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# Association between Stress-Coping Strategy and Functional Disability in the General Older Adult Population: The Takashima Study

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## Keywords

Cohort study · Asian population · Positive thought · Problem-solving

## Abstract

**Background:** Both physical and psychological factors have been associated with functional disability. However, the associations between stress-coping strategies and future functional disability remain unclear. **Methods:** We analyzed 2,924 participants who did not have incidence of functional disability or death within the first 3 years of the baseline survey and were aged 65 years or more at the end of follow-up. Stress-coping strategies were assessed via a self-administered questionnaire (emotional expression, emotional support seeking, positive thought, problem-solving, and disengagement) in a baseline survey from 2006 to 2014. Levels of coping strategies were classified as low, middle, and high based of frequency. Functional disability decline was followed up using the long-term-care insurance program until November 1, 2019. Functional dis-

ability decline was defined as a new long-term-care insurance program certification. Cox proportional hazards model with competing risk analysis for death was used to evaluate associations between coping strategy levels and functional disability. **Results:** During the follow-up period, we observed 341 cases of functional disability and 73 deaths without previous incidence of functional disability. A significant inverse association between “positive thought” and “problem-solving” and future functional disability was observed. Multivariable adjusted hazard ratios (95% confidence interval) for functional disability were 0.68 (0.51–0.92) for high levels of “positive thought” and 0.73 (0.55–0.95) for high levels of “problem-solving,” compared with low levels of the coping strategies. The inverse association was stronger in men. **Conclusions:** Some sub-components of stress-coping strategies might be associated with future incidence of functional disability among older adults.

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## Introduction

Japan is currently the most aged society in the world with a reported percentage of the population aged 65 years and over (aging rate) of 28.1% in 2018 [1]. The average period with no impediment to daily life was estimated to be 72 years in men and 75 years in women, and the average period with impediment to daily life was estimated to be 8.8 years in men and 12.3 years in women in 2016 [1]. The World Population Prospects 2019 reported that the aging rate in developed countries will be 28.2% in 2060, while the aging rate in East Asia and Southern Europe will exceed 30% in 2060 [2]. Other developed countries, particularly in East Asia and Europe, will undergo super-aging, indicating that the expansion of healthy life expectancy is becoming an increasingly urgent issue.

Stress-coping strategy has been associated with both chronic disease and psychological health [3]. Approach-oriented coping strategies were related to the volume of the hippocampus [4], and the decreased risk of stroke [5] and depression [6]. On the other hand, avoidance coping strategies were associated with increased risk of depression [6]. Both physical status [7] such as smoking [8, 9], high blood pressure (BP) [10], and physical frailty [11], and psychological factors, including depression [7, 12] were related to future functional decline. A recent study in Japan found that mild or moderate psychological distress was associated with the incidence of functional disability [13]. The major estimated causes of long-term care in Japan were dementia (17.6%), stroke (16.1%), and infirmity due to aging (12.8%) [14]. These results might strongly suggest that stress-coping strategies might be associated with future functional disability via these risk factors. However, to the best of our knowledge, no previous studies have examined the association between (or subcomponents of) stress-coping strategies and future functional disability in the general older adult population. The current study aimed to examine the association between stress-coping strategies and future functional disability in the general Japanese older adult population using the Takashima study, an ongoing population-based cohort study in Japan [15, 16].

## Participants and Methods

### *Participants and Follow-Up*

The Takashima study is an ongoing population-based cohort study of risk factors for lifestyle-related disease [15, 16] and is part of the Japan Multi-Institutional Collaborative Cohort (J-MICC) study [17, 18]. From 2006 to 2014, a total of 4,760 residents in Ta-

kashima City aged 20 years or more who underwent the annual health check-up agreed to participate in the baseline survey.

To minimize reverse causation as much as possible, we excluded participants with a history of cardiovascular disease (CVD) ( $N = 169$ ) and those with missing information ( $N = 153$ ) in the baseline survey. We further excluded participants aged <65 years at the end of follow-up ( $N = 1,420$ ), those who died or exhibited incident functional disability within the first 3 years of follow-up ( $N = 78$ ), and those who were lost to follow-up ( $N = 16$ ) due to incomplete data. Consequently, 2,924 participants (1,195 men and 1,729 women) were included in the current analysis.

