*Circ J* 2018; **82:** 1302–1308
doi:10.1253/circj.CJ-17-1201

**ORIGINAL ARTICLE**
**Epidemiology**

# "Ikigai", Subjective Wellbeing, as a Modifier of the Parity-Cardiovascular Mortality Association
## — The Japan Collaborative Cohort Study —

Sumiyo Yasukawa; Eri Eguchi, PhD; Keiki Ogino, MD, PhD;
Akiko Tamakoshi, MD, PhD; Hiroyasu Iso, MD, PhD

***Background:*** Nulliparity is associated with an excess risk of cardiovascular disease (CVD). "Ikigai", subjective wellbeing in Japan, is associated with reduced risk of CVD. The impact of ikigai on the association between parity and the risk of CVD, however, has not been reported.

***Methods and Results:*** A total of 39,870 Japanese women aged 40–79 years without a history of CVD, cancer or insufficient information at baseline in 1988–1990, were enrolled and followed until the end of 2009. They were categorized into 7 groups according to parity number 0–≥6. Using Cox regression hazard modeling, the associations between parity and mortality from stroke, coronary artery disease, and total CVD were investigated. During the follow-up period, 2,121 total CVD deaths were documented. No association was observed between parity and stroke and CVD mortality in women with ikigai, but there was an association in those without ikigai. The multivariable hazard ratios of stroke and total CVD mortality for nulliparous women without ikigai vs. those with 1 child were 1.87 (95% CI: 1.15–3.05) and 1.46 (95% CI: 1.07–2.01), respectively, and that for stroke mortality in high parity women without ikigai was 1.56 (95% CI: 1.00–2.45).

***Conclusions:*** Nulliparous or high parity women without ikigai had higher mortality from stroke and/or total CVD, suggesting that ikigai attenuated the association between parity and CVD mortality in Japanese women.

**Key Words:** Cardiovascular disease; Ikigai; Mortality; Parity

Cardiovascular disease (CVD) is a leading cause of mortality in both Western countries and in Japan. Reproductive factors are one of the important factors associated with the risk of CVD. In the Framingham Heart Study and the National Health and Nutrition Examination Survey National Epidemiologic Follow-up Study conducted in 1993, Ness et al reported that high parity, as compared with nulliparity, increased the mortality from coronary artery disease (CAD) and CVD.[1] In the American Cancer Society Cancer Prevention Survey II cohort study involving 585,445 subjects, Steenland et al showed that nulliparous women were at a higher risk for CVD than were parous women.[2] A study of 119,963 US women, however, reported no association between parity and the risk of CVD mortality.[3] A meta-analysis of 10 cohort studies in Western and Asian countries reported that parous women had a lower risk of CVD mortality than did nulliparous women.[4]

There is growing evidence that positive psychological factors are associated with lower risk of CVD mortality.[5–9] For example, Giltay et al reported that having high optimism resulted in a 77% reduction in CVD mortality as compared with having high pessimism, in a prospective population-based cohort study of 941 subjects in the Netherlands.[5] Similarly, several Japanese studies showed that having "ikigai", culturally defined as a comprehensive concept describing subjective wellbeing in Japan,[10] was associated with reduced risk of CVD incidence and mortality.[11–14] Ikigai means, briefly, something to live for, the joy and goal of living, a life worth living, and the happiness and benefit of being alive.[10–12]

Lifestyle behaviors, such as having habitual physical activity and not currently smoking, and socioeconomic factors such as higher education level, social support or networks were associated with lower CVD mortality.[15–19] Women may experience more of those factors through their

Received October 30, 2017; revised manuscript received February 7, 2018; accepted February 12, 2018; released online April 3, 2018 Time for primary review: 28 days
Department of Public Health, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama (S.Y., E.E., K.O.); Department of Nursing, Okayama University Graduate School of Health Sciences, Okayama (S.Y.); Department of Public Health, Hokkaido University Graduate School of Medicine, Hokkaido (A.T.); and Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Osaka (H.I.), Japan
Mailing address: Eri Eguchi, MPH, PhD, Department of Public Health, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan. E-mail: eri_eguchi@okayama-u.ac.jp
ISSN-1346-9843 

regular jobs, caring for their children or social activities, which they often see as ikigai in their life. In contrast, nulliparous women are less likely to have a larger social network,[20] and high parity women are more likely to have physical and psychological problems due to childbearing and child rearing,[21] or lower socioeconomic status,[1,22] which are associated with increased risk of CVD mortality.[18] Hence, we hypothesized that the negative impact of nulliparity or high parity on CVD mortality may be influenced by ikigai. No study, to date, however, has investigated the influence of ikigai on the association between parity and CVD mortality. Therefore, the purpose of this study was to investigate ikigai's impact on the association between nulliparity or high parity and CVD mortality.

