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Vascular pathology and trajectories of late-life major depressive disorder in secondary psychiatric care

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Abstract

Objective—To examine 5-year trajectories of psychiatrist-treated late-life major depressive disorder (MDD), and evaluate whether previous vascular pathology is associated with more severe trajectories of late-life MDD.

Methods—Data were obtained from nationally representative civil, psychiatric, hospital and prescription registers in Denmark. The sample included 11,092 older adults (≥ 60 years) who received their first diagnosis of MDD in a psychiatric facility in Denmark between 2000 and 2007. Trajectories of in- or outpatient contact at psychiatric hospitals for MDD over the 5-year period following index MDD diagnosis were modeled using latent class growth analysis. Measures of vascular disease (stroke, heart disease, vascular dementia) and vascular risk factors (hypertension, diabetes) were defined based on medication prescriptions and hospital-based diagnoses. Other predictors included demographic characteristics and characteristics of the index MDD diagnosis.

Results—The final model included 4 trajectories with *consistently low* (66% of the sample), *high decreasing* (19%), *consistently high* (9%), and *moderate fluctuating* (6%) probabilities of contact at a psychiatric hospital for MDD during the 5-year period following the index MDD diagnosis, respectively. We found no significant associations between any form of vascular pathology and trajectory class membership. Relative to the *consistently low* class, older age, greater severity and

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>12 months of prior antidepressant medication use predicted membership in the other three classes.

Conclusions—A notable proportion (34%) of individuals diagnosed with MDD in late-life require specialized psychiatric treatment for extended time periods. We did not find evidence that vascular pathology predicts hospital contact trajectories in secondary-treated late-life MDD.

Keywords

major depression; vascular disease; vascular risk factors; trajectories

INTRODUCTION

There is reason to believe that depression occurring in late life may be a distinct clinical and/or etiological entity from earlier-onset depression. Epidemiological studies using both register-based (1) and community (2) samples find that the age of onset distribution of major depressive disorder (MDD) is bimodal, with one peak in early adulthood and a second, smaller peak in older adulthood. This suggests that individuals are at increased risk for developing MDD at two very different points in the lifespan. Studies also suggest that late-onset depression may have a smaller genetic component than earlier onset depression (3,4), which implies that environment or lifestyle factors play a larger role in precipitating late-life MDD. One well-developed hypothesis regarding the etiology of late-life depression is the vascular depression hypothesis (5–9), which posits that vascular pathologies can lead to white matter lesions in the brain that “predispose, precipitate or perpetuate a depressive syndrome in many elderly patients” (Alexopoulos et al., 1997, pg. 915). According to this hypothesis, vascular pathology can both precipitate the onset of depression among older adults with no previous depression episodes, and precipitate recurrent episodes among older adults with a prior history of MDD (8). Consistent with this hypothesis, studies have demonstrated that MDD is more common among individuals who have had a stroke (10), and that late-onset MDD is associated with increased risk for vascular disease in relatives (11).

Evidence suggests that vascular pathology may be associated with more severe long-term trajectories of depressive symptoms in general population samples of older adults. Byers and colleagues (12) found that stroke, hypertension and diabetes were associated with high and increasing 20-year depressive symptom trajectories in older women. Kooistra and colleagues (13) examined depressive symptoms over 8 years among patients with vascular disease and found that cerebrovascular disease in particular was associated with symptom chronicity. These studies support the idea that vascular pathology may perpetuate depressive symptoms among older adults. However, it is unclear to what extent this association pertains to trajectories of clinically diagnosed MDD.

Our goal in this study was twofold: first, we aimed to characterize trajectories of clinically diagnosed late-life MDD in a sample of older adults treated in secondary psychiatric care. To accomplish this, we used information from the Danish Central Psychiatric Research Register (DCPRR), which includes records of all inpatient and outpatient treatment in psychiatric hospitals in Denmark. As the vast majority of psychiatric treatment in Denmark

is provided by the public sector, this register provides a highly comprehensive view of users of the secondary psychiatric treatment system (1). Second, we aimed to evaluate whether a prior diagnosis with vascular disease or vascular risk factors predicts the course trajectory of secondary-treated late-life MDD. We hypothesized that individuals with a history of vascular disease or vascular risk factors would be more likely to experience a chronic course.