The Takashima study conducted follow-up surveys until November 1, 2019. Vital status and functional disability of the participants were determined from the basic resident registry and long-term-care insurance program of the local government. The long-term-care insurance program is a public social health program providing long-term care in Japan [19, 20]. An individual aged 65 years or more is eligible for long-term care. To receive long-term-care services through the long-term-care insurance program, the individual is assessed for functional disability using the standardized questionnaire developed by the Ministry of Health, Labour, and Welfare of Japan. If the individual is eligible for care, the committee decides the level of care, ranging from Requiring-support 1, Requiring-support 2, Care level 1, to Care level 5 according to the national standardized criteria [21]. During the follow-up period, the criteria for the long-term-care program were not changed. Functional disability decline in the current study was defined as a new long-term-care insurance program certification of requiring support (Requiring-support 1 and higher) in accordance with the methods used in the previous studies [13, 22, 23]. Several previous studies have used long-term-care insurance program certification as an outcome of incidence of functional disability in older adults [13, 22–27], and 1 previous study reported a correlation between long-term-care insurance program certification, activities of daily living, and Mini-Mental State Examination scores [28].

### *Baseline Examinations*

Baseline BP was measured twice by trained observers using a standard electrical sphygmomanometer BP103iII (Omron Healthcare, Kyoto, China) applied to the right arm of seated participants after at least 5 min of rest. Body mass index (BMI) was calculated as weight divided by height squared ( $\text{kg}/\text{m}^2$ ). We used a self-administered questionnaire that included lifestyle, clinical history, family history, smoking, and alcohol drinking habits. The questionnaire was checked and collected by trained observers.

Nonfasting blood samples were obtained at the baseline survey. Blood samples were shipped to 1 laboratory (Kinkiyoken, Otsu, Japan) for blood measurements. Hemoglobin A1c (HbA1c) level (JDS) was measured by latex agglutination immunoassay. HbA1c (NGSP) levels were calculated using a formula ( $1.02 \times \text{HbA1c [JDS]} + 0.25$ ) [29]. Serum triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels were measured by direct enzymatic assays (Sekisui Medical Co., Ltd., Tokyo, Japan) using standardized protocol certification by the Cholesterol Reference Method Laboratory Network.

### *Coping Strategies*

Coping strategies at the baseline survey were assessed using a self-administered questionnaire. The questionnaire to assess

stress-coping strategies used by the J-MICC study has been described elsewhere [30]. Briefly, participants were asked “How do you cope with daily life?” and requested to report the frequency (seldom, occasionally, often, and very often) of using 5 coping strategies (emotional expression, emotional support seeking, positive thought, problem-solving, and disengagement) selected from the Brief COPE [31] or the General Coping Questionnaire [32]. The 5 coping strategies were evaluated with the following items: (1) “To express your feeling or your undesirable emotion” (emotional expression); (2) “To consult someone close to you and to ask for encouragement” (emotional support seeking); (3) “To interpret that problem positively” (positive thought); (4) “To work hard to resolve the problem” (problem-solving); and (5) “To let the problem take its own course” (disengagement).

### Statistical Analysis

Cox proportional hazards models with competing risk analysis for death [33] were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of the incidence of functional disability based on the levels of each stress-coping strategy with low level as a reference. The level of each coping strategy was classified as follows: low for a frequency of “seldom,” middle for a frequency of “occasionally,” and high for a frequency of “often” or “very often.” Age- and sex-adjusted HRs for the incidence of functional disability were estimated using models adjusted for age and sex (model 1). Multivariable-adjusted HRs for the incidence of functional disability were estimated using models adjusted for age, sex, systolic BP, BMI, HbA1c (NGSP) level, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, drinking habits (nondrinker, past-drinker, or current drinker), smoking habits (nonsmoker, past-smoker, or current smoker), antihypertensive medication, and medication for dyslipidemia and diabetes (model 2). We added the number of years of education as a covariate in an additional model (model 3). Similarly, we conducted a subgroup analysis by sex. All tests were 2-tailed, and *p* values of <0.05 were considered to indicate statistical significance. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

## Results

The total person-years of observation were 27,270, and the mean follow-up period was 9.33 years. Participants' baseline characteristics are shown in Table 1. The mean age was 66.3 years, and mean systolic BP and diastolic BP were 129.6 mm Hg and 76.3 mm Hg, respectively. The mean number of years of education was 11.2 years. During the follow-up period, 366 participants had functional disability, and 73 participants died without incidence of functional disability.

