Patterns of late-life depression: On the nature of depressive subtypes and the role of aging

Veltman, E.M.

CHAPTER 4

Stability and transition of depressive subtypes in older adults

E.M. Veltman, MD[a] | A.A.L. Kok, PhD[b] | F. Lamers, PhD[b] | M.L. Stek, MD PhD[b c]
R.C. van der Mast, MD PhD[a d] | D. Rhebergen, MD PhD[b c]

[a] Department of Psychiatry, Leiden University Medical Center, The Netherlands
[b] Amsterdam University Medical Center, Vrije Universiteit, Psychiatry, Amsterdam Public Health research institute, the Netherlands
[c] GGZ inGeest Specialized Mental Health Care, Amsterdam, the Netherlands
[d] Department of Psychiatry, CAPRI-University of Antwerp, Belgium

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Background: The heterogeneity of late-life depression hampers diagnosis and treatment. Data-driven methods have identified several subtypes of depression in older persons, but the longitudinal stability of these subtypes remains unknown.

Methods: In total 111 older persons with a major depressive disorder both at baseline and 2-year follow-up from the Netherlands Study of Depression in Older persons (NESDO) were included. Latent class analysis was performed to identify subtypes of depression at baseline and at 2-year follow-up, and latent transition analysis was used to examine the stability of these subtypes over time. Transition rates between subtypes and characteristics of groups were examined.

Results: Two subtypes were identified in both baseline (T0) and follow-up data (T1), including a 'melancholic' subtype (prevalence 80.2% (T0) and 62.2% (T1)), and an 'atypical' subtype (prevalence 19.8% (T0) and 37.8% (T1)). The melancholic subtype was characterized by decreased appetite and weight and had a stability of 0.86. The atypical subtype was characterized by increased appetite and weight and had a stability of 0.93, although the discriminating power of different symptoms had decreased at T1. Mean age and education differed significantly between stable and transitioning subgroups, other characteristics did not differ between subgroups.

Limitations: Limited sample size might have hampered the analyses.

Conclusions: Subtypes of late-life depression are relatively stable, but symptoms of depression (like weight loss) seem to blur with symptoms of (patho)physiological aging. This underlines the clinical relevance of depression subtyping, but also the importance of further research into subtypes and the influence of aging.

Keywords: latent transition analysis; late-life depression; depression subtypes; stability of depressive subtypes; atypical depression; melancholic depression

Abstract

Introduction

Late-life depression is a common disorder, with a prevalence ranging from 1-16% (Djernes, 2006). Especially late-life depression is associated with a poorer course (Schaakxs et al., 2018), and comes with a high disease burden for both patients (Gallo et al., 2007) and their caregivers (Scazufca et al., 2002). Better insight into the aetiology and treatment options is therefore of great importance. However, to date research is being hindered by the heterogeneity of depression (Lux and Kendler, 2010; Goldberg, 2011), since the diagnosis of major depressive disorder (MDD) does not reflect the wide array of possible depressive symptom combinations. A diagnosis of MDD is made if 5 out of 9 DSM criteria are met, and since several of these symptoms are opposites (e.g. weight gain or loss), two patients diagnosed with MDD could have zero symptoms overlapping. In addition, previous, longitudinal studies demonstrated low longitudinal stability of depression categories described in the Diagnostic and Statistical Manual of Mental Disorders (DSM) edition 5 (American Psychiatry Association, 2013) such as major depressive disorder, dysthymia, and subthreshold depression (Angst et al., 1997, 2000). Acknowledging this heterogeneity, the DSM 5 contains several specifiers such as depression with atypical or melancholic features, but these have not proved sufficient to predict prognosis and treatment response (Parker et al., 2010; Lojko and Rybakowski, 2017).

A different approach to examine the heterogeneity of depression is through data-driven methods (Lubke and Muthén, 2005), such as latent class analysis (LCA). These techniques cluster patients based on their congregate of different depressive symptoms, without a pre-conceived hypothesis. Studies in younger adults using LCA identified an 'atypical' subtype characterized by increased sleep and appetite, and a 'typical' or 'melancholic' subtype characterized by decreased sleep and appetite, and the presence of psychomotor symptoms (Kendler et al., 1996; Sullivan et al., 1998, 2002; Lamers et al., 2010; Rodgers et al., 2013; Li et al., 2014). In addition, these empirically-derived subtypes and their most distinguishing symptoms as appetite and weight have been linked to distinct biological and genetic correlates, and different neural activity on functional MRI (Lamers et al., 2013; Milaneschi et al., 2017; Simmons et al., 2018). In older adults, earlier data-driven studies have found subtypes mainly based on severity, probably due to inclusion of persons without a formal diagnosis of depression (Hybels et al., 2009, 2013; Lee et al., 2012; Mezuk and Kendler, 2012). Furthermore, not all of these studies distinguished between increase and decrease of sleep, appetite, weight and psychomotor symptoms, while these distinctions appeared to be crucial in identifying subtypes of depression in both younger (Lamers et al., 2010; Alexandrino et al., 2013; Rodgers et al., 2013). We have performed an LCA on older depressed adults taking this symptom distinction into account, and have found an atypical, melancholic, and moderately severe subtype (Veltman et al., 2017), similar to the aforementioned studies in younger adults. To further examine the validity and clinical usefulness of these subtypes, insight is needed into the stability and the potential transition rate of subjects across subtypes over time.

