Psychological Medicine

cambridge.org/psm

Original Article

Cite this article: Oh KY, Van Dam NT, Doucette JT, Murrough JW (2019). Effects of chronic physical disease and systemic inflammation on suicide risk in patients with depression: a hospital-based case–control study. *Psychological Medicine* 1–9. https://doi.org/10.1017/S0033291718003902

Received: 2 August 2018
Revised: 11 November 2018
Accepted: 27 November 2018

Key words:
Depression; suicide; inflammation; C-reactive protein; medical comorbidity; hospital-based study

Author for correspondence:
James W. Murrough, E-mail: james.murrough@mssm.edu

Effects of chronic physical disease and systemic inflammation on suicide risk in patients with depression: a hospital-based case–control study

Kyu Young Oh[1], Nicholas T. Van Dam[1,2], John T. Doucette[3] and James W. Murrough[1,4,5]

[1]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [2]School of Psychological Sciences, University of Melbourne, Parkville, VIC 3010, Australia; [3]Department of Environmental Medicine & Public Health, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [4]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA and [5]Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

Abstract

Background. Few studies have examined the concurrent effects of physical disease and systemic inflammation on suicide risk in patients with depression. The authors investigated the independent contributions of chronic physical disease and systemic inflammation as indexed by C-reactive protein (CRP), on risk of suicide attempt.

Methods. In this case–control study, 1468 cases of suicide attempters and 14 373 controls, both aged 18–65 years with a diagnosis of depression during 2011–2015, were identified from the hospital-wide database. Regression models were implemented to identify separate effects of physical diseases and systemic inflammation indexed by CRP, on risk of suicide attempt.

Results. Compared with having no physical disease, having one, two, and three or more physical diseases was associated with a 3.6-, 6.4-, and 14.9-fold increase in odds of making a suicide attempt, respectively, after adjusting for age, sex, and race/ethnicity. In a sub-sample of cases and controls with available CRP values, patients with high CRP (>3 mg/L) had 1.9 times the odds of suicide attempt compared with patients with low CRP (<1 mg/L). This association was no longer significant when controlling for the effect of physical disease.

Conclusions. The presence of physical disease is an important risk factor for suicide attempt among patients with depression. Systemic inflammation is likewise associated with increased risk for suicide attempt, however, this association appears to be accounted for by the presence of physical disease among patients receiving care in a medical center setting. Healthcare providers should consider the risk of suicide attempt in depressed patients burdened with multiple comorbidities.

Introduction

Suicide accounts for nearly 800 000 deaths worldwide each year (World Health Organization, 2014). More than 90% of patients who die by suicide have a mental disorder, most commonly major depression, occurring in half to two-thirds the suicide victims (Mann, 2003; Hawton *et al.*, 2013). Among patients with depression, comorbidity with other mental disorders including alcohol abuse, anxiety disorders, and personality disorders has been recognized as risk factors for suicide (Henriksson *et al.*, 1993; Hawton *et al.*, 2013). Physical diseases, especially chronic diseases such as chronic obstructive pulmonary disease, cancer, spine disorders, asthma, and stroke, are also known to be important contributors to suicide risk (Waern *et al.*, 2002; Webb *et al.*, 2012; Crump *et al.*, 2014). Depression is highly prevalent and most individuals who die by suicide receive some form of medical care in the year preceding their death (Ahmedani *et al.*, 2014). Therefore, the identification of risk factors for suicide attempt among patients with depression in healthcare settings is essential.

Beyond medical co-morbidities, pro-inflammatory states have been linked to suicidal ideation and suicide attempt in recent studies. Increased blood levels of inflammatory markers such as tumor necrosis factor-alpha, and interleukin-6, have been reported in patients with a history of suicidal ideation or behavior compared with non-suicidal control subjects (Dieperink *et al.*, 2004; Black and Miller, 2015). Several studies to date have investigated the association between suicide risk and C-reactive protein (CRP) specifically, an acute-phase protein known to index systemic inflammation. While two studies with small sample sizes showed no significant association between CRP and suicide (Karlovic *et al.*, 2012; Vargas *et al.*, 2013),

CAMBRIDGE UNIVERSITY PRESS

several other studies demonstrated a positive association (O'Donovan *et al.*, 2013; Courtet *et al.*, 2015; Batty *et al.*, 2016; Gibbs *et al.*, 2016; Loas *et al.*, 2016; Priya *et al.*, 2016; Melhem *et al.*, 2017; Park and Kim, 2017; Caceda *et al.*, 2018).

While the presence of chronic disease and elevated levels of systemic inflammation are both risk factors for suicide, the independent contribution of these factors to risk remains unclear (Turecki and Brent, 2016). In the aforementioned studies that demonstrated a positive association between CRP and suicide risk, two cross-sectional studies and one prospective cohort study have compared individuals with suicidal ideation (Park and Kim, 2017), attempt (Priya *et al.*, 2016), and suicide completers (Batty *et al.*, 2016), with the general population. Other cross-sectional studies examined the association of CRP and various levels of suicidal behavior in a psychiatric inpatient sample (Gibbs *et al.*, 2016; Loas *et al.*, 2016; Melhem *et al.*, 2017). Several studies examined the association between CRP and suicidal behavior within an inpatient population with depression (O'Donovan *et al.*, 2013; Courtet *et al.*, 2015; Chang *et al.*, 2017; Caceda *et al.*, 2018). While these studies all found that elevated CRP was associated with an increased risk of suicidal ideation or attempt, there was only limited examination of the role of mental and physical diseases, which may have led to limitations in accurate estimation of the magnitude of the relationship between inflammation and suicide.

