

Association between C-Reactive Protein Levels and Functional Disability in the General Older-Population: The Takashima Study

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Aims: High-sensitivity C-reactive protein (hsCRP) associates with atherosclerotic diseases such as stroke. However, previous results on the association between hsCRP levels and functional disability were controversial.

Methods: We analyzed 2,610 men and women who did not exhibit functional disability or death within the first 3 years of the baseline survey and those aged 65 years or older at the end of follow-up. The levels of hsCRP were assessed using latex agglutination assay at baseline survey from 2006 to 2014. Functional disability was followed up using the long-term care insurance (LTCI) program until November 1, 2019. Functional disability was defined as a new LTCI program certification. Cox proportional hazards model with competing risk analysis for death was used to evaluate the association between hsCRP levels and future functional disability.

Results: During a 9-year follow-up period, we observed 328 cases of functional disability and 67 deaths without prior functional disability incidence. The multivariable-adjusted hazard ratio (HR, 95% confidence interval [CI]) of functional disability in log-transformed hsCRP levels was 1.43 (1.22–1.67) in men and 0.97 (0.81–1.15) in women. When hsCRP level was analyzed as a categorical variable, low hsCRP levels (< 1.0 mg/l) as the reference, the multivariable-adjusted HR (95% CI) of functional disability in high hsCRP levels (\geq 3.0 mg/l) was 2.37 (1.56–3.62). Similar results were observed when stratified by sex, but it was not significant in women.

Conclusions: This study demonstrates that low-grade systemic inflammation to assess hsCRP might predict the future incidence of functional disability, especially in men.

Key words: Functional disability, Systemic inflammatory, C-reactive protein

Japan is the most aged society with a population percentage of individuals aged 65 and above (aging rate) of 28.1% in 2018¹⁾. In Japan, the estimated average period with no independent to everyday life in men and women was 72 and 75 years, respectively, and the estimated average period with independent to everyday life in men and women was 8.8 and 12.3 years, respectively¹⁾. By 2060, the mean aging rate was

estimated to be 28%²⁾ in developed countries. The estimated aging rate in 2060 is similar to the aging rate in 2016 in Japan. Therefore, the prevention act on disability might be important not only for Japan but also for other countries.

Cardiometabolic risk factors such as smoking, obesity, hypertension, diabetes, and dyslipidemia are established risk factors for atherosclerotic diseases³⁾.

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These factors are associated with high sensitivity C-reactive protein (hsCRP) levels as a marker for low-grade systemic inflammation⁴⁻⁷. The levels of hsCRP were reported to be associated with atherosclerotic diseases such as stroke, atherosclerosis, and myocardial infarction⁸⁻¹². Some of these diseases were reported to be one of the leading causes of the long-term care in Japan¹³. Previous cross-sectional studies reported the significant association between hsCRP and functional disability¹⁴⁻¹⁷. However, longitudinal studies did not find a significant association between hsCRP and future functional decline in the general elderly population^{16, 17}. Therefore, the previous results of longitudinal studies and cross-sectional studies were controversial.

The aim of the present study was to examine the association between baseline hsCRP levels and future functional disability in the Japanese general population using the Takashima Study, an ongoing population-based cohort study in Japan¹⁸. We also examined whether the associations differed according to those cardiometabolic risk factors.

Methods

Participants and Follow-Up

The Takashima Study is an ongoing population-based cohort study^{18, 19} and is also a part of the Japan Multi-Institutional Collaborative Cohort Study (J-MICC Study)²⁰. The baseline survey was conducted from 2006 to 2014. A total of 4,760 residents in Takashima City aged 20 years or above participated in the annual health check-up and agreed to participate in the study. In this analysis, we excluded participants younger than 65 years at the end of follow-up (N=1,420), those with a history of cardiovascular disease (CVD) (N=169), those with higher CRP levels (>10.0 mg/l) or those who reported with common cold or injury within 2 weeks before the baseline survey (N=378), and those with missing information (N=101) at baseline survey. We further excluded participants who died or those with incident functional disability that occurred within the first 3 years of follow-up (N=60) and those who were lost to follow-up (N=11) due to incomplete data. Consequently, 2,610 participants (1,056 men and 1,554 women) were included in this analysis.

