3．参加対象者及び会場について

	参加者※1	男性	女性	会場	対象範囲※2
特定高齢者	１７名	６名	１１名	岩沼市総合福祉センター	岩沼小学校学区
要支援者	７名	１名	６名	デイサービスさとのもり	デイサービスさとのもり利用者

※1　参加者はやむを得ない事由により、特定高齢者14名・要支援者6名で終了した。

※2　岩沼市社会福祉協議会の協力のもとで地域包括支援センターの対象範囲及びデイサービスを選定した。

4．モデル事業への参加及び送迎について

○同意書　①事業用チラシ　②事業説明書　③参加同意書
　　④研究協力のお願い　⑤研究協力同意書

・特定高齢者への同意取付　⇒　市保健師、市歯科衛生士、地域包括支援センター職員

・要支援者への同意取付　⇒　デイサービス職員、地域包括支援センター職員

○傷害保険の付帯【特定高齢者】

○各戸方式の送迎【特定高齢者】

5．主要ツールについて

◎総合

・介護予防手帳

・健幸だより（対象者家族向）

◎口腔機能向上用

・咀嚼力判定ガム

・岩沼健幸体操（口腔体操）

◎栄養改善用

・食生活診断シート[岩沼市管理栄養士作成システム]

・バランスBINGO

・ご長寿パン、大地のスコーン・きなごまクッキー

・４つのお皿のランチョンマット

6．評価方法について

◎主観的健康感

◎口腔機能向上、栄養改善のアセスメント・評価シート

◎顔写真（事業前後）

◎SF８　[→東北大学へ依頼]

7．教室の構成について

☆講義形態（講習型）　⇒　サロン的形態（体験型）

・特定高齢者　　口腔(運動)＋**休憩**＋栄養＋口腔(清掃)

	時間帯	メインテーマ	口腔機能向上	栄養改善
第1回（10/1）	10：00～13：00		アセスメント、 寸劇『息・いき生き』	アセスメント、 「外食の選び方その1」
第2回（10/8）	10：00～13：15	舌	「舌の観察･口腔乾燥と味覚チェック」「唾液腺マッサージ」	「若さを保つ肉・魚・たまご・大豆のおかず」「はやくて簡単バランス食その1」
第3回（10/22）	10：00～13：15	唾液	「口腔内エステ」「唾液腺マッサージ」	「エネルギーのもと、ごはん」「はやくて簡単バランス食その2」
第4回（11/5）	10：00～13：10	咀嚼	「かみかみ30」「ゴックンらくらく体操」	「からだの調子をよくする野菜のおかず」「楽しんでつくるバランス食その1」
第5回（11/19）	10：00～13：00	嚥下	「すっきりゴックン」「唾液腺マッサージ」	「朝食は一日のはじまり」「楽しんでつくるバランス食その2」
第6回（12/3）	10：00～13：10	歯	歯科医師講話、「歯みがきのススメと虫歯の実験」「クチミズキ体操」	「お通じは健康のバロメーター」「ひと手間かけたバランス食その1」
第7回（12/17）	10：00～13：10	笑顔	「すてきな笑顔をつくろう」「パタカラ体操」	「上手にとりたい油と脂」「ひと手間かけたバランス食その2」
第8回（12/22）	10：00～13：30		評価、「ゴックンらくらく体操」、振り返り	評価、「間食の取り方」「外食の選び方その2」、振り返り

・要支援者

	時間帯（目安）	メインテーマ	口腔機能向上	栄養改善
第1回（9/24）	9:30～14:30		アセスメント	アセスメント
第2回（10/1）	11:00～14:30	舌	「舌の観察･口腔乾燥と味覚チェック」「唾液腺マッサージ」	「ワンポイントアドバイス」 (一汁三菜でバランスの良い食事)
第3回（10/15）	11:50～14:30	唾液	「口腔内エステ」「唾液腺マッサージ」	「ワンポイントアドバイス」 (口腔乾燥のための食事ポイント)
第4回（10/29）	11:00～14:30	咀嚼	「かみかみ30」「ゴックンらくらく体操」	「楽しんでつくろうご長寿パン」「ワンポイントアドバイス」
第5回（11/12）	11:50～14:30	嚥下	「すっきりゴックン」「クチミズキ体操」	「体の調子を良くする野菜のおかず」「ワンポイントアドバイス」
第6回（11/26）	11:00～14:30	歯	「歯みがきのススメと虫歯の実験」「パタカラ体操」	「若さを保つ肉・魚・たまご・大豆のおかず」「ワンポイントアドバイス」
第7回（12/10）	11:50～14:30	笑顔	「すてきな笑顔をつくろう」「ゴックンらくらく体操」	「エネルギーのもと、ごはん」「ワンポイントアドバイス」
第8回（12/24）	9:30～14:30		評価、「ゴックンらくらく体操」	評価、「間食の取り方」

Ⅳ．研究成果の刊行に関する一覧表

（1）論文発表

1) Sone T, Nakaya N, Ohmori K, Shimazu T, Higashiguchi M, Kakizaki M, Kikuchi N, Kuriyama S, Tsuji I.
Sense of Life Worth Living (ikigai) and Mortality in Japan: The Ohsaki Study (Sense of Life WorthLiving [ikigai] and Mortality).
Psychosomatic Medicine, 2008;70:709-715.