Latent transition analysis (LTA) is a data-driven method useful for examining the longitudinal stability and transition of subtypes of depression. In younger depressed adults, studies performing LTA have found a relatively high stability of subtypes (48-90%),

with the atypical subtype being the most stable (71-79%) (Lamers et al., 2012; Rodgers et al., 2014). In older depressed adults, so far one earlier LTA has been performed (Ni et al., 2017). Their sample consisted of outpatients aged 60 to 96 years, and they demonstrated moderate stability of subtypes during 2-year follow-up (46-61%), with the highest stability in the subtype characterized by a moderate severity and a lack of positive affect. However, they did not differentiate between increasing and decreasing sleep, appetite, weight, and psychomotor symptoms, and as shown before, these symptoms are important in differentiating between subtypes of depression.

The Netherlands Study on Depression in Older persons (NESDO) provides an excellent opportunity to examine the stability of late-life depression subtypes, with recognition of the importance of differentiation between increase and decrease in sleep, appetite and psychomotor symptoms. This paper is a follow-up of an earlier cross-sectional study that identified three subtypes of depression using latent class analysis, including an atypical, a melancholic, and a moderate subtype (Veltman et al., 2017). The atypical subtype was characterized by a high severity, and an increase in sleep, appetite and weight. The melancholic subtype was characterized by a high severity, but a decrease in sleep, appetite and weight. The moderate subtype was characterized by an overall lower prevalence of depressive symptoms. To examine the 2-year longitudinal stability of these subtypes, in this study we perform a latent transition analysis on persons derived from the NESDO-cohort with a major depressive disorder (MDD) both at baseline and at 2-year follow-up. This study population differs from the population in Veltman et al. (2017) in chronicity, since a diagnosis of MDD on both time points was needed for inclusion. Nevertheless, considering the three identified subtypes in our previous study (Veltman et al., 2017), as well as the findings from LTA studies on younger adults identifying similar subtypes (Lamers et al., 2012; Rodgers et al., 2014), we hypothesize to find three subtypes among older depressed people using LTA, including a melancholic, atypical, and moderate subtype, with considerable stability during 2-year follow-up.

Methods

Study population

Data were derived from the baseline and 2-year follow-up measurements of the Netherlands Study of Depression in Older persons (NESDO), a longitudinal multi-site naturalistic cohort study, examining course and consequences of depression in older persons. The NESDO cohort (n=510) consists of persons aged 60-93 years, including 378 persons with a depressive disorder in the previous 6 months at baseline, and 132 non-depressed controls. Depressed older persons were recruited from both mental health care institutes and general practitioners in five regions in the Netherlands, in order to include persons with current late-life depression in various developmental and severity stages. Depression included a 6-month diagnosis of Major Depressive Disorder (MDD) (95%) and/ or 6 month dysthymic disorder (26.5%), or minor depression (two to four depressive symptoms lasting at least two weeks, 5.0%) according to DSM-IV-R criteria. Non-depressed older persons were recruited from general practices and were included when no lifetime

diagnosis of depression was present. Exclusion criteria were (suspected) dementia, and insufficient command of the Dutch language. The study design of NESDO is described in detail elsewhere (Comijs et al., 2011).

For the present study, persons with a 6-month diagnosis of MDD at baseline (T0), and a 6-month diagnosis of MDD at 2-year follow-up (T1), were included. Persons with dysthymia or minor depression only were excluded. We chose to include only persons with a present diagnosis of MDD on both T0 and T1 because we specifically wanted to examine the longitudinal stability of depression subtypes.

