – 24.9)**	**Obese (≥ 25.0)**	
Number	70,071	2,195	32,765	20,310	14,801	
Age (years)*	37.0(8.0)	36.5(9.4)	36.8(8.2)	37.4(7.9)	37.2(7.6)	<0.001
Systolic BP (mmHg)*	110.7(8.3)	107.5(8.9)	109.8(8.4)	111.2(8.1)	112.4(7.9)	<0.001
Diastolic BP (mmHg)*	71.5(6.9)	69.5(7.1)	70.9(6.9)	71.7(6.8)	72.6(6.7)	<0.001
Glucose (mg/dl)*	89.4(6.2)	87.8(6.7)	89.0(6.3)	89.7(6.1)	90.1(6.1)	<0.001
Total cholesterol (mg/dl)*	190.3(31.0)	174.7(27.9)	185.5(30.0)	193.6(30.8)	198.8(31.2)	<0.001
LDL-C (mg/dl)*	115.1(28.5)	95.8(24.4)	109.6(27.2)	119.0(27.9)	125.1(28.4)	<0.001
HDL-C (mg/dl)*	56.3(10.8)	62.0(12.3)	57.9(11.2)	55.1(10.1)	53.3(9.3)	<0.001
Triglycerides (mg/dl)†	90(70-114)	74(58-93)	84(65-107)	94(73-117)	102(81-123)	<0.001
ALT†	21(16-29)	17(14-22)	19(15-25)	23(18-30)	27(20-37)	<0.001
AST†	22(19-26)	21(18-25)	21(18-25)	22(19-27)	24(20-29)	<0.001
GGT†	22(16-32)	18(14-24)	19(15-27)	23(17-34)	28(20-42)	<0.001
hsCRP(mg/l)†	0.4(0. 1-0. 8)	0.1(0.1-0.5)	0.3(0.1-0.7)	0.5(0.3-0.9)	0.6(0.4-1.2)	<0.001
HOMA-IR†	1.32(0.90-1.72)	1.06(0.64-1.49)	1.21(0.81-1.60)	1.35(0.95-1.76)	1.51(1.10-1.93)	<0.001
Current smoker (%)	42.9	53.5	44.1	40.7	41.9	<0.001
Alcohol intake, 20g/day (%)	21.4	15.9	19.2	22.3	26.0	<0.001
Regular exercise (%)§	16.6	6.8	14.5	18.3	20.2	<0.001
High education level (%)	84.4	77.4	83.2	85.6	86.2	<0.001
Seoul center (%)	32.7	35.0	34.7	31.2	29.8	<0.001

Data are *mean (standard deviation), †median (interquartile range), or percentage.

Abbreviations: BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; hs CRP , high-sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment -Insulin resistance. Between group differences for normalized data were tested by ANOVA.

§ ≥ 1 time per week

Table 3 Baseline characteristics according to group (women)

