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

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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 mortality¹⁻⁶. 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-being⁷. 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 status⁸.

"*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 life¹⁰. *Ikigai* involves more than enjoyment, pleasure, or happiness and provides significance for one's value in life, including subjective motivation for a living¹¹. 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 women¹². Unemployment has been shown to affect health adversely¹³. 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 not¹⁴. Some studies showed an increased incidence of cardiovascular events such as coronary heart disease (CHD) and stroke associated with unemployment status¹⁵⁻¹⁷. 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 disorders¹⁸. Many studies have suggested that poor health is a direct

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3 or indirect consequence of unemployment and that this causal relationship is mediated by health behaviors such
4 as tobacco or alcohol consumption¹⁹⁻²². Unemployed people were more likely to have higher stress and lower
5 psychological well-being, which may also lead to a decline in physical health²³.
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10 A panel study of 6 739 US adults (mean age 68.8 years) over four years showed that a higher purpose in
11 life is associated with lower mortality from stroke, adjusted for age, gender, race/ethnicity, and socioeconomic
12 status²⁴. In a study of 230 retired Japanese men and 98 women (mean age 65.5 years) examining the
13 relationship between work and *Ikigai*, men who were actively engaged in work were associated with greater
14 well-being than inactive¹¹. However, no study has focused on the impact of *Ikigai* and mortality risk by
15 employment status to our knowledge. We hypothesized that *Ikigai* has a positive impact on cardiovascular
16 health and examined effect modification of employment status considering the effect of having *Ikigai* is
17 prominent even under an unemployed situation. We aimed to assess the impact of *Ikigai* and employment status
18 on cardiovascular mortality in Japanese, using 19.1 years follow-up of a large-scale prospective cohort study.
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33 **Methods**

34 **Study population**

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36 The Japan Collaborative Cohort Study for the Evaluation of Cancer Risks (JACC study) was enrolled
37 between 1988 and 1990 in 45 areas in Japan. Participants were required to conduct self-administered
38 questionnaires about their lifestyle and previous medical history concerning cardiovascular disease (CVD) and
39 cancer at baseline. The details of the study procedure are described elsewhere²⁵. Briefly, a total of 1 105 85
40 subjects (46 395 men and 64 190 women) aged 40 to 79 years old participated in the JACC study at baseline
41 survey. Among the participants, 7 692 were excluded due to a past history of CVD or cancer at baseline. An
42 additionally, we excluded 31 392 excluded for 25 730 participants in areas with no questions about *Ikigai* and 5
43 662 participants who lacked information about *Ikigai*. Finally, 71 501 subjects (29 517 men and 41 984 women)
44 were eligible for inclusion in the analyses (figure 1). Prior to the completion of the questionnaire, the participants
45 were provided informed consent to be involved in this epidemiological study. Individual informed consent was
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3 obtained from each participant in 36 out of the 45 study areas (written consent in 35 areas and oral consent in 1
4 area). In the remaining nine areas, group consent was obtained from each community representative. Ethical
5 approval for the present study was given by Osaka University and Hokkaido University.
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11 **Mortality surveillance**

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

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

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3 We compared sex-specific and age-adjusted mean or prevalence of baseline variables of risk factors for CVD
4 according to the perceived level of *Ikigai* among participants using analysis of covariance or chi-square test.
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8 The *P*-value of the covariate for trends across the perceived level of *Ikigai* was calculated using the mean value
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10 of each variable and the median value among the categories. For each participant, we calculated the person-years
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12 of follow-up from baseline in 1988 and 1990 to the first endpoint of death, moving from the community, or the
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14 end of 2009. Mortality rates for CVD were estimated according to the perceived levels of *Ikigai*.
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17 In the analysis, we calculated the association between *Ikigai* and risk of mortality from CVD by sex,
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19 with hazard ratios (HRs) and 95% confidence intervals (CIs), using the Cox proportional hazards model. The
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21 analysis was performed adjusted for age and then for other potential confounders: BMI (< 18.5, 18.5 to
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23 <25.0, 25.0 to 30.0, 30.0 to 35.0, and ≥ 35.0 kg/m²), smoking status (never, ex-smoker, and current
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25 smoker), alcohol consumption (never, ex-drinker, 1–20 and ≥ 20.0 g ethanol/ day), sports activity time per week
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27 (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),
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29 education level (<13, 13–15, 16–18, and ≥ 19 years), marital status (living with a spouse, divorced, bereaved and
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31 single), sleep duration per day (<5, 5, 6, 7, 8, 9 and ≥ 10 h/day), perceived mental stress (low, moderate, high,
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33 very high), sense of life enjoyment (always, sometimes, moderate, never) and medical history of hypertension
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35 and diabetes (yes or no). Missing values for these covariates were treated as additional missing categories, and
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37 the model contained these dummy variables. Furthermore, the stratified analysis was performed for six
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39 categories of employment status; employed, self-employed, part-time worker, unemployed, homemaker, and
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41 other. In addition, we conducted a sensitivity analysis to exclude those who died early and those who moved and
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43 were censored in the first five years of follow-up. The following analysis calculated the association between
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45 *Ikigai* and risk of mortality from CVD among unemployed persons by type of CVD: total stroke, ischemic
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47 stroke, hemorrhagic stroke, CHD, and heart failure.
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54 Probability values for statistical significance were two-tailed, and a *P*-value <0.05 was regarded as
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56 statistically significant. The statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary,
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58 NC, USA).
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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 mortality²⁸⁻³⁰. 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 levels³¹. 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

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3 mortality and stroke incidence were stronger in men than in women^{32,33}. Another analysis used JACC study data
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5 on 3 004 CVD deaths recorded during the mean 12.5-years follow-up period. It showed that men with higher
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7 *Ikigai* had a reduced risk of CVD mortality after adjusting CVD risk factors, but not stroke and CHD³⁴. In the
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9 present study, the inverse association between having *Ikigai* and CVD mortality risk was more pronounced in
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11 men than in women, as in previous studies. However, with a large study population and a more extended follow-
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13 up period than the previous study, it demonstrated that among the unemployed, those with high *Ikigai* had
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15 significantly lower mortality risk from CVD, stroke, and CHD regardless of gender. Our findings showed that
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17 having *Ikigai* can reduce the risk of mortality from stroke and CHD, even among unemployment. A previous
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19 study, which followed 297 construction workers for two years and observed changes in their blood pressure,
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21 showed that the longer the unemployment, the greater the rise in blood pressure. A previous study may imply a
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23 causal link between the increase in blood pressure and the length of unemployment³⁵. Positive psychological
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25 factors are associated with a lower prevalence of hypertension³⁶. Therefore, *Ikigai* may have reduced the risk of
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27 mortality from stroke by positively affecting blood pressure changes in unemployed people. The better health
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29 impacts of having *Ikigai* may be apparent, even among the unemployed with much evidence of poor health.
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36 The present study has several strengths compared to previous studies. First, a population-based cohort
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38 study with a large sample size and a more extended follow-up period allowed us to assess the risk of
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40 cardiovascular mortality according to a level of *Ikigai*, stratified by employment status. Second, we adjusted for
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42 confounding factors, including lifestyle habits, social and psychological factors, and past medical histories such
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44 as hypertension and diabetes mellitus.
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48 There were some limitations to our study. First, psychological factors such as *Ikigai* were evaluated by a
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50 self-administered single-item questionnaire. Second, we used mortality as an endpoint, but the onset of CVD
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52 could have induced lifestyle changes and *Ikigai*. There could be reverse causality that the occurrence of disease
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54 or illness had influenced *Ikigai* at baseline. Therefore, we excluded histories of CVD and cancer and conducted a
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56 sensitivity analysis in which individuals who died or moved during the first five years of follow-up were
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58 censored and found that the inverse association between *Ikigai* and risk of CVD mortality remained unchanged.
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3 Lastly, although we adjusted for numerous potential confounders, some unmeasured confounders, such as the
4 usage of medical services, may still be present. A previous study using a national panel study of 7 168 US adults
5 showed that having a purpose in life was associated with a higher likelihood of using health care services such as
6 cholesterol tests, colonoscopies, mammogram/X-ray, pap smear, and prostate examinations ³⁷.
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14 **Conclusion**

