Intelligence 68 (2018) 30–36

Contents lists available at ScienceDirect

Intelligence

journal homepage: www.elsevier.com/locate/intell

Does general intelligence moderate the association between inflammation and psychological distress?

Emily Midouhas*, Eirini Flouri, Efstathios Papachristou, Theodora Kokosi

Department of Psychology and Human Development, UCL Institute of Education, University College London, UK

ARTICLE INFO

Keywords:
Inflammation
Intelligence
Psychological distress
Understanding society

ABSTRACT

Research has shown that inflammation is implicated in the pathogenesis of mental health disorders, but not all individuals with such disorders have raised inflammatory markers. This study examined whether general intelligence may be a protective factor for 9666 adults aged 18–97 with elevated inflammation, measured with C-reactive protein (CRP), using data from the UK's Understanding Society. In multigroup analyses for males and females, multiple linear regression was used to model psychological distress dependent upon CRP, adjusting for a host of possible confounders including alcohol consumption, smoking status, history of cardiovascular disease or diabetes, physical exercise and obesity. Moderation by intelligence was tested with a multiplicative interaction term. Results showed that, in adjusted models, CRP was related to an increase in psychological distress in males ($\beta = .049$) but not females. Furthermore, intelligence moderated the effect of CRP on psychological distress in males ($\beta = -.037$), such that males with higher CRP levels were at lower risk with increased intelligence. In conclusion, general intelligence may protect male adults from the negative effects of inflammation on psychological distress.

1. Introduction

The link between inflammation and psychological distress was first made by Robert Smith (1991). His "macrophage theory of depression" proposed that enhanced production of proinflammatory cytokines is related to the pathogenesis of depression. Indeed, empirical studies have found significantly higher levels of circulating inflammatory markers including proinflammatory cytokines [e.g., interleukin 6 (IL-6)], as well as C-reactive protein (CRP), an acute phase protein synthesized in the liver, among clinical patients with psychiatric disorders, especially depression (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Kiecolt-Glaser, Derry, & Fagundes, 2015). Although few longitudinal studies have examined inflammatory markers and psychiatric problems (Khandaker, Pearson, Zammit, Lewis, & Jones, 2014), a much-cited meta-analysis (Howren, Lamkin, & Suls, 2009) of cross-sectional studies showed that effect sizes for depression are moderate, around $d = 0.25$ (for IL-6) and $d = 0.15$ (for CRP).

There are three main pathways through which inflammation may bring about mental health problems, mainly evidenced by animal models (Dantzer et al., 2008; Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011; Miller, Maletic, & Raison, 2009). Firstly, inflammation has been found to reduce the availability of serotonin and other neurotransmitters in the brain, associated with depression and anxiety. Secondly, it may be related to activation of the hypothalamic-pituitary-adrenal (HPA) axis. Thirdly, it may cause oxidative stress dysfunction in the brain including abnormal total antioxidant capacity, antioxidants, free radicals, oxidative damage and autoimmune response products (Liu et al., 2015 for a review). These effects may contribute to impaired mood, cognition and perception, all of which are associated with depression (Miller et al., 2009).

Although inflammation may be a risk factor for depression, not everyone with high levels of inflammatory markers develop depressive symptoms (Dantzer et al., 2008; Kiecolt-Glaser et al., 2015). Raison and Miller (2011) indicated that inflammatory markers are noticeably higher in roughly a third of depressed patients compared to comparison participants who are non-depressed. Therefore, inflammation is not required nor sufficient to bring on depressive symptoms (Glassman & Miller, 2007).

Intelligence is one individual characteristic that may be associated with such emotional resilience to inflammatory responses to illness, injury or stress, yet, to our knowledge, there has been no attempt to explore this possibility. There are two main reasons why we might see a moderating role for intelligence. Firstly, intelligence has been shown to enhance individuals' care of their own health and well-being through effective learning and good reasoning skills (Deary, Weiss, & Batty, 2010; Deary, Whiteman, Starr, Whalley, & Fox, 2004). Such skills are

* Corresponding author at: Department of Psychology and Human Development, UCL Institute of Education, University College London, 25 Woburn Square, London WC1H 0AA, UK.
E-mail address: emily.midouhas@ucl.ac.uk (E. Midouhas).

https://doi.org/10.1016/j.intell.2018.03.002
Received 20 April 2017; Received in revised form 24 January 2018; Accepted 1 March 2018
Available online 08 March 2018

useful in protecting against depressive symptoms through positive behaviours such as exercise, a healthy diet as well as minimizing alcohol and drug consumption. They are also important for adhering to complex treatment regimens to manage appropriately longstanding or other illnesses and physical conditions, also associated with depression. Secondly, stress brought on by negative life events is a cause of inflammation. Individuals with higher intelligence have been found to cope better with such stressors through superior problem-solving abilities and self-regulatory functioning (Breslau, Lucia, & Alvarado, 2006; Masten et al., 1999), which can reduce depressive symptoms or psychological distress, in general.

In the present study, we used data from Understanding Society, an annual longitudinal survey of around 40,000 households in the UK, to explore if, indeed, intelligence buffers the effect of inflammation (measured with CRP) on psychological distress (measured with the General Health Questionnaire). We adjusted for selected characteristics to rule out confounders, including education (Khandaker et al., 2014), age (Franceschi et al., 2000), history of cardiovascular disease or diabetes, smoking status, alcohol consumption, physical exercise and obesity. Elevated inflammation characterises several disorders and diseases (e.g., cardiovascular disease, diabetes, metabolic syndrome) related to a higher risk for depression or psychological distress (Shelton & Miller, 2010). Alcohol dependence and smoking have been found to be comorbid with depression as well as have inflammatory effects (Leclercq, De Saeger, Delzenne, de Timary, & Stärkel, 2014). Physically active individuals have lower inflammatory markers than their sedentary counterparts (Lancaster & Febbraio, 2014) and exercise's benefits for reductions in depressive or anxiety symptoms may be via lowering inflammation levels (Gleeson et al., 2011). Moreover, obesity is associated with depression (Luppino et al., 2010) and has been characterised as a state of chronic inflammation (Shelton & Miller, 2010).