2) Funada S, Shimazu T, Kakizaki M, Kuriyama S, Sato Y, Matsuda-Ohmori K, Nishino Y, Tsuji I.
Body mass index and cardiovascular disease mortality in Japan: The Ohsaki Study.
Preventive Medicine, 2008;47(1):66-70.

3) 東口みづか，中谷直樹，大森　芳，島津太一，曽根稔雅，寶澤　篤，栗山進一，辻　一郎.
低栄養と介護保険認定・死亡リスクに関するコホート研究：鶴ヶ谷プロジェクト.
日本公衆衛生雑誌，2008;55:433-439.

4) Hayashi A, Kayama M, Ando K, Ono M, Suzukamo Y, Michimata A, Onishi Akiyama M, Fukuhara S, Izumi S.
Analysis of Subjective Evaluations of the Functions of Tele-Coaching Intervention in Patients with Spinocerebellar Degeneration.
NeuroRehabilitation, 2008;23(2): 159-69.

5) 出江紳一，鈴鴨よしみ.
コーチング技術を応用した神経難病患者に対する心理社会的介入.
別冊・医学のあゆみ，2008:65-70.

6) 出江紳一，鈴鴨よしみ，道又　顕，田邊素子.
コーチング.
臨床リハビリテーション，2008;17(9):886-888.

7) 小坂　健.
口腔ケアの実際.
調剤と情報，2008;15:146-149.

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

Toshimasa Sone, OTR, BA, Naoki Nakaya, PhD, Kaori Ohmori, MD, PhD, Taichi Shimazu, MD, PhD, Mizuka Higashiguchi, PhD, Masako Kakizaki, MS, Nobutaka Kikuchi, MD, PhD, Shinichi Kuriyama, MD, PhD, and Ichiro Tsuji, MD, PhD

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.

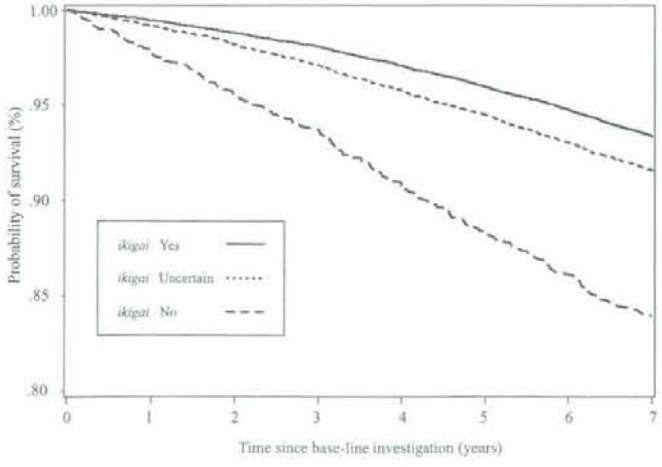

Figure 1. Kaplan-Meier curves of all-cause mortality according to *ikigai* (n = 43,391).

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 (≤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, 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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REFERENCES

