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

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# CHAPTER 2

# Depressive subtypes in an elderly cohort identified using latent class analysis

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**Background:** Clinical findings indicate heterogeneity of depressive disorders, stressing the importance of subtyping depression for research and clinical care. Subtypes of the common late life depression are however seldom studied. Data-driven methods may help provide a more empirically-based classification of late-life depression.

**Methods:** Data were used from the Netherlands Study of Depression in Older People (NESDO) derived from 359 persons, aged 60 years or older, with a current diagnosis of major depressive disorder. Latent class analysis (LCA) was used to identify subtypes of depression, using ten CIDI-based depression items. Classes were then characterized using various sociodemographic and clinical characteristics.

**Results:** The most prevalent class, as identified by LCA, was a moderate-severe class (prevalence 46.5%), followed by a severe melancholic class (prevalence 38.4%), and a severe atypical class (prevalence 15.0%). The strongest distinguishing features between the three classes were appetite and weight and, to a lesser extent, psychomotor symptoms and loss of interest. Compared with the melancholic class, the severe atypical class had the highest prevalence of females, the lowest mean age, the highest BMI, and highest prevalence of both cardiovascular disease, and metabolic syndrome.

**Limitations:** The strongest distinguishing symptoms, appetite and weight, could be correlated. Further, only longitudinal studies could demonstrate whether the identified classes are stable on the long term.

**Discussion:** In older persons with depressive disorders, three distinct subtypes were identified, similar to subtypes found in younger adults. The strongest distinguishing features were appetite and weight; moreover, classes differed strongly on prevalence of metabolic syndrome and cardiovascular disease. These findings suggest differences in the involvement of metabolic pathways across classes, which should be considered when investigating the pathogenesis and (eventually) treatment of depression in older persons.

**Key words:** latent class analysis, depression subtypes, atypical depression, melancholic depression, metabolic syndrome

Abstract

## Background

Late-life depression is a very common disorder. In older persons living in different settings (e.g. from private households to institutions) prevalence rates of major depressive disorder (MDD) are estimated at 1-16% (Djernes 2006). In addition, depressive disorders among older persons are frequently of a chronic nature, with a high burden for both patients (Gallo et al., 2007) and their caregivers (Scazufca et al., 2002) and with high societal costs (Hughes et al., 1997; Unützer et al., 2009). Insight into the pathogenesis and possible treatment options is therefore of paramount importance. However, research on the aetiology and pathogenesis is impeded by the heterogeneity of depression and differences in biological underpinnings across subtypes, as demonstrated in younger adults (Marijnissen et al., 2011; Lamers et al., 2013; Liu et al., 2014; Vogelzangs et al., 2014; Mansur et al., 2015; Milaneschi et al., 2016).



Data-driven techniques are a fruitful way to investigate heterogeneity in depressive disorders (Lubke and Muthén 2005). These techniques cluster patients based on their congregate of different depressive symptoms, without a pre-conceived hypothesis. Studies using latent class analysis (LCA) in depressed, younger adult populations (Kendler et al., 1996; Sullivan et al., 1998; Lamers et al., 2010; Li et al., 2014) identified an 'atypical' class, characterized by increased appetite and increased sleep, and a 'typical' (often named 'melancholic') class, characterized by loss of appetite and weight, and by the presence of psychomotor symptoms. Subsequently, these empirically-derived classes could be linked to distinct biological correlates (Lamers et al., 2010, 2013; Milaneschi et al., 2015) as well as different genetic profiles (Milaneschi et al., 2016).

To what extent similar subtypes can be identified in late-life major depression needs to be established. Some studies have implemented LCA in late-life depression (Hybels et al., 2009, 2011, 2013; Lee et al., 2012; Mezuk and Kendler 2012), finding subtypes based mainly on severity. However, most of these studies also included non-depressed persons (Hybels et al., 2009, 2013; Mezuk and Kendler 2012), or persons with at least one depressive symptom (Lee et al., 2012), without a formal diagnosis of major depression. Whereas inclusion of subthreshold depressive disorders may generate insight into the heterogeneity of depression, it impedes examination of the assumed heterogeneity of particularly major depressive disorder (MDD). Furthermore, in populations with depression of varying severity, data-driven techniques are at risk to detect classes that are mainly driven by different levels of severity. Furthermore, because most studies included persons from community samples, no insight was provided into clinical (outpatient) populations (Lee et al., 2012; Mezuk and Kendler 2012; Hybels et al., 2013). Lastly, previously demonstrated in younger depressed adults, a differentiation between increased or decreased appetite, weight and/or sleep served as a core feature for differentiation between atypical and melancholic subtypes (Kendler et al., 1996; Sullivan et al., 1998; Lamers et al., 2010; Li et al., 2014). However, few studies among older, depressed persons distinguished between increased and decreased appetite, weight and sleep (Hybels et al., 2009, 2013; Lee et al., 2012), and the majority of data-driven studies in the older population identified subtypes primarily based on depression severity only (Hybels et al., 2009, 2011; Mezuk and Kendler 2012).