## Methods

### Subjects

The Japan Collaborative Cohort (JACC) Study, sponsored by the Ministry of Education, Culture, Sports, Science, and Technology of Japan, is a nationwide multicenter collaborative study to evaluate prospectively the various risks and/or protective factors on cancer mortality and incidence. The details of the study procedures have been described elsewhere.[23] Briefly, a baseline survey was conducted from 1988 to 1990. In total, 110,585 healthy subjects (46,395 men and 64,190 women), aged 40–79 years, in 45 areas, 7 of 8 districts in Japan, completed self-administered questionnaires. In the present study, we enrolled subjects who were residents living in 22 target areas. In 20 areas, enrollees were those who had undertaken a basic health examination that was conducted under the Health and Medical Service Law for the Aged, and, in 2 areas, enrollees were identified based on a health check-up for atomic bomb survivors. Informed consent was obtained individually from all subjects in 36 areas (written consent in 35 areas and oral consent in 1 area), whereas written group consent was obtained from the subjects in the remaining 9 areas. The present study was approved by the ethics committees of Nagoya University School of Medicine, University of Tsukuba, and Osaka University.

Of the 64,190 women enrolled, 3,276 were excluded because of stroke history, CAD, or cancer. Furthermore, we excluded 21,044 women because of a lack of information about delivery and/or ikigai. Therefore, a total of 39,870 women were enrolled in the present study. There was no substantial difference in CVD risk factors between individuals with information on parity and/or ikigai and those with missing information.

### Mortality Surveillance

Follow-up surveys were conducted annually to verify the vital status of the participants. The causes and dates of death were identified by reviewing all death certificates in each area. According to the International Classification of Diseases (ICD), 10th revision, cause-specific mortality was determined in terms of stroke (ICD 160–169), CAD (ICD120–125), and total CVD (ICD 101–199). From baseline until 31 December 2009, except for several areas where follow-up was terminated at the end of 1999 (4 areas), 2003 (4 areas), and 2008 (2 areas), a total of 6,389 subjects were censored because of death, while 2,350 subjects were censored because of having moved out of the targeted areas. The median follow-up period was 19.4 years (IQR, 11.6–21.0 years).

### Data Collection

A self-administered questionnaire was used to assess subject baseline characteristics. It included medical histories and lifestyle-related items such as physical activity, smoking, drinking, sleeping hours, history of hypertension, history of diabetes, subjective mental stress, education level, and regular employment. For women, the following reproductive variables were obtained: parity number, marital status, age at menopause, and history of hormone drug use.

### Categories of Parity Status

Self-reported parity number was assessed using a single question, "How many was your parity?" Parity number was then classified into 7 categories: 0, 1, 2, 3, 4, 5, and ≥6.

### Evaluation of Ikigai

As already noted, ikigai is culturally defined, as a comprehensive concept describing subjective wellbeing in Japan.[10–12] In the present study, ikigai status was assessed using a single question, "Do you have ikigai in your life?" The following 4 possible answers were provided: "definitely yes", "yes", "not particularly", and "no". For the analysis, these responses were categorized into 2 groups as follows: subjects who answered, "definitely yes" or "yes" were defined as those with ikigai; and subjects who answered "not particularly" or "no" were defined as those without ikigai.

### Statistical Analysis

We first determined the mean age, age-adjusted mean, and the prevalence of cardiovascular risk factors according to the parity number and ikigai using analysis of covariance for means, and the logistic regression model for prevalence. Cox regression hazard modeling was used to determine the age-adjusted and multivariable-adjusted hazard ratios (HR) and 95% CI to determine associations between parity number (nulliparity and higher parity, as compared with parity 1) and mortality from stroke, CAD, and total CVD. To evaluate the impact of ikigai on the association between parity and mortality from stroke, CAD, and total CVD, we conducted the same analysis for women with and without ikigai and evaluated the effect of the modification using the cross-product terms of parity and ikigai.

On multivariate analysis, at baseline, we adjusted for several factors known to be associated with cardiovascular mortality: age (years); body mass index (BMI; kg/m$^2$); history of hormone drug use, "Have you ever used a hormone drug?" (yes or no); habitual exercise or walking, hours of exercise (almost never and for 1–2, 3–4, and ≥5 h per week); hours of walking (almost never and for 0.5, 0.6–0.9, and ≥1 h per day), smoking status (never, ex-smoker, current smoker 1–19 cigarettes per day, and current smoker ≥20 cigarettes per day), alcohol consumption (non-drinker, ex-drinker, current drinker 0.1–22.9, 23.0–45.9, 46.0–68.9, and ≥69.0 g ethanol per day); duration of sleeping hours (<4.5, 4.5–5.4, 5.5–6.4, 6.5–7.4, 7.5–8.4, 8.5–9.4, and ≥9.5 h); history of hypertension (yes or no), history of diabetes (yes or no); level of perceived mental stress (high, medium, or low); education level (attended school until 13, 13–15, 16–18, or >19 years of age), and regular employment (yes or no).