In order to examine the influence of chronic physical diseases and biological markers of systemic inflammation (i.e. CRP) on suicide attempt in patients with depression, we conducted a case–control study drawn from a sample of 15 841 patients with a diagnosis of a depressive disorder who received evaluation or treatment at an academic medical center between 2011 and 2015. In line with prior work, we hypothesized that a higher number of chronic physical diseases and mental disorders among patients with depression is associated with a higher risk of suicide attempt (Henriksson *et al.*, 1993; Crump *et al.*, 2014). In addition, we hypothesized that elevated markers of systemic inflammation are associated with a higher risk of suicide attempt (Black and Miller, 2015). Finally, we modeled the contributions of inflammatory markers and chronic physical diseases together in order to estimate the independent contribution of these factors to suicide risk.

Methods

Participants

This retrospective study utilized data extracted from the electronic medical records (EMR) of an academic medical center. Cases and controls were selected from all patients aged 18–65 with a diagnosis of depression during the period of 1 January 2011–31 December 2015. To define depression, International Classification of Diseases, Ninth Revision (ICD-9) codes 296.2, 296.20–26, 296.3, 296.30–36, 296.82, 300.4, 311 (National Center for Health Statistics, Atlanta;, 2010) representing Major Depressive Affective Disorder Single or Recurrent Episodes, Atypical Depressive Disorder, Dysthymic Disorder, and Depressive Disorder Not Elsewhere Classified were used. In addition, our case definition of suicide attempters was individuals with at least one of ICD-9 codes E950–E959 or E980–E989 (Suicide and Self-inflicted Injury and Injury Undetermined whether Accidentally or Purposely Inflicted, respectively) given during 2011–2015, consistent with previous work (Gorton *et al.*, 2016). Our control definition was individuals without any of the suicide attempt codes, in addition to an absence of documented suicide attempt per medical records. A total of 1468 cases (depressed, suicide attempt+) and 14 737 controls (depressed, suicide attempt−) were thus identified; cases and controls were not matched. All research involved the collection of existing data that was provided to the investigators in a fully de-identified manner, and otherwise met criteria for exempt status according to the Program for the Protection of Human Subjects at Mount Sinai. Additional details of participant inclusion and exclusion criteria are discussed in the online Supplemental Methods in the Supplement.

Data extraction

De-identified demographic, clinical, and laboratory data were acquired from a hospital-wide database containing data available from the EMR. Demographic data included age, gender, and race/ethnicity. Clinical data included diagnoses of both physical diseases and mental disorders. Chronic physical disease codes were categorized as follows: neoplasm, diabetes mellitus, chronic lung disease (asthma, chronic obstructive pulmonary disease), chronic heart disease (atherosclerosis, coronary artery disease, congestive heart failure, myocardial infarction), arthritis (rheumatoid, osteoarthritis), and stroke. Mental disorder codes were categorized as follows: dementia, psychotic disorders, bipolar disorders, anxiety disorders, obsessive-compulsive disorder, alcohol use disorders, and substance use disorders other than alcohol. Laboratory data of inflammatory markers were as follows: high-sensitivity CRP, white blood cell count (WBC) with differential, erythrocyte sedimentation rate (ESR), and vitamin D level, all of which have been associated with depression or suicide in previous studies (Garcia-Rizo *et al.*, 2013; Grudet *et al.*, 2014; Lopresti *et al.*, 2014). We focused on CRP as our primary biological marker of systemic inflammation, given its known association with depression and established validity of indexing systemic inflammation (Harrison, 2015). Additional details of data collection are discussed in the online Supplemental Methods in the Supplement.

Data analysis

All available variables were compared between the cases and controls. These comparisons were done in the full sample (cases: $N = 1468$; controls: $N = 14\,373$) and in the sub-sample of individuals who had CRP data available (cases: $N = 172$; controls: $N = 1158$). To examine the association between candidate risk factors and suicide attempt, we implemented logistic regression models with the stepwise addition of covariates. First, in the full sample, we sought to identify associations between chronic physical diseases and mental disorders (predictors), and suicide attempt (outcome), adjusting for demographic covariates including age, sex, and race/ethnicity. Then, in the sub-sample with available CRP values, we sought to examine the association between CRP level and suicide attempt, adjusting for the same demographic covariates as used in the full sample. Finally, we modeled the effects of CRP, chronic physical diseases, mental disorders, and demographic covariates on suicide attempt together in a single model in order to determine the magnitude of these effects while adjusting for the others. Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained from logistic regression models. CRP level was treated as an ordinal variable with three levels corresponding to low (<1 mg/L), intermediate (1–3 mg/L), and high (>3 mg/L) according to the CDC guidelines (Pearson *et al.*,

2003), as well as a continuous variable in separate models. In analyses using continuous CRP level, natural log-transformed CRP was used due to a positively skewed distribution. Two-sided p values of <0.05 were considered statistically significant. All analyses were performed using the statistical package R version 3.2.3 (R Core Team, 2015). Study methods and reporting conform to established standards for observational studies as defined by the STROBE statement (The PLOS Medicine Editors, 2014).

Results

Demographic and clinical characteristics of the sample are reported in Table 1. Chronic physical diseases were more common among patients with depression who made a suicide attempt (i.e. cases) compared with patients with depression who did not make a suicide attempt (i.e. controls), with 56.0% of the cases exhibiting at least one chronic physical disease compared with 26.6% of the controls ($p < 0.001$). Among the largest group differences in disease types were chronic lung disease (34.9% *v.* 12.2% in cases and controls, respectively), and diabetes (21.6% *v.* 5.4%). Comorbid mental disorders were significantly more common in the cases compared with the controls: 74.9% of cases had at least one mental disorder in addition to depression, compared with 29.1% of controls ($p < 0.001$). The most notable differences were in the presence of a substance use disorder other than alcohol (44.3% *v.* 6.0% in cases and controls, respectively), anxiety disorder (40.8% *v.* 14.4%), and alcohol use disorder (26.2% *v.* 3.8%). Comparisons between the full study sample and the CRP-available sample are presented in the online Supplemental Results 1 in the Supplement.