Characteristics	Overall	BMI categories (kg/m^2)				*P*
		Underweight (< 18.5)	**Normal weight (18.5 – 22.9)**	**Overweight (23.0 – 24.9)**	**Obese (≥ 25.0)**	
Number	92,123	11,510	62,580	11,889	6,144	
Age (years)*	36.9(7.9)	33.7(6.0)	36.4(7.3)	40.3(8.9)	41.6(9.6)	<0.001
Systolic BP (mmHg)*	103.7(10.0)	101.1(9.9)	103.3(9.9)	106.1(9.8)	108.2(9.7)	<0.001
Diastolic BP (mmHg)*	66.2(7.6)	64.8(7.3)	65.9(7.5)	67.7(7.6)	69.1(7.7)	<0.001
Glucose (mg/dl)*	87.8(6.3)	86.7(6.6)	87.7(6.3)	88.7(6.1)	89.3(6.0)	<0.001
Total cholesterol (mg/dl)*	185.7(30.5)	177.6(27.5)	184.1(29.6)	194.2(32.1)	200.4(32.6)	<0.001
LDL-C (mg/dl)*	102.9(26.8)	93.8(22.9)	101.3(25.8)	112.0(28.5)	118.9(29.5)	<0.001
HDL-C (mg/dl)*	66.4(11.6)	69.1(12.2)	66.7(11.6)	64.3(10.8)	62.8(10.1)	<0.001
Triglycerides (mg/dl)†	67(53-87)	62(50-78)	66(52-84)	75(58-96)	82(64-105)	<0.001
ALT†	14(11-18)	13(11-17)	14(11-18)	16(12-20)	17(13-23)	<0.001
AST†	19(16-22)	19(16-22)	19(16-22)	20(17-23)	20(17-24)	<0.001
GGT†	12(9-15)	12(9-15)	11(9-15)	12(9-16)	14(10-19)	<0.001
hsCRP†(mg/l)†	0.3(0.1-0.6)	0.1(0.1-0.4)	0.3(0.1-0.5)	0.4(0.1-0.8)	0.6(0.3-1.2)	<0.001
HOMA-IR†	1.32(0.87-1.74)	1.14(0.70-1.58)	1.30(0.85-1.71)	1.45(1.04-1.87)	1.57(1.16-1.97)	<0.001
Current smoker (%)	5.13	6.05	5.11	4.44	4.91	<0.001
Alcohol intake, 20g/day (%)	3.20	2.69	3.18	3.22	4.30	<0.001
Regular exercise (%)§	14.0	7.4	13.9	18.4	18.7	<0.001
High education level (%)	71.6	82.9	74.1	59.2	51.3	<0.001
Seoul center (%)	31.7	30.6	31.8	31.7	32.3	0.044

Data are *mean (standard deviation), †median (interquartile range), or percentage.

Abbreviations: BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; hs CRP , high-sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment -Insulin resistance.

§ ≥ 1 time per week. Between group differences for normalized data were tested by ANOVA.

TABLE 4 Number of events, mortality rate and hazard ratios (HRs) for all cause mortality in underweight, normal weight and overweight and obese subjects

	Person-years	Number of events	Mortality rate (10,000 person-year)	Age- adjusted HRs (95% CI)*	Multivariate HR (95% CI)*
Total (N=162,194)					
Under	61,508.2	33	5.4	1.48(1.03-2.13)	1.53(1.06-2.20)
Normal	483,143.6	242	5.0	1.00(reference)	1.00(reference)
Overweight	174,134.7	92	5.2	0.75(0.59-0.96)	0.74(0.58-0.95)
Obese	111,797.3	69	6.2	0.85(0.65-1.11)	0.81(0.61-1.07)
Men (N=70,071)					
Under	12,801.3	16	12.5	1.48(0.88-2.48)	1.50(0.89-2.52)
Normal	181,919.7	138	7.6	1.00(reference)	1.00(reference)
Overweight	111,210.4	67	5.9	0.78(0.58-1.04)	0.81(0.60-1.09)
Obese	79,440.7	52	6.5	0.89(0.65-1.22)	0.91(0.65-1.26)
Women (N=92,123)					
Under	48,706.9	17	0.3	1.38(0.83-2.32)	1.43(0.85-2.40)
Normal	301,223.9	104	3.5	1.00(reference)	1.00(reference)

Overweight	62,924.3	25	4.0	0.77(0.50-1.21)	0.71(0.44-1.13)
Obese	32,356.7	17	5.3	0.85(0.50-1.44)	0.74(0.41-1.31)

***Estimated from Cox proportional hazard model.**

Adjustments: Age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, and education level

TABLE 5 Number of events, mortality rate and hazard ratios (HRs) for cancer mortality in underweight, normal weight and overweight and obese subjects

	Person-years	Number of events	Mortality rate (10,000 person-year)	Age- adjusted HRs (95% CI)*	Multivariate HR (95% CI)*
Total (N=162,194)					
Under	**61,508.2**	**13**	**2.1**	**1.15(0.65-2.04)**	**1.21(0.68-2.14)**
Normal	**483,143.6**	**121**	**2.5**	**1.00(reference)**	**1.00(reference)**
Overweight	**174,134.7**	**40**	**2.3**	**0.64(0.45-0.92)**	**0.67(0.46-0.95)**
Obese	**111,797.3**	**40**	**3.6**	**0.95(0.67-1.37)**	**0.94(0.65-1.37)**
Men (N=70,071)					
Under	**12,801.3**	**6**	**4.7**	**0.94(0.41-2.15)**	**1.01(0.44-2.31)**
Normal	**181,919.7**	**74**	**4.1**	**1.00(reference)**	**1.00(reference)**
Overweight	**111,210.4**	**29**	**2.6**	**0.65(0.42-0.99)**	**0.69(0.45-1.06)**
Obese	**79,440.7**	**29**	**3.7**	**0.95(0.62-1.46)**	**0.99(0.63-1.55)**

