ORIGINAL ARTICLE

Cohort study of long working hours and increase in blood high-sensitivity C-reactive protein (hsCRP) concentration: Mechanisms of overwork and cardiovascular disease

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Abstract

Objectives: We aimed to find evidence of the inflammation-mediated mechanism by which long working hours contribute to cardiovascular disease (CVD).

Methods: This cohort study was performed in 56 953 Korean adults free of CVD who underwent a comprehensive screening examination and were followed for up to 7 years. An increase in blood high-sensitivity C-reactive protein (hsCRP) of 1 mg/L or more at the follow-up visit was defined as an incidence. The average weekly working hours in the past year were categorized as ≤40, 41–52, 53–60, and ≥60 h per week. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using generalized estimating equations to calculate the risk of an incidental increase of hsCRP.

Results: Participants with longer working hours had a higher incidence of hsCRP. Multivariable-adjusted ORs (95% CIs) of incident cases for ≥61 h compared with ≤40 h was 1.69 (1.04–2.75). In subgroup analyses according to sex and the presence of hypertension and diabetes, the risk of hsCRP incidence were highest in the group working more than 61 h in all subgroups, but none of them were statistically significant.

Conclusions: Working hours are independently associated with increased risk of elevated hsCRP in a dose–response relationship. Excessive long-time work is a risk factor for CVD, and it was found that an increase in hsCRP was associated with the pathogenesis.

KEYWORDS
cardiovascular disease, cohort study, high-sensitivity C-reactive protein, longitudinal study, working hours

1 | INTRODUCTION

Atherosclerosis is the result of a more complex cellular and molecular inflammatory reaction beyond accumulation of lipids within the walls of blood vessels.[1] Atherosclerosis proceeds from initial endothelial dysfunction to fatty-streak formation, advanced lesion formation, and eventual unstable fibrous plaques. All stages of arteriosclerosis

proceed on the basis of inflammation; and immune cells such as monocytes and lymphocytes secrete various hydrolytic enzymes, cytokines, chemokines, and growth factors.[2]

Various inflammatory biomarkers, such as high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-6, and IL-1β, have been used to evaluate the degree of atherosclerosis or predict the occurrence of cardiovascular disease (CVD).[3,4] C-reactive protein (CRP) is an acute inflammatory substance mainly produced by hepatocytes but is also synthesized by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes.[5] In 2007, hsCRP was included in the Reynolds Risk Score, an alternative global risk algorithm of the traditional Framingham model. This score is designed to predict the risk of CVD in the next 10 years.[6,7]

According to the latest statistics from the Organization for Economic Cooperation and Development (OECD), Korean workers work an average of 1908 h per year, ranking fourth among member countries.[8] Overwork is one of the major causes of threats to workers′ health and is associated with diseases such as cerebro-cardiovascular disease,[9,10] high blood pressure,[11] and diabetes.[12]

A systematic review of 25 cohort studies in the United States, Europe, and Australia concluded that long working hours were a risk factor for incident coronary heart disease and stroke.[10] In particular, employees who work more than 36–40 h per week have a higher risk of stroke in a dose–response relationship.[10] However, the mechanism between long working hours and CVD is unknown. There are some reports that long working hours are related to an increase in metabolic factors such as blood pressure, diabetes, and hyperlipidemia; however, these findings are not consistent.[13,14]

In this large-scale cohort study, we studied the relationship between long working hours and increased concentration of hsCRP in the blood, and we aimed to find evidence of the inflammation-mediated mechanism by which long working hours contribute to CVD.

2 | METHOD

2.1 | Study population

The Kangbuk Samsung Health Study was a cohort study of South Korean adults aged 18 years and older who underwent a comprehensive annual or biennial health examination at Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon, South Korea.[15] More than 80% of participants were employees of various companies and local governmental organizations and their spouses. In South Korea, the Occupational Safety and Health Law requires annual or biennial health screening examinations of all employees free of charge. Other examinees voluntarily underwent health examinations at the health care center.[15]

The present study included a total of 173 791 participants who underwent comprehensive health examinations from January 1, 2012 to December 31, 2017 and had undergone at least one other examination before December 31, 2018. We excluded 15 054 participants based on the following criteria at the first visit: missing data on average working hours per week; presence of increased hsCRP equal to or higher than 1 mg/L; history of malignancy; history of stroke; history of cardiovascular diseases; use of aspirin, warfarin, amiodarone, or medications for arrhythmia; and aged >65 years or <19 years. Some participants met more than one exclusion criterion. In addition, 101 784 subjects whose weekly working hours group had changed in the self-administered questionnaire at each visit were also excluded from the study. A total of 56 953 participants was eligible for this study. (Figure 1).