We explored these relationships in males and females separately. Females are more at risk of psychological distress as well as of persistently high levels of CRP (Ishii et al., 2012). On the other hand, males are more susceptible than females to the effects of inflammation on psychological distress (Ramsey et al., 2016). There may be an increased susceptibility among males to dysregulation of acute inflammation and pro-inflammatory immune response (Fairweather, Frisancho-Kiss, & Rose, 2008) and greater proneness to infection. Furthermore, there may be different pathways from stress to inflammation for males and females (Toker, Shirom, Shapira, Berliner, & Melamed, 2005). As well as inflammation and psychological distress, cognitive ability has been shown to differ by gender, especially over time, albeit not consistently or in the same direction. Some studies suggest that women have greater age-related declines (Karlamangla et al., 2009; Van Dijk, Van Gerven, Van Boxtel, Van der Elst, & Jolles, 2008; Wu et al., 2012). Other studies have found that men do (Salthouse, 2014; Zelinski & Gilewski, 2003). Still other research shows similar patterns in both (Ferreira, Ferreira Santos-Galduróz, Ferri, & Fernandes Galduróz, 2014).

2. Method

2.1. Sample

Understanding Society is an annual longitudinal survey of over 40,000 households (at wave 1) in all four UK countries. It comprises the larger General Population Sample (GPS), a stratified (by Government Office Region [GOR], population density and minority ethnic density) clustered (within postal sectors) random sample of households recruited in 2009–2010 (wave 1) and a smaller component from the pre-existing British Household Panel Survey (BHPS). There have been six waves of interviews thus far. Biomedical measures including CRP and body mass index were taken during a nurse visit approximately five months after the main wave 2 interview (GPS participants) or wave 3 interview (BHPS participants) (McFall, Conolly, & Burton, 2014). Respondents were eligible to participate in the nurse visit if they had taken part in the corresponding main interview in English, were aged 16+, lived in England, Wales or Scotland and were not pregnant. Of these 35,875, 57.5% took part in the nurse visit. Further details of the sampling and timelines associated with data collection can be found at www.understandingsociety.ac.uk/documentation.

This study used data from GPS and BHPS participants taking part in either wave 2 or 3 (as this was when the inflammatory marker and mental health measures were taken). Our study participants were at least age 18 (ages ranged 18–97), had appropriate data from the nurse health assessment on CRP (see further information in Measures) as well as on the General Health Questionnaire (GHQ) at either wave 2 or 3 and had data on cognitive ability tests (taken in English) at wave 3 (n = 9666). In this sample, 4344 participants were male and 5322 were female.

2.2. Measures

C-reactive protein (*CRP*) was analysed from serum using the N latex CRP mono immunoassay on the Behring Nephelometer II Analyzer (Dade Behring, Milton Keynes, UK). Intra and inter assay coefficients of variation were < 2%. Systemic inflammation is defined as CRP > 3 mg/L levels. In line with previous research on CRP and depression (Valkanova, Ebmeier, & Allan, 2013), participants with CRP levels higher than 10 mg/L (likely due to infection) were excluded. We modelled CRP as a continuous indicator. We log transformed the variable for our main regression analyses given that it has a positively skewed distribution. We present the untransformed CRP data in the descriptive tables to aid in interpretation.

Psychological distress was measured with the General Health Questionnaire-12 (GHQ-12; Goldberg, 1972), a self-administered 12-item screening measure for minor psychiatric disorders. The questionnaire detects changes in normal functioning and caseness (the strong probability that an individual has a minor psychiatric disorder). The items focus on the inability to carry out normal activities and the appearance of new and distressing symptoms. They also cover feelings of strain, depression, inability to cope, anxiety-based insomnia and lack of confidence. Each item asks whether the respondent has recently experienced a particular symptom or behaviour, rated on 4-point frequency scales. We created a continuous variable using the established approach (Goldberg & Williams, 1991), as follows. The first two of the four response categories were scored as 0 and the latter two as 1. The total number of times a person indicated that their psychological state was worse than usual was then summed, giving a possible score ranging 0–12.

To measure *general intelligence* (*IQ*), a component score was derived from principal components analysis of the z-transformed scores on the five cognitive ability measures[1] (described below) administered in Understanding Society to those aged 16+. These multiple well-validated assessments are thought to measure general intelligence (or 'g'), which has been shown not to be dependent on the use of specific mental ability tasks (Johnson, Bouchard, Krueger, McGue, & Gottesman, 2004). Verbal declarative memory was measured with a summary score on tasks measuring immediate and delayed recall. Verbal fluency was measured with a test of semantic or category fluency. Working memory was measured with the Serial 7 Subtraction test (Huppert, Brayne, Gill, Paykel, & Beardsall, 1995). A number series test assessed fluid reasoning (Fisher, McArdle, McCammon, Sonnega, & Weir, 2013). Lastly, numerical problem solving was measured with a test that assesses skills in solving numerical problems encountered in everyday life. (For more details on the tests see Whitley et al., 2016.) The component score (using the first unrotated component) was transformed into a

[1] Only individuals completing the cognitive ability component in English were included in this analysis to avoid issues with comparability of tests in different languages. Roughly 1% of respondents had tests translated into other languages.

Table 1
Bias analysis of study variables between the analytic and the non-analytic samples.