1. Maier H, Smith J. Psychological predictors of mortality in old age. J Gerontol B Psychol Sci Soc Sci 1999;54:P44–P54.
2. Meinow B, Kareholt I, Parker MG, Thorslund M. The effect of the duration of follow-up in mortality analysis: the temporal pattern of different predictors. J Gerontol B Psychol Sci Soc Sci 2004;59:S181–9.
3. Koivumaa-Honkanen H, Honkanen R, Viinamaki H, Heikkila K, Kaprio J, Koskenvuo M. Self-reported life satisfaction and 20-year mortality in healthy Finnish adults. Am J Epidemiol 2000;152:983–91.
4. Gustafsson TM, Isacson DG, Thorslund M. Mortality in elderly men and women in a Swedish municipality. Age Ageing 1998;27:585–93.
5. Everson SA, Goldberg DE, Kaplan GA, Cohen RD, Pukkala E, Tuomilehto J, Salonen JT. Hopelessness and risk of mortality and incidence of myocardial infarction and cancer. Psychosom Med 1996;58: 113–21.
6. Stern SL, Dhanda R, Hazuda HP. Hopelessness predicts mortality in older Mexican and European Americans. Psychosom Med 2001;63: 344–51.
7. Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. J Health Soc Behav 1997;38:21–37.
8. DeSalvo KB, Bloser N, Reynolds K, He J, Muntner P. Mortality prediction with a single general self-rated health question. A meta-analysis. J Gen Intern Med 2006;21:267–75.
9. Singh-Manoux A, Gueguen A, Martikainen P, Ferrie J, Marmot M, Shipley M. Self-rated health and mortality: short- and long-term associations in the Whitehall II study. Psychosom Med 2007;69: 138–43.
10. Seki N. Relationships between walking hours, sleeping hours, meaningfulness of life (*ikigai*) and mortality in the elderly: prospective cohort study. Nippon Eiseigaku Zasshi 2001;56:535–40. (in Japanese)
11. Sakata K, Yoshimura N, Tamaki J, Hashimoto T. Ikigai, sutoresu, tayorarekan to jyunkankishikkan, akuseishinseibutsu shibou tono kanren. Journal of Health and Welfare Statistics 2002;49:14–8. (in Japanese)
12. Nakanishi N, Fukuda H, Takatorige T, Tatara K. Relationship between self-assessed masticatory disability and 9-year mortality in a cohort of community-residing elderly people. J Am Geriatr Soc 2005;53:54–8.
13. Pijls LT, Feskens EJ, Kromhout D. Self-rated health, mortality, and chronic diseases in elderly men. The Zutphen study, 1985–1990. Am J Epidemiol 1993;138:840–8.
14. Benjamins MR, Hummer RA, Eberstein IW, Nam CB. Self-reported health and adult mortality risk: an analysis of cause-specific mortality. Soc Sci Med 2004;59:1297–306.
15. Anda R, Williamson D, Jones D, Macera C, Eaker E, Glassman A, Marks J. Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of U.S. adults. Epidemiology 1993;4:285–94.
16. Heidrich J, Liese AD, Lowel H, Keil U. Self-rated health and its relation to all-cause and cardiovascular mortality in southern Germany. Results from the MONICA Augsburg cohort study 1984–1995. Ann Epidemiol 2002;12:338–45.
17. Wakai K, Kojima M, Nishio K, Suzuki S, Niwa Y, Lin Y, Kondo T, Yatsuya H, Tamakoshi K, Yamamoto A, Tokudome S, Toyoshima H, Tamakoshi A for the JACC Study Group. Psychological attitudes and risk of breast cancer in Japan: a prospective study. Cancer Causes Control 2007;18:259–67.
18. Shinmura I. Koujien (Japanese dictionary). 3rd ed. Tokyo, Japan: Iwanamishoten; 1987.
19. Tsuji I, Nishino Y, Ohkubo T, Kuwahara A, Ogawa K, Watanabe Y, Tsubono Y, Bando T, Kanemura S, Izumi Y, Sasaki A, Fukao A, Nishikori M, Hisamichi S. A prospective cohort study on National Health Insurance beneficiaries in Ohsaki, Miyagi Prefecture, Japan: study design, profiles of the subjects and medical cost during the first year. J Epidemiol 1998;8:258–63.
20. Tsuji I, Kuwahara A, Nishino Y, Ohkubo T, Sasaki A, Hisamichi S. Medical cost for disability: a longitudinal observation of national health insurance beneficiaries in Japan. J Am Geriatr Soc 1999;47:470–6.
21. Anzai Y, Kuriyama S, Nishino Y, Takahashi K, Ohkubo T, Ohmori K, Tsubono Y, Tsuji I. Impact of alcohol consumption upon medical care utilization and costs in men: 4-year observation of National Health Insurance beneficiaries in Japan. Addiction 2005;100:19–27.
22. Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, Tsubono Y, Tsuji I. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA 2006;296:1255–65.
23. World Health Organization. International Statistical Classification of Diseases and Related Health Problems. 10th ed. Geneva, Switzerland: World Health Organization; 1992.
24. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. J Psychosom Res 2002;53:897–902.
25. Lekander M, Elofsson S, Neve IM, Hansson LO, Unden AL. Self-rated health is related to levels of circulating cytokines. Psychosom Med 2004;66:559–63.
26. Horsten M, Wamala SP, Vingerhoets A, Orth-Gomer K. Depressive symptoms, social support, and lipid profile in healthy middle-aged women. Psychosom Med 1997;59:521–8.

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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 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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References

Calle, E.E., Thun, M.J., Petrelli, J.M., et al., 1999. Body-mass index and mortality in a prospective cohort of U.S. adults. N. Engl. J. Med. 341, 1097–1105.
Chen, Z., Yang, G., Zhou, M., et al., 2006. Body mass index and mortality from ischaemic heart disease in a lean population: 10 year prospective study of 220,000 adult men. Int. J. Epidemiol. 35, 141–150.
Cui, R., Iso, H., Toyoshima, H., JACC Study Group, et al., 2005. Body mass index and mortality from cardiovascular disease among Japanese men and women: the JACC study. Stroke 36, 1377–1382.
Danesh, J., Collins, R., Peto, R., 1997. Chronic infections and coronary heart disease: is there a link? Lancet 350, 430–436.
de Simone, G., Scalfi, L., Galderisi, M., et al., 1994. Cardiac abnormalities in young women with anorexia nervosa. Br. Heart J. 71, 287–292.
Epstein, S.E., Zhou, Y.F., Zhu, J., 1999. Infection and atherosclerosis: emerging mechanistic paradigms. Circulation 100, 20–28.
Field, C.J., Gougeon, R., Marliss, E.B., 1991. Changes in circulating leukocytes and mitogen responses during very-low-energy all-protein reducing diets. Am. J. Clin. Nutr. 54, 123–129.

