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

| | BMI ($kg/m^2$) | | | | | | | 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 ($kg/m^2$) (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 $kg/m^2$ 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/m$^2$) | | | | | | | *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/m$^2$) (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/m$^2$) | | | | | | | 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/m$^2$) (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 | 1.49 | 1.19 | 1.00 | 0.90 | 0.90 | 1.11 |
| | (2.42–3.18) | (1.35–1.64) | (1.09–1.22) | (reference) | (0.81–1.00) | (0.76–1.06) | (0.87–1.43) |
| Multivariate HRs1[c] | 1.42 | 1.10 | 1.04 | 1.00 | 1.01 | 1.10 | 1.44 |
| | (1.23–1.65) | (0.99–1.22) | (0.95–1.14) | (reference) | (0.90–1.13) | (0.92–1.31) | (1.11–1.87) |
| Multivariate HRs2[d] | 1.52 | 1.14 | 1.06 | 1.00 | 1.00 | 1.06 | 1.39 |
| | (1.31–1.76) | (1.03–1.26) | (0.96–1.16) | (reference) | (0.89–1.12) | (0.89–1.26) | (1.07–1.81) |
| Multivariate HRs3[e] | 1.35 | 1.06 | 1.01 | 1.00 | 0.99 | 1.05 | 1.42 |
| | (1.15–1.59) | (0.95–1.19) | (0.92–1.12) | (reference) | (0.88–1.12) | (0.87–1.26) | (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 | 1.25 | 1.17 | 1.00 | 1.07 | 1.17 | 1.54 |
| | (1.29–2.39) | (1.05–1.49) | (1.01–1.37) | (reference) | (0.90–1.28) | (0.91–1.51) | (1.08–2.21) |
| Multivariate HRs1[c] | 1.26 | 1.07 | 1.11 | 1.00 | 1.14 | 1.27 | 1.71 |
| | (0.92–1.73) | (0.89–1.28) | (0.95–1.30) | (reference) | (0.95–1.37) | (0.97–1.66) | (1.17–2.50) |
| Multivariate HRs2[d] | 1.32 | 1.09 | 1.12 | 1.00 | 1.12 | 1.22 | 1.64 |
| | (0.96–1.82) | (0.91–1.31) | (0.96–1.32) | (reference) | (0.93–1.35) | (0.93–1.60) | (1.12–2.40) |
| Multivariate HRs3[e] | 1.24 | 1.11 | 1.13 | 1.00 | 1.16 | 1.20 | 1.62 |
| | (0.87–1.78) | (0.92–1.35) | (0.95–1.34) | (reference) | (0.96–1.41) | (0.90–1.61) | (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 | 1.26 | 1.06 | 1.00 | 0.91 | 0.96 | 1.21 |
| | (1.61–2.20) | (1.12–1.41) | (0.94–1.18) | (reference) | (0.79–1.05) | (0.77–1.19) | (0.86–1.71) |
| Multivariate HRs1[c] | 1.49 | 1.11 | 1.01 | 1.00 | 0.94 | 1.01 | 1.25 |
| | (1.26–1.76) | (0.98–1.26) | (0.90–1.14) | (reference) | (0.81–1.09) | (0.80–1.27) | (0.87–1.80) |
| Multivariate HRs2[d] | 1.59 | 1.16 | 1.03 | 1.00 | 0.93 | 0.97 | 1.23 |
| | (1.35–1.89) | (1.03–1.32) | (0.92–1.16) | (reference) | (0.80–1.07) | (0.77–1.23) | (0.86–1.76) |
| Multivariate HRs3[e] | 1.48 | 1.09 | 0.98 | 1.00 | 0.88 | 0.91 | 1.22 |
| | (1.23–1.78) | (0.96–1.25) | (0.87–1.11) | (reference) | (0.76–1.03) | (0.71–1.17) | (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<br>(2.23–3.18) | 1.48<br>(1.28–1.70) | 1.12<br>(0.98–1.28) | 1.00<br>(reference) | 1.07<br>(0.93–1.23) | 1.13<br>(0.94–1.36) | 1.59<br>(1.27–1.99) |
| Multivariate HRs1[c] | 1.49<br>(1.24–1.80) | 1.15<br>(0.99–1.33) | 0.99<br>(0.87–1.14) | 1.00<br>(reference) | 1.03<br>(0.89–1.19) | 1.07<br>(0.89–1.30) | 1.33<br>(1.05–1.69) |
| Multivariate HRs2[d] | 1.58<br>(1.31–1.91) | 1.19<br>(1.03–1.38) | 1.01<br>(0.88–1.15) | 1.00<br>(reference) | 1.00<br>(0.87–1.16) | 1.04<br>(0.85–1.26) | 1.24<br>(0.97–1.57) |
| Multivariate HRs3[e] | 1.44<br>(1.17–1.78) | 1.18<br>(1.01–1.38) | 1.02<br>(0.88–1.18) | 1.00<br>(reference) | 1.06<br>(0.91–1.24) | 1.09<br>(0.88–1.34) | 1.37<br>(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<br>(1.43–3.10) | 1.30<br>(0.99–1.70) | 1.16<br>(0.91–1.48) | 1.00<br>(reference) | 0.99<br>(0.76–1.28) | 1.11<br>(0.80–1.54) | 1.59<br>(1.06–2.39) |
| Multivariate HRs1[c] | 1.46<br>(0.96–2.22) | 1.10<br>(0.82–1.47) | 1.09<br>(0.85–1.40) | 1.00<br>(reference) | 1.00<br>(0.77–1.31) | 1.06<br>(0.75–1.51) | 1.47<br>(0.94–2.27) |
| Multivariate HRs2[d] | 1.55<br>(1.02–2.36) | 1.14<br>(0.85–1.52) | 1.10<br>(0.86–1.41) | 1.00<br>(reference) | 0.98<br>(0.75–1.28) | 1.01<br>(0.71–1.43) | 1.38<br>(0.89–2.14) |
| Multivariate HRs3[e] | 1.78<br>(1.13–2.81) | 1.36<br>(1.00–1.86) | 1.21<br>(0.92–1.59) | 1.00<br>(reference) | 1.02<br>(0.76–1.36) | 0.99<br>(0.68–1.45) | 1.32<br>(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<br>(1.37–2.05) | 1.26<br>(1.07–1.48) | 1.00<br>(0.85–1.17) | 1.00<br>(reference) | 1.02<br>(0.86–1.21) | 1.07<br>(0.86–1.34) | 1.33<br>(1.02–1.73) |
| Multivariate HRs1[c] | 1.47<br>(1.19–1.82) | 1.14<br>(0.96–1.36) | 0.95<br>(0.81–1.12) | 1.00<br>(reference) | 1.04<br>(0.87–1.24) | 1.07<br>(0.85–1.35) | 1.26<br>(0.95–1.68) |
| Multivariate HRs2[d] | 1.56<br>(1.26–1.93) | 1.19<br>(1.00–1.41) | 0.96<br>(0.82–1.13) | 1.00<br>(reference) | 1.01<br>(0.85–1.21) | 1.04<br>(0.83–1.31) | 1.17<br>(0.88–1.55) |
| Multivariate HRs3[e] | 1.45<br>(1.15–1.83) | 1.17<br>(0.97–1.40) | 0.96<br>(0.81–1.15) | 1.00<br>(reference) | 1.04<br>(0.86–1.25) | 1.07<br>(0.83–1.37) | 1.24<br>(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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# 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