Table 2 shows adjusted HRs (95% CI) for all participants based on the level of stress-coping strategies. Compared with low levels for the coping strategy, the multivariable-adjusted HRs for functional disability with high levels of “positive thought” and “problem-solving” were 0.68 (95% CI, 0.51, 0.92) and 0.73 (95% CI, 0.55, 0.95),

**Table 1.** Baseline characteristics of study population: the Takashima Study, Japan, 2006–2014

Participants		
Total number	2,924	
Age, years, mean (SD)	66.27	(5.57)
Men, <i>N</i> (%)	1,195	(40.87)
Systolic BP, mm Hg, mean (SD)	129.57	(19.54)
Diastolic BP, mm Hg, mean (SD)	76.31	(11.20)
BMI, kg/m <sup>2</sup> , mean (SD)	23.07	(2.99)
HbA1c, NGSP, %, mean (SD)	5.61	(0.65)
LDL cholesterol, mmol/L, mean (SD)	3.32	(0.83)
HDL cholesterol, mmol/L, mean (SD)	1.60	(0.40)
Education year, year, mean (SD)	11.13	(2.21)
Drinking status		
Nondrinker, <i>N</i> (%)	1,541	(52.70)
Past-drinker, <i>N</i> (%)	58	(1.98)
Current drinker, <i>N</i> (%)	1,325	(45.31)
Smoking status		
Nonsmoker, <i>N</i> (%)	2,106	(72.02)
Past-smoker, <i>N</i> (%)	471	(16.11)
Current smoker, <i>N</i> (%)	347	(11.87)
Medication		
Hypertension, <i>N</i> (%)	882	(30.16)
Dyslipidemia, <i>N</i> (%)	510	(17.44)
Diabetes, <i>N</i> (%)	180	(6.16)

*N*, number; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

respectively. The significant associations between future functional disability and these coping strategies remained after additional adjustment for the number of years of education. However, other coping strategies were not associated with future functional disability.

Adjusted HRs (95% CI) based on the level of coping strategies stratified by sex are shown in Table 3 for men and Table 4 for women. High levels of both “positive thought” and “problem-solving” were significantly associated with increased risk of future functional disability in men. Compared with low levels of coping strategies, the multivariable-adjusted HRs of future functional disability in men were 0.61 (95% CI, 0.41, 0.92) for high levels of “positive thought” and 0.63 (95% CI: 0.43, 0.94) for high levels of “problem-solving.” In women, the multivariable-adjusted HRs were 0.72 (95% CI: 0.48, 1.09) for high levels of “positive thought” and 0.81 (95% CI: 0.55, 1.21) for high levels of “problem-solving.” Similar results were observed in both men and women, but no reach statistical significance was noted in women. Other coping strategies in both men and women were not associated with future functional disability.

**Table 2.** HRs for functional disability based on the levels of coping strategies in all participants: the Takashima Study, Japan, 2006–2014