	Analytic sample (n = 9666)		Non-analytic sample (n = 50,492)		
	Continuous variables				
	n	*M(SD)*	n	*M(SD)*	*T*
Age	9666	52.10(16.12)	3583	50.08(19.77)	−5.98*
IQ	9663	101.74(14.12)	31,260	99.46(15.22)	−13.08*
CRP	9666	2.07(2.00)	2153	2.10(2.03)	0.53
GHQ	9666	1.67(2.97)	41,733	1.87(3.04)	5.01*
Low alcohol consumption	9221	1.68(0.97)	32,109	1.89(1.08)	16.17*
	Categorical variables				
	n	%	n	%	X^2
CVD or diabetes status	715	10.8	3680	16.3	119.23*
Obesity	258	2.7	424	4.1	26.66*
Moderate physical activity	1256	15.2	4988	14.6	1.51
Former regular smoker	3935	68.7	13,327	55.8	317.52*
Current regular smoker	1701	29.7	9147	38.3	146.63*

Note: Means, %s and Ns are unweighted. CRP = C-reactive protein; CRP not log transformed. CVD = cardiovascular disease. GHQ = general health questionnaire. Non-analytic sample = Individuals who participated in waves 2 or 3 and who did not have data on CRP, IQ and GHQ.
* $p < 0.001$.

standardised IQ score with a mean of 100 and a standard deviation of 15 (Hanscombe et al., 2012).

Key covariates were age in years when CRP was measured and health-related behaviours and conditions. The health-related behaviours and conditions were *smoking status*, *cardiovascular disease (CVD) or diabetes status, physical activity*, *low alcohol consumption* and *obesity*. *Smoking status* indicated whether or not the participant was a current regular smoker, a former regular smoker or had never been a regular smoker (of at least one cigarette per week). Participants with a history of *cardiovascular disease* or *diabetes* (self-reported) had a cardiovascular disease or diabetes. *Physical activity* was defined as whether the participant engaged in one or more activities considered to be of moderate intensity at least three times per week. *Low alcohol consumption* was measured with the question 'how often have you had an alcoholic drink during the last 12 months?' with responses ranging 1 (*weekly*) to 4 (*never*). *Obesity* was defined as a body mass index of 30 or higher.

2.3. Analytic strategy

First, we investigated whether adults in our analytic sample ($n = 9666$) were different from adults not in the analytic sample ($n = 50{,}492$) on our study variables. Then we examined the descriptives of the sample of females and males as we stratified all of our analyses by gender. Following that, we inspected the Spearman's correlations between all variables in the regression models stratified by gender. Lastly, we carried out three linear regression multigroup models in Mplus 7.4 using maximum likelihood estimation with robust standard errors (MLR), computed using a sandwich estimator. In fitting the regression models, missing information was taken into account using the Full Information Maximum Likelihood (FIML) method provided by Mplus. FIML assumes that data are missing at random for continuous and categorical variables. Variances were specified for all independent variables with any missingness in order to retain the full analytic sample in the models. All models accounted for the complex sampling design of Understanding Society.[2] Standard errors and a chi-square test of model fit were computed taking into account stratification (by GOR, population density and minority ethnic density) and non-independence of observations due to cluster sampling (Asparouhov & Muthen, 2006).

All models were run for females and males in multigroup models. Model 1 tests the association between CRP and psychological distress adjusting for age. We tested whether the effect of age on GHQ was non-linear as there is existing evidence that risk of psychological distress peaks in middle adulthood and then again in late adulthood (ONS, 2016; ONS, 2013). This may be due to variations in roles and responsibilities during the different life phases. For example, middle adulthood for many individuals is characterised by caring for children and parents alongside managing work and other personal commitments, which can increase stress levels and therefore impinge on well-being. In the younger years and during retirement, individuals tend to have more free time to spend on endeavours which promote their well-being (ONS, 2016; ONS, 2013). Alternatively, there may be a cohort effect whereby the distributions of psychological distress for a given cohort are due to the unique social, economic and cultural experiences of that cohort, which will differ for other cohorts. There is some research supporting this in the UK (Sacker & Wiggins, 2002). In our sample, too, the age-GHQ association was non-linear for both males and females. Hence we also included an age-squared term in all models. Model 2 adjusts for the remaining covariates including CVD or diabetes status, obesity, physical activity, alcohol consumption, smoking status and IQ. Model 3 includes the interaction term for CRP and IQ. In order to avoid multicollinearity (i.e., Variance Inflation Factors (VIFs) > 4) in the regression models resulting from the strong correlation between IQ and CRP with their interaction term, and between age and its square, IQ, CRP, age and age^2 variables were mean centred by subtracting the overall mean from the respective variable values. The CRP × IQ interaction term therefore is the product of the centred IQ and CRP variables. Standardised regression coefficients are reported to allow for effect size comparisons.

3. Results

3.1. Descriptives

Table 1 shows the differences in all study variables for those in the analytic sample compared to those in the non-analytic sample (estimates were unweighted). The analytic sample had older participants and participants with higher IQ and lower psychological distress compared to the non-analytic sample. They were also less likely to have a

[2] The Mplus commands used were TYPE = COMPLEX in the ANALYSIS command along with the STRATIFICATION, CLUSTER AND WEIGHT options of the VARIABLE command.

Table 2
Descriptives of the study variables in the analytic sample by gender.

	Females (n = 5322)		Males (n = 4344)	
	n	%	n	%
CVD or diabetes status	321	8.2	394	10.9
Obesity	174	3.3	84	1.9
Moderate physical activity	711	15.2	545	14.8
Former regular smoker	1117	24.3	1415	29.0
Current regular smoker	908	19.8	795	21.9
	n	*M(SD)*	n	*M(SD)*
GHQ	5322	1.98(3.18)	4344	1.48(2.80)
CRP	5322	2.22(2.08)	4344	1.84(1.87)
IQ	5320	99.19(14.65)	4343	102.67(14.18)
Age	5322	48.61(17.50)	4344	48.20(17.59)
Low alcohol consumption	5067	1.90(1.05)	4154	1.54(0.91)

Note: Means and %s are weighted. Ns are unweighted. CVD = cardiovascular disease. GHQ = general health questionnaire. CRP = C-reactive protein; CRP not log transformed.

cardiovascular disease, to be obese and a current smoker. They also had a higher level of alcohol consumption. Table 2 contains the descriptive statistics for all study variables in the analytic sample (estimates were weighted). In the analytic sample, females and males had average psychological distress scores of 2 and 1.5 respectively. Average CRP for both females and males was 2. Females had a mean IQ of roughly 99 and males had a mean IQ of around 103. Statistically significant, albeit weak, Spearman's correlations (Tables 3 and 4) were found between lower psychological distress and higher CRP among both males and females. IQ was negatively associated with psychological distress and CRP (males) but only with CRP and not psychological distress (females). All covariates were also significantly related to psychological distress and CRP in both genders, except physical activity and smoking status (females).