We used SAS V.9.4 (SAS Institute Inc., Cary, NC, USA) for all statistical analysis. All probability values for statistical tests were 2-tailed, and $P<0.05$ was regarded as statistically significant.

**Table 1. Mean Subject Characteristics and Prevalence of Cardiovascular Risk Factors vs. Parity**

| Cardiovascular risk factors | Parity (n=39,870 women) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 (n=1,466; 3.7%) | 1 (n=3,087; 7.7%) | 2 (n=15,530; 38.9%) | 3 (n=12,475; 31.3%) | 4 (n=4,331; 10.9%) | 5 (n=1,744; 4.4%) | ≥6 (n=1,237; 3.1%) | P-value for trend |
| Age (years) | 59.0 | 56.7 | 53.6 | 56.4 | 63.0 | 67.6 | 71.4 | <0.0001 |
| BMI (kg/m$^2$) | 22.6 | 22.6 | 22.8 | 23.1 | 23.3 | 23.1 | 23.3 | <0.0001 |
| Married (%) | 69.0 | 76.0 | 86.1 | 87.6 | 84.5 | 82.7 | 79.0 | <0.0001 |
| Age at menopause (years) | 47.4 | 48.1 | 48.9 | 48.9 | 48.6 | 48.2 | 47.7 | 0.73 |
| History of hormone drug use (%) | 10.0 | 7.9 | 4.8 | 4.0 | 4.0 | 3.0 | 5.0 | <0.0001 |
| Habitual exercise or walking (%) | 62.1 | 66.6 | 67.9 | 69.3 | 70.5 | 68.4 | 64.5 | 0.0002 |
| Current smoker (%) | 9.9 | 8.3 | 4.6 | 3.9 | 4.3 | 4.6 | 6.8 | <0.0001 |
| Current alcohol drinker (%) | 24.5 | 24.0 | 24.0 | 22.9 | 23.4 | 23.3 | 24.7 | 0.20 |
| Sleep (h/day) | 7.2 | 7.1 | 7.1 | 7.1 | 7.1 | 7.2 | 7.4 | <0.0001 |
| History of hypertension (%) | 20.2 | 20.8 | 21.8 | 22.1 | 22.5 | 22.4 | 23.3 | 0.63 |
| History of diabetes (%) | 4.1 | 4.6 | 3.7 | 4.0 | 3.3 | 3.6 | 5.6 | 0.19 |
| High perceived mental stress (%) | 21.9 | 21.6 | 20.1 | 19.5 | 19.3 | 20.9 | 22.8 | 0.05 |
| College or higher education (%) | 15.9 | 11.9 | 11.4 | 9.7 | 8.6 | 7.6 | 7.1 | <0.0001 |
| Regular employment (%) | 33.3 | 29.4 | 31.0 | 34.7 | 34.3 | 34.8 | 34.3 | <0.0001 |

BMI, body mass index.

**Table 2. Mean Subject Characteristics and Prevalence of CV Risk Factors vs. Ikigai Status**

| CV risk factors | Women without/with ikigai (n=39,870) | | |
|---|---|---|---|
| | Without ikigai (n=22,632; 56.8%) | With ikigai (n=17,238; 43.2%) | P-value |
| Age (years) | 57.5 | 56.6 | <0.0001 |
| BMI (kg/m$^2$) | 22.9 | 23.0 | <0.0001 |
| Married (%) | 84.2 | 85.1 | 0.02 |
| Age at menopause (years) | 48.6 | 48.8 | <0.0001 |
| History of hormone drug use (%) | 4.5 | 5.1 | 0.004 |
| Habitual exercise or walking (%) | 67.3 | 69.4 | <0.0001 |
| Current smoker (%) | 5.0 | 4.8 | 0.30 |
| Current alcohol drinker (%) | 21.7 | 26.0 | <0.0001 |
| Sleep (h/day) | 7.1 | 7.0 | 0.0007 |
| History of hypertension (%) | 22.5 | 21.1 | 0.0005 |
| History of diabetes (%) | 4.2 | 3.5 | 0.001 |
| High perceived mental stress (%) | 21.7 | 18.0 | <0.0001 |
| College or higher education (%) | 8.6 | 13.0 | <0.0001 |
| Regular employment (%) | 30.6 | 35.6 | <0.0001 |

Ikigai, something to live for, the joy and goal of living, a life worth living, and the happiness and benefit of being alive. BMI, body mass index; CV, cardiovascular.

