Psychoneuroendocrinology 110 (2019) 104443

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Inflammatory and metabolic disturbances are associated with more severe trajectories of late-life depression

Alejandro de la Torre-Luque[a,b,c], Jose Luis Ayuso-Mateos[a,b,c,*], Yolanda Sanchez-Carro[a,b,c], Javier de la Fuente[a,b,c], Pilar Lopez-Garcia[a,b,c]

[a] Centre for Biomedical Research in Mental Health (CIBERSAM), Spain
[b] Department of Psychiatry, Universidad Autónoma de Madrid, Spain
[c] Department of Psychiatry, Instituto de Investigación Sanitaria Princesa (IIS Princesa), Spain

ARTICLE INFO

Keywords:
Depression
Inflammation
Metabolic disease risk
Longitudinal trajectories
Healthy ageing

ABSTRACT

Late-life depression is a highly prevalent mental health condition with devastating consequences even from its earliest stages. Alterations in physiological functions, such as inflammatory and metabolic, have been described in patients with depression. However, little is known on the association between depression symptom course and metabolic and inflammation dysregulation. This study aimed to depict the course of depression symptoms while ageing, taking into consideration inter-individual heterogeneity. Moreover, it intended to study the associations between inflammatory and metabolic risk profiles and symptom trajectories. To do so, data from 13,203 adults aged 50–90 years (52.75% women; mean age at baseline = 65.07, *SD* = 10.00) were used. Blood sample and blood pressure measures were taken from 1536 participants (56.58% women; mean age at baseline = 61.73 years, *sd* = 7.64). Depression symptoms were assessed every two years across a 10-year follow-up. Trajectories were identified by means of latent class mixed modelling. Inflammation and metabolic risk profile scores were obtained from plasma and diagnostic-based indicators in the follow-up, using a robust latent-factor approach. Multigroup modelling was used to study the associations between the profiles and symptom trajectories. As a result, three heterogeneous trajectories of symptoms were identified (low-symptom, moderate-symptom and high-symptom trajectory). Participants depicting a high-symptom trajectory showed the greatest inflammation profile score and high metabolic risk. Moderate-symptom trajectory was also related to high inflammation and metabolic risk. To sum up, at-risk trajectories of symptoms were associated with high inflammation and risk of metabolic diseases. This study provides valuable evidence to advance personalised medicine and mental health precision, considering person-specific profiles and physiological concomitants.

1. Introduction

Depression constitutes a public health concern because of its high prevalence, affecting 300 million people, and its impact, being one of the leading causes of disability worldwide (GBD, 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; Ustun et al., 2004; World Health Organization, 2017). Depression influence becomes more evident as people age. Some studies have shown prevalence rates of late-life depression of 30–40%, being higher in elderly women and in population with low levels of education (Andreas et al., 2017; Braam et al., 2014; Dias et al., 2019; Sonnenberg et al., 2000). The interaction of social and physiological factors associated to ageing (e.g., loneliness, widowhood, cumulative burden of chronic diseases, upregulation of inflammatory processes (Alexopoulos and Morimoto, 2011; Kiecolt-Glaser et al., 2015) could explain the high rates of depression in the elderly. For instance, a poor health status (e.g., having multiple chronic diseases) and limited functional status (e.g., limitations in activities of daily living) involve substantial loss in autonomy and reward on a daily basis, with a subsequent impact on emotional state and mental health (Chui et al., 2015; Marengoni et al., 2011; Riddle et al., 2015).

How does depression symptomatology evolve while ageing is a question still under debate. Many studies have highlighted a significant influence of clinically subthreshold depression on health-related outcomes in old age (Carrière et al., 2017; Cuijpers et al., 2013). A unitary course of symptoms has been proved to be insufficient to cover inter-individual heterogeneity over the adulthood and old age (Byers et al.,

* Corresponding author at: Centre for Biomedical Research in Mental Health (CIBERSAM), Department of Psychiatry, School of Medicine, Universidad Autónoma de Madrid, 4 Arzobispo Morcillo Street, Madrid, 28029, Spain.
E-mail address: joseluis.ayuso@uam.es (J.L. Ayuso-Mateos).

https://doi.org/10.1016/j.psyneuen.2019.104443
Received 21 June 2019; Received in revised form 10 September 2019; Accepted 11 September 2019

2012; Montagnier et al., 2014; Musliner et al., 2016).

There are consistent data supporting the association between inflammation and depression. Inflammation seems to be involved in pathophysiologic underpinnings of depression symptomatology (Köhler et al., 2017; Miller and Raison, 2016). Alterations in pro-inflammatory response (e.g., increased cytokine release, increased levels of acute-phase reactants, chemokines and soluble adhesion molecules) have been well documented in patients with depression and high levels of symptoms (Rozing et al., 2019; Valkanova et al., 2013). Low-grade inflammation agents (e.g., fibrinogen and C-reactive protein) may be upregulated in acute stages of depression and over a heightened course of depression symptoms (Ambrosio et al., 2018; Raison and Miller, 2013; Uher et al., 2014; Von Kanel et al., 2009). Moreover, treatment with anti-inflammatory medication may lead to depression symptom amelioration (Raison and Miller, 2013). Moreover, mounting evidence has corroborated the association between depressive conditions and inflammatory disturbances in old age (Brown et al., 2016; White et al., 2017).

On the other hand, metabolic processes have also been considered when studying depression over the old age. The burden of metabolic diseases (e.g., diabetes, hypertension, hypercholesterolemia) is considerable in old age, in terms of epidemiological (e.g., a twofold risk of metabolic diseases is expected in the old age), social (metabolic diseases are highly associated with increased disability) and economic issues (health care service utilisation) (Scholze et al., 2010; Suastika et al., 2011). There is growing evidence pointing to a bidirectional association between increased risk of metabolic diseases and diagnosed depression (Pan et al., 2012; Van Reedt Dortland et al., 2010; Viinamäki et al., 2009). In a same line, numerous studies have found that older adults with depression may show altered levels of metabolic markers (Almeida et al., 2007; Marijnissen et al., 2017). However, little is known about how longitudinal trajectories of depressive symptoms may be related to metabolic disease burden in old age.

Evidence on the association between inflammatory markers and metabolic syndrome risk and depression symptom course is limited and inconsistent. Also, most of these findings predominantly raised from cross-sectional studies. Longitudinal studies are needed to explain how depression symptom course may be linked with specific inflammation and metabolic risk profiles. This study aimed to depict the heterogeneous course of depression symptoms while ageing and its sociodemographic and health-related concomitants. Also, it intended to analyse the association between symptom trajectories and inflammation and metabolic risk profiles. We hypothesised that at least two heterogeneous trajectories of depressive symptoms (e.g., a normative course and a trajectory featured by high symptoms) would be identified in the elderly. Factors related to more severe trajectories of symptoms would be being women, showing lower educational attainment and poorer health status (i.e., multimorbidity, disability and history of psychiatric problems). Finally, trajectories with elevated levels of symptoms would be related to inflammation and metabolic risk profiles; that is, profiles featured by high inflammation and metabolic scores.

