Data supplement for Frank et al., Association Between Systemic Inflammation and Individual Symptoms of Depression: A Pooled Analysis of 15 Population-Based Cohort Studies. Am J Psychiatry (doi: 10.1176/appi.ajp.2021.20121776)

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Appendix 1: Description of the Included Cohort Studies With Individual-Participant Data

Costa Rican Longevity and Healthy Aging Study (CRELES)(1)

The Costa Rican Longevity and Healthy Aging Study (CRELES) is a nationally representative, longitudinal survey which was established in 2005 to explore the health and lifecourse experiences of 2,827 Costa Rican adults aged \geq 60 years. Baseline household interviews were conducted between 2004 and 2006, with two-year follow-up interviews in 2007 and 2009. CRELES has collected data on variety of biological, psychological, and sociological measures to assess the causes and consequences of health-related outcomes. Plasma C-reactive protein (CRP) was collected at baseline (2005) from fasting blood samples. Depressive symptoms were measured at baseline and two years later, using the Geriatric Depression Scale.(2) Written informed consent was obtained prior to the study. Ethical approval was granted by the Ethical Science Committee of the University of Costa Rica (http://ccp.ucr.ac.cr/creles).

English Longitudinal Study of Ageing (ELSA)(3)

The English Longitudinal Study of Ageing (ELSA) is an ongoing, nationally representative, longitudinal, population study of adults aged \geq 50 years living in England. ELSA was established in 2002. Since then, participants have been followed up biannually. Thus far, there have been 9 waves of data collection in ELSA. For the present study, baseline levels of plasma CRP were measured at wave 6 (2012/13) from fasting blood samples. Depressive symptoms were ascertained at baseline and wave 8 (2016/17), using the 8-item version of the Centre for Epidemiological Studies Depression Scale.(4) Written informed consent was obtained at each data collection wave. Ethical approval was obtained from the London Multi-Centre Research Ethics Committee (https://www.elsa-project.ac.uk).

Midlife in the United States (MIDUS)(5)

The Midlife in the United States (MIDUS) study is a nationally representative, longitudinal survey of health and well-being of non-institutionalised, English-speaking adults aged 25 - 74 years in the United States. Participant selection was based on random digit dialling conducted between 1995 and 1996. The total original sample (n=7108) includes the main respondents (n=3487), their siblings (n=950), an oversample from five metropolitan areas in the United States (n=757), and a twin subsample (n=1914). The collection of psychosocial data was primarily based on telephone interviews and questionnaires distributed via email to study participants. A follow-up study of the cohort was conducted between 2004-2009 (MIDUS II), which included the *Biomarker Project*. Biological and neurological data of 1,255 respondents was collected from two distinct subsamples: the longitudinal survey sample of 1,054 participants, and the Milwaukee sample of 201 participants who participated in the baseline MIDUS Milwaukee study initiated in 2005. In the present multi-cohort study, we included individuals with complete data on two inflammatory markers (interleukin-6 [IL-6] or CRP), covariates, and depressive symptoms. Serum CRP and IL-6 measures were obtained from fasting blood samples. Depressive symptoms were assessed using the 20-item CES-D(4) questionnaire (http://www.midus.wisc.edu).

Whitehall II(6)

The Whitehall II study is a prospective cohort study comprising 10,308 men and woman aged 35 to 55 years, who were recruited from 20 London-based civil service departments in 1985. To date, there have been 11 phases of data collection. Since 1985, data has been collected every two to five years, using a wide range of self-report measures and clinical assessments to explore social, psychological, biological and behavioural factors determinants of health, illness, and social inequalities. In the present analyses, we used measures of fasting serum CRP and IL-6 at wave 7 (2002/04, baseline). Depressive symptoms were assessed at baseline and three years later (2007/2009) using the 20-item version of the CES-D.(4) Written informed consent from participants was obtained at each wave of data collection. Ethical approval has been granted by the University College London Medical School Committee on the Ethics of Human Research (https://www.ucl.ac.uk/iehc/research/epidemiology-public-health/research).

Understanding Society (UKHLS)(7)

Understanding Society, the UK Household Longitudinal Study (UKHLS), is a large-scale prospective cohort study that has followed people from over 40,000 households throughout the UK. It captures a representative sample of people of all age ages and ethnicities. UKHLS was launched in 2009, building on and including data from the British Household Panel Survey (BHPS). To date, there have been 8 waves of data collection. UKHLS has collected a variety of biopsychosocial measures, including information about participants' social and economic circumstances, psychological well-being, attitudes and beliefs, physical illness, and genetics. Psychosocial data and general health information were collected via annual face-to-face interviews and a self-completion online survey. Biomedical data

(e.g., weight, height, blood samples) were collected during the nurse health assessments. Serum levels of CRP were measured at wave 2 (2010-12, baseline) from non-fasting blood samples. Depressive symptoms were ascertained at wave 2 and 3 (2011-13), using the 12-item General Health Questionnaire (GHQ-12).(8) Written informed consent was obtained at each wave of data collection. UKHLS has been granted ethical approval by the University of Essex Ethics Committee; approval for the nurse health assessment was granted by the National Research Ethics Service approved the nurse health assessment (https://www.understandingsociety.ac.uk).

National Health and Nutrition Survey (NHANES) - 2005/06, 2007/08, 2009/10, 2015/16, and 2017/18(9)

The National Health and Nutrition Examination Survey (NHANES) is a series of studies designed to ascertain nationally representative information on health and the nutritional status of children and adults in the United States. NHANES was initially established by the National Centre for Health Statistics (NCHS) in the 1960s, and became continuous in 1999, collecting data from a nationally representative sample of approximately 5000 people each year. For the present analyses, we focused on 5 independent NHANES cohorts with complete data on CRP, covariates, and depressive symptoms from 2005/06, 2007/08, 2009/10, 2015/16, and 2017/18. In each cohort, measures on systemic inflammation were based on serum high-sensitivity CRP collected from participants' fasting blood samples. Depressive symptoms were measured using 9 items of the Patient Health Questionnaire (PHQ-9).(10) Written informed consent was provided prior to each study. Ethical approval was granted by the NCHS Research Ethics Review Board (ERB) (https://wwwn.cdc.gov/Nchs/Nhanes/2009-2010/CRP_F.htm).

Social Environment and Biomarkers of Aging Study (SEBAS)(11)

The Social Environment and Biomarkers of Ageing Study (SEBAS) is a nationally representative, longitudinal survey of both middle-aged and older adults living in Taiwan. The first wave of data collection was conducted in 2000 and participants were followed up in 2006. SEBAS provides a rich variety of social, environmental, psychological and biological data. Baseline measures of systemic inflammation included fasting serum samples of CRP and IL-6. Depressive symptoms were assessed at baseline and six years later, using a 10-item version of the CES-D.(4) SEBAS was approved by ethical committees in Taiwan, at Georgetown University, and at Princeton University. Written informed consent was obtained prior to the study. More information about the Social Environment and Biomarkers of Aging Study can be found at the Georgetown University Centre for Populations and Health website (https://cph.georgetown.edu/research/taiwan/).

Health and Retirement Study (HRS)(12)

The Health and Retirement Study (HRS) is a nationally representative, longitudinal, biannual, population-based cohort study of approximately 20,000 people aged \geq 51 years in the United States. HRS was launched in 1992 by the University of Michigan and is funded by the National Institute on Aging. Since then, HRS has collected information about income, work, assets, pension plans, health insurance, disability, physical health and functioning, mental health, cognitive functioning, and health care expenditures (<u>https://hrs.isr.umich.edu/about</u>). CRP levels (dried blood spots) were collected after face-to-face interviews and subsequently analysed using an enzyme-linked immunosorbent assay. The 20-item version of the CES-D(4) to assess depressive symptoms. Participants provided written informed consent prior to the study, and ethical approval was granted by the University of Michigan Institutional Review Board.

The Irish Longitudinal Study of Ageing (TILDA)(13)

The Irish Longitudinal Study of Ageing (TILDA) is a prospective cohort study exploring the economic, social, age-, and health-related experiences of community-dwelling adults aged \geq 50 years in the Republic of Ireland. The first wave of data collection was conducted between October 2009 and July 2011 in a representative sample of 8,175 adults. Sampling was based on a three-stage selection process using the Geodirectory (i.e., an extensive list of all addresses registered in Ireland) as a sampling frame. First, subdivisions of electoral districts stratified by socioeconomic status, age, and geographical location were used as the primary sampling unit. Second, a random probability sample of 40 addresses was selected from within each cluster, resulting in an initial sample of 25,600 addresses. The third stage involved asking all adults aged \geq 50 years of selected households to participate. Participants completed a computer assisted personal interview (CAPI) and a self-administered questionnaire and were then invited to attend one of two test centres for the collection of physical samples and bio-medical measures. High-sensitivity CRP was measured in non-fasting blood plasma using a third-generation particle enhanced immunoturbidimetric assay. Depressive symptoms were assessed using the 20-item version of the CES-D.(4) All participants provided written informed consent prior to the study. Ethical approval was granted by the Research Ethics Committee of Trinity College Dublin (https://tilda.tcd.ie).

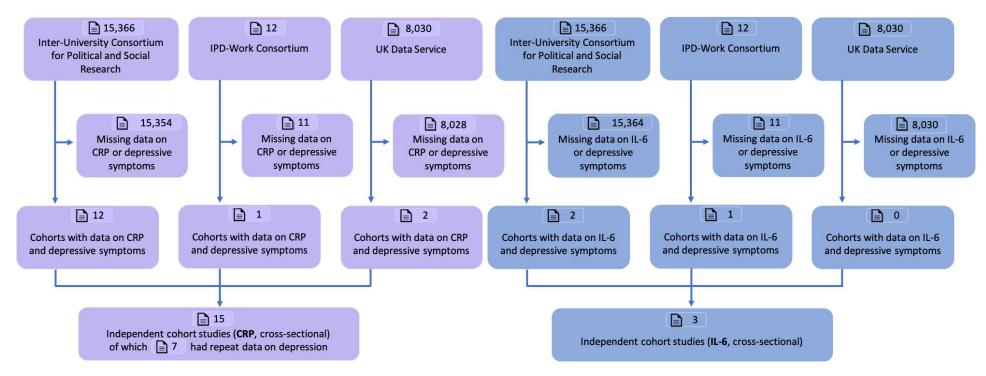
The National Social Life, Health, and Aging Project (NSHAP)(14)

The National Social Life, Health, and Aging Project (NSHAP) is a nationally representative, longitudinal cohort study of community-dwelling older adults in the United States. NSHAP aims to examine the interactions among and relationships between physical health and illness, mental health, medication use, health behaviours, cognitive functioning, social relationships, and sexuality. Thus far, there have been three waves of data collection. The first wave of NSHAP was conducted between 2005 and 2006 by NORC and Principal Investigators at the University of Chicago, completing more than 3,000 interviews with a sample of adults born between 1920 and 1947 (aged 57 to 85 at the time of Wave 1 interview). Approximately 3,400 interviews were conducted for wave 1 with wave 2 respondents, wave 1 non-interviewed respondents, and their spouses or cohabiting romantic partners between 2010 and 2011. Wave 3 was conducted from September 2015 to November 2016, including 2,409 wave 2 respondents, and a refresher cohort consisting of adults born between 1948 and 1965 together with their spouses or romantic partners. A total 4,777 respondents were interviewed in Wave 3. Data on high-sensitivity CRP was derived from dried blood spots collected at participants' homes during the interview. Depressive symptoms were ascertained from the 11 items of the CES-D.(4) All participants gave their written informed consent prior to participation in the study. The study protocol was approved by NORC, the Institutional Review Boards of the University of Chicago, and the University of Arizona.

The Mexican Health and Aging Study (MHAS)(15)

The Mexican Health and Aging Study (MHAS) is a nationally representative, longitudinal cohort study of adults aged \geq 50 years living in both urban and rural areas in Mexico. MHAS was designed to explore health and ageing-related biopsychosocial mechanisms and outcomes. To date, five waves of data collection have been conducted; a baseline wave of adults born in 1951 or earlier was conducted in 2001 with follow-up interviews held in 2003, 2012, 2015, and 2018. Data on biomarkers were collected from 2012 onwards, including serum levels of high-sensitivity CRP obtained from dried blood spots. Depressive symptoms were ascertained from 9-items of the CES-D.(4) All participants provided written informed consent prior to each wave of data collection. Ethical approval for MHAS study protocols and instruments were granted by the Institutional Review Board or Ethics Committee of the University of Texas Medical Branch, the Instituto Nacional de Estadistica y Geografia (INEGI) in Mexico, and the Instituto Nacional de Salud Publica (INSP) in Mexico (http://www.mhasweb.org).

FIGURE S1. Selection of studies for individual-participant pooled analysis of the association between systemic inflammation and individual symptoms of depression



Study	Method of CRP ascertainment	Time interval blood collection and measurement of depressive symptoms at baseline	Method of depression symptoms ascertainment	Cut-off depression measures	Prevalence
SEBAS	Serum (fasting)	24 days (mean lag)	Centre for Epidemiological Studies Depression Scale	≥10	17.61%
MHAS	Dried blood spot	Same day	Centre for Epidemiological Studies Depression Scale	≥4	36.65%
MIDUS	Serum (fasting)	1 day	Centre for Epidemiological Studies Depression Scale	≥16	13.17%
CRELES	Plasma (fasting)	Same day	Geriatric Depression Scale	≥10	9.95%
NSHAP	Dried blood spots	Same day	Centre for Epidemiological Studies Depression Scale	≥9	24.07%
NHANES 2005	Serum (fasting)	Same day	Depression Screener Questionnaire	≥10	6.10%
NHANES 2007	Serum (fasting)	Same day	Depression Screener Questionnaire	≥10	9.53%
NHANES 2009	Serum (fasting)	Same day	Depression Screener Questionnaire	≥ 10	9.42%
NHANES 2015	Serum (fasting)	Same day	Depression Screener Questionnaire	≥10	8.14%
NHANES 2017	Serum (fasting)	Same day	Depression Screener Questionnaire	≥10	8.65%
Whitehall II	Serum (fasting)	14 days (mean lag)	Centre for Epidemiological Studies Depression Scale (20-item version)	≥16	15.10%
TILDA	Plasma (non-fasting)	≥ 1 week	Centre for Epidemiological Studies Depression Scale	≥16	8.23%
ELSA	Plasma (fasting)	2 -6 weeks	Centre for Epidemiological Studies Depression Scale (8-item version)	≥4	11.31%
UKHLS	Serum (non-fasting)	5 months	General Health Questionnaire	≥4	16.90%
HRS	Dried blood spots	No date	Centre for Epidemiological Studies Depression Scale	≥4	14.56%
Total					13.96%

 TABLE S1. Method of exposure (C-reactive protein) and outcome (depressive symptoms) ascertainment

TABLE S2. Method of exposure ascertainment (interleukin-6)

Study	Method of IL-6 ascertainment	Time of blood collection	Fasting status	Analytical method
SEBAS	Serum	Morning	Fasting	High-sensitivity enzyme-linked immunosorbent assay (ELISA)
MIDUS	Serum	Morning	Fasting	High-sensitivity enzyme-linked immunosorbent assay (ELISA)
WHII	Serum	Morning	Fasting	High-sensitivity enzyme-linked immunosorbent assay (ELISA)

TABLE S3. Study-specific measures of adverse childhood experiences (ACEs)

	Cohorts	MHAS	ELSA	CRELES	WHII	HRS	NSHAP	MIDUS
		1 Serious health problems	Ever lived in children's home or with foster parents	Poverty	Hospitalization for four or more weeks	Physical abuse by a parent	Family life happy growing up	Emotional abuse
s l		2 Lived with grandparents	Separation from mother for ≥6 months at age ≤16 years	Health Problems	Parental divorce	Parents' drinking/drug use caused problems	Family well off from age 6-16	Physical abuse
2 2		3 Had typhoid fever	Victim of serious physical attack/assault at age ≤16 years	Tuberculosis	Unintentional parental unemployment	Repeating a school year	Lived with both parents from age 6-16	Sexgual abuse
i.		4 Had blow to head	Victim of sexual assault at age ≤16 years	Rheumatic fever	Parental mental illness/problematic alcohol consumption	n	Health status from age 6-16	Emotional neglect
ğ		5 Had tuberculosis	Physically abusive parents at age <16 years	Poliomyelitis	Physical abuse by someone close		Experienced violent event from age 6-16	Physical neglegt
de de		6 Had rheumatic fever	Parents with substance abuse/mental health problems at age <16 years	Malaria	Exposure to frequent parental arguments or fights		Witnessed violent event from age 6-16	
ê		7 Had polio	Parents argued or fought very often at age <16 years	Asthma	Orphanage/children's home			
l le		8 Health compared to other children	Serious illness <16 years	No bathroom				
5		9 Had no toilet inside home	Loss of parent <16 years	No shoes				
ers		10 Went hungry to bed	Foster care <16 years	No electircity				
- P		11 No shoes						
		12 Dropped out of school						
		13 Family slept in same room where food prepared						
		14 Family received financial assistance						

Appendix 2. Study Characteristics

TABLE S4. Study characteristics

Study	Baseline (year)	Country	Number of participants	Number (%) of women	Mean age at baseline (years)	Geometric mean CRP (mg/L) [mean (CI)]	Method of depression symptoms ascertainment	Number of symptoms by domain (physical/cognitive/emotional/self- perception/self-harm) **			
CRP COHORTS	CRP COHORTS										
SEBAS	2000	Taiwan	602	263 (43.7%)	65.9	0.74 (0.57 - 0.97)	Centre for Epidemiological Studies Depression Scale	4/1/1/0/0			
MHAS *	2012	Mexico	865	527 (60.9%)	54.8	0.96 (0.90 - 1.03)	Centre for Epidemiological Studies Depression Scale	3/0/5/0/0			
MIDUS	2004-2009	USA	949	509 (53.6%)	45.8	0.74 (0.67 - 0.80)	Centre for Epidemiological Studies Depression Scale	5/4/7/4/0			
CRELES	2005	Costa Rica	1186	662 (55.8%)	71.9	1.27 (1.24 - 1.30)	Geriatric Depression Scale	1/1/2/0/0			
NSHAP *	2005-2006	USA	1807	934 (51.7%)	69.3	0.82 (0.77 - 0.87)	Centre for Epidemiological Studies Depression Scale	4/1/5/1/0			
NHANES 2005	2005-2006	USA	3933	2037 (51.8%)	47.9	1.10 (1.07 - 1.14)	Depression Screener Questionnaire	4/2/1/1/1			
Whitehall II *	2002-2004	UK	4133	1123 (27.2%)	60.8	0.64 (0.62 - 0.67)	Centre for Epidemiological Studies Depression Scale	5/4/7/4/0			
NHANES 2017	2017-2018	USA	4325	2206 (51.0%)	51.2	0.87 (0.84 - 0.90)	Depression Screener Questionnaire	4/2/1/1/1			
NHANES 2015	2015-2016	USA	4497	2309 (51.4%)	49.7	1.03 (1.00 - 1.06)	Depression Screener Questionnaire	4/2/1/1/1			
TILDA *	2009-2011	Ireland	4704	2590 (55.1%)	62.1	0.73 (0.70 - 0.76)	Centre for Epidemiological Studies Depression Scale	5/4/7/4/0			
NHANES 2007	2007-2008	USA	4751	2404 (50.6%)	50.4	1.02 (1.00 - 1.05)	Depression Screener Questionnaire	4/2/1/1/1			
NHANES 2009	2009-2010	USA	4914	2474 (50.4%)	49.3	1.00 (0.97 - 1.02)	Depression Screener Questionnaire	4/2/1/1/1			
ELSA *	2012-2013	UK	5490	3027 (55.1%)	66.8	0.78 (0.76 - 0.80)	Centre for Epidemiological Studies Depression Scale	3/0/5/0/0			
UKHLS *	2010-2012	UK	5615	3121 (55.6%)	53	0.81 (0.79 - 0.84)	General Health Questionnaire	1/1/3/0/0			
HRS *	2006-2008	USA	8580	5040 (58.7%)	68.3	0.90 (0.88 - 0.92)	Centre for Epidemiological Studies Depression Scale	3/1/5/0/0			
Total			56351	29226 (51.5%)	57.8 (12.0)	0.89 (0.85 - 0.94)					

Table S4 (continued)

Study	Baseline (year)	Country	Number of participants	Number (%) of women	Mean age at baseline (years)	Geometric mean CRP (pg/mL) [mean (CI)]	Method of depression symptoms ascertainment	Number of symptoms by domain (physical/cognitive/emotional/self- perception/self-harm) **			
IL-6 COHORTS	IL-6 COHORTS										
SEBAS	2000	Taiwan	600	261 (43.5%)	66	1.01 (0.96 - 1.06)	Centre for Epidemiological Studies Depression Scale	4/1/1/0/0			
MIDUS	2004-2009	USA	953	511 (53.6%)	45.8	0.65 (0.61 - 0.70)	Centre for Epidemiological Studies Depression Scale	5/4/7/4/0			
Whitehall II	2002-2004	UK	3820	1005 (26.3%)	60.6	0.55 (0.54 - 0.57)	Centre for Epidemiological Studies Depression Scale	5/4/7/4/0			
Total			5373	1777 (41.1%)	57.5	0.74 (0.70 - 0.78)					

* Studies with repeated measures of depression symptoms ** Physical symptoms / Cognitive symptoms / Emotional symptoms / Symptoms of self-perception / Self-harm symptoms

	High CRP (≥ 3mg/L) & high levels of identified symptoms (top tertile)	Others	p-value
	N = 3,587	N= 52,764	
Age	59.66 (15.3)	57.53 (16.1)	< 0.001
Sex			< 0.001
Men	33.65%	49.12%	
Women	66.35%	50.88%	
Education			< 0.001
None/Elementary	27.43%	20.56%	
Secondary	47.87%	43.53%	
Tertiary	24.70%	35.91%	
Smoking			< 0.001
Yes	32.14%	28.11%	
No	67.86%	71.89%	
Physically inactive			< 0.001
Yes	58.91%	34.54%	
No	41.09%	65.46%	
Alcohol			< 0.001
None/low	61.40%	39.26%	
Moderate	31.89%	48.92%	
High	6.71%	11.82%	
Body mass index	32.37 (7.8)	28.27 (5.8)	< 0.001
Systolic blood pressure	129.70 (20.23)	128.83 (19.3)	0.001
Diastolic blood pressure	75.24 (13.6)	74.48 (12.7)	< 0.001
Diabetes			< 0.001
Yes	24.78%	10.93%	
No	75.22%	89.07%	
Cancer			< 0.001
Yes	14.08%	9.46%	
No	85.92%	90.54%	
CHD			< 0.001
Yes	18.34%	7.63%	
No	81.66%	92.37%	
Stroke			< 0.001
Yes	7.75%	3.50%	
No	92.25%	96.50%	

 TABLE S5. Study characteristics of individuals with high CRP and high levels of the identified symptoms versus other study members

Note: Number (percentage) and mean (standard deviation).

	High CRP (≥ 3mg/L) & high levels of identified symptoms (top tertile)	Others	p-value
	N = 1,963	N=4,851	
Age	58.26 (14.74)	57.70 (15.15)	0.162
Sex			< 0.001
Men	30.92%	39.72%	
Women	69.08%	60.28%	
Education			0.271
None/Elementary	31.89%	30.10%	
Secondary	44.22%	44.60%	
Tertiary	23.89%	25.30%	
Smoking			0.702
Yes	36.12%	36.61%	
No	63.88%	63.39%	
Physically inactive			< 0.001
Yes	61.49%	42.75%	
No	38.51%	57.25%	
Alcohol			< 0.001
None/low	62.21%	44.84%	
Moderate	30.21%	40.34%	
High	7.58%	14.82%	
Body mass index	32.58 (8.08)	28.14 (5.88)	< 0.001
Systolic blood pressure	129.16 (20.1)	128.11 (19.27)	0.043
Diastolic blood pressure	75.75 (13.25)	75.27 (12.31)	0.157
Diabetes			< 0.001
Yes	25.06%	13.75%	
No	74.94%	86.25%	
Cancer			< 0.001
Yes	12.53%	9.48%	
No	87.47%	90.52%	
CHD			< 0.001
Yes	16.96%	10.37%	
No	83.04%	89.63%	
Stroke			0.002
Yes	8.00%	5.92%	
No	92.00%	94.08%	

TABLE S6. Study characteristics of individuals with high CRP and high levels of the identified symptoms versus other study members among people with overall elevated levels of depressive symptoms

Note: Number (percentage) and mean (standard deviation).

Appendix 3. Study Specific Estimates for Random-Effect Meta-Analyses of C-Reactive Protein and Individual Depression

FIGURE S2a. Random-effects meta-analysis of the cross-sectional association between C-reactive protein and individual depression symptoms (adjusted for age & sex)

Study	Ν	Cases		OR	95%-CI
Bothered by things			I		
MIDUS	949	44		0.98	[0.75; 1.28]
WHII	4133	285		1.00	[0.90; 1.12]
TILDA	4704	322	T III	1.14	[0.99; 1.31]
Overall effect			-	1.05	[0.94; 1.16]
Heterogeneity: $I^2 = 14\%$ [0%; 91%], $\tau^2 = 0.0027$, $p = 0.31$, $R_b = 32\%$ [0%; 100%]					
Changes in appetite					
SEBAS	602	80		1.23	[0.95; 1.59]
MIDUS	949	33		1.27	[0.94; 1.72]
NSHAP	1807	209		1.25	[1.11; 1.41]
NHANES 2005	3933	250		1.20	[1.08; 1.33]
WHII	4133	129		1.21	[1.03; 1.42]
NHANES 2017	4325	418		1.21	[1.11; 1.32]
NHANES 2015	4497	411		1.24	[1.14; 1.34]
TILDA	4704	164		1.26	[1.05; 1.52]
NHANES 2007	4751	430		1.16	[1.07; 1.25]
NHANES 2009	4914	454		1.30	[1.20; 1.40]
Overall effect			•	1.23	[1.18; 1.27]
Heterogeneity: $l^2 = 0\% [0\%; 29\%], \tau^2 = 0.0003, p = 0.86, R_b = 9\% [0\%; 100\%]$					
Could not get going/energy					
SEBAS	602	95		1.02	[0.78; 1.34]
MHAS	865	462		1.16	[1.01; 1.33]
MIDUS	949	87		1.34	[1.10; 1.63]
CRELES	1186	170	— •—	1.23	[0.98; 1.54]
NSHAP	1807	313		1.12	[1.01; 1.24]
NHANES 2005	3933	563		1.19	[1.11; 1.28]
WHII	4133	314		1.15	[1.04; 1.28]
NHANES 2017	4325	754		1.15	[1.07; 1.24]
NHANES 2015	4497	781		1.22	[1.15; 1.30]
TILDA	4704	226		1.36	[1.17; 1.58]
NHANES 2007	4751	810		1.22	[1.15; 1.30]
NHANES 2009	4914	807		1.20	[1.13; 1.27]
ELSA	5490	888		1.30	[1.21; 1.39]
HRS	8580	3674		1.17	[1.13; 1.22]
Overall effect Heterogeneity: <i>I</i> ² = 21% [0%; 58%], τ^2 = 0.0023, <i>p</i> = 0.22, <i>R</i> _b = 49% [0%; 100%]			•	1.20	[1.16; 1.24]
Could not shake off the blues	040	45		1.00	10 04 4 441
MIDUS	949	45		1.09	[0.84; 1.41]
WHII	4133	211		1.13	[0.99; 1.28]
TILDA	4704	169		1.26	[1.05; 1.51]
Overall effect Heterogeneity: $I^2 = 0\% [0\%; 82\%], \tau^2 = 0.0016, p = 0.55, R_b = 17\% [0\%; 100\%]$			-	1.16	[1.04; 1.29]
Did not enjoy life MHAS	865	193		1.00	[0.85; 1.17]
MIDUS	949	123		1.07	[0.90; 1.27]
CRELES	1186	42	and the second	1.30	[0.87; 1.95]
NSHAP	1807	202		1.08	[0.95; 1.22]
WHI	4133	603		1.00	[0.92; 1.08]
TILDA	4704	436	Ĩ — 	1.19	[1.06; 1.34]
ELSA	5490	462		1.17	[1.07; 1.28]
UKHLS	5615	885		1.11	[1.04; 1.18]
HRS	8580	600	-10-	1.10	[1.03; 1.18]
Overall effect	0000	000	•	1.10	[1.04; 1.15]
Heterogeneity: $l^2 = 29\%$ [0%; 67%], $\tau^2 = 0.0028$, $p = 0.18$, $R_b = 46\%$ [0%; 100%]					[]
Feeling bad about yourself					
NHANES 2005	3933	148	— <u>—</u>	1.16	[1.02; 1.32]
NHANES 2017	4325	219	- •	1.12	[0.99; 1.27]
NHANES 2017	4323	250		1.12	[1.07; 1.31]
NHANES 2007	4751	279		1.22	[1.11; 1.34]
NHANES 2009	4914	286		1.18	[1.07; 1.30]
Overall effect		200	•	1.18	[1.12; 1.24]
Heterogeneity: $l^2 = 0\% [0\%; 32\%], \tau^2 = 0.0002, p = 0.87, R_b = 6\% [0\%; 100\%]$					L
			0.75 1 15		
			0.75 1 1.5		
			Decreased risk Increased risk		

Figure S2a (continued)