Compared with having no chronic physical disease, having one (OR 3.62, CI 3.15–4.16), two (OR 6.40, CI 5.27–7.76), and three or more (OR 14.94, CI 11.84–18.82) diseases was significantly associated with increased odds of suicide attempt, adjusting for age, sex, and race/ethnicity (Table 2). Modeling disease type revealed that the largest effect of disease by type on suicide attempt was diabetes (OR 4.42, CI 3.73–5.22), followed by chronic lung disease (OR 3.70, CI 3.24–4.22). Compared with having no comorbid mental disorder, having one (OR 3.89, CI 3.37–4.49), two (OR 11.78, CI 9.94–13.97), and three or more (OR 56.67, CI 45.71–70.52) was associated with a large increase in odds of suicide attempt, adjusting for age, sex, and race/ethnicity. Among mental disorder types, having a substance use disorder other than alcohol was associated with the largest magnitude of increased odds for suicide attempt (OR 7.06, CI 6.10–8.17). Detailed analyses that take into account types of physical disease and mental disorder are presented in online Table S1 in the Supplement.

Next, we examined the association between systemic inflammation indexed by biological markers in the blood, and risk of suicide attempt. Among the markers we tested (CRP, ESR, WBC, and vitamin D), only CRP and ESR levels were found to be significantly different between the cases and controls (online Table S2 in the Supplement). The distribution of raw and log-transformed CRP values is shown in Fig. 1.

In the unadjusted model, patients with CRP > 3 mg/L had about twice the odds of suicide attempt compared with the patients with CRP < 1 mg/L (OR 1.90, CI 1.24–3.02; Table 3). The association between CRP and suicide attempt remained significant after controlling for age, sex, and race/ethnicity (OR 1.84, CI 1.18–2.95). When controlling for a number of mental disorders, CRP remained significantly associated with suicide attempt (OR 1.71, CI 1.05–2.89).

When modeling the influence of both CRP and the presence of physical disease on suicide attempt, the association between CRP and suicide attempt was no longer significant ($p = 0.24$). Having one (OR 4.07, CI 2.43–6.97), two (OR 7.40, CI, 4.20–13.35), or three or more (OR 16.20, CI 8.89–30.35) physical diseases still conferred increasingly greater risk of suicide attempt (Table 3). When age, sex, race/ethnicity, number of chronic physical diseases, and number of mental disorders were all included in a single regression, CRP was again not a significant predictor of suicide attempt risk (OR 1.30, CI 0.77–2.25). A similar pattern of results was obtained when the effect of individual types of physical diseases on suicide risk was modeled (online Supplementary Table S3), and when CRP was treated as a continuous rather than a categorical variable (online Supplementary Tables S4 and S5).

As the time lapse between the measurement of CRP and the outcome event may affect the results, we performed separate analyses using only CRP values that were measured within 6 months ($N = 386$), 6 months to 2 years ($N = 436$), and 2 to 5 years ($N = 508$) preceding the outcome event. The descriptive statistics of these time lapses are reported in online Supplementary Table S6. The magnitude of the association between CRP level and suicide attempt was similar across the different timeframes (online Table S6 in the Supplement).

Linear regression models of CRP and chronic physical disease are presented in online Supplemental Results 2 and Table S7 in the Supplement.

Discussion

In a large sample ($N = 15\,841$) drawn from a population of patients with depression receiving care at an urban medical center, we found that physical disease comorbidity was a large risk factor for suicide attempt. The presence of one, two, and three or more physical diseases increased the odds of a suicide attempt by a factor of 3.6, 6.4, and 14.9, respectively. Comorbidity between depression and other mental disorders was likewise associated with a large increase in the odds of making a suicide attempt. The presence of one, two, and three or more mental disorders in addition to depression increased the odds of a suicide attempt by a factor of 3.9, 11.8, and 56.7, respectively. Patients with a CRP value >3 mg/L had approximately twice the odds of suicide attempt compared with patients with a CRP value of <1 mg/L. However, CRP was no longer associated with suicide attempt after adjusting for the presence of chronic physical diseases. Our findings confirm physical and mental disorders, and systemic inflammation, as important risk factors for suicide attempt among treatment-seeking patients with depression, and further estimate the relative magnitude of these effects.

Our findings replicate and extend previous studies examining risk factors for suicide. Our sample with depression had a higher proportion of females, consistent with prior results (Weissman *et al.*, 1993), and had 29% comorbidity between depression and chronic diseases, similar to 23% comorbidity reported worldwide (Moussavi *et al.*, 2007). In the current study, diabetes, chronic lung disease, neoplasm, and arthritis were significantly associated with increased suicide attempt risk, consistent with prior work (Waern *et al.*, 2002; Webb *et al.*, 2012). Prior work showing an association between physical disease and suicide did not necessarily control for the potential confounding effect of depression,

