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# Participation in health check-ups and mortality using propensity score matched cohort analyses

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ABSTRACT

*Objective.* All Japanese aged ≥40 years are eligible for free annual health check-ups including blood pressure and cholesterol measurements. It is well known that health check-up screenees are more likely to have healthy lifestyles and better health conditions than non-screenees. Therefore, controlling these factors is required to investigate whether screenees have a lower mortality risk than non-screenees independent of their lifestyles or health conditions.

*Methods.* We followed 48,775 Japanese National Health Insurance beneficiaries aged 40–79 years since 1994 for 11 years. We used Cox proportional hazard models adjusted for possible confounding factors. We also performed propensity for use of the health check-up matched cohort analyses.

*Results.* Compared to non-screenees, multiple-adjusted hazard ratios (95% confidence intervals) for all-cause and cardiovascular disease mortality among screenees were 0.74 (0.62–0.88) and 0.65 (0.44–0.95) for men and 0.69 (0.52–0.91) and 0.61 (0.36–1.04) for women, respectively. These relations were also observed when we used propensity matched cohort analyses.

*Conclusion.* This is the first study to show that mortality rates are lower among screenees than non-screenees in Japanese health check-ups when propensity matched cohort analyses were used for adjusting confounding factors. Further prospective studies, including randomized controlled trials, are required to confirm whether screening lowers mortality.



## Introduction

Japanese have the longest life span in the world, and this has increased remarkably (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare, 2007). The reduction of stroke mortality in Japan is one explanation for the current status of Japanese longevity (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare, 2008).

One strategy to reduce stroke in Japan has been the national health check-up system. The Health Services for the Elderly Act 1982 provides for six health services including general health checks (Tatara et al., 1991). These services are inexpensive or free for all who reside anywhere in Japan and hold a resident card, who are aged ≥40 years, and who do not have access to other health examinations in the workplace. Thus, all Japanese adults aged ≥40 years can attend annual health check-ups. Height, weight, blood pressure (BP), lipids, glucose, liver function, and renal function are measured during these health check-ups (Tatara et al., 1991). Specific cancer screenings are not included in the health check-up examination. After the check-ups, depending on the results, the screenees can receive health education in a group setting or ask for individual health counseling (Tatara et al., 1991).

The U.S. Preventive Task Force (USPSTF) recommends regular monitoring for high BP, lipid disorders, and obesity in adults (U.S. Preventive Services Task Force, 2009), and these risk factors are included in the national health check system. Thus, this Japanese system of health check-up coupled with follow-up treatment of abnormalities should contribute to lowering stroke mortality among Japanese.

However, estimating the effect of health check-ups on mortality is difficult because no randomized trial exists, and participants who attend annual health check-ups are more likely to have healthy lifestyles or health conditions than those who do not.

Although previous studies did not adjust for these lifestyles or health conditions (Iwasaki et al., 2006; Lannerstad et al., 1997;

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Wilhelmsen et al., 1986), recent Japanese studies reported the relationship between health check-up and risk of mortality adjusted for possible confounding factors (Khan et al., 2004; Ikeda et al., 2005). Khan et al. (2004) investigated 3185 men and women for about 15 years and found an inverse relationship between screening and all-cause mortality. Ikeda et al. (2005) also investigated 68,825 men and women for 10 years and reported an inverse relationship between participation in screening and all-cause and cause-specific mortality only in women. However, neither of the studies adjusted for information on diet, self-rated health, nor physical function, which should also be different between participants who used health check-up (screenees) and those who did not (non-screenees).

The Ohsaki National Health Insurance (NHI) Cohort Study investigated lifestyles of the general population with very high response rate and determined whether participants used the annual health check system in 1995 (Hozawa et al., 2009; Kuriyama et al., 2006; Ohmori-Matsuda et al., 2007; Sone et al., 2008. Tsuji et al., 1998). Because the Ohsaki study had several detailed lifestyle information than the previous report, such as diet, physical function, or self-rated health, we could control for these important confounding factors.

Recently, propensity scores have been widely used in cardiovascular research (D'Agostino, 2007). This approach was used to reduce bias in observational studies. Therefore, in this study, we also used this approach to investigate the relationship between health check-up and mortality.

The present study compares general and specific mortality rates among screenees and non-screenees, after 11 years of follow-up, controlling lifestyle, and other risk factors.

## Methods

### *Study cohort*

Details of the Ohsaki NHI Cohort Study have been described elsewhere (Hozawa et al., 2009; Kuriyama et al., 2006; Ohmori-Matsuda et al., 2007; Sone et al., 2008; Tsuji et al., 1998). In brief, we sent a self-administered questionnaire between October and December 1994 to all NHI beneficiaries aged 40–79 years living in the catchment area of the Ohsaki Public Health Center. The NHI in Japan is used by farmers, self-employed individuals, pensioners, and their dependents. Because these populations usually do not have access to any other health examinations, they could all be considered targets of health check-ups. Of the 54,996 eligible individuals mailed the questionnaire, 52,029 (95%) responded. To ascertain the date of and reason for withdrawal from the NHI, we started the prospective collection of NHI withdrawal history files on January 1, 1995. We excluded 774 participants who had withdrawn from the NHI before the baseline questionnaire survey. Thus, 51,255 participants ultimately formed the study cohort. Among the participants of the Ohsaki NHI Cohort Study, 16,515 (32.2%) had undergone an annual health check between April and December 1995. In Japan, calendar year started in April, and health check-ups were usually carried out from April to December. To exclude bias from participants who died before being able to attend a health check, we further excluded 2480 participants who died or moved from the area before the health check ended on December 6, 1995 (Fig. 1). Thus, our study participants comprised of 48,775 men and women (men, 23,451; women, 25,324). We defined 15,985 of them as screenees and 32,790 as non-screenees of the health check in 1995.

The ethics committee of Tohoku University School of Medicine reviewed and approved the study protocol. We considered that returning signed, self-administered questionnaires implied written consent to participate in this study.

### *Exposure data*

The questionnaire included items about cigarette smoking, alcohol consumption, self-reported weight and height, histories of diseases, participation in sports or exercise, time spent walking, sense that life is worth living (*ikigai*) (Sone et al., 2008), self-rated health, physical function, the frequency of recent average consumption of 4 beverages (green tea, oolong tea, black tea, and coffee) and 36 food items, and cancer screening within the previous 5 years. Validation of the questionnaire for time spent walking (Tsubono et al., 2002) or the food frequency questionnaire (Ogawa et al., 2003) has already been reported. The physical function status was assessed using the six-item measure of the Medical Outcomes Study (MOS) Short-form General Health Survey (Stewart et al., 1988): able to perform vigorous activity (MOS scores of 5 or 6); capable of moderate but not vigorous activity (MOS scores of 2–4); and capable of only low physical activity (MOS scores of 0 or 1). We defined MOS 0 or 1 as limited physical function.

### *Follow-up*

The end points among the cohort of 48,775 were all-cause mortality and cause-specific mortality from December 6, 1995, to December 31, 2006. The

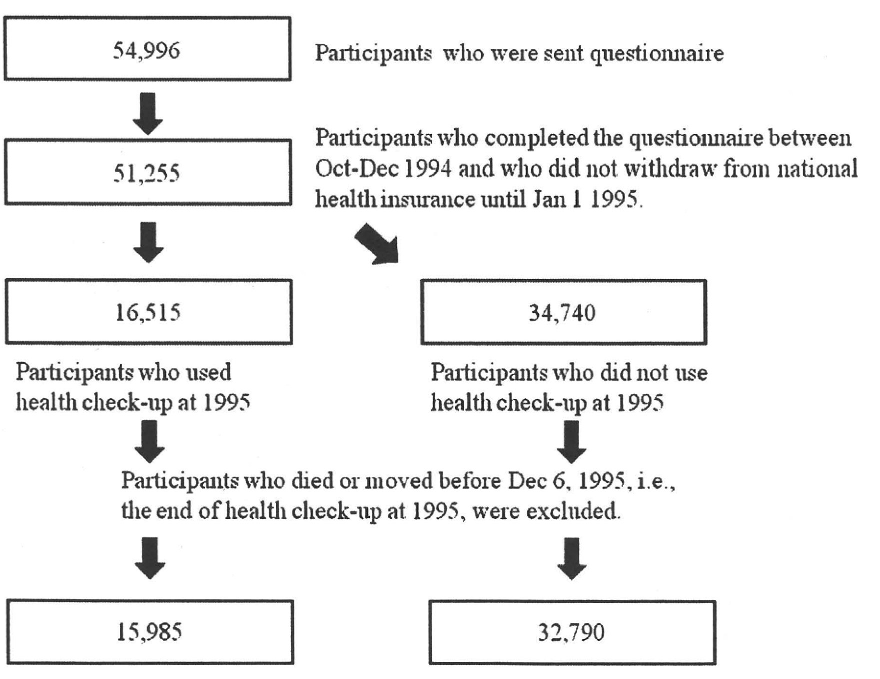


**Fig. 1.** Flowchart of the study participants.

details of follow-up and certification of death causes have been described in previous reports (Hozawa et al., 2009; Kuriyama et al., 2006; Ohmori-Matsuda et al., 2007, Sone et al., 2008).

*Statistical analysis*

To compare the baseline characteristics, we used the Student's *t*-test and the chi-squared test for continuous and categorical variables, respectively. We used the Cox proportional hazards regression analysis with age as the time scale, using left and right censoring, to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and cause-specific mortality (Korn et al., 1997). All data were analyzed using the SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Non-screenees were considered as the reference category. Because smoking habit or alcohol consumption is largely different between men and women in Japan, we separately analyzed men and women in all analyses. One exception was the propensity score matched cohort analysis. Because the pairs were matched both by sex and propensity score, we showed men only, women only, and men and women combined information in this analysis.

We used two models to estimate the difference in mortality between screenees and non-screenees. Model 1 used the following lifestyles and conditions as potential confounders: body mass index (BMI); participation in sports or exercise; time spent walking; sense of life worth living (*ikigai*); self-rated health; physical function; history of any extant diseases; smoking status; alcohol consumption; daily consumption of meat, fish, green and yellow vegetables, and green tea; job status; education; residential area; and history of screening for lung, gastric, colon, breast, and uterine cancer. To minimize the possibility that participants did not attend health check-ups because of illness or moving restriction, we used Model 2: excluding participants with any extant diseases, those with limited physical function, and those who died within the first 3 years of follow-up.

For the propensity score matched cohort analyses, we used participants who did not have any extant diseases, those without limited physical function, and those who did not die within the first 3 years of follow-up ($N = 7732$ for men and $N = 7435$ for women). Among the participants, we calculated the propensity score, which was determined without regard to outcome, using multivariable logistic regression analysis using possible confounding factors in Model 2 together with age categories at baseline (40–49, 50–59, 60–69, and 70–79). *C* statistics of these models were 0.79 for men and 0.78 for women. Then, we made propensity score categories for every 5% (Table 1). The number of pairs was defined as the minimum of the number of screenees and non-screenees in each propensity score category. We randomly selected the participants from each category. Finally, we sorted screenees and non-screenees according to the propensity score. As a result, 1800 and 2087 propensity matched pairs (1:1) for men and women were selected. The relation between the use of the health check-up and all-cause and cause-specific mortality was calculated using the Cox proportional hazard model stratified on the propensity score matched pairs. All reported *p* values are 2-tailed.

**Table 1**
Selection of pair for propensity matched cohort analyses. The Ohsaki Cohort Study.

| Men | | | | Women | | |
|---|---|---|---|---|---|---|
| Propensity score | Non-screenees | Screenees | Pair selected | Non-screenees | Screenees | Pair selected |
| 0–0.049 | 423 | 17 | 17 | 74 | 3 | 3 |
| 0.05–0.099 | 1093 | 83 | 83 | 445 | 37 | 37 |
| 0.1–0.149 | 994 | 148 | 148 | 492 | 76 | 76 |
| 0.15–0.199 | 759 | 154 | 154 | 508 | 117 | 117 |
| 0.2–0.249 | 508 | 157 | 157 | 555 | 155 | 155 |
| 0.25–0.299 | 348 | 125 | 125 | 465 | 152 | 152 |
| 0.3–0.349 | 264 | 108 | 108 | 391 | 166 | 166 |
| 0.35–0.399 | 192 | 143 | 143 | 270 | 146 | 146 |
| 0.4–0.449 | 177 | 136 | 136 | 211 | 197 | 197 |
| 0.45–0.499 | 175 | 149 | 149 | 199 | 203 | 199 |
| 0.5–0.549 | 152 | 163 | 152 | 176 | 213 | 176 |
| 0.55–0.599 | 129 | 181 | 129 | 178 | 199 | 178 |
| 0.6–0.649 | 108 | 183 | 108 | 126 | 235 | 126 |
| 0.65–0.699 | 84 | 187 | 84 | 120 | 217 | 120 |
| 0.7–0.749 | 69 | 161 | 69 | 89 | 267 | 89 |
| 0.75–0.799 | 29 | 94 | 29 | 78 | 298 | 78 |
| 0.8–0.849 | 9 | 26 | 9 | 57 | 233 | 57 |
| 0.85–0.899 | 0 | 2 | 0 | 15 | 70 | 15 |
| 0.9– | 0 | 2 | 0 | 0 | 2 | 0 |
| Total | 5513 | 2219 | 1800 | 4449 | 2986 | 2087 |

We used participants who did not have any extant diseases, those without limited physical function, and those who did not die within the first 3 years of follow-up ($N = 7732$ for men and $N = 7435$ for women).
Number of pair was defined as the minimum of the number of screenees and non-screenees in each propensity score category.

