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Chronic and remitting trajectories of depressive symptoms in the elderly. Characterization and risk factors.

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None

Abstract

Aims

In elderly general population sub-syndromal clinically significant levels of depressive symptoms are highly prevalent and associated with high co-morbidity and increased mortality risk. However changes in depressive symptoms over time and etiologic factors have been difficult to characterize notably due to methodological shortcomings. Our objective was to differentiate trajectories of depressive symptoms over 10 years in community-dwelling elderly men and women using statistical modelling methods which take into account intra-subject correlation and individual differences as well as to examine current and life-time risk factors associated with different trajectories.

Methods

Participants aged 65 and over were administered standardised questionnaires and underwent clinical examinations at baseline and after 2, 4, 7 and 10 years. Trajectories over time of the Center for Epidemiologic Studies Depression scores were modelled in 517 men and 736 women separately with latent class mixed models which include both a linear mixed model to describe latent classes of trajectories and a multinomial logistic model to characterize the latent trajectories according to baseline covariates (socio-demographic, lifestyle, clinical, genetic characteristics and stressful life events).

Results

In both genders two different profiles of symptom changes were observed over the 10-year follow-up. For 9.1% of men and 25% of women a high depressive symptom trajectory was found with a trend toward worsening in men. The majority of the remaining men and women showed decreasing symptomatology over time, falling from clinically significant to very low levels of depressive symptoms. In large multivariate class membership models, mobility limitations (odds ratio (OR)=4.5, 95% confidence interval (CI) 1.6-12.9 and OR=4.9, 95% CI 2.3-10.7, in men and women respectively), ischemic pathologies (OR=2.9, 95% CI 1.0-8.3 and OR=3.1, 95% CI 1.0-9.9), and recent stressful events (OR=4.5, 95% CI 1.1-18.5, OR=3.2, 95% CI 1.6-6.2) were associated with a poor

symptom course in both gender as well as diabetes in men (OR=3.5, 95% CI 1.1-10.9) and childhood traumatic experiences in women (OR=3.1, 95% CI 1.6-5.8).

Conclusions

This prospective study was able to differentiate patterns of chronic and remitting depressive symptoms in elderly people with distinct symptom courses and risk factors for men and women. These findings may inform prevention programmes designed to reduce the chronic course of depressive symptomatology.

Keywords: depressive symptoms, aged, risk factors, cohort studies

INTRODUCTION

Most community-dwelling elderly people who have clinically significant levels of depressive symptomatology do not meet the full diagnostic criteria for major depressive episodes (Blazer, 2003; Cuijpers *et al.*, 2013). Studies of depression in the elderly have thus increasingly focused on levels of depressive symptomatology rather than diagnostic categories, as this takes into account clinically significant sub-syndromal states; the latter being not only highly prevalent in the elderly (12-15%), but also associated with high co-morbidity, high mortality, and treatment resistance (Helmchen & Linden, 2000; Kirsch *et al.*, 2008; Olfson *et al.*, 1996).

Previous studies have suggested that depressive states in the elderly may have a highly variable course due to their diverse origins. Very few studies in the general elderly population have undertaken the complex task of characterizing dimensional symptom trajectories over a long time period. One study considered *a priori* trajectory groups instead of estimating them (Chen *et al.*, 2011), while others used methods such as non-parametric K-means clustering (Cui *et al.*, 2008) or a semi-parametric latent class growth analysis (Andreescu *et al.*, 2008; Byers *et al.*, 2012; Hsu, 2012; Jones & Nagin, 2007; Liang *et al.*, 2011) which do not fully take into account intra-subject correlation (correlation between repeated evaluations of the same subject). One recent study (Kuchibhatla *et al.*, 2012) used a more complex method, the generalized growth mixture model (Muthen *et al.*, 2002), which takes into account both intra-subject correlation and individual variability in depressive symptom curves over time within each trajectory group. This study included covariates such as self-rated health, cognition, functional disability, social network, and recent stressful events, but not other major risk factors for depression in the elderly such as chronic diseases and early-life stressors (Cole & Dendukuri, 2003; Ritchie *et al.*, 2009; Vink *et al.*, 2008). Possible gender differences in clinical trajectories were also not examined, although such differences have consistently been observed in the levels, characteristics, and course of depressive symptoms (Carriere *et al.*, 2011; Piccinelli & Wilkinson, 2000; Ryan *et al.*, 2008). In women symptom levels tend to be higher and chronicity of depression appears to have a greater impact, perhaps due to over reporting of symptoms, psychological, neurochemical, hormonal, genetic, and personality factors, and higher stress reactivity (Grigoriadis & Robinson, 2007). Given

these differences it would be clinically more useful to examine the course of depressive symptoms separately in men and women. This would furthermore enable the establishment of thresholds for the early detection of persons at high risk of a severe and unremitting disease course.

The present study has two aims: i) to examine trajectories of depressive symptoms over a 10-year period for men and women separately, using statistical modelling methods which take into account intra-subject correlation and individual differences, and ii) to examine a wide range of current and life-time risk and protective factors potentially associated with different trajectories. Identifying factors contributing to depressive symptom chronicity and remission in men and women may subsequently be useful to indicate potential intervention windows.

MATERIAL AND METHODS

Study sample

Participants of the ESPRIT study were recruited over a 2-year period from 1999 to 2001 (Ritchie *et al.*, 2004), by random selection from the electoral rolls in Montpellier, France. Eligible people, who were at least 65 years of age and non-institutionalised, were invited to participate and provided written informed consent. Of the people initially drawn at random, 27.3% did not participate. Those who refused to participate were replaced by another person drawn at random from the same electoral division to ensure representativeness. Participants were administered a number of standardised questionnaires by trained staff and underwent clinical examinations at baseline, 2, 4, 7, and 10 years of follow-up. Ethics approval was granted by the Ethics Committee of the University Hospital of Kremlin-Bicêtre (France). Informed consent was obtained from all individual participants included in the study.

Of the 2259 participants included in the cohort, 1988 subjects (816 men and 1172 women) with at least two repeated measures of depressive symptoms throughout the 10-year period were at first selected. Of these, 735 subjects with missing data for at least one baseline covariate were excluded (of them 481 had incomplete responses to the childhood event questionnaire) leaving 1253 (517 men and

736 women) in the main analysis. Sensitivity analysis for detection of trajectories was also performed on the full sample of 1988 participants.