We followed up all participants until November 1, 2019. Vital status was determined from the basic resident register, and functional disability was determined from the long-term care insurance (LTCI) program. The LTCI in Japan was a public health insurance program for long-term care was started in 2000. By law, all Japanese or aliens residing in Japan

who are aged 40 or more participated in the LTCI, and aged 65 or more are eligible for the long-term care²¹. All individuals receive long-term care services; the LTCI assesses functional disability using the standardized questionnaire developed by the Ministry of Health, Labour, and Welfare of Japan. According to the standardized questionnaire, the committee decided the level ranging from Requiring support 1, Requiring support 2, Care level 1, to Care level 5 according to the national standardized criteria. During the follow-up period, the criteria for the long-term care program was not changed²². In the present study, functional disability decline was defined as a new LTCI certification to require any support (Requiring support 1 and higher) according to the previous studies^{19, 23, 24, 25}. The LTCI certificate correlates with the Activities of Daily Living (ADLs) and the Mini-Mental States Examination²⁶. This study protocol followed the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation and was approved by the Institutional Review Boards of Tsuruga Nursing University (No. 19002), Shiga University of Medical Science (No. G2005-103), and Kinki University Faculty of Medicine (No. 31-165). The data that support the findings of this study are not available due to ethical restrictions.

Baseline Examinations

Baseline blood pressure (BP) was measured twice by trained observers using a standard electrical sphygmomanometer BP103iII (Omron Health Care, Kyoto) applied to the right arm of seated participants after at least 5 min of rest. Body mass index (BMI, kg/m²) was calculated as weight divided by height squared. Non-fasting blood samples were obtained at the baseline survey. Blood samples were shipped to one laboratory (Kinkiyoken, Otsu, Japan) for measurements. Hemoglobin A1c (HbA1c) (JDS) and hsCRP were measured using latex agglutination immunoassay. HbA1c (NGSP) levels were calculated using the formula: $1.02 \times \text{HbA1c [JDS]} + 0.25$ ²⁷. Serum triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were measured by direct enzymatic assays using standardized protocols certified by the Cholesterol Reference Method Laboratory Network.

We used a self-administered questionnaire that included lifestyle, clinical history, family history, smoking habits (never smoker, past smoker, or current smoker), and alcohol drinking habits (never drinker, past drinker, or current drinker). Additionally, the questionnaire included common cold or injury within 2 weeks before the baseline survey. The questionnaire

Table 1. Baseline characteristics of study population according to the high sensitivity C-reactive Protein level: the Takashima Study, 2006 to 2014

	High sensitivity C-reactive Protein levels (mg/l)			Total	P value
	Low (< 1.0)	Middle (1.0 to 3.0)	High (≥ 3.0)		
Number	2,143	372	95	2,610	
Age (year)	66.2 (5.6)	66.9 (5.6)	67.0 (5.4)	66.3 (5.6)	0.046
Men (N)	828 (38.6)	182 (48.9)	46 (48.4)	1,056 (40.5)	< 0.001
SBP (mmHg)	128.6 (19.5)	133.4 (19.5)	131.1 (19.1)	129.4 (19.5)	< 0.001
DBP (mmHg)	75.9 (11.2)	78.1 (10.8)	76.2 (11.4)	76.2 (11.2)	0.002
Body mass index (kg/m ²)	22.8 (2.8)	24.3 (3.4)	24.2 (3.4)	23.0 (3.0)	< 0.001
HbA1c (NGSP) (%)	5.57 (0.58)	5.75 (0.79)	5.72 (0.78)	5.60 (0.62)	< 0.001
LDL cholesterol (mmol/L)	128.0 (31.7)	130.7 (34.0)	130.1 (35.7)	128.4 (32.2)	0.276
HDL cholesterol (mmol/L)	63.0 (15.5)	56.7 (15.5)	57.7 (16.6)	61.9 (15.7)	< 0.001
Education year (year)	11.3 (2.2)	10.8 (2.1)	10.8 (2.2)	11.1 (2.2)	0.004
Drinking Status					
Never drinker	1,129 (52.7)	191 (51.3)	46 (48.4)	1,366 (45.8)	0.638
Past drinker	43 (2.0)	4 (1.1)	2 (2.1)	49 (1.9)	
Current drinker	971 (45.3)	177 (47.6)	47 (49.5)	1,195 (52.3)	
Smoking status					
Never smoker	1,577 (73.6)	238 (64.0)	65 (68.4)	1,880 (72.0)	< 0.001
Past smoker	339 (15.8)	63 (16.9)	16 (16.8)	418 (16.0)	
Current smoker	227 (10.6)	71 (19.1)	14 (14.7)	312 (12.0)	
Treatment					
BP lowering medication	606 (28.3)	129 (34.7)	33 (34.7)	768 (29.4)	0.023
Lipid lowering medication	380 (17.7)	63 (16.9)	11 (11.6)	454 (17.4)	0.292
Glucose lowering therapy	122 (5.7)	34 (9.1)	10 (10.5)	166 (6.4)	0.010

BP: blood pressure, DBP: Diastolic blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein, SBP: Systolic blood pressure. Values are number, rate (%), or mean (SD).

was checked and collected by trained observers.