Women (N=92,123)					
Under	**48,706.9**	**7**	**1.4**	**1.33(0.60-2.92)**	**1.28(0.58-2.83)**
Normal	**301,223.9**	**47**	**0.2**	**1.00(reference)**	**1.00(reference)**
Overweight	**62,924.3**	**11**	**1.7**	**0.69(0.36-1.33)**	**0.71(0.36-1.42)**
Obese	**32,356.7**	**11**	**0.0**	**1.07(0.55-2.09)**	**1.00(0.47-2.12)**

***Estimated from competing risk regression model.**

Adjustments: Age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, and education level

Table 6. Number of events, mortality rate and hazard ratios (HRs) for CVD mortality in underweight, normal weight and overweight and obese subjects

	Person-years	Number of events	Mortality rate (10,000 person-year)	Age- adjusted HRs (95% CI)*	Multivariate HR (95% CI)*
Total (N=162,194)					
Under	**61,508.2**	**3**	**0.5**	**1.32(0.40-4.35)**	**1.34(0.40-4.49)**
Normal	**483,143.6**	**24**	**0.5**	**1.00(reference)**	**1.00(reference)**
Overweight	**174,134.7**	**9**	**0.5**	**0.74(0.35-1.59)**	**0.77(0.35-1.71)**
Obese	**111,797.3**	**5**	**0.4**	**0.61(0.23-1.60)**	**0.61(0.23-1.65)**
Men (N=70,071)					
Under	**12,801.3**	**1**	**0.8**	**0.80(0.11-5.73)**	**0.84(0.12-6.19)**
Normal	**181,919.7**	**14**	**0.1**	**1.00(reference)**	**1.00(reference)**
Overweight	**111,210.4**	**7**	**0.6**	**0.82(0.33-2.03)**	**0.94(0.37-2.45)**
Obese	**79,440.7**	**4**	**0.5**	**0.68(0.22-2.09)**	**0.75(0.25-2.28)**

Women (N=92,123)					
Under	**48,706.9**	**2**	**0.4**	**1.64(0.39-6.94)**	**-**
Normal	**301,223.9**	**10**	**0.3**	**1.00(reference)**	**1.00(reference)**
Overweight	**62,924.3**	**2**	**0.3**	**0.66(0.15-2.85)**	**-**
Obese	**32,356.7**	**1**	**0.3**	**0.55(0.07-4.24)**	**-**

***Estimated from competing risk regression.**

Adjustments: Age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, and education level

Table 7. Major causes of death by BMI category

	BMI categories (kg/m^2)			
Characteristics	**Underweight (< 18.5)**	**Normal weight (18.5 – 22.9)**	**Overweight (23 – 24.9)**	**Obese (≥25.0)**
Total deaths	33	242	92	69
CVD	3	24	9	5
Cancer other site	13	120	40	41
Oesophagus/gastric	5	25	15	5
Liver/bile duct cancer	-	26	5	9
Intestine/rectum	-	8	1	3
Bronchus/lung cancer	4	20	6	8
Cerebral	-	7	2	4
Breast/ovary	3	11	4	6
Kidney	-	1	2	-
Heart/ mediastinal	-	2	-	-
Bone/connective tissue	-	5	2	1
Peritoneal/retroperitoneal	-	-	-	1
Leukemia/lymphoma	1	14	3	3
Unknown original site	-	1	-	1
Infection	1	3	-	-
GI disease	-	2	2	1
Liver disease	-	2	2	1
Respiratory disease	2	2	3	-
Kidney disease	1	-	-	-
Musculoskeletal disease	1	3	1	-
Alzheimer, Parkinsons disease	-	2	1	-
Anemia	-	-	1	-
Others*	12	84	33	21