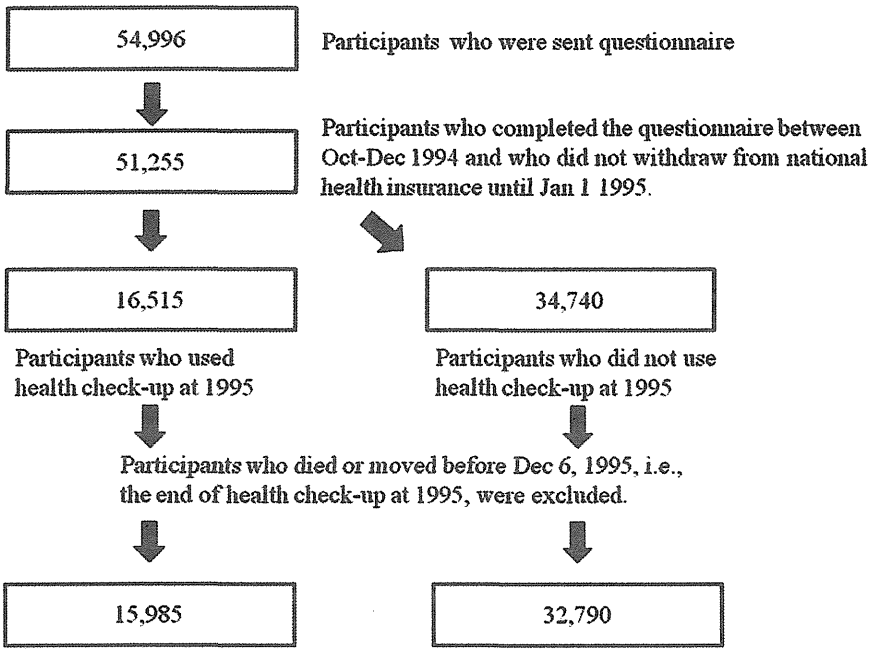

**Fig. 1.** Flowchart of the study participants.

**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.

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.

## 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<br>(0.67–0.77) | 1 | 0.68<br>(0.58–0.79) | 1 | 0.75<br>(0.66–0.84) | 1 | 0.71<br>(0.63–0.81) | 1 |
| | Hazard ratio (95% CI) Model 2 | 0.73<br>(0.61–0.87) | 1 | 0.64<br>(0.43–0.94) | 1 | 0.76<br>(0.58–0.997) | 1 | 0.77<br>(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<br>(0.59–0.73) | 1 | 0.70<br>(0.58–0.84) | 1 | 0.66<br>(0.55–0.79) | 1 | 0.62<br>(0.51–0.74) | 1 |
| | Hazard ratio (95% CI) Model 2 | 0.66<br>(0.50–0.86) | 1 | 0.60<br>(0.36–1.006) | 1 | 0.64<br>(0.41–0.98) | 1 | 0.70<br>(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<br>(0.56–0.88) | 1 | 0.63<br>(0.38–1.03) | 1 | 0.79<br>(0.55–1.12) | 1 | 0.67<br>(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<br>(0.53–0.99) | 1 | 0.68<br>(0.37–1.26) | 1 | 0.73<br>(0.45–1.17) | 1 | 0.77<br>(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<br>(0.59–0.86) | 1 | 0.65<br>(0.44–0.95) | 1 | 0.76<br>(0.58–1.01) | 1 | 0.70<br>(0.51–0.95) | 1 |

