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Relationship between Ikigai and longitudinal changes in serum HDL cholesterol levels: the Circulatory Risk in Communities Study (CIRCS)

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Abstract

Background Having positive psychological well-being has been associated with serum high-density lipoprotein cholesterol (HDLC), but no longitudinal study to date has examined the association between Ikigai and serum HDLC. Therefore, we examined the association between Ikigai and change in serum HDLC over time using a cohort dataset spanning 2010–2018.

Methods The study included 471 men and 776 women aged 40–74 years who underwent a cardiovascular examination in 2010 and were asked their levels of Ikigai. We combined "definitely yes" and "yes" as "with Ikigai" and recorded "a little" as "with a little Ikigai" and "no" as "without Ikigai". We measured serum HDLC using direct methods. The association between Ikigai and serum HDLC levels at baseline, and changes in this relationship during an eight-year period, were analyzed using linear mixed-effect models.

Results At the baseline, relative to those without Ikigai, women with Ikigai had higher serum HDLC (baseline difference in those with a little Ikigai = 7.52 mg/dl, 95% confidence interval [CI]: 1.12 to 13.9 and in those with Ikigai = 8.11 mg/dl, 95% CI: 1.54 to 14.7). The difference in serum HDLC between women with and without Ikigai remained over the eight-year follow-up period. There were no similar Ikigai-associated differences in the serum HDLC of men.

Conclusions Women with Ikigai showed differences in serum HDLC that were observed at baseline and persisted over time.

Keywords Ikigai, HDL cholesterol, Stress, Longitudinal study, Positive psychology

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Introduction

Lower serum high-density lipoprotein cholesterol (HDLC) levels are known to be an indicator of cardiovascular disease risk [1, 2]. Recent reviews have suggested that elevated serum HDLC levels can have a direct positive effect on reverse cholesterol transport [3] and anti-inflammatory processes [4], both of which may prevent the development of atherosclerotic diseases. In particular, a growing body of research suggests that higher serum HDLC levels predict cardiovascular health independent of other lipids [5].

Having a positive psychological well-being has been reported to prevent adverse mental and physical health conditions by reducing stress reactions [6] and enhancing risk aversion (e.g., by reducing smoking and drinking and improving physical activity levels and diet) [7]. In fact, Soo et al. [5] reported that a healthier psychological well-being (assessed using control, autonomy, satisfaction, and pleasure scales) was associated with higher serum HDLC [5]. Radler et al. (2018) found that high-stability trajectories of well-being, comprising self-acceptance, environmental mastery, personal growth, and purpose in life, were associated with high serum HDLC, but not with serum low-density lipoprotein cholesterol (LDLC) [8]. Similarly, higher levels of optimism were found to be associated with higher serum HDLC, but no significant difference was found for serum LDLC [9]. Thus, there is increasing evidence that improved psychological well-being is associated with enhanced serum HDLC levels.

In recent years, increasing numbers of studies examining the impacts of "Ikigai" on health have been conducted, not only in the field of positive psychology, but also in preventive medicine [10, 11]. The word "Ikigai" originated in the Heian period (the years between 794 and 1185) and is made up of two Japanese words, "iki," meaning life, and "gai," a suffix from the word "kai" (shellfish), which has been valued as a precious object or treasure since the Heian period [12, 13]. Ikigai is the concept of something to live for, the joy and goal of living, a life worth living, and the happiness and benefit of being alive; it is similar to the concepts of "purpose in life", "meaning of life", and "reason to live" [14]. While several English words can be used to describe Ikigai, there is no English word or phrase that translates exactly to Ikigai [15]. The phrase Ikigai has spread based on the 2017 publication "Ikigai" [13] and is now used worldwide. It is a comprehensive concept that includes not only enjoyment and happiness, but also the meaning of life and self-actualization, and it has important impacts on physical and psychological well-being [16]. In a study of about 40,000 Japanese citizens, those without Ikigai were at significantly higher risk of all causes of mortality than those with Ikigai [17]. Other cohort studies have suggested that Ikigai is significantly associated with the risk of mortality due to cardiovascular disease [18, 19].