We followed all related tenets of the Declaration of Helsinki, and this study was approved by the Institutional Review Board of Kangbuk Samsung Hospital. The requirement for informed consent was waived because we accessed only de-identified data routinely collected as part of health screening examinations (IRB No: KBSMC2020-12-035).

2.2 | Measurements

Working hours were identified using the following question: "How many average hours did you work in a week for the past year including overtime?" The Labor Standards Act of Korea states that working hours of adults should not exceed 40 per week excluding breaks. With permission of the worker, an additional 12 h per week can be added, for a maximum of 52 h per week since 2019. However, at the time of this study in 2012, the Korean Industrial Accident Insurance Act was in effect. This set working hours exceeding 60 per week as the standard for chronic overwork. Based on this, the average weekly working hours in the past year were categorized as ≤40, 41–52, 53–60, and ≥60 h per week.

Blood specimens were sampled from the antecubital vein after a fast of least 10 h. Serum hsCRP was determined using a particle-enhanced immunoturbidimetric assay on a Modular Analytics P800 apparatus (Roche Diagnostics). The Laboratory Medicine Department of Kangbuk Samsung Hospital is accredited by the Korean Society of Laboratory Medicine (KSLM) and the Korean Association of Quality Assurance for Clinical Laboratories (KAQACL) and participates in the College of American
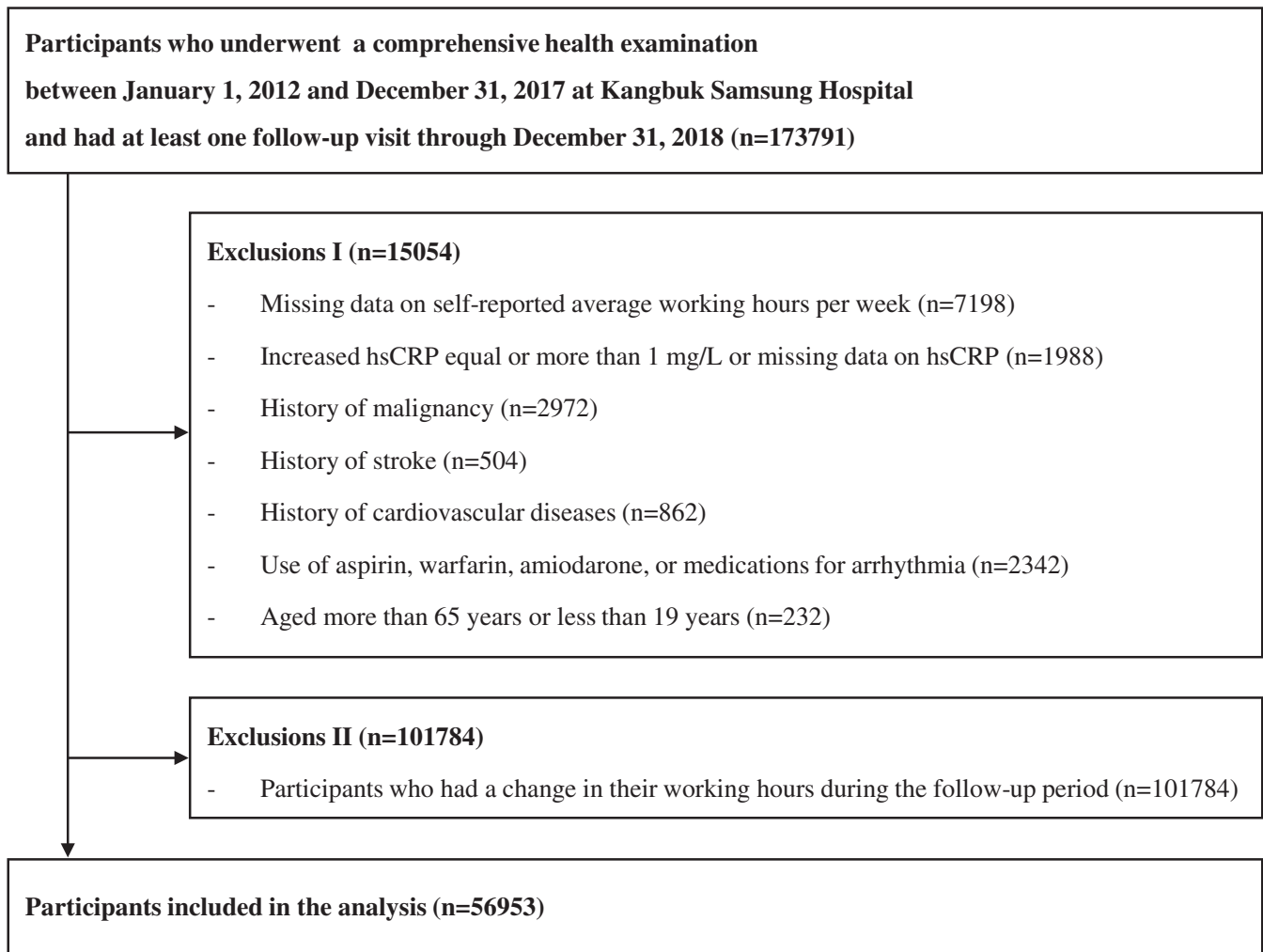

