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TITLE

Purpose in life (*Ikigai*) and employment status in relation to cardiovascular mortality

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Abstract

Objectives: To investigate if having a purpose in life (*Ikigai*) is associated with cardiovascular mortality and assess whether the association varies by employment status.

Design: Prospective cohort study.

Setting: The Japan Collaborative Cohort Study (JACC Study, 1988-2009).

Participants: Cohort analyses included 29 517 men and 41 984 women (40-79 years at baseline 1988-90) from the JACC Study, free of cardiovascular disease and cancer at baseline.

Primary outcome measures: The association between purpose in life (*Ikigai)* and the risk of mortality from CVD by employment status was examined by hazard ratios (HRs) using a Cox proportional hazards model, adjusting cardiovascular risk factors.

Results: During the median 19.1-year follow-up, there were 4 680 deaths (men 2 393 and women 2 287) from CVD, including 2 053 (1 047 and 1 006) from total stroke, 716 (398 and 318) from ischemic stroke, 739 (344 and 395) from hemorrhagic stroke, 975 (550 and 425) from coronary heart disease (CHD), and 792 (361 and 431) from heart failure. Compared with unemployed people with low *Ikigai*, those with moderate and high *Ikigai* had a lower risk of CVD mortality. Multivariable HRs (95% CIs) were 0.74 (0.57 to 0.97), 0.69 (0.52 to 0.93); *P* for trend = 0.044, respectively in men, and 0.78 (0.64 to 0.95), 0.77 (0.61 to 0.97); *P* for trend = 0.039 in women. Such an inverse association was more evident for men than women and remained even after excluding early deaths that occurred within five years of the baseline survey. The inverse association with *Ikigai* was observed to remain statistically significant for total stroke and CHD after adjustment for CVD risk factors.

Conclusion: Having *Ikigai* was associated with a lower risk of CVD mortality for all study participants, especially unemployed men and women.

Article Summary

Strengths and limitations of this study

The strength of this study is that it is a population-based cohort study with a large sample size and a long follow-up period.

The association between the level of purpose in life (*Ikigai*) and the risk of cardiovascular mortality was assessed by stratification of employment status.

The limitation of this study is that psychological factors such as "the purpose of life (*Ikigai*)" were assessed using a self-administered single-item questionnaire.

An analysis that censored people who died or moved during the first five years of follow-up and examined possible adverse causal relationships from CVD development did not change the conclusions of this study.

Introduction

Recently, there has been growing evidence that positive psychological factors, such as life satisfaction, happiness, life enjoyment, optimism, and purpose in life have been associated with favorable health outcomes, including reduced risk of cardiovascular disease, the activities of daily living, cognitive impairment, and all-cause mortality [1-6]. A meta-analysis of 17 studies (mainly from the United States, Canada, and Europe) reported that psychological factors, such as meaning in life, purpose of life, life satisfaction, positive affect, and self-esteem, were considered essential components of well-being [7]. In another meta-analysis, high life purpose was associated with a 17% lower risk of all-cause mortality and cardiovascular events such as myocardial infarction, cardiac death, and stroke, even after adjusting for sociodemographic, health, and functional status [8].

"*Ikigai*" is a Japanese concept similar to "purpose in life," "meaning of life," "life worth living," and "reason to live," which can be translated as "that which most makes one's life seem worth living" [9]. In Japanese, *Ikigai* is defined as a comprehensive concept related to life satisfaction, self-esteem, self-efficacy, morale, and cognitive evaluation of the meaning of one's life [10]. *Ikigai* involves more than enjoyment, pleasure, or happiness and provides significance for one's value in life, including subjective motivation for a living [11]. Thus, *Ikigai* is considered an essential positive psychological factor rooted in Japanese culture. In a previous prospective cohort study over 7-years' follow-up on 43 391 Japanese adults, the presence of a sense of *Ikigai* was associated with decreased risk of all-cause and cardiovascular mortality among middle-aged and elderly Japanese men and women [12]. Unemployment has been shown to affect health adversely [13]. A meta-analysis of 42 cross-sectional and prospective cohort studies providing data on more than 20 million people showed that unemployment was associated with an increased risk of all-cause mortality, with a 63% higher risk for those who experienced unemployment than those who did not [14]. Some studies showed an increased incidence of cardiovascular events such as coronary heart disease (CHD) and stroke associated with unemployment status [15-17]. A study based on a population-wide dataset, consisting of a record linkage between 3 084 137 Belgian individuals aged 25 to 59 years at the 2001 census, has shown that unemployment status was associated with health problems such as cardiovascular, endocrine, and psychiatric disorders [18]. Many studies have suggested that poor health is a direct or indirect consequence of unemployment and that this causal relationship is mediated by health behaviors such as tobacco or alcohol consumption [19-22]. Unemployed people were more likely to have higher stress and lower psychological well-being, which may also lead to a decline in physical health [23].

A panel study of 6 739 US adults (mean age 68.8 years) over four years showed that a higher purpose in life is associated with lower mortality from stroke, adjusted for age, gender, race/ethnicity, and socioeconomic status[24]. In a study of 230 retired Japanese men and 98 women (mean age 65.5 years) examining the relationship between work and *Ikigai*, men who were actively engaged in work were associated with greater well-being than inactive [11]. However, no study has focused on the impact of *Ikigai* and mortality risk by employment status to our knowledge. We hypothesized that *Ikigai* has a positive impact on cardiovascular health and examined effect modification of employment status considering the effect of having *Ikigai* is prominent even under an unemployed situation. We aimed to assess the impact of *Ikigai* and employment status on cardiovascular mortality in Japanese, using 19.1 years follow-up of a large-scale prospective cohort study.

Methods

Study population

The Japan Collaborative Cohort Study for the Evaluation of Cancer Risks (JACC study) was enrolled between1988 and 1990 in 45 areas in Japan. Participants were required to conduct self-administered questionnaires about their lifestyle and previous medical history concerning cardiovascular disease (CVD) and cancer at baseline. The details of the study procedure are described elsewhere [25]. Briefly, a total of 110 585 subjects (46 395 men and 64 190 women) aged 40 to 79 years old participated in the JACC study at baseline survey. Among the participants, 7 692 were excluded due to a past history of CVD or cancer at baseline. An additionally, we excluded 31 392 excluded for 25 730 participants in areas with no questions about *Ikigai* and 5 662 participants who lacked information about *Ikigai*. Finally, 71 501 subjects (29 517 men and 41 984 women) were eligible for inclusion in the analyses (figure 1). Prior to the completion of the questionnaire, the participants were provided informed consent to be involved in this epidemiological study. Individual informed consent was obtained from each participant in 36 out of the 45 study areas (written consent in 35 areas and oral consent in 1 area). In the remaining nine areas, group consent was obtained from each community representative. Ethical approval for the present study was given by Osaka University and Hokkaido University.

Mortality surveillance

The date and cause of death for participants were determined by reviewing all death certificates from each area. According to the International Classification of Diseases, 10th revision, cause-specific mortality was defined within total CVD mortality (I01 to I99). From baseline until December 31, 2009, a total of 15 801 participants were censored because of death, and 3986 were censored because they moved out of their original residential area; follow-up was terminated at the end of 1999 (four areas), 2003 (four areas), and 2008 (two areas). The median follow-up period was 19.1 years (interquartile range, 10.4 - 20.7).

Baseline Measurement

At baseline, we used a self-administered questionnaire to obtain information on age, body mass index (BMI) (calculated by dividing body weight in kilograms by height squared in meters), smoking status, alcohol consumption, sleep duration, walking time per day, sports activity time per week, education level, marital status, employment status, and psychological conditions such as *Ikigai,* perceived mental stress, sense of life enjoyment, and medical history of hypertension and diabetes mellitus. *Ikigai* was assessed using the question "How much '*Ikigai*' do you feel in your daily life?" and responses were assessed using a four-point Likert scale: "low," "moderate," "high," and "very high." We collapsed "very high" into "high" for the analyses, as did previous studies [26 27], and the three categories for perceived levels of *Ikigai* were "low," "moderate," and "high." Other psychological conditions were evaluated by single-item questions using four points Likert scale.

Statistical analysis

We compared sex-specific and age-adjusted mean or prevalence of baseline variables of risk factors for CVD according to the perceived level of *Ikigai* among participants using analysis of covariance or chi-square test. The *P*-value of the covariate for trends across the perceived level of *Ikigai* was calculated using the mean value of each variable and the median value among the categories. For each participant, we calculated the person-years of follow-up from baseline in 1988 and 1990 to the first endpoint of death, moving from the community, or the end of 2009. Mortality rates for CVD were estimated according to the perceived levels of *Ikigai*.

In the analysis, we calculated the association between *Ikigai* and risk of mortality from CVD by sex, with hazard ratios (HRs) and 95% confidence intervals (CIs), using the Cox proportional hazards model. The analysis was performed adjusted for age and then for other potential confounders: BMI (< 18.5, 18.5 to <25.0, 25.0 to 30.0, 30,0 to 35.0, and ≥35.0 kg/m^2), smoking status (never, ex-smoker, and current smoker), alcohol consumption (never, ex-drinker, 1–20 and ≥20.0 g ethanol/ day), sports activity time per week (almost never, 1–2, 3–4 and ≥5 h/week), walking time per day (almost never, 0.5, 0.6–0.9, and ≥1 h/day), education level (<13, 13–15, 16–18, and ≥19 years), marital status (living with a spouse, divorced, bereaved and single), sleep duration per day (<5, 5, 6, 7, 8, 9 and ≥10 h/day), perceived mental stress (low, moderate, high, very high), sense of life enjoyment (always, sometimes, moderate, never) and medical history of hypertension and diabetes (yes or no). Missing values for these covariates were treated as additional missing categories, and the model contained these dummy variables. Furthermore, the stratified analysis was performed for six categories of employment status; employed, self-employed, part-time worker, unemployed, homemaker, and other. In addition, we conducted a sensitivity analysis to exclude those who died early and those who moved and were censored in the first five years of follow-up. The following analysis calculated the association between *Ikigai* and risk of mortality from CVD among unemployed persons by type of CVD: total stroke, ischemic stroke, hemorrhagic stroke, CHD, and heart failure.