2. Materials and methods

Data from 13,615 participants (52.50% women; mean age at baseline = 65.24, *SD* = 10.08) of the English Longitudinal Study of Ageing (ELSA), a biannual, nationally representative, prospective cohort study of health and ageing, were used (NatCen Social Research, 2012; Steptoe et al., 2013). All the participants were between 50 years and 90 years and provided a written consent form to participate. None of them showed either a diagnosis of dementia or antecedents of cancer or immunology diseases.

2.1. Data collection and procedures

Data were collected by face-to-face surveys with trained researchers. Participants were surveyed every two years along a 10-year follow-up, comprising six waves (2002–2012). Baseline survey consisted of a wide battery of questions on sociodemographic features (e.g., marital status, education attainment, household income), disease history (disease burden and history of emotional problems) and health-related conditions. Antidepressant use, chronic diseases and disability details were collected at the 6th wave survey (2012). Three indexes were made to account for disease morbidity and disability (see further details in the Supplementary material): the chronic disease index, activities of daily living difficulty index (ADL) and the instrumental activities of daily living difficulty index (IADL).

Depression symptomatology was assessed across all waves by means of the 8-item version of the Center for Epidemiologic Studies Depression Scale (CES-D 8; Karim et al., 2015; Turvey et al., 1999). This tool evaluates the presence of key symptoms of depressive disorders by means of a dichotomous (yes/no) scale of response. Two components (i.e., depressed mood and somatic symptom component) and a composite score, stating the total number of symptoms, can be derived from the CES-D 8. This short version of the questionnaire has good internal consistency across waves in our sample (Kuder-Richardson 20 index between 0.78 and 0.81 in our sample) and comparable psychometric properties to the full 20-item CES-D (Karim et al., 2015; Van de Velde et al., 2009). The cut-off point for clinical symptomatology was set at more than 3 symptoms (Turvey et al., 1999).

Body mass index (BMI), blood pressure and blood sample data were collected at the 6th ELSA wave (see the Supplementary material for further details). A blood sample was taken in a subsample of 1536 participants (56.58% women; mean age at baseline = 61.73 years, *sd* = 7.64). Individuals with a history of clotting or bleeding disorders or with pharmacological prescription of anticoagulant drugs were excluded from blood sample tests. Blood storage and analysis were carried out at the Royal Victoria Infirmary (Newcastle-upon-Tyne, United Kingdom). Among inflammatory biomarkers white blood cell count, C-reactive protein (CRP), and fibrinogen were assessed. As metabolic biomarkers, we considered: high density lipoprotein (HDL) cholesterol, triglycerides, and glycated haemoglobin (HbA1c). Further details on blood sample analysis is described in the Supplementary material.

2.2. Data analysis

Attrition analyses were conducted to test for differences between the analytical sample and the dropout sample (see further details on analytic approach in the Supplementary data). Latent class mixed modelling (LCMM) was used to depict the course of depression symptoms while ageing, allowing for latent person-specific trajectory identification (Proust-Lima et al., 2015; Proust-Lima and Jacqmin-Gadda, 2005). Model estimation relied on robust maximum likelihood and full information methods (this enabled the depiction of heterogeneous trajectories even when intermittent missing data were present). First, symptom course models depicting either linear or quadratic growth in the fixed and random component were examined. Afterwards, models with increasing trajectory classes were compared in order to identify the model with optimal class enumeration (see the Supplementary material for further details on model selection criteria).

Multinomial regression was used to study how baseline sociodemographic and health-related factors were associated with trajectory class membership. Finally, the fit of multigroup multiple-indicators multiple-causes (MIMIC) models was compared to study the association between depression trajectory class membership and inflammation and metabolic risk profiles. The inflammation and metabolic risk profile models relied on robust plasma-derived and diagnosis-based indicators (see the Supplementary material). Models with increasing parameter constraints across trajectory class groups (each constraint involved

Table 1
Descriptive statistics and attrition analyses.

	Descriptive statistics		Attrition analyses			
			Initial vs. DEP sample		DEP vs. BLOOD sample	
	DEP sample	BLOOD sample	Statistic	*ES*	Statistic	*ES*
n	13203	1536				
Sex (% men)	47.25	43.42	10.15	0.03	10.06	0.03
Age	65.07 (10)	61.73 (7.64)	11.10	−0.76	17.57	0.40
Marital status (%)			23.09	0.03	27.22	0.03
Never married	5.01	4.04				
Married/partnered	69.23	73.54				
Separated/divorced	8.77	9.51				
Widowed	16.99	12.91				
Education level (%)			55.95	0.04	148.30	0.07
No qualifications	34.99	37.37				
Primary-school graduate	19.57	8.59				
Secondary-school graduate	15.2	18.16				
Some college education	16.67	21.62				
University graduate or higher	13.57	14.26				
Household income (£)	18,092 (20,587.71)	21,203.10 (34,526.84)	−2.73	0.19	−4.02	−0.18
History of emotional problems (% yes)	4.62	7.36	2.29^{ns}	0.01	28.84	0.04
Antidepressant prescription (% yes)	13.68	11.91	1.12^{ns}	0.01	5.74^{ns}	0.01
CES-D 8[†]	1.58 (1.98)	1.33 (1.85)	–	–	5.44	0.14
GHQ-12	5.10 (0.98)	4.99 (0.90)	2.25	−0.37	4.94	0.13
Multimorbidity	1.02 (1.01)	0.84 (0.83)	5.23	−0.36	8.61	0.21
ADL	0.4 (0.97)	0.24 (0.73)	4.94	−0.47	8.49	0.19
IADL	0.24 (0.71)	0.11 (0.41)	5.37	−0.51	12.15	0.23
BP						
Systolic (mmHg)		134.05 (17.72)				
Diastolic (mmHg)		72.79 (10.53)				
BMI		27.98 (4.69)				
Inflammatory plasma markers						
WBC (10^9 cell/l)		6.44 (1.89)				
Fib (mg/l)		2.99 (0.52)				
CRP (mg/l)		3.58 (11.44)				
Metabolic plasma markers						
Trig (mmol/l)		1.45 (0.76)				
HDL (mmol/l)		1.68 (0.47)				
HbA1c (%)		41.4 (8.15)				

Note. Percentage of cases are displayed for dichotomous and categorical variables. Means and standard deviation (between brackets) are displayed for continuous variables. Data from all variables were taken at baseline, except BMI, BP, antidepressant prescription, inflammatory and metabolic markers (wave 6).
Initial sample constituted the sample of all participants with more than 50 years and no history of cancer nor immunological diseases (N = 13,615). DEP sample = sample under analysis for depression trajectory class identification. BLOOD sample = sample with blood sample collected.
For attrition analyses, t tests (continuous outcomes) and χ^2 tests (non-continuous outcomes) were used as contrast statistics. All these tests were significant ($p < 0.01$) except those with superscript ^{ns}. ES = effect size estimates (Cohen's d for continuous outcomes and Cramer's V for non-continuous outcomes).
CES-D 8 = Center for Epidemiologic Studies Depression Scale, 8-item version. GHQ-12 = General Health Questionnaire, 12-item version. ADL = Activities of daily living difficulty index. IADL = Instrumental activities of daily living difficulty index. BP = Blood pressure. BMI = Body mass index. WBC = White blood cell count. Fib = Fibrinogen. CRP = C-reactive protein. Trig = Triglycerides. HDL = High-density lipoprotein cholesterol. HbA1c = Glycated haemoglobin.
[†] Attrition analysis for this variable was not conducted between the initial sample and DEP sample due to lack of scores from the dropped sample.

parameter being equal across groups) were compared. Thus, the influence of symptom trajectory on the profile was proved when a more constrained model fitted better fit to data. Diagonally weighted least squares methods were used for inflammation profile and metabolic risk profile estimation.