Compared with the participants included in the analysis, those excluded were older, with a lower level of education, and were more likely to be treated with antidepressants and to have mobility limitations, ischemic pathologies, low cognitive performance, and depressive symptomatology. They were also more likely to have lack of support during childhood ($p < 0.001$ for all comparisons). There were no significant differences regarding gender, past major depressive episode and 5-HTTLPR genotype.

Depressive symptoms

Depressive symptoms were evaluated at each wave using the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977), a 20-item self-report rating scale designed to evaluate the frequency and severity of depressive symptoms and validated in French (Fuhrer & Rouillon, 1989; Morin *et al.*, 2011). Response to each item was on a 4-point scale varying from 0 to 3 and the total score ranged from 0 to 60. Participants with a CES-D score ≥ 16 are considered as having high levels of depressive symptomatology which would warrant clinical intervention (Radloff, 1977).

Baseline covariables

The standardized interview included questions on demographic characteristics, level of education and mode of living. Detailed medical questionnaires included history of diabetes and ischemic pathologies. Participants with a body mass index (BMI) over 25 kg/m^2 were classified as overweight. At baseline and follow-up examinations, the general questionnaire included an inventory of all drugs (including antidepressant drugs) used during the preceding month which were systematically coded using the Anatomical Therapeutic Chemical (ATC) classification system (WHO Collaborating Centre, 2013). Purpose of treatment was not recorded. Mobility was assessed according to the Rosow and Breslau scale (Rosow & Breslau, 1966) which evaluates ability to do heavy housework, walk half a mile, and climb stairs. Cognitive functioning was assessed using a modified version of the Isaacs Verbal Fluency test (Isaacs & Kennie, 1973). This timed test of lexical access draws on conceptual, linguistic and mnemonic abilities, and is thus sensitive to pathologies in both frontal and posterior brain regions

(Schlosser *et al.*, 1998). The participants were asked to generate as many words as possible in 30 seconds within a given semantic category such as colors, animals, fruits or cities. In the absence of a validated cut-off, low cognitive performance was a priori defined in our study as scoring in the lower tertile and corresponded to a total score lower than 43.

A retrospective self-report questionnaire (Ritchie *et al.*, 2009) examining traumatic experiences during childhood and adolescence (covering 25 adverse and 8 protective factors), was given to subjects for completion in the third wave of the study (four years after recruitment by which time the interviewer had established a close relationships with the participants). These factors were combined in three variables: parental mental problems, lack of support (less than 6 positive items among the following: paternal and maternal affection, availability of an adult friend, raised by both parents, impression of having had a happy childhood, a normal education, feeling happy at school and the impression that parents did their best) and adverse childhood events (at least one negative item among: poverty, neglected, verbal, physical or sexual abuse, humiliation or mental cruelty, excessive punishment, or parents too often sharing their problems with children). Exposure to stressful life events in the past year was also assessed at baseline using the Gospel Oak 12-item questionnaire including bereavement, rupture in a close relationship, severe illness and serious financial or legal problems (Harwood *et al.*, 1998). The Mini International Neuropsychiatric Interview (MINI) (Sheehan *et al.*, 1998), a standardized psychiatric examination was used for the diagnosis of past major depressive episodes, according to DSM-IV criteria.

Blood samples for DNA collection were taken after the baseline clinical interview. The serotonin-transporter-promoter region (5-HTTLPR) was genotyped as previously reported (Ritchie *et al.*, 2009) having previously been found to moderate the relationship between stress and depression (Karg *et al.*, 2011; Miller *et al.*, 2013).

Statistical analyses

The χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables were used to identify gender differences and to compare the included and excluded participants. The latent class mixed model (LCMM) was used to identify trajectory groups of CES-D score over time. This

model seeks potential latent profiles in heterogeneous populations. It combines a latent class model to identify homogenous latent groups of subjects and a mixed model to describe the mean trajectory over time in each latent group, while taking into account the individual correlation between repeated measures. In the latent class submodel, a multinomial logistic model was used to characterize the latent classes according to baseline covariates. The function LCMM (Proust-Lima *et al.*, 2014) of the R-package version 3.1.3 was used to estimate the model parameters.

As the CES-D distribution is skewed to the left, the original scale was transformed with a beta cumulative distribution function simultaneously estimated with the LCMM model. The class-specific trajectories of depressive symptoms were described according to years since entry in the cohort using a quadratic polynomial without adjustment for baseline covariates. All analyses were stratified by gender. The optimal number of latent classes and the shape of the class-specific trajectories were determined by sequentially increasing the number of model parameters (one- to four- latent classes with a linear or quadratic time trajectory, a diagonal or unstructured random-effect covariance matrix and a class-specific or proportional random-effect covariance matrix (Proust-Lima *et al.*, 2014)). This sequential procedure screened a total of 180 models for each gender (*supplementary material*). The Bayesian information criteria (BIC) were used to select the best model. For each model, fifty sets of random starting values were tested to ensure that an adequate solution was obtained.

Covariates were firstly introduced separately in the class-membership model adjusted for baseline age. Significant covariates with a p-value <0.20 in the age-adjusted model were then put together in the multivariate models. Two nested adjusted models were built. The first (Model 1) included age, mobility, diabetes, obese or overweight and ischemic pathologies for both genders and also 5-HTTLPR genotype for men and cognitive performance for women. The second (Model 2) further included recent stressful life events as well as childhood lack of support, adverse events, and parental mental problems.

RESULTS

At baseline, the median age (IQR) of the 1253 participants (517 men and 736 women) was 72 years (68-76) and the median time (IQR) of follow-up was 8.9 (7.6-9.0) years. Women were more likely to

live alone, have mobility restriction, and reporting parental mental problems during childhood (*Table 1*). They also reported more frequently high levels of depressive symptoms, antidepressant use and past major depressive episodes. Diabetes, ischemic pathologies, high BMI, and low cognitive performance were more frequent in men.

Trajectories of depressive symptoms

In both genders two sub-populations were identified corresponding to two different profiles of symptom change over the 10-year follow-up. The final mathematical expressions (*supplementary material*) of the estimated class-specific linear mixed models differed for men and women.

