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Abstract

Background

Biological markers of suicide risk have the potential to inform prevention and treatment efforts. It has recently been hypothesised that inflammation may influence mood and in turn suicide risk. We investigated the association between indicators of systemic inflammation and suicide in a large cohort of Taiwanese adults.

Methods

White blood cell (WBC) count and levels of C-reactive protein (CRP) were measured in 462,747 and 359,849 adults in the Taiwan MJ cohort, respectively. The associations between WBC, CRP and suicide risk were investigated using Cox proportional hazards models adjusting for a range of potential confounding factors.

Results

During a mean 15.1 and 15.8 years of follow-up, 687 and 605 suicides were identified in participants who had information on WBC and CRP respectively. There was an association of suicide with WBC count (adjusted hazard ratio [aHR] = 1.13 per 1 standard deviation increase of log-transformed WBC, 95% confidence interval [CI] 1.09, 1.77). The association was driven by the highest quintile of WBC count (aHR = 1.39, 95% CI 1.09, 1.77; reference: the lowest quintile). No association between CRP and suicide was found.

Limitations

Our cohort was from a privately-run health check-up programme and had a lower suicide rate than that in the general population.

Conclusions

Individuals with the highest WBC counts may have increased risk of suicide. Peripheral markers of inflammation are potential biomarkers of suicide risk; however, this seems to vary by population and the marker investigated and could be influenced by a range of confounding factors.

Key words (3-6)

Inflammation, suicide, white blood cell count, C-reactive protein, Taiwan, cohort

Evidence for an association between inflammatory markers and suicide: a cohort study based on 359,849 to 462,747 Taiwanese adults

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[1]Evidence for an association between inflammatory markers and suicide: a cohort study based on 359,849 to 462,747 Taiwanese adults

Introduction

Suicide is a leading cause of death and a major public health concern (World Health Organization, 2014). Biological markers of suicide risk have the potential to inform the identification and management of those at risk. Elevated levels of circulating inflammatory markers, indicating an activation of the immune system, have been found to be associated with suicide in cross-sectional, post-mortem and clinical studies (Black and Miller, 2015; Brundin et al., 2017; Brundin et al., 2015). Due to the biological plausibility of inflammation causally influencing mood and neurobiological physiology and processes related to suicidal behaviour (Brundin et al., 2017; Felger et al., 2016), large prospective cohorts have been used to investigate the association between inflammatory markers and suicidal behaviour. Two recent cohort studies suggested that systematic inflammation, indicated by increased levels of white blood cell (WBC) count or serum C-reactive protein (CRP), was associated with later risk of suicide (Batty et al., 2016; Batty et al., 2018). We aimed to investigate whether there was an association between peripheral indicators of systemic inflammation and the likelihood of dying by suicide in a large cohort of adults from Taiwan.

Methods

Sample

The study sample was drawn from the Taiwan MJ cohort: a prospective cohort of over half a million Taiwanese adults aged 20 years or older who participated in a large health check-up programme run by MJ Health Management Institution, Taipei (http://www.mjclinic.com.tw/) (Strand et al., 2018; Wu et al., 2017). From 1996, the programme included a self-completed questionnaire to collect baseline information on sociodemographic and health-related factors. In 1996-2017, 561,495 individuals participated. After excluding those with missing information on covariates, data on 462,747 (82%) and 359,849 (64%) participants with information on WBC count and CRP, respectively, were used in the current analysis. Data for CRP were less complete as a number of participants chose not to pay for testing. Amongst participants with information on WBC count (n=462,747), those who also had information on CRP level (n=354,078) were older (mean age 41.2 vs 35.5 years) and more likely to be females (51.8% vs 47.4%) than those who did not have CRP information (n=108,669). The China Medical University Hospital Ethics Committee approved the research protocol. The study was also

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approved by National Health Research Institutes, Taiwan, and the MJ Health Management Institution.

Exposures

We utilised two measures of inflammation: WBC count and CRP, measured in blood samples taken at enrollment. WBC count was calculated from the number of neutrophils, lymphocytes, eosinophils, monocytes and basophils in the blood sample per litre. Participants (males and females separately), were divided into quintiles based on WBC count after excluding individuals with values $<3.5 \times 10^9$/L or $\geqslant 12.5\times 10^9$/L that would indicate reduced immune function or acute infections respectively (Tong et al., 2004). CRP is an acute phase protein released by the liver in response to upstream release of inflammatory markers (Clyne and Olshaker, 1999). Participants were grouped into the following categories based on their CRP levels: <1.1, 1.1-2.0, 2.1-3.0, 3.1-5.0, and 5.1-10.0 mg/L. We excluded individuals with values >10 mg/L, considered to indicate acute infections (Clyne and Olshaker, 1999).

Outcome

Suicides were identified through linkage to Taiwan's national cause-of-death registry up to 12th June 2019, the latest date when data were available, using the national identification numbers. The following International Classification of Diseases, Ninth (ICD-9) or Tenth (ICD-10) Revision codes were used to identify suicides: ICD-9 E950–E959 and ICD-10 X60-X84. We also included deaths that were likely to be misclassified suicides, including deaths of undetermined intent (ICD-9 E980–E989; ICD-10 Y10-Y34), accidental pesticide poisoning (ICD-9 E863; ICD-10 X48), and accidental suffocation (ICD-9 E913; ICD-10 W75, W76, W83, W84) (Chang et al., 2010).