Table 1. Demographic and clinical characteristics of study sample

	Full sample					CRP-available sample				
	Cases (n = 1468)		Controls (n = 14 373)		p value	Cases (n = 172)		Controls (n = 1158)		p value
	Mean	S.D.	Mean	S.D.		Mean	S.D.	Mean	S.D.	
Age	43.1	14.2	43.1	14.3	>0.99	49.2	12.9	47.3	13.3	0.08
	N	%	*N*	%		*N*	%	*N*	%	
Sex					<0.001					0.04
Male	640	43.6	5422	37.7		72	41.9	394	34	
Female	828	56.4	8950	62.3		100	58.1	764	66	
Race/ethnicity					<0.001					0.73
Caucasian (White)	366	24.9	3682	25.6		39	22.7	290	25	
Hispanic/Latino[a]	506	34.5	4132	28.7		66	38.4	472	40.8	
African American (Black)	360	24.5	3345	23.3		49	28.5	274	23.7	
Asian	27	1.8	240	1.7		2	1.2	12	1	
Other	209	14.2	2974	20.7		16	9.3	110	9.5	
Suicide attempt codes										
E95	593	40.4				23	13.4			
E98	1008	68.7				156	90.7			
No. of chronic physical diseases					<0.001					<0.001
0	646	44	10 554	73.4		25	14.5	538	46.5	
1	453	30.9	2693	18.7		50	29.1	336	29	
2	206	14	819	5.7		45	26.2	175	15.1	
3 or more	163	11.1	307	2.1		52	30.2	109	9.4	
Chronic physical diseases types					<0.001					0.03
Neoplasm	181	12.3	833	5.8		51	29.7	136	11.7	
Diabetes	317	21.6	779	5.4		64	37.2	151	13	
Chronic lung disease	512	34.9	1748	12.2		93	54.1	292	25.2	
Chronic heart disease	204	13.9	942	6.6		52	30.2	234	20.2	
Arthritis	160	10.9	735	5.1		48	27.9	170	14.7	
Stroke	50	3.4	300	2.1		15	8.7	68	5.9	
No. of mental disorders[b]					<0.001					<0.001
0	368	25.1	10 188	70.9		44	25.6	795	68.7	
1	453	30.9	3263	22.7		51	29.7	286	24.7	
2	314	21.4	754	5.2		40	23.3	61	5.3	
3 or more	333	22.7	168	1.2		37	21.5	16	1.4	
Mental disorders types					<0.001					<0.001
Depression	1468	100	14 373	100		172	100	1158	100	
Dementia	42	2.9	75	0.5		7	4.1	13	1.1	
Psychosis	312	21.3	1011	7		36	20.9	95	8.2	
Bipolar	218	14.9	493	3.4		18	10.5	25	2.2	
Anxiety	599	40.8	2063	14.4		90	52.3	181	15.6	
Obsessive-compulsive disorder	25	1.7	251	1.7		1	0.6	17	1.5	
Alcohol use disorder	384	26.2	544	3.8		30	17.4	40	3.5	
Other substance use disorder	650	44.3	863	6		75	43.6	88	7.6	

E95, Suicide and Self-inflicted Injury; E98, Injury Undetermined whether Accidentally or Purposely Inflicted.

[a]Race and ethnicity were not clearly separated in the records, with representation in both categories. In the majority of instances, classification of race and ethnicity were consistent. For practical purposes and purposes of statistical power, the categories were collapsed. Unidentified race or ethnicity data were considered 'Other.'

[b]Number of mental disorders excludes depression, which is present in all individuals.

Table 2. Effect of chronic physical disease and mental disorder on odds of suicide attempt among patients with depression

	Model 1		Model 2		Model 3		Model 4	
	Age, sex		Age, sex, race		Age, sex, race, no. of chronic physical diseases		Age, sex, race, no. of mental disorders	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age	1.00	1.00–1.00	1.00	1.00–1.00	0.97***	0.97–0.98	0.99*	0.99–1.00
Sex (female)	0.78***	0.70–0.87	0.76***	0.68–0.85	0.70***	0.63–0.79	1.10	0.97–1.25
Race/ethnicity								
Caucasian			1	(reference)	1	(reference)	1	(reference)
Hispanic/Latino			1.28***	1.11–1.48	1.00	0.86–1.16	1.23*	1.05–1.44
African American			1.12	0.96–1.31	0.91	0.78–1.07	0.97	0.82–1.15
Asian			1.15	0.74–1.70	1.07	0.69–1.61	1.34	0.84–2.05
Other			0.72***	0.60–0.86	0.77**	0.64–0.92	0.82*	0.68–1.00
No. of chronic physical diseases								
0					1	(reference)		
1					3.62***	3.15–4.16		
2					6.40***	5.27–7.76		
3 or more					14.94***	11.84–18.82		
No. of mental disorders								
0							1	(reference)
1							3.89***	3.37–4.49
2							11.78***	9.94–13.97
3 or more							56.67***	45.71–70.52
N	15 841		15 841		15 841		15 841	

OR, odds ratio; CI, confidence interval.
N is full sample (1468 cases, 14 373 controls).
***0.001, **0.01, *0.05.

which is independently associated with both the presence of chronic disease and with suicide risk (Webb *et al.*, 2012). Since all subjects in the current study had depression, our results show that the presence of chronic physical disease is a large risk factor for suicide attempt, over and above depression. Furthermore, while several previous studies looked at the association between suicide and specific individual diseases (Waern *et al.*, 2002), our results suggest that comorbidity of multiple diseases confers substantially higher odds of suicide attempt than would be anticipated from a simple additive model of risk. Separately, we found that the presence of a mental disorder in addition to depression increased the risk for suicide attempt dramatically; one additional diagnosis increased the odds of a suicide attempt nearly 4-fold. Prior work has shown anxiety (OR 1.59), alcohol abuse (OR 2.47), and substance abuse (OR 2.66) to be associated with suicide in depressed patients (Hawton *et al.*, 2013); our results also highlight dementia, psychosis, and bipolar disorder as important risk factors for suicide attempt in patients who initially received a diagnosis of depression.

We found an association between elevated CRP and ESR with increased risk of suicide attempt, replicating previous smaller scale findings of CRP and suicide (Courtet *et al.*, 2015; Gibbs *et al.*, 2016) in a larger number of suicide attempters. In our study, the association between CRP and suicide attempt was no longer significant when controlling for types or number of chronic physical diseases. Although some prior studies have reported a positive association between CRP and suicide risk without explicitly controlling for chronic medical conditions (O'Donovan *et al.*, 2013; Gibbs *et al.*, 2016; Priya *et al.*, 2016), there has been four studies that found CRP as an independent contributor to suicide risk even after controlling for physical diseases to a varied extent (Courtet *et al.*, 2015; Batty *et al.*, 2016; Park and Kim, 2017; Caceda *et al.*, 2018).