METHODS

Data Sources

Data for this study were obtained from the following Danish national registers: the Danish Civil Registration System [DCRS] (14,15), the DCPRR (16), the Danish National Patient Register [DNPR] (17) and the Danish National Prescription Register [DNpreR] (18). Information from these registers was linked using the civil personal register (CPR) number, a unique ID number assigned to all legal residents of Denmark. The DCRS includes information on date of birth, sex, place of birth, and date of death or emigration (if no longer alive and/or living in Denmark). The DCPRR includes information (e.g. admission date, discharge date, main and auxiliary diagnoses) for all inpatient admissions to psychiatric hospitals in Denmark since 1969 and all outpatient and emergency admissions since 1995. Diagnoses in the DCPRR are given at discharge by the treating psychiatrist based on the International Classification of Diseases 8th Revision (ICD-8) (19) from 1969–1993 and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (20) from 1994 onwards. The DNPR includes similar information for all inpatient admissions to somatic hospitals since 1977 and all outpatient and emergency admissions since 1995. The DNpreR includes complete information on all prescriptions written by general practitioners and filled in non-hospital pharmacies in Denmark since 1995.

Study Sample

Individuals were selected for inclusion in the study sample based on the following criteria:

- a. They were living legally (by birth or by legal residency/naturalization) in Denmark and had a CPR number.
- b. They received their first (i.e. index) diagnosis of MDD (ICD-10 codes F32, F33) in secondary care in Denmark between 2000–2007. Individuals with an MDD diagnosis prior to 2000 [ICD-10 codes F32, F33; ICD-8 codes 296.09, 296.29, 298.09, 300.49] were excluded. We specifically selected individuals who received their index MDD diagnosis between 2000 and 2007 for the following reasons: first, the DCPRR started recording outpatient visits to psychiatric hospitals in 1995, therefore by excluding individuals who received an MDD diagnosis before 2000, we could be more confident that the MDD diagnosis was not reflective of ongoing treatment for a prior episode. Previous studies of the incidence of psychiatric disorders in the Danish registers have used this same 5-year buffer period (1). Second, as information on GP prescriptions and outpatient visits to somatic hospitals in Denmark are also only available from 1995 onwards, we needed to allow time during which vascular pathology could be assessed before the index MDD diagnosis. As the available version of the DCRS

is current up through 2012, we excluded individuals with an index MDD diagnosis after 2007 to allow 5-years of follow-up time for the trajectory analyses.

- c. They were at least 60 years old at the time of their index MDD diagnosis.
- d. They never received a diagnosis of bipolar disorder (ICD-8 codes 296.19, 296.39, 298.19; ICD-10 codes F30, F31) or schizophrenia spectrum disorder (ICD-8 codes 295.xx, 296.89, 297.09, 298.29–298.99, 299.04–299.09, 301.83; ICD-10 codes F20–F29) either before or after their MDD diagnosis. Individuals with other comorbid psychiatric conditions were not excluded.
- e. They survived for at least 6 months after their initial MDD diagnosis, and therefore contributed at least one data-point of follow-up time to the trajectory analysis.
- f. They did not emigrate from Denmark within 5 years after their initial MDD diagnosis.
- g. They had a known place of birth.

Figure 1 shows a flow-chart of the sample-selection process, including the numbers of individuals excluded for each criterion. The final study sample included 11,092 individuals.

Measures

Vascular pathology—We examined five different forms of vascular pathology, including two vascular risk factors (hypertension, diabetes) and three forms of vascular disease (stroke, heart disease, vascular dementia). Information on these five types of vascular pathology was obtained from the DNPR, DNPreR and, for vascular dementia, also the DPCRR. Individuals were considered to have a history of a given form of vascular pathology if they either a) were treated in a somatic hospital with a primary, secondary or ‘underlying cause’ diagnosis of that pathology during the 5-year period preceding their index MDD diagnosis or b) filled a prescription from their GP for a medication used to treat that pathology during the same period. ICD-10 and Anatomical Therapeutic Chemical (ACT) codes used to define the different types of vascular pathology are listed in Supplemental Table 1. ICD-10 and ACT codes were selected based on prior research using the Danish registers (21–23). Each form of vascular pathology was operationalized as a dichotomous variable, with a score of 1 indicating that the individual had received a diagnosis of, or been prescribed medication for, that type of vascular pathology during the 5-year period preceding his or her index MDD diagnosis. The variables were not mutually exclusive. Given that vascular risk factors and disease frequently co-occur and affect depression via similar biological mechanisms (24), we also created a measure of vascular burden equal to the number (0–5) of vascular diagnoses received by each individual during the 5-year period prior to his or her index MDD diagnosis.