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16 We found that *Ikigai* was associated with a lower risk of CVD mortality for all participants, particularly
17 unemployed men and women. Having *Ikigai* could reduce the risk of CVD mortality among unemployed
18 persons.
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33 **Author Contributions:** HI and AT conceived and designed the study; JM, and KS drafted the plan for the data
34
35 analyses; JM and TK conducted data analysis; SI and TK provided statistical expertise and interpreted the data;
36
37 JM drafted the manuscript; HI and KS analyzed and interpreted the data, and critically revised the manuscript;
38
39 JM, KS, and HI had primary responsibility for final content; and all authors were involved in interpretation of
40
41 the results and revision of the manuscript and approved the final version of the manuscripts. JM, KS, and HI are
42
43 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.

REFERENCES

1. Collins AL, Gleib DA, Goldman N. The role of life satisfaction and depressive symptoms in all-cause mortality. *Psychology and aging* 2009;24(3):696-702. doi: 10.1037/a0016777
[published Online First: 2009/09/11]
2. Koivumaa-Honkanen H, Honkanen R, Viinamaki H, et al. Self-reported life satisfaction and 20-year mortality in healthy Finnish adults. *American journal of epidemiology* 2000;152(10):983-91.
3. Steptoe A. Happiness and Health. *Annual review of public health* 2019;40:339-59. doi: 10.1146/annurev-publhealth-040218-044150 [published Online First: 2019/01/03]
4. Shirai K, Iso H, Ohira T, et al. Perceived level of life enjoyment and risks of cardiovascular disease incidence and mortality: the Japan public health center-based study. *Circulation* 2009;120(11):956-63. doi: 10.1161/CIRCULATIONAHA.108.834176
5. Rozanski A, Bavishi C, Kubzansky LD, et al. Association of Optimism With Cardiovascular Events and All-Cause Mortality: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2019;2(9):e1912200. doi: 10.1001/jamanetworkopen.2019.12200 [published Online First: 2019/09/29]
6. Tomioka K, Kurumatani N, Hosoi H. Relationship of Having Hobbies and a Purpose in Life With Mortality, Activities of Daily Living, and Instrumental Activities of Daily Living Among Community-Dwelling Elderly Adults. *Journal of epidemiology* 2016;26(7):361-70. doi: 10.2188/jea.JE20150153

- 1
2
3 7. Tang M, Wang D, Guerrien A. A systematic review and meta-analysis on basic psychological
4
5 need satisfaction, motivation, and well-being in later life: Contributions of self-determination
6
7 theory. *PsyCh journal* 2019 doi: 10.1002/pchj.293 [published Online First: 2019/06/10]
8
9
- 10
11 8. Cohen R, Bavishi C, Rozanski A. Purpose in Life and Its Relationship to All-Cause Mortality and
12
13 Cardiovascular Events: A Meta-Analysis. *Psychosomatic medicine* 2016;78(2):122-33. doi:
14
15 10.1097/PSY.0000000000000274 [published Online First: 2015/12/03]
16
17
- 18
19 9. Mathews G. What Makes Life Worth Living? How Japanese and Americans Make Sense of Their
20
21 Worlds. *Berkeley: University of California Press* 1996
22
23
- 24
25 10. Shirai K, Iso H, Fukuda H, et al. Factors associated with "Ikigai" among members of a public
26
27 temporary employment agency for seniors (Silver Human Resources Centre) in Japan; gender
28
29 differences. *Health and quality of life outcomes* 2006;4:12. doi: 10.1186/1477-7525-4-12
30
31
- 32
33 11. Weiss RS, Bass SA, Heimovitz HK, et al. Japan's silver human resource centers and participant
34
35 well-being. *Journal of cross-cultural gerontology* 2005;20(1):47-66. doi: 10.1007/s10823-
36
37 005-3797-4
38
39
- 40
41 12. Sone T, Nakaya N, Ohmori K, et al. Sense of life worth living (ikigai) and mortality in Japan:
42
43 Ohsaki Study. *Psychosomatic medicine* 2008;70(6):709-15. doi:
44
45 10.1097/PSY.0b013e31817e7e64
46
47
- 48
49 13. Sloane E, Schrenker R. Conceptual Design and Resources for a General-Purpose Safety and
50
51 Performance Verification and Validation Toolkit (V2T) for Life-Critical Wireless Medical
52
53 Device Networks (WMDN). *Conf Proc IEEE Eng Med Biol Soc* 2005;1:178-81. doi:
54
55 10.1109/IEMBS.2005.1616371 [published Online First: 2007/02/07]
56
57
58
59
60

- 1
2
3 14. Roelfs DJ, Shor E, Davidson KW, et al. Losing life and livelihood: a systematic review and
4
5 meta-analysis of unemployment and all-cause mortality. *Social science & medicine*
6
7 2011;72(6):840-54. doi: 10.1016/j.socscimed.2011.01.005 [published Online First:
8
9 2011/02/19]
10
11
12
13 15. Meneton P, Kesse-Guyot E, Mejean C, et al. Unemployment is associated with high
14
15 cardiovascular event rate and increased all-cause mortality in middle-aged socially privileged
16
17 individuals. *International archives of occupational and environmental health*
18
19 2015;88(6):707-16. doi: 10.1007/s00420-014-0997-7
20
21
22
23 16. Gallo WT. Evolution of research on the effect of unemployment on acute myocardial infarction
24
25 risk. *Archives of internal medicine* 2012;172(22):1737-8. doi:
26
27 10.1001/jamainternmed.2013.1835 [published Online First: 2012/11/21]
28
29
30
31 17. Brenner MH. The impact of unemployment on heart disease and stroke mortality in European
32
33 Union Countries. *EU publications* 2016 doi: 10.2767/81253
34
35
36
37 18. Vanthomme K, Gadeyne S. Unemployment and cause-specific mortality among the Belgian
38
39 working-age population: The role of social context and gender. *PloS one*
40
41 2019;14(5):e0216145. doi: 10.1371/journal.pone.0216145
42
43
44
45 19. Weden MM, Astone NM, Bishai D. Racial, ethnic, and gender differences in smoking cessation
46
47 associated with employment and joblessness through young adulthood in the US. *Social*
48
49 *science & medicine* 2006;62(2):303-16. doi: 10.1016/j.socscimed.2005.06.009 [published
50
51 Online First: 2005/07/21]
52
53
54
55 20. Janlert U. Unemployment as a disease and diseases of the unemployed. *Scandinavian journal of*
56
57 *work, environment & health* 1997;23 Suppl 3:79-83. [published Online First: 1997/01/01]
58
59
60

