on men or on composite results,[7–10,12–16] whereas sex-specific studies have been few and their results inconsistent.[17–20]

To our knowledge, no prospective study has reported the relationship between weight change since early adulthood and specific causes of CVD mortality including ischemic heart disease (IHD) and stroke. The objective of the present study was to investigate weight change since age 20 in relation to the risks of total CVD mortality and mortality due to type of CVD, using data obtained from a large prospective population-based cohort study in Japan.

Methods

Subjects

The present data were derived from the Ohsaki Cohort Study, the study design of which has been described in detail previously.[26–29] The subjects were all National Health Insurance (NHI) beneficiaries, aged 40–79 years, living in the catchment area of the Ohsaki Public Health Center, Miyagi Prefecture, north-east 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. The NHI is a community-based health insurance system for farmers, the self-employed, pensioners, and their dependants. The study area is a typical rural area and the main industry is agriculture. Thirty-nine percent of men were farmers, 28% were self-employed, and 28% were retired. Among women, 31% were housewives, 25% were farmers, and 15% were self-employed.[27]

We conducted a baseline survey of various lifestyle habits during the period from October through December 1994. Trained survey personnel visited the subjects and informed them of the survey objectives, the fact that subjects were treated anonymously at the data analysis stage, and their freedom to decline. The subjects were asked to complete the questionnaires by themselves and return them to the same personnel member within 1 week. Return of the self-administered questionnaires signed by the participants was considered to imply their consent to participate in the study. In order to protect the subjects' privacy, their personal names were deleted from all NHI Claims History files, Withdrawal History files, and our baseline data files in the subsequent follow-up record linkage. The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine.

Among the 54,996 eligible individuals, 52,029 (95%) responded to the questionnaires. Participants who withdrew from the NHI before 1 January 1995, the time when the prospective collection of data on NHI withdrawals began, were excluded (n=776). Thus, the study cohort consisted of the remaining 51,253 participants. For the present analysis, participants with histories of myocardial infarction or stroke (n=2,510) or cancer (n=1,638) were excluded. After further excluding participants for whom data were missing, or who had extreme values for current height, current weight or weight at age 20 (n=5,741), we included 41,364 subjects (men, n=20,112; women, n=21,252) in the analysis.

Classification of Exposure

The self-administered questionnaire included questions on current height at baseline (in cm), current weight at baseline and recalled weight at age 20 (in kg). For the present analysis, weight change (in kg) was defined as the difference between current weight and recalled weight. The participants were categorized into 5 groups according to weight change since age 20: weight loss ≥10.0 kg; weight loss 5.0–9.9 kg; stable weight (±4.9 kg change); weight gain 5.0–9.9 kg; and weight gain ≥10.0 kg. BMI at baseline and at age 20 was also calculated as current weight and recalled weight at age 20 divided by the square of current height (kg/m^2), respectively.

The self-reported current height and weight data were highly correlated with measured data (correlation coefficient: 0.96 for weight and 0.93 for height) in a subsample who received health examinations in 1995 (n=14,883), the year after the baseline survey.[28]

Follow-up

The primary endpoints for the present analysis were CVD mortality, including IHD and stroke mortality, occurring between 1 January 1995 and 31 March 2008. All participants were followed up for mortality and emigration by reviewing the NHI withdrawal history files. 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 subsequent information on participants who withdrew from the NHI because of emigration or employment was unavailable, their follow-ups were discontinued. As of 31 March 2008, the follow-up rate in the Ohsaki NHI Cohort Study was 85.2% (80.7% among non-deceased subjects).

For all the decedents, we investigated the causes of death by reviewing the death certificates filed at Ohsaki Public Health Center with permission from the Ministry of Health, Labour, and Welfare, Japan. Causes of death were encoded by trained physicians in accordance with the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), for total CVD (group I), IHD (I20–25), total stroke (I60–69), ischemic stroke (I63), and hemorrhagic stroke (I61).

Statistical Analysis

The person-years of follow-up were calculated from 1 January 1995 to the date of death, withdrawal from the NHI, or 31 March 2008, whichever occurred first. Cox proportional hazards regression analysis was used to investigate the sex-specific hazard ratios (HRs) and 95% confidence intervals (CIs) between weight change since age 20 and CVD mortality.

The following variables were considered as potential confounders: age (in years), current height (in cm), body weight at age 20 (in kg), educational levels (junior high school or less, high school and college or higher), baseline job status (employed and not employed), smoking status at age 20 (yes/no), smoking status at baseline (never smoked, smoked in the past, currently smoking <20 cigarettes/day and currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past, currently drinking <45.6 g ethanol/day and current drinking ≥45.6 g ethanol/day), time spent walking (≥1 h/day and <1 h/day). For women, menopausal status (yes/no), oral contraceptive use (yes/no) and hormone replacement therapy (yes/no) were also considered as confounders.

To assess whether the risk of CVD death associated with weight change differed between subjects who were underweight, normal weight and overweight, we cross-classified the participants into groups according to their BMI at age 20 (<22.5 kg/m^2, underweight; 22.5–24.9 kg/m^2, normal weight; and ≥25.0 kg/m^2, overweight), treating BMI 22.5–24.9 kg/m^2 at age 20 with subsequent stable weight as the reference group. Furthermore, we repeated the analysis after exclusion of deaths in the first 3 years of follow-up. Other stratified analyses were conducted according to the age at study entry (40–59 years vs. 60–79 years) and smoking status at baseline (never-smokers

Table 1. Subject Characteristics vs. Weight Change Since Age 20

	Weight change since age 20					P-value
	Loss		Stable	Gain		
	≥10.0kg	5.0–9.9kg	±4.9kg	5.0–9.9kg	≥10.0kg	
Men (n=20,112)						
No. subjects	1,609	3,117	7,578	3,880	3,928	
Age (years)	66.9±8.3	63.9±9.0	58.2±10.4	56.2±10.2	55.4±9.9	<0.0001
BMI at age 20 (kg/m²)	26.1±4.1	24.2±2.4	22.5±2.1	21.7±2.0	21.1±2.1	<0.0001
BMI at baseline (kg/m²)	20.9±2.7	21.8±2.3	22.4±2.1	24.2±2.0	26.3±2.4	<0.0001
Hypertension	28.3	24.3	20.2	22.6	26.7	<0.0001
Diabetes mellitus	12.7	8.7	5.1	7.0	7.0	<0.0001
Education until age 15	72.5	72.1	60.6	54.9	52.8	<0.0001
Unemployed at baseline	32.8	22.9	16.3	15.7	13.7	<0.0001
Smoker at age 20	35.4	37.3	41.3	42.3	42.3	<0.0001
Current smoker	62.5	60.3	59.3	51.7	49.3	<0.0001
Current drinker	63.0	69.7	75.4	75.0	76.7	<0.0001
Walking <1 h/day	52.6	48.1	47.4	55.0	55.3	<0.0001
Women (n=21,252)						
No. subjects	1,192	2,822	7,417	4,865	4,956	
Age (years)	67.0±9.1	63.7±9.7	59.2±10.0	58.5±9.5	58.7±9.3	<0.0001
BMI at age 20 (kg/m²)	26.5±3.9	24.4±2.7	22.4±2.5	21.5±2.2	20.7±2.3	<0.0001
BMI at baseline (kg/m²)	20.7±2.8	21.6±2.6	22.5±2.4	24.4±2.3	26.9±2.7	<0.0001
Hypertension	26.9	26.1	22.4	26.5	36.1	<0.0001
Diabetes mellitus	8.0	6.2	4.5	4.3	5.7	<0.0001
Education until age 15	68.7	62.0	52.8	53.7	56.3	<0.0001
Unemployed at baseline	61.4	57.2	46.2	48.5	51.6	<0.0001
Smoker at age 20	1.5	1.4	1.4	1.3	1.8	<0.0001
Current smoker	14.1	8.8	8.5	7.2	9.7	<0.0001
Current drinker	18.8	20.6	23.0	24.6	26.5	<0.0001
Walking <1 h/day	58.1	56.4	55.0	57.2	60.4	<0.0001

Data given as mean±SD or %. BMI, body mass index.

vs. former smokers and current smokers in men; never-smokers vs. ever-smokers in women, because the number of former smokers was too few). The statistical evidence for the difference in effect between these subgroup participants was assessed by computing log-likelihood ratio tests of the interaction. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

The mean BMI at age 20 was 22.5±2.8 kg/m² and at study entry it was 23.5±3.0 kg/m². The mean change in body weight from age 20 to study entry was a gain of 2.0±8.8 kg in men and a gain of 3.3±8.4 kg in women.

The sex-specific baseline characteristics of participants according to the weight change categories are summarized in **Table 1**. The participants who had lost ≥10.0 kg in weight were older, and were more likely to have hypertension and diabetes, to have been educated until age 15, to have been unemployed at baseline, and to be current smokers. In contrast, the participants who had gained ≥10.0 kg in weight were more likely to be smokers at age 20, current drinkers, and to walk <1 h a day. The proportions of current smokers and current drinkers among women, however, were much lower than among men.

During the 13.3 years of follow-up (451,081 person-years), we documented 1,756 CVD deaths (1,017 men and 739 women), including 408 IHD deaths (253 men and 155 women) and 790 stroke deaths (436 men and 354 women). **Table 2** lists the multivariate-adjusted HRs for CVD mortality according to the weight change categories. There was an L-shaped association in men and a U-shaped association in women between weight change and CVD mortality (P=0.006 for interaction with sex). In men, the multivariate-adjusted HR relative to the stable weight group was 1.52 (95% CI: 1.25–1.85) for the weight loss ≥10.0 kg group, and no significant risks were observed in the other weight change groups. In women, the multivariate-adjusted HR relative to the stable weight group was 1.62 (95% CI: 1.25–2.11) for the weight loss ≥10.0 kg group and 1.36 (95% CI: 1.09–1.69) for the weight gain ≥10.0 kg group.