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

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# Impact of walking on life expectancy and lifetime medical expenditure: the Ohsaki Cohort Study

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## ABSTRACT

**Objective:** People who spend a longer time walking have lower demands for medical care. However, in view of their longer life expectancy, it is unclear whether their lifetime medical expenditure increases or decreases. The present study examined the association between time spent walking, life expectancy and lifetime medical expenditure.

**Method:** The authors followed up 27 738 participants aged 40–79 years and prospectively collected data on their medical expenditure and survival covering a 13-year-period. Participants were classified into those walking $<1$ and $\geq 1$ h per day. The authors constructed life tables and estimated the life expectancy and lifetime medical expenditure from 40 years of age using estimate of multiadjusted mortality and medical expenditure using a Poisson regression model and linear regression model, respectively.

**Results:** Participants who walked $\geq 1$ h per day have a longer life expectancy from 40 years of age than participants who walked $<1$ h per day. The multiadjusted life expectancy for those who walked $\geq 1$ h per day was 44.81 years, significantly lower by 1.38 years in men ($p=0.0073$) in men and 57.78 years in women, non-significantly lower by 1.16 years in women ($p=0.2351$). In addition to their longer life expectancy, participants who walked $\geq 1$ h per day required a lower lifetime medical expenditure from 40 years of age than participants who walked $<1$ h per day. The multiadjusted lifetime medical expenditure for those who walked $\geq 1$ h per day was £99 423.6, significantly lower by 7.6% in men ($p=0.0048$) and £128 161.2, non-significantly lower by 2.7% in women ($p=0.2559$).

**Discussion:** Increased longevity resulting from a healthier lifestyle does not necessarily translate into an increased amount of medical expenditure throughout life. Encouraging people to walk may extend life expectancy and decrease lifetime medical expenditure, especially for men.

### ARTICLE SUMMARY

**Article focus**

- Medical expenditure per month was reduced when the amount of time spent walking was increased.
- Walking is associated with a decreased risk of mortality.
- In view of the increased life expectancy of those who walk longer, it is unclear whether lifetime medical expenditure increases or decreases as a result.

**Key messages**

- Lifetime medical expenditure from the age of 40 years for men and women who walked $\geq 1$ h per day was reduced by 7.6% and 2.7%, respectively, in comparison with those who walked $<1$ h per day.
- Years of life added as a result of a healthy lifestyle did not necessarily translate into an increased amount of lifetime medical expenditure.

**Strengths and limitations of this study**

- This is the first study to investigate the association between walking, life expectancy and lifetime medical expenditure.
- We assessed walking using a simple questionnaire, in which we asked the participants to report only the time spent walking, and did not ask about walking pace, distance walked or any distinction between walking for exercise and other reasons.

## INTRODUCTION

Previous studies have agreed that a higher level of physical activity extends life expectancy.[1–4] Walking is part of a physically active lifestyle. Previous studies have indicated that a longer time spent walking,[5–13] walking pace[8 14–16] and a longer distance walked[17 18] are significantly associated with a decreased risk of mortality.

We previously reported that medical expenditure per month was significantly reduced among those who spent a longer time walking, based on the same cohort dataset as that used here.[19] Similar findings have been reported worldwide.[20 21] However, in view of the increased life expectancy of those who walk for a longer time, it is unclear whether lifetime medical expenditure increases or decreases as a result. In other words, the question to be answered here is whether a lifelong healthy lifestyle eventually increases lifetime medical expenditure because of extended life expectancy.

So far, only one study has examined the association between physical activity and lifetime costs.[4] This revealed that people with a high physical activity level tended to live longer than people with a lower physical activity level, and that the former had lower lifetime medical costs than the latter. However, that study was only a simulation analysis based on assumed variations in the health and economic effects of active and sedentary lifestyles.

The objective of the present study was to examine the association between walking, life expectancy and lifetime medical expenditure using actual individual data derived from a population-based 13-year prospective observation period. The population comprised 27 738 Japanese adults aged 40–79 years living in the community who were free of any functional limitations or chronic conditions interfering with physical activity, with an accrued total of 285 342 person-years. This cohort study has been monitoring survival and medical care utilisation, and its costs, for all participants.[19] [22] Using this dataset, we constructed a life table to estimate life expectancy and lifetime medical expenditure according to the time spent walking.[24] [25]

## MATERIALS AND METHODS

### Study cohort

The present data were derived from the Ohsaki National Health Insurance (NHI) Cohort Study.[19] [22] [25] We conducted a self-administered questionnaire survey of various lifestyle habits between October and December 1994 for all NHI beneficiaries aged 40–79 years who lived in the catchment area of Ohsaki Public Health Center, Miyagi Prefecture, northeastern Japan. Out of 54 996 eligible individuals, 52 029 (95%) responded.

