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Systemic inflammation and risk of completed suicide in the general population

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Introduction

There is a growing *prima facie* case for inflammation being a determinant of suicide. In cohort studies, elevated levels of inflammatory markers have been linked to the future occurrence of depression,[1] a known risk factor for suicide. In psychiatric patients, inflammation is positively correlated with the intensity of self-reported suicidal ideation[2] and, *post mortem*, relative to controls, victims of suicide have higher cytokine levels.[3] Furthermore, individuals with asthma, a condition characterised by inflammation, experience higher rates of suicide mortality than non-atopic counterparts.[4]

While these various lines of evidence may implicate inflammation in the pathophysiology of suicide, there has been no prospective examination of the link between inflammation and future suicide events.

Methods

Data from a series of independent, geographically-representative, near-identical surveys of individuals living in private households, conducted between 1998 and 2006 in the UK, were pooled.[5] In seven (1998, 1999, 2003, 2004, 2006 Health Survey for England [HSE]; 1998, 2003 Scottish Health Survey [SHS]), serum CRP was ascertained using the N-Latex CRP mono-immunoassay on the Behring Nephelometer II Analyser. Study members were linked to national cause-of-death registers until 14th February 2011 (HES) or 31st December 2009 (SHS). Death certification for suicide has a high level of agreement with other sources of evidence (forensic reports, police reports, toxicological and histological data).[6] Covariates included psychological distress which comprised 'caseness' on 12-item General Health Questionnaire, self-reported long-standing mental illness, and use of psychotropic

medication. Ethical approval for each survey was granted by local Research Ethics Committees, and study members provided informed consent.

Results

A mean duration of 8.6 years of follow-up (339,727 person-years) gave rise to 26 deaths ascribed to suicide (7.7 events per 100,000 person-years) in an analytical sample with data on inflammation, age, sex, and mortality (N=39,349). Of the study covariates, cigarette smoking (age- and gender-adjusted hazard ratio; 95% confidence interval: current vs. never/former: 9.67; 3.82, 24.52), gender (male vs. female: 2.64; 1.15, 6.07), socioeconomic status (manual social class vs. non-manual: 4.02; 1.60, 10.13), and psychological distress ('caseness' vs. not: 4.89; 2.22, 10.80) were related to an elevated rate of suicide.

After basic adjustment, people in the highest inflammation group were four times more likely to die from suicide relative to those in the lowest group (4.20; 1.44, 12.25) (table 1). A graded association was apparent across the three categories (p-value[trend]=0.007) with a 1-SD-increase in inflammation associated with a 55% increase in suicide risk (1.55; 1.05-2.30). This gradient was attenuated somewhat after adjustment for smoking, although accounting for other covariates had little impact.

Excluding people at various thresholds of high CRP (4, 6, 8, 10 mg/L) did not materially alter our findings. While a positive association between CRP and suicide rates was apparent across the full duration of follow-up (figure 1), on partitioning (<=5 vs. >5 years), the magnitude of this relationship was somewhat stronger in the early (multivariable-adjusted hazard ratio for a 1-SD increase in CRP: 1.63; 0.87, 3.05) relative to the later phases (1.17; 0.69, 1.96).

Discussion

We found up to a 4-fold increased risk of completed suicide in individuals with elevated inflammation compared with those having low levels. That this gradient was not explained by controlling for a series of covariates raises the likelihood that other mechanisms underlie the association. Our finding that suicide was related to a series of known risk factors gives us some confidence in our novel results for inflammation.

Despite a large sample size, the number of completed suicide cases herein was modest leading to low statistical power. Our results therefore warrant testing using the present study design and other approaches such as Mendelian Randomisation and large-scale pharmacological trials of inflammation reduction.

Author contributions: Study concept and design: GDB; Acquisition and preparation of the dataset (including mortality linkage): ES; Statistical analysis: SB; Interpretation of the data: All authors; Drafting of the manuscript: GDB; Critical revision of the manuscript for important intellectual content: All authors. ES, GDB and SB had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors saw and agreed on the final manuscript as well as the decision to submit for publication.

Conflicts of Interest and Financial Disclosures: None to declare.