The risk of IHD and stroke mortality had trends similar to overall CVD mortality. In men, the weight loss ≥10.0 kg group had a significantly higher risk of death due to all forms of stroke (HR, 1.38; 95% CI: 1.01–1.89) and ischemic stroke (HR, 1.54; 95% CI: 1.00–2.37). A noticeably lower risk of IHD mortality was observed among men with weight gain ≥10.0 kg (HR, 0.59; 95% CI: 0.37–0.94). In women, the relationship tended to be U-shaped for IHD and for stroke mortality. These excess risks for all CVD and IHD mortality related to weight loss were persistently observed even after exclusion of early deaths in the first 3 years of follow-up.

Table 3 lists the multivariate-adjusted HRs for CVD mortality according to BMI at age 20 and weight change categories, treating subjects with a BMI 22.5–24.9 kg/m² at age 20 and subsequent stable weight (±4.9 kg change) as the reference

Table 2. CVD Mortality vs. Weight Change Since Age 20

	Weight change since age 20				
	Loss		Stable	Gain	
	≥10.0 kg	5.0–9.9 kg	±4.9 kg	5.0–9.9 kg	≥10.0 kg
Men (n=20,112)					
Person-years	14,652	31,798	83,070	43,485	44,506
All CVD					
No. deaths	189	211	345	139	133
HR1 (95% CI)	1.52 (1.25–1.85)‡	1.04 (0.87–1.24)	1 (Reference)	0.95 (0.78–1.16)	0.99 (0.80–1.21)
HR2 (95% CI)	1.36 (1.08–1.70)†	0.99 (0.81–1.20)	1 (Reference)	0.97 (0.78–1.21)	0.96 (0.76–1.20)
IHD					
No. deaths	45	49	97	39	23
HR1 (95% CI)	1.41 (0.95–2.10)	0.92 (0.64–1.31)	1 (Reference)	0.92 (0.63–1.35)	0.59 (0.37–0.94)*
HR2 (95% CI)	1.27 (0.80–1.99)	0.79 (0.52–1.18)	1 (Reference)	0.86 (0.57–1.31)	0.54 (0.32–0.92)*
All strokes					
No. deaths	74	83	148	68	63
HR1 (95% CI)	1.38 (1.01–1.89)*	0.96 (0.73–1.26)	1 (Reference)	1.08 (0.81–1.45)	1.08 (0.80–1.47)
HR2 (95% CI)	1.24 (0.86–1.78)	0.96 (0.70–1.30)	1 (Reference)	1.19 (0.87–1.63)	1.03 (0.73–1.45)
Ischemic stroke					
No. deaths	43	38	65	35	30
HR1 (95% CI)	1.54 (1.00–2.37)*	0.90 (0.60–1.36)	1 (Reference)	1.34 (0.88–2.04)	1.25 (0.80–1.96)
HR2 (95% CI)	1.24 (0.74–2.06)	0.85 (0.54–1.35)	1 (Reference)	1.56 (1.00–2.41)*	1.16 (0.70–1.91)
Hemorrhagic stroke					
No. deaths	15	20	49	15	17
HR1 (95% CI)	1.16 (0.61–2.21)	0.84 (0.49–1.44)	1 (Reference)	0.66 (0.37–1.18)	0.78 (0.44–1.39)
HR2 (95% CI)	0.91 (0.39–2.10)	0.82 (0.43–1.56)	1 (Reference)	0.66 (0.33–1.32)	0.87 (0.45–1.65)
Women (n=21,252)					
Person-years	12,266	30,175	82,206	53,797	55,126
All CVD					
No. deaths	104	173	195	110	157
HR1 (95% CI)	1.62 (1.25–2.11)‡	1.52 (1.23–1.88)‡	1 (Reference)	0.98 (0.77–1.24)	1.36 (1.09–1.69)†
HR2 (95% CI)	1.48 (1.09–2.00)*	1.54 (1.21–1.95)‡	1 (Reference)	1.08 (0.84–1.41)	1.48 (1.16–1.89)†
IHD					
No. deaths	24	42	35	25	29
HR1 (95% CI)	1.98 (1.11–3.53)*	2.02 (1.27–3.22)†	1 (Reference)	1.24 (0.74–2.08)	1.39 (0.84–2.31)
HR2 (95% CI)	1.92 (1.00–3.71)*	2.01 (1.20–3.39)†	1 (Reference)	1.31 (0.74–2.33)	1.29 (0.72–2.30)
All strokes					
No. deaths	42	83	98	57	74
HR1 (95% CI)	1.39 (0.93–2.07)	1.49 (1.10–2.01)*	1 (Reference)	0.99 (0.71–1.38)	1.24 (0.90–1.69)
HR2 (95% CI)	1.28 (0.80–2.05)	1.71 (1.21–2.41)†	1 (Reference)	1.20 (0.83–1.73)	1.42 (0.99–2.03)
Ischemic stroke					
No. deaths	21	35	39	25	26
HR1 (95% CI)	1.23 (0.68–2.22)	1.30 (0.81–2.08)	1 (Reference)	1.19 (0.72–1.98)	1.21 (0.72–2.02)
HR2 (95% CI)	0.97 (0.49–1.93)	1.41 (0.85–2.35)	1 (Reference)	1.18 (0.67–2.08)	1.41 (0.81–2.44)
Hemorrhagic stroke					
No. deaths	7	29	15	11	20
HR1 (95% CI)	1.00 (0.40–2.50)	1.43 (0.77–2.68)	1 (Reference)	0.71 (0.35–1.46)	1.26 (0.68–2.33)
HR2 (95% CI)	–§	1.83 (0.88–3.81)	1 (Reference)	1.21 (0.55–2.65)	1.70 (0.80–3.58)

*P≤0.05; †P≤0.01; ‡P≤0.001. §No. deaths <3.

HR1 adjusted for age (in years), current height (in cm), body weight at age 20 (in kg), education (junior high school or less, high school, and college or higher), baseline job status (employed and unemployed), smoking status at age 20 (yes/no), smoking status at baseline (never smoked, smoked in the past, currently smoking <20 cigarettes/day and currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past, currently drinking <45.6 g ethanol/day and current drinking ≥45.6 g ethanol/day), time spent walking (≥1 h/day and <1 h/day); women plus menopause status (yes/no), oral contraceptive use (yes/no) and hormone replacement therapy (yes/no); HR2, participants excluded from HR1: those who died <3 years after baseline.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IHD, ischemic heart disease.

Table 3. CVD Mortality vs. Weight Change Since Age 20 and BMI at Age 20

BMI at age 20	Weight change since age 20				
	Loss		Stable	Gain	
	≥10.0kg	5.0–9.9kg	±4.9kg	5.0–9.9kg	≥10.0kg
Men (n=20,112)					
<22.5kg/m²					
No. deaths	22	47	157	88	100
HR1 (95% CI)	2.02 (1.27–3.20)†	1.17 (0.83–1.65)	1.11 (0.86–1.43)	1.02 (0.76–1.37)	1.05 (0.78–1.41)
HR2 (95% CI)	1.71 (0.98–2.97)	1.13 (0.77–1.66)	1.10 (0.83–1.45)	1.01 (0.73–1.40)	1.03 (0.74–1.43)
22.5–24.9kg/m²					
No. deaths	68	91	132	39	25
HR1 (95% CI)	1.84 (1.36–2.47)‡	1.11 (0.85–1.45)	1 (Reference)	0.99 (0.69–1.41)	1.05 (0.69–1.62)
HR2 (95% CI)	1.60 (1.13–2.26)†	1.02 (0.75–1.38)	1 (Reference)	1.05 (0.71–1.55)	0.97 (0.60–1.59)
≥25.0kg/m²					
No. deaths	99	73	56	12	8
HR1 (95% CI)	1.50 (1.10–2.04)†	1.14 (0.84–1.54)	1.32 (0.95–1.83)	1.48 (0.81–2.69)	1.83 (0.89–3.77)
HR2 (95% CI)	1.53 (1.08–2.16)*	1.24 (0.88–1.73)	1.49 (1.05–2.13)*	1.67 (0.89–3.14)	1.43 (0.58–3.54)
Women (n=21,252)					
<22.5kg/m²					
No. deaths	16	39	101	67	115
HR1 (95% CI)	4.32 (2.45–7.62)‡	2.18 (1.42–3.34)‡	1.49 (1.04–2.12)*	1.25 (0.85–1.83)	1.70 (1.18–2.45)†
HR2 (95% CI)	4.04 (2.06–7.92)‡	2.29 (1.42–3.72)‡	1.55 (1.04–2.30)*	1.51 (0.99–2.30)	1.91 (1.28–2.86)†
22.5–24.9kg/m²					
No. deaths	19	56	54	27	33
HR1 (95% CI)	1.68 (0.99–2.85)	1.84 (1.26–2.68)†	1 (Reference)	1.12 (0.70–1.77)	2.08 (1.35–3.21)‡
HR2 (95% CI)	1.40 (0.74–2.67)	1.83 (1.20–2.81)†	1 (Reference)	0.97 (0.56–1.68)	2.13 (1.30–3.47)†
≥25.0kg/m²					
No. deaths	69	78	40	16	9
HR1 (95% CI)	1.86 (1.23–2.81)†	1.86 (1.27–2.71)†	1.33 (0.86–2.05)	1.86 (1.05–3.30)*	1.90 (0.93–3.89)
HR2 (95% CI)	1.84 (1.16–2.93)*	2.01 (1.32–3.05)†	1.40 (0.87–2.25)	2.32 (1.28–4.19)†	2.39 (1.15–4.97)*