The mechanisms that underly the association between Ikigai and health outcomes have not been completely elucidated, including those that pertain to cardiovascular disease, for which the evidence is strongest. Plausible explanations for increased health risks in those without Ikigai include poor adherence to medical regimens, engaging in unhealthy behaviors (e.g., smoking, heavy drinking, sedentary lifestyle, and poor diet), and direct toxic neuroendocrine effects [20]. Moreover, it has been hypothesized that biological dysregulation can occur because a lack of Ikigai activates stress-response systems, leading to heightened anticipation of stress, which exacerbates negative affective reactions to stressful events [21]. Chronic high levels of stress have been linked to impaired hypothalamus–pituitary–adrenal (HPA) axis function, higher sympathetic activation, and lower parasympathetic autonomic tone, all of which can contribute to dysregulation across a range of biological processes [22–24]. Previous studies have suggested that negative affect, such as anxiety or depressed mood [25] and hostility [26], was associated with the prevalence of serum HDLC.

Given the findings that the level of psychological well-being has remained unchanged over the years and has been associated with serum HDLC [8], we hypothesized that Ikigai could be associated with higher serum HDLC levels and that the association would persist over time. Therefore, we conducted a longitudinal study to examine the long-term association of Ikigai with serum HDLC levels. Furthermore, since previous studies on Ikigai have suggested the existence of sex-specific differences in perceptions [27], lifestyle (e.g., smoking and drinking alcohol) [28] and mortality [14], we stratified our analyses by sex. In addition, since women undergo significant changes in serum HDLC levels after menopause [29], we further stratified the analyses by menopause status.

Methods

Study population

The Circulatory Risk in Communities Study (CIRCS) is an ongoing community-based cohort study of cardiovascular disease involving approximately 12,000 persons per 4-to-6-year period (more than 65,000 people in total) covering five regions of Japan [30]. Within the study, annual evaluations of the cardiovascular disease risk factors have been conducted from November to February since 1981 [30–33]. In the present study, we used the CIRCS medical examination data from 2010–2018 for men and women aged 40–74 years who lived in the Kyowa district of Chikusei City, Ibaraki Prefecture in Japan, one of the districts covered by CIRCS, and

participated in the cardiovascular examinations in 2010. In 2010 there were 1463 participants who completed Ikigai questionnaires, including 594 men and 869 women in the target age range. We excluded 110 participants who had histories of heart disease and stroke and 106 participants who did not have measured Ikigai at baseline. Consequently, 1,247 participants (471 men, 776 women) were included in the study.

A total of 1,247 participants (471 men and 776 women) participated in the study from the baseline year and qualified for inclusion in this study. These were 461 (37.0%) followed for 8 years, 164 (13.2%) for 7 years, 109 (8.7%) for 6 years, 98 (7.9%) for 5 years, 69 (5.5%) for 4 years, 75 (6.0%) for 3 years, 71 (5.7%) for 2 years, 86 (6.9%) for 1 year, 114 (9.1%) for only for baseline.

Questionnaire survey on Ikigai

Participants were asked the following question regarding Ikigai using a self-administered questionnaire at baseline: "Do you have Ikigai in your life?" They responded on a four-point Likert scale with the following options: "definitely yes", "yes", "a little", and "no". This question on Ikigai in the present study has been widely used in large cohort studies [34, 35].

In this study, we combined "definitely yes" and "yes" as "with Ikigai" because the number of participants who answered "definitely yes" was small (50 men and 70 women). Additionally, we combined "a little" as "with a little Ikigai". Participants who answered "no" were categorized as "without Ikigai" and used as the reference category.

Lipids measurements

Serum total cholesterol (TC) and HDLC of the participants were measured by the Liebermann–Burchard direct method annually from 2010 (our study baseline) until 2018. The external quality control for the measurements of lipids was provided by the Standardization Program of the Japan Medical Association. The laboratories participated in the program of the Osaka Medical Center for Health Science and Promotion, a member of the Cholesterol Reference Method Laboratory Network, to standardize lipids measurements and implement international quality control [36]. Non-high-density lipoprotein cholesterol (non-HDLC) was calculated as TC minus HDLC.

