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Incontinence

Association between Physical Activity and Urinary Incontinence in a Community-Based Elderly Population Aged 70 Years and Over

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Abstract

Objectives: The objective of the present study was to evaluate the association between physical activity (PA) levels and urinary incontinence (UI) in a community-based elderly population aged ≥70 yr.
Methods: This population-based cross-sectional survey was conducted in 2003 using an extensive health interview for each participant. A self-reported single-item questionnaire was used to estimate different levels of PA in each subject. The prevalence of UI was estimated by the self-administered International Consultation on Incontinence Questionnaire. The study population included 676 Japanese men and women.
Results: The prevalence of UI was 25% (34% in women and 16% in men). After adjustment for potential confounding factors, the odds ratio (95% confidence interval) of UI compared with the lowest PA group was 0.71 (0.47–1.09) and 0.58 (0.35–0.96) in subjects exhibiting middle and high levels of PA, respectively (p for trend = 0.02).
Conclusions: High PA level was independently related to a lower self-reported prevalence of UI in a community-dwelling elderly population aged ≥70 yr. Although this cross-sectional study cannot demonstrate a temporal relationship between PA and the onset of UI, the findings suggest that PA may have a potentially beneficial effect on the prevention of UI. A prospective study or randomized trials are required to clarify the causality.

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1. Introduction

Urinary incontinence (UI) is a frequent and bothersome symptom that is common in the elderly population [1]. Population-based estimates of the prevalence of UI among elderly subjects (age ≥60 yr) is 47.6% for women and 14.5% for men in Japan [2]. UI is increasingly recognized as a health and economic problem that affects the physical, psychological, social, and economic well-being of individuals and their families and poses a substantial economic burden on health and social services [3,4].

Understanding the risk factors of UI is an important step toward developing direct treatment resources and providing preventive care for UI. Based on many epidemiologic studies on UI in various populations, a number of risk factors have been identified. Some chronic medical conditions, such as diabetes and Hypertension, have also been found to be associated with the occurrence of UI [2,5], and obesity is an especially well-established factor that can cause UI or contribute to the severity of the condition [6]. Regular physical activity (PA) was confirmed to be effective for the primary and secondary prevention of these chronic diseases or conditions (eg, diabetes, hypertension, and obesity) [7]. Furthermore, pelvic floor muscle dysfunction is also a risk factor for UI. Burgio et al have shown that pelvic floor exercise is an effective treatment for both stress and urge incontinence [8]. Because PA is a determinant of muscle strength including abdominal muscles [9], and abdominal muscle training indirectly strengthens the pelvic floor muscles [10], PA may prevent UI through an improvement in abdominal muscle strength.

Therefore, it is conceivable that PA may have a potentially beneficial effect on the prevention of UI. However, to our knowledge, only a few studies that have investigated the relationship between PA and UI [11–16], and their results have not suggested any beneficial effect of PA on the prevention of UI. Moreover, no studies fully assessed the relationship between PA and UI in a community-dwelling elderly population. Thus, it is still unclear how PA relates to UI in community-dwelling elderly adults aged ≥70 yr among whom this condition is highly prevalent.

Thus, we designed a cross-sectional study to investigate the relationship between PA and UI in community-dwelling elderly aged ≥70 yr.

2. Methods

2.1. Subjects

Our study population comprised subjects aged ≥70 yr who were living in the Tsurugaya area of Sendai, one of the major cities in the Tohoku area of Japan. The Tsurugaya investigators conducted two cross-sectional surveys in 2002 and 2003 [17]. We used 2003 data in this study because the 2002 survey did not collect information on UI. In 2003, 2625 persons aged ≥70 yr lived in Tsurugaya. We invited all of them to participate in a comprehensive geriatric assessment of medical status, physical function, cognitive function, severity of UI, and dental status, and 948 (36.1%) of them did so, giving their informed consent for analysis of the data. All assessments were carried out in nonclinical public facility. The protocol of this study was approved by the Institutional Review Board of the Tohoku University Graduate School of Medicine.

We excluded subjects who did not complete the questionnaire items regarding PA ($n = 73$). We also excluded participants who had the potential for PA restriction, that is, those who reported they were incapable of walking 50 m independently ($n = 77$) or who had a history of stroke ($n = 28$) or depression (Geriatric Depression Scale scores of ≥14; $n = 94$). As a result, we analyzed 346 women and 330 men (mean age ± standard deviation, 75.5 ± 4.4 yr).

2.2. Assessment of UI

The International Consultation Incontinence Questionnaire (ICIQ) was used to assess the prevalence and types of UI and to determine UI scores [18]. The ICIQ is a new subjective measure for evaluating the frequency, amount of leakage, and quality-of-life (QOL) impact of UI using four questions. This questionnaire was developed under the auspices of the International Consultation on Incontinence and the content validity, reproducibility, and responsiveness of the test have been investigated [18]. Linguistic validation of the Japanese translation of ICIQ was also confirmed [19].

2.3. PA questionnaire

A self-reported single-item questionnaire was used to estimate different levels of PA in each subject. The question asked whether the subject had performed any activities from the following categories in the previous 12 mo: walking, brisk walking, or sports (eg, aerobics, tennis, swimming, jogging, etc). If they had participated in a given activity, the frequency and duration spent in the activity were ascertained using the following categories: for frequency, (1) 1–2 times/mo, (2) 1–2 times/wk, (3) 3–4 times/wk, or (4) almost every day; and for duration (per walk or workout), (1) 0–30 min, (2) 0.5–1 h, (3) 1–2 h, (4) 2–3 h, (5) 3–4 h, or (6) ≥4 h. Among the levels of exercise intensity, sports were considered the highest, followed in order by brisk walking and walking. Each of the three types was further classified into three subcategories according to the frequency and duration of the walks or workouts as follows [20]: (1) high, at least 3–4 times/wk for at least 30 min each time; (2) low, reporting some activity in the past year, but not enough to meet high levels; and (3) none, no PA. Finally, we used these categories and subcategories to define the following three levels of PA: (1) "low," no walking or low walking, no brisk walking, no sports; (2) "middle," high walking, low brisk walking, no sports; and (3) "high," any walking, high brisk walking, low or high sports.

2.4. Assessment of other variables

Anthropometrics (height, body weight) were recorded by a standardized protocol. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Blood pressure was measured at the left upper arm two times using an automatic device (HEM747IC; Omron Life Science, Tokyo, Japan) following 5 min rest in the resting position.

Blood samples were drawn from the antecubital vein of the seated subject with minimal tourniquet use. Specimens were collected in siliconized vacuum glass tubes containing sodium fluoride for blood glucose and no additives for lipids analyses.

Blood glucose concentration was measured by enzymatic methods (Shino-Test, Tokyo, Japan). Information on smoking status, drinking status, medication, delivery, and histories of diseases were obtained from the questionnaire survey. The drug information was confirmed by a well-trained pharmacist.

2.5. Statistical analysis

On the basis of the positive answers to question 4 in the ICIQ, "leaks when you cough or sneeze" and/or "leaks when you are physically active/exercising" were defined as stress incontinence, "leaks before you can get to the toilet" as urge incontinence, and the combinations as mixed incontinence. Other positive answers, such as to "leaks when you are asleep," "when you have finished urinating and are dressed," "for no obvious reason," and "all the time," were regarded as other incontinence, irrespective of the presence of stress, urge, or mixed incontinence. If the participants claimed one of these symptoms, we treated them as having UI. A single summed score associated with the degree of UI was also calculated based on the ICIQ [18]. The score ranged from 0 to 21 with greater values indicating increased severity. Because the distribution of the ICIQ scores was rather skewed, log-transformed ICIQ scores were used to assess the relationship between PA levels and ICIQ score [21]. When we calculated log-transformed ICIQ scores, 1.0 was added (ICIQ score + 1) before transformation.

Hypertension was defined as a systolic blood pressure of $\geq$140 mm Hg and/or a diastolic blood pressure of $\geq$90 mm Hg or use of nondiuretic antihypertensive agents. Diabetes was defined as a casual blood glucose concentration of $\geq$200 mg/dl or current use of antidiabetic medication.

Descriptive data are presented as means $\pm$ standard error or percentages. The age- and sex-adjusted variable differences according to continence status were examined by analysis of covariance (ANCOVA) for continuous variables or by the multiple logistic regression analysis for variables of proportion. The odds ratio (OR) and 95% confidence interval (CI) of UI (0: no incontinence; 1: urinary incontinence) compared with the lowest PA level were calculated using multiple logistic regression analysis. Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit statistic. For all models, the test was not significant ($p \geq 0.54$). ANCOVA was used to examine the adjusted relation of PA with log-transformed ICIQ score. We used age, sex, BMI, diabetes, hypertension (nondiuretic drugs), history of coronary heart disease (CHD) or nephropathy, alcohol consumption, use of tranquilizers, use of hypnotics, use of diuretics, and history of delivery as covariates for multiple adjustments. For sex-specific analyses, we used age, BMI, diabetes, hypertension (including diuretic drugs), history of CHD or nephropathy, use of tranquilizers, use of hypnotics, and history of delivery in women and adjustment for age, BMI, hypertension (including diuretic drugs), history of nephropathy in men as covariates. When men and women were analyzed separately, the amount of variables was limited to $\leq$(amount of cases)/10 (ie, $\leq$11 in women and $\leq$5 in men) in multiple regression models [22]. All p values for linear trend were calculated by using the category

Table 1 – Characteristics of the population according to urinary continence status

	No incontinence (n = 507)	Urinary incontinence (n = 169)	p^*
Age, yr†	75.17 ± 0.19	76.34 ± 0.34	<0.01
Sex (women, %)	45.0	69.8	<0.01
BMI, kg/m^2†	24.03 ± 0.15	24.13 ± 0.26	0.74
Diabetes, %	7.9	11.2	0.10
Hypertension (nondiuretic drugs; %)	67.7	70.4	0.34
Drinking status			
Current drinker, %	49.8	44.2	0.06
Ex-drinker, %	11.9	9.7	0.64
Nondrinker, %	38.4	46.1	0.12
Self-reported illness			
Renal, %	5.1	7.7	0.43
CHD, %	8.7	10.1	0.33
Use of tranquilizers, %	9.5	11.8	0.59
Use of hypnotics, %	7.1	4.1	0.16
Use of diuretics, %	5.1	4.7	0.48
History of delivery, % in women	89.5	92.5	0.45

BMI = body mass index; CHD = coronary heart disease.