Statistical Analysis

We categorized the hsCRP levels into three categories, namely, low: <1.0 mg/l, middle: 1.0–3.0 mg/l, and high: ≥ 3.0 mg/l, according to the Centers for Disease Control and Prevention and the American Heart Association statement²⁸⁾ and a previous study¹¹⁾. The Cox proportional hazards models with competing risk analysis for death²⁹⁾ were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of the functional disability incidence in the log-transformed hsCRP levels or according to the hsCRP categories. Multivariable-adjusted HRs for the incidence of functional disability were estimated using models adjusted for age, sex, systolic BP, BMI, HbA1c (NGSP), LDL cholesterol, HDL cholesterol, drinking habits, smoking habits, BP-lowering medication, lipid-lowering medication, and glucose-lowering therapy (model 2). We added education year as covariates in an additional model (model 3). As a sensitivity analysis, we conducted subgroup analysis by smoking status or cardiometabolic risk factors. We

defined hypertension as BP ≥ 140/90 or BP-lowering medication, high blood glucose as HbA1c (NGSP) ≥ 5.6% or glucose-lowering therapy, dyslipidemia as cholesterol ≥ 3.62 mmol/l, HDL cholesterol ≤ 1.03 mmol/l or lipid-lowering medication, and obesity as BMI ≥ 25 kg/m². All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). All tests were two-tailed, and a *p*-value of <0.05 was considered statistically significant.

Results

Total person-years was 24,337, and the mean follow-up period was 9.34 years. The baseline characteristics of the participants are shown in **Table 1**, and the baseline characteristics of the participants stratified by sex are shown in **Supplemental Table 1**. The mean age was 66.3 years, and the mean systolic BP and diastolic BP levels were 129.4 and 76.2 mmHg, respectively. The mean education year was 11.2 years. According to the higher hsCRP categories, systolic and diastolic BP, BMI, LDL cholesterol levels, and age were increasing, and HDL cholesterol levels

Table 2. Hazard ratios (95%CI) for functional disability for a 1-unit increase in log-transformed high sensitivity CRP levels: the Takashima Study, Japan, 2006–2014

	Model 1	Model 2	Model 3
Men and Women			
HR (95% CI)	1.17 (1.05-1.31)	1.18 (1.05-1.33)	1.18 (1.05-1.33)
Men			
HR (95% CI)	1.35 (1.16-1.58)	1.41 (1.21-1.66)	1.43 (1.22-1.67)
Women			
HR (95% CI)	1.01 (0.85-1.19)	0.97 (0.81-1.15)	0.97 (0.81-1.15)

CI: confidence interval, HDL: high density lipoprotein, LDL: low density lipoprotein.

Hazard ratios estimated using the Cox proportional hazards model with competing risk of death. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, systolic blood pressure, body mass index, HbA1c (NGSP), LDL cholesterol, HDL cholesterol, drinking habits, smoking habits, blood pressure lowering medication, lipid lowering medication, and glucose lowering therapy. Model 3 was adjusted for covariates in model 2 and education year.

Table 3. Hazard ratios (95%CI) for functional disability based on the levels of high sensitivity CRP levels: the Takashima Study, Japan, 2006–2014

