Association Between C-Reactive Protein and Suicidal Ideation: A Large-Scale Cross-Sectional Study

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ABSTRACT

Studies of C-reactive protein (CRP) levels and suicidal behaviours have shown inconsistent results previously. This study investigated the relationship between CRP levels and suicidal ideation in a large population-based cohort in Korea to enhance the understanding of the biological aspects of suicide and inform more accurate risk assessment models in clinical applications. A multivariate regression model was used to estimate the CRP levels by suicidal ideation and calculate the odds ratio (OR) for suicidal ideation per increase in CRP. People with suicidal ideation had higher CRP levels than those without suicidal ideation (1.35 mg/dL *vs*. 1.17 mg/dL). In the age- and gender-adjusted model, the OR for suicidal ideation per 1-SD increase in log (CRP) was 1.14 (p = 0.029). However, the fully adjusted model did not reach statistical significance. The relationship between CRP levels and suicide might not be evident among Korean adults.

Key Words: *C-reactive protein, Inflammation, Socioeconomic factors, Suicidal ideation, Public health problem*.

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Suicide is a serious public health problem with an urgent need for prevention. The WHO projects that nearly one million suicide deaths will occur annually by 2030, constituting 1.4% of all deaths.[1] Timely identification of people vulnerable to suicide is a crucial but extremely difficult task. Although the psychosocial origins of suicide are now well understood, its biological origins remain relatively obscure. The fundamental biological mechanisms of suicidal behaviours are currently considered to involve abnormalities in serotonergic neurotransmission and a dysfunctional hypothalamic–pituitary–adrenal axis. Identifying biomarkers for suicide will enhance the understanding of its pathophysiology and help clinicians support patients at risk.[2]

Mounting evidence implicates inflammation in the suicidality pathophysiology. Increased levels of initial inflammatory markers are associated with depression and psychological distress, both well-known as significant risk factors for suicide. Several studies examined the relationship between CRP levels and suicidal behaviours. However, most were limited by small sample sizes,[3] and findings were contradictory. Therefore, the relationship between CRP levels and suicidal ideation was estimated using large, population-based Korean data, considering critical confounders.

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Suicide should be understood within the cultural context. For example, the Confucian norm of familism is the core concept for understanding suicidal behaviours in Korea. Strong bonds with family members usually prevent suicide, and dysfunctional family relationships can have a converse effect.[4] Additionally, characteristics associated with suicide might be different across cultures. The goal of this study was to evaluate the relationship between CRP levels and suicide ideation, considering critical confounders using large, population-based Korean data.

Data from the Korea National Health and Nutrition Examination Survey (KNHANES, 2015–2017), an annual nationally representative survey conducted by the Korea Disease Control and Prevention Agency, were used. Of the 10,822 participants aged >19 years with data on suicidal ideation and CRP, 473 were excluded due to a history of cancer or cardiovascular events, including myocardial infarction and stroke. After excluding any missing data on the below covariates, 8,654 individuals were included for the analysis.

CRP levels were quantified using the immunoturbidimetric method (Cobas, Roche, Germany), and suicidal ideation was evaluated through a binary (yes/no) question, "Have you ever thought about committing suicide in the past 12 months?" Information on covariates was also collected.

Data were presented as mean ± standard deviation or number (%). Multivariate regression models were used to examine the association between CRP levels and suicidal ideation. In each model with adjustment for various potential confounders, the authors estimated the CRP levels by suicidal ideation and calculated the odds ratio (OR) for suicidal ideation per CRP increase.

Table I: Association between CRP (mg/dL) and suicidal ideation (n = 8,654).

Adjustment variable	Estimated level of CRP (SE)[a]			Suicidal ideation per 1-SD increase in log (CRP)[b]	
	No suicidal ideation	Suicidal ideation	p-value	OR (95% CI)	p-value
None	1.17 (0.02)	1.35 (0.11)	0.068	1.15 (1.02–1.28)	0.017
Age and gender	1.17 (0.02)	1.34 (0.10)	0.091	1.14 (1.01–1.27)	0.029
Age, gender, and obesity	1.17 (0.02)	1.32 (0.10)	0.134	1.12 (0.99–1.26)	0.066
Age, gender, and hypertension	1.17 (0.02)	1.33 (0.10)	0.099	1.13 (1.01–1.27)	0.033
Age, gender, and Type 2 diabetes	1.17 (0.02)	1.34 (0.10)	0.092	1.13 (1.01–1.27)	0.031
Age, gender, and current smoking	1.17 (0.02)	1.32 (0.10)	0.123	1.11 (0.99–1.25)	0.068
Age, gender, and frequent drinking	1.17 (0.02)	1.32 (0.10)	0.085	1.13 (1.01–1.27)	0.031
Age, gender, and regular exercise	1.17 (0.02)	1.33 (0.10)	0.116	1.12 (1.00–1.26)	0.047
Age, gender, and income level	1.17 (0.02)	1.32 (0.10)	0.143	1.12 (1.00–1.25)	0.054
Age, gender, and educational attainment	1.17 (0.02)	1.31 (0.10)	0.178	1.11 (0.99–1.24)	0.078
Age, gender, and stress	1.17 (0.02)	1.31 (0.10)	0.170	1.11 (0.99–1.25)	0.079
Age, gender, and depression	1.17 (0.02)	1.35 (0.10)	0.101	1.13 (1.00–1.28)	0.050
All[c]	1.17 (0.02)	1.29 (0.10)	0.268	1.10 (0.96–1.25)	0.171