## Results

Mean ages (standard deviation, SD) of screenees and non-screenees were 61.7 (10.0) and 59.6 (10.7) years for men and 61.4 (8.9) and 62.0 (10.5) years for women, respectively. Mean BMIs (SD) of screenees and non-screenees were 23.4 (2.9) and 23.3 (3.2) kg/m$^2$ for men and 23.8 (3.2) and 23.8 (3.7) kg/m$^2$ for women, respectively. The proportions who never smoked, who often consumed green and yellow vegetables, and who had been screened for cancer were much higher among screenees than non-screenees (Table 2). The proportions of participants who considered that life was worth living, who had unlimited physical functions, or who had good/excellent self-rated health were also higher among screenees than non-screenees. Table 2 also shows the proportion with a history of severe diseases such as stroke, myocardial infarction, or cancer was higher among non-screenees than screenees. Thus, screenees were in better health than non-screenees, probably because, as we have been able to check using other analyses, they tended to have healthier lifestyles.

During 11 years of follow-up, the all-cause mortality rate (per 1000 person-years) was lower among screenees (men, 15.8; women, 5.7) than that among non-screenees (men, 23.8; women, 14.0). This tendency was similar for cause-specific mortality. Both male and female screenees had a reduced multiple-adjusted HR of death due to all-causes, CVD, cancer, and other causes (Model 1) (Table 3). For men, if we used more detailed categories of current smoking (≥20 cigarettes/day and <20 cigarettes/day) and current drinking (≥69 g of ethanol/day, 46–68.9 g of ethanol /day, 23–45.9 g of ethanol/day, and 0–22.9 g of ethanol/day), the HRs were unchanged (data not shown).

When we excluded participants with any extant diseases, those with restricted movement, and those who died during the first 3 years of follow-up (Model 2), this approach did not alter the point estimate of the relative risk substantially.

For the propensity matched cohort analyses, significant differences were not found in the characteristics between screenees and non-screenees at baseline when the propensity matched cohort analyses were made (data not shown). Screenees consistently showed a reduced HR of all-cause and cause-specific mortality when we used propensity matched cohort analysis (Table 4). When we combined men and women in the same model, screenees had a significantly reduced HR of death due to all-cause and cause-specific mortality, except for cancer mortality.

## Discussion

We found that screenees of a health check-up in 1995 had healthier lifestyles than non-screenees. We also found that all-cause and cause-specific mortality risks were lower among screenees than non-screenees. The difference in mortality between screenees and non-screenees persisted, despite attenuation when adjusted for lifestyle or when participants with extant diseases were excluded. Furthermore, except for cancer mortality, propensity matched analyses also showed significantly lower all-cause and cause-specific mortality risks among screenees than non-screenees, even though propensity matched screenees and non-screenees had identical baseline characteristics.

The strengths of this study are the large sample cohort and the high (95%) response rate to the questionnaire. Thus, we considered our screenees and non-screenees to be representatives of the target

**Table 2**
Baseline characteristics of participants who used health check-up in 1995 and those who did not. The Ohsaki Cohort Study, 1994.

| | | Men | | | Women | | |
|---|---|---|---|---|---|---|---|
| | | Screenees | Non-screenees | *P* | Screenees | Non-screenees | *P* |
| *N* | | 6814 | 16,637 | | 9171 | 16,153 | |
| Age category | 40–49 years (%) | 16.9 | 24.4 | <0.001 | 12.9 | 17.3 | <0.001 |
| | 50–59 years (%) | 20.1 | 22.1 | | 26.3 | 21.6 | |
| | 60–69 years (%) | 42.3 | 36.0 | | 45.2 | 36.1 | |
| | 70–79 years (%) | 20.8 | 17.5 | | 15.7 | 25.1 | |
| Body mass index | <18.5 kg/m$^2$ (%) | 2.9 | 4.1 | <0.001 | 2.9 | 5.0 | <0.001 |
| | 18.5–21.9 kg/m$^2$ (%) | 28.4 | 30.1 | | 25.7 | 26.6 | |
| | 22–24.9 kg/m$^2$ (%) | 43.5 | 40.4 | | 40.0 | 36.1 | |
| | 25–29.9 kg/m$^2$ (%) | 23.7 | 23.2 | | 28.8 | 27.9 | |
| | ≥30 kg/m$^2$ (%) | 1.6 | 2.2 | | 2.5 | 4.4 | |
| Smoking | Current (%) | 48.2 | 57.8 | <0.001 | 4.9 | 10.5 | <0.001 |
| | Former (%) | 30.5 | 24.8 | | 1.7 | 3.2 | |
| | Never (%) | 21.3 | 17.4 | | 93.4 | 86.3 | |
| Alcohol drinking | Current (%) | 76.1 | 70.3 | <0.001 | 22.0 | 22.7 | <0.001 |
| | Former (%) | 8.3 | 12.8 | | 3.1 | 5.4 | |
| | Never (%) | 15.6 | 17.0 | | 75.0 | 71.9 | |
| Engaging in sports or exercise | ≥1 hour/week (%) | 29.9 | 35.3 | <0.001 | 30.2 | 25.5 | <0.001 |
| Time spent walking | ≥1 hour/day (%) | 48.0 | 48.4 | <0.001 | 44.2 | 41.4 | <0.001 |
| Sense of life worth living | Yes (%) | 68.1 | 58.4 | <0.001 | 60.3 | 53.7 | <0.001 |
| Self-rated health | Excellent (%) | 9.2 | 10.7 | <0.001 | 7.9 | 7.5 | <0.001 |
| | Good (%) | 64.2 | 53.4 | | 60.0 | 49.7 | |
| | Fair (%) | 13.6 | 14.9 | | 14.1 | 15.8 | |
| | Poor (%) | 10.5 | 14.3 | | 14.8 | 18.9 | |
| | Bad (%) | 2.5 | 6.7 | | 3.4 | 8.1 | |
| Physical function | Unlimited (%) | 93.6 | 86.6 | <0.001 | 92.3 | 85.4 | <0.001 |
| Meat consumption | ≥3–4 times/week (%) | 26.1 | 27.3 | <0.001 | 29.9 | 26.0 | <0.001 |
| Fish | Almost everyday (%) | 39.1 | 35.3 | <0.001 | 41.9 | 35.3 | <0.001 |
| Green and yellow vegetables | Almost everyday (%) | 36.3 | 28.9 | <0.001 | 48.3 | 39.2 | <0.001 |
| Green tea | ≥5 cups/day (%) | 30.5 | 25.5 | <0.001 | 34.3 | 33.4 | <0.001 |
| Education | Until 15 years of age (%) | 59.6 | 63.5 | <0.001 | 55.1 | 60.2 | <0.001 |
| | Until 16–18 years of age (%) | 32.1 | 29.3 | | 36.5 | 32.2 | |
| | Until ≥19 years of age (%) | 8.3 | 7.2 | | 8.3 | 7.6 | |
| Job status | Working (%) | 57.2 | 56.4 | <0.001 | 35.1 | 30.8 | <0.001 |
| Living area | City (%) | 14.8 | 27.3 | <0.001 | 15.5 | 30.2 | <0.001 |
| Cancer screening/lung | ≥1/5 years (%) | 92.5 | 77.6 | <0.001 | 90.8 | 77.0 | <0.001 |
| Cancer screening/gastric | ≥1/5 years (%) | 80.6 | 49.8 | <0.001 | 77.3 | 48.6 | <0.001 |
| Cancer screening/colon | ≥1/5 years (%) | 57.3 | 28.6 | <0.001 | 53.3 | 27.4 | <0.001 |
| Cancer screening/uterus | ≥1/5 years (%) | - | - | | 71.4 | 43.4 | <0.001 |
| Cancer screening/breast | ≥1/5 years (%) | - | - | | 62.3 | 34.9 | <0.001 |
| History of diseases | Stroke (%) | 1.7 | 3.4 | <0.001 | 0.7 | 2.3 | <0.001 |
| | Hypertension (%) | 24.4 | 24.6 | 0.73 | 24.6 | 31.0 | <0.001 |
| | Myocardial infarction (%) | 2.7 | 3.6 | <0.001 | 1.8 | 2.8 | <0.001 |
| | Kidney diseases (%) | 3.7 | 3.8 | 0.64 | 3.6 | 4.6 | <0.001 |
| | Liver diseases (%) | 7.0 | 7.0 | 0.85 | 4.1 | 4.6 | 0.08 |
| | Cholecystitis or cholelithiasis (%) | 5.8 | 4.9 | 0.003 | 6.6 | 7.6 | 0.004 |
| | Diabetes (%) | 6.4 | 7.9 | <0.001 | 3.5 | 7.1 | <0.001 |
| | Gastric ulcer (%) | 23.5 | 18.6 | <0.001 | 12.3 | 10.2 | <0.001 |
| | Tuberculosis (%) | 5.7 | 4.3 | <0.001 | 3.1 | 3.0 | 0.60 |
| | Hearing problem (%) | 5.6 | 4.7 | 0.003 | 3.1 | 4.1 | <0.001 |
| | Cataract (%) | 5.7 | 4.7 | 0.002 | 11.2 | 11.8 | 0.14 |
| | Arthritis (%) | 6.6 | 6.1 | 0.13 | 12.0 | 13.0 | 0.02 |
| | Osteoporosis (%) | 1.1 | 1.2 | 0.55 | 6.9 | 7.0 | 0.71 |
| | Cancer (%) | 2.5 | 3.1 | 0.01 | 3.3 | 4.0 | <0.01 |
| | Blood transfusion (%) | 10.8 | 11.6 | 0.09 | 11.8 | 13.5 | <0.01 |

population in this area. Although it is unknown whether this information could be directly applicable for participants who had other insurance for employees and their dependents or who lived in other countries or other areas in Japan, our information might be important for other settings.

Several important confounding factors should be considered when comparing mortality rates between screenees and non-screenees of health check-ups. Firstly, screenees had healthier habits on important lifestyle factors such as smoking or green and yellow vegetable consumption. Secondly, we found that participants with a history of diseases were less likely to undergo the health check-up. This may be because they were feeling too bad to attend or they often visited a physician anyway. Thirdly, screenees were more active, had better self-rated health, and had a greater sense that life is worth living. These characteristics are associated with lower mortality (Sone et al., 2008; Idler and Benyamini, 1997). However, although we considered them as confounding factors, these factors could not fully account for the difference in mortality. Finally, our result did not change substantially when we used propensity matched cohort analyses to minimize the self-selection bias. Therefore, we concluded that the difference in mortality rates between screenees and non-screenees was observed, even though we used detailed lifestyle information, extant diseases, or propensity for participating in health check-up. However, as with all prospective cohort studies, unknown confounding factors might exist. Although the effect of unknown and unmeasured confounding factors on mortality might be reduced by using propensity matched cohort analyses, only randomized controlled trials can provide an unbiased estimate of the effect.