Other covariates

The participants' body mass index (BMI) was calculated from their weight (kg) and height (m) according to the formula: BMI = Weight (kg)/ Height (m^2). All participants wore socks and light clothing during weight measurements. Each participant was interviewed to determine their smoking status and history, and the number of cigarettes they currently smoked per day. They were also asked about their usual weekly alcohol consumption in "go" units (a traditional Japanese unit of volume equivalent to 23 g of ethanol). Histories of coronary heart disease and stroke were also established during the interviews. Female participants were also asked about their menopausal status and responded by "yes" or "no".

The participants were asked about stress, declining interest and depressed in mood as depression. As a measure of stress, we asked a single question: "Do you feel stressed in your work or daily life?" The response categories were "all the time", "much of the time", "a little", and "almost never"; the first three responses were categorized as "having stress" and the last was categorized as "without stress". The questions regarding depression were "Have you had little interest or pleasure in doing things in the past month?" and "Have you felt depressed or hopeless in the past month?", to both of which the participants could respond only "yes" or "no".

The ENRICHD social support instrument [37] was also used during the interview. The items were rated on a five-point Likert scale (0 = none of the time, 4 = all the time). The total scores ranged from 6 to 30 and were divided using tertiles into low, medium, and high social support groups.

The covariates included baseline age, years (the difference in age between the baseline and the time at which the outcome was measured), health-related lifestyle information such as smoking status (never smoker, former smoker, current smoker of 1–19 cigarettes/day, current smoker of ≥ 20 cigarettes/day), drinking status (never drinker, former drinker, current drinker of ethanol at 1 to 22 g/day, or current drinker of ethanol at ≥ 23 g/day), psychosocial factors such as presence of stress (having stress or without stress), declining interest (yes or no), and depressed in mood (yes or no), other psychological factors such as social support level (low, medium, or high), occupational status (unemployed or employed) and menopause (yes or no) in relation to Ikigai and serum HDLC levels. All covariates were assessed at baseline.

Statistical analysis

We used ANOVA to compare means and chi-squared tests to compare the proportions of various lifestyle and psychological factors to baseline data. We used linear mixed-effect models to investigate the association of changes in Ikigai with changes in serum HDLC over time. This is a generally accepted method for processing longitudinal data and explaining the correlations among measurements taken from the same individual [31]. In addition, we obtained the variance inflation factor (VIF) to examine multicollinearity between Ikigai and depression.

Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA). All p values of <0.05 (two-tailed) were considered statistically significant.

Results

Table 1 shows the sex-specific baseline characteristics of the participants according to their Ikigai levels. Compared to those with Ikigai, men without Ikigai reported less social support, higher rates of subjective mental stress, declining interest, and depressed in mood, and they were also more likely to be unemployed. Similarly, women without Ikigai reported less social support, higher rates of subjective mental stress, declining interest, and depressed in mood compared to those with Ikigai. In addition, women without Ikigai had a lower average age and were more likely to be current smokers than women with Ikigai. Men with and without Ikigai showed significant differences in social support, subjective mental stress, declining interest, and depressed in mood related to depression and employment. Women with and without Ikigai showed significant differences in age, smoking status, drinking status, social support, subjective mental stress, declining interest, and depressed in mood (Table 1).

Table 2 shows the sex-specific changes in serum HDLC levels according to Ikigai. At baseline, compared to those without Ikigai, women with Ikigai had higher serum HDLC (baseline difference in those with a little Ikigai = 7.52 mg/dl, 95% confidence interval [CI]: 1.12 to 13.9 and baseline difference in those with Ikigai = 8.11 mg/dl, 95% CI: 1.54 to 14.7). VIF ranged from 1.000 to 2.790, and no multicollinearity was found among the psychological variables included in the models (data not shown). The difference in serum HDLC between women with and without Ikigai persisted over the eight-year follow-up period (Table 2).

The menopausal status-specific associations between Ikigai and serum HDLC levels are presented in Table 3. There were no differences in the associations between Ikigai and serum HDLC in groups with different menopausal status. For example, the baseline differences and 95% CIs stratified by menopausal status were: 13.7 mg/dl, 95% CI = 0.74 to 26.6 for non-menopausal women with a little Ikigai; 13.3 mg/dl, 95% CI = -0.15 to 26.7 for non-menopausal women with Ikigai; 6.85 mg/dl, 95% CI = -0.29 to 14.0 for menopausal women with a little Ikigai; 7.53 mg/dl, 95% CI = 0.23 to 14.8 for menopausal women with Ikigai (Table 3).