*P≤0.05; †P≤0.01; ‡P≤0.001.
HR1 adjusted for age (in years), current height (in cm), body weight at age 20 (in kg), education (junior high school or less, high school, and college or higher), baseline job status (employed and unemployed), smoking status at age 20 (yes/no), smoking status at baseline (never smoked, smoked in the past, currently smoking <20 cigarettes/day and currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past, currently drinking <45.6g ethanol/day and current drinking ≥45.6g ethanol/day), time spent walking (≥1h/day and <1h/day); women plus menopause status (yes/no), oral contraceptive use (yes/no) and hormone replacement therapy (yes/no); HR2, participants excluded from HR1: those who died <3 years after baseline.
Abbreviations as in Tables 1,2.

group. For those whose BMI had been <25kg/m² at age 20, there was an L shaped association in men and a U-shaped association in women between weight change and CVD mortality. For those whose BMI had been ≥25kg/m² at age 20, the associations tended to be U-shaped in both men and women; the multivariate HR (95% CI) for men was 1.50 (1.10–2.04) for the weight loss ≥10.0kg group and 1.83 (0.89–3.77) for the weight gain ≥10.0kg group, while for women it was 1.86 (1.23–2.81) for the weight loss ≥10.0kg group and 1.90 (0.93–3.89) for the weight gain ≥10.0kg group. These excess risks for CVD mortality were persistently observed even after exclusion of early deaths in the first 3 years of follow-up. In summary, the association tended to be U-shaped except for men whose BMI had been <25kg/m² at age 20.

Table 4 lists the associations between weight change and CVD mortality, after stratification by age at study entry (40–59 years vs. 60–79 years) and smoking status. For the participants aged 60–79 years, the associations remained L-shaped in men and U-shaped in women. The risks of CVD mortality among the weight loss ≥10.0kg groups were not altered significantly by smoking habit. The multivariate HR (95% CI) for men was 1.67 (0.92–3.03) among never-smokers, 1.60 (1.10–2.33) among former smokers, and 1.52 (1.16–2.00) among current smokers; the interaction was not statistically significant (P=0.15).

Discussion

In this large population-based prospective study of Japanese men and women, we observed that the associations between weight change and CVD mortality differed by gender. Weight loss since age 20 was associated with significantly higher risk of CVD mortality in both men and women. Weight gain ≥10.0kg was a predictor of CVD mortality in women, but not in men. In cross-classification analysis based on BMI at age 20 and weight change, the association tended to be U-shaped, except for men whose BMI had been <25kg/m² at age 20. This excess risk among the participants who had lost weight persisted after we excluded deaths within 3 years of follow-up.

Previous studies have recognized different association between weight change and CVD mortality according to the life stage at which weight change occurred, being L-shaped in studies examining middle-aged men,[16,17,19,20] and U-shaped in studies examining elderly populations.[14,15] Higher CVD mor-

Table 4. CVD Mortality vs. Weight Change Since Age 20, Age and Baseline Smoking Status

	Weight change since age 20				
	Loss		Stable	Gain	
	≥10.0 kg	5.0–9.9 kg	±4.9 kg	5.0–9.9 kg	≥10.0 kg
Men (n=20,112)					
Age					
40–59					
No. deaths	10	20	55	28	41
HR (95% CI)	1.85 (0.86–3.97)	1.37 (0.80–2.34)	1 (Reference)	0.93 (0.59–1.48)	1.26 (0.83–1.91)
60–79					
No. deaths	179	191	290	111	92
HR (95% CI)	1.46 (1.19–1.80)‡	1.00 (0.83–1.20)	1 (Reference)	0.97 (0.78–1.22)	0.92 (0.72–1.17)
Baseline smoking status					
Never					
No. deaths	20	22	45	16	25
HR (95% CI)	1.67 (0.92–3.03)	0.83 (0.49–1.41)	1 (Reference)	0.88 (0.49–1.58)	1.29 (0.78–2.14)
Former					
No. deaths	52	58	92	38	37
HR (95% CI)	1.60 (1.10–2.33)*	1.06 (0.76–1.49)	1 (Reference)	0.82 (0.56–1.21)	0.77 (0.52–1.15)
Current					
No. deaths	101	118	187	75	67
HR (95% CI)	1.52 (1.16–2.00)†	1.09 (0.86–1.38)	1 (Reference)	1.04 (0.79–1.36)	1.08 (0.81–1.45)
Women (n=21,252)					
Age					
40–59					
No. deaths	3	13	19	17	19
HR (95% CI)	1.86 (0.50–6.85)	2.49 (1.19–5.22)*	1 (Reference)	1.28 (0.66–2.48)	1.16 (0.60–2.24)
60–79					
No. deaths	101	160	176	93	138
HR (95% CI)	1.53 (1.17–2.01)†	1.44 (1.15–1.79)†	1 (Reference)	0.95 (0.74–1.23)	1.40 (1.11–1.76)†
Baseline smoking status					
Never					
No. deaths	63	116	139	78	119
HR (95% CI)	1.50 (1.08–2.08)*	1.48 (1.14–1.90)†	1 (Reference)	1.00 (0.75–1.32)	1.50 (1.17–1.94)†
Ever					
No. deaths	18	16	20	11	9
HR (95% CI)	1.83 (0.87–3.84)	1.31 (0.65–2.61)	1 (Reference)	1.01 (0.48–2.12)	0.59 (0.26–1.33)

*P≤0.05; †P≤0.01; ‡P≤0.001.
HR adjusted for age (in years), current height (in cm), body weight at age 20 (in kg), education (junior high school or less, high school, and college or higher), baseline job status (employed and unemployed), smoking status at age 20 (yes/no), smoking status at baseline (never smoked, smoked in the past, currently smoking <20 cigarettes/day and currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past, currently drinking <45.6 g ethanol/day and current drinking ≥45.6 g ethanol/day), time spent walking (≥1 h/day and <1 h/day); women plus menopause status (yes/no), oral contraceptive use (yes/no) and hormone replacement therapy (yes/no).
Abbreviations as in Table 2.

tality associated with weight loss might be a direct consequence of ill health[14,16,17] or be confounded by smoking and changes in smoking habits since age 20. In the present study, the higher risk in subjects who had lost weight was persistently observed in the subgroup without self-reported histories of hypertension and diabetes mellitus at baseline (data not shown), or after exclusion of early deaths in the first 3 years of follow-up. Furthermore, the higher risk of CVD mortality was not altered by smoking status at age 20 or at baseline. Therefore, the excess risk of CVD mortality associated with weight loss could not be totally explained by pre-existing disease or smoking status. BMI at study entry, however, was low (men, 20.9 kg/m^2; women, 20.7 kg/m^2) among those participants who had lost weight, while low BMI has been reported as an unfavorable prognostic factor among Japanese patients with congestive heart failure[30] or those who have undergone first coronary revascularization.[31] The higher case-fatality rate among those subjects may be 1 possible reason for the excess risk of CVD mortality associated with weight loss.

In men, the present study yielded mixed results among weight gain groups. The risk of CVD mortality for the weight gain groups tended to be higher than that among the stable weight groups, except for men who were aged >60 years at study entry or whose BMI at age 20 had been <25 kg/m^2. Older men who had gained weight since young adulthood, or those who had not been overweight at age 20, might receive a beneficial effect. In other words, weight gain appeared to be harmful to younger men, or those whose BMI had been ≥25 kg/m^2 at age

20. Furthermore, there was a noticeably lower risk of IHD mortality among men with a weight gain ≥10.0 kg, the majority of whom had a BMI <22.5 kg/m^2 at age 20. A previous study also reported that high BMI in middle age may be the most important weight-related risk factor for IHD mortality in old age,[15] because atherosclerosis begins in the first decade of life, even though its clinical manifestations most often occur in the fifth decade and beyond.[32] According to the National Health and Nutrition Survey conducted by the Ministry of Health, Labour, and Welfare, Japan, the prevalence of being overweight among men aged 20–29 years has increased from 12% to 21% during the last 20 years,[33] indicating that the unfavorable effect of weight gain might impose a substantial public health burden on Japan in the near future.

In this study, we observed that the associations between weight change and CVD mortality differed by gender (P=0.006 for interaction with sex), in that weight gain was associated with a higher mortality in women but not in men. Few studies have examined sex-specific effects on the association between weight change and CVD mortality.[17,19,20] In Norway, Drøyvold et al reported that both men and women who lost weight had a higher CVD mortality than those who were weight-stable,[17] whereas Wilsgaard et al showed that weight loss was associated with excess mortality only in men.[20] A previous study has suggested that weight change is associated with more relative changes in fat-free mass in men than in women,[24] and body fat percentage has been reported as highly indicative of CVD risk factors in another study.[34] In other words, weight gain in women is associated with a higher degree of fat mass gain than is the case in men, possibly leading to unfavorable metabolic and health consequences. In Japanese women, Saito et al reported that there was no significant association between weight change since age 20 and CVD mortality,[19] although we observed a U-shaped relationship for women in the present study. The difference may be explained by the age of the subjects, in that most of the present female subjects were >60 years old and thus post-menopausal, lacking the estrogen protection effect.[35]

The present study had several strengths in addition to its prospective nature and high response rate. First, we assessed the effects of several important confounding factors on weight change and CVD mortality: smoking status at age 20 and at baseline; alcohol drinking; and physical activity. Subgroup analysis of smoking status was also conducted to clarify that there was no interaction between smoking and weight loss with CVD mortality. Second, to our knowledge, this is the first reported study to have examined the association of weight change since young adulthood with specific causes of CVD mortality.