Therefore, this study aimed to gain more insight into the assumed heterogeneity of MDD in older persons by performing LCA, based on depressive symptoms. If distinct classes are identified, these are examined to establish whether they differ with respect to demographic and clinical characteristics, as well as other risk factors and comorbidity patterns.

## Methods

### Sample

Data were derived from the baseline measurements of the Netherlands Study of Depression in Older persons (NESDO), a longitudinal multi-site naturalistic cohort study, examining the course and consequences of depression in older people. The NESDO cohort (n=510) consists of persons aged 60-93 years, including 378 persons with a depressive disorder in the previous 6 months, 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. Age-of-onset of depression did not serve as an selection criterion. Non-depressed older persons were recruited from general practices and were included when no lifetime diagnosis of depression was present. Exclusion criteria are (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 current study, we selected all persons with a 6-month DSM-IV diagnosis of major depression, as assessed with the Dutch version of the Composite International Diagnostic Interview (CIDI) lifetime version 2.1 (World Health Organization 1997; Andrews and Peters 1998). The CIDI was conducted by specially trained clinical research staff. Persons with a diagnosis of minor depression (n=13) or dysthymia only (n=6) were excluded. In addition, individuals with incomplete data on CIDI items for depressive disorder were excluded (n=10), thus retaining a data set of 359 persons. Attrition was non-differential with respect to age and gender but, compared to included persons, individuals with missing data had more years of education (OR 1.55; 95% CI 1.06-2.17) and lower severity of depression, as measured by the Inventory of Depression Symptomatology (IDS) (OR 0.21; 95% CI 0.13-0.36).

### Method

#### Assessment of indicator variables for LCA items

Ten depressive symptoms (Table 1) were used as indicator variables in the LCA analyses, including the depression key symptoms of the DSM-IV as assessed with the CIDI (World Health Organization 1997; Andrews and Peters 1998). The items were coded as 'not present' or 'present', except for the four items regarding change in appetite, weight, sleep

and psychomotor disturbance. For these latter items, four categories were created and coded as 'no change', 'decrease', 'increase' or 'both increase and decrease'.

Finally, in order to check the assumption of local independence, required for LCA, we examined the magnitude of bivariate correlation using Spearman's rho. Correlations ranging from <0.001 to 0.29 were found. Since these correlations are only small to moderate, we assume that the assumption of local independence for LCA was sufficiently met.

*Subject characteristics*

Classes were characterized using sociodemographic and clinical characteristics. Sociodemographic variables included age, gender and years of education. Clinical characteristics included age-of-onset of the depressive disorder, presence of a 6-month comorbid anxiety disorder, severity of depressive symptoms as assessed with the 30-item Inventory of Depressive Symptomatology (IDS) (Rush et al., 1996), and apathy as assessed with the Apathy Scale (Starkstein et al., 1992). Psychosocial variables included overall functioning, personality measures, childhood adversity, and life events, all as continuous measurements. Overall functioning was measured with the World Health Organization Disability Assessment Schedule II (WHODAS) (Chwastiak and Von Korff 2003; Buist-Bouwman et al., 2008). Personality measures included levels of neuroticism and extraversion, assessed using the Neo Five-Factor Inventory (NEO-FFI) (Costa and McCrae 1995; Hoekstra et al., 1996). Childhood adversity/trauma was assessed using a structured inventory derived from a Dutch longitudinal cohort study (NEMESIS) (De Graaf 2002). An index (range 0-4) was constructed incorporating the occurrence and frequency of 4 types of abuse before age 16 years (emotional neglect, psychological abuse, physical abuse, and sexual abuse). The number of negative life events in the last year was assessed by the Brugha questionnaire (Brugha 1985). Physical health indicators included current smoking status (current versus not smoking), pain, body mass index (BMI), metabolic syndrome, presence of cardiovascular disease, and ankle brachial pressure index. Pain was measured using the number of pain locations (range 0-7) listed in the Chronic Graded Pain scale (Von Korff 1992). Height and weight were measured and BMI was calculated as kilograms divided by meter squared. In addition, both the presence of metabolic syndrome (yes/no) and its individual components were measured, including waist circumference, plasma triglycerides, plasma high-density lipoprotein cholesterol (HDL-cholesterol), blood pressure and fasting plasma glucose. 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 < 50 mg/dl, systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or use of antihypertensive 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. The presence of cardiovascular disease was determined as assessed by self-report of coronary disease, angina pectoris, heart failure or a history of stroke, supported by appropriate medication use or being currently under treatment by a physician (see Vogelzangs et al., 2010 for details). Ankle brachial pressure index was used as an indicator of possible peripheral vascular disease.