## Results

During the median 19.4-year follow-up period, 6,389 of the 39,870 women enrolled, died. Cause of death included stroke (n=940), CAD (n=392), and total CVD (n=2,121). The proportions of women with parity 0, 1, 2, 3, 4, 5, and ≥6 were 3.7%, 7.7%, 38.9%, 31.3%, 10.9%, 4.4%, and 3.1%, respectively. The mean parity number was 2.7, and range for parity number was 0–13. We used the category of parity 1 as the reference. The proportion of women with ikigai was 43.2%, and that of women without ikigai was 56.8%.

**Table 1** lists the mean age, age-adjusted mean, and the prevalence of cardiovascular risk factors according to parity category. Compared with women with 1 child, nulliparous women were less likely to perform habitual exercise or walking and were more likely to be current smokers, have a high education level and regular employment. Compared with women with 1 child, high parity women (≥6) were less likely to perform habitual exercise or walking and have a high education level and were more likely to be regularly employed.

**Table 2** lists mean age, age-adjusted mean, and prevalence of cardiovascular risk factors for women according to ikigai status. Compared with women without ikigai, women with ikigai were more likely to be married, perform habitual exercise or walking, drink alcohol, and have a high education level and regular employment. Moreover, they were less likely to have a history of hypertension and diabetes or a high level of perceived mental stress.

**Table 3** lists age- and multivariable-adjusted HR (95%

**Table 3. CVD Mortality According to Parity**

| | Parity (n=39,870 women) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 (n=1,466; 3.7%) | 1 (n=3,087; 7.7%) | 2 (n=15,530; 38.9%) | 3 (n=12,475; 31.3%) | 4 (n=4,331; 10.9%) | 5 (n=1,744; 4.4%) | ≥6 (n=1,237; 3.1%) |
| **Person-years** | 23,659 | 48,807 | 263,512 | 211,975 | 68,889 | 25,590 | 16,772 |
| **Stroke** | | | | | | | |
| n | 55 | 51 | 194 | 243 | 178 | 104 | 115 |
| Age-adjusted HR (95% CI) | 1.60 (1.09–2.33) | 1.00 | 1.07 (0.78–1.45) | 1.11 (0.82–1.50) | 1.26 (0.92–1.73) | 1.33 (0.95–1.89) | 1.49 (1.07–2.10) |
| Multivariable HR (95% CI) | 1.55 (1.06–2.27) | 1.00 | 1.08 (0.79–1.48) | 1.11 (0.82–1.50) | 1.22 (0.89–1.67) | 1.25 (0.89–1.76) | 1.35 (0.96–1.89) |
| **CAD** | | | | | | | |
| n | 22 | 28 | 67 | 108 | 70 | 43 | 54 |
| Age-adjusted HR (95% CI) | 1.12 (0.64–1.96) | 1.00 | 0.72 (0.46–1.13) | 0.92 (0.61–1.39) | 0.85 (0.55–1.33) | 0.91 (0.56–1.47) | 1.10 (0.69–1.75) |
| Multivariable HR (95% CI) | 1.07 (0.61–1.87) | 1.00 | 0.72 (0.46–1.12) | 0.92 (0.60–1.39) | 0.84 (0.54–1.30) | 0.87 (0.54–1.30) | 1.01 (0.63–1.63) |
| **Total CVD** | | | | | | | |
| n | 120 | 134 | 444 | 549 | 390 | 234 | 250 |
| Age-adjusted HR (95% CI) | 1.29 (1.01–1.66) | 1.00 | 0.96 (0.79–1.17) | 0.96 (0.80–1.16) | 1.02 (0.83–1.24) | 1.08 (0.87–1.34) | 1.14 (0.92–1.41) |
| Multivariable HR (95% CI) | 1.25 (0.97–1.60) | 1.00 | 0.97 (0.80–1.18) | 0.96 (0.79–1.16) | 0.99 (0.81–1.21) | 1.02 (0.83–1.27) | 1.06 (0.85–1.32) |

Multivariable adjustment for age, body mass index, history of hormone drug use, habitual exercise or walking, smoking status, alcohol consumption, duration of sleep hours, history of hypertension and diabetes, perceived mental stress, education level, and regular employment. CAD, coronary artery disease; CVD, cardiovascular disease.

CI) for CVD mortality according to parity category. Compared with women with 1 child, nulliparous women had higher age-adjusted HR of mortality from stroke and total CVD. These associations remained statistically significant or borderline significant after adjustment for other cardiovascular risk factors. The multivariable HR of mortality from stroke for nulliparous women, as compared with women with 1 child, was 1.55 (95% CI: 1.06–2.27). Compared with women with 1 child, women with >6 children had higher age-adjusted HR of mortality from stroke, but this association had only borderline significance after adjustment for other cardiovascular risk factors.