Study	N	Cases		OR	95%-CI
Felt depressed MHAS MIDUS NSHAP NHANES 2005 WHI NHANES 2017 NHANES 2015 TILDA NHANES 2007 NHANES 2009 ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 43\%$ [0%; 70%], $\tau^2 = 0.0026$, $p = 0.05$, $R_b = 51\%$ [0%; 100%]	865 949 1807 3933 4133 4325 4497 4704 4751 4914 5490 5615 8580	303 72 270 234 300 325 325 229 363 390 602 1028 1118		1.05 1.18 1.04 1.16 1.02 1.10 1.14 1.27 1.13 1.22 1.23 1.07 1.14 1.13	$\begin{matrix} [0.91; 1.21]\\ [0.96; 1.46]\\ [0.94; 1.16]\\ [1.05; 1.29]\\ [0.92; 1.14]\\ [0.99; 1.22]\\ [1.05; 1.24]\\ [1.03; 1.23]\\ [1.12; 1.32]\\ [1.14; 1.33]\\ [1.14; 1.33]\\ [1.01; 1.14]\\ [1.08; 1.20]\\ [1.09; 1.18] \end{matrix}$
Felt everything was an effort SEBAS MHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: I^2 = 79% [59%; 89%], τ^2 = 0.0142, $p < 0.01$, R_p = 76% [30%; 100%]	602 865 949 1807 4133 4704 5490 8580	116 313 68 295 394 284 907 1954		1.09 0.98 1.28 1.32 1.10 1.48 1.36 1.26 1.23	[0.85; 1.39] [0.85; 1.12] [1.03; 1.59] [1.19; 1.47] [1.00; 1.21] [1.29; 1.69] [1.27; 1.45] [1.21; 1.32] [1.12; 1.36]
Felt fearful MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 61% [0%; 89%], τ^2 = 0.0131, p = 0.08, R_b = 54% [0%; 100%]	949 4133 4704	24 165 178		0.93 0.94 1.21 1.03	[0.65; 1.33] [0.81; 1.09] [1.01; 1.44] [0.87; 1.23]
Felt hopeless about the future MIDUS CRELES WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 80%], $\tau^2 = 0.0016$, $p = 0.50$, $R_b = 33\%$ [0%; 100%]	949 1186 4133 4704	220 132 855 788		0.95 1.12 1.04 1.07 1.04	[0.83; 1.09] [0.86; 1.45] [0.97; 1.12] [0.97; 1.18] [0.97; 1.11]
Felt lonely SEBAS MIHAS MIDUS NSHAP WHII TIIDA ELSA HRS Overall effect Heterogeneity: $I^2 = 0\% [0\%; 3\%], \tau^2 = 0.0002, p = 0.94, R_b = 7\% [0\%; 100\%]$	602 865 949 1807 4133 4704 5490 8580	57 255 69 311 286 318 564 1261		1.15 1.16 1.10 1.06 1.14 1.13 1.15 1.13	[0.83; 1.59] [1.00; 1.34] [0.88; 1.37] [1.00; 1.21] [0.95; 1.18] [1.00; 1.30] [1.04; 1.22] [1.10; 1.21] [1.09; 1.17]
Felt sad MHAS MIDUS NSHAP WHI TILDA ELSA HRS Overall effect Heterogeneity: $l^2 = 21\%$ [0%; 65%], $\tau^2 = 0.0017$, $p = 0.27$, $R_b = 39\%$ [0%; 100%]	865 949 1807 4133 4704 5490 8580	368 68 336 250 322 926 1467	0.75 1 1.5 Decreased risk	1.11 1.03 1.03 0.95 1.13 1.06 1.11 1.07	[0.97; 1.27] [0.83; 1.28] [0.93; 1.14] [0.98; 1.30] [0.99; 1.13] [1.06; 1.16] [1.01; 1.12]

Figure S2a (continued)

Study	N	Cases		OR	95%-CI
Felt unhappy MHAS MIDUS CRELES NSHAP WHI TILDA ELSA UKHLS HRS Overall effect Heterogeneity: I^2 = 49% [0%; 76%], τ^2 = 0.0068, p = 0.05, R_b = 66% [0%; 100%]	865 949 1186 1807 4133 4704 5490 5615 8580	171 125 106 313 696 517 514 706 1014		1.06 1.14 1.49 1.14 1.01 1.21 1.11 1.04 1.08 1.11	[0.90; 1.25] [0.96; 1.35] [1.14; 1.94] [1.03; 1.27] [0.94; 1.09] [1.08; 1.35] [1.02; 1.20] [0.97; 1.12] [1.02; 1.14] [1.04; 1.18]
Felt worse than others MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 88%], τ^2 = 0.0016, p = 0.41, R_b = 35% [0%; 100%]	949 4133 4704	142 687 503		1.15 1.02 1.03 1.05	[0.98; 1.35] [0.95; 1.10] [0.92; 1.16] [0.97; 1.13]
Had crying spells MIDUS WHII TILDA Overall effect Heterogeneity: J^2 = 36% [0%; 79%], τ^2 = 0.0180, ρ = 0.21, R_b = 53% [0%; 100%]	949 4133 4704	21 74 150		1.58 1.08 1.25 1.24	[1.08; 2.32] [0.88; 1.33] [1.03; 1.52] [1.00; 1.53]
Life had been a failure MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 62% [0%; 89%], τ^2 = 0.0160, ρ = 0.07, R_b = 58% [0%; 100%]	949 4133 4704	29 169 143		1.36 0.99 1.24 1.15	[0.98; 1.88] [0.86; 1.14] [1.02; 1.50] [0.95; 1.38]
Little interest in doing things/unmotivated NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 HRS Overall effect Heterogeneity: $I^2 = 22\%$ [0%; 66%], $\tau^2 = 0.0010$, $p = 0.27$, $R_b = 39\%$ [0%; 100%]	3933 4325 4497 4751 4914 8580	232 393 419 337 409 1675	- - = - = - = - = - = - = - = - = - = -	1.18 1.26 1.12 1.21 1.26 1.23 1.21	[1.06; 1.31] [1.15; 1.39] [1.04; 1.21] [1.11; 1.32] [1.16; 1.36] [1.18; 1.29] [1.16; 1.26]
Moving or speaking slowly or too fast NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $I^2 = 0\% [0\%; 78\%], \tau^2 = 0.0015, p = 0.44, R_b = 26\% [0\%; 100\%]$	3933 4325 4497 4751 4914	92 173 172 180 196		1.20 1.10 1.11 1.08 1.24 1.14	[1.02; 1.41] [0.96; 1.26] [0.98; 1.25] [0.96; 1.22] [1.11; 1.39] [1.07; 1.22]
People dislike me MIDUS NSHAP WHII TILDA Overall effect Heterogeneity: I^2 = 57% [0%; 86%], τ^2 = 0.0326, p = 0.07, R_b = 65% [0%; 100%]	949 1807 4133 4704	26 101 77 71		1.24 1.29 1.14 0.78 1.12	[0.88; 1.74] [1.09; 1.53] [0.93; 1.39] [0.56; 1.09] [0.90; 1.39]
People were unfriendly SEBAS MIDUS NSHAP WHII TILDA Overall effect Heterogeneity: I^2 = 36% [0%; 76%], τ^2 = 0.0189, p = 0.18, R_b = 52% [0%; 100%]	602 949 1807 4133 4704	17 14 147 101 97	0.5 1 2 Decreased risk	1.61 1.29 1.08 0.97 1.24 1.15	[1.03; 2.51] [0.82; 2.03] [0.94; 1.24] [0.81; 1.16] [0.98; 1.56] [0.97; 1.36]

Figure S2a (continued)

Study	N	Cases		OR	95%-CI
Sleep problems			T-		
SEBAS	602	191	.	1.05	[0.85; 1.29]
MHAS	865	389		1.02	[0.89; 1.17]
MIDUS	949	213		1.13	[0.99; 1.29]
NSHAP	1807	427		1.11	[1.01; 1.21]
NHANES 2005	3933	479		1.24	[1.15; 1.34]
WHII	4133	919		0.99	[0.93; 1.06]
NHANES 2017	4325	704		1.22	[1.13; 1.31]
NHANES 2015	4497	667		1.13	[1.06; 1.20]
TILDA	4704	832		1.21	[1.11; 1.32]
NHANES 2007	4751	816		1.17	[1.10; 1.25]
NHANES 2009	4914	817		1.17	[1.10; 1.24]
ELSA	5490	1860		1.16	[1.10; 1.22]
UKHLS	5615	921		1.06	[0.99; 1.13]
HRS	8580	2599	-8-	1.10	[1.06; 1.15]
Overall effect			•	1.13	[1.09; 1.17]
Heterogeneity: $l^2 = 67\%$ [42%; 81%], $\tau^2 = 0.0031$, $p < 0.01$, $R_b = 64\%$ [35%; 94%]					
Talked less than usual					
MIDUS	949	94		1.06	[0.88; 1.27]
WHII	4133	370	+	1.07	[0.97; 1.18]
TILDA	4704	217		1.05	[0.89; 1.24]
Overall effect			-	1.06	[0.99; 1.15]
Heterogeneity: $l^2 = 0\%$ [<0%; <0%], $\tau^2 = < 0.0001$, $p = 0.98$, $R_b = 0\%$ [<0%; <100%]					
Thought you would be better off dead					
NHANES 2005	3933	31		1.10	[0.84; 1.45]
NHANES 2017	4325	42		1.00	[0.75; 1.33]
NHANES 2015	4497	57		1.34	[1.09; 1.65]
NHANES 2007	4751	59		1.40	[1.13; 1.73]
NHANES 2009	4914	54		1.18	[0.95; 1.46]
Overall effect				1.22	[1.06; 1.39]
Heterogeneity: $l^2 = 19\% [0\%; 83\%], \tau^2 = 0.0095, p = 0.29, R_b = 40\% [0\%; 100\%]$					
Trouble concentrating					
MIDUS	949	121		1.15	[0.97; 1.36]
NHANES 2005	3933	171		1.12	[0.99; 1.27]
WHII	4133	694	+ <u>-</u>	1.06	[0.98; 1.14]
NHANES 2017	4325	271		1.11	[1.00; 1.24]
NHANES 2015	4497	276		1.22	[1.11; 1.34]
TILDA	4704	405	— <u>—</u> —	0.98	[0.86; 1.11]
NHANES 2007	4751	272		1.17	[1.06; 1.29]
NHANES 2009	4914	303		1.23	[1.12; 1.35]
UKHLS	5615	785		1.08	[1.01; 1.16]
Overall effect			-	1.12	[1.07; 1.18]
Heterogeneity: $l^2 = 47\%$ [0%; 76%], $\tau^2 = 0.0031$, $p = 0.05$, $R_b = 53\%$ [0%; 100%]			r		
			0.75 1 1.5		
			0.70 1 1.0		

0.75 1 1.5 Decreased risk Increased risk

FIGURE S2b. Random-effects meta-analysis of the cross-sectional association between C-reactive protein and individual depression symptoms (adjusted for age, sex & education)

Study	N	Cases		OR	95%-CI
Bothered by things MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 88%], τ^2 = 0.0016, p = 0.42, R_b = 22% [0%; 100%]	949 4133 4704	44 285 322		0.99 1.00 1.12 1.04	[0.76; 1.29] [0.90; 1.12] [0.98; 1.28] [0.95; 1.15]
Changes in appetite SEBAS MIDUS NSHAP NHANES 2005 WHI NHANES 2017 NHANES 2015 TILDA NHANES 2007 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $I^2 = 0\% [0\%; 0\%], \tau^2 = 0.0002, p = 0.97, R_b = 5\% [0\%; 100\%]$	602 949 1807 3933 4133 4325 4497 4704 4751 4914	80 33 209 250 129 418 411 164 430 454		1.16 1.24 1.20 1.18 1.21 1.21 1.21 1.22 1.15 1.25 1.20	$\begin{matrix} [0.89; 1.51] \\ [0.91; 1.68] \\ [1.06; 1.36] \\ [1.07; 1.31] \\ [1.04; 1.41] \\ [1.07; 1.28] \\ [1.12; 1.31] \\ [1.02; 1.46] \\ [1.06; 1.24] \\ [1.16; 1.24] \\ \hline \end{matrix}$
Could not get going/energy SEBAS MHAS MIDUS CRELES NSHAP NHANES 2005 WHI NHANES 2015 TILDA NHANES 2015 TILDA NHANES 2007 NHANES 2009 ELSA HRS Overall effect Heterogeneity: $I^2 = 15\%$ [0%; 53%], $\tau^2 = 0.0021$, $p = 0.29$, $R_b = 47\%$ [0%; 100%]	602 865 949 1186 1807 3933 4133 4325 4497 4704 4751 4914 5490 8580	95 462 87 170 313 563 314 754 781 226 810 807 888 3674		1.04 1.16 1.32 1.10 1.18 1.15 1.13 1.20 1.37 1.20 1.17 1.27 1.16 1.18	$\begin{matrix} [0.79; 1.37] \\ [1.01; 1.33] \\ [1.09; 1.62] \\ [0.97; 1.53] \\ [0.99; 1.22] \\ [1.10; 1.27] \\ [1.04; 1.27] \\ [1.05; 1.21] \\ [1.13; 1.28] \\ [1.17; 1.60] \\ [1.13; 1.28] \\ [1.10; 1.24] \\ [1.19; 1.36] \\ [1.12; 1.21] \\ [1.14; 1.23] \end{matrix}$
Could not shake off the blues MIDUS WHII TILDA Overall effect Heterogeneity: $I^2 = 0\% [0\%; 64\%], \tau^2 = 0.0005, p = 0.75, R_b = 7\% [0\%; 100\%]$	949 4133 4704	45 211 169		1.08 1.13 1.21 1.14	[0.83; 1.40] [1.00; 1.28] [1.01; 1.45] [1.04; 1.26]
Did not enjoy life MHAS MIDUS CRELES NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 27\%$ [0%; 66%], $\tau^2 = 0.0029$, $p = 0.21$, $R_b = 46\%$ [0%; 100%]	865 949 1186 1807 4133 4704 5490 5615 8580	193 123 42 202 603 436 462 885 600		0.98 1.05 1.29 1.04 1.00 1.17 1.16 1.10 1.07 1.08	[0.83; 1.15] [0.89; 1.24] [0.86; 1.94] [0.92; 1.08] [1.04; 1.32] [1.06; 1.26] [1.03; 1.17] [1.00; 1.15] [1.02; 1.14]
Feeling bad about yourself NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: I^2 = 0% [0%; 45%], τ^2 = 0.0003, p = 0.83, R_b = 8% [0%; 100%]	3933 4325 4497 4751 4914	148 219 250 279 286	0.75 1 1.5 Decreased risk	1.13 1.09 1.15 1.20 1.14 1.15	[0.99; 1.29] [0.96; 1.23] [1.04; 1.27] [1.09; 1.33] [1.03; 1.26] [1.09; 1.21]

Figure S2b (continued)

Study	Ν	Cases		OR	95%-CI
Felt depressed MHAS MIDUS NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2015 TILDA NHANES 2007 NHANES 2009 ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 26\%$ [0%; 62%], $\tau^2 = 0.0020$, $p = 0.18$, $R_b = 44\%$ [865 949 1807 3933 4133 4325 4497 4704 4751 4914 5490 5615 8580	303 72 270 234 300 325 325 229 363 390 602 1028 1118		1.03 1.17 1.02 1.12 1.03 1.06 1.10 1.24 1.11 1.20 1.06 1.08 1.10	[0.90; 1.18] [0.95; 1.44] [0.91; 1.14] [1.01; 1.25] [0.93; 1.15] [0.96; 1.18] [1.00; 1.20] [1.06; 1.45] [1.01; 1.21] [1.07; 1.27] [1.11; 1.29] [1.00; 1.13] [1.02; 1.14] [1.06; 1.14]
Felt everything was an effort SEBAS MHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: I^2 = 76% [52%; 88%], τ^2 = 0.0122, $p < 0.01$, R_b = 73% [602 865 949 1807 4133 4704 5490 8580 26%; 100%]	116 313 68 295 394 284 907 1954		1.10 0.96 1.27 1.28 1.11 1.44 1.33 1.20 1.21	[0.86; 1.41] [0.83; 1.11] [1.02; 1.58] [1.15; 1.42] [1.01; 1.22] [1.26; 1.65] [1.24; 1.42] [1.15; 1.26] [1.11; 1.32]
Felt fearful MIDUS WHI TILDA Overall effect Heterogeneity: I^2 = 59% [0%; 88%], τ^2 = 0.0131, p = 0.09, R_b = 54% [949 4133 4704 0%; 100%]	24 165 178		0.91 0.94 1.20 1.03	[0.64; 1.30] [0.82; 1.08] [1.00; 1.43] [0.86; 1.22]
Felt hopeless about the future MIDUS CRELES WHII TILDA Overall effect Heterogeneity: $l^2 = 7\% [0\%; 86\%], \tau^2 = 0.0025, p = 0.36, R_b = 41\% [0]$	949 1186 4133 4704 %; 100%]	220 132 855 788		0.92 1.11 1.04 1.05 1.02	[0.80; 1.05] [0.85; 1.44] [0.97; 1.12] [0.95; 1.16] [0.95; 1.10]
Felt lonely SEBAS MHAS MIDUS NSHAP WHII TIIDA ELSA HRS Overall effect Heterogeneity: $l^2 = 0\%$ [<0%; <0%], $\tau^2 = < 0.0001$, $p = 0.99$, $R_b = 3\%$ [:	602 865 949 1807 4133 4704 5490 8580 <0%; <100%]	57 255 69 311 286 318 564 1261		1.11 1.14 1.09 1.07 1.06 1.13 1.10 1.10 1.10	[0.81; 1.53] [0.98; 1.32] [0.88; 1.35] [0.97; 1.19] [0.95; 1.18] [0.98; 1.30] [1.01; 1.19] [1.05; 1.16] [1.06; 1.14]
Felt sad MHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 60%], $\tau^2 = 0.0010$, $p = 0.63$, $R_b = 28\%$ [0	865 949 1807 4133 4704 5490 8580 %; 100%]	368 68 336 250 322 926 1467	0.75 1 1.5	1.10 1.03 1.03 0.95 1.11 1.05 1.07 1.05	[0.96; 1.26] [0.83; 1.28] [0.93; 1.14] [0.84; 1.07] [0.97; 1.28] [0.98; 1.12] [1.02; 1.12] [1.01; 1.10]

Decreased risk Increased risk

Figure S2b (continued)

Study	N	Cases		OR	95%-CI
Felt unhappy MHAS MIDUS CRELES NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: I^2 = 39% [0%; 72%], τ^2 = 0.0063, p = 0.11, R_B = 65% [0%; 100%]	865 949 1186 1807 4133 4704 5490 5615 8580	171 125 106 313 696 517 514 706 1014		1.05 1.13 1.48 1.11 1.01 1.18 1.10 1.04 1.06 1.09	[0.89; 1.24] [0.96; 1.34] [1.13; 1.93] [1.00; 1.23] [0.94; 1.09] [1.06; 1.32] [1.01; 1.19] [0.96; 1.12] [1.00; 1.12] [1.03; 1.17]
Felt worse than others MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 77%], τ^2 = 0.0006, p = 0.63, R_b = 16% [0%; 100%]	949 4133 4704	142 687 503		1.10 1.01 1.01 1.02	[0.94; 1.29] [0.93; 1.09] [0.90; 1.14] [0.96; 1.10]
Had crying spells MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 33% [0%; 93%], τ^2 = 0.0195, p = 0.22, R_b = 54% [0%; 100%]	949 4133 4704	21 74 150		1.59 1.08 1.20 1.22	[1.08; 2.35] [0.88; 1.33] [0.99; 1.46] [0.98; 1.51]
Life had been a failure MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 53% [0%; 86%], τ^2 = 0.0123, p = 0.12, R_b = 52% [0%; 100%]	949 4133 4704	29 169 143		1.34 1.00 1.22 1.14	[0.97; 1.86] [0.87; 1.15] [1.00; 1.49] [0.95; 1.35]
Little interest in doing things/unmotivated NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 HRS Overall effect Heterogeneity: $I^2 = 13\% [0\%; 78\%], \tau^2 = 0.0010, p = 0.33, R_b = 37\% [0\%; 100\%]$	3933 4325 4497 4751 4914 8580	232 393 419 337 409 1675	-=- -=- =- =- =- = =	1.14 1.22 1.09 1.20 1.22 1.19 1.18	[1.02; 1.27] [1.11; 1.34] [1.01; 1.18] [1.09; 1.32] [1.12; 1.32] [1.14; 1.25] [1.13; 1.23]
Moving or speaking slowly or too fast NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $I^2 = 0\% [0\%; 70\%], \tau^2 = 0.0010, \rho = 0.60, R_b = 19\% [0\%; 100\%]$	3933 4325 4497 4751 4914	92 173 172 180 196		1.17 1.07 1.08 1.06 1.19 1.11	[0.99; 1.38] [0.93; 1.24] [0.95; 1.22] [0.94; 1.19] [1.06; 1.34] [1.04; 1.19]
People dislike me MIDUS NSHAP WHII TILDA Overall effect Heterogeneity: I^2 = 49% [0%; 83%], τ^2 = 0.0303, p = 0.12, R_b = 63% [0%; 100%]	949 1807 4133 4704	26 101 77 71		1.23 1.20 1.15 0.76 1.09	[0.87; 1.73] [1.01; 1.42] [0.94; 1.41] [0.54; 1.07] [0.88; 1.35]
People were unfriendly SEBAS MIDUS NSHAP WHI TILDA Overall effect Heterogeneity: I^2 = 25% [0%; 70%], τ^2 = 0.0162, p = 0.25, R_b = 48% [0%; 100%]	602 949 1807 4133 4704	17 14 147 101 97	0.5 1 2 Decreased risk	1.55 1.27 1.02 0.98 1.20 1.11	[0.99; 2.43] [0.81; 2.00] [0.88; 1.18] [0.82; 1.18] [0.95; 1.52] [0.95; 1.31]

Figure S2b (continued)

Study	N	Cases		OR	95%-CI
Sleep problems	600	101	Ŀ	4.04	10 04 4 001
SEBAS MHAS	602 865	191 389		1.04 1.01	[0.84; 1.29]
MIAS	949	213		1.13	[0.88; 1.15] [0.98; 1.30]
NSHAP	1807	427		1.09	[1.00; 1.19]
NHANES 2005	3933	479		1.22	[1.13; 1.32]
WHI	4133	919		0.99	[0.93; 1.06]
NHANES 2017	4325	704		1.19	[1.11; 1.28]
NHANES 2015	4497	667		1.10	[1.03; 1.17]
TILDA	4704	832		1.19	[1.09; 1.30]
NHANES 2007	4751	816		1.16	[1.09; 1.24]
NHANES 2009	4914	817		1.14	[1.07; 1.21]
ELSA	5490	1860		1.13	[1.07; 1.19]
UKHLS	5615	921		1.05	[0.99; 1.12]
HRS Overall effect	8580	2599	-8-	1.07	[1.03; 1.12]
Overall effect Heterogeneity: <i>I</i> ² = 63% [33%; 79%], τ^2 = 0.0027, <i>p</i> < 0.01, <i>R_b</i> = 61% [29%; 93%]			•	1.11	[1.07; 1.15]
Heterogeneity, $T = 65\% [55\%, 75\%], \tau = 0.0027, p < 0.01, R_b = 61\% [25\%, 55\%]$					
Talked less than usual					
MIDUS	949	94		1.03	[0.85; 1.24]
WHII	4133	370		1.07	[0.97; 1.18]
TILDA	4704	217		1.03	[0.86; 1.23]
Overall effect			-	1.05	[0.98; 1.14]
Heterogeneity: $I^2 = 0\% [0\%; 3\%], \tau^2 = < 0.0001, p = 0.90, R_b = 1\% [0\%; 100\%]$					
Thought you would be better off dead					
NHANES 2005	3933	31		1.05	[0.80; 1.38]
NHANES 2017	4325	42	<u>-</u> -	0.99	[0.74; 1.32]
NHANES 2015	4497	57		1.31	[1.06; 1.62]
NHANES 2007 NHANES 2009	4751 4914	59 54		1.37 1.13	[1.11; 1.70]
Overall effect	4914	54		1.13	[0.91; 1.41] [1.03; 1.36]
Heterogeneity: $I^2 = 21\% [0\%; 67\%], \tau^2 = 0.0098, p = 0.28, R_b = 40\% [0\%; 100\%]$				1.10	[1.05, 1.50]
Trouble concentrating					
MIDUS	949	121		1.14	[0.96; 1.35]
NHANES 2005	3933	171		1.10	[0.97; 1.24]
WHII	4133	694		1.06	[0.99; 1.14]
NHANES 2017	4325	271		1.08	[0.97; 1.21]
NHANES 2015	4497	276		1.19	[1.08; 1.32]
TILDA	4704	405		0.97	[0.85; 1.11]
NHANES 2007	4751	272		1.15	[1.04; 1.27]
NHANES 2009	4914	303		1.20	[1.09; 1.32]
UKHLS Overall effect	5615	785		1.07 1.11	[1.00; 1.14]
Overall effect Heterogeneity: $I^2 = 33\%$ [0%; 69%], $\tau^2 = 0.0024$, $p = 0.15$, $R_b = 47\%$ [0%; 100%]			-	1.11	[1.05; 1.16]
Hereingenergy, $r = 35\% [0\%, 03\%], r = 0.0024, p = 0.15, n_b = 47\% [0\%, 100\%]$					
			0.75 1 1.5		

0.75 1 1.5 Decreased risk Increased risk

FIGURE S2c. Random-effects meta-analysis of the cross-sectional association between C-reactive protein and individual depression symptoms (adjusted for age, sex & chronic illness-related factors)

Study	N	Cases		OR	95%-CI
Bothered by things MIDUS WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 89%], $\tau^2 = 0.0020$, $p = 0.38$, $R_b = 25\%$ [0%; 100%]	949 4133 4704	44 285 322		0.99 1.00 1.13 1.05	[0.75; 1.30] [0.89; 1.12] [0.98; 1.30] [0.95; 1.16]
Changes in appetite SEBAS MIDUS NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2015 TILDA NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $l^2 = 0\%$ [0%; 28%], $r^2 = 0.0003$, $p = 0.86$, $R_b = 10\%$ [0%; 100%]	602 949 1807 3933 4133 4325 4497 4704 4751 4914	80 33 209 250 418 411 164 430 454		1.24 1.26 1.24 1.19 1.20 1.21 1.25 1.14 1.28 1.21	$\begin{matrix} [0.95; 1.62] \\ [0.93; 1.71] \\ [1.09; 1.41] \\ [1.08; 1.32] \\ [1.02; 1.41] \\ [1.09; 1.32] \\ [1.12; 1.31] \\ [1.04; 1.50] \\ [1.05; 1.23] \\ [1.18; 1.38] \\ [1.17; 1.26] \end{matrix}$
Could not get going/energy SEBAS MHAS MIDUS CRELES NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2015 TILDA NHANES 2007 NHANES 2009 ELSA HRS Overall effect	602 865 949 1186 1807 3933 4133 4133 4325 4497 4704 4751 4914 5490 8580	95 462 87 170 313 563 314 754 781 226 810 807 888 3674		1.02 1.15 1.28 1.21 1.10 1.18 1.14 1.14 1.21 1.37 1.20 1.18 1.29 1.15 1.19	$\begin{matrix} [0.77; 1.35] \\ [1.01; 1.31] \\ [1.05; 1.56] \\ [0.96; 1.52] \\ [0.99; 1.22] \\ [1.10; 1.27] \\ [1.03; 1.27] \\ [1.06; 1.22] \\ [1.14; 1.29] \\ [1.14; 1.29] \\ [1.13; 1.27] \\ [1.11; 1.25] \\ [1.20; 1.38] \\ [1.11; 1.19] \\ [1.14; 1.23] \end{matrix}$
Heterogeneity: $l^2 = 28\% [0\%; 62\%], \tau^2 = 0.0022, p = 0.16, R_b = 48\% [0\%; 100\%]$ Could not shake off the blues MIDUS WHII TILDA Overall effect Heterogeneity: $l^2 = 0\% [0\%; 84\%], \tau^2 = 0.0017, p = 0.53, R_b = 18\% [0\%; 100\%]$	949 4133 4704	45 211 169		1.09 1.12 1.26 1.16	[0.83; 1.43] [0.98; 1.27] [1.05; 1.51] [1.04; 1.29]
Did not enjoy life MHAS MIDUS CRELES NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 24\%$ [0%; 64%], $\tau^2 = 0.0030$, $p = 0.23$, $R_b = 46\%$ [0%; 100%]	865 949 1186 1807 4133 4704 5490 5615 8580	193 123 42 202 603 436 462 885 600		0.98 1.06 1.29 1.07 1.00 1.19 1.16 1.10 1.07 1.08	[0.83; 1.15] [0.89; 1.26] [0.86; 1.94] [0.94; 1.21] [0.92; 1.09] [1.05; 1.34] [1.06; 1.27] [1.03; 1.17] [1.00; 1.15] [1.03; 1.14]
Feeling bad about yourself NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $l^2 = 0\%$ [0%; 46%], $\tau^2 = 0.0003$, $p = 0.82$, $R_b = 9\%$ [0%; 100%]	3933 4325 4497 4751 4914	148 219 250 279 286	0.75 1 1.5 Decreased risk	1.14 1.08 1.15 1.19 1.15 1.15	[1.00; 1.30] [0.96; 1.22] [1.04; 1.27] [1.08; 1.31] [1.05; 1.26] [1.09; 1.20]

Decreased risk Increased risk

Figure S2c (continued)

