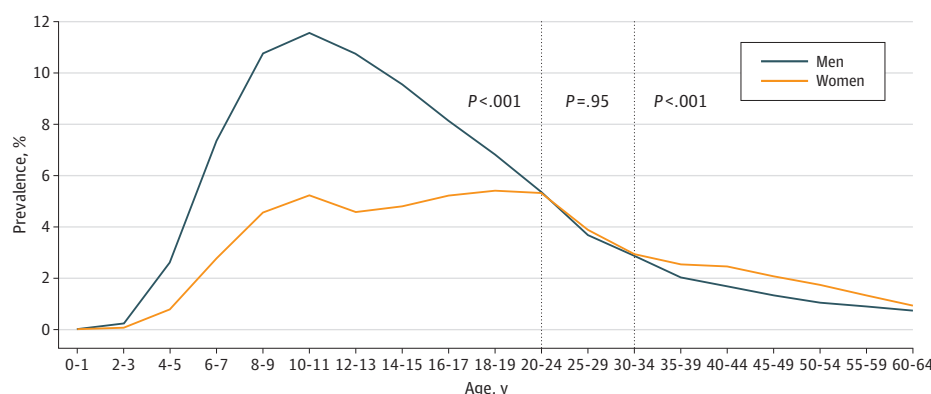


Figure. Percentage of Male and Female Populations With Stimulant Medication Use by Age, 2014



P values were estimated from multivariable logistic regression models comparing boys/men with girls/women in the annual prevalence of stimulant use (2014) in ages 0 through 19 years, 20 through 34 years, and 35 through 64 years, adjusting for race/ethnicity, plan state, urbanicity of area of residence, and annual household income.

In 2014, as a percentage of total stimulant dispensings, amphetamine-related products predominated in adults (83.6% [488 322/583 885]), whereas methylphenidate was more common in youth (52.5% [247 710/472 248]) (data not shown). Among those treated with stimulants, a clinician-reported ADHD diagnosis was more common among youths than adults (62.0% [40 055/64 626] vs 45.5% [33 790/74 269]) (data not shown).

Discussion | In a commercially insured population, in just 5 years, between 2010 and 2014, the proportion of adults treated with stimulants grew rapidly in contrast to youths, who had a modest increase in stimulant use. The increase in adult stimulant use may be largely driven by increases in outpatient diagnoses of adult ADHD.³ However, consistent with previous reports,⁴ we show that a large proportion of stimulant-treated adults lacked an ADHD diagnosis, potentially reflecting off-label use. This raises concerns regarding potential nonmedical use of prescription stimulants.^{5,6}

The study limitations include dispensings that may not represent actual consumption and limited data on clinical appropriateness of treatment. Finally, the findings may not be nationally representative. Nevertheless, our study reports a prominent expansion in stimulant use among adults in a large, commercially insured population and supports further research to better understand outcomes of stimulant use, particularly among adult women.

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Association of Systemic Inflammation With Risk of Completed Suicide in the General Population

There is a growing *prima facie* case for inflammation being associated with suicide. In cohort studies,¹ elevated levels of inflammatory markers have been linked to the future occurrence of depression, a known risk factor for suicide. In