Other measures—We examined other potential correlates of trajectory class membership including sex (male/female), place of birth (urban area within Denmark, rural area within Denmark, birthplace outside Denmark), age at index MDD diagnosis (60–69, 70–79, 80+),

severity/psychosis at index MDD diagnosis (mild [F32.0, F33.0], moderate [F32.1, F33.1], severe without psychotic symptoms [F32.2, F33.2], severe with psychotic symptoms [F32.3, F33.3]), inpatient treatment at index MDD diagnosis, and number of months (0, 1–12, >12) of antidepressant medication (Anatomical Therapeutic Chemical [ATC] category N06A) prescribed for each individual by his or her primary care doctor during the 5-year period before the index MDD diagnosis.

Analytic design and statistical methods

We assessed vascular pathology during the 5-year period before each individual's index MDD diagnosis. We then modeled trajectories of MDD during the subsequent 5-year period following the index MDD diagnosis (See Figure 2). Trajectories were modeled using latent class growth analysis [LCGA] (25,26) in SAS PROC TRAJ (27,28). The primary response variable was in- or outpatient psychiatric contact (yes/no) with a primary diagnosis of MDD during each 6-month interval in the 5-year period following the index MDD diagnosis.

In LCGA, the optimal number of classes is determined by fitting models with different numbers of classes and comparing fit statistics (25,26). We fit models with 1–7 classes, but the 7-class model would not converge. We allowed for non-linearity of trajectories by including up to cubic polynomial terms for each class in each model. If a term was not significant ($p < .05$), or if the model failed to converge, we refit the model with quadratic or linear terms. Not surprisingly given the age of the sample, attrition due to death during the 5-year follow-up period was high (37.5%). To avoid bias due to non-random participant attrition (29), we incorporated a dropout model in which the probability of death at each time point was allowed to depend on the previous two time periods, age at index MDD diagnosis, inpatient treatment and somatic illness (vascular pathology and cancer) during the 5 years before index MDD diagnosis.

After selecting the final number of classes, we fit LCGA models in PROC TRAJ that included a structural component (i.e., a multinomial regression with class membership as the outcome variable) to assess the effects of different measures of vascular pathology on the odds of trajectory class membership. The largest class was used as the reference category. We present results from two conditional LCGA models: one which included the 5 individual measures of vascular pathology, and one which included our aggregate measure of vascular burden. This 'one-step approach' accounts for uncertainty in class assignment because the two parts of the model (the structural component and the measurement component) are estimated simultaneously (30). Both models were adjusted for sex, birthplace, age, severity, inpatient vs. outpatient treatment, number of months on antidepressant medication, and calendar year at index MDD diagnosis.

Sensitivity analyses

To assess whether it is the experience of having a serious somatic illness, rather than vascular pathology per se, that influences trajectories of late-life MDD, we also examined the impact of a cancer diagnosis (ICD-10 codes C00-C97) within the 5-year period preceding the index MDD diagnosis.

RESULTS

Model selection

When selecting the final model, we took into consideration AIC and BIC values (31), average posterior probabilities of class membership (a measure of the precision with which individuals are assigned to latent classes) and clinical utility. Characteristics of models with 1–6 classes are shown in Supplemental Table 2. We selected the 4-class model because it was adequately precise (minimum average posterior probability of group membership was 86%), each class contained >5% of the population, and it represented an improvement over the 3-class model in terms of AIC and BIC values. Most importantly, the model captured 4 distinct patterns of contact with the secondary psychiatric treatment system. Adding more classes resulted in groups that reflected only minor deviations from patterns already represented in the 4-class model.