* Analysis of covariance (age and BMI) or multiple logistic regression adjusted for age and sex where appropriate.

† Adjusted least squares mean ± standard error.

of the PA levels (low: 1; median: 2; high: 3). A significant difference was defined as $p < 0.05$. SAS software (version 9.1) was used for analyses.

3. Results

In this study, the overall prevalence of UI was 30.5% (289 of 948). Among 676 subjects who were available to be analyzed, 169 (25.0%) had self-reported UI, including 118 women (34.2%) women and 51 men (15.5%). Among them, 61 (36.1%; 56 women and 5 men) had stress UI, 62 (36.7%; 33 women and 29 men) had urge incontinence, 31 (18.3%; 25 women and 6 men) had mixed UI, and 15 (8.9%; 4 women and 11 men) had other UI.

3.1. *Age- and sex-adjusted baseline characteristics according to continence status*

The mean age was higher in the UI groups than in the non-UI groups ($p < 0.01$) (Table 1). The proportion of women was significantly greater in the UI groups ($p < 0.01$). Although not statistically significant, the proportions of diabetics appeared to be higher among the UI groups ($p = 0.10$). Otherwise, no significant difference was observed between the non-UI groups and the UI groups.

3.2. *Relationships between PA levels and UI prevalence*

In a crude model, the ORs of occurrence of UI across the PA levels low, middle, and high were 1.00 (reference), 0.63 (95%CI, 0.42–0.94), and 0.43 (95%CI, 0.26–0.68), respectively (Table 2). These results were unchanged when we adjusted for age, sex, or multiple confounding factors. Although not statistically significant, the positive relation of BMI (OR = 1.003; 95%CI, 0.95–1.06) and diabetes (OR = 1.60; 95%CI, 0.84–2.94) with UI were observed in multiple model. Furthermore, although p for trend was statistically significant only in women, similar relations were also observed in men (p for interaction = 0.66).

3.3. *Relationships between PA levels and log-transformed ICIQ score*

In this study population, the median (interquartile range) ICIQ score was 0 (0–3) in low PA level, 0 (0–3) in

Table 2 – Adjusted relationships of PA levels to the occurrence of urinary incontinence

	PA levels			p for trend
	Low level	Middle level	High level	
All, n = 676				
No. of participants	276	232	168	—
No. of urinary incontinence*	88	53	28	—
Odds ratio (95% CI)				
Crude	1.00	0.63 (0.42–0.94)	0.43 (0.26–0.68)	<0.01
Age- and sex-adjusted	1.00	0.71 (0.47–1.07)	0.56 (0.33–0.91)	0.01
Multiple adjusted†	1.00	0.71 (0.47–1.09)	0.58 (0.35–0.96)	0.02
Women, n = 346				
No. of participants	168	108	70	—
No. of urinary incontinence*	64	41	13	—
Odds ratio (95% CI)				
Crude	1.00	0.99 (0.60–1.63)	0.37 (0.18–0.71)	0.01
Age-adjusted	1.00	0.99 (0.60–1.63)	0.43 (0.21–0.84)	0.04
Multiple adjusted‡	1.00	0.98 (0.58–1.64)	0.44 (0.21–0.87)	0.046
Men, n = 330				
No. of participants	108	124	98	—
No. of urinary incontinence*	24	12	15	—
Odds ratio (95% CI)				
Crude	1.00	0.38 (0.17–0.78)	0.63 (0.31–1.28)	0.15
Age-adjusted	1.00	0.38 (0.17–0.79)	0.66 (0.31–1.34)	0.18
Multiple adjusted§	1.00	0.38 (0.18–0.80)	0.66 (0.31–1.35)	0.18

PA, physical activity; CI = confidence interval.

* Had a self-reported urinary incontinence including stress urinary incontinence, urge incontinence, mixed urinary incontinence, and other urinary incontinence.

† Adjusted for potential confounding factors (see Methods section).

‡ Adjusted for potential confounding factors (see Methods section).

§ Adjusted for potential confounding factors (see Methods section).

Table 3 – Adjusted PA level in relation to log-transformed ICIQ* score among the subjects

	PA levels			p for trend
	Low level	Middle level	High level	
All, n = 676				
No. of participants	276	232	168	
Crude log ICIQ score†	0.50 ± 0.04	0.37 ± 0.05	0.27 ± 0.06	<0.01
Age-adjusted log ICIQ score†	0.47 ± 0.04	0.38 ± 0.05	0.32 ± 0.60	0.03
Multiple adjusted log ICIQ score†,‡	0.46 ± 0.04	0.38 ± 0.05	0.33 ± 0.06	0.06
Women, n = 346				
No. of participants	168	108	70	
Crude log ICIQ score†	0.60 ± 0.06	0.60 ± 0.07	0.28 ± 0.09	<0.01
Age-adjusted log ICIQ score†	0.59 ± 0.06	0.59 ± 0.08	0.34 ± 0.10	0.02
Multiple adjusted log ICIQ score†,§	0.59 ± 0.06	0.59 ± 0.08	0.34 ± 0.10	0.02
Men, n = 330				
No. of participants	108	124	98	
Crude log ICIQ score†	0.35 ± 0.06	0.17 ± 0.05	0.27 ± 0.06	0.35
Age-adjusted log ICIQ score†,‖	0.35 ± 0.06	0.17 ± 0.05	0.27 ± 0.06	0.40
Multiple adjusted log ICIQ score†,¶	0.34 ± 0.06	0.18 ± 0.06	0.27 ± 0.06	0.40

PA = physical activity; ICIQ = International Consultation Incontinence Questionnaire.
* Before log transformation, 1.0 was added to the ICIQ score.
† Variables are presented as least squares means ± standard error.
‡ Adjusted for potential confounding factors (see Methods section).
§ Adjusted for potential confounding factors (see Methods section).
‖ Adjusted for potential confounding factors (see Methods section).
¶ Adjusted for potential confounding factors (see Methods section).

middle PA level, and 0 (0–0) in high PA level. In all subjects, in a crude, age-adjusted model, increasing PA levels showed a significantly inverse relationship with mean log ICIQ score (p for trend <0.01 and 0.03, respectively; Table 3). In a multiple model, although not statistically significant, increasing PA levels were inversely related to mean log ICIQ score (p for trend = 0.06). In the multivariate model, although increasing PA levels showed a significantly inverse relationship with mean log ICIQ score in women only (p for trend 0.02 in women and 0.40 in men), no significant interaction between sex and PA for UI was observed.

4. Discussion

In this cross-sectional study, we examined the relationship between PA and UI among community-dwelling elderly population aged ≥70 yr, among whom this condition is highly prevalent. These results suggested that high PA was independently related to a lower self-reported prevalence of UI and lower degree of UI in community-dwelling elderly population aged ≥70 yr.

Although regular PA was confirmed to be effective in the primary and secondary prevention of factors in UI such as diabetes, hypertension, obesity, and pelvic floor muscle dysfunctions [7,9], it was also considered that high-impact PA may be a potential risk factor associated with UI because high-impact PA (eg, jogging, tennis) also increases abdominal pressure, which is an important factor associated with the occurrence of stress incontinence [16,23]. In this study, the highest PA level including sports was not related to a higher prevalence of UI. Moreover, we also assessed the relationship between ICIQ score, which is an indicator of the degree of UI. The results did not indicate that higher PA levels increased the degree of UI. However, because information about high-impact PA such as jogging and tennis was not derived specifically from our questionnaire [20], we cannot establish that any specific high-impact PA had an effect on UI.

In this study, we have hypothesized that PA may have a potentially beneficial effect on the prevention of UI. Although several studies [6,11,12,14–16] investigated the relationship between PA and UI, only one study [13] used a community-based population including older (73–79 yr) women. However, they did not adjust for any confounding factors when they analyzed the relationship between PA and UI. Incidentally, these studies have not suggested any beneficial effect of PA on UI in contrast to our hypothesis and our results. Although the reason for this discrepancy is unclear, because high-impact PA is a risk factor for UI [16,23] and age was associated with a decline in jump peak performance according to peak leg muscle power [24], the difference in the age of the subjects may partly explain this discrepancy.

UI prevalence rises in elderly adults regardless of sex [25]. In this study, women had a higher prevalence of UI (34.2%) compared with men (15.5%) as seen in other studies; for example, the prevalence of UI in community-dwelling elderly ≥60 yr of age in Europe is 19.3% in women and 10.4% in men [26]. Although interaction between sex and PA for UI was not significant, p for trend of the relation between PA and UI was statistically significant only in women. Prostate diseases may explain the weaker association observed in men [27]. However, since we did not have information on prostate diseases, we could not answer the issue. Further study is required to clarify the discrepancy.

UI is a major elderly health problem. Gasquet et al [3] indicated that stress UI is frequent in French women, causing embarrassment and negatively affecting their QOL. A recent study also indicated that UI severity was the single most important predictor of QOL and bother in a large group of European women, regardless of type of UI [28]. In this study, we found that PA was independently related to ICIQ score, which is an indicator of the QOL. This result suggested that PA may have a potentially beneficial effect on the QOL associated with UI.

This study had several limitations. First, because all assessment was carried out in a public facility, participants were sufficiently active and healthy. In addition, we have excluded the subjects who had a potential for PA restriction. Moreover, because depressive symptoms might influence the frequency and degree of PA [29] and UI can be a reason for depression, we also excluded participants with depression. Therefore, our results may not represent an elderly general population. However, we believe that these exclusions were necessary to investigate the relation of PA with UI. Second, because this study was a cross-sectional study, we could not conclude that PA decreases the occurrence of UI or that UI leads to impairment of PA among subjects aged ≥70 yr. Therefore, a prospective study or trial should be undertaken to confirm the relationship between PA and UI. Third, because the question of PA is focused on some activities such as walking, brisk walking, and sports, we could not infer the influence of other sorts of exercise on UI. Fourth, although we adjusted for several confounders related to UI, we could not adjust some factors associated with UI, such as genitourinary surgery or prostate disease status because of lack of information. Finally, a self-reported single-item question and corresponding response sets were used to estimate different levels (not a quantitative) of PA. Moreover, we did not directly measure the exercise intensities of walking, brisk walking, and sports by our subjects. Still, one may easily discriminate one's own "brisk walking" from ordinary walking. We therefore believe that the categorization of relative walking intensity based on the subjects' own perceptions was reliable. It is well known that ratings of perceived exertion correspond well to exercise intensity as measured by oxygen uptake [30].