	High sensitivity C-reactive Protein levels (mg/l)		
	Low (< 1.0)	Middle (1.0 to 3.0)	High (≥ 3.0)
Men and Women			
Person-years	20,130	3,398	849
Event (N)	249	54	25
Model 1	1.00 (Reference)	1.22 (0.91, 1.65)	2.37 (1.57, 3.56)
Model 2	1.00 (Reference)	1.23 (0.91, 1.67)	2.38 (1.56, 3.63)
Model 3	1.00 (Reference)	1.22 (0.90, 1.66)	2.37 (1.56, 3.62)
Men			
Person-years	7,800	1,630	413
Event (N)	98	33	16
Model 1	1.00 (Reference)	1.57 (1.06, 2.32)	2.79 (1.62, 4.80)
Model 2	1.00 (Reference)	1.68 (1.12, 2.51)	2.94 (1.66, 5.23)
Model 3	1.00 (Reference)	1.68 (1.13, 2.52)	2.99 (1.68, 5.34)
Women			
Person-years	12,330	1,768	436
Event (N)	151	21	9
Model 1	1.00 (Reference)	0.93 (0.58, 1.49)	1.97 (1.04, 3.74)
Model 2	1.00 (Reference)	0.90 (0.55, 1.47)	1.78 (0.93, 3.40)
Model 3	1.00 (Reference)	0.90 (0.55, 1.48)	1.78 (0.92, 3.42)

CI: confidence interval, HDL: high density lipoprotein, LDL: low density lipoprotein. Hazard ratios estimated using the Cox proportional hazards model with competing risk of death. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, systolic blood pressure, body mass index, HbA1c(NGSP), LDL cholesterol, HDL cholesterol, drinking habits, smoking habits, blood pressure lowering medication, lipid lowering medication, and glucose lowering therapy. Model 3 was adjusted for covariates in model 2 and education year.

were decreasing. Additionally, the higher prevalence of men and smokers was observed according to the higher hsCRP categories. During the follow-up period, a total of 328 participants had a functional disability, and 67 participants died without incidence of functional disability.

Table 2 shows the adjusted HRs (95% CIs) in log-transformed hsCRP levels using the Cox proportional hazards model with competing risk of

death. The age- and sex-adjusted HR (95% CI) for a 1-unit increase in log-transformed hsCRP levels was 1.17 (1.05–1.31). When stratified by sex, the HR (95% CI) was 1.35 (1.16–1.58) in men and 1.01 (0.85–1.19) in women. After adjustment for potential confounders including education year, the HR (95% CI) of functional disability was 1.43 (1.22–1.67) in men and 0.97 (0.81–1.15) in women.

Table 3 shows the adjusted HRs (95% CIs)

Table 4. Hazard ratios (95%CI) for functional disability based on the levels of high sensitivity CRP levels stratified by smoking status: the Takashima Study, Japan, 2006–2014

	High sensitivity C-reactive Protein levels (mg/l)			<i>P</i> for interaction
	Low (< 1.0)	Middle (1.0 to 3.0)	High (≥ 3.0)	
Men and Women				
Never smoker	1.00 (Reference)	1.03 (0.69, 1.54)	2.01 (1.16, 3.51)	0.267
Past smoker	1.00 (Reference)	1.71 (0.81, 3.61)	1.40 (0.46, 4.24)	
Current smoker	1.00 (Reference)	2.00 (0.88, 4.58)	5.02 (1.81, 13.93)	
Men				
Never smoker	1.00 (Reference)	2.10 (1.00, 4.37)	2.55 (0.90, 7.22)	0.155
Past smoker	1.00 (Reference)	1.47 (0.70, 3.07)	1.28 (0.42, 3.91)	
Current smoker	1.00 (Reference)	2.05 (0.88, 4.80)	4.64 (1.70, 12.69)	
Women*				
Never smoker	1.00 (Reference)	0.87 (0.53, 1.42)	1.76 (0.91, 3.38)	

CI: confidence interval, HDL: high density lipoprotein, LDL: low density lipoprotein. Hazard ratios estimated using the Cox proportional hazards model with competing risk of death. Adjusted for age, systolic blood pressure, body mass index, HbA1c (NGSP), LDL cholesterol, HDL cholesterol, drinking habits, blood pressure lowering medication, lipid lowering medication, glucose lowering therapy, and education year.

*Due to the small number of women current or past smokers, analysis could not be conducted for women.

according to the hsCRP levels using the Cox proportional hazards model with competing risk of death. Compared with low hsCRP level (< 1.0 mg/l), the age- and sex-adjusted HR (95% CI) of functional disability in high hsCRP level (≥ 3.0 mg/l) was 2.37 (1.57–3.56). When stratified by sex, similar results were observed (men: 2.79 [95% CI: 1.62–4.80] and women: 1.97 [1.04–3.74]). After adjustment for potential confounders including education year, the HR (95% CI) of functional disability in high hsCRP level was 2.37 (1.56–3.62). There was no significant interaction between sex and hsCRP level (*P* for interaction 0.193 in model 3). When stratified by sex, similar results were observed.