- 1
2
3 21. Backhans MC, Balliu N, Lundin A, et al. Unemployment Is a Risk Factor for Hospitalization
4
5 Due to Alcohol Problems: A Longitudinal Study Based on the Stockholm Public Health
6
7 Cohort (SPHC). *Journal of studies on alcohol and drugs* 2016;77(6):936-42. doi:
8
9 10.15288/jsad.2016.77.936 [published Online First: 2016/11/01]
10
11
12
13 22. Hammarstrom A. Health consequences of youth unemployment--review from a gender
14
15 perspective. *Social science & medicine* 1994;38(5):699-709.
16
17
18 23. Schaller J, Stevens AH. Short-run effects of job loss on health conditions, health insurance, and
19
20 health care utilization. *Journal of health economics* 2015;43:190-203. doi:
21
22 10.1016/j.jhealeco.2015.07.003
23
24
25 24. Kim ES, Sun JK, Park N, et al. purpose in life and reduced incidence of stroke in older adults:
26
27 'The Health and Retirement Study'. *Journal of psychosomatic research* 2013;74(5):427-32.
28
29 doi: 10.1016/j.jpsychores.2013.01.013 [published Online First: 2013/04/20]
30
31
32
33 25. Tamakoshi A, Ozasa K, Fujino Y, et al. Cohort profile of the Japan Collaborative Cohort Study
34
35 at final follow-up. *Journal of epidemiology* 2013;23(3):227-32.
36
37
38
39 26. Yasukawa S, Eguchi E, Ogino K, et al. "Ikigai", Subjective Wellbeing, as a Modifier of the
40
41 Parity-Cardiovascular Mortality Association- The Japan Collaborative Cohort Study.
42
43 *Circulation journal : official journal of the Japanese Circulation Society* 2018;82(5):1302-
44
45 08. doi: 10.1253/circj.CJ-17-1201
46
47
48
49 27. Tanno K, Sakata K, Japan Collaborative Cohort Study for Evaluation of C. Psychological factors
50
51 and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC).
52
53 *Asian Pacific journal of cancer prevention : APJCP* 2007;8 Suppl:113-22.
54
55
56
57
58
59
60

- 1
2
3 28. De Martinis M, Franceschi C, Monti D, et al. Inflammation markers predicting frailty and
4 mortality in the elderly. *Experimental and molecular pathology* 2006;80(3):219-27. doi:
5 10.1016/j.yexmp.2005.11.004 [published Online First: 2006/02/08]
6
7
8
9
10
11 29. Harris TB, Ferrucci L, Tracy RP, et al. Associations of elevated interleukin-6 and C-reactive
12 protein levels with mortality in the elderly. *The American journal of medicine*
13 1999;106(5):506-12. [published Online First: 1999/05/21]
14
15
16
17
18
19 30. Reuben DB, Cheh AI, Harris TB, et al. Peripheral blood markers of inflammation predict
20 mortality and functional decline in high-functioning community-dwelling older persons.
21 *Journal of the American Geriatrics Society* 2002;50(4):638-44. [published Online First:
22 2002/05/02]
23
24
25
26
27
28
29 31. Zilioli S, Slatcher RB, Ong AD, et al. purpose in life predicts allostatic load ten years later.
30 *Journal of psychosomatic research* 2015;79(5):451-7. doi: 10.1016/j.jpsychores.2015.09.013
31 [published Online First: 2015/11/04]
32
33
34
35
36
37 32. Giltay EJ, Geleijnse JM, Zitman FG, et al. Dispositional optimism and all-cause and
38 cardiovascular mortality in a prospective cohort of elderly dutch men and women. *Archives*
39 *of general psychiatry* 2004;61(11):1126-35. doi: 10.1001/archpsyc.61.11.1126 [published
40 Online First: 2004/11/03]
41
42
43
44
45
46
47 33. Ostir GV, Markides KS, Peek MK, et al. The association between emotional well-being and the
48 incidence of stroke in older adults. *Psychosomatic medicine* 2001;63(2):210-5. [published
49 Online First: 2001/04/09]
50
51
52
53
54
55 34. Tanno K, Sakata K, Ohsawa M, et al. Associations of ikigai as a positive psychological factor
56 with all-cause mortality and cause-specific mortality among middle-aged and elderly
57
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59
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53
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55
56
57
58
59
60

Japanese people: findings from the Japan Collaborative Cohort Study. *Journal of psychosomatic research* 2009;67(1):67-75. doi: 10.1016/j.jpsychores.2008.10.018

35. Janlert U. Unemployment and blood pressure in Swedish building labourers. *Journal of internal medicine* 1992;231(3):241-6. doi: 10.1111/j.1365-2796.1992.tb00530.x [published Online First: 1992/03/01]
36. Ostir GV, Berges IM, Markides KS, et al. Hypertension in older adults and the role of positive emotions. *Psychosomatic medicine* 2006;68(5):727-33. doi: 10.1097/01.psy.0000234028.93346.38 [published Online First: 2006/10/03]
37. Kim ES, Strecher VJ, Ryff CD. Purpose in life and use of preventive health care services. *Proceedings of the National Academy of Sciences of the United States of America* 2014;111(46):16331-6. doi: 10.1073/pnas.1414826111 [published Online First: 2014/11/05]

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

	Men				Women			
	Low	Moderate	High	<i>P</i> -Value	Low	Moderate	High	<i>P</i> -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)	

1		≥5 h/w	73 (3.5)	687 (5.9)	1307 (9.0)		79 (2.2)	720 (3.8)	956 (5.7)	
2	Walking time, n (%)					<0.001				<.0001
3		never	294 (18.8)	1354 (11.6)	1307 (9.5)		390 (14.3)	1852 (9.7)	1221 (7.7)	
4		0.5 h/day	302 (19.3)	2268 (19.4)	2453 (17.8)		525 (19.3)	3444 (18.0)	2596 (16.4)	
5		0.5-1 h/day	271 (17.3)	2339 (20.0)	2788 (20.3)		558 (20.5)	4198 (21.9)	3249 (20.5)	
6		≥1 h/day	695 (44.5)	5757 (49.1)	7195 (52.4)		1246 (45.8)	9690 (50.5)	8777 (55.4)	
7	Sleep duration, h/d		7.6	7.5	7.4	0.009	7.2	7.1	7.1	0.008
8	Perceived mental stress, n (%)					<0.001				<0.001
9		Low	378 (17.7)	1382 (11.4)	3107 (20.9)		541 (14.6)	2319 (11.6)	4300 (24.4)	
10		Moderate	1029 (48.1)	8237 (68.2)	8332 (55.9)		1838 (49.8)	13907 (69.8)	10169 (57.6)	
11		High	733 (34.3)	2451 (20.3)	3458 (23.2)		1315 (35.6)	3699 (18.6)	3184 (18.0)	
12	Sense of life enjoyment, n (%)					<0.001				<0.001
13		Low	417 (19.2)	399 (3.3)	193 (1.3)		775 (20.7)	686 (3.4)	184 (1.0)	
14		Moderate	965 (44.4)	9101 (75.0)	5612 (37.5)		1753 (46.7)	15044 (75.2)	5937 (33.5)	
15		High	230 (10.6)	2640 (21.7)	8265 (55.2)		315 (8.4)	4288 (21.4)	10234 (57.8)	
16	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
17	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	<i>P</i> _{Trend}	Low	Moderate	High	<i>P</i> _{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.