Field, A.E., Coakley, E.H., Must, A., et al., 2001. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch. Intern. Med. 161, 1581–1586.
Garg, A., 2004. Acquired and inherited lipodystrophies. N. Engl. J. Med. 350, 1220–1234.
Garnett, E.S., Barnard, D.L., Ford, J., et al., 1969. Gross fragmentation of cardiac myofibrils after therapeutic starvation for obesity. Lancet 1, 914–916.
Gu, D., He, J., Duan, X., et al., 2006. Body weight and mortality among men and women in China. JAMA 295, 776–783.
Iso, H., Jacobs Jr., D.R., Wentworth, D., et al., 1989. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. N. Engl. J. Med. 320, 904–910.
Jacobs, D., Blackburn, H., Higgins, M., et al., 1992. Report of the Conference on Low Blood Cholesterol: Mortality Associations. Circulation 86, 1046–1060.
Jee, S.H., Pastor-Barriuso, R., Appel, L.J., et al., 2005. Body Mass Index and incident ischemic heart disease in South Korea men and women. Am. J. Epidemiol. 162, 42–48.
Kiechl, S., Egger, G., Mayr, M., et al., 2001. Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study. Circulation 103, 1064–1070.
Kuriyama, S., Hozawa, A., Ohmori, K., et al., 2004. Joint impact of health risks on health care charges: 7-year follow-up of National Health Insurance beneficiaries in Japan (the Ohsaki Study). Prev. Med. 39, 1194–1199.
Kuriyama, S., Shimazu, T., Ohmori, K., et al., 2006. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA. 296, 1255–1265.
Kuriyama, S., Tsuji, I., Ohkubo, T., et al., 2002. Medical care expenditure associated with body mass index in Japan: the Ohsaki Study. Int. J. Obes. Relat. Metab. Disord. 26, 1069–1074.
Marcos, A., Varela, P., Toro, O., et al., 1997. Interactions between nutrition and immunity in anorexia nervosa: a 1-y follow-up study. Am. J. Clin. Nutr. 66, 485S–490S.
Niedhammer, I., Bugel, I., Bonenfant, S., et al., 2000. Validity of self-reported weight and height in the French GAZEL cohort. Int. J. Obes. Relat. Metab. Disord 24, 1111–1118 Sep.
Ni Mhurchu, C., Rodgers, A., Pan, W.H., et al., 2004. Body mass index and cardiovascular disease in the Asia-Pacific Region: an overview of 33 cohorts involving 310,000 participants. Int. J. Epidemiol. 33, 751–758.
Oki, I., Nakamura, Y., Okamura, T., et al., 2006. Body mass index and risk of stroke mortality among a random sample of Japanese adults: 19-year follow-up of NIPPON DATA80. Cerebrovasc Dis. 22, 409–415.
Rimm, E.B., Stampfer, M.J., Giovannucci, E., et al., 1995. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. Am. J. Epidemiol. 141, 1117–1127.
SAS Institute Inc., 2004 SAS Institute Inc., SAS/STAT 9.1 User's Guide, SAS Institute Inc, Cary, NC (2004).
Shaper, A.G., Wannamethee, S.G., Walker, M., 1997. Body weight: implications for the prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of middle aged men. BMJ. 314, 1311–1317.
Shor, A., Phillips, J.I., 1999. Chlamydia pneumoniae and atherosclerosis. JAMA 282, 2071–2073.
Song, Y.M., Sung, J., 2001. Body mass index and mortality: a twelve-year prospective study in Korea. Epidemiology 12, 173–179.
Song, Y.M., Sung, J., Davey Smith, G., et al., 2004. Body mass index and ischemic and hemorrhagic stroke: a prospective study in Korean men. Stroke 35, 831–836.
Swenne, I., 2001. Changes in body weight and body mass index (BMI) in teenage girls prior to the onset and diagnosis of an eating disorder. Acta Paediatr. 90, 677–681.
Tsubono, Y., Tsuji, I., Fujita, K., et al., 2002. Validation of walking questionnaire for population-based prospective studies in Japan: comparison with pedometer. J. Epidemiol. 12, 305–309.
Tsuji, I., Kuwahara, A., Nishino, Y., et al., 1999. Medical cost for disability: a longitudinal observation of national health insurance beneficiaries in Japan. J. Am. Geriatr. Soc. 47, 470–476.
Tsuji, I., Nishino, Y., Ohkubo, T., et al., 1998. A prospective cohort study on National Health Insurance beneficiaries in Ohsaki, Miyagi Prefecture, Japan: study design, profiles of the subjects and medical cost during the first year. J. Epidemiol. 8, 258–263.
Wilson, P.W., D'Agostino, R.B., Sullivan, L., et al., 2002. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch. Intern. Med. 162, 1867–1872.
World Health Organization, 1992. International statistical classification of diseases and related health problems. 10th revision. ed. World Health Organization, Geneva.
World Health Organization, 1995. The use and interpretation of anthropometry: report of a WHO expert committee. WHO Tech. Rep. Ser. 854, 312–409.
Zhang, X., Shu, X.O., Gao, Y.T., et al., 2004. Anthropometric predictors of coronary heart disease in Chinese women. Int. J. Obes. 28, 734–740.
Zhu, J., Nieto, F.J., Horne, B.D., et al., 2001. Prospective study of pathogen burden and risk of myocardial infarction or death. Circulation. 103, 45–51.