Several limitations should also be noted. First, body weight at age 20 was based on recall and could not be validated in the present subjects. The accuracy of long-term recall of previous body weight, however, has been verified in a study involving middle-aged Japanese subjects, and that had indicated high correlation (r=0.85).[36] Regarding the validity of self-reported past body weight in the elderly population, previous studies showed that persons with a higher current BMI tended to underestimate their past weight, whereas those with a lower current BMI tended to overestimate their past weight.[37,38] This potential for overestimation of weight change may have weakened, but not substantially distorted the association between weight change and risk of CVD mortality in the present study. Second, information about weight was available only at 2 time points: age 20 and study entry, and there was no information about whether any weight loss was intentional or unintentional. Because long-term weight change is an indicator of long-term energy balance, while negative energy balance could occur as a result of high expenditure such as a debilitating condition or low calorie intake such as that associated with dieting, the present findings should not be interpreted as evidence against the benefit of intentional weight reduction. Third, the validity of cause of death information based on death certificates, which were encoded by trained physicians, was somewhat limited. Possible misclassification should be noted because cause of death encoded as heart failure (code I50) or cardiac arrest (code I46) may also include death due to other underlying diseases.[39] The association between weight change and the risk of CVD mortality, however, did not alter even when we omitted those deceased subjects.

Conclusion

Weight loss since young adulthood was found to be associated with excess risk of CVD mortality in men, while a U-shaped relationship was observed for women. Men and women whose BMI had been <22.5 kg/m^2 at age 20 and then lost ≥10 kg in weight had the highest risk of CVD mortality. The present results suggest that if lean young people maintain a stable weight, and overweight young people do not gain weight as they age, then the risk of mortality due to CVD may be reduced.

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Original Article

Association between sleep duration, weight gain, and obesity for long period

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ABSTRACT

Background: Although previous studies showed the long-term effects of sleep duration on risk of weight gain, Western tends to gain weight irrespective of sleep duration over a long period. Conversely, it is showed that body mass index (BMI) decreases during a long period in Japanese and thus, the long-term effect of sleep duration on weight gain and obesity is still unclear in Asia.
Methods: We followed up 13,629 participants aged 40–79 years and prospectively collected data from 1995 to 2006. We divided the participants into five groups according to their self-reported sleep duration: ⩽5 h (short sleep), 6 h, 7 h (reference), 8 h, and ⩾9 h (long sleep). The main outcome was ⩾5 kg weight gain or BMI ⩾ 25 kg/m^2 (obesity). We used logistic regression analyses to derive odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for several confounding factors.
Results: We observed no association between sleep duration and risk of ⩾5 kg weight gain and obesity. After stratification by BMI, long sleepers had a significantly increased risk of ⩾5 kg weight gain (OR: 1.36, 95%CI: 1.09–1.70) in obese participants.
Conclusions: Among community-dwelling Japanese, only obese long sleepers have a significantly increased long-term risk of ⩾5 kg weight gain.

1. Introduction

Obesity is increasing worldwide and its associated health problems are now widely recognized. According to the World Health Organization, Asia has a low prevalence of obesity in comparison to other areas of the world [1]. They recommended that obesity should be defined lower in Asia than Western [2]. In Japan, the prevalence of obesity is only 3%, and severe obesity almost never exists [3]. However, the percentage age of body fat is higher in Asian than in Western with the same body mass index (BMI) [4]. Meanwhile, according to the Organisation for Economic Co-operation and Development, Koreans have the shortest mean sleep duration in the world, followed by the Japanese [5].

The associations between sleep duration, weight gain, and/or obesity have been examined previously in seven meta-analyses and a systematic review [6–12]. However, almost all of the populations studied were Western, with longer mean sleep durations and higher prevalence of obesity than Asian populations. In Asia, three prospective studies, all from Japan, have examined the association between sleep duration and obesity [13–15]. However, the study participants were recruited from among people who were undergoing health checkups. The effect of sleep duration on weight gain and obesity has not yet been examined in an Asian population or recruited from the general community.

In addition, some previous studies have examined the long-term effects of sleep duration on weight gain and obesity from data accumulated over periods of at least 10 years [16,17]. Even though these studies showed that short sleepers were at risk of weight gain and obesity, Patel et al. showed that their study participants gained weight irrespective of sleep duration over a 16 year period [16]. In contrast, Matsushita et al. showed that mean BMI tended to decrease during a 10 year follow-up period in Japanese participants aged ⩾50 years [18]. Thus, the long-term association between sleep duration, weight gain, and obesity might differ between Western and Japanese populations, and the long-term effect of sleep duration on weight gain and obesity is still unclear in Asia.

In the present study, therefore, we examined the long-term association between sleep duration, weight gain, and obesity in Japanese subjects recruited from the general community based on data accumulated over 12 years.

2. Methods

2.1. Study cohort

Between October and December 1994, we distributed a self-administered questionnaire survey of various lifestyle habits to all National Health Insurance (NHI) beneficiaries aged 40–79 years

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who lived in the catchment area of Ohsaki Public Health Center, Miyagi Prefecture, northeastern Japan [19]. Among 54,996 eligible individuals, 52,029 (95%) responded. We followed-up with the participants from January 1, 1995 through December 31, 2008 and recorded any mortality or migration by reviewing the NHI withdrawal history files. On December 1, 2006, we distributed another questionnaire to all community-dwelling individuals aged over 40 years in Ohsaki City [20]. Among the 77,325 eligible individuals, 40,027 individuals who participated in the survey in 1994, were included without death or lost to follow-up until December 1, 2006. By combining the data for these two surveys, we were able to use the questionnaire responses for 16,982 participants (response rate 42.4%).

For the present analysis, we excluded 3116 participants who did not provide information about body weight and height, and 237 participants who did not provide information about sleep duration. As a result, a final total of 13,629 participants were included.

The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine. We considered the return of self-administered questionnaires signed by the participants to imply their consent to participate in the study.

2.2. Sleep duration

The self-administered questionnaire included question on sleep duration. Sleep duration was assessed through each participant's response to the question, "How many hours on average do you sleep per day ?" The participants entered the mean integer number representing the hours of sleep taken per day during the previous year. We divided the participants into five groups according to their sleep duration: $\leqslant$5 h (short sleep), 6 h, 7 h (reference), 8 h, and $\geqslant$9 h (long sleep).

2.3. Outcome measures

The main outcome measure was $\geqslant$5 kg weight gain calculated as weight (kg) in the NHI Cohort Study minus self-reported weight (kg) recorded in the Ohsaki Cohort 2006 Study. We also assessed BMI $\geqslant$ 25.0 kg/m^2 (obesity) calculated as weight (kg) divided by the square of height (m^2). These self-reported heights, weights, and BMI in the questionnaire were considered to be sufficiently valid [21]. The Pearson's correlation coefficient (r) between 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 $r = 0.88$ ($p < 0.01$) for BMI.

2.4. Statistical analysis

We used logistic regression analyses to derive odds ratios (ORs) and 95% confidence intervals (CIs) for $\geqslant$5 kg weight gain and obesity according to each sleep duration category and to adjust for potentially confounding factors, using the SAS version 9.2 statistical software package. The 7 h sleep duration category was selected as the reference. All p values were two-tailed and differences at $p < 0.05$ were accepted as statistically significant.

We considered the following variables to be potential confounding factors: sex (men or women), age (continuous), BMI (<18.5, 18.5–24.9, 25.0–29.9, or $\geqslant$30.0 kg/m^2), education (junior high school or less, high school, or college/university or higher), smoking status (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 h, or 1 h or longer), sports and physical exercise time per week (less than 1 h, 1–2 h, 3–4 h, or 5 h or longer), job status (employed, or no occupation or housewife), marital status (married or unmarried), menopausal status (premenopausal or postmenopausal), coffee consumption (never or occasionally, 1–2 cups/day, 3–4 cups/day, $\geqslant$5 cups/day), and self-rated health (good or not good). We further adjusted for energy consumption (kcal/day) in the multivariate models 2.

In addition, we repeated analyses after excluding participants who had functional limitation, poor self-rated health, or history of disease. Physical function status was assessed using the 6 item measure of the Medical Outcomes Study (MOS) Short-form General Health Survey [22]. Participants were excluded if they stated on the MOS questionnaire that they were unable to perform moderate or vigorous activities ($n = 3576$), walk one block ($n = 25$), or perform self-care activities such as eating, dressing, bathing, or using the toilet ($n = 2$). We excluded participants who reported severe bodily pain ($n = 246$), poor self-rated health ($n = 896$), or history of cancer ($n = 160$), myocardial infarction ($n = 100$), or stroke ($n = 45$). The remaining 8579 participants were apparently healthy and their sleep duration was not affected these physical conditions.

3. Results

3.1. Baseline characteristics in terms of sleep duration categories

Table 1 shows the baseline characteristics of the study participants according to the categories of sleep duration.

The mean age was highest in the long sleep category. The proportions of women decreased linearly as the sleep duration category increased. Even though the mean weight was the lowest in the short sleep category, the mean BMI showed no significant difference. The mean weight change increased linearly as the sleep duration category increased. The proportion of participants who were employed was lowest in the short sleep category, whereas the proportions of participants who were current drinkers and consumed $\geqslant$3 cups/day of coffee were lowest in the long sleep category. The proportions of participants who walked $\geqslant$1 h/day and did $\geqslant$3 h/week sports and physical exercise were highest in the long sleep category. Mean energy consumption was lowest in the short sleep category.