	Level of coping strategies			<i>p</i> trend
	low	middle	high	
<b>Emotional expression</b>				
Person-years	8,120	15,351	3,799	
Events, <i>N</i>	143	173	50	
Model 1	1.00 (reference)	0.97 (0.77–1.22)	1.13 (0.82–1.55)	0.635
Model 2	1.00 (reference)	0.99 (0.78–1.24)	1.19 (0.87–1.63)	0.459
Model 3	1.00 (reference)	0.99 (0.78–1.25)	1.20 (0.87–1.64)	0.429
<b>Emotional support seeking</b>				
Person-years	12,305	10,901	4,064	
Events, <i>N</i>	186	137	43	
Model 1	1.00 (reference)	1.03 (0.82–1.29)	0.97 (0.69–1.37)	0.979
Model 2	1.00 (reference)	1.09 (0.87–1.38)	0.96 (0.68–1.37)	0.895
Model 3	1.00 (reference)	1.09 (0.87–1.37)	0.96 (0.67–1.36)	0.910
<b>Positive thought</b>				
Person-years	3,180	9,989	14,101	
Events, <i>N</i>	67	132	167	
Model 1	1.00 (reference)	0.82 (0.61–1.11)	0.67 (0.50–0.89)	0.004
Model 2	1.00 (reference)	0.85 (0.62–1.15)	0.68 (0.51–0.92)	0.007
Model 3	1.00 (reference)	0.85 (0.62–1.15)	0.69 (0.51–0.93)	0.009
<b>Problem-solving</b>				
Person-years	3,826	9,406	14,038	
Events, <i>N</i>	88	110	168	
Model 1	1.00 (reference)	0.81 (0.60–1.09)	0.74 (0.56–0.96)	0.031
Model 2	1.00 (reference)	0.78 (0.57–1.06)	0.73 (0.55–0.95)	0.030
Model 3	1.00 (reference)	0.78 (0.58–1.06)	0.73 (0.56–0.96)	0.034
<b>Disengagement</b>				
Person-years	5,647	12,299	9,324	
Events, <i>N</i>	79	159	128	
Model 1	1.00 (reference)	1.06 (0.81–1.4)	1.15 (0.86–1.52)	0.339
Model 2	1.00 (reference)	1.11 (0.85–1.47)	1.18 (0.88–1.58)	0.264
Model 3	1.00 (reference)	1.12 (0.85–1.47)	1.19 (0.89–1.59)	0.252

Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, systolic BP, body mass index, HbA1c(NGSP), LDL cholesterol, HDL cholesterol, drinking habits, smoking habits, antihypertensive medication, medication for dyslipidemia, and medication for diabetes. Model 3 was adjusted for covariates in model 2 and number of years of education. BP, blood pressure; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HR, hazard ratio.

## Discussion

In the present study, we found that several components of stress-coping strategies were associated with future functional disability defined as long-term-care insurance program certification. The levels of “positive thought” and “problem solving” were inversely associated with future functional disability in the general Japanese older adult population. The associations were more prominent in men. However, no significant association between future functional disability and “emotional expression,” “emotional support seeking,” and “disengagement” were observed in this study.

Previous studies reported an association between functional disability and lifestyle-related factors, psychological health, and physical health [7, 11, 12]. Coping strategies were associated with lifestyle, psychological health, and physical health [3, 5, 6, 30, 34]. These studies suggested that coping strategies might be associated with functional disability through these factors. However, to the best of our knowledge, there is little evidence regarding the association between coping strategies and future functional disability, and this is the first study to examine the association between components of coping strategies and future functional disability using a population-based cohort study.

**Table 3.** HRs for functional disability based on the levels of coping strategies in men: the Takashima Study, Japan, 2006–2014

	Level of coping strategies			<i>p</i> trend
	low	middle	high	
<b>Emotional expression</b>				
Person-years	3,292	6,355	1,521	
Events, <i>N</i>	56	88	20	
Model 1	1.00 (reference)	1.09 (0.77–1.54)	1.16 (0.71–1.89)	0.517
Model 2	1.00 (reference)	1.12 (0.79–1.59)	1.19 (0.72–1.96)	0.436
Model 3	1.00 (reference)	1.14 (0.80–1.61)	1.21 (0.74–2.00)	0.375
<b>Emotional support seeking</b>				
Person-years	7,218	3,160	791	
Events, <i>N</i>	113	43	8	
Model 1	1.00 (reference)	0.98 (0.69–1.39)	0.73 (0.35–1.56)	0.506
Model 2	1.00 (reference)	0.95 (0.66–1.36)	0.78 (0.36–1.70)	0.527
Model 3	1.00 (reference)	0.92 (0.64–1.32)	0.76 (0.35–1.66)	0.441
<b>Positive thought</b>				
Person-years	1,530	4,018	5,620	
Events, <i>N</i>	38	54	72	
Model 1	1.00 (reference)	0.77 (0.50–1.18)	0.61 (0.40–0.91)	0.014
Model 2	1.00 (reference)	0.78 (0.51–1.19)	0.61 (0.41–0.92)	0.018
Model 3	1.00 (reference)	0.78 (0.51–1.20)	0.63 (0.41–0.95)	0.025
<b>Problem-solving</b>				
Person-years	1,618	3,396	6,154	
Events, <i>N</i>	45	40	79	
Model 1	1.00 (reference)	0.70 (0.45–1.11)	0.67 (0.45–0.98)	0.056
Model 2	1.00 (reference)	0.64 (0.40–1.02)	0.63 (0.43–0.94)	0.046
Model 3	1.00 (reference)	0.64 (0.40–1.03)	0.65 (0.44–0.97)	0.064
<b>Disengagement</b>				
Person-years	2,904	5,062	3,202	
Events, <i>N</i>	45	71	48	
Model 1	1.00 (reference)	1.01 (0.69–1.47)	1.05 (0.7–1.57)	0.831
Model 2	1.00 (reference)	1.05 (0.72–1.55)	1.14 (0.74–1.74)	0.551
Model 3	1.00 (reference)	1.05 (0.72–1.55)	1.15 (0.75–1.76)	0.519

