Association between high sensitivity CRP and suicidal ideation in the Korean general population

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Abstract
Inflammation has been linked with a potential critical role in suicide. The purpose of this study is to examine the relation of CRP with suicidal behavior in the Korean population. We conducted a cross-sectional study in 4693 Korean adults aged 20–81 years who participated in the 2015 Korea National Health and Nutrition Examination Survey. High sensitivity CRP levels were measured by immunoturbidimetric method. Suicidal ideation and suicide attempt were assessed by using a questionnaire. Data were analyzed in 2017. Multiple logistic regression analysis was used to compute odds ratios (ORs) and 95% confidence intervals (CIs). The prevalence of suicidal ideation was 4.9% and that of suicide attempt was 0.4%. Suicidal ideation was more prevalent in the highest compared with the lowest serum CRP quartile (OR, 1.79; 95% CI, 1.11–2.89) after adjustment for age, sex, household income, educational level, marital status, employment status, alcohol dependency, current smoking, physical activity, BMI, sleep duration, number of chronic diseases, restriction on activity, subjective health status, perceived stress, depression and depressive mood (p for trend < 0.05). In conclusion, elevated levels of CRP were associated with an increased risk of suicidal ideation among South Korean adults.
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1. Introduction

Suicide is the 14th leading cause of death worldwide (Mortality and Causes of Death, 2015). Over 800,000 people die due to suicide every year and there are many more who attempt suicide. Korea's suicide rate is the highest in the OECD (Organization for Economic Cooperation and Development) countries. The age-standardized suicide rate of Korea was 26.5 (per 100,000) in 2015 (Statistics Korea, 2016). Suicide is a complex public health problem of global importance (Turecki and Brent, 2016). A variety of risk factors for suicide have been established in the scientific literature (Sinyor et al., 2017). In the light of the apparent weakness of clinical risk factors in suicide risk assessment (Chan et al., 2016; Large et al., 2016), biological risk factors have the potential importance. However, the neurobiological mechanisms of suicide are still not fully understood.

Inflammation has been linked with a potential critical role in suicidal behavior (Brundin et al., 2017; Brundin et al., 2015; Janelidze and Brundin, 2013; Lund-Sorensen et al., 2016). Suicidal behavior refers to a continuum of behaviors from suicidal ideation to completed suicide (O'Carroll et al., 1996). High sensitivity C-reactive protein (CRP) is a sensitive marker of low grade systemic inflammation (Pepys and Hirschfield, 2003). Studies on the association between CRP and suicidal behavior are scarce, and studies have yielded inconsistent results (Courtet et al., 2015; Gibbs et al., 2016; Loas et al., 2016; O'Donovan et al., 2013; Priya et al., 2016; Vargas et al., 2013). There has been no study examining the association between CRP and suicidal behavior in Korea.

We investigated the relation between CRP and suicidal behavior from the Korea National Health and Nutrition Examination Survey (KNHANES), a large nationally representative survey.

2. Experimental procedures

2.1. Study population

The present study used the data from the 2015 Korea National Health and Nutrition Examination Survey (KNHANES). The KNHANES periodically collected representative data on the health and nutritional status of the civilian, non-institutionalized Korean general population to monitor trends toward the prevalence, treatment, and control of selected chronic diseases, and analyze risk factors for chronic diseases. Survey items were selected from review of previous KNHANES and similar foreign surveys by the Korea Centers for Disease Control and Prevention, and then items were confirmed by an advisory committee. The KNHANES comprises a health interview survey, a health examination survey, and a nutrition survey that are administered by trained investigators. A stratified multistage clustered probability design was used to select representative samples of non-institutionalized Korean civilians for the KNHANES (Korea Center for Disease Control and Prevention, 2017). The survey data were publicly available. This survey was completed by 7380 participants (77.6% of the total target population of 9507). The present analysis was restricted to participants aged at least 20 years whose CRP levels were available ($n=5267$). After excluding those who had missing values for study variables ($n=574$), the final sample for the present study was composed of 4693 individuals. The study was approved by the Korea Centers for Disease Control and Prevention Institutional Review Board. Written informed consent was obtained from all study participants.

2.2. Assessment of suicidal behavior

Suicidal ideation was assessed by participants' positive answer to the question "In the last 12 months, did you think about committing suicide seriously?" If the subject answered "yes," they were asked about their suicide attempts, if any. This indicator is a well-documented predictor of suicide attempts that has been previously used in other surveys (Gaynes et al., 2004) and in previous KNHANES studies (Song and Lee 2016).

2.3. Measurement of CRP levels

Blood samples were collected in 3 ml EDTA coated tubes (BD Vacutainer, Franklin Lakes, NJ). We used the immunoturbidimetric method for quantifying serum concentration of high-sensitivity CRP (Cobas, Roche, Germany), which is calibrated daily with reference standards between 1.0 and 200.0 mg/L. All clinical analyses were performed by the Neodin Medical Institute, a laboratory certified by the Korean Ministry of Health and Welfare.

2.4. Covariates

Anthropometric measurements of the participants were conducted at local community health centers and clinics as a part of the health examination. The anthropometric variables (height and body weight) were recorded using a standard protocol. Body mass index was calculated as weight in kilograms divided by height in meters squared, and classified into three categories: <18.5, 18.5-24.9, and $\geq 25.0 \text{ kg/m}^2$.

Sociodemographic, lifestyle behavior, and comorbidity information were collected using a questionnaire. Participants were asked about their household income, educational level, marital and employment status. Household income was divided by quartiles. Total household income was estimated by dividing the total household income by the square root of number of people in household (equivalized household income=total household income (Korean won)/$\sqrt{}$number of people in household). The educational level was divided into four categories (under elementary school, middle school, high school and above college/university). Marital status was classified into three categories (married, single, and divorced/separated/widowed). Employment status was classified into two categories (employed and unemployed).

Drinking was classified into drinkers who had at least one alcoholic beverage in their lifetime and non-drinkers who had never consumed alcohol. Dependence on alcohol was assessed using the Alcohol Use Disorders Identification Test (AUDIT) scores ≥ 20 (Babor et al., 2001). People who reported having smoked fewer than 100 cigarettes in their lives were classified as never smokers, and the remainders were asked whether they were current or former smokers (Agaku et al., 2014). Level of physical activity was calculated using metabolic equivalent of task values (MET) based on self-reported frequency and duration of activities during the week. MET-minutes per week was computed by multiplying the MET value of a particular activity (walking=3.3 METs, moderate physical activity=4.0 METs, and vigorous physical activity=8.0 METs) with minutes spent in that particular activity (Ainsworth et al., 2000). Total weekly physical activity was calculated by summing MET-minutes per week of walking, moderate, and vigorous activity. Participants who had ≥ 3000 MET-minutes per week were classified as vigorous physical activity. Sleep duration was self-reported in integers, and classified into five categories: ≤ 5, 6, 7, 8, and $\geq 9 \text{ h/}$day.