An important difference between our design and two of these four studies is that all 15 841 individuals in our study had depression, which is one of the highest risk factors for suicide, and is itself associated with inflammation (Raison and Miller, 2011). These studies, Batty *et al.* (2016) and Park and Kim (2017), examined individuals within the general population, potentially failing to differentiate suicidal ideation or attempt from depression, which exhibit an overlap of at least 50% (Holma *et al.*, 2014). The remaining study of Courtet *et al.* examined 600 depressed inpatients, but defined suicide attempt as 'having a lifetime history of suicide attempt,' and excluded all patients with CRP > 10 mg/L from the analysis, for the possibility that high CRP likely indicates acute infection (Courtet *et al.*, 2015). In our study, patients with CRP > 10 mg/L represented 29% of patients with available CRP values. High CRP (>10 mg/L) is known to provide

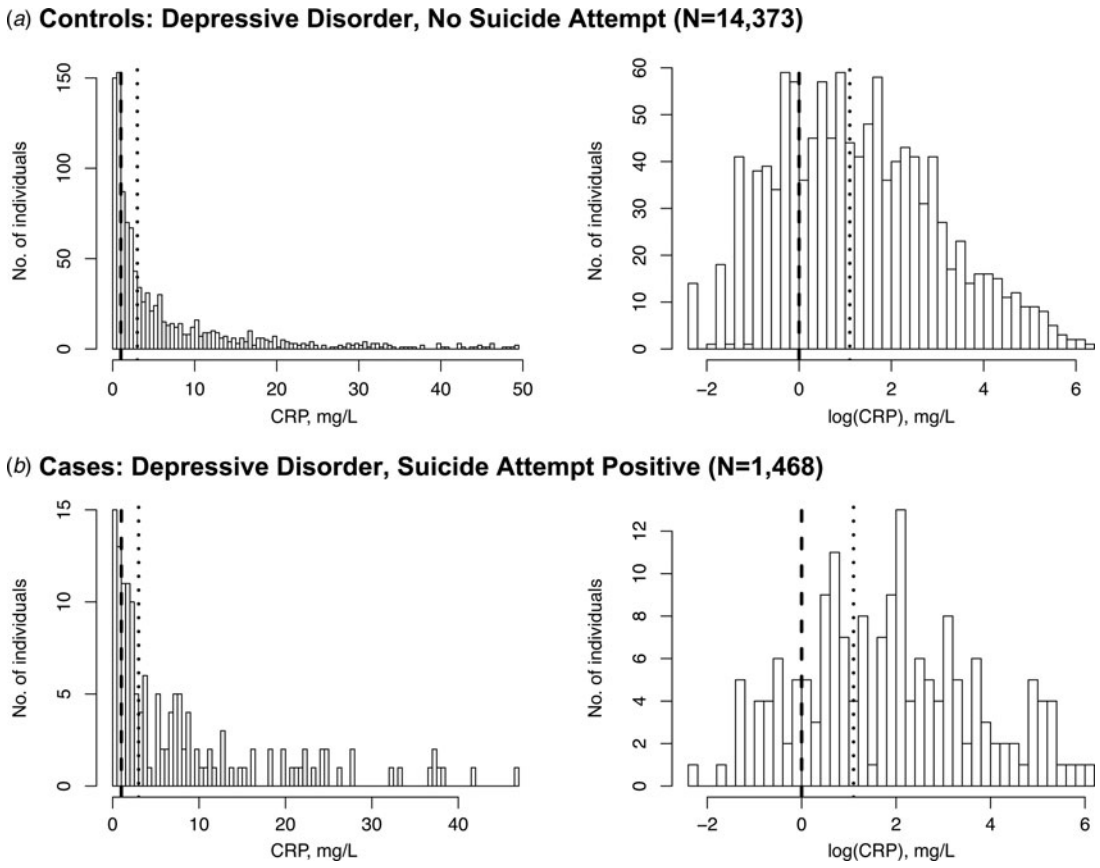

Fig. 1. Distribution of CRP values in study sample. Figure depicts the distribution of raw (left) and log-transformed (right) CRP values in both cases and controls. (*a*) Top row. Controls: depressive disorder, no suicide attempt ($N = 14\,373$). (*b*) Bottom row. Cases: depressive disorder, suicide attempt positive ($N = 1468$). Vertical dashed line represents cutoff value (1 mg/L) between low and intermediate CRP categories, and vertical dotted line represents cutoff value (3 mg/L) between intermediate and high CRP categories.

meaningful information about inflammation and all-cause mortality (Hamer *et al.*, 2010), and excluding these individuals disproportionally selects for those with lower chronic disease risk, healthier behaviors, and fewer psychological characteristics linked to increased disease risk (Shanahan *et al.*, 2014). Furthermore, even though high CRP may indicate acute infection, hospitalization with infection has been associated with suicide deaths in a recent nationwide cohort study (Lund-Sorensen *et al.*, 2016). Therefore, excluding certain thresholds of CRP to rule out infection can potentially distort true associations between CRP and suicide risk.

Another important difference between our findings and those of past studies is a definition of 'chronic physical disease.' Courtet *et al.* defined chronic physical disease as a dichotomous variable – none *v.* having at least one disease (Courtet *et al.*, 2015). Considering that we found higher risk with increasing comorbidity of diseases and certain types of diseases, previous results may not have captured the full range of influence of chronic diseases. Park *et al.* also controlled for number (but not types) of chronic diseases (Park and Kim, 2017). Batty *et al.* and Caceda *et al.* both controlled for many types of physical diseases similar to our methods, yet direct comparison of results is difficult because of distinct study population. In contrast to a relatively sicker and older patient population of our study, Batty *et al.* focused on the general population and Caceda *et al.* on younger psychiatric inpatients. Caceda *et al.* used suicidal ideation, not attempt, as a dependent variable.