Covariates

At enrollment, cohort members completed a questionnaire reporting age, sex, educational level, smoking (non-smoker, ex-smoker, current smoker), alcohol drinking (non-drinker, occasional drinker, frequent drinker), physical activity (inactive, low, medium or above), and history of cancer, hypertension, diabetes, and heart diseases (yes/no). Physical activity was defined as in (Wu et al., 2017), classifying individuals by exercise volume calculated from self-reported exercise frequency, duration and intensity into inactive, low active [90 min/week or 15 min/day or 3.75-7.49 metabolic equivalents (MET)-h/week] and fully active (150min/week or 30 min/ day or 7.5MET-h/week). Hypertension was defined as the presence of any of the following: reporting a history of hypertension, taking any hypertensive drugs, a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg. Diabetes was defined as the presence of any of the following: reporting

a history of diabetes, taking diabetes medications or a fasting blood sugar ≥126 mmol/L. Height and weight were measured at baseline and were used to calculate body mass index (BMI).

Statistical analysis

Cox proportional hazards regression models were used to first investigate the risk of suicide for individuals in each WBC or CRP category, relative to individuals with the lowest levels of inflammatory markers. Hazard ratios (HRs) for risk of suicide and their 95% confidence intervals (CIs) were estimated. We also estimated HRs for suicide for each 1 standard deviation (SD) increase in log-transformed data of WBC and CRP. Non-linearity of association was investigated using a likelihood ratio test by comparing the goodness of fit of models including the WBC or CRP categories as a linear term and as a categorical variable. Time of entry was recruitment date; time of exit was 12th June 2019 or the date of death if earlier. Separate analyses were run for WBC count and CRP. The proportional hazards assumption was examined by plotting Schoenfeld residuals with time and examining their correlations. A total of 354,078 participants were included in both WBC-suicide analysis (77% of 462,747) and CRP-suicide analysis (98% of 359,849). Nearly all participants included in the CRP-suicide analysis were also included in the WBC-suicide analysis.

We first estimated models adjusted for age and/or sex only (model 1 in Appendix Table 1), with further models additionally adjusted for education (model 2), smoking (model 3), drinking (model 4), physical activity (model 5), BMI, its quadratic term and physical disease status (model 6), and finally all the above covariates (fully adjusted model; model 7). We examined any evidence for sex differences by including appropriate interaction terms in the regression models and estimating models separately for males and females. Finally, we repeated the analysis including those with extreme WBC and CRP levels (WBC count of <3.5 × 109/L or ≥ 12.5× 109/L; CRP >10 mg/L) to investigate whether findings were changed when including these participants.

Results

The study sample comprised 561,495 individuals: 462,747 (82%) and 359,849 (64%) had information on WBC count and CRP, respectively. Appendix Tables 2 and 3 show the distributions of covariates by WBC quintile and CRP level respectively. Increasing age (CRP only), higher BMI, low educational level, smoking, drinking, physical inactivity, and a history of cancer (CRP only), hypertension, diabetes, or heart diseases were found to be associated with higher levels of inflammation. The strongest associations were with smoking and diabetes (WBC) and education, hypertension, diabetes, and heart disease (CRP).

During a mean 15.1 and 15.8 years of follow-up, 687 and 605 suicides were identified in the 462,747 and 359,849 participants who had information on WBC count and CRP respectively. In the sex and

age-adjusted model, there was an association between WBC and suicide – hazard ratio for suicide was 1.21 (95% CI 1.12, 1.31) per 1 SD increase of log-transformed WBC data (Table 1). However, only participants in the highest WBC count quintile were at increased risk of suicide (HR 1.66, 95% CI 1.31, 2.11), relative to the lowest WBC count quintile.

The WBC-suicide association was weakened after controlling for potential confounding factors, particularly smoking (model 3 in Appendix Table 1), but there was still statistical evidence for a 13% increase in suicide risk per 1 SD increase of log-transformed WBC count (HR 1.13, 95% CI 1.05-1.22) after adjusting all covariates. Given that both education and smoking attenuated the association, we explored whether those who had less education were also more likely to be smokers and found this to be the case (Appendix Table 4). In the sample with complete information on WBC count, current smokers were more likely to have below university education than non-smokers (72.3% vs 58.8%).

The association with WBC count was mainly due to increased suicide risk amongst individuals in the highest WBC quintile (HR 1.39, 95% CI 1.09, 1.77) – test of non-linearity showed a better model fit when WBC quintiles were included as a categorical than continuous variable (p=0.042; Table 1). When restricting the analysis to participants who had information on both WBC count and CRP (n=354,078), the results were similar (HR per 1 SD increase in log-transformed WBC = 1.11, 95% CI 1.02, 1.21). There was statistical evidence for variations in the WBC-suicide association over the follow-up time – Schoenfeld residuals were associated with time (p=0.008). Analyses stratified by follow-up time showed that the WBC-suicide association was mainly observed in 0-4 and 5-9 years but not ≥10 years from the start of follow-up (Appendix Table 5). During 5-9 years of follow-up, WBC quintiles 2, 3, and 4 were also associated with suicide relative to the lowest quintile (HRs ranged 1.93-1.97), although the highest quintile still showed the strongest association (HR 3.14, 95% CI 2.00, 4.92).