**Statistical analysis**

LCA was performed, using Mplus version 5 (Muthén and Muthén 2007). Free from any a priori assumptions, data-driven techniques such as LCA cluster persons based on a given outcome. LCA, often described as a 'categorical equivalent' of factor analysis, assumes that an unobserved, latent categorical variable explains the association among a set of observed symptoms, like depressive symptoms. Data-driven calculations start with one class, suggesting one classification fitting for all persons. The persons are then successively allocated to an ascending number of classes, here up to 5 classes. To determine the number of classes best fitting the data, we examined the Bayesian Information Criterion (BIC), sample size adjusted BIC (ssaBIC), entropy, the Lo-Mendell-Rubin likelihood ratio test (LMR), the bootstrapped likelihood ratio test (BLRT), the proportion of respondents in each computed class, and the interpretability and clinical relevance of the latent classes.

Of the traditionally used 'information criteria', the BIC performs best (Nylund et al., 2007). Lower BIC and ssaBIC values indicate better model fit. The Lo-Mendell-Rubin test (LMR) provides a p-value, which indicates whether the k-1 class model is rejected in favor of the k class model. Entropy, as a measure of the quality of classification, is presented for models with more than one class. Values for entropy can range from 0 to 1, with values closer to 1 indicating greater classification accuracy. In order to identify clinically relevant classes, we aimed to identify classes greater than 5% of the sample. Currently there is no consensus as to which criterion best identifies the best fitting number of classes, although reasons exist to regard the BLRT as superior compared to other parameters of fit (Nylund et al., 2007).

After identification of the classes and assignment of participants to their most likely class, the probability of occurrence of each depressive symptom per class was examined using Cramer's V as a measurement of a symptom's distinguishing power. Next, the distribution of the aforementioned characteristics across the identified classes was examined, using two-tailed chi-square statistics for categorical variables, one-way-analysis of variance statistics (ANOVA) for continuous variables, and Kruskal-Wallis tests for nonparametric continuous variables. Additional comparisons were performed to test for differences between pairs of classes. Multinomial logistic regression analyses were conducted to examine multivariable determinants of identified classes. All models were first adjusted for sociodemographic items (age, gender, years of education), with additional adjustment for all variables being significantly associated in bivariate analyses. For this purpose, a p-value $<0.10$ was considered statistically significant. All comparisons were conducted using SPSS version 21.0 for Windows (51).

## Results

The total sample consisted of 359 depressed older people, of whom 66.0% were females, with a mean age of 70.5 (± SD 7.4) years and a mean age of depression onset of 48.5 (± SD 20.3) years.

Considering the various parameters of fit (data available upon request), the best-fitting model was the three-class model, with the lowest ssaBIC (4593.2) and a significant BLRT (p<0.001). From the four-class model onwards, the BLRT was no longer significant, indicating that adding more classes to the model did not improve model fit. Although some parameters pointed at a two-class model (highest entropy = 0.87; lowest BIC 4724.1; and a significant LMRT; p=0.001), the superiority of the BLRT has been reported (Nylund et al., 2007). In addition, the two-class model lumped together the moderate and melancholic class and was, therefore, considered clinically less relevant.



**Table 1** shows the probability of the occurrence of different depressive symptoms in the three identified latent classes. The first class (prevalence 15.0%) showed a symptom pattern with the highest occurrence of both weight gain and increased appetite. The second class (prevalence 38.4%) was characterized by the highest occurrence of weight loss, decreased appetite, less sleep, and psychomotor changes. The third class (prevalence 46.5%) had the lowest occurrence of all ten depressive symptoms; hereafter, these classes are labeled "atypical", "melancholic" class, and "moderate severe" class, respectively. Although these labels resemble specific DSM specifiers, we explicitly do not intend to refer to these DSM specifiers. These labels were chosen to facilitate comparisons with previous data-driven studies in younger adults, finding a comparable class that has been dubbed 'atypical' (Lamers et al., 2010; 2013; 2015; Rodgers et al. 2014; Alexandrino et al. 2015). Strong distinguishing symptoms between classes were weight (Cramer's V= 0.59) and appetite (Cramer's V=0.79) and, to a lesser extent, psychomotor changes (Cramer's V=0.26) and loss of interest (Cramer's V=0.25).

**Table 2** shows the sociodemographic and clinical characteristics of the three identified latent classes. Within the severe atypical class, there was a preponderance of females, with a slightly lower mean age compared to both other classes (p=0.002). The moderate class had the lowest depression severity and the lowest number of current anxiety disorders, confirming the lower severity in this class. There were no significant group differences for the psychosocial variables. As for physical health characteristics, metabolic syndrome was most prevalent within the atypical class, and least prevalent within the melancholic class (p=0.003). BMI was significantly higher in the severe atypical class compared to both the severe melancholic and moderate class (p<0.001). Presence of heart disease was significantly lower in the melancholic class compared to both other classes.