Overall, our findings may be explained by several factors. The experience of a chronic physical illness is a known stressor, and stress from multiple sources is a critical component of modern theories of suicide (Mann, 2003; van Heeringen and Mann, 2014). It has long been known that physical diseases are linked to psychological risk factors that may increase the risk of suicide, such as hopelessness (Beevers and Miller, 2004), entrapment (Taylor *et al.*, 2011), and burdensomeness (Cukrowicz *et al.*, 2011). Inflammation, which commonly accompanies physical diseases, is itself associated with suicide risk (O'Donovan *et al.*, 2013; van Heeringen and Mann, 2014; Black and Miller, 2015). Therefore, physical illness may lead to increased suicide risk through multiple pathways, including by acting as a non-specific stressor, by exacerbating specific psychological risk factors for suicide, and by increasing systemic inflammatory signaling. While we found that the effect of inflammation on risk of suicide attempt was explained by chronic physical disease, more research is warranted to clarify the mechanism of how inflammation influences suicide risk in different populations such as physically healthy populations with depression.

An important question remains whether CRP is a 'state' marker of risk, associated with acute suicidality, or a 'trait' marker of risk, associated with chronic elevated risk. Recent literature has reported conflicting findings on this topic (Chang *et al.*, 2017; Caceda *et al.*, 2018). Our results show that CRP measured within three different time frames, within 6 months of suicide attempt (prior to the event), between 6 months and 2 years, and between

Table 3. Effect of CRP, chronic physical disease and mental disorder on odds of suicide attempt among patients with depression

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	CRP		CRP, age, sex		CRP, age, sex, race		CRP, age, sex, race, no. of chronic physical diseases		CRP, age, sex, race, no. of mental disorders		CRP, age, sex, race, o. of chronic disease and mental disorders	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
CRP – low	1	(reference)	1	(reference)	1	(reference)	1	(reference)	1	(reference)	1	(reference)
CRP – intermediate	1.38	0.82–2.34	1.33	0.79–2.27	1.32	0.79–2.26	1.33	0.77–2.32	1.43	0.80–2.59	1.46	0.80–2.70
CRP – high	1.90**	1.24–3.02	1.88**	1.22–3.00	1.84**	1.18–2.95	1.34	0.84–2.19	1.71*	1.05–2.89	1.30	0.77–2.25
Age			1.01	1.00–1.02	1.01	1.00–1.02	0.97***	0.96–0.99	1.01	0.99–1.02	0.98**	0.96–0.99
Sex (female)			0.70*	0.51–0.98	0.69*	0.50–0.97	0.62**	0.44–0.89	0.94	0.65–1.38	0.83	0.56–1.23
Race/ethnicity												
Caucasian					1	(reference)	1	(reference)	1	(reference)	1	(reference)
Hispanic/Latino					1.07	0.70–1.67	0.80	0.51–1.27	0.80	0.50–1.30	0.64	0.38–1.06
African American					1.32	0.83–2.10	0.94	0.58–1.54	1.01	0.60–1.69	0.81	0.47–1.40
Asian					1.42	0.21–5.55	1.32	0.19–5.46	1.95	0.29–7.96	2.05	0.30–8.55
Other					1.09	0.57–2.00	0.97	0.49–1.83	1.35	0.68–2.59	1.29	0.64–2.54
No. of chronic physical diseases												
0							1	(reference)			1	(reference)
1							4.07***	2.43–6.97			3.50***	2.01–6.26
2							7.40***	4.20–13.35			6.40***	3.46–12.13
3 or more							16.20***	8.89–30.35			12.68***	6.60–25.05
No. of mental disorders												
0									1	(reference)	1	(reference)
1									3.13***	2.04–4.81	2.84***	1.83–4.44
2									11.43***	6.82–19.22	9.77***	5.69–16.83
3 or more									45.07***	23.29–91.00	40.71***	20.12–86.15
N	1330		1330		1330		1330		1330		1330	

OR, odds ratio; CI, confidence interval.
N is CRP-available sample (172 cases, 1158 controls).
***0.001, **0.01, *0.05.

2 years and 5 years, is similarly associated with elevated risk, suggesting that CRP may represent a relatively stable risk factor. Future research will be required to further characterize the time course of CRP or other inflammatory markers as risk factors.

Our study has several strengths. It is unique in its design focusing exclusively on patients with depression, and inclusion of a relatively large sample compared with previous studies. Drawn from a hospital-wide database, our sample was not limited to inpatients, and consisted of patients receiving care at various clinical settings. We also used CRP values preceding outcome, defined as suicide attempt in cases and last medical documentation of non-suicidality in controls, which can preclude falsely elevated CRP due to tissue damage after suicide attempt. The EMR data allowed us to run additional analyses controlling for the time lapse between the CRP measurement and the outcome event. We were able to include a variety of routine clinical markers as variables potentially associated with a risk of suicide attempt. Finally, we included a full range of types and numbers of chronic physical diseases and mental disorders as covariates in our analysis.

This study has several limitations. Given the use of EMR, it was difficult to obtain data for all potentially confounding variables regarding the relationship between CRP and other predictor variables and suicide attempt. Factors such as depression severity, body mass index (Visser *et al.*, 1999), history of abuse (Danese *et al.*, 2008), socioeconomic status, rating of physical pain, lifetime history of suicide attempts, and extent of suicidal risk or ideation would have improved the robustness of our model, but were often missing or partially present in the EMR. Furthermore, creating a sample based on ICD-9 codes and laboratory values available on EMR had certain limitations. Using specific codes for suicide attempt, although common (Gorton *et al.*, 2016), can result in false positives and false negatives because it is difficult to differentiate accidents from purposeful self-injury in many acute patient settings. As the sample was defined as patients receiving evaluation and treatment at a medical center (inpatient or outpatient), our study may include patients who are sicker than the average population with depression. The sub-sample with available CRP data may also have been sicker compared with patients with depression in the general population, or patients in our full sample that did not have CRP available. Therefore, it may be difficult to generalize our findings to all patients with depression. Furthermore, because we limited our patient population to individuals with depression, our findings may not be applicable to individuals with other psychiatric disorders, including bipolar disorder, schizophrenia, alcoholism, substance abuse, and personality disorders (Mann, 2002), as well as individual without any psychiatric diagnosis. Despite these limitations, the current approach allowed us to examine a wide range of types and numbers of chronic physical diseases and mental disorders as covariates.