5. Conclusions

A high PA level was independently related to a lower self-reported prevalence of UI in community-dwelling elderly population aged ≥70 yr. Although this cross-sectional study cannot demonstrate temporal relationship between PA and the onset of UI, the findings suggest that PA may have a potentially beneficial effect on the prevention of UI. A prospective study or randomized trials are required to clarify the causality.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Editorial Comment on: Association between Physical Activity and Urinary Incontinence in a Community-Based Elderly Population Aged 70 Years and Over

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Because urinary incontinence among the elderly consumes a considerable part of health care costs and often leads to personal suffering and lowered quality of life, it is essential to use preventive solutions that are cost effective but also have other positive effects, such as increased physical functioning and improved quality of life. Interventions that may prolong time without health care or time

to be able to live independently on one's own are extremely important from a personal viewpoint but also from the perspective of the whole society. It is time to test interventions in a wide health economic overview, in multicentre studies focusing on different groups of elderly, to prove that staff-intensive prophylactic physical training is a good investment in the care of older people.

Urinary incontinence among the elderly is complex; it has several causative factors and a potential impact on daily life for the individual and also for relatives. Additionally, urinary incontinence is related to nursing home admittance or increased need for health care and help in performing daily activities. Older persons performing regular physical activities reported lower prevalence of urinary incontinence episodes [1]. Several other studies have pointed out similar findings. For instance, impaired mobility, such as difficulties in walking or moving the arms and hands, as well as oedema in the legs were factors strongly related to urinary incontinence and faecal incontinence in older women and men [2]. Furthermore, studies have shown the positive effects of physical training on the frequency of leakage among nursing home populations [3,4] but not on cost reduction [5]. Improving mobility function has many other effects apart from urinary incontinence, such as reducing the incidence of falls and improving balance, coordination, cardiorespiratory fitness, and quality of life [6]. These positive outcomes have to be considered as well.

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Sense of Life Worth Living (*Ikigai*) and Mortality in Japan: Ohsaki Study

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Objective: To investigate the association between the sense of "life worth living (*ikigai*)" and the cause-specific mortality risk. The psychological factors play important roles in morbidity and mortality risks. However, the association between the negative psychological factors and the risk of mortality is inconclusive. **Methods:** The Ohsaki Study, a prospective cohort study, was initiated on 43,391 Japanese adults. To assess if the subjects found a sense of *ikigai*, they were asked the question, "*Do you have ikigai in your life?*" We used Cox regression analysis to calculate the hazard ratio of the all-cause and cause-specific mortality according to the sense of *ikigai* categories. **Results:** Over 7 years' follow-up, 3048 of the subjects died. The risk of all-cause mortality was significantly higher among the subjects who did not find a sense of *ikigai* as compared with that in the subjects who found a sense of *ikigai*; the multivariate adjusted hazard ratio (95% confidence interval) was 1.5 (1.3–1.7). As for the cause-specific mortality, subjects who did not find a sense of *ikigai* were significantly associated with an increased risk of cardiovascular disease (1.6; 1.3–2.0) and external cause mortality (1.9; 1.1–3.3), but not of the cancer mortality (1.3; 1.0–1.6). **Conclusions:** In this prospective cohort study, subjects who did not find a sense of *ikigai* were associated with an increased risk of all-cause mortality. The increase in mortality risk was attributable to cardiovascular disease and external causes, but not cancer. **Key words:** sense of life worth living (*ikigai*), Japanese, all-cause mortality, cause-specific mortality.

CVD = cardiovascular disease; **NHI** = National Health Insurance; **PHC** = Public Health Center; **IHD** = ischemic heart disease; **HR** = hazard ratio; **CI** = confidence interval; **BMI** = body mass index.

INTRODUCTION

The psychological factors of people play important roles in the morbidity and mortality risks (1–17). Studies in the US and Europe have reported that the negative psychological factors, as represented by factors such as a low subjective sense of well-being (1), dissatisfaction (2–4), hopelessness (5,6), and self-perception of ill health (7–9), were associated with an increased risk of all-cause mortality. The association between the negative psychological factors and the mortality risk has been reported to be independent of the objective health status, socioeconomic status, or the health-related lifestyle.

In Japanese culture, having a sense of "life worth living (*ikigai*)" is the most commonly used indicator of subjective well-being. The sense of "life worth living (*ikigai*)" does not merely reflect an individual's psychological factors (well-being, hopes) but also an individual's consciousness of the motivation for living, because it has a meaning akin to having a "purpose in life" and "reason for living." The term *ikigai* is commonly used in such phrases as "this hobby is what makes my life worth living (*ikigai*)" or "raising children makes my life worth living (*ikigai*)". In the most authoritative dictionary in Japan, the sense of *ikigai* is described as "joy and a sense of well-being from being alive" and of "realizing the value of being alive" (18). Three earlier studies in Japan have reported that the lack of *ikigai* was significantly associated with an increased risk of all-cause mortality (10–12).

The association between the negative psychological factors and the risk of cause-specific mortality is, however, inconclusive (11,13–16). Some studies have indicated an association with cancer mortality, whereas others have denied any such association (11,13,14). As for cardiovascular disease (CVD) mortality, no agreement has been reached among past studies (11,14–16). A Japanese study reported that the lack of *ikigai* was significantly associated with CVD mortality, but not cancer mortality (11). On the other hand, another study reported that the lack of *ikigai* was associated with an increased risk of breast cancer (17).

Because the causes differ between CVD and cancer, the impact of the psychological factors on mortality risk may also differ between CVD and cancer. Determination of this difference would strengthen our understanding of the mechanism underlying the impact of the psychological factors on physical health and illness. In this study, we attempted to test the hypothesis that the association between *ikigai* and mortality risk is dependent on the specific cause of death. To test this hypothesis, we investigated the association between *ikigai* and the cause-specific mortality in a population-based prospective cohort study in Japan. Among all the studies conducted until now in Japan (10–12), the present study had the largest number of subjects, the largest number of decedents, and the most comprehensive set of covariates for multivariate adjustment.

METHODS

The present data were derived from the Ohsaki National Health Insurance (NHI) Cohort Study. The study design has been reported previously (19–22). A self-administered questionnaire was distributed between October and December 1994 to all NHI beneficiaries aged 40 to 79 years and living in the catchment areas of the Ohsaki Public Health Center (PHC) (n = 54,996). The Ohsaki PHC, a local governmental agency, provides preventive health services for the residents of 14 municipalities in Miyagi Prefecture in northeastern Japan. The questionnaires were delivered to the subjects' residences by public health officials in each municipality. This procedure yielded a high response rate of 94.6% (n = 52,029). We excluded 811 subjects because they had died or withdrawn from the NHI before January 1, 1995, when we started

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the prospective collection of NHI claim history files, and finally, a total of 51,218 subjects formed the study cohort. This study was approved by the Ethics Committee of Tohoku University School of Medicine. We considered the return of self-administered questionnaires signed by the subjects to imply their consent to participate in the study.

The 93-item questionnaire at the baseline survey consisted of questions related to the following ten factors: past medical history, family history, physical health status, drinking habit, smoking habit, dietary habit, job, marital status, education, and other health-related factors, including *ikigai* (19).

Ikigai was assessed through the subject's response to the question, *"Do you have ikigai in your life?"* The subjects were asked to choose one of three answers: "yes," "uncertain," or "no."

The endpoints were all-cause mortality and cause-specific mortality. To follow up the subjects for mortality and migration, we reviewed the NHI withdrawal history files. When a subject was withdrawn from the NHI system because of death, emigration, or employment, the withdrawal data and its reason were coded on the NHI withdrawal history files. Because we were unable to obtain subsequent information on the subjects who withdrew from the NHI, we discontinued follow-up of the subjects who withdrew from the NHI system because of emigration or employment.

For the decedents, we investigated the cause of death by reviewing the death certificates filed at the Ohsaki PHC. Cause of death was classified according to the International Classification of Diseases, 10th Revision (23). We identified deaths from cancer as codes C00–C97, CVD as codes I00–I99 (including ischemic heart disease (IHD) as codes I20–I25 and stroke as codes I60–I69), pneumonia as codes J10–J18, and external causes as codes V01–V99, W00–W99, X00–X99 (including suicide as codes X60–X84), and Y01–Y34. None of the subjects died of unknown causes. Because the Family Registration Law in Japan requires registration of death, death certificates confirmed all the deaths that occurred in the study area.

Of the 51,218 subjects who participated in the baseline survey, we excluded 2939 subjects who had not indicated any response to the question about *ikigai* and the 4888 subjects who had a history of cancer, myocardial infarction, or stroke. Consequently, our final analysis included the data of 43,391 subjects (20,625 men and 22,766 women).

We counted the person-years of follow-up for each subject from January 1, 1995 until the date of death, date of withdrawal from the NHI, or the end of the study period (December 31, 2001), whichever occurred first. We accrued 269,989 person-years of follow-up. During the follow-up, 3048 (7.0%) subjects died and 5187 (12.0%) subjects were lost to follow-up.

The Kaplan-Meier survival curves were used to obtain estimates of survival at 7 years, and the log-rank test was used to test for significant differences between survival curves for the various response categories for *ikigai*, using the SAS LIFETEST procedure on SAS, version 9.1 (SAS Institute, Cary, North Carolina). Cox proportional hazards regression analysis was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and cause-specific mortality according to the response categories for *ikigai* and to adjust for potential confounders, using the SAS PHREG procedure on SAS, version 9.1. The validity of the proportional hazard assumption was verified by adding a time-dependent variable to each model to confirm that the HR for each covariate did not increase or decrease over time. All p values were two-sided, and differences at $p < .05$ were considered to be statistically significant. Interaction between each variable and *ikigai* was tested by a multiplicative model.