Probability values for statistical significance were two-tailed, and a *P*-value <0.05 was regarded as statistically significant. The statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Patient and Public Involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Results

During a follow-up of 1 160 648 person-years, the deaths of 4 680 (men and women: 2 393 and 2 287) due to total CVD were documented. Other deaths from major CVD types were: 2 053 (1 047 and 1 006) from total stroke, 716 (398 and 318) from ischemic stroke, 739 (344 and 395) from hemorrhagic stroke, 975 (550 and 425) from CHD, and 792 (361 and 431) from heart failure.

Table 1 shows the mean values or prevalence of cardiovascular risk factors and health behaviors at baseline according to *Ikigai* level. In both men and women, those with high *Ikigai* tended to have a higher level of the following factors: BMI, self-employed, higher education (≥ 16 years), current alcohol consumption, never smoking, living with a spouse, sports activity (≥1-2 h/week), walking time (≥1 h/day), low perceived mental stress and high life enjoyment. Unlike men, women with high *Ikigai* tended to be employed or part-time workers.

Table 2 shows the sex-specific risk of mortality from total CVD according to the level of *Ikigai*, stratified by employment status. Men who had moderate and high *Ikigai* had a lower mortality risk from total CVD than those with low *Ikigai*. Multivariable HRs (95% CIs) were 0.80 (0.68 to 0.93) and 0.74 (0.64 to 0.87); *P* for trend < 0.001, respectively. A similar inverse association was observed among unemployed men. Multivariable HRs (95% CIs) were 0.74 (0.57 to 0.97) and 0.69 (0.52 to 0.93); *P* for trend = 0.044, respectively. Women who had moderate and high *Ikigai* levels tended to have lower mortality risk from total CVD than those with low *Ikigai*. However, tests for trend were not statistically significant: multivariable HRs (95% CI) were 0.87 (0.75 to 1.00) and 0.88 (0.76 to 1.03); *P* for trend = 0.136, respectively. Among unemployed women, those who had moderate and high *Ikigai* had lower mortality risk from total CVD than those who had low *Ikigai*; tests for trend were statistically significant: multivariable HRs (95% CI) were 0.78 (0.64 to 0.95) and 0.77 (0.61 to

0.97); *P* for trend = 0.039, respectively. Table 3 shows the sensitivity analysis in which we censored individuals who died and those who moved during the first five years of follow-up, having already excluded individuals who had an early death. The inverse association was more evident for men than for women and remained even after excluding early deaths that occurred within five years of the baseline survey.

Table 4 shows the risk of mortality from CVD types according to the level of *Ikigai* among unemployed people. Unemployed individuals with high *Ikigai* had lower risk of mortality from total stroke, ischemic and hemorrhagic strokes, CHD, and heart failure than those with low *Ikigai*. After adjusting for CVD risk factors, the inverse association with *Ikigai* remained statistically significant for total stroke and CHD.

Discussion

Having *Ikigai* was associated with a lower risk of mortality from CVD for all study participants, especially unemployed men and women, in a longitudinal large cohort study. The risk reduction for CVD mortality was observed even after excluding early deaths within five years from the baseline survey. Furthermore, the mortality risk reduction was evident for total stroke and CHD among the unemployed.

The underlying biological mechanisms for the potential preventive effect of *Ikigai* on mortality remained unclear, but some reasons have been addressed. Elevated levels of inflammatory markers such as C-reactive protein and interleukin-6 were associated with an increased risk of mortality [28-30]. A previous study using data from a 10-year panel survey of 985 adults aged 25-74 years residing in the United States showed that people with higher life purpose had lower physiological function scores, calculated by summarizing biomarkers such as resting blood pressure, heart rate variability, low-density lipoprotein cholesterol, glycosylated hemoglobin, plasma C-reactive protein, interleukin-6, urinary measures of epinephrine/norepinephrine and cortisol levels [31]. These may explain how *Ikigai* reduces the risk of mortality in people by lowering the higher stress and inflammatory response.

Two other prospective cohort studies using 9-year follow-up data for 999 persons and 6-year follow-up data for 2 478 persons have demonstrated that the risk reductions by positive psychological factors in all-cause mortality and stroke incidence were stronger in men than in women [32 33]. Another analysis used JACC study data on 3 004 CVD deaths recorded during the mean 12.5-years follow-up period. It showed that men with higher *Ikigai* had a reduced risk of CVD mortality after adjusting CVD risk factors, but not stroke and CHD [34]. In the present study, the inverse association between having *Ikigai* and CVD mortality risk was more pronounced in men than in women, as in previous studies. However, with a large study population and a more extended follow-up period than the previous study, it demonstrated that among the unemployed, those with high *Ikigai* had significantly lower mortality risk from CVD, stroke, and CHD regardless of gender. Our findings showed that having *Ikigai* can reduce the risk of mortality from stroke and CHD, even among unemployment. A previous study, which followed 297 construction workers for two years and observed changes in their blood pressure, showed that the longer the unemployment, the greater the rise in blood pressure. A previous study may imply a causal link between the increase in blood pressure and the length of unemployment [35]. Positive psychological factors are associated with a lower prevalence of hypertension [36]. Therefore, *Ikigai* may have reduced the risk of mortality from stroke by positively affecting blood pressure changes in unemployed people. The better health impacts of having *Ikigai* may be apparent, even among the unemployed with much evidence of poor health.

The present study has several strengths compared to previous studies. First, a population-based cohort study with a large sample size and a more extended follow-up period allowed us to assess the risk of cardiovascular mortality according to a level of *Ikigai*, stratified by employment status. Second, we adjusted for confounding factors, including lifestyle habits, social and psychological factors, and past medical histories such as hypertension and diabetes mellitus.

There were some limitations to our study. First, psychological factors such as *Ikigai* were evaluated by a self-administered single-item questionnaire. Second, we used mortality as an endpoint, but the onset of CVD could have induced lifestyle changes and *Ikigai*. There could be reverse causality that the occurrence of disease or illness had influenced *Ikigai* at baseline. Therefore, we excluded histories of CVD and cancer and conducted a sensitivity analysis in which individuals who died or moved during the first five years of follow-up were censored and found that the inverse association between *Ikigai* and risk of CVD mortality remained unchanged.

Lastly, although we adjusted for numerous potential confounders, some unmeasured confounders, such as the usage of medical services, may still be present. A previous study using a national panel study of 7 168 US adults showed that having a purpose in life was associated with a higher likelihood of using health care services such as cholesterol tests, colonoscopies, mammogram/X-ray, pap smear, and prostate examinations [37].

Conclusion

We found that *Ikigai* was associated with a lower risk of CVD mortality for all participants, particularly unemployed men and women. Having *Ikigai* could reduce the risk of CVD mortality among unemployed persons.

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Author Contributions: HI and AT conceived and designed the study; JM, and KS drafted the plan for the data analyses; JM and TK conducted data analysis; SI and TK provided statistical expertise and interpreted the data; JM drafted the manuscript; HI and KS analyzed and interpreted the data, and critically revised the manuscript; JM, KS, and HI had primary responsibility for final content; and all authors were involved in interpretation of the results and revision of the manuscript and approved the final version of the manuscripts. JM, KS, and HI are guarantors.

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Ethical approval: This study was approved by Osaka University and Hokkaido University. The participants were provided informed consent to be involved in this epidemiological study. Individual informed consent was obtained from each participant in 36 out of the 45 study areas (written consent in 35 areas and oral consent in 1 area). In the remaining nine areas, group consent was obtained from each community representative.

Transparency: JM, KS, and HI affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: No additional data available.

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Table 1. Sex-specific, mean values and proportions of baseline characteristics according to the perceived levels of *Ikigai*.

