inflammation and individual symptoms of depression 15,366 12 8,030 15,366 12 8,030 Inter-University Consortium Inter-University Consortium IPD-Work Consortium IPD-Work Consortium UK Data Service UK Data Service for Political and Social for Political and Social Research Research 15,354 11 15,364 11 8,028 8,030 Missing data on Missing data on IL-6 Missing data on Missing data on Missing data on IL-6 Missing data on IL-6 CRP or depressive CRP or depressive CRP or depressive or depressive or depressive or depressive symptoms symptoms symptoms symptoms symptoms symptoms 12 1 2 2 1 0 Cohorts with data on CRP Cohorts with data on CRP Cohorts with data on CRP Cohorts with data on IL-6 Cohorts with data on IL-6 Cohorts with data on IL-6 and depressive symptoms 15 3 Independent cohort studies (CRP, cross-sectional) Independent cohort studies (IL-6, cross-sectional) of which 7 had repeat data on depression

Figure 1. Selection of studies for individual-participant pooled analysis of the association between systemic inflammation and individual symptoms of depression

Figure 2. Unadjusted and scrially adjusted cross-sectional association between C-reactive protein (CRP) and 24 symptoms of depression (random-effects meta-analysis).

Outcome	N (participants)/ N (studies)	Odds ratio (95% CI) per 1SD higher CRP*						
		Crude	Model 1	Model 2	Model 3	Model 4	Model 5	
Depression	56220 / 15		1.18 (1.14 - 1.22)	1.15 (1.11 - 1.18)	1.16 (1.12 - 1.20)	1.06 (1.03 - 1.10)	1.05 (1.02 - 1.09	
Depressive symptoms								
Had crying spells	9786/3	I	1.24 (1.00 - 1.53)	1.22 (0.98 - 1.51)	1.22 (0.99 - 1.51)	1.12 (0.92 - 1.36)	1.10 (0.94 - 1.30	
Changes in appetite †	34615 / 10	-	1.23 (1.18 - 1.27)	1.20 (1.16 - 1.24)	1.21 (1.17 - 1.26)	1.12 (1.07 - 1.18)	1.14 (1.09 - 1.19	
Felt everything was an effort †	27130 / 8	-	1.23 (1.12 - 1.36)	1.21 (1.11 - 1.32)	1.21 (1.10 - 1.34)	1.11 (1.04 - 1.19)	1.12 (1.04 - 1.2	
Thought you would be better off dead	22420 / 5	<del></del>	1.22 (1.06 - 1.39)	1.18 (1.03 - 1.36)	1.18 (1.03 - 1.34)	1.10 (0.95 - 1.27)	1.07 (0.93 - 1.24	
Little insterest in doing things †	31000/6	-	1.21 (1.16 - 1.26)	1.18 (1.13 - 1.23)	1.19 (1.14 - 1.24)	1.10 (1.05 - 1.15)	1.09 (1.04 - 1.14	
Could not get going †	50736 / 14		1.20 (1.16 - 1.24)	1.18 (1.14 - 1.23)	1.19 (1.14 - 1.23)	1.09 (1.06 - 1.13)	1.08 (1.05 - 1.12	
Feeling bad about yourself	22420 / 5		1.18 (1.12 - 1.24)	1.15 (1.09 - 1.21)	1.15 (1.09 - 1.20)	1.05 (0.99 - 1.11)	1.03 (0.97 - 1.09	
Could not shake off the blues	9786 / 3		1.16 (1.04 - 1.29)	1.14 (1.04 - 1.26)	1.16 (1.04 - 1.29)	1.03 (0.91 - 1.16)	1.03 (0.91 - 1.1	
