Systemic inflammation and suicide risk: cohort study of 419 527 Korean men and women

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ABSTRACT

Background Data from only one study have been used to examine the relationship between systemic inflammation and later suicide risk, and a strong positive association was apparent. More research is needed, particularly looking at gender, not least because women are seemingly more vulnerable to inflammation-induced mood changes than men.
Methods The Korean Cancer Prevention Study had a cohort of over 1 million individuals aged 30–95 years at baseline examination between 1992 and 1995, when white blood cell count, our marker of systemic inflammation, was assessed.
Results A mean of 16.6 years of mortality surveillance gave rise to 1010 deaths from suicide in 106 643 men, and 1019 deaths from suicide in 312 884 women. There was little evidence of an association between our inflammation marker and suicide mortality in men after multiple adjustments. In women, however, those in the second inflammation quartile and higher experienced around 30% increase risk of death (HR 1.35; 95% CI: 1.11–1.64).
Conclusions Higher levels of systemic inflammation were moderately related to an elevated risk of suicide death in women but not in men.

INTRODUCTION

The global burden of suicidal ideation, hospitalisation, and completion is considerable.[1] While the psychosocial origins of suicide are becoming increasing well understood,[2–5] with the exception of selected characteristics,[6 7] comparatively little is known about its biological origins. Findings from studies using different designs have implicated systemic inflammation in the occurrence of suicide. Thus, in cohort studies, elevated levels of baseline inflammatory markers have been linked to depression and psychological distress[8] which themselves are well-established risk factors for suicide.[5 9] Additionally, pathological studies reveal that victims of suicide have higher cytokine levels relative to non-suicide controls.[10]

There is also some evidence of gender differentials in these observations. Thus, although it is not a universal observation,[11] there is a suggestion that women tend to be more vulnerable to inflammation-induced mood changes, with transient elevations seemingly eliciting a more pronounced sense of loneliness and social disconnection.[12] We therefore hypothesised that inflammation may be more strongly associated with suicide risk in women than in men.

We recently reported a three-fold elevated risk of suicide death in people in the highest inflammation group;[13] however, owing to a low number of events we were not able to examine gender-specific effects and the generalisability of this finding from a European population to non-Western countries is uncertain. Our objective in the present study, therefore, was to examine the association of inflammation with suicide mortality in a cohort study of over 400 000 Korean men and women. With South Korean women having the highest suicide death rate worldwide and men being ranked third, the country provides an ideal setting in which to enhance understanding of suicide aetiology.[14]

METHODS

Described in detail elsewhere,[15] the Korean Cancer Prevention Study is a prospective cohort study established to identify environmental risk factors for major causes of death in more than 1 million people. In brief, the cohort comprises government employees and their dependents who were registered with the Korea National Health Insurance Service.

At study baseline (1992–1995), blood samples were obtained after an overnight fast with white blood cell counts, our marker of inflammation, quantified by automated blood cell counters (Beckman Coulter, Fullerton, California) in hospital laboratories. Cell counts are expressed in Système International d'Unités ($\times 10^9$ cells/L). Each hospital followed the quality control procedures of the Korean Association of Laboratory Quality Control.

Covariate data were assessed using standard protocols. Weight and height of each study member were measured directly in light clothing with shoes removed, and body mass index calculated in the usual manner (weight in kilograms divided by height in metres squared). Based on existing definitions,[16] diabetes mellitus was denoted by a blood glucose of ≥ 126 mg/dL and/or self-report of either physician diagnosis or medication usage, and hypertension by a systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg, or the use of blood pressure lowering medication. With the study member present, completed questionnaires were scrutinised by research workers and, where necessary, clarification sought. Smoking (current smokers, former and never) and exercise (yes, no) were self-reported as was current total daily alcohol consumption, expressed as number of glasses per week of 'Soju'. Comparable to vodka, soju is the most popular alcoholic beverage in Korea (one glass contains about 12 g of ethanol). Alcohol consumption was categorised: non-drinker (0 g/day), light

Table 1 Association of white blood cell count with suicide risk in the Korean Cancer Prevention Study (n=419 527)

	Number of suicides	Number at risk	Age adjustment	Multiple adjustment*	Multiple adjustment†
Men					
Quartile 1 (<5.9)‡	237	24 828	1.0 (ref)	1.0	1.0
Quartile 2 (≥5.9 to <7.0)	267	28 168	1.00 (0.84, 1.19)	0.98 (0.82, 1.17)	1.03 (0.86, 1.24)
Quartile 3 (≥7.0 to <8.2)	229	26 416	0.93 (0.78, 1.12)	0.91 (0.75, 1.09)	0.91 (0.75, 1.11)
Quartile 4 (≥8.2)	277	27 231	1.15 (0.97, 1.37)	1.10 (0.92, 1.31)	1.10 (0.91, 1.33)
P value for trend	–	–	0.0852	0.2688	0.3212
Women					
Quartile 1 (<5.4)	201	76 280	1.0 (ref)	1.0	1.0
Quartile 2 (≥5.4 to <6.3)	251	73 263	1.30 (1.08, 1.57)	1.32 (1.09, 1.59)	1.35 (1.11, 1.64)
Quartile 3 (≥6.3 to <7.4)	282	81 350	1.31 (1.09, 1.57)	1.32 (1.10, 1.58)	1.34 (1.10, 1.62)
Quartile 4 (≥7.4)	285	81 991	1.30 (1.09, 1.56)	1.30 (1.08, 1.56)	1.32 (1.09, 1.60)
P value for trend	–	–	0.0195	0.0243	0.0248
P value for interaction by gender	–	–	0.4999	0.2714	0.2375