3.2. Linear regression models

3.2.1. Relationship between CRP and psychological distress (unadjusted model)

In both males and females, an increase in CRP (log transformed and centred) was associated with greater psychological distress, adjusting for age (centred) and its square (centred; Model 1, Tables 4 and 5). In males and females, an increase in one year of age was related to a decrease, by, respectively, 0.07 and 0.05 standard deviation units, in psychological distress. Moreover, age was associated non-linearly to psychological distress for both males and females, as expected.

3.2.2. Relationship between CRP and psychological distress (adjusted model)

After adjusting for key covariates in Model 2 (Tables 5 and 6), the effect of CRP was attenuated for females. However, in males it remained statistically significant. The effect size reduced only slightly from 0.07 to 0.05. Among males, having a history of cardiovascular disease or diabetes, low alcohol consumption and being a current regular smoker were related significantly to more psychological distress. Having a higher IQ (centred) was associated with lower psychological distress. Among females, having a history of cardiovascular disease or diabetes, low alcohol consumption and being a current regular smoker were associated with more psychological distress. Engaging in moderate physical activity was related to less psychological distress. IQ failed marginally to be predictive of lower psychological distress in females.

3.2.3. Moderation of the relationship between CRP and psychological distress by IQ

Model 3 was fitted to test the (centred) interaction effect of CRP and IQ (Tables 5 and 6). VIF values in this fully adjusted model were very low, ranging from 1.01 to 1.12, indicating that none of the variables were highly collinear, including the CRP × IQ interaction term with the CRP and IQ main effects. Among males, the interaction term was significant and negative. We examined whether the main effects of CRP and IQ and their interaction were gender invariant in the fully adjusted models using Wald tests. The results suggested that only the interaction term (Wald $\chi^2(1) = 5.47$; $p = .02$) but not the main effects of CRP (Wald $\chi^2(1) = 1.65$; $p = .20$) or IQ (Wald $\chi^2(1) = 0.44$; $p = .51$) differed significantly between males and females.

To unpack the interactions between CRP and IQ in males, we plotted the predicted values of psychological distress for illustrative cases with high vs. medium/low CRP levels by IQ (Fig. 1). As the figure shows, differences in psychological distress by CRP are more prominent among those with a lower level of IQ.

Notes: High CRP refers to being in the top third of cases according to CRP levels. Low or medium CRP refers to being in the bottom or middle third of cases. IQ and CRP are grand mean centred.

3.2.4. Sensitivity analysis

Psychological distress measures were taken at either wave 2 or 3 but our cognitive tests were administered at wave 3 only. We therefore tested whether our results were the same when using the wave 2 compared with the wave 3 psychological distress measure. As IQ is fairly stable over time, we felt it was valid to regress psychological distress at wave 2 on IQ at wave 3. Our sensitivity analysis showed that results did not differ when using the wave 2 compared with the wave 3 measure of psychological distress.

Table 3
Spearman's correlations for main study variables (males).

Variables	1	2	3	4	5	6	7	8	9	10
1. GHQ	1	0.05**	−0.04*	0.02	−0.01	0.07**	0.03*	−0.11**	0.05**	0.07***
2. CRP		1	−0.12***	0.07***	−0.04*	0.06***	0.12***	0.19***	0.07***	0.09***
3. IQ			1	−0.18***	0.06**	−0.13***	−0.01	−0.30***	−0.09***	−0.09***
4. CVD or diabetes status				1	−0.08***	0.10***	0.09**	0.31**	0.13***	0.01
5. Moderate physical activity					1	−0.05**	−0.02	−0.07***	−0.02	−0.01
6. Low alcohol consumption						1	0.09***	−0.00	−0.04*	0.04
7. Obesity							1	−0.02	0.01	−0.01
8. Age								1	0.28***	−0.17***
9. Former regular smoker									1	−0.34***
10. Current regular smoker										1

Note. GHQ = general health questionnaire. CRP = C-reactive protein. CRP not log transformed. CVD = cardiovascular disease.
Former regular smoker (1 = yes, 0 = no) and current regular smoker (1 = yes, 0 = no).
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 4
Spearman's correlations for main study variables (females).

Variables	1	2	3	4	5	6	7	8	9	10
1. GHQ	1	0.03**	−0.01	0.08***	−0.05**	0.06***	0.06***	−0.10**	−0.00	0.09**
2. CRP		1	−0.13***	0.10***	−0.11***	0.11***	0.11***	0.13***	0.03*	0.04**
3. IQ			1	−0.17***	0.06***	−0.19***	−0.02	−0.29***	−0.02	−0.07***
4. CVD or diabetes status				1	−0.05**	0.15***	0.08***	0.25***	0.03	−0.01
5. Moderate physical activity					1	−0.06***	−0.04*	−0.07***	−0.01	−0.04**
6. Low alcohol consumption						1	0.08***	0.07***	−0.05**	0.03*
7. Obesity							1	−0.01	0.01	0.00
8. Age								1	0.10***	−0.16***
9. Former regular smoker									1	−0.27***
10. Current regular smoker										1

Note. GHQ = general health questionnaire. CRP = C-reactive protein. CRP not log transformed. CVD = cardiovascular disease. Former regular smoker (1 = yes, 0 = no) and current regular smoker (1 = yes, 0 = no).
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

4. Discussion

To the best of our knowledge, this is the first study to explore the role of general intelligence in moderating the association between inflammatory markers (CRP) and psychological distress in adults. We found that CRP was associated with greater psychological distress in males, but not females, after accounting for a range of confounders, including health behaviours (e.g., smoking and alcohol intake), history of cardiovascular disease and other physical health indicators (e.g., physical activity) often left out of studies examining inflammation and psychopathology (Miller et al., 2009).