A beneficial effect of health checks on mortality rates might be attributable to early detection of risk factors and early intervention

**Table 3**
Relation between using a health check-up in 1995 and cause-specific mortality. The Ohsaki Cohort Study, 1995–2006.

| | | All-cause mortality | | CVD mortality | | Cancer mortality | | Mortality due to other causes | |
|---|---|---|---|---|---|---|---|---|---|
| | | Screenees | Non-screenees | Screenees | Non-screenees | Screenees | Non-screenees | Screenees | Non-screenees |
| Men | *n* | 6814 | 16,637 | 6814 | 16,637 | 6814 | 16,637 | 6814 | 16,637 |
| | Number of deaths | 1052 | 3589 | 261 | 1043 | 418 | 1219 | 373 | 1327 |
| | Mortality rate (per 1000 person-years) | 15.8 | 23.8 | 3.9 | 6.9 | 6.3 | 8.1 | 5.6 | 8.8 |
| | Hazard ratio (95% CI) Model 1 | 0.72 (0.67–0.77) | 1 | 0.68 (0.58–0.79) | 1 | 0.75 (0.66–0.84) | 1 | 0.71 (0.63–0.81) | 1 |
| | Hazard ratio (95% CI) Model 2 | 0.73 (0.61–0.87) | 1 | 0.64 (0.43–0.94) | 1 | 0.76 (0.58–0.997) | 1 | 0.77 (0.57–1.04) | 1 |
| Women | *n* | 9171 | 16,153 | 9171 | 16,153 | 9171 | 16,153 | 9171 | 16,153 |
| | Number of deaths | 519 | 2125 | 174 | 758 | 179 | 574 | 166 | 793 |
| | Mortality rate (per 1000 person-years) | 5.7 | 14.0 | 1.9 | 5.0 | 2.0 | 3.8 | 1.8 | 5.2 |
| | Hazard ratio (95% CI) Model 1 | 0.66 (0.59–0.73) | 1 | 0.70 (0.58–0.84) | 1 | 0.66 (0.55–0.79) | 1 | 0.62 (0.51–0.74) | 1 |
| | Hazard ratio (95% CI) Model 2 | 0.66 (0.50–0.86) | 1 | 0.60 (0.36–1.006) | 1 | 0.64 (0.41–0.98) | 1 | 0.70 (0.43–1.14) | 1 |

*n*: number of participants; CVD: cardiovascular diseases; CI: confidence interval; Model 1: we used Cox proportional hazards model with age as the time scale. In the model, we adjusted for body mass index (calculated as weight in kilograms divided by height in meters squared; <18.5, 18.5–21.9, 22.0–24.9, 25.0–29.9, and ≥30); participation in sports or exercise (<1 hour/week and ≥1 hour/week); time spent walking (<1 or ≥1 hour/day); sense of life worth living (*ikigai*); self-rated health; physical function; history of any extant diseases; smoking status (never, former, and current); alcohol consumption (never, former, and current); daily consumption of meat, fish, green and yellow vegetables, and green tea; job status; education (until 15 years of age, between 16 and 18 years of age, and ≥19 years of age); residential area; and history of screening for lung, gastric, colon, breast, and uterine cancer. Model 2: excluding participants with any extant diseases, those with limited physical function, and those who died within the first 3 years of follow-up.

including treatment. Risk factors such as high BP, abnormal liver function, and excessive alcohol consumption can be identified earlier among screenees of health check-ups. When risk factors are identified, participants are advised to visit a physician or to alter their lifestyle. If participants follow such advice, risk factors might be better controlled and lead to a reduction in future mortality rates. Although the health check-ups mainly screen risk factors for CVD, this process is also applicable to non-CVD mortality. Changes in smoking status or alcohol consumption could reduce rates of not only CVD diseases but also of cancer, liver, and respiratory diseases. Education about decreasing salt intake to lower BP might contribute to reducing salt-related diseases such as gastric cancer and kidney disease. However, our study did not collect detailed information about whether screenees with abnormal findings determined through health check-ups actually visited clinicians, changed their lifestyles, or controlled their risk factors appropriately through medication or lifestyle modification. This is a study limitation.

We had another limitation in this study. Except for several questionnaires, we generally relied on the self-reported questionnaire. We also rely on the data from secondary sources, such as death certificate. Usage of this information might yield uncontrolled errors and imprecision (Doria-Rose et al., 2010).

In conclusion, we found that the mortality risk was lower among screenees than non-screenees when we adjusted for possible confounding factors, such as lifestyle and extant diseases. This is also true when we used propensity matched cohort analyses. However, this study could not clarify whether the health check processes actually lead to a decreased risk of mortality. Further studies including randomized controlled trials are required to confirm our findings, but such trials could not be performed in Japan, since the national health check-up service is available to all. Therefore, we believe that the present findings represent the best available information regarding the relationship between the Japanese health check system and mortality.

**Conflict of interest statement**

The authors declare that there are no conflicts of interest.

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This study is not related with any industry.

**Table 4**
Relation between using health check-up in 1995 and all-cause and cause-specific mortality using propensity for undergoing health check-up matched cohort. The Ohsaki Cohort Study, 1995–2006.

| | | All-cause mortality | | CVD mortality | | Cancer mortality | | Mortality due to other causes | |
|---|---|---|---|---|---|---|---|---|---|
| | | Screenees | Non-screenees | Screenees | Non-screenees | Screenees | Non-screenees | Screenees | Non-screenees |
| Men | *n* of participants | 1800 | 1800 | 1800 | 1800 | 1800 | 1800 | 1800 | 1800 |
| | Number of deaths | 137 | 189 | 26 | 43 | 59 | 76 | 52 | 70 |
| | HR (95% CI) | 0.70 (0.56–0.88) | 1 | 0.63 (0.38–1.03) | 1 | 0.79 (0.55–1.12) | 1 | 0.67 (0.46–0.97) | 1 |
| Women | *n* of participants | 2087 | 2087 | 2087 | 2087 | 2087 | 2087 | 2087 | 2089 |
| | Number of deaths | 72 | 99 | 18 | 27 | 29 | 40 | 25 | 32 |
| | HR (95% CI) | 0.73 (0.53–0.99) | 1 | 0.68 (0.37–1.26) | 1 | 0.73 (0.45–1.17) | 1 | 0.77 (0.45–1.32) | 1 |
| Men and women combined | *n* of participants | 3887 | 3887 | 3887 | 3887 | 3887 | 3887 | 3887 | 3887 |
| | Number of deaths | 209 | 288 | 44 | 70 | 88 | 116 | 77 | 102 |
| | HR (95% CI) | 0.71 (0.59–0.86) | 1 | 0.65 (0.44–0.95) | 1 | 0.76 (0.58–1.01) | 1 | 0.70 (0.51–0.95) | 1 |

*n*: number; HR: hazard ratio; CI: confidence interval.

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Original Article

# Effect of Age on the Association between Body Mass Index and All-Cause Mortality: The Ohsaki Cohort Study

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## ABSTRACT

**Background:** To clarify the effect of age on the association between body mass index (BMI) and all-cause mortality.

**Methods:** We followed 43 972 Japanese participants aged 40 to 79 years for 12 years. Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs), using the following BMI categories: <18.5 (underweight), 18.5–20.9, 21.0–22.9, 23.0–24.9 (reference), 25.0–27.4, 27.5–29.9, and ≥30.0 kg/m$^2$ (obese). Analyses were stratified by age group: middle-aged (40–64 years) vs elderly (65–79 years).

**Results:** We observed a significantly increased risk of mortality in underweight elderly men: the multivariate HR was 1.26 (0.92–1.73) in middle-aged men and 1.49 (1.26–1.76) in elderly men. In addition, we observed a significantly increased risk of mortality in obese middle-aged men: the multivariate HR was 1.71 (1.17–2.50) in middle-aged men and 1.25 (0.87–1.80) in elderly men. In women, there was an increased risk of mortality irrespective of age group in the underweight: the multivariate HR was 1.46 (0.96–2.22) in middle-aged women and 1.47 (1.19–1.82) in elderly women. There was no excess risk of mortality with age in obese women: the multivariate HR was 1.47 (0.94–2.27) in middle-aged women and 1.26 (0.95–1.68) in elderly women.

**Conclusions:** As compared with the reference category, obesity was associated with a high mortality risk in middle-aged men, whereas underweight, rather than obesity, was associated with a high mortality risk in elderly men. In women, obesity was associated with a high mortality risk during middle age; underweight was associated with a high mortality risk irrespective of age. The mortality risk due to underweight and obesity may be related to sex and age.

*Key words:* body mass index; mortality; age effect; underweight; obesity

## INTRODUCTION

Epidemiological studies have indicated that the association between body mass index (BMI) and all-cause mortality is dependent upon age.[1–18] While almost all studies have agreed that the excess risk of mortality due to obesity attenuates with age,[1–14,17,18] there is long-standing disagreement regarding the effect of age on the association between underweight and all-cause mortality.[1–15] Some studies have shown that the excess risk of mortality due to underweight attenuates with age.[2,3,6–12,15] Other studies have indicated that the excess risk of mortality due to underweight increases with age[5,13] or remains high irrespective of age.[3,4,10,14] This inconsistency may be partly due to the inability to control for history of cancer and cardiovascular disease,[4,6,7,10,12] and to inadequate adjustment for several other confounders such as cigarette smoking,[14] alcohol consumption,[7–9,12,14] physical activity,[7–10,12,14] and socioeconomic status.[2,8,10,12,14,15] Additionally, several studies failed to include a category for the lowest BMI (<18.5) because of the small proportion of such underweight participants,[1,3,8,9,13–15] or neglected to recruit a study population from the general population.[2,10,12,15]

Serena et al concluded that it is necessary to develop appropriate BMI cut-off points that are country- and ethnic-specific for Asians.[19] Among 4 Asian studies of the effect of age on the association between BMI and all-cause mortality,[2,6,7,10] one was conducted in Japan.[10] In that study, however, multivariate analysis failed to adjust adequately for several confounders. Therefore, the effect of age on the

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association between underweight and all-cause mortality remains to be clarified.

To further examine the effect of age on the association between BMI and all-cause mortality, we conducted a cohort study among middle-aged and elderly Japanese who were recruited from the general population. We obtained information about their medical history, smoking status, and other possible confounders. In addition, our study overcomes problems in previous studies because we adjusted for several confounders after excluding participants with subclinical disease. We believe that by clarifying the effect of age on the association between BMI and all-cause mortality, it might be possible to improve public health measures by targeting body weight control according to life stage.

## METHODS

### Study cohort

The details of the Ohsaki National Health Insurance (NHI) Cohort Study have been described previously.[20–22] Briefly, we delivered a self-administered questionnaire requesting information on various lifestyle habits during the period from October through December 1994 to all NHI beneficiaries aged 40 to 79 years living in the catchment area of the Ohsaki Public Health Center, Miyagi Prefecture, in northeastern Japan. The Ohsaki Public Health Center is a local government agency that provides preventive health services to the residents of 14 municipalities in Miyagi Prefecture. Of 54 996 eligible individuals, 52 029 (95%) responded.

We excluded 776 participants who withdrew from the NHI before 1 January 1995, when we started prospective collection of data on NHI withdrawals. Thus, the study cohort comprised the remaining 51 253 participants. The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine. We considered the return of the self-administered questionnaires signed by the participants to imply their consent to participate in the study.

For the current analysis, we also excluded 1767 participants with a history of cancer, 1384 participants with a history of myocardial infarction, and 997 participants with a history of stroke, because the presence of these diseases at baseline could have affected their BMI. In addition, we excluded 3133 participants who did not provide information about body weight or height. As a result, a total of 43 972 adults (21 038 men and 22 934 women) participated. After 12 years of follow-up, there were 5707 deaths (3685 men and 2022 women).

### Body mass index

The self-administered questionnaire included questions on weight and height. BMI was calculated as weight in kilograms divided by the square of height in meters ($kg/m^2$). We used BMI as a measure of total adiposity and divided the participants into groups according to the following BMI categories: <18.5 (underweight), 18.5–20.9, 21.0–22.9, 23.0–24.9, 25.0–27.4, 27.5–29.9, and ≥30.0 $kg/m^2$ (obese). These weight categories correspond to the cut-off points proposed by the World Health Organization (WHO), ie, normal BMI range (18.5–24.9 $kg/m^2$), grade 1 overweight (25.0–29.9 $kg/m^2$), grade 2 overweight (30.0–39.9 $kg/m^2$), and grade 3 overweight (≥40.0 $kg/m^2$).[23]

We previously evaluated the validity of self-reported weight and height.[22] Briefly, the weight and height of 14 883 participants, who were a subsample of the cohort, were measured during health examinations in 1995. The Pearson correlation coefficient ($r$) and weighted kappa ($\kappa$) for the self-reported values and measured values were $r = 0.96$ ($P < 0.01$) for weight, $r = 0.93$ ($P < 0.01$) for height, and $r = 0.88$ ($P < 0.01$) and $\kappa = 0.72$ for BMI. Thus, the self-reported heights and weights in the baseline questionnaire were considered sufficiently valid.

### Follow-up

We followed the participants from 1 January 1995 through 31 December 2006 and recorded any mortality or migration by reviewing data on NHI withdrawals. When a participant withdrew from the NHI system because of death, emigration, or employment, the date of and reason for withdrawal were coded in the NHI withdrawal history files. Because we were unable to obtain subsequent information on participants who withdrew from the NHI because of emigration or employment, we discontinued follow-up of these participants.

The end point was all-cause mortality. Data on the death of participants were based on the death certificates filed at Ohsaki Public Health Center.

The person-years of follow-up were counted for each participant, until either the date of death, withdrawal from the NHI, or the end of the study period, whichever occurred first. The total number of person-years accrued was 440 175.

### Statistical analysis

We used Cox proportional hazards regression analysis to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality according to BMI category, and to adjust for potential confounding factors, using the SAS version 9.1 statistical software package.[24] To enable detailed examination of the association of BMI and all-cause mortality by WHO categories, the normal weight and overweight categories were divided into 3 and 2 categories, respectively. The BMI category 23.0–24.9 $kg/m^2$ was selected as the reference because it is the median of the 7 categories.