To evaluate whether characteristics were independently associated with class membership, multinomial logistic regression analyses were performed, comparing the two severe classes with the moderate class, and the two severe classes with each other (**Table 3**). Analyses were first adjusted for sociodemographic items (gender, age, years of education) and for variables that differed across classes in bivariate analyses with a p-value

=< 0.10, including age-of-onset, depression severity, presence of 1-year anxiety diagnosis, presence of heart disease and BMI. To avoid multicollinearity, metabolic syndrome was not included as this was highly correlated to both BMI (rs=0.52, p<0.001) and cardiovascular disease (rs=0.12, p=0.03). Using post-hoc tests we explored whether the results would differ if BMI and cardiovascular disease were replaced by metabolic syndrome; however, the results were similar. In the fully adjusted models, female sex (OR=4.57; 95% CI=1.96-10.66), lower age (OR=0.57; 95% CI=0.38-0.88), and higher BMI (OR=1.66; 95% CI=1.17-2.36) were significantly associated with the atypical class as compared to the moderate class. Likewise, female sex (OR=2.93; 95% CI=1.22-7.05), lower age (OR=0.63, 95% CI=0.41-0.98), higher BMI (OR=2.38; 95% CI=1.63-3.48) and cardiovascular disease (OR=2.78; 95% CI=1.09-7.09) were significantly associated with the atypical class as compared to the severe melancholic class. On the other hand, higher depression severity (OR=1.33; 95% CI=1.03-1.73), a lower BMI (OR=0.70; 95% CI=0.52-0.93) and a lower number of cardiovascular disease (OR=0.41; 95% CI=0.20-0.83) were significantly associated with melancholic class, as compared to the moderate class.

Since both BMI and metabolic syndrome showed a significant difference between groups, and since atypical depression is thought to be associated with metabolic syndrome (Lamers et al., 2010; Vogelzangs et al., 2011; Mansur et al., 2015), in post-hoc analyses we further explored the association between the separate criteria of metabolic syndrome and class membership (**Table 4**). Multinomial logistic regression analyses were performed to compare both severe classes with the moderate class, and the severe classes with each other. The covariates used were similar to those used in Table 3, except for BMI. The prevalence of metabolic syndrome was significantly higher in the atypical class compared to both the melancholic class (OR=3.12; 95% CI=1.52-6.40) and the moderate class (OR=2.08; 95% CI=1.02-4.22). A higher waist circumference was significantly higher in the atypical class compared to both the melancholic class (OR=1.84; 95% CI=1.27-2.66) and the atypical class (OR=1.44; 95% CI=1.01-2.06). Higher systolic blood pressure (OR=1.44; 95% CI=1.01-2.05) was significantly associated with the atypical class, as compared to the melancholic class. A lower blood glucose was significantly associated with the melancholic class (OR=0.64; 95% CI=0.47-0.86) as compared to the moderate class.

Next, to examine whether weight gain was induced by antidepressant use, instead of being an indicator of a specific depression subtype, we performed post-hoc analyses to explore whether including current antidepressant in the multivariate analyses had any significant effect on the odds ratios. Antidepressants included were selective serotonin-reuptake inhibitors (ATC-code N06AB), non-selective monoamine reuptake inhibitors (ATC-code N06AA), non-selective monoamine oxidase inhibitors (ATC-code N06AF), or other antidepressants (ATC-code N06AX). Prevalence of current antidepressant use was 72.1% in the entire population, 63% in the atypical subtype, 81.9% in the melancholic subtype, and 67.1 in the moderate subtype ($\chi 2$(df)=11.88(4), p=0.02). After additional adjustment of regression analyses for antidepressant use, odds ratios remained largely similar (results available upon request). In contrast to the expectations, that antidepressant use may induce weight gain, and hence would be associated with atypical class, antidepressant use was only significantly associated with melancholic class (OR=2.12; 95%CI 1.18-3.85, as compared to the moderate class; and OR=2.50; 95% CI 1.12-5.60, as compared to atypical

class). Notably, antidepressant use entailed current use, whereas lifetime depression symptoms served as indicator variables for the LCA. Therefore, antidepressant use were only included in post-hoc analyses, and not in the main analyses in this study.

## Discussion

This study aimed to empirically identify distinct depressive subtypes among depressed older persons, and to investigate whether these subtypes differ with respect to sociodemographic and clinical characteristics. The most prevalent class, as identified by LCA, was a moderate severe class (prevalence 46.5%), followed by a severe melancholic class (prevalence 38.4%) and a severe atypical class (prevalence 15.0%). The strongest distinguishing features between the three classes were appetite and weight and, to a lesser extent, psychomotor symptoms and loss of interest. The severe atypical class had the highest prevalence of females, the lowest mean age, the highest BMI and highest prevalence of both cardiovascular disease and metabolic syndrome, as compared to the melancholic class.



Our findings are in line with previous studies. To date, several data-driven studies have been performed and, although the number and symptom patterns of identified classes vary between studies (depending on their design/methods), there is increasing evidence that within the heterogeneity of depressive disorders, atypical and melancholic subtypes may constitute clinically relevant subtypes (Kendler et al., 1996; Sullivan et al., 1998; Alexandrino et al., 2014; Li et al., 2014; Rodgers et al., 2014; Lamers et al., 2015). Although our atypical group does not exactly matches the DSM definition of atypical depression, we found similar symptoms (increased weight and appetite), characteristics (higher prevalence of female, lower mean age, lower age-of-onset) and co-occurring pathophysiology (higher prevalence of metabolic syndrome). Furthermore, previous data-driven studies have found similar classes, labeling them atypical, with similar characteristics (Novick et al. 2005; Lamers et al. 2010; Li et al. 2014; Rodgers et al. 2014; Alexandrino et al. 2014) and biological disturbances(Lamers et al. 2013; Lasserre et al. 2016; Rethorst et al. 2016), that largely correspond with the DSM-based atypical depression. This underlines the idea both approaches distinguish the same atypical subtype.