Model 1 was adjusted for age. Model 2 was adjusted for age, systolic BP, body mass index, HbA1c(NGSP), LDL cholesterol, HDL cholesterol, drinking habits, smoking habits, antihypertensive medication, medication for dyslipidemia, and medication for diabetes. Model 3 was adjusted for covariates in model 2 and the number of years of education. BP, blood pressure; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HR, hazard ratio.

In the current study, high levels of “positive thought” and “problem-solving” were significantly associated with a lower risk of future functional disability. Previous studies have shown that problem-solving and positive reappraisal strategies are inversely associated with depression [6] and mental health [35]. Other studies have revealed that the approach-oriented coping strategies are positively associated with the volume of the whole hippocampus [4]. Moreover, depression, mental health, and cognitive impairment are reported to be risk factors of functional disability [12]. The current results are consistent with these previous findings. The preventive effects of coping

strategies for depression, mental health, and cognitive impairment may be mechanisms associated with coping strategies and future functional disability.

In Japan, a previous study reported that dementia, stroke, and frailty due to aging were the main causes of functional disability decline, defined as long-term-care insurance program certification of requiring any support, which was the same definition of functional disability used in the current study [14]. In the Japan Public Health Center cohort study, stroke incidence was inversely associated with the approach-oriented coping strategy [5]. These previous findings were also consistent with the cur-

**Table 4.** HRs for functional disability based on the levels of coping strategies in women: the Takashima Study, Japan, 2006–2014

	Level of coping strategies			<i>p</i> trend
	low	middle	high	
<b>Emotional expression</b>				
Person-years	4,828	8,995	2,279	
Events, <i>N</i>	87	85	30	
Model 1	1.00 (reference)	0.89 (0.65–1.22)	1.11 (0.73–1.68)	0.911
Model 2	1.00 (reference)	0.88 (0.65–1.20)	1.09 (0.71–1.67)	0.977
Model 3	1.00 (reference)	0.88 (0.64–1.20)	1.08 (0.71–1.66)	0.991
<b>Emotional support seeking</b>				
Person-years	5,087	7,742	3,274	
Events, <i>N</i>	73	94	35	
Model 1	1.00 (reference)	1.08 (0.79–1.48)	1.09 (0.73–1.64)	0.612
Model 2	1.00 (reference)	1.20 (0.88–1.63)	1.08 (0.71–1.65)	0.543
Model 3	1.00 (reference)	1.19 (0.87–1.63)	1.08 (0.70–1.65)	0.549
<b>Positive thought</b>				
Person-years	1,649	5,972	8,481	
Events, <i>N</i>	29	78	95	
Model 1	1.00 (reference)	0.86 (0.55–1.33)	0.71 (0.47–1.09)	0.088
Model 2	1.00 (reference)	0.89 (0.58–1.37)	0.72 (0.48–1.09)	0.077
Model 3	1.00 (reference)	0.88 (0.57–1.36)	0.72 (0.47–1.09)	0.073
<b>Problem-solving</b>				
Person-years	2,208	6,010	7,884	
Events, <i>N</i>	43	70	89	
Model 1	1.00 (reference)	0.89 (0.60–1.33)	0.79 (0.54–1.16)	0.211
Model 2	1.00 (reference)	0.92 (0.61–1.38)	0.81 (0.55–1.21)	0.274
Model 3	1.00 (reference)	0.91 (0.61–1.37)	0.81 (0.55–1.19)	0.255
<b>Disengagement</b>				
Person-years	2,743	7,237	6,122	
Events, <i>N</i>	34	88	80	
Model 1	1.00 (reference)	1.14 (0.76–1.73)	1.28 (0.84–1.93)	0.231
Model 2	1.00 (reference)	1.22 (0.81–1.84)	1.34 (0.88–2.03)	0.180
Model 3	1.00 (reference)	1.22 (0.81–1.83)	1.33 (0.88–2.02)	0.183