[a]Multivariate regression analysis. [b]Multivariate logistic regression analysis. [c]Adjusted for comorbidities (obesity, hypertension, and Type 2 diabetes), health-related habits (current smoking, frequent drinking, and regular exercise), socioeconomic status (income level and educational attainment), and mental health (stress and depression). CRP = C-reactive protein; SE = Standard error; SD = Standard deviation; OR = Odds ratio = CI, Confidence interval.

If a statistical significance value changed after adjusting for variable categories, additional analyses were performed for each variable. The CRP data were skewed and showed the following distribution (mg/dL): Median, 0.6; interquartile range, 0.39–1.10; and range: 0.09–20.01. Log-transformed CRP for logistic analysis was used to estimate ORs per 1-standard deviation (SD) increase in log (CRP).[5] Analyses were conducted using the STATA SE 9.2 (Stata Corp., College Station, TX), and p-values of ≤0.05 were considered statistically significant. KNHANES adhered to the guidelines set forth in the Declaration of Helsinki. Written informed consent was obtained from all participants. The study protocol was approved by the Institutional Review Board of Gachon University Gil Medical Centre, Incheon, Korea (GCIRB2020-255).

Approximately 4.3% of participants reported experiencing suicidal ideation. People with suicidal ideation were older, had higher CRP levels (1.17 mg/dL *vs*. 1.35 mg/dL; p = 0.068) and multimorbidity (HTN and DM). They were also more likely to be women, obese, of low socioeconomic status (poor, and less educated), and had unhealthy habits (current smoking and no regular exercise) with poor mental health (stress and depression. Data not shown).

Table I shows the bidirectional association between CRP levels and suicidal ideation. There was no significance in the models with CRP as dependent variable, but some significance was found in the reverse direction. In the age- and sex-adjusted model, the OR for suicidal ideation per 1-SD increase in log (CRP) was 1.14 (p = 0.029). The associations varied across the additionally adjusted covariates, and the significance disappeared in several variables adjusted models, such as obesity, smoking, socioeconomic status, and mental health. The fully adjusted model did not reach statistical significance.

It is exceedingly hard for clinicians to recognise signs of suicide. Presently, they must rely on a patient's personal and/or familial history of suicidal behaviours, primarily based on their voluntary self-report. However, the credibility of self-reporting is problematic for patients who are most determined to die, and the social stigma associated with suicide can shake their veracity. Therefore, clinicians need a more objective and biologically based model of suicidal risk assessment that can yield biomarkers with high prediction accuracy so they can identify high-risk individuals and provide them with intensive support.

While mood disorders are recognised as significant risk factors for suicide-related behaviour, suicidal behaviours may also occur independently of depression. Much less is known about whether inflammatory states are independently associated with suicide-related behaviours beyond depression. Recent evidence suggests that a unique immunobiological profile is linked to increased suicide risk, irrespective of depressive symptoms.[6] Other evidence indicates that the kynurenine pathway is a unique mechanism connecting inflammation to suicide, separate from its association with depression.[7] Findings from the most relevant works on this issue[5] and those of the present study support this notion: Depression had little effect on the association between CRP levels and suicidal ideation. Instead of depression, the authors identified other potential mediators, raising the likelihood that other mechanisms underlie the association.

This study has several limitations. First, mental health including suicidal ideation was evaluated using a very simplified question, not a validated scale. However, a single screening question is brief and straightforward for a nationwide survey. Additionally, the participants may have underreported their suicidal ideation; however, the authors expect that this bias would move the results toward rather than away from the null. Finally, the effect sizes in this study are small, which need consideration of other potential confounders, such as childhood abuse.

Despite these limitations, this large, comprehensive, population-based cohort study examined the relationship between CRP levels and suicidal behaviours. Prior studies conducted within specific clinical settings were fundamentally vulnerable

to confounding factors such as access to healthcare or the severity of cases. Further approaches, such as Mendelian randomisation, are needed to clarify the associations.

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ETHICAL APPROVAL:
The Institutional Review Board of the Korea Centres for Disease Control and Prevention approved the survey, and the Institutional Review Board of Gachon University Gil Medical Centre approved the study protocol (GCIRB2020-255).

PATIENTS' CONSENT:
All participants provided written informed consent.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
ICH: Conception of the manuscript, acquisition, analysis, interpretation of the data, drafting, and critical revision of the manuscript for important intellectual content.
HYA: Drafting of the work, analysis, and interpretation of the data.
YP: Conception of idea and critical revision of the manuscript for important intellectual content.
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