Trajectories of late-life MDD

Five-year trajectories of secondary-treated late-life MDD are shown in Figure 3. The largest class (66%) had a *consistently low* probability of in- or outpatient MDD treatment during the 5-year period following their index MDD diagnosis. The next largest class (19%) had a *high* probability of being treated by a psychiatrist during the first year after their index MDD diagnosis, a *decreasing* probability during years 2–3 and a low probability during years 4–5. An additional 9% of the sample had a *consistently high* probability of being in secondary treatment for MDD throughout the 5-year period following their index MDD diagnosis. Finally, the smallest class (6%) had a *moderate fluctuating* probability of secondary treatment for MDD during the 5 years following their index MDD diagnosis. The probability of contact in this group fluctuated between 20–50%, with a higher probability towards the end of the 5-year follow-up period.

Vascular pathology and other correlates

Frequencies of sample characteristics overall and within each trajectory class are shown in Table 1. The sample was 68% female, with an average at index MDD diagnosis of 75 years ($SD = 9$ years). 72% of the sample received a diagnosis for at least one type of vascular pathology. Because so few (<5) individuals received diagnoses within all 5 categories, data protection laws in Denmark prohibit us from reporting results for this group. Instead, these individuals are included along with individuals who received 4 diagnoses. The most common form of vascular pathology was hypertension (67%) followed by heart disease (19%), stroke (13%), diabetes (8%) and vascular dementia (2%). Vascular pathology was more common among individuals who died during the study follow-up period relative to those who survived (80% vs. 67%, $\chi^2=192.8$, $df = 1$, $p < .0001$). Individuals excluded from the study sample because they died within 6 months of their index MDD diagnosis were more likely than included participants to have vascular pathology (84% vs. 72%, $\chi^2=69.6$, $df = 1$, $p < .0001$) across all diagnoses other than vascular dementia. Almost 88% of the sample filled at least one prescription for an antidepressant medication during the 5-year period preceding their index MDD diagnosis.

Figure 4 displays odds ratios (ORs) and 95% confidence intervals (CIs) for correlates of trajectory class membership, with the *consistently low* class as the reference category. None of the measures of vascular pathology were significantly associated with trajectory class membership (p value range: .06 – .94). Older age was associated with higher odds of membership in the *high decreasing* class (70–80 years: OR = 1.31, 95% CI [1.14, 1.50]; 80+: OR = 1.44, [1.24, 1.66]) and the *consistently high* class (70–80 years: 1.72, [1.43, 2.08]; 80+ years: 1.70 [1.38, 2.09]). Inpatient treatment at index MDD diagnosis was associated with decreased odds of membership in the *high decreasing* class (0.62, [0.55, 0.71]), but increased odds of membership in the *moderate fluctuating* class (1.41 [1.14, 1.75]). There was a dose response relationship between severity at index MDD diagnosis and membership in the *high decreasing* and *consistently high* classes, such that as severity increased, the odds of membership increased from a 1.33–1.41 fold increase for moderate MDD to a 2.39–2.82 fold increase for severe MDD with psychotic features. The association between severity and membership in the *moderate fluctuating* class was less pronounced; moderate MDD did not significantly increase the odds of membership in the class, and the increase in odds associated for severe (1.68 [1.19, 2.37]) and psychotic (1.87 [1.25, 2.79]) MDD were not as large. More than 12 months of antidepressant use prior to index MDD diagnosis was associated with increased odds of membership in the *high decreasing* class (1.27 [1.06, 1.54]), the *consistently high* class (1.29, [1.02, 1.64]) and particularly the *moderate fluctuating* class (2.12, [1.48, 3.06]).

Sensitivity analysis

A cancer diagnosis during the 5-year period prior to the index MDD diagnosis was not significantly associated with trajectory class membership (data not shown).

DISCUSSION

The goals of this study were to characterize 5-year trajectories of secondary-treated late-life MDD using data from Danish national registers, and examine the extent to which vascular disease and vascular risk factors are associated with different trajectories among older secondary-treated MDD patients. Latent class growth analysis yielded a 4-class model with the following groups: *consistently low* (66% of the sample) probability of subsequent secondary care for MDD during the 5-year period following the index MDD diagnosis, *high decreasing* probability (19%), *consistently high* probability (9%) and *moderate fluctuating* probability (6%). Older age, greater severity of the index MDD episode and > 12 months of antidepressant medication use in the 5-year period preceding the first MDD diagnosis in secondary care were associated with increased odds of membership in the *high decreasing*, *consistently high* and *moderate fluctuating* classes relative to the *consistently low class*. We found no significant associations between any form of vascular pathology and trajectory of secondary-treated late-life MDD.