We excluded 776 participants who had withdrawn from the NHI before 1 January 1995 because their cost data were not available. Thus, the remaining 51 253 participants formed the study cohort. The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine. Participants who had returned the self-administered questionnaires and signed them were considered to have consented to participate.

For the present analysis, we excluded participants who had functional limitation or chronic conditions interfering with physical activity. Physical function status was assessed using the six-item measure of the Medical Outcomes Study Short-form General Health Survey.[26] Participants were excluded if they stated on the Medical Outcomes Study questionnaire that they were unable to perform moderate or vigorous activities (n=15 916). We excluded participants who reported severe bodily pain (n=949), or any history of stroke (n=474), myocardial infarction (n=585) or arthritis (n=2176). We also excluded those who died within the first year (n=174) or did not provide complete responses in the walking status questionnaire (n=3241). Thus, a total of 27 738 participants (15 521 men and 12 217 women) remained. These participants were apparently healthy enough to walk for as long as they wished.

### Time spent walking

The self-administered questionnaire included items on time spent walking. Time spent walking was assessed through the subject's response to the question, 'About how much time do you walk per day on average?' The participants were asked to choose one of three answers: '1 h or more,' '30 min—1 h' or '30 min or less.' In Japan, the Ministry of Health, Labour and Welfare recommended to walk ≥1 h per day in Exercise and Physical Activity Reference for Health Promotion 2006. Then, we divided the participants into two groups according to the time spent walking daily: <1 h and ≥1 h. We had previously evaluated and reported the validity of self-reported time spent walking.[5] [19] [27] This validation study had indicated that self-reported walking time was reasonably reproducible and sufficiently valid for studying the health effects of walking.

### Health-insurance system in Japan

Details of the Japanese NHI system have been described previously.[22] [28] [29] Briefly, everyone living in Japan is required to enrol in a health-insurance system. The NHI covers 35% of the Japanese population, mainly farmers, self employed or retired people. The NHI covers almost all medical treatment, including diagnostic tests, medication, surgery, supplies and materials, physicians and other personnel costs, inpatient care and most dental treatment. It covers treatment by physicians and nurses but not that by other professionals such as home health aides. Payment to medical providers is made on a fee-for-service basis, where the price of each service is determined by a uniform national fee schedule.

When a participant withdraws from the NHI system because of death, emigration or employment, the withdrawal date and its reason are coded in the NHI withdrawal history files. We recorded any mortality or migration by reviewing the NHI withdrawal history files and collected data on the death of participants by reviewing the death certificates filed at Ohsaki Public Health Center. We thus followed up the participants and prospectively collected data on medical care utilisation and its costs for all individuals in the cohort from 1 January 1995 to 31 December 2007. Study participants (16.3%) were lost to follow-up, so their vital status was unknown.

### Statistical analysis

Using the Ohsaki NHI cohort database, we estimated mortality and medical expenditure for individual age groups, and for the categories of time spent walking, for both men and women. We divided age into the following groups: 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84 and ≥85 years. The multiadjusted mortalities for each age category were estimated from a Poisson regression model based on person-years and the number of deaths from 1996 until 2007. The dependent variable was mortality, and the independent variables were age groups, categories of time spent walking and the following covariates: smoking status (current and past smoker, or never smoker), alcohol consumption (current drinker consuming 1–499 g/week, current drinker consuming ≥450 g/week, or never and past drinker), body mass index (BMI: $<21$ kg/m$^2$, 21–24.9 kg/m$^2$ or $\geq 25$ kg/m$^2$), self-rated health (good or not good), sports and physical activity (≥3 h/week or <3 h/week), history of hypertension disease (presence or absence), history of diabetes mellitus (presence or absence), history of cancer (presence or absence), history of liver disease (presence or absence) and history of kidney disease (presence or absence).[19] The data on all covariates were obtained from a self-administered questionnaire. We estimated the mortality of participants aged ≥85 years by multiplying the estimated mortality for the 85–89-year age group by the ratio of mortality for the same age group relative to the mortality for ≥85 years from complete life tables for the year 2000, as there were few person-years for participants aged over 90 years in our dataset.[30]

Because medical expenditure increases before death, we separately calculated medical expenditure for participants who survived through the index year and for those who died. The multiadjusted medical expenditure per year for survivors and decedents, respectively, was estimated for each of the age groups and the categories of time spent walking using a linear regression model adjusted for the above covariates.