Stratified analyses were conducted using 2 age groups: middle-aged participants (40–64 years) and elderly participants (65–79 years). The classification of elderly participants was based on a report by the WHO.[25] All $P$ values were 2-tailed, and a $P$ value of <0.05 was considered statistically significant.

The following variables were selected as potential confounding factors: 5-year age group, weight change since age 20 years (loss of ≥10.0 kg, loss of 5.0–9.9 kg, change of less than 5.0 kg, gain of 5.0–9.9 kg, or gain of ≥10.0 kg), education (junior high school or less, high school, or college/university or higher), marital status (married or unmarried), cigarette smoking (never smoker, past smoker, current smoker consuming 1–19 cigarettes per day, or current smoker consuming at least 20 cigarettes per day), alcohol consumption (never drinker, past drinker, or current drinker), time spent walking per day (less than 1 hour or 1 hour or longer), sports and physical exercise time per week (less than 1 hour, 1–2 hours, 3–4 hours, or 5 hours or longer), history of kidney disease (yes or no), and history of liver disease (yes or no). We further adjusted for hypertension and diabetes mellitus in multivariate model 2. Before including the above potential confounders into the multivariate models, we examined interactions between all-cause mortality and all potential confounders through the addition of cross-product terms to the multivariate model. Based on the results of these analyses (data not shown), we included all the above variables into the multivariate models. In addition, we repeated the analyses after excluding the 739 participants who died within 2 years of baseline.

## RESULTS

### Baseline characteristics by BMI category

The baseline characteristics of the study participants according to the 7 BMI categories are shown for middle-aged men (Table 1), elderly men (Table 2), middle-aged women (Table 3), and elderly women (Table 4). Among middle-aged men and women, 2.3% and 2.9%, respectively, were underweight, about 50% of each had a BMI from 21.0 to 24.9 kg/m$^2$; 25.7% and 28.5% had a BMI from 25.0 to 29.9 kg/m$^2$, and 2.3% and 3.4% were obese, respectively. Among elderly men and women, 5.8% and 5.9%, respectively, were underweight, about half of each had a BMI from 21.0 to 24.9 kg/m$^2$; 19.2% and 27.9% had a BMI from 25.0 to 29.9 kg/m$^2$, and 1.4% and 4.0% were obese, respectively.

In men, mean age decreased linearly with an increase in BMI category. In women, middle-aged women with a BMI from 25.0 to 27.4 kg/m$^2$ and elderly women who were underweight were oldest. The proportions of men and women who had lost ≥5 kg of body weight since age 20 years decreased with increasing BMI category. Participants with the highest level of education were middle-aged men with a BMI from 25.0 to 27.4 kg/m$^2$, middle-aged women with a BMI from 18.5 to 20.9 kg/m$^2$, and underweight elderly men and women. The proportions of unmarried men and women were higher among those who were underweight and obese. The proportions of men and women who were current smokers decreased with increasing BMI. The proportions of men and women who had never drunk alcohol were highest in the underweight, with the exception of middle-aged women. Underweight and obese men and women were less likely to walk 1 hour or longer per day and to participate in <1 hour of sports or physical exercise per week. The proportions of men and women who had histories of hypertension and diabetes increased with an increase in BMI category. The proportions of middle-aged men and elderly women who had histories of kidney disease and liver disease did not significantly differ across BMI categories. The proportions of participants with histories of liver disease and kidney disease were highest among elderly obese men and underweight middle-aged women, respectively.

### All-cause mortality by BMI category

Table 5 (for men) and Table 6 (for women) show person-year totals, numbers of all-cause deaths, and HRs of all-cause mortality with 95% CIs according to BMI category and age group.

In men, we observed significantly increased risks of mortality in the underweight and obese: the model 1 multivariate HRs (95% CI) were 1.42 (1.23–1.65) and 1.44 (1.11–1.87), respectively. After stratification by age group, we observed a significantly increased risk of mortality in elderly underweight men: the model 1 multivariate HRs were 1.26 (0.92–1.73) in middle-aged men and 1.49 (1.26–1.76) in elderly men. There was also a significantly increased risk of mortality in middle-aged obese men: the model 1 multivariate HRs were 1.71 (1.17–2.50) in middle-aged men and 1.25 (0.87–1.80) in elderly men.

In women, we observed significantly increased risks of mortality in the underweight and obese: the model 1 multivariate HRs were 1.49 (1.24–1.80) and 1.33 (1.05–1.69), respectively. After stratification by age group, we observed an increased risk of mortality irrespective of age group in the underweight category: the model 1 multivariate HRs were 1.46 (0.96–2.22) in middle-aged women and 1.47 (1.19–1.82) in elderly women. However, we did not observe an excess risk of mortality with age in the obese: the model 1 multivariate HRs were 1.47 (0.94–2.27) in middle-aged women and 1.26 (0.95–1.68) in elderly women.

The inclusion of covariates for histories of hypertension and diabetes (model 2) attenuated the HR in adults with a BMI ≥25.0 kg/m$^2$ and increased the HR in those with a BMI <23.0 kg/m$^2$. However, model 2 multivariate HRs were similar to model 1 HRs. After the exclusion of participants who died during the first 2 years of follow-up (model 3), multivariate HRs were similar to model 2 HRs in men and obese women. In underweight women, however, there was no excess risk of mortality with age: the model 3 multivariate HRs were 1.78 (1.13–2.81) in middle-aged adults and 1.45 (1.15–1.83) in elderly adults.

We also calculated model 1 multivariate HRs after changing the reference category to 18.5 ≤ BMI ≤ 24.9 kg/m$^2$ from

**Table 1. Baseline characteristics by BMI[a] category in 13764 men aged 40–64 years**

| | BMI (kg/m²) | | | | | | | P value[b] |
|---|---|---|---|---|---|---|---|---|
| | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | 27.5–29.9 | ≥30.0 | |
| No. of subjects | 310 | 2159 | 3591 | 3852 | 2637 | 903 | 312 | |
| Mean age (years) (SD[a]) | 54.2 (7.7) | 53.0 (8.0) | 53.1 (7.8) | 53.2 (7.6) | 52.8 (7.6) | 52.1 (7.4) | 52.0 (7.6) | <0.0001 |
| Mean weight (kg) (SD) | 48.9 (4.8) | 54.6 (4.6) | 59.4 (4.7) | 64.6 (5.2) | 70.3 (5.8) | 77.4 (6.3) | 86.9 (14.8) | <0.0001 |
| Mean height (cm) (SD) | 166.3 (7.6) | 164.9 (6.6) | 164.0 (6.3) | 164.1 (6.2) | 164.1 (6.5) | 164.8 (6.5) | 163.6 (19.1) | <0.0001 |
| Mean BMI (kg/m²) (SD) | 17.6 (0.9) | 20.1 (0.7) | 22.1 (0.5) | 24.0 (0.6) | 26.1 (0.7) | 28.5 (0.7) | 32.4 (4.7) | <0.0001 |
| Weight change since age 20 years (%) | | | | | | | | |
| ≤−10.0 kg | 24.4 | 8.5 | 4.0 | 2.8 | 1.5 | 2.5 | 0.7 | <0.0001 |
| −9.9 to −5.0 kg | 26.8 | 21.9 | 14.2 | 8.0 | 4.5 | 3.3 | 3.0 | |
| −4.9 to +4.9 kg | 43.5 | 61.2 | 57.2 | 36.1 | 15.5 | 6.6 | 4.3 | |
| +5.0 to +9.9 kg | 4.4 | 7.1 | 19.9 | 32.9 | 28.1 | 12.3 | 7.2 | |
| ≥+10.0 kg | 1.0 | 1.3 | 4.6 | 20.2 | 50.4 | 75.2 | 84.9 | |
| Education (%) | | | | | | | | |
| Junior high school or less | 57.2 | 56.6 | 55.8 | 55.1 | 52.3 | 54.2 | 55.8 | NS[a] |
| High school | 35.7 | 35.9 | 36.8 | 37.2 | 39.0 | 37.3 | 35.6 | |
| College/university or higher | 7.1 | 7.5 | 7.5 | 7.7 | 8.7 | 8.6 | 8.6 | |
| Marital status (%) | | | | | | | | |
| Married | 84.3 | 87.0 | 88.8 | 89.7 | 88.6 | 90.4 | 82.4 | 0.0072 |
| Unmarried | 15.7 | 13.0 | 11.2 | 10.3 | 11.4 | 9.6 | 17.6 | |
| Smoking status (%) | | | | | | | | |
| Never smoker | 13.1 | 13.1 | 18.2 | 21.5 | 24.9 | 24.9 | 23.6 | <0.0001 |
| Past smoker | 16.8 | 14.1 | 17.2 | 19.4 | 22.9 | 21.2 | 19.5 | |
| Current smoker, 1–19 cigarettes/day | 23.4 | 26.6 | 20.9 | 19.0 | 14.7 | 13.3 | 13.8 | |
| Current smoker, ≥20 cigarettes/day | 46.7 | 46.3 | 43.7 | 40.2 | 37.5 | 40.7 | 43.1 | |
| Alcohol drinking (%) | | | | | | | | |
| Never drinker | 20.7 | 14.7 | 14.3 | 14.5 | 14.7 | 15.2 | 19.7 | <0.0001 |
| Past drinker | 14.4 | 7.3 | 7.3 | 5.9 | 7.0 | 5.8 | 8.9 | |
| Current drinker | 64.9 | 78.0 | 78.4 | 79.7 | 78.3 | 79.1 | 71.5 | |
| Time spent walking (%) | | | | | | | | |
| ≥1 hour/day | 44.3 | 55.9 | 53.8 | 53.0 | 49.1 | 46.1 | 45.3 | <0.0001 |
| <1 hour/day | 55.8 | 44.1 | 46.2 | 47.0 | 50.9 | 53.9 | 54.7 | |
| Sports and physical exercise (%) | | | | | | | | |
| ≥5 hours/week | 2.4 | 5.8 | 5.4 | 5.8 | 4.5 | 4.4 | 5.9 | 0.0367 |
| 3–4 hours/week | 3.8 | 4.1 | 4.7 | 5.2 | 5.0 | 4.8 | 3.0 | |
| 1–2 hours/week | 11.9 | 12.1 | 14.2 | 14.1 | 14.3 | 15.8 | 12.9 | |
| <1 hour/week | 81.9 | 78.1 | 75.7 | 75.0 | 76.2 | 75.0 | 78.2 | |
| History of hypertension (%) | | | | | | | | |
| Yes | 10.0 | 12.6 | 14.6 | 17.2 | 21.2 | 26.8 | 25.3 | <0.0001 |
| No | 90.0 | 87.4 | 85.4 | 82.8 | 78.8 | 73.2 | 74.7 | |
| History of diabetes (%) | | | | | | | | |
| Yes | 6.1 | 4.5 | 5.9 | 5.9 | 6.6 | 7.3 | 9.6 | 0.0015 |
| No | 93.9 | 95.6 | 94.2 | 94.1 | 93.4 | 92.7 | 90.4 | |
| History of kidney disease (%) | | | | | | | | |
| Yes | 4.5 | 4.3 | 3.3 | 3.0 | 3.5 | 4.7 | 2.6 | NS |
| No | 95.5 | 95.7 | 96.7 | 97.0 | 96.6 | 95.4 | 97.4 | |
| History of liver disease (%) | | | | | | | | |
| Yes | 6.1 | 6.4 | 6.2 | 7.0 | 7.4 | 7.6 | 8.0 | NS |
| No | 93.9 | 93.7 | 93.8 | 93.0 | 92.6 | 92.4 | 92.0 | |

[a]BMI, body mass index; SD, standard deviation; NS, not significant.
[b]P values were calculated by using the chi-square test (for categorical variables) or ANOVA (for continuous variables).

$23.0 \le BMI \le 24.9\,kg/m^2$ (model 4). The HRs were similar to model 1 HRs: the model 4 multivariate HRs in underweight men were 1.18 (0.88–1.60) in middle-aged men and 1.42 (1.26–1.76) in elderly men, in obese men they were 1.64 (1.13–2.38) in middle-aged men and 1.25 (0.87–1.80) in elderly men, in underweight women they were 1.38 (0.94–1.99) in middle-aged women and 1.43 (1.19–1.71) in elderly women, and in obese women they were 1.41 (0.92–2.16) in middle-aged women and 1.25 (0.95–1.64) in elderly women.

## DISCUSSION

The present results indicate that the mortality risk associated with underweight and obesity might be dependent upon sex and age group. We noted significant increased risks of mortality only in middle-aged obese men and elderly underweight men. In women, there was no significant excess risk of mortality with age in the obese, and no significant increased risk of mortality, irrespective of age group, in the underweight.