		<i>Ikigai</i>			<i>P</i> _{Trend}
		Low	Moderate	High	
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 cardiovascular diseases types according to the perceived levels of *Ikigai* among unemployed persons.

		<i>Ikigai</i>			<i>P</i> _{Trend}
		Low	Moderate	High	
	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.



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.

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

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of 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	3-4
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

1	Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
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3				
4	Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6-7
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7	Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	6-7
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11	Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
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17	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
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26	Bias	#9	Describe any efforts to address potential sources of bias	7
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28	Study size	#10	Explain how the study size was arrived at	7
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30	Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8
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34	Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	
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40	Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	8
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44	Statistical methods	#12c	Explain how missing data were addressed	8
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48	Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	8
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52	Statistical methods	#12e	Describe any sensitivity analyses	
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56	8			
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Results

1	Participants	#13a	Report numbers of individuals at each stage of study—eg numbers	9
2			potentially eligible, examined for eligibility, confirmed eligible,	
3			included in the study, completing follow-up, and analysed. Give	
4			information separately for for exposed and unexposed groups if	
5			applicable.	
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9	Participants	#13b	Give reasons for non-participation at each stage	9
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11	Participants	#13c	Consider use of a flow diagram	
12				
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14	27			
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16	Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical,	9, 21-22
17			social) and information on exposures and potential confounders. Give	
18			information separately for exposed and unexposed groups if	
19			applicable.	
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23	Descriptive data	#14b	Indicate number of participants with missing data for each variable of	
24			interest	
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29	Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
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34	Outcome data	#15	Report numbers of outcome events or summary measures over time.	
35			Give information separately for exposed and unexposed groups if	
36			applicable.	
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39	9-10			
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41	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted	9-10
42			estimates and their precision (eg, 95% confidence interval). Make	
43			clear which confounders were adjusted for and why they were	
44			included	
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48	Main results	#16b	Report category boundaries when continuous variables were	9
49			categorized	
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52	Main results	#16c	If relevant, consider translating estimates of relative risk into absolute	
53			risk for a meaningful time period	
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1	Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
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5	Discussion			
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7	Key results	#18	Summarise key results with reference to study objectives	10
8				
9	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
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15	Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10-11
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20	Generalisability	#21	Discuss the generalisability (external validity) of the study results	11-12
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23	Other			
24	Information			
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26	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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BMJ Open

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

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3 1 **TITLE**
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5 2 Purpose in life (*Ikigai*) and employment status in relation to cardiovascular mortality: the Japan Collaborative
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8 3 Cohort Study
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12 5 **AUTHOR NAMES AND AFFILIATIONS**
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38 16
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40 17 **KEYWORDS**
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42 18 purpose in life (*Ikigai*), employment status, cardiovascular disease, stroke, coronary heart disease, mortality,
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44 19 prospective study
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49 21 **NUMBER OF TABLES**
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WORD COUNT

237 words (abstract)

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For peer review only

1
2
3 **32 Abstract**
4

5 **33 Objectives:** To investigate whether having a purpose in life (*Ikigai*) is associated with risk of cardiovascular
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7
8 **34** disease mortality and whether the association varies by employment status.
9

10 **35 Design:** Prospective cohort study
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12 **36 Setting:** Residents in 45 municipalities, Japan.
13

14
15 **37 Participants:** 29 517 men and 41 984 women aged 40 to 79 years, free of cardiovascular disease (CVD) and
16
17 **38** cancer at baseline from 1988 to 1990.
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19 **39 Primary outcome measures:** CVD mortality
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21
22 **40 Results:** During the median follow-up of 19.1 years, 4 680 deaths (2 393 men and 2 287 women) from total
23
24 **41** CVD were observed. Greater *Ikigai* was associated with a lower risk of CVD mortality, and the result was
25
26 **42** stronger for men than for women. Stratified by employment status, the inverse association was confined to
27
28 **43** unemployed persons. Among unemployed persons, the multivariable HRs of total CVD were higher for
29
30 moderate and high versus low levels of *Ikigai*. Multivariable HRs (95% CIs) were 0.74 (0.57 to 0.97) and 0.69
31 **44**
32 (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
33 **45**
34 trend = 0.039 in women. No association was observed among the employed, including part-time workers, self-
35 **46**
36 employed, and homemakers for both men and women. Such an inverse association remained even after
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38 **47** excluding early deaths within five years from the baseline survey.
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40 **48**

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42 **49 Conclusion:** Higher levels of *Ikigai* were associated with a lower risk of CVD mortality, especially for
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44 **50** unemployed men and women.
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52 **Article Summary**

53 **Strengths and limitations of this study**

54 - Strengths included a population-based cohort study, a large sample size, and a long follow-up period.

55 - Another strength was the adjustment for many confounding factors including lifestyle habits, social and
56 psychological factors, and past medical histories such as hypertension and diabetes mellitus.

57 - Limitation was a self-administered single-item questionnaire on the purpose in life (*Ikigai*) to assess exposure at
58 the baseline survey.

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59 Introduction

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

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

78 A meta-analysis of 42 cross-sectional and prospective cohort studies providing data on more than 20
79 million people showed that unemployment was associated with an increased risk of all-cause mortality, with a
80 63% higher risk for those who experienced unemployment than those who did not.¹⁴ Unemployment status was
81 associated with an increased incidence of cardiovascular events such as coronary heart disease and stroke
82 associated with.¹⁵⁻¹⁷ A study based on a population-wide dataset of 3 084 137 Belgian individuals aged 25 to 59
83 at the 2001 census showed that unemployment status was associated with health problems such as

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3 84 cardiovascular, endocrine, and psychiatric disorders.¹⁸ According to a study of 297 construction workers
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5 85 followed for two years, the longer the unemployment, the greater rise in blood pressure levels.¹⁹ Poor health is a
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7 86 direct or indirect consequence of unemployment, and this causal relationship was mediated by health behaviors
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9
10 87 such as tobacco or alcohol consumption.²⁰⁻²³
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12 88 No study, however, has focused on the impact of *Ikigai* on mortality risk by employment status. We
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15 89 hypothesize that *Ikigai* positively impacts cardiovascular health even in an unemployed situation. We aimed to
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17 90 test this hypothesis using a long-term follow-up of a large-scale prospective cohort study of Japanese adults.
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19 91