低栄養と介護保険認定・死亡リスクに関するコホート研究

鶴ヶ谷プロジェクト

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目的　介護保険認定および死亡リスク予測の観点から，血清アルブミン値を特定高齢者の決定基準として用いる場合の基準値の妥当性を検討すること。

方法　仙台市宮城野区鶴ヶ谷地区の70歳以上住民に対し，高齢者総合機能評価「寝たきり予防健診」を平成15年に行った。受診者のうち，同意が得られ介護保険認定非該当であった者832人を対象とした。血清アルブミンの基準値について，3.5 g/dLから4.0 g/dLまでの範囲で0.1 g/dLごとに基準値を変化させて，各基準値以下群の介護保険認定および死亡リスク（Cox比例ハザードモデルにより算出），該当率，感度，特異度，陽性反応適中度を算出し，基準値間で比較検討した。

結果　3年間の追跡調査で，介護保険認定者111人，死亡者33人を確認した。重複者を除いた合計は130人であった。介護保険認定および死亡リスクは，血清アルブミン値3.5 g/dLから4.0 g/dLの基準値すべてで有意に上昇した。各基準値の該当率は，3.5 g/dLで1.3%，3.8 g/dLで9.6%，4.0 g/dLで29.6%であった。感度は3.5 g/dLで5.4%，3.8 g/dLで18.5%，4.0 g/dLで45.4%であった。特異度は3.5 g/dLで99.4%，3.8 g/dLで92.0%，4.0 g/dLで73.4%であった。陽性反応適中度は3.5 g/dLで63.6%，3.8 g/dLで30.0%，4.0 g/dLで24.0%であった。血清アルブミン値3.8 g/dLを基準値とした時の，最大3分位群（4.4 g/dL以上）をreferenceとした場合の性・年齢補正ハザード比（95% CI）は，基準値以下群（3.8 g/dL以下）で2.1（1.1–3.9），最小3分位群（3.9–4.1 g/dL）で1.5（0.9–2.5），中間3分位群（4.2–4.3 g/dL）で1.0（0.6–1.7）であった。

結論　該当率および感度，特異度の点から，血清アルブミン値3.8 g/dLを基準値とすることの妥当性が示唆された。

Key words：地域高齢者，基準値，介護保険認定，血清アルブミン

I　緒　　言

介護保険法改正を受けて，介護保険制度は平成18年度より予防重視型システムへ転換し，その一環として地域支援事業が始められた。地域支援事業における介護予防事業特定高齢者施策は，要支援または要介護状態となるリスクの高い高齢者（特定高齢者）を地域の中から把握して，適切な介護予防事業を提供するものである。

栄養改善プログラムは，運動器機能向上プログラム，口腔機能向上プログラム，うつ・閉じこもり・認知症の各予防・支援プログラム等とともに，介護予防事業の一つに位置付けられている。制度発足当時（平成18年4月時点），栄養改善プログラムへの参加が望ましいとされる決定基準は，基本チェックリストにおいて「体重が6か月で2～3 kg以上の減少」および「Body Mass Index（BMI）が18.5未満」，または生活機能評価において「血清アルブミン値が3.5 g/dL以下」とされた[1]。これら決定基準のエビデンスとして，BMI18.5未満[2]あるいは血清アルブミン値3.5 g/dL未満[3]の者で，日常生活活動（ADL）遂行能力・運動機能が有意に低いという横断研究の報告，低栄養状態の者でADL遂行能力・運動機能の悪化リスクや死亡リスクが有意に上昇するという前向きコホート研究の報告がある[4～9]。

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しかし，栄養改善プログラムへの参加が望ましいとされる特定高齢者の決定基準「血清アルブミン値3.5 g/dL以下」については，地域高齢者でそれに該当する者は少ないのではないかとの指摘がある。事実，平成16年の国民健康・栄養調査[10]によると，わが国の70歳以上の者で血清アルブミン値3.6 g/dL未満であった者の頻度は，男性2.3%，女性1.3%に過ぎなかった（3.5 g/dL以下の頻度は示されず）。