All the analyses were conducted using STATA and R software and packages lcmm and lavaan (R Core Team, 2017).

3. Results

Descriptive statistics of participants in analysis are displayed in Table 1. Data from 13,203 participants were used to study the course of depression symptoms while ageing (participants in analysis). A sample of 412 participants (55.34% men; m = 73.26 years at baseline, sd = 10.84; 64.55% married and 69.05% with less than secondary education attainment) was excluded from analyses due to the lack of CES-D measurement. Attrition analyses revealed the presence of significant differences across samples. However, only differences in age and IADL were meaningfully significant (i.e., with at least a medium effect size) when comparing the initial and the analytical sample.

3.1. Depression symptom trajectories

Three trajectories of depressive symptoms while ageing were found (Fig. 1). LCMM revealed that the growth solution comprising three heterogeneous trajectories of depression symptoms, linear fixed and mixture component, fitted better than the other nested models (see Table S1 and S2 in the Supplementary material). This model presented low fit indexes (CAIC = 183,177.42; SABIC = 183,145.64) and high mean of posterior probabilities of belonging to each trajectory class (.81–.95). The three identified trajectories were: 1) a low-symptom trajectory or normative trajectory featured by a trajectory of minimal levels of symptoms but slightly rising (time loading B = 0.07, $SE < 0.01$, Wald's Z = 9.82, $p < 0.01$), depicted in 74.57% of participants in analysis (n = 9846); 2) a moderate-symptom trajectory class (17.99% of participants, n = 2375) with rising levels of symptomatology, that surpassed the cut-off point of clinical meaningfulness over time (time loading B = 0.07, SE = 0.01, Wald's Z = 3.83, $p < 0.01$)

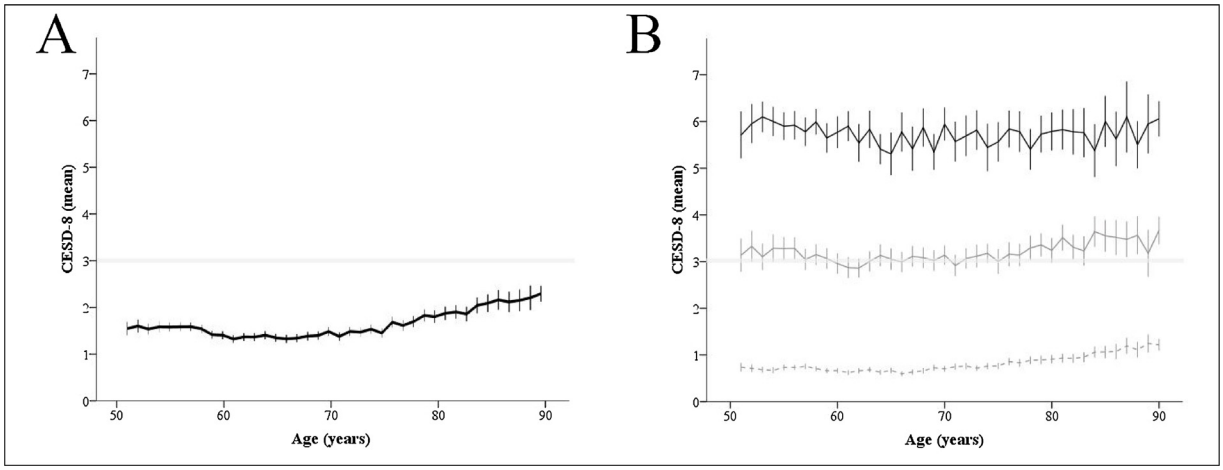

Fig. 1. Overall course and underlying person-specific trajectories of depression symptomatology over the old age.
Note. Figure in the A box depicts the overall course of depression symptoms while ageing. Figure in the B box depicts the underlying trajectories of symptoms identified.
Error bars depict the 95% confidence interval of the mean.
The shaded area refers to the cut-off point for clinical symptomatology.
For the figure in the B box: Grey dashed line = low-symptom trajectory class. Grey solid line = moderate-symptom trajectory class. Dark solid line = high-symptom trajectory class.

and 3) a high-symptom trajectory (7.44% of participants, $n = 982$) with heightened levels of symptoms (always above the cut-off point for clinical meaningfulness) over time, but slightly decreasing (time loading $B = -0.05$, $SE = 0.02$, Wald's $Z = -2.25$, $p < 0.03$).

3.2. Sociodemographic and clinical factors associated to depression trajectories

The multinomial logistic regression revealed a better fit regarding the model with predictors (AIC = 4254.14; $R^2 = .24$), in comparison with the unconditional model (AIC = 19,035.25; $R^2 = .00$). Regression coefficients by predictor is displayed in Table 2. Moderate-symptom trajectory (in comparison to low symptom class) was explained by sex (being woman), civil status (being separated or widowed), education (not having got secondary school certificate or above), but especially by exhibiting a history of emotional problems, multimorbidity and functioning limitations, and having prescribed antidepressant medication. High-symptom trajectory was explained by the same factors (but also by younger age). However, membership for this class involved higher relative ratio values across factors.

3.3. Inflammatory and metabolic risk and depression trajectories

Fig. 2 displays inflammation and metabolic risk profile scores according to symptom trajectory class. Positive correlations were found between the inflammation profile score and the CES-D 8 components across measurement waves (for the depressed mood component, r between 0.05, wave 2, to .11, wave 6; for the somatic symptom component, r between 0.14, wave 2, to .20, wave 6). Higher correlations were observed between the matabolic profile score and the CES-D 8 components (for the depressed mood component, r between 0.18, wave 3, to .22, wave 2; for the somatic symptom component, r between 0.22, wave 3, to .28, wave 6). Correlation between the metabolic and inflammation profile scores was positive, but low, $r = 0.25$, $p < 0.01$.

Multigroup testing revealed that the inflammation profile solution with constraints on indicator loadings, intercepts and residuals fitted better to data than the nested models., ΔCFI = .004, ΔRMSEA = -0.005. This pointed to a moderating effect of depressive symptom trajectory group on the inflammation profile scores. Regarding the metabolic risk profile model, the loss of fit was not significant for the model with loadings and thresholds constrained, ΔCFI = .003, ΔRMSEA = -.002, in comparison to the unconstrained model. This finding provided some evidence on the moderating role of depressive symptom trajectory group in the metabolic profile scores. Fit indexes for all the nested models are shown in Table S3 (Supplementary material).