Participants who underwent a comprehensive health examination between January 1, 2012 and December 31, 2017 at Kangbuk Samsung Hospital and had at least one follow-up visit through December 31, 2018 (n=173791)

Exclusions I (n=15054)

- Missing data on self-reported average working hours per week (n=7198)
- Increased hsCRP equal or more than 1 mg/L or missing data on hsCRP (n=1988)
- History of malignancy (n=2972)
- History of stroke (n=504)
- History of cardiovascular diseases (n=862)
- Use of aspirin, warfarin, amiodarone, or medications for arrhythmia (n=2342)
- Aged more than 65 years or less than 19 years (n=232)

Exclusions II (n=101784)

- Participants who had a change in their working hours during the follow-up period (n=101784)

Participants included in the analysis (n=56953)

FIGURE 1 Flow chart of study participants.

Pathologists (CAP) Survey Proficiency Testing. In this study, participant hsCRP endpoint value was set at 1 mg/L or higher based on the moderately increasing criteria of the American Heart Association and Centers for Disease Control and Prevention.[16]

Height and weight were measured by trained nurses using a stadiometer and a bioimpedance analyzer with the participants wearing a lightweight hospital gown and no shoes (InBody 3.0 and InBody 720, Biospace Co.).[17] Obesity was defined as body mass index (BMI) $\geq 25 \, \mathrm{kg/m^2}$. Hypertension, diabetes, and dyslipidemia were defined as previously diagnosed with or currently taking medications for these disorders. These cases were identified through a self-reported questionnaire. Smoking status was categorized as never, former, or current smokers. Alcohol consumption was categorized as ≥ 10 g/day or <10 g/day. The weekly frequency of moderate- or vigorous-intensity physical activity was assessed and categorized as <3 or ≥ 3 times per week, respectively. Education level was categorized as less than college graduate or college graduate or more.

2.3 | Statistical analysis

The chi-square test and one-way ANOVA were used to compare characteristics of study participants stratified by working hours at baseline. Participants were followed from the baseline visit to the last available visit before December 31, 2018. Generalized estimating equations (GEEs) was used to deal with cluster effect among working hour groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated to calculate the risk of an incidental increase of hsCRP. Serum hsCRP was measured whenever subjects visited the health center. Even if the hsCRP value is higher than the cutoff value of 1 mg/dL, it may decrease later. In order to consider the repeatedly measured value, we calculated the odds ratios using the GEE method. We initially analyzed the risk of hsCRP increase according to working hours without any adjustment (model 1). In model 2, age, sex, and baseline hsCRP were adjusted. In model 3, the following variables were additionally adjusted: year of visit, smoking status; alcohol intake; education level; physical activity level; history

of or medication for hypertension, diabetes, and dyslipidemia; and obesity. To determine the linear trend of incidence, the number of categories was used as a continuous variable and tested in each model. In addition, stratified analyses in predefined subgroups were performed by sex and presence of hypertension or diabetes at baseline.

Statistical analyses were performed using STATA version 17.0 (StataCorp LP). All reported *P* values were two-tailed. A *P* value <.05 was considered statistically significant.

3 | RESULTS

At baseline, the mean (standard deviation) age of the 56 953 participants was 36.8 years (7.3 years). Most of the subjects worked fewer than 52 h per week, and only about 1.6% of the total subjects were distributed in the highest group of 61 h or more per week. Weekly working hours were positively associated with male sex, baseline hsCRP, current smoking status, alcohol intake, history of or medication for dyslipidemia, and obesity. Weekly working hours were inversely associated with regular exercise (Table 1).