However, whereas most data-driven studies were performed in younger adult persons, data on older persons are less abundant. To our knowledge, previous data-driven studies in older persons were mainly community based (Lee et al., 2012; Mezuk and Kendler 2012; Hybels et al., 2013). Further, these studies either used appetite and weight change as one aggregated item (Lee et al., 2012), did not distinguish 'increased appetite' (Hybels et al., 2011, 2012; Mezuk and Kendler 2012), did only use 'decreased appetite' and 'weight loss' (Hybels et al., 2009), or used none of these items except for 'decreased appetite' (Hybels et al., 2013). However, not including both increased and decreased appetite and weight may hamper identification of specific subtypes as found in adults, characterized by, e.g., an increase in appetite or weight (e.g. atypical subtype). Our findings extend previous findings by showing that in late-life depression (using disaggregated symptoms) an

atypical and a melancholic subtype can be distinguished, and a relation with metabolic disease was found. This is in line with previous findings in younger adults (Kendler et al., 1996; Sullivan et al., 1998; Lamers et al., 2010; Li et al., 2014).

Considering the distribution of the classes identified with LCA, our prevalence rates seem to differ from previous studies that also investigated disaggregated symptoms in LCA. Studies in younger adults demonstrated a relatively higher prevalence of atypical depression, with rates as high as 24.6% (Lamers et al., 2010, 2012; Rodgers et al., 2013). Since increased appetite and weight gain are prominent differentiating features to identify atypical depressive subtypes (Lamers et al., 2010, 2013; Li et al., 2014), frequently occurring frailty in older persons, being associated with weight loss (and the development of depression) (Andrew and Rockwood 2007; Hegeman et al., 2012; Collard et al., 2014, 2015a, 2015b), may impact on prevalence rates of atypical subtypes in this population. Second, the prevalence of moderate severe depression is about 1.5 times as high in our older sample (46.5%) compared to younger adult studies [prevalence rates: 29.1-34.2% (Lamers et al., 2012a; Rodgers et al., 2014, respectively)]. This is in line with previous findings indicating that depression may become less severe with age, although these latter findings are based on the DSM criteria (Judd et al., 2002; Fiske et al., 2009). Alternatively, depressive symptom endorsement may change across ages, resulting in lower depression severity on instruments validated for use in younger adults and, hence, the risk of underestimating depression severity in older persons. For example, a decline of DSM-IV symptoms (such as guilt and anhedonia) was shown in older persons as compared to younger adults (Caine et al., 1994; meta-analysis Hegeman et al., 2012). Since these items are at the core of commonly used instruments like the Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Depression (HDRS), it is conceivable that this influences measurement of the level of severity in older persons. Finally, late-onset depression may be of a different nature than early-onset depression. Whereas early-onset depression may be characterized by a relatively higher percentage of atypical depression, the pathogenesis and phenomenology of late-onset depression may differ, therefore reducing the proportion of atypical depression within the depressed older population.

Earlier studies found a higher prevalence of psychomotor symptoms in depressed older persons compared to depressed younger persons, but only for agitation (Hegeman et al., 2012), whereas we found a higher prevalence for both retardation alone and co-occurring with agitation. In the present cohort of depressed older persons, psychomotor symptoms were more prevalent than in several younger adult studies, in which the prevalence of psychomotor changes ranged from 46.5-59.6% (Lamers et al., 2010; Rodgers et al., 2014), compared to 27.6% in our study. However, we found that psychomotor symptoms were only moderately distinguishing features between the classes (Cramer's V= 0.26). This is remarkable, since psychomotor symptoms are commonly seen as a feature of melancholic depression (Parker et al., 2010). An explanation for our finding might be that the MADRS and CIDI are unable to reliably measure psychomotor symptoms. Use of a measurement that focuses on psychomotor symptoms of depression, such as the CORE (Parker et al., 1994; Parker 2007; Rhebergen et al., 2011; Attu et al., 2012), may further differentiate depressive subtypes. Notably, apathy differed neither across classes, whereas loss of

interest and psychomotor symptoms were moderately strong distinguishing features between classes. In clinical practice apathy may mimic psychomotor retardation or loss of interest, whereas our results suggest that apathy (as measured with the Apathy Scale) measures different clinical features/phenomena.