Significant differences across classes were revealed for all indicators and latent factor scores, especially when comparing the low-symptom trajectory with the others (see Table S4 for further details on estimated parameters). More severe symptom trajectories showed higher levels of inflammatory biomarkers and higher latent factor scores (observing significant *post hoc* differences between all the groups) as well as higher metabolic risk considering its indicators and latent factor score.

4. Discussion

In this prospective, large cohort study of old individuals, we found three different depression symptoms trajectories while ageing considering inter-individual heterogeneity: low depressive symptoms, moderate depressive symptoms and high depressive symptoms. The factors that better predicted the membership to clinically relevant trajectories were female gender, lower educational attainment, being separated or widowed, multimorbidity, disability and history of emotional problems in adulthood. Finally, we found an association between more severe symptom trajectories and the presence of inflammatory and metabolic factors.

Our study revealed that the course of depression while ageing follows different trajectories differentiated by symptom intensity and trend. We found that three heterogeneous trajectories depicted the depression symptom course more optimally. These results are in line with current approaches claiming for integrating longitudinal and person-centred corollaries into epidemiology and psychiatry research and practice, as a contribution to advance personalised medicine and mental health precision (Costello and Angold, 2016; Redekop and Mladsi, 2013). Some studies with older adults have found a similar symptom trajectory class enumeration, highlighting a course of elevated symptoms over the studied period and a normative class (comprising the bulk of participants) with low levels of symptoms over time (Hybels et al., 2016; Montagnier et al., 2014; Rote et al., 2015). According to Musliner et al. (2016), most of older adults may show a course featured by low levels of symptoms, with a minimal impact on health and related outcomes. However, a low proportion of individuals may show very high, even chronic, depression symptoms over time. Our

Table 2
Regression predictors of depression symptom trajectory class membership.

	Moderate-symptom trajectory (n = 2375)			High-symptom trajectory (n = 982)		
	RRR	*CI*	*Z*	*RRR*	*CI*	*Z*
(intercept)	0.35	(0.15, 0.83)	−2.39*	0.09	(0.02, 0.44)	−3.00**
Sex (reference = man)	1.71	(1.41, 2.17)	5.42**	1.89	(1.28, 2.78)	3.24**
Age	0.99	(0.98, 1.00)	−1.70	0.97	(0.95, 0.99)	−2.50*
Marital Status (reference = married)						
Never married	1.02	(0.62, 1.68)	0.10	2.13	(0.95, 4.80)	1.83
Separated/divorced	1.41	(1.05, 1.88)	2.26*	2.51	(1.55, 4.04)	3.77**
Widowed	1.45	(1.11, 1.91)	2.71**	2.16	(1.33, 3.49)	3.14**
Household income	1.00	(1.00, 1.00)	−4.07**	1.00	(1.00, 1.00)	−0.58
Education level (reference = no qualifications)						
Primary-school graduate	0.96	(0.69, 1.34)	−0.22	0.89	(0.48, 1.62)	−0.39
Secondary-school graduate	0.71	(0.54, 0.93)	−2.47*	0.49	(0.30, 0.82)	−2.70**
Some college education	0.87	(0.66, 1.13)	−1.07	0.36	(0.20, 0.64)	−3.46**
University graduate or higher	0.68	(0.48, 0.97)	−2.15*	0.26	(0.12, 0.57)	−3.36**
History of emotional problems (reference = no)	2.45	(1.78, 3.38)	5.50**	5.44	(3.46, 8.57)	7.32**
Multimorbidity	1.15	(1.04, 1.27)	2.70**	1.56	(1.31, 1.86)	5.04**
ADL	1.39	(1.24, 1.57)	5.49**	1.54	(1.32, 1.81)	5.37**
IADL	1.65	(1.36, 2.01)	5.03**	2.04	(1.60, 2.61)	5.72**
Antidepressant prescription (reference = no)	1.93	(1.51, 2.46)	5.24**	2.65	(1.80, 3.92)	4.93**

Note. Moderate-symptom and high-symptom class membership were compared with low-symptom class membership (n = 9846; reference class). Data from all variables were taken at baseline, except antidepressant prescription (wave 6).
ADL = Activities of daily living difficulty index. IADL = Instrumental activities of daily living difficulty index.
RRR = relative risk ratio. *CI* = 95% confidence interval of the *RRR*. *Z* = Wald's *Z* test statistic.
* $p < 0.05$; ** $p < 0.01$.

study showed a proportion of individuals with very high levels of symptoms over time (comprising the high-symptom trajectory class), but also a group of individuals with rising symptoms (the moderate-symptom trajectory class adults). Taking together participants from both classes, one in four individuals may show clinical levels of depression symptoms in their late life.

We found risk factors highly associated to the moderate-symptom trajectory (i.e., being woman, low educational attainment, being separated or widowed, multimorbidity, disability, history of emotional problems in adulthood and antidepressant consumption). Similar predictors were observed regarding the high-symptom trajectory class membership, but the relative influence of these factors on class membership prediction was higher. Moreover, high-symptom trajectory individuals showed elevated symptomatology from earlier in life, due to the significant effect of age on class membership prediction. These results provide additional evidence on the cumulative impact of multimorbidity, disability and emotional problem history to show a more severe symptom trajectory in old age (Byers et al., 2012; Chui et al., 2015; Montagnier et al., 2014).

Regarding the inflammation and metabolic risk profiles, our results supported the association between more severe forms of depression (moderate- and high-symptom trajectories) in old individuals and inflammatory and metabolic dysregulation. In this regard, latent-factor multigroup-based procedures revealed that participants with a high-symptom trajectory while ageing showed a higher inflammation score compared to the other less severe trajectories. Besides, metabolic risk profile scores were significantly higher in individuals showing both at-risk trajectories (high and moderate symptoms trajectories) in comparison to those showing the normative one.

Our results are in line with some studies that show an association between inflammatory and metabolic dysregulation and more severe cases of depression in clinical samples (i.e., more episodes, chronic course and more resistance to antidepressant medication; Kim et al., 2015; Pan et al., 2012; Raison and Miller, 2013; Viinamäki et al., 2009; Vogelzangs et al., 2014). It has been proposed a longitudinal and bi-directional association between dysregulated inflammatory and metabolic processes and late-life depression emergence and persistence, at a diagnosis and symptom level (Eswarappa et al., 2019; Hamer et al., 2013; Marijnissen et al., 2017). Epidemiological cohort studies on large community samples have demonstrated that increased inflammation serves as a risk factor for the development of depression. Higher levels of baseline inflammatory markers (C-reactive protein) and metabolic disturbances (high triglycerides and glucose levels, larger waist circumference and lower levels of HDL cholesterol) have been associated with an increased risk of chronic depression in older participants later in life (Rozing et al., 2019; Sonsin-Diaz et al., 2019; Vogelzangs et al., 2010). Conversely, it has been shown that presence of depressive symptoms (especially somatic symptoms) predicts increased inflammation in old age (Martinez-Cengotitabengoa et al., 2016; Niles et al., 2018; Sonsin-Diaz et al., 2019).