The estimates of multiadjusted mortality and medical expenditure for each age group were used for estimating life expectancy and lifetime medical expenditure from 40 years of age. Life expectancy was calculated using Chiang's analytical method on the basis of the latest published complete life tables of Japan for the year 2000.[23 30] Lifetime medical expenditure was estimated from the sum obtained by multiplying the static population in life table by the medical expenditure for survivors and the number of deaths in the life table by the increased medical expenditure owing to death, which was calculated by subtracting the medical expenditure in year of survivors from that in the period of 1 year before death. That is, the life expectancy ($e_x$) and lifetime medical expenditure ($M_e$) for each age group (x) were estimated using the numbers of survivors ($l_x$), deaths ($d_x$), static population ($L_x$), multiadjusted medical expenditure for survivors ($a_y$) and multiadjusted medical expenditure for the deceased ($b_y$) as follows:

$\sum$ is the sum of $y \geq x$

$$e_x = \frac{\sum L_y}{l_x}$$

$$M_x = \frac{\sum (L_y a_y + d_y b_y)}{l_x}$$

The 95% CIs were estimated using a Monte Carlo simulation with 100 000 replicates based on a Poisson regression model and linear regression model. All analyses were used the SAS V.9.1 statistical software package.

We used a purchasing-power parity rate (British pounds to Japanese yen) of £1.00=¥140.

## RESULTS

After 13 years of follow-up, we observed 2936 deaths (2193 men and 743 women) among the 27 738 participants (15 521 men and 12 217 women). The mean medical expenditure per year for survivors who walked ≥1 h per day was £1714.2 in men and £1621.4 in women, significantly lower than for those who walked <1 h per day (men: £2064.3, $p<0.0001$; women: £1878.6, $p<0.0001$). Also, the mean medical expenditure in the year of death for participants who walked ≥1 h per day was £16 878.6 in men and £17 464.3 in women, which was not significantly different from those who walked <1 h per day (men: £16 650.0, $p=0.7315$; women: £17 742.9, $p=0.8330$).

### Baseline characteristics in terms of categories for time spent walking

Table 1 shows the baseline characteristics of the study participants according to the categories of time spent walking for men and women, respectively.

As compared with those who walked <1 h per day, participants who walked ≥1 h per day were less likely to be smokers and obese. Self-reported histories of hypertension, diabetes mellitus and liver disease were all significantly less prevalent in those who walked ≥1 h per day.

### Mortality in terms of categories for time spent walking

Figure 1A (for men) and Figure 1B (for women) show the multiadjusted mortality (per 1000) in each of the age groups according to the categories of time spent walking.

In men in each age group, the multiadjusted mortality was lower in participants who walked ≥1 h per day than in those who walked <1 h per day. In women in all age groups except for the aged 40–44 and 45–49 year groups, the multiadjusted mortality was lower in participants who walked ≥1 h per day than in those who walked <1 h per day.

**Table 1** Baseline characteristics by time-spent-walking categories in 27 738 participants

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Time spent walking | | | Time spent walking | | |
| | <1 h | ≥1 h | p Value* | <1 h | ≥1 h | p Value* |
| No of subjects | 7363 | 8158 | 0.2784 | 6303 | 5914 | 0.0714 |
| Mean (SD) age | 57.4 (10.6) | 57.2 (10.2) | | 57.9 (10.1) | 57.6 (9.7) | |
| Smoking status (%) | | | | | | |
| Current and past smoker | 81.9 | 79.8 | 0.0011 | 12.6 | 9.9 | <0.0001 |
| Never smoker | 18.1 | 20.2 | | 87.5 | 90.1 | |
| Alcohol drinking (%) | | | | | | |
| Never and past drinker | 26.5 | 25.1 | 0.1117 | 74.7 | 75.4 | 0.1380 |
| Current drinker, 1–449 g/week | 61.3 | 62.2 | | 24.3 | 23.9 | |
| Current drinker, ≥450 g/week | 12.2 | 12.8 | | 1.1 | 0.7 | |
| Body mass index (%) | | | | | | |
| <21 kg/m$^2$ | 18.5 | 20.5 | <0.0001 | 18.6 | 19.4 | 0.0019 |
| 21–24.9 kg/m$^2$ | 53.3 | 55.8 | | 50.7 | 52.9 | |
| ≥25 kg/m$^2$ | 28.3 | 23.7 | | 30.7 | 27.7 | |
| Self-rated health (%) | | | | | | |
| Good | 73.1 | 79.3 | <0.0001 | 72.5 | 78.2 | <0.0001 |
| Not good | 26.9 | 20.7 | | 27.5 | 21.8 | |
| Sports and physical activity (%) | | | | | | |
| ≥3 h/week | 13.2 | 18.7 | <0.0001 | 10.7 | 16.6 | <0.0001 |
| <3 h/week | 86.8 | 81.3 | | 89.3 | 83.4 | |
| History of hypertension (%) | | | | | | |
| Presence | 21.5 | 18.6 | <0.0001 | 24.2 | 20.1 | <0.0001 |
| Absence | 78.5 | 81.4 | | 75.8 | 79.9 | |
| History of diabetes mellitus (%) | | | | | | |
| Presence | 7.4 | 4.8 | <0.0001 | 5.1 | 3.2 | <0.0001 |
| Absence | 92.6 | 95.2 | | 94.9 | 96.8 | |
| History of cancer (%) | | | | | | |
| Presence | 2.1 | 1.8 | 0.2563 | 2.8 | 2.8 | 0.9032 |
| Absence | 97.9 | 98.2 | | 97.2 | 97.2 | |
| History of liver disease (%) | | | | | | |
| Presence | 6.9 | 5.7 | 0.0013 | 3.7 | 2.9 | 0.0223 |
| Absence | 93.1 | 94.4 | | 96.3 | 97.1 | |
| History of kidney disease (%) | | | | | | |
| Presence | 2.9 | 2.7 | 0.3493 | 3.6 | 2.7 | 0.0049 |
| Absence | 97.1 | 97.3 | | 96.4 | 97.3 | |

*p Values were calculated using the $\chi^2$ test.