In the present study, the differences in characteristics found between our melancholic and atypical classes are in line with other studies (Schotte et al., 1997; Lamers et al., 2010, 2012). Considering the preponderance of females in the atypical subtype, it has been suggested that, especially in women, obesity co-occurs with depression (Luppino et al., 2010; Marijnissen et al., 2011; Milaneschi et al., 2014), which could explain the higher prevalence of females in the atypical class. The lower use of antidepressants in the atypical class compared to both other classes further adds to the idea that increased weight and appetite are part of the symptom profile rather than a result of antidepressant use. In post-hoc analyses we found that additional adjustment for antidepressant use did not alter our findings. However, our database only includes current antidepressant use, while we used lifetime symptoms for the determining the classes. Furthermore, in a study with a naturalistic design like we used, no reliable statement can be made regarding the impact of antidepressant use. Lastly, we used a cross-sectional design, making it impossible to draw causal inferences. Although the lower age within the atypical group is also in accordance with others (Angst et al., 2002; Novick et al., 2005; Halbreich and Kahn. 2007; Lamers et al., 2010), an explanation for this is lacking.

Finally, notable findings are the low prevalence of cardiovascular disease within the melancholic class, and the high prevalence of metabolic syndrome within the atypical class. Studies including younger adults also found a higher prevalence of metabolic syndrome within atypical depression (Lamers et al., 2010, 2013; Vogelzangs et al., 2014), but did not find a higher number of cardiovascular diseases. It is possible that atypical depression, which more often co-occurs with metabolic syndrome at a younger age, constitutes a phenotype with a higher risk of cardiovascular disease at an older age. In younger adults, studies have found that treating components of metabolic syndrome might also benefit depressive symptoms: persons with atypical depression benefit the most from exercise (Rethorst et al. 2016), and addition of the anti-inflammatory drug celecoxib lowers IL-6 rates (Abbasi et al. 2012), which are elevated in atypical depression (Lamers et al. 2013). Our finding stresses the importance of preventive cardiovascular management in persons with atypical depression, as well as studies on the effect of treating metabolic syndrome components and inflammation in depressed older persons.

The results of this study should be interpreted in the context of various strengths and limitations. A strength is that this study is the first to demonstrate depression subtypes, both in severity and symptom profile, in an older population with major depression. In addition, a wide selection of characteristics were examined.

However, some limitations also need to be addressed. The strongest distinguishing symptoms between classes were weight (Cramer's V= 0.59) and appetite (Cramer's V=0.79). One could argue that (in theory) these constructs are highly correlated, as was also the case in a study using factor mixture modelling (an extension of LCA) in a general population

sample (Ten Have et al., 2016); however, the correlation coefficient was small (rs =0.293). Albeit this seems counterintuitive, we hypothesize that, in older persons, these putative correlating items may be less correlated than in younger adults, since weight loss is a common problem and is associated with a broad range of physiological and pathological factors in aging. Also, using weight and appetite as separate items in LCA allows comparison with a large body of literature on adult LCA (Kendler et al., 1996; Sullivan et al., 1998; Lamers et al., 2010; Hybels et al., 2012; Mezuk and Kendler 2012; Rodgers et al., 2013; Alexandrino et al., 2014). However, despite potential issues with violation of the local independence assumption in adult studies, atypical and melancholic subtypes found in these latter studies had differential biology (Mansur et al., 2011; Lamers et al., 2013; Liu et al., 2014; Vogelzangs et al., 2014) and genetic differences (Milaneschi et al., 2016), highlighting the relevance of the distinction by appetite and weight. Further, due to the cross-sectional design of the study, it remains unknown to what extent the identified classes are stable over time. In addition, the lack of a comparison group of persons in the same age cohort without current depression limits thorough examination to what extent current depression state or age may impact on the identified classes, based on lifetime symptoms. However, studies in younger adults demonstrated a high diagnostic stability of LCA-derived subtypes (Lamers et al., 2012b; Rodgers et al., 2013), with especially great stability of the atypical class ranging from 70-79%, thus suggesting etiologically distinct entities. Schaakxs et al. (2017) found stability of depression severity with aging, albeit with different symptom prominence. Symptoms more prominent in older age were early awakening and problems with sleeping during the night, while symptoms occurring more often in younger age were interpersonal sensitivity and sleeping too much. Future longitudinal studies should examine whether classes are stable over time in older adults, too.

In addition, persons with missing data had lower depression severity and a higher education level. Had they not been excluded, they would probably have been allocated to the moderate class; this would have had an impact on the distribution of classes. Regarding education, the attrition presumably does not impact our findings, as there was no significant difference in education across the classes.

To conclude, this study applied data-driven methods to identify classes of depressive disorder in a large cohort of older persons. In line with studies in younger adults, three classes were identified (i.e. an atypical, melancholic and moderate severe depression), with appetite and weight being the main distinguishing features. The increased prevalence of metabolic syndrome within the atypical class, and the decreased prevalence of cardiovascular disease within the melancholic subtype (the latter not previously found in younger adult populations) illustrates the importance of differentiating into depressive subtypes, particularly in the older population. Furthermore, differentiation into depressive subtypes in late-life depression may facilitate further research on the underlying etiology of depression, the role of metabolic abnormalities, and the predictive value of subtypes on treatment response.

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**Conflict of interest**
All authors declare that they have no conflict of interests.