In men, both curves start at a low level of depressive symptoms (below the CES-D threshold of 16 at baseline). The upper curve (9.1% of men) increases over time with a marked quadratic shape at the end of the follow-up (*Fig. 1A - solid curves*). The confidence interval is large due to the relatively small number of subjects in this trajectory. The lower curve (90.9% of men) shows decreasing CES-D scores with a very low final level (5.2). In women, the upper curve (25.0% of women) shows a steady high level over the 10 years (mean CES-D at inclusion equal to 17.3) (*Fig. 1B - solid curves*) while the lower curve (75.0% of women) clearly decreases from 11.6 at the beginning to 5.4 at the end of the follow-up. The same patterns of symptom course were also found on the full sample of 1988 participants (816 men and 1172 women which included those with missing covariate data) (*Fig. 1A and Fig. 1B - dashed curves*), which further strengthens our results.

Of the 517 men and 736 women included in the main analysis, 57 men (11%) and 161 women (21.9%) were treated with antidepressant at least once over the 10-year follow-up. When trajectories of depressive symptoms were analyzed in the sub-group of treated women two trajectories with identical profiles were again found (*Fig. 2*), although they were shifted upwards in comparison with the overall sample. The group of treated men was too small to investigate their specific trajectories.

Factors associated with specific trajectories

In both genders the age-adjusted probability of being in the at risk upper trajectory was significantly increased with mobility limitations, diabetes, ischemic pathologies, recent stressful life event, parental

mental problems, lack of support during childhood and past major depressive episode. Low cognitive performance and adverse childhood events in women and 5-HTTLPR genotype in men were also significant (*Table 2*). Baseline characteristics were then entered in the multivariate models with the exception of past major depressive episode and antidepressant use which may constitute intermediate factors between childhood events and depressive symptoms in late life.

In men, the odds of being in the upper increasing curve were higher when they had mobility limitations and diabetes with odds ratios of 3.98 and 3.10 respectively (*Table 3, Model 1*). The S allele of the 5-HTTLPR polymorphism tended to be negatively associated with the odds of a poor symptom course but the association did not reach the level of significance ($p=0.09$). When recent or adverse childhood events were further included in the model (*Table 3, Model 2*), mobility limitations, diabetes and ischemic pathologies as well as recent stressful events and marginally parental mental problem were associated with the upper curve. The association with 5-HTTLPR was no more significant and no significant interactions were found with recent or early childhood adverse environment ($p\text{-value} >0.25$).

In women, mobility limitations and ischemic pathologies were significantly associated with poor symptom course (*Table 3, Model 1*). When recent or adverse childhood events were further included in the model (*Table 3, Model 2*), these results remained unchanged. In addition, recent stressful events, adverse childhood events and parental mental problems were significant, with particularly high odds ratios for recent stressful events and adverse events during childhood (OR of 3.16 and 3.09, $p \leq 0.0008$).

DISCUSSION

Modeling symptom trajectories

Using 10-year follow-up data from a large general population cohort established specifically for the prospective study of psychiatric disorder in the elderly, we clearly differentiated pathways of chronic and remitting depressive symptoms for men and women. For a small group of men (9.1%), we observed an increase in depressive symptoms and a trend towards worsening at the end of the follow-up. A larger female group, comprising a quarter of women, was observed to have a constantly high level of symptoms (above the threshold of 16). In contrast to these two patterns showing persistent symptoms, the remaining majority of men and women showed decreasing symptomatology over time, falling from clinically significant to very low levels. When the analysis was restricted to the women treated with antidepressants the same pattern was found with a sub-group showing a steady high level of symptoms, but this was higher than in overall sample which raises the question of treatment efficacy, adequacy and/or compliance.

Comparing our methodology with previous attempts to characterize depression trajectories in elderly population, past studies have mostly used a semi-parametric latent class growth analysis (LCGA) with the SAS procedure TRAJ (Jones & Nagin, 2007). This exploratory analysis is a specific case of LCMM in which the repeated measures within a subject are assumed to be independent. Applying the proc TRAJ to our data (data not shown) gives five trajectories in women and men. This overestimation of the number of latent classes is typical of LCGA (Muthén & Asparouhov, 2008). This may be explained by the neglected within subject correlation (modeled in the LCMM by subject-specific random-effects) which is captured by additional trajectory groups. A consequence of this is that inferences regarding covariates may be biased.

LCMM is similar to the Growth Mixture Modelling (GMM) implemented in M-Plus software (Muthén *et al.*, 2002) with the exception that M-plus does not normalize the scores using parameterized transformations. Using this methodology with a modified CES-D scale ranging from 0 to 20 (Kuchibhatla *et al.*, 2012), Kuchibhatla *et al.* found four groups of trajectories (stable high, stable low, increasing and decreasing). The study was not, however, stratified by gender although in the final

multinomial logistic model, female gender was reported to be associated with the downward and stable high trajectories; this being consistent with our findings.

Risk factors for chronic trajectories in men and women

Examining a large range of covariates commonly associated with depression in the elderly across the life-span, we observed that a chronic course was associated with both distal and proximal risk factors. With regard to early-life factors, having reported parents with psychiatric disorders and adverse events during childhood in women, were significantly associated with a severe and chronic course of illness in late life. Adverse childhood experiences are associated with later affective vulnerability (Chapman *et al.*, 2004). Possible explanations of this association could involve a genetic pathway (particularly when parents had mental problems), early structural and functional changes of the nervous system (functional changes of corticotropic hypothalamic-pituitary-adrenal axis and alterations in brain structures like the hippocampus) (Frodl & O'Keane, 2013), stress related inflammation and metabolic dysfunctions (Vamosi *et al.*, 2010) as well as epigenetic changes (Klengel *et al.*, 2014) and telomere shortening (Kiecolt-Glaser *et al.*, 2011). In the same cohort, we previously reported an association between past traumatic life event and alteration in metabolic or vascular disorders (Chaudieu *et al.*, 2011) as well as cortisol secretion (Chaudieu *et al.*, 2008) and a permanent alteration in hypothalamic-pituitary-adrenal axis in the participants with a history of depression (Beluche *et al.*, 2009). Our results remained significant in women despite possible over-adjustment on intermediate factors (obesity, diabetes, ischemic pathologies, and recent stressful events). In men, the associations with parental mental problems and lack of support during childhood became non significant after multiple adjustment but this may be due to lack of statistical power and/or possible over-adjustment. While previous research has shown that adverse childhood exposures may induce on-going vulnerability to depression persisting into late-life (Ritchie *et al.*, 2009) we further extend these findings by suggesting they also contribute to depressive symptom chronicity.