21 92 **Methods**

24 93 **Study population**

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26 94 The Japan Collaborative Cohort Study for the Evaluation of Cancer Risks (JACC study) enrolled residents in 45
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28 95 area around Japan between 1988 and 1990. Participants were required to conduct self-administered
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30
31 96 questionnaires about their lifestyle and previous medical history concerning cardiovascular disease (CVD) and
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33 97 cancer at baseline. The details of the study procedure are described elsewhere.²⁴ Briefly, a total of 1 10 585
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35 98 subjects (46 395 men and 64 190 women) aged 40 to 79 years old participated in the JACC study at the baseline
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38 99 survey. Among the participants, 7 692 were excluded due to a past history of CVD or cancer at baseline.
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40 100 Additionally, we excluded 31 392 excluded for 25 730 participants in areas with no questions about *Ikigai* and 5
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42 101 662 participants who lacked information about *Ikigai*. Finally, 71 501 subjects (29 517 men and 41 984 women)
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44
45 102 were eligible for inclusion in the analyses (Figure 1). Prior to the completion of the questionnaire, the
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47 103 participants were provided informed consent to be involved in this epidemiological study. Individual informed
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49 104 consent was obtained from each participant in 36 out of the 45 study areas (written consent in 35 areas and oral
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51 105 consent in 1 area). In the remaining nine areas, group consent was obtained from each community
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53
54 106 representative. Ethical approval for the present study was given by the ethical committees of Osaka University
55
56 107 and Hokkaido University.
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58 108
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60

109 **Mortality surveillance**

110 The date and cause of death for participants were determined by reviewing all death certificates from each area.
111 According to the International Classification of Diseases, 10th revision, cause-specific mortality was defined
112 within total CVD mortality (I01 to I99). Type-specific CVD mortality was defined as I60.0 to I69.8 for total
113 stroke, I20.0 to I25.5 for coronary heart disease, I50.0 to I50.9 for heart failure, and other CVDs. Total stroke
114 was divided into three subtypes: cerebral infarction (I63.0 to I63.9), hemorrhagic stroke (I60.0 to I61.9), and
115 stroke of undetermined type (I62.0 to I62.9 and I64 to I69.8). From baseline until December 31, 2009, a total of
116 15 801 participants were censored because of death, and 3 986 were censored because they moved out of their
117 original residential area; follow-up was terminated at the end of 1999 (four areas), 2003 (four areas), and 2008
118 (two areas). The median follow-up period was 19.1 years (interquartile range, 10.4 to 20.7).

120 **Baseline Measurement**

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

131 **Statistical analysis**

132 For each participant, we calculated the person-years of follow-up from the baseline surveys between 1988 and
133 1990 to the first endpoint of death, moving from the community, or the end of 2009. Mortality rates for CVD

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3 134 were estimated according to the perceived levels of *Ikigai* at baseline. We compared sex-specific and age-
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5 135 adjusted mean or prevalence of baseline risk characteristics according to perceived levels of *Ikigai* among
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8 136 participants using the linear regression or mantel-haenszel test.
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10 137 The analysis used a Cox proportional hazards model to calculate sex-specific hazard ratios
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12 138 (HRs) and 95% confidence intervals (CIs) of CVD according to perceived levels of *Ikigai* at baseline
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14
15 139 and the risk of mortality from CVD at follow-up. The adjustment was done for age and then for other
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17 140 potential confounders: BMI (< 18.5, 18.5 to <25.0, 25.0 to 30.0, 30.0 to 35.0, and ≥ 35.0 kg/m²),
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19 141 smoking status (never, ex-smoker, and current smoker), alcohol consumption (never, ex-drinker, 1–20 and ≥ 20.0
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21 142 g ethanol per day), sports activity time per week (almost never, 1–2, 3–4 and ≥ 5 hour per week), walking time
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24 143 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),
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26 144 marital status (living with a spouse, divorced, bereaved and single), sleep duration per day (<5, 5, 6, 7, 8, 9 and
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28 145 ≥ 10 hour per day), perceived mental stress (low, moderate, high, very high), sense of life enjoyment (always,
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31 146 sometimes, moderate, never) and medical history of hypertension and diabetes (yes or no). Missing values for
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33 147 these covariates were treated as additional missing categories, and the model contained these dummy variables.
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35 148 Furthermore, the stratified analysis was performed for six categories of employment status; employed, self-
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38 149 employed, part-time workers, homemakers, unemployed, and others. Homemakers were regarded as the
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40 150 category of employed because they were primarily women, and many of them were assumed to have motivation
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42 151 for children and housework in Japan. In addition, we conducted a sensitivity analysis to exclude those who died
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45 152 early and those who moved and were censored in the first five years of follow-up and the type-specific CVD
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47 153 analysis for total stroke, ischemic stroke, hemorrhagic stroke, stroke of undetermined type, coronary heart
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49 154 disease, heart failure, and other CVDs. To test for linear trends across the *Ikigai* categories for baseline risk
50
51 155 characteristics and hazard ratios, and ordering variable of *Ikigai* (1: low, 2: moderate, 3: high) was used.
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54 156 Probability values for statistical significance were two-tailed, and a *P*-value <0.05 was regarded as statistically
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56 157 significant. The statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).
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58 158 **Patient and Public Involvement**

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3 159 Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this
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5
6 160 research.

10 162 **Results**

11
12 163 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
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15 164 total CVD were documented. Other deaths from major CVD types were 2 053 (1 047 and 1 006) total strokes,
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17 165 716 (398 and 318) ischemic strokes, 739 (344 and 395) hemorrhagic strokes, 598 (305 and 293) strokes of
18
19 166 undetermined type, 975 (550 and 425) coronary heart diseases, 792 (361 and 431) heart failures, and 860 (435
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21
22 167 and 425) other CVDs.

23
24 168 Table 1 shows the mean values or prevalence of cardiovascular risk factors and health behaviors at
25
26 169 baseline according to *Ikigai* level. In both men and women, those with high *Ikigai* tended to have higher levels of
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28
29 170 the following factors: BMI, self-employed, higher education (≥ 16 years), current alcohol consumption, never
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31 171 smoking, living with a spouse, sports activity (≥ 1 -2 h/week), walking time (≥ 1 h/day), low perceived mental
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33 172 stress and high life enjoyment. Unlike men, women with high *Ikigai* tended to be employed or part-time
34
35 173 workers.