Table 2 shows the mortality ratio with 95% CIs according to the categories of time spent walking. In men, the multiadjusted mortality ratio for participants who walked ≥1 h per day was significantly lower than that for participants who walked <1 h per day (0.90, 95% CI 0.82 to 0.98, p=0.0153). In women, the multiadjusted mortality ratio for participants who walked ≥1 h per day was non-significantly lower than that for participants who walked <1 h per day (0.95, 95% CI 0.82 to 1.10, p=0.4693).

### Life expectancy and lifetime medical expenditure in terms of time spent walking

Table 3 shows the life expectancy and lifetime medical expenditure from 40 years of age with 95% CIs according to the categories of time spent walking.

In men, the multiadjusted life expectancy of those who walked ≥1 h per day was 44.81 years (95% CI 43.66 to 45.94), which was significantly longer by 1.38 years (p=0.0073) than for those who walked <1 h per day (43.43 years; 95% CI 42.39 to 44.41). In women, the same results were observed, although the differences did not reach statistical significance.

In spite of their longer life expectancy, their lifetime medical expenditure from 40 years of age was significantly lower in men and non-significantly lower in women. The multiadjusted lifetime medical expenditure for participants who walked ≥1 h per day was £99 423.6 (95% CI 92 515.9 to 106 694.7), significantly lower by 7.6% (p=0.0048) than for those who walked <1 h per day (£107 544.2; 95% CI 101 234.0 to 114 044.6). In women, the multiadjusted lifetime medical expenditure for participants who walked ≥1 h per day was £128 161.2 (95% CI 111 335.0 to 148 494.7), non-significantly lower by 2.7% (p=0.2559) than for

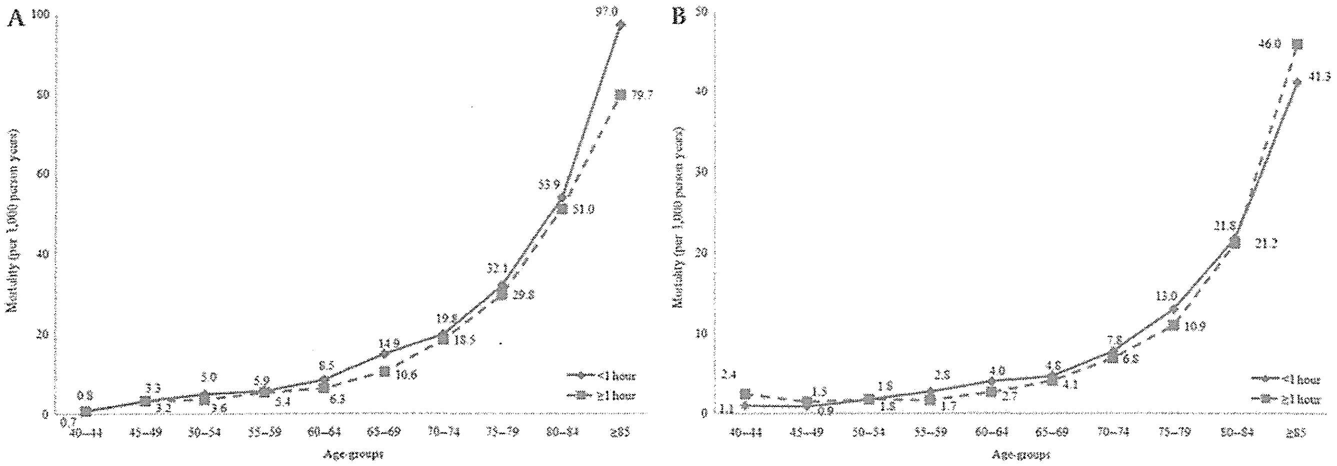

**Figure 1** Multiadjusted mortality by time-spent-walking categories in each age group in (A) men and (B) women.

those who walked <1 h per day (£131 766.8; 95% CI 115 902.4 to 150 714.3).

## DISCUSSION

The present results indicate that the multiadjusted lifetime medical expenditure from the age of 40 years for those who walked ≥1 h per day was significantly lower by 7.6% in men and non-significantly lower by 2.7% in women than for those who walked <1 h per day. This decrease in lifetime medical expenditure was observed in spite of a longer life expectancy (1.38 years for men and 1.16 years for women) among those who walked ≥1 h per day. Thus, a healthy lifestyle not only extended longevity but also decreased the amount of lifetime medical expenditure, especially men.

We observed statistically significant differences for men but not for women. Although the differences did not reach statistical significance, the same results were observed for women. The reason why the impact of walking was smaller in women than in men was unknown. In women, other factors such as obesity and postmenopausal change might have a stronger impact on life expectancy and lifetime medical expenditure than walking.