There was no evidence for an association between CRP and suicide in any models (Table 1 and Appendix Table 1). In the fully adjusted model, the hazard ratio for suicide was 1.01 (95% CI 0.93, 1.10) per SD increase in log-transformed CRP. Finally, there was no evidence for sex difference in any associations (p values for interaction ranged 0.71-0.89 for WBC and 0.98-0.99 for CRP) (Appendix Table 1).

Our findings are robust to inclusion of extreme values of WBC ($<3.5 \times 10^9$/L or $\geq 12.5\times 10^9$/L) or CRP (>10 mg/L). When including an additional 7950 participants who had extreme values of WBC count (n=470,697), fully adjusted analyses showed a similar association between WBC count and suicide (HR per 1 SD increase in log-transformed WBC = 1.13, 95% CI 1.05, 1.22). When including an additional 10,001 participants who had extreme values of CRP (n=369,850), fully adjusted analyses

still showed no association between CRP and suicide (HR per 1 SD increase in log-transformed CRP = 1.04, 95% CI 0.97, 1.12).

Discussion

In this large cohort of Taiwanese adults, we found an association between systemic inflammation, indexed by the highest level of WBC count, and suicide after controlling for a range of potential confounding factors. The WBC-suicide association was mainly seen within 10 years of follow-up. In contrast, no association was found between CRP and suicide.

Our findings on WBC count are consistent with those from another large cohort that found an association between suicide risk and WBC count in Korean women (Batty et al., 2018) and a recent cross-sectional study that showed links between WBC count and increased suicide risk in adult women (Keaton et al., 2019). However, the Korean study found an increased risk of suicide in all WBC quartiles relative to the lowest quartile, and such associations were observed in women only (Batty et al., 2018). By contrast, we found an association mainly for the highest quintile of WBC count and no evidence of sex difference. Furthermore, the Korean study found little impact on their findings of controlling for a wide range of potential confounding factors, such as smoking. By contrast, we found marked attenuation of the WBC-suicide association after controlling for confounding factors, particularly education and smoking (see Appendix Table 1, models 2 and 3); this may suggest that socioeconomic factors such as education, which are closely related to smoking, are important potential confounding factors. Studies have also shown that those from socioeconomically deprived backgrounds are at an increased risk of suicide (Li et al., 2011). Smoking has been shown to be associated with WBC count in prior studies, with those who currently smoke having the highest WBC count, ex-smokers a lower count, and never-smokers the lowest (Higuchi et al., 2016; Smith et al., 2003). In addition, those who discontinue smoking have been shown to have falls in WBC count over the following years. The distribution of smokers across the WBC quintiles in our study reflects these previous findings, with 14.0% of the lowest quintile reporting current smoking compared with 33.2% in the highest quintile. The mechanism through which smoking impacts on WBC count in the long term is currently unknown; smoking and passive exposure to smoke are associated with increased risk of respiratory infections (Jayes et al., 2016). In the short term it is thought that nicotine stimulates the release of catecholamines and cortisol, which may both trigger increased WBC count (Smith et al., 2003). Of interest, both smoking and education attenuated the association in the same direction, with those who currently smoked being more likely to also have lower educational qualifications, and these factors may be markers for other factors associated with suicide risk but not measured in this study (e.g. diet, socioeconomic position).

The 39% increase in suicide risk associated with the highest quintile of WBC count is small compared to some other well-recognised risk factors, e.g. a previous suicide attempt, a history of psychiatric inpatient care, and low socioeconomic position (Franklin et al., 2017); nevertheless, suicide is complex and a recent systematic review of research published in 1965-2015 showed that the overall weighted odds ratio of all the potential predictors of suicide studied was 1.51 (95% CI 1.49, 1.54), i.e. a 51% increase in suicide risk (Franklin et al., 2017).

Our findings on CRP are inconsistent with a similar study exploring relationships between suicide and CRP in a UK sample; in particular, our study did not replicate the high hazard ratio of 4.2 for the highest CRP category reported by the investigators (Batty et al., 2016). It is possible that the factors (such as infections) leading to systemic inflammation differ by population, and that the association between inflammatory markers and suicide varies across populations. Studies have reported lower levels of CRP in East Asian populations compared with Caucasian populations (Saito et al., 2014), and if suicide risk is conferred by high absolute levels of CRP rather than relative levels, this may explain the discrepancy in our findings. By contrast, another study reported no significant difference in WBC count between Asian and white participants (Lim et al., 2015). This has implications for using peripheral inflammatory markers to index suicide risk across the globe, as some biomarkers may be population-specific and others may not.

Systemic inflammation is affected by many factors that may confound the association between inflammation and suicidal behaviour; failure to adequately control for these is a limitation in the field (Black and Miller, 2015). Potential confounders include ethnicity, smoking, alcohol and substance use, BMI, dietary habits, medication use, and inflammatory diseases (Bergmans et al., 2019; Black and Miller, 2015). However, we still found evidence of an association between the highest WBC count and suicide after adjusting for several of these factors. The relationship between inflammation and suicide is likely to be complex: inflammation has also been hypothesised to be a mediating mechanism underlying the association between infection and suicidal behaviour, and it may be that those who have raised WBC counts have a history of prior infections. Associations between hospitalisation for infections and self-harm or suicidal behaviour have been reported in studies utilising the Danish longitudinal registers (Gjervig Hansen et al., 2019; Lund-Sorensen et al., 2016).