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37
38 174 Table 2 shows the sex-specific risk of mortality from total CVD according to the level of *Ikigai*,
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40 175 stratified by employment status. Men who had moderate and high *Ikigai* had a lower risk of mortality from total
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42 176 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);
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44
45 177 *P* for trend < 0.001 , respectively. A similar inverse association was observed among unemployed men,
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47 178 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.
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49 179 Women who had moderate and high *Ikigai* levels tended to have a lower risk of mortality from total CVD than
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51 180 those with low *Ikigai*. But, tests for trend were not statistically significant: multivariable HRs (95% CI) were
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53
54 181 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
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56 182 who had moderate and high *Ikigai* had a lower risk of mortality from total CVD than those who had low *Ikigai*;
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58 183 tests for trend were statistically significant: multivariable HRs (95% CI) were 0.78 (0.64 to 0.95) and 0.77 (0.61
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3 184 to 0.97); P for trend = 0.039, respectively. No associations were observed among the unemployed, including
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5 185 part-time workers, self-employed, and homemakers for both men and women.
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7
8 186 Table 3 shows the sensitivity analysis in which we censored individuals who died and those who moved
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10 187 during the first five years of follow-up, having excluded individuals who had an early death. The inverse
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12 188 associations did not differ materially for both men and women.
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15 189 Table 4 shows the risk of mortality from CVD types according to the perceived levels of *Ikigai* among
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17 190 the unemployed. Unemployed men and women with high *Ikigai* had lower risks of mortality from total stroke,
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19 191 stroke subtypes (ischemic stroke, hemorrhagic stroke, and stroke of determined type), coronary heart disease,
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21 heart failure, and other CVDs than those with low *Ikigai*. After adjusting for CVD risk factors, the inverse
22 192 association remained statistically significant for total stroke, stroke of determined type, and coronary heart
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24 193 disease.
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28 195 29 30 31 196 **Discussion**

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33 197 In a large prospective cohort study, higher levels of *Ikigai* were associated with a lower risk of mortality from
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35 198 total CVD among unemployed men and women after adjustment for known cardiovascular risk factors, but such
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37 as inverse association was not observed for the employed. The lower risk of CVD mortality among the
38 199 unemployed was observed even after excluding early deaths within five years from the baseline survey.
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40 200 Furthermore, the risk reduction was evident for total stroke and coronary heart disease among the unemployed
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42 201 people.
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47 203 The underlying biological mechanisms for the potential preventive effect of *Ikigai* on mortality from
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49 204 CVD remained unclear, but some reasons have been addressed. Elevated levels of inflammatory markers such
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51 205 as C-reactive protein and interleukin-6 were associated with an increased CVD risk.²⁷⁻²⁹ A previous study using
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53 data from a 10-year panel survey of 985 adults aged 25 to 74 years residing in the United States showed that
54 206 people with a higher purpose in life had lower physiological function scores, calculated by summarizing
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56 207 biomarkers such as resting blood pressure, heart rate variability, low-density lipoprotein cholesterol, glycosylated
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3 209 hemoglobin, plasma C-reactive protein, interleukin-6, urinary measures of epinephrine/norepinephrine and
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5 210 cortisol levels.³⁰ Another study of 135 older women aged 61 to 91 years found that those with higher scores of
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8 211 purpose in life had lower levels of the soluble IL-6 receptor, an inflammatory marker for stroke, coronary heart
9
10 212 disease as well as rheumatoid arthritis and Alzheimer's disease.³¹

11
12 213 Two other prospective cohort studies using 9.1-year follow-up data for 941 persons and 6-year follow-
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14
15 214 up data for 2 478 persons showed that the risk reductions associated with positive psychological factors in all-
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17 215 cause mortality and stroke incidence were stronger in men than in women.^{32 33} A previous report of the JACC
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19 216 study with a 12.5-year follow-up showed that men with higher *Ikigai* had a reduced risk of CVD mortality but
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21
22 217 not women.³⁴ We observed a similar inverse association of CVD mortality risk in the present study and extended
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24 218 the evidence that the inverse association between *Ikigai* and CVD mortality risk was confined to unemployed
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26 219 men and women.

27
28 220 The present study has several strengths compared to previous studies. First, a population-based cohort
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31 221 study with a large sample size and a more extended follow-up period allowed us to assess the risk of
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33 222 cardiovascular mortality according to the perceived levels of *Ikigai*, stratified by employment status. Second, we
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35 223 adjusted for many confounding factors including lifestyle habits, social and psychological factors, and past
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38 224 medical histories such as hypertension and diabetes mellitus. There were some limitations to our study. First,
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40 225 psychological factors such as *Ikigai* were evaluated by a self-administered single-item questionnaire. It has been
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42 226 noted that *Ikigai* encompasses not only eudaimonic well-being, i.e., well-being that pertains to internal virtue and
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44
45 227 pursuing human capacity³⁵, but also aspects of hedonic well-being characterized by pleasure and satisfaction not
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47 228 necessarily resulting from a virtuous activity³⁶. Unemployed persons with *Ikigai* were possibly likely to have
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49 229 available eudaimonic or hedonic well-being in their daily lives. However, the present study did not provide
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51
52 230 information on the details of *Ikigai*. Second, the presence of illness and preclinical conditions may have
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54 231 influenced *Ikigai* at baseline, which could lead to reverse causality. Therefore, we excluded histories of CVD
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56 232 and cancer and also conducted a sensitivity analysis in which individuals who died or moved during the first five
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58 233 years of follow-up were censored and found that the inverse association between *Ikigai* and the risk of CVD
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3 234 mortality remained unchanged. Lastly, although we adjusted for numerous potential confounders, some
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5 235 unmeasured confounders, such as the usage of medical services, may still be present. A previous study using a
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8 236 national panel study of 7 168 US adults showed that having a purpose in life was associated with a higher
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10 237 likelihood of using health care services such as cholesterol tests, colonoscopies, mammogram/X-ray, pap smear,
11
12 238 and prostate examinations.³⁷
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17 240 **Conclusion**

18
19 241 We found that higher levels of *Ikigai* were associated with a lower risk of CVD mortality, specifically for
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21 242 unemployed men and women. Having *Ikigai* might be useful for the risk reduction of CVD mortality among the
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24 243 unemployed.
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34
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36
37 274 analyses; JM and TK conducted data analysis; SI and TK provided statistical expertise and interpreted the data;
38
39
40 275 JM drafted the manuscript; HI and KS analyzed and interpreted the data, and critically revised the manuscript;
41
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44
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46
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REFERENCES

1. Collins AL, Gleib DA, Goldman N. The role of life satisfaction and depressive symptoms in all-cause mortality. *Psychol Aging* 2009;24:696-702.
2. Koivumaa-Honkanen H, Honkanen R, Viinamaki H, *et al.* Self-reported life satisfaction and 20-year mortality in healthy Finnish adults. *Am J Epidemiol* 2000;152:983-91.
3. Steptoe A. Happiness and Health. *Annu Rev Public Health* 2019;40:339-59.
4. Shirai K, Iso H, Ohira T, *et al.* Perceived level of life enjoyment and risks of cardiovascular disease incidence and mortality: the Japan public health center-based study. *Circulation* 2009;120:956-63.
5. Rozanski A, Bavishi C, Kubzansky LD, *et al.* Association of optimism with cardiovascular events and all-cause mortality: a systematic review and meta-analysis. *JAMA Netw Open* 2019;2:e1912200.
6. Tomioka K, Kurumatani N, Hosoi H. Relationship of having hobbies and a purpose in life with mortality, activities of daily living, and instrumental activities of daily living among community-dwelling elderly adults. *J Epidemiol* 2016;26:361-70.
7. Tang M, Wang D, Guerrien A. A systematic review and meta-analysis on basic psychological need satisfaction, motivation, and well-being in later life: Contributions of self-determination theory. *Psych J* 2020;9:5-33.
8. Cohen R, Bavishi C, Rozanski A. Purpose in life and Its relationship to all-cause mortality and cardiovascular events: a meta-analysis. *Psychosom Med* 2016;78:122-33.
9. Mathews G. What Makes Life Worth Living? How Japanese and Americans Make Sense of Their Worlds. *Berkeley: University of California Press* 1996