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**Table 1.** Estimated symptom profile probabilities of endorsing depressive symptoms from LCA (n=359)

| Class Description | Total sample | Class 1, Severe atypical | Class 2, Severe melancholic | Class 3, Moderate severity | Cramer V Statistic | P-value(df) |
|---|---|---|---|---|---|---|
| Prevalence | 359 (100%) | 54 (15.0%) | 138 (38.4%) | 167 (46.5%) | | |
| **DSM-IV criterion symptoms** | | | | | | |
| Depressed mood | 0.97 | 0.94 | 1.00 | 0.95 | 0.14 | 0.028(2) |
| Loss of interest | 0.92 | 0.96 | 0.99 | 0.86 | 0.25 | <.001(2) |
| Weight | | | | | 0.59 | <.001(8) |
| No weight change | 0.57 | 0.54 | 0.27 | 0.84 | | |
| Weight loss | 0.34 | 0.00 | 0.71 | 0.14 | | |
| Weight gain | 0.06 | 0.37 | 0.01 | 0.00 | | |
| Both gain and loss | 0.03 | 0.09 | 0.01 | 0.02 | | |
| Appetite | | | | | 0.79 | <.001(8) |
| No change in appetite | 0.30 | 0.04 | 0.02 | 0.61 | | |
| Decreased appetite | 0.53 | 0.00 | 0.92 | 0.38 | | |
| Increased appetite | 0.12 | 0.80 | 0.00 | 0.00 | | |
| Both increase and decrease | 0.05 | 0.17 | 0.06 | 0.01 | | |
| Sleep | | | | | 0.16 | 0.004(8) |
| No change in sleep | 0.10 | 0.09 | 0.04 | 0.14 | | |
| Less sleep | 0.60 | 0.48 | 0.66 | 0.59 | | |
| More sleep | 0.08 | 0.06 | 0.09 | 0.08 | | |
| Both less and more sleep | 0.22 | 0.37 | 0.22 | 0.17 | | |
| Psychomotor | | | | | 0.26 | <.001(8) |
| No psychomotor change | 0.28 | 0.28 | 0.11 | 0.41 | | |
| Psychomotor retardation | 0.30 | 0.24 | 0.33 | 0.30 | | |
| Psychomotor agitation | 0.15 | 0.17 | 0.17 | 0.16 | | |
| Both agitation and retardation | 0.26 | 0.32 | 0.39 | 0.13 | | |
| Fatigue/energy loss | 0.91 | 0.94 | 0.98 | 0.84 | 0.22 | <.001(2) |
| Guilt/worthlessness | 0.79 | 0.85 | 0.87 | 0.71 | 0.19 | 0.002(2) |
| Concentration/ indecisiveness | 0.96 | 1.00 | 0.98 | 0.94 | 0.12 | 0.063(2) |
| Suicidal ideation | 0.69 | 0.70 | 0.79 | 0.59 | 0.20 | 0.001(2) |

**Table 2.** Characteristics of latent classes (n=359)

| | Total sample | Class 1, Severe atypical (n=54) | Class 2, Severe melancholic (n=138) | Class 3, Moderate severity (n=167) | X2, F, (df), overall P-value |
|---|---|---|---|---|---|
| Prevalence | 359 (100%) | 54 (15.0%) | 138 (38.4%) | 167 (46.5%) | |
| **Sociodemographics** | | | | | |
| Sex, female, % | 66.0 | 83.3 | 68.8 | 58.1 | 12.39(2), 0.002[1] |
| Age, mean (SD), years | 70.5(7.4) | 68.3(6.7) | 70.5(7.1) | 71.5(7.7) | 3.95(2), 0.02[2] |
| Education, mean (SD), years | 10.4(3.4) | 11.0(3.7) | 10.1(3.2) | 10.4(3.4) | 1.21(2), 0.30[2] |
| Clinical characteristics | | | | | |
| Age onset, mean (SD) years | 48.5(20.3) | 41.7(20.7) | 49.6(19.1) | 49.9(20.8) | 3.58(2), 0.04[2] |
| Severity (IDS), mean (SD) | 30.5(13.0) | 32.2(11.8) | 32.6(14.2) | 28.0(11.8) | 5.20(2), 0.01[2] |
| Presence 1 year anxiety diagnosis, % | 40.1 | 38.9 | 48.6 | 33.5 | 7.13(2), 0.03[1] |
| Apathy, mean (SD) | 17.2(5.6) | 17.2(5.9) | 17.2(5.7) | 17.3(5.5) | 0.02(2), 0.98[2] |
| **Psychosocial** | | | | | |
| Functioning, mean (SD) | 33.3(15.8) | 34.7(16.4) | 35.0(16.3) | 31.4(15.2) | 2.23(2), 0.12[2] |
| Neuroticism, mean (SD) | 39.0(7.0) | 40.3(7.2) | 38.7(6.7) | 38.8(7.3) | 1.00(2), 0.37[2] |
| Extraversion, mean (SD) | 33.7(6.5) | 34.3(6.9) | 34.2(6.8) | 33.2(6.2) | 0.79(2), 0.46[2] |
| Childhood trauma index, mean (SD) | 1.0(1.2) | 1.2(1.3) | 1.1(1.2) | 0.9(1.2) | 1.75(2), 0.18[2] |
| No. negative life events, median (IQR) | 0.0(1) | 0.0(1) | 1.0(1) | 0.0(1) | 3.94(2), 0.14[3] |
| **Physical health** | | | | | |
| Current smoking, % | 27.0 | 31.5 | 26.5 | 26.5 | 0.64(2), 0.75[1] |
| Chronic pain grade, median (IQR) | 2.00(2) | 2.00(3) | 2.00(2) | 2.00(2) | 4.90(2), 0.09[3] |
| Presence of metabolic syndrome, % | 44.0 | 63.0 | 35.5 | 44.9 | 11.98(2), <0.01[1] |
| Body mass index, median (IQR) | 26.3(4.4) | 27.7 (5.9) | 25.3 (5.65) | 25.3 (5.32) | 23.74(2), <0.01[3] |
| Cardiovascular disease, % | 17.8 | 24.1 | 10.1 | 22.2 | 9.13(2), 0.01[1] |
| Diabetes, % | 12.8 | 11.1 | 9.4 | 13.9 | 1.35(2), 0.48[1] |
| Ankle brachial index, median (IQR) | 1.1(0.2) | 1.1(0.4) | 1.1(0.2) | 1.1(0.2) | 0.37(2), 0.83[3] |