Among 56 953 subjects, 1323 (2.3%) experienced at least one increase in serum hsCRP of 1 mg/L or more. Participants with longer working hours had a higher incidence of hsCRP (Figure 2).

Across all models, working 61 h or more was associated with a significantly higher risk of incident cases than was working ≤40 h. In the fully adjusted model, multivariable-adjusted OR (95% CI) of incident cases for ≥61 h compared with ≤40 h was 1.69 (1.04–2.75). In addition, a dose–response relationship was observed in which the strength of the association between working hours and serum hsCRP also increased as the working hour group increased (Table 2).

In subgroup analyses according to sex and the presence of hypertension and diabetes, the risk of hsCRP incidence were highest in the group working more than 61 h in all subgroups, but none of them were statistically significant (Table 3).

Meanwhile, in the same study subject, if hsCRP increased by 1 mg/L or more, it was defined as failure of survival, and then hazard ratios were calculated by the method of COX regression. In all groups, long working hours of more than 61 h were significantly associated with

TABLE 1 Baseline characteristics of study participants by weekly working hours

| | Weekly working hours | | | | *P* for trend |
Characteristics	≤40 h	41–52 h	53–60 h	≥61 h	
Number	28 990	24 958	2114	891	
Age (years)*	38.3 (7.4)	35.2 (6.6)	36.9 (7.4)	37.1 (7.4)	<.001
Male	33.7	75.8	81.4	82.5	<.001
Baseline hsCRP (mg/L)	0.075 (0.110)	0.083 (0.115)	0.088 (0.115)	0.095 (0.123)	<.001
Smoking status					
Never	63.8	46.9	41.5	38.2	<.001
Former	18.0	30.2	25.0	21.3	<.001
Current	12.3	21.0	30.7	37.4	<.001
Alcohol intake[a]	29.0	43.6	51.5	53.9	<.001
Regular exercise[b]	13.3	12.3	11.0	10.8	<.001
High education level[c]	77.8	88.3	87.3	82.3	<.001
Hypertension[d]	5.4	6.6	9.3	6.5	<.001
Diabetes[e]	1.8	1.5	2.8	2.7	.482
Dyslipidemia[f]	9.7	13.1	15.8	12.9	<.001
Obesity[g]	22.8	31.6	37.7	39.5	<.001

Note: Data are expressed as *mean (standard deviation), or percentage.

[a]≥10 g/day.

[b]≥3 times/week.

[c]≥ College graduate.

[d]Past history of hypertension or medication for hypertension.

[e]Past history of diabetes or medication for diabetes.

[f]Past history of dyslipidemia or medication for dyslipidemia.
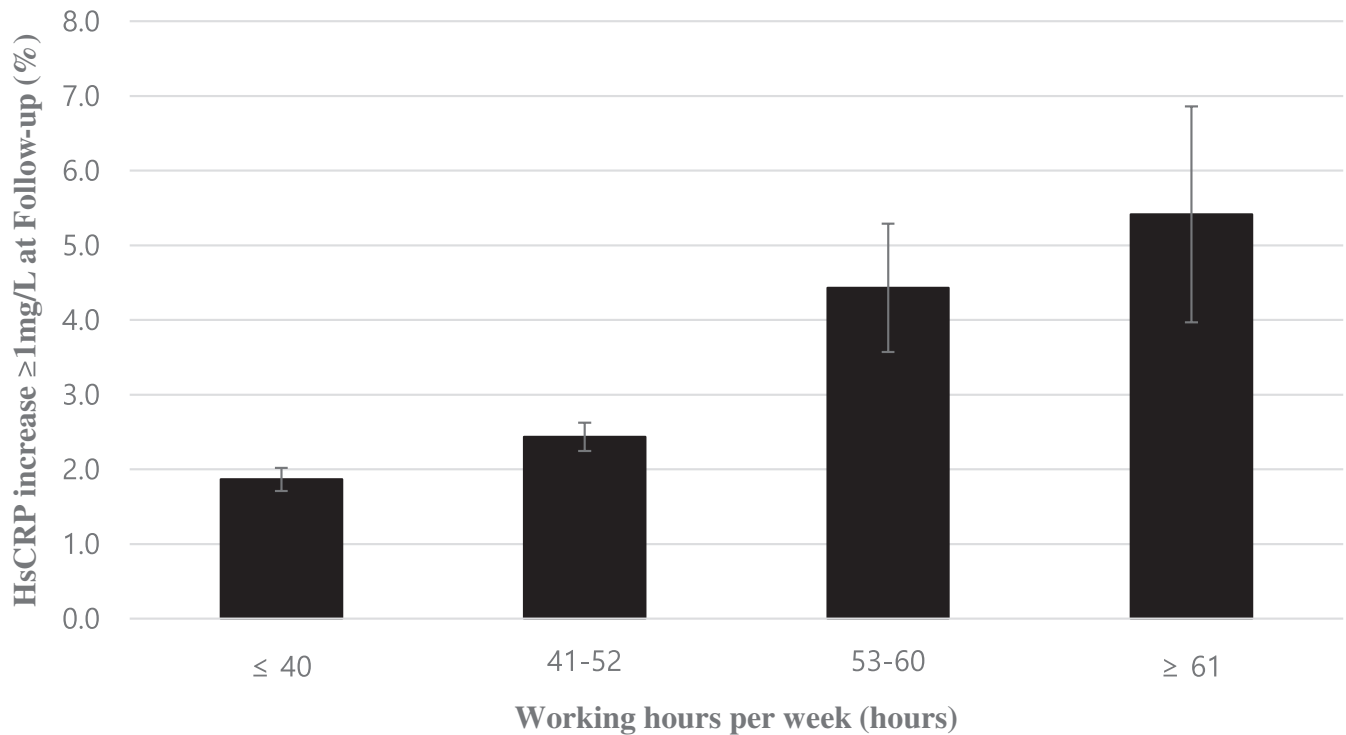
[g]Body mass index ≥25.