Vulnerability to depression following adverse childhood exposures has been observed to be modulated by 5-HTTLPR polymorphism, with carriers of the short (S) allele having increased risk although not consistently (Karg *et al.*, 2011; Risch *et al.*, 2009). The reverse risk has been also observed, with

carriers of the L allele being more vulnerable, and this has been related to insecure attachment, family adversity, and lower resilience capacity in younger (Carli *et al.*, 2011; Laucht *et al.*, 2009; Olsson *et al.*, 2005) as well as in older populations (Ritchie *et al.*, 2009; Surtees *et al.*, 2006). We only found a weak association in men with the S allele being protective which disappeared after adjustment for early adverse events including parental risk.

With regard to more proximal risk factors, we found very recent stressful events (disease, death, divorce and financial and judicial problems in the past year) to be associated with adverse trajectories in men and women in the multivariate model independently of early adverse environment. Only one previous trajectory study (Kuchibhatla *et al.*, 2012) also found recent stressful life events to be a risk factor for chronic course. In relation to other proximal factors we found mobility limitations and ischemic pathologies in men and women, as well as diabetes in men to be linked to adverse trajectories.

Diabetes, heart disease and global burden of chronic diseases were associated with a high risk of developing depression in other trajectory studies (Byers *et al.*, 2012; Chen *et al.*, 2011). Depression has consistently been associated with vascular risk including ischemia and diabetes, it is present in around 20% of patients with cardiovascular disease and in 18-39% of type 2 diabetic patients (Roy & Lloyd, 2012) and is associated with adverse cardiovascular outcomes (Rudisch & Nemeroff, 2003). A number of biological mechanisms (neuroendocrine dysfunction, hemodynamic factors, immune activation, thrombotic predisposition) (Parissis *et al.*, 2007) and behavioral factors (smoking, obesity, poor self-care) (Joynt *et al.*, 2003) can link depression and cardiovascular disease in a bidirectional relationship. In diabetic patients, specific risk factors such as diabetes complications, poor glycemic control, and burden of insulin therapy can also increase the risk of depression (Renn *et al.*, 2011). In our study the risk increase associated with ischemic pathologies persisted after multiple adjustments while that association with diabetes persisted only in men. Icks *et al.* also found no significant association between diabetes and depressive symptoms in women after controlling for co-morbidities (Icks *et al.*, 2008).

In women poor cognitive performance in verbal fluency was also at risk in the age-adjusted model. However, this association became non significant after controlling for physical comorbidity and mobility limitations. Three trajectory studies in the elderly failed to demonstrate a significant association between cognitive performance evaluated with the Mini Mental State Examination or the Trail Making Test and unfavorable trajectories (Andreescu *et al.*, 2008; Byers *et al.*, 2012; Cui *et al.*, 2008). Only one study showed that poor mental status measured with the Short Portable Mental Status Questionnaire (a very brief dementia screening test) increased the odds of being in the worsening symptom class (Kuchibhatla *et al.*, 2012). Depressive symptoms may be a reaction to early cognitive deficit, chronic depression may impair cognitive functions, and depression may be a risk factor or a prodromal stage of dementia for a subset of older adults (Byers & Yaffe, 2011).

Our results indicate that mobility limitation is a highly significant risk factor for chronic symptomatology in both men and women with a 4-5-fold increase in the odds of being in the increasing symptoms class or in the chronic but stable high symptom class, respectively. Activities of daily living or physical functioning were also found to predict poor outcome in previous studies of the course of depressive symptoms (Andreescu *et al.*, 2008; Byers *et al.*, 2012; Chen *et al.*, 2011; Cui *et al.*, 2008; Hsu, 2012; Kuchibhatla *et al.*, 2012; Liang *et al.*, 2011). A range of mediators have been suggested to explain the association between disability and the development of depression, notably decreased self-esteem, loss of sense of control, restriction of the social network, and isolation (Carriere *et al.*, 2009).

Altogether, our study highlighted distinct baseline thresholds of CES-D scores in elderly women and men which predict future adverse trajectories; the upper trajectory initiated at 17.3 (95%CI: 15.2-19.4) in women and slightly lower in men, at 13.2 (95%CI: 10.4-16.4), and these baseline levels were significantly higher from those of the remitting trajectories (*Fig. 1*). Our study also enabled the characterization of risk factors for a poor course of depressive symptoms in the elderly. This may help to detect elderly people who could benefit from an early intervention, thus preventing them from late-life depression and subsequent consequences in terms of co-morbidity and functional disability.

Limits and strengths

Our study has several limitations. Although repeated examinations have been performed with five time points over 10 years, between-wave transitory changes in depressive symptoms may not have been detected. As in all other trajectory studies, the effect of missing data and study attrition was not addressed in this study. Our statistical models assumed such effects to be negligible (ignorable missing response assumption (Little & Rubin, 1987)) however a possible link may exist between loss to follow-up and worsening of depressive symptoms which may have affected trajectory estimates. Since the depressive trajectory groups were different on baseline depressive symptoms, the relationships between risk factors and depressive symptom trajectories could be partly due to associations with baseline depressive levels. The two worst trajectories included 25% women and only 9.1% men which suggests lower statistical power and lack of statistical significance for some exposures in men. Furthermore stratifying analyses by gender precluded drawing conclusions with regard to gender difference in risk factors. Finally information based on retrospective recall, especially for childhood events, could not be independently validated; however, the observed associations were very strong.

Our study presents several strengths. We used a robust statistical method taking into account the highly skewed distribution of the CES-D scale with the beta distribution function and within-subject correlation with subject-specific random effects. We checked that the profiles of symptom course were the same in the whole original sample and in the restricted sample without missing data for covariates. We used data over ten years from a prospective general population study specifically designed to examine the course of psychiatric symptomatology in the elderly. We used a symptom scale with a wide score range and examined a wide range of depression-related risk factors including for the first time, early life exposures and genetic factors. We stratified by gender in order to observe gender-specific course and risk factors of depressive symptoms.