介護予防事業特定高齢者施策が全国の市町村で実施されるなかで，特定高齢者数が当初の想定よりも少ないことが明らかとなった。そこで特定高齢者の決定基準が見直され，栄養改善プログラムへの参加が望ましいとされる決定基準については，平成19年3月に開催された，厚生労働省第2回介護予防継続的評価分析等検討会において，「血清アルブミン値3.8 g/dL以下」とされた。

本研究の目的は，介護保険認定および死亡リスク予測の観点から，血清アルブミン値を特定高齢者の決定基準として用いる場合の基準値の妥当性を検討することである。そのため，仙台市宮城野区鶴ヶ谷地区の70歳以上住民を3年間追跡し，血清アルブミン値と介護保険認定および死亡リスクとの関連について検討を行った。

Ⅱ　研究方法

1.　対象者

仙台市宮城野区鶴ヶ谷地区の70歳以上住民に対し，高齢者総合機能評価「寝たきり予防健診」を平成15年7月から8月に行った。同地区は，昭和40年代に開発された住宅地で，現在では高齢化の進んだ地区である。平成12年における仙台市全体の高齢化率13%[11]に対し，本地区は24%[12]であった。

「寝たきり予防健診」の調査項目は，ソーシャル・サポート[13]，生活習慣，抑うつ尺度（Geriatric Depression Scale，以下GDSと略す）[14]，認知機能検査（Mini-Mental State Examination，以下MMSEと略す）[15]，疾患既往歴，身長・体重測定，血液検査，栄養摂取状況等に関する聞き取り調査，服薬情報，運動機能測定，歯科健診，骨密度検査，動脈硬化関連検査，呼吸器機能検査等である。

平成15年7月，同地区の70歳以上住民（2,925人）に「寝たきり予防健診」の案内状を郵送した。「寝たきり予防健診」を受診した者は958人（対象の32.8%）で，そのうち研究および介護保険利用状況に関する追跡調査に同意した者は927人（対象の31.7%）であった。

2.　調査項目

本研究で用いた調査項目は，血清アルブミン値，教育歴，配偶者の有無，ソーシャル・サポート，喫煙状況，飲酒状況，抑うつ，認知機能，疾患既往歴，主観的健康度である。血清アルブミン値は，非空腹時に肘前静脈から真空採血した血液検体を，株式会社ビー・エム・エルに委託し測定した。その他の調査項目については，訓練を受けた調査員が，調査票を対象者に提示しながら聞き取り調査を行った。

ソーシャル・サポートに関する調査には，村岡らによる評価項目を用いた[13]。質問は(1)困ったときの相談相手がいますか，(2)体の具合の悪いときの相談相手がいますか，(3)日常生活を援助してくれる人がいますか，(4)具合が悪いとき病院へ連れて行ってくれる人がいますか，(5)寝込んだとき身のまわりの世話をしてくれる人がいますか，の5項目のそれぞれについて「はい」または「いいえ」のいずれかで回答するよう求めた。

GDSは，うつ症状等に関する30項目の質問に対して「はい」または「いいえ」で回答するものである。各項目でうつ症状を示す回答に1点を加え，その合計点を評価した[14]。

MMSEは，認知症のスクリーニングテストとして世界で最も多く用いられている。11項目の質問により構成され，全項目の合計点（最高30点）を評価した[15]。

3.　追跡調査

本研究では，介護保険の初回認定（要支援・要介護）または死亡をエンドポイントとした。なお，介護保険に認定された者の中で，その後に認定区分の変更や死亡が発生した場合においても，初回認定の時点をもってエンドポイントとした。

仙台市と東北大学大学院医学系研究科社会医学講座公衆衛生学分野との調査実施協定に基づき，文書による同意が得られた者を対象として，上記のエンドポイントに関する情報が提供された。具体的には，仙台市健康福祉局介護保険課職員が同意書との照合を行ったうえで，平成15年7月1日から平成18年6月30日までの要支援・要介護認定の有無，要介護状態区分および初回認定年月日，異動の有無，異動年月日およびその理由（市外転居または死亡）に関する情報を本分野に提供した。

4.　統計解析

平成15年に「寝たきり予防健診」を受診し，研究および介護保険利用状況に関する追跡調査に同意した者927人のうち，すでに介護保険認定を受けていた者78人，採血データが欠損していた者17人を除く，832人（同意した者の89.8%）を解析対象とした。