Appendix Table 4 shows that women with Ikigai had lower serum non-HDLC compared to those without Ikigai (baseline difference in those with a little Ikigai = -19.2 mg/dl, 95% CI: -31.9 to -6.57 and baseline difference in those with Ikigai = -19.0 mg/dl, 95% CI: -31.9 to -5.98). However, no association of Ikigai with change in serum non-HDLC over time was evident; no statistically significant interactions between Ikigai and time (Appendix Table 4). We did not find similar association with serum TC in women and Ikigai was not associated with any of outcomes we measured in men (Appendix Table 5).

Discussion

Our results showed that, at baseline, women who had Ikigai had significantly higher serum HDLC levels than those without Ikigai. However, we found no significant changes in the serum HDLC levels of women over time. No similar Ikigai-associated differences were found in men. Previous studies have observed that people with higher levels of purpose in life, personal growth, and positive affect also had significantly higher levels of serum HDLC [38]. Similarly, individuals with persistently higher psychological well-being have been found to have higher serum HDLC levels than those with persistently lower psychological well-being [8]. Furthermore, the evidence presented here shows that Ikigai is as closely related to serum HDLC levels as to serum non-HDLC levels, and that differences in serum HDLC levels that were observed at baseline and are explained by Ikigai persisted over time.

There are several mechanisms that may explain the positive relationship between Ikigai and serum HDLC. The first is the association with psychological distress. Our results showed that both men and women with Ikigai had a lower prevalence of depression than those without Ikigai. This is supported by a study examining the association between Ikigai and depression, which found that the level of Ikigai was positively correlated with well-being and inversely correlated with depression [39]. Indeed, the development of positive emotions has been found to result in better psychological function and reduce depression [40]. Furthermore, our study agreed with the finding from a previous study which found that serum HDLC levels were lower in the depressed group than in the control group [41]. Overall, our study suggested that people with Ikigai suffer from less depression, which may be positively associated with their serum HDLC levels.

The second potential mechanism is biological, possibly stemming from the association between Ikigai and psychological stress. Few studies that have investigated positive psychological well-being indicators, such as Ikigai, and their relation to cardiovascular health, have explicitly addressed whether positive psychological well-being influences stress levels directly or buffers the association with stress. However, when researchers have considered the mechanisms by which psychological well-being

Table 1 Sex-specific baseline characteristics of the participants stratified by presence of Ikigai

	Men ($n = 471$)				Women ($n = 776$)			
Ikigai levels	**Without**	**With a little**	**With**	***p* for difference**	**Without**	**With a little**	**With**	***p* for difference**
Number	18	245	208		24	414	338	
Age, mean (SD)	57.6(11.7)	61.5(8.2)	62.1(8.9)	0.10	55.0(7.8)	60.2(8.0)	61.5(8.1)	<0.001*
BMI, mean (SD)	24.9(4.8)	23.5(2.8)	23.9(2.6)	0.09	23.7(3.4)	23.0(3.5)	23.0(3.0)	0.60
Former smoker, % (n)	61.1(11)	54.7(134)	55.3(115)	0.87	4.2(1)	5.3(22)	5.3(18)	0.97
Current smoker of 1-19 cigarettes/day, % (n)	22.2(4)	21.2(52)	19.7(41)	0.91	8.3(2)	3.4(14)	2.7(9)	0.30
Current smoker of ≥ 20 cigarettes/day, % (n)	0(0)	6.5(16)	6.3(13)	0.54	8.3(2)	0.2(1)	0(0)	<0.001*
Former drinker, % (n)	22.2(4)	11.8(29)	13.5(28)	0.43	20.8(5)	6.0(25)	5.9(20)	0.01*
Current drinker of ethanol at 1 to 22 g/day, % (n)	0(0)	4.9(12)	4.3(9)	0.62	4.2(1)	5.5(23)	6.5(22)	0.80
Current drinker of ethanol at ≥ 23 g/day, % (n)	61.1(11)	58.4(143)	63.5(132)	0.54	16.7(4)	8.2(34)	8.0(27)	0.33
Social support (low), % (n)	61.1(11)	45.3(111)	29.3(61)	<0.001*	70.8(17)	44.7(185)	20.7(70)	<0.001*
Subjective mental stress, % (n)	77.8(14)	67.0(164)	54.8(114)	0.01*	91.7(22)	72.0(298)	63.0(213)	<0.001*
Declining interest, % (n)	38.9(7)	4.1(10)	2.4(5)	<0.001*	20.8(5)	5.1(21)	2.7(9)	<0.001*
Depressed in mood, % (n)	50.0(9)	5.7(14)	1.0(2)	<0.001*	29.2(7)	5.3(22)	3.6(12)	<0.001*
Menopause, % (n)	-	-	-	-	70.8(17)	84.3(349)	86.4(292)	0.11
Unemployed, % (n)	61.1(11)	33.6(82)	28.9(60)	0.02*	8.3(2)	16.0(66)	16.1(54)	0.60