Model 1 was adjusted for age. Model 2 was adjusted for age, systolic BP, BMI, HbA1c(NGSP), LDL cholesterol, HDL cholesterol, drinking habits, smoking habits, antihypertensive medication, medication for dyslipidemia, and medication for diabetes. Model 3 was adjusted for covariates in model 2 and number of years of education. BP, blood pressure; BMI, body mass index; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HR, hazard ratio.

rent results, and the preventive effect of approach-oriented coping strategies for stroke might also provide a potential mechanism underlying our observations.

In the present study, we could not find any significant association between emotional expression, emotional support seeking, or avoidance-oriented behaviors. A previous study showed to be no significant association between BMI and emotional expression or emotional support seeking [30]. Furthermore, depression was not associated with emotional support seeking [6]. Avoidance-oriented behaviors were successful for coping with short-term uncontrollable stress and related to chronic disease progression or

mortality [3]. Another study from Japan reported that avoidance-oriented behaviors were not associated with CVD-related death or incidence [5]. These results suggested that these coping strategies might not be effective for coping with long-term stress.

Significant inverse associations between “positive thought” and “problem-solving” and future functional disability were found in men, but in women, a similar but not significant association was found. Sex differences in the association between these coping strategies and C-reactive protein (CRP) level [34] were reported to be observed. These coping strategies were associated with CRP

level in men. CRP is a predictor for future CVD-related death [36]. Another study reported that these coping strategies resulted in lower risk of depression in both men and women, but the adjusted odds ratios for depression in men was 0.52, which was lower than that in women (0.64) [6]. The previous studies suggested that these coping strategies might be more strongly influenced by both physical and psychological factors that could be considered potential risk factors for functional disability in men compared with women.

The strengths of the current study include its prospective design and complete follow-up of functional disability using the long-term-care insurance program of the local government. We excluded men and women who had incident functional disability or died within the first 3 years of the baseline survey from the analysis to minimize bias due to reverse causation. Follow-up of functional disability using the long-term-care insurance program might minimize bias due to loss to follow-up bias. However, the present study involved several limitations that should be considered. First, we did not consider income in our analysis. Education and income are considered major components of socioeconomic status. In the current study, we considered only education, and the association between components of stress-coping strategies and functional disability was not significantly affected by the education level. Second, we did not consider changes in coping strategies during the follow-up period. Third, due to a lack of data, we did not consider depression and dementia at baseline as potential confounders. Lastly, due to insufficient data, we did not consider the presence or absence of a family member living with the participants.

## Conclusion

The present study demonstrated that some subcomponents of coping strategies (“positive thought” and “problem-solving”) are independent predictors of future functional disability defined as long-term-care insurance program certification in the general Japanese older adult population. These findings potentially indicate that improved coping strategies may prevent future functional disability.

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## Statement of Ethics

This study protocol adhered to the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation. All participants provided written informed consent, and this study protocol was approved by the Institutional Review Board of Tsuruga Nursing University (No. 19002), Shiga University of Medical Science (No. G2005-103), and Kinki University Faculty of Medicine (No. 31-165).

## Conflict of Interest Statement

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## Author Contributions

Kita Y. and Ueshima H. contributed to the design of Takashima Cohort Study, and Takashima N. and Kita Y. contributed to the conception and design of this study. Takashima N., Nakamura Y., Miyagawa N., Kadota A., Tanaka-Mizuno S., Matsui K., Miura K., Ueshima H., and Kita Y. collected the data. Takashima N. analyzed data and wrote the manuscript draft. All authors discussed the results and contributed to the final manuscript. All authors have approved the submitted manuscript. The manuscript has not been submitted elsewhere nor published elsewhere in whole.

## Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise research participant privacy but are available from the corresponding author (N.T.) upon reasonable request within the limitations of informed consent by the research committee of Takashima Study upon acceptance.



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