Table. Association of C-Reactive Protein With Completed Suicide^a

Adjustment	No. of Events	No. at Risk	CRP, HR (95% CI) ^b			P Value	1-SD. Increase in CRP, HR (95% CI) ^c
			Low (<1 mg/L)	Intermediate (1-3 mg/L)	High (>3 mg/L)		
No. of events/No. at risk	26	39 349	5/14 241	9/13 660	12/11 448	NA	NA
Age- and sex-adjusted	26	39 349	1 [Reference]	2.16 (0.71-6.51)	4.20 (1.44-12.25)	.007	1.55 (1.05-2.30)
Age-, sex-, and socioeconomic status-adjusted	26	37 392	1 [Reference]	2.09 (0.69-6.32)	3.86 (1.32-11.32)	.01	1.50 (1.01-2.23)
Age-, sex-, and somatic illness-adjusted	26	39 339	1 [Reference]	2.15 (0.71-6.50)	4.16 (1.42-12.18)	.007	1.55 (1.04-2.29)
Age-, sex-, and psychological distress-adjusted	25	38 114	1 [Reference]	2.60 (0.79-8.52)	4.56 (1.43-14.55)	.008	1.53 (1.03-2.29)
Age-, sex- and smoking-adjusted	26	39 200	1 [Reference]	1.83 (0.60-5.54)	3.03 (1.03-8.94)	.04	1.36 (0.91-2.03)
Multivariable-adjusted ^d	25	36 267	1 [Reference]	2.23 (0.68-7.35)	3.31 (1.02-10.73)	.04	1.33 (0.89-2.01)

Abbreviations: CRP, C-reactive protein (to convert to nanomoles per liter, multiply by 9.524); HR, hazard ratio; NA, not applicable.

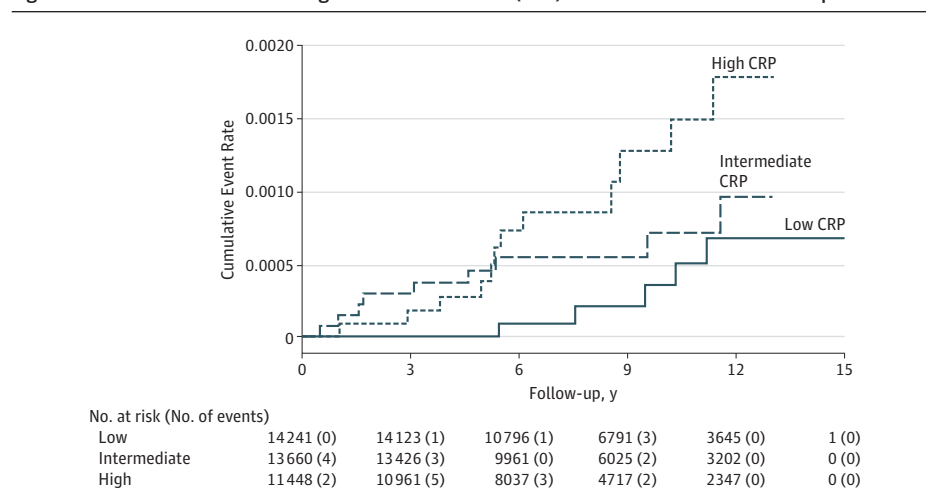
^a Suicide mortality was denoted by any mention of the following events on death certificates (*International Classification of Diseases, Ninth Revision and Tenth Revision*): suicide and self-inflicted poisoning by solid or liquid substances (E950-E959), injury undetermined whether accidentally or purposely inflicted (E980-E989), 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).

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

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

^d Adjusted for age, sex, socioeconomic status, psychological distress, cigarette smoking, and somatic illness (ie, neoplasms, diabetes, other endocrine disorders, cerebrovascular disease, myocardial infarction, angina, hypertension, any other heart disease, respiratory diseases, and any other nonmental health condition).

Figure. Suicide Death Rates According to C-Reactive Protein (CRP) Level and Duration of Follow-up



The proportion of deaths by suicide in each of the 3 CRP categories (low [<1 mg/L], intermediate [$1-3$ mg/L], or high [>3 mg/L]) over the duration of follow-up (0-17 years). Each step signals at least 1 death by suicide. To convert to nanomoles per liter, multiply by 9.524.