Interest in the links between inflammation and suicidal behaviour stems from studies reporting immunological dysfunction in relation to psychopathology (Beumer et al., 2012; Black and Miller, 2015), and psychopathology may in turn lead to increased suicide risk; namely psychopathology may mediate the association between inflammation and suicide (Brundin et al., 2017). However,

although psychopathology is an important risk factor for suicide, not all deaths by suicide occur in the presence of psychiatric disorders (Milner et al., 2013). There is also an increasing body of evidence demonstrating the associations between inflammation and suicidal thought or behaviour independent of psychopathology (Courtet et al., 2016; Ganança et al., 2016). Prospective studies with repeated measures on inflammatory markers, psychopathology, and suicide outcomes are needed to study these relationships in order to better understand if they lie on interrelated causal pathways or are independent mechanisms conferring risk.

Limitations

There are several limitations of the study. First, study participants were drawn from a privately-run health programme and may have been more affluent than Taiwan's general population. The overall suicide rate in our cohort was lower than that in the general population (9.8-10.6 vs 14.8 per 100,000). However, the cohort showed similar characteristics such as the prevalence of smoking (23%) to that of the general population (Wen et al., 2005). Second, only the levels of the inflammatory markers measured at baseline assessment were investigated; repeated measures of inflammatory markers may provide further information about their associations with suicide. We also did not include potentially important factors such as past suicidal behaviour in the analysis as the data were not collected in the MJ cohort; however, past suicidal behaviour could itself be an outcome of inflammation rather than a confounding factor for the inflammation-suicide association and thus its adjustment may not be needed (Schisterman et al., 2009).

Our findings indicate that peripheral markers of inflammation may be potential biomarkers of suicide risk, and high WBC count is a candidate worth further exploration. However, the inflammation-suicide association may vary by population and the marker investigated and could be influenced by a range of confounding factors, e.g. smoking. Studies aimed at elucidating the pathophysiology of suicidal behaviour in order to identify biomarkers of risk should explore whether these vary by population, considering residual confounding, and continue to investigate alternative biomarkers beyond peripheral indicators of systemic inflammation.

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Tables

Table 1. Hazard ratio for suicide by white blood cell count (N=462,747) and C-reactive protein (N=359,849) level

Inflammation markers	Participants (N)	Suicide (n)	Age and sex adjusted HR	(95% CI)	Fully adjusted[a] HR	(95% CI)
White blood cell (WBC) count						
Quintile 1 (Q1)[b]	93,200	107	1.00		1.00	
Quintile 2 (Q2)[b]	93,565	127	1.12	(0.87 , 1.45)	1.10	(0.85 , 1.42)
Quintile 3 (Q3)[b]	88,299	132	1.23	(0.95 , 1.59)	1.16	(0.90 , 1.50)
Quintile 4 (Q4)[b]	95,967	127	1.05	(0.81 , 1.36)	0.95	(0.73 , 1.23)
Quintile 5 (Q5)[b]	91,716	194	1.66	(1.31 , 2.11)	1.39	(1.09 , 1.77)
p for non-linearity[c]					0.042	
Per 1 SD increase in log(WBC)[d]			1.21	(1.12 , 1.31)	1.13	(1.05 , 1.22)
C-reactive protein (CRP)						
<1.1 (mg/L)	242,628	393	1.00		1.00	
1.1-2.0 (mg/L)	54,433	95	1.01	(0.81 , 1.26)	1.02	(0.81 , 1.28)
2.1-3.0 (mg/L)	25,861	48	1.07	(0.79 , 1.45)	1.03	(0.78 , 1.43)
3.1-5.0 (mg/L)	21,966	45	1.18	(0.86 , 1.60)	1.15	(0.84 , 1.58)
5.1-10.0 (mg/L)	14,961	24	0.92	(0.61 , 1.39)	0.88	(0.58 , 1.33)
p for non-linearity[c]					0.830	
Per 1 SD increase in log(CRP)[d]			1.02	(0.94 , 1.10)	1.01	(0.93 , 1.10)

Note: Q: quintile; HR: hazard ratio; CI: confidence interval; SD: standard deviation

[a]Adjusted for age, sex, education, smoking, drinking, physical activity, body mass index (and its quadratic term) and history of cancer, hypertension, diabetes, and heart diseases.

[b]Participants, for males and females separately, were divided into quintiles based on white blood cell counts - values of quintiles 1-5 were 3.5-5.1, 5.2-5.9, 6.0-6.6, 6.7-7.7, and 7.8-12.4 10^9/L respectively in males and 3.5-4.7, 4.8-5.5, 5.6-6.2, 6.3-7.2, and 7.3-12.4 10^9/L respectively in females.

[c]p value of likelihood ratio test for non-linearity comparing the goodness of fit of models including the quintiles as a categorical variable and as a linear term. A smaller p value indicates stronger statistical evidence for non-linearity.

[d]Hazard ratios per 1 SD increase in log-transformed values of WBC or CRP. 1 SD change in log[WBC (10⁹/L)] = 0.24. 1 SD change in log[CRP (mg/L)] = 0.57.