	Men				Women			
	Low	Moderate	High	*P*-Value	Low	Moderate	High	*P*-Value
No. at risk, n (%)	2197(7.4)	12240(41.5)	15080(51.1)		3819(9.1)	20308(48.4)	17857(42.5)	
Age, years	57.4	57.2	56.8	<0.001	58.1	57.7	56.8	<0.001
Body Mass Index, kg/m^2	22.5	22.5	22.8	<0.001	23.1	22.8	23.1	<0.001
Employment status, n (%)				<0.001				<0.001
Employed	560 (25.5)	4658 (38.1)	5362 (35.6)		385 (10.1)	2714 (13.4)	2550 (14.3)	
Self-employed	423 (19.3)	3860 (31.5)	5669 (37.6)		367 (9.6)	3137 (15.4)	3321 (18.6)	
Part-time worker	24 (1.1)	267 (2.2)	282 (1.9)		290 (7.6)	1987 (9.8)	1779 (10.0)	
Unemployed	436 (19.8)	2262 (18.5)	1802 (11.9)		894 (23.4)	4364 (21.5)	2637 (14.8)	
Homemaker	2 (0.1)	13 (0.1)	9 (0.1)		685 (17.9)	6201 (30.5)	4908 (27.5)	
Other	752 (34.2)	1180 (9.6)	1956 (13)		1198 (31.4)	1905 (9.4)	2662 (14.9)	
Education level, n (%)				<0.001				<0.001
<16 years	714 (48.0)	4465 (39.1)	4079 (30.2)		1329 (49.8)	7686 (40.7)	4826 (30.6)	
16-18 years	556 (37.4)	5252 (46)	6515 (48.3)		1128 (42.3)	9580 (50.7)	8874 (56.3)	
≥ 19 years	217 (14.6)	1712 (15)	2891 (21.4)		210 (7.9)	1639 (8.7)	2052 (13.0)	
Alcohol consumption, n (%)				<0.001				<0.001
Never	412 (19.6)	2225 (19.0)	2514 (17.3)		2691 (77.2)	14305 (76.2)	12042 (72.0)	
Past	221 (10.5)	694 (5.9)	738 (5.1)		97 (2.8)	294 (1.6)	283 (1.7)	
Current	1468 (69.9)	8814 (75.1)	11264 (77.6)		697 (20.0)	4173 (22.2)	4408 (26.3)	
Smoking status, n (%)								0.007
Never	413 (19.6)	2322 (19.9)	3153 (21.8)		3053 (91.6)	16664 (93.5)	14943 (93.6)	
Past	507 (24.1)	2945 (25.2)	3627 (25.0)		68 (2.0)	253 (1.4)	214 (1.3)	
Current	1186 (56.3)	6416 (54.9)	7708 (53.2)		212 (6.4)	911 (5.1)	814 (5.1)	
Marital status, n (%)				<0.001				<0.001
Living with a spouse	1708 (86.0)	10358 (93.0)	13424 (95.4)		2530 (75.4)	15317 (83.9)	14081 (84.8)	
Widowed	127 (6.4)	391 (3.5)	368 (2.6)		620 (18.5)	2257 (12.4)	2009 (12.1)	
Divorced	56 (2.8)	182 (1.6)	149 (1.1)		90 (2.7)	417 (2.3)	344 (2.1)	
Single	95 (4.8)	210 (1.9)	134 (1)		114 (3.4)	276 (1.5)	176 (1.1)	
Sports activity time, n (%)				<0.001				<0.001
never	1705 (81.2)	8431 (72.5)	9060 (62.6)		3105 (86.6)	14951 (79.3)	11876 (70.6)	
1-2 h/w	213 (10.1)	1787 (15.4)	2807 (19.4)		272 (7.6)	2343 (12.4)	2803 (16.7)	
3-4 h/w	108 (5.1)	721 (6.2)	1302 (9.0)		129 (3.6)	851 (4.5)	1188 (7.1)	

≥5 h/w	73 (3.5)	687 (5.9)	1307 (9.0)		79 (2.2)	720 (3.8)	956 (5.7)	
Walking time, n (%)				<0.001				<.0001
never	294 (18.8)	1354 (11.6)	1307 (9.5)		390 (14.3)	1852 (9.7)	1221 (7.7)	
0.5 h/day	302 (19.3)	2268 (19.4)	2453 (17.8)		525 (19.3)	3444 (18.0)	2596 (16.4)	
0.5-1 h/day	271 (17.3)	2339 (20.0)	2788 (20.3)		558 (20.5)	4198 (21.9)	3249 (20.5)	
≥1 h/day	695 (44.5)	5757 (49.1)	7195 (52.4)		1246 (45.8)	9690 (50.5)	8777 (55.4)	
Sleep duration, h/d	7.6	7.5	7.4	0.009	7.2	7.1	7.1	0.008
Perceived mental stress, n (%)				<0.001				<0.001
Low	378 (17.7)	1382 (11.4)	3107 (20.9)		541 (14.6)	2319 (11.6)	4300 (24.4)	
Moderate	1029 (48.1)	8237 (68.2)	8332 (55.9)		1838 (49.8)	13907 (69.8)	10169 (57.6)	
High	733 (34.3)	2451 (20.3)	3458 (23.2)		1315 (35.6)	3699 (18.6)	3184 (18.0)	
Sense of life enjoyment, n (%)				<0.001				<0.001
Low	417 (19.2)	399 (3.3)	193 (1.3)		775 (20.7)	686 (3.4)	184 (1.0)	
Moderate	965 (44.4)	9101 (75.0)	5612 (37.5)		1753 (46.7)	15044 (75.2)	5937 (33.5)	
High	230 (10.6)	2640 (21.7)	8265 (55.2)		315 (8.4)	4288 (21.4)	10234 (57.8)	
History of hypertension, n (%)	485 (24.7)	2305 (20.5)	2698 (19.2)	0.050	975 (28)	4107 (22.3)	3433 (20.8)	0.188
History of diabetes mellitus, n (%)	153 (8.1)	729 (6.6)	895 (6.5)	0.888	197 (5.9)	735 (4.1)	566 (3.5)	0.062

Table 2. Sex-specific, age-adjusted, and multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) of cardiovascular mortality according to the perceived levels of *Ikigai*, stratified by employment status.

	Men				Women			
	Low	Moderate	High	P_{Trend}	Low	Moderate	High	P_{Trend}
All								
No. at risk	2197	12240	15080		3819	20308	17857	
No. of person-years	32824	191424	244694		61744	330980	298982	
No. of deaths	251	1007	1135		307	1129	851	
Age-adjusted HR (95%CI)	1.00	**0.66 (0.58 to 0.76)**	**0.57 (0.50 to 0.65)**	**<0.001**	1.00	**0.75 (0.66 to 0.86)**	**0.68 (0.60 to 0.78)**	**<0.001**
Multivariable * HR (95%CI)	1.00	**0.80 (0.68 to 0.93)**	**0.74 (0.64 to 0.87)**	**<0.001**	1.00	0.87 (0.75 to 1.00)	0.88 (0.76 to 1.03)	0.136
Employed								
No. at risk	560	4658	5362		385	2714	2550	
No. of person-years	9479	80287	92997		6695	48860	46328	
No. of deaths	22	193	192		7	43	44	
Age-adjusted HR (95%CI)	1.00	0.92 (0.59 to 1.44)	0.73 (0.47 to 1.14)	0.051	1.00	0.85 (0.38 to 1.89)	0.89 (0.40 to 1.97)	0.916
Multivariable * HR (95%CI)	1.00	1.02 (0.63 to 1.63)	0.80 (0.49 to 1.31)	0.116	1.00	0.82 (0.35 to 1.95)	1.01 (0.41 to 2.48)	0.679
Self-employed								
No. at risk	423	3860	5669		367	3137	3321	
No. of person-years	6347	61848	93546		6025	53663	56797	
No. of deaths	35	290	425		9	113	102	
Age-adjusted HR (95%CI)	1.00	0.76 (0.54 to 1.08)	0.71 (0.50 to 1.00)	0.120	1.00	1.14 (0.58 to 2.25)	0.98 (0.50 to 1.94)	0.523
Multivariable * HR (95%CI)	1.00	0.86 (0.60 to 1.24)	0.85 (0.59 to 1.22)	0.682	1.00	1.30 (0.62 to 2.73)	1.29 (0.60 to 2.76)	0.782
Part-time worker								
No. at risk	24	267	282		290	1987	1779	
No. of person-years	336	4037	4344		4941	34182	30244	
No. of deaths	2	27	24		7	28	33	
Age-adjusted HR (95%CI)	1.00	0.78 (0.18 to 3.28)	0.51 (0.12 to 2.20)	0.287	1.00	0.55 (0.24 to 1.25)	0.73 (0.32 to 1.65)	0.279
Multivariable * HR (95%CI)	1.00	0.91 (0.17 to 4.76)	0.70 (0.12 to 4.06)	0.762	1.00	0.88 (0.34 to 2.25)	0.79 (0.30 to 2.04)	0.866
Unemployed								
No. at risk	436	2262	1802		894	4364	2637	
No. of person-years	4821	27595	23334		11864	62898	38599	
No. of deaths	84	368	250		145	555	306	
Age-adjusted HR (95%CI)	1.00	**0.63 (0.50 to 0.80)**	**0.48 (0.37 to 0.61)**	**<0.001**	1.00	**0.70 (0.58 to 0.84)**	**0.62 (0.51 to 0.76)**	**<0.001**
Multivariable * HR (95%CI)	1.00	**0.74 (0.57 to 0.97)**	**0.69 (0.52 to 0.93)**	**0.044**	1.00	**0.78 (0.64 to 0.95)**	**0.77 (0.61 to 0.97)**	**0.039**

Homemaker								
No. at risk	2	13	9		685	6201	4908	
No. of person-years	33	164	137		10963	100252	80823	
No. of deaths	0	0	0		46	266	184	
Age-adjusted HR (95%CI)	-	-	-	-	1.00	**0.67 (0.49 to 0.91)**	**0.57 (0.41 to 0.78)**	**0.003**
Multivariable * HR (95%CI)	-	-	-	-	1.00	0.83 (0.59 to 1.17)	0.84 (0.58 to 1.22)	0.576
Other								
No. at risk	752	1180	1956		1198	1905	2662	
No. of person-years	11808	17493	30335		21257	31124	46191	
No. of deaths	108	129	244		93	124	182	
Age-adjusted HR (95%CI)	1.00	**0.62 (0.48 to 0.80)**	**0.67 (0.53 to 0.84)**	**<0.001**	1.00	0.81 (0.62 to 1.06)	0.83 (0.65 to 1.06)	0.253
Multivariable * HR (95%CI)	1.00	**0.64 (0.47 to 0.87)**	**0.76 (0.59 to 0.97)**	**0.016**	1.00	0.91 (0.64 to 1.29)	1.00 (0.76 to 1.31)	0.813

* Adjusted for age, body mass index, smoking status, alcohol consumption, sports activity, walking time, sleep duration, education level, employment status, marital status, sense of life enjoyment, perceived mental stress, medical history of hypertension, and diabetes mellitus.