*Multiple adjustment is adjustment for: age, body mass index, smoking status, alcohol consumption, exercise, hypertension, diabetes and health insurance premium.

†Same variables as in prior statistical model but the analytical sample is based on exclusions of suicide deaths in the first 5 years of follow-up (893 suicide deaths in 95 364 men; 945 such deaths in 304 727 women).

‡White cell counts are multiples of 10^9 cells/L.

drinking (1–24.9), moderate drinking (25–49.9), heavy drinking (50–99) and very heavy drinking (>99). Our measure of socioeconomic status was the monetary contribution per year, in South Korean 'Won' (₩1112=US$1.00), made by the employee to their medical insurance scheme. This is means derived, being based on employee's income plus assets, such as ownership of property and an automobile; a higher contribution therefore denotes higher socioeconomic status.

A computerised search of death certificate data from the National Statistical Office in Korea was performed and trained recorders extracted cause according to the International Classification of Diseases, Tenth Revision (suicide codes: E95, and X60–X84). Of a total of 1 329 525 study members, 878 367 had data on white cell count. Exclusions of people with implausible values and those with a baseline diagnosis of cancer or cardiovascular disease resulted in an analytical sample of 419 527. We summarised the relation between white cell count and suicide mortality using Cox proportional hazards regression. To examine if gender was an effect modifier in the inflammation–suicide relation, we created an interaction term and compared this more complex model with that in which the interaction term had been removed. Irrespective of the p value for interaction, all results were presented separately for men and women.

RESULTS

During a mean of 16.6 years of follow-up there were 1010 deaths from suicide in 106 643 men, and 1019 such deaths in 312 884 women. In men, after adjustment for age, there was little evidence of an association between our inflammation marker and suicide mortality (table 1). In women, however, those in the second inflammation quartile, and higher, experienced around a 30% increased risk of death. Controlling for a range of covariates which included cigarette smoking, alcohol intake and socioeconomic status—all known risk factors for suicide—had essentially no impact on the magnitude of these relationships. There was, however, no strong statistical evidence of a difference in the inflammation–suicide gradient in men and women (p value for interaction: 0.27). Finally, with subclinical disease potentially influencing levels of inflammation, we dropped suicide deaths in the first 5 years of follow-up, reasoning that some of these deaths may have been ascribed to a diagnosis of major morbidity during this period. Our results were essentially unchanged.

DISCUSSION

We found a degree of support for our hypothesis that higher levels of inflammation were more predictive of suicide risk in women than men. As speculated, it may be that women experience more acute changes in mood in response to alterations in systemic inflammation,[12] and so have a greater risk of suicide. Relative to the only other study in this field which was insufficiently powered to explore differential effects by gender,[13] in that study we found markedly stronger inflammation–suicide associations although we captured systemic inflammation using C-reactive protein as opposed to white blood cell count.

The present study has some strengths including its size which facilitates analyses by gender. It is also of course not without its shortcomings. With inflammation being related to depression as described,[11] and other mental health problems, as well as being implicated in the occurrence of suicide,[4] it is a possible mediating factor in the inflammation–suicide relation. Unfortunately, we did not have sufficiently good indicators of mental health in the present study to explore this issue. Second, white blood cell count is likely to be elevated in the presence of an infection like the common cold on which we did not collect data. If the positive relation between white blood cell count and suicide in women was generated by acute infection one would anticipate an elevated risk in the highest blood cell count group only; however, raised suicide rates are in fact apparent across quartiles 2–4, so confounding by infection seems very unlikely.

Using the present data set, we have previously confirmed known relationships such as an association of smoking, high alcohol consumption and poverty with suicide mortality.[15] While these results increase our confidence in the present novel findings for inflammation and suicide, our hypothesis requires further testing. With suicide mortality being rare, the utilisation of the more common suicide attempt via, for instance, hospital admission, would therefore have utility in this context, as would the use of other markers of systemic inflammation such as C-reactive protein and interleukin 6.

What is already known on this subject

► Data from one study have been used to explore the relation of systemic inflammation with later suicide risk and a strong positive association was apparent. There were insufficient suicide events in that study to examine gender differentials in this relationship.

What this study adds

► In a cohort of a general population sample from South Korea, higher levels of systemic inflammation were moderately related to an elevated risk of suicide death in women but not in men.

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