3.2. Weight gain and obesity by sleep duration category

Table 2 shows the numbers of participants who had $\geqslant$5 kg weight gain and obesity and the ORs of $\geqslant$5 kg weight gain and obesity with 95% CIs according to the sleep duration categories.

We observed no association between sleep duration, $\geqslant$5 kg weight gain, and obesity. The multivariate OR1 for $\geqslant$5 kg weight gain was 0.93 (95%CIs; 0.73–1.19) in short sleeper and 1.05 (0.91–1.20) in long sleepers (p for trend = 0.3087). Similarly, the multivariate OR1 for obesity was 1.08 (0.77–1.52) in short sleeper and 1.06 (0.86–1.30) in long sleeper (p for trend = 0.3712). After further adjustments of multivariate ORs1 for energy consumption, the multivariate ORs2 showed associations similar to those for ORs1 ($\geqslant$5 kg weight gain; p for trend = 0.3097, obesity; p for trend = 0.3655). In addition, after stratification by BMI, the present study also demonstrated a null association between sleep duration and $\geqslant$5 kg weight gain in normal weight participants (p for trend = 0.6236). However, among obese participants, long sleepers had a significantly increased risk of $\geqslant$5 kg weight gain (OR: 1.36, 95%CI: 1.09–1.70).

Table 3 shows the numbers of healthy participants who had $\geqslant$5 kg weight and obesity and ORs with 95% CIs according to the sleep duration categories. We also observed no association between sleep duration, $\geqslant$5 kg weight gain, and obesity in participants who had no physical limitations or history of disease. The multivariate OR1 for $\geqslant$5 kg weight gain was 0.88 (0.61–1.26) in

Table 1
Baseline characteristics by sleep duration in 13,629 participants aged 40–79 years.

	Sleep duration (h/day)					*p* Value[b]
	⩽5	6	7	8	⩾9	
No. of subjects	453	1831	4291	5265	1789	
Mean age (years) (SD[a])	57.5 (9.7)	56.3 (9.6)	56.2 (9.3)	58.4 (9.1)	61.9 (8.5)	<.0001
Women (%)	70.0	66.3	58.4	51.2	45.6	<.0001
Mean weight (kg) (SD)	56.9 (10.1)	57.6 (9.2)	58.7 (9.3)	58.8 (9.4)	58.5 (10.0)	<.0001
Mean BMI (kg/m^2) (SD)	23.6 (3.3)	23.6 (3.0)	23.7 (3.0)	23.7 (3.0)	23.7 (3.6)	NS
Mean weight change (kg) (SD)	0.7 (5.7)	0.8 (5.0)	1.0 (5.4)	1.1 (5.8)	1.8 (7.4)	<.0001
Education (%)						
Junior high school or less	48.9	42.8	46.2	56.7	69.7	<.0001
High school	40.7	43.9	42.4	35.7	25.9	
College/university or higher	10.5	13.3	11.4	7.6	4.4	
Job status (%)						
Employed	54.8	58.8	65.6	63.4	58.3	<.0001
No occupation or housewife	45.2	41.2	34.4	36.6	41.7	
Smoking status (%)						
Never smoker	63.7	62.9	60.6	53.1	49.0	<.0001
Past smoker	12.3	12.2	12.6	15.1	18.1	
Current smoker <20	10.8	11.4	9.3	12.8	15.3	
Current smoker ⩾20	13.1	13.5	17.5	19.0	17.7	
Alcohol drinking (%)						
Never drinker	48.7	48.4	48.6	50.6	54.1	<.0001
Past drinker	6.3	5.7	4.8	6.7	6.8	
Current drinker	45.0	45.9	46.7	42.8	39.2	
Time spent walking (%)						
⩾1 h/day	42.5	45.2	45.9	47.4	50.2	0.0054
<1 h/day	57.5	54.8	54.1	52.6	49.8	
Sports and physical exercise (%)						
⩾5 h/week	8.2	5.3	5.8	6.9	8.5	0.0083
3–4 h/week	6.1	6.5	6.2	6.2	7.0	
1–2 h/week	13.9	16.2	16.2	16.8	15.0	
<1 h/week	71.8	72.0	71.8	70.1	69.5	
Marital status (%)						
Married	77.1	83.4	86.7	86.6	84.2	<.0001
Unmarried	22.9	16.6	13.3	13.4	15.8	
Menopause status (%)						
Premenopausal	25.6	30.0	28.0	18.0	8.6	<.0001
Postmenopausal	74.4	70.0	72.0	82.0	91.3	
Coffee consumption (%)						
⩾5 cups/day	6.8	5.2	3.2	3.1	1.7	<.0001
3–4 cups/day	7.8	9.5	9.5	7.6	5.4	
1–2 cups/day	27.8	34.6	36.8	34.1	29.1	
<1 cup/day	57.6	50.7	50.6	55.3	63.8	
Self-rated health (%)						
Good	56.7	69.0	71.6	71.4	67.9	<.0001
Not good	43.3	31.0	28.5	28.6	32.1	
Mean energy consumption/day (kcal) (SD)	1405.2 (528.9)	1488.7 (550.8)	1554.3 (565.4)	1595.8 (598.4)	1572.4 (600.3)	<.0001

[a] BMI, body mass index; SD, standard deviation; NS, not significant.
[b] *p* Values were calculated by chi-squared test (categorical variables), or ANOVA (continuous variables).

short sleepers and 1.06 (0.88–1.27) in long sleepers (*p* for trend = 0.5539). Similarly, the multivariate OR1 for obesity was 0.96 (0.59–1.57) in short sleepers and 1.06 (0.82–1.37) in long sleepers (*p* for trend = 0.3267). After stratification by BMI, only obese long sleepers also had a significantly increased risk of ⩾5 kg weight gain (OR: 1.41, 95%CI: 1.04–1.92).

4. Discussion

The present results indicate that the association between sleep duration, ⩾5 kg weight gain and obesity showed no significant association over a long period in Japanese subjects recruited from the community. After stratification by BMI, obese long sleepers showed a significantly increased risk of ⩾5 kg weight gain (OR: 1.36, 95%CI: 1.09–1.70).

The mean age in the long sleep category was oldest and the proportion of women in the short sleep category was highest in the sleep duration categories, but the association between sleep duration, ⩾5 kg weight gain, and obesity also showed no significant associations after stratification by the age categories (<65 years or ⩾65 years) and sexes (data not shown).

There is a possibility that the long sleep category would have included participants who were bedridden due to physical limitation. Short sleep is associated with poor self-rated health [23]. Therefore, we conducted additional analysis after excluding participants who had functional limitation, poor self-rated health, or history of disease in order to eliminate any bias due to these effects. However, only obese long sleepers also showed a significantly increased risk of weight gain (OR: 1.41, 95%CI: 1.04–1.92).

These results were different from those of previous studies conducted in Japan [13–15]. However, the participants of those studies had been recruited from among individuals undergoing health checkups. Also, the previous studies had examined the short-term effect of sleep duration on obesity, whereas, the present study examined the long-term effect. On the other hand, the present results were also different from those of previous studies that had examined the long-term effects of sleep duration on weight gain

Table 2
The association between sleep duration, ⩾5 kg weight gain, and obesity.

	Sleep duration					
	⩽5	6	7	8	⩾9	*p* for trend[a]
⩾5 kg weight gain						
Total number	453	1,831	4,291	5,265	1,789	
Case	95	355	876	1113	468	
Crude	1.03(0.82–1.31)	0.94(0.82–1.08)	1.00 (reference)	1.05(0.95–1.15)	1.38(1.21–1.57)	<.0001
Age-sex adjusted ORs	0.98(0.77–1.25)	0.93(0.81–1.07)	1.00 (reference)	0.94(0.85–1.04)	1.07(0.93–1.22)	0.2032
Multivariate ORs1[b]	0.93(0.73–1.19)	0.95(0.82–1.09)	1.00 (reference)	0.94(0.84–1.04)	1.05(0.91–1.20)	0.3087
Multivariate ORs2[c]	0.93(0.73–1.20)	0.95(0.82–1.09)	1.00 (reference)	0.94(0.84–1.04)	1.05(0.91–1.20)	0.3093
Stratified analyses (BMI)						
<25 kg/m^2	0.99(0.72–1.35)	0.94(0.78–1.12)	1.00 (reference)	0.93(0.81–1.06)	0.91(0.76–1.08)	0.6236
⩾25 kg/m^2	0.86(0.58–1.29)	0.96(0.76–1.23)	1.00 (reference)	0.95(0.80–1.13)	1.36(1.09–1.70)	0.0145
Obesity[d]						
Total number	311	1,329	3,038	3,724	1,256	
Case	44	177	413	539	162	
Crude	1.05(0.75–1.47)	0.98(0.81–1.18)	1.00 (reference)	1.08(0.94–1.24)	0.94(0.78–1.14)	0.9454
Age-sex adjusted ORs	1.07(0.76–1.49)	0.98(0.81–1.18)	1.00 (reference)	1.12(0.98–1.29)	1.05(0.86–1.29)	0.3125
Multivariate ORs1	1.08(0.77–1.52)	0.99(0.82–1.20)	1.00 (reference)	1.12(0.97–1.29)	1.06(0.86–1.30)	0.3712
Multivariate ORs2	1.08(0.77–1.51)	0.99(0.81–1.19)	1.00 (reference)	1.12(0.97–1.29)	1.06(0.86–1.29)	0.3655

[a] *p* for trend values were calculated by sleep duration as a continuous variable.
[b] Multivariate ORs1 was adjusted for sex (men or women); age (continuous); body mass index (<18.5, 18.5–24.9, 25.0–29.9, or ⩾30.0 kg/m^2); education (junior high school or less, high school, or college/university or higher); smoking status (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/day (less than 1 h, or 1 h or longer); job status (employed, or no occupation or housewife); marital status (married or unmarried); menopause (premenopausal or postmenopausal); coffee (never or occasionally, 1–2 cups/day, 3–4 cups/day, ⩾5 cups/day); self-rated health (good or not good).
[c] Multivariate ORs2 was further adjusted multivariate ORs1 for energy consumption/day (tertile category).
[d] Analyses of obesity excluded the 3971 participants who was obesity from the 13,629 participants.