FIGURE 2 Prevalence of incident hsCRP increase by 1 mg/L or more at follow-up by weekly working hours.

TABLE 2 Odds ratio (95% CI) for incident hsCRP increase by 1 mg/L or more by weekly working hours

Weekly working hours	Incidence (%)	Unadjusted	Age, sex and baseline hsCRP adjusted	Fully adjusted[a]
≤40 h	551 (1.89)	1	1	1
41–52 h	623 (2.48)	1.20 (1.05–1.37)	1.04 (0.89–1.22)	1.00 (0.85–1.18)
53–60 h	98 (4.49)	1.15 (0.79–1.66)	0.97 (0.66–1.41)	1.03 (0.70–1.51)
≥61 h	51 (5.53)	1.78 (1.11–2.84)	1.49 (0.92–2.41)	1.69 (1.04–2.75)

[a]Adjustment for age, sex, baseline hsCRP, year of visit, smoking, alcohol, physical activity, education, hypertension, diabetes, dyslipidemia, and obesity.

an increase in hsCRP, and the hazard ratio was greater in multivariate analysis than in the crude model and the age, sex-adjusted model (Table S1).

4 | DISCUSSION

Arteriosclerosis is a common condition in which plaques originating from the inner layer of the artery and smooth muscle grow with proliferation of fibrous tissue leading to decreased blood flow, coagulation, and thrombosis.[2,18] Risk factors for atherosclerosis include high blood cholesterol, high blood pressure, diabetes, smoking, obesity, inactive lifestyle, and age. Inflammation contributes to the progression of arteriosclerosis, and inflammatory signs such as high CRP level are associated with arteriosclerosis.[1,3,4] As a result, the predictive usefulness of biomarkers such as hsCRP has been established.[19–21]

In this large cohort study of relatively healthy men and women, a higher risk of increased hsCRP was present in the group working more than 61 h weekly compared to the group working less than 40 h per week. Even after adjusting for behavioral factors such as smoking, alcohol, and physical activity and metabolic factors such as obesity, high blood pressure, and diabetes that might be the cause of the increase in hsCRP, long working hours were an independent risk factor for increased hsCRP.