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Table 1. Hazard ratios (95% CI) for the association of C-reactive protein with completed suicide: pooling of data from seven UK general population-based longitudinal studies

	N events	N at risk	C-reactive protein			P-value for trend	1 SD increase in CRP
			Low (<1mg/L)	Intermediate (1-3mg/L)	High (>3mg/L)		
N of events / N at risk	26	39349	5 / 14241	9 / 13660	12 / 11448		
Age- and sex-adjusted	26	39349	1.0 (ref.)	2.16 (0.71, 6.51)	4.20 (1.44, 12.25)	0.007	1.55 (1.05, 2.30)
Age-, sex-, and socioeconomic status-adjusted	26	37392	1.0	2.09 (0.69, 6.32)	3.86 (1.32, 11.32)	0.01	1.50 (1.01, 2.23)
Age-, sex-, and somatic illness-adjusted	26	39339	1.0	2.15 (0.71, 6.50)	4.16 (1.42, 12.18)	0.007	1.55 (1.04, 2.29)
Age-, sex-, and psychological distress-adjusted	25	38114	1.0	2.60 (0.79, 8.52)	4.56 (1.43, 14.55)	0.008	1.53 (1.03, 2.29)
Age-, sex- and smoking-adjusted	26	39200	1.0	1.83 (0.60, 5.54)	3.03 (1.03, 8.94)	0.04	1.36 (0.91, 2.03)
Multivariable-adjusted	25	36267	1.0	2.23 (0.68, 7.35)	3.31 (1.02, 10.73)	0.04	1.33 (0.89, 2.01)

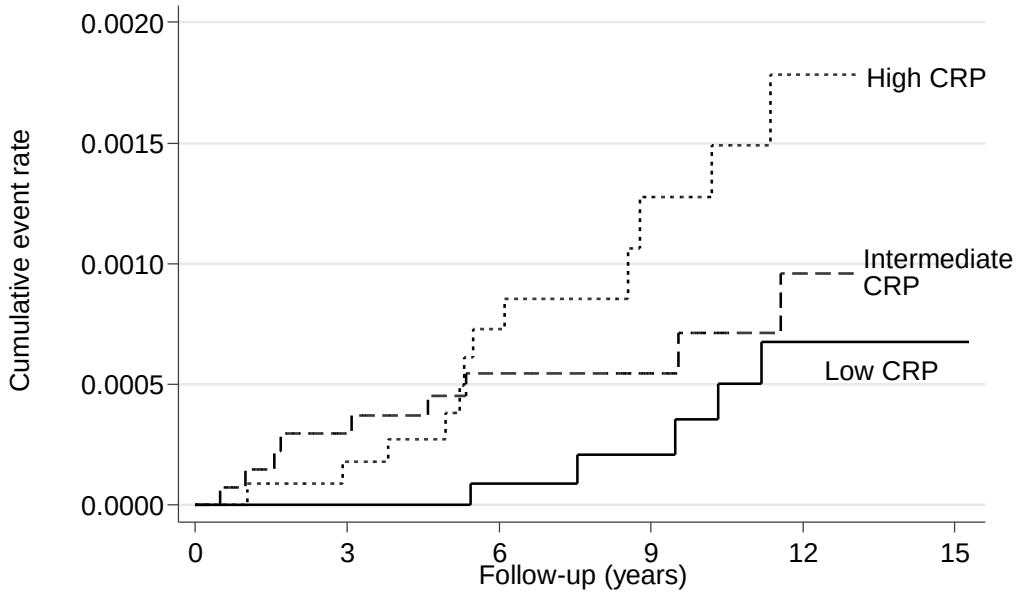
Multivariable adjustment is adjustment for age, sex, socioeconomic status, psychological distress, cigarette smoking, and somatic illness (neoplasms, diabetes, other endocrine disorders, cerebrovascular disease, myocardial infarction, angina, hypertension, any other heart disease, respiratory diseases and any other non-mental health condition).

Suicide mortality was denoted by any mention of the following events on death certificates (international classification of diseases (ICD) 9th and 10th revisions): ICD-9 suicide and self-inflicted poisoning by solid or liquid substances (E950-E959) and injury undetermined whether accidentally or purposely inflicted (E980-E989), and ICD-10 terrorism (U03.1 and U03.9), intentional self-harm (X60-X84), event of undetermined intent (Y10-Y34), sequelae of intentional self-harm, assault and events of undetermined intent (Y87), and sequelae of unspecified external cause (Y89.9).

For the computation of hazard ratios per 1-SD-increase in CRP, CRP data were log-transformed (loge[CRP] 1.25).

In all analyses the baseline hazard function was stratified by study.

Figure 1. Suicide death rates according to CRP level and duration of follow-up: pooling of data from seven UK general population-based longitudinal studies



Number at risk (n events)

Low	14241	(0)	14123	(1)	10796	(1)	6791	(3)	3645	(0)	1
Intermediate	13660	(4)	13426	(3)	9961	(0)	6025	(2)	3202	(0)	0
High	11448	(2)	10961	(5)	8037	(3)	4717	(2)	2347	(0)	0

Legend: The figure displays the proportion of deaths by suicide (each 'step' signals at least one event) in each of the three CRP categories (Low [<1mg/L], Intermediate [1-3mg/L], High [>3mg/L]) over the duration of follow-up (0-17 years).