Symptoms of depression

Ten depressive symptoms were used as indicator variables in the LCA analyses in order to identify depression subtypes. Nine depression key symptoms of the DSM-IV were based on the Dutch version of the Composite International Diagnostic Interview (CIDI) lifetime version 2.1, (World Health Organization, 1997; Andrews and Peters 1998) which were used to diagnose depressive and anxiety disorders according to DSM-IV criteria and conducted by specially trained clinical research staff. Changes in appetite and weight were used as two separate variables. All items were coded as 'not present' or 'present', except for the items regarding changes in appetite, weight, sleep and psychomotor disturbance. Here we created four categories, so for example for weight the categories were: absence of weight changes, weight loss, weight gain, and both gain and loss.

Covariates

Several socio-demographic, clinical, psychosocial, and physical health indicators were used to characterize subtypes, equal to the covariates used in our baseline paper (Veltman et al., 2017) and mostly overlapping with similar studies in younger adults (Lamers et al., 2012) to enable comparison.

Socio-demographic variables, including age, gender and years of education, were collected during the baseline interview. *Clinical characteristics* such as age of onset of the depressive disorder and comorbid anxiety disorders were assessed by the CIDI. Severity of depressive symptoms was assessed with the of the 30-item Inventory of Depressive Symptomatology (IDS) (Rush et al., 1996). Further, we assessed several *psychosocial variables*. Overall daily functioning was measured with the World Health Organization Disability Assessment Schedule II (WHODAS) (Chwastiak and Von Korff, 2003); Buist-Bouwman et al., 2008). Apathy was measured using the Apathy Scale (Starkstein et al., 1992), and cognitive functioning by the Mini Mental State Examination (MMSE) (Folstein et al., 1975). *Physical health indicators* were included. Respondents were asked whether they were currently smoking (yes/no). In addition, their alcohol intake was calculated as number of drinks per week. Pain was measured using a count of pain locations (range 0-7) listed in the Chronic Graded Pain scale (Von Korff et al., 1992). The presence of metabolic syndrome (yes/no) was measured. Cut-off values for metabolic syndrome were based on the adjusted Adult Treatment Panel (ATP III) criteria (Expert panel, 2001), including waist circumference ≥88 cm, triglycerides ≥150 mg/dl, HDL-cholesterol < 50mg/dl, systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or use of anti-hypertensive drugs, fasting blood glucose ≥100 mg/dl or use of a hypoglycemic drug. Persons scoring positive on ≥3

criteria were considered to have a metabolic syndrome. Diabetes was defined as fasting plasma glucose level ≥ 7.0 mmol/l. Objective and standardized assessments of height and weight were performed. Body mass index (BMI) was calculated as kilograms divided by meter squared and categorized as underweight-normal (BMI<25), overweight (25≤BMI<30) and obese (BMI≥30). The number of chronic diseases, presence of cardiovascular disease (assessed by self-report supported by appropriate medication use (see Vogelzangs et al. (2010) for a detailed description), the presence of diabetes (based on fasting plasma glucose level ≥ 7.0 mmol/l or use of anti-diabetic medication [ATC-code A10] (WHO 2007)) was determined. Muscle weakness as an indicator of frailty was measured with a hand-held dynamometer. This was considered present if persons scored below the cut off score after their performance was stratified by gender and BMI, according to Fried et al. (2001).

Outline of analyses

First, latent class analyses, using 10 CIDI-items as indicator variables, were performed at T0 and T1 separately. The conditional probability of occurrence of each depressive symptom, given class membership was examined using Cramer's V. After identification of classes, latent transition analysis was performed, to examine the stability of the identified classes. Characteristics of all classes were examined. In univariate analyses, repeated measurement T-tests were used for normally distributed variables, McNemar tests for dichotomous variables, and Wilcoxon paired rank tests for non-parametric variables. In multivariable analyses, the two stable subtypes were compared, and analyses were corrected for variables that significantly changed the bivariate associations, when added separately (change odd's ratio >10%).

Latent Class Analyses

To determine and identify subtypes of depressive disorders, we performed Latent Class Analysis (LCA). Free from any a priori assumptions about the number and characterization of subtypes, data-driven techniques such as LCA cluster persons into unobserved ('latent') classes, based on their values on several observed variables. Analysis starts with one class, suggesting one class fitting for all persons. Then, iteratively, one class is added to the model, and the best fitting number of classes is determined on the basis of several statistical indicators and interpretability. The LCAs were conducted using M*plus* version 5 (Muthén and Muthén, 2007).