**Table 4** lists HR (95% CI) for CVD mortality according to parity categories stratified by ikigai. In women without ikigai, nulliparous women had higher age-adjusted mortality from stroke and total CVD, as compared with women with 1 child. These associations remained statistically significant after adjustment for other risk factors. The multivariable HR of mortality from stroke and total CVD for nulliparous women, as compared with women with 1 child, were 1.87 (95% CI: 1.15–3.05) and 1.46 (95% CI: 1.07–2.01), respectively. Moreover, women with >6 children had higher age-adjusted mortality from stroke as compared with women with 1 child. These associations remained statistically significant after adjustment for other risk factors. The multivariable HR of mortality from stroke was 1.56 (95% CI: 1.00–2.45). For women with ikigai, there was no association between parity and CVD mortality, and there was no significant interaction between ikigai and the association between parity and CVD mortality.

## Discussion

To our knowledge, this is the first large-scale prospective study to show that nulliparous or high parity women had an increased risk of mortality from stroke, as compared with women with 1 child, in only women without ikigai.

The present findings of the association between nulliparity or high parity and CVD mortality were similar to those of previous studies.[1,2,4,24–26] The Israel Longitudinal Mortality Study II showed that nulliparous women had a 2.4-fold higher rate of CVD mortality, and women with >8 children had 1.6-fold higher rate, as compared with women with 2 children.[25] In the first National Health and Nutrition Examination Survey Epidemiology Follow-up Study of 3,852 US women aged 45–74 years, followed for 20 years, women with ≥6 pregnancies had a 1.7-fold higher risk of stroke, as compared with nulliparous women.[26] The magnitude of associations between parity and CVD mortality in the present study were smaller than those in the aforementioned studies. One reason for this disparity is that the number of subjects in these studies was not large enough; moreover, calculations of some studies were not adjusted for enough potential confounders.

The mechanism of the association between nulliparity and higher CVD mortality is unclear, but nulliparity has been associated with higher estradiol, which leads to elevated blood pressure,[27,28] and enhanced stiffness of the blood vessels.[29,30] Moreover, nulliparous women with infertility often have polycystic ovary syndrome,[31] which can lead to an increased risk of CVD mortality. Regarding high parity, repeated pregnancy and delivery induce physical and psychological stress and add strain to the cardiovascular system.[22] Moreover, high parity women are likely to be more vulnerable socioeconomically, for example, having a low education level and not having regular employment, which affects higher CVD mortality.[18,32]

In the present study, ikigai served as a factor attenuating

**Table 4. CVD Mortality According to Parity and Ikigai Status**

| | Parity (n=39,870 women) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 (n=1,466; 3.7%) | 1 (n=3,087; 7.7%) | 2 (n=15,530; 38.9%) | 3 (n=12,475; 31.3%) | 4 (n=4,331; 10.9%) | 5 (n=1,744; 4.4%) | ≥6 (n=1,237; 3.1%) |
| **Women with ikigai** | | | | | | | |
| **Person-years** | 8,672 | 21,377 | 116,145 | 96,438 | 30,086 | 9,931 | 6,712 |
| **Stroke** | | | | | | | |
| n | 16 | 23 | 76 | 96 | 69 | 32 | 39 |
| Age-adjusted HR (95% CI) | 1.21 (0.64–2.29) | 1.00 | 0.91 (0.57–1.46) | 0.97 (0.61–1.52) | 1.20 (0.75–1.93) | 1.10 (0.64–1.89) | 1.34 (0.79–2.27) |
| Multivariable HR (95% CI) | 1.09 (0.57–2.08) | 1.00 | 0.89 (0.56–1.44) | 0.95 (0.60–1.50) | 1.10 (0.68–1.76) | 1.01 (0.58–1.75) | 1.08 (0.63–1.84) |
| **CAD** | | | | | | | |
| n | 10 | 12 | 30 | 41 | 27 | 10 | 15 |
| Age-adjusted HR (95% CI) | 1.41 (0.61–3.28) | 1.00 | 0.71 (0.36–1.40) | 0.80 (0.42–1.52) | 0.86 (0.44–1.71) | 0.61 (0.26–1.42) | 0.89 (0.41–1.93) |
| Multivariable HR (95% CI) | 1.31 (0.56–3.07) | 1.00 | 0.71 (0.36–1.39) | 0.82 (0.43–1.56) | 0.83 (0.42–1.66) | 0.63 (0.27–1.49) | 0.84 (0.38–1.87) |
| **Total CVD** | | | | | | | |
| n | 38 | 61 | 174 | 220 | 150 | 80 | 80 |
| Age-adjusted HR (95% CI) | 1.05 (0.70–1.57) | 1.00 | 0.83 (0.62–1.11) | 0.84 (0.64–1.12) | 0.94 (0.70–1.27) | 0.96 (0.68–1.34) | 0.92 (0.66–1.30) |
| Multivariable HR (95% CI) | 0.98 (0.65–1.47) | 1.00 | 0.83 (0.62–1.11) | 0.85 (0.64–1.13) | 0.89 (0.66–1.21) | 0.92 (0.66–1.30) | 0.81 (0.57–1.14) |
| **Women without ikigai** | | | | | | | |
| **Person-years** | 14,987 | 27,430 | 147,367 | 115,537 | 38,803 | 15,659 | 10,061 |
| **Stroke** | | | | | | | |
| n | 39 | 28 | 118 | 147 | 109 | 72 | 76 |
| Age-adjusted HR (95% CI) | 1.84 (1.13–3.00) | 1.00 | 1.19 (0.79–1.81) | 1.23 (0.82–1.85) | 1.31 (0.87–2.00) | 1.49 (0.96–2.31) | 1.61 (1.03–2.51) |
| Multivariable HR (95% CI) | 1.87 (1.15–3.05) | 1.00 | 1.23 (0.81–1.86) | 1.25 (0.83–1.87) | 1.33 (0.88–2.02) | 1.47 (0.95–2.30) | 1.56 (1.00–2.45) |
| **CAD** | | | | | | | |
| n | 12 | 16 | 37 | 67 | 43 | 33 | 39 |
| Age-adjusted HR (95% CI) | 0.95 (0.45–2.01) | 1.00 | 0.72 (0.40–1.30) | 1.01 (0.58–1.74) | 0.84 (0.47–1.49) | 1.05 (0.58–1.92) | 1.19 (0.65–2.16) |
| Multivariable HR (95% CI) | 0.96 (0.45–2.03) | 1.00 | 0.72 (0.40–1.31) | 1.02 (0.59–1.76) | 0.84 (0.47–1.50) | 1.01 (0.55–1.86) | 1.08 (0.59–1.99) |
| **Total CVD** | | | | | | | |
| n | 82 | 73 | 270 | 329 | 240 | 154 | 170 |
| Age-adjusted HR (95% CI) | 1.46 (1.07–2.00) | 1.00 | 1.08 (0.83–1.40) | 1.06 (0.82–1.37) | 1.07 (0.83–1.40) | 1.16 (0.88–1.54) | 1.29 (0.97–1.71) |
| Multivariable HR (95% CI) | 1.46 (1.07–2.01) | 1.00 | 1.11 (0.85–1.44) | 1.07 (0.83–1.38) | 1.08 (0.83–1.41) | 1.15 (0.86–1.52) | 1.27 (0.96–1.69) |