The prolonged exposure to inflammatory agents, especially in brain, may have devastating consequences in terms of mood dysregulation and depression symptom emergence (e.g., anorexia, fatigue), altered neuroplasticity (associated with an increased vulnerability to further depressive episode) and cognitive impairment, due to reduced synaptic availability of monoamines (e.g., increased uptake of serotonin by an upregulation of the mitogen-activated protein kinase) and neurotoxicity effects (e.g., increased levels of reactive oxygen species, astrocyte-mediated glutamate metabolism alterations) (Eisenberger et al., 2010; Felger et al., 2016; Raison and Miller, 2013). Likewise, anti-depressant effects have been found after administering some anti-inflammatory medications (Kohler et al., 2016). This could be especially relevant while ageing as inflammation may speed up ageing-related processes (Gabuzda and Yankner, 2013).

On the other hand, metabolic disturbances have been linked to depression both in cross-sectional and in prospective cohort studies, showing a bidirectional association between metabolic syndrome and late-life depression (Almeida et al., 2009; Pan et al., 2012; Viinamäki

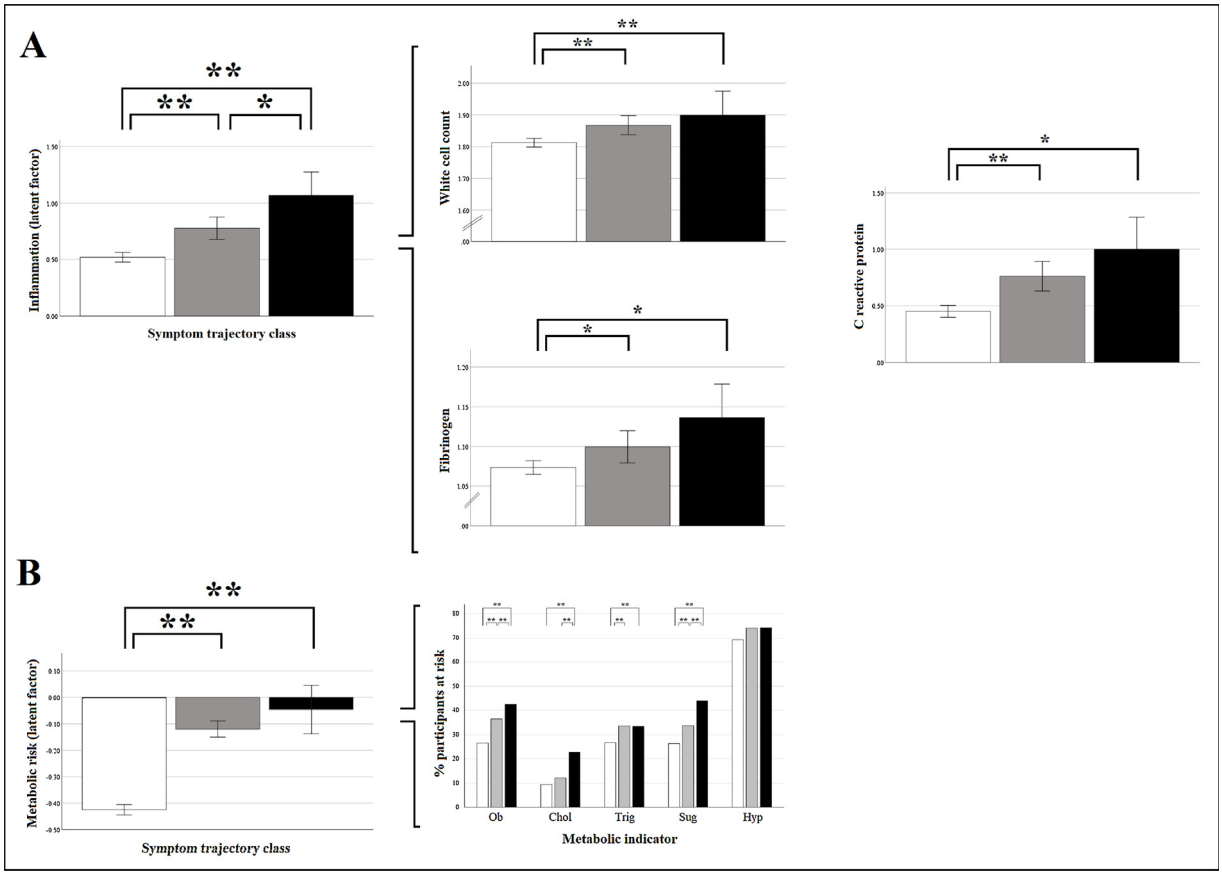

Fig. 2. Inflammatory and metabolic risk profile and indicators according to depression symptom trajectory class.
Note. Figure in the A box depicts the scores in the inflammatory profile latent factor (indicators on the right side). Figure in the B box displays the scores in the metabolic risk profile latent factor (indicators on the right side).
Inflammation indicators are in loglineal scale. Error bars depict the 95% confidence interval of the mean for the continuous variables.
Ob = obesity risk. Chol = high cholesterol risk. Trig = high triglycerides risk. Sug = high blood sugar risk. Hyp = High hypertension risk.
Comparisons between groups relied on Bonferroni correction. * $p < 0.05$; ** $p < 0.01$.
White bar = low-symptom trajectory class. Grey bar = moderate-symptom trajectory class. Dark bar = high-symptom trajectory class.

et al., 2009; Vogelzangs et al., 2011). Metabolic disturbances in depression could be explained by a dysregulation of the hypothalamic-pituitary-adrenocortical axis, a neurobiological signature of depression (de la Torre-Luque et al., 2016; Mansur et al., 2015; Van Reedt Dortland et al., 2010). Thus, for instance, glucocorticoid-mediated insulin resistance has been identified as a significant mediator in the well-known association between diabetes and depression. Also, leptin (a circulating hormone produced by adipose tissue and highly associated with obesity) synthesis is significantly increased in patients with depression due to the influence of glucocorticoids.

5. Conclusions

Our results highlight that, person-specific trajectories of depression symptoms should be considered while ageing. Therefore, a more comprehensive psychiatric screening, exploring multiple domains (i.e., taking into consideration longitudinal aspects as well as patient's sociodemographic and health profile), becomes essential to make a more accurate diagnosis and to choose the optimal therapeutic option. Moreover, an assessment of inflammation and metabolic profiles could particularly be valuable to improve mental health precision in older population, as mounting evidence stresses the role of these profiles as early peripheral markers of depression (Mansur et al., 2015; Raison and Miller, 2013). Our findings are derived from a sophisticated, robust methodology, relying on latent factors which capture the common variability from some observable indicators and allowing studying underlying profiles or processes. Additionally, our large sample (coming from a nationally-representative population) allows for ensuring finding generalisability. As a shortcoming, other more specific inflammation and metabolic markers (e.g., specific cytokines or oxidative stress markers [Rozing et al., 2019; Vogelzangs et al., 2014]) could have been studied to provide further insight on specific underpinnings of depression symptom course. Additionally, longitudinal assessment of inflammation and metabolic markers was missing. However, this study aimed at providing some body of evidence that allows clinicians and practitioners implementing screening protocols even at its earliest stages (e.g., on a primary care basis). On the other hand, sample with blood markers was much lower than the sample used for depressive symptom trajectory identification. Attrition analysis revealed the lack of meaningful differences (i.e., differences with at least medium effect size, considered as an optimal cut-off point when sample size is very large; Lin et al., 2013) between these both samples, except in terms of age. Participants with blood sample were younger. This fact may hinder generalisability of our results to older samples. Further research should be done to corroborate our findings with very-old samples. Secondly, our study did not focus on clinical samples (i.e., participants with a diagnosed depression). In this regard, we opted for providing some insight on how inflammatory and metabolic profile on a community basis to advance in depression diagnosis accuracy and prevention in the older age (Aragonès et al., 2006; Kok and Reynolds, 2017). Finally, most of the profile factors that have been explored in this study (e.g., multimorbidity, ADL, IADL) relied on self-reports.