Study	N	Cases		OR	95%-CI
Felt depressed MHAS MIDUS NSHAP NHANES 2005 WHI NHANES 2017 NHANES 2015 TILDA NHANES 2007 NHANES 2009 ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 45\%$ [0%; 71%], $\tau^2 = 0.0033$, $p = 0.04$, $R_b = 56\%$ [0%; 100%]	865 949 1807 3933 4133 4325 4497 4704 4751 4914 5490 5615 8580	303 72 270 234 300 325 325 229 363 390 602 1028 1118		1.02 1.19 1.03 1.13 0.98 1.07 1.12 1.28 1.10 1.19 1.21 1.06 1.11 1.11	[0.88; 1.18] [0.96; 1.47] [0.93; 1.15] [1.02; 1.26] [0.88; 1.09] [1.02; 1.22] [1.09; 1.50] [1.01; 1.20] [1.09; 1.50] [1.12; 1.31] [0.99; 1.13] [1.06; 1.17] [1.06; 1.16]
Felt everything was an effort SEBAS MHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: I^2 = 81% [63%; 90%], τ^2 = 0.0157, $p < 0.01$, R_b = 77% [32%; 100%]	602 865 949 1807 4133 4704 5490 8580	116 313 68 295 394 284 907 1954		1.08 0.95 1.25 1.31 1.08 1.46 1.36 1.23 1.21	[0.84; 1.39] [0.82; 1.10] [1.00; 1.56] [1.18; 1.46] [0.98; 1.19] [1.27; 1.67] [1.27; 1.45] [1.18; 1.28] [1.10; 1.34]
Felt fearful MIDUS WHI TILDA Overall effect Heterogeneity: $I^2 = 66\% [0\%; 90\%], \tau^2 = 0.0178, p = 0.05, R_b = 59\% [3\%; 100\%]$	949 4133 4704	24 165 178		0.89 0.93 1.22 1.02	[0.61; 1.29] [0.80; 1.08] [1.02; 1.46] [0.84; 1.25]
Felt hopeless about the future MIDUS CRELES WHII TILDA Overall effect Heterogeneity: $I^2 = 0\% [0\%; 64\%], \tau^2 = 0.0006, p = 0.74, R_b = 16\% [0\%; 100\%]$	949 1186 4133 4704	220 132 855 788		0.97 1.10 1.04 1.06 1.04	[0.84; 1.12] [0.84; 1.44] [0.97; 1.12] [0.96; 1.17] [0.98; 1.10]
Felt lonely SEBAS MHAS MIDUS NSHAP WHII TIIDA ELSA HRS Overall effect Heterogeneity: $I^2 = 0\%$ [<0%; <0%], $\tau^2 = < 0.0001$, $p = 0.99$, $R_b = 3\%$ [<0%; <100%]	602 865 949 1807 4133 4704 5490 8580	57 255 69 311 286 318 564 1261		1.14 1.14 1.15 1.10 1.06 1.13 1.12 1.13 1.12	[0.82; 1.58] [0.98; 1.33] [0.92; 1.44] [0.99; 1.22] [0.95; 1.19] [1.03; 1.21] [1.03; 1.21] [1.07; 1.19] [1.08; 1.16]
Felt sad MHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 71%], $\tau^2 = 0.0013$, $p = 0.42$, $R_b = 33\%$ [0%; 100%]	865 949 1807 4133 4704 5490 8580	368 68 336 250 322 926 1467	0.75 1 1.5 Decreased risk	1.08 1.04 1.03 0.94 1.11 1.05 1.09 1.05	[0.94; 1.24] [0.84; 1.29] [0.93; 1.14] [0.83; 1.06] [0.97; 1.28] [0.98; 1.12] [1.04; 1.14] [1.01; 1.10]

Figure S2c (continued)

Study	N	Cases		OR	95%-CI
Felt unhappy MHAS MIDUS CRELES NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 52\%$ [0%; 77%], $\tau^2 = 0.0076$, $p = 0.03$, $R_b = 68\%$ [0%; 100%]	865 949 1186 1807 4133 4704 5490 5615 8580	171 125 106 313 696 517 514 706 1014		1.04 1.14 1.49 1.12 1.01 1.21 1.10 1.02 1.06 1.10	[0.87; 1.24] [0.96; 1.35] [1.14; 1.94] [1.01; 1.24] [0.94; 1.09] [1.08; 1.35] [1.01; 1.20] [0.95; 1.10] [1.00; 1.12] [1.02; 1.18]
Felt worse than others MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 23% [0%; 92%], τ^2 = 0.0029, p = 0.27, R_b = 47% [0%; 100%]	949 4133 4704	142 687 503		1.17 1.01 1.03 1.05	[0.99; 1.38] [0.94; 1.09] [0.92; 1.16] [0.96; 1.15]
Had crying spells MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 38% [0%; 80%], τ^2 = 0.0187, p = 0.20, R_b = 53% [0%; 100%]	949 4133 4704	21 74 150		1.56 1.06 1.24 1.22	[1.06; 2.30] [0.86; 1.31] [1.02; 1.51] [0.99; 1.51]
Life had been a failure MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 58% [0%; 88%], τ^2 = 0.0148, p = 0.09, R_b = 55% [0%; 100%]	949 4133 4704	29 169 143		1.36 1.00 1.25 1.15	[0.98; 1.89] [0.86; 1.16] [1.02; 1.53] [0.96; 1.39]
Little interest in doing things/unmotivated NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 HRS Overall effect Heterogeneity: $I^2 = 18\% [0\%; 63\%], \tau^2 = 0.0010, p = 0.29, R_B = 39\% [0\%; 100\%]$	3933 4325 4497 4751 4914 8580	232 393 419 337 409 1675	-=- -=- =- -=- == =	1.16 1.24 1.10 1.20 1.24 1.20 1.19	[1.04; 1.29] [1.13; 1.36] [1.02; 1.19] [1.09; 1.32] [1.14; 1.34] [1.15; 1.26] [1.14; 1.24]
Moving or speaking slowly or too fast NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: I^2 = 11% [0%; 81%], τ^2 = 0.0021, p = 0.34, R_b = 32% [0%; 100%]	3933 4325 4497 4751 4914	92 173 172 180 196		1.18 1.07 1.06 1.06 1.22 1.11	[1.00; 1.39] [0.93; 1.23] [0.94; 1.20] [0.94; 1.20] [1.09; 1.37] [1.04; 1.20]
People dislike me MIDUS NSHAP WHII TILDA Overall effect Heterogeneity: I^2 = 49% [0%; 83%], τ^2 = 0.0258, p = 0.12, R_b = 60% [0%; 100%]	949 1807 4133 4704	26 101 77 71		1.19 1.26 1.14 0.79 1.11	[0.84; 1.68] [1.06; 1.49] [0.93; 1.40] [0.56; 1.11] [0.90; 1.35]
People were unfriendly SEBAS MIDUS NSHAP WHII TILDA Overall effect Heterogeneity: I^2 = 40% [0%; 78%], τ^2 = 0.0204, p = 0.15, R_b = 52% [0%; 100%]	602 949 1807 4133 4704	17 14 147 101 97	0.5 1 2 Decreased risk	1.57 1.33 1.06 0.95 1.24 1.14	[1.01; 2.44] [0.84; 2.11] [0.92; 1.22] [0.79; 1.15] [0.98; 1.57] [0.96; 1.35]

Figure S2c (continued)

Study	N	Cases		OR	95%-CI
Sleep problems SEBAS MHAS MIDUS NSHAP NHANES 2005 WHI NHANES 2017 NHANES 2015 TILDA NHANES 2007 NHANES 2009 ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 61\%$ [30%; 78%], $\tau^2 = 0.0028$, $p < 0.01$, $R_p = 61\%$ [24%; 98%]	602 865 949 1807 3933 4133 4325 4497 4704 4751 4914 5490 5615 8580	191 389 213 427 479 919 704 667 832 816 817 1860 921 2599		$\begin{array}{c} 1.04\\ 1.00\\ 1.09\\ 1.10\\ 1.22\\ 0.99\\ 1.19\\ 1.11\\ 1.21\\ 1.15\\ 1.15\\ 1.15\\ 1.15\\ 1.06\\ 1.08\\ 1.11 \end{array}$	
Talked less than usual MIDUS WHII TILDA Overall effect Heterogeneity: $l^2 = 0\% [0\%; 0\%], \tau^2 = < 0.0001, p = 0.96, R_b = 0\% [0\%; 100\%]$	949 4133 4704	94 370 217		1.04 1.07 1.05 1.06	[0.86; 1.25] [0.97; 1.18] [0.88; 1.25] [0.98; 1.15]
Thought you would be better off dead NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $I^2 = 10\% [0\%; 81\%], \tau^2 = 0.0082, p = 0.35, R_b = 36\% [0\%; 100\%]$	3933 4325 4497 4751 4914	31 42 57 59 54		1.06 0.98 1.27 1.36 1.15 1.18	[0.80; 1.40] [0.73; 1.31] [1.03; 1.57] [1.10; 1.68] [0.93; 1.43] [1.03; 1.34]
Trouble concentrating MIDUS NHANES 2005 WHII NHANES 2017 NHANES 2015 TILDA NHANES 2007 NHANES 2009 UKHLS Overall effect Heterogeneity: $I^2 = 36\% [0\%; 71\%], \tau^2 = 0.0024, p = 0.13, R_b = 46\% [0\%; 100\%]$	949 3933 4133 4325 4497 4704 4751 4914 5615	121 171 694 271 276 405 272 303 785		1.12 1.11 1.05 1.09 1.19 0.98 1.15 1.21 1.07 1.11	[0.94; 1.33] [0.98; 1.25] [0.97; 1.13] [0.97; 1.22] [1.08; 1.31] [0.86; 1.12] [1.04; 1.27] [1.11; 1.32] [1.00; 1.15] [1.06; 1.16]
Heterogeneity: I^{2} = 36% [0%; 71%], τ^{2} = 0.0024, p = 0.13, R_{b} = 46% [0%; 100%]			0.75 1 1.5		

0.75 1 1.5 Decreased risk Increased risk

FIGURE S2d. Random-effects meta-analysis of the cross-sectional association between C-reactive protein and individual depression symptoms (adjusted for age, sex & behavioural factors)

Study	N	Cases		OR	95%-CI
Bothered by things MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 49% [0%; 85%], τ^2 = 0.0054, p = 0.14, R_b = 41% [0%; 100%]	949 4133 4704	44 285 322		0.96 0.88 1.07 0.96	[0.71; 1.30] [0.78; 1.00] [0.92; 1.24] [0.85; 1.09]
Changes in appetite SEBAS MIDUS NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2015 TILDA NHANES 2007 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $I^2 = 0\% [0\%; 59\%], \tau^2 = 0.0019, p = 0.51, R_b = 30\% [0\%; 100\%]$	602 949 1807 3933 4133 4325 4497 4704 4751 4914	80 33 209 250 129 418 411 164 430 454		1.23 1.24 1.23 1.10 1.18 1.09 1.06 1.25 1.05 1.14 1.12	[0.94; 1.61] [0.88; 1.75] [1.09; 1.39] [0.98; 1.23] [0.99; 1.40] [0.96; 1.17] [1.03; 1.51] [0.96; 1.15] [1.04; 1.24] [1.07; 1.18]
Could not get going/energy SEBAS MHAS MIDUS CRELES NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2017 TILDA NHANES 2015 TILDA NHANES 2007 NHANES 2009 ELSA HRS Overall effect Heterogeneity: $l^2 = 15\% [0\%; 54\%], \tau^2 = 0.0012, p = 0.29, R_b = 33\% [0\%; 100\%]$	602 865 949 1186 1807 3933 4133 4325 4497 4704 4751 4914 5490 8580	95 462 87 170 313 563 314 754 781 226 810 807 888 3674		1.01 1.13 1.11 1.17 1.07 1.11 1.05 1.02 1.10 1.24 1.16 1.08 1.12 1.04 1.09	$ \begin{bmatrix} 0.76; 1.34] \\ 0.98; 1.31] \\ 0.98; 1.39 \\ 0.92; 1.48] \\ 0.96; 1.20] \\ 1.02; 1.20] \\ 1.02; 1.20] \\ 1.02; 1.18] \\ 1.05; 1.18] \\ 1.05; 1.46] \\ 1.08; 1.24] \\ 1.01; 1.16] \\ 1.04; 1.20] \\ 1.00; 1.08] \\ 1.06; 1.13] $
Could not shake off the blues MIDUS WHII TILDA Overall effect Heterogeneity: $l^2 = 0\% [0\%; 81\%], \tau^2 = 0.0020, p = 0.58, R_b = 17\% [0\%; 100\%]$	949 4133 4704	45 211 169		0.94 1.01 1.12 1.03	[0.69; 1.28] [0.88; 1.16] [0.92; 1.37] [0.91; 1.16]
Did not enjoy life MHAS MIDUS CRELES NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 15\%$ [0%; 57%], $\tau^2 = 0.0030$, $p = 0.31$, $R_b = 44\%$ [0%; 100%]	865 949 1186 1807 4133 4704 5490 5615 8580	193 123 42 202 603 436 462 885 600		1.05 0.96 1.26 1.05 0.96 1.16 1.07 1.02 0.98 1.03	[0.88; 1.25] [0.79; 1.17] [0.84; 1.89] [0.92; 1.19] [0.88; 1.05] [1.02; 1.32] [0.97; 1.18] [0.95; 1.10] [0.91; 1.05] [0.97; 1.09]
Feeling bad about yourself NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2009 Overall effect Heterogeneity: $l^2 = 0\%$ [<0%; <0%], $\tau^2 = < 0.0001$, $p = 0.98$, $R_b = 1\%$ [<0%; <100%]	3933 4325 4497 4751 4914	148 219 250 279 286	0.75 1 1.5	1.06 1.04 1.02 1.07 1.04 1.05	[0.92; 1.23] [0.90; 1.20] [0.91; 1.15] [0.96; 1.19] [0.93; 1.16] [0.99; 1.11]

0.75 1 1.5 Decreased risk Increased risk

Figure S2d (continued)

Study	Ν	Cases		OR	95%-CI
Felt depressed MHAS MIDUS NSHAP NHANES 2005 WHI NHANES 2017 NHANES 2015 TILDA NHANES 2007 NHANES 2009 ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 53%], $\tau^2 = 0.0012$, $p = 0.53$, $R_b = 30\%$]	865 949 1807 3933 4133 4325 4497 4704 4704 4751 4914 5490 5615 8580	303 72 270 234 300 325 325 229 363 390 602 1028 1118		1.04 1.07 0.97 1.07 0.95 1.02 1.04 1.15 1.01 1.11 1.08 0.98 1.03 1.03	[0.89; 1.21] [0.84; 1.37] [0.86; 1.09] [0.95; 1.20] [0.94; 1.07] [0.91; 1.15] [0.94; 1.16] [0.97; 1.36] [0.91; 1.12] [1.01; 1.21] [0.99; 1.18] [0.92; 1.05] [0.98; 1.09] [1.00; 1.07]
Felt everything was an effort SEBAS MHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: I^2 = 48% [0%; 77%], τ^2 = 0.0052, p = 0.06, R_b = 55%	602 865 949 1807 4133 4704 5490 8580	116 313 68 295 394 284 907 1954		1.04 0.96 1.13 1.08 1.04 1.30 1.19 1.14 1.11	[0.81; 1.34] [0.83; 1.12] [0.88; 1.45] [0.98; 1.19] [0.94; 1.16] [1.12; 1.50] [1.10; 1.28] [1.09; 1.19]
Felt fearful MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 63% [0%; 89%], τ^2 = 0.0253, p = 0.07, R_b = 62%	949 4133 4704	24 165 178		0.77 0.91 1.17 0.97	[0.50; 1.18] [0.78; 1.07] [0.97; 1.42] [0.77; 1.22]
Felt hopeless about the future MIDUS CRELES WHII TILDA Overall effect Heterogeneity: l^2 = 14% [0%; 87%], τ^2 = 0.0034, p = 0.32, R_b = 44%	949 1186 4133 4704 ,[0%; 100%]	220 132 855 788		0.89 1.09 1.01 1.05 1.00	[0.76; 1.04] [0.83; 1.43] [0.94; 1.09] [0.95; 1.17] [0.92; 1.09]
Felt lonely SEBAS MHAS MIDUS NSHAP WHI TIIDA ELSA HRS Overall effect Heterogeneity: $I^2 = 0\% [0\%; 51\%], \tau^2 = 0.0022, p = 0.70, R_b = 35\%$	602 865 949 1807 4133 4704 5490 8580 (0%; 100%]	57 255 69 311 286 318 564 1261		1.13 1.15 0.89 1.04 1.01 1.12 1.02 1.06 1.05	[0.81; 1.57] [0.97; 1.36] [0.69; 1.15] [0.93; 1.16] [0.90; 1.14] [0.97; 1.30] [0.93; 1.11] [1.00; 1.12] [0.99; 1.11]
Felt sad MHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 70%], $\tau^2 = 0.0018$, $p = 0.43$, $R_b = 36\%$	865 949 1807 4133 4704 5490 8580	368 68 336 250 322 926 1467	0.75 1 1.5 Decreased risk	1.04 0.98 0.99 0.88 1.08 0.98 1.02 0.99	[0.90; 1.21] [0.77; 1.25] [0.89; 1.11] [0.77; 1.00] [0.93; 1.26] [0.91; 1.05] [0.97; 1.08] [0.94; 1.05]

Decreased risk Increased risk

Figure S2d (continued)

Study	Ν	Cases		OR	95%-CI
Felt unhappy MHAS MIDUS CRELES NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 54\%$ [2%; 78%], $\tau^2 = 0.0089$, $p = 0.03$, $R_b = 68\%$ [0%; 100%]	865 949 1186 1807 4133 4704 5490 5615 8580	171 125 106 313 696 517 514 706 1014		1.09 1.05 1.45 1.08 0.98 1.16 1.02 0.96 0.98 1.05	[0.91; 1.30] [0.87; 1.27] [1.11; 1.90] [0.97; 1.21] [0.90; 1.06] [1.03; 1.31] [0.93; 1.12] [0.88; 1.04] [0.93; 1.04] [0.97; 1.13]
Felt worse than others MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 86%], τ^2 = 0.0015, p = 0.49, R_b = 29% [0%; 100%]	949 4133 4704	142 687 503		1.13 1.01 1.00 1.03	[0.95; 1.35] [0.93; 1.10] [0.88; 1.14] [0.95; 1.12]
Had crying spells MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 13% [0%; 91%], τ^2 = 0.0103, p = 0.32, R_b = 35% [0%; 100%]	949 4133 4704	21 74 150		1.33 0.97 1.19 1.12	[0.85; 2.09] [0.77; 1.23] [0.96; 1.47] [0.92; 1.36]
Life had been a failure MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 28% [0%; 92%], τ^2 = 0.0068, p = 0.25, R_b = 35% [0%; 100%]	949 4133 4704	29 169 143		1.20 0.96 1.17 1.06	[0.82; 1.75] [0.82; 1.12] [0.95; 1.45] [0.91; 1.25]
Little interest in doing things/unmotivated NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 HRS Overall effect Heterogeneity: $I^2 = 9\% [0\%; 77\%], \tau^2 = 0.0012, p = 0.36, R_b = 38\% [0\%; 100\%]$	3933 4325 4497 4751 4914 8580	232 393 419 337 409 1675	-⊞- -⊞- -⊞- -⊞ -⊞ €	1.08 1.17 1.01 1.11 1.14 1.10 1.10	[0.96; 1.22] [1.05; 1.30] [0.92; 1.10] [1.00; 1.23] [1.04; 1.25] [1.05; 1.15] [1.05; 1.15]
Moving or speaking slowly or too fast NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: I^2 = 0% [0%; 71%], τ^2 = 0.0013, p = 0.57, R_b = 19% [0%; 100%]	3933 4325 4497 4751 4914	92 173 172 180 196		1.09 1.08 1.05 0.96 1.12 1.06	[0.91; 1.31] [0.92; 1.26] [0.92; 1.20] [0.84; 1.10] [0.98; 1.27] [0.98; 1.13]
People dislike me MIDUS NSHAP WHII TILDA Overall effect Heterogeneity: I^2 = 64% [0%; 88%], τ^2 = 0.0350, p = 0.04, R_b = 62% [5%; 100%]	949 1807 4133 4704	26 101 77 71		0.95 1.25 0.99 0.71 0.99	[0.63; 1.44] [1.04; 1.50] [0.79; 1.25] [0.49; 1.02] [0.78; 1.25]
People were unfriendly SEBAS MIDUS NSHAP WHI TILDA Overall effect Heterogeneity: I^2 = 13% [0%; 82%], τ^2 = 0.0174, p = 0.33, R_b = 47% [0%; 100%]	602 949 1807 4133 4704	17 14 147 101 97	0.5 1 2 Decreased risk	1.58 1.09 0.99 0.97 1.13 1.07	[1.00; 2.49] [0.62; 1.91] [0.85; 1.15] [0.81; 1.17] [0.87; 1.46] [0.90; 1.27]

Figure S2d (continued)

Study	N	Cases		OR	95%-CI
Sleep problems					
SEBAS	602	191		1.05	[0.85; 1.30]
MHAS	865	389		0.98	[0.84; 1.14]
MIDUS	949	213		1.09	[0.94; 1.27]
NSHAP	1807	427		1.08	[0.98; 1.19]
NHANES 2005	3933	479		1.20	[1.10; 1.31]
WHII	4133	919		0.95	[0.88; 1.02]
NHANES 2017	4325	704		1.10	[1.01; 1.20]
NHANES 2015	4497	667		1.02	[0.95; 1.10]
TILDA	4704	832		1.15	[1.04; 1.27]
NHANES 2007	4751	816		1.08	[1.01; 1.16]
NHANES 2009	4914	817		1.08	[1.01; 1.15]
ELSA	5490	1860		1.07	[1.01; 1.14]
UKHLS HRS	5615	921		0.96	[0.89; 1.03]
Overall effect	8580	2599		1.03 1.06	[0.99; 1.08]
Heterogeneity: $l^2 = 58\%$ [23%; 77%], $\tau^2 = 0.0028$, $p < 0.01$, $R_b = 58\%$ [21%; 95%]			-	1.00	[1.02; 1.10]
Herefore the second state of the second state					
Talked less than usual					
MIDUS	949	94	<u> </u>	0.99	[0.80; 1.22]
WHI	4133	370		1.00	[0.90; 1.12]
TILDA	4704	217		1.03	[0.86; 1.24]
Overall effect			-	1.00	[0.92; 1.09]
Heterogeneity: $I^2 = 0\% [0\%; 0\%], \tau^2 = < 0.0001, p = 0.95, R_b = 0\% [0\%; 100\%]$					
Thought you would be better off dead					
NHANES 2005	3933	31		0.97	[0.71; 1.32]
NHANES 2017	4325	42		0.96	[0.69; 1.33]
NHANES 2015	4497	57		1.17	[0.91; 1.50]
NHANES 2007	4751	59		1.32	[1.05; 1.66]
NHANES 2009	4914	54		1.01	[0.80; 1.28]
Overall effect Heterogeneity: <i>I</i> ² = 11% [0%; 82%], τ ² = 0.0090, <i>p</i> = 0.34, <i>R_b</i> = 33% [0%; 100%]				1.10	[0.95; 1.27]
Here observes $r = 11\% [0\%, 02\%], r = 0.0000, p = 0.34, R_b = 33\% [0\%, 100\%]$					
Trouble concentrating	0.10	404		4.00	10.00.4.003
MIDUS	949	121		1.09	[0.90; 1.33]
NHANES 2005	3933	171		1.06	[0.93; 1.21]
WHII	4133	694		1.06	[0.97; 1.15]
NHANES 2017 NHANES 2015	4325 4497	271 276		1.10 1.16	[0.97; 1.25]
TILDA	4497	405		1.10	[1.04; 1.30] [0.87; 1.17]
NHANES 2007	4704	272		1.01	[0.95; 1.19]
NHANES 2007 NHANES 2009	4914	303		1.12	[1.01; 1.25]
UKHLS	5615	785	···	0.99	[0.92; 1.07]
Overall effect	0010	100		1.07	[1.02; 1.11]
Heterogeneity: $I^2 = 0\%$ [0%; 62%], $\tau^2 = 0.0010$, $p = 0.49$, $R_b = 24\%$ [0%; 100%]				1101	[
			r 1 1		
			075 4 45		

0.75 1 1.5 Decreased risk Increased risk

FIGURE S3a. Random-effects meta-analysis of the longitudinal association between C-reactive protein and individual depression symptoms (adjusted for age, sex & individual baseline symptom)

Study	N	Cases		OR	95%-CI
Bothered by things WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0002$, $p = 0.60$, $R_b = 3\%$ [0%; 100%]	3636 4327	179 297		1.07 1.13 1.10	[0.93; 1.23] [0.98; 1.31] [0.99; 1.22]
Changes in appetite NSHAP WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 52%], $\tau^2 = 0.0003$, $p = 0.80$, $R_b = 3\%$ [0%; 100%]	1370 3636 4327	134 70 143		1.14 1.10 1.21 1.15	[0.97; 1.33] [0.89; 1.36] [0.99; 1.47] [1.03; 1.28]
Could not get going/energy MHAS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $l^2 = 45\%$ [0%; 78%], $\tau^2 = 0.0037$, $p = 0.11$, $R_b = 54\%$ [0%; 100%]	755 1370 3636 4327 4853 6090	369 232 235 197 828 2,720		1.00 1.05 1.02 1.21 1.19 1.13 1.10	[0.87; 1.15] [0.93; 1.19] [0.90; 1.16] [1.02; 1.44] [1.10; 1.28] [1.08; 1.19] [1.03; 1.18]
Could not shake off the blues WHII TILDA Overall effect Heterogeneity: I^2 = 46%, τ^2 = 0.0075, p = 0.18, R_b = 47% [0%; 100%]	3636 4327	126 158		1.03 1.23 1.12	[0.87; 1.22] [1.02; 1.49] [0.94; 1.34]
Did not enjoy life MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 59\%$ [5%; 82%], $\tau^2 = 0.0044$, $p = 0.02$, $R_b = 56\%$ [10%; 100%]	755 1370 3636 4327 4853 4978 6090	145 134 546 333 366 725 409		1.04 1.13 0.93 1.21 1.07 1.11 1.12 1.08	[0.87; 1.24] [0.96; 1.33] [0.85; 1.02] [1.06; 1.39] [0.96; 1.19] [1.03; 1.20] [1.02; 1.22] [1.01; 1.15]
Felt depressed MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 54\%$ [0%; 80%], $\tau^2 = 0.0058$, $p = 0.04$, $R_b = 62\%$ [0%; 100%]	755 1370 3636 4327 4853 4978 6090	229 180 224 220 483 787 628		1.21 0.90 1.02 1.07 1.12 1.07 1.16 1.08	[1.03; 1.43] [0.78; 1.03] [0.90; 1.16] [0.90; 1.27] [1.02; 1.23] [1.00; 1.15] [1.07; 1.25] [1.00; 1.16]
Felt everything was an effort MHAS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $l^2 = 0\%$ [0%; 0%], $\tau^2 = 0.0002$, $p = 0.96$, $R_b = 6\%$ [0%; 100%]	755 1370 3636 4327 4853 6090	249 203 277 252 780 1,178	0.8 1 1.25 Decreased risk	1.10 1.20 1.15 1.10 1.16 1.15 1.15	[0.94; 1.29] [1.05; 1.37] [1.03; 1.29] [0.94; 1.29] [1.07; 1.25] [1.08; 1.22] [1.10; 1.20]

Figure S3a (continued)

Study	N	Cases		OR	95%-CI
Felt fearful WHII TILDA Overall effect Heterogeneity: <i>I</i> ² = 59% [0%; 90%], τ ² = 0.0097, <i>p</i> = 0.12, <i>R</i> _b = 58% [0%; 100%]	3636 4327	152 169		0.97 1.17 1.06	[0.84; 1.13] [0.98; 1.40] [0.88; 1.26]
Felt hopeless about the future WHII TILDA Overall effect Heterogeneity: I^2 = 78% [4%; 95%], τ^2 = 0.0065, p = 0.03, R_b = 76% [22%; 100%]	3636 4327	855 683		1.02 1.17 1.09	[0.95; 1.10] [1.06; 1.30] [0.96; 1.24]
Felt lonely MHAS NSHAP WHII TIIDA ELSA HRS Overall effect Heterogeneity: $I^2 = 53\%$ [0%; 81%], $\tau^2 = 0.0030$, $p = 0.06$, $R_b = 45\%$ [0%; 94%]	755 1370 3636 4327 4853 6090	227 227 233 235 447 811		1.06 1.03 1.03 1.17 1.07 1.22 1.10	[0.90; 1.25] [0.91; 1.17] [0.91; 1.17] [1.00; 1.37] [0.97; 1.19] [1.14; 1.31] [1.03; 1.18]
Felt sad MHAS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $I^2 = 56\% [0\%; 82\%], \tau^2 = 0.0035, p = 0.04, R_b = 51\% [0\%; 100\%]$	755 1370 3636 4327 4853 6090	307 260 195 261 742 918		0.99 1.00 0.93 1.08 1.07 1.15 1.05	[0.85; 1.15] [0.89; 1.13] [0.81; 1.07] [0.92; 1.26] [0.99; 1.16] [1.08; 1.22] [0.98; 1.12]
Felt unhappy MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 61\%$ [11%; 83%], $\tau^2 = 0.0038$, $\rho = 0.02$, $R_b = 56\%$ [15%; 97%]	755 1370 3636 4327 4853 4978 6090	130 201 670 430 424 565 651		1.10 0.94 0.97 1.10 1.07 1.08 1.17 1.06	[0.91; 1.33] [0.82; 1.07] [0.99; 1.05] [0.97; 1.25] [0.97; 1.18] [0.99; 1.17] [1.09; 1.26] [1.00; 1.13]
Felt worse than others WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.92$, $R_b = 0\%$ [0%; 100%]	3636 4327	530 271		1.08 1.09 1.08	[0.99; 1.18] [0.93; 1.27] [1.00; 1.17]
Had crying spells WHII TILDA Overall effect Heterogeneity: I^2 = 0%, τ^2 = 0.0028, ρ = 0.38, R_b = 18% [0%; 100%]	3636 4327	64 134		0.99 1.14 1.07	[0.78; 1.25] [0.92; 1.41] [0.90; 1.27]
Life had been a failure WHII TILDA Overall effect Heterogeneity: I^2 = 60% [0%; 91%], τ^2 = 0.0135, p = 0.12, R_b = 59% [0%; 100%]	3636 4327	137 109	0.75 1 1.5 Decreased risk	0.97 1.21 1.07	[0.83; 1.14] [0.97; 1.51] [0.86; 1.32]