Multivariable adjustment for age, body mass index, history of hormone drug use, habitual exercise or walking, smoking status, alcohol consumption, duration of sleep hours, history of hypertension and diabetes, perceived mental stress, education level, and regular employment. CAD, coronary artery disease; CVD, cardiovascular disease.

the association between nulliparity and CVD mortality. Positive psychological conditions,[33] health-related behaviors,[17] social networks,[34,35] connections,[36] and support[37] resulting from having ikigai were all important in lowering CVD mortality. Emotional support from children is related to health benefits at older ages,[38] and it has also been reported that there is no association between childlessness and social integration and life satisfaction.[39,40] Another study concluded that higher education level, living in the city, and having better access to medical services are associated with life satisfaction and psychological wellbeing in elderly women.[41] As we show in **Table 2**, women with ikigai were more likely to be married, have habitual exercise and a high education level, regular job, and lower proportions of high perceived mental stress, lifestyle behaviors and socioeconomic factors that are reportedly associated with a lower risk of CVD mortality.[15,17–19,42,43] Women with ikigai may have a lower risk of CVD mortality through those lifestyle behaviors and socioeconomic factors even though they had nulliparity or high parity.

The strengths of the present study include the fact that it was a large-scale prospective cohort study that enrolled participants from all over Japan. It included 2,121 cases of mortality in all participants with CVD during the long-term follow-up (median, 19.4 years). Additionally, the prospective design helped to make the study more robust

by eliminating selection and recall bias. Finally, we collected data on a large number of variables at baseline and adjusted for potential confounding variables such as cardiovascular risk factors and socioeconomic factors. These strengths allowed us to estimate the impact of ikigai on the association between parity and CVD mortality.

The study also had the following limitations. First, the exposure data on ikigai were obtained at baseline only; therefore, it is possible that changes in ikigai status occurred during the follow-up period. Second, because we used single questions in the self-administered questionnaire, there may have been non-differential bias in variables such as ikigai or history of hormone drug use. This study, however, included a large number of subjects; therefore, the effects of those biases were considered to be minimal. Third, although we adjusted for potential confounding factors such as perceived mental stress at baseline, the subjective nature of health might have confounded the findings. Fourth, there were no data on certain CVD risk factors such as measured blood pressure, blood glucose, and lipids. To reduce the effect of this lack of data, we adjusted for a history of hypertension as well as a history of diabetes mellitus in the analyses. Last, there might be a concern about selection bias, because we excluded participants who had missing information. The baseline characteristics of those with missing data, however, were similar to those included in the cohort for analysis.