Table 3. Sex-specific, multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) of cardiovascular mortality according to the perceived levels of *Ikigai* after exclusion of deaths occurred 1 to 5 years from the baseline among unemployed persons.

	Ikigai			
	Low	**Moderate**	**High**	P_{Trend}
Men				
At Risk	436	2262	1802	
Person-years	4821	27595	23334	
No. of deaths	84	368	250	
Multivariable HR	1.00	**0.74 (0.57 to 0.97)**	**0.69 (0.52 to 0.93)**	**0.044**
	79	358	243	
Deaths within 1 y exclude	1.00	**0.74 (0.56 to 0.97)**	**0.68 (0.51 to 0.92)**	**0.044**
	73	343	232	
Deaths within 2 y exclude	1.00	0.77 (0.58 to 1.02)	**0.71 (0.52 to 0.96)**	0.087
	67	318	223	
Deaths within 3 y exclude	1.00	0.75 (0.56 to 1.01)	**0.71 (0.52 to 0.98)**	0.104
	60	299	210	
Deaths within 4 y exclude	1.00	0.78 (0.57 to 1.06)	0.72 (0.52 to 1.01)	0.157
	56	282	201	
Deaths within 5 y exclude	1.00	0.75 (0.55 to 1.04)	**0.69 (0.49 to 0.98)**	0.115
Women				
No. at risk	894	4364	2637	
No. of person-years	11864	62898	38599	
No. of deaths	145	555	306	
Multivariable HR	1.00	**0.78 (0.64 to 0.95)**	**0.77 (0.61 to 0.97)**	**0.039**
	138	540	299	
Deaths within 1 y excluded	1.00	**0.78 (0.64 to 0.96)**	**0.78 (0.62 to 0.98)**	0.056
	134	526	290	
Deaths within 2 y excluded	1.00	**0.79 (0.64 to 0.97)**	**0.78 (0.61 to 0.98)**	0.061
	125	498	281	
Deaths within 3 y excluded	1.00	**0.77 (0.62 to 0.96)**	0.78 (0.61 to 1.00)	0.057
	113	480	273	
Deaths within 4 y excluded	1.00	0.81 (0.65 to 1.02)	0.83 (0.65 to 1.08)	0.193
	112	462	267	
Deaths within 5 y excluded	1.00	**0.78 (0.62 to 0.97)**	0.80 (0.62 to 1.04)	0.092

* Adjusted for age, body mass index, smoking status, alcohol consumption, sports activity, walking time, sleep duration, education level, employment status, marital status, sense of life enjoyment, perceived mental stress, medical history of hypertension, and diabetes mellitus.

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Table 4. Age- and sex-adjusted and multivariable hazard ratios (HRs) and 95 % confidence intervals (CIs) of mortality from cardiovascular diseases types according to the perceived levels of *Ikigai* among unemployed persons.

		Ikigai			
		Low	**Moderate**	**High**	P_{Trend}
	No. at risk	1330	6626	4439	
	No. of person-years	16684	90493	61933	
Total stroke	No. of deaths	107	375	242	
	Age-, sex-adjusted HR (95%CI)	1.00	**0.58 (0.47 to 0.72)**	**0.51 (0.41 to 0.65)**	**<0.001**
	Multivariable * HR (95%CI)	1.00	**0.72 (0.57 to 0.91)**	**0.74 (0.56 to 0.96)**	**0.022**
Ischemic stroke	No. of deaths	37	157	91	
	Age-, sex- adjusted HR (95%CI)	1.00	0.70 (0.49 to 1.00)	**0.54 (0.37 to 0.80)**	**0.007**
	Multivariable * HR (95%CI)	1.00	0.82 (0.56 to 1.20)	0.80 (0.51 to 1.24)	0.555
Hemorrhagic stroke	No. of deaths	30	95	67	
	Age-, sex- adjusted HR (95%CI)	1.00	**0.54 (0.36 to 0.82)**	**0.54 (0.35 to 0.83)**	**0.008**
	Multivariable * HR (95%CI)	1.00	0.74 (0.47 to 1.19)	0.84 (0.49 to 1.42)	0.425
Coronary heart disease	No. of deaths	43	196	99	
	Age-, sex- adjusted HR (95%CI)	1.00	0.75 (0.54 to 1.05)	**0.51 (0.36 to 0.74)**	**<0.001**
	Multivariable * HR (95%CI)	1.00	0.77 (0.54 to 1.10)	**0.64 (0.43 to 0.97)**	0.103
Heart failure	No. of deaths	43	187	120	
	Age-, sex- adjusted HR (95%CI)	1.00	0.73 (0.52 to 1.01)	**0.65 (0.46 to 0.92)**	0.055
	Multivariable * HR (95%CI)	1.00	0.90 (0.63 to 1.30)	1.01 (0.67 to 1.52)	0.663

* Adjusted for age, sex, body mass index, smoking status, alcohol consumption, sports activity, walking time, sleep duration, education level, employment status, marital status, sense of life enjoyment, perceived mental stress, medical history of hypertension, and diabetes mellitus.

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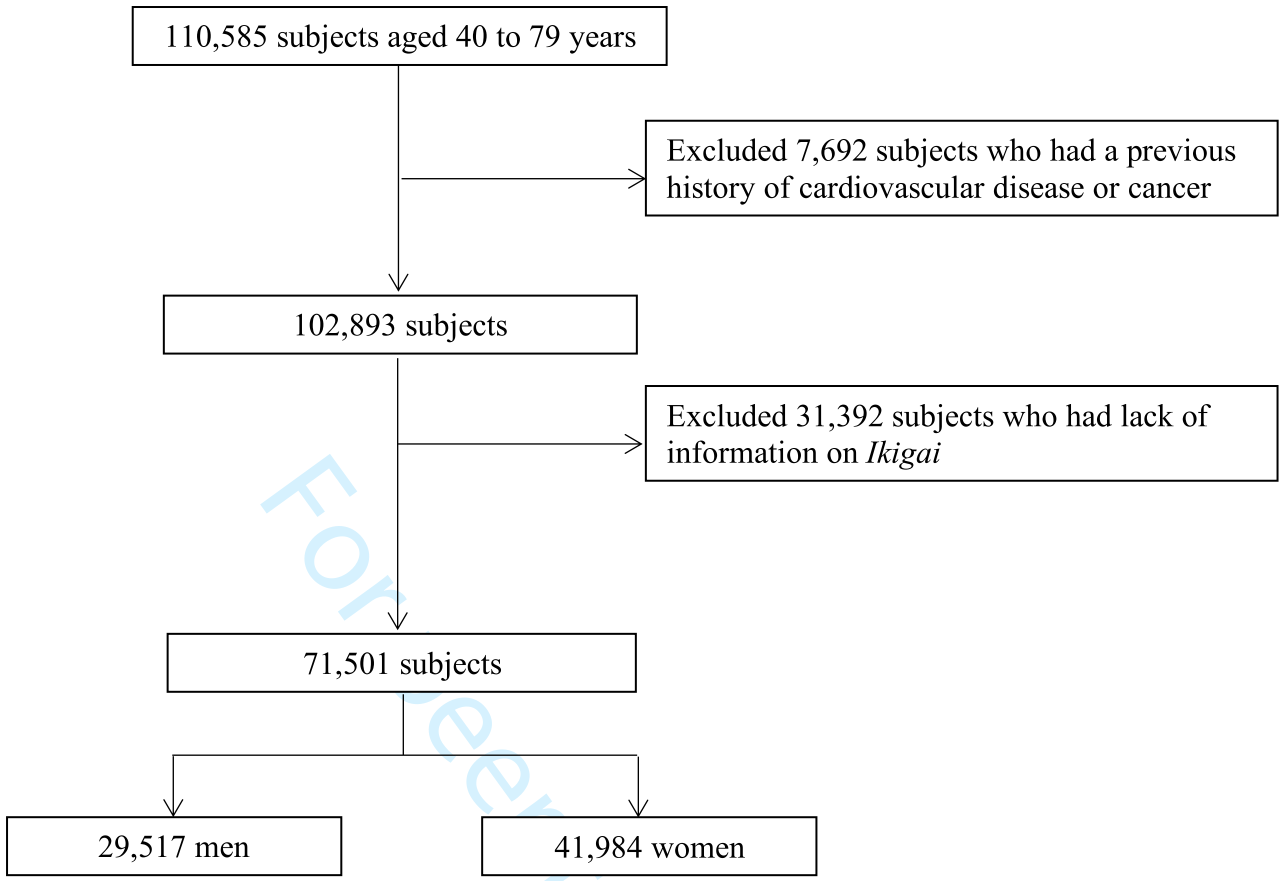
110,585 subjects aged 40 to 79 years
Excluded 7,692 subjects who had a previous history of cardiovascular disease or cancer
102,893 subjects
Excluded 31,392 subjects who had lack of information on *Ikigai*
71,501 subjects
29,517 men
41,984 women

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6-7

Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6-7
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	7
Bias	#9	Describe any efforts to address potential sources of bias	7
Study size	#10	Explain how the study size was arrived at	7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	

8

Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	8
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	8
Statistical methods	#12e	Describe any sensitivity analyses	

8

Results

Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	9
Participants	#13b	Give reasons for non-participation at each stage	9
Participants	#13c	Consider use of a flow diagram	
27			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9, 21-22
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
6-7, 27			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
9			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
9-10			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
Main results	#16b	Report category boundaries when continuous variables were categorized	9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
9-10			

Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	11
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10-11
Generalisability	#21	Discuss the generalisability (external validity) of the study results	11-12
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13-14

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Purpose in life (Ikigai) and employment status in relation to cardiovascular mortality: the Japan Collaborative Cohort Study

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TITLE

Purpose in life (*Ikigai*) and employment status in relation to cardiovascular mortality: the Japan Collaborative Cohort Study

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Abstract

Objectives: To investigate whether having a purpose in life (*Ikigai*) is associated with risk of cardiovascular disease mortality and whether the association varies by employment status.