We considered the following variables as potential confounders; age at baseline (continuous variable), sex (men or women), marital status (married, widowed/divorced, or single), education (junior high school or higher), job (employed or unemployed), self-rated health (bad or poor, fair, or good or excellent), perceived mental stress (high, moderate, or low), bodily pain (severe or moderate, mild or very mild, or none), physical function (limited or unlimited), body mass index (BMI) in kg/m^2 (≤18.4, 18.5–24.9, or ≥25.0), smoking status (never, former, currently smoking 1–19 cigarettes/day, or ≥20 cigarettes/day), alcohol consumption (never, former, current ethanol intake of ≤22.7 g/day, 22.8–45.5 g/day, 45.6–68.3 g/day, or ≥68.4 g/day), time spent walking (<1 hour/day or ≥1 hour/day), sleep duration (≤6 hours/day, 7–8 hours/day, or ≥9 hours/day), and history of hypertension, diabetes mellitus,

TABLE 1. Characteristics of Study Subjects According to *Ikigai* (n = 43,391)

	Ikigai		
	Yes	Uncertain	No
No. of subjects	25,596	15,782	2013
Age at baseline, years (mean ± SD)	60.3 ± 10.2	59.6 ± 10.5	61.4 ± 11.1
Women (%)	50.1	55.6	57.4
Marital status (%)			
Married	84.8	79.2	68.9
Widowed/divorced	12.8	15.0	21.7
Single	2.5	5.7	9.4
Education (%)			
Junior high school	56.9	62.4	67.1
Higher	43.1	37.6	32.9
Job (%)			
Employed	67.3	60.0	47.6
Unemployed	32.7	40.0	52.4
Self-rated health (%)			
Bad or poor	12.3	24.8	46.6
Fair	10.8	20.8	16.9
Good or excellent	76.9	54.5	36.5
Perceived mental stress (%)			
High	12.4	19.2	36.3
Moderate	65.6	70.4	43.2
Low	22.0	10.3	20.5
Bodily pain (%)			
Severe or moderate	13.4	20.0	33.3
Mild or very mild	50.3	54.1	40.9
None	36.3	25.9	25.8
Physical function (%)			
Limited	18.9	29.6	48.6
Unlimited	81.1	70.4	51.4
BMI, kg/m^2 (%)			
≤18.4	3.0	4.0	6.6
18.5–24.9	67.6	67.5	65.1
≥25.0	29.5	28.5	28.4
Smoking status (%)			
Never	53.0	55.0	54.9
Former	14.9	13.1	14.0
Current, 1–19 cigarettes/day	11.8	12.2	12.3
Current, ≥20 cigarettes/day	20.3	19.8	18.9
Alcohol consumption (%)			
Never	42.6	47.0	49.8
Former	6.3	8.3	11.3
Current, ≤22.7 g/day ethanol	21.9	19.2	16.9
Current, 22.8–45.5 g/day ethanol	10.4	8.6	7.6
Current, 45.6–68.3 g/day ethanol	12.5	10.1	7.2
Current, ≥68.4 g/day ethanol	6.3	6.7	7.2
Time spent walking (%)			
<1 hr/day	50.7	57.5	65.0
≥1 hr/day	49.3	42.5	35.0
Sleep duration (%)			
≤6 hrs/day	15.2	16.7	19.5
7–8 hrs/day	69.2	65.9	55.7
≥9 hrs/day	15.6	17.4	24.8

(*Continued*)

TABLE 1. Continued

	Ikigai		
	Yes	Uncertain	No
History of illness (%)			
Hypertension	24.4	26.5	30.0
Diabetes mellitus	5.7	6.1	9.2
Kidney disease	3.5	3.9	5.0
Liver disease	5.1	5.6	6.0
Gastric or duodenal ulcer	14.5	14.2	14.0
Arthritis	8.8	10.0	12.3
Osteoporosis	3.4	4.0	6.0

SD = standard deviation; BMI = body mass index.

kidney disease, liver disease, gastric or duodenal ulcer, arthritis, or osteoporosis (presence or absence).

In addition, we repeated all analyses after excluding the deaths that occurred within the first 2 years of follow-up (644 all-cause deaths), because subjects who died within the first 2 years of follow-up might have been in poor health at baseline. Stratified analyses according to confounders were conducted in relationship to the association between *ikigai* and the mortality risk, because *ikigai* may be associated with the risk of all-cause mortality independent of socioeconomic factors, other psychological factors, physical function, lifestyle habits, or history of illness.

RESULTS

Over the 7 years of follow-up, the total number of deaths was 3048. This number included 1100 deaths from cancer, 971 deaths from CVD (including 207 from IHD and 479 from stroke), 241 deaths from pneumonia, and 186 deaths from external causes (including 90 from suicide).

Among the 43,391 subjects enrolled, 25,596 (59.0%) indicated that they found a sense of *ikigai*, 15,782 (36.4%) indicated they were uncertain, and 2013 (4.6%) indicated they did not find a sense of *ikigai*. As compared with those who found a sense of *ikigai*, those who did not were more likely to be unmarried, unemployed, have a lower educational level, have bad or poor self-rated health, have a high level of perceived mental stress, have severe or moderate bodily pain, have limitation of physical function, and less likely to walk (Table 1).

The Kaplan-Meier curves indicated that those who did not find a sense of *ikigai* were associated with an increased risk of all-cause mortality ($p < .001$) (Figure 1). Table 2 shows the HR (95% CI) of all-cause and cause-specific mortality according to the response categories for *ikigai*. There was a statistically significant association between *ikigai* and the risk of all-cause mortality. As compared with subjects who found a sense of *ikigai*, the multivariate adjusted HR (95% CI) of all-cause mortality was 1.1 (1.0–1.2) for those who were uncertain, and 1.5 (1.3–1.7) for those who did not find a sense of *ikigai*. This finding remained basically unchanged even after excluding the deaths that occurred within the first 2 years of follow-up.

The above-mentioned increase in the all-cause mortality risk was attributable to an increased risk of mortality from CVD, pneumonia, and external causes. However, *ikigai* was not associated with the risk of cancer mortality. As compared with those who found a sense of *ikigai*, the multivariate HR (95% CI) in those who did not find a sense of *ikigai* was 1.6 (1.3–2.0) for CVD, 1.8 (1.2–2.7) for pneumonia, 1.9 (1.1–3.3) for external causes, and 1.3 (1.0–1.6) for cancer.

We further investigated the risk of mortality from IHD and stroke among the CVD mortality. As compared with those who found a sense of *ikigai*, those who did not find a sense of *ikigai* were significantly associated with an increased risk of stroke mortality, but not of IHD mortality. The multivariate HR (95% CI) in those who did not find a sense of *ikigai* was 2.1 (1.6–2.9) for stroke and 0.9 (0.5–1.7) for IHD.

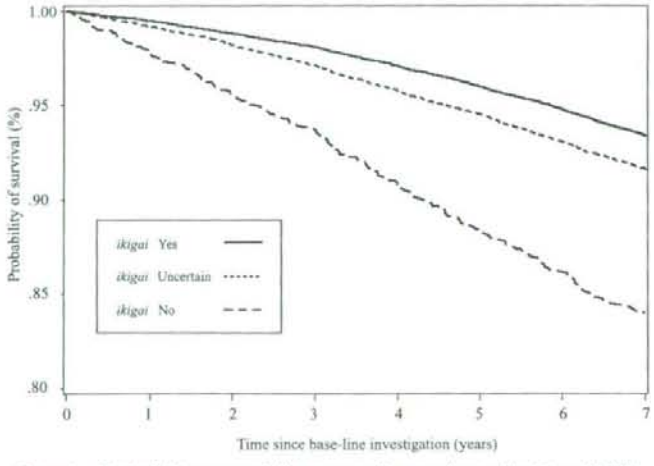

Figure 1. Kaplan-Meier curves of all-cause mortality according to *ikigai* (n = 43,391).

TABLE 2. Hazard Ratios (HRs) of Mortality According to *Ikigai* (n = 43,391)

	Ikigai		
	Yes	Uncertain	No
Person-years of follow-up	160,910	97,232	11,847
All-cause			
No. of cases	1547	1206	295
Age and sex adjusted HR (95% CI)	1.0 (reference)	1.4 (1.3–1.5)	2.5 (2.2–2.9)
p-values	—	<.001	<.001
Multivariate HR1 (95% CI)	1.0 (reference)	1.1 (1.0–1.2)	1.5 (1.3–1.7)
p-values	—	.006	<.001
Multivariate HR2 (95% CI)	1.0 (reference)	1.1 (1.0–1.2)	1.4 (1.2–1.6)
p-values	—	.082	<.001
Cancer			
No. of cases	653	374	73
Age and sex adjusted HR (95% CI)	1.0 (reference)	1.1 (0.9–1.2)	1.5 (1.2–2.0)
p-values	—	.45	<.001
Multivariate HR1 (95% CI)	1.0 (reference)	0.9 (0.8–1.1)	1.3 (1.0–1.6)
p-values	—	.36	.061
Multivariate HR2 (95% CI)	1.0 (reference)	0.9 (0.8–1.1)	1.2 (0.9–1.6)
p-values	—	.41	.22
Cardiovascular disease			
No. of cases	460	399	112
Age and sex adjusted HR (95% CI)	1.0 (reference)	1.5 (1.4–1.8)	3.0 (2.5–3.7)
p-values	—	<.001	<.001
Multivariate HR1 (95% CI)	1.0 (reference)	1.2 (1.0–1.4)	1.6 (1.3–2.0)
p-values	—	.014	<.001
Multivariate HR2 (95% CI)	1.0 (reference)	1.1 (0.9–1.3)	1.6 (1.2–2.0)
p-values	—	.24	<.001
Ischemic heart disease			
No. of cases	96	97	14
Age and sex adjusted HR (95% CI)	1.0 (reference)	1.8 (1.4–2.4)	1.9 (1.1–3.3)
p-values	—	<.001	.029
Multivariate HR1 (95% CI)	1.0 (reference)	1.4 (1.0–1.8)	0.9 (0.5–1.7)
p-values	—	.048	.81
Multivariate HR2 (95% CI)	1.0 (reference)	1.4 (1.0–2.1)	0.9 (0.4–1.9)
p-values	—	.048	.73
Stroke			
No. of cases	222	192	65
Age and sex adjusted HR (95% CI)	1.0 (reference)	1.5 (1.3–1.9)	3.6 (2.7–4.8)
p-values	—	<.001	<.001
Multivariate HR1 (95% CI)	1.0 (reference)	1.2 (1.0–1.5)	2.1 (1.6–2.9)
p-values	—	.035	<.001
Multivariate HR2 (95% CI)	1.0 (reference)	1.1 (0.9–1.4)	1.9 (1.3–2.7)
p-values	—	.37	<.001
Pneumonia			
No. of cases	102	105	34
Age and sex adjusted HR (95% CI)	1.0 (reference)	1.9 (1.5–2.5)	4.0 (2.7–5.9)
p-values	—	<.001	<.001
Multivariate HR1 (95% CI)	1.0 (reference)	1.3 (1.0–1.7)	1.8 (1.2–2.7)
p-values	—	.091	.008
Multivariate HR2 (95% CI)	1.0 (reference)	1.3 (0.9–1.7)	1.3 (0.8–2.2)
p-values	—	.13	.30
External cause			
No. of cases	91	76	19
Age and sex adjusted HR (95% CI)	1.0 (reference)	1.5 (1.1–2.0)	3.0 (1.8–4.9)
p-values	—	.011	<.001
Multivariate HR1 (95% CI)	1.0 (reference)	1.3 (0.9–1.7)	1.9 (1.1–3.3)
p-values	—	.15	.018
Multivariate HR2 (95% CI)	1.0 (reference)	1.2 (0.8–1.8)	2.4 (1.3–4.4)
p-values	—	.27	.003