## Conclusions

Nulliparous women with ikigai had no increased risk of CVD mortality, while nulliparous or high parity women without ikigai had an increased risk of CVD mortality. This suggests that ikigai may attenuate the potential for CVD mortality in nulliparous and high parity women.

### Name of Grants

This study was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (Monbusho), 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, 18014011, 20014026, 20390156, and 26293138 as well as from the Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H26 Jyunkankitou [Seikaku]-Ippan-001.

### Disclosures

The authors declare no conflicts of interest.

### References

1. Ness RB, Harris T, Cobb J, Flegal KM, Kelsey JL, Balanger A, et al. Number of pregnancies and the subsequent risk of cardiovascular disease. *N Engl J Med* 1993; **328:** 1528–1533.
2. Steenland K, Lally C, Thun M. Parity and coronary heart disease among women in the American Cancer Society CPS II population. *Epidemiology* 1996; **7:** 641–643.
3. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. A prospective study of age at menarche, parity, age at first birth, and coronary heart disease in women. *Am J Epidemiol* 1987; **126:** 861–870.
4. Lv H, Wu H, Yin J, Qian J, Ge J. Parity and cardiovascular disease mortality: A dose-response meta-analysis of cohort studies. *Sci Rep* 2015; **5:** 13411.
5. Giltay EJ, Geleijnse JM, Zitman FG, Hoekstra T, Schouten EG. Dispositional optimism and all-cause and cardiovascular mortality in a prospective cohort of elderly Dutch men and women. *Arch Gen Psychiatry* 2004; **61:** 1126–1135.
6. Giltay EJ, Kamphuis MH, Kalmijn S, Zitman FG, Kromhout D. Dispositional optimism and the risk of cardiovascular death: The Zutphen Elderly Study. *Arch Intern Med* 2006; **166:** 431–436.
7. Shirai K, Iso H, Ohira T, Ikeda A, Noda H, Honjo K, 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:** 956–963.
8. Tindle HA, Chang YF, Kuller LH, Manson JE, Robinson JG, Rosal MC, et al. Optimism, cynical hostility, and incident coronary heart disease and mortality in the Women's Health Initiative. *Circulation* 2009; **120:** 656–662.
9. Nabi H, Koskenvuo M, Singh-Manoux A, Korkeila J, Suominen S, Korkeila K, et al. Low pessimism protects against stroke: The Health and Social Support (HeSSup) prospective cohort study. *Stroke* 2010; **41:** 187–190.
10. Shirai K, Iso H, Fukuda H, Toyoda Y, Takatorige T, Tatara K. Factors associated with "Ikigai" among members of a public temporary employment agency for seniors (Silver Human Resources Centre) in Japan; gender differences. *Health Qual Life Outcomes* 2006; **4:** 12.
11. Sone T, Nakaya N, Ohmori K, Shimazu T, Higashiguchi M, Kakizaki M, et al. Sense of life worth living (ikigai) and mortality in Japan: Ohsaki Study. *Psychosom Med* 2008; **70:** 709–715.
12. Tanno K, Sakata K, Ohsawa M, Onoda T, Itai K, Yaegashi Y, et al. Associations of ikigai as a positive psychological factor with all-cause mortality and cause-specific mortality among middle-aged and elderly Japanese people: Findings from the Japan Collaborative Cohort Study. *J Psychosom Res* 2009; **67:** 67–75.
13. Chida Y, Steptoe A. Positive psychological well-being and mortality: A quantitative review of prospective observational studies. *Psychosom Med* 2008; **70:** 741–756.
14. Koizumi M, Ito H, Kaneko Y, Motohashi Y. Effect of having a sense of purpose in life on the risk of death from cardiovascular diseases. *J Epidemiol* 2008; **18:** 191–196.
15. Noda H, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, et al. Walking and sports participation and mortality from coronary heart disease and stroke. *J Am Coll Cardiol* 2005; **46:** 1761–1767.
16. Iso H, Date C, Yamamoto A, Toyoshima H, Watanabe Y, Kikuchi S, et al. Smoking cessation and mortality from cardiovascular disease among Japanese men and women: The JACC Study. *Am J Epidemiol* 2005; **161:** 170–179.
17. Mackenbach JP, Cavelaars AE, Kunst AE, Groenhof F. Socioeconomic inequalities in cardiovascular disease mortality; an international study. *Eur Heart J* 2000; **21:** 1141–1151.
18. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: A review of the literature. *Circulation* 1993; **88:** 1973–1998.
19. Eguchi E, Iso H, Tanabe N, Wada Y, Yatsuya H, Kikuchi S, et al. Healthy lifestyle behaviours and cardiovascular mortality among Japanese men and women: The Japan collaborative cohort study. *Eur Heart J* 2012; **33:** 467–477.
20. Seeman TE, Kaplan GA, Knudsen L, Cohen R, Guralnik J. Social network ties and mortality among the elderly in the Alameda County Study. *Am J Epidemiol* 1987; **126:** 714–723.
21. Lawlor DA, Emberson JR, Ebrahim S, Whincup PH, Wannamethee SG, Walker M, et al. Is the association between parity and coronary heart disease due to biological effects of pregnancy or adverse lifestyle risk factors associated with child-rearing?: Findings from the British Women's Heart and Health Study and the British Regional Heart Study. *Circulation* 2003; **107:** 1260–1264.
22. Grundy E, Tomassini C. Fertility history and health in later life: A record linkage study in England and Wales. *Soc Sci Med* 2005; **61:** 217–228.
23. Tamakoshi A, Ozasa K, Fujino Y, Suzuki K, Sakata K, Mori M, et al. Cohort profile of the Japan Collaborative Cohort Study at final follow-up. *J Epidemiol* 2013; **23:** 227–232.
24. Sakauchi F. Reproductive history and health screening for women and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). *Asian Pac J Cancer Prev* 2007; **8**(Suppl)**:** 129–134.
25. Jaffe DH, Eisenbach Z, Manor O. The effect of parity on cause-specific mortality among married men and women. *Matern Child Health J* 2011; **15:** 376–385.
26. Qureshi AI, Giles WH, Croft JB, Stern BJ. Number of pregnancies and risk for stroke and stroke subtypes. *Arch Neurol* 1997; **54:** 203–206.
27. Fisch IR, Frank J. Oral contraceptives and blood pressure. *JAMA* 1977; **237:** 2499–2503.
28. Paganini-Hill A, Ross RK, Gerkins VR, Henderson BE, Arthur