Figure S3a (continued)

Study	N	Cases		OR	95%-CI
Little interest in doing things/unmotivated HRS Overall effect Heterogeneity: not applicable	6090	1,153	•	1.15 1.15	[1.09; 1.22] [1.09; 1.22]
People dislike me NSHAP WHI TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 88%], τ^2 = 0.0061, p = 0.41, R_b = 27% [0%; 100%]	1370 3636 4327	69 73 48		0.96 1.13 0.87 1.01	[0.78; 1.19] [0.91; 1.40] [0.58; 1.30] [0.85; 1.20]
People were unfriendly NSHAP WHII TILDA Overall effect Heterogeneity: I^2 = 34% [0%; 78%], τ^2 = 0.0090, p = 0.22, R_b = 39% [0%; 100%]	1370 3636 4327	75 73 74		1.22 0.95 0.99 1.06	[0.99; 1.50] [0.77; 1.18] [0.74; 1.33] [0.89; 1.26]
Sleep problems MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: I^2 = 55% [0%; 81%], τ^2 = 0.0025, p = 0.04, R_b = 57% [1%; 100%]	755 1370 3636 4327 4853 4978 6090	327 323 781 786 1,896 771 1,696		1.01 1.09 1.09 1.22 1.06 1.04 1.16 1.10	[0.87; 1.17] [0.98; 1.22] [1.01; 1.18] [1.11; 1.35] [1.00; 1.13] [0.97; 1.12] [1.10; 1.22] [1.05; 1.15]
Talked less than usual WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.67$, $R_b = 2\%$ [0%; 100%]	3636 4327	264 197		1.09 1.14 1.11	[0.97; 1.22] [0.96; 1.36] [1.00; 1.22]
Trouble concentrating WHII TILDA UKHLS Overall effect Heterogeneity: $I^2 = 0\% [0\%; 85\%], \tau^2 = 0.0008, p = 0.50, R_b = 23\% [0\%; 100\%]$	3636 4327 4978	346 366 786	0.75 1 1.5 Decreased risk	1.08 1.00 1.10 1.07	[0.98; 1.20] [0.87; 1.15] [1.02; 1.19] [1.01; 1.15]

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FIGURE S3b. Random-effects meta-analysis of the longitudinal association between C-reactive protein and individual depression symptoms (adjusted for age, sex, individual baseline symptom & education)

Study	N	Cases		OR	95%-CI
Appetite was poor NSHAP WHII TILDA Overall effect Heterogeneity: $I^2 = 0\% [0\%; 0\%], \tau^2 = < 0.0001, p = 0.94, R_b = 0\% [0\%; 100\%]$	1370 3636 4327	134 70 143		1.15 1.10 1.15 1.14	[0.98; 1.34] [0.89; 1.36] [0.94; 1.40] [1.02; 1.27]
Bothered by things WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.73$, $R_b = 1\%$ [0%; 100%]	3636 4327	179 297		1.07 1.11 1.09	[0.93; 1.24] [0.96; 1.29] [0.98; 1.21]
Could not get going/energy MHAS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $I^2 = 25\%$ [0%; 69%], $\tau^2 = 0.0024$, $p = 0.25$, $R_b = 45\%$ [0%; 100%]	755 1370 3636 4327 4853 6090	369 232 235 197 828 2,720		1.00 1.05 1.02 1.18 1.16 1.13 1.10	[0.87; 1.15] [0.93; 1.19] [0.90; 1.16] [0.99; 1.40] [1.07; 1.25] [1.08; 1.19] [1.04; 1.16]
Could not shake off the blues WHII TILDA Overall effect Heterogeneity: $I^2 = 26\%$, $\tau^2 = 0.0047$, $p = 0.25$, $R_b = 35\%$ [0%; 100%]	3636 4327	126 158		1.03 1.20 1.11	[0.87; 1.22] [0.99; 1.45] [0.94; 1.30]
Did not enjoy life MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 56\%$ [0%; 81%], $\tau^2 = 0.0040$, $p = 0.03$, $R_b = 54\%$ [5%; 100%]	755 1370 3636 4327 4853 4978 6090	145 134 546 333 366 725 409		1.03 1.10 0.93 1.20 1.06 1.10 1.12 1.07	[0.86; 1.23] [0.94; 1.29] [0.85; 1.02] [1.05; 1.38] [0.96; 1.18] [1.02; 1.19] [1.02; 1.22] [1.00; 1.14]
Felt depressed MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: I^2 = 44% [0%; 76%], τ^2 = 0.0049, p = 0.10, R_b = 58% [0%; 100%]	755 1370 3636 4327 4853 4978 6090	229 180 224 220 483 787 628		1.21 0.90 1.03 1.03 1.10 1.05 1.12 1.06	[1.03; 1.42] [0.78; 1.03] [0.90; 1.17] [0.87; 1.22] [1.00; 1.21] [0.98; 1.13] [1.04; 1.21] [0.99; 1.14]
Felt everything was an effort MHAS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $l^2 = 0\% [0\%; 7\%], \tau^2 = 0.0002, p = 0.93, R_b = 8\% [0\%; 100\%]$	755 1370 3636 4327 4853 6090	249 203 277 252 780 1,178	0.8 1 1.25 Decreased risk	1.09 1.17 1.16 1.07 1.13 1.11 1.12	[0.93; 1.27] [1.03; 1.33] [1.03; 1.30] [0.92; 1.25] [1.04; 1.22] [1.05; 1.18] [1.08; 1.17]

Figure S3b (continued)

Study	N	Cases		OR	95%-CI
Felt fearful WHII TILDA Overall effect Heterogeneity: J^2 = 49%, τ^2 = 0.0072, p = 0.16, R_b = 50% [0%; 100%]	3636 4327	152 169		0.97 1.15 1.05	[0.84; 1.13] [0.96; 1.38] [0.89; 1.24]
Felt hopeless about the future WHII TILDA Overall effect Heterogeneity: I^2 = 72% [0%; 94%], τ^2 = 0.0046, p = 0.06, R_b = 70% [2%; 100%]	3636 4327	855 683		1.02 1.15 1.08	[0.95; 1.10] [1.04; 1.27] [0.96; 1.21]
Felt lonely MHAS NSHAP WHII TIIDA ELSA HRS Overall effect Heterogeneity: I^2 = 37% [0%; 75%], τ^2 = 0.0023, p = 0.16, R_b = 38% [0%; 100%]	755 1370 3636 4327 4853 6090	227 227 233 235 447 811		1.05 1.02 1.03 1.17 1.07 1.19 1.10	[0.89; 1.24] [0.89; 1.16] [0.91; 1.17] [0.99; 1.38] [0.97; 1.19] [1.11; 1.28] [1.03; 1.17]
Felt sad MHAS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: I^2 = 41% [0%; 76%], τ^2 = 0.0025, p = 0.13, R_b = 44% [0%; 100%]	755 1370 3636 4327 4853 6090	307 260 195 261 742 918		0.98 1.02 0.94 1.08 1.07 1.13 1.05	[0.84; 1.15] [0.90; 1.15] [0.82; 1.07] [0.92; 1.26] [0.99; 1.16] [1.06; 1.20] [0.99; 1.12]
Felt unhappy MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 54\%$ [0%; 81%], $\tau^2 = 0.0035$, $p = 0.04$, $R_b = 54\%$ [2%; 100%]	755 1370 3636 4327 4853 4978 6090	130 201 670 430 424 565 651		1.09 0.92 0.98 1.09 1.06 1.08 1.15 1.05	[0.90; 1.33] [0.81; 1.05] [0.90; 1.06] [0.96; 1.23] [0.96; 1.17] [0.99; 1.18] [1.07; 1.24] [0.99; 1.12]
Felt worse than others WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.83$, $R_b = 0\%$ [0%; 100%]	3636 4327	530 271		1.08 1.06 1.08	[0.99; 1.17] [0.91; 1.24] [1.00; 1.16]
Had crying spells WHII TILDA Overall effect Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0.0010$, $p = 0.51$, $R_b = 7\%$ [0%; 100%]	3636 4327	64 134		0.99 1.10 1.05	[0.78; 1.25] [0.89; 1.36] [0.89; 1.24]
Life had been a failure WHI TILDA Overall effect Heterogeneity: J^2 = 43%, τ^2 = 0.0082, p = 0.19, R_b = 46% [0%; 100%]	3636 4327	137 109	0.8 1 1.25 Decreased risk Increased risk	0.97 1.17 1.05	[0.83; 1.14] [0.93; 1.47] [0.87; 1.26]

Figure S3b (continued)

Study	Ν	Cases		OR	95%-CI
Little interest in doing things/unmotivated HRS Overall effect Heterogeneity: not applicable	6090	1,153		1.12 1.12	[1.05; 1.19] [1.05; 1.19]
People dislike me NSHAP WHI TILDA Overall effect Heterogeneity: I^2 = 20% [0%; 92%], τ^2 = 0.0104, p = 0.29, R_b = 37% [0%; 100%]	1370 3636 4327	69 73 48		0.93 1.13 0.83 0.99	[0.75; 1.15] [0.91; 1.40] [0.55; 1.25] [0.82; 1.19]
People were unfriendly NSHAP WHII TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 86%], τ^2 = 0.0030, p = 0.49, R_b = 17% [0%; 100%]	1370 3636 4327	75 73 74		1.14 0.96 0.97 1.03	[0.92; 1.41] [0.78; 1.19] [0.72; 1.30] [0.89; 1.19]
Sleep problems MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 54\%$ [0%; 80%], $\tau^2 = 0.0024$, $p = 0.04$, $R_b = 56\%$ [0%; 100%]	755 1370 3636 4327 4853 4978 6090	327 323 781 786 1,896 771 1,696		1.00 1.08 1.09 1.20 1.04 1.03 1.15 1.09	[0.86; 1.16] [0.97; 1.21] [1.01; 1.18] [1.09; 1.33] [0.98; 1.11] [0.95; 1.11] [1.09; 1.21] [1.04; 1.14]
Talked less than usual WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0002$, $p = 0.61$, $R_b = 3\%$ [0%; 100%]	3636 4327	264 197		1.08 1.14 1.10	[0.96; 1.21] [0.96; 1.36] [1.00; 1.21]
Trouble concentrating WHII TILDA UKHLS Overall effect Heterogeneity: $I^2 = 0\% [0\%; 85\%], \tau^2 = 0.0007, p = 0.50, R_b = 22\% [0\%; 100\%]$	3636 4327 4978	346 366 786	0.75 1 1.5 Decreased risk	1.07 1.00 1.10 1.07	[0.97; 1.19] [0.87; 1.15] [1.02; 1.19] [1.00; 1.14]

Decreased risk Increased risk

FIGURE S3c. Random-effects meta-analysis of the longitudinal association between C-reactive protein and individual depression symptoms (adjusted for age, sex, individual baseline symptom & chronic illness-related factors)

Study	N	Cases		OR	95%-CI
Bothered by things WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0002$, $\rho = 0.60$, $R_b = 3\%$ [0%; 100%]	3636 4327	179 297		1.06 1.12 1.09	[0.92; 1.22] [0.97; 1.30] [0.98; 1.21]
Changes in appetite NSHAP WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 61%], $\tau^2 = 0.0004$, $\rho = 0.77$, $R_b = 4\%$ [0%; 100%]	1370 3636 4327	134 70 143		1.11 1.07 1.19 1.12	[0.95; 1.30] [0.86; 1.33] [0.97; 1.45] [1.00; 1.25]
Could not get going/energy MHAS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $I^2 = 51\%$ [0%; 80%], $\tau^2 = 0.0049$, $\rho = 0.07$, $R_b = 59\%$ [0%; 100%]	755 1370 3636 4327 4853 6090	369 232 235 197 828 2,720		0.96 1.05 1.01 1.21 1.18 1.12 1.09	[0.83; 1.11] [0.92; 1.19] [0.89; 1.15] [1.02; 1.44] [1.09; 1.27] [1.07; 1.18] [1.02; 1.17]
Could not shake off the blues WHII TILDA Overall effect Heterogeneity: I^2 = 26%, τ^2 = 0.0047, p = 0.25, R_b = 35% [0%; 100%]	3636 4327	126 158		1.03 1.20 1.11	[0.87; 1.22] [0.99; 1.45] [0.94; 1.30]
Did not enjoy life MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 58\%$ [2%; 82%], $\tau^2 = 0.0041$, $p = 0.03$, $R_b = 55\%$ [7%; 100%]	755 1370 3636 4327 4853 4978 6090	145 134 546 333 366 725 409		1.02 1.08 0.93 1.20 1.05 1.11 1.12 1.07	[0.85; 1.23] [0.92; 1.27] [0.85; 1.02] [1.05; 1.38] [0.95; 1.17] [1.03; 1.19] [1.02; 1.22] [1.00; 1.14]
Feit depressed MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: I^2 = 42% [0%; 76%], τ^2 = 0.0048, p = 0.11, R_b = 57% [0%; 100%]	755 1370 3636 4327 4853 4978 6090	229 180 224 220 483 787 628		1.20 0.90 1.02 1.06 1.11 1.06 1.13 1.07	[1.02; 1.42] [0.78; 1.04] [0.89; 1.16] [0.90; 1.25] [1.01; 1.22] [0.98; 1.14] [1.05; 1.22] [1.00; 1.14]
Felt everything was an effort MHAS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $l^2 = 0\%$ [0%; 17%], $\tau^2 = 0.0003$, $p = 0.91$, $R_b = 10\%$ [0%; 100%]	755 1370 3636 4327 4853 6090	249 203 277 252 780 1,178	0.8 1 1.25 Decreased risk	1.06 1.18 1.15 1.10 1.16 1.13 1.14	[0.90; 1.24] [1.03; 1.35] [1.02; 1.29] [0.94; 1.28] [1.07; 1.25] [1.06; 1.20] [1.09; 1.19]

Figure S3c (continued)

Study	N	Cases		OR	95%-CI
Felt fearful WHII TILDA Overall effect Heterogeneity: J^2 = 55% [0%; 89%], τ^2 = 0.0091, p = 0.13, R_b = 55% [0%; 100%]	3636 4327	152 169		0.98 1.18 1.07	[0.84; 1.15] [0.98; 1.42] [0.89; 1.28]
Felt hopeless about the future WHII TILDA Overall effect Heterogeneity: $I^2 = 66\%$ [0%; 92%], $\tau^2 = 0.0036$, $p = 0.09$, $R_b = 64\%$ [0%; 100%]	3636 4327	855 683		1.03 1.15 1.08	[0.96; 1.11] [1.04; 1.28] [0.97; 1.20]
Felt lonely MHAS NSHAP WHII TIIDA ELSA HRS Overall effect Heterogeneity: f^2 = 48% [0%; 79%], τ^2 = 0.0031, p = 0.09, R_b = 44% [0%; 100%]	755 1370 3636 4327 4853 6090	227 227 233 235 447 811		1.01 1.03 1.03 1.18 1.06 1.20 1.09	[0.85; 1.20] [0.90; 1.17] [0.90; 1.17] [1.00; 1.39] [0.96; 1.18] [1.12; 1.29] [1.02; 1.17]
Felt sad MHAS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: I^2 = 47% [0%; 79%], τ^2 = 0.0030, p = 0.09, R_b = 48% [0%; 100%]	755 1370 3636 4327 4853 6090	307 260 195 261 742 918		0.96 1.01 0.93 1.06 1.07 1.13 1.04	[0.82; 1.12] [0.89; 1.14] [0.81; 1.07] [0.90; 1.24] [0.99; 1.15] [1.06; 1.20] [0.98; 1.11]
Felt unhappy MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 51\%$ [0%; 79%], $\tau^2 = 0.0030$, $p = 0.06$, $R_b = 50\%$ [0%; 100%]	755 1370 3636 4327 4853 4978 6090	130 201 670 430 424 565 651		1.05 0.92 0.97 1.08 1.06 1.06 1.14 1.04	[0.86; 1.28] [0.80; 1.05] [0.95; 1.05] [0.96; 1.17] [0.97; 1.15] [1.06; 1.23] [0.98; 1.10]
Felt worse than others WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.92$, $R_b = 0\%$ [0%; 100%]	3636 4327	530 271		1.08 1.07 1.08	[0.99; 1.18] [0.91; 1.25] [1.00; 1.16]
Had crying spells WHII TILDA Overall effect Heterogeneity: l^2 = 0%, τ^2 = 0.0016, p = 0.46, R_b = 11% [0%; 100%]	3636 4327	64 134		1.00 1.13 1.07	[0.79; 1.27] [0.91; 1.40] [0.90; 1.27]
Life had been a failure WHII TILDA Overall effect Heterogeneity: J^2 = 59% [0%; 90%], τ^2 = 0.0138, p = 0.12, R_b = 59% [0%; 100%]	3636 4327	137 109	0.8 1 1.25 Decreased risk	0.96 1.20 1.06	[0.81; 1.13] [0.96; 1.50] [0.86; 1.31]

Figure S3c (continued)

Study	N	Cases		OR	95%-CI
Little interest in doing things/unmotivated HRS Overall effect Heterogeneity: not applicable	6090	1,153	•	1.13 1.13	[1.07; 1.20] [1.07; 1.20]
People dislike me NSHAP WHI TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 88%], τ^2 = 0.0062, p = 0.42, R_b = 27% [0%; 100%]	1370 3636 4327	69 73 48		0.95 1.11 0.85 1.00	[0.77; 1.18] [0.89; 1.38] [0.57; 1.27] [0.84; 1.18]
People were unfriendly NSHAP WHI TILDA Overall effect Heterogeneity: I^2 = 19% [0%; 92%], τ^2 = 0.0070, p = 0.29, R_b = 33% [0%; 100%]	1370 3636 4327	75 73 74		1.21 0.97 0.98 1.06	[0.98; 1.49] [0.78; 1.21] [0.73; 1.32] [0.90; 1.25]
Sleep problems MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 56\%$ [0%; 81%], $\tau^2 = 0.0030$, $p = 0.04$, $R_b = 61\%$ [0%; 100%]	755 1370 3636 4327 4853 4978 6090	327 323 781 786 1,896 771 1,696		0.97 1.08 1.09 1.21 1.06 1.03 1.15 1.09	[0.83; 1.13] [0.97; 1.21] [1.00; 1.18] [1.10; 1.34] [0.96; 1.13] [0.96; 1.11] [1.09; 1.21] [1.03; 1.15]
Talked less than usual WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0003$, $p = 0.56$, $R_b = 5\%$ [0%; 100%]	3636 4327	264 197		1.06 1.13 1.08	[0.94; 1.20] [0.95; 1.35] [0.98; 1.20]
Trouble concentrating WHII TILDA UKHLS Overall effect Heterogeneity: I^2 = 0% [0%; 85%], τ^2 = 0.0009, p = 0.49, R_b = 25% [0%; 100%]	3636 4327 4978	346 366 786	0.75 1 1.5 Decreased risk	1.08 0.99 1.09 1.07	[0.97; 1.20] [0.86; 1.14] [1.01; 1.18] [1.00; 1.14]

FIGURE S3d. Random-effects meta-analysis of the longitudinal association between C-reactive protein and individual depression symptoms (adjusted for age, sex, individual baseline symptom & behavioural factors)

Study	N	Cases		OR	95%-CI
Bothered by things WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\rho = 1.00$, $R_b = 0\%$ [0%; 100%]	3636 4327	179 297		1.09 1.09 1.09	[0.94; 1.27] [0.93; 1.28] [0.98; 1.22]
Changes in appetite NSHAP WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 64%], $\tau^2 = 0.0006$, $p = 0.75$, $R_b = 6\%$ [0%; 100%]	1370 3636 4327	134 70 143		1.17 1.08 1.22 1.16	[0.99; 1.38] [0.85; 1.37] [0.99; 1.51] [1.03; 1.31]
Could not get going/energy MHAS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 74%], $\tau^2 = 0.0016$, $p = 0.43$, $R_b = 33\%$ [0%; 100%]	755 1370 3636 4327 4853 6090	369 232 235 197 828 2,720		0.95 0.94 0.99 1.07 1.08 1.05 1.03	[0.81; 1.11] [0.82; 1.07] [0.86; 1.14] [0.88; 1.30] [0.99; 1.17] [1.00; 1.11] [0.97; 1.08]
Could not shake off the blues WHII TILDA Overall effect Heterogeneity: $I^2 = 14\%$, $\tau^2 = 0.0042$, $p = 0.28$, $R_b = 30\%$ [0%; 100%]	3636 4327	126 158		1.04 1.21 1.12	[0.86; 1.25] [0.99; 1.48] [0.95; 1.32]
Did not enjoy life MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 56\%$ [0%; 81%], $\tau^2 = 0.0052$, $p = 0.04$, $R_b = 56\%$ [2%; 100%]	755 1370 3636 4327 4853 4978 6090	145 134 546 333 366 725 409		1.07 1.08 0.93 1.24 1.00 1.05 1.12 1.06	[0.88; 1.30] [0.91; 1.28] [0.84; 1.02] [1.07; 1.44] [0.89; 1.12] [0.97; 1.14] [1.02; 1.23] [0.99; 1.14]
Felt depressed MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 34\%$ [0%; 72%], $\tau^2 = 0.0042$, $p = 0.17$, $R_b = 51\%$ [0%; 100%]	755 1370 3636 4327 4853 4978 6090	229 180 224 220 483 787 628		1.16 0.87 1.04 1.00 1.03 1.00 1.09 1.02	[0.97; 1.39] [0.75; 1.01] [0.90; 1.20] [0.93; 1.14] [0.92; 1.08] [1.00; 1.18] [0.96; 1.10]
Felt everything was an effort MHAS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $l^2 = 0\%$ [0%; 30%], $\tau^2 = 0.0005$, $p = 0.87$, $R_b = 15\%$ [0%; 100%]	755 1370 3636 4327 4853 6090	249 203 277 252 780 1,178	0.75 1 1.5 Decreased risk	1.11 1.12 1.13 0.99 1.08 1.10 1.09	[0.93; 1.32] [0.97; 1.29] [0.99; 1.28] [0.84; 1.17] [0.99; 1.17] [1.03; 1.17] [1.04; 1.15]

Figure S3d (continued)

Study	N	Cases		OR	95%-CI
Felt fearful WHII TILDA Overall effect Heterogeneity: l^2 = 6%, τ^2 = 0.0032, p = 0.30, R_b = 27% [0%; 100%]	3636 4327	152 169		1.03 1.18 1.09	[0.87; 1.21] [0.97; 1.44] [0.94; 1.27]
Felt hopeless about the future WHII TILDA Overall effect Heterogeneity: $I^2 = 62\%$ [0%; 91%], $\tau^2 = 0.0035$, $p = 0.11$, $R_b = 61\%$ [0%; 100%]	3636 4327	855 683		1.02 1.14 1.07	[0.94; 1.10] [1.02; 1.27] [0.96; 1.19]
Felt lonely MHAS NSHAP WHII TIIDA ELSA HRS Overall effect Heterogeneity: $I^2 = 36\% [0\%; 75\%], \tau^2 = 0.0024, p = 0.17, R_b = 35\% [0\%; 100\%]$	755 1370 3636 4327 4853 6090	227 227 233 235 447 811		1.06 1.01 1.01 1.14 0.98 1.15 1.06	[0.88; 1.27] [0.88; 1.16] [0.88; 1.16] [0.96; 1.36] [0.88; 1.10] [1.07; 1.24] [0.99; 1.13]
Felt sad MHAS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: l^2 = 41% [0%; 77%], τ^2 = 0.0029, ρ = 0.13, R_b = 44% [0%; 100%]	755 1370 3636 4327 4853 6090	307 260 195 261 742 918		0.96 1.00 0.90 1.08 1.01 1.10 1.02	[0.81; 1.13] [0.88; 1.13] [0.78; 1.04] [0.91; 1.28] [0.93; 1.10] [1.03; 1.17] [0.96; 1.09]
Felt unhappy MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $l^2 = 62\%$ [14%; 83%], $\tau^2 = 0.0054$, $p = 0.01$, $R_b = 60\%$ [16%; 100%]	755 1370 3636 4327 4853 4978 6090	130 201 670 430 424 565 651		1.07 0.87 0.96 1.10 1.00 1.00 1.14 1.02	[0.86; 1.33] [0.75; 1.00] [0.88; 1.05] [0.90; 1.26] [0.90; 1.11] [0.91; 1.10] [1.05; 1.23] [0.95; 1.09]
Felt worse than others WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0009$, $p = 0.40$, $R_b = 19\%$ [0%; 100%]	3636 4327	530 271		1.05 1.14 1.08	[0.95; 1.16] [0.96; 1.35] [0.98; 1.18]
Had crying spells WHII TILDA Overall effect Heterogeneity: $I^2 = 47\%$, $\tau^2 = 0.0149$, $p = 0.17$, $R_b = 48\%$ [0%; 100%]	3636 4327	64 134		0.89 1.14 1.02	[0.68; 1.16] [0.90; 1.44] [0.80; 1.30]
Life had been a failure WHII TILDA Overall effect Heterogeneity: I^2 = 29%, τ^2 = 0.0070, p = 0.24, R_b = 38% [0%; 100%]	3636 4327	137 109	0.8 1 1.25 Decreased risk	0.94 1.13 1.01	[0.79; 1.12] [0.88; 1.45] [0.84; 1.22]

Figure S3d (continued)

Study	Ν	Cases		OR	95%-CI
Little interest in doing things/unmotivated HRS Overall effect Heterogeneity: not applicable	6090	1,153		1.08 1.08	[1.02; 1.15] [1.02; 1.15]
People dislike me NSHAP WHI TILDA Overall effect Heterogeneity: I^2 = 21% [0%; 92%], τ^2 = 0.0096, p = 0.28, R_b = 33% [0%; 100%]	1370 3636 4327	69 73 48		0.87 1.11 0.85 0.96	[0.69; 1.09] [0.88; 1.40] [0.55; 1.31] [0.79; 1.16]
People were unfriendly NSHAP WHII TILDA Overall effect Heterogeneity: I^2 = 31% [0%; 93%], τ^2 = 0.0102, p = 0.23, R_b = 38% [0%; 100%]	1370 3636 4327	75 73 74		1.18 0.91 0.93 1.01	[0.95; 1.47] [0.72; 1.16] [0.68; 1.27] [0.84; 1.22]
Sleep problems MHAS NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 59\%$ [4%; 82%], $\tau^2 = 0.0034$, $p = 0.02$, $R_b = 60\%$ [6%; 100%]	755 1370 3636 4327 4853 4978 6090	327 323 781 786 1,896 771 1,696		0.94 1.05 1.06 1.18 1.01 1.01 1.13 1.06	[0.80; 1.10] [0.93; 1.18] [0.97; 1.15] [1.06; 1.32] [0.94; 1.08] [0.93; 1.09] [1.07; 1.19] [1.00; 1.12]
Talked less than usual WHII TILDA Overall effect Heterogeneity: I^2 = 14%, τ^2 = 0.0029, p = 0.28, R_b = 32% [0%; 100%]	3636 4327	264 197		1.04 1.18 1.09	[0.91; 1.18] [0.98; 1.43] [0.95; 1.25]
Trouble concentrating WHII TILDA UKHLS Overall effect Heterogeneity: $I^2 = 0\% [0\%; 83\%], \tau^2 = 0.0009, p = 0.54, R_b = 23\% [0\%; 100\%]$	3636 4327 4978	346 366 786	0.75 1 1.5	1.08 0.97 1.05 1.04	[0.97; 1.21] [0.83; 1.13] [0.97; 1.14] [0.97; 1.12]

Decreased risk Increased risk

FIGURE S4a. Random-effects meta-analysis of the cross-sectional association between Creactive protein (low-grade) and individual depression symptoms (adjusted for age & sex)