Appendix (online supplementary material)

Appendix table 1. Hazard ratio for suicide by white blood cell count (N=462,747) and C-reactive protein (N=359,849) level after adjusting for a series of covariates

Inflammation markers	Participants (N)	Suicide (n)	Age and/or sex adjusted[a] (model 1)		Adjusted for age, sex and education (model 2)		Adjusted for age, sex and smoking (model 3)		Adjusted for age, sex and drinking (model 4)		Adjusted for age, sex and physical activity (model 5)		Adjusted for age, sex, BMI/BMI^2 and physical diseases (model 6)		Fully adjusted[b] (model 7)	
			HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
White blood cell count																
Total																
Quintile 1 (Q1)[c]	93,200	107	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Quintile 2 (Q2)[c]	93,565	127	1.12	(0.87 , 1.45)	1.10	(0.85 , 1.42)	1.09	(0.84 , 1.41)	1.12	(0.87 , 1.45)	1.13	(0.87 , 1.46)	1.14	(0.88 , 1.48)	1.10	(0.85 , 1.42)
Quintile 3 (Q3)[c]	88,299	132	1.23	(0.95 , 1.59)	1.18	(0.91 , 1.52)	1.16	(0.90 , 1.50)	1.22	(0.95 , 1.57)	1.23	(0.95 , 1.59)	1.26	(0.98 , 1.63)	1.16	(0.90 , 1.50)
Quintile 4 (Q4)[c]	95,967	127	1.05	(0.81 , 1.36)	0.97	(0.75 , 1.26)	0.95	(0.74 , 1.23)	1.03	(0.80 , 1.33)	1.05	(0.81 , 1.36)	1.09	(0.84 , 1.41)	0.95	(0.73 , 1.23)
Quintile 5 (Q5)[c]	91,716	194	1.66	(1.31 , 2.11)	1.47	(1.16 , 1.86)	1.42	(1.12 , 1.80)	1.61	(1.27 , 2.04)	1.66	(1.31 , 2.10)	1.73	(1.36 , 2.20)	1.39	(1.09 , 1.77)
Male																
Q1 (3.5-5.1 10^9/L)	43,891	58	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Q2 (5.2-5.9 10^9/L)	48,225	79	1.20	(0.85 , 1.68)	1.15	(0.82 , 1.62)	1.15	(0.82 , 1.62)	1.20	(0.85 , 1.68)	1.20	(0.85 , 1.68)	1.22	(0.87 , 1.71)	1.15	(0.82 , 1.61)
Q3 (6.0-6.6 10^9/L)	43,079	74	1.24	(0.88 , 1.76)	1.17	(0.83 , 1.65)	1.16	(0.82 , 1.63)	1.23	(0.87 , 1.73)	1.24	(0.88 , 1.75)	1.27	(0.90 , 1.79)	1.14	(0.81 , 1.61)
Q4 (6.7-7.7 10^9/L)	48,121	69	1.00	(0.70 , 1.42)	0.90	(0.64 , 1.28)	0.89	(0.63 , 1.26)	0.98	(0.69 , 1.39)	0.99	(0.70 , 1.40)	1.02	(0.72 , 1.46)	0.86	(0.61 , 1.23)
Q5 (7.8-12.4 10^9/L)	44,662	111	1.71	(1.24 , 2.35)	1.45	(1.05 , 1.99)	1.42	(1.03 , 1.97)	1.65	(1.20 , 2.27)	1.68	(1.22 , 2.32)	1.74	(1.26 , 2.41)	1.33	(0.96 , 1.85)
Female																
Q1 (3.5-4.7 10^9/L)	49,309	49	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Q2 (4.8-5.5 10^9/L)	45,340	48	1.03	(0.69 , 1.53)	1.01	(0.68 , 1.51)	1.01	(0.68 , 1.51)	1.02	(0.69 , 1.53)	1.03	(0.69 , 0.54)	1.05	(0.70 , 1.56)	1.02	(0.69 , 1.53)
Q3 (5.6-6.2 10^9/L)	45,220	58	1.22	(0.84 , 1.79)	1.18	(0.81 , 1.73)	1.19	(0.81 , 1.74)	1.21	(0.83 , 1.78)	1.23	(0.84 , 1.80)	1.26	(0.86 , 1.84)	1.20	(0.82 , 1.75)
Q4 (6.3-7.2 10^9/L)	47,846	58	1.12	(0.77 , 1.64)	1.06	(0.73 , 1.56)	1.07	(0.73 , 1.56)	1.10	(0.75 , 1.61)	1.13	(0.77 , 1.65)	1.16	(0.79 , 1.71)	1.08	(0.73 , 1.58)
Q5 (7.3-12.4 10^9/L)	47,054	83	1.61	(1.13 , 2.29)	1.48	(1.04 , 2.11)	1.45	(1.02 , 2.07)	1.56	(1.10 , 2.22)	1.62	(1.14 , 2.31)	1.69	(1.18 , 2.43)	1.45	(1.01 , 2.10)
p value for sex interaction			0.88		0.86		0.71		0.87		0.88		0.89		0.71	
C-reactive protein																
Total																
<1.1 (mg/L)	242,628	393	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
1.1-2.0 (mg/L)	54,433	95	1.01	(0.81 , 1.26)	1.00	(0.80 , 1.26)	1.00	(0.80 , 1.26)	1.01	(0.81 , 1.27)	1.01	(0.81 , 1.26)	1.02	(0.81 , 1.28)	1.02	(0.81 , 1.28)
2.1-3.0 (mg/L)	25,861	48	1.07	(0.79 , 1.45)	1.05	(0.78 , 1.42)	1.05	(0.78 , 1.42)	1.07	(0.79 , 1.44)	1.07	(0.79 , 1.45)	1.09	(0.80 , 1.47)	1.03	(0.78 , 1.43)
3.1-5.0 (mg/L)	21,966	45	1.18	(0.86 , 1.60)	1.15	(0.85 , 1.57)	1.15	(0.84 , 1.56)	1.17	(0.86 , 1.59)	1.18	(0.86 , 1.60)	1.19	(0.86 , 1.62)	1.15	(0.84 , 1.58)
5.1-10.0 (mg/L)	14,961	24	0.92	(0.61 , 1.39)	0.88	(0.58 , 1.34)	0.88	(0.58 , 1.33)	0.91	(0.60 , 1.37)	0.92	(0.61 , 1.39)	0.92	(0.60 , 1.39)	0.88	(0.58 , 1.33)