Table 3
The association between sleep duration, 5 kg weight gain, and obesity in healthy participants aged 40–79 years.

	Sleep duration					
	⩽5	6	7	8	⩾9	*p* for trend[a]
5 kg weight gain						
Total number	228	1185	2830	3305	1031	
Case	41	222	522	652	251	
Multivariate ORs1[b]	0.88(0.61–1.26)	1.01(0.85–1.21)	1.00 (reference)	0.95(0.83–1.09)	1.06(0.88–1.27)	0.5539
Stratified analyses (BMI)						
<25 kg/m^2	1.00(0.64–1.56)	1.07(0.86–1.33)	1.00 (reference)	0.90(0.76–1.07)	0.91(0.73–1.15)	0.2253
⩾25 kg/m^2	0.71(0.38–1.33)	0.92(0.68–1.26)	1.00 (reference)	1.06(0.85–1.32)	1.41(1.04–1.92)	0.0073
Obesity[c]						
Total number	160	852	2,041	2362	747	
Case	20	123	282	341	101	
Multivariate ORs1	0.96(0.59–1.57)	1.09(0.87–1.38)	1.00 (reference)	1.08(0.90–1.28)	1.06(0.82–1.37)	0.3267

[a] *p* for trend values were calculated by sleep duration as a continuous variable.
[b] Multivariate ORs1 was adjusted for sex (men or women); age (continuous); body mass index (<18.5, 18.5–24.9, 25.0–29.9, or ⩾30.0 kg/m^2); education (junior high school or less, high school, or college/university or higher); smoking status (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/day (less than 1 h, or 1 h or longer); sports and physical exercise time/week (less than 1 h, 1–2 h, 3–4 h, or 5 h or longer); job status (employed, or no occupation or housewife); marital status (married or unmarried); menopause (premenopausal or postmenopausal); coffee consumption (never or occasionally, 1–2 cups/day, 3–4 cups/day, ⩾5 cups/day).
[c] Analyses of obesity excluded the 2417 participants who was obesity from the 8579 participants.

and obesity [16,17]. This may have been due to differences in long-term BMI or weight change trends between Japanese and Americans; the former show a decreasing long-term trend for BMI [18], and the latter an increasing long-term trend for weight increases [16]. Over short periods, short sleep is also a risk factor for obesity in Japanese [13–15]. Thus, after short sleepers have increased weight, they might show a weight reduction in the long term. Therefore, the present study found no association between short sleep and the risk of weight gain and obesity. However, we were unable to demonstrate whether our study participants exhibited such weight changes during the observation period because we only had data for their weight at the baseline and the end of follow up.

The biological mechanism responsible for the association between short sleep, weight gain, and obesity has mainly been considered attributable to a decreased leptin level and an increased ghrelin level with shorter sleep duration [24–26]. Appetite increases as the level of the satiety-promoting hormone falls and that of the appetite-promoting hormone increases. Thus, short sleep induces an increase of daily energy consumption and, thereby, weight gain. However, although we did not obtain data on leptin and ghrelin levels, daily energy consumption was lowest in short sleepers. The proportion of women in the short sleep category was higher than that in the long sleep category, but the above trend was also observed after separation of the sexes (data not shown). Manini et al. and St-Onge et al. demonstrated no association between sleep duration and energy expenditure as measured using doubly labeled water [27,28]. Therefore, the lack of association between short sleep, weight gain, and obesity in the present study might have been attributable to the lack of a relationship between short sleep duration and

increased energy consumption. However, although the Nurses' Health Study also showed that daily energy consumption was lowest in short sleepers [16], lack of sleep duration was associated with a risk of ⩾15 kg weight gain. The association between changes in hormone levels, increasing daily energy consumption, weight gain, and obesity due to short sleep duration might be related to not only the above mechanism, but also other unknown mechanisms.

A major strength of the present study was that it was the first to have investigated the long-term association between sleep duration, weight gain, and obesity in an Asian general population showing different long-term trends of weight change from Western populations [16,18]. Asians have a lower prevalence of obesity and a shorter mean sleep duration than Westerners [1,5]. To exclude the effects of physical condition on sleep duration, weight gain, and obesity, we repeated our analyses after excluding participants who had functional limitation or history of disease.

On the other hand, several limitations should also be considered. First, we had no information about sleep quality, the timing of sleep, the use of sleep medication, the presence of sleeping disorders, rotating shift work, or night work that can influence sleep duration and thereby affect the risk of weight gain and obesity. Although we had no information about rotating shift work and night work, since 18.2% of our participants were housewives, 32.6% farmers, and 14.8% retired, such details would have been unlikely to have changed the results. Second, the assessment of weight was done only at the baseline and at the end of follow-up. We had no information about the trends of weight change during the follow-up period. Third, we used self-reported weight, height, and BMI. There is a systematic bias in self-reported weight and height. Because of this bias, there is possibility that we observed no association between short sleep duration, weight gain, and obesity. However, we demonstrated a high correlation and appropriate agreement between self-reported values and measured values (weight: $r = 0.96$, height: $r = 0.93$, BMI: $r = 0.88$).

In conclusion, the present study showed that only obese long sleepers have a significantly increased risk of ⩾5 kg weight gain in the long term among Japanese recruited from the community. Short sleep did not carry a risk of weight gain and obesity. Further research is needed to clarify the long-term association between sleep duration, weight gain, and obesity in Asian populations.

Conflict of Interest

This was not an industry supported study. The authors declare that they have no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2012.09.024.

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Relationships between changes in time spent walking since middle age and incident functional disability

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ABSTRACT

Objective. To examine the relationship between changes in time spent walking since middle age and incident functional disability.

Method. In 2006, we conducted a prospective cohort study of 7177 disability-free Japanese individuals aged ≥65 years who lived in Ohsaki City, Miyagi Prefecture, Japan. Participants were categorized into four groups according to changes in time spent walking based on two questionnaire surveys conducted in 1994 and in 2006. Incident functional disability was retrieved from the public Long-term Care Insurance database, and the subjects were followed up for 5 years. The Cox proportional hazards model was used to investigate the association between changes in time spent walking and the risk of incident functional disability.

Results. Compared with subjects who remained sedentary, the multivariate-adjusted hazard ratios (95% confidence intervals) were 0.69 (0.49–0.98) among those who became active and 0.64 (0.50–0.82) among those who remained active. These results did not alter when analyses were stratified by gender, age and motor function status.

Conclusion. An increase in time spent walking among sedentary adults is significantly associated with a lower risk of incident functional disability.

Introduction

Physical activity is a well-known modifiable behavior associated with lower risks of mortality (Haskell et al., 2009; Leitzmann Mf, 2007; Nelson et al., 2007; Wagner and Brath, 2012; Wen et al., 2011). In addition to keeping physically active, increasing physical activity is also known to be beneficial in terms of cardiovascular risk and longevity (Aadahl et al., 2009; Balboa-Castillo et al., 2011; Gregg et al., 2003; Petersen et al., 2012; Schnohr et al., 2003; Talbot et al., 2007; Wannamethee et al., 1998). Previous longitudinal studies have shown that, in comparison with individuals who remain sedentary, those who increase their physical activity have a total mortality risk reduction of more than 40% (Balboa-Castillo et al., 2011; Gregg et al., 2003; Schnohr et al., 2003; Wannamethee et al., 1998).

In countries with rapidly aging populations, such as Japan, the health and economic impacts of disability have been attracting increasing attention (Fried et al., 2001). Disability is the endpoint of the disablement process, which includes four distinct but correlated concepts: active pathology, impairment, functional limitation, and disability (Nagi, 1991). According to the Nagi's disablement model, functional limitation is a limitation in performance at the level of the whole organism or person, which includes motor dysfunction; disability is an inability or limitation in performing socially defined roles and tasks expected of an individual within a sociocultural and physical environment. During the disablement process, not only physical inactivity could be a predisposing risk factor, but changes in physical behavior may avoid, retard or reverse the outcomes (Verbrugge and Jette, 1994). However, data are limited regarding the effects of changes in physical activity on disability or functional status. One study of older American women has shown that in comparison with women who remained inactive after middle age, those who remained active or became active had fewer difficulties with activities of daily living (ADL), better scores in the Physical Performance Test, and faster walking speeds (Brach Js, 2003). Another two recent studies have also observed that increasing physical activity from middle age was associated with a lower disability score in old age (Berk et al., 2006; Gretebeck et al., 2012). Otherwise, the British Regional Heart Study has also shown that in comparison with men who had remained inactive, those who became active or remained active had a lower risk of mobility limitation (Wannamethee et al., 2005).

However, those studies mostly employed self-reported endpoints (Berk et al., 2006; Gretebeck et al., 2012; Wannamethee et al., 2005), and some had small numbers of participants (Berk et al., 2006; Brach Js, 2003); furthermore, none of them measured the incidence of disability. In Japan, Long-term Care Insurance (LTCI) certification of requiring assistance with ADL, based on a nationally uniform standard of functional disability, has been frequently used in previous epidemiological

Abbreviations: ADL, activities of daily living; LTCI, Long-term Care Insurance.