Our finding regarding the association between CRP and psychological distress for men reflects evidence from other cross-sectional research linking inflammatory markers to psychopathology (Miller et al., 2009; Slavich & Irwin, 2014). A recent study, notably using longitudinal data, found links between high serum IL-6 at age 9 years and depressive and psychotic symptoms at 18 years, but did not find that CRP levels at age 9 predicted these symptoms (Khandaker et al., 2014). Our study looked at an older adult population, examining individuals from ages 18 to 97, which might explain the difference in findings. Furthermore, that study used a large sample ($n = 4585$) that was roughly half the size of our study's sample, which may also help to explain why they did not find this effect. The fact that we did not find this relationship in women is surprising given that women are more prone to both psychological distress (Bromet et al., 2011) and inflammation (Yang & Kozloski, 2011), as well as the negative mood and behaviour effects of inflammation (Derry, Padin, Kuo, Hughes, & Kiecolt-Glaser, 2015). However, as previously noted, a number of studies have found that inflammation is more strongly linked to psychological distress in males than in females (Ramsey et al., 2016). Although a number of possible reasons have been put forward, the mechanisms of this association need to be examined further.

Notably, we also found that among males having a higher IQ (relative to a lower IQ) was associated with less psychological distress. This was particularly the case for males with high CRP levels, such that males with high CRP levels were less affected in terms of their psychological distress if they had higher levels of general intelligence. Intelligence is a problem-solving capacity which has been shown to assist individuals in coping with their adverse situations and related stressors (Masten et al., 1999). Additionally, individuals with higher intelligence may better educate themselves about how to manage their health, both physical and mental, which means they are more likely to engage in behaviours that prevent ill health (or help with disease management), such as exercising more, eating more healthily, avoiding tobacco use and taking medication and treatments as prescribed (Deary et al., 2010; Mõttus et al., 2014; Murray, Johnson, Wolf, & Deary, 2011). Keeping healthy and managing one's physical health problems may help to stave off psychological distress. We adjusted for a number of these variables in our study. However, there are additional health-promoting behaviours for which we did not have data that may explain our finding. These include the extent to which participants might engage in identification of their own symptoms of psychological distress and consultation of a doctor for diagnosis and advice regarding treatment (Beier & Ackerman, 2003; Gottfredson, 2004).

Table 5
Standardised regression coefficients for psychological distress (males).

Predictors	Model 1			Model 2			Model 3		
	Coefficient	SE	95% CI	Coefficient	SE	95% CI	Coefficient	SE	95% CI
CRP log	0.072**	0.018	[0.036, 0.108]	0.049**	0.018	[0.013, 0.084]	0.051**	0.018	[0.015, 0.087]
Age	−0.066**	0.017	[−0.099, −0.032]	−0.081**	0.020	[−0.120, −0.041]	−0.082**	0.020	[−0.121, −0.043]
Age^2	−0.039*	0.019	[−0.077, −0.001]	−0.056**	0.019	[−0.094, −0.018]	−0.057**	0.019	[−0.095, −0.020]
CVD or diabetes status				0.042*	0.020	[0.003, 0.081]	0.041*	0.020	[0.002, 0.079]
Obesity				0.047	0.030	[−0.011, 0.105]	0.048	0.030	[−0.10, 0.106]
Moderate physical activity				0.001	0.019	[−0.036, 0.038]	−0.003	0.018	[−0.038, 0.031]
Low alcohol consumption				0.071**	0.021	[0.029, 0.113]	0.070**	0.022	[0.028, 0.112]
Former regular smoker				−0.004	0.018	[−0.039, 0.031]	−0.003	0.018	[−0.038, 0.031]
Current regular smoker				0.065**	0.021	[0.025, 0.106]	0.067**	0.021	[0.026, 0.107]
IQ				−0.052*	0.021	[−0.094, −0.010]	−0.055*	0.021	[−0.097, −0.013]
CRP log × IQ							−0.037*	0.018	[−0.073, −0.002]
Constant	1.576**	0.074	[1.430, 1.722]	1.095**	0.138	[0.823, 1.366]	1.086**	0.139	[0.814, 1.358]

Note. CRP log = C-reactive protein log transformed. CVD = cardiovascular disease. CRP log, IQ, CRP log × IQ, age and age^2 were grand mean centred.
* $p < 0.05$.
** $p < 0.01$.

Table 6
Standardised regression coefficients for psychological distress (females).

Predictors	Model 1			Model 2			Model 3		
	Coefficient	SE	95% CI	Coefficient	SE	95% CI	Coefficient	SE	95% CI
CRP log	0.046*	0.019	[0.008, 0.083]	0.015	0.019	[−0.022, 0.052]	0.018	0.019	[−0.018, 0.054]
Age	−0.090**	0.017	[−0.123, −0.056]	−0.122**	0.020	[−0.161, −0.084]	−0.121**	0.020	[−0.159, −0.082]
Age^2	−0.060**	0.020	[−0.098, −0.021]	−0.080**	0.019	[−0.118, −0.043]	−0.081**	0.019	[−0.118, −0.043]
CVD or diabetes status				0.088**	0.022	[0.045, 0.131]	0.088**	0.022	[0.045, 0.131]
Obesity				0.039	0.023	[−0.005, 0.083]	0.038	0.023	[−0.006, 0.082]
Moderate physical activity				−0.051**	0.017	[−0.085, −0.017]	−0.051**	0.017	[−0.085, −0.017]
Low alcohol consumption				0.063**	0.019	[0.027, 0.100]	0.063**	0.019	[0.027, 0.100]
Former regular smoker				0.032	0.018	[−0.003, 0.066]	0.032	0.018	[−0.003, 0.067]
Current regular smoker				0.120**	0.021	[0.079, 0.161]	0.120**	0.021	[0.079, 0.161]
IQ				−0.034	0.018	[−0.070, 0.001]	−0.036	0.018	[−0.071, 0.000]
CRP log × IQ							0.020	0.017	[−0.013, 0.053]
Constant	2.085**	0.071	[1.945, 2.225]	1.490**	0.130	[1.236, 1.744]	1.498**	0.130	[1.243, 1.753]

Note. CRP log = C-reactive protein log transformed. CVD = cardiovascular disease. CRP log, IQ, CRP log × IQ, age and age^2 were grand mean centred.
* $p < 0.05$.
** $p < 0.01$.