Tests used: [1]Chi-square ($\chi 2$); [2]Anova (F); [3]Kruskal-Wallis ($\chi 2$)

**Table 3.** Odds Ratios and 95% CIs for the Multivariable Comparison of the three Latent Classes (N=359)

| | Comparison of severe classes to moderate class (=reference) | | Severe Atypical vs Severe Melancholic (=ref) OR (95% CI) |
|---|---|---|---|
| | Severe Atypical, OR (95% CI) | Severe Melancholic, OR (95% CI) | |
| **Sociodemographics** | | | |
| Female | 4.55(1.95-10.59) | 1.60(0.94-2.71) | 2.93(1.22-7.05) |
| Age | 0.58(0.38-0.89) | 0.90(0.69-1.19) | 0.65(0.42-1.00) |
| Education in years | 1.38(0.96-2.00) | 1.02(0.79-1.33) | 1.35(0.93-1.97) |
| **Clinical characteristics** | | | |
| Age of onset | 0.81(0.56-1.18) | 1.03(0.78-1.35) | 0.79(0.54-1.16) |
| Presence 1-year anxiety diagnosis | 0.87(0.42-1.82) | 1.47(0.87-2.48) | 0.55(0.26-1.15) |
| Severity | 0.95(0.65-1.40) | 1.33(1.03-1.73) | 0.71(0.48-1.06) |
| Antidepressant use | 1.17(0.49-2.58) | 2.12(1.18-3.85) | 2.50(1.12-5.60) |
| **Physical health** | | | |
| Chronic pain grade | 1.20(0.82-1.76) | 1.10(0.83-1.44) | 1.09(0.74-1.62) |
| Body mass index | 1.67(1.18-2.36) | 0.68(0.51-0.91) | 2.45(1.67-3.59) |
| Cardiovascular disease | 1.13(0.49-2.58) | 0.44(0.21-0.89) | 2.58(1.00-6.64) |

Corrected for every other item in the table: gender, age, years of education, age of onset, presence of 1-year anxiety diagnosis, severity, antidepressant use, chronic pain grade, body mass index, cardiovascular disease. Exp(B) and 95% CI for Exp(B)

**Table 4.** Odds Ratios and 95% CIs for Metabolic Syndrome and the Separate Criteria (N=359)

| | Comparison of severe classes to moderate class (=reference) | | Severe Atypical vs Severe Melancholic (=ref), OR (95% CI) |
|---|---|---|---|
| | Severe Atypical, OR (95% CI) | Severe Melancholic, OR (95% CI) | |
| Metabolic syndrome | 2.08(1.02-4.22) | 0.63(0.38-1.05) | 3.32(1.60-6.88) |
| Waist circumference | 1.44(1.01-2.06) | 0.76(0.57-1.01) | 1.89(1.30-2.76) |
| Triglycerides | 1.08(0.77-1.52) | 1.02(0.79-1.32) | 1.06(0.75-1.49) |
| HDL cholesterol | 0.89(0.62-1.28) | 1.03(0.80-1.33) | 0.85(0.59-1.22) |
| Systolic pressure | 1.24(0.87-1.76) | 0.85(0.66-1.10) | 1.45(1.02-2.08) |
| Diastolic pressure | 1.21(0.84-1.72) | 0.88(0.68-1.14) | 1.37(0.96-1.96) |
| Blood glucose | 0.73(0.50-1.07) | 0.64(0.48-0.87) | 1.14(0.75-1.75) |

Corrected for variables in Table 3 except BMI: gender, age, years of education, age of onset, presence of 1-year anxiety diagnosis, severity, antidepressant use, chronic pain grade and presence of cardiovascular disease