In conclusion, the analyses suggest for the first time distinct patterns of chronic and remitting symptomatology course in men and women and that a chronic disease course is associated with exposure to recent life stressors, disability and disease co-morbidity in both genders as well as to childhood adversity in women.

References

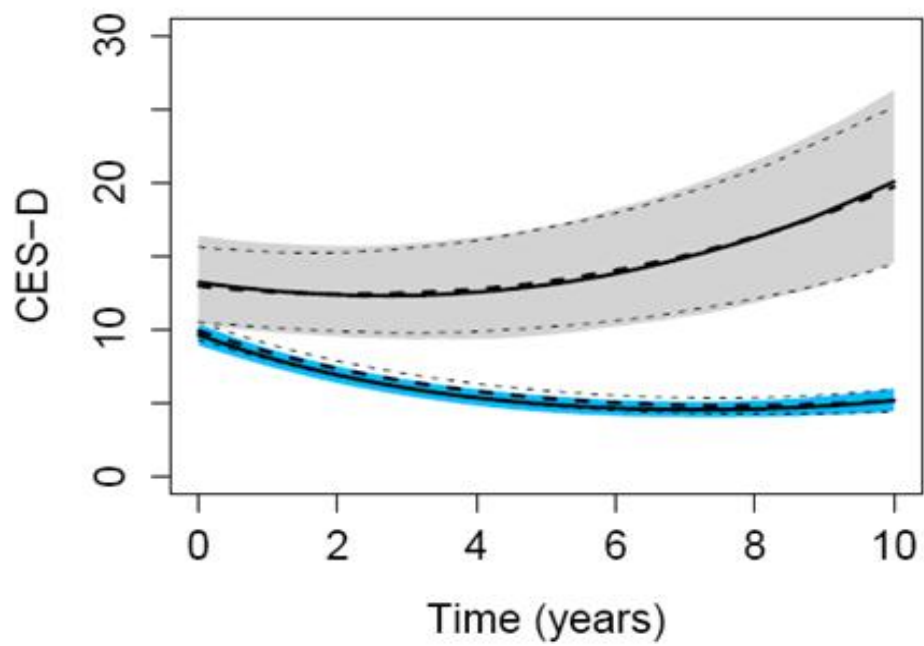
- Andreescu C, Chang CC, Mulsant BH, Ganguli M** (2008). Twelve-year depressive symptom trajectories and their predictors in a community sample of older adults. *International Psychogeriatrics* **20**, 221-36.
- Beluche I, Chaudieu I, Norton J, Carriere I, Boulenger JP, Ritchie K, Ancelin ML** (2009). Persistence of abnormal cortisol levels in elderly persons after recovery from major depression. *Journal of Psychiatric Research* **43**, 777-83.
- Blazer DG** (2003). Depression in late life: review and commentary. *The journals of Gerontology. Series A, Biological Sciences and Medical Sciences* **58**, 249-65.
- Byers AL, Vittinghoff E, Lui LY, Hoang T, Blazer DG, Covinsky KE, Ensrud KE, Cauley JA, Hillier TA, Fredman L, Yaffe K** (2012). Twenty-year depressive trajectories among older women. *Archives of General Psychiatry* **69**, 1073-9.
- Byers AL, Yaffe K** (2011). Depression and risk of developing dementia. *Nature Reviews Neurology* **7**, 323-31.
- Carli V, Mandelli L, Zaninotto L, Roy A, Recchia L, Stoppia L, Gatta V, Sarchiapone M, Serretti A** (2011). A protective genetic variant for adverse environments? The role of childhood traumas and serotonin transporter gene on resilience and depressive severity in a high-risk population. *European Psychiatry* **26**, 471-8.
- Carriere I, Gutierrez LA, Peres K, Berr C, Barberger-Gateau P, Ritchie K, Ancelin ML** (2011). Late life depression and incident activity limitations: influence of gender and symptom severity. *Journal of Affective Disorders* **133**, 42-50.
- Carriere I, Villebrun D, Peres K, Stewart R, Ritchie K, Ancelin ML** (2009). Modelling complex pathways between late-life depression and disability: evidence for mediating and moderating factors. *Psychological Medicine* **39**, 1587-90.
- Chapman DP, Whitfield CL, Felitti VJ, Dube SR, Edwards VJ, Anda RF** (2004). Adverse childhood experiences and the risk of depressive disorders in adulthood. *Journal of Affective Disorders* **82**, 217-25.
- Chaudieu I, Beluche I, Norton J, Boulenger JP, Ritchie K, Ancelin ML** (2008). Abnormal reactions to environmental stress in elderly persons with anxiety disorders: evidence from a population study of diurnal cortisol changes. *Journal of Affective Disorders* **106**, 307-13.
- Chaudieu I, Norton J, Ritchie K, Birmes P, Vaiva G, Ancelin ML** (2011). Late-life health consequences of exposure to trauma in a general elderly population: the mediating role of reexperiencing posttraumatic symptoms. *Journal of Clinical Psychiatry* **72**, 929-35.
- Chen CM, Mullan J, Griffiths D, Kreis IA, Lan TY, Chiu HC** (2011). Trajectories of depression and their relationship with health status and social service use. *Archives of Gerontology and Geriatrics* **53**, e118-24.
- Cole MG, Dendukuri N** (2003). Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *American Journal of Psychiatry* **160**, 1147-56.
- Cui X, Lyness JM, Tang W, Tu X, Conwell Y** (2008). Outcomes and predictors of late-life depression trajectories in older primary care patients. *American Journal of Geriatric Psychiatry* **16**, 406-15.
- Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW** (2013). Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. *British Journal of Psychiatry* **202**, 22-7.
- Frodl T, O'Keane V** (2013). How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. *Neurobiology of Disease* **52**, 24-37.
- Fuhrer R, Rouillon F** (1989). La version française de l'échelle CES-D (Center for Epidemiologic Studies-Depression Scale). Description et traduction de l'échelle d'autoévaluation. *Psychiatrie & psychobiologie* **4**, 163-166.
- Grigoriadis S, Robinson GE** (2007). Gender issues in depression. *Annals of Clinical Psychiatry* **19**, 247-55.