People were unfriendly	12195 / 5	-	1.15 (0.97 - 1.36)	1.11 (0.95 - 1.31)	1.14 (0.96 - 1.35)	1.07 (0.90 - 1.27)	1.03 (0.85 - 1.2	
Life had been a failure	9786/3	-	1.15 (0.95 - 1.38)	1.14 (0.95 - 1.35)	1.15 (0.96 - 1.39)	1.06 (0.91 - 1.25)	1.07 (0.92 - 1.2	
Moving or speaking slowly or too fast	22420 / 5		1.14 (1.07 - 1.22)	1.11 (1.04 - 1.19)	1.11 (1.04 - 1.20)	1.06 (0.98 - 1.13)	1.04 (0.97 - 1.1	
Felt lonely	27130 / 8	-	1.13 (1.09 - 1.17)	1.10 (1.06 - 1.14)	1.12 (1.08 - 1.16)	1.05 (0.99 - 1.11)	1.04 (0.99 - 1.09	
Sleep problems †	55165 / 14		1.13 (1.09 - 1.17)	1.11 (1.07 - 1.15)	1.11 (1.08 - 1.15)	1.06 (1.02 - 1.10)	1.05 (1.01 - 1.09	
Felt depressed	54563 / 13		1.13 (1.09 - 1.18)	1.10 (1.06 - 1.14)	1.11 (1.06 - 1.16)	1.03 (1.00 - 1.07)	1.02 (0.98 - 1.0	
Trouble concentrating †	37821/9		1.12 (1.07 - 1.18)	1.11 (1.05 - 1.16)	1.11 (1.06 - 1.16)	1.07 (1.02 - 1.11)	1.07 (1.01 - 1.1	
People dislike me	11593 / 4		1.12 (0.90 - 1.39)	1.09 (0.88 - 1.35)	1.11 (0.90 - 1.35)	0.99 (0.78 - 1.25)	0.98 (0.78 - 1.2	
Felt unhappy	33329 / 9		1.11 (1.04 - 1.18)	1.09 (1.03 - 1.17)	1.10 (1.02 - 1.18)	1.05 (0.97 - 1.13)	1.04 (0.96 - 1.1	
Did not enjoy life	33329/9	-	1.10 (1.04 - 1.15)	1.08 (1.02 - 1.14)	1.08 (1.03 - 1.14)	1.03 (0.97 - 1.09)	1.02 (0.97 - 1.0	
Felt sad	26528 / 7		1.07 (1.01 - 1.12)	1.05 (1.01 - 1.10)	1.05 (1.01 - 1.10)	0.99 (0.94 - 1.05)	1.00 (0.95 - 1.0	
Talked less than usual	9786 / 3	-	1.06 (0.99 - 1.15)	1.05 (0.98 - 1.14)	1.06 (0.98 - 1.15)	1.00 (0.92 - 1.09)	1.00 (0.92 - 1.0	
Felt worse than others	9786 / 3		1.05 (0.97 - 1.13)	1.02 (0.96 - 1.10)	1.05 (0.96 - 1.15)	1.03 (0.95 - 1.12)	1.02 (0.95 - 1.1	
Bothered by things	9786 / 3		1.05 (0.94 - 1.16)	1.04 (0.95 - 1.15)	1.05 (0.95 - 1.16)	0.96 (0.85 - 1.09)	0.96 (0.86 - 1.0	
Felt hopeless about the future	10972 / 4		1.04 (0.97 - 1.11)	1.02 (0.95 - 1.10)	1.04 (0.98 - 1.10)	1.00 (0.92 - 1.09)	1.00 (0.92 - 1.0	
Felt fearful	9786/3		1.03 (0.87 - 1.23)	1.03 (0.86 - 1.22)	1.02 (0.84 - 1.25)	0.97 (0.77 - 1.22)	0.97 (0.76 - 1.2	

<sup>\*</sup>Model 1: adjusted for age and sex; Model 2: as Model 1 and additionally adjusted for education; Model 2: as Model 1 and additionally adjusted for health-related factors; Model 4: as Model 1 and additionally adjusted for behavioural factors; Model 5: adjusted for all of the above covariates.

<sup>†</sup> Statistically significant after all adjustments

Figure 3. Association between C-reactive protein (CRP) and 6 depression symptoms in subgroups, after additional adjustments and longitudinally (random-effects meta-analysis).