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studies as a measure of incident functional disability in the elderly (Aida et al., 2012; Hozawa et al., 2010; Tomata et al., 2012). As the economic burden of taking care of older people with disability is increasing (Ministry of Health, 2012), studies of modifiable risk factors of functional disability have become necessary. To our knowledge, no prospective study has yet investigated the relationship between changes in physical activity since middle age and the risk of incident functional disability. Furthermore, the doubts of benefits of increasing or maintaining physical activity could result from younger age, better motor function or higher intensity of physical activity in men which allow those subjects to be more active than the others have not been well clarified.

In the present study, we chose to focus on walking, which is the most common type of physical activity among middle-aged or older individuals. Our previous studies have shown that spending a longer time walking per day is associated with lower medical costs and increased longevity (Fujita et al., 2004; Nagai et al., 2011; Tsuji et al., 2003). The objective of the present study was to investigate changes in time spent walking in relation to the risks of incident functional disability in a large community-dwelling population in Japan.

Methods

Study cohort

The present investigation used data from a population-based longitudinal study conducted in Ohsaki, a northern non-coastal rural area of Miyagi Prefecture, northeastern Japan. Between October and December 1994, all National Health Insurance beneficiaries aged 40 to 79 years who lived in the catchment area of Ohsaki Public Health Center (including one city and 13 towns) were invited to take part in a health survey with self-administered questionnaire on various lifestyle habits (1994 Survey) (Nagai et al., 2011; Tsuji et al., 2003). Among 54,996 eligible individuals, 52,029 (94.6%) responded.

During a period when a municipal merger occurred, one city and 6 towns in the study area were merged into a single new municipality, Ohsaki City, on 31 March 2006. Thereafter, we conducted a health survey on the citizens of Ohsaki City. Between 1 December and 15 December 2006, a self-administered questionnaire was distributed to subjects aged 65 years or older based on the Residential Registry for Ohsaki City (2006 Survey) (Koyama et al., 2010; Kuriyama et al., 2010; Nakaya et al., 2013; Tomata et al., 2012). Among 23,132 eligible individuals (aged 53 years or older in 1994 Survey), 12,676 (54.8%) responded. We considered the return of completed questionnaires to imply consent to participate in the 2006 Survey, and subsequent death and emigration were followed up. We also confirmed information regarding LTCI certification status after obtaining written consent from the subjects. The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine.

For the present analysis, we further excluded 3610 persons who did not provide written consent for review of their LTCI information, one person who had been died, 973 persons who had already been certified as having disability by the LTCI at the time of the baseline survey, and 915 persons for whom responses to the questions on walking were missing. Thus, a final total of 7177 responses were analyzed for the purposes of this study.

Classification of exposures

Time spent walking was evaluated on the basis of the response to a specific question, 'How long do you walk a day, on average?' in both the 1994 and 2006 Surveys, and the subjects were asked to choose one out of three responses: '1 h or more', '30 min to 1 h' or '30 min or less'. The validity of self-reported time spent walking had been reported previously, which indicated that self-reported walking time was reasonably reproducible and sufficiently valid for studying the health effects of walking (Fujita et al., 2004; Nagai et al., 2011; Tsubono et al., 2002; Tsuji et al., 2003). According to the "Global Recommendations of Physical Activity for Health" developed by the WHO, at least a total of 150 min or 30 min of moderate-intensity activity 5 times per week is suggested for all adults (WHO, 2010). Therefore, participants who spent more than 30 min per day walking were considered to be active in this study. As shown in Table 1, four categories of changes in time spent walking were defined for each participant by his/her answers in 1994 and 2006: remained inactive (<30 min in both 1994 and 2006); became inactive (≥30 min in 1994 and <30 min in 2006); became active (<30 min in 1994 and ≥30 min in 2006); and remained active (≥30 min in both 1994 and 2006).

Table 1
Categories of changes in time spent walking (December 2006, Ohsaki City, Miyagi Prefecture, Northeastern Japan).

Time spent walking per day		2006 survey	
		≥30 min	≥30 min
1994 survey	<30 min	Remained inactive	Became active
	<30 min	Became inactive	Remained active

Follow-up and case ascertainment

The primary endpoint for the present analysis was incident functional disability defined as newly qualifying for LTCI certification and registration on the public LTCI database between 16 December 2006 and 30 November 2011. We collected LTCI certification data every year from the public LTCI database maintained by Ohsaki City. LTCI is a form of mandatory social insurance aimed at assisting the frail and elderly with daily activities (Ikegami, 1997; Imai et al., 2008; Ministry of Health, 2012; Tsutsui and Muramatsu, 2005). People aged 65 years or older who require assistance with ADL are eligible to apply for formal caregiving services, and undergo assessment by well-trained care managers based on a questionnaire developed by the Ministry of Health, Labour and Welfare. On the basis of standardized scores for functional and cognitive impairment calculated from the questionnaire and based on physician's judgment report including the elderly's disease status, physical and cognitive status and performance-based measures, the eligibility of applicants for insurance benefits is judged by the Municipal Certification Committee. LTCI certification has been used in previous epidemiological studies as a measure of incident functional disability in the elderly (Aida et al., 2012; Hozawa et al., 2010; Tomata et al., 2012).

All participants were followed up by reviewing information on the date of LTCI certification, death, or emigration from Ohsaki City, which had been transferred yearly each December from the Ohsaki City Government under an agreement related to Epidemiological Research and Privacy Protection.

Statistical analysis

The person-years of follow-up were calculated from 16 December 2006 to the date of incident functional disability, date of emigration from Ohsaki City, date of death, or 30 November 2011, whichever occurred first. Cox proportional hazards regression analysis was used to investigate the hazard ratios (HRs) and 95% confidence intervals (CIs) for incident functional disability according to changes in time spent walking, treating participants who had remained inactive as the reference category.

The following variables in the 2006 Survey, which were thought to be unfavorable conditions for being active and may be related to incident functional disability, were considered as potential confounders: age (in years), sex (men or women), body mass index (in kg/m^2), history of diseases (stroke, hypertension, myocardial infarction, arthritis, osteoporosis, cancer, falls or fractures), education level (junior high school, high school, or college or higher), smoking status (never smoked, smoked in the past, currently smoking <20 cigarettes/day or currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past or currently drinking), pain (none or mild pain, moderate pain or more), and motor function score based on the Kihon Checklist.

To assess whether the risk of incident functional disability associated with changes in time spent walking differed by gender, age or subjects' motor function, we further stratified the participants according to gender (men versus women), age at the time of the 2006 Survey (65–74 years versus ≥75 years) and motor function (without limitation versus with limitation). Motor function limitation was defined by a motor function score of 3 points or more based on the Kihon Checklist completed in the 2006 Survey. The motor function score based on the Kihon Checklist has been evaluated previously and shown to have predictive validity for functional disability (Fukutomi et al., 2013; Tomata et al., 2011). Statistical evidence for differences in effect between these subgroups was assessed on the basis of log-likelihood ratio tests of interaction.

All statistical analyses were performed using the SAS software package (version 9.2; SAS Institute, Inc., Cary, North Carolina, USA). All statistical tests described here were 2-sided, and differences at $P < 0.05$ were accepted as significant.

Results

From 1994 to 2006, 13.0% of the study participants remained inactive, 22.5% became inactive, 11.6% became active, and 52.9% remained active. The baseline characteristics of participants according to the changes in time spent walking categories are summarized in Table 2. Compared with the rest of the study participants, those who had become active were younger, included a higher proportion of men, included a higher proportion of current drinkers, were less likely to have a history of myocardial infarction, osteoporosis or cancer, and were less likely to have pain and motor function limitation.

During the 5 years of follow-up from 16 December 2006, we documented 712 incident functional disability (9.9%), 619 deaths (8.6%) and 59 losses to follow-up (0.8%) because of emigration. Table 3 shows the multivariate-adjusted HRs for incident functional disability according to the changes in time spent walking categories. In comparison with individuals who remained inactive, those who became active had a 31% lower risk of incident functional disability (HR = 0.69, 95% CI: 0.49–0.98), and those who remained active had a 36% lower risk of incident functional disability (HR = 0.64, 95% CI: 0.50–0.82). The risk of incident functional disability among individuals who became inactive was similar to that for individuals who remained inactive. Furthermore, we repeated the analyses after excluding individuals whose disability event occurred in the first year of follow-up (Model 3). When we excluded 253 such participants, the associations became slightly weaker but did not change substantially. The multivariate-adjusted HRs (95% CIs) for incident functional disability were 0.89 (0.66–1.19) for individuals who became inactive, 0.75 (0.50–1.12) for those who became active, and 0.64 (0.48–0.85) for those who remained active.

Table 4 shows the associations between changes in time spent walking and incident functional disability, after stratification by gender (men versus women), age at the time of the 2006 Survey (65–74 years versus ≥75 years) and motor function (without limitation versus with limitation). The associations did not vary substantially between men and women (p for interaction = 0.71). In women, became active or remained active was associated with a lower risk of incident functional disability, with HRs (95% CIs) of 0.61 (0.39–0.96) and 0.60 (0.44–0.80), respectively. Similar results were observed in men, but were not statistically significant. The risks of incident functional disability were not altered significantly by age (p for interaction = 0.10). The multivariate-adjusted HRs (95% CIs) for individuals who became active were 0.58 (0.24–1.37) for those aged 65–74 years and 0.73 (0.50–1.06) for those aged ≥75 years. Furthermore, irrespective of whether or not participants had motor function limitation, those who became active tended to have a lower risk of incident functional disability (p for interaction = 0.97). The multivariate-adjusted HRs (95% CIs) for became active were 0.75 (0.47–1.19) for individuals without motor function limitation and 0.69 (0.41–1.18) for those with motor function limitation, although this was not statistically significant.