Male																
<1.1 (mg/L)	112,315	217	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
1.1-2.0 (mg/L)	28,352	54	0.98	(0.73 , 1.32)	0.98	(0.73 , 1.32)	0.97	(0.72 , 1.30)	0.98	(0.73 , 1.32)	0.98	(0.72 , 1.32)	0.97	(0.72 , 1.31)	0.97	(0.72 , 1.31)
2.1-3.0 (mg/L)	13,427	28	1.07	(0.72 , 1.59)	1.06	(0.71 , 1.57)	1.05	(0.71 , 1.56)	1.07	(0.72 , 1.58)	1.07	(0.72 , 1.59)	1.06	(0.71 , 1.58)	1.03	(0.69 , 1.53)
3.1-5.0 (mg/L)	11,142	27	1.24	(0.83 , 1.85)	1.22	(0.82 , 1.83)	1.20	(0.80 , 1.79)	1.23	(0.82 , 1.83)	1.23	(0.83 , 1.84)	1.21	(0.80 , 1.81)	1.18	(0.78 , 1.77)
5.1-10.0 (mg/L)	7,537	13	0.87	(0.50 , 1.53)	0.84	(0.48 , 1.48)	0.84	(0.48 , 1.47)	0.86	(0.49 , 1.50)	0.87	(0.50 , 1.53)	0.85	(0.48 , 1.49)	0.81	(0.46 , 1.42)
Female																
<1.1 (mg/L)	130,313	176	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
1.1-2.0 (mg/L)	26,081	41	1.08	(0.77 , 1.53)	1.07	(0.76 , 1.51)	1.09	(0.78 , 1.54)	1.09	(0.77 , 1.54)	1.09	(0.77 , 1.53)	1.11	(0.79 , 1.57)	1.11	(0.79 , 1.57)
2.1-3.0 (mg/L)	12,434	20	1.11	(0.70 , 1.78)	1.09	(0.68 , 1.73)	1.11	(0.70 , 1.78)	1.12	(0.70 , 1.78)	1.12	(0.70 , 1.78)	1.15	(0.72 , 1.84)	1.14	(0.71 , 1.83)
3.1-5.0 (mg/L)	10,824	18	1.14	(0.70 , 1.87)	1.11	(0.68 , 1.81)	1.12	(0.69 , 1.82)	1.13	(0.70 , 1.85)	1.15	(0.70 , 1.87)	1.18	(0.72 , 1.95)	1.14	(0.69 , 1.89)
5.1-10.0 (mg/L)	7,424	11	1.02	(0.55 , 1.88)	0.97	(0.53 , 1.80)	0.98	(0.53 , 1.82)	1.01	(0.55 , 1.87)	1.03	(0.56 , 1.90)	1.04	(0.56 , 1.96)	1.02	(0.54 , 1.91)
p value for sex interaction			0.99		0.98		0.98		0.98		0.99		0.99		0.98	

Note: BMI: body mass index; HR: hazard ratio; CI: confidence interval

aAge and sex adjusted for the total sample; age-adjusted only for sex-specific samples.

[b]Adjusted for age, sex, education, smoking, drinking, physical activity, body mass index (and its quadratic term) and history of cancer, hypertension, diabetes, and heart diseases.

[c]Participants, for males and females separately, were divided into quintiles based on white blood cell counts.

Appendix table 2. Distributions of covariates by quintile[a] of white blood cell count in the MJ cohort (N=462,747).