- Harwood RH, Prince MJ, Mann AH, Ebrahim S** (1998). The prevalence of diagnoses, impairments, disabilities and handicaps in a population of elderly people living in a defined geographical area: the Gospel Oak project. *Age and Ageing* **27**, 707-14.
- Helmchen H, Linden M** (2000). Subthreshold disorders in psychiatry: clinical reality, methodological artifact, and the double-threshold problem. *Comprehensive Psychiatry* **41**, 1-7.
- Hsu HC** (2012). Group-based trajectories of depressive symptoms and the predictors in the older population. *International Journal of Geriatric Psychiatry* **27**, 854-62.
- Icks A, Kruse J, Dragano N, Broecker-Preuss M, Slomiany U, Mann K, Jockel KH, Erbel R, Giani G, Moebus S** (2008). Are symptoms of depression more common in diabetes? Results from the Heinz Nixdorf Recall study. *Diabetes and Metabolism* **25**, 1330-6.
- Isaacs B, Kennie AT** (1973). The Set test as an aid to the detection of dementia in old people. *British Journal of Psychiatry* **123**, 467-70.
- Jones BL, Nagin DS** (2007). Advances in group-based trajectory modelling and an SAS procedure for estimating them. *Sociological methods & research* **35**, 542-571.
- Joynt KE, Whellan DJ, O'Connor CM** (2003). Depression and cardiovascular disease: mechanisms of interaction. *Biological Psychiatry* **54**, 248-61.
- Karg K, Burmeister M, Shedden K, Sen S** (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Archives of General Psychiatry* **68**, 444-54.
- Kiecolt-Glaser JK, Gouin JP, Weng NP, Malarkey WB, Beversdorf DQ, Glaser R** (2011). Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. *Psychosomatic Medicine* **73**, 16-22.
- Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT** (2008). Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS medicine* **5**, e45.
- Klengel T, Pape J, Binder EB, Mehta D** (2014). The role of DNA methylation in stress-related psychiatric disorders. *Neuropharmacology* **80**, 115-32.
- Kuchibhatla MN, Fillenbaum GG, Hybels CF, Blazer DG** (2012). Trajectory classes of depressive symptoms in a community sample of older adults. *Acta Psychiatrica Scandinavica* **125**, 492-501.
- Laucht M, Treutlein J, Blomeyer D, Buchmann AF, Schmid B, Becker K, Zimmermann US, Schmidt MH, Esser G, Rietschel M, Banaschewski T** (2009). Interaction between the 5-HTTLPR serotonin transporter polymorphism and environmental adversity for mood and anxiety psychopathology: evidence from a high-risk community sample of young adults. *The international journal of neuropsychopharmacology* **12**, 737-47.
- Liang J, Xu X, Quinones AR, Bennett JM, Ye W** (2011). Multiple trajectories of depressive symptoms in middle and late life: racial/ethnic variations. *Psychology and Aging* **26**, 761-77.
- Little R, Rubin D** (1987). *Statistical Analysis with Missing Data*. John Wiley & Sons, Inc.: New York.
- Miller R, Wankerl M, Stalder T, Kirschbaum C, Alexander N** (2013). The serotonin transporter gene-linked polymorphic region (5-HTTLPR) and cortisol stress reactivity: a meta-analysis. *Molecular Psychiatry* **18**, 1018-24.
- Morin AJ, Moullec G, Maiano C, Layet L, Just JL, Ninot G** (2011). Psychometric properties of the Center for Epidemiologic Studies Depression Scale (CES-D) in French clinical and nonclinical adults. *Revue d'épidémiologie et de santé publique* **59**, 327-40.
- Muthén B, Asparouhov T** (2008). Growth mixture modeling: Analysis with non-Gaussian random effects. In *Longitudinal Data Analysis* (ed. G. Fitzmaurice, Davidian, M., Verbeke, G. & Molenberghs, G.), pp. 143-165. Boca Raton: Chapman & Hall/CRC Press.
- Muthen B, Brown CH, Masyn K, Jo B, Khoo ST, Yang CC, Wang CP, Kellam SG, Carlin JB, Liao J** (2002). General growth mixture modeling for randomized preventive interventions. *Biostatistics* **3**, 459-75.
- Olfson M, Broadhead WE, Weissman MM, Leon AC, Farber L, Hoven C, Kathol R** (1996). Subthreshold psychiatric symptoms in a primary care group practice. *Archives of General Psychiatry* **53**, 880-6.