- 1
2
3 332 10. Shirai K, Iso H, Fukuda H, *et al.* Factors associated with "Ikigai" among members of a public
4
5
6 333 temporary employment agency for seniors (Silver Human Resources Centre) in Japan; gender
7
8 334 differences. *Health Qual Life Outcomes* 2006;4:12.
9
10
11 335 11. Weiss RS, Bass SA, Heimovitz HK, *et al.* Japan's silver human resource centers and participant
12
13 336 well-being. *J Cross Cult Gerontol* 2005;20:47-66.
14
15
16
17 337 12. Sone T, Nakaya N, Ohmori K, *et al.* Sense of life worth living (ikigai) and mortality in Japan:
18
19 338 Ohsaki Study. *Psychosom Med* 2008;70:709-15.
20
21
22 339 13. Kim ES, Sun JK, Park N, *et al.* Purpose in life and reduced incidence of stroke in older adults:
23
24
25 340 'The Health and Retirement Study'. *J Psychosom Res* 2013;74:427-32.
26
27
28 341 14. Roelfs DJ, Shor E, Davidson KW, *et al.* Losing life and livelihood: a systematic review and
29
30 342 meta-analysis of unemployment and all-cause mortality. *Soc Sci Med* 2011;72:840-54.
31
32
33 343 15. Meneton P, Kesse-Guyot E, Mejean C, *et al.* Unemployment is associated with high
34
35
36 344 cardiovascular event rate and increased all-cause mortality in middle-aged socially privileged
37
38 345 individuals. *Int Arch Occup Environ Health* 2015;88:707-16.
39
40
41 346 16. Gallo WT. Evolution of research on the effect of unemployment on acute myocardial infarction
42
43
44 347 risk. *Arch Intern Med* 2012;172:1737-8.
45
46
47 348 17. Brenner MH. The impact of unemployment on heart disease and stroke mortality in European
48
49 349 Union Countries. *EU publications* 2016
50
51
52 350 18. Vanthomme K, Gadeyne S. Unemployment and cause-specific mortality among the Belgian
53
54
55 351 working-age population: The role of social context and gender. *PLoS One* 2019;14:e0216145.
56
57
58
59
60

- 1
2
3 352 19. Janlert U. Unemployment and blood pressure in Swedish building labourers. *J Intern Med*
4
5 353 1992;231:241-6.
6
7
8
9 354 20. Weden MM, Astone NM, Bishai D. Racial, ethnic, and gender differences in smoking cessation
10
11 355 associated with employment and joblessness through young adulthood in the US. *Soc Sci*
12
13 356 *Med* 2006;62:303-16.
14
15
16
17 357 21. Janlert U. Unemployment as a disease and diseases of the unemployed. *Scand J Work Environ*
18
19 358 *Health* 1997;23 Suppl 3:79-83.
20
21
22 359 22. Backhans MC, Balliu N, Lundin A, *et al.* Unemployment is a risk factor for hospitalization due
23
24 360 to alcohol problems: a longitudinal study based on the Stockholm Public Health Cohort
25
26 (SPHC). *J Stud Alcohol Drugs* 2016;77:936-42.
27 361
28
29
30 362 23. Hammarstrom A. Health consequences of youth unemployment--review from a gender
31
32 363 perspective. *Soc Sci Med* 1994;38:699-709.
33
34
35
36 364 24. Tamakoshi A, Ozasa K, Fujino Y, *et al.* Cohort profile of the Japan Collaborative Cohort Study
37
38 365 at final follow-up. *J Epidemiol* 2013;23:227-32.
39
40
41 366 25. Yasukawa S, Eguchi E, Ogino K, *et al.* "Ikigai", subjective wellbeing, as a modifier of the parity-
42
43 367 cardiovascular mortality association- The Japan Collaborative Cohort Study. *Circ J*
44
45 368 2018;82:1302-08.
46
47
48
49 369 26. Tanno K, Sakata K. Psychological factors and mortality in the Japan Collaborative Cohort Study
50
51 370 for Evaluation of Cancer (JACC). *Asian Pac J Cancer Prev* 2007;8:113-22.
52
53
54
55 371 27. De Martinis M, Franceschi C, Monti D, *et al.* Inflammation markers predicting frailty and
56
57 372 mortality in the elderly. *Exp Mol Pathol* 2006;80:219-27.
58
59
60

- 1
2
3 373 28. Harris TB, Ferrucci L, Tracy RP, *et al.* Associations of elevated interleukin-6 and C-reactive
4
5 374 protein levels with mortality in the elderly. *Am J Med* 1999;106:506-12.
6
7
8
9 375 29. Reuben DB, Cheh AI, Harris TB, *et al.* Peripheral blood markers of inflammation predict
10
11 376 mortality and functional decline in high-functioning community-dwelling older persons. *J Am*
12
13 377 *Geriatr Soc* 2002;50:638-44.
14
15
16
17 378 30. Zilioli S, Slatcher RB, Ong AD, *et al.* Purpose in life predicts allostatic load ten years later. *J*
18
19 379 *Psychosom Res* 2015;79:451-7.
20
21
22 380 31. Friedman EM, Hayney M, Love GD, *et al.* Plasma interleukin-6 and soluble IL-6 receptors are
23
24 381 associated with psychological well-being in aging women. *Health Psychol* 2007;26:305-13.
25
26
27
28 382 32. Giltay EJ, Geleijnse JM, Zitman FG, *et al.* Dispositional optimism and all-cause and
29
30 383 cardiovascular mortality in a prospective cohort of elderly Dutch men and women. *Arch Gen*
31
32 384 *Psychiatry* 2004;61:1126-35.
33
34
35
36 385 33. Ostir GV, Markides KS, Peek MK, *et al.* The association between emotional well-being and the
37
38 386 incidence of stroke in older adults. *Psychosom Med* 2001;63:210-5.
39
40
41 387 34. Tanno K, Sakata K, Ohsawa M, *et al.* Associations of ikigai as a positive psychological factor
42
43 388 with all-cause mortality and cause-specific mortality among middle-aged and elderly
44
45 389 Japanese people: findings from the Japan Collaborative Cohort Study. *J Psychosom Res*
46
47 390 2009;67:67-75.
48
49
50
51 391 35. Ryff CD. Psychological well-being revisited: advances in the science and practice of eudaimonia.
52
53 392 *Psychother Psychosom* 2014;83:10-28.
54
55
56
57
58
59
60

- 1
2
3 393 36. Trudel-Fitzgerald C, Millstein RA, von Hippel C, *et al.* Psychological well-being as part of the
4
5 394 public health debate? Insight into dimensions, interventions, and policy. *BMC Public Health*
6
7 2019;19:1712.
8 395
9
10
11 396 37. Kim ES, Strecher VJ, Ryff CD. Purpose in life and use of preventive health care services. *Proc*
12
13 397 *Natl Acad Sci U S A* 2014;111:16331-6.
14
15
16 398
17
18 399
19
20
21
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23
24
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Table 1 Sex-specific mean values and proportions of baseline characteristics according to the perceived levels of *Ikigai*.