Design: Prospective cohort study

Setting: Residents in 45 municipalities, Japan.

Participants: 29 517 men and 41 984 women aged 40 to 79 years, free of cardiovascular disease (CVD) and cancer at baseline from 1988 to 1990.

Primary outcome measures: CVD mortality

Results: During the median follow-up of 19.1 years, 4 680 deaths (2 393 men and 2 287 women) from total CVD were observed. Greater *Ikigai* was associated with a lower risk of CVD mortality, and the result was stronger for men than for women. Stratified by employment status, the inverse association was confined to unemployed persons. Among unemployed persons, the multivariable HRs of total CVD were higher for moderate and high versus low levels of *Ikigai*. Multivariable HRs (95% CIs) were 0.74 (0.57 to 0.97) and 0.69 (0.52 to 0.93), P for trend < 0.044, respectively in men, and 0.78 (0.64 to 0.95) and 0.77 (0.61 to 0.97), P for trend = 0.039 in women. No association was observed among the employed, including part-time workers, self-employed, and homemakers for both men and women. Such an inverse association remained even after excluding early deaths within five years from the baseline survey.

Conclusion: Higher levels of *Ikigai* were associated with a lower risk of CVD mortality, especially for unemployed men and women.

Article Summary

Strengths and limitations of this study

- Strengths included a population-based cohort study, a large sample size, and a long follow-up period.
- Another strength was the adjustment for many confounding factors including lifestyle habits, social and psychological factors, and past medical histories such as hypertension and diabetes mellitus.
- Limitation was a self-administered single-item questionnaire on the purpose in life (*Ikigai*) to assess exposure at the baseline survey.

Introduction

Recently, there has been growing evidence that positive psychological factors, such as life satisfaction, happiness, life enjoyment, optimism, and purpose in life have been associated with favorable health outcomes, including reduced risk of cardiovascular disease, in activities of daily living, cognitive impairment, and all-cause mortality.[1-6] A meta-analysis of 17 studies (mainly from the United States, Canada, and Europe) reported that psychological factors, such as meaning in life, purpose of life, life satisfaction, positive affect, and self-esteem, were considered essential components of well-being.[7] In another meta-analysis, high life purpose was associated with a 17% lower risk of all-cause mortality and cardiovascular events such as myocardial infarction, cardiac death, and stroke.[8]

"*Ikigai*" is a Japanese concept similar to "purpose in life," "meaning of life," "life worth living," and "reason to live," which can be translated as "that which most makes one's life seem worth living".[9] In Japanese, *Ikigai* is defined as a comprehensive concept related to life satisfaction, self-esteem, self-efficacy, morale, and cognitive evaluation of the meaning of one's life.[10] *Ikigai* involves more than enjoyment, pleasure, or happiness and provides significance for one's value in life, including subjective motivation for a living.[11] In a previous prospective cohort study of 43 391 Japanese adults over 7-years' follow-up, the presence of a sense of *Ikigai* was associated with decreased risk of all-cause and cardiovascular mortality among middle-aged and elderly Japanese men and women.[12] A panel study of 6 739 US adults aged 53 to 105 years over a four-year follow-up showed that a higher level of purpose in life was associated with a 22% reduced incidence of stroke after adjustment for age, gender, race/ethnicity, and socioeconomic status.[13]

A meta-analysis of 42 cross-sectional and prospective cohort studies providing data on more than 20 million people showed that unemployment was associated with an increased risk of all-cause mortality, with a 63% higher risk for those who experienced unemployment than those who did not.[14] Unemployment status was associated with an increased incidence of cardiovascular events such as coronary heart disease and stroke associated with.[15-17] A study based on a population-wide dataset of 3 084 137 Belgian individuals aged 25 to 59 at the 2001 census showed that unemployment status was associated with health problems such as cardiovascular, endocrine, and psychiatric disorders.[18] According to a study of 297 construction workers followed for two years, the longer the unemployment, the greater rise in blood pressure levels.[19] Poor health is a direct or indirect consequence of unemployment, and this causal relationship was mediated by health behaviors such as tobacco or alcohol consumption.[20-23]

No study, however, has focused on the impact of *Ikigai* on mortality risk by employment status. We hypothesize that *Ikigai* positively impacts cardiovascular health even in an unemployed situation. We aimed to test this hypothesis using a long-term follow-up of a large-scale prospective cohort study of Japanese adults.

Methods

Study population

The Japan Collaborative Cohort Study for the Evaluation of Cancer Risks (JACC study) enrolled residents in 45 area around Japan between1988 and 1990. Participants were required to conduct self-administered questionnaires about their lifestyle and previous medical history concerning cardiovascular disease (CVD) and cancer at baseline. The details of the study procedure are described elsewhere.[24] Briefly, a total of 110 585 subjects (46 395 men and 64 190 women) aged 40 to 79 years old participated in the JACC study at the baseline survey. Among the participants, 7 692 were excluded due to a past history of CVD or cancer at baseline. Additionally, we excluded 31 392 excluded for 25 730 participants in areas with no questions about *Ikigai* and 5 662 participants who lacked information about *Ikigai*. Finally, 71 501 subjects (29 517 men and 41 984 women) were eligible for inclusion in the analyses (Figure 1). Prior to the completion of the questionnaire, the participants were provided informed consent to be involved in this epidemiological study. Individual informed consent was obtained from each participant in 36 out of the 45 study areas (written consent in 35 areas and oral consent in 1 area). In the remaining nine areas, group consent was obtained from each community representative. Ethical approval for the present study was given by the ethical committees of Osaka University and Hokkaido University.

Mortality surveillance

The date and cause of death for participants were determined by reviewing all death certificates from each area. According to the International Classification of Diseases, 10th revision, cause-specific mortality was defined within total CVD mortality (I01 to I99). Type-specific CVD mortality was defined as I60.0 to I69.8 for total stroke, I20.0 to I25.5 for coronary heart disease, I50.0 to I50.9 for heart failure, and other CVDs. Total stroke was divided into three subtypes: cerebral infarction (I63.0 to I63.9), hemorrhagic stroke (I60.0 to I61.9), and stroke of undetermined type (I62.0 to I62.9 and I64 to I69.8). From baseline until December 31, 2009, a total of 15 801 participants were censored because of death, and 3 986 were censored because they moved out of their original residential area; follow-up was terminated at the end of 1999 (four areas), 2003 (four areas), and 2008 (two areas). The median follow-up period was 19.1 years (interquartile range, 10.4 to 20.7).

Baseline Measurement

At baseline, we used a self-administered questionnaire to obtain information on age, body mass index (BMI) (calculated by dividing body weight in kilograms by height squared in meters), smoking status, alcohol consumption, sleep duration, walking time per day, sports activity time per week, education level, marital status, employment status, and psychological conditions such as *Ikigai,* perceived mental stress, sense of life enjoyment, and medical history of hypertension and diabetes mellitus. *Ikigai* was assessed using the question 'How much *Ikigai* do you feel in your daily life?' and responses were assessed using a four-point Likert scale: 'low,' 'moderate,' 'high,' and 'very high.' We collapsed 'very high' into 'high' for the analyses, as did previous studies.[25 26] Other psychological conditions were evaluated by single-item questions using four points Likert scale.

Statistical analysis

For each participant, we calculated the person-years of follow-up from the baseline surveys between 1988 and 1990 to the first endpoint of death, moving from the community, or the end of 2009. Mortality rates for CVD were estimated according to the perceived levels of *Ikigai* at baseline. We compared sex-specific and age-adjusted mean or prevalence of baseline risk characteristics according to perceived levels of *Ikigai* among participants using the linear regression or mantel-haenszel test.

The analysis used a Cox proportional hazards model to calculate sex-specific hazard ratios (HRs) and 95% confidence intervals (CIs) of CVD according to perceived levels of *Ikigai* at baseline and the risk of mortality from CVD at follow-up. The adjustment was done for age and then for other potential confounders: BMI (< 18.5, 18.5 to <25.0, 25.0 to 30.0, 30,0 to 35.0, and ≥35.0 kg/m^2), smoking status (never, ex-smoker, and current smoker), alcohol consumption (never, ex-drinker, 1–20 and ≥20.0 g ethanol per day), sports activity time per week (almost never, 1–2, 3–4 and ≥5 hour per week), walking time per day (almost never, 0.5, 0.6–0.9, and ≥1 hour per day), education levels (<13, 13–15, 16–18, and ≥19 years), marital status (living with a spouse, divorced, bereaved and single), sleep duration per day (<5, 5, 6, 7, 8, 9 and ≥10 hour per day), perceived mental stress (low, moderate, high, very high), sense of life enjoyment (always, sometimes, moderate, never) and medical history of hypertension and diabetes (yes or no). Missing values for these covariates were treated as additional missing categories, and the model contained these dummy variables. Furthermore, the stratified analysis was performed for six categories of employment status; employed, self-employed, part-time workers, homemakers, unemployed, and others. Homemakers were regarded as the category of employed because they were primarily women, and many of them were assumed to have motivation for children and housework in Japan. In addition, we conducted a sensitivity analysis to exclude those who died early and those who moved and were censored in the first five years of follow-up and the type-specific CVD analysis for total stroke, ischemic stroke, hemorrhagic stroke, stroke of undetermined type, coronary heart disease, heart failure, and other CVDs. To test for linear trends across the *Ikigai* categories for baseline risk characteristics and hazard ratios, and ordering variable of *Ikigai* (1: low, 2: moderate, 3: high) was used. Probability values for statistical significance were two-tailed, and a *P*-value <0.05 was regarded as statistically significant. The statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Patient and Public Involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Results

During a follow-up of 1 160 648 person-years, the deaths of 4 680 (men and women: 2 393 and 2 287) due to total CVD were documented. Other deaths from major CVD types were 2 053 (1 047 and 1 006) total strokes, 716 (398 and 318) ischemic strokes, 739 (344 and 395) hemorrhagic strokes, 598 (305 and 293) strokes of undetermined type, 975 (550 and 425) coronary heart diseases, 792 (361 and 431) heart failures, and 860 (435 and 425) other CVDs.