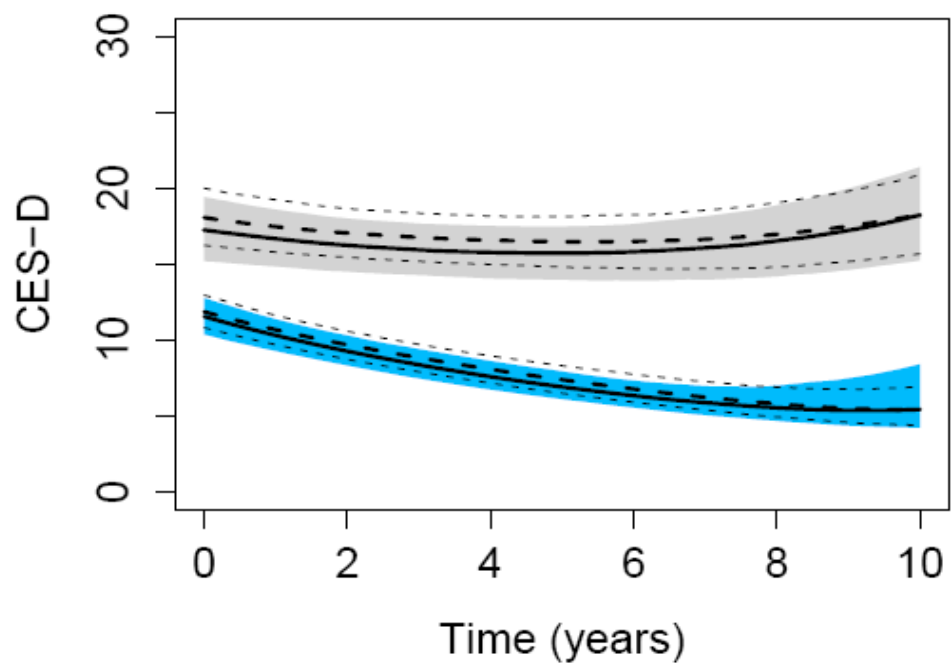
- Olsson CA, Byrnes GB, Lotfi-Miri M, Collins V, Williamson R, Patton C, Anney RJ** (2005). Association between 5-HTTLPR genotypes and persisting patterns of anxiety and alcohol use: results from a 10-year longitudinal study of adolescent mental health. *Molecular Psychiatry* **10**, 868-76.
- Parissis JT, Fountoulaki K, Filippatos G, Adamopoulos S, Paraskevaidis I, Kremastinos D** (2007). Depression in coronary artery disease: novel pathophysiologic mechanisms and therapeutic implications. *International Journal of Cardiology* **116**, 153-60.
- Piccinelli M, Wilkinson G** (2000). Gender differences in depression. Critical review. *British Journal of Psychiatry* **177**, 486-92.
- Proust-Lima C, Philipps V, Diakite A, Lique B** (2014). LCMM: Estimation of extended mixed models using latent classes and latent processes. *R Package* <http://cran.r-project.org/web/packages/lcmm/lcmm.pdf>.
- Radloff L** (1977). The CES-D scale: a self-report depression scale for research in the general population. *Applied psychological measurement* **1**, 385-401.
- Renn BN, Feliciano L, Segal DL** (2011). The bidirectional relationship of depression and diabetes: a systematic review. *Clinical Psychology Review* **31**, 1239-46.
- Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR** (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *JAMA* **301**, 2462-71.
- Ritchie K, Artero S, Beluche I, Ancelin ML, Mann A, Dupuy AM, Malafosse A, Boulenger JP** (2004). Prevalence of DSM-IV psychiatric disorder in the French elderly population. *British Journal of Psychiatry* **184**, 147-52.
- Ritchie K, Jaussent I, Stewart R, Dupuy AM, Courtet P, Ancelin ML, Malafosse A** (2009). Association of adverse childhood environment and 5-HTTLPR Genotype with late-life depression. *Journal of Clinical Psychiatry* **70**, 1281-8.
- Rosow I, Breslau N** (1966). A Guttman health scale for the aged. *The journals of gerontology. Series B, Psychological sciences and social sciences* **21**, 556-9.
- Roy T, Lloyd CE** (2012). Epidemiology of depression and diabetes: a systematic review. *Journal of Affective Disorders* **142 Suppl**, S8-21.
- Rudisch B, Nemeroff CB** (2003). Epidemiology of comorbid coronary artery disease and depression. *Biological Psychiatry* **54**, 227-40.
- Ryan J, Carriere I, Ritchie K, Stewart R, Toulemonde G, Dartigues JF, Tzourio C, Ancelin ML** (2008). Late-life depression and mortality: influence of gender and antidepressant use. *British Journal of Psychiatry* **192**, 12-8.
- Schlosser R, Hutchinson M, Joseffer S, Rusinek H, Saarimaki A, Stevenson J, Dewey SL, Brodie JD** (1998). Functional magnetic resonance imaging of human brain activity in a verbal fluency task. *Journal of Neurology, Neurosurgery and Psychiatry* **64**, 492-8.
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC** (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* **59 Suppl 20**, 22-33.
- Surtees PG, Wainwright NW, Willis-Owen SA, Luben R, Day NE, Flint J** (2006). Social adversity, the serotonin transporter (5-HTTLPR) polymorphism and major depressive disorder. *Biological Psychiatry* **59**, 224-9.
- Vamosi M, Heitmann BL, Kyvik KO** (2010). The relation between an adverse psychological and social environment in childhood and the development of adult obesity: a systematic literature review. *Obesity reviews* **11**, 177-84.
- Vink D, Aartsen MJ, Schoevers RA** (2008). Risk factors for anxiety and depression in the elderly: a review. *Journal of Affective Disorders* **106**, 29-44.
- WHO Collaborating Centre fDSM** (2013). Anatomical Therapeutic Chemical (ATC) Classification System.

Fig. 1 Depressive symptom trajectories in men and women

1A: Men



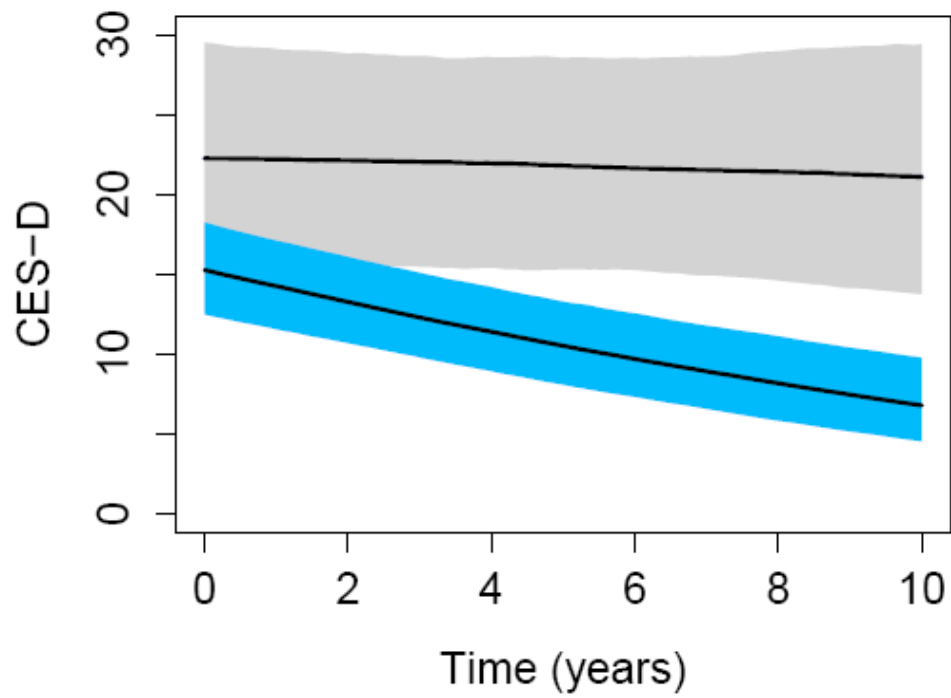
1B: Women



Solid line: estimated trajectories and corresponding confidence interval (shaded area) for the selected sample of 517 men and 736 women having data for risk factors.

Dashed line: estimated trajectories and corresponding confidence interval (dashed limits) for the overall sample of 816 men and 1172 women.