Study	N	Cases		OR	95%-CI
Appetite was poor TILDA Overall effect Heterogeneity: not applicable	4492	149		1.15 1.15	[0.90; 1.47] [0.90; 1.47]
Bothered by things MIDUS WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 56%], $\tau^2 = 0.0004$, $p = 0.79$, $R_b = 5\%$ [0%; 100%]	921 3990 4492	42 275 301		0.95 1.00 1.06 1.01	[0.71; 1.27] [0.88; 1.13] [0.89; 1.27] [0.91; 1.12]
Changes in appetite SEBAS MIDUS NSHAP NHANES 2005 WHI NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $I^2 = 0\% [0\%; 0\%], \tau^2 = 0.0003, p = 0.97, R_b = 6\% [0\%; 100\%]$	598 921 1714 3467 3990 3990 4062 4259 4433	79 29 186 211 121 373 349 371 377		1.22 1.11 1.15 1.23 1.18 1.23 1.23 1.23 1.17 1.27 1.21	[0.92; 1.62] [0.78; 1.58] [1.00; 1.33] [1.08; 1.41] [1.09; 1.38] [1.11; 1.36] [1.05; 1.30] [1.15; 1.41] [1.16; 1.27]
Could not get going/energy SEBAS MHAS MIDUS CRELES NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2017 NHANES 2015 NHANES 2009 TILDA ELSA HRS Overall effect	598 804 921 1055 1714 3467 3990 3990 4062 4259 4433 4492 5199 7768	94 426 79 145 286 472 297 687 667 687 693 205 814 3229	*	0.99 1.16 1.22 1.19 1.06 1.20 1.11 1.21 1.18 1.20 1.19 1.21 1.32 1.13 1.18	
Heterogeneity: $l^2 = 20\% [0\%; 57\%], \tau^2 = 0.0020, p = 0.24, R_b = 37\% [0\%; 100\%]$ Could not shake off the blues MIDUS WHII TILDA Overall effect Heterogeneity: $l^2 = 0\% [0\%; 80\%], \tau^2 = 0.0024, p = 0.59, R_b = 18\% [0\%; 100\%]$	921 3990 4492	42 205 156		1.02 1.20 1.21 1.17	[0.76; 1.36] [1.04; 1.38] [0.95; 1.54] [1.03; 1.33]
Did not enjoy life MHAS MIDUS CRELES NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $l^2 = 0\%$ [0%; 64%], $\tau^2 = 0.0045$, $p = 0.46$, $R_b = 47\%$ [0%; 100%]	804 921 1055 1714 3990 4492 5199 5317 7768	180 118 35 185 579 404 424 829 523		1.02 1.04 0.68 1.04 0.99 1.10 1.14 1.13 1.06 1.07	[0.85; 1.23] [0.86; 1.25] [0.90; 1.20] [0.90; 1.20] [0.90; 1.08] [0.94; 1.28] [1.02; 1.27] [1.04; 1.22] [0.97; 1.16] [1.00; 1.14]
Feeling bad about yourself NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $l^2 = 0\% [0\%; 0\%], \tau^2 = < 0.0001, p = 0.97, R_b = 1\% [0\%; 100\%]$	3467 3990 4062 4259 4433	124 197 213 235 246		1.16 1.13 1.15 1.21 1.17 1.17	[0.98; 1.38] [0.97; 1.32] [1.01; 1.30] [1.06; 1.38] [1.04; 1.32] [1.10; 1.24]

Figure S4a (continued)

Study	N	Cases		OR	95%-CI
Felt depressed MHAS MIDUS NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2017 NHANES 2017 NHANES 2007 NHANES 2009 TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 55%], $\tau^2 = 0.0015$, $p = 0.49$, $R_b = 30\%$ [0%; 100%]	804 921 1714 3467 3990 3990 4062 4259 4433 4492 5199 5317 7768	283 68 253 198 298 288 281 304 334 209 549 971 974		1.12 1.17 1.03 1.16 1.00 1.13 1.12 1.05 1.23 1.14 1.19 1.12 1.12 1.12	[0.95; 1.32] [0.92; 1.48] [0.91; 1.17] [1.01; 1.33] [0.89; 1.13] [1.00; 1.25] [0.94; 1.17] [1.11; 1.37] [0.92; 1.41] [1.08; 1.31] [1.04; 1.20] [1.08; 1.16]
Felt everything was an effort SEBAS MIHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: I^2 = 74% [47%; 87%], τ^2 = 0.0123, $p < 0.01$, R_b = 67% [28%; 100%]	598 804 921 1714 3990 4492 5199 7768	115 287 65 261 367 253 816 1668		1.09 0.94 1.34 1.21 1.02 1.28 1.35 1.22 1.17	[0.83; 1.43] [0.80; 1.10] [1.05; 1.72] [1.06; 1.38] [0.91; 1.14] [1.06; 1.54] [1.24; 1.46] [1.16; 1.29] [1.07; 1.29]
Felt fearful MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 88%], τ^2 = 0.0037, p = 0.41, R_b = 23% [0%; 100%]	921 3990 4492	24 161 166		0.99 0.96 1.16 1.02	[0.68; 1.45] [0.82; 1.12] [0.92; 1.46] [0.88; 1.18]
Felt hopeless about the future MIDUS CRELES WHII TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 72%], τ^2 = 0.0006, p = 0.64, R_b = 13% [0%; 100%]	921 1055 3990 4492	217 110 828 743		1.00 0.96 1.08 1.00 1.04	[0.86; 1.16] [0.60; 1.53] [1.00; 1.17] [0.89; 1.13] [0.97; 1.11]
Felt lonely SEBAS MIHAS MIDUS NSHAP WHI TIIDA ELSA HRS Overall effect Heterogeneity: $I^2 = 0\% [0\%; 48\%], \tau^2 = 0.0015, \rho = 0.73, R_b = 25\% [0\%; 100\%]$	598 804 921 1714 3990 4492 5199 7768	57 237 65 287 274 302 526 1101		1.21 1.24 1.03 1.06 1.06 1.19 1.15 1.14 1.13	[0.86; 1.70] [1.04; 1.48] [0.81; 1.31] [0.93; 1.20] [1.00; 1.42] [1.04; 1.27] [1.07; 1.22] [1.07; 1.19]
Felt sad MHAS MIDUS NSHAP WHI TILDA ELSA HRS Overall effect Heterogeneity: l^2 = 12% [0%; 74%], τ^2 = 0.0022, p = 0.34, R_b = 36% [0%; 100%]	804 921 1714 3990 4492 5199 7768	342 65 315 241 300 868 1292	0.75 1 1.5 Decreased risk	1.17 1.00 1.01 0.94 1.05 1.05 1.10 1.05	[1.00; 1.37] [0.79; 1.27] [0.90; 1.14] [0.82; 1.07] [0.88; 1.26] [0.97; 1.14] [1.03; 1.17] [0.99; 1.11]

Figure S4a (continued)

Study	N	Cases		OR	95%-CI
Felt unhappy MHAS MIDUS CRELES NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 46%], $\tau^2 = 0.0013$, $p = 0.74$, $R_b = 26\%$ [0%; 100%]	804 921 1055 1714 3990 4492 5199 5317 7768	157 120 84 286 668 482 477 674 897		1.08 1.07 1.32 1.10 1.00 1.16 1.07 1.10 1.06 1.07	[0.89; 1.31] [0.87; 1.31] [0.78; 2.22] [0.97; 1.24] [0.92; 1.08] [1.00; 1.34] [0.97; 1.19] [1.01; 1.20] [0.99; 1.14] [1.02; 1.12]
Felt worse than others MIDUS WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 88%], $\tau^2 = 0.0020$, $p = 0.43$, $R_b = 33\%$ [0%; 100%]	921 3990 4492	136 662 476		1.15 1.02 1.00 1.04	[0.96; 1.37] [0.94; 1.11] [0.86; 1.16] [0.95; 1.14]
Had crying spells MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 87%], τ^2 = 0.0114, p = 0.45, R_b = 34% [0%; 100%]	921 3990 4492	19 72 138		1.56 1.15 1.13 1.20	[0.99; 2.46] [0.91; 1.45] [0.88; 1.46] [0.98; 1.48]
Life had been a failure MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 80%], τ^2 = 0.0018, ρ = 0.59, R_b = 12% [0%; 100%]	921 3990 4492	26 162 131		1.14 0.97 1.10 1.02	[0.79; 1.65] [0.83; 1.14] [0.85; 1.43] [0.89; 1.18]
Little interest in doing things/unmotivated NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 HRS Overall effect Heterogeneity: I^2 = 48% [0%; 79%], τ^2 = 0.0038, p = 0.09, R_b = 56% [0%; 100%]	3467 3990 4062 4259 4433 7768	193 352 367 274 355 1432	-œ- -œ- -œ- -œ- ⊕ - œ- -œ- - œ-	1.16 1.31 1.13 1.11 1.34 1.18 1.20	[1.01; 1.34] [1.16; 1.48] [1.02; 1.25] [0.98; 1.25] [1.20; 1.49] [1.11; 1.25] [1.12; 1.28]
Moving or speaking slowly or too fast NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $I^2 = 28\%$ [0%; 72%], $\tau^2 = 0.0047$, $p = 0.23$, $R_b = 40\%$ [0%; 100%]	3467 3990 4062 4259 4433	79 159 148 155 167		1.24 1.14 1.06 1.03 1.28 1.14	[0.99; 1.55] [0.96; 1.36] [0.92; 1.23] [0.89; 1.20] [1.10; 1.48] [1.03; 1.25]
People dislike me MIDUS NSHAP WHII TILDA Overall effect Heterogeneity: I^2 = 61% [0%; 87%], τ^2 = 0.0472, p = 0.05, R_b = 67% [0%; 100%]	921 1714 3990 4492	25 95 73 69		1.27 1.42 1.15 0.76 1.15	[0.87; 1.86] [1.15; 1.75] [0.91; 1.46] [0.51; 1.13] [0.89; 1.50]
People were unfriendly SEBAS MIDUS NSHAP WHI TILDA Overall effect Heterogeneity: I^2 = 56% [0%; 84%], τ^2 = 0.0406, p = 0.06, R_b = 61% [0%; 100%]	598 921 1714 3990 4492	17 14 137 96 92	0.5 1 2 Decreased risk	1.78 1.48 1.07 0.93 1.31 1.20	[1.10; 2.89] [0.89; 2.47] [0.91; 1.26] [0.76; 1.14] [0.97; 1.77] [0.95; 1.50]

Decreased risk Increased risk

Figure S4a (continued)

Study	N	Cases		OR	95%-CI
Sleep problems			Ĭ.		
SEBAS	598	190		1.06	[0.85; 1.33]
MHAS	804	361		1.05	[0.90; 1.23]
MIDUS	921	205		1.14	[0.98; 1.32]
NSHAP	1714	397		1.07	[0.97; 1.19]
NHANES 2005	3467	400		1.26	[1.14; 1.40]
WHII	3990	882		0.98	[0.91; 1.06]
NHANES 2017	3990	4062		1.23	[1.12; 1.36]
NHANES 2015	4062	579		1.10	[1.02; 1.19]
NHANES 2007	4259	699		1.14	[1.05; 1.23]
NHANES 2009	4433	716		1.20	[1.11; 1.29]
TILDA	4492	773		1.14	[1.01; 1.28]
ELSA	5199	1745		1.18	[1.11; 1.26]
UKHLS	5317	863		1.07	[0.99; 1.16]
HRS	7768	2305	-83-	1.08	[1.03; 1.14]
Overall effect			•	1.12	[1.08; 1.17]
Heterogeneity: $I^2 = 59\%$ [26%; 77%], $\tau^2 = 0.0031$, $p < 0.01$, $R_b = 56\%$ [23%; 89%]					
Talked less than usual					
MIDUS	921	91		1.07	[0.87; 1.31]
WHII	3990	357	+	1.10	[0.98; 1.23]
TILDA	4492	205		1.01	[0.81; 1.26]
Overall effect				1.08	[0.98; 1.18]
Heterogeneity: $l^2 = 0\% [0\%; 55\%], \tau^2 = 0.0002, p = 0.79, R_b = 4\% [0\%; 100\%]$					
Thought you would be better off dead					
NHANES 2005	3467	26		1.09	[0.76; 1.57]
NHANES 2017	3990	38		0.90	[0.64; 1.27]
NHANES 2015	4062	50	<u>H</u>	1.55	[1.16; 2.07]
NHANES 2007	4259	46		1.33	[0.98; 1.80]
NHANES 2009	4433	48		1.27	[0.96; 1.68]
Overall effect Heterogeneity: <i>l</i> ² = 37% [0%; 77%], τ ² = 0.0239, <i>ρ</i> = 0.17, <i>R_b</i> = 48% [0%; 100%]				1.23	[1.01; 1.49]
Trouble concentrating					
MIDUS	921	115	m	1.13	[0.94; 1.36]
NHANES 2005	3467	146	-	1.13	[0.97; 1.33]
WHI	3990	668		1.07	[0.98; 1.16]
NHANES 2017	3990	245	-	1.10	[0.96; 1.27]
NHANES 2015	4062	237		1.23	[1.09; 1.39]
NHANES 2007	4259	234		1.17	[1.03; 1.33]
NHANES 2009	4433	269		1.35	[1.20; 1.52]
TILDA	4492	384		0.90	[0.76; 1.06]
UKHLS	5317	734		1.09	[1.00; 1.18]
Overall effect	00000000	10.07050/	~	1.13	[1.05; 1.22]
Heterogeneity: $I^2 = 61\%$ [19%; 81%], $\tau^2 = 0.0081$, $p < 0.01$, $R_b = 65\%$ [17%; 100%]					-
			0.5 1 2		

0.5 1 2 Decreased risk Increased risk

FIGURE S4b. Random-effects meta-analysis of the cross-sectional association between C-reactive protein (low-grade) and individual depression symptoms (adjusted for age, sex & education)

Study	N	Cases		OR	95%-CI
Appetite was poor SEBAS MIDUS NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 TILDA Overall effect Heterogeneity: $I^2 = 0\%$ [<0%; <0%], $\tau^2 = 0.0003$, $p = 0.99$, $R_b = 5\%$ [<0%; <100%	598 921 1714 3467 3990 3990 4062 4259 4433 4492	79 29 186 211 373 349 371 377 149		1.15 1.09 1.10 1.20 1.19 1.19 1.19 1.15 1.22 1.11 1.18	[0.86; 1.54] [0.76; 1.56] [0.95; 1.27] [1.05; 1.38] [0.99; 1.44] [1.06; 1.34] [1.07; 1.32] [1.04; 1.28] [1.10; 1.35] [0.87; 1.42] [1.12; 1.23]
Bothered by things MIDUS WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 27%], $\tau^2 = 0.0002$, $p = 0.87$, $R_b = 2\%$ [0%; 100%]	921 3990 4492	42 275 301		0.95 1.00 1.04 1.01	[0.71; 1.28] [0.88; 1.13] [0.87; 1.25] [0.91; 1.11]
Could not get going/energy SEBAS MHAS MIDUS CRELES NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2017 NHANES 2015 NHANES 2009 TILDA ELSA HRS Overall effect Heterogeneity: $I^2 = 5\% [0\%; 57\%], \tau^2 = 0.0015, p = 0.39, R_b = 32\% [0\%; 100\%]$	598 804 921 1055 1714 3467 3990 3990 4062 4259 4433 4492 5199 7768	94 426 79 145 286 472 297 687 667 687 693 205 814 3229		1.01 1.16 1.21 1.17 1.04 1.19 1.11 1.18 1.16 1.22 1.29 1.12 1.16	[0.75; 1.36] [0.99; 1.35] [0.97; 1.51] [0.77; 1.77] [1.08; 1.21] [1.08; 1.22] [1.09; 1.28] [1.07; 1.25] [1.09; 1.28] [1.07; 1.25] [0.99; 1.51] [1.18; 1.41] [1.07; 1.17] [1.12; 1.20]
Could not shake off the blues MIDUS WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 62%], $\tau^2 = 0.0003$, $p = 0.76$, $R_b = 3\%$ [0%; 100%]	921 3990 4492	42 205 156		1.09 1.19 1.15 1.15	[0.91; 1.31] [1.03; 1.38] [0.90; 1.46] [1.03; 1.28]
Did not enjoy life MHAS MIDUS CRELES NSHAP WHI TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 64%], $\tau^2 = 0.0048$, $p = 0.46$, $R_b = 49\%$ [0%; 100%]	804 921 1055 1714 3990 4492 5199 5317 7768	180 118 35 185 579 404 424 829 523		1.01 1.02 0.65 1.00 0.99 1.07 1.11 1.12 1.02 1.04	[0.84; 1.21] [0.85; 1.23] [0.28; 1.52] [0.86; 1.16] [0.91; 1.08] [1.00; 1.24] [1.03; 1.24] [1.03; 1.21] [0.93; 1.11] [0.98; 1.11]
Feeling bad about yourself NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $l^2 = 0\% [0\%; 0\%], \tau^2 = 0.0001, p = 0.95, R_b = 2\% [0\%; 100\%]$	3467 3990 4062 4259 4433	124 197 213 235 246	0.5 1 2 Decreased risk	1.13 1.09 1.11 1.18 1.12 1.13	[0.95; 1.34] [0.93; 1.28] [0.98; 1.26] [1.04; 1.34] [0.99; 1.27] [1.06; 1.20]

Decreased risk Increased risk

Figure S4b (continued)

Study	Ν	Cases		OR	95%-CI
Felt depressed MHAS MIDUS NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2017 NHANES 2015 NHANES 2009 TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 0\% [0\%; 46\%], \tau^2 = 0.0011, p = 0.64, R_b = 24\% [0\%; 100\%]$	804 921 1714 3467 3990 3990 4062 4259 4433 4492 5199 5317 7768	283 68 253 198 298 288 281 304 334 209 549 971 974		1.11 1.16 1.00 1.12 1.02 1.09 1.07 1.02 1.18 1.09 1.15 1.11 1.04 1.08	[0.94; 1.31] [0.91; 1.47] [0.88; 1.14] [0.90; 1.15] [0.96; 1.20] [0.96; 1.20] [0.91; 1.14] [1.06; 1.32] [0.88; 1.35] [1.04; 1.27] [1.03; 1.19] [0.97; 1.11] [1.04; 1.12]
Felt everything was an effort SEBAS MHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $I^2 = 66\%$ [28%; 84%], $\tau^2 = 0.0097$, $p < 0.01$, $R_b = 63\%$ [16%; 100%]	598 804 921 1714 3990 4492 5199 7768	115 287 65 261 367 253 816 1668		1.09 0.92 1.32 1.16 1.03 1.24 1.30 1.14 1.14	[0.83; 1.43] [0.78; 1.08] [1.02; 1.32] [0.93; 1.15] [1.03; 1.50] [1.19; 1.42] [1.05; 1.24]
Felt fearful MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 87%], τ^2 = 0.0035, p = 0.44, R_b = 21% [0%; 100%]	921 3990 4492	24 161 166		0.97 0.96 1.15 1.02	[0.66; 1.42] [0.82; 1.13] [0.91; 1.45] [0.88; 1.18]
Felt hopeless about the future MIDUS CRELES WHII TILDA Overall effect Heterogeneity: $I^2 = 0\% [0\%; 80\%], \tau^2 = 0.0011, p = 0.51, R_b = 19\% [0\%; 100\%]$	921 1055 3990 4492	217 110 828 743		0.97 0.93 1.07 0.98 1.02	[0.84; 1.13] [0.58; 1.50] [0.99; 1.16] [0.87; 1.11] [0.95; 1.10]
Felt lonely SEBAS MHAS MIDUS NSHAP WHI TIIDA ELSA HRS Overall effect Heterogeneity: $I^2 = 0\% [0\%; 42\%], \tau^2 = 0.0013, \rho = 0.79, R_b = 22\% [0\%; 100\%]$	598 804 921 1714 3990 4492 5199 7768	57 237 65 287 274 302 526 1101		1.18 1.22 1.03 1.03 1.06 1.17 1.12 1.08 1.09	[0.84; 1.65] [1.02; 1.46] [0.81; 1.30] [0.91; 1.16] [0.94; 1.20] [0.98; 1.40] [1.01; 1.24] [1.01; 1.15] [1.04; 1.15]
Felt sad MHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $I^2 = 0\% [0\%; 61\%], \tau^2 = 0.0015, p = 0.62, R_b = 29\% [0\%; 100\%]$	804 921 1714 3990 4492 5199 7768	342 65 315 241 300 868 1292	0.75 1 1.5 Decreased risk	1.16 1.00 1.02 0.94 1.03 1.04 1.05 1.03	[0.99; 1.36] [0.79; 1.27] [0.91; 1.15] [0.83; 1.07] [0.86; 1.24] [0.96; 1.13] [0.99; 1.12] [0.98; 1.09]

Figure S4b (continued)

Study	N	Cases		OR	95%-CI
Felt unhappy MHAS MIDUS CRELES NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $J^2 = 0\%$ [0%; 46%], $\tau^2 = 0.0014$, $p = 0.73$, $R_b = 26\%$ [0%; 100%]	804 921 1055 1714 3990 4492 5199 5317 7768	157 120 84 286 668 482 477 674 897		1.06 1.12 1.30 1.06 0.99 1.13 1.06 1.10 1.03 1.06	[0.87; 1.29] [0.93; 1.34] [0.77; 2.19] [0.94; 1.20] [0.98; 1.31] [0.96; 1.18] [1.00; 1.20] [0.96; 1.11] [1.01; 1.11]
Felt worse than others MIDUS WHII TILDA Overall effect Heterogeneity: $I^2 = 0\% [0\%; 0\%], \tau^2 = < 0.0001, p = 0.94, R_b = 0\% [0\%; 100\%]$	921 3990 4492	136 662 476		1.01 1.01 0.98 1.00	[0.75; 1.36] [0.92; 1.10] [0.85; 1.13] [0.93; 1.08]
Had crying spells MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 89%], τ^2 = 0.0146, ρ = 0.39, R_b = 39% [0%; 100%]	921 3990 4492	19 72 138		1.56 1.16 1.08 1.19	[0.99; 2.46] [0.92; 1.47] [0.83; 1.40] [0.96; 1.48]
Life had been a failure MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 65%], τ^2 = 0.0007, p = 0.74, R_b = 5% [0%; 100%]	921 3990 4492	26 162 131		1.12 0.99 1.09 1.03	[0.77; 1.63] [0.84; 1.16] [0.84; 1.42] [0.90; 1.18]
Little interest in doing things/unmotivated NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 HRS Overall effect Heterogeneity: $I^2 = 49\%$ [0%; 80%], $\tau^2 = 0.0039$, $p = 0.08$, $R_b = 57\%$ [0%; 100%]	3467 3990 4062 4259 4433 7768	193 352 367 274 355 1432	-œ- -œ- -œ- -œ- -œ- -œ-	1.12 1.27 1.08 1.08 1.29 1.13 1.16	[0.97; 1.29] [1.12; 1.44] [0.98; 1.20] [0.96; 1.22] [1.16; 1.44] [1.07; 1.20] [1.08; 1.24]
Moving or speaking slowly or too fast NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $I^2 = 16\%$ [0%; 83%], $\tau^2 = 0.0039$, $p = 0.31$, $R_b = 35\%$ [0%; 100%]	3467 3990 4062 4259 4433	79 159 148 155 167		1.18 1.11 1.01 0.99 1.21 1.09	[0.95; 1.47] [0.93; 1.32] [0.87; 1.18] [0.85; 1.16] [1.04; 1.41] [0.99; 1.20]
People dislike me MIDUS NSHAP WHII TILDA Overall effect Heterogeneity: I^2 = 53% [0%; 84%], τ^2 = 0.0424, p = 0.10, R_b = 64% [0%; 100%]	921 1714 3990 4492	25 95 73 69		1.27 1.31 1.17 0.74 1.12	[0.86; 1.87] [1.06; 1.62] [0.92; 1.49] [0.50; 1.10] [0.87; 1.45]
People were unfriendly SEBAS MIDUS NSHAP WHII TILDA Overall effect Heterogeneity: $I^2 = 53\%$ [0%; 83%], $\tau^2 = 0.0389$, $p = 0.08$, $R_b = 60\%$ [0%; 100%]	598 921 1714 3990 4492	17 14 137 96 92	0.5 1 2 Decreased risk	1.73 1.47 1.01 0.94 1.28 1.17	[1.06; 2.83] [0.88; 2.45] [0.85; 1.20] [0.77; 1.15] [0.94; 1.74] [0.93; 1.46]

Figure S4b (continued)

Study	N	Cases		OR	95%-CI
Sleep problems SEBAS MHAS MIDUS NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2015 NHANES 2015 NHANES 2009 TILDA ELSA UKHLS HRS OVerall effect Heterogeneity: $I^2 = 52\%$ [11%; 74%], $\tau^2 = 0.0025$, $p = 0.01$, $R_b = 51\%$ [12%; 89%]	598 804 921 1714 3467 3990 3990 4062 4259 4433 4492 5199 5317 7768	190 361 205 397 400 882 4062 579 699 716 773 1745 863 2305		$\begin{array}{c} 1.06\\ 1.04\\ 1.14\\ 1.05\\ 1.23\\ 0.98\\ 1.20\\ 1.07\\ 1.13\\ 1.17\\ 1.12\\ 1.14\\ 1.06\\ 1.05\\ 1.10\\ \end{array}$	[0.84; 1.33] [0.89; 1.21] [0.98; 1.32] [0.95; 1.17] [1.11; 1.36] [0.91; 1.06] [1.09; 1.32] [0.99; 1.16] [1.04; 1.22] [1.08; 1.26] [1.07; 1.22] [0.99; 1.26] [1.07; 1.22] [0.98; 1.15] [1.00; 1.10] [1.06; 1.14]
Talked less than usual MIDUS WHII TILDA Overall effect Heterogeneity: $J^2 = 0\%$ [0%; 77%], $\tau^2 = 0.0008$, $p = 0.63$, $R_b = 10\%$ [0%; 100%]	921 3990 4492	91 357 205		1.04 1.10 0.98 1.06	[0.84; 1.28] [0.98; 1.23] [0.79; 1.22] [0.96; 1.17]
Thought you would be better off dead NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $I^2 = 37\% [0\%; 76\%], \tau^2 = 0.0245, p = 0.18, R_b = 48\% [0\%; 100\%]$	3467 3990 4062 4259 4433	26 38 50 46 48		1.03 0.88 1.52 1.28 1.22 1.18	[0.72; 1.48] [0.62; 1.25] [1.13; 2.04] [0.95; 1.73] [0.91; 1.63] [0.97; 1.44]
Trouble concentrating MIDUS NHANES 2005 WHI NHANES 2017 NHANES 2017 NHANES 2015 NHANES 2009 TILDA UKHLS Overall effect Heterogeneity: $l^2 = 52\%$ [0%; 78%], $\tau^2 = 0.0069$, $p = 0.03$, $R_b = 60\%$ [0%; 100%]	921 3467 3990 3990 4062 4259 4433 4492 5317	115 146 668 245 237 234 269 384 734		1.14 1.11 1.07 1.06 1.19 1.14 1.31 0.89 1.08 1.11	[0.94; 1.38] [0.94; 1.31] [0.98; 1.17] [1.05; 1.35] [1.00; 1.30] [1.16; 1.48] [0.75; 1.05] [0.99; 1.18] [1.03; 1.19]
Heterogeneity: $l^2 = 52\%$ [0%; 78%], $\tau^2 = 0.0069$, $p = 0.03$, $R_b = 60\%$ [0%; 100%]			0.5 1 2 Decreased risk Increased risk		Management - SOCOR

FIGURE S4c. Random-effects meta-analysis of the cross-sectional association between C-reactive protein (low-grade) and individual depression symptoms (adjusted for age, sex & chronic illness-related factors)

Study	N	Cases		OR	95%-CI
Bothered by things MIDUS WHII TILDA Overall effect Heterogeneity: $l^2 = 0\%$ [0%; 42%], $\tau^2 = 0.0002$, $p = 0.84$, $R_b = 3\%$ [0%; 100%]	921 3990 4492	42 275 301		0.97 1.00 1.06 1.01	[0.72; 1.31] [0.88; 1.13] [0.88; 1.27] [0.92; 1.12]
Changes in appetite SEBAS MIDUS NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2015 NHANES 2015 NHANES 2007 NHANES 2009 TILDA Overall effect Heterogeneity: $I^2 = 0\%$ [<0%; <0%], $\tau^2 = 0.0003$, $p = 0.98$, $R_b = 5\%$ [<0%; <100%]	598 921 1714 3467 3990 3990 4062 4259 4433 4492	79 29 186 211 373 349 371 377 149		1.23 1.14 1.23 1.16 1.21 1.21 1.21 1.25 1.26 1.14 1.20	$\begin{matrix} [0.92; 1.64] \\ [0.79; 1.64] \\ [0.99; 1.32] \\ [1.07; 1.41] \\ [1.07; 1.36] \\ [1.10; 1.34] \\ [1.04; 1.28] \\ [1.14; 1.39] \\ [0.89; 1.46] \\ [1.15; 1.25] \end{matrix}$
Could not get going/energy SEBAS MHAS MIDUS CRELES NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2017 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 TILDA ELSA HRS Overall effect Heterogeneity: $I^2 = 28\% [0\%; 62\%], \tau^2 = 0.0022, p = 0.16, R_b = 39\% [0\%; 100\%]$	598 804 921 1055 1714 3467 3990 3990 4062 4259 4433 4492 5199 7768	94 426 79 145 286 472 297 687 667 687 693 205 814 3229		0.98 1.17 1.22 1.05 1.20 1.10 1.20 1.18 1.18 1.18 1.17 1.23 1.32 1.12 1.17	[0.72; 1.33] [1.00; 1.37] [0.97; 1.53] [0.93; 1.71] [0.93; 1.18] [1.09; 1.32] [1.09; 1.22] [1.09; 1.22] [1.09; 1.28] [1.08; 1.27] [1.00; 1.52] [1.21; 1.43] [1.07; 1.17] [1.12; 1.22]
Could not shake off the blues MIDUS WHII TILDA Overall effect Heterogeneity: $I^2 = 0\% [0\%; 73\%], \tau^2 = 0.0016, p = 0.68, R_b = 13\% [0\%; 100\%]$	921 3990 4492	42 205 156		1.03 1.17 1.22 1.16	[0.76; 1.39] [1.01; 1.35] [0.96; 1.55] [1.02; 1.31]
Did not enjoy life MHAS MIDUS CRELES NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 0\% [0\%; 60\%], \tau^2 = 0.0050, p = 0.54, R_b = 49\% [0\%; 100\%]$	804 921 1055 1714 3990 4492 5199 5317 7768	180 118 35 185 579 404 424 829 523		1.02 1.05 0.65 1.02 0.99 1.09 1.12 1.12 1.12 1.04 1.05	[0.84; 1.23] [0.87; 1.27] [0.28; 1.51] [0.88; 1.18] [0.90; 1.08] [0.93; 1.27] [1.00; 1.25] [1.03; 1.21] [0.95; 1.13] [0.99; 1.13]
Feeling bad about yourself NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $I^2 = 0\%$ [<0%; <0%], $\tau^2 = < 0.0001$, $p = 0.98$, $R_b = 1\%$ [<0%; <100%]	3467 3990 4062 4259 4433	124 197 213 235 246	0.5 1 2 Decreased risk	1.15 1.10 1.14 1.17 1.13 1.14	[0.97; 1.36] [0.94; 1.29] [1.00; 1.29] [1.03; 1.33] [1.00; 1.28] [1.07; 1.21]