To determine which model best fitted the data, we examined the sample size adjusted BIC (ssaBIC), entropy (i.e., classification accuracy), the bootstrapped Lo-Mendell-Rubin likelihood ratio test (LMR) (number of bootstraps used = 1000), the bootstrapped likelihood ratio test (BLRT) and the proportion of respondents in each class. Lower ssaBIC values indicate better model fit (Nylund et al., 2007a). Entropy, as a measure of classification accuracy, is presented for models with more than one subtype. Values for entropy can range between 0 and 1 with values closer to 1 indicating greater accuracy. The Lo-Mendell-Rubin test (LMR) provides a p-value, which indicates whether the *k*-1 subtype model is rejected in favor of the *k* subtype model. Similar to the LMR test, a p-value below .05 for the bootstrapped likelihood ratio test (BLRT) indicates that the present model fits the data better than the model with one class less; a p-value exceeding .05 indicates that the model with one class less should be preferred (Nylund et al., 2007a). There is no

consensus yet as to which criterion best identifies the best fitting number of classes, but the BLRT seems to be superior to other model fit indices (Nylund et al., 2007a).Finally, we only accepted models in which all classes contained at least five percent of the sample.

Latent transition analysis

Latent transition analysis is a longitudinal mixture model that explores change in latent classes of individuals over time. Latent class analysis on two time points is used as a measurement model in LTA, from which individual-level change among these classes over time is defined by the transition analyses (Nylund, 2007b). Depending on the outcome of the two separate latent class analyses performed for T0 and T1, the latent transition analysis was modelled according to Nylund (2007b). In case of an equal number of subtypes for both latent classes analyses, these subtypes were compared in order to see to what extent they were similar. The latent transition model, calculating the movement of subjects between subtypes across time points, was modelled with respect to the comparability of subtypes found on T0 and T1. First, the degree of similarity between subtypes was compared through loglikelihood tests. For this purpose, we examined the extent of (in)variance of the subtypes in different models: a model where all conditional probabilities of variables were constrained to be equal across time, a model where all conditional probabilities were estimated freely across time, and models in which all conditional probabilities started out as variant, and were gradually coded as invariant (testing for partial invariance). The higher the number of conditional probabilities that were invariant across time, the higher the similarity of identified classes over time.

Results

The total sample consisted of 111 depressed older people, of whom 67% were females, with a mean age of 70.9 (SD ±7.7) years at baseline and a mean age of depression onset of 44.2 (SD ±20.1) years.

In **Table 1**, demographics of the total sample at baseline (T0) and 2-year follow-up (T1) are shown.

Severity significantly decreased over time ($p<0.01$), as did body mass index ($p=0.01$), while muscle weakness increased ($p=0.04$).

Table 2 shows the model fit indices for 1 to 4 classes on both T0 and T1. The best fitting model for the analysis on both baseline and 2-year follow-up was the 2-class model, with a significant Lo-Mendell-Rubin test (LMR) (T0 $p=0.01$; T1 $p<0.01$), a significant bootstrapped likelihood ratio test (BLRT) (T0 $p<0.01$; T1 $p=0.01$), lowest BIC and highest entropy. There is no consensus yet as to which criterion best identifies the best fitting number of classes, but the BLRT seems to be superior to other model fit indices (Nylund et al., 2007a). From the 3-class model onwards, the BLRT was no longer significant, indicating that adding more than two classes to the model did not improve model fit. Classification accuracy was

high, with average posterior probabilities for subgroups ranging between 0.825 – 1.000 (n=111, data not shown), further indicating a reasonable classification quality.

Table 3 shows the estimated symptom profile probabilities for the two-class model on both T0 and T1. Variables are dichotomous (present or not present), except for the variables appetite, weight, sleep, and psychomotor symptoms, which are nominally divided into four categories (increase, decrease, both, or no change). In both subtypes weight and appetite, and to a lesser extent sleep and psychomotor symptoms, are the main significantly differing symptoms between subtypes. The first subtype in both T0 and T1 shows an atypical symptom pattern, with the highest occurrence of both weight gain and increased appetite, and is therefore labeled 'atypical'. The second subtype in both T0 and T1 is characterized by a more typical or melancholic symptom pattern with symptoms such as weight loss and decreased appetite, and is therefore labeled 'melancholic'. Although especially the 'atypical' label resembles a specific DSM diagnosis, we explicitly do not intend to refer to this DSM diagnosis. Rather, the label is chosen to facilitate comparisons with our previous data-driven study on older depressed adults (Veltman et al., 2017), and with earlier latent class and latent transition analyses in younger depressed adults (Lamers et al., 2012; Rodgers et al., 2014).

We then performed a latent transition analysis to examine the stability of these subtypes between T0 and T1. The best fitting model included appetite as invariant symptom, and all other symptoms as variant. Both subtypes showed high stability (atypical subtype N=15, stability =0.93; melancholic subtype N=62, stability=0.87). The estimated transition probability of melancholic to atypical (N=27) was 0.14, and of atypical to melancholic (N=7) was 0.07.