**Table 2. Baseline characteristics by BMI[a] category in 7274 men aged 65–79 years**

| | BMI (kg/m²) | | | | | | | P value[b] |
|---|---|---|---|---|---|---|---|---|
| | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | 27.5–29.9 | ≥30.0 | |
| No. of subjects | 422 | 1518 | 2026 | 1805 | 1089 | 310 | 104 | |
| Mean age (years) (SD[a]) | 71.5 (4.2) | 70.4 (4.2) | 70.2 (4.0) | 69.9 (4.0) | 69.6 (3.9) | 69.5 (3.8) | 69.9 (4.3) | <0.0001 |
| Mean weight (kg) (SD) | 47.1 (4.9) | 52.0 (4.4) | 56.5 (4.7) | 61.6 (5.0) | 66.7 (5.4) | 72.4 (6.5) | 81.0 (21.6) | <0.0001 |
| Mean height (cm) (SD) | 164.5 (8.0) | 161.1 (6.4) | 160.1 (6.5) | 160.4 (6.3) | 159.9 (6.2) | 159.6 (7.2) | 153.8 (13.7) | <0.0001 |
| Mean BMI (kg/m²) (SD) | 17.4 (1.0) | 20.0 (0.7) | 22.0 (0.6) | 23.9 (0.6) | 26.0 (0.7) | 28.4 (0.6) | 34.3 (8.1) | <0.0001 |
| Weight change since age 20 years (%) | | | | | | | | |
| ≤−10.0 kg | 55.0 | 29.9 | 13.5 | 6.9 | 3.1 | 3.1 | 4.0 | <0.0001 |
| −9.9 to −5.0 kg | 28.9 | 37.1 | 30.5 | 16.6 | 8.4 | 5.9 | 5.0 | |
| −4.9 to +4.9 kg | 15.4 | 29.9 | 43.6 | 43.0 | 26.1 | 13.8 | 12.0 | |
| +5.0 to +9.9 kg | 0.8 | 2.3 | 9.7 | 22.1 | 29.1 | 19.3 | 8.0 | |
| ≥+10.0 kg | 0.0 | 0.8 | 2.7 | 11.4 | 33.4 | 57.9 | 71.0 | |
| Education (%) | | | | | | | | |
| Junior high school or less | 69.4 | 73.9 | 75.4 | 72.1 | 73.2 | 72.9 | 69.6 | 0.0107 |
| High school | 20.9 | 19.4 | 18.5 | 19.2 | 20.9 | 22.4 | 24.5 | |
| College/university or higher | 9.8 | 6.7 | 6.1 | 8.8 | 6.0 | 4.7 | 5.9 | |
| Marital status (%) | | | | | | | | |
| Married | 89.8 | 90.3 | 90.0 | 89.2 | 91.7 | 91.4 | 89.6 | NS[a] |
| Unmarried | 10.2 | 9.7 | 10.0 | 10.9 | 8.3 | 8.6 | 10.4 | |
| Smoking status (%) | | | | | | | | |
| Never smoker | 12.7 | 14.0 | 14.6 | 18.5 | 18.6 | 23.4 | 29.4 | <0.0001 |
| Past smoker | 32.7 | 31.7 | 34.9 | 38.9 | 43.1 | 42.3 | 35.9 | |
| Current smoker, 1–19 cigarettes/day | 34.8 | 30.7 | 29.2 | 24.5 | 21.0 | 15.7 | 18.5 | |
| Current smoker, ≥20 cigarettes/day | 19.8 | 23.6 | 21.4 | 18.1 | 17.3 | 18.5 | 16.3 | |
| Alcohol drinking (%) | | | | | | | | |
| Never drinker | 21.3 | 19.3 | 19.9 | 19.2 | 18.4 | 20.1 | 20.8 | <0.0001 |
| Past drinker | 24.0 | 18.1 | 15.0 | 14.0 | 14.9 | 12.3 | 18.8 | |
| Current drinker | 54.8 | 62.6 | 65.1 | 66.7 | 66.7 | 67.6 | 60.4 | |
| Time spent walking (%) | | | | | | | | |
| ≥1 hour/day | 36.9 | 47.1 | 46.0 | 43.0 | 37.6 | 41.7 | 34.8 | <0.0001 |
| <1 hour/day | 63.1 | 52.9 | 54.0 | 57.0 | 62.4 | 58.3 | 65.2 | |
| Sports and physical exercise (%) | | | | | | | | |
| ≥5 hours/week | 16.2 | 15.4 | 17.0 | 17.4 | 15.3 | 15.4 | 10.7 | NS |
| 3–4 hours/week | 9.2 | 9.8 | 10.4 | 10.4 | 11.4 | 8.8 | 7.1 | |
| 1–2 hours/week | 14.8 | 17.0 | 18.9 | 17.6 | 20.4 | 24.2 | 26.2 | |
| <1 hour/week | 59.9 | 57.9 | 53.7 | 54.5 | 52.9 | 51.7 | 56.0 | |
| History of hypertension (%) | | | | | | | | |
| Yes | 21.6 | 27.8 | 32.8 | 38.2 | 43.3 | 48.4 | 52.9 | <0.0001 |
| No | 78.4 | 72.2 | 67.2 | 61.8 | 56.7 | 51.6 | 47.1 | |
| History of diabetes (%) | | | | | | | | |
| Yes | 6.2 | 6.7 | 9.2 | 9.7 | 9.7 | 12.9 | 11.5 | 0.0010 |
| No | 93.8 | 93.3 | 90.8 | 90.3 | 90.3 | 87.1 | 88.5 | |
| History of kidney disease (%) | | | | | | | | |
| Yes | 5.0 | 4.0 | 3.4 | 4.5 | 3.5 | 2.9 | 3.9 | NS |
| No | 95.0 | 96.1 | 96.6 | 95.5 | 96.5 | 97.1 | 96.2 | |
| History of liver disease (%) | | | | | | | | |
| Yes | 8.3 | 7.7 | 5.8 | 5.7 | 6.5 | 7.4 | 11.5 | 0.0284 |
| No | 91.7 | 92.3 | 94.2 | 94.4 | 93.5 | 92.6 | 88.5 | |

[a]BMI, body mass index; SD, standard deviation; NS, not significant.
[b]P values were calculated by using the chi-square test (for categorical variables) or ANOVA (for continuous variables).

We considered several important confounding factors: cigarette smoking, alcohol consumption, and physical activity are major confounding factors associated with both BMI and mortality.[1–15,17,18] We also considered education level and marital status as potential confounding factors, as in past studies.[1,3,4,6,7,9,11,17] Furthermore, the presence of subclinical disease or a history of illness could induce weight loss and increase the risk of death.[1–4,8,9,11,14,15,17,18] To eliminate any effect of medical history, we excluded participants with a history of cancer, myocardial infarction, or stroke, and adjusted for weight change since age 20 years, history of kidney disease, and history of liver disease, in multivariate analysis.

Multivariate adjustment attenuated the HR estimates associated with a BMI of 27.5–29.9 or ≥30.0 kg/m² in women, but not in men. No single covariate resulted in significant attenuation, although an increase in body weight of 5 kg or more since age 20 years, current drinking, and ≥1 hour physical activity per week attenuated hazard ratios. In contrast, a decrease in body weight of 5 kg or less since age 20 years, past drinking, being unmarried, <1 hour spent

**Table 3. Baseline characteristics by BMI[a] category in 14457 women aged 40–64 years**

| | BMI (kg/m²) | | | | | | | P value[b] |
|---|---|---|---|---|---|---|---|---|
| | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | 27.5–29.9 | ≥30.0 | |
| No. of subjects | 425 | 2135 | 3521 | 3770 | 2890 | 1227 | 489 | |
| Mean age (years) (SD[a]) | 54.1 (7.7) | 53.5 (7.7) | 53.9 (7.5) | 54.4 (7.2) | 55.6 (6.9) | 55.4 (6.8) | 54.9 (7.0) | <0.0001 |
| Mean weight (kg) (SD) | 42.1 (4.1) | 47.3 (3.7) | 51.4 (3.7) | 55.9 (4.0) | 60.4 (4.4) | 65.6 (4.9) | 73.0 (11.0) | <0.0001 |
| Mean height (cm) (SD) | 154.8 (7.7) | 153.6 (5.4) | 152.7 (5.2) | 152.6 (5.2) | 152.0 (5.2) | 151.5 (5.5) | 149.6 (8.6) | <0.0001 |
| Mean BMI (kg/m²) (SD) | 17.5 (0.9) | 20.0 (0.7) | 22.0 (0.6) | 24.0 (0.6) | 26.1 (0.7) | 28.5 (0.7) | 32.6 (4.6) | <0.0001 |
| Weight change since age 20 years (%) | | | | | | | | |
| ≤−10.0 kg | 19.1 | 8.2 | 3.2 | 1.2 | 0.4 | 0.9 | 0.9 | <0.0001 |
| −9.9 to −5.0 kg | 31.4 | 22.5 | 14.0 | 5.6 | 2.6 | 1.3 | 1.5 | |
| −4.9 to +4.9 kg | 46.8 | 58.6 | 52.7 | 35.6 | 15.0 | 7.1 | 4.3 | |
| +5.0 to +9.9 kg | 2.2 | 9.5 | 24.3 | 36.9 | 33.7 | 17.4 | 6.1 | |
| ≥+10.0 kg | 0.5 | 1.3 | 5.8 | 20.8 | 48.3 | 73.4 | 87.2 | |
| Education (%) | | | | | | | | |
| Junior high school or less | 49.4 | 42.8 | 45.7 | 49.2 | 55.1 | 58.8 | 63.9 | <0.0001 |
| High school | 40.2 | 45.0 | 43.3 | 41.6 | 37.8 | 34.1 | 31.1 | |
| College/university or higher | 10.4 | 12.2 | 11.0 | 9.3 | 7.0 | 7.1 | 5.0 | |
| Marital status (%) | | | | | | | | |
| Married | 74.4 | 81.7 | 83.6 | 84.8 | 84.1 | 84.1 | 81.1 | <0.0001 |
| Unmarried | 25.6 | 18.3 | 16.4 | 15.2 | 15.9 | 15.9 | 18.9 | |
| Smoking status (%) | | | | | | | | |
| Never smoker | 79.4 | 82.8 | 88.8 | 90.1 | 89.1 | 88.0 | 87.9 | <0.0001 |
| Past smoker | 2.3 | 2.5 | 1.8 | 2.0 | 2.3 | 2.4 | 2.1 | |
| Current smoker, 1–19 cigarettes/day | 12.4 | 9.6 | 6.4 | 5.3 | 6.2 | 5.7 | 5.1 | |
| Current smoker, ≥20 cigarettes/day | 5.9 | 5.1 | 3.0 | 2.6 | 2.5 | 3.8 | 4.9 | |
| Alcohol drinking (%) | | | | | | | | |
| Never drinker | 66.9 | 64.7 | 68.4 | 68.0 | 68.2 | 69.2 | 64.8 | 0.0002 |
| Past drinker | 6.4 | 5.1 | 3.4 | 3.6 | 4.4 | 5.6 | 8.5 | |
| Current drinker | 26.7 | 30.2 | 28.3 | 28.3 | 27.4 | 25.2 | 26.7 | |
| Time spent walking (%) | | | | | | | | |
| ≥1 hour/day | 41.0 | 47.5 | 46.8 | 47.9 | 45.2 | 39.9 | 39.4 | <0.0001 |
| <1 hour/day | 59.0 | 52.5 | 53.2 | 52.1 | 54.8 | 60.1 | 60.6 | |
| Sports and physical exercise (%) | | | | | | | | |
| ≥5 hours/week | 3.6 | 3.5 | 4.4 | 3.7 | 3.9 | 3.0 | 3.6 | NS[a] |
| 3–4 hours/week | 4.1 | 4.3 | 4.9 | 5.1 | 5.1 | 4.5 | 3.4 | |
| 1–2 hours/week | 14.0 | 14.6 | 14.1 | 14.7 | 16.4 | 14.7 | 11.7 | |
| <1 hour/week | 78.4 | 77.6 | 76.6 | 76.5 | 74.6 | 77.8 | 81.4 | |
| History of hypertension (%) | | | | | | | | |
| Yes | 10.6 | 11.0 | 15.2 | 20.7 | 28.8 | 35.6 | 41.3 | <0.0001 |
| No | 89.4 | 89.0 | 84.8 | 79.3 | 71.2 | 64.4 | 58.7 | |
| History of diabetes (%) | | | | | | | | |
| Yes | 3.3 | 3.4 | 3.2 | 3.5 | 4.5 | 4.5 | 6.1 | 0.0043 |
| No | 96.7 | 96.6 | 96.9 | 96.6 | 95.5 | 95.5 | 93.9 | |
| History of kidney disease (%) | | | | | | | | |
| Yes | 6.4 | 5.3 | 3.9 | 3.2 | 2.7 | 3.9 | 4.9 | <0.0001 |
| No | 93.7 | 94.7 | 96.1 | 96.8 | 97.3 | 96.1 | 95.1 | |
| History of liver disease (%) | | | | | | | | |
| Yes | 5.2 | 3.2 | 3.6 | 3.9 | 3.7 | 4.5 | 5.7 | NS |
| No | 94.8 | 96.8 | 96.4 | 96.1 | 96.3 | 95.5 | 94.3 | |

[a]BMI, body mass index; SD, standard deviation; NS, not significant.
[b]*P* values were calculated by using the chi-square test (for categorical variables) or ANOVA (for continuous variables).

walking per day, and histories of kidney disease and liver disease significantly increased HRs in men.