### Comparison with other studies

Four studies have addressed the association between physical activity level and life expectancy.[1–4] Additionally, studies investigating associations between time spent walking,[5–13] or distance walked[17 18] and mortality have consistently shown that participants who have a higher physical activity have a longer life expectancy and lower mortality than participants who have a lower physical activity. Only one study has reported the association between physical activity and lifetime medical expenditure.[4] In a simulation study, Keeler *et al* demonstrated that if participants with a sedentary lifestyle had exercised regularly, the additional exercise would have increased their life expectancy by 300 days and saved £1900 in lifetime costs. Even though there is a difference between physical activity and walking, this result is consistent with the present finding that participants who walked ≥1 h per day lived longer and had a lower lifetime medical expenditure.

We previously calculated life expectancy and lifetime medical expenditure in relation to smoking and BMI from age 40 years using the same dataset as that for the present study.[24] The results indicated that lifetime medical expenditure was lower for smokers than for non-smokers, reflecting the 3.5-year shorter life expectancy of smokers.[24] On the other hand, lifetime medical expenditure was higher for participants who were obese (BMI≥30.0) than for those who were of normal weight (18.5≤BMI<25.0), even though the former lived 2 years less than the latter (Nagai M, Kuriyama S, Kakizaki M, *et al.* Impact of obesity, overweight and underweight on life expectancy and lifetime medical expenditures. *Popul Health Metr*, under review). In fact, both smokers and obese participants had a shorter life expectancy than non-smokers and normal-weight participants, whereas

**Table 2** Mortality ratio for time-spent-walking categories in 27 738 participants

| Time spent walking | | Univariate<br>Mortality ratio (95% CI) | Univariate<br>p Value | Multiadjusted*<br>Mortality ratio (95% CI) | Multiadjusted*<br>p Value |
|---|---|---|---|---|---|
| Men | <1 h | 1.00 | | 1.00 | |
| | ≥1 h | 0.87 (0.80 to 0.94) | 0.0009 | 0.90 (0.82 to 0.98) | 0.0153 |
| Women | <1 h | 1.00 | | 1.00 | |
| | ≥1 h | 0.89 (0.77 to 1.03) | 0.1135 | 0.95 (0.82 to 1.10) | 0.4693 |

*Adjusted for age groups, smoking status, alcohol drinking, body mass index, self-rated health, sports and physical activity, and history of hypertension, diabetes mellitus, cancer, liver disease and kidney disease.

**Table 3** Life expectancy and lifetime medical expenditure at age 40 years for time-spent-walking categories in 27 738 participants

| | Time spent walking | Univariate Estimate | Univariate 95% CI | Univariate p Value | Multiadjusted* Estimate | Multiadjusted* 95% CI | Multiadjusted* p Value |
|---|---|---|---|---|---|---|---|
| Men | Life expectancy (years) at age 40 years | | | | | | |
| | <1 h | 42.41 | 41.45 to 43.26 | 0.0004 | 43.43 | 42.39 to 44.41 | 0.0073 |
| | ≥1 h | 44.19 | 43.15 to 45.19 | | 44.81 | 43.66 to 45.94 | |
| | Lifetime medical expenditure (£) at age 40 years | | | | | | |
| | <1 h | 107 023.2 | 101 093.6 to 113 066.3 | <0.0001 | 107 544.2 | 101 234.0 to 114 044.6 | 0.0048 |
| | ≥1 h | 94 402.1 | 87 812.3 to 101 248.0 | | 99 423.6 | 92 515.9 to 106 694.7 | |
| Women | Life expectancy (years) at age 40 years | | | | | | |
| | <1 h | 52.25 | 49.79 to 54.92 | 0.0569 | 56.62 | 53.17 to 60.62 | 0.2351 |
| | ≥1 h | 54.25 | 51.38 to 57.48 | | 57.78 | 54.02 to 62.22 | |
| | Lifetime medical expenditure (£) at age 40 years | | | | | | |
| | <1 h | 123 553.0 | 111 619.5 to 137 549.6 | 0.0644 | 131 766.8 | 115 902.4 to 150 714.3 | 0.2559 |
| | ≥1 h | 115 896.0 | 102 406.6 to 131 792.1 | | 128 161.2 | 111 335.0 to 148 494.7 | |

*Adjusted for age groups, smoking status, alcohol drinking, body mass index, self-rated health, sports and physical activity, and history of hypertension, diabetes mellitus, cancer, liver disease and kidney disease as same as table 2.

their lifetime medical expenditure was conversely increased. These differences could be explained by the impact of these risk factors on quality of life. Using prospective data for 16 176 adult Caucasians in the USA,[31] Reuser *et al* estimated life expectancy and years of life with and without activities of daily-living disability in relation to smoking and BMI, respectively. The results indicated that smoking decreased both life expectancy and years of life with activities of daily-living disability, whereas obesity decreased the former but increased the latter, thus leading to the conclusion that 'smoking kills, and obesity disables'. Reuser's conclusion is concordant with the impact of walking on life expectancy and lifetime medical expenditure. Physical activity decreases not only mortality but also disability,[5–13 17 18 32] leading to lower medical expenditure.[33] For instance, walking has been significantly associated with a lower risk of cardiovascular disease,[7] stroke,[34] coronary heart disease,[35 36] type 2 diabetes[37] and hypertension.[38] Consequently, walking also reduces expenditure on medication needed for these conditions.[39]