Further research should incorporate more objective measures of these variables to complement the results aforementioned.

Individualised medicine has provided a valuable insight on uniqueness of older patient, as evidenced by heterogeneity in disease expression and health profiles and treatment response. Our study highlights how important is to incorporate person-centred assessment protocols, covering issues across multiple domains (e.g., subjective, immunological) and considering the longitudinal nature of depression, in order to contribute to diagnosis precision and intervention decision-making optimisation. Also, it suggests that inflammation and metabolic markers may help old people with depression syndromes be monitored in terms of symptom course and treatment prognosis. Finally, this study aims at encouraging new lines of treatments for depression, based on new anti-inflammatory agents (Kohler et al., 2016).

Funding and conflict of interests

This study was supported by the European Commission Horizon 2020 under grant number 635316 (ATHLOS) and Instituto de Salud CarlosIII- PI16/00218 FIS research grant co-funded by the European Union European Regional Development Fund (ERDF)"A Way to Build Europe". The ELSA waves used in this study were funded jointly by the UK government departments and the US National Institute on Aging.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.104443.

References

Alexopoulos, G., Morimoto, S., 2011. The inflamation hypothesis in geriatric depression. Int. J. Geriatr. Psychiatry 26, 1109–1118. https://doi.org/10.1002/gps.2672.THE.

Almeida, O.P., Calver, J., Jamrozik, K., Hankey, G.J., Flicker, L., 2009. Obesity and metabolic syndrome increase the risk of incident depression in older men: the Health in Men Study. Am. J. Geriatr. Psychiatry 17, 889–898. https://doi.org/10.1097/JGP.0b013e3181b047e3.

Almeida, O.P., Flicker, L., Norman, P., Hankey, G.J., Vasikaran, S., Van Bockxmeer, F.M., Jamrozik, K., 2007. Association of cardiovascular risk factors and disease with depression in later life. Am. J. Geriatr. Psychiatry 15, 506–513. https://doi.org/10.1097/01.JGP.0000246869.49892.77.

Ambrosio, G., Kaufmann, F.N., Manosso, L., Platt, N., Ghisleni, G., Lúcia, A., Rodrigues, S., Rieger, D.K., Kaster, M.P., 2018. Depression and peripheral inflammatory profile of patients with obesity. Psychoneuroendocrinology 91, 132–141. https://doi.org/10.1016/j.psyneuen.2018.03.005.

Andreas, S., Schulz, H., Volkert, J., Dehoust, M., Sehner, S., Suling, A., Ausín, B., Canuto, A., Crawford, M., Da Ronch, C., Grassi, L., Hershkovitz, Y., Muñoz, M., Quirk, A., Rotenstein, O., Santos-Olmo, A.B., Shalev, A., Strehle, J., Weber, K., Wegscheider, K., Wittchen, H.U., Härter, M., 2017. Prevalence of mental disorders in elderly people: the European MentDis-ICF65+ study. Br. J. Psychiatry 210, 125–131. https://doi.org/10.1192/bjp.bp.115.180463.

Aragonès, E., Piñol, J.L., Labad, A., 2006. The overdiagnosis of depression in non-depressed patients in primary care. Fam. Pract. 23, 363–368. https://doi.org/10.1093/fampra/cmi120.

Braam, A.W., Copeland, J.R.M., Delespaul, P.A.E.G., Beekman, A.T.F., Como, A., Dewey, M., Fichter, M., Holwerda, T.J., Lawlor, B.A., Lobo, A., Magnússon, H., Prince, M.J., Reischies, F., Wilson, K.C., Skoog, I., 2014. Depression, subthreshold depression and comorbid anxiety symptoms in older Europeans: results from the EURODEP concerted action. J. Affect. Disord. 155, 266–272. https://doi.org/10.1016/j.jad.2013.11.011.

Brown, P.J., Roose, S.P., Zhang, J., Wall, M., Rutherford, B.R., Ayonayon, H.N., Butters, M.A., Harris, T., Newman, A.B., Satterfield, S., Simonsick, E.M., Yaffe, K., 2016. Inflammation, depression, and slow gait: a high mortality phenotype in later life. Journals Gerontol. Med. Sci. 71, 221–227. https://doi.org/10.1093/gerona/glv156.

Byers, A.L., Vittinghoff, E., Lui, L.-Y., Hoang, T., Blazer, D.G., Covinsky, K.E., Ensrud, K.E., Cauley, J.A., Hillier, T.A., Fredman, L., Yaffe, K., 2012. Twenty-year depressive trajectories among older women. Arch. Gen. Psychiatry 69, 1073–1079.

Carrière, I., Farré, A., Proust-Lima, C., Ryan, J., Ancelin, M.L., Ritchie, K., 2017. Chronic and remitting trajectories of depressive symptoms in the elderly. Characterisation and risk factors. Epidemiol. Psychiatr. Sci. 26, 146–156. https://doi.org/10.1017/S2045796015001122.

Chui, H., Gerstorf, D., Hoppmann, C.A., Luszcz, M.A., 2015. Trajectories of depressive symptoms in old age: integrating age-, pathology-, and montality-related changes. Psychol. Aging 30, 940–951. https://doi.org/10.1037/pag0000054.

Costello, E.J., Angold, A., 2016. Developmental epidemiology. In: Cicchetti, D. (Ed.), Epidemiologic Reviews. John Wiley & Sons Inc., Amsterdam, pp. 74–82. https://doi.org/10.1007//978-1-4614-9608-3.

Cuijpers, P., Vogelzangs, N., Twisk, J., Kleiboer, A., Li, J., Penninx, B.W.J.H., 2013. Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. Br. J. Psychiatry 202, 22–27. https://doi.org/10.1192/bjp.bp.112.112169.

de la Torre-Luque, A., Bornas, X., Balle, M., Fiol-Veny, A., 2016. Complexity and non-linear biomarkers in emotional disorders: a meta-analytic study. Neurosci. Biobehav. Rev. 68, 410–422. https://doi.org/10.1016/j.neubiorev.2016.05.023.

Dias, F.L.C., Teixeira, A.L., Guimarães, H.C., Santos, A.P.B., Ritter, S.R.F., Machado, J.C.B., Barbosa, M.T., Caramelli, P., 2019. Prevalence of late-life depression and its correlates in a community-dwelling low-educated population aged 75+ years: the Pietà study. J. Affect. Disord. 242, 173–179. https://doi.org/10.1016/j.jad.2018.08.012.