Figure S4c (continued)

Study	N	Cases		OR	95%-CI
Felt depressed MHAS MIDUS NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2017 NHANES 2017 NHANES 2007 NHANES 2009 TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 7\%$ [0%; 60%], $\tau^2 = 0.0021$, $p = 0.37$, $R_b = 36\%$ [0%; 100%]	804 921 1714 3467 3990 3990 4062 4259 4433 4492 5199 5317 7768	283 68 253 198 298 288 288 304 334 209 549 971 974		1.10 1.19 1.02 1.14 0.96 1.10 1.02 1.21 1.15 1.17 1.10 1.10 1.10	$ \begin{bmatrix} 0.93; 1.30 \\ 0.94; 1.51 \\ 0.90; 1.16 \\ 0.99; 1.31 \\ 0.85; 1.09 \\ 0.97; 1.25 \\ 0.99; 1.23 \\ 0.91; 1.14 \\ 1.09; 1.35 \\ 0.93; 1.42 \\ 1.06; 1.29 \\ 1.02; 1.19 \\ 1.02; 1.18 \\ 1.05; 1.15 \\ \end{bmatrix} $
Felt everything was an effort SEBAS MHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: I^2 = 77% [54%; 88%], τ^2 = 0.0152, ρ < 0.01, R_b = 71% [32%; 100%]	598 804 921 1714 3990 4492 5199 7768	115 287 65 261 367 253 816 1668		1.06 0.91 1.36 1.20 0.99 1.26 1.34 1.19 1.15	[0.81; 1.39] [0.77; 1.07] [1.05; 1.76] [1.05; 1.37] [0.89; 1.11] [1.04; 1.52] [1.23; 1.46] [1.13; 1.26] [1.04; 1.28]
Felt fearful MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 7% [0%; 90%], τ^2 = 0.0056, p = 0.34, R_b = 28% [0%; 100%]	921 3990 4492	24 161 166		0.95 0.94 1.16 1.01	[0.64; 1.41] [0.80; 1.11] [0.92; 1.47] [0.86; 1.18]
Felt hopeless about the future MIDUS CRELES WHI TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 66%], τ^2 = 0.0010, p = 0.72, R_b = 19% [0%; 100%]	921 1055 3990 4492	217 110 828 743		1.02 0.89 1.07 1.00 1.04	[0.88; 1.19] [0.55; 1.44] [0.99; 1.16] [0.88; 1.13] [0.96; 1.11]
Felt lonely SEBAS MHAS MIDUS NSHAP WHI TIIDA ELSA HRS Overall effect Heterogeneity: $I^2 = 0\% [0\%; 34\%], \tau^2 = 0.0010, \rho = 0.84, R_b = 18\% [0\%; 100\%]$	598 804 921 1714 3990 4492 5199 7768	57 237 65 287 274 302 526 1101		1.21 1.23 1.09 1.06 1.06 1.19 1.14 1.12 1.12	[0.86; 1.70] [1.03; 1.47] [0.85; 1.39] [0.94; 1.19] [0.93; 1.20] [0.99; 1.43] [1.03; 1.26] [1.05; 1.20] [1.06; 1.18]
Felt sad MHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $I^2 = 0\% [0\%; 67\%], \tau^2 = 0.0015, p = 0.51, R_b = 30\% [0\%; 100\%]$	804 921 1714 3990 4492 5199 7768	342 65 315 241 300 868 1292	0.75 1 1.5 Decreased risk	1.14 1.03 1.02 0.93 1.04 1.04 1.04	[0.97; 1.34] [0.81; 1.31] [0.91; 1.15] [0.81; 1.06] [0.87; 1.25] [0.96; 1.12] [1.02; 1.15] [0.99; 1.10]

Figure S4c (continued)

Study	Ν	Cases		OR	95%-CI
Felt unhappy MHAS MIDUS CRELES NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 55%], $\tau^2 = 0.0022$, $p = 0.62$, $R_b = 35\%$ [0%; 100%]	804 921 1055 1714 3990 4492 5199 5317 7768	157 120 84 286 668 482 477 674 897		1.06 1.16 1.35 1.08 0.99 1.17 1.06 1.08 1.05 1.07	[0.87; 1.29] [0.96; 1.40] [0.79; 2.30] [0.96; 1.22] [0.91; 1.08] [1.01; 1.35] [0.96; 1.18] [0.99; 1.18] [0.98; 1.12] [1.02; 1.12]
Felt worse than others MIDUS WHII TILDA Overall effect Heterogeneity: $I^2 = 24\%$ [0%; 92%], $\tau^2 = 0.0040$, $p = 0.27$, $R_b = 47\%$ [0%; 100%]	921 3990 4492	136 662 476		1.18 1.01 1.00 1.04	[0.99; 1.41] [0.93; 1.10] [0.86; 1.16] [0.94; 1.16]
Had crying spells MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 17% [0%; 91%], τ^2 = 0.0239, p = 0.30, R_b = 50% [0%; 100%]	921 3990 4492	19 72 138		1.68 1.13 1.12 1.22	[1.05; 2.70] [0.89; 1.44] [0.87; 1.45] [0.95; 1.56]
Life had been a failure MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 0% [0%; 87%], τ^2 = 0.0043, ρ = 0.45, R_b = 23% [0%; 100%]	921 3990 4492	26 162 131		1.23 0.98 1.12 1.05	[0.85; 1.78] [0.83; 1.15] [0.85; 1.47] [0.90; 1.23]
Little interest in doing things/unmotivated NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 HRS Overall effect Heterogeneity: I^2 = 46% [0%; 78%], τ^2 = 0.0036, p = 0.10, R_b = 55% [0%; 100%]	3467 3990 4062 4259 4433 7768	193 352 367 274 355 1432	-œ- -œ- -œ- -œ- €	1.15 1.29 1.12 1.09 1.32 1.16 1.18	[1.00; 1.32] [1.14; 1.46] [1.01; 1.24] [0.97; 1.23] [1.18; 1.47] [1.09; 1.23] [1.11; 1.26]
Moving or speaking slowly or too fast NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: $I^2 = 26\% [0\%; 71\%], \tau^2 = 0.0046, p = 0.25, R_B = 39\% [0\%; 100\%]$	3467 3990 4062 4259 4433	79 159 148 155 167		1.22 1.10 1.04 1.01 1.25 1.11	[0.98; 1.52] [0.92; 1.31] [0.90; 1.21] [0.87; 1.18] [1.08; 1.45] [1.01; 1.22]
People dislike me MIDUS NSHAP WHII TILDA Overall effect Heterogeneity: $I^2 = 55\%$ [0%; 85%], $\tau^2 = 0.0409$, $p = 0.08$, $R_b = 63\%$ [0%; 100%]	921 1714 3990 4492	25 95 73 69		1.25 1.37 1.16 0.76 1.14	[0.85; 1.84] [1.12; 1.68] [0.91; 1.48] [0.51; 1.14] [0.89; 1.47]
People were unfriendly SEBAS MIDUS NSHAP WHI TILDA Overall effect Heterogeneity: I^2 = 58% [0%; 85%], τ^2 = 0.0455, p = 0.05, R_b = 63% [0%; 100%]	598 921 1714 3990 4492	17 14 137 96 92	0.5 1 2 Decreased risk	1.79 1.50 1.06 0.91 1.30 1.19	[1.10; 2.91] [0.89; 2.52] [0.90; 1.25] [0.74; 1.12] [0.96; 1.77] [0.94; 1.51]

Figure S4c (continued)

Study	N	Cases		OR	95%-CI
Sleep problems					
SEBAS	598	190		1.05	[0.83; 1.32]
MHAS	804	361		1.03	[0.88; 1.21]
MIDUS	921	205		1.12	[0.96; 1.31]
NSHAP	1714	397		1.06	[0.96; 1.18]
NHANES 2005	3467	400		1.24	[1.12; 1.38]
WHII	3990	882		0.97	[0.90; 1.05]
NHANES 2017	3990	4062		1.21	[1.10; 1.33]
NHANES 2015	4062	579		1.10	[1.01; 1.19]
NHANES 2007	4259	699		1.12	[1.03; 1.21]
NHANES 2009	4433	716 773		1.19	[1.10; 1.28]
TILDA ELSA	4492 5199	1745		1.14 1.17	[1.01; 1.28]
UKHLS	5317	863		1.17	[1.10; 1.25] [0.98; 1.16]
HRS	7768	2305		1.07	[1.02; 1.12]
Overall effect	1100	2305	•	1.11	[1.07; 1.15]
Heterogeneity: $I^2 = 57\%$ [22%; 76%], $\tau^2 = 0.0029$, $p < 0.01$, $R_b = 54\%$ [20%; 89%]				1.11	[1.07, 1.10]
Talked less than usual					
MIDUS	921	91		1.06	[0.86; 1.31]
WHII	3990	357		1.10	[0.98; 1.23]
TILDA	4492	205		1.01	[0.81; 1.25]
Overall effect			-	1.08	[0.98; 1.18]
Heterogeneity: $l^2 = 0\%$ [0%; 58%], $\tau^2 = 0.0003$, $p = 0.78$, $R_b = 4\%$ [0%; 100%]					
Thought you would be better off dead					
NHANES 2005	3467	26		1.06	[0.74; 1.52]
NHANES 2017	3990	38		0.88	[0.62; 1.25]
NHANES 2015	4062	50		1.49	[1.12; 1.99]
NHANES 2007 NHANES 2009	4259	46		1.31 1.24	[0.97; 1.77]
Overall effect	4433	48		1.24	[0.93; 1.65] [0.99; 1.45]
Heterogeneity: $I^2 = 33\%$ [0%; 75%], $\tau^2 = 0.0224$, $p = 0.20$, $R_b = 46\%$ [0%; 100%]				1.20	[0.55, 1.45]
Trouble concentrating					
MIDUS	921	115		1.13	[0.93; 1.37]
NHANES 2005	3467	146		1.13	[0.97; 1.32]
WHII	3990	668	-00-	1.05	[0.96; 1.15]
NHANES 2017	3990	245		1.07	[0.93; 1.23]
NHANES 2015	4062	237		1.22	[1.08; 1.38]
NHANES 2007	4259	234		1.15	[1.01; 1.31]
NHANES 2009	4433	269		1.33	[1.18; 1.50]
TILDA	4492	384		0.91	[0.77; 1.07]
UKHLS Overall effect	5317	734		1.09	[1.00; 1.19]
Overall effect Heterogeneity: $l^2 = 57\%$ [11%; 80%], $\tau^2 = 0.0072$, $p = 0.02$, $R_h = 61\%$ [12%; 100%]			-	1.12	[1.04; 1.20]
Hereingeneity. $I = 57\%$ [11%, 00%], $\tau = 0.0072$, $p = 0.02$, $R_b = 61\%$ [12%; 100%]			r		
			0.75 1 1.5		

Decreased risk Increased risk

FIGURE S4d. Random-effects meta-analysis of the cross-sectional association between C-reactive protein (low-grade) and individual depression symptoms (adjusted for age, sex & behavioural factors)

Study	N	Cases		OR	95%-CI
Bothered by things					
MIDUS	921	42		0.96	[0.69; 1.33]
WHII	3990	275		0.87	[0.76; 1.00]
TILDA Overall effect	4492	301		1.01 0.92	[0.83; 1.22] [0.82; 1.04]
Heterogeneity: $l^2 = 0\%$ [0%; 87%], $\tau^2 = 0.0020$, $p = 0.45$, $R_b = 18\%$ [0%; 100%]				0.52	[0.02, 1.04]
Changes in appetite SEBAS	598	79		1.21	[0.90; 1.62]
MIDUS	921	29		1.14	[0.77; 1.69]
NSHAP	1714	186		1.13	[0.97; 1.32]
NHANES 2005	3467	211		1.09	[0.94; 1.27]
WHI	3990	121		1.16	[0.94; 1.43]
NHANES 2017 NHANES 2015	3990 4062	373 349		1.07 1.03	[0.94; 1.22]
NHANES 2017	4002	371	-	1.03	[0.92; 1.16] [0.95; 1.19]
NHANES 2009	4433	377	- 11 -	1.13	[1.01; 1.27]
TILDA	4492	149		1.17	[0.90; 1.53]
Overall effect Heterogeneity: $l^2 = 0\%$ [0%; 0%], $\tau^2 = 0.0005$, $p = 0.97$, $R_b = 8\%$ [0%; 100%]			•	1.09	[1.04; 1.15]
Could not get going/energy					
SEBAS	598	94		0.96	[0.71; 1.30]
MHAS MIDUS	804 921	426 79		1.10	[0.93; 1.31]
CRELES	1055	145		1.03 1.07	[0.80; 1.32] [0.70; 1.64]
NSHAP	1714	286		1.02	[0.89; 1.16]
NHANES 2005	3467	472		1.11	[1.00; 1.23]
WHII	3990	297		1.00	[0.87; 1.14]
NHANES 2017 NHANES 2015	3990 4062	687 667		1.05 1.06	[0.95; 1.17]
NHANES 2015 NHANES 2007	4062	687		1.13	[0.97; 1.16] [1.03; 1.23]
NHANES 2009	4433	693		1.09	[1.00; 1.19]
TILDA	4492	205		1.08	[0.86; 1.36]
ELSA	5199	814		1.13	[1.03; 1.24]
HRS Overall effect	7768	3229		0.99 1.06	[0.94; 1.04] [1.02; 1.10]
Heterogeneity: $l^2 = 4\%$ [0%; 57%], $\tau^2 = 0.0009$, $p = 0.41$, $R_b = 21\%$ [0%; 100%]			ľ	1.00	[1.02, 1.10]
Could not shake off the blues					
MIDUS	921	42	— <u>— </u>	0.90	[0.65; 1.25]
WHII	3990	205		1.05	[0.89; 1.23]
TILDA Overall effect	4492	156		1.07 1.03	[0.83; 1.38] [0.90; 1.18]
Heterogeneity: $I^2 = 0\%$ [0%; 73%], $\tau^2 = 0.0018$, $p = 0.68$, $R_b = 12\%$ [0%; 100%]				1100	[0:00] 1110]
Did not enjoy life MHAS	804	180		1.07	[0.87; 1.32]
MIDUS	921	118		0.95	[0.77; 1.17]
CRELES	1055	35	· · · · · ·	0.62	[0.26; 1.49]
NSHAP	1714	185		1.00	[0.86; 1.16]
WHII	3990	579 404		0.95	[0.86; 1.05]
TILDA ELSA	4492 5199	404		1.05 1.04	[0.89; 1.24] [0.92; 1.17]
UKHLS	5317	829	E .	1.05	[0.96; 1.14]
HRS	7768	523		0.93	[0.85; 1.02]
Overall effect			+	1.00	[0.93; 1.07]
Heterogeneity: $l^2 = 0\%$ [0%; 61%], $\tau^2 = 0.0054$, $p = 0.52$, $R_b = 48\%$ [0%; 100%]					
Feeling bad about yourself	0407	104		1.00	10 00 4 001
NHANES 2005 NHANES 2017	3467 3990	124 197		1.06 1.04	[0.88; 1.28] [0.87; 1.24]
NHANES 2017 NHANES 2015	4062	213	-	1.04	[0.89; 1.17]
NHANES 2007	4259	235	- <u>-</u>	1.05	[0.91; 1.22]
NHANES 2009	4433	246		1.03	[0.90; 1.18]
Overall effect z = 200 z = 200 z = 200 z = 200 z = 100 z = 200 z			†	1.04	[0.97; 1.11]
Heterogeneity: $l^2 = 0\%$ [<0%; <0%], $\tau^2 = < 0.0001$, $p = 1.00$, $R_b = 0\%$ [<0%; <100%]					
			0.5 1 2		
			Decreased risk Increased risk		

Figure S4d (continued)

Study	Ν	Cases		OR	95%-CI
Felt depressed MHAS MIDUS NSHAP NHANES 2005 WHII NHANES 2017 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 48%], $\tau^2 = 0.0018$, $p = 0.62$, $R_b = 28\%$ [0%; 100%]	804 921 1714 3467 3990 3990 4062 4259 4433 4492 5199 5317 7768	283 68 253 198 298 288 281 304 334 209 549 971 974		$\begin{array}{c} 1.12\\ 1.08\\ 0.95\\ 1.07\\ 0.93\\ 1.03\\ 1.05\\ 0.93\\ 1.14\\ 1.00\\ 1.04\\ 1.03\\ 1.01\\ 1.02 \end{array}$	$ \begin{bmatrix} 0.93; 1.34 \\ 0.83; 1.41 \\ 0.83; 1.09 \\ 0.92; 1.24 \\ 0.81; 1.07 \\ 0.89; 1.19 \\ 0.93; 1.19 \\ 0.93; 1.19 \\ 0.93; 1.10 \\ 1.01; 1.29 \\ 0.79; 1.26 \\ 0.93; 1.16 \\ 0.95; 1.12 \\ 0.94; 1.09 \\ 0.98; 1.07 \\ \end{array} $
Felt everything was an effort SEBAS MHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: I^2 = 40% [0%; 74%], τ^2 = 0.0048, ρ = 0.11, R_b = 45% [0%; 100%]	598 804 921 1714 3990 4492 5199 7768	115 287 65 261 367 253 816 1668		1.02 0.90 1.15 1.14 0.95 1.07 1.16 1.09 1.06	[0.78; 1.34] [0.75; 1.07] [0.87; 1.52] [1.00; 1.30] [0.84; 1.07] [0.87; 1.32] [1.05; 1.28] [1.03; 1.16] [0.99; 1.14]
Felt fearful MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 13% [0%; 91%], τ^2 = 0.0112, p = 0.32, R_b = 39% [0%; 100%]	921 3990 4492	24 161 166		0.81 0.93 1.13 0.97	[0.52; 1.26] [0.78; 1.11] [0.88; 1.45] [0.80; 1.18]
Felt hopeless about the future MIDUS CRELES WHII TILDA Overall effect Heterogeneity: $J^2 = 0\% [0\%; 64\%], \tau^2 = 0.0005, p = 0.73, R_b = 9\% [0\%; 100\%]$	921 1055 3990 4492	217 110 828 743		0.93 0.95 1.03 0.99 1.00	[0.79; 1.10] [0.58; 1.55] [0.95; 1.12] [0.87; 1.13] [0.93; 1.07]
Felt lonely SEBAS MHAS MIDUS NSHAP WHI TIIDA ELSA HRS Overall effect Heterogeneity: I^2 = 10% [0%; 71%], τ^2 = 0.0069, ρ = 0.35, R_b = 50% [0%; 100%]	598 804 921 1714 3990 4492 5199 7768	57 237 65 287 274 302 526 1101		1.19 1.24 0.85 1.00 1.01 1.18 1.04 1.05 1.06	[0.84; 1.68] [1.02; 1.51] [0.64; 1.12] [0.88; 1.13] [0.98; 1.16] [0.98; 1.43] [0.94; 1.16] [0.98; 1.12] [0.97; 1.15]
Felt sad MHAS MIDUS NSHAP WHII TILDA ELSA HRS Overall effect Heterogeneity: $I^2 = 0\% [0\%; 60\%], \tau^2 = 0.0015, p = 0.63, R_b = 27\% [0\%; 100\%]$	804 921 1714 3990 4492 5199 7768	342 65 315 241 300 868 1292	0.75 1 1.5 Decreased risk	1.09 0.96 0.98 0.88 1.01 0.98 1.01 0.99	[0.92; 1.30] [0.73; 1.26] [0.87; 1.11] [0.76; 1.01] [0.83; 1.22] [0.89; 1.07] [0.95; 1.08] [0.93; 1.04]

Figure S4d (continued)

Study	N	Cases		OR	95%-CI
Felt unhappy MHAS MIDUS CRELES NSHAP WHII TILDA ELSA UKHLS HRS Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 56%], $\tau^2 = 0.0023$, $p = 0.60$, $R_b = 33\%$ [0%; 100%]	804 921 1055 1714 3990 4492 5199 5317 7768	157 120 84 286 668 482 477 674 897		1.10 1.05 1.27 1.05 0.95 1.08 0.98 1.02 0.95 1.00	[0.88; 1.37] [0.85; 1.29] [0.75; 2.16] [0.92; 1.19] [0.87; 1.04] [0.92; 1.26] [0.88; 1.10] [0.92; 1.13] [0.88; 1.02] [0.95; 1.06]
Felt worse than others MIDUS WHII TILDA Overall effect Heterogeneity: I^2 = 1% [0%; 90%], τ^2 = 0.0034, p = 0.36, R_b = 40% [0%; 100%]	921 3990 4492	136 662 476		1.14 1.02 0.95 1.02	[0.94; 1.39] [0.93; 1.12] [0.81; 1.11] [0.92; 1.14]
Had crying spells MIDUS WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 64%], $\tau^2 = 0.0022$, $p = 0.75$, $R_b = 8\%$ [0%; 100%]	921 3990 4492	19 72 138		1.29 1.03 1.08 1.08	[0.77; 2.17] [0.79; 1.35] [0.82; 1.43] [0.89; 1.31]
Life had been a failure MIDUS WHII TILDA Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 0%], $\tau^2 = < 0.0001$, $p = 0.93$, $R_b = 0\%$ [0%; 100%]	921 3990 4492	26 162 131		0.98 0.94 1.00 0.96	[0.64; 1.50] [0.79; 1.12] [0.75; 1.34] [0.83; 1.10]
Little interest in doing things/unmotivated NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 HRS Overall effect Heterogeneity: I^2 = 50% [0%; 80%], τ^2 = 0.0045, ρ = 0.07, R_b = 56% [0%; 100%]	3467 3990 4062 4259 4433 7768	193 352 367 274 355 1432	∎- -®- -⊕- -⊕- ⊕ ⊕	1.03 1.21 1.03 1.01 1.21 1.03 1.08	[0.88; 1.20] [1.06; 1.39] [0.92; 1.15] [0.89; 1.15] [1.07; 1.36] [0.97; 1.10] [1.00; 1.16]
Moving or speaking slowly or too fast NHANES 2005 NHANES 2017 NHANES 2015 NHANES 2007 NHANES 2009 Overall effect Heterogeneity: I^2 = 22% [0%; 67%], τ^2 = 0.0050, p = 0.27, R_b = 36% [0%; 100%]	3467 3990 4062 4259 4433	79 159 148 155 167		1.07 1.11 1.03 0.90 1.17 1.05	[0.84; 1.36] [0.91; 1.35] [0.87; 1.22] [0.76; 1.07] [0.99; 1.38] [0.95; 1.16]
People dislike me MIDUS NSHAP WHII TILDA Overall effect Heterogeneity: I^2 = 68% [7%; 89%], τ^2 = 0.0564, p = 0.02, R_b = 66% [13%; 100%]	921 1714 3990 4492	25 95 73 69		1.03 1.38 1.00 0.68 1.03	[0.66; 1.60] [1.11; 1.72] [0.77; 1.30] [0.44; 1.05] [0.77; 1.37]
People were unfriendly SEBAS MIDUS NSHAP WHI TILDA Overall effect Heterogeneity: $l^2 = 60\%$ [0%; 85%], $\tau^2 = 0.0531$, $p = 0.04$, $R_b = 63\%$ [0%; 100%]	598 921 1714 3990 4492	17 14 137 96 92	0.5 1 2 Decreased risk	1.73 1.22 0.99 0.79 1.16 1.07	[1.06; 2.83] [0.67; 2.24] [0.83; 1.18] [0.63; 0.99] [0.83; 1.62] [0.83; 1.39]

Figure S4d (continued)

Study	Ν	Cases		OR	95%-CI
Sleep problems			Ĩ.		
SEBAS	598	190		1.07	[0.85; 1.35]
MHAS	804	361		0.99	[0.84; 1.17]
MIDUS	921	205		1.09	[0.92; 1.29]
NSHAP	1714	397	— — ——	1.01	[0.90; 1.13]
NHANES 2005	3467	400		1.22	[1.09; 1.36]
WHII	3990	882		0.93	[0.86; 1.01]
NHANES 2017	3990	4062		1.09	[0.98; 1.21]
NHANES 2015	4062	579	- <mark>e</mark> -	1.00	[0.91; 1.09]
NHANES 2007	4259	699		1.04	[0.95; 1.13]
NHANES 2009	4433	716		1.13	[1.04; 1.23]
TILDA	4492	773		1.09	[0.96; 1.24]
ELSA	5199	1745		1.08	[1.01; 1.16]
UKHLS	5317	863		0.96	[0.88; 1.05]
HRS	7768	2305		1.01	[0.96; 1.07]
Overall effect			◆	1.04	[1.00; 1.09]
Heterogeneity: $l^2 = 53\%$ [13%; 74%], $\tau^2 = 0.0032$, $p = 0.01$, $R_b = 53\%$ [14%; 91%]					
Talked less than usual					
MIDUS	921	91		1.04	[0.82; 1.31]
WHII	3990	357		1.03	[0.91; 1.16]
TILDA	4492	205		1.00	[0.79; 1.27]
Overall effect			-	1.03	[0.93; 1.13]
Heterogeneity: $I^2 = 0\% [0\%; 0\%], \tau^2 = < 0.0001, p = 0.97, R_b = 0\% [0\%; 100\%]$					
Thought you would be better off dead					
NHANES 2005	3467	26		0.91	[0.61; 1.35]
NHANES 2017	3990	38		0.75	[0.50; 1.12]
NHANES 2015	4062	50		1.33	[0.96; 1.84]
NHANES 2007	4259	46		1.30	[0.94; 1.79]
NHANES 2009	4433	48		1.15	[0.85; 1.56]
Overall effect				1.09	[0.87; 1.36]
Heterogeneity: $l^2 = 42\%$ [0%; 79%], $\tau^2 = 0.0351$, $p = 0.14$, $R_b = 53\%$ [0%; 100%]					
Trouble concentrating	001			4.07	10.07 1.007
MIDUS	921	115		1.07	[0.87; 1.32]
NHANES 2005	3467	146		1.04	[0.88; 1.23]
WHIL	3990	668	- (3) -	1.06	[0.97; 1.16]
NHANES 2017	3990	245		1.08	[0.92; 1.26]
NHANES 2015	4062	237		1.20	[1.05; 1.38]
NHANES 2007	4259	234		1.07	[0.93; 1.23]
NHANES 2009	4433	269		1.27	[1.11; 1.45]
TILDA UKHLS	4492	384		0.92	[0.77; 1.10]
Overall effect	5317	734		0.99	[0.90; 1.08]
Overall effect Heterogeneity: $I^2 = 46\% [0\%; 75\%], \tau^2 = 0.0054, p = 0.06, R_b = 51\% [0\%; 100\%]$				1.08	[1.01; 1.15]
Heterogeneity. $r = 46\% [0\%; 75\%], \tau = 0.0054, p = 0.06, R_b = 51\% [0\%; 100\%]$			r		
			0.75 1 1.5		

Decreased risk Increased risk

FIGURE S5a. Random-effects meta-analysis of the cross-sectional association between interleukin-6 and individual depression symptoms (adjusted for age & sex)

Study	N	Cases		OR	95%-CI
Bothered by things MIDUS WHII Overall effect Heterogeneity: I^2 = 47%, τ^2 = 0.0277, p = 0.17, R_b = 53% [0%; 100%]	953 3820	44 265		0.82 1.15 1.03	[0.53; 1.27] [0.93; 1.42] [0.75; 1.41]
Changes in appetite SEBAS MIDUS WHII Overall effect Heterogeneity: I^2 = 0% [0%; 55%], τ^2 = 0.0013, p = 0.79, R_b = 4% [0%; 100%]	600 953 3820	80 33 112		1.46 1.28 1.55 1.47	[1.08; 1.97] [0.80; 2.05] [1.16; 2.07] [1.21; 1.78]
Could not get going/energy SEBAS MIDUS WHII Overall effect Heterogeneity: $I^2 = 50\%$ [0%; 86%], $\tau^2 = 0.0270$, $p = 0.14$, $R_b = 60\%$ [0%; 100%]	600 953 3820	95 88 279		1.03 1.58 1.37 1.31	[0.76; 1.40] [1.16; 2.15] [1.13; 1.66] [1.03; 1.67]
Could not shake off the blues MIDUS WHII Overall effect Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0.0007$, $\rho = 0.64$, $R_b = 3\%$ [0%; 100%]	953 3820	45 191		1.15 1.29 1.26	[0.76; 1.75] [1.02; 1.63] [1.02; 1.54]
Did not enjoy life MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0002$, $p = 0.65$, $R_b = 3\%$ [0%; 100%]	953 3820	123 554		1.15 1.07 1.09	[0.88; 1.50] [0.92; 1.25] [0.95; 1.25]
Felt depressed MIDUS WHII Overall effect Heterogeneity: I^2 = 67% [0%; 93%], τ^2 = 0.0357, p = 0.08, R_b = 66% [0%; 100%]	953 3820	73 271		1.51 1.07 1.24	[1.09; 2.10] [0.87; 1.31] [0.90; 1.71]
Felt everything was an effort SEBAS MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 76%], $\tau^2 = 0.0012$, $p = 0.65$, $R_b = 8\%$ [0%; 100%]	600 953 3820	116 68 354		1.57 1.57 1.38 1.46	[1.20; 2.05] [1.12; 2.20] [1.16; 1.64] [1.27; 1.68]
Felt fearful MIDUS WHII Overall effect Heterogeneity: I^2 = 43%, τ^2 = 0.0455, ρ = 0.19, R_b = 51% [0%; 100%]	953 3820	24 148		0.63 0.98 0.85	[0.35; 1.14] [0.74; 1.30] [0.56; 1.28]
Felt hopeless about the future MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0004$, $p = 0.56$, $R_b = 6\%$ [0%; 100%]	953 3820	221 777		1.03 1.11 1.09	[0.83; 1.27] [0.97; 1.27] [0.97; 1.22]
Felt lonely SEBAS MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 64%], $\tau^2 = 0.0016$, $p = 0.75$, $R_b = 7\%$ [0%; 100%]	600 953 3820	57 69 257		0.99 1.19 1.15 1.13	[0.68; 1.45] [0.85; 1.67] [0.94; 1.41] [0.95; 1.33]
Felt sad MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0003$, $p = 0.68$, $R_b = 2\%$ [0%; 100%]	953 3820	68 226		1.18 1.08 1.11	[0.83; 1.67] [0.86; 1.36] [0.92; 1.35]
			0.5 1 2 Decreased risk Increased risk		