Table 1 shows the mean values or prevalence of cardiovascular risk factors and health behaviors at baseline according to *Ikigai* level. In both men and women, those with high *Ikigai* tended to have higher levels of the following factors: BMI, self-employed, higher education (≥ 16 years), current alcohol consumption, never smoking, living with a spouse, sports activity (≥1-2 h/week), walking time (≥1 h/day), low perceived mental stress and high life enjoyment. Unlike men, women with high *Ikigai* tended to be employed or part-time workers.

Table 2 shows the sex-specific risk of mortality from total CVD according to the level of *Ikigai*, stratified by employment status. Men who had moderate and high *Ikigai* had a lower risk of mortality from total CVD than those with low *Ikigai*. Multivariable HRs (95% CIs) were 0.80 (0.68 to 0.93) and 0.74 (0.64 to 0.87); *P* for trend < 0.001, respectively. A similar inverse association was observed among unemployed men, multivariable HRs (95% CIs) were 0.74 (0.57 to 0.97) and 0.69 (0.52 to 0.93); *P* for trend = 0.044, respectively. Women who had moderate and high *Ikigai* levels tended to have a lower risk of mortality from total CVD than those with low *Ikigai*. But, tests for trend were not statistically significant: multivariable HRs (95% CI) were 0.87 (0.75 to 1.00) and 0.88 (0.76 to 1.03); *P* for trend = 0.136, respectively. Among unemployed women, those who had moderate and high *Ikigai* had a lower risk of mortality from total CVD than those who had low *Ikigai*; tests for trend were statistically significant: multivariable HRs (95% CI) were 0.78 (0.64 to 0.95) and 0.77 (0.61

to 0.97); *P* for trend = 0.039, respectively. No associations were observed among the unemployed, including part-time workers, self-employed, and homemakers for both men and women.

Table 3 shows the sensitivity analysis in which we censored individuals who died and those who moved during the first five years of follow-up, having excluded individuals who had an early death. The inverse associations did not differ materially for both men and women.

Table 4 shows the risk of mortality from CVD types according to the perceived levels of *Ikigai* among the unemployed. Unemployed men and women with high *Ikigai* had lower risks of mortality from total stroke, stroke subtypes (ischemic stroke, hemorrhagic stroke, and stroke of determined type), coronary heart disease, heart failure, and other CVDs than those with low *Ikigai*. After adjusting for CVD risk factors, the inverse association remained statistically significant for total stroke, stroke of determined type, and coronary heart disease.

Discussion

In a large prospective cohort study, higher levels of *Ikigai* were associated with a lower risk of mortality from total CVD among unemployed men and women after adjustment for known cardiovascular risk factors, but such as inverse association was not observed for the employed. The lower risk of CVD mortality among the unemployed was observed even after excluding early deaths within five years from the baseline survey. Furthermore, the risk reduction was evident for total stroke and coronary heart disease among the unemployed people.

The underlying biological mechanisms for the potential preventive effect of *Ikigai* on mortality from CVD remained unclear, but some reasons have been addressed. Elevated levels of inflammatory markers such as C-reactive protein and interleukin-6 were associated with an increased CVD risk.[27-29] A previous study using data from a 10-year panel survey of 985 adults aged 25 to 74 years residing in the United States showed that people with a higher purpose in life had lower physiological function scores, calculated by summarizing biomarkers such as resting blood pressure, heart rate variability, low-density lipoprotein cholesterol, glycosylated hemoglobin, plasma C-reactive protein, interleukin-6, urinary measures of epinephrine/norepinephrine and cortisol levels.[30] Another study of 135 older women aged 61 to 91 years found that those with higher scores of purpose in life had lower levels of the soluble IL-6 receptor, an inflammatory marker for stroke, coronary heart disease as well as rheumatoid arthritis and Alzheimer's disease.[31]

Two other prospective cohort studies using 9.1-year follow-up data for 941 persons and 6-year follow-up data for 2 478 persons showed that the risk reductions associated with positive psychological factors in all-cause mortality and stroke incidence were stronger in men than in women.[32 33] A previous report of the JACC study with a 12.5-year follow-up showed that men with higher *Ikigai* had a reduced risk of CVD mortality but not women.[34] We observed a similar inverse association of CVD mortality risk in the present study and extended the evidence that the inverse association between *Ikigai* and CVD mortality risk was confined to unemployed men and women.

The present study has several strengths compared to previous studies. First, a population-based cohort study with a large sample size and a more extended follow-up period allowed us to assess the risk of cardiovascular mortality according to the perceived levels of *Ikigai*, stratified by employment status. Second, we adjusted for many confounding factors including lifestyle habits, social and psychological factors, and past medical histories such as hypertension and diabetes mellitus. There were some limitations to our study. First, psychological factors such as *Ikigai* were evaluated by a self-administered single-item questionnaire. It has been noted that *Ikigai* encompasses not only eudaimonic well-being, i.e., well-being that pertains to internal virtue and pursuing human capacity[35], but also aspects of hedonic well-being characterized by pleasure and satisfaction not necessarily resulting from a virtuous activity[36]. Unemployed persons with *Ikigai* were possibly likely to have available eudaimonic or hedonic well-being in their daily lives. However, the present study did not provide information on the details of *Ikigai*. Second, the presence of illness and preclinical conditions may have influenced *Ikigai* at baseline, which could lead to reverse causality. Therefore, we excluded histories of CVD and cancer and also conducted a sensitivity analysis in which individuals who died or moved during the first five years of follow-up were censored and found that the inverse association between *Ikigai* and the risk of CVD mortality remained unchanged. Lastly, although we adjusted for numerous potential confounders, some unmeasured confounders, such as the usage of medical services, may still be present. A previous study using a national panel study of 7 168 US adults showed that having a purpose in life was associated with a higher likelihood of using health care services such as cholesterol tests, colonoscopies, mammogram/X-ray, pap smear, and prostate examinations.[37]

Conclusion

We found that higher levels of *Ikigai* were associated with a lower risk of CVD mortality, specifically for unemployed men and women. Having *Ikigai* might be useful for the risk reduction of CVD mortality among the unemployed.

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Author Contributions HI and AT conceived and designed the study; JM, and KS drafted the plan for the data analyses; JM and TK conducted data analysis; SI and TK provided statistical expertise and interpreted the data; JM drafted the manuscript; HI and KS analyzed and interpreted the data, and critically revised the manuscript; JM, KS, and HI had primary responsibility for final content; and all authors were involved in interpretation of the results and revision of the manuscript and approved the final version of the manuscripts. JM, KS, and HI are guarantors.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethical approval This study was approved by the ethics committees of Hokkaido University, Hokkaido, Japan, and Osaka University, Osaka, Japan. number/ID 14285-6.

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Data availability statement The raw/processed data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

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Table 1 Sex-specific mean values and proportions of baseline characteristics according to the perceived levels of *Ikigai*.

	Men				Women			
	Low	Moderate	High	P_{Trend}	Low	Moderate	High	P_{Trend}
No. at risk, n (%)	2197 (7.4)	12240 (41.5)	15080 (51.1)		3819 (9.1)	20308 (48.4)	17857 (42.5)	
Age, years, mean (SD)	57.4 (10.5)	57.2 (10.1)	56.8 (10.2)	<0.001	58.1 (10.8)	57.7 (10.0)	56.8 (9.9)	<0.001
Body Mass Index, kg/m^2, mean (SD)	22.5 (2.9)	22.5 (2.8)	22.8 (2.8)	<0.001	23.1 (3.5)	22.8 (3.1)	23.1 (3.1)	<0.001
Employment status, n (%)				<0.001				<0.001
Employed	560 (25.5)	4658 (38.1)	5362 (35.6)		385 (10.1)	2714 (13.4)	2550 (14.3)	
Self-employed	423 (19.3)	3860 (31.5)	5669 (37.6)		367 (9.6)	3137 (15.4)	3321 (18.6)	
Part-time worker	24 (1.1)	267 (2.2)	282 (1.9)		290 (7.6)	1987 (9.8)	1779 (10.0)	
Unemployed	436 (19.8)	2262 (18.5)	1802 (11.9)		894 (23.4)	4364 (21.5)	2637 (14.8)	
Homemaker	2 (0.1)	13 (0.1)	9 (0.1)		685 (17.9)	6201 (30.5)	4908 (27.5)	
Other	752 (34.2)	1180 (9.6)	1956 (13)		1198 (31.4)	1905 (9.4)	2662 (14.9)	
Education level, n (%)				<0.001				<0.001
<16 years	714 (48.0)	4465 (39.1)	4079 (30.2)		1329 (49.8)	7686 (40.7)	4826 (30.6)	
16-18 years	556 (37.4)	5252 (46.0)	6515 (48.3)		1128 (42.3)	9580 (50.7)	8874 (56.3)	
≥ 19 years	217 (14.6)	1712 (15.0)	2891 (21.4)		210 (7.9)	1639 (8.7)	2052 (13.0)	
Alcohol consumption, n (%)				<0.001				<0.001
Never	412 (19.6)	2225 (19.0)	2514 (17.3)		2691 (77.2)	14305 (76.2)	12042 (72.0)	
Past	221 (10.5)	694 (5.9)	738 (5.1)		97 (2.8)	294 (1.6)	283 (1.7)	
Current	1468 (69.9)	8814 (75.1)	11264 (77.6)		697 (20.0)	4173 (22.2)	4408 (26.3)	
Smoking status, n (%)								0.007
Never	413 (19.6)	2322 (19.9)	3153 (21.8)		3053 (91.6)	16664 (93.5)	14943 (93.6)	
Past	507 (24.1)	2945 (25.2)	3627 (25.0)		68 (2.0)	253 (1.4)	214 (1.3)	
Current	1186 (56.3)	6416 (54.9)	7708 (53.2)		212 (6.4)	911 (5.1)	814 (5.1)	
Marital status, n (%)				<0.001				<0.001
Living with a spouse	1708 (86.0)	10358 (93.0)	13424 (95.4)		2530 (75.4)	15317 (83.9)	14081 (84.8)	
Widowed	127 (6.4)	391 (3.5)	368 (2.6)		620 (18.5)	2257 (12.4)	2009 (12.1)	
Divorced	56 (2.8)	182 (1.6)	149 (1.1)		90 (2.7)	417 (2.3)	344 (2.1)	
Single	95 (4.8)	210 (1.9)	134 (1.0)		114 (3.4)	276 (1.5)	176 (1.1)	
Sports activity time, n (%)				<0.001				<0.001
Never	1705 (81.2)	8431 (72.5)	9060 (62.6)		3105 (86.6)	14951 (79.3)	11876 (70.6)	
1-2 h/w	213 (10.1)	1787 (15.4)	2807 (19.4)		272 (7.6)	2343 (12.4)	2803 (16.7)	
3-4 h/w	108 (5.1)	721 (6.2)	1302 (9.0)		129 (3.6)	851 (4.5)	1188 (7.1)	
≥5 h/w	73 (3.5)	687 (5.9)	1307 (9.0)		79 (2.2)	720 (3.8)	956 (5.7)	
Walking time, n (%)				<0.001				<.0001