Eisenberger, N.I., Berkman, E.T., Inagaki, T.K., Rameson, L.T., Mashal, N.M., Irwin, M.R., 2010. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. Biol. Psychiatry 68, 748–754. https://doi.org/10.1016/j.biopsych.2010.06.010.

Eswarappa, M., Neylan, T.C., Whooley, M.A., Metzler, T.J., Cohen, B.E., 2019. Inflammation as a predictor of disease course in posttraumatic stress disorder and depression: a prospective analysis from the Mind your Heart Study. Brain Behav. Immun. 75, 220–227. https://doi.org/10.1016/j.bbi.2018.10.012.

Felger, J.C., Li, Z., Haroon, E., Woolwine, B.J., Jung, M.Y., Hu, X., Miller, A.H., 2016. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol. Psychiatry 21, 1358–1365. https://doi.org/10.1038/mp.2015.168.

Gabuzda, D., Yankner, B.A., 2013. Physiology: inflammation links ageing to the brain. Nature 497, 197–198. https://doi.org/10.1038/nature12100.

GBD, 2016. Disease and Injury Incidence and Prevalence Collaborators, 2017. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990 – 2016 : a systematic analysis for the Global Burden of Disease Study 2016. Lancet 390, 1211–1259. https://doi.org/10.1016/S0140-6736(17)32154-2.

Hamer, M., Batty, G.D., Kivimaki, M., 2013. Risk of future depression in people who are obese but metabolically healthy: The English Longitudinal Study of Ageing. Mol Psychiatry 17, 940–945. https://doi.org/10.1038/mp.2012.30.Risk.

Hybels, C.F., Bennett, J.M., Landerman, L.R., Liang, J., Plassman, B.L., Wu, B., 2016. Trajectories of depressive symptoms and oral health outcomes in a community sample of older adults. Int. J. Geriatr. Psychiatry 31, 83–91. https://doi.org/10.1002/gps.4292.

Karim, J., Weisz, R., Bibi, Z., ur Rehman, S., 2015. Validation of the eight-item center for epidemiologic studies depression scale (CES-D) among older adults. Curr. Psychol. 34, 681–692. https://doi.org/10.1007/s12144-014-9281-y.

Kiecolt-Glaser, J.K., Derry, H.M., Fagundes, C.P., 2015. Inflammation: depression fans the flames and feasts on the heat. Am. J. Psychiatry 172, 1075–1091. https://doi.org/10.1176/appi.ajp.2015.15020152.

Kim, E.Y., Kim, S.H., Ha, K., Lee, H.J., Yoon, D.H., Ahn, Y.M., 2015. Depression trajectories and the association with metabolic adversities among the middle-aged adults. J. Affect. Disord. 188, 14–21. https://doi.org/10.1016/j.jad.2015.08.024.

Kohler, O., Krogh, J., Mors, O., Eriksen Benros, M., 2016. Inflammation in depression and the potential for anti-inflammatory treatment. Curr. Neuropharmacol. 14, 732–742. https://doi.org/10.2174/1570159X14666151208113700.

Köhler, O., Sylvia, L.G., Bowden, C.L., Calabrese, J.R., Thase, M., Shelton, R.C., McInnis, M., Tohen, M., Kocsis, J.H., Ketter, T.A., Friedman, E.S., Deckersbach, T., Ostacher, M.J., Iosifescu, D.V., McElroy, S., Nierenberg, A.A., 2017. White blood cell count correlates with mood symptom severity and specific mood symptoms in bipolar disorder. Aust. N. Z. J. Psychiatry 51, 355–365. https://doi.org/10.1177/0004867416644508.

Kok, R.M., Reynolds, C.F., 2017. Management of depression in older adults: a review. JAMA - J. Am. Med. Assoc. 317, 2114–2122. https://doi.org/10.1001/jama.2017.5706.

Lin Jr., M., Shmueli, H.C.L., Lin, G., M, 2013. Too big to fail : large samples and the p -Value problem. Inf. Syst. Res. 7047, 1–12. https://doi.org/10.1287/isre.2013.0480.

Mansur, R.B., Brietzke, E., McIntyre, R.S., 2015. Is there a "metabolic-mood syndrome"? A review of the relationship between obesity and mood disorders. Neurosci. Biobehav. Rev. 52, 89–104. https://doi.org/10.1016/j.neubiorev.2014.12.017.

Marengoni, A., Angleman, S., Melis, R., Mangialasche, F., Karp, A., Garmen, A., Meinow, B., Fratiglioni, L., 2011. Aging with multimorbidity: a systematic review of the literature. Ageing Res. Rev. 10, 430–439. https://doi.org/10.1016/j.arr.2011.03.003.

Marijnissen, R.M., Vogelzangs, N., Mulder, M.E., van den Brink, R.H.S., Comijs, H.C., Oude Voshaar, R.C., 2017. Metabolic dysregulation and late-life depression: a prospective study. Psychol. Med. 47, 1041–1052. https://doi.org/10.1017/S0033291716003196.

Martinez-Cengotitabengoa, M., Carrascon, L., O'Brien, J.T., Diaz-Gutierrez, M.J., Bermudez-Ampudia, C., Sanada, K., Arrasate, M., Gonzalez-Pinto, A., 2016. Peripheral inflammatory parameters in late-life depression: a systematic review. Int. J. Mol. Sci. 17. https://doi.org/10.3390/ijms17122022.

Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16, 22–34. https://doi.org/10.1038/nri.2015.5.

Montagnier, D., Dartigues, J.F., Rouillon, F., Pérès, K., Falissard, B., Onen, F., 2014.