In conclusion, we found that the presence of physical and mental comorbid disorders substantially increases the risk of making a suicide attempt among treatment-seeking patients with depression in a medical center setting. Elevations in circulating markers of systemic inflammation like CRP are likewise associated with risk of suicide attempt, however, these markers do not appear to contribute additional information regarding risk among patients with chronic physical diseases. Our findings suggest that health care providers, especially primary care providers who manage a wide array of chronic conditions, should carefully consider the risk of suicide attempt in patients who present with depression and co-occurring chronic physical diseases. Moreover, mental health providers caring for patients with depression should likewise monitor the course of chronic physical diseases. The routine use of CRP measurement in the assessment of suicide risk is not supported by our study.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718003902.

Author ORCIDs. James W Murrough, 0000-0001-6286-1242.

Acknowledgements. We thank Ezra Fass for help with data extraction, and Jane Pirkis for her comments on this manuscript.

Author contributions. Ms Oh and Drs Van Dam, Doucette, and Murrough made substantial contributions to the conception or design of the work, analysis and interpretation of data for the work, and drafting of the work or revising it critically for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work.

Financial support. Funding for this work was provided by the Friedman Brain Institute and the Ehrenkranz Laboratory for Human Resilience, both components of the Icahn School of Medicine at Mount Sinai (grant number 02856865). The funding bodies had no role in the design, conduct, analysis, interpretation of the work, or in the preparation or approval of the manuscript.

Conflict of interest. In the past 3 years, Dr Murrough has provided consultation services to Allergan, Fortress Biotech, Novartis, Janssen Research and Development, Genentech, ProPhase, and Global Medical Education and has received research support from Avanir Pharmaceuticals. All other authors disclose no conflict of interest.

References

Ahmedani BK, Simon GE, Stewart C, Beck A, Waitzfelder BE, Rossom R, Lynch F, Owen-Smith A, Hunkeler EM, Whiteside U, Operskalski BH, Coffey MJ and Solberg LI (2014) Health care contacts in the year before suicide death. *Journal of General Internal Medicine* **29**, 870–877.

Batty GD, Bell S, Stamatakis E and Kivimaki M (2016) Association of systemic inflammation with risk of completed suicide in the general population. *JAMA Psychiatry* **73**, 993–995.

Beevers CG and Miller IW (2004) Perfectionism, cognitive bias, and hopelessness as prospective predictors of suicidal ideation. *Suicide and Life-Threatening Behavior* **34**, 126–137.

Black C and Miller BJ (2015) Meta-analysis of cytokines and chemokines in suicidality: distinguishing suicidal versus nonsuicidal patients. *Biological Psychiatry* **78**, 28–37.

Caceda R, Griffin WST and Delgado PL (2018) A probe in the connection between inflammation, cognition and suicide. *Journal of Psychopharmacology* **32**, 482–488.

Chang CC, Tzeng NS, Kao YC, Yeh CB and Chang HA (2017) The relationships of current suicidal ideation with inflammatory markers and heart rate variability in unmedicated patients with major depressive disorder. *Psychiatry Research* **258**, 449–456.

Courtet P, Jaussent I, Genty C, Dupuy AM, Guillaume S, Ducasse D and Olie E (2015) Increased CRP levels may be a trait marker of suicidal attempt. *European Neuropsychopharmacology* **25**, 1824–1831.

Crump C, Sundquist K, Sundquist J and Winkleby MA (2014) Sociodemographic, psychiatric and somatic risk factors for suicide: a Swedish national cohort study. *Psychological Medicine* **44**, 279–289.

Cukrowicz KC, Cheavens JS, Van Orden KA, Ragain RM and Cook RL (2011) Perceived burdensomeness and suicide ideation in older adults. *Psychology and Aging* **26**, 331–338.

Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R and Caspi A (2008) Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Archives of General Psychiatry* **65**, 409–415.

Dieperink E, Ho SB, Tetrick L, Thuras P, Dua K and Willenbring ML (2004) Suicidal ideation during interferon-alpha2b and ribavirin treatment of patients with chronic hepatitis C. *General Hospital Psychiatry* **26**, 237–240.

Garcia-Rizo C, Fernandez-Egea E, Miller BJ, Oliveira C, Justicia A, Griffith JK, Heaphy CM, Bernardo M and Kirkpatrick B (2013) Abnormal glucose tolerance, white blood cell count, and telomere length in newly diagnosed, antidepressant-naive patients with depression. *Brain, Behavior, and Immunity* **28**, 49–53.

Gibbs HM, Davis L, Han X, Clothier J, Eads LA and Caceda R (2016) Association between C-reactive protein and suicidal behavior in an adult inpatient population. *Journal of Psychiatric Research* **79**, 28–33.

Gorton HC, Webb RT, Kapur N and Ashcroft DM (2016) Non-psychotropic medication and risk of suicide or attempted suicide: a systematic review. *BMJ Open* **6**, e009074.

Grudet C, Malm J, Westrin A and Brundin L (2014) Suicidal patients are deficient in vitamin D, associated with a pro-inflammatory status in the blood. *Psychoneuroendocrinology* **50**, 210–219.

Hamer M, Chida Y and Stamatakis E (2010) Association of very highly elevated C-reactive protein concentration with cardiovascular events and all-cause mortality. *Clinical Chemistry* **56**, 132–135.