(*Continued*)

TABLE 2. Continued

	Ikigai		
	Yes	Uncertain	No
Suicide			
No. of cases	44	38	8
Age and sex adjusted HR (95% CI)	1.0 (reference)	1.5 (1.0–2.3)	2.7 (1.3–5.7)
p-values	—	.067	.011
Multivariate HR1 (95% CI)	1.0 (reference)	1.4 (0.9–2.2)	2.0 (0.9–4.4)
p-values	—	.15	.11
Multivariate HR2 (95% CI)	1.0 (reference)	1.4 (0.8–2.5)	2.5 (0.9–6.7)
p-values	—	.21	.079

HR1 denotes the HR with death from all-causes included in the model.
HR2 denotes the HR with death from all-causes in the first two years of follow-up (644 deaths) excluded from analysis in the model.
Multivariate HR are adjusted for age (continuous variable), sex (men or women), marital status (married, widowed/divorced, or single), education (junior high school or higher), job (employed or unemployed), self-rated health (bad or poor, fair, or good or excellent), perceived mental stress (high, moderate, or low), bodily pain (severe or moderate, mild or very mild, or none), physical function (limited or unlimited), body mass index in kg/m^2 ($\leq$18.4, 18.5–24.9, or $\geq$25.0), smoking status (never, former, currently smoking 1–19 cigarettes/day, or $\geq$20 cigarettes/day), alcohol consumption (never, former, current ethanol intake of $\leq$22.7 g/day, 22.8–45.5 g/day, 45.6–68.3 g/day, or $\geq$68.4 g/day), time spent walking (<1 hour/day or $\leq$1 hour/day), sleep duration ($\geq$6 hours/day, 7–8 hours/day, or $\geq$9 hours/day), and history of hypertension, diabetes mellitus, kidney disease, liver disease, gastric or duodenal ulcer, arthritis, or osteoporosis (presence or absence).
Numbers in parentheses are 95% confidence intervals (CIs).
CI = confidence interval.

Regarding the external causes of death (186 deaths), suicide (90 deaths) was the most commonly encountered cause. The risk of suicide mortality was associated with the sense of *ikigai* at an almost significant level. As compared with those who found a sense of *ikigai*, the multivariate HR (95% CI) in those who did not find a sense of *ikigai* was 2.0 (0.9–4.4) for suicide.

The association between *ikigai* and pneumonia mortality disappeared after excluding the deaths that occurred within the first 2 years of follow-up. As compared with those who found a sense of *ikigai*, the multivariate HR (95% CI) in those who did not find a sense of *ikigai* was 1.3 (0.8–2.2) for pneumonia. The risk of other cause-specific mortality remained basically unchanged after excluding the deaths that occurred within the first 2 years of follow-up. The results obtained after excluding the deaths that occurred within 3 to 4 years of follow-up also showed an increase in the all-cause mortality risk among the subjects lacking a sense of *ikigai*.

We found that those who did not find a sense of *ikigai* were associated with an increased risk of all-cause mortality, independent of socioeconomic factors, other psychological factors, physical function, lifestyle habits, and history of illness. As shown in Table 1, the lack of *ikigai* was associated with poorer psychosocial status and poorer physical health status. We conducted stratified analyses to examine whether the association between the *ikigai* and mortality was dependent on the variables listed in Table 1. As shown in Table 3, there were no differences across age strata (p for interaction = .80). Likewise, no significant effect modification of other confounding variables was shown either (p for interaction = >.05). The lack of *ikigai* was associated with an increased risk of all-cause mortality, independent of the sex, marital status, educational level, employment, self-rated health, perceived mental stress, bodily pain, and physical function. We also attempted to conduct stratified analyses according to lifestyle variables and history of illness. The lack of *ikigai* was associated with an increased risk of all-cause mortality, independent of the BMI, smoking status, alcohol consumption, time spent walking, sleep duration, and a history of illness (data not shown).

DISCUSSION

In this population-based prospective cohort study in Japan, those who did not find a sense of *ikigai* were significantly associated with an increased risk of all-cause mortality. The increase in mortality risk was attributed to an increase in the mortality from CVD (mainly stroke) and external causes, but not to the morality risk from cancer. In our study subjects, those who did not find a sense of *ikigai* were likely to have a poorer socioeconomic status and poorer objective health status. However, the mortality risk in those who did not find a sense of *ikigai* was consistently increased, irrespective of socioeconomic factors, other psychological factors, physical function, lifestyle habits, and a history of illness.

Although many studies have reported an association between the psychological factors and all-cause mortality risk (1–12), the association between the negative psychological factors and the risk of cause-specific mortality remains inconsistent. In Japan, only one study has investigated the association between *ikigai* and the risk of cause-specific mortality (11). The lack of *ikigai* was associated an increased risk of CVD mortality, but not of cancer mortality. Our findings were consistent with this previous report. In addition, we have shown new evidence indicating that the lack of *ikigai* may also be associated with an increased risk of mortality from external causes, but not from pneumonia.

TABLE 3. Multivariate Hazard Ratios (HRs) of All-Cause Mortality According to *Ikigai* Stratified by Socioeconomic Factors, Other Psychological Factors, or Physical Function

	No. of Subjects	No. of Cases	*Ikigai*			*p* for Interaction*
			Yes	Uncertain	No	
Age, yr						
≤64	28,002	959	1.0 (reference)	1.1 (0.9–1.2)	1.1 (0.8–1.4)	.80
≥65	15,389	2089	1.0 (reference)	1.1 (1.0–1.2)	1.6 (1.4–1.9)	
Sex						
Men	20,625	1874	1.0 (reference)	1.1 (1.0–1.2)	1.4 (1.2–1.7)	.20
Women	22,766	1174	1.0 (reference)	1.1 (1.0–1.3)	1.6 (1.3–2.0)	
Marital status						
Married	32,089	2043	1.0 (reference)	1.1 (1.0–1.2)	1.6 (1.3–1.9)	.47
Widowed/divorced or single	7003	632	1.0 (reference)	1.2 (1.0–1.4)	1.5 (1.1–1.9)	
Education						
Junior high school	24,621	1971	1.0 (reference)	1.1 (1.0–1.2)	1.5 (1.2–1.7)	.24
Higher	16,893	858	1.0 (reference)	1.2 (1.0–1.4)	1.6 (1.2–2.2)	
Job						
Employed	20,372	995	1.0 (reference)	1.2 (1.1–1.4)	1.8 (1.4–2.4)	.43
Unemployed	11,566	1163	1.0 (reference)	1.1 (1.0–1.3)	1.5 (1.2–1.8)	
Self-rated health						
Good or excellent	28,893	1496	1.0 (reference)	1.2 (1.1–1.3)	1.6 (1.3–2.1)	.71
Bad to fair	14,312	1524	1.0 (reference)	1.1 (0.9–1.2)	1.5 (1.3–1.7)	
Perceived mental stress						
Low	7600	593	1.0 (reference)	1.1 (0.9–1.3)	1.7 (1.3–2.2)	.32
High or moderate	35,342	2380	1.0 (reference)	1.1 (1.0–1.2)	1.4 (1.2–1.7)	
Bodily pain						
None	12,983	795	1.0 (reference)	1.1 (1.0–1.3)	1.3 (1.0–1.8)	1.00
Severe to very mild	27,487	1997	1.0 (reference)	1.1 (1.0–1.3)	1.6 (1.4–1.9)	
Physical function						
Unlimited	32,161	1584	1.0 (reference)	1.1 (1.0–1.3)	1.3 (1.0–1.6)	.10
Limited	10,245	1348	1.0 (reference)	1.1 (1.0–1.3)	1.6 (1.3–1.9)	

Multivariate HR are adjusted for age (continuous variable), sex (men or women), marital status (married, widowed/divorced, or single), education (junior high school or higher), job (employed or unemployed), self-rated health (bad or poor, fair, or good or excellent), perceived mental stress (high, moderate, or low), bodily pain (severe or moderate, mild or very mild, or none), physical function (limited or unlimited), body mass index in kg/m^2 (≤18.4, 18.5–24.9, or ≥25.0), smoking status (never, former, currently smoking 1–19 cigarettes/day, or ≥20 cigarettes/day), alcohol consumption (never, former, current ethanol intake of ≤22.7 g/day, 22.8–45.5 g/day, 45.6–68.3 g/day, or ≥68.4 g/day), time spent walking (<1 hr/day or ≥ 1 hr/day), sleep duration (≤6 hr /day, 7–8 hr/day, or ≥9 hr/day), and history of hypertension, diabetes mellitus, kidney disease, liver disease, gastric or duodenal ulcer, arthritis, or osteoporosis (presence or absence). Numbers in parentheses are 95% confidence intervals (CIs).