Ageing and trajectories of depressive symptoms in community-dwelling men and women. Int. J. Geriatr. Psychiatry 29, 720–729. https://doi.org/10.1002/gps.4054.
Musliner, K.L., Munk-Olsen, T., Eaton, W.W., Zandi, P.P., 2016. Heterogeneity in long-term trajectories of depressive symptoms: patterns, predictors and outcomes. J. Affect. Disord. 192, 199–211. https://doi.org/10.1037/0021-9010.81.6.628.
NatCen Social Research, T, 2012. English Longitudinal Study of Ageing (ELSA). Wave One to Wave Five. User Guide to the Datasets.
Niles, A.N., Smirnova, M., Lin, J., O'Donovan, A., 2018. Gender differences in longitudinal relationships between depression and anxiety symptoms and inflammation in the Health and Retirement Study. Psychoneuroendocrinology 95, 149–157. https://doi.org/10.1016/j.psyneuen.2018.05.035.
Pan, A., Keum, N., Okereke, O.I., Sun, Q., Kivimaki, M., Rubin, R.R., Hu, F.B., 2012. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. Diabetes Care 35, 1171–1180. https://doi.org/10.2337/dc11-2055.
Proust-Lima, C., Jacqmin-Gadda, H., 2005. Estimation of linear mixed models with a mixture of distribution for the random effects. Comput. Methods Programs Biomed. 78, 165–173. https://doi.org/10.1016/j.cmpb.2004.12.004.
Proust-Lima, C., Philipps, V., Liquet, B., 2015. Estimation of Extended Mixed Models Using Latent Classes and Latent Processes: the R Package Lcmm. https://doi.org/10.18637/jss.v078.i02.
R Core Team, 2017. R: a Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna.
Raison, C.L., Miller, A.H., 2013. The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). Mol. Psychiatry 18, 15–37. https://doi.org/10.1038/mp.2012.2.
Redekop, W.K., Mladsi, D., 2013. The faces of personalized medicine: a framework for understanding its meaning and scope. Value Heal. 16, S4–S9. https://doi.org/10.1016/j.jval.2013.06.005.
Riddle, M., McQuoid, D.R., Potter, G.G., Steffens, D.C., Taylor, W.D., 2015. Disability but not social support predicts cognitive deterioration in late-life depression. Int. Psychogeriatrics 27, 707–714. https://doi.org/10.1017/S1041610214002543.
Rote, S., Chen, N.W., Markides, K., 2015. Trajectories of depressive symptoms in elderly Mexican Americans. J. Am. Geriatr. Soc. 63, 1324–1330. https://doi.org/10.1111/jgs.13480.
Rozing, M.P., Veerhuis, R., Westendorp, R.G.J., Eikelenboom, P., Stek, M., 2019. Inflammation in older subjects with early- and late-onset depression in the NESDO study: a cross-sectional and longitudinal case-only design. Psychoneuroendocrinology 99, 20–27. https://doi.org/10.1016/j.psyneuen.2018.08.029.
Scholze, J., Alegria, E., Ferri, C., Langham, S., Stevens, W., Jeffries, D., Uhl-Hochgraeber, K., 2010. Epidemiological and economic burden of metabolic syndrome and its consequences in patients with hypertension in Germany, Spain and Italy; A prevalence-based model. BMC Public Health 10. https://doi.org/10.1186/1471-2458-10-529.
Sonnenberg, C.M., Beekman, A.T.F., Deeg, D.J.H., Van Tilburg, W., 2000. Sex differences in late-life depression. Acta Psychiatr. Scand. 101, 286–292. https://doi.org/10.1034/j.1600-0447.2000.101004286.x.
Sonsin-Diaz, N., Gottesman, R.F., Fracica, E., Walston, J., Windham, B.G., Knopman, D.S., Walker, K.A., 2019. Chronic systemic inflammation is associated with symptoms of late-life depression: the ARIC study. Am. J. Geriatr. Psychiatry 1–12. https://doi.org/10.1016/j.jagp.2019.05.011.
Steptoe, A., Breeze, E., Banks, J., Nazroo, J., 2013. Cohort profile: the english longitudinal study of ageing. Int. J. Epidemiol. 42, 1640–1648. https://doi.org/10.1093/ije/dys168.
Suastika, K., Dwipayana, P., Ratna Saraswati, I.M., Kuswardhani, T., Astika, N., Putrawan, I.B., Matsumoto, K., Kajiwara, N., Taniguchi, H., 2011. Relationship between age and metabolic disorders in the population of Bali. J. Clin. Gerontol. Geriatr. 2, 47–52. https://doi.org/10.1016/j.jcgg.2011.03.001.
Turvey, C.L., Wallace, R.B., Herzog, R., 1999. A revised CES-D measure of depressive symptoms and a DSM-based measure of major depressive episodes in the elderly. Int. Psychogeriatrics 11, 139–148. https://doi.org/10.1017/S1041610299005694.
Uher, R., Tansey, K.E., Dew, T., Maier, W., Mors, O., Hauser, J., Dernovsek, M.Z., Henigsberg, N., Souery, D., McGuffin, P., 2014. An Inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. Am. J. Psychiatry 171, 1278–1286. https://doi.org/10.1176/appi.ajp.2014.14010094.
Ustun, T.B., Ayuso-Mateos, J.L., Chatterji, S., Mathers, C., Murray, C.J.L., 2004. Global burden of depressive disorders in the year 2000. Br. J. Psychiatry 184, 386–392.
Valkanova, V., Ebmeier, K.P., Allan, C.L., 2013. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. J. Affect. Disord. 150, 736–744. https://doi.org/10.1016/j.jad.2013.06.004.
Van de Velde, S., Levecque, K., Bracke, P., 2009. Measurement equivalence of the CES-D 8 in the general population in Belgium: a gender perspective. Arch. Public Heal. 67, 15. https://doi.org/10.1186/0778-7367-67-1-15.
Van Reedt Dortland, A.K.B., Giltay, E.J., Van Veen, T., Zitman, F.G., Penninx, B.W.J.H., 2010. Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use. Acta Psychiatr. Scand. 122, 30–39. https://doi.org/10.1111/j.1600-0447.2010.01565.x.
Viinamäki, H., Heiskanen, T., Lehto, S.M., Niskanen, L., Koivumaa-Honkanen, H., Tolmunen, T., Honkalampi, K., Saharinen, T., Haatainen, K., Hintikka, J., 2009. Association of depressive symptoms and metabolic syndrome in men. Acta Psychiatr. Scand. 120, 23–29. https://doi.org/10.1111/j.1600-0447.2008.01333.x.
Vogelzangs, N., Beekman, A.T.F., Boelhouwer, I.G., Bandinelli, S., Milaneschi, Y., Ferrucci, L., Penninx, B.W.J.H., 2011. Metabolic depression: a chronic depressive subtype? Findings from the InCHIANTI Study of older persons. J. Clin. Psychiatry 72, 598–604. https://doi.org/10.4088/JCP.10m06559.
Vogelzangs, N., Beekman, A.T.F., Van Reedt Dortland, A.K.B., Schoevers, R.A., Giltay, E.J., De Jonge, P., Penninx, B.W.J.H., 2014. Inflammatory and metabolic dysregulation and the 2-year course of depressive disorders in antidepressant users. Neuropsychopharmacology 39, 1624–1634. https://doi.org/10.1038/npp.2014.9.
Vogelzangs, N., Kritchevsky, S.B., Beekman, A.T.F., Brenes, G.A., Newman, A.B., Satterfield, S., Yaffe, K., Harris, T.B., Penninx, B.W.J.H., 2010. Obesity and onset of significant depressive symptoms: results from a community-based cohort of older men and women. J. Clin. Psychiatry 71, 391–399. https://doi.org/10.4088/JCP.08m04743blu.
Von Kanel, R., Bellingrath, S., Kudielka, B.M., 2009. Association of vital exhaustion and depressive symptoms with changes in fibrin D-dimer to acute psychosocial stress. J. Psychosom. Res. 67, 93–101. https://doi.org/10.1016/j.jpsychores.2008.12.009.
White, J., Kivimäki, M., Jokela, M., Batty, G.D., 2017. Association of inflammation with specific symptoms of depression in a general population of older people: the English Longitudinal Study of Ageing. Brain Behav. Immun. 61, 27–30. https://doi.org/10.1016/j.bbi.2016.08.012.
World Health Organization, 2017. Depression and Other Common Mental Disorders. Global Health Estimates. World Health Organization, Geneva. https://doi.org/CC BY-NC-SA 3.0 IGO.