Consistent with previous studies (32,33), our findings suggest that a substantial proportion of older MDD patients experience persistent or recurring MDD over extended periods of time: 34% of the individuals in our sample were in secondary treatment with a primary diagnosis of MDD at various periods and for various lengths of time during the 5-year

period following their index MDD diagnosis. Additional members of the sample may have experienced subclinical depressive symptoms that did not bring them back into secondary treatment. These findings highlight the burden of MDD among the elderly, and reaffirm that this population, particularly those who enter the secondary treatment system at an older age, with a more severe clinical presentation and recent prolonged antidepressant medication use, requires special attention from clinicians and policymakers.

Our hypothesis that pre-existing vascular pathology would be associated with greater chronicity in 5-year course trajectories of clinically diagnosed MDD in older adults was not supported. There is substantial evidence demonstrating an association between, for example, stroke and the incidence or prevalence of depression (see Robinson & Jorge, 2015 for a review), including evidence from Danish registers (34). However the evidence suggesting an association between vascular pathology and chronicity of depression is less robust. The most widely documented and heavily researched findings in this area suggest differences in executive function and cognitive impairment among patients with so-called vascular depression (8). Although some research found that executive dysfunction was associated with relapse and recurrence (35) others found no such effect (36). It is possible, therefore, that while vascular pathology is associated with the *occurrence* of MDD, it has less of an impact on the course of illness after the initial syndrome has converted to onset meeting complete diagnostic criteria. A second interpretation of these findings is that vascular pathologies may contribute to differences in the course of depressive symptoms as suggested previously (12,13,37), but not in a way that translates into differences in long-term contact patterns with the secondary psychiatric treatment system. For example, vascular pathology may increase the chronicity of subclinical depressive symptoms (12,13), which either go untreated or are more likely to be treated solely in a primary care setting.

Methodological considerations

Several important methodological features should be taken into account when interpreting these results. First, we were unable to examine the impact of all vascular risk factors because the registers do not include information on diet, physical activity, obesity or smoking. Second, individuals who did not receive MDD treatment, or received only medication management via their primary care doctors, were not included in our analyses. Our research goal was to examine trajectories of MDD treated in specialty psychiatric settings. Because the majority of secondary psychiatric care in Denmark is provided by the public sector, and all psychiatric treatment in the public sector is recorded in the registry, we are confident that our sample is representative of this population. However, it should be noted that our results may not necessarily generalize to all individuals with MDD.

Third, we could not distinguish in this study between truly first-onset MDD cases and individuals experiencing recurrent MDD episodes. Because this was an older sample, and the DCPRR only includes records of inpatient visits since 1969 and outpatient visits since 1995, we can only be sure these individuals had not received treatment from a psychiatrist within the past 5 years. According to the vascular depression hypothesis, vascular pathology could theoretically precipitate either a first-onset or a recurrent MDD episode (8), however it

is unclear to what, if any, extent it might influence subsequent course trajectories differently for first-onset vs. recurrent MDD cases. Further research is needed to investigate this issue.

Fourth, we were unable to measure depressive symptoms directly, or to account for other factors influencing secondary treatment such as adherence to doctor recommendations. It should be noted that the dates on which individuals enter and exit secondary treatment do not correspond perfectly with the onset or remission of depressive symptoms; as our own data attest, nearly 90% of individuals in our sample received a prescription for antidepressants before their index diagnosis, indicating they were already experiencing symptoms. Denmark has a gatekeeper healthcare system in which individuals seek care first from their primary care doctors and are then referred for specialty care if needed, therefore this pattern was expected.

Finally, it is worth noting that vascular pathology was more common among individuals who died during the 5-year follow-up period compared to individuals who survived for at least 5 years following their index MDD diagnosis. Although we fit a conditional dropout model as part of our trajectory analysis, this may not have entirely eliminated bias due to differential attrition. In addition, the 1,016 older adults with late-life MDD who were excluded because they died within 6 months of receiving their index MDD diagnosis were also significantly more likely than individuals included in the study sample to have prior cerebrovascular disease across all categories except for vascular dementia. Therefore, there may have been some bias created by the fact that the individuals included in our analyses were less likely than the population of older adults with late-life MDD overall to have cerebrovascular disease.