Almost all previous studies agree that the excess risk of mortality due to obesity decreases with age,[1–14,17,18] and our results accord with this. In underweight adults, the results of past studies have been inconsistent.[1–15] Our results are in agreement with 2 of 14 studies of men,[5,13] and 4 of 13 studies of women.[3,4,10,14]

In Japan, Matsuo et al reported the effect of age on the association between BMI and all-cause mortality.[10] Their findings agree with ours, except for underweight men. They adjusted only for age, alcohol intake, and smoking status in multivariate analysis; however, physical activity and socioeconomic status have also been identified as confounding factors for the risk of all-cause mortality.[1–15,17,18] Although their result differ from ours for underweight men, our study was more careful in adjusting for physical activity, socioeconomic status, weight change since age 20 years, marital status, and histories of kidney disease and liver disease.

**Table 4. Baseline characteristics by BMI[a] category in 8477 women aged 65–79 years**

| | BMI (kg/m²) | | | | | | | P value[b] |
|---|---|---|---|---|---|---|---|---|
| | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | 27.5–29.9 | ≥30.0 | |
| No. of subjects | 503 | 1383 | 1977 | 1906 | 1666 | 702 | 340 | |
| Mean age (years) (SD[a]) | 72.0 (4.3) | 70.9 (4.3) | 70.4 (4.2) | 70.0 (4.0) | 70.0 (4.0) | 70.0 (4.1) | 70.0 (4.0) | <0.0001 |
| Mean weight (kg) (SD) | 39.6 (4.5) | 44.6 (3.7) | 48.8 (3.7) | 53.6 (4.0) | 58.1 (4.7) | 62.5 (5.2) | 68.7 (12.0) | <0.0001 |
| Mean height (cm) (SD) | 151.9 (8.8) | 149.5 (5.8) | 148.8 (5.3) | 149.3 (5.3) | 149.0 (5.6) | 147.8 (5.9) | 144.6 (10.3) | <0.0001 |
| Mean BMI (kg/m²) (SD) | 17.2 (1.2) | 19.9 (0.7) | 22.0 (0.6) | 24.0 (0.6) | 26.1 (0.7) | 28.6 (0.7) | 33.0 (5.6) | <0.0001 |
| Weight change since age 20 years (%) | | | | | | | | |
| ≤−10.0 kg | 41.9 | 22.7 | 12.0 | 4.5 | 3.3 | 1.5 | 1.3 | <0.0001 |
| −9.9 to −5.0 kg | 33.3 | 35.1 | 25.4 | 16.1 | 8.7 | 4.5 | 2.6 | |
| −4.9 to +4.9 kg | 22.7 | 36.9 | 46.3 | 39.0 | 21.6 | 15.3 | 6.2 | |
| +5.0 to +9.9 kg | 1.8 | 4.9 | 12.7 | 26.6 | 29.9 | 22.7 | 13.1 | |
| ≥+10.0 kg | 0.2 | 0.3 | 3.6 | 13.8 | 36.5 | 56.0 | 76.8 | |
| Education (%) | | | | | | | | |
| Junior high school or less | 65.7 | 68.8 | 68.4 | 67.1 | 72.6 | 75.2 | 82.1 | <0.0001 |
| High school | 28.6 | 26.4 | 25.0 | 26.2 | 22.1 | 19.2 | 14.7 | |
| College/university or higher | 5.7 | 4.8 | 6.6 | 6.7 | 5.2 | 5.6 | 3.3 | |
| Marital status (%) | | | | | | | | |
| Married | 59.8 | 61.7 | 62.9 | 62.8 | 63.9 | 65.5 | 62.0 | NS[a] |
| Unmarried | 40.2 | 38.4 | 37.1 | 37.2 | 36.1 | 34.5 | 38.0 | |
| Smoking status (%) | | | | | | | | |
| Never smoker | 84.1 | 90.0 | 90.0 | 91.1 | 92.3 | 91.4 | 89.8 | 0.0016 |
| Past smoker | 4.1 | 2.6 | 3.0 | 3.6 | 2.9 | 3.0 | 5.1 | |
| Current smoker, 1–19 cigarettes/day | 10.5 | 6.3 | 6.1 | 4.8 | 3.9 | 4.7 | 3.9 | |
| Current smoker, ≥20 cigarettes/day | 1.3 | 1.1 | 1.0 | 0.5 | 0.8 | 1.0 | 1.2 | |
| Alcohol drinking (%) | | | | | | | | |
| Never drinker | 82.0 | 81.1 | 81.8 | 81.4 | 82.0 | 78.3 | 80.4 | NS |
| Past drinker | 4.6 | 4.5 | 4.9 | 4.4 | 3.4 | 4.8 | 5.8 | |
| Current drinker | 13.5 | 14.4 | 13.3 | 14.2 | 14.6 | 16.9 | 13.8 | |
| Time spent walking (%) | | | | | | | | |
| ≥1 hour/day | 34.3 | 40.4 | 39.8 | 38.7 | 35.5 | 34.7 | 28.5 | 0.0002 |
| <1 hour/day | 65.7 | 59.6 | 60.2 | 61.3 | 64.5 | 65.3 | 71.5 | |
| Sports and physical exercise (%) | | | | | | | | |
| ≥5 hours/week | 4.6 | 8.4 | 6.9 | 9.2 | 8.5 | 7.2 | 9.7 | 0.0003 |
| 3–4 hours/week | 6.7 | 7.6 | 8.5 | 8.1 | 8.1 | 7.8 | 6.6 | |
| 1–2 hours/week | 12.7 | 14.9 | 19.3 | 19.4 | 18.2 | 18.1 | 13.1 | |
| <1 hour/week | 76.0 | 69.0 | 65.3 | 63.3 | 65.2 | 66.9 | 70.7 | |
| History of hypertension (%) | | | | | | | | |
| Yes | 24.7 | 29.9 | 35.0 | 39.8 | 45.8 | 50.7 | 54.7 | <0.0001 |
| No | 75.4 | 70.1 | 65.0 | 60.2 | 54.2 | 49.3 | 45.3 | |
| History of diabetes (%) | | | | | | | | |
| Yes | 5.8 | 6.1 | 8.7 | 7.5 | 8.2 | 9.0 | 12.9 | 0.0004 |
| No | 94.2 | 93.9 | 91.4 | 92.6 | 91.8 | 91.0 | 87.1 | |
| History of kidney disease (%) | | | | | | | | |
| Yes | 4.4 | 4.3 | 4.5 | 4.0 | 5.0 | 4.4 | 2.1 | NS |
| No | 95.6 | 95.7 | 95.5 | 96.0 | 95.0 | 95.6 | 97.9 | |
| History of liver disease (%) | | | | | | | | |
| Yes | 4.0 | 4.8 | 5.5 | 5.0 | 3.8 | 4.6 | 6.2 | NS |
| No | 96.0 | 95.2 | 94.5 | 95.0 | 96.2 | 95.4 | 93.8 | |

[a]BMI, body mass index; SD, standard deviation; NS, not significant.
[b]P values were calculated by using the chi-square test (for categorical variables) or ANOVA (for continuous variables).

Development of measures to address underweight has been slower than for obesity. However, Grabowski et al and Sergi et al showed that a low BMI in elderly adults was a predictor of mortality.[26,27] Okoro et al found that underweight was associated with subsequent disability in elderly adults.[28] Our study also found that underweight is associated with a high mortality risk in elderly men and women, irrespective of age group.

A major strength of the present study was that the participants were recruited from the general Japanese population. According to the Global Database on Body Mass Index of the WHO, the prevalence of underweight participants is higher in Japan (10%–20%) than in Western populations (0%–5%). Therefore, the Japanese population is one of the best in which to examine the excess risk of mortality due to underweight.

Several limitations of our study should be considered. First, although BMI has been accepted as satisfactory index of underweight and obesity, it cannot be used to identify distributions of fat and muscle tissue. Second, we used self-

**Table 5. HRs[a] and 95% CIs[a] of all-cause mortality in 21 038 men by BMI[a] category, stratified by age group**

| | BMI | | | | | | |
|---|---|---|---|---|---|---|---|
| | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | 27.5–29.9 | ≥30.0 |
| Total | | | | | | | |
| No. | 732 | 3677 | 5617 | 5657 | 3726 | 1213 | 416 |
| Person-years | 6282 | 35 339 | 55 681 | 57 157 | 37 954 | 12 484 | 4162 |
| No. of deaths | 270 | 805 | 1004 | 861 | 513 | 165 | 67 |
| Mortality rate[b] | 43.0 | 22.8 | 18.0 | 15.1 | 13.5 | 13.2 | 16.1 |
| Age-smoking-adjusted HRs | 2.78 (2.42–3.18) | 1.49 (1.35–1.64) | 1.19 (1.09–1.22) | 1.00 (reference) | 0.90 (0.81–1.00) | 0.90 (0.76–1.06) | 1.11 (0.87–1.43) |
| Multivariate HRs1[c] | 1.42 (1.23–1.65) | 1.10 (0.99–1.22) | 1.04 (0.95–1.14) | 1.00 (reference) | 1.01 (0.90–1.13) | 1.10 (0.92–1.31) | 1.44 (1.11–1.87) |
| Multivariate HRs2[d] | 1.52 (1.31–1.76) | 1.14 (1.03–1.26) | 1.06 (0.96–1.16) | 1.00 (reference) | 1.00 (0.89–1.12) | 1.06 (0.89–1.26) | 1.39 (1.07–1.81) |
| Multivariate HRs3[e] | 1.35 (1.15–1.59) | 1.06 (0.95–1.19) | 1.01 (0.92–1.12) | 1.00 (reference) | 0.99 (0.88–1.12) | 1.05 (0.87–1.26) | 1.42 (1.07–1.88) |
| 40–64 y | | | | | | | |
| No. | 310 | 2159 | 3591 | 3852 | 2637 | 903 | 312 |
| Person-years | 3053 | 21 992 | 36 885 | 40 026 | 27 421 | 9425 | 3221 |
| No. of deaths | 47 | 224 | 340 | 305 | 211 | 75 | 33 |
| Mortality rate[b] | 15.4 | 10.2 | 9.2 | 7.6 | 7.7 | 8.0 | 10.2 |
| Age-smoking-adjusted HRs | 1.76 (1.29–2.39) | 1.25 (1.05–1.49) | 1.17 (1.01–1.37) | 1.00 (reference) | 1.07 (0.90–1.28) | 1.17 (0.91–1.51) | 1.54 (1.08–2.21) |
| Multivariate HRs1[c] | 1.26 (0.92–1.73) | 1.07 (0.89–1.28) | 1.11 (0.95–1.30) | 1.00 (reference) | 1.14 (0.95–1.37) | 1.27 (0.97–1.66) | 1.71 (1.17–2.50) |
| Multivariate HRs2[d] | 1.32 (0.96–1.82) | 1.09 (0.91–1.31) | 1.12 (0.96–1.32) | 1.00 (reference) | 1.12 (0.93–1.35) | 1.22 (0.93–1.60) | 1.64 (1.12–2.40) |
| Multivariate HRs3[e] | 1.24 (0.87–1.78) | 1.11 (0.92–1.35) | 1.13 (0.95–1.34) | 1.00 (reference) | 1.16 (0.96–1.41) | 1.20 (0.90–1.61) | 1.62 (1.07–2.45) |
| 65–79 y | | | | | | | |
| No. | 422 | 1518 | 2026 | 1805 | 1089 | 310 | 104 |
| Person-years | 3229 | 13 347 | 18 796 | 17 131 | 10 533 | 3059 | 941 |
| No. of deaths | 223 | 581 | 664 | 556 | 302 | 90 | 34 |
| Mortality rate[b] | 69.1 | 43.5 | 35.3 | 32.5 | 28.7 | 29.4 | 36.1 |
| Age-smoking-adjusted HRs | 1.88 (1.61–2.20) | 1.26 (1.12–1.41) | 1.06 (0.94–1.18) | 1.00 (reference) | 0.91 (0.79–1.05) | 0.96 (0.77–1.19) | 1.21 (0.86–1.71) |
| Multivariate HRs1[c] | 1.49 (1.26–1.76) | 1.11 (0.98–1.26) | 1.01 (0.90–1.14) | 1.00 (reference) | 0.94 (0.81–1.09) | 1.01 (0.80–1.27) | 1.25 (0.87–1.80) |
| Multivariate HRs2[d] | 1.59 (1.35–1.89) | 1.16 (1.03–1.32) | 1.03 (0.92–1.16) | 1.00 (reference) | 0.93 (0.80–1.07) | 0.97 (0.77–1.23) | 1.23 (0.86–1.76) |
| Multivariate HRs3[e] | 1.48 (1.23–1.78) | 1.09 (0.96–1.25) | 0.98 (0.87–1.11) | 1.00 (reference) | 0.88 (0.76–1.03) | 0.91 (0.71–1.17) | 1.22 (0.83–1.79) |