		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Covariates		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age		40.17 (13.0)	39.80 (13.1)	39.62 (13.2)	39.77 (13.3)	39.98 (13.6)
BMI (z-score)		-0.25 (0.8)	-0.10 (0.9)	0.00 (0.9)	0.11 (1.0)	0.28 (1.1)
		n (%)	n (%)	n (%)	n (%)	n (%)
Sex	Male	43891 (47.1)	48225 (51.5)	43079 (48.8)	48121 (50.1)	44662 (48.7)
	Female	49309 (52.9)	45340 (48.5)	45220 (51.2)	47846 (49.9)	47054 (51.3)
Education	Middle school or below	16948 (18.2)	17375 (18.6)	17463 (19.8)	20269 (21.1)	22142 (24.1)
	High school	17410 (18.7)	18378 (19.6)	17973 (20.4)	21483 (22.4)	22594 (24.6)
	Junior college	18965 (20.3)	19650 (21.0)	18743 (21.2)	20467 (21.3)	19015 (20.7)
	University or higher	39877 (42.8)	38162 (40.8)	34120 (38.6)	33748 (35.2)	27965 (30.5)
Smoking	Non-smoker	74179 (79.6)	69944 (74.8)	64243 (72.8)	65352 (68.1)	56460 (61.6)
	Ex-smoker	6008 (6.4)	6498 (6.9)	5654 (6.4)	5917 (6.2)	4773 (5.2)
	Current smoker	13013 (14.0)	17123 (18.3)	18402 (20.8)	24698 (25.7)	30483 (33.2)
Drinking	Non-drinker	77304 (82.9)	76002 (81.2)	71368 (80.8)	75781 (79.0)	70601 (77.0)
	Occasional drinker	9075 (9.7)	10150 (10.8)	9803 (11.1)	11440 (11.9)	11311 (12.3)
	Frequent drinker	6821 (7.3)	7413 (7.9)	7128 (8.1)	8746 (9.1)	9804 (10.7)
Physical activity	Inactive	41639 (44.7)	43492 (46.5)	43075 (48.8)	48596 (50.6)	49507 (54.0)
	Low	25976 (27.9)	25842 (27.6)	23762 (26.9)	25205 (26.3)	22879 (24.9)
	Medium or above	25585 (27.5)	24231 (25.9)	21462 (24.3)	22166 (23.1)	19330 (21.1)
History of cancer	No	91977 (98.7)	92611 (99.0)	87414 (99.0)	95048 (99.0)	90838 (99.0)
	Yes	1223 (1.3)	954 (1.0)	885 (1.0)	919 (1.0)	878 (1.0)
History of hypertension	No	80809 (86.7)	78824 (84.2)	72992 (82.7)	77430 (80.7)	70857 (77.3)
	Yes	12391 (13.3)	14741 (15.8)	15307 (17.3)	18537 (19.3)	20859 (22.7)
History of diabetes	No	90478 (97.1)	89999 (96.2)	84281 (95.4)	90641 (94.5)	84546 (92.2)
	Yes	2722 (2.9)	3566 (3.8)	4018 (4.6)	5326 (5.5)	7170 (7.8)
History of heart diseases	No	90445 (97.0)	90659 (96.9)	85432 (96.8)	92602 (96.5)	88132 (96.1)
	Yes	2755 (3.0)	2906 (3.1)	2867 (3.2)	3365 (3.5)	3584 (3.9)

[a]Participants, for males and females separately, were divided into quintiles based on white blood cell counts - values of quintiles 1-5 were 3.5-5.1, 5.2-5.9, 6.0-6.6, 6.7-7.7, and 7.8-12.4 109/L respectively in males and 3.5-4.7, 4.8-5.5, 5.6-6.2, 6.3-7.2, and 7.3-12.4 109/L respectively in females.

Appendix table 3. Distributions of covariates by level of C-reactive protein in the MJ cohort (N=359,849).

		<1.1 (mg/L)	1.1-2.0 (mg/L)	2.1-3.0 (mg/L)	3.1-5.0 (mg/L)	5.1-10.0 (mg/L)
Covariates		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age		39.78 (13.2)	43.45 (14.1)	44.41 (14.4)	45.35 (14.7)	45.89 (15.1)
BMI (z-score)		-0.16 (0.8)	0.25 (1.0)	0.43 (1.0)	0.58 (1.1)	0.67 (1.3)
		n (%)	n (%)	n (%)	n (%)	n (%)
Sex	Male	112315 (46.3)	28352 (52.1)	13427 (51.9)	11142 (50.7)	7537 (50.4)
	Female	130313 (53.7)	26081 (47.9)	12434 (48.1)	10824 (49.3)	7424 (49.6)
Education	Middle school or below	52098 (21.5)	15667 (28.8)	8250 (31.9)	7458 (34.0)	5435 (36.3)
	High school	59116 (24.4)	12691 (23.3)	6027 (23.3)	4925 (22.4)	3384 (22.6)
	Junior college	51399 (21.2)	10714 (19.7)	4688 (18.1)	3958 (18.0)	2534 (16.9)
	University or higher	80015 (33.0)	15361 (28.2)	6896 (26.7)	5625 (25.6)	3608 (24.1)
Smoking	Non-smoker	174555 (71.9)	37435 (68.8)	17586 (68.0)	14839 (67.6)	9964 (66.6)
	Ex-smoker	14980 (6.2)	3859 (7.1)	1759 (6.8)	1559 (7.1)	1071 (7.2)
	Current smoker	53093 (21.9)	13139 (24.1)	6516 (25.2)	5568 (25.3)	3926 (26.2)
Drinking	Non-drinker	192447 (79.3)	42442 (78.0)	19995 (77.3)	17002 (77.4)	11473 (76.7)
	Occasional drinker	28367 (11.7)	6362 (11.7)	2982 (11.5)	2468 (11.2)	1721 (11.5)
	Frequent drinker	21814 (9.0)	5629 (10.3)	2884 (11.2)	2496 (11.4)	1767 (11.8)
Physical activity	Inactive	119422 (49.2)	26912 (49.4)	12948 (50.1)	11117 (50.6)	7850 (52.5)
	Low	62777 (25.9)	13045 (24.0)	6147 (23.8)	5194 (23.6)	3535 (23.6)
	Medium or above	60429 (24.9)	14476 (26.6)	6766 (26.2)	5655 (25.7)	3576 (23.9)
History of cancer	No	240024 (98.9)	53702 (98.7)	25444 (98.4)	21615 (98.4)	14688 (98.2)
	Yes	2604 (1.1)	731 (1.3)	417 (1.6)	351 (1.6)	273 (1.8)
History of hypertension	No	205282 (84.6)	41124 (75.5)	18606 (71.9)	15054 (68.5)	9984 (66.7)
	Yes	37346 (15.4)	13309 (24.5)	7255 (28.1)	6912 (31.5)	4977 (33.3)
History of diabetes	No	233958 (96.4)	50601 (93.0)	23519 (90.9)	19413 (88.4)	12917 (86.3)
	Yes	8670 (3.6)	3832 (7.0)	2342 (9.1)	2553 (11.6)	2044 (13.7)
History of heart diseases	No	233095 (96.9)	52022 (95.6)	24523 (94.8)	20717 (94.3)	13987 (93.5)
	Yes	7533 (3.1)	2411 (4.4)	1338 (5.2)	1249 (5.7)	974 (6.5)