* In calculating *p* for interaction, we treated age as continuous variable and others as dichotomous variable.

The present study had several methodological advantages as compared with previous studies on the association between *ikigai* and mortality. First, we investigated a variety of causes of death (all-cause; cancer; CVD including IHD or stroke; pneumonia and external causes including suicide). Second, we controlled extensively for potential confounders, including socioeconomic factors, other psychological factors, physical function, lifestyle habits, and a history of illness. We repeated all the analyses after excluding the deaths that occurred within the first 2 years of follow-up, and we attempted to conduct stratified analyses by confounders. In addition, the subjects with a history of cancer, myocardial infarction, and stroke were more likely to answer the lack of *ikigai*. If we included these subjects, the association between *ikigai* and the mortality risk would have been overestimated because of confounding. Thus, we excluded from our analysis the subjects with a history of cancer, myocardial infarction, and stroke. Based on our findings after taking the above details into consideration, we concluded that the association between the negative psychological factors and the mortality risk was independent of socioeconomic factors, other psychological factors, physical function, lifestyle habits, and a history of illness.

On the other hand, the present study also had some limitations. First, we had no information on the prevalence of mental illnesses, such as depression. Second, the sense of *ikigai* among our study subjects may have been altered positively or negatively during the follow-up period. However, we had no information on such changes. Third, we excluded those who failed to respond to the question on whether or not the subjects found a sense of *ikigai*. As compared with the characteristics of those who were included in this study (43,391 subjects), those who did not indicate their response to the question on *ikigai* (2939 subjects) tended to be older (mean age in years: 60.1 versus 65.1) and were more likely to have bad or poor self-rated health (18.4% versus 30.1%), severe or moderate bodily pain (16.7% versus 22.0%), and limitation of physical function (24.2% versus 49.1%). Thus, the association between

ikigai and mortality could have been underestimated, assuming that the missing respondents were in poor health with more pain, limited physical function, and/or older in age.

The increased risk of all-cause mortality among those who did not find a sense of *ikigai* was mainly attributable to an increased risk of mortality from CVD. There have been no reports on the reasons for the increase in the mortality from CVD in subjects lacking a sense of *ikigai* for the time being. However, a previous study reported that subjects with hopelessness tended to have abnormal platelet functions and reduced heart rate variability (6). The negative psychological factors in relationship to *ikigai* was associated with increased serum levels of C-reactive protein and inflammatory cytokines, and decreased serum levels of high-density lipoprotein (24–26)—all of which are known risk markers for CVD mortality.

In conclusion, this population-based prospective, cohort study in Japan demonstrated that the lack of *ikigai* was associated with an increased risk of all-cause mortality. This increase was mainly attributable to an increased mortality from CVD (mainly stroke) and that from external causes.

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Body mass index and cardiovascular disease mortality in Japan: The Ohsaki Study

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ABSTRACT

Objective. Although there is a clear positive association between obesity and the incidence and severity of cardiovascular disease, the association between underweight and cardiovascular disease is unclear. The objective of this study was to examine the relation between body mass index (BMI) and cardiovascular disease in Japan, where the proportion of the population that is underweight is relatively high.

Method. A total of 43,916 Japanese adults (21,003 men and 22,913 women) aged 40 to 79 years who had no history of cancer, ischemic heart disease (IHD), or stroke participated in the baseline survey in 1994. Hazard ratios (HR) and their 95% confidence intervals (CIs) for death due to total cardiovascular disease, all strokes, ischemic stroke, hemorrhagic stroke, and IHD were calculated according to BMI by using Cox's proportional hazards regression models. The 22.5–24.9 kg/m^2 BMI category was used as the reference category in all analyses.

Results. There were U-shaped associations between BMI and total cardiovascular disease, all stroke, hemorrhagic stroke, and IHD mortality, and a J-shaped association between BMI and ischemic stroke mortality. Participants with a BMI <18.5 kg/m^2 had a significantly increased risk of total cardiovascular disease, all stroke, hemorrhagic stroke, and IHD mortality, and the multivariate HR (95% CI) was 1.62 (1.19–2.19), 1.50 (1.02–2.21), 2.11 (1.07–4.17), 1.83 (1.11–3.01), respectively.

Conclusion. Underweight was substantially associated with hemorrhagic stroke and IHD mortality in Japan, while obesity was associated with increased risk of total cardiovascular disease mortality and mortality from individual cardiovascular diseases.

Introduction

Although obesity is an important risk factor for cardiovascular disease (Wilson et al., 2002; Field et al., 2001; Calle et al., 1999; Shaper et al., 1997; Rimm et al., 1995), whether there is the association between underweight and cardiovascular disease remains a matter of controversy.

Several studies in Asia, where the proportion of the population that is underweight is relatively high, have provided data on associations between low Body Mass Index (BMI) and cardiovascular disease, including stroke subtypes and ischemic heart disease (IHD) (Cui et al., 2005; Song et al., 2004; Chen et al., 2006; Oki et al., 2006; Ni Mhurchu et al., 2004; Zhang et al., 2004; Song and Sung, 2001; Gu et al., 2006; Jee et al., 2005). Some of them have reported finding that low BMI was associated with an increased risk of hemorrhagic stroke (Cui et al., 2005; Song et al., 2004), IHD (Cui et al., 2005) and of ischemic stroke (Oki et al., 2006), while other studies reported that it was not associated with an increased risk of ischemic stroke (Cui et al., 2005; Song et al., 2004), hemorrhagic stroke (Oki et al., 2006; Ni Mhurchu et al., 2004), or IHD (Ni Mhurchu et al., 2004; Zhang et al., 2004; Song and Sung, 2001; Jee et al., 2005), and thus that results have been inconsistent.

We therefore conducted a population-based, prospective cohort study among Japanese adults to clearly define the relationships between BMI and total cardiovascular disease mortality and mortality from individual cardiovascular diseases.

Method

Study cohort

The details of the Ohsaki National Health Insurance (NHI) Cohort Study have been described previously (Tsuji et al., 1998; Tsuji et al., 1999; Kuriyama et al., 2004; Kuriyama et al., 2006). In brief, between October and December 1994, we delivered a self-administered questionnaire on various health habits to all NHI beneficiaries aged 40–79 years living in the catchment area of Ohsaki Public Health Center, Miyagi Prefecture, in the northeast region of Japan. Ohsaki Public Health Center is a local government agency that provides preventive health services to the residents of 14 municipalities in Miyagi Prefecture. Of the 54,996 eligible individuals to whom questionnaires were delivered, 52,029 (95%) responded.

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On January 1, 1995, we began the prospectively collecting data on dates of death and withdrawal from NHI by obtaining NHI withdrawal history files from the local NHI Association. We excluded 774 participants because they had withdrawn from NHI before the start of the start of collection of the NHI withdrawal history files, and the remaining 51,255 participants formed the study cohort. The study protocol was reviewed and approved by the Ethics Committee of Tohoku University School of Medicine. We considered the return of the self-administered questionnaire signed by the participant to imply consent to participation in the study.

For current analysis, we excluded participants who died before collection of the NHI claim history files ($n=37$), participants who did not answer the question about body weight and height ($n=3543$). In addition, because of the possibility that atypical diseases associated with both the BMI extremes might have been present, we excluded patients ($n=51$) who were below the 0.05th percentile (below 14.41 kg/m^2 for men; below 13.67 kg/m^2 for women) and above the 99.95th percentile (above 58.46 kg/m^2 for men; above 62.00 kg/m^2 for women).

We also excluded participants who have a history of cancer ($n=1596$), IHD ($n=1322$), or stroke ($n=1048$) in self-reported clinical histories that records were not reviewed. As a result, there were 43,916 subjects of the analysis and among them there was a total of 680 cardiovascular disease deaths.

Self-reported BMI

The self-administered questionnaire included questions on body weight and height and was used as a baseline survey. We used BMI as a measure of total adiposity to assess underweight and obesity. BMI was calculated as body weight divided by the square of body height (kg/m^2). We divided the participants into groups according to following BMI values: <18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, and ≥30.0 kg/m^2 for hazard ratios (HRs) of cardiovascular disease, all stroke, and ischemic stroke, and <18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–27.4, and ≥27.5 kg/m^2 for HRs of hemorrhagic stroke and IHD. We used BMI values of 18.5, 25.0, and 30.0 kg/m^2 to categorize participants, because these numbers are used in the World Health Organization (WHO) weight categories (World Health Organization, 1995). We further divided 18.5–24.9 kg/m^2 into three equal categories, and 25.0–29.9 kg/m^2 into two equal categories. The 22.5–24.9 kg/m^2 BMI category was used as the reference category in all analyses.

We had previously evaluated the validity of self-reported body weight and height (Kuriyama et al., 2002). In brief, in 1995 the body weight and height of 14,883 participants, who were a subsample of the cohort, were measured during a basic health examination provided by the local governments. The Pearson's correlation coefficient (r) for the self-reported values and measured values was 0.96 ($P<0.0001$) for body weight, 0.93 ($P<0.0001$) for body height, and 0.88 ($P<0.0001$) for BMI. Thus, the self-reported heights and weights in the baseline questionnaire were considered to be sufficiently valid.

Follow-up

The end points were cardiovascular disease mortality, stroke mortality, and IHD mortality. We followed up the participants for mortality and emigration by reviewing the NHI withdrawal history files. When a participant was withdrawn from the NHI system because of death, emigration, or employment, the date of withdrawal and the reason were coded on the NHI withdrawal history files. Because we were unable to obtain subsequent information on the participants who withdrew from the NHI, we discontinued their follow-up.

For deaths thus identified, we investigated cause of death by reviewing the death certificates filed at Ohsaki Public Health Center. Cause of death was coded by trained physicians according to the International Classification of Diseases and Related Health Problems, the Tenth Revision [ICD-10] (World Health Organization, 1992). We identified deaths from cardiovascular disease (codes I20–I25 or I60–I69), all strokes (codes I60–I69), ischemic strokes (codes I63), hemorrhagic strokes (codes I61–I62), and IHD (codes I20–I25).