Table 4 shows the characteristics of the stable subjects and transitioning subjects. The group transitioning from atypical to melancholic has the lowest mean age, followed by the stable atypical subtype. The stable melancholic subtype has the lowest years of education. Prevalence of diabetes was lowest in the stable atypical group and highest in the group transitioning from atypical to melancholic. Further group differences in demographic characteristics did not reach significance. Multivariable comparison of the stable atypical and the stable melancholic subgroup showed no significant differences (data not shown). Due to low numbers in the transitioning groups (melancholic to atypical, N=27, and atypical to melancholic, N=7), power limited multivariable analyses across all four groups. Next, multivariable comparison of the stable subjects, including both atypical and melancholic subtypes (N=77), versus the transitioning subjects, including persons transitioning from melancholic towards atypical and vice versa (N=32), did not yield significant findings.

Discussion

In this study, data-driven subtypes of old age depression and their stability over two-year follow-up were examined. Both at baseline and 2-year follow-up, two depression subtypes were identified. The first, melancholic subtype was mainly characterized by a decrease in appetite and weight. The second, atypical subtype was predominantly characterized by an increase in appetite and weight. Both subtypes had high temporal stability, with a slightly higher stability for the atypical subtype. Whereas transition rates between subtypes were low, subjects were more likely to shift from the melancholic subtype to the atypical subtype than vice versa. The stable atypical subtype had a lower mean age and a lower age of onset than the stable melancholic subtype, but this difference disappeared in multivariable analyses. Diabetes was lowest in the stable atypical group and highest in the group transitioning from atypical to melancholic. Other demographic variables were not significantly correlated to subtypes, neither in univariate, nor in multivariable regression analyses. No variables predicting transitioning, as compared to stable class membership, were discovered in multivariable analyses.

In contrast to our hypothesis and our previously published LCA (Veltman et al., 2017), based on data derived from the same cohort (N=359), we now identified two subtypes (atypical and melancholic) instead of three. The previously identified moderate subtype is now absent, which may be caused by a decline in study population and thereby a decrease in power. Since we specifically wanted to examine the longitudinal stability of depression subtypes, persons were only eligible for inclusion in the current study if they fulfilled DSM-criteria for MDD both at baseline and 2-year follow-up. Hence, a study population of chronic or recurrent MDD was selected, whereas in the former study (Veltman et al., 2017) persons with non-chronic MDD were also included. Since chronic depression has been associated with higher depression severity (Reisinger Walker and Druss, 2015), this selection procedure may have resulted in a study sample with higher mean depression severity, and hence, the absence of a moderately severe subtype. Severity scores of the different cohorts indeed reveal a higher severity in the current study towards, with an IDS sum score of 34.9 (SD ± 13.1) in the present study and of 30.5 (SD ± 13.0) in our previous LCA study. In post-hoc analyses, we further explored the characteristics of the subjects that were included in our earlier LCA (Veltman et al., 2017), but not in our current LTA. These were subjects with either missing data on T0, or with MDD on T0 but not on T1 (N=248). First, we found that participants in the current study were equally selected with respect to original subtypes (p=0.12); persons from all three LCA-derived classes were equally selected for inclusion in the current study. This suggests that the absence of a moderate severe subtype might be (partly) caused by a relatively small sample (N= 111), with less power for complex modelling. Furthermore, included subjects had a higher MDD severity on T0 (p=0.02) compared to excluded subjects. Of the 248 excluded subjects, 64.1% (N=159) did not reach the criteria for MDD, and 35.9% (N=89) had dropped out. Reasons for drop-out were dropout due to unknown reasons between T0 and T1 (8.0%, N=20), refusal to participate at T1 (5.2%, N=13), not eligible due to physical or mental reasons (16.5%, N=41), no contact could be made (2.0%, N=5), or passing away (4.0%, N=10).

Next, the symptom profiles of the identified atypical and melancholic subgroup in both T0 and T1, and their high temporal stabilities correspond to earlier studies on younger depressed adults (Lamers et al., 2012; Rodgers et al., 2014). In line with studies on younger adults, the atypical subtype was characterized by increased appetite and weight, and the melancholic subtype by decreased appetite and weight. In the current study however, the difference in appetite and weight symptoms between both subtypes was smaller at T1 as compared to T0. The reduced item discriminating power and very small number of invariable symptoms (1 out of 10) in the LTA model might imply that the nature of the atypical and melancholic subtypes is not completely stable over time. This might be because old age and aging are often associated with diminishing physical health (e.g. weight loss and muscle weakness) and somatic comorbidity, especially in depressed older persons (Holvast et al., 2017). These (patho)physiological processes might influence the presentation of late-life depression, and decrease the distinguishing power of symptoms such as appetite and weight over time. This hypothesis is supported by our finding that BMI and muscle strength significantly decreased during 2-year follow-up (see **Table 1**). This indicates the dwindling health of our subjects and may complicate the identification of depressive subtypes in an older population where depressive symptom presentation might be clouded by (patho)physiological aging.