Figure S5a (continued)

Study	N	Cases		OR	95%-CI
Felt unhappy MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0001$, $p = 0.70$, $R_b = 1\%$ [0%; 100%]	953 3820	125 636	<u>∎</u> ◆	1.22 1.15 1.17	[0.94; 1.59] [1.00; 1.33] [1.03; 1.32]
Felt worse than others MIDUS WHII Overall effect Heterogeneity: I^2 = 0%, τ^2 = 0.0026, p = 0.37, R_b = 23% [0%; 100%]	953 3820	142 608	■ ■	1.28 1.12 1.17	[1.00; 1.64] [0.97; 1.30] [1.01; 1.35]
Had crying spells MIDUS WHII Overall effect Heterogeneity: l^2 = 58% [0%; 90%], τ^2 = 0.0797, p = 0.12, R_b = 58% [0%; 100%]	953 3820	21 66		2.18 1.27 1.59	[1.24; 3.84] [0.87; 1.86] [0.95; 2.66]
Life had been a failure MIDUS WHII Overall effect Heterogeneity: I^2 = 69% [0%; 93%], τ^2 = 0.0878, p = 0.07, R_b = 69% [0%; 100%]	953 3820	29 151		1.60 0.94 1.17	[0.97; 2.65] [0.71; 1.24] [0.71; 1.92]
People dislike me MIDUS WHII Overall effect Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0.0006$, $p = 0.70$, $R_b = 1\%$ [0%; 100%]	953 3820	26 71		1.57 1.38 1.44	[0.92; 2.68] [0.96; 1.99] [1.06; 1.95]
People were unfriendly SEBAS MIDUS WHII Overall effect Heterogeneity: I^2 = 57% [0%; 88%], τ^2 = 0.1207, p = 0.10, R_b = 61% [0%; 100%]	600 953 3820	17 14 87		1.41 2.69 1.13 1.52	[0.78; 2.54] [1.33; 5.43] [0.79; 1.61] [0.92; 2.51]
Sleep problems SEBAS MIDUS WHII Overall effect Heterogeneity: I^2 = 5% [0%; 90%], τ^2 = 0.0035, p = 0.35, R_b = 29% [0%; 100%]	600 953 3820	190 216 840	- □ - -= = ◆	1.17 1.31 1.09 1.16	[0.93; 1.48] [1.06; 1.62] [0.96; 1.24] [1.03; 1.31]
Talked less than usual MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.83$, $R_b = 0\%$ [0%; 100%]	953 3820	94 330		1.30 1.25 1.26	[0.97; 1.75] [1.04; 1.51] [1.08; 1.48]
Trouble concentrating MIDUS WHI Overall effect Heterogeneity: I^2 = 23%, τ^2 = 0.0061, p = 0.25, R_b = 40% [0%; 100%]	953 3820	122 632	0.2 0.5 1 2 5 Decreased risk Increased risk	1.36 1.14 1.20	[1.04; 1.78] [0.99; 1.31] [1.01; 1.43]

FIGURE S5b. Random-effects meta-analysis of the cross-sectional association between interleukin-6 and individual depression symptoms (adjusted for age, sex & education)

Ν	Cases		OR	95%-CI
953 3820	44 265		0.83 1.15 1.04	[0.53; 1.29] [0.93; 1.42] [0.76; 1.40]
600 953 3820	80 33 112		1.39 1.24 1.56 1.43	[1.02; 1.89] [0.77; 2.00] [1.17; 2.07] [1.17; 1.75]
600 953 3820	95 88 279		1.01 1.55 1.38 1.30	[0.74; 1.37] [1.14; 2.11] [1.14; 1.68] [1.02; 1.66]
953 3820	45 191		1.14 1.28 1.24	[0.75; 1.73] [1.01; 1.62] [1.01; 1.53]
953 3820	123 554		1.13 1.07 1.08	[0.86; 1.48] [0.92; 1.25] [0.95; 1.24]
953 3820	73 271		1.49 1.09 1.24	[1.07; 2.07] [0.88; 1.35] [0.92; 1.66]
600 953 3820	116 68 354		1.55 1.54 1.39 1.45	[1.18; 2.04] [1.10; 2.16] [1.17; 1.66] [1.26; 1.67]
953 3820	24 148		0.62 0.99 0.84	[0.34; 1.12] [0.75; 1.31] [0.55; 1.31]
953 3820	221 777		0.99 1.10 1.07	[0.80; 1.23] [0.97; 1.25] [0.94; 1.21]
600 953 3820	57 69 257		0.95 1.19 1.16 1.12	[0.64; 1.40] [0.84; 1.68] [0.94; 1.43] [0.94; 1.34]
953 3820	68 226	0.5 1 2 Decreased risk	1.19 1.08 1.11	[0.84; 1.68] [0.86; 1.35] [0.92; 1.34]
	953 3820 600 953 3820 953 3820 953 3820 953 3820 953 3820 953 3820 953 3820 953 3820 953 3820 953 3820	953 44 3820 265 600 80 953 33 3820 112 600 95 953 279 953 45 3820 123 953 123 3820 271 953 73 953 271 600 116 953 354 953 354 953 24 3820 148 953 24 3820 241 953 257 600 57 953 257 953 257 953 68	953 44 600 80 953 333 3820 112 600 95 953 88 953 879 953 879 953 279 953 123 953 123 953 123 953 271 953 68 953 24 953 24 953 24 953 221 3820 277 600 57 953 221 3820 257 953 68 953 226	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

Figure S5b (continued)

Study	Ν	Cases		OR	95%-CI
Felt unhappy MIDUS WHII Overall effect Heterogeneity: $J^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.74$, $R_b = 1\%$ [0%; 100%]	953 3820	125 636	- <u>□</u> □	1.21 1.15 1.16	[0.93; 1.58] [1.00; 1.33] [1.03; 1.32]
Felt worse than others MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0005$, $p = 0.56$, $R_b = 6\%$ [0%; 100%]	953 3820	142 608		1.21 1.11 1.14	[0.94; 1.56] [0.96; 1.29] [0.99; 1.30]
Had crying spells MIDUS WHII Overall effect Heterogeneity: I^2 = 59% [0%; 90%], τ^2 = 0.0836, ρ = 0.12, R_b = 59% [0%; 100%]	953 3820	21 66		2.22 1.28 1.62	[1.26; 3.92] [0.87; 1.89] [0.96; 2.72]
Life had been a failure MIDUS WHII Overall effect Heterogeneity: I^2 = 65% [0%; 92%], τ^2 = 0.0741, p = 0.09, R_b = 65% [0%; 100%]	953 3820	29 151		1.57 0.95 1.16	[0.94; 2.62] [0.72; 1.26] [0.73; 1.85]
People dislike me MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0004$, $\rho = 0.73$, $R_b = 1\%$ [0%; 100%]	953 3820	26 71		1.57 1.40 1.45	[0.91; 2.70] [0.98; 2.01] [1.07; 1.96]
People were unfriendly SEBAS MIDUS WHI Overall effect Heterogeneity: $I^2 = 53\%$ [0%; 86%], $\tau^2 = 0.1088$, $p = 0.12$, $R_b = 59\%$ [0%; 100%]	600 953 3820	17 14 87		1.35 2.62 1.15 1.49	[0.75; 2.43] [1.30; 5.29] [0.81; 1.63] [0.92; 2.42]
Sleep problems SEBAS MIDUS WHI Overall effect Heterogeneity: $I^2 = 4\% [0\%; 90\%], \tau^2 = 0.0037, p = 0.35, R_b = 30\% [0\%; 100\%]$	600 953 3820	190 216 840	-⊞- -⊞- - -⊞-	1.14 1.31 1.09 1.16	[0.90; 1.45] [1.06; 1.62] [0.96; 1.24] [1.02; 1.31]
Talked less than usual MIDUS WHII Overall effect Heterogeneity: $f^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.96$, $R_b = 0\%$ [0%; 100%]	953 3820	94 330		1.26 1.25 1.25	[0.94; 1.69] [1.04; 1.51] [1.07; 1.47]
Trouble concentrating MIDUS WHII Overall effect Heterogeneity: I^2 = 24%, τ^2 = 0.0062, p = 0.25, R_b = 39% [0%; 100%]	953 3820	122 632	0.2 0.5 1 2 5 Decreased risk Increased risk	1.36 1.14 1.21	[1.04; 1.77] [0.99; 1.32] [1.01; 1.43]

Decreased risk Increased risk

FIGURE S5c. Random-effects meta-analysis of the cross-sectional association between interleukin-6 and individual depression symptoms (adjusted for age, sex & chronic illness-related factors)

Study	Ν	Cases		OR	95%-CI
Bothered by things MIDUS WHII Overall effect Heterogeneity: $I^2 = 42\%$, $\tau^2 = 0.0252$, $p = 0.19$, $R_b = 51\%$ [0%; 100%]	953 3820	44 265		0.82 1.14 1.02	[0.53; 1.27] [0.92; 1.41] [0.75; 1.39]
Changes in appetite SEBAS MIDUS WHII Overall effect Heterogeneity: I^2 = 0% [0%; 56%], τ^2 = 0.0014, ρ = 0.79, R_b = 5% [0%; 100%]	600 953 3820	80 33 112		1.40 1.22 1.49 1.41	[1.03; 1.90] [0.75; 1.99] [1.11; 2.00] [1.15; 1.72]
Could not get going/energy SEBAS MIDUS WHII Overall effect Heterogeneity: I^2 = 50% [0%; 85%], τ^2 = 0.0275, p = 0.14, R_b = 58% [0%; 100%]	600 953 3820	95 88 279		0.96 1.45 1.35 1.25	[0.70; 1.32] [1.06; 1.98] [1.11; 1.65] [0.98; 1.60]
Could not shake off the blues MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0007$, $p = 0.63$, $R_b = 3\%$ [0%; 100%]	953 3820	45 191		1.09 1.23 1.19	[0.71; 1.68] [0.97; 1.56] [0.96; 1.48]
Did not enjoy life MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.77$, $R_b = 0\%$ [0%; 100%]	953 3820	123 554		1.12 1.07 1.08	[0.85; 1.47] [0.92; 1.25] [0.95; 1.24]
Felt depressed MIDUS WHII Overall effect Heterogeneity: I^2 = 73% [0%; 94%], τ^2 = 0.0510, p = 0.05, R_b = 72% [8%; 100%]	953 3820	73 271		1.47 0.99 1.18	[1.05; 2.06] [0.80; 1.23] [0.81; 1.70]
Felt everything was an effort SEBAS MIDUS WHII Overall effect Heterogeneity: I^2 = 0% [0%; 75%], τ^2 = 0.0012, p = 0.66, R_b = 7% [0%; 100%]	600 953 3820	116 68 354		1.53 1.49 1.33 1.41	[1.16; 2.01] [1.06; 2.10] [1.11; 1.59] [1.22; 1.63]
Felt fearful MIDUS WHII Overall effect Heterogeneity: I^2 = 68% [0%; 93%], τ^2 = 0.1140, p = 0.08, R_b = 69% [0%; 100%]	953 3820	24 148		0.52 0.96 0.76	[0.28; 0.97] [0.72; 1.28] [0.43; 1.33]
Felt hopeless about the future MIDUS WHII Overall effect Heterogeneity: I^2 = 0%, τ^2 = 0.0004, p = 0.57, R_b = 5% [0%; 100%]	953 3820	221 777	- = +	1.02 1.10 1.08	[0.82; 1.27] [0.96; 1.26] [0.96; 1.21]
Felt lonely SEBAS MIDUS WHII Overall effect Heterogeneity: I^2 = 0% [0%; 79%], τ^2 = 0.0043, p = 0.61, R_b = 16% [0%; 100%]	600 953 3820	57 69 257		0.96 1.24 1.16 1.14	[0.65; 1.42] [0.87; 1.76] [0.94; 1.44] [0.94; 1.37]
Felt sad MIDUS WHII Overall effect Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0.0006$, $p = 0.62$, $R_b = 3\%$ [0%; 100%]	953 3820	68 226	0.5 1 2 Decreased risk	1.18 1.06 1.10	[0.83; 1.67] [0.84; 1.33] [0.90; 1.33]

Figure S5c (continued)

Study	N	Cases		OR	95%-CI
Felt unhappy MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.87$, $R_b = 0\%$ [0%; 100%]	953 3820	125 636	 □ ◆ 	1.18 1.15 1.16	[0.90; 1.55] [1.00; 1.33] [1.02; 1.31]
Felt worse than others MIDUS WHII Overall effect Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0.0021$, $p = 0.40$, $R_b = 19\%$ [0%; 100%]	953 3820	142 608	<u>∎</u> ₽	1.27 1.12 1.16	[0.99; 1.63] [0.97; 1.30] [1.01; 1.34]
Had crying spells MIDUS WHII Overall effect Heterogeneity: <i>I</i> ² = 58% [0%; 90%], τ ² = 0.0859, <i>p</i> = 0.12, <i>R</i> _b = 58% [0%; 100%]	953 3820	21 66		2.19 1.25 1.59	[1.22; 3.92] [0.84; 1.87] [0.93; 2.70]
Life had been a failure MIDUS WHII Overall effect Heterogeneity: I^2 = 67% [0%; 92%], τ^2 = 0.0830, p = 0.08, R_b = 67% [0%; 100%]	953 3820	29 151		1.59 0.94 1.16	[0.94; 2.68] [0.71; 1.25] [0.71; 1.89]
People dislike me MIDUS WHII Overall effect Heterogeneity: I^2 = 0%, τ^2 = < 0.0001, p = 0.89, R_b = 0% [0%; 100%]	953 3820	26 71		1.47 1.40 1.42	[0.84; 2.57] [0.97; 2.03] [1.04; 1.93]
People were unfriendly SEBAS MIDUS WHII Overall effect Heterogeneity: I^2 = 61% [0%; 89%], τ^2 = 0.1440, p = 0.08, R_b = 65% [0%; 100%]	600 953 3820	17 14 87		1.36 2.74 1.08 1.48	[0.76; 2.43] [1.32; 5.68] [0.76; 1.54] [0.87; 2.53]
Sleep problems SEBAS MIDUS WHII Overall effect Heterogeneity: I^2 = 0% [0%; 84%], τ^2 = 0.0017, p = 0.53, R_b = 17% [0%; 100%]	600 953 3820	190 216 840	- □ - - ⊕ ◆	1.12 1.25 1.08 1.13	[0.88; 1.42] [1.00; 1.56] [0.95; 1.23] [1.01; 1.26]
Talked less than usual MIDUS WHII Overall effect Heterogeneity: I^2 = 0%, τ^2 = < 0.0001, ρ = 0.96, R_b = 0% [0%; 100%]	953 3820	94 330		1.25 1.24 1.24	[0.92; 1.69] [1.03; 1.50] [1.06; 1.46]
Trouble concentrating MIDUS WHII Overall effect Heterogeneity: l^2 = 0%, τ^2 = 0.0035, p = 0.35, R_b = 26% [0%; 100%]	953 3820	122 632	0.2 0.5 1 2 5 Decreased risk Increased risk	1.29 1.11 1.16	[0.98; 1.70] [0.96; 1.29] [0.99; 1.36]

Decreased risk Increased risk

FIGURE S5d. Random-effects meta-analysis of the cross-sectional association between interleukin-6 and individual depression symptoms (adjusted for age, sex & behavioural factors)

			8 /		· · · ·
Study	Ν	Cases		OR	95%-CI
Bothered by things MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0068$, $p = 0.40$, $R_b = 22\%$ [0%; 100%]	953 3820	44 265		0.78 0.98 0.93	[0.48; 1.26] [0.78; 1.23] [0.73; 1.19]
Changes in appetite SEBAS MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 58%], $\tau^2 = 0.0016$, $p = 0.78$, $R_b = 5\%$ [0%; 100%]	600 953 3820	80 33 112		1.50 1.21 1.37 1.39	[1.09; 2.07] [0.72; 2.04] [1.01; 1.86] [1.13; 1.72]
Could not get going/energy SEBAS MIDUS WHI Overall effect Heterogeneity: I^2 = 0% [0%; 83%], τ^2 = 0.0046, p = 0.55, R_b = 19% [0%; 100%]	600 953 3820	95 88 279		1.00 1.28 1.19 1.16	[0.73; 1.37] [0.91; 1.81] [0.97; 1.46] [0.97; 1.38]
Could not shake off the blues MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0003$, $p = 0.72$, $R_b = 1\%$ [0%; 100%]	953 3820	45 191		0.95 1.05 1.03	[0.59; 1.53] [0.81; 1.37] [0.81; 1.29]
Did not enjoy life MIDUS WHII Overall effect Heterogeneity: $J^2 = 0\%$, $\tau^2 = < 0.0001$, $\rho = 0.91$, $R_b = 0\%$ [0%; 100%]	953 3820	123 554		1.02 1.00 1.00	[0.76; 1.37] [0.85; 1.18] [0.87; 1.16]
Felt depressed MIDUS WHII Overall effect Heterogeneity: $I^2 = 66\% [0\%; 92\%], \tau^2 = 0.0423, p = 0.09, R_b = 66\% [0\%; 100\%]$	953 3820	73 271		1.37 0.94 1.10	[0.95; 1.97] [0.75; 1.18] [0.77; 1.57]
Felt everything was an effort SEBAS MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$ [0%; 81%], $\tau^2 = 0.0022$, $\rho = 0.58$, $R_b = 11\%$ [0%; 100%]	600 953 3820	116 68 354		1.52 1.37 1.27 1.35	[1.15; 2.01] [0.94; 1.99] [1.05; 1.53] [1.16; 1.58]
Felt fearful MIDUS WHII Overall effect Heterogeneity: I^2 = 74% [0%; 94%], τ^2 = 0.1736, p = 0.05, R_b = 74% [18%; 100%]	953 3820	24 148		0.46 0.95 0.71	[0.24; 0.89] [0.70; 1.28] [0.36; 1.38]
Felt hopeless about the future MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0005$, $p = 0.56$, $R_b = 6\%$ [0%; 100%]	953 3820	221 777		0.95 1.03 1.01	[0.75; 1.20] [0.90; 1.18] [0.89; 1.14]
Felt lonely SEBAS MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\% [0\%; 47\%], \tau^2 = 0.0005, p = 0.82, R_b = 2\% [0\%; 100\%]$	600 953 3820	57 69 257		0.96 0.95 1.07 1.02	[0.64; 1.43] [0.64; 1.40] [0.86; 1.34] [0.86; 1.22]
Felt sad MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0026$, $p = 0.48$, $R_b = 11\%$ [0%; 100%]	953 3820	68 226		1.14 0.97 1.02	[0.78; 1.66] [0.76; 1.23] [0.82; 1.27]
			0.5 1 2 Decreased risk Increased risk		

Decreased risk Increased risk

Figure S5d (continued)

Study	N	Cases		OR	95%-CI
Felt unhappy MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.91$, $R_b = 0\%$ [0%; 100%]	953 3820	125 636	•	1.11 1.09 1.09	[0.83; 1.48] [0.94; 1.27] [0.96; 1.25]
Felt worse than others MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0004$, $p = 0.59$, $R_b = 5\%$ [0%; 100%]	953 3820	142 608	<u>∎</u> ◆	1.24 1.14 1.16	[0.95; 1.62] [0.98; 1.33] [1.02; 1.34]
Had crying spells MIDUS WHII Overall effect Heterogeneity: I^2 = 50%, τ^2 = 0.0778, p = 0.16, R_b = 52% [0%; 100%]	953 3820	21 66		1.87 1.07 1.34	[0.98; 3.58] [0.70; 1.63] [0.78; 2.28]
Life had been a failure MIDUS WHII Overall effect Heterogeneity: I^2 = 52% [0%; 88%], τ^2 = 0.0584, p = 0.15, R_b = 56% [0%; 100%]	953 3820	29 151		1.37 0.85 1.01	[0.78; 2.41] [0.62; 1.16] [0.65; 1.59]
People dislike me MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.95$, $R_b = 0\%$ [0%; 100%]	953 3820	26 71		1.17 1.20 1.19	[0.63; 2.18] [0.80; 1.79] [0.85; 1.67]
People were unfriendly SEBAS MIDUS WHII Overall effect Heterogeneity: I^2 = 59% [0%; 88%], τ^2 = 0.1537, p = 0.09, R_b = 63% [0%; 100%]	600 953 3820	17 14 87		1.33 2.59 0.96 1.37	[0.73; 2.43] [1.16; 5.78] [0.65; 1.42] [0.78; 2.40]
Sleep problems SEBAS MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\% [0\%; 90\%], \tau^2 = 0.0032, p = 0.37, R_b = 26\% [0\%; 100\%]$	600 953 3820	190 216 840	- □- □- □- □-	1.18 1.25 1.05 1.13	[0.93; 1.49] [1.00; 1.56] [0.92; 1.20] [1.00; 1.28]
Talked less than usual MIDUS WHII Overall effect Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0006$, $p = 0.60$, $R_b = 4\%$ [0%; 100%]	953 3820	94 330	- ■ ◆	1.24 1.12 1.15	[0.90; 1.71] [0.92; 1.37] [0.97; 1.37]
Trouble concentrating MIDUS WHII Overall effect Heterogeneity: I^2 = 0%, τ^2 = 0.0038, p = 0.35, R_b = 27% [0%; 100%]	953 3820	122 632	0.2 0.5 1 2 5 Decreased risk Increased risk	1.31 1.12 1.17	[0.98; 1.75] [0.96; 1.30] [0.99; 1.38]

Decreased risk Increased risk

Appendix 4. Supplementary Analyses

FIGURE S6. Serially adjusted cross-sectional associations between CRP (low-grade) and 24 individual symptoms of depression (random-effects meta-analysis)

Depressive symptom	N (participants)/	participants)/ Odds ratio (95% CI) per 1SD higher CRP*								
(outcome)	N (studies)	Model 1	Model 1	Model 2	Model 3	Model 4	Model 5			
Had crying spells	9403 / 3		1.20 (0.98 - 1.48)	1.19 (0.96 - 1.48)	1.22 (0.95 - 1.56)	1.08 (0.89 - 1.31)	1.09 (0.89 - 1.32)			
Changes in appetite	31926 / 10	-0-	1.21 (1.16 - 1.27)	1.18 (1.12 - 1.23)	1.20 (1.15 - 1.25)	1.09 (1.04 - 1.15)	1.08 (1.02 - 1.13)			
Felt everything was an effort	25486 / 8		1.17 (1.07 - 1.29)	1.14 (1.05 - 1.24)	1.15 (1.04 - 1.28)	1.06 (0.99 - 1.14)	1.05 (0.97 - 1.13)			
Thought you would be better off dead	20211 / 5		1.23 (1.01 - 1.49)	1.18 (0.97 - 1.44)	1.20 (0.99 - 1.45)	1.09 (0.87 - 1.36)	1.07 (0.85 - 1.34)			
Little insterest in doing things	27979 / 6		1.20 (1.12 - 1.28)	1.16 (1.08 - 1.24)	1.18 (1.11 - 1.26)	1.08 (1.00 - 1.16)	1.07 (1.00 - 1.15)			
Could not get going	46752 / 14	-8-	1.18 (1.13 - 1.22)	1.16 (1.12 - 1.20)	1.17 (1.12 - 1.22)	1.06 (1.02 - 1.10)	1.06 (1.02 - 1.09)			
Feeling bad about yourself	20211 / 5		1.17 (1.10 - 1.24)	1.13 (1.06 - 1.20)	1.14 (1.07 - 1.21)	1.04 (0.97 - 1.11)	1.02 (0.96 - 1.10)			
Could not shake off the blues	9403 / 3		1.17 (1.03 - 1.33)	1.15 (1.03 - 1.28)	1.16 (1.02 - 1.31)	1.03 (0.90 - 1.18)	1.03 (0.90 - 1.18)			
People were unfriendly	11715 / 5		1.20 (0.95 - 1.50)	1.17 (0.93 - 1.46)	1.19 (0.94 - 1.51)	1.07 (0.83 - 1.33)	1.06 (0.82 - 1.36)			
Life had been a failure	9403 / 3		1.02 (0.89 - 1.18)	1.03 (0.90 - 1.18)	1.05 (0.90 - 1.23)	0.96 (0.83 - 1.10)	0.97 (0.84 - 1.12)			
Moving or speaking slowly or too fast	20211 / 5		1.14 (1.03 - 1.25)	1.09 (0.99 - 1.20)	1.11 (1.01 - 1.22)	1.05 (0.95 - 1.16)	1.04 (0.94 - 1.15)			
Felt lonely	25486 / 8		1.13 (1.07 - 1.19)	1.09 (1.04 - 1.15)	1.12 (1.06 - 1.18)	1.06 (0.97 - 1.15)	1.04 (0.97 - 1.12)			
Sleep problems	51014 / 14	-@-	1.12 (1.08 - 1.17)	1.10 (1.06 - 1.14)	1.11 (1.07 - 1.15)	1.04 (1.00 - 1.09)	1.04 (1.00 - 1.08)			
Felt depressed	50416 / 13	-8-	1.12 (1.08 - 1.16)	1.08 (1.04 - 1.12)	1.10 (1.05 - 1.15)	1.02 (0.98 - 1.07)	1.01 (0.97 - 1.05)			
Trouble concentrating	34931 / 9		1.13 (1.05 - 1.22)	1.11 (1.03 - 1.19)	1.12 (1.04 - 1.20)	1.08 (1.01 - 1.15)	1.07 (1.00 - 1.14)			
People dislike me	11117 / 4		1.15 (0.89 - 1.50)	1.12 (0.87 - 1.45)	1.14 (0.89 - 1.47)	1.03 (0.77 - 1.37)	1.03 (0.78 - 1.35)			
Felt unhappy	31260 / 9		1.07 (1.02 - 1.12)	1.06 (1.01 - 1.11)	1.07 (1.02 - 1.12)	1.00 (0.95 - 1.06)	1.00 (0.95 - 1.06)			
Did not enjoy life	31260 / 9		1.07 (1.00 - 1.14)	1.04 (0.98 - 1.11)	1.05 (0.99 - 1.13)	1.00 (0.93 - 1.07)	0.99 (0.92 - 1.07)			
Felt sad	24888 / 7		1.05 (0.99 - 1.11)	1.03 (0.98 - 1.09)	1.04 (0.99 - 1.10)	0.99 (0.93 - 1.04)	0.98 (0.93 - 1.03)			
Talked less than usual	9403 / 3		1.08 (0.98 - 1.18)	1.06 (0.96 - 1.17)	1.08 (0.98 - 1.18)	1.03 (0.93 - 1.13)	1.03 (0.93 - 1.13)			
Felt worse than others	9403 / 3		1.04 (0.95 - 1.14)	1.00 (0.93 - 1.08)	1.04 (0.94 - 1.16)	1.02 (0.92 - 1.14)	1.02 (0.92 - 1.12)			
Bothered by things	9403 / 3		1.01 (0.91 - 1.12)	1.01 (0.91 - 1.11)	1.01 (0.92 - 1.12)	0.92 (0.82 - 1.04)	0.93 (0.82 - 1.04)			
Felt hopeless about the future	10458 / 4	<u> </u>	1.04 (0.97 - 1.11)	1.02 (0.95 - 1.10)	1.04 (0.96 - 1.11)	1.00 (0.93 - 1.07)	1.00 (0.92 - 1.08)			
Felt fearful	9403 / 3		1.02 (0.88 - 1.18)	1.02 (0.88 - 1.18)	1.01 (0.86 - 1.18)	0.97 (0.80 - 1.18)	0.97 (0.80 - 1.17)			
	0.	8 1.0 1.5								

*Model 1: Adjusted for age, sex and baseline depression symptom; Model 2: As Model 1 and additionally adjusted for education; Model 3: As Model 1 and additionally adjusted for chronic illness-related risk factors; Model 4: as Model 1 and additionally adjusted for behavioural risk factors; Model 5: adjusted for all of the above covariates.