Harrison M (2015) Erythrocyte sedimentation rate and C-reactive protein. *Australian Prescriber* **38**, 93–94.

Hawton K, Casanas ICC, Haw C and Saunders K (2013) Risk factors for suicide in individuals with depression: a systematic review. *Journal of Affective Disorders* **147**, 17–28.

Henriksson MM, Aro HM, Marttunen MJ, Heikkinen ME, Isometsa ET, Kuoppasalmi KI and Lonnqvist JK (1993) Mental disorders and comorbidity in suicide. *American Journal of Psychiatry* **150**, 935–940.

Holma KM, Haukka J, Suominen K, Valtonen HM, Mantere O, Melartin TK, Sokero TP, Oquendo MA and Isometsa ET (2014) Differences in incidence of suicide attempts between bipolar I and II disorders and major depressive disorder. *Bipolar Disorders* **16**, 652–661.

Karlovic D, Serretti A, Vrkic N, Martinac M and Marcinko D (2012) Serum concentrations of CRP, IL-6, TNF-alpha and cortisol in major depressive disorder with melancholic or atypical features. *Psychiatry Research* **198**, 74–80.

Loas G, Dalleau E, Lecointe H and Yon V (2016) Relationships between anhedonia, alexithymia, impulsivity, suicidal ideation, recent suicide attempt, C-reactive protein and serum lipid levels among 122 inpatients with mood or anxious disorders. *Psychiatry Research* **246**, 296–302.

Lopresti AL, Maker GL, Hood SD and Drummond PD (2014) A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **48**, 102–111.

Lund-Sorensen H, Benros ME, Madsen T, Sorensen HJ, Eaton WW, Postolache TT, Nordentoft M and Erlangsen A (2016) A nationwide cohort study of the association between hospitalization with infection and risk of death by suicide. *JAMA Psychiatry* **73**, 912–919.

Mann JJ (2002) A current perspective of suicide and attempted suicide. *Annals of Internal Medicine* **136**, 302–311.

Mann JJ (2003) Neurobiology of suicidal behaviour. *Nature Reviews Neuroscience* **4**, 819–828.

Melhem NM, Munroe S, Marsland A, Gray K, Brent D, Porta G, Douaihy A, Laudenslager ML, DePietro F, Diler R, Driscoll H and Gopalan P (2017) Blunted HPA axis activity prior to suicide attempt and increased inflammation in attempters. *Psychoneuroendocrinology* **77**, 284–294.

Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V and Ustun B (2007) Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *The Lancet* **370**, 851–858.

National Center for Health Statistics (Atlanta; 2010) International Classification of Diseases, Ninth Revision, Clinical Modification. CDC.

O'Donovan A, Rush G, Hoatam G, Hughes BM, McCrohan A, Kelleher C, O'Farrelly C and Malone KM (2013) Suicidal ideation is associated with elevated inflammation in patients with major depressive disorder. *Depression and Anxiety* **30**, 307–314.

Park RJ and Kim YH (2017) Association between high sensitivity CRP and suicidal ideation in the Korean general population. *European Neuropsychopharmacology* **27**, 885–891.

Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon III RO, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith Jr SC, Taubert K, Tracy RP and Vinicor F (2003) Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* **107**, 499–511.

Priya PK, Rajappa M, Kattimani S, Mohanraj PS and Revathy G (2016) Association of neurotrophins, inflammation and stress with suicide risk in young adults. *Clinica Chimica Acta* **457**, 41–45.

R Core Team (2015) R: A Language and Environment for Statistical Computing. *R Foundation for Statistical Computing*.

Raison CL and Miller AH (2011) Is depression an inflammatory disorder? *Current Psychiatry Reports* **13**, 467–475.

Shanahan L, Freeman J and Bauldry S (2014) Is very high C-reactive protein in young adults associated with indicators of chronic disease risk? *Psychoneuroendocrinology* **40**, 76–85.

Taylor PJ, Gooding P, Wood AM and Tarrier N (2011) The role of defeat and entrapment in depression, anxiety, and suicide. *Psychological Bulletin* **137**, 391–420.

The PLOS Medicine Editors (2014) Observational studies: getting clear about transparency. *PLoS Medicine* **11**, e1001711.

Turecki G and Brent DA (2016) Suicide and suicidal behaviour. *The Lancet* **387**, 1227–1239.

van Heeringen K and Mann JJ (2014) The neurobiology of suicide. *The Lancet Psychiatry* **1**, 63–72.

Vargas HO, Nunes SO, Pizzo de Castro M, Bortolasci CC, Sabbatini Barbosa D, Kaminami Morimoto H, Venugopal K, Dodd S, Maes M and Berk M (2013) Oxidative stress and lowered total antioxidant status are associated with a history of suicide attempts. *Journal of Affective Disorders* **150**, 923–930.

Visser M, Bouter LM, McQuillan GM, Wener MH and Harris TB (1999) Elevated C-reactive protein levels in overweight and obese adults. *JAMA* **282**, 2131–2135.

Waern M, Rubenowitz E, Runeson B, Skoog I, Wilhelmson K and Allebeck P (2002) Burden of illness and suicide in elderly people: case–control study. *BMJ* **324**, 1355.

Webb RT, Kontopantelis E, Doran T, Qin P, Creed F and Kapur N (2012) Suicide risk in primary care patients with major physical diseases: a case–control study. *Archives of General Psychiatry* **69**, 256–264.

Weissman MM, Bland R, Joyce PR, Newman S, Wells JE and Wittchen H-U (1993) Sex differences in rates of depression: cross-national perspectives. *Journal of Affective Disorders* **29**, 77–84.

World Health Organization (2014) Preventing suicide: a global imperative. (http://www.who.int/mental_health/suicide-prevention/world_report_2014/en/). Accessed 9 November 2018.