Nevertheless, taking these possible (patho)physiological alterations in aging into account by freeing conditional probabilities across time, the stability of the identified subtypes was high, and several characteristics were in line with earlier studies on subtypes of depression. Age was significantly lower in the stable atypical subgroup and in the subgroup transitioning from atypical to melancholic, compared to the stable melancholic subgroup and the subgroup transitioning from melancholic to atypical. In earlier studies among younger adults identifying a similar atypical subtype, age and age of depression onset were also lowest in the atypical subtype (Lamers et al., 2010; Veltman et al., 2017). In contrast with previous studies, however, in our study prevalence of metabolic syndrome and cardiovascular disease did not differ between the atypical and melancholic subtype, and prevalence of diabetes was lowest in our stable atypical subtype. It was previously demonstrated that chronic depression, in particular in older age, is associated with a wide array of somatic illnesses (Hegeman et al., 2017; Holvast et al., 2017). Likewise, in non-depressed older persons, prevalence of somatic illnesses is higher in older age. Hence, competing pathways, other than pathways associated with depression subtype, may result in onset of diabetes and cardiovascular disease in older persons. To conclude, we hypothesize that in our chronically depressed cohort of older persons, the lack of significant difference in metabolic and cardiovascular disturbances may rather reflect pathophysiological disturbances associated with either chronicity of depression or aging processes that are not linearly correlated with depression subtypes in late-life. In addition to this, the limited sample size and 2-year follow-up period might have been insufficient to find the true diversity in depression subtypes and their underlying pathophysiological pathways. Future research on the longitudinal stability of late-life depression subtypes with larger sample sizes and longer follow-up is warranted.

Strengths and limitations

The results of this study should be interpreted in the light of various strengths and limitations. A strength of this study is that it is the first latent transition analysis on older depressed persons taking both increase and decrease of weight, appetite, sleep, and psychomotor changes into account. This differentiation of symptoms has been especially distinguishing in earlier found data-driven subtypes, and it enables comparison with several studies on both younger and older adults. Furthermore, a wide selection of characteristics was examined. The limited sample size is an important limitation of the current study. Due to both selection of patients with chronic or recurrent MDD and to dropout due to morbidity and mortality in this older population, only a small number of the original population in our earlier study was included. This may decrease the reliability of our LTA, and may hamper our univariate and multivariable analyses. Another limitation is the possible violation of the local independence assumption (correlation between variables in a class is accounted for by the latent variable). This could occur if separate variables are included that measure different expressions of the same underlying symptom.

Conclusion

To conclude, this is the first study that examined the temporal stability of data-driven subtypes of late-life depression taking into account both increase and decrease in sleep, appetite, weight, and psychomotor symptoms. An atypical and a melancholic subtype were found, both with a high stability over 2-year follow-up. Appetite and weight were main distinguishing symptoms, but their discriminating ability decreased over time. Since the overall cohort significantly declined in weight and physical health during 2-year follow-up, the process of (patho)physiological aging might blur the differentiation of depression subtypes in older age. These findings stress the importance of taking the pathophysiological tangle of aging into account when searching for a better approach to diagnosis, treatment and prevention of late-life depression.

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Table 1. Characteristics of total sample at baseline (T0) and 2-year follow-up (T1) (N=111)

	T0	T1	Overall p-value (df)
Socio-demographics			
Sex, female, %	66.7	*	*
Age, mean (SD), y	70.7(7.6)	*	*
Education, mean (SD), y	10.5(3.8)	*	*
Clinical characteristics			
Age of onset, mean (SD) y	43.8(19.7)	*	*
Severity (IDS), mean (SD)	34.9(13.1)	32.1(12.3)	0.01(110)[1]
Anxiety dx last year, %	46.8	37.8	0.13[2]
Psychosocial			
Functioning sx, mean (SD)	35.7(16.4)	37.4(16.1)	0.26(105)[1]
Apathy score, mean (SD)	18.3(5.1)	19.7(6.2)	0.09(108)[1]
MMSE score, median (IQR)	28.0(2.0)	28.0(2.0)	0.67[3]
Physical health			
Current smoking, %	27.0	#	#
# alcohol/ week, median (IQR)	0.3(4.9)	#	#
Chronic pain grade, mean (SD)	2.3(1.3)	2.2(1.1)	0.53(100)[1]
Body mass index, median (IQR)	26.6(5.4)	26.3(6.2)	0.01[3]
Cardiovascular disease, yes, %	26.1	27.0	1.00[2]
Diabetes, yes, %	17.1	19.1	0.32[1]
# chronic diseases, mean(SD)	2.9(1.9)	2.2(1.1)	0.80(109)[1]
Metabolic syndrome, yes, %			
Muscle weakness, %	21.6	27.9	0.04[2]