Appendix table 4. Cross tabulation of smoking and education covariates

		Non-smoker		Former-smoker		Current smoker	
		n	(%)	n	(%)	n	(%)
Education	Males and females						
	Middle school or below	67,277	(20.38)	6,467	(22.42)	20,453	(19.72)
	High school	59,704	(18.08)	6,990	(24.23)	31,144	(30.03)
	Junior college	67,201	(20.35)	6,207	(21.51)	23,432	(22.59)
	University or higher	135,996	(41.19)	9,186	(31.84)	28,690	(27.66)
	Male						
	Middle school or below	12,942	(11.15)	5,753	(23.55)	17,267	(19.73)
	High school	16,327	(14.07)	5,368	(21.97)	24,408	(27.89)
	Junior college	23,692	(20.42)	5,270	(21.57)	20,470	(23.39)
	University or higher	63,070	(54.36)	8,038	(32.90)	25,373	(28.99)
	Female						
	Middle school or below	54,335	(25.37)	714	(16.15)	3,186	(19.67)
	High school	43,377	(20.26)	1,622	(36.69)	6,736	(41.58)
	Junior college	43,509	(20.32)	937	(21.19)	2,962	(18.28)
	University or higher	72,926	(34.05)	1,148	(25.97)	3,317	(20.47)

Appendix table 5. Hazard ratio for suicide by the level of white blood cell count (N=462,747) and C-reactive protein (N=359,849) as well as the duration of follow-up (0-4, 5-9, and 10 years or more) after adjusting for potential confounding factors[a]

	0-4 years		5-9 years		10+ years	
Inflammation markers	HR[a]	(95% CI)	HR[a]	(95% CI)	HR[a]	(95% CI)
White blood cell (WBC) count						
Quintile 1 (Q1)[b]	1.00		1.00		1.00	
Quintile 2 (Q2)[b]	1.27	(0.73 , 2.19)	1.93	(1.21 , 3.09)	0.81	(0.56 , 1.17)
Quintile 3 (Q3)[b]	1.25	(0.72 , 2.15)	1.97	(1.22 , 3.19)	0.90	(0.63 , 1.29)
Quintile 4 (Q4)[b]	1.42	(0.83 , 2.44)	1.95	(1.21 , 3.15)	0.69	(0.48 , 1.00)
Quintile 5 (Q5)[b]	1.90	(1.14 , 3.14)	3.14	(2.00 , 4.92)	0.87	(0.61 , 1.23)
Per 1 SD increase in log(WBC)[c]	1.25	(1.07 , 1.46)	1.42	(1.25 , 1.61)	0.97	(0.86 , 1.09)
C-reactive protein (CRP)						
<1.1 (mg/L)	1.00		1.00		1.00	
1.1-2.0 (mg/L)	1.16	(0.73 , 1.84)	1.39	(0.96 , 2.00)	0.83	(0.59 , 1.18)
2.1-3.0 (mg/L)	1.01	(0.53 , 1.93)	1.51	(0.95 , 2.39)	0.78	(0.47 , 1.28)
3.1-5.0 (mg/L)	1.30	(0.71 , 2.37)	1.34	(0.81 , 2.24)	0.96	(0.59 , 1.57)
5.1-10.0 (mg/L)	0.24	(0.06 , 0.99)	0.92	(0.46 , 1.83)	1.00	(0.56 , 1.77)
Per 1 SD increase in log(CRP)[c]	0.93	(0.78 , 1.11)	1.08	(0.95 , 1.23)	0.96	(0.85 , 1.09)

Note: Q: quintile; HR: hazard ratio; CI: confidence interval; SD: standard deviation

[a]Adjusted for age, sex, education, smoking, drinking, physical activity, body mass index (and its quadratic term) and history of cancer, hypertension, diabetes, and heart diseases.

[b]Participants, for males and females separately, were divided into quintiles based on white blood cell counts - values of quintiles 1-5 were 3.5-5.1, 5.2-5.9, 6.0-6.6, 6.7-7.7, and 7.8-12.4 10^9/L respectively in males and 3.5-4.7, 4.8-5.5, 5.6-6.2, 6.3-7.2, and 7.3-12.4 10^9/L respectively in females.

[c]Hazard ratios per 1 SD increase in log-transformed values of WBC or CRP. 1 SD change in log[WBC (109/L)] = 0.24. 1 SD change in log[CRP (mg/L)] = 0.57.

Conflict of interest

None.

Author Statement

The research data are confidential and thus could not be provided.

Contributors

All authors have approved the final article. Contributions: AER, interpretation of data, wrote manuscript; BM, contributed to writing the manuscript, interpretation of data; CPW and SSC, study conceptualisation, conducting analysis and interpretation, critical revision of manuscript; DG study conceptualisation, analytic method, interpretation of data, critical revision of manuscript

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