## Strengths and limitations

This is the first study to have investigated the association between walking, life expectancy and lifetime medical expenditure. A major strength of this study was that we collected individual data on medical expenditure based on a cohort study of survival and medical-care utilisation, and its cost, for all participants,[19 22 24 28] and the NHI covers almost all medical treatment in Japan. Second, we conducted a 13-year prospective observation of 27 738 Japanese adults aged 40–79 years living in the community who were free of any functional limitations or chronic conditions interfering with physical activity, with an accrued total of 285 342 person-years. Third, in order to reduce bias or reverse causation in that people did not walk because of functional limitations that also required medical expenditure, we excluded participants who, at the baseline, reported limited physical function or conditions interfering with physical activity. Additionally, to control for confounders, we also included various covariates in our Poisson regression model and linear regression model.

On the other hand, several limitations should also be considered. First, we assessed walking using a simple questionnaire in which we asked the participants to report only the time spent walking and did not ask about walking pace, distance walked or any distinction between walking for exercise and other reasons. Second, a longer time spent walking may be a reflection of performing more vigorous activity, making it difficult to distinguish the impact of walking from other types of physical activity. However, the present result did not change after multivariate adjustment.

## Conclusions and policy implication

In summary, lifetime medical expenditure was shown to be decreased in participants who walked ≥1 h per day, despite the fact that they lived longer. Increased longevity resulting from a healthier lifestyle did not necessarily translate into an increased amount of medical expenditure throughout life. However, in the present study, around 50% of study participants walk <1 h per day. To increase their walking time, the recommendation of walking with a pedometer may be useful.[40] An increase in walking time at the population level would bring about a tremendous change in people's health and medical cost. A campaign to encourage people to walk for longer and a program to make walking environments safer and more pleasant should be implemented. This intervention may extend life expectancy without apparently increasing lifetime medical expenditure, especially for men.

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**Patient consent** Obtained.

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**ORIGINAL ARTICLE**
**Epidemiology**

# Impact of Weight Change Since Age 20 and Cardiovascular Disease Mortality Risk

## – The Ohsaki Cohort Study –

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***Background:*** It is unclear whether weight change since young adulthood affects the risk of mortality due to cardiovascular disease (CVD). The aim of this study was to investigate weight change since age 20 in relation to the risk of CVD mortality.

***Methods and Results:*** A total of 41,364 eligible Japanese men and women aged 40–79 years participated in the Ohsaki Cohort Study baseline survey in 1994. Hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD mortality were calculated according to weight change since age 20 (loss ≥10.0 kg; loss 5.0–9.9 kg; stable [±4.9 kg]; gain 5.0–9.9 kg; gain ≥10.0 kg). During 13.3 years of follow-up, 1,756 participants died of CVD. The association between weight change and CVD mortality was L-shaped in men and U-shaped in women; the multivariate HR (95% CI) for men with weight loss ≥10.0 kg was 1.52 (1.25–1.85), and that for women with weight loss ≥10.0 kg and weight gain ≥10.0 kg was 1.62 (1.25–2.11) and 1.36 (1.09–1.69), respectively. Cross-classification analysis based on body mass index (BMI) at age 20 and weight change tended to be U-shaped, except for men whose BMI had been <25 kg/m$^2$ at age 20, in which case it was L-shaped.

***Conclusions:*** Weight loss since young adulthood is associated with excess risk of mortality due to CVD in men, while a U-shaped relationship was observed for women. (*Circ J* 2013; **77:** 679–686)

**Key Words:** Body mass index; Cardiovascular disease mortality; Japan; Weight change; Young adulthood

Obesity is an established risk factor for cardiovascular disease (CVD) morbidity[1–3] and mortality.[4–6] In addition to a high body mass index (BMI), weight gain also adversely affects CVD risk factors.[7–10] The effect of weight change on CVD mortality has been assessed in several studies, but the results have varied. Some studies have reported weight gain associated with CVD mortality,[11,12] or that there was a U-shaped association,[13–15] whereas others have shown that only weight loss was associated with CVD mortality.[16–20]

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These differences in results could have been due to differences in the age composition of the study participants, the life stage at which weight change occurred, the duration of the weight change, or the length of follow-up among the studies.[21] The elevated mortality risk associated with recent weight loss due to antecedent disease, especially in studies of older people or those with short follow-up periods may easily lead to biased results. Monitoring long-term weight change, which represents the transition of weight trajectories during the course of life, may help to clarify the mixed results for CVD mortality among older subjects.[22] Both being persistently obese since early adulthood and having an increase in BMI category from normal to obese were associated with higher all-cause mortality in the Ohsaki Cohort Study.[23] An inverse relationship in men and L-shaped association in women between weight change and all-cause and CVD mortality, however, were observed in another study among middle-aged Japanese individuals.[19]

Additionally, a previous study has suggested that the metabolic and health consequences of weight change may differ between men and women.[24] Furthermore, sex differences in major cardiovascular risk factors have been noted as a substantial reason for the sex difference in CVD risk.[25] Previous studies of the association between weight change and subsequent CVD morbidity or mortality, however, were based mainly

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