Table 4 shows the multivariable-adjusted HRs (95% CIs) of functional disability stratified by smoking status. There was no significant interaction between smoking status and hsCRP level (*P* for interaction 0.367). Compared with low hsCRP levels, multivariable-adjusted HRs for high hsCRP were 2.01 (1.16–3.51) in never smokers and 5.02 (1.81–13.93) in current smokers. When stratified by sex, similar results were observed in men. Owing to the smaller number of women smokers and past smokers, we could not examine the association stratified by women current smoker and past smoker.

Table 5 shows the multivariable-adjusted HRs (95% CIs) of functional disability stratified by cardiometabolic risk factors. There was an interaction between high glucose and hsCRP levels (*P* for interaction 0.046), but there were no significant interactions between other cardiometabolic risk factors and hsCRP levels. In the groups with or without high

glucose or dyslipidemia, significantly increased risks of future functional disability in high hsCRP were observed. There was an increased risk of future functional disability in middle hsCRP levels in the participants with high glucose but not in the participants without high glucose. In the groups without hypertension and with obesity, similar but insignificant increases in the risk of functional disability were observed.

Discussion

In the present population-based longitudinal study, we found that low-grade systemic inflammation evaluated by hsCRP levels was associated with future incidence of functional disability defined as LTCI certification, especially in men. The association was independent of the cardiometabolic risk factors.

In the current study, we found that baseline hsCRP levels as a marker for low-grade systemic inflammation predicted the future functional disability in the Japanese population. To the best of our knowledge, this is the first study to observe the significant positive association between hsCRP levels and future functional disability based on a population-based longitudinal study. Similar results were observed in previous cross-sectional studies^{14–17}. Although these cross-sectional studies reported the significant association between CRP levels and functional disability, previous longitudinal studies in the general population did not find any significant association between hsCRP and future functional disability^{16, 17}. A longitudinal study reported that increasing CRP but

Table 5. Hazard ratios (95%CI) for functional disability based on the levels of high sensitivity CRP levels stratified by cardio metabolic risk factors: the Takashima Study, Japan, 2006–2014

	High sensitivity C-reactive Protein levels (mg/l)			<i>P</i> for interaction
	Low (< 1.0)	Middle (1.0 to 3.0)	High (≥ 3.0)	
High Glucose				
No	1.00 (Reference)	0.85 (0.53, 1.37)	2.78 (1.54, 5.04)	0.046
Yes	1.00 (Reference)	1.76 (1.15, 2.69)	2.41 (1.35, 4.27)	
Hypertension				
No	1.00 (Reference)	1.10 (0.65, 1.86)	1.06 (0.46, 2.45)	0.065
Yes	1.00 (Reference)	1.33 (0.91, 1.94)	3.42 (2.03, 5.77)	
Dyslipidemia				
No	1.00 (Reference)	1.32 (0.84, 2.08)	2.39 (1.23, 4.65)	0.893
Yes	1.00 (Reference)	1.12 (0.74, 1.69)	2.51 (1.48, 4.24)	
Obesity				
No	1.00 (Reference)	1.06 (0.72, 1.57)	2.67 (1.58, 4.51)	0.581
Yes	1.00 (Reference)	1.36 (0.78, 2.37)	1.79 (0.85, 3.79)	

CI: confidence interval, LDL: low density lipoprotein, HDL: high density lipoprotein. Hazard ratios estimated using the Cox proportional hazards model with competing risk of death.

We defined high glucose as HbA1c (NGSP) ≥ 5.6 % or glucose lowering therapy, hypertension as BP ≥ 140/90 mmHg or blood pressure lowering medication, dyslipidemia as LDL cholesterol ≥ 3.62 mmol/l, HDL cholesterol ≤ 1.03 mmol/l, or lipid lowering medication, and obesity as BMI ≥ 25 kg/m². Adjusted for age, systolic blood pressure, body mass index, HbA1c(NGSP), LDL cholesterol, HDL cholesterol, drinking habits, blood pressure lowering medication, lipid lowering medication, glucose lowering therapy, and education year.

not stable high CRP during 10 years was associated with functional disability¹⁷). These previous longitudinal studies were evaluated for functional disability by follow-up examination. Compared with previous studies, there might be less chance of follow-up loss due to the functional disability in this study, because we followed up using a certification in the public health insurance program for long-term care. Another possible reason is the difference in the risk factor contributing to functional disability among Japanese and other populations. Further longitudinal studies might be needed to confirm the association between hsCRP levels and future functional disability.