Note: These analyses excluded participants with CRP values ≥ 10 mg/L. (i.e., low-grade inflammation)

FIGURE S7. Serially adjusted cross-sectional associations between interleukin-6 and 21 individual symptoms of depression (random-effects meta-analysis)

Depressive symptom	N (participants)/ Odds ratio (95% CI) per 1SD higher IL-6*						
outcome)	N (studies)	Model 1	Model 1	Model 2	Model 3	Model 4	Model 5
Had crying spells	4773 / 2	ļ	1.59 (0.95 - 2.66)	1.62 (0.96 - 2.72)	1.59 (0.93 - 2.70)	1.34 (0.78 - 2.28)	1.34 (0.78 - 2.28)
Changes in appetite	5373/3	_	1.33 (0.33 - 2.88)	1.43 (1.17 - 1.75)	1.41 (1.15 - 1.72)	1.39 (1.13 - 1.72)	1.31 (1.06 - 1.63)
	5373/3		1.46 (1.27 - 1.68)	1.45 (1.26 - 1.67)	1.41 (1.22 - 1.63)	1.35 (1.16 - 1.58)	1.31 (1.12 - 1.53)
elt everything was an effort		_	1.46 (1.27 - 1.68)	1.45 (1.20 - 1.67)	1.41 (1.22 - 1.05)	1.35 (1.16 - 1.58)	1.51 (1.12 - 1.55)
hought you would be better off dead	No data						
ittle insterest in doing things	No data		4 24 (4 22 4 67)	4 22 (4 22 4 55)	4 35 (0 00 4 60)	4 4 6 40 07 4 00	4 4 2 4 0 0 2 4 2 5
ould not get going	5373 / 3		1.31 (1.03 - 1.67)	1.30 (1.02 - 1.66)	1.25 (0.98 - 1.60)	1.16 (0.97 - 1.38)	1.12 (0.92 - 1.35)
eeling bad about yourself	No data	_					
ould not shake off the blues	4773 / 2		1.26 (1.02 - 1.54)	1.24 (1.01 - 1.53)	1.19 (0.96 - 1.48)	1.03 (0.81 - 1.29)	1.00 (0.78 - 1.26)
eople were unfriendly	5373 / 3		1.52 (0.92 - 2.51)	1.49 (0.92 - 2.42)	1.48 (0.87 - 2.53)	1.37 (0.78 - 2.40)	1.33 (0.75 - 2.34)
fe had been a failure	4773 / 2		1.17 (0.71 - 1.92	1.16 (0.73 - 1.85)	1.16 (0.71 - 1.89)	1.01 (0.65 - 1.59)	1.00 (0.66 - 1.52)
loving or speaking slowly or too fast	No data						
elt lonely	5373 / 3	+- o	1.13 (0.95 - 1.33)	1.12 (0.94 - 1.34)	1.14 (0.94 - 1.37)	1.02 (0.86 - 1.22)	1.02 (0.85 - 1.22)
leep problems	5373 / 3		1.16 (1.03 - 1.31)	1.16 (1.02 - 1.31)	1.13 (1.01 - 1.26)	1.13 (1.00 - 1.28)	1.09 (0.97 - 1.22)
elt depressed	4773/2		1.24 (0.90 - 1.71)	1.24 (0.92 - 1.66)	1.18 (0.81 - 1.70)	1.10 (0.77 - 1.57)	1.05 (0.75 - 1.47)
rouble concentrating	4773/2		1.20 (1.01 - 1.43)	1.21 (1.01 - 1.43)	1.16 (0.99 - 1.36)	1.17 (0.99 - 1.38)	1.13 (0.98 - 1.30)
eople dislike me	4773 / 2		1.44 (1.06 - 1.95)	1.45 (1.07 - 1.96)	1.42 (1.04 - 1.93)	1.19 (0.85 - 1.67)	1.19 (0.85 - 1.68)
elt unhappy	4773 / 2	— e —	1.17 (1.03 - 1.32)	1.16 (1.03 - 1.32)	1.16 (1.02 - 1.31)	1.09 (0.96 - 1.25)	1.08 (0.95 - 1.24)
id not enjoy life	4773/2	+ <u>-</u> -	1.09 (0.95 - 1.25)	1.08 (0.95 - 1.24)	1.08 (0.95 - 1.24)	1.00 (0.87 - 1.16)	1.00 (0.87 - 1.15)
elt sad	4773/2		1.11 (0.92 - 1.35)	1.11 (0.92 - 1.34)	1.10 (0.90 - 1.33)	1.02 (0.82 - 1.27)	1.00 (0.81 - 1.26)
alked less than usual	4773/2		1.26 (1.08 - 1.48)	1.25 (1.07 - 1.47)	1.24 (1.06 - 1.46)	1.15 (0.97 - 1.37)	1.13 (0.96 - 1.34)
elt worse than others	4773/2		1.17 (1.01 - 1.35)	1.14 (0.99 - 1.30)	1.16 (1.01 - 1.34)	1.16 (1.02 - 1.34)	1.14 (1.00 - 1.31)
othered by things	4773/2		1.03 (0.75 - 1.41)	1.04 (0.76 - 1.40)	1.02 (0.75 - 1.39)	0.93 (0.73 - 1.19)	0.93 (0.71 - 1.21)
elt hopeless about the future	4773/2	 +	1.09 (0.97 - 1.22)	1.07 (0.94 - 1.21)	1.08 (0.96 - 1.21)	1.01 (0.89 - 1.14)	0.99 (0.86 - 1.14)
	4773/2	T ^u	0.85 (0.56 - 1.28)	0.84 (0.55 - 1.31)	0.76 (0.43 - 1.33)	0.71 (0.36 - 1.38)	0.62 (0.86 - 1.14)

*Model 1: Adjusted for age, sex and baseline depression symptom; Model 2: As Model 1 and additionally adjusted for education; Model 3: As Model 1 and additionally adjusted for chronic illness-related risk factors; Model 4: as Model 1 and additionally adjusted for behavioural risk factors; Model 5: adjusted for all of the above covariates.

FIGURE S8. Serially adjusted longitudinal associations between CRP and 21 individual symptoms of depression (random-effects meta-analysis)

N (studies) Had crying spells 7963 / 2 Changes in appetite 9333 / 3 Felt everything was an effort 21031 / 6 Thought you would be better off dead No data Little insterest in doing things 6090 / 1 Could not strest in doing things 6090 / 1 Could not strest in doing things 6090 / 1 Could not stake off the blues 7963 / 2 People were unfriendly 9333 / 3 Life had been a failure 7963 / 2 Moving or speaking slowly or too fast No data Felt lonely 21031 / 6 Sleep problems 26009 / 7 Folt depressed 26009 / 7 Trouble concentrating 12941 / 3 People dislike me 9333 / 3 Folt unhappy 26009 / 7 Did not enjoy life 26009 / 7	Model 1	Model 1 1.07 (0.90 - 1.27) 1.15 (1.03 - 1.28) 1.15 (1.10 - 1.20) 1.15 (1.09 - 1.22) 1.10 (1.03 - 1.18)	Model 2 1.05 (0.89 - 1.24) 1.14 (1.02 - 1.27) 1.12 (1.08 - 1.17) 1.12 (1.05 - 1.19)	Model 3 1.07 (0.90 - 1.27) 1.12 (1.00 - 1.25) 1.14 (1.09 - 1.19) 1.13 (1.07 - 1.20)	Model 4 1.02 (0.80 - 1.30) 1.16 (1.03 - 1.31) 1.09 (1.04 - 1.15)	Model 5 1.02 (0.81 - 1.29) 1.15 (1.02 - 1.31) 1.09 (1.04 - 1.14)
Changes in appetite 9333 / 3 Felt everything was an effort 21031 / 6 Thought you would be better off dead No data Little insterest in doing things 6090 / 1 Could not get going 21031 / 6 Feeling bad about yourself No data Could not shake off the blues 7963 / 2 People were unfriendly 9333 / 3 Life had been a failure 7963 / 2 Moving or speaking slowly or too fast No data Feit lonely 21031 / 6 Sleep problems 26009 / 7 Foit depressed 26009 / 7 Trouble concentrating 12941 / 3 People dislike me 9333 / 3 Feit unhappy 26009 / 7 Did not enjoy life 26009 / 7		1.15 (1.03 - 1.28) 1.15 (1.10 - 1.20) 1.15 (1.09 - 1.22)	1.14 (1.02 - 1.27) 1.12 (1.08 - 1.17) 1.12 (1.05 - 1.19)	1.12 (1.00 - 1.25) 1.14 (1.09 - 1.19)	1.16 (1.03 - 1.31)	1.15 (1.02 - 1.31)
Changes in appetite 9333 / 3 Felt everything was an effort 21031 / 6 Thought you would be better off dead No data Little insterest in doing things 6090 / 1 Could not get going 21031 / 6 Feeling bad about yourself No data Could not shake off the blues 7963 / 2 People were unfriendly 9333 / 3 Life had been a failure 7963 / 2 Moving or speaking slowly or too fast No data Feit lonely 21031 / 6 Sleep problems 26009 / 7 Foit depressed 26009 / 7 Trouble concentrating 12941 / 3 People dislike me 9333 / 3 Feit unhappy 26009 / 7 Did not enjoy life 26009 / 7		1.15 (1.03 - 1.28) 1.15 (1.10 - 1.20) 1.15 (1.09 - 1.22)	1.14 (1.02 - 1.27) 1.12 (1.08 - 1.17) 1.12 (1.05 - 1.19)	1.12 (1.00 - 1.25) 1.14 (1.09 - 1.19)	1.16 (1.03 - 1.31)	1.15 (1.02 - 1.31)
Felt everything was an effort 21031 / 6 Thought you would be better off dead No data Little insterest in doing things 6090 / 1 Could not get going 21031 / 6 Feeling bad about yourself No data Could not shake off the blues 7963 / 2 People were unfriendly 9333 / 3 Life had been a failure 7963 / 2 Moving or speaking slowly or too fast No data Felt lonely 21031 / 6 Sleep problems 26009 / 7 Fould dislike me 9333 / 3 Felt darpressed 26009 / 7 Fouble dislike me 9333 / 3 Felt unhappy 26009 / 7 Did not enjoy life 26009 / 7	+ + +	1.15 (1.10 - 1.20) 1.15 (1.09 - 1.22)	1.12 (1.08 - 1.17) 1.12 (1.05 - 1.19)	1.14 (1.09 - 1.19)		
Thought you would be better off dead No data Little insterest in doing things 6090 / 1 Could not get going 21031 / 6 Feeling bad about yourself No data Could not shake off the blues 7963 / 2 People were unfriendly 9333 / 3 Life had been a failure 7963 / 2 Moving or speaking slowly or too fast No data Feit lonely 21031 / 6 Sleep problems 26009 / 7 Fould beinses 26009 / 7 Fould blikke me 9333 / 3 Felt unhappy 26009 / 7 Dub of enjoy life 26009 / 7	+ + +	1.15 (1.09 - 1.22)	1.12 (1.05 - 1.19)		1.09 (1.04 - 1.15)	1.09 (1.04 - 1.14)
Little Insterest in doing things 6090 / 1 Could not get going 21031 / 6 Feeling bad about yourself No data Could not shake off the blues 7963 / 2 People were unfriendly 9333 / 3 Life had been a failure 7963 / 2 Voving or speaking slowly or too fast No data Felt lonely 21031 / 6 Sleep problems 26009 / 7 Filt denessed 26009 / 7 Folt denessed 9333 / 3 People dislike me 9333 / 3 Felt unhappy 26009 / 7 Joid not enjoy life 26009 / 7				1.13 (1.07 - 1.20)		
Could not get going 21031 / 6 Feeling bad about yourself No data Could not shake off the blues 7963 / 2 People were unfriendly 9333 / 3 Life had been a failure 7963 / 2 Voving or speaking slowly or too fast No data Felt lonely 21031 / 6 Sleep problems 26009 / 7 Fielt depressed 26009 / 7 Trouble concentrating 12941 / 3 People dislike me 9333 / 3 Feit unpappy 26009 / 7 Jid not enjoy life 26009 / 7	-#- -#-			1.13 (1.07 - 1.20)		
Feeling bad about yourself No data Could not shake off the blues 7963 / 2 People were unfriendly 9333 / 3 Life had been a failure 7963 / 2 Moving or speaking slowly or too fast No data Felt lonely 21031 / 6 Sleep problems 26009 / 7 For uble concentrating 12941 / 3 Paolule collisities me 9333 / 3 Felt unhappy 26009 / 7 Did not enjoy life 26009 / 7		1.10 (1.03 - 1.18)	4 40 (4 04 4 4 6)		1.08 (1.02 - 1.15)	1.08 (1.01 - 1.15)
Could not shake off the blues 7963 / 2 People were unfriendly 9333 / 3 Life had been a failure 7963 / 2 Woving or speaking slowly or too fast No data Felt lonely 21031 / 6 Sleep problems 26009 / 7 Filt depressed 26009 / 7 For uble concentrating 12941 / 3 People dislike me 9333 / 3 Felt unhappy 26009 / 7 Did not enjoy life 26009 / 7			1.10 (1.04 - 1.16)	1.09 (1.02 - 1.17)	1.03 (0.97 - 1.08)	1.02 (0.96 - 1.09)
People were unfriendly 9333 / 3 .ife had been a failure 7963 / 2 Joving or speaking slowly or too fast No data Feit lonely 21031 / 6 Sleep problems 26009 / 7 -eit depressed 26009 / 7 Prouble concentrating 12941 / 3 People dislike me 9333 / 3 -eit unhappy 26009 / 7						
Life had been a failure 7963 / 2 Moving or speaking slowly or too fast No data Felt lonely 21031 / 6 Sleep problems 26009 / 7 Felt depressed 26009 / 7 Trouble concentrating 12941 / 3 People dislike me 9333 / 3 Felt unhappy 26009 / 7 Did not enjoy life 26009 / 7		1.12 (0.94 - 1.34)	1.11 (0.94 - 1.30)	1.11 (0.94 - 1.30)	1.12 (0.95 - 1.32)	1.12 (0.95 - 1.32)
Moving or speaking slowly or too fast No data Felt lonely 21031 / 6 Sleep problems 26009 / 7 Felt depressed 26009 / 7 Trouble concentrating 12941 / 3 People dislike me 9333 / 3 Felt unhappy 26009 / 7 Did not enjoy life 26009 / 7	_	1.06 (0.89 - 1.26)	1.03 (0.89 - 1.19)	1.06 (0.90 - 1.25)	1.01 (0.84 - 1.22)	1.02 (0.85 - 1.22)
Felt Ionely 21031 / 6 Sleep problems 26009 / 7 Filt depressed 26009 / 7 Frouble concentrating 12941 / 3 People dislike me 9333 / 3 Felt unhappy 26009 / 7 Joint of enjoy life 26009 / 7		1.07 (0.86 - 1.32)	1.05 (0.87 - 1.26)	1.06 (0.86 - 1.31)	1.01 (0.84 - 1.22)	1.01 (0.84 - 1.22)
Sleep problems 26009 / 7 Felt depressed 26009 / 7 Trouble concentrating 12941 / 3 People dislike me 9333 / 3 =elt unhappy 26009 / 7 Did not enjoy life 26009 / 7						
Sleep problems 26009 / 7 Felt depressed 26009 / 7 Trouble concentrating 12941 / 3 People dislike me 9333 / 3 Felt unhappy 26009 / 7 Did not enjoy life 26009 / 7	_ 	1.10 (1.03 - 1.18)	1.10 (1.03 - 1.17)	1.09 (1.02 - 1.17)	1.06 (0.99 - 1.13)	1.06 (0.99 - 1.13)
Felt depressed 26009 / 7 Trouble concentrating 12941 / 3 People dislike me 9333 / 3 Felt unhappy 26009 / 7 Did not enjoy life 26009 / 7		1.10 (1.05 - 1.15)	1.09 (1.04 - 1.14)	1.09 (1.03 - 1.15)	1.06 (1.00 - 1.12)	1.05 (0.99 - 1.12)
People dislike me 9333 / 3 Felt unhappy 26009 / 7 Did not enjoy life 26009 / 7		1.08 (1.00 - 1.16)	1.06 (0.99 - 1.14)	1.07 (1.00 - 1.14)	1.02 (0.96 - 1.10)	1.02 (0.96 - 1.09)
Felt unhappy 26009 / 7 Did not enjoy life 26009 / 7	_ _ _	1.07 (1.01 - 1.15)	1.07 (1.00 - 1.14)	1.07 (1.00 - 1.14)	1.04 (0.97 - 1.12)	1.04 (0.97 - 1.12)
Did not enjoy life 26009 / 7		1.01 (0.85 - 1.20)	0.99 (0.82 - 1.22)	1.00 (0.84 - 1.18)	0.96 (0.79 - 1.16)	0.96 (0.79 - 1.15)
		1.06 (1.00 - 1.13)	1.05 (0.99 - 1.12)	1.04 (0.98 - 1.10)	1.02 (0.95 - 1.09)	1.01 (0.95 - 1.08)
		1.08 (1.01 - 1.15)	1.07 (1.00 - 1.14)	1.07 (1.00 - 1.14)	1.06 (0.99 - 1.14)	1.05 (0.98 - 1.13)
Felt sad 21031 / 6		1.05 (0.98 - 1.12)	1.05 (0.99 - 1.12)	1.04 (0.98 - 1.11)	1.02 (0.96 - 1.09)	1.02 (0.95 - 1.08)
Talked less than usual 7963 / 2		1.11 (1.00 - 1.22)	1.10 (1.00 - 1.21)	1.08 (0.98 - 1.20)	1.09 (0.95 - 1.25)	1.08 (0.93 - 1.25)
Felt worse than others 7963 / 2		1.08 (1.00 - 1.17)	1.08 (1.00 - 1.16)	1.08 (1.00 - 1.16)	1.08 (0.98 - 1.18)	1.07 (0.98 - 1.17)
Bothered by things 7963 / 2		1.10 (0.99 - 1.22)	1.09 (0.98 - 1.21)	1.09 (0.98 - 1.21)	1.09 (0.98 - 1.22)	1.09 (0.97 - 1.21
Felt hopeless about the future 7963 / 2		1.09 (0.96 - 1.24)	1.08 (0.96 - 1.21)	1.08 (0.97 - 1.20)	1.07 (0.96 - 1.19)	1.07 (0.96 - 1.18)
Felt fearful 7963 / 2		1.06 (0.88 - 1.26)	1.05 (0.89 - 1.24)	1.07 (0.89 - 1.28)	1.09 (0.94 - 1.27)	1.09 (0.94 - 1.27)

*Model 1: Adjusted for age, sex and baseline depression symptom; Model 2: As Model 1 and additionally adjusted for education; Model 3: As Model 1 and additionally adjusted for chronic illness-related risk factors; Model 4: as Model 1 and additionally adjusted for behavioural risk factors; Model 5: adjusted for all of the above covariates.

FIGURE S9. Unadjusted and serially adjusted cross-sectional association between C-reactive protein (CRP) and, depression status, symptom domains, and 24 symptoms of depression (random-effects meta-analysis)

	N (participants)/	ticipants)/ Odds ratio (95% CI) per 1SD higher CRP*								
Outcome	N (studies)	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)			
Symptom domains										
Physical symptoms			1.17 (1.12 -1.22)	1.15 (1.10 - 1.20)	1.15 (1.10 - 1.20)	1.08 (1.05 - 1.11)	1.08 (1.04 - 1.11)			
Had crying spells	9786 / 3		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 - 1.21)			
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)			
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 - 1.11)			
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)			
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 - 1.09)			
Cognitive symptoms			1.17 (1.11 - 1.23)	1.14 (1.09 - 1.20)	1.15 (1.10 - 1.21)	1.08 (1.05 - 1.12)	1.08 (1.04 - 1.12)			
ittle 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)			
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 - 1.24)			
rouble 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 - 1.13)			
Self-perception-related symptoms			1.13 (1.06 - 1.20)	1.10 (1.03 - 1.17)	1.12 (1.07 - 1.19)	1.04 (1.00 - 1.09)	1.02 (0.99 - 1.07)			
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 - 1.15)			
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 - 1.22)			
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 - 1.10)			
Emotional symptoms		-8-	1.10 (1.07 - 1.13)	1.08 (1.05 - 1.10)	1.08 (1.05 - 1.11)	1.02 (0.99 - 1.05)	1.02 (0.99 - 1.05)			
ife 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 - 1.23)			
elt 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)			
elt 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 - 1.06)			
elt 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 - 1.12)			
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 - 1.08)			
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 - 1.04)			
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 - 1.08)			
elt 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 - 1.09			
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 - 1.23)			

*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.

Depressive symptom N (participants)/ N (studies) (outcome) Odds ratio (95% CI) per 1SD higher CRP* Men Bothered by things 5564/3 1.05 (0.78 - 1.40) Hopeless about the future 6088/4 1.03 (0.90 - 1.17) 5564/3 0.94 (0.67 - 1.30) Felt fearful Life had been a failure 5564/3 1.25 (0.99 - 1.25) Women 4222/3 1.03 (0.92 - 1.16) Bothered by things 4884/4 Hopeless about the future 1.03 (0.93 - 1.14) Felt fearful 4222/3 1.09 (0.88 -1.36) Life had been a failure 4222/3 1.02 (0.81 - 1.28) Age group <60 years 4992/3 Bothered by things 1.02 (0.90 - 1.16) Hopeless about the future 4992/3 1.06 (0.97 - 1.15) 4992/3 0.99 (0.83 - 1.19) Felt fearful Life had been a failure 4174/2 1.10 (0.80 - 1.51) Age group ≥60 years 4794/3 1.07 (0.92 - 1.23) Bothered by things Hopeless about the future 5980/4 1.01 (0.88 - 1.16) Felt fearful 4794/3 1.13 (0.94 - 1.36) Life had been a failure 4663/2 1.09 (0.92 - 1.30) **Depressed patients** Bothered by things 1136/3 0.97 (0.85 - 1.10) Hopeless about the future 1241/4 0.95 (0.79 - 1.14) Felt fearful 1136/3 0.88 (0.71 - 1.10) Life had been a failure 1136/3 0.98 (0.83 - 1.16) Individuals without chronic illnesses** 5137/3 Bothered by things 1.05 (0.93 - 1.18) 5520/4 Hopeless about the future 1.03 (0.92 - 1.15) Felt fearful 5137/3 0.97 (0.75 - 1.25) Life had been a failure 5137/3 1.04 (0.89 - 1.20) Longitudinal association‡ 7963/2 1.10 (0.99 - 1.22) Bothered by things Hopeless about the future 7963/2 1.09 (0.96 - 1.24) Felt fearful 7963/2 1.06 (0.88 - 1.26) Life had been a failure 7963/2 1.07 (0.86 - 1.32) 0.5 2.0 1.0

FIGURE S10. Association between C-reactive protein (CRP) and 4 depression symptoms in subgroups, after additional adjustments and longitudinally (random-effects meta-analysis)

*Adjusted for age and sex as appropriate

† Adjusted for age, sex and adverse childhood experiences

‡ Adjusted for age, sex and depressive symptom at baseline

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

TABLE S7. Random-effects meta-analysis of the cross-sectional associations between CRP and 6 individual symptoms of depression, stratified by time of exposure and outcome ascertainment

Symptom	Studies with no time lag			Studies with time lag		
	OR	LCI	UCI	OR	LCI	UCI
Changes in appetite	1.23	1.18	1.28	1.23	1.1	1.37
Could not get going	1.19	1.14	1.23	1.21	1.11	1.33
Felt everything was an effort	1.18	0.98	1.42	1.26	1.13	1.41
Little insterest in doing things	1.2	1.14	1.27	1.23	1.18	1.29
Sleep problems	1.16	1.11	1.21	1.1	1.03	1.16
Trouble concentrating	1.17	1.12	1.23	1.05	0.99	1.12

Effect estimates adjusted for age & sex

TABLE S8. Age- and sex-adjusted random-effects meta-analysis of the cross-sectional association between CRP and individual symptoms of depression in people with an overall elevated level of depressive symptoms

		Model 1		N (Sample /Studies)
Symptom	OR	LCI	UCI	
Had crying spells	1.13	0.93	1.37	1136 / 3
Changes in appetite	1.11	1.02	1.2	3573 / 10
Felt everything was an effort	1.15	0.99	1.34	3864 / 8
Thought you would be better off dead	1.07	0.93	1.21	1896 / 5
Little insterest in doing things	1.11	1.04	1.19	3145 / 6
Could not get going	1.17	1.1	1.25	5864 / 14
Feeling bad about yourself	1.05	0.97	1.14	1896 / 5
Could not shake off the blues	1.03	0.89	1.19	1136 / 3
People were unfriendly	1.04	0.89	1.22	1677 / 5
Life had been a failure	0.98	0.83	1.16	1136 / 3
Moving or speaking slowly or too fast	0.97	0.87	1.08	1896 / 5
Felt lonely	1.05	0.96	1.14	3864 / 8
Sleep problems	1.08	1.02	1.14	6709 / 14
Felt depressed	1.02	0.96	1.08	6603 / 13
Trouble concentrating	1.03	0.95	1.13	3981 / 9
People dislike me	1.03	0.8	1.33	1571 / 4
Felt unhappy	0.99	0.91	1.07	4812 / 9
Did not enjoy life	0.99	0.89	1.09	4812 / 9
Felt sad	0.96	0.87	1.05	3758 / 7
Talked less than usual	0.87	0.7	1.08	1136 / 3
Felt worse than others	1.03	0.91	1.16	1136 / 3
Bothered by things	0.97	0.85	1.1	1136 / 3
Felt hoopeless about the future	0.95	0.79	1.14	1241 / 4
Felt fearful	0.88	0.71	1.1	1136 / 3

Model 1: effect estimates adjusted for age and sex

Appendix 5. Statistical Code

Statistical Code R: Random-effects analysis of the cross-sectional associations between C-reactive protein and individual symptoms of depression (RStudio)

```
2
   ### Preparation meta-analysis
3 library(meta)
4 library(metafor)
   CRPmeta<- read.csv("Meta-analysis_CRP_DEP.csv") #read csv file with simple model results
   # log_transform effect size data
6
   CRPmeta$OR <- log(CRPmeta$OR)
   CRPmeta$lower <- log(CRPmeta$lower)</pre>
8
   CRPmeta$upper <- log(CRPmeta$upper)</pre>
9
10
   # Calculate standard error seTE
11 CRPmeta$seTE <- (CRPmeta$upper - CRPmeta$lower)/3.92
12
   # metagen function - to reconvert effect sizes to original scale
13 m <- metagen(OR,seTE, studlab = paste(Study), method.tau = "", sm = "OR", data = CRPmeta)
14 # Forest plot
   forest(m,rightlabs = c("OR", "95% CI", "weight"), leftlabs = c("Symptoms"), layout = "JAMA", digits.sd = 2)
15
16
   ## subgroups
17
    forest.subgroup<-update.meta(m,byvar=Symptom,comb.random = TRUE,comb.fixed = FALSE)</pre>
18
    forest.subgroup
    forest(forest.subgroup, study.results = TRUE, bysort = FALSE, print.subgroup.labels = TRUE,
19
           print.byvar = FALSE,print.Rb = TRUE,print.Rb.ci = TRUE,
20
           leftcols = c("studlab", "N", "Cases"),
21
           smlab = "CRP - crude model", pooled.totals = TRUE,comb.random = TRUE,
22
23
           comb.fixed = FALSE, text.random = "Overall effect",print.tau2 = TRUE, col.square = "grey",
           colgap = "10mm", col.square.lines = "blue", col.diamond = "blue",
24
           col.diamond.lines = "black",col.inside = "black", col.predict = "green",
25
           print.I2.ci = TRUE, overall = FALSE, hetstat = TRUE, overall.hetstat = FALSE,
26
           calcwidth.hetstat = TRUE, label.right = "Increased risk", col.label.right = "darkblue",
27
           label.left = "Decreased risk", col.label.left = "darkblue",
28
29
           digits.sd = 4)
```

Statistical Code STATA: Loop for multivariate logistic regression analyses (example)

The following code is an example syntax (i.e., loop) used to calculate the odds ratios and accompanying 95% confidence intervals for the cross-sectional association between C-reactive protein and individual depression symptoms in Whitehall II.


```
capture program drop prog_getpred
         args row outcome title
         matrix B=r(table)
         local b=round(B[1,1],.01)
local lci=round(B[5,1],.01)
local uci=round(B[6,1],.01)
local string "`b' (`lci',`uci')"
        putexcel A row'="'outcome"

putexcel B`row'="`title'"

putexcel C`row'="`string'"

putexcel D`row'="`b'"

putexcel E`row'="`lci'"

putexcel F`row'="`uci'"
  end
   putexcel set "TILDA_data_CRP_cross_cov.xlsx", modify sheet("Sheet1", replace)
   local options
                                   , nolog or
   local extras
                                   if codcrp==1
                                  wlbothbi wlappbi wlbluesbi wlgoodbi wlconcbi ///
wldepbi wleffbi wlhpebi wlfailbi wlfearbi ///
wlslpebi wlhpybi wltlkbi wllonebi wlunfrbi wlenjoybi ///
   local outcomes
                                   w1crybi w1sadbi w1dislbi w1nmuchbi w1deptotbi
   local exposure
                                   w1crpLog
   local row=0
   local num=0
Foreach outcome of local outcomes{
   // local baseLine: subinstr local outcome "8" "6"
// local num=`num'+1
        local baseline: word `num' of `baselines'
         logistic 'outcome' 'exposure' 'if' 'options'
prog_getpred 'row' 'outcome' "Baseline"
          forval i=1/5{
               if 'i'==1
if 'i'==2
if 'i'==3
if 'i'==4
if 'i'==5
                                                             wlage i.wlsex
                                                            wlage i.wlsex i.edu1
wlage i.wlsex i.edu1
wlage i.wlsex bmi1 i.smoked1 i.nopa1 i.alcc1
wlage i.wlsex i.chd1 i.stroke1 i.cancer1 sbp1 dbp1 i.diab1
wlage i.wlsex i.edu1 bmi1 i.smoked1 i.nopa1 i.alcc1 i.chd1 i.stroke1 i.cancer1 sbp1 dbp1 i.diab1
                                   local extras
                                    local extras
                                   local extras
                local row='row'+1
logistic 'outcome' 'exposure' 'extras' 'if' 'options'
prog_getpred 'row' 'outcome' "'extras'"
                foreach var of local extras{
                     local row=`row'+1
logistic `outcome' `exposure' `var' `if' `options'
prog_getpred `row' `outcome' "`var'"
E,
   import excel using "TILDA_data_CRP_cross_cov.xlsx", sheet(Sheet1) clear
   reshape wide C, i(B) j(A) string
rename C* *
   rename B extra
```

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