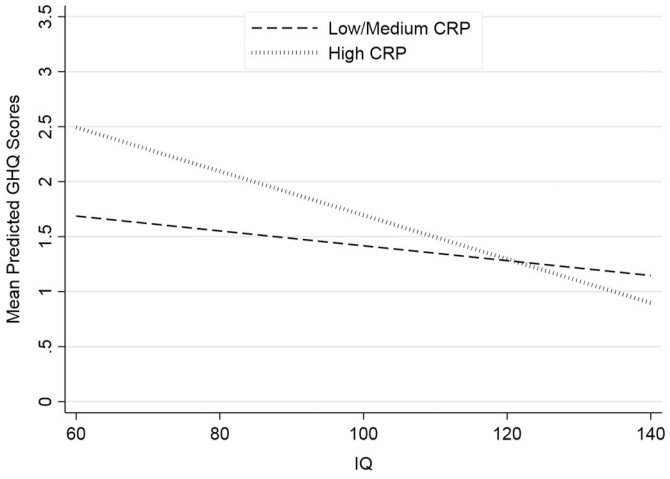

Fig. 1. Predicted values of psychological distress (GHQ) due to high vs. low/medium CRP by IQ (males).

Why was this effect seen only in males, however? We think this may be due to sex differences in biological mechanisms (beyond the scope of this study) and/or gender differences in confounders we did not consider, such as social integration. Social integration may refer to being married or in a partnership, participating in the labour force and having strong social networks. Research shows that marital or civil partnership status, labour force participation (and income) - all linked with intelligence (Strenze, 2007) - are more strongly related to psychological distress (depression in particular) in men than in women (Van de Velde, Bracke, & Levecque, 2010). Importantly, our finding that higher intelligence weakened the link between inflammation and psychological distress was also found for males only. Although a greater proportion of women than men in our sample had elevated inflammation, inflammation did not predict psychological distress in women. Future theory-driven research is needed to understand why.

The effects we identified for CRP, IQ and their interaction among male participants were small. They ranged from 0.04 to 0.06 standard deviation units. Confidence intervals further demonstrated the likely small effects of inflammation, IQ and their interplay. For example, the 95% CI for the interaction of inflammation and IQ was −0.002 to −0.073. Nevertheless, these associations are still important with regard to our understanding of the complexities of how biological and cognitive factors may work together to influence mental health.

The findings of the study should be considered in light of several additional limitations. First, the study is correlational and cross-sectional. Therefore, we are unable to infer the direction of the associations or establish whether there is a causal relationship between inflammation, IQ and psychological distress. For example, psychological distress may affect cognitive performance and inflammation. Future research should explore longitudinally the associations between these three variables, including the possible bidirectional links between them, using cross-lagged models of repeated measures. Second, there were some possible confounders left out of our study that might be accounted for in future research, such as adverse life events. Third, we could not test for the mechanisms through which general intelligence may protect adults who are psychologically at-risk due to high levels of inflammation, such as health management behaviour and positive coping responses to illness and stress, a priority for future research using longitudinal data. Lastly, we used only one inflammatory marker. Future studies should explore additional inflammatory markers, including IL-6.

Despite these limitations, our study has many strengths. In addition to examining a novel question about the protective role of intelligence in the inflammation-psychopathology link, these include the use of a large, nationally representative sample of adults at various ages across the lifespan and adjustment for important confounders of the associations tested.

5. Conclusions

In sum, higher intelligence may act as a buffer of the effect of inflammation, measured with CRP levels, on psychological distress in men. Longitudinal research is required, however, to establish the directionality of the associations between inflammation, psychological distress and cognitive ability.

Acknowledgements

This research was supported by a UK Economic and Social Research Council grant (ES/P001742/1).

References

Asparouhov, T., & Muthen, B. (2006). Comparison of estimation methods for complex survey data analysis. *Mplus web notes*.

Beier, M. E., & Ackerman, P. L. (2003). Determinants of health knowledge: An investigation of age, gender, abilities, personality, and interests. *Journal of Personality and Social Psychology, 84*(2), 439. http://dx.doi.org/10.1037/0022-3514.84.2.439.

Breslau, N., Lucia, V. C., & Alvarado, G. F. (2006). Intelligence and other predisposing factors in exposure to trauma and posttraumatic stress disorder: A follow-up study at age 17 years. *Archives of General Psychiatry, 63*(11), 1238–1245. http://dx.doi.org/10.1001/archpsyc.63.11.1238.

Bromet, E., Andrade, L. H., Hwang, I., Sampson, N. A., Alonso, J., De Girolamo, G., ...

Karam, A. N. (2011). Cross-national epidemiology of DSM-IV major depressive episode. *BMC Medicine, 9*(1), 90. http://dx.doi.org/10.1186/1741-7015-9-90.

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience, 9*(1), 46–56. http://dx.doi.org/10.1038/nrn2297.

Deary, I. J., Weiss, A., & Batty, G. D. (2010). Intelligence and personality as predictors of illness and death: How researchers in differential psychology and chronic disease epidemiology are collaborating to understand and address health inequalities. *Psychological Science in the Public Interest, 11*(2), 53–79. http://dx.doi.org/10.1177/1529100610387081.

Deary, I. J., Whiteman, M. C., Starr, J. M., Whalley, L. J., & Fox, H. C. (2004). The impact of childhood intelligence on later life: Following up the Scottish mental surveys of 1932 and 1947. *Journal of Personality and Social Psychology, 86*(1), 130. http://dx.doi.org/10.1037/0022-3514.86.1.130.