We combined "definitely yes" and "yes" as "with Ikigai", and recorded "a little" as "with a little Ikigai" and "no" as "without Ikigai"

We used ANOVA to compare means and chi-squared tests to compare the proportions

BMI body mass index, *SD* standard deviation, *n* number

*$p < 0.05$

Table 2 Ikigai-associated sex-specific changes in serum HDLC

	Men					Women				
Ikigai levels	**Without (reference)**	**With a little**		**With**		**Without (reference)**	**With a little**		**With**	
Serum HDLC (Baseline difference)[a]		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value
Model1	0	5.13(-1.55,11.8)	0.13	4.25(-2.47,11.0)	0.21	0	7.86(1.52,14.2)	0.02*	8.21(1.80,14.6)	0.01*
Model2	0	5.27(-1.13,11.7)	0.11	4.47(-2.01,11.0)	0.18	0	8.06(1.78,14.4)	0.01*	8.61(2.17,15.1)	0.01*
Model3	0	3.89(-3.10,10.9)	0.27	2.95(-4.19,10.1)	0.42	0	7.52(1.12,13.9)	0.02*	8.11(1.54,14.7)	0.02*
Serum HDLC (Time-dependent difference)[b]		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value
Model1	0	-0.06(-0.51,0.38)	0.78	0.16(-0.29,0.61)	0.49	0	0.32(-0.01,0.66)	0.06	0.38(0.04,0.72)	0.03*
Model2	0	-0.09(-0.69,0.51)	0.77	0.11(-0.50,0.71)	0.73	0	0.35(-0.12,0.82)	0.14	0.38(-0.09,0.86)	0.12
Model3	0	-0.09(-0.69,0.51)	0.77	0.11(-0.50,0.71)	0.73	0	0.35(-0.12,0.83)	0.14	0.38(-0.09,0.86)	0.11

We combined "definitely yes" and "yes" as "with Ikigai", and recorded "a little" as "with a little Ikigai" and "no" as "without Ikigai"

We used linear mixed-effect models to investigate the association of changes in Ikigai with changes in serum HDLC over time

Model1 is adjusted for age

Model2 is adjusted for age, former smoker, current smoker of 1-19 cigarettes/day, current smoker of ≥ 20 cigarettes/day, former drinker, current drinker of ethanol at 1 to 22 g/day, current drinker of ethanol at ≥ 23 g/day, social support, menopause and unemployed at baseline

Model3 is adjusted for age, former smoker, current smoker of 1-19 cigarettes/day, current smoker of ≥ 20 cigarettes/day, former drinker, current drinker of ethanol at 1 to 22 g/day, current drinker of ethanol at ≥ 23 g/day, social support, declining interest, depressed in mood, menopause and unemployed at baseline

CI confidence interval, *HDLC* high-density lipoprotein cholesterol

**p < 0.05*

[a] Baseline difference is the association of Ikigai at baseline with serum HDLC

[b] Time-dependent difference is the association of Ikigai with the slope describing the linear relationship between serum HDLC levels and time (serum HDLC changes per year)