Tests used: 1=paired-samples t-test; 2=McNemar; 3=Wilcoxon paired rank test

** = no change over time/ no added value in mentioning*

 # = no data available on T1

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Table 2. Model fit indices for different classes at T0 and T1

Model fit indices for different classes, T0											
Classes	**Maximum likelihood**	**BIC**	**ssaBIC**	**Entropy**	**Lo-Mendell-Rubin**		**BLRT**	**Proportion per class**			
					2LL	p	p	1	2	3	4
1	-680.618	1446.007	1389.123	-	-	-	-	1.000			
2	-649.427	1473.107	1356.180	0.888	62.381	0.0100	0.00	0.198	0.802		
3	-633.110	1529.953	1352.982	0.814	32.635	0.0939	0.1750	0.243	0.568	0.189	
4	-620.831	1594.877	1357.862	0.803	30.650	1.000	0.0900	0.270	0.189	0.432	0.108

Model fit indices for different classes, T1											
Classes	**Maximum likelihood**	**BIC**	**ssaBIC**	**Entropy**	**Lo-Mendell-Rubin**		**BLRT**	**Proportion per class**			
					2LL	p	p	1	2	3	4
1	-683.285	1451.342	1394.458	-	-	-	-	1.000			
2	-660.989	1496.230	1379.303	0.764	44.593	0.0082	0.0130	0.378	0.622		
3	-648.750	1559.323	1382.352	0.780	26.338	0.9855	0.7130	0.423	0.252	0.324	
4	-643.177	1625.251	1388.237	0.864	26.549	0.8232	0.4140	0.360	0.243	0.297	0.099

Table 3. Estimated symptom profile probabilities of endorsing depressive symptoms from LCA T0 and T1 (n=111)

	T0					T1				
	Total sample	T0 Class 1 Atypical	T0 Class 2 Melancholic	Cramer's V	P-value T0(df)	Total sample	T1 Class 1 Atypical	T1 Class 2 Melancholic	Cramer's V	P-value T1(df)
Prevalence		**22 (19.8%)**	**89 (80.2%)**				**42 (37.8%)**	**69 (62.2%)**		
DSM-IV criterion symptoms		**Symptom probabilities**					**Symptom probabilities**			
Depressed mood	99.1	1.00	0.99	0.05	0.62(1)	95.5	1.00	0.93	<0.01	0.07(1)
Loss of interest	93.7	0.96	0.93	0.04	0.70(1)	91.0	1.00	0.86	<0.01	0.01(1)
Weight				0.78	<0.01(3)				0.43	<0.01(3)
No weight change	55.9	0.36	0.61			77.5	0.81	0.75		
Weight loss	31.5	0.00	0.39			16.2	0.05	0.23		
Weight gain	10.8	0.55	0.00			5.4	0.14	0.00		
Both gain and loss	1.8	0.09	0.00			0.9	0.00	0.01		
Appetite				0.80	<0.01(3)				0.47	<0.01(3)
No change in appetite	26.1	0.09	0.30			37.8	0.57	0.26		
Decreased appetite	55.0	0.14	0.65			43.2	0.00	0.70		
Increased appetite	15.3	0.73	0.01			16.2	0.43	0.00		
Both increase and decrease	3.6	0.05	0.03			2.7	0.00	0.04		
Sleep				0.28	0.03(3)				0.13	0.02(3)
No change in sleep	9.0	0.05	0.10			13.5	0.24	0.07		
Less sleep	65,8	0.59	0.67			64.0	0.60	0.67		
More sleep	8.1	0.00	0.10			11.7	0.14	0.10		
Both less and more sleep	17.1	0.36	0.12			10.8	0.08	0.16		
Psychomotor				0.25	0.07(3)				0.06	<0.01(3)
No psychomotor change	22.5	0.14	0.25			27.9	0.29	0.28		