M, Mack TM. Menopausal estrogen therapy and hip fractures. *Ann Intern Med* 1981; **95:** 28–31.
29. Bourne T, Hillard TC, Whitehead MI, Crook D, Campbell S. Oestrogens, arterial status, and postmenopausal women. *Lancet* 1990; **335:** 1470–1471.
30. Prentice RL. On the ability of blood pressure effects to explain the relation between oral contraceptives and cardiovascular disease. *Am J Epidemiol* 1988; **127:** 213–219.
31. Wild RA. Polycystic ovary syndrome: A risk for coronary artery disease? *Am J Obstet Gynecol* 2002; **186:** 35–43.
32. Hurt LS, Ronsmans C, Thomas SL. The effect of number of births on women's mortality: Systematic review of the evidence for women who have completed their childbearing. *Popul Stud (Camb)* 2006; **60:** 55–71.
33. Rozanski A, Kubzansky LD. Psychologic functioning and physical health: A paradigm of flexibility. *Psychosom Med* 2005; **67**(Suppl 1)**:** S47–S53.
34. Orth-Gomer K, Johnson JV. Social network interaction and mortality: A six year follow-up study of a random sample of the Swedish population. *J Chronic Dis* 1987; **40:** 949–957.
35. Iwasaki M, Otani T, Sunaga R, Miyazaki H, Xiao L, Wang N, et al. Social networks and mortality based on the Komo-Ise cohort study in Japan. *Int J Epidemiol* 2002; **31:** 1208–1218.
36. Kaplan GA, Salonen JT, Cohen RD, Brand RJ, Syme SL, Puska P. Social connections and mortality from all causes and from cardiovascular disease: Prospective evidence from eastern Finland. *Am J Epidemiol* 1988; **128:** 370–380.
37. Broadhead WE, Kaplan BH, James SA, Wagner EH, Schoenbach VJ, Grimson R, et al. The epidemiologic evidence for a relationship between social support and health. *Am J Epidemiol* 1983; **117:** 521–537.
38. Alexander BB, Rubinstein RL, Goodman M, Luborsky M. A path not taken: A cultural analysis of regrets and childlessness in the lives of older women. *Gerontologist* 1992; **32:** 618–626.
39. Pollmann-Schult M. Social integration and life satisfaction of childless women and men in mid- and late-life. *Z Gerontol Geriatr* 2011; **44:** 411–416.
40. Shi L. Elderly support in rural and suburban villages: Implications for future support system in China. *Soc Sci Med* 1994; **39:** 265–277.
41. Zhang W, Liu G. Childlessness, psychological well-being, and life satisfaction among the elderly in China. *J Cross Cult Gerontol* 2007; **22:** 185–203.
42. Ikeda A, Iso H, Toyoshima H, Fujino Y, Mizoue T, Yoshimura T, et al. Marital status and mortality among Japanese men and women: The Japan Collaborative Cohort Study. *BMC Public Health* 2007; **7:** 73.
43. Iso H, Date C, Yamamoto A, Toyoshima H, Tanabe N, Kikuchi S, et al. Perceived mental stress and mortality from cardiovascular disease among Japanese men and women: The Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study). *Circulation* 2002; **106:** 1229–1236.