血清アルブミンの基準値について，3.5 g/dLから4.0 g/dLまでの範囲で0.1 g/dLごとに基準値を

変化させた。その際，基準値より上の者については，対象者数が均等になるよう3分割して，それぞれ最小3分位群，中間3分位群，最大3分位群とした。最大3分位群をreferenceとし，それ以外の3群（基準値以下群・最小3分位群・中間3分位群）の介護保険認定および死亡リスクをCox比例ハザードモデルにより算出した。算出にあたっては性・年齢を補正したモデルに加え，以下の4つの共変量モデルを構築した。第1に社会的要因を補正したモデルであり，教育歴（19歳以上，16–18歳，15歳以下），配偶者の有無（あり，なし），ソーシャル・サポートの有無（あり，なし）により構成された。第2に生活習慣を補正したモデルであり，喫煙状況（現在喫煙者，過去喫煙者，非喫煙者），飲酒状況（現在飲酒者，過去飲酒者，非飲酒者）により構成された。第3に精神・身体的要因を補正したモデルであり，抑うつ（GDS；10点以下，11–13点，14点以上），認知機能（MMSE；18–24点，25–27点，28点以上），疾患既往歴（脳卒中，高血圧，心筋梗塞，糖尿病，がん：あり，なし），主観的健康度（非常に健康である/まあ健康な方である，どちらとも言えない/あまり健康ではない/健康ではない）により構成された。第4のモデルは，社会的要因，生活習慣，精神・身体的要因のすべてにより構成された。

血清アルブミンの各基準値について，該当率，感度，特異度，陽性反応適中度を算出し，そのバランスから特定高齢者の決定基準としての妥当性を比較検討した。

本研究において該当率は，解析対象者における血清アルブミン値が基準値以下の者の割合と定義した。感度は，介護保険認定または死亡を発生した者における血清アルブミン値が基準値以下の者の割合と定義した。特異度は，介護保険認定を発生していない生存者における血清アルブミン値が基準値以上の者の割合と定義した。陽性反応適中度は，血清アルブミン値が基準値以下の者における介護保険認定または死亡を発生した者の割合と定義した。

統計解析にはSAS Version9.1（SAS Inc, Cary, NC, USA）を用い，$P<0.05$を統計学的有意水準とした。

5. 倫理的配慮

本調査研究は，東北大学大学院医学系研究科倫理委員会の承認を得ている。対象者に対しては「寝たきり予防健診」の受診時に書面と口頭により調査の目的を説明した上で，書面による同意を得た。

Ⅲ 結　　果

1. 対象者の基本特性

対象者の基本特性を示す（表1）。

解析対象者832人のうち，男性は47.8%であった。平均年齢（標準偏差）は75.6（4.5）歳であり，70歳から75歳の者の割合が49.0%と最も多かった。現在喫煙者の割合は10.5%，現在飲酒者の割合は42.8%であった。疾患既往歴を持つ者の割合は，脳卒中で3.3%，高血圧で41.5%，心筋梗塞で10.2%，糖尿病で14.9%，がんで8.9%であった。

3年間の追跡調査により，介護保険認定を新規に受けた者は111人（解析対象者の13.3%），死亡者は33人（同4.0%）であり，そこから重複者14人を除いた合計130人（同15.6%）を介護保険認定および死亡者として確認した。介護保険認定を新規に受けた者の内訳は，要支援54人，要介護57人であった。

表1　対象者の基本特性（n＝832）

男性（%）	47.8
年齢（%）	
70–74歳	49.0
75–79歳	32.8
80–84歳	13.2
85歳以上	4.9
教育歴15歳以下（%）	20.1
配偶者なし（%）	32.2
ソーシャル・サポートなし（%）	
困ったときの相談相手なし	8.4
体の具合の悪いときの相談相手なし	5.9
日常生活を援助してくれる人なし	24.8
具合が悪いとき病院へ連れて行ってくれる人なし	9.6
寝込んだとき身のまわりの世話をしてくれる人なし	11.9
現在喫煙者（%）	10.5
現在飲酒者（%）	42.8
抑うつ14点以上（%）	12.6
認知機能24点以下（%）	4.8
疾患既往歴あり（%）	
脳卒中	3.3
高血圧	41.5
心筋梗塞	10.2
糖尿病	14.9
がん	8.9
主観的健康度（%）	
どちらとも言えない/あまり健康ではない/健康ではない	26.9

2. 血清アルブミンの基準値を変化させた時の基準値以下群における介護保険認定および死亡リスク

血清アルブミンの基準値を3.5 g/dLから4.0 g/dLまでの範囲で0.1 g/dLごとに変化させ，各基準値の最大3分位群をreferenceとした時の，他群のハザード比と95%信頼区間（95% CI）を算出した。基準値以下群の結果を示す（表2）。

性・年齢補正ハザード比（95% CI）は，血清アルブミンの基準値が3.5 g/dLで5.4（2.3–12.4），3.6 g/dLで3.3（1.7–6.8），3.7 g/dLで2.9（1.6–5.2），3.8 g/dLで2.1（1.1–3.9），3.9 g/dLで2.0（1.1–3.5），4.0 g/dLで1.8（1.1–3.1）であり，すべての基準値で有意なリスクの上昇が示された。また，多変量モデルすべてにおいて，この結果は大きくは変わらなかった。なお，男女別の解析においても，リスクの上昇の程度は男女でほぼ同程度であった（結果は示さず）。