Derry, H. M., Padin, A. C., Kuo, J. L., Hughes, S., & Kiecolt-Glaser, J. K. (2015). Sex differences in depression: Does inflammation play a role? *Current Psychiatry Reports, 17*(10), 78. http://dx.doi.org/10.1007/s11920-015-0618-5.

Fairweather, D., Frisancho-Kiss, S., & Rose, N. R. (2008). Sex differences in autoimmune disease from a pathological perspective. *The American Journal of Pathology, 173*(3), 600–609. http://dx.doi.org/10.2353/ajpath.2008.071008.

Ferreira, L., Ferreira Santos-Galduróz, R., Ferri, C. P., & Fernandes Galduróz, J. C. (2014). Rate of cognitive decline in relation to sex after 60 years of age: A systematic review. *Geriatrics & Gerontology International, 14*(1), 23–31. http://dx.doi.org/10.1111/ggi.12093.

Fisher, G. G., McArdle, J. J., McCammon, R. J., Sonnega, A., & Weir, D. (2013). *New measures of fluid intelligence in the HRS.* Ann Arbor, Michigan: Institute for Social Research, University of Michigan.

Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., & De Benedictis, G. (2000). Inflamm-aging: An evolutionary perspective on immunosenescence. *Annals of the New York Academy of Sciences, 908*(1), 244–254. http://dx.doi.org/10.1111/j.1749-6632.2000.tb06651.x.

Glassman, A. H., & Miller, G. E. (2007). Where there is depression, there is inflammation… sometimes!. *Biological Psychiatry, 62*(4), 280–281. http://dx.doi.org/10.1016/j.biopsych.2007.05.032.

Gleeson, M., Bishop, N. C., Stensel, D. J., Lindley, M. R., Mastana, S. S., & Nimmo, M. A. (2011). The anti-inflammatory effects of exercise: Mechanisms and implications for the prevention and treatment of disease. *Nature Reviews Immunology, 11*(9), 607–615. http://dx.doi.org/10.1038/nri3041.

Goldberg, D. P. (1972). The detection of psychiatric illness by questionnaire. *Maudsley monograph. 21*. Oxford: Oxford University Press.

Goldberg, D., & Williams, P. (1991). *A user's guide to the General Health Questionnaire.* Windsor: NFER-Nelson.

Gottfredson, L. S. (2004). Intelligence: Is it the epidemiologists' elusive "fundamental cause" of social class inequalities in health? *Journal of Personality and Social Psychology, 86*(1), 174. http://dx.doi.org/10.1037/0022-3514.86.1.174.

Hanscombe, K. B., Trzaskowski, M., Haworth, C. M., Davis, O. S., Dale, P. S., & Plomin, R. (2012). Socioeconomic status (SES) and children's intelligence (IQ): In a UK-representative sample SES moderates the environmental, not genetic, effect on IQ. *PLoS One, 7*(2), e30320. http://dx.doi.org/10.1371/journal.pone.0030320.

Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosomatic Medicine, 71*(2), 171–186. http://dx.doi.org/10.1097/PSY.0b013e3181907c1b.

Huppert, F. A., Brayne, C., Gill, C., Paykel, E. S., & Beardsall, L. (1995). CAMCOG—A concise neuropsychological test to assist dementia diagnosis: Socio-demographic determinants in an elderly population sample. *British Journal of Clinical Psychology, 34*(4), 529–541. http://dx.doi.org/10.1111/j.2044-8260.1995.tb01487.x.

Ishii, S., Karlamangla, A. S., Bote, M., Irwin, M. R., Jacobs, D. R., Jr., Cho, H. J., & Seeman, T. E. (2012). Gender, obesity and repeated elevation of C-reactive protein: Data from the CARDIA cohort. *PLoS One, 7*(4), e36062. http://dx.doi.org/10.1371/journal.pone.0036062.

Johnson, W., Bouchard, T. J., Krueger, R. F., McGue, M., & Gottesman, I. I. (2004). Just one g: Consistent results from three test batteries. *Intelligence, 32*(1), 95–107. http://dx.doi.org/10.1016/S0160-2896(03)00062-X.

Karlamangla, A. S., Miller-Martinez, D., Aneshensel, C. S., Seeman, T. E., Wight, R. G., & Chodosh, J. (2009). Trajectories of cognitive function in late life in the United States: Demographic and socioeconomic predictors. *American Journal of Epidemiology, 170*(3), 331–342. http://dx.doi.org/10.1093/aje/kwp154.

Khandaker, G. M., Pearson, R. M., Zammit, S., Lewis, G., & Jones, P. B. (2014). Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: A population-based longitudinal study. *JAMA Psychiatry, 71*(10), 1121–1128. http://dx.doi.org/10.1001/jamapsychiatry.2014.1332.

Kiecolt-Glaser, J. K., Derry, H. M., & Fagundes, C. P. (2015). Inflammation: Depression fans the flames and feasts on the heat. *American Journal of Psychiatry, 172*(11), 1075–1091. http://dx.doi.org/10.1176/appi.ajp.2015.15020152.

Lancaster, G. I., & Febbraio, M. A. (2014). The immunomodulating role of exercise in metabolic disease. *Trends in Immunology, 35*(6), 262–269. http://dx.doi.org/10.1016/j.it.2014.02.008.

Leclercq, S., De Saeger, C., Delzenne, N., de Timary, P., & Stärkel, P. (2014). Role of inflammatory pathways, blood mononuclear cells, and gut-derived bacterial products in alcohol dependence. *Biological Psychiatry, 76*(9), 725–733. http://dx.doi.org/10.1016/j.biopsych.2014.02.003.

Liu, T., Zhong, S., Liao, X., Chen, J., He, T., Lai, S., & Jia, Y. (2015). A meta-analysis of oxidative stress markers in depression. *PLoS One, 10*(10), e0138904. http://dx.doi.org/10.1371/journal.pone.0138904.

Luppino, F. S., de Wit, L. M., Bouvy, P. F., Stijnen, T., Cuijpers, P., Penninx, B. W., & Zitman, F. G. (2010). Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. *Archives of General Psychiatry, 67*(3), 220–229. http://dx.doi.org/10.1001/archgenpsychiatry.2010.2.