Statistical analysis

Between 1 January 1995 and 31 December 2001, we prospectively counted the number of person-years of follow-up for each participant from the beginning of follow-up until the date of death, withdrawal from the NHI, or the end of the follow-up, whichever occurred first. The total number of person-years accrued was 272,863.

We used the Cox proportional hazards regression analysis and SAS software (SAS Institute Inc., 2004) to calculate HRs and 95% confidence intervals (CIs) for cardiovascular disease mortality according to category of BMI and to adjust for

Table 1
Baseline characteristics according to Body Mass Index (BMI) categories, the Ohsaki Study in Japan, 1995–2001

Variables	BMI (kg/m^2)														
	<18.5 ($n=1627$)		18.5–19.9 ($n=3111$)		20.0–22.4 ($n=12257$)		22.5–24.9 ($n=14259$)		25.0–27.4 ($n=8280$)		27.5–29.9 ($n=3156$)		≥30.0 ($n=1226$)		P value[a]
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Sex															
Male	718	44.1	1580	50.8	6293	51.3	7076	49.6	3723	45.0	1209	38.3	404	33.0	<.0001
Female	909	55.9	1531	49.2	5964	48.7	7183	50.4	4557	55.0	1947	61.7	822	67.0	
Age±SD (years)	64.4±10.7		61.0±11.0		60.1±10.6		59.7±10.1		59.9±9.8		59.6±9.8		60.0±10.0		<.0001
Weight change since 20 years old															
Lost ≥5 kg	842	55.9	1118	38.6	2525	23.2	1292	10.7	310	4.3	93	3.3	27	2.4	<.0001
No change	648	43.1	1701	58.8	7194	66.0	6050	50.0	1631	22.8	332	11.7	74	6.6	
Gained ≥5 kg	15	1.0	74	2.6	1185	10.9	4750	39.3	5207	72.8	2413	85.0	1018	91.0	
Smoking status															
Never	684	50.5	1210	46.4	5093	49.0	6444	53.4	3983	57.8	1632	62.5	661	66.6	<.0001
Former	195	14.4	352	13.5	1481	14.3	1823	15.1	1106	16.0	341	13.1	109	11.0	
Current (<20 cigarettes/day)	235	17.4	443	17.0	1511	14.5	1381	11.4	609	8.8	187	7.2	59	5.9	
Current (≥20 cigarettes/day)	240	17.7	604	23.2	2302	22.2	2419	20.0	1194	17.3	451	17.3	164	16.5	
Alcohol drinking															
Never	698	49.6	1170	42.8	4573	42.5	5337	42.8	3263	45.6	1331	49.5	557	54.0	<.0001
Former	181	12.9	256	9.4	833	7.7	837	6.7	484	6.8	172	6.4	94	9.1	
Current (<45.6 g ethanol/day)	350	24.9	779	28.5	3300	30.7	3960	31.8	2190	30.6	766	28.5	255	24.7	
Current (≥45.6 g ethanol/day)	177	12.6	527	19.3	2051	19.1	2325	18.7	1211	16.9	422	15.7	125	12.1	
Hypertension															
Yes	283	17.4	584	18.8	2459	20.1	3584	25.1	2622	31.7	1184	37.5	521	42.5	<.0001
No	1344	82.6	2527	81.2	9798	79.9	10675	74.9	5658	68.3	1972	62.5	705	57.5	
Diabetes mellitus															
Yes	86	5.3	144	4.6	672	5.5	879	6.2	552	6.7	224	7.1	115	9.4	<.0001
No	1541	94.7	2967	95.4	11585	94.5	13380	93.8	7728	93.3	2932	92.9	1111	90.6	
Walking duration															
<1 h	892	61.2	1485	51.8	5757	51.5	6836	52.4	4250	56.2	1707	59.3	688	62.4	<.0001
≥1 h	566	38.8	1382	48.2	5414	48.5	6206	47.6	3308	43.8	1172	40.7	414	37.6	
Education															
Until age up to 15 years	931	61.2	1761	59.2	6832	58.2	7974	58.2	4774	60.0	1881	62.4	774	66.9	<.0001
Until age 16–18 years	472	31.0	972	32.7	3943	33.6	4630	33.8	2619	32.9	926	30.7	320	27.7	
Until age ≥19 years	118	7.8	244	8.2	959	8.2	1090	8.0	567	7.1	208	6.9	63	5.4	

[a] P values were calculated by chi-squared test (categorical variables), or ANOVA (continuous variables).

confounding factors. The proportional hazards assumptions were tested graphically before we carried out the Cox regression analyses. Interaction between sex and BMI category was tested by addition of cross-product terms to the multivariate model. The association between BMI category and cardiovascular disease mortality did not vary by sex. The p-values for interaction between sex and BMI categories for cardiovascular disease, all stroke, ischemic stroke, hemorrhagic stroke, and IHD were 0.22, 0.11, 0.20, 0.85, and 0.95, respectively. All reported P values are two-tailed, and differences at $P<0.05$ were considered statistically significant.

We considered the following variables to be potential confounders: age (in years), sex, smoking status (never, former, 1–19 cigarettes/day, ≥20 cigarettes/day), drinking status (never, former, <45.6 g ethanol/day, ≥45.6 g ethanol/day), walking duration (≥1 h/day, <1 h/day), and education (up to 15 years of age, up to 16–18 years of age, up to ≥19 years of age). We also adjusted for weight change since 20 years old of age (5 kg or more loss, no change, 5 kg or more gain), to account for weight change due to subclinical diseases. Walking duration was used as measurement of physical activity, because walking is the most common type of physical activity among middle-aged and older individuals in rural Japan. The validity and reproducibility of the questionnaire in regard to walking time have been reported elsewhere (Tsubono et al., 2002). We also analyzed the interactions between walking duration and BMI categories, tested by addition of cross-product terms to the multivariate model. The association between BMI categories and cardiovascular disease mortality did not differ according to walking status (P for interaction = 0.20). We repeated all analysis after excluding of participants had died from cardiovascular disease during the first three years of follow-up. Since we considered history of hypertension and diabetes mellitus as intermediate in the etiologic pathway between BMI and cardiovascular disease mortality, we did not include them in the model.

Results

The baseline characteristics according to BMI category are shown in Table 1. The proportion of females was higher in the high BMI categories ($P<0.0001$). The participants with a BMI ≥30.0 kg/m^2 were more hypertensive, more diabetic, less educated, smoked less, drank less, and walked less than the participants in the lower BMI categories ($P<0.0001$). The participants with a BMI <18.5 kg/m^2 were older, less hypertensive, and less diabetic than those in the higher BMI categories ($P<0.0001$).

Table 2 shows the age, sex-adjusted and multivariate-adjusted HRs for cardiovascular disease mortality according to BMI category. There was a U-shaped association between BMI and cardiovascular disease mortality. After adjustment for age, sex, smoking status, alcohol drinking, walking duration, and education, the multivariate HR (95% CI) for cardiovascular disease mortality relative to a BMI of 22.5–24.9 kg/m^2 was 1.81 (1.35–2.42) for BMI <18.5 kg/m^2 1.45 (1.11–1.90) for BMI of 18.5–19.9 kg/m^2, and 1.74 (1.15–2.63) for BMI ≥30.0 kg/m^2.

After further adjustment for weight change since 20 years of age, the multivariate HRs for cardiovascular disease mortality decreased in the BMI categories <18.5 kg/m^2 and 18.5–19.9 kg/m^2, but a U-shaped association was still observed. Relative to a BMI of 22.5–24.9 kg/m^2, the multivariate HR was 1.62 (1.19–2.19) for BMI <18.5 kg/m^2, 1.34 (1.01–1.76) for BMI of 18.5–19.9 kg/m^2, and 1.88 (1.23–2.87) for BMI ≥30.0 kg/m^2.

The BMI category had U-shaped relations with total cardiovascular disease, and all stroke mortality. In hemorrhagic stroke mortality and IHD mortality, there was increased risk in the low categories of BMI, and a tendence for an increased risk in the high categories of BMI. In addition, for ischemic stroke mortality, there was an increased risk tendency for the lowest BMI category, and an increased risk in the highest BMI category. Participants with a BMI ≥30.0 kg/m^2 had an increased risk of all stroke mortality, and ischmeic stroke mortality, and the multivariate HR (95% CI) was 1.74 (1.04–2.89), and 2.28 (1.13–4.61) respectively. Participants with a BMI <18.5 kg/m^2 had significantly increased risk of all stroke mortality, hemorrhagic stroke mortality, and IHD mortality, and the multivariate HR (95% CI) was 1.50 (1.02–2.21), 2.11 (1.07–4.17), 1.83 (1.11–3.01), respectively. In addition, we adjusted for dietary intake (salt intake, beef, green and yellow vegetable, and fruit consumption), marital status, and job status, accompany multivariate HRs. However, result did not change substantially as a consequence (data not shown).