Table 3 Ikigai-associated menopause-specific changes in serum HDLC

	Non-menopausal women					Menopausal women				
Ikigai levels	**Without(reference)**	**With a little**		**With**		**Without(reference)**	**With a little**		**With**	
Serum HDLC (Baseline difference)[a]		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value
Model1	0	13.1(0.74,25.5)	0.04*	12.2(-0.44,24.8)	0.06	0	6.83(-0.23,13.9)	0.06	7.26(0.14,14.4)	0.04*
Model2	0	13.7(0.74,26.6)	0.04*	13.3(-0.15,26.7)	0.05	0	6.85(-0.29,14.0)	0.06	7.53(0.23,14.8)	0.04*
Serum HDLC (Time-dependent difference)[b]		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value
Model1	0	1.59(0.21,2.96)	0.02*	0.64(-0.72,1.99)	0.35	0	0.20(-0.30,0.70)	0.44	0.30(-0.20,0.80)	0.24
Model2	0	1.02(-0.52,2.56)	0.19	0.07(-1.46,1.59)	0.93	0	0.27(-0.24,0.77)	0.30	0.36(-0.14,0.87)	0.16

We combined "definitely yes" and "yes" as "with Ikigai", and recorded "a little" as "with a little Ikigai" and "no" as "without Ikigai"

We used linear mixed-effect models to investigate the association of changes in Ikigai with changes in serum HDLC over time

Model1 is adjusted for age

Model2 is adjusted for age, former smoker, current smoker of 1-19 cigarettes/day, current smoker of ≥ 20 cigarettes/day, former drinker, current drinker of ethanol at 1 to 22 g/day, current drinker of ethanol at ≥ 23 g/day, social support, declining interest, depressed in mood and unemployed at baseline

CI confidence interval, *HDLC* high-density lipoprotein cholesterol

*$p < 0.05$

[a] Baseline difference is the association of Ikigai at baseline with serum HDLC

[b] Time-dependent difference is the association of Ikigai with the slope describing the linear relationship between serum HDLC levels and time (serum HDLC changes per year)

affects health, usually using a stress-buffering model, they have often assumed that well-being prevents the onset of cardiovascular disease [7]. Here, in theoretical terms, we also considered that, when stress increases, the hypothalamus generally secretes corticotropin-releasing hormone (CRH). This hormone stimulates adrenocorticotropic hormone secretion from the pituitary gland, which in turn stimulates the secretion of glucocorticoids from the adrenal cortex (HPA axis). It has been shown that, through this HPA axis sequence, people with higher levels of psychological well-being produce lower levels of cortisol, one of the glucocorticoids [42, 43]. In addition, compared to those with a weaker sense of purpose and a poorer personal-growth profile, those with a stronger sense of purpose and who continue to engage in self-development tend to start their days with lower cortisol levels because of their lower psychological stress levels, and their cortisol levels remain lower throughout the day [44]. Chronic increases in glucocorticoids elevate glucose levels and reduce the activity of lipoprotein lipase (LPL), which consequently lowers serum HDLC levels [45]. Moreover, several studies have demonstrated the associations between Ikigai and psychological states such as anxiety and depression [46]. In other words, Ikigai may buffer against accumulating stress response (e.g., the activation of the HPA axis) and improve serum HDLC levels.

The level of Ikigai may change over time. However, we only had one measure of Ikigai over the follow-up period. A previous longitudinal study examined the multiple aspects of psychological well-being including autonomy, environmental mastery, personal growth, positive relations with others, purpose in life, and self-acceptance and about 80% of participants were highly stable in these six dimensions of well-being over 10 years [8]. Eudaimonic motivation such as Ikigai has been known to increase until the 30 s and did not change significantly thereafter [15, 47]. Since the average age of our study subjects at the baseline was around 60 years old, their Ikigai levels were unlikely to change during the study period. Therefore, the level of Ikigai could be associated with serum HDLC levels, and the association persisted for a long period of time.

Many studies of Ikigai indicate the presence of sex differences in the associations [14, 18, 19, 28, 48]. In a previous study, the risk of cardiovascular disease mortality was reduced in men with higher levels of Ikigai, but not in women [14]. Moreover, risk reductions driven by Ikigai in all-cause mortality and stroke incidence were found to be stronger in men than in women [18]. These sex-differences may be due to the differing perceptions of Ikigai between men and women. They may also be related to lifestyle differences (e.g., smoking, alcohol drinking) between men and women [28, 49]. Although we did not collect perceptional information of Ikigai in the present study, we found Ikigai-related lifestyle differences such as smoking in women, but not in men. Thus, the sex differences might affect on the associations between Ikigai and serum HDLC levels.