Previous studies reported that low-grade systemic inflammation is associated with smoking^{5, 6} and atherosclerotic diseases such as stroke, atherosclerosis, and myocardial infarction⁸⁻¹²). Moreover, smoking is a well-known risk factor for functional disability³⁰⁻³²), and stroke might be one of the leading causes of long-term care in Japan¹³). A population-based stroke registry in Japan reported that approximately half of the patients with stroke were dependent at discharge³³). Therefore, these previous results were consistent with our findings and suggest that low-grade systemic inflammation due to smoking or atherosclerotic diseases might lead to disability.

Cardiometabolic risk factors are known to be a risk factor for low-grade systemic inflammation⁴⁻⁷). When stratified by cardiometabolic risk factors,

similar associations between hsCRP and future functional disability were observed. These results might indicate that hsCRP predicted future functional disability independently of these cardiometabolic risk factors. Previous studies reported that hsCRP predicted CVD event independently of cardiometabolic risk factors^{8, 11}). These results might indicate that evaluation for low-grade systemic inflammation might be useful to predict not only future CVD events but also future functional disability.

Sarcopenia is associated with disability³⁴) and is the third leading cause of the long-term care in Japan as estimated by the infirmity due to aging¹³). A previous study reported that high hsCRP was associated with poor physical performance or muscle strength³⁵). In the current study, we found a significant association between hsCRP and functional disability after adjustment for cardiovascular risk factors. These mechanisms might also be used to explain these observations.

In the present study, we could not find any significant association between log-transformed hsCRP levels and future functional disability in women. In the categorical analysis, age-adjusted HR in the highest hsCRP group in women was significantly increasing. The association between hsCRP categories and future functional disability was more prominent in men. However, there was no

significant interaction between hsCRP categories and sex on future functional disability. These results might indicate the nonlinear association between hsCRP levels and future functional disability in the lower hsCRP levels. Another possible reason was due to the small number of events in high hsCRP categories in women. Average hsCRP levels in women were lower than those in men. Lower smoking rate and prevalence of several risk factors for atherosclerosis in women might contribute to the lower CRP levels. Moreover, the mortality rate of stroke in women was reported to be higher than that in men due to the elder mean onset age^{33, 36}. Lower survival rate for an acute or subacute phase in women might lead to a lower receiving rate for long-term care services. Further study might be needed to examine the detail of the mechanism.

The strength of the current study is its longitudinal design, and it uses the LTCI of the local government. Therefore, follow-up of functional disability using the LTCI might minimize bias due to loss of follow-up bias. However, this study has several limitations. First, although education and income were considered as two major components of socioeconomic status, we could not consider income. Second, we did not evaluate the participants who did not receive long-term care services. Therefore, it might be underestimating the risk for functional disability. Third, the participants in this study were in suburban or rural areas of Japan. Fourth, owing to lack of data, we could not consider baseline physical performance levels. Fifth, owing to the small number of events, we could not analyze the association between hsCRP levels and the reason for functional disability, such as cognitive impairment and basal and instrumental ADLs.

Conclusion

Our study demonstrated that low-grade systemic inflammation evaluated by hsCRP might predict the incidence of future functional disability defined as LTCI certification in Japanese independently of potential confounders including smoking and education year, especially in men. These findings suggest that hsCRP is a predictive factor for future functional disability, and that improvement of low-grade systemic inflammation through the improvement of risk factors for atherosclerosis or physical performance and smoking cessation in smokers might prevent future functional disability.

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Conflict of Interest

The Takashima Study was partially supported by Omron Health Care Co. Ltd. The study's had no role in the study design, conduct of the study, data collection, data interpretation or preparation of the report. No other author has reported a potential conflict of interest relevant to this article. All authors have full access to all the data and take responsibility for their integrity and the accuracy of the analysis.