psychiatric patients, inflammation is positively associated with the intensity of self-reported suicidal ideation,² and those who commit suicide have higher cytokine levels post mortem relative to control patients.³ Furthermore, individuals with asthma, a condition characterized by inflammation, experience higher rates of suicide mortality than their nonatopic 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 were pooled from a series of independent, geographically representative, near-identical surveys of individuals living in private households, conducted from January 1998

to May 2007 in the United Kingdom.⁵ In 7 surveys (the 1998, 1999, 2003, 2004, and 2006 Health Surveys for England; the 1998 and 2003 Scottish Health Surveys), serum C-reactive protein (CRP) levels were ascertained using the N Latex CRP monoimmunoassay on the Behring Nephelometer II analyzer (Dade Behring). Study members were linked to national cause-of-death registers until February 2011 for the Health Survey for England or December 2009 for the Scottish Health Survey. Death certification for suicide has a high level of agreement with other sources of evidence (eg, forensic reports, police reports, and toxicological and histological data).⁶ Covariates included psychological distress, which was determined by caseness (ie, a score greater than 3) on the 12-item General Health Questionnaire, self-reported long-standing mental illness, and the use of psychotropic medication. Ethical approval for each survey

was granted by local research ethics committees, and study members provided informed consent at the time of the survey. Approval and informed consent were not required for the present analyses.

Results | In an analytical sample of 39 349 participants with data on inflammation, age, sex, and mortality, a mean (SD) duration of 8.6 (3.3) years of follow-up gave rise to 26 deaths ascribed to suicide (7.7 events per 100 000 person-years). Age- and sex-adjusted hazard ratios (HRs) and 95% CIs were calculated for study covariates; being a cigarette smoker (current vs never/former: HR, 9.67; 95% CI, 3.82-24.52), male (male vs female: HR, 2.64; 95% CI, 1.15-6.07), socioeconomically disadvantaged (manual vs nonmanual social class: HR, 4.02; 95% CI, 1.60-10.13), and psychologically distressed (score >3 vs ≤3: HR, 4.89; 95% CI, 2.22-10.80) were associated with an elevated rate of suicide.

After basic adjustment, people in the highest inflammation group were 4 times more likely to die by suicide relative to those in the lowest group (HR, 4.20; 95% CI, 1.44-12.25) (Table). A graded association was apparent across the 3 categories (P value = .007), with a 1-SD increase in inflammation associated with a 55% increase in suicide risk (HR, 1.55; 95% CI, 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 (ie, at 4, 6, 8, and 10 mg/L [to convert to nanomoles per liter, multiply by 9.524]) 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), on partitioning (≤5 vs >5 years), the magnitude of this association was somewhat stronger in the early phase (multivariable-adjusted HR for a 1-SD increase in CRP: HR, 1.63; 95% CI, 0.87-3.05) relative to the later phases (HR, 1.17; 95% CI, 0.69-1.96).

Discussion | We found up to a 4-fold increased risk of completed suicide in individuals with elevated levels of inflammation compared with those with low levels. That this gradient was only partially explained by controlling for a series of covariates raises the likelihood that other mechanisms underlie the association. Our finding that suicide was associated with a series of known risk factors gives us some confidence in our novel results for inflammation.

Conclusions | In conclusion, this is the first prospective cohort study to examine the link between systemic inflammation and future suicide risk, but it is not without its shortcomings. Despite a large sample size, the number of completed suicides herein was modest, leading to low statistical power. Our results warrant testing using the present study design and other approaches, such as mendelian randomization and large-scale pharmacological trials of inflammation reduction.

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COMMENT & RESPONSE

Effects of Cannabis Use on Human Behavior: A Call for Standardization of Cannabis Use Metrics

To the Editor With rapidly shifting legislation worldwide in relation to recreational and medicinal cannabis use, the review by Volkow et al¹ is timely. We highlight several additional noteworthy issues for consideration.

While further evidence has emerged that acute and long-term exposure to cannabis impairs cognition,² there is still grossly insufficient evidence for recovery of function with abstinence. Neither the parameters of cannabis exposure nor the neural mechanisms subserving persistence or recovery have been elucidated. Well-controlled prospective studies monitoring restoration of brain function and structure from current use through prolonged abstinence are required to delineate the time course and moderators of potential recovery of cognitive function.