* Injuries, accidents, poisonings, senility, mental disorders and unknown causes

TABLE 8. Subgroup analyses: all cause mortality according to BMI categories

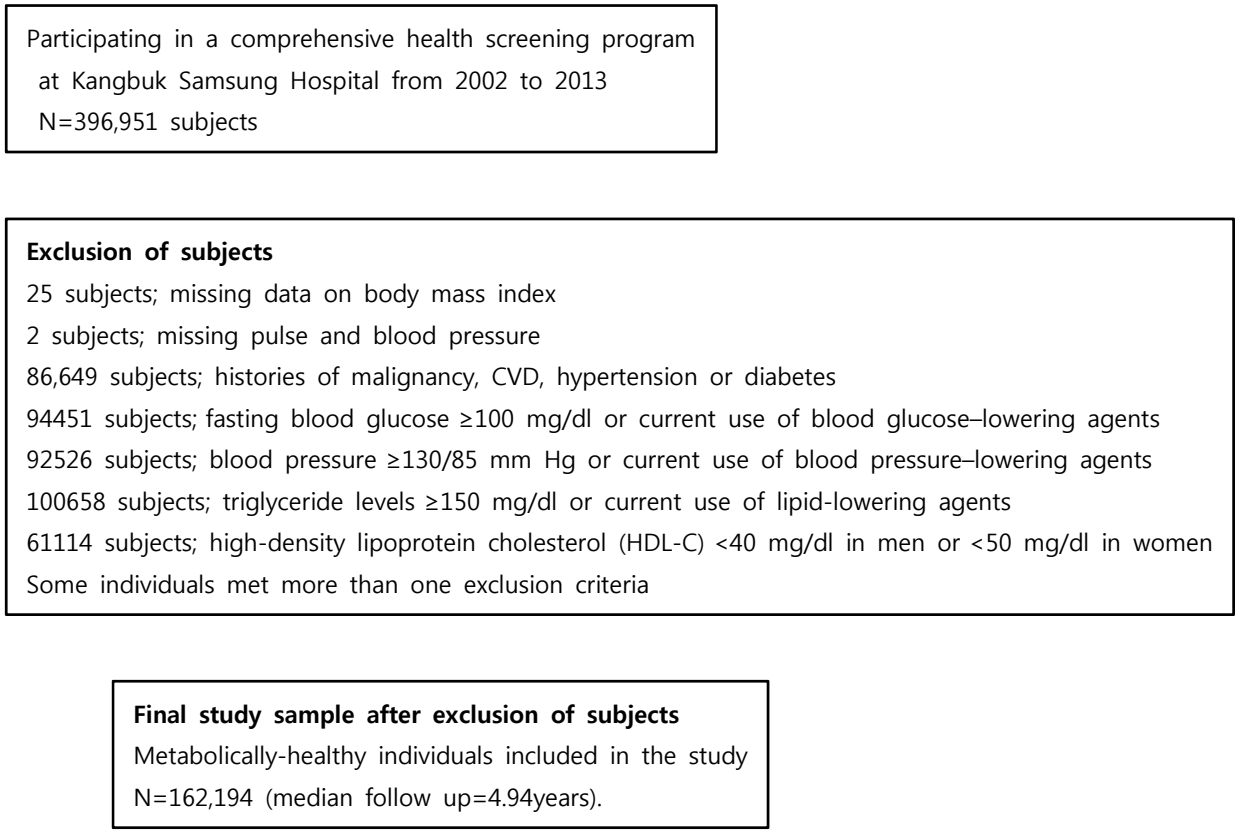
	BMI categories (kg/m^2)				*p* for trend	*p* for interaction
	Underweight (< 18.5)	**Normal weight (18.5 – 22.9)**	**Overweight (23.0 – 24.9)**	**Obese (≥ 25.0)**		
Women (*n*=92,123) aHR[a] (95% CI)	1.43(0.85-2.40)	1.00(reference)	0.71(0.44-1.13)	0.74(0.41-1.31)	0.040	0.7502
Men (*n*=70,071) aHR[a] (95% CI)	1.50(0.89-2.52)	1.00(reference)	0.81(0.60-1.09)	0.91(0.65-1.26)	0.128	
Age <50 years (*n*=150,075) aHR[a] (95% CI)	1.15(0.73-1.82)	1.00(reference)	0.91(0.67-1.22)	0.87(0.61-1.25)	0.274	0.0557
Age ≥50 years (*n*=12,119) aHR[a] (95% CI)	2.25(1.22-4.15)	1.00(reference)	0.59(0.38-0.93)	0.86(0.54-1.36)	0.020	
No current smoker (*n*=120,536) aHR[a] (95% CI)	2.00(1.32-3.02)	1.00(reference)	0.76(0.55-1.04)	0.90(0.63-1.28)	0.013	0.1588
Current smoker (*n*=33,802) aHR[a] (95% CI)	0.72(0.32-1.65)	1.00(reference)	0.77(0.52-1.14)	0.75(0.47-1.19)	0.255	
CRP<1.0mg/dl (*n*=77,120) aHR[a] (95% CI)	1.61(0.91-2.85)	1.00(reference)	0.64(0.41-1.00)	0.72(0.43-1.20)	0.011	0.7417
CRP≥1.0mg/dl (n=16,483) aHR[a] (95% CI)	2.55(1.20-5.41)	1.00(reference)	0.68(0.38-1.22)	0.73(0.39-1.34)	0.017	
Alcohol>20g/d(n=136,563) aHR[a] (95% CI)	1.66(1.12-2.45)	1.00(reference)	0.84(0.64-1.11)	0.88(0.64-1.21)	0.029	0.2319
Alcohol<20g/d (*n*=17,401) aHR[a] (95% CI)	0.61(0.15-2.53)	1.00(reference)	0.50(0.27-0.93)	0.63(0.33-1.18)	0.107	
No regular exercise(*n*=135,634) aHR[a] (95% CI)	1.63(1.12-2.37)	1.00(reference)	0.68(0.51-0.90)	0.84(0.61-1.14)	0.002	0.2913
Regular exercise(*n*=24,142) aHR[a] (95% CI)	0.50(0.07-3.67)	1.00(reference)	0.98(0.59-1.62)	0.72(0.38-1.36)	0.488	
Low education(*n*=25,343) aHR[a] (95% CI)	1.37(0.71-2.63)	1.00(reference)	0.78(0.53-1.17)	0.78(0.48-1.26)	0.093	0.7880