[a]HR, hazard ratio; CI, confidence interval; BMI, body mass index.
[b]Mortality rate was defined as number of deaths per 1000 person-years.
[c]Multivariate HRs1 were adjusted for age in 5-year categories; weight change since age 20 years (loss of 10.0 kg or more, loss of 5.0–9.9 kg, change of less than ±5.0 kg, gain of 5.0–9.9 kg, or gain of 10.0 kg or more); education (junior high school or less, high school, or college/university or higher); marital status (married or unmarried); cigarette smoking (never smoker, past smoker, current smoker consuming 1–19 cigarettes per day, or current smoker consuming at least 20 cigarettes per day); alcohol drinking (never drinker, past drinker, or current drinker); time spent walking per day (less than 1 hour, or 1 hour or longer); sports and physical exercise time per week (less than 1 hour, 1–2 hours, 3–4 hours, or 5 hours or longer); history of kidney disease (yes or no); history of liver disease (yes or no).
[d]Multivariate HRs2 were further adjusted for history of hypertension (yes or no) and history of diabetes (yes or no).
[e]Multivariate HRs3 excluded from multivariate HRs2 the 473 men who died within the 2 years after baseline.

reported BMI at baseline. Niedhammer et al showed that there is a systematic bias in self-reported weight and height.[29] However, we previously evaluated the validity of self-reported BMI, and demonstrated a high correlation and appropriate agreement between self-reported BMI and measured BMI in a subsample of 14 883 participants ($r = 0.88$, $\kappa = 0.72$). We consider this bias to be a nondifferential misclassification that is not dependent upon all-cause death. This misclassification weakens the true association toward the null. Third, as a result of stratification by age group, there was a possibility of beta error because of inadequate numbers of participants and events. Finally, there is a possibility of residual confounding by physical activity.

In summary, obesity increases mortality risk in middle-aged men, whereas underweight, rather than obesity, is associated with high mortality risk in elderly men. In women, obesity increases mortality risk in middle age, and underweight increases mortality risk irrespective of age. Although there

**Table 6. HRs[a] and 95% CIs[a] of all-cause mortality in 22 934 women by BMI[a] category, stratified by age group**

| | BMI | | | | | | |
|---|---|---|---|---|---|---|---|
| | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | 27.5–29.9 | ≥30.0 |
| Total | | | | | | | |
| No. | 928 | 3518 | 5498 | 5676 | 4556 | 1929 | 829 |
| Person-years | 9011 | 34 782 | 55 716 | 57 537 | 46 281 | 19 477 | 8313 |
| No. of deaths | 174 | 371 | 451 | 415 | 357 | 159 | 95 |
| Mortality rate[b] | 19.3 | 10.7 | 8.1 | 7.2 | 7.7 | 8.2 | 11.4 |
| Age-smoking-adjusted HRs | 2.66 (2.23–3.18) | 1.48 (1.28–1.70) | 1.12 (0.98–1.28) | 1.00 (reference) | 1.07 (0.93–1.23) | 1.13 (0.94–1.36) | 1.59 (1.27–1.99) |
| Multivariate HRs1[c] | 1.49 (1.24–1.80) | 1.15 (0.99–1.33) | 0.99 (0.87–1.14) | 1.00 (reference) | 1.03 (0.89–1.19) | 1.07 (0.89–1.30) | 1.33 (1.05–1.69) |
| Multivariate HRs2[d] | 1.58 (1.31–1.91) | 1.19 (1.03–1.38) | 1.01 (0.88–1.15) | 1.00 (reference) | 1.00 (0.87–1.16) | 1.04 (0.85–1.26) | 1.24 (0.97–1.57) |
| Multivariate HRs3[e] | 1.44 (1.17–1.78) | 1.18 (1.01–1.38) | 1.02 (0.88–1.18) | 1.00 (reference) | 1.06 (0.91–1.24) | 1.09 (0.88–1.34) | 1.37 (1.07–1.77) |
| 40–64 y | | | | | | | |
| No. | 425 | 2135 | 3521 | 3770 | 2890 | 1227 | 489 |
| Person-years | 4416 | 21 274 | 35 734 | 38 262 | 29 435 | 12 484 | 4999 |
| No. of deaths | 32 | 92 | 137 | 128 | 104 | 49 | 28 |
| Mortality rate[b] | 7.2 | 4.3 | 3.8 | 3.3 | 3.5 | 3.9 | 5.6 |
| Age-smoking-adjusted HRs | 2.10 (1.43–3.10) | 1.30 (0.99–1.70) | 1.16 (0.91–1.48) | 1.00 (reference) | 0.99 (0.76–1.28) | 1.11 (0.80–1.54) | 1.59 (1.06–2.39) |
| Multivariate HRs1[c] | 1.46 (0.96–2.22) | 1.10 (0.82–1.47) | 1.09 (0.85–1.40) | 1.00 (reference) | 1.00 (0.77–1.31) | 1.06 (0.75–1.51) | 1.47 (0.94–2.27) |
| Multivariate HRs2[d] | 1.55 (1.02–2.36) | 1.14 (0.85–1.52) | 1.10 (0.86–1.41) | 1.00 (reference) | 0.98 (0.75–1.28) | 1.01 (0.71–1.43) | 1.38 (0.89–2.14) |
| Multivariate HRs3[e] | 1.78 (1.13–2.81) | 1.36 (1.00–1.86) | 1.21 (0.92–1.59) | 1.00 (reference) | 1.02 (0.76–1.36) | 0.99 (0.68–1.45) | 1.32 (0.82–2.15) |
| 65–79 y | | | | | | | |
| No. | 503 | 1383 | 1977 | 1906 | 1666 | 702 | 340 |
| Person-years | 4595 | 13 508 | 19 982 | 19 275 | 16 845 | 6994 | 3314 |
| No. of deaths | 142 | 279 | 314 | 287 | 253 | 110 | 67 |
| Mortality rate[b] | 30.9 | 20.7 | 15.7 | 14.9 | 15.0 | 15.7 | 20.2 |
| Age-smoking-adjusted HRs | 1.67 (1.37–2.05) | 1.26 (1.07–1.48) | 1.00 (0.85–1.17) | 1.00 (reference) | 1.02 (0.86–1.21) | 1.07 (0.86–1.34) | 1.33 (1.02–1.73) |
| Multivariate HRs1[c] | 1.47 (1.19–1.82) | 1.14 (0.96–1.36) | 0.95 (0.81–1.12) | 1.00 (reference) | 1.04 (0.87–1.24) | 1.07 (0.85–1.35) | 1.26 (0.95–1.68) |
| Multivariate HRs2[d] | 1.56 (1.26–1.93) | 1.19 (1.00–1.41) | 0.96 (0.82–1.13) | 1.00 (reference) | 1.01 (0.85–1.21) | 1.04 (0.83–1.31) | 1.17 (0.88–1.55) |
| Multivariate HRs3[e] | 1.45 (1.15–1.83) | 1.17 (0.97–1.40) | 0.96 (0.81–1.15) | 1.00 (reference) | 1.04 (0.86–1.25) | 1.07 (0.83–1.37) | 1.24 (0.92–1.68) |

[a]HR, hazard ratio; CI, confidence interval; BMI, body mass index.
[b]Mortality rate was defined as number of deaths per 1000 person-years.
[c]Multivariate HRs1 were adjusted for age in 5-year categories; weight change since age 20 years (loss of 10.0 kg or more, loss of 5.0–9.9 kg, change of less than ±5.0 kg, gain of 5.0–9.9 kg, or gain of 10.0 kg or more); education (junior high school or less, high school, or college/university or higher); marital status (married or unmarried); cigarette smoking (never smoker, past smoker, current smoker consuming 1–19 cigarettes per day, or current smoker consuming at least 20 cigarettes per day); alcohol drinking (never drinker, past drinker, or current drinker); time spent walking per day (less than 1 hour, or 1 hour or longer); sports and physical exercise time per week (less than 1 hour, 1–2 hours, 3–4 hours, or 5 hours or longer); history of kidney disease (yes or no); history of liver disease (yes or no).
[d]Multivariate HRs2 were further adjusted for history of hypertension (yes or no) and history of diabetes (yes or no).
[e]Multivariate HRs3 excluded from multivariate HRs2 the 266 women who died within the 2 years after baseline.

was no significant interaction by age group or sex, the mortality risks associated with underweight and obesity may nevertheless be dependent on sex and age group.

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Original Article

# Dietary Glycemic Index, Glycemic Load and Blood Lipid Levels in Middle-Aged Japanese Men and Women

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***Aims***: This study investigated the association between dietary glycemic index (GI)/glycemic load (GL) and serum lipids in middle-aged Japanese men and women.

***Methods***: The study participants were employees of a metal products factory in Japan: 2,257 men and 1,598 women aged 35 years or older. Dietary GI and GL were assessed using a self-administered diet history questionnaire. Serum lipid levels, adjusted for age, body mass index, alcohol consumption, smoking, physical activity, menopause status, and dietary intake of total energy, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, cholesterol and fiber, were compared among GI/GL quintiles for each gender.

***Results***: No significant associations were observed between GI and adjusted serum lipids in men or women. In contrast, GL was inversely associated with HDL-cholesterol in men and women ($p$ for trend = 0.001 for men and < 0.001 for women), and positively associated with non-HDL-cholesterol ($p$ for trend = 0.010), LDL-cholesterol ($p$ for trend = 0.035) and triglycerides ($p$ for trend = 0.011) in women; however, alcohol drinking affected these associations; there was no association between GL and serum lipids in male nondrinkers and between GL and LDL-cholesterol in female nondrinkers.

***Conclusion***: GL was inversely associated with HDL-cholesterol and positively associated with non-HDL-cholesterol in Japanese women. These associations in men were not observed in nondrinkers. A high-GL diet for women may have an atherogenic effect through these serum lipid abnormalities.

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**Key words**; Glycemic index, Glycemic load, HDL-cholesterol, LDL-cholesterol, Japanese

## Introduction

In 1981, Jenkins *et al.* noticed that foods with an equivalent carbohydrate content were associated with a variable rise in postprandial glucose and reported glycemic indices (GIs) representing a numerical measure of hyperglycemic response to glucose load for 51 different kinds of food[1]. Dietary GI can be calculated based on the GI for each food and the carbohydrate contribution of each food to the overall diet. Glycemic load (GL) is a measure that considers both dietary GI and the amount of carbohydrate intake[2]. Recently, an association between dietary GI/GL and several diseases, including type 2 diabetes and cancer, has been

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reported[3].

The association between GI and high-density lipoprotein cholesterol (HDL-C) was reported in previous studies involving Western and Asian populations[4-10]; however, some studies conducted in Western countries[11, 12] have reported no significant association between GI/GL and HDL-C. In contrast, a recent U.S. study in middle-aged women reported not only a significant inverse association between GI and HDL-C but also a significant positive association between GI and low-density lipoprotein cholesterol (LDL-C)[7]. Reports on the association between GI/GL and serum lipids are limited, and the results are largely inconsistent.

Previous studies have frequently been conducted in the U.S. and Europe, and only a few reports are from Asian populations[8-10] with higher rice intake and lower fat intake, which is significantly different, in terms of the foods contributing to dietary GI, to the intake of Western populations[13]. Studies from Japan are limited to women, and there are no studies available regarding middle-aged Japanese men. Furthermore, only one study from an Asian population examined the association between GI/GL and LDL-C, and there are no reports evaluating the association between GI/GL and non-HDL-C.

The present study was designed to determine the association between dietary GI/GL and serum lipids in a large population comprised of Japanese middle-aged men and women who had different dietary habits to Western populations.

## Methods

### Participants

The participants were 4,593 employees (2,813 men and 1,780 women), aged 35-years or older, of a manufacturer that produces zippers and aluminum sashes in Toyama Prefecture, Japan. In 2003, a regular mass health examination and a self-administered diet history questionnaire were conducted. Of the 4,593 employees, 4,327 (94%) (2,590 men and 1,737 women) underwent the health examination and responded to the diet survey. Employees with total caloric intake below 500 kcal or above 5,000 kcal ($n$ = 16), those with extremely high triglycerides (>400 mg/dL) and inadequately calculated LDL-C ($n$ = 46), and those on medication for hyperlipidemia ($n$ = 136), hypertension ($n$ = 226), and diabetes mellitus ($n$ = 48) were excluded. Thus, 3,855 participants (2,257 men and 1,598 women) were analyzed in this report.