Conclusions

A notable proportion (34%) of older adults diagnosed with MDD in a secondary care setting require specialized psychiatric treatment for extended periods of time. These individuals tend to be older and have a more severe clinical presentation at index MDD diagnosis than individuals with a better prognosis. We found no evidence that vascular pathology during the 5-year period prior to the index MDD diagnosis was associated with differences in the subsequent course trajectory of psychiatric hospital contacts for MDD in older patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Pedersen CB, Mors O, Bertelsen A, Waltoft BL, Agerbo E, McGrath JJ, et al. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry*. 2014 May; 71(5):573–581. [PubMed: 24806211]
2. Eaton WW, Anthony JC, Gallo J, Cai G, Tien A, Romanoski A, et al. Natural history of Diagnostic Interview Schedule/DSM-IV major depression. The Baltimore Epidemiologic Catchment Area follow-up. *Arch Gen Psychiatry*. 1997 Nov; 54(11):993–999. [PubMed: 9366655]
3. Grayson L, Thomas A. A systematic review comparing clinical features in early age at onset and late age at onset late-life depression. *J Affect Disord*. 2013 Sep 5; 150(2):161–170. [PubMed: 23623421]
4. Musliner KL, Trabjerg BB, Waltoft BL, Laursen TM, Mortensen PB, Zandi PP, et al. Parental history of psychiatric diagnoses and unipolar depression: a Danish National Register-based cohort study. *Psychol Med*. 2015 Oct; 45(13):2781–2791. [PubMed: 25920726]
5. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. *Arch Gen Psychiatry*. 1997 Oct; 54(10):915–922. [PubMed: 9337771]
6. Alexopoulos GS, Meyers BS, Young RC, Kakuma T, Silbersweig D, Charlson M. Clinically defined vascular depression. *Am J Psychiatry*. 1997 Apr; 154(4):562–565. [PubMed: 9090349]
7. Alexopoulos GS. The vascular depression hypothesis: 10 years later. *Biol Psychiatry*. 2006 Dec 15; 60(12):1304–1305. [PubMed: 17157096]
8. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry*. 2013 Sep; 18(9):963–974. [PubMed: 23439482]
9. Sheline YI, Pieper CF, Barch DM, Welsh-Bohmer K, McKinstry RC, MacFall JR, et al. Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Arch Gen Psychiatry*. 2010 Mar; 67(3):277–285. [PubMed: 20194828]
10. Robinson RG, Jorge RE. Post-Stroke Depression: A Review. *Am J Psychiatry*. 2016 Mar 1; 173(3):221–231. [PubMed: 26684921]
11. Kendler KS, Fiske A, Gardner CO, Gatz M. Delineation of two genetic pathways to major depression. *Biol Psychiatry*. 2009 May 1; 65(9):808–811. [PubMed: 19103442]
12. Byers AL, Vittinghoff E, Lui LY, Hoang T, Blazer DG, Covinsky KE, et al. Twenty-year depressive trajectories among older women. *Arch Gen Psychiatry*. 2012 Oct; 69(10):1073–1079. [PubMed: 23026957]
13. Kooistra M, van der Graaf Y, Grool AM, Zuithoff NP, Jan Biessels G, Geerlings MI, et al. The natural course of elevated levels of depressive symptoms in patients with vascular disease over eight years of follow-up. The SMART-Medea study. *J Affect Disord*. 2016 Sep 15; 202:95–101. [PubMed: 27259081]
14. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011 Jul; 39(7 Suppl):22–25. [PubMed: 21775345]
15. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull*. 2006 Nov; 53(4):441–449. [PubMed: 17150149]
16. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health*. 2011 Jul; 39(7 Suppl):54–57. [PubMed: 21775352]
17. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011 Jul; 39(7 Suppl):30–33. [PubMed: 21775347]
18. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scandinavian Journal of Public Health*. 2011; 39(Suppl 7):38–41. [PubMed: 21775349]
19. Danish National Board of Health. Classification of diseases: extended Danish-Latin version of the World Health Organization International Statistical Classification of Diseases and Related Health Problems. 8th. Copenhagen, Denmark: Danish National Board of Health; 1971.
20. World Health Organization. Diagnostic criteria for research. Geneva: 1993. The ICD-10 classification of mental and behavioural disorders.

21. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011 May 28;11:83-2288-11-83.
22. Johannessen L, Strudsholm U, Foldager L, Munk-Jorgensen P. Increased risk of hypertension in patients with bipolar disorder and patients with anxiety compared to background population and patients with schizophrenia. *J Affect Disord*. 2006 Oct; 95(1-3):13-17. [PubMed: 16777235]
23. Horsdal HT, Benros ME, Köhler O, Krogh J, Gasse C. Metabolic profile at first-time schizophrenia diagnosis - a population-based cross-sectional study. *Neuropsychiatric Disease and Treatment*. (in press).
24. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology*. 2005 Aug 23; 65(4):545-551. [PubMed: 16116114]
25. Nagin DS. Analyzing developmental trajectories: A semiparametric, group-based approach. *Psychological Methods*. 1999; 4(2):139-157.
26. Nagin, DS. Group-based modeling of development Cambridge, Massachusetts: Harvard University Press; 2005.
27. Jones BL, Nagin DS, Roeder K. A SAS procedure based on mixture models for estimating developmental trajectories. *Sociological Methods & Research*. 2001; 29(3):374-393.
28. Jones BL, Nagin DS. Advances in group-based trajectory modeling and an SAS procedure for estimating them. *Sociological Methods & Research*. 2007; 35(4):542-571.
29. Haviland AM, Jones BL, Nagin DS. Group-based trajectory modeling extended to account for nonrandom participant attrition. *Sociological Methods & Research*. 2011; 40(2):367-390.
30. Vermunt JK. Latent Class Modeling with Covariates: Two Improved Three-Step Approaches. *Political Analysis*. 2010; 18:450-469.
31. Nylund KL, Asparouhov T, Muthen BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: A monte carlo simulation study. *Structural Equation Modeling*. 2007; 14(4):535-569.
32. Luppá M, Luck T, König HH, Angermeyer MC, Riedel-Heller SG. Natural course of depressive symptoms in late life. An 8-year population-based prospective study. *J Affect Disord*. 2012 Dec 15; 142(1-3):166-171. [PubMed: 22840627]
33. Beekman AT, Geerlings SW, Deeg DJ, Smit JH, Schoevers RS, de Beurs E, et al. The natural history of late-life depression: a 6-year prospective study in the community. *Arch Gen Psychiatry*. 2002 Jul; 59(7):605-611. [PubMed: 12090813]
34. Jørgensen TS, Wium-Andersen IK, Wium-Andersen MK, Jørgensen MB, Prescott E, Maartensson S, et al. Incidence of depression after stroke, and associated risk factors and mortality outcomes in a large cohort of danish patients. *JAMA Psychiatry*. 2016; 73(10):1032-1040. [PubMed: 27603000]
35. Alexopoulos GS, Meyers BS, Young RC, Kalayam B, Kakuma T, Gabrielle M, et al. Executive dysfunction and long-term outcomes of geriatric depression. *Arch Gen Psychiatry*. 2000 Mar; 57(3):285-290. [PubMed: 10711915]
36. Butters MA, Bhalla RK, Mulsant BH, Mazumdar S, Houck PR, Begley AE, et al. Executive functioning, illness course, and relapse/recurrence in continuation and maintenance treatment of late-life depression: is there a relationship? *Am J Geriatr Psychiatry*. 2004 Jul-Aug;12(4):387-394. [PubMed: 15249276]
37. Hickie I, Scott E, Wilhelm K, Brodaty H. Subcortical hyperintensities on magnetic resonance imaging in patients with severe depression—a longitudinal evaluation. *Biol Psychiatry*. 1997 Sep 1; 42(5):367-374. [PubMed: 9276077]

Highlights

- We examined 5-year trajectories of clinically diagnosed depression in a large, representative sample of older adults treated in secondary psychiatric care in Denmark.
- Latent class growth analysis identified four trajectory patterns: consistently low (66%), high decreasing (19%), consistently high (9%), and moderate fluctuating (6%) probability of psychiatric hospital contact following the index depression.
- Older age, greater severity, inpatient treatment and >12 months of prior antidepressant medication use predicted hospital contact trajectories.
- Vascular pathology was not significantly associated with trajectory class membership

Figure 1.

Sample selection

*Does not include individuals living in Greenland

Figure 2.
Study design
MDD = Major depressive disorder

Figure 3.
5-year trajectories of late-life MDD in secondary psychiatric care
Bands represent 95% confidence intervals

Figure 4.
Correlates of 5-year trajectories of MDD
Note: p values generated by 2-sided t tests, df=11,091.