High education(*n*=85,732) aHR[a] (95% CI)	1.93(1.15-3.26)	1.00(reference)	0.75(0.50-1.12)	0.89(0.57-1.38)	0.052	
No fatty liver (*n*=146,251) aHR[a] (95% CI)	1.53(1.05-2.22)	1.00(reference)	0.71(0.54-0.93)	0.84(0.61-1.16)	0.005	0.5534
fatty liver (*n*=15,880) aHR[a] (95% CI)	2.16(0.26-17.91)	1.00(reference)	0.70(0.35-1.40)	0.54(0.27-1.07)	0.055	

Cox proportional hazard models

Models adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, and education level

Figure 1


Participating in a comprehensive health screening program at Kangbuk Samsung Hospital from 2002 to 2013
N=396,951 subjects
Exclusion of subjects
25 subjects; missing data on body mass index
2 subjects; missing pulse and blood pressure
86,649 subjects; histories of malignancy, CVD, hypertension or diabetes
94451 subjects; fasting blood glucose ≥100 mg/dl or current use of blood glucose–lowering agents
92526 subjects; blood pressure ≥130/85 mm Hg or current use of blood pressure–lowering agents
100658 subjects; triglyceride levels ≥150 mg/dl or current use of lipid-lowering agents
61114 subjects; high-density lipoprotein cholesterol (HDL-C) <40 mg/dl in men or <50 mg/dl in women
Some individuals met more than one exclusion criteria
Final study sample after exclusion of subjects
Metabolically-healthy individuals included in the study
N=162,194 (median follow up=4.94years).