	T0					T1				
	Total sample	T0 Class 1 Atypical	T0 Class 2 Melancholic	Cramer's V	P-value T0(df)	Total sample	T1 Class 1 Atypical	T1 Class 2 Melancholic	Cramer's V	P-value T1(df)
Prevalence		**22 (19.8%)**	**89 (80.2%)**				**42 (37.8%)**	**69 (62.2%)**		
DSM-IV criterion symptoms		**Symptom probabilities**					**Symptom probabilities**			
Psychomotor retardation	36.0	0.32	0.37			32.4	0.36	0.31		
Psychomotor agitation	20.7	0.14	0.23			22.5	0.05	0.34		
Both agitation and retardation	20.7	0.41	0.16			16.2	0.31	0.07		
Fatigue/energy loss	94.6	1.00	0.93	0.12	0.21(1)	98.2	1.00	0.97	0.07	0.27(1)
Guilt/worthlessness	83.8	1.00	0.80	0.22	0.02(1)	70.3	0.88	0.59	0.18	<0.01(1)
Concentration/ indecisiveness	95.5	1.00	0.94	0.11	0.26(1)	96.4	1.00	0.94	0.10	0.11(1)
Suicidal ideation	74.8	1.00	0.69	0.29	<0.01(1)	70.3	0.74	0.68	0.03	0.52(1)

The left half of the table shows the symptom probabilities of the entire cohort and of the two different subtypes at T0 (ranging from 0-1), and the p-value for the difference in probability. The right half of the table shows the symptom probabilities of the two subtypes at T1, again with their corresponding p-values. All symptoms are dichotomous, except for the symptoms weight, appetite, sleep and psychomotor symptoms. These are nominally divided into four categories: no change, increase, decrease, and both increase and decrease.

Table 4. Characteristics of stable and transitioning subtypes at baseline

	Stable atypical (N=15)	Stable melancholic (N=62)	Atypical » Melancholic (N=7)	Melancholic » Atypical (N=27)	Overall p-value (df)
Socio-demographics					
Sex, female, %	80.0	64.5	71.4	63.0	0.67(3)[1]
Age, mean (SD), y	67.6(6.7)	71.8(8.0)	65.7(5.0)	71.2(6.8)	0.04(3)[2]
Education, mean (SD), y	11.1(3.7)	9.6(3.7)	11.4(4.7)	11.8(3.6)	0.05(3)[2]
Clinical characteristics					
Age onset, mean (SD) y	35.1(21.4)	45.8(19.2)	44.3(15.1)	44.1(20.6)	0.28(3)[2]
Severity sx, mean (SD)	37.2(11.9)	33.3(14.4)	37.4(7.1)	36.8(11.8)	0.43(3)[2]
Anxiety dx last year, %	53.3	48.4	57.1	37.0	0.65(3)[1]
Psychosocial					
Functioning, mean (SD)	37.1(15.4)	36.6(16.1)	41.1(12.6)	31.1(18.3)	0.65(3)[2]
Apathy score, mean (SD)	19.6(4.1)	17.5(4.6)	16.7(5.8)	19.8(6.1)	0.17(3)[2]
MMSE score, mean (SD)	28.3(1.6)	27.5(1.9)	27.6(1.3)	27.9(2.2)	0.41(3)[2]
Physical health					
Current smoking, %	33.3	29.0	28.6%	18.5%	0.70(3)[1]
# alcohol/ week, median (IQR)	1.0(3.7)	0.4(3.7)	0.0(1.0)	0.2(8.2)	0.73(3)[3]
Chronic pain grade, mean (SD)	2.5(1.2)	2.2(1.3)	2.3(1.3)	2.2(1.4)	0.95(3)[2]
Presence of metabolic syndrome, %	73.3	50.0	57.1	37.0	0.16(3)[1]
Body mass index, median (IQR)	27.8(9.2)	26.6(6.2)	27.4(1.7)	25.5(5.3)	0.22(3)[3]
Cardiovascular disease, yes, %	33.3	22.6	57.1	22.2	0.21(3)[1]
Diabetes, %	0.0	22.6	42.9	3.7	0.01(3)[1]
# chronic diseases, mean (SD)	3.1(1.8)	2.8(1.9)	3.6(2.9)	2.7(1.7)	0.76(3)[2]
Muscle weakness, %	20.0	27.9	0.0	14.8	0.25(3)[1]

Estimated transition probabilities: atypical to atypical=0.928; atypical to melancholic=0.072; melancholic to atypical=0.135; melancholic to melancholic =0.865
Statistical tests used: 1) chi-square; 2) Anova; 3) Kruskal-Wallis