Table 2
Hazard Ratio (HR) and 95% Confidence Interval (CI) of cardiovascular disease mortality according to Body Mass Index (BMI) categories, the Ohsaki Study in Japan, 1995–2001

Variables	BMI (kg/m^2)						
	<18.5	18.5–19.9	20.0–22.4	22.5–24.9	25.0–27.4	27.5–29.9	≥30.0
Person-years	9623	19013	75625	89271	51957	19780	7594
CVD							
Case, n	60	76	187	192	95	44	26
Age, sex-adjusted HR (95%CI)	1.94 (1.45–2.60)	1.52 (1.17–1.99)	1.05 (0.86–1.29)	1.00	0.90 (0.70–1.15)	1.17 (0.84–1.62)	1.81 (1.20–2.73)
Multivariate HR1 (95%CI)[a]	1.81 (1.35–2.42)	1.45 (1.11–1.90)	1.03 (0.85–1.27)	1.00	0.90 (0.70–1.15)	1.16 (0.83–1.61)	1.74 (1.15–2.63)
Multivariate HR2 (95%CI)[b]	1.62 (1.19–2.19)	1.34 (1.01–1.76)	0.98 (0.79–1.21)	1.00	0.94 (0.73–1.21)	1.19 (0.85–1.66)	1.88 (1.23–2.87)
All strokes							
Case, n	36	54	126	132	72	29	18
Age, sex-adjusted HR (95%CI)	1.68 (1.16–2.43)	1.58 (1.15–2.16)	1.03 (0.81–1.32)	1.00	0.98 (0.74–1.31)	1.10 (0.73–1.64)	1.77 (1.08–2.91)
Multivariate HR1 (95%CI)[a]	1.59 (1.09–2.30)	1.54 (1.12–2.11)	1.03 (0.80–1.31)	1.00	0.98 (0.73–1.30)	1.08 (0.72–1.62)	1.69 (1.03–2.77)
Multivariate HR2 (95%CI)[b]	1.50 (1.02–2.21)	1.48 (1.06–2.05)	1.00 (0.78–1.29)	1.00	0.99 (0.74–1.34)	1.07 (0.71–1.62)	1.74 (1.04–2.89)
Ischemic stroke							
Case, n	17	21	61	62	34	13	10
Age, sex-adjusted HR (95%CI)	1.41 (0.82–2.42)	1.15 (0.70–1.90)	1.01 (0.71–1.44)	1.00	1.04 (0.68–1.58)	1.13 (0.62–2.06)	2.28 (1.17–4.47)
Multivariate HR1 (95%CI)[a]	1.33 (0.78–2.29)	1.11 (0.68–1.83)	1.00 (0.70–1.43)	1.00	1.02 (0.67–1.55)	1.09 (0.60–1.99)	2.13 (1.09–4.18)
Multivariate HR2 (95%CI)[b]	1.17 (0.67–2.05)	1.02 (0.61–1.70)	0.95 (0.66–1.36)	1.00	1.07 (0.69–1.64)	1.15 (0.62–2.13)	2.28 (1.13–4.61)
Hemorrhagic stroke							
Case, n	12	18	36	40	19	15	
Age, sex-adjusted HR (95%CI)	2.25 (1.18–4.31)	1.91 (1.09–3.34)	1.02 (0.65–1.59)	1.00	0.85 (0.49–1.46)	1.35 (0.74–2.44)	
Multivariate HR1 (95%CI)[a]	2.13 (1.11–4.09)	1.87 (1.07–3.27)	1.01 (0.64–1.59)	1.00	0.84 (0.49–1.45)	1.31 (0.72–2.39)	
Multivariate HR2 (95%CI)[b]	2.11 (1.07–4.17)	1.81 (1.01–3.24)	0.98 (0.62–1.55)	1.00	0.90 (0.51–1.57)	1.45 (0.77–2.72)	
Ischemic heart disease							
Case, n	24	22	61	60	23	23	
Age, sex-adjusted HR (95%CI)	2.54 (1.57–4.09)	1.41 (0.86–2.30)	1.10 (0.77–1.56)	1.00	0.71 (0.44–1.15)	1.45 (0.89–2.34)	
Multivariate HR1 (95%CI)[a]	2.28 (1.41–3.68)	1.29 (0.79–2.10)	1.06 (0.74–1.51)	1.00	0.72 (0.44–1.17)	1.48 (0.91–2.41)	
Multivariate HR2 (95%CI)[b]	1.83 (1.11–3.01)	1.08 (0.65–1.78)	0.94 (0.65–1.36)	1.00	0.81 (0.49–1.33)	1.74 (1.04–2.91)	

[a] Multivariate HR1 (95%CI) has been adjusted for age, sex, smoking status (never, former, 1–19 cigarettes/day, ≥20 cigarettes/day), alcohol drinking (never, former, <45.6 g ethanol/day, ≥45.6 g ethanol/day), walking duration (≥1 h, <1 h) and education (until age up to 15 years, until age 16–18 years, until age ≥19 years).

[b] Multivariate HR2 (95%CI) has been adjusted for age, sex, smoking status (never, former, 1–19 cigarettes/day, ≥20 cigarettes/day), alcohol drinking (never, former, <45.6 g ethanol/day, ≥45.6 g ethanol/day), walking duration (≥1 h, <1 h), education (until age up to 15 years, until age 16–18 years, until age ≥19 years) and weight change since 20y old (lost 5 kg or more, no change, gained 5 kg or more).

After excluding the 267 participants who died from cardiovascular disease in the first 3 years of follow-up, the point estimate of the HR for cardiovascular disease among participants with a BMI <18.5 kg/m^2 was essentially unchanged. Participants with a BMI <18.5 kg/m^2 had an increased risk of cardiovascular disease, all stroke, hemorrhagic stroke, and IHD mortality, and the multivariate HR (95% CI) was 1.71 (1.17–2.49), 1.64 (1.03–2.61), 2.22 (0.95–5.21), and 1.87 (0.98–3.58), respectively.

The results of the analysis of the association between BMI and cardiovascular disease mortality among participants with a BMI <18.5 kg/m^2 stratified by sex were similar to the results of main analysis. The multivariate HR for cardiovascular disease, all stroke, and IHD mortality was 1.91 (1.29–2.81), 1.62 (0.97–2.70), 2.47 (1.35–4.52), respectively for men, and 1.68 (1.07–2.63), 1.51 (0.88–2.62), and 2.12 (0.96–4.64), respectively for women. The association between BMI and cardiovascular disease mortality was not significantly modified by smoking status (P for interaction >0.05).

Discussion

The results of this prospective cohort study indicated that underweight was significantly associated with increased risk of hemorrhagic stroke mortality and IHD mortality, but not of ischemic stroke mortality, while obesity was associated with increased risk of hemorrhagic stroke, IHD, and ischemic stroke mortality. These increases in risk among the underweight participants persisted after adjustment for weight change since 20 years of age and after exclusion of the participants who died from cardiovascular disease in the first 3 years of follow-up, which should minimize the impact of underlying diseases.

An excess risk of hemorrhagic stroke has been reported among Japanese with a BMI <18.5 kg/m^2 (Cui et al., 2005) and among Korean men with a BMI <18.0 kg/m^2 (Song et al., 2004). Our results were consistent with these studies. Several studies indicated an association between low serum total cholesterol values and hemorrhagic stroke (Iso et al., 1989; Jacobs et al., 1992). Because of the positive correlation between cholesterol values and BMI, these studies also indicated that low BMI increases the risk of hemorrhagic stroke.

The reported excess risk of IHD mortality among Japanese women with a BMI <18.5 kg/m^2 (Cui et al., 2005) and Chinese men with a BMI <18.0 kg/m^2 (Chen et al., 2006) is consistent with our results. By contrast, the lowest risk of IHD was observed in the lowest BMI category in two studies conducted in Korea accounting for weight loss (Song and Sung, 2001; Jee et al., 2005). What would explain the difference in the results for the risk of IHD in the lowest BMI category? It may be that the endpoint in the Japanese study (Cui et al., 2005), the Chinese study (Chen et al., 2006), and our own study was mortality, whereas it was incidence in the Korean studies (Song and Sung, 2001; Jee et al., 2005). Individuals with IHD who have a low BMI may be too weak to survive, and if that were true, case-fatality would be higher among them. That mechanism may be responsible for the difference in the results for risk of IHD mortality in the lowest BMI category.

Other mechanisms have been suggested to explain the risk of cardiovascular disease in underweight persons. In previous studies individuals with a low BMI have been found to have an increased risk of several cardiovascular abnormalities, reduced ventricular mass (de Simone et al., 1994), valvular dysfunction (Swenne et al., 2001), electrocardiographic changes (Garnettet al., 1969), and cardiac myofibril damage (Danesh et al., 1997). Individuals with a low BMI tend to have compromised immunity (Shor and Phillips, 1997; Epstein et al., 1999) and to beat increased risk of chronic infection, which may contribute to IHD (Zhu et al., 2001; Kiechl et al., 2001; Marcos et al., 1997; Field et al., 1991; Garg et al., 2004).

Study limitations and strengths

Our study has several limitations. First, the BMI values were based on self-report. Although a study of a Western population demonstrated that the small error that exists is generally a systematic overestimation of height and underestimation of weight, which leads underestimation of BMI, especially at higher weights (Niedhammer et al., 2000), it is uncertain whether the same was true in our population. Therefore, we were unable to estimate the effect of self-reported weight and height on our estimates of the effects of excess weight on cardiovascular disease risk. Second, we excluded 3543 subjects who did not respond to the questions on self-reported height or weight. We compared these 3543 individuals with 43,916 subjects of the analysis. In this group, 123 cases of cardiovascular disease death, 88 cases of all stroke death, 39 cases of ischemic stroke death, 25 cases of hemorrhagic stroke death, and 35 cases of IHD death were diagnosed. The multivariate HRs (95% CIs) for cardiovascular diseases, all stroke, ischemic stroke, hemorrhagic stroke, and IHD mortality upon comparison with subjects who provided a complete report, were 0.94 (0.68–1.30), 1.07 (0.71–1.60), 0.89 (0.49–1.61), 1.00 (0.48–2.07), and 0.75 (0.43–1.30), respectively. The HRs were not statistically significant. Third, there was a possibility of residual confounding by smoking status. The association between BMI and cardiovascular disease mortality was not significantly modified by smoking status (P for interaction >0.05). However, this issue could not be addressed in stratified analysis by smoking status due to the insufficient numbers of deaths.

Our study also has several strengths. First, we followed up a large number of participants over a 7-year period, and the study subjects were highly representative of the target population, because the response rate was 95%. Second, the cohort contained an adequate proportion of subjects who with a low BMI and normal BMI. The prevalence of BMI = 18.5–24.9 kg/m^2 in the cohort was 67% and much higher than in Western populations (less than 30% in Framingham study [Wilson et al., 2002]). Third, we adjusted for weight change since 20 years of age and conducted an analysis after exclusion of the first 3 years of follow-up, which should have minimized the impact of underlying diseases.

Conclusion

Underweight was found to be significantly associated with increased risk of hemorrhagic stroke mortality and IHD mortality, while obesity was associated with increased risk of hemorrhagic stroke, IHD mortality, and ischemic stroke mortality. Our data indicate that greater attention should be paid to underweight in order to promote public health, at least in countries where a large or moderately high proportion of the population is still underweight.

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