Depressive symptom N (participants)/							
outcome)	N (studies)	Odds ratio (95% CI)	per 1SD higher CRP*				
Men	(**************************************	1					
elt everything was an effort	13117 / 8		1.24 (1.06 - 1.4				
Changes in appetite	17766 / 10	_	1.27 (1.19 - 1.3				
ould not get going	24631 / 14		1.21 (1.13 - 1.2				
ttle interest in doing things	14530 / 6		1.26 (1.17 - 1.3				
leep problems	26601 / 14		1.15 (1.08 - 1.2				
rouble concentrating	19048 / 9		1.13 (1.05 - 1.2				
g			(				
omen	44040./0	_	4 24 /4 45 4 2				
elt everything was an effort	14013 / 8	_	1.24 (1.15 - 1.3				
hanges in appetite	16849 / 10		1.20 (1.12 - 1.2				
ould not get going	26105 / 14		1.19 (1.14 - 1.2				
ttle interest in doing things	16470 / 6		1.19 (1.13 - 1.2				
leep problems	28564 / 14	-	1.12 (1.08 - 1.1				
rouble concentrating	18773 / 9	_	1.12 (1.04 - 1.2				
ge group <60 years							
elt everything was an effort	9253 / 8		1.26 (1.13 - 1.4				
hanges in appetite	20139 / 10		1.27 (1.13 - 1.4				
ould not get going	24037 / 13	_	1.20 (1.13 - 1.2				
ttle interest in doing things	16725 / 6		1.20 (1.13 - 1.2				
leep problems	27550 / 14	-	1.15 (1.10 - 1.2				
rouble concentrating	23289 / 9		1.12 (1.03 - 1.2				
_			•				
ge group ≥60 years	17077 / 0		1 22 /1 07 1 4				
elt everything was an effort	17877 / 8		1.22 (1.07 - 1.4				
changes in appetite	14476 / 10		1.25 (1.17 - 1.3				
ould not get going	26568 / 13	_	1.21 (1.15 - 1.2				
ttle interest in doing things	14275 / 6		1.24 (1.17 - 1.3				
leep problems	27615 / 14	-	1.11 (1.03 - 1.1				
rouble concentrating	14532 / 9	_ <del>-</del>	1.13 (1.03 - 1.2				
epressed individuals							
elt everything was an effort	3864 / 8		1.15 (0.99 - 1.3				
hanges in appetite	3573 / 10		1.11 (1.02 - 1.2				
Could not get going	5864 / 14		1.17 (1.10 - 1.2				
ittle interest in doing things	3145 / 6	<del></del>	1.11 (1.04 - 1.1				
leep problems	6709 / 14	<b></b>	1.08 (1.02 - 1.1				
rouble concentrating	3981 / 9	-	1.03 (0.95 - 1.1				
djustment for ACE† elt everything was an effort	5737 / 3		1 10 /1 07 1 2				
hanges in appetite	17454 / 7	I	1.19 (1.07 - 1.3				
ould not get going			1.18 (1.05 - 1.3				
0 0 0	16352 / 6		1.19 (1.12 - 1.2				
ittle interest in doing things	8457 / 1		1.23 (1.18 - 1.2				
leep problems rouble concentrating	16352 / 6 4586 / 2		1.08 (1.01 - 1.1 1.07 (0.98 - 1.1				
rouble concentrating	4300 / 2	-	1.07 (0.98 - 1.1				
dividuals without chronic illnesses**							
elt everything was an effort	12006 / 8		1.21 (1.07 - 1.3				
hanges in appetite	20056 / 10	-	1.21 (1.14 - 1.2				
Could not get going	26554 / 14	-	1.17 (1.13 - 1.2				
ittle interest in doing things	17077 / 6	_	1.16 (1.10 - 1.2				
leep problems	30483 / 14	-	1.11 (1.06 - 1.1				
rouble concentrating	23614 / 9	-	1.11 (1.05 - 1.1				
ongitudinal association‡							
elt everything was an effort	21031 / 6	_	1 15 /1 10 1 2				
	21031 / 6		1.15 (1.10 - 1.2)				
hanges in appetite	9333 / 3		1.15 (1.03 - 1.2				
ould not get going	21031 / 6		1.10 (1.03 - 1.1				
ttle interest in doing things	6090 / 1		1.15 (1.09 - 1.2				
leep problems	26009 / 7	-	1.10 (1.05 - 1.1				
rouble concentrating	12941 / 3	_	1.07 (1.01 - 1.1				
			_				

<sup>†</sup> Adjusted for age, sex and adverse childhood experiences; ‡ Adjusted for age, sex and depressive symptom at baseline

<sup>\*\*</sup> Note: These analyses excluded individuals with a self-reported history of coronary heart disease, stroke, cancer, hypertension, and/or diabetes.