The absence of any link between Ikigai and serum HDLC levels in the male participants may have stemmed from sex-specific stress responses. In general, women are more likely to manage and cope with their emotional responses to stress than men are, which may explain the stronger relationship between cholesterol variability and stress in women than in men [50]. In a previous study, women with highly perceived mental stress had a higher risk of death from cardiovascular disease than women with less perceived mental stress, but no similar association was found in men [51].

Moreover, women undergo significant changes in serum HDLC levels during menopause, which occurs around the age of 45–55 [29]. However, in CIRCS, serum HDLC did not change significantly during menopause [52]. Besides, our results did not reveal the influence of menopause, because 84.8% of the women in this study were already menopausal status at baseline, which made it difficult to detect the influence of the transition to menopause.

This study holds particular value due to its large sample size and the inclusion of a long-term follow-up period of eight years. Moreover, we used lipids measurements standardized by the Cholesterol Reference Method Laboratory Network. This justified our assumption that misclassification bias due to errors in lipids measurements was minimal and the resulting accuracy allowed us to compare our lipids measurements with previous well-standardized studies [36].

The present study had some limitations. First, the survey only included one question regarding Ikigai, which may have resulted in misclassification. Second, Ikigai was measured only at one point in time; therefore, we were not able to examine the effect of well-being on lipid profiles over time. Third, there was no medical history information on the participants' past mental illnesses, such as depression. Since both the men and the women without Ikigai had a high percentage of depressive symptoms, they may already have had a mental illness, which may have affected their level of Ikigai. Fourth, there may be residual confounding effects from factors such as diet [53, 54] and physical activity levels [55], which were associated with serum cholesterol levels at the baseline, and social factors such as education [56] and income [56]. In particular, physical activity levels have been found to be associated with a higher level of Ikigai [57]. Similarly, diet quality and motivation to eat healthily are also associated with Ikigai [58, 59]. These observations suggest that both

physical activity and diet are associated with improvements in HDL function [55, 60]. In other words, it is possible that persons with Ikigai tend to have a healthy diet and engage in moderate physical activity, both of which could maintain high serum HDLC levels over time. Thus, while diet and physical activity levels are closely related to Ikigai and serum cholesterol levels, we were unable to consider their effects in this study because the necessary information was not available. Fifth, the small number of participants in the without-Ikigai group resulted in limited precision and detection power. Sixth, as this study was conducted in a homogenously Japanese population, the results may be difficult to generalize to other populations. Future replications using a larger sample size and non-Japanese populations are therefore required.

Conclusions

In conclusion, the present study suggests that having Ikigai can contribute to higher levels of serum HDLC at baseline and that this association persists over time. In addition, Ikigai may also provide new avenues for enhancing lifestyle by promoting healthy behaviors and improving mental health conditions.

Appendix

Table 4 Ikigai-associated sex-specific changes in serum non-HDLC

Ikigai levels	Men					Women				
	Without (reference)	With a little		With		Without (reference)	With a little		With	
Serum non-HDLC (Baseline difference)[a]		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value
Model1	0	1.91(-12.7,16.5)	0.80	3.90(-10.8,18.6)	0.60	0	-17.6(-30.2,-5.00)	0.01*	-17.4(-30.1,-4.72)	0.01*
Model2	0	2.16(-13.4,17.9)	0.78	2.10(-13.8,17.9)	0.80	0	-19.2(-31.9,-6.57)	0.01*	-19.0(-31.9,-5.98)	0.01*
Serum non-HDLC (Time-dependent difference)[b]		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value
Model1	0	0.59(-0.94,2.13)	0.45	0.15(-1.39,1.70)	0.85	0	0.49(-0.72,1.69)	0.43	0.42(-0.79,1.63)	0.50
Model2	0	0.55(-1.39,2.49)	0.58	0.27(-1.69,2.22)	0.79	0	0.46(-1.17,2.09)	0.58	0.50(-1.14,2.14)	0.55

We combined "definitely yes" and "yes" as "with Ikigai", and recorded "a little" as "with a little Ikigai" and "no" as "without Ikigai"