Fig. 2 Depressive symptom trajectories in women treated with antidepressant



Estimated trajectories and corresponding confidence interval (shaded area) for the selected sample of 161 women treated with antidepressant at least once over the follow-up (n=35 in the upper curve and n=126 in the lowest curve).

TABLE 1. Sample description at baseline (n=1253)

	Men n=517	Women n=736	P-value Chi ² test
Age (years) median (IQR)	71 (68-75)	72 (68-76)	0.33 ^a
Educational level (%)	19.73	20.79	0.65
≤ 5 years of education			
Living alone (%)	7.54	39.40	<0.0001
Mobility limitations ^b (%)	18.57	45.52	<0.0001
Diabetes ^c (%)	12.57	6.52	0.0002
BMI: obese or over-weighted ^d (%)	55.71	36.55	<0.0001
Ischemic pathologies ^e (%)	18.57	8.29	<0.0001
Cognitive impairment ^f (%)	31.72	24.59	0.005
5HTTLPR polymorphism, S allele (%)	70.02	71.74	0.51
Recent stressful life event (%)	55.71	61.01	0.06
Adverse childhood event (%)	38.49	38.59	0.97
Parental mental problems (%)	16.44	22.55	0.008
Lack of support during childhood (%)	13.15	15.63	0.22
Depressive symptomatology (%)			
CES-D > 16	19.34	32.88	<0.0001
Past major depressive episode (%)	15.69	32.66	<0.0001
Antidepressant use (%)	2.13	7.47	<0.0001

^a Wilcoxon test

^b Inability to do heavy housework, walk half a mile, and climb stairs

^c Diabetes defined as fasting glycemia ≥ 7 mmol/l or treated.

^d body mass index over or equal to 25

^e History of stroke, myocardial infarction, angina pectoris, arteritis, or cardio-vascular surgery

^f Isaacs Verbal Fluency test score at 30 seconds < 43

BMI: body mass index, IQR: inter quartile range, CES-D: Center for Epidemiologic Studies

Depression Scale

TABLE 2. ASSOCIATIONS BETWEEN BASELINE COVARIATES AND THE PROBABILITY OF BEING IN THE UPPER TRAJECTORY - AGE ADJUSTED CLASS-MEMBERSHIP MODELS

	Men N=517		Women N=736	
	OR [95%CI]	p value	OR [95%CI]	p value
Educational level \leq 5 years	0.89 [0.31;2.62]	0.84	0.87 [0.48;1.56]	0.63
Living alone	1.80 [0.53;6.10]	0.34	1.04 [0.63;1.74]	0.87
Mobility limitations	4.45 [1.79;11.02]	0.001	5.28 [1.88;14.79]	0.002
Diabetes	3.74 [1.37;10.26]	0.01	2.80 [1.18;6.63]	0.02
BMI: obese or over-weighted	1.99 [0.81;4.88]	0.13	1.52 [0.94;2.47]	0.09
Ischemic pathologies	2.81 [1.19;6.62]	0.02	3.20 [1.41;7.23]	0.005
5-HTTLPR polymorphism, S allele	0.46 [0.21;1.00]	0.05	0.74 [0.45;1.22]	0.23
Cognitive impairment	1.05 [0.45;2.46]	0.91	1.85 [1.06;3.21]	0.03
Recent stressful life event	3.25 [1.02;10.33]	0.05	2.60 [1.40;4.84]	0.002
Adverse childhood event	1.95 [0.88;4.30]	0.10	3.75 [2.23;6.31]	<0.0001
Parental mental problems	2.95 [1.21;7.20]	0.02	2.55 [1.43;4.53]	0.002
Lack of support during childhood	3.03 [1.12;8.22]	0.03	2.47 [1.30;4.68]	0.006
Past major depressive episode	12.81 [4.00;40.96]	<0.0001	4.21 [2.27;7.80]	<0.0001

OR: Odds ratio; CI: Confidence Interval, BMI: Body mass index

Table 3. ASSOCIATIONS BETWEEN BASELINE COVARIATES AND THE PROBABILITY OF BEING IN THE UPPER TRAJECTORY– MULTIVARIATE CLASS-MEMBERSHIP MODELS

	Model 1		Model 2	
	OR [95%CI]	p value	OR [95%CI]	p value
MEN, N=517				
Age (years)	1.07 [0.98;1.16]	0.13	1.07 [0.97;1.17]	0.16
Mobility limitations	3.98 [1.54;10.28]	0.004	4.48 [1.56;12.87]	0.005
Diabetes	3.10 [1.09;8.77]	0.03	3.50 [1.13;10.87]	0.03
BMI: obese or over-weighted	1.37 [0.56;3.36]	0.49	1.11 [0.43;2.87]	0.83
Ischemic pathologies	2.01 [0.79;5.10]	0.14	2.91 [1.03;8.26]	0.04
5-HTTLPR polymorphism: S allele	0.46 [0.19;1.13]	0.09	0.63 [0.24;1.65]	0.35
Recent stressful life event			4.50 [1.09;18.50]	0.04
Adverse childhood event			1.39 [0.49;3.93]	0.53
Parental mental problems			2.96 [0.88;9.93]	0.08
Lack of support during childhood			2.48 [0.81;7.59]	0.11
WOMEN, n=736				
Age (years)	1.00 [0.96;1.04]	0.99	1.02 [0.96;1.08]	0.59
Mobility limitations	4.54 [2.23;9.24]	<0.0001	4.95 [2.30;10.68]	<0.0001
Diabetes	2.16 [0.79;5.94]	0.13	2.24 [0.71;7.03]	0.17
BMI: obese or over-weighted	0.97 [0.56;1.68]	0.91	0.87 [0.47;1.63]	0.67
Ischemic pathologies	3.06 [1.11;8.38]	0.03	3.14 [1.00;9.86]	0.05
Cognitive impairment	1.60 [0.86;2.97]	0.14	1.47 [0.77;2.83]	0.25
Recent stressful life event			3.16 [1.62;6.17]	0.0008
Adverse childhood event			3.09 [1.64;5.81]	0.0005
Parental mental problems			2.52 [1.15;5.52]	0.02
Lack of support during childhood			1.57 [0.72;3.41]	0.25

OR: Odds ratio; CI: Confidence Interval, BMI: Body mass index