Table 1

Sample characteristics

Characteristics	Trajectory class									
	Total Sample (N = 11,092)		Consistently low (n = 7,435)		High decreasing (n = 2,204)		Consistently high (n = 936)		Moderate fluctuating (n = 517)	
	Number	%	Number	%	Number	%	Number	%	Number	%
Sex										
Male	3,540	31.91	2,460	33.09	665	30.17	274	29.27	141	27.27
Female	7,552	68.09	4,975	66.91	1,539	69.83	662	70.73	376	72.73
Age at index MDD diagnosis										
60–69	3,462	31.21	2,486	33.44	555	25.18	237	25.32	184	35.59
70–79	3,950	35.61	2,566	34.51	784	35.57	384	41.03	216	41.78
80+	3,680	33.18	2,383	32.05	865	39.25	315	33.65	117	22.63
Geographic area of birth										
Urban area within Denmark	5,640	50.85	3,910	52.59	1,069	48.50	413	44.12	248	47.97
Rural area within Denmark	5,060	45.62	3,259	43.83	1,070	48.55	481	51.39	250	48.36
Born outside Denmark	392	3.53	266	3.58	65	2.95	42	4.49	19	3.68
Months on antidepressants										
0 months on antidepressants	1,376	12.41	980	13.18	233	10.57	118	12.61	45	8.70
Up to 12 months on antidepressants	5,417	48.84	3,651	49.11	1,085	49.23	443	47.33	238	46.03
Over 12 months on antidepressants	4,299	38.76	2,804	37.71	886	40.20	375	40.06	234	45.26
Treatment setting at index MDD diagnosis										
Inpatient	4,017	36.22	2,781	37.40	618	28.04	373	39.85	245	47.39
Outpatient	7,075	63.78	4,654	62.60	1,586	71.96	563	60.15	272	52.61
Severity at index MDD diagnosis										
Mild	1,887	17.01	1,364	18.35	317	14.38	130	13.89	76	14.70
Moderate	4,911	44.28	3,282	44.14	1,016	46.10	397	42.41	216	41.78
Severe without psychotic features	1,531	13.80	934	12.56	330	14.97	166	17.74	101	19.54
Severe with psychotic features	958	8.64	548	7.37	220	9.98	132	14.10	58	11.22
Severity unspecified	1,805	16.27	1,307	17.58	321	14.56	111	11.86	66	12.77
Vascular pathology										

Characteristics	Trajectory class									
	Total Sample (N = 11,092)		Consistently low (n = 7,435)		High decreasing (n = 2,204)		Consistently high (n = 936)		Moderate fluctuating (n = 517)	
	Number	%	Number	%	Number	%	Number	%	Number	%
Hypertension	7,440	67.08	5,016	67.46	1,480	67.15	604	64.53	340	65.76
Diabetes	877	7.91	599	8.06	180	8.17	67	7.16	31	6.00
Stroke	1,445	13.03	991	13.33	291	13.20	103	11.00	60	11.61
Heart disease	2,117	19.09	1,447	19.46	439	19.92	152	16.24	79	15.28
Vascular dementia	229	2.06	155	2.08	49	2.22	20	2.14	5	0.97
Vascular burden										
0	3,111	28.05	2,034	27.35	621	28.10	302	32.33	154	30.08
1	4,850	43.73	3,258	43.81	943	42.67	401	42.93	248	48.44
2	2,259	20.37	1,555	20.91	462	20.90	163	17.45	79	15.43
3	752	6.78	513	6.90	158	7.15	57	6.10	24	4.69
4+	120	1.08	76	1.02	26	1.18	11	1.18	7	1.37

Note. Class assignment based on maximum posterior probability of class membership. Results for individual measures of vascular pathology and other covariates obtained from a single model including all of these variables. Results for the aggregate measure of vascular burden obtained from a separate model, also adjusted for sex, age at index MDD diagnosis, geographic area of birth, number of months on antidepressant medication and severity at index MDD diagnosis. The numbers of individuals assigned to each class based on posterior probabilities in this model are 7,436 for the consistently low class, 2,210 for the high decreasing class, 934 for the consistently high class and 512 for the moderate fluctuating class.