We used linear mixed-effect models to investigate the association of changes in Ikigai with changes in serum non-HDLC over time

Model1 is adjusted for age

Model2 is adjusted for age, former smoker, current smoker of 1-19 cigarettes/day, current smoker of ≥ 20 cigarettes/day, former drinker, current drinker of ethanol at 1 to 22 g/day, current drinker of ethanol at ≥ 23 g/day, social support, declining interest, depressed in mood, menopause and unemployed at baseline

CI confidence interval, *non-HDLC* non-high-density lipoprotein cholesterol

*$p < 0.05$

[a] Baseline difference is the association of Ikigai at baseline with serum non-HDLC

[b] Time-dependent difference is the association of Ikigai with the slope describing the linear relationship between serum non-HDLC levels and time (serum non-HDLC changes per year)

Table 5 Ikigai-associated sex-specific changes in serum TC

Ikigai levels	Men					Women				
	Without (reference)	With a little		With		Without (reference)	With a little		With	
Serum TC (Baseline difference)[a]		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value
Model1	0	7.05(-7.83,21.9)	0.35	8.10(-6.88,23.1)	0.29	0	-9.78(-22.6,3.02)	0.13	-9.28(-22.2,3.64)	0.16
Model2	0	6.16(-9.78,22.1)	0.45	5.03(-11.3,21.3)	0.54	0	-11.6(-24.3,1.15)	0.07	-10.7(-23.8,2.32)	0.11
Serum TC (Time-dependent difference)[b]		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value		*β* (95% CI)	*p* value	*β* (95% CI)	*p* value
Model1	0	0.52(-1.06,2.09)	0.52	0.28(-1.30,1.87)	0.72	0	0.79(-0.45,2.04)	0.21	0.78(-0.47,2.03)	0.22
Model2	0	0.45(-1.52,2.43)	0.65	0.36(-1.63,2.34)	0.72	0	0.80(-0.83,2.43)	0.33	0.87(-0.77,2.50)	0.30

We combined "definitely yes" and "yes" as "with Ikigai", and recorded "a little" as "with a little Ikigai" and "no" as "without Ikigai"

We used linear mixed-effect models to investigate the association of changes in Ikigai with changes in serum TC over time

Model1 is adjusted for age

Model2 is adjusted for age, former smoker, current smoker of 1-19 cigarettes/day, current smoker of ≥ 20 cigarettes/day, former drinker, current drinker of ethanol at 1 to 22 g/day, current drinker of ethanol at ≥ 23 g/day, social support, declining interest, depressed in mood, menopause and unemployed at baseline

CI confidence interval, *TC* total cholesterol

*$p < 0.05$

[a] Baseline difference is the association of Ikigai at baseline with serum TC

[b] Time-dependent difference is the association of Ikigai with the slope describing the linear relationship between serum TC levels and time (serum TC changes per year)

Abbreviations

HDLC	High-density lipoprotein cholesterol
LDLC	Low-density lipoprotein cholesterol
HPA	Hypothalamus–pituitary–adrenal
CIRCS	Circulatory Risk in Communities Study
TC	Total cholesterol
non-HDLC	Non-high-density lipoprotein cholesterol
BMI	Body mass index
VIF	Variance inflation factor
CI	Confidence interval
CRH	Corticotropin-releasing hormone
LPL	Lipoprotein lipase

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Authors' contributions
S.I. analyzed the data and drafted the manuscript. A.I. provided technical assistance for the data analysis. S.I., A.I., K.Y., H.I., and T.T. designed and coordinated the study. H.I. obtained the funding. All authors were involved in data collection, interpretation of the data, and critical revision of the manuscript.

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Availability of data and materials
The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author upon reasonable request and with the permission of the cohort committee.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the ethics committees of the University of Tsukuba (approval no. 66–10), Osaka University (approval no. 14285–9), the ethics review board of Juntendo University's Faculty of Medicine (approval no. 2016091), and the institutional review board of Osaka Center for Cancer and Cardiovascular Disease Prevention (approval no. R2-Rinri-4). We obtained informed consent for the use of existing data from representatives in communities, but not from each research participant since the current study is the secondary use of the data obtained for public health practice on cardiovascular disease prevention in local communities.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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