Table 2
Baseline characteristics of participants according to the changes in time spent walking categories (December 2006, Ohsaki City, Miyagi Prefecture, Northeastern Japan).

	Remained inactive	Became inactive	Became active	Remained active	P-value[a]
Number at risk	937	1614	832	3794	
Age, mean (SD), years	75.8 (5.7)	76.1 (5.8)	74.0 (5.5)	74.2 (5.5)	<0.0001
Men (%)	43.3	41.3	46.9	45.9	0.0072
Body mass index, mean (SD), kg/m^2	23.9 (3.5)	23.6 (3.8)	23.7 (3.3)	23.4 (3.3)	0.0011
Current smoker (%)	12.4	14.0	12.4	13.5	0.7339
Current drinker (%)	33.6	30.2	38.8	37.3	<0.0001
Education until age 15 (%)	29.3	33.6	31.5	30.1	0.2239
History of diseases (%)					
Stroke	3.7	3.9	3.3	2.2	0.0021
Hypertension	47.1	50.7	42.2	40.1	<0.0001
Myocardial infarction	6.2	6.3	4.2	4.7	0.0244
Arthritis	20.3	19.0	15.1	14.8	<0.0001
Osteoporosis	14.1	13.4	8.5	9.7	<0.0001
Cancer	12.0	10.2	6.9	7.4	<0.0001
Falls or fractures	17.8	18.9	18.0	15.2	0.0036
Moderate pain or more (%)	36.8	37.4	24.0	24.7	<0.0001
Motor function limitation (%)[b]	38.3	40.6	18.0	16.7	<0.0001

[a] P-values were calculated by analysis of variance or chi-square test.

[b] With three points or more to the following five motor function questions in Kihon Checklist: 'Are you able to go upstairs without holding rail or wall?', 'Are you able to stand up from the chair without any aids?', 'Are you able to keep walking for about 15 min?', 'Have you fallen down during the past year?', 'Do you worry about falling down?'.

Discussion

In this large longitudinal population-based study of Japanese community-dwelling elderly, we observed that an increase in time spent walking among sedentary middle-aged adults was significantly associated with a lower risk of incident functional disability. Even in those who were very old or with limited motor function, becoming active from middle age tended to be associated with a lower risk of incident functional disability.

These results were consistent with previous longitudinal studies based on self-reported physical activity levels at different time points and subsequent functional status (Berk et al., 2006; Brach Js, 2003; Gretebeck et al., 2012; Wannamethee et al., 2005). Those studies found that in comparison with people who had always been inactive since middle age, those who increased their physical activity had better physical performance or lower disability scores in old age. In the present study, after 5 years of follow-up, we noticed that in a senior population aged more than 65 years, not only those who remained active also those who became active had lower risks of incident functional disability, than those who remained inactive for the previous 12 years. Furthermore, for those who became inactive, the risk of incident functional disability was similar to those who remained inactive, which was consistent with those of previous studies about changes in physical activity level and mortality (Balboa-Castillo et al., 2011; Gregg et al., 2003).

The British Regional Heart Study observed that the protective effects of maintaining or increasing physical activity against risks of mobility limitation were largely attenuated following adjustment for chronic diseases and clinical symptoms (Wannamethee et al., 2005). In the present study, after adjusting for possible confounders including history of diseases, body pain and motor function status, we found that an increase in time spent walking among sedentary middle-aged adults was still significantly associated with a lower risk of incident functional disability. Furthermore, the associations did not vary substantially by gender, age or motor function. This is important because it suggested that the lower risks of incident functional disability associated with increasing or maintaining physical activity level was not only a result of younger age, better motor function or higher intensity of physical activity in men. In our study population, even among individuals who were more than 75 years old or with motor function limitation, older adults who remained active since middle age had a significantly lower risk of incident functional disability. Therefore, even for those who may find it difficult to be physically active, maintaining or adopting an active lifestyle should be continuously promoted.

Most previous studies examining the health effect of changes in physical activity were focused on longevity (Balboa-Castillo et al., 2011; Gregg et al., 2003; Petersen et al., 2012; Schnohr et al., 2003; Talbot et al., 2007; Wannamethee et al., 1998). In the present study, we also observed that in comparison with individuals who remained inactive, those who became active tended to have lower risk of all-cause mortality (HR = 0.78, 95% CI: 0.54–1.09) (data not shown). We further observed that individuals who became active and those who remained active were also associated with a reduced risk of incident functional disability. The present study has expanded knowledge in this field because it showed that maintaining or adopting an active lifestyle not

Table 3
Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident disability according to the changes in time spent walking categories (December 2006, Ohsaki City, Miyagi Prefecture, Northeastern Japan).

	No. of cases	Person-years	Model 1	Model 2	Model 3
			HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Remained inactive	134	3924	1.00	1.00	1.00
Became inactive	252	6679	1.14 (0.96–1.36)	0.98 (0.78–1.25)	0.89 (0.66–1.19)
Became active	62	3779	0.62 (0.46–0.84)	0.69 (0.49–0.98)	0.75 (0.50–1.12)
Remained active	264	17,266	0.56 (0.45–0.68)	0.64 (0.50–0.82)	0.64 (0.48–0.85)

[a] Model 1 was adjusted for age (years), sex.
[b] Model 2 was adjusted for age (years), sex, BMI (kg/m^2), history of stroke (yes/no), history of hypertension (yes/no), history of myocardial infarction (yes/no), history of arthritis (yes/no), history of osteoporosis (yes/no), history of cancer (yes/no), history of falls or fractures (yes/no), education (junior high school or less, high school, or college or higher), smoking status (never smoked, smoked in the past, currently smoking <20 cigarettes/day or currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past or currently drinking), pain (none or mild pain, moderate pain or more) and motor function limitations (yes/no).
[c] Model 3 was further excluded people whose event of disability occurred in the first year of follow-up.

only improved longevity, also resulted in healthier aging. Thus, for healthy aging, our message to those who are currently sedentary is that it is never too late to start walking.

This study had several strengths in addition to its prospective nature and large community-dwelling population base. First, we assessed the effects of several important confounding factors on changes in time spent walking and incident functional disability: history of diseases, body pain and motor function status. Subgroup analysis of motor function status was also conducted to confirm that there was no interaction between motor function limitation and time spent walking with incident functional disability. Second, the data on incident functional disability were more accurate than self-reported information because the outcome was obtained from the public LTCI database, which is based on uniform nationwide criteria of functional disability, and thus the data were considered reliable.

Several limitations should also be noted. 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, and there was no information about the reason of any change in time spent walking. However, physical activity level was noted to be affected by psychological distress and mental disorder in previous studies (Bonnet et al., 2005; Muhsen et al., 2010). It may be one reason for being or becoming inactive, where reverse causation may not be totally avoided. Second, we did not investigate the causes of functional disability in subjects who received LTCI certification. Thus, the most effective component responsible for reduction of functional disability by becoming or remaining active will need to be clarified in the future. Third, our endpoint could have been underestimated because the qualification process for obtaining LTCI benefit requires voluntary application. Furthermore, non-response bias and survival bias should be considered because the incidence rate of functional disability in the present study (9.9%) was much lower than that for all Japan (17.3%) (Ministry of Health, 2012).

Conclusion

An increase in time spent walking among sedentary middle-aged adults was significantly associated with a lower risk of incident functional disability. Even in those who were very old or with limited motor function, becoming active from middle age tended to be associated with a lower risk of incident functional disability. Our results suggest that, for healthy aging, active people should remain active as they age, and for those who are currently sedentary, it is never too late to start walking.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Table 4
Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident disability according to the changes in time spent walking categories, by gender, age and motor function status (December 2006, Ohsaki City, Miyagi Prefecture, Northeastern Japan).

	Gender		Age		Motor function	
	Men	Women	65–74	≥75	No limitation	With limitation
Remained inactive (cases/n)	49/406	85/531	21/385	113/552	50/578	84/359
HR (95% CI)[a]	1.00	1.00	1.00	1.00	1.00	1.00
Became inactive (cases/n)	95/666	157/948	42/671	210/943	88/958	164/656
HR (95% CI)[a]	1.16 (0.77–1.74)	0.88 (0.65–1.18)	1.17 (0.64–2.15)	0.96 (0.74–1.25)	0.98 (0.67–1.43)	0.99 (0.72–1.35)
Became active (cases/n)	31/390	31/442	10/447	52/385	38/682	24/150
HR (95% CI)[a]	0.83 (0.48–1.43)	0.61 (0.39–0.96)	0.58 (0.24–1.37)	0.73 (0.50–1.06)	0.75 (0.47–1.19)	0.69 (0.41–1.18)
Remained active (cases/n)	103/1740	161/2054	52/2036	212/1758	169/3162	95/632
HR (95% CI)[a]	0.72 (0.48–1.09)	0.60 (0.44–0.80)	0.65 (0.36–1.18)	0.63 (0.48–0.82)	0.69 (0.49–0.98)	0.62 (0.44–0.88)
p for interaction	0.71		0.10		0.97	

[a] Model was adjusted for age (years), sex, BMI (kg/m^2), history of stroke (yes/no), history of hypertension (yes/no), history of myocardial infarction (yes/no), history of arthritis (yes/no), history of osteoporosis (yes/no), history of cancer (yes/no), history of falls or fractures (yes/no), education (junior high school or less, high school, or college or higher), smoking status (never smoked, smoked in the past, currently smoking <20 cigarettes/day or currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past or currently drinking), pain (none or mild pain, moderate pain or more) and motor function limitations (yes/no).

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