Masten, A. S., Hubbard, J. J., Gest, S. D., Tellegen, A., Garmezy, N., & Ramirez, M. (1999). Competence in the context of adversity: Pathways to resilience and maladaptation from childhood to late adolescence. *Development and Psychopathology, 11*(1), 143–169.

McFall, S. L., Conolly, A., & Burton, J. (2014, March). Collecting biomarkers using trained interviewers. Lessons learned from a pilot study. *Survey Research Methods. 8. Survey Research Methods* (pp. 57–66). . No. 1 10.18148/srm/2014.v8i1.5471.

Miller, B. J., Buckley, P., Seabolt, W., Mellor, A., & Kirkpatrick, B. (2011). Meta-analysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. *Biological Psychiatry, 70*(7), 663–671. http://dx.doi.org/10.1016/j.biopsych.2011.04.013.

Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biological Psychiatry, 65*(9), 732–741. http://dx.doi.org/10.1016/j.biopsych.2008.11.029.

Mõttus, R., Johnson, W., Murray, C., Wolf, M. S., Starr, J. M., & Deary, I. J. (2014). Towards understanding the links between health literacy and physical health. *Health Psychology, 33*(2), 164. http://dx.doi.org/10.1037/a0031439.

Murray, C., Johnson, W., Wolf, M. S., & Deary, I. J. (2011). The association between cognitive ability across the lifespan and health literacy in old age: The Lothian Birth Cohort 1936. *Intelligence, 39*(4), 178–187. http://dx.doi.org/10.1016/j.intell.2011.04.001.

Office for National Statistics (2013). *Measuring national well-being – Health, 2013*.

Office for National Statistics (2016). *Measuring national well-being – at what age is personal well-being the highest?* .

Raison, C. L., & Miller, A. H. (2011). Is depression an inflammatory disorder? *Current Psychiatry Reports, 13*(6), 467–475. http://dx.doi.org/10.1007/s11920-011-0232-0.

Ramsey, J. M., Cooper, J. D., Bot, M., Guest, P. C., Lamers, F., Weickert, C. S., ... Bahn, S. (2016). Sex differences in serum markers of major depressive disorder in the Netherlands Study of Depression and Anxiety (NESDA). *PLoS One, 11*(5), e0156624. http://dx.doi.org/10.1371/journal.pone.0156624.

Sacker, A., & Wiggins, R. D. (2002). Age-period-effect on inequalities in psychological distress, 1981–2000. *Psychological Medicine, 32*, 977–990. http://dx.doi.org/10.1017/S0033291702006013.

Salthouse, T. A. (2014). Correlates of cognitive change. *Journal of Experimental Psychology: General, 143*(3), 1026. http://dx.doi.org/10.1037/a0034847.

Shelton, R. C., & Miller, A. H. (2010). Eating ourselves to death (and despair): The contribution of adiposity and inflammation to depression. *Progress in Neurobiology, 91*(4), 275–299. http://dx.doi.org/10.1016/j.pneurobio.2010.04.004.

Slavich, G. M., & Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological Bulletin, 140*(3), 774. http://dx.doi.org/10.1037/a0035302.

Smith, R. S. (1991). The macrophage theory of depression. *Medical Hypotheses, 35*(4), 298–306. http://dx.doi.org/10.1016/0306-9877(91)90272-Z.

Strenze, T. (2007). Intelligence and socioeconomic success: A meta-analytic review of longitudinal research. *Intelligence, 35*(5), 401–426. http://dx.doi.org/10.1016/j.intell.2006.09.004.

Toker, S., Shirom, A., Shapira, I., Berliner, S., & Melamed, S. (2005). The association between burnout, depression, anxiety, and inflammation biomarkers: C-reactive protein and fibrinogen in men and women. *Journal of Occupational Health Psychology, 10*(4), 344. http://dx.doi.org/10.1037/1076-8998.10.4.344.

Valkanova, V., Ebmeier, K. P., & Allan, C. L. (2013). CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies. *Journal of Affective Disorders, 150*(3), 736–744. http://dx.doi.org/10.1016/j.jad.2013.06.004.

Van de Velde, S., Bracke, P., & Levecque, K. (2010). Gender differences in depression in 23 European countries: Cross-national variation in the gender gap in depression. *Social Science & Medicine, 71*(2), 305–313. http://dx.doi.org/10.1016/j.socscimed.2010.03.035.

Van Dijk, K. R., Van Gerven, P. W., Van Boxtel, M. P., Van der Elst, W., & Jolles, J. (2008). No protective effects of education during normal cognitive aging: Results from the 6-year follow-up of the Maastricht Aging Study. *Psychology and Aging, 23*(1), 119. http://dx.doi.org/10.1037/0882-7974.23.1.119.

Whitley, E., Deary, I. J., Ritchie, S. J., Batty, G. D., Kumari, M., & Benzeval, M. (2016). Variations in cognitive abilities across the life course: Cross-sectional evidence from Understanding Society: The UK Household Longitudinal Study. *Intelligence, 59*, 39–50. http://dx.doi.org/10.1016/j.intell.2016.07.001.

Wu, Y., Zhang, D., Pang, Z., Oksuzyan, A., Jiang, W., Wang, S., ... Tan, Q. (2012). Gender-specific patterns in age-related decline in general health among Danish and Chinese: A cross-national comparative study. *Geriatrics & Gerontology International, 12*(3), 431–439. http://dx.doi.org/10.1111/j.1447-0594.2011.00784.x.

Yang, Y., & Kozloski, M. (2011). Sex differences in age trajectories of physiological dysregulation: Inflammation, metabolic syndrome, and allostatic load. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 66*((5), 493–500. http://dx.doi.org/10.1093/gerona/glr003.

Zelinski, E. M., & Gilewski, M. J. (2003). Effects of demographic and health variables on Rasch scaled cognitive scores. *Journal of Aging and Health, 15*(3), 435–464. http://dx.doi.org/10.1177/0898264303253499.