Never	294 (18.8)	1354 (11.6)	1307 (9.5)		390 (14.3)	1852 (9.7)	1221 (7.7)	
0.5 h/day	302 (19.3)	2268 (19.4)	2453 (17.8)		525 (19.3)	3444 (18.0)	2596 (16.4)	
0.5-1 h/day	271 (17.3)	2339 (20.0)	2788 (20.3)		558 (20.5)	4198 (21.9)	3249 (20.5)	
≥1 h/day	695 (44.5)	5757 (49.1)	7195 (52.4)		1246 (45.8)	9690 (50.5)	8777 (55.4)	
Sleep duration, hour per day, mean (SD)	7.6 (1.3)	7.5 (1.1)	7.4 (1.1)	0.009	7.2 (1.3)	7.1 (1.1)	7.1 (1.0)	0.008
Perceived mental stress, n (%)				<0.001				<0.001
Low	378 (17.7)	1382 (11.4)	3107 (20.9)		541 (14.6)	2319 (11.6)	4300 (24.4)	
Moderate	1029 (48.1)	8237 (68.2)	8332 (55.9)		1838 (49.8)	13907 (69.8)	10169 (57.6)	
High	733 (34.3)	2451 (20.3)	3458 (23.2)		1315 (35.6)	3699 (18.6)	3184 (18.0)	
Sense of life enjoyment, n (%)				<0.001				<0.001
Low	417 (19.2)	399 (3.3)	193 (1.3)		775 (20.7)	686 (3.4)	184 (1.0)	
Moderate	965 (44.4)	9101 (75.0)	5612 (37.5)		1753 (46.7)	15044 (75.2)	5937 (33.5)	
High	230 (10.6)	2640 (21.7)	8265 (55.2)		315 (8.4)	4288 (21.4)	10234 (57.8)	
History of hypertension, n (%)	485 (24.7)	2305 (20.5)	2698 (19.2)	0.050	975 (28.0)	4107 (22.3)	3433 (20.8)	0.188
History of diabetes mellitus, n (%)	153 (8.1)	729 (6.6)	895 (6.5)	0.888	197 (5.9)	735 (4.1)	566 (3.5)	0.062

SD : Standard deviation

Table 2 Sex-specific, age-adjusted, and multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) of total cardiovascular mortality according to the perceived levels of *Ikigai*, stratified by employment status.

	Men				Women			
	Low	Moderate	High	P_{Trend}	Low	Moderate	High	P_{Trend}
All								
No. at risk	2197	12240	15080		3819	20308	17857	
No. of person-years	32824	191424	244694		61744	330980	298982	
No. of deaths	251	1007	1135		307	1129	851	
Age-adjusted HR (95%CI)	1.00	**0.66 (0.58 to 0.76)**	**0.57 (0.50 to 0.65)**	**<0.001**	1.00	**0.75 (0.66 to 0.86)**	**0.68 (0.60 to 0.78)**	**<0.001**
Multivariable * HR (95%CI)	1.00	**0.80 (0.68 to 0.93)**	**0.74 (0.64 to 0.87)**	**<0.001**	1.00	0.87 (0.75 to 1.00)	0.88 (0.76 to 1.03)	0.136
Employed								
No. at risk	560	4658	5362		385	2714	2550	
No. of person-years	9479	80287	92997		6695	48860	46328	
No. of deaths	22	193	192		7	43	44	

Age-adjusted HR (95%CI)	1.00	0.92 (0.59 to 1.44)	0.73 (0.47 to 1.14)	0.051	1.00	0.85 (0.38 to 1.89)	0.89 (0.40 to 1.97)	0.916
Multivariable * HR (95%CI)	1.00	1.02 (0.63 to 1.63)	0.80 (0.49 to 1.31)	0.116	1.00	0.82 (0.35 to 1.95)	1.01 (0.41 to 2.48)	0.679
Self-employed								
No. at risk	423	3860	5669		367	3137	3321	
No. of person-years	6347	61848	93546		6025	53663	56797	
No. of deaths	35	290	425		9	113	102	
Age-adjusted HR (95%CI)	1.00	0.76 (0.54 to 1.08)	0.71 (0.50 to 1.00)	0.120	1.00	1.14 (0.58 to 2.25)	0.98 (0.50 to 1.94)	0.523
Multivariable * HR (95%CI)	1.00	0.86 (0.60 to 1.24)	0.85 (0.59 to 1.22)	0.682	1.00	1.30 (0.62 to 2.73)	1.29 (0.60 to 2.76)	0.782
Part-time workers								
No. at risk	24	267	282		290	1987	1779	
No. of person-years	336	4037	4344		4941	34182	30244	
No. of deaths	2	27	24		7	28	33	
Age-adjusted HR (95%CI)	1.00	0.78 (0.18 to 3.28)	0.51 (0.12 to 2.20)	0.287	1.00	0.55 (0.24 to 1.25)	0.73 (0.32 to 1.65)	0.279
Multivariable * HR (95%CI)	1.00	0.91 (0.17 to 4.76)	0.70 (0.12 to 4.06)	0.762	1.00	0.88 (0.34 to 2.25)	0.79 (0.30 to 2.04)	0.866
Homemakers								
No. at risk	2	13	9		685	6201	4908	
No. of person-years	33	164	137		10963	100252	80823	
No. of deaths	0	0	0		46	266	184	
Age-adjusted HR (95%CI)	-	-	-	-	1.00	**0.67 (0.49 to 0.91)**	**0.57 (0.41 to 0.78)**	**0.003**
Multivariable * HR (95%CI)	-	-	-	-	1.00	0.83 (0.59 to 1.17)	0.84 (0.58 to 1.22)	0.576
Unemployed								
No. at risk	436	2262	1802		894	4364	2637	
No. of person-years	4821	27595	23334		11864	62898	38599	
No. of deaths	84	368	250		145	555	306	
Age-adjusted HR (95%CI)	1.00	**0.63 (0.50 to 0.80)**	**0.48 (0.37 to 0.61)**	**<0.001**	1.00	**0.70 (0.58 to 0.84)**	**0.62 (0.51 to 0.76)**	**<0.001**
Multivariable * HR (95%CI)	1.00	**0.74 (0.57 to 0.97)**	**0.69 (0.52 to 0.93)**	**0.044**	1.00	**0.78 (0.64 to 0.95)**	**0.77 (0.61 to 0.97)**	**0.039**
Others								
No. at risk	752	1180	1956		1198	1905	2662	
No. of person-years	11808	17493	30335		21257	31124	46191	
No. of deaths	108	129	244		93	124	182	
Age-adjusted HR (95%CI)	1.00	**0.62 (0.48 to 0.80)**	**0.67 (0.53 to 0.84)**	**<0.001**	1.00	0.81 (0.62 to 1.06)	0.83 (0.65 to 1.06)	0.253
Multivariable * HR (95%CI)	1.00	**0.64 (0.47 to 0.87)**	**0.76 (0.59 to 0.97)**	**0.016**	1.00	0.91 (0.64 to 1.29)	1.00 (0.76 to 1.31)	0.813

* Adjusted for age, body mass index, smoking status, alcohol consumption, sports activity, walking time, sleep duration, education level, employment status, marital status, sense of life enjoyment, perceived mental stress, medical history of hypertension, and diabetes mellitus.

Table 3 Sex-specific, multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) of total cardiovascular mortality according to the perceived levels of *Ikigai* after exclusion of deaths occurred 1 to 5 years from the baseline among unemployed persons.