3. 血清アルブミンの各基準値における該当率，感度，特異度，陽性反応適中度

血清アルブミンの各基準値における，該当率，感度，特異度，陽性反応適中度を算出した（表3）。

該当率は基準値を上げるにつれ上昇し，基準値が3.5 g/dLで1.3%，4.0 g/dLで29.6%であった。感度も基準値を上げるにつれ上昇し，基準値が3.5 g/dLで5.4%，4.0 g/dLで45.4%であった。特異度は基準値を上げるにつれ低下し，基準値が3.5 g/dLで99.4%，4.0 g/dLで73.4%であった。陽性反応適中度も基準値を上げるにつれ低下し，基準値が3.5 g/dLで63.6%，4.0 g/dLで24.0%であった。一方，基準値が3.8 g/dLでは，該当率は9.6%（男性12.1%，女性7.4%），感度は18.5%，特異度は92.0%，陽性反応適中度は30.0%であった。

血清アルブミン値3.8 g/dLを基準値とした時の，最大3分位群（4.4 g/dL以上）をreferenceとした場合の，他群のハザード比と95%信頼区間（95% CI）を算出した（表4）。

性・年齢補正ハザード比（95% CI）は基準値以下群（3.8 g/dL以下）で2.1（1.1–3.9），最小3分位群（3.9–4.1 g/dL）で1.5（0.9–2.5），中間3分位群（4.2–4.3 g/dL）で1.0（0.6–1.7）であり，有意な量反応関係が示された（P for Trend＝0.004）。また，最小3分位群，中間3分位群でリスクの有意な上昇

表3　血清アルブミンの各基準値における該当率，感度，特異度，陽性反応適中度（%）

	血清アルブミン基準値（g/dL）					
	3.5	3.6	3.7	3.8	3.9	4.0
該当率	1.3	2.6	4.8	9.6	17.8	29.6
感度	5.4	8.5	13.1	18.5	31.5	45.4
特異度	99.4	98.4	96.7	92.0	84.8	73.4
陽性反応適中度	63.6	50.0	42.5	30.0	27.7	24.0

該当率：解析対象者における血清アルブミン値が基準値以下の者の割合
感　度：介護保険認定または死亡を発生した者における血清アルブミン値が基準値以下の者の割合
特異度：介護保険認定を発生していない生存者における血清アルブミン値が基準値以上の者の割合
陽性反応適中度：血清アルブミン値が基準値以下の者における介護保険認定または死亡を発生した者の割合

表2　血清アルブミンの基準値を変化させた時の基準値以下群における介護保険認定および死亡リスク（n＝832）

	血清アルブミン基準値（g/dL）					
	3.5	3.6	3.7	3.8	3.9	4.0
イベント数/対象者数	7/11	11/22	17/40	24/80	41/148	59/246
性・年齢補正 HR	5.4(2.3–12.4)	3.3(1.7–6.8)	2.9(1.6–5.2)	2.1(1.1–3.9)	2.0(1.1–3.5)	1.8(1.1–3.1)
HR1	6.0(2.4–14.9)	3.6(1.7–7.7)	3.1(1.6–5.7)	2.2(1.2–4.2)	2.0(1.2–3.6)	1.9(1.1–3.2)
HR2	5.5(2.3–12.9)	3.3(1.6–6.7)	2.8(1.5–5.1)	2.0(1.1–3.7)	1.9(1.1–3.4)	1.8(1.1–3.0)
HR3	5.7(2.3–14.1)	3.2(1.5–7.0)	2.7(1.4–5.1)	2.1(1.1–4.0)	2.3(1.3–4.1)	2.1(1.2–3.6)
HR4	7.1(2.7–18.9)	3.8(1.6–8.7)	3.0(1.5–5.8)	2.3(1.2–4.5)	2.4(1.3–4.3)	2.2(1.3–3.8)

注）referenceはそれぞれ最大3分位群とし，基準値以下群につきHRを算出した。すなわち，3.5 g/dLおよび3.6 g/dLを基準値とした時は4.3 g/dL以上群を，3.7g/dLから4.0g/dLを基準値とした時は4.4 g/dL以上群をreferenceとした。
性・年齢補正 HR（95%信頼区間）
HR1：性，年齢，教育歴，配偶者の有無，ソーシャル・サポートの有無を補正
HR2：性，年齢，喫煙状況，飲酒状況を補正
HR3：性，年齢，抑うつ，認知機能，疾患既往歴，主観的健康度を補正
HR4：性，年齢，教育歴，配偶者の有無，ソーシャル・サポートの有無，喫煙状況，飲酒状況，抑うつ，認知機能，疾患既往歴，主観的健康度を補正