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Supplemental Table 1. Baseline characteristics of study population stratified by sex according to the high sensitivity C-reactive Protein level: the Takashima Study, 2006 to 2014

	High sensitivity C-reactive Protein levels (mg/l)				P value
	Low (< 1.0)	Middle (1.0 to 3.0)	High (≥ 3.0)	Total	
Men (N)	828	182	46	1056	
Age (year)	67.1 (5.5)	67.7 (5.6)	68.0 (6.0)	67.2 (5.6)	0.295
SBP (mmHg)	130.2 (19.4)	132.3 (19.0)	135.0 (18.0)	130.8 (19.3)	0.130
DBP (mmHg)	78.5 (11.0)	78.7 (11.0)	78.8 (11.2)	78.5 (11.0)	0.952
Body mass index (kg/m ²)	23.2 (2.7)	24.43 (2.9)	24.38 (3.0)	23.45 (2.8)	< 0.001
HbA1c (NGSP) (%)	5.59 (0.70)	5.75 (0.79)	5.83 (0.99)	5.63 (0.74)	0.005
LDL cholesterol (mmol/L)	121.0 (30.5)	124.27 (35.8)	127.0 (33.4)	121.9 (31.6)	0.240
HDL cholesterol (mmol/L)	58.5 (14.9)	53.05 (14.4)	52.4 (12.9)	57.3 (14.9)	< 0.001
Education year (year)	11.12 (2.4)	10.98 (2.3)	10.89 (2.4)	11.09 (2.4)	0.638
Drinking Status					
Never drinker	183 (22.1)	41 (22.5)	9 (19.6)	233 (22.1)	0.958
Past drinker*	25 (3.0)	-	-	30 (2.8)	
Current drinker	620 (74.9)	137 (75.3)	36 (78.3)	793 (75.1)	
Smoking status					
Never smoker	322 (38.9)	53 (29.1)	17 (37.0)	392 (37.1)	< 0.001
Past smoker	321 (38.8)	60 (33.0)	16 (34.8)	397 (37.6)	
Current smoker	185 (22.3)	69 (37.9)	13 (28.3)	267 (25.3)	
Treatment					
BP lowering medication	253 (30.6)	70 (38.5)	16 (34.8)	339 (32.1)	0.109
Lipid lowering medication	89 (10.8)	20 (11.0)	-	111 (10.5)	0.377
Glucose lowering therapy*	67 (8.1)	22 (12.1)	6 (13.0)	95 (9.0)	0.144
Women (N)	1315	190	49	1554	
Age (year)	65.7 (5.5)	66.12 (5.5)	66.2 (4.7)	65.7 (5.5)	0.463
SBP (mmHg)	127.6 (19.5)	134.44 (20.0)	127.4 (19.7)	128.5 (19.7)	< 0.001
DBP (mmHg)	74.2 (11.1)	77.49 (10.6)	73.7 (11.3)	74.6 (11.1)	< 0.001
Body mass index (kg/m ²)	22.5 (2.9)	24.09 (3.7)	24.0 (3.7)	22.7 (3.1)	< 0.001
HbA1c (NGSP) (%)	5.56 (0.48)	5.75 (0.80)	5.62 (0.50)	5.58 (0.53)	< 0.001
LDL cholesterol (mmol/L)	132.3 (31.6)	136.91 (31.2)	132.9 (37.9)	132.9 (31.8)	0.180
HDL cholesterol (mmol/L)	65.9 (15.1)	60.16 (15.8)	62.6 (18.3)	65.1 (15.4)	< 0.001
Education year (year)	11.2 (2.1)	10.64 (2.0)	10.8 (2.1)	11.1 (2.1)	< 0.001
Drinking Status					
Never drinker	946 (71.9)	150 (79.0)	37 (75.5)	1133 (72.9)	0.181
Past drinker*	18 (1.4)	-	-	19 (1.2)	
Current drinker	351 (26.7)	40 (21.1)	11 (22.5)	402 (25.9)	
Smoking status					
Never smoker	1255 (95.4)	185 (97.4)	48 (98.0)	1488 (95.8)	0.465
Past smoker*	18 (1.4)	-	-	21 (1.4)	
Current smoker*	42 (3.2)	-	-	45 (2.9)	
Treatment					
BP lowering medication	353 (26.8)	59 (31.1)	17 (34.7)	429 (27.6)	0.254
Lipid lowering medication	291 (22.1)	43 (22.6)	9 (18.4)	343 (22.1)	0.807
Glucose lowering therapy*	55 (4.2)	12 (6.3)	-	71 (4.6)	0.199

BP: blood pressure, DBP: Diastolic blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein, Ni: Number, SBP: Systolic blood pressure. Values are number, rate (%), or mean (SD).

* -: The actual number is less than 5.