	Men				<i>P</i> _{Trend}	Women			
	Low	Moderate	High			Low	Moderate	High	<i>P</i> _{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	

1	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
2	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
3	Self-employed								
4	No. at risk	423	3860	5669		367	3137	3321	
5	No. of person-years	6347	61848	93546		6025	53663	56797	
6	No. of deaths	35	290	425		9	113	102	
7	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
8	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
9	Part-time workers								
10	No. at risk	24	267	282		290	1987	1779	
11	No. of person-years	336	4037	4344		4941	34182	30244	
12	No. of deaths	2	27	24		7	28	33	
13	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
14	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
15	Homemakers								
16	No. at risk	2	13	9		685	6201	4908	
17	No. of person-years	33	164	137		10963	100252	80823	
18	No. of deaths	0	0	0		46	266	184	
19	Age-adjusted HR (95%CI)	-	-	-	-	1.00	0.67 (0.49 to 0.91)	0.57 (0.41 to 0.78)	0.003
20	Multivariable * HR (95%CI)	-	-	-	-	1.00	0.83 (0.59 to 1.17)	0.84 (0.58 to 1.22)	0.576
21	Unemployed								
22	No. at risk	436	2262	1802		894	4364	2637	
23	No. of person-years	4821	27595	23334		11864	62898	38599	
24	No. of deaths	84	368	250		145	555	306	
25	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
26	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
27	Others								
28	No. at risk	752	1180	1956		1198	1905	2662	
29	No. of person-years	11808	17493	30335		21257	31124	46191	
30	No. of deaths	108	129	244		93	124	182	
31	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
32	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.

		<i>Ikigai</i>			<i>P</i> _{Trend}
		Low	Moderate	High	
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.

		<i>Ikigai</i>			<i>P</i> _{Trend}
		Low	Moderate	High	
	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.

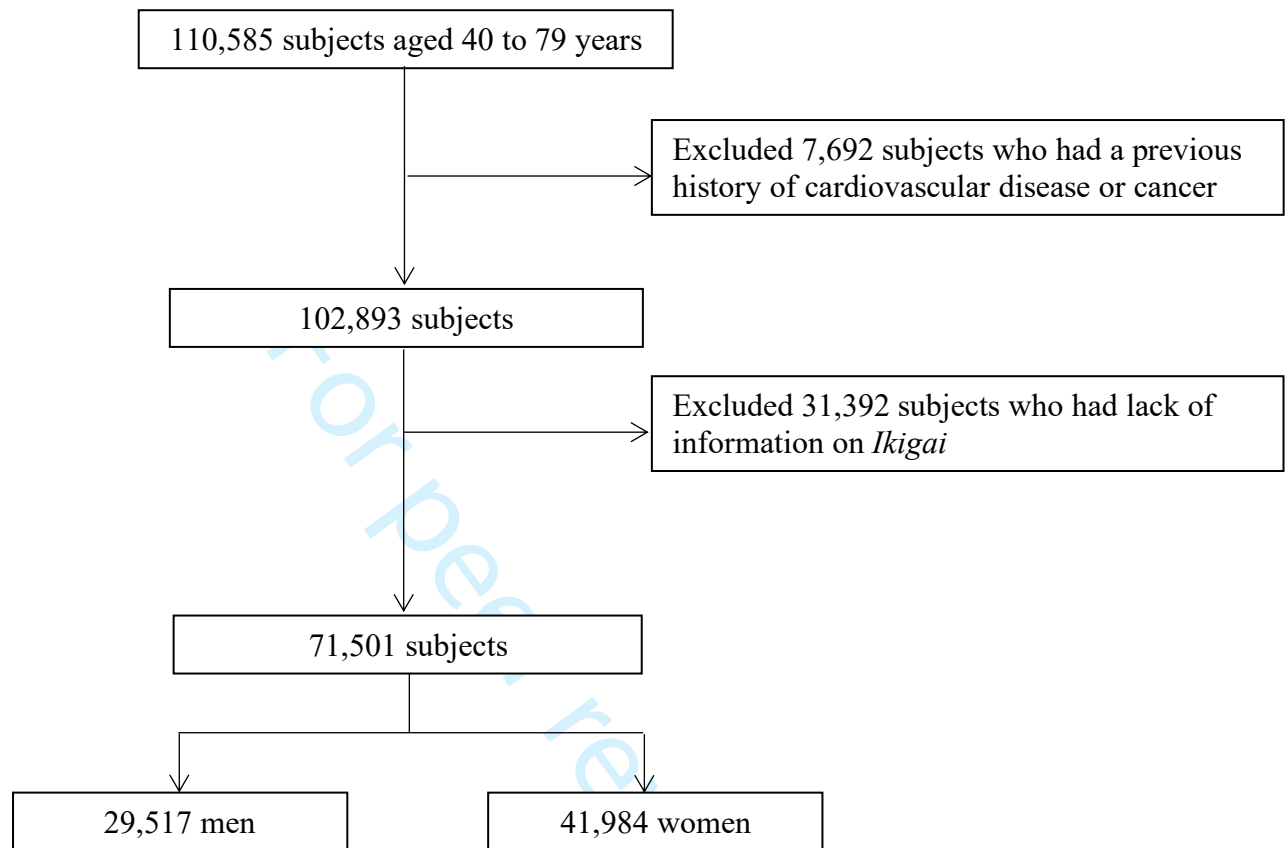


Figure 1 Flowchart for the selection of the study subjects.

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 cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of 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

1	Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6-7
2				
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4	Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	6-7
5				
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7				
8	Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
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14	Data sources /	#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
15	measurement			
16				
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22	Bias	#9	Describe any efforts to address potential sources of bias	7
23				
24	Study size	#10	Explain how the study size was arrived at	7
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27	Quantitative	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8
28	variables			
29				
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31	Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7-8
32				
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34	Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7-8
35				
36				
37	Statistical methods	#12c	Explain how missing data were addressed	8
38				
39	Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	8
40				
41	Statistical methods	#12e	Describe any sensitivity analyses	8
42				
43				
44	Results			
45				
46	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
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54	Participants	#13b	Give reasons for non-participation at each stage	9
55				
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57	Participants	#13c	Consider use of a flow diagram	6
58				
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1	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
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8	Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	6
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11	Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	7
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14	Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9
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19	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
20				
21				
22				
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26	Main results	#16b	Report category boundaries when continuous variables were categorized	7-9
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30	Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
31				
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34	Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
35				
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38	Discussion			
39				
40	Key results	#18	Summarise key results with reference to study objectives	10
41				
42	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
43				
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47	Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10-11
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53	Generalisability	#21	Discuss the generalisability (external validity) of the study results	11-12
54				
55	Other Information			
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1 Funding #22 Give the source of funding and the role of the funders for the 13-14
2 present study and, if applicable, for the original study on which
3 the present article is based
4
5

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7 This checklist was completed on 29. November 2021 using <https://www.goodreports.org/>, a tool made by the
8 EQUATOR Network in collaboration with [Penelope.ai](https://www.penelope.ai)
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