### Data Collection

Body height and weight were measured during a regular annual health examination conducted at the company in 2003. Body mass index (BMI) was calculated as the weight (kg) divided by the height squared ($m^2$). Total cholesterol, triglycerides, and HDL-C were measured using fasting blood samples. Total cholesterol and triglycerides were measured enzymatic ally, and HDL-C was measured directly. Quality control was conducted for the lipid measurements based on the Centers for Disease Control and Prevention / US Cholesterol Reference Method Laboratory Network. LDL-C was calculated using the Friedewald formula as described below[14]:

LDL-C (mg/dL) = total cholesterol (mg/dL) − HDL-C (mg/dL) − triglycerides (mg/dL) × 0.2

Non-HDL cholesterol (non-HDL-C) was calculated as total cholesterol minus HDL-C.

Smoking status (presence or absence of a smoking habit), intensity of physical activity (none, mild, moderate or severe), and the menopause status for women were determined based on a health examination questionnaire.

### Dietary Assessment

Dietary habits during the preceding month were assessed using a self-administered diet history questionnaire (DHQ)[15]. The DHQ was developed to estimate the dietary intake of macronutrients and micronutrients for epidemiological studies in Japan. A detailed description of the methods used for calculating dietary intake and the validity of the DHQ have been published previously[13, 16-18]. Estimates of dietary intake for 147 food and beverage items, energy and nutrients were calculated using an ad hoc computer algorithm developed for the DHQ based on the Standard Tables of Food Composition in Japan.

### Calculation of Dietary GI and GL

The GI of a food is defined as the 2-hour incremental area under the blood glucose response curve after consumption of a food portion containing a specific amount (usually 50 g) of available carbohydrate, divided by the corresponding area after consumption of a portion of a reference food (usually glucose or white bread) containing the same amount of available carbohydrate, and multiplied by 100 to be expressed as a percentage[2]. We calculated dietary GI by multiplying the percentage contribution of each individual food to daily available carbohydrate intake by the GI value of the food and summed these products. Available carbohydrate was calculated as total carbohydrate minus dietary fiber[2]. We also calculated dietary GL by multiplying the dietary GI by the total amount of daily available carbohydrate intake (divided by 100). Of the 147 food and beverage items included in the DHQ, six (4.1%) are alcoholic beverages, eight (5.4%) contain no available carbohydrate and 63 (42.9%) contain less than 3.5 g available carbohydrate per serving. The calculation of dietary GI and GL was thus based on the remaining 70 items with GI values ranging from 16 to 91. A detailed description of the calculation of dietary GI and GL used in the present study as well as a table of GI values for each item have been published elsewhere[9, 13].

**Statistical Analysis**

The gender-specific mean values of age, height, weight, BMI, and serum lipids (total cholesterol, triglycerides, HDL-C, LDL-C, and non-HDL-C) in each GI/GL quintile were determined. The mean serum lipid levels were calculated in each GI/GL quintile adjusted for age and BMI (model 2) or for multiple variables (i.e. age, BMI, alcohol consumption, smoking status, degree of habitual exercise, menopausal status (women), total energy intake, dietary intakes of saturated fatty acid (SFA), monounsaturated fatty acid (MUFA), n-3 polyunsaturated fatty acids (PUFA), n-6 PUFA, dietary cholesterol and dietary fiber) (model 3) through analysis of covariance. For each variable, categorization and dummy variable adjustment were performed; three categories of alcohol consumption determined by the DHQ for men (nondrinker, consumed less than 20 g/day, consumed 20 g or more) and two categories of alcohol consumption for women (nondrinker or drinker), two categories of smoking status (current smoker or not), three categories for the degree of habitual exercise (no, light, moderate to strong), and five categories (quintile) for total energy intake (kcal/day), SFA (g/day), MUFA (g/day), n-3 PUFA (g/day), n-6 PUFA (g/day), dietary cholesterol (mg/day) and dietary fiber intake (g/day). Triglycerides were converted logarithmically for analysis. Linear trends with increasing levels of dietary GI and GL were tested by assigning each participant the median value for the category and modeling this value as a continuous variable. Similar analyses were conducted in subgroups based on drinking status (nondrinkers or drinkers) in both men and women, and in subgroups based on the menopausal status (pre- or postmenopause) in women. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS version 17.0J; SPSS, Tokyo, Japan). $P<0.05$ was considered significant.

## Results

The characteristics of the study participants are shown in **Supplemental Table 1**. The mean ages were 47.4 years for men and 47.0 years for women. The mean BMIs were 23.3 kg/m$^2$ for men and 22.4 kg/m$^2$ for women. Thirty-nine percent of women were postmenopausal. The mean carbohydrate and fat intake (% of energy) were 57.8% and 21.4% for men and 59.2% and 25.8% for women, respectively. The mean dietary GIs were 69.3 for men and 68.0 for women. The mean dietary GLs (/1,000 kcal) were 88.2 for men and 89.2 for women. White rice was the largest contributor to dietary GI/GL (61.6% for men and 53.6% for women), followed by bread (6.9%), noodles (5.5%), and confectionery (5.1%) for men and confectionery (10.1%), bread (8.9%), and sugar (5.3%) for women (data shown in **Supplemental Table 2**).

In men and women, being in the higher GI and GL quintiles was associated with a significantly higher mean age, and no significant association between either GI or GL and BMI was observed (GL results are shown in **Table 1** and **2**). Higher GL was also associated with less alcohol, a lower habitual exercise rate, lower dietary energy intake, lower fatty acid intake, and higher carbohydrate intake.

GI was not significantly associated with serum lipids in men, and higher GI was associated with significantly higher triglycerides and non-HDL-C in women (data shown in **Supplemental Table 3**). When the mean serum lipid levels in the GI quintiles adjusted for multiple variables were determined, GI was significantly and inversely associated only with TG for men ($p$ for trend$=0.029$), and no significant association between GI and serum lipids was observed for women (data not tabulated).

The mean serum lipid levels in each GL quintile are shown in **Table 3** and **4**. In men (**Table 3**), higher GL was associated with significantly lower HDL-C and higher LDL-C and non-HDL-C in the univariate analyses (model 1) and age and BMI-adjusted models (model 2). When adjusted for multiple variables (model 3), higher GL was significantly associated only with lower HDL-C. The association between GL and LDL-C or non-HDL-C was not significant when drinking status was included in the model (data not tabulated), and also in the multivariate-adjusted model (model 3). In women (**Table 4**), higher GL was associated with significantly lower HDL-C, higher total cholesterol, triglycerides, LDL-C, and non-HDL-C (model 1). Higher GL was significantly associated with lower HDL-C and with higher triglycerides, LDL-C, and non-HDL-C in the age and BMI-

**Table 1.** Baseline characteristics of male study participants according to glycemic load quintiles

| | Quintiles of dietary glycemic load | | | | | |
|---|---|---|---|---|---|---|
| Glycemic load (/1,000 kcal) | Q1 (lowest) $n=452$ ≤73.0 | Q2 $n=451$ 73.1–83.4 | Q3 $n=452$ 83.5–91.9 | Q4 $n=451$ 92.0–103.3 | Q5 (highest) $n=451$ ≥103.4 | $p$ |
| Age (years) | 46.7±6.9 | 47.6±6.8 | 47.0±6.8 | 47.7±6.9 | 47.9±6.9 | 0.010 |
| Body height (cm) | 169.1±6.1 | 169.7±6.1 | 169.4±5.9 | 168.9±6.1 | 168.5±6.5 | 0.041 |
| Body weight (kg) | 67.0±9.4 | 67.5±9.3 | 67.5±9.8 | 65.9±8.7 | 66.5±9.8 | 0.076 |
| Body mass index (kg/m²) | 23.3±2.7 | 23.4±2.8 | 23.4±3.0 | 23.0±2.8 | 23.3±3.1 | 0.481 |
| Current smoker (%) | 58.8 | 53.7 | 54.2 | 47.0 | 54.1 | 0.011 |
| Alcohol drinker (%) | | | | | | <0.001 |
| Nondrinkers | 2.2 | 8.4 | 13.7 | 22.6 | 36.6 | |
| Light drinkers (<20 g/day) | 20.4 | 36.8 | 45.4 | 50.3 | 50.3 | |
| Moderate/heavy drinkers (≥20 g/day) | 77.4 | 54.8 | 40.9 | 27.1 | 13.1 | |
| Habitual exercise (%) | | | | | | 0.003 |
| No | 65.9 | 65.6 | 68.1 | 67.0 | 74.9 | |
| Light | 19.2 | 20.4 | 18.4 | 19.5 | 16.0 | |
| Moderate/Strong | 14.2 | 14.0 | 13.1 | 12.9 | 8.6 | |
| Energy intake (kcal/day) | 2,417±625 | 2,268±554 | 2,191±582 | 2,103±548 | 2,024±644 | <0.001 |
| Carbohydrate intake (g/day) | 278.5±72.6 | 303.1±75.7 | 316.9±87.5 | 326.1±87.1 | 350.6±113.6 | <0.001 |
| Fat intake (g/day) | 69.3±30.9 | 60.0±21.9 | 54.1±20.5 | 46.8±16.2 | 35.2±14.9 | <0.001 |
| Protein intake (g/day) | 77.5±27.1 | 71.0±23.2 | 65.5±21.3 | 61.1±17.6 | 52.5±18.4 | <0.001 |
| Carbohydrate intake (%Energy) | 46.3±5.6 | 53.4±3.1 | 57.8±2.7 | 62.0±2.9 | 69.3±4.5 | <0.001 |
| Fat intake (%Energy) | 25.5±7.5 | 23.6±5.7 | 22.0±5.2 | 19.9±4.4 | 15.6±4.3 | <0.001 |
| SFA (g/day) | 17.3±8.2 | 15.1±6.0 | 13.9±5.8 | 12.1±4.5 | 9.2±4.3 | <0.001 |
| MUFA (g/day) | 25.6±12.4 | 21.7±8.3 | 19.4±7.5 | 16.5±6.2 | 12.1±5.5 | <0.001 |
| n3PUFA (g/day) | 3.6±1.8 | 3.0±1.3 | 2.6±1.1 | 2.3±0.9 | 1.7±0.8 | <0.001 |
| n6PUFA (g/day) | 13.6±6.0 | 11.9±4.3 | 10.6±3.8 | 9.3±3.3 | 7.3±3.0 | <0.001 |
| Dietary cholesterol (mg/day) | 353.2±171.1 | 301.4±140.6 | 259.2±124.6 | 226.5±106.8 | 158.6±94.2 | <0.001 |
| Fiber intake (g/day) | 12.3±4.9 | 11.8±4.5 | 11.2±4.2 | 10.6±3.9 | 9.6±4.0 | <0.001 |
| Dietary glycemic index | 67.1±4.5 | 68.4±3.6 | 69.1±3.4 | 70.1±3.2 | 71.5±3.1 | <0.001 |
| Glycemic index-white rice (%) | 52.8±23.7 | 58.0±20.6 | 60.3±20.1 | 65.1±19.6 | 71.3±19.6 | <0.001 |
| Glycemic index-bread (%) | 7.1±8.4 | 7.8±8.3 | 7.4±8.3 | 6.6±7.9 | 5.4±7.7 | <0.001 |
| Glycemic index-noodles (%) | 7.2±7.4 | 5.9±5.1 | 5.5±5.1 | 4.6±4.9 | 4.0±4.4 | <0.001 |
| Glycemic index-confectioneries (%) | 6.1±5.7 | 5.4±4.7 | 5.0±4.0 | 4.7±3.8 | 3.2±3.9 | <0.001 |
| Glycemic index-sugar (%) | 6.1±4.0 | 5.2±3.5 | 5.0±3.5 | 4.3±3.2 | 3.5±2.7 | <0.001 |
| White rice intake (g/day) | 285.9±148.4 | 359.4±148.1 | 403.6±159.7 | 463.4±175.1 | 579.8±244.6 | <0.001 |

Values are the mean ± standard deviation or %.

adjusted model (model 2) and also in the multivariate-adjusted model (model 3).

Because drinking status had a large effect on the multivariate-adjusted model results, we analyzed the subgroups separately based on drinking status in men and women. Compared to nondrinkers, dietary GL and carbohydrate intake were lower in both male and female drinkers, while fat intake was higher in male drinkers but lower in female drinkers (data in **Supplement Table 4**). In male nondrinkers ($n=377$), no associations between GL and serum lipid levels were observed (**Table 5**). In male drinkers ($n=1,880$) the associations between GL and serum lipid levels were similar to those of all men. In female nondrinkers ($n=949$), higher GL was associated with significantly lower HDL-C, higher triglycerides, and higher non-HDL-C, but was not associated with LDL-C (**Table 6**). In female drinkers ($n=649$), higher GL was associated with significantly lower HDL-C, higher non-HDL-C and higher LDL-C.