The main strength of our study was that, while most previous studies have observed an association between long working hours and the occurrence of stroke and CVD, our study analyzed the risk of increased systemic inflammation markers that could explain the mechanism of the process. Also, while previous studies on the link between working hours and hsCRP are cross-sectional,[22,23] our study has the advantage of being a cohort study in

	Weekly working hours				
Subgroups	**≤40 h**	**41–52 h**	**53–60 h**	**≥61 h**	***P* for trend**
Sex[a]					
Male	Reference	0.95 (0.78–1.15)	0.93 (0.61–1.44)	1.59 (0.93–2.70)	.624
Female	Reference	1.12 (0.83–1.51)	1.57 (0.64–3.82)	2.03 (0.61–6.70)	.168
Hypertensive or Diabetic patients[b]					
None	Reference	1.00 (0.84–1.18)	0.94 (0.61–1.43)	1.64 (1.01–2.67)	.429
Both or either	Reference	1.01 (0.55–1.85)	1.81 (0.67–4.88)	1.98 (0.25–15.67)	.424

TABLE 3 Odds ratio (95% CI) for incident hsCRP increase by 1 mg/L or more by weekly working hours in subgroups

[a]Adjustment for age, baseline hsCRP, year of visit, smoking, alcohol, physical activity, education, hypertension, diabetes, dyslipidemia, and obesity.

[b]Adjustment for age, sex, baseline hsCRP, year of visit, smoking, alcohol, physical activity, education, dyslipidemia, and obesity.

which approximately 60 000 subjects were followed for up to 7 years.

Both of the previous studies used data from the Korean National Health and Nutrition Survey (KNHANES), an annual cross-sectional survey representing the entire Korean population since 1998; but the survey subjects are different from year to year. In 2015, the hsCRP level of the adult participants was included in the KNHANES for the first time. Based on this, two previous studies on working hours and hsCRP recently reported somewhat inconsistent results.[22,23] These studies were cross-sectional, with one including 3060 people in 2015 and the other consisting of 7470 individuals between 2015 and 2018. The first study reported that the ratio of hsCRP measured at 3 mg/L or more was significantly higher for subjects who worked for more than 55 h per week only among those aged 60 or older; no significant results were obtained in the middle-aged group.[23] In the second study, analyzed with data from a different year of the same survey, those aged 60 or older were excluded. The 40- to 59-year-old male subjects who worked over 52 h were reported to have a significantly higher ratio of hsCRP of 1 mg/L or more. No significant results were obtained in the female or younger group.[22]

The pathways leading to an increase in systemic inflammation after long working hours are various, including lack of sleep, secretion of corticosteroids, oxidative stress, and high-risk health behaviors. In previous studies, long working hours were closely linked to daily sleep restrictions.[24–27] Acute sleep deprivation, such as a night on call for medical residents, could affect disruption of autonomic responses and changes in immune levels.[28] Night-shift work increases the secretion of the stress hormone cortisol and also increases blood pressure.[29] This suggests that changes in the hypothalamic pituitary axis and autonomic nervous system

are related to work stress. In a study concerning the relationship between work shift and oxidative stress, parameters related to oxidative stress damage were higher in the night shift group compared to the daytime group. These parameters included thiobarbituric acid reactive substances such as carbonyls, hydrogen peroxide, and nitrite. Conversely, parameters related to antioxidant functions such as ferric-reducing/antioxidant power, catalase, superoxide dismutase, and glutathione peroxidase were lower for those working night shifts.[30] Since the above studies reported results from night-shift work, there is a limitation in the ability to generalize to long working hours.

There are some limitations to this study. First, self-reported working hours can differ from visit to visit, and there is a possibility of misclassification bias in association with increased hsCRP. Therefore, we tried to reduce bias by analyzing only the study subjects belonging to the same working hours group throughout the study. Second, the cutoff value of hsCRP increase was defined as 1 mg/L or more. Since our study consisted of relatively healthy people, when the cutoff value was increased, the incidence rapidly decreased. Therefore, sensitivity analysis could not be performed. Moreover, the potential for bias related to residual confounding exists whether measured or not in the associations observed in this study. Finally, as our study was conducted in young, healthy Korean adults, generalization to population groups of different ages, races, and ethnicities is difficult.

5 | CONCLUSION

To our knowledge, this is the first cohort study to report that working hours are independently associated with

increased risk of elevated hsCRP in a dose–response relationship. Working hours are an important factor in prevention of CVD, and hsCRP measurement plays an important role in health examination of workers.

AUTHOR CONTRIBUTIONS

W.L. and H.W.Y. conceived the ideas; W.L. and Y.L. collected the data; W.L., H.W.Y. and Y.L. analyzed the data; and W.L. and H.W.Y. led the writing.

DISCLOSURE

Conflict of interest: The authors have no conflicts of interest to disclose. *Approval of the research protocol*: The study was approved by the Institutional Review Board of Kangbuk Samsung Hospital. *Informed consent*: waived because we accessed only de-identified data. *Registry and the Registration No. of the study/Trial*: N/A. *Animal Studies*: N/A.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.