	Ikigai			
	Low	**Moderate**	**High**	P_{Trend}
Men				
At risk	436	2262	1802	
Person-years	4821	27595	23334	
No. of deaths	84	368	250	
Multivariable HR	1.00	**0.74 (0.57 to 0.97)**	**0.69 (0.52 to 0.93)**	**0.044**
	79	358	243	
Deaths within 1 y exclude	1.00	**0.74 (0.56 to 0.97)**	**0.68 (0.51 to 0.92)**	**0.044**
	73	343	232	
Deaths within 2 y exclude	1.00	0.77 (0.58 to 1.02)	**0.71 (0.52 to 0.96)**	0.087
	67	318	223	
Deaths within 3 y exclude	1.00	0.75 (0.56 to 1.01)	**0.71 (0.52 to 0.98)**	0.104
	60	299	210	
Deaths within 4 y exclude	1.00	0.78 (0.57 to 1.06)	0.72 (0.52 to 1.01)	0.157
	56	282	201	
Deaths within 5 y exclude	1.00	0.75 (0.55 to 1.04)	**0.69 (0.49 to 0.98)**	0.115
Women				
No. at risk	894	4364	2637	
No. of person-years	11864	62898	38599	
No. of deaths	145	555	306	
Multivariable HR	1.00	**0.78 (0.64 to 0.95)**	**0.77 (0.61 to 0.97)**	**0.039**
	138	540	299	
Deaths within 1 y excluded	1.00	**0.78 (0.64 to 0.96)**	**0.78 (0.62 to 0.98)**	0.056
	134	526	290	
Deaths within 2 y excluded	1.00	**0.79 (0.64 to 0.97)**	**0.78 (0.61 to 0.98)**	0.061
	125	498	281	
Deaths within 3 y excluded	1.00	**0.77 (0.62 to 0.96)**	0.78 (0.61 to 1.00)	0.057
	113	480	273	

Deaths within 4 y excluded	1.00	0.81 (0.65 to 1.02)	0.83 (0.65 to 1.08)	0.193
	112	462	267	
Deaths within 5 y excluded	1.00	**0.78 (0.62 to 0.97)**	0.80 (0.62 to 1.04)	0.092

* Adjusted for age, body mass index, smoking status, alcohol consumption, sports activity, walking time, sleep duration, education level, employment status, marital status, sense of life enjoyment, perceived mental stress, medical history of hypertension, and diabetes mellitus.

Table 4 Age- and sex-adjusted and multivariable hazard ratios (HRs) and 95 % confidence intervals (CIs) of mortality from type-specific cardiovascular diseases according to the perceived levels of *Ikigai* among unemployed persons.

		Ikigai			
		Low	**Moderate**	**High**	**P_{Trend}**
	No. at risk	1330	6626	4439	
	No. of person-years	16684	90493	61933	
Total stroke	No. of deaths	107	375	242	
	Age-, sex-adjusted HR (95%CI)	1.00	**0.58 (0.47 to 0.72)**	**0.51 (0.41 to 0.65)**	**<0.001**
	Multivariable * HR (95%CI)	1.00	**0.72 (0.57 to 0.91)**	**0.74 (0.56 to 0.96)**	**0.022**
Ischemic stroke	No. of deaths	37	157	91	
	Age-, sex- adjusted HR (95%CI)	1.00	0.70 (0.49 to 1.00)	**0.54 (0.37 to 0.80)**	**0.007**
	Multivariable * HR (95%CI)	1.00	0.82 (0.56 to 1.20)	0.80 (0.51 to 1.24)	0.555
Hemorrhagic stroke	No. of deaths	30	95	67	
	Age-, sex- adjusted HR (95%CI)	1.00	**0.54 (0.36 to 0.82)**	**0.54 (0.35 to 0.83)**	**0.008**
	Multivariable * HR (95%CI)	1.00	0.74 (0.47 to 1.19)	0.84 (0.49 to 1.42)	0.425
Stroke of undetermined type	No. of deaths	40	123	84	.
	Age-, sex- adjusted HR (95%CI)	1.00	**0.51 (0.36 to 0.73)**	**0.47 (0.32 to 0.69)**	**<0.001**
	Multivariable * HR (95%CI)	1.00	**0.61 (0.41 to 0.90)**	**0.61 (0.39 to 0.96)**	**0.041**
Coronary heart disease	No. of deaths	43	196	99	
	Age-, sex- adjusted HR (95%CI)	1.00	0.75 (0.54 to 1.05)	**0.51 (0.36 to 0.74)**	**<0.001**

	Multivariable * HR (95%CI)	1.00	0.77 (0.54 to 1.10)	**0.64 (0.43 to 0.97)**	0.103
Heart failure	No. of deaths	43	187	120	
	Age-, sex- adjusted HR (95%CI)	1.00	0.73 (0.52 to 1.01)	**0.65 (0.46 to 0.92)**	0.055
	Multivariable * HR (95%CI)	1.00	0.90 (0.63 to 1.30)	1.01 (0.67 to 1.52)	0.663
Other CVDs	No. of deaths	36	165	95	.
	Age-, sex- adjusted HR (95%CI)	1.00	0.75 (0.52 to 1.08)	**0.60 (0.40 to 0.87)**	**0.023**
	Multivariable * HR (95%CI)	1.00	0.75 (0.51 to 1.11)	0.64 (0.42 to 1.00)	0.144

* Adjusted for age, sex, body mass index, smoking status, alcohol consumption, sports activity, walking time, sleep duration, education level, employment status, marital status, sense of life enjoyment, perceived mental stress, medical history of hypertension, and diabetes mellitus.

Figure legends

Figure 1 Flowchart for the selection of the study subjects.

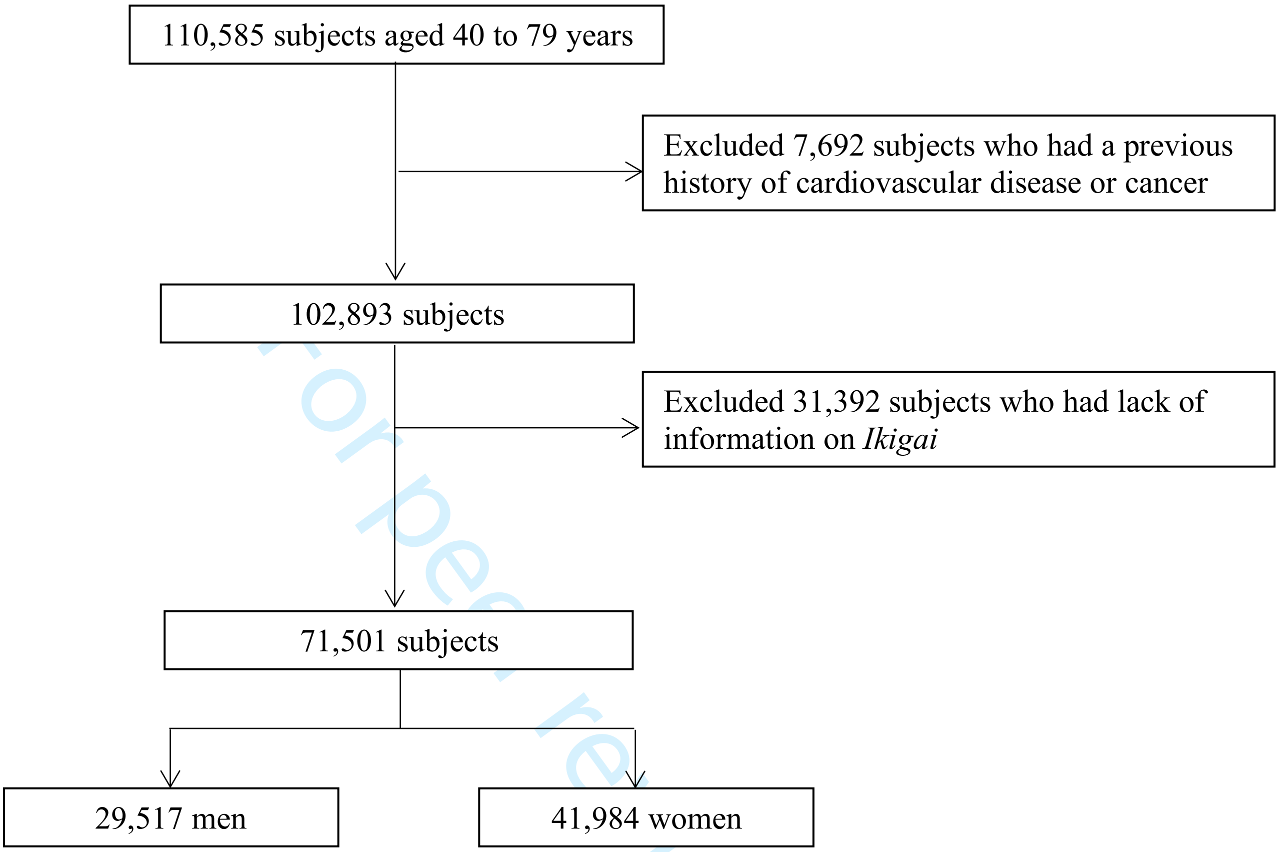

Figure 1 Flowchart for the selection of the study subjects.

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6-7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7

Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6-7
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	7
Bias	#9	Describe any efforts to address potential sources of bias	7
Study size	#10	Explain how the study size was arrived at	7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7-8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7-8
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	8
Statistical methods	#12e	Describe any sensitivity analyses	8
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	9
Participants	#13b	Give reasons for non-participation at each stage	9
Participants	#13c	Consider use of a flow diagram	6

Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9, 20-21
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	6
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	7
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
Main results	#16b	Report category boundaries when continuous variables were categorized	7-9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	11-12
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10-11
Generalisability	#21	Discuss the generalisability (external validity) of the study results	11-12
Other Information			

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13-14

 This checklist was completed on 29. November 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai