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### **Citation**

Veltman, E. M. (2020, March 3). *Patterns of late-life depression: On the nature of depressive subtypes and the role of aging*. Retrieved from <https://hdl.handle.net/1887/86067>

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**Issue Date:** 2020-03-03

# 3

**CHAPTER 3**

# Inflammatory markers and cortisol parameters across depressive subtypes in an older cohort

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**Background:** There is growing evidence that inflammatory and cortisol dysregulation are underlying pathophysiological mechanisms in the aetiology of major depressive disorder, particularly in younger adults. However, findings of biological disturbances in late-life depression have been divergent, probably due to the even greater heterogeneity of depression in older adults with aging processes influencing biological factors. Using empirically derived subtypes may enable the identification of biological disturbances underlying depression in older adults.

**Methods:** Data were used from the Netherlands Study of Depression in Older Persons (NESDO) of 359 persons aged 60 years or older, with a current diagnosis of major depressive disorder (MDD). Depressive subtypes (severe atypical, severe melancholic, and moderate severe subtype) that were previously identified through latent class analysis (LCA), were examined on differences in inflammatory markers including C-reactive protein (CRP), interleukin-6 (IL-6), and neutrophil gelatinase-associated lipocalin (NGAL), as well as cortisol parameters.

**Results:** No differences in measures for inflammation and cortisol across subtypes were observed in uncorrected or for putative confounders corrected models.

**Limitations:** Several subjects had missing cortisol and inflammatory data, decreasing the power. However, results did not change after imputation analysis.

**Discussion:** In this cohort of depressed older adults, no differences in inflammation and cortisol measures between depression subtypes were observed. This is probably due to the many (patho) physiological processes that are involved in aging, thereby clouding the results.

**Key words:** latent class analysis; depression subtypes; inflammation; cortisol; atypical depression; melancholic depression

## Background

Major depressive disorder is a common disease, with prevalence rates in the older population ranging from 1-16% (Djernes 2006). However, the aetiology and pathogenesis of major depressive disorder remain largely unknown. Studies have suggested that possible underlying biological mechanisms include disturbances in inflammation pathways and the hypothalamic-pituitary-adrenal (HPA)-axis, which could predict course and treatment response (Berk et al., 2013; Miller et al., 2015; Martinez et al., 2016; Zalli et al., 2016). However, to date findings are inconsistent.

Regarding inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6), studies in older depressed adults have found mainly higher inflammatory markers in depressed persons compared to healthy controls (Biggelaar et al., 2007; Bremmer et al., 2008; Martinez et al., 2016). A meta-analysis concluded that of several inflammation markers, only IL-6 had a consistent positive correlation with late-life depression (Martinez et al., 2016). Findings on cortisol measures in older depressed persons are inconsistent too, with some studies finding higher cortisol measures (Balardin et al., 2011; Kuo et al., 2011; Belvederi Murri et al., 2014; Rhebergen et al., 2015), whereas others reported a U-shaped association between cortisol and depression in older adults (Bremmer et al., 2007; Penninx et al., 2007).

There are indications that these inconsistent findings might be due to the considerable heterogeneity of depression in older adults, stressing the importance of subtyping depression when researching underlying pathophysiological mechanisms. Within younger adults, inflammatory and cortisol dysregulations have been linked to specific subtypes of depression (Gold and Chrousos 2002; Stetler and Miller 2011; Lamers et al., 2013; Penninx et al., 2013). A melancholic subtype, identified by data-driven techniques, was linked to higher cortisol measures compared to other subtypes and healthy controls. An atypical subtype, characterized by increased appetite and weight, was linked to increased inflammatory markers (Lamers et al., 2013), and seemed to have a differential genetic profile (Milaneschi et al., 2016). Within older people, there are indications as well that the degree and quality of biological dysregulation may be correlated with both the severity of depression (Viinamäki et al., 2009; Duivis et al., 2011; Kahl et al., 2012) and depression characteristics (Vogelzangs et al., 2014). Data-driven subtypes of depression in older adults have been identified previously (Hybels et al., 2009; Lee et al., 2012; Mezuk & Kendler 2012; Veltman et al., 2017), but research on biological disturbances within these subtypes is lacking.

Therefore, to gain more insight into the role of immunometabolism and functioning of the HPA-axis within depressed older adults, we examined inflammatory markers and cortisol parameters within different subtypes of depression, as determined previously in this cohort of older people by latent class analysis (LCA) (Veltman et al., 2017). We hypothesized that inflammatory markers are higher in the atypical subtype compared to the other subtypes, and that cortisol parameters are higher in the melancholic subtype of depression.

## 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 predictors of 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. The study protocol of NESDO has been approved centrally by the Ethical Review Board of the VU University Medical Center, and subsequently by the local ethical review boards of all participating universities. Written informed consent was obtained from all participants at the start of the baseline assessment. 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 (n=359), as assessed with the Dutch version of the Composite International Diagnostic Interview (CIDI) lifetime version 2.1 (World Health Organization 1997; Andrews & Peters 1998). The CIDI was conducted by trained clinical research staff. None of the participants used corticosteroids. Seventy-seven persons had missing data on all cortisol measures and were excluded from the cortisol analyses. Ten persons had missing data on all inflammatory markers and were excluded from the inflammation analyses. Four persons had missing values on all inflammatory markers and cortisol measures, and were excluded from all analyses, thus retaining a final study population of 355 persons on baseline characteristics, 349 persons on inflammatory markers, and 282 persons on cortisol measures. Attrition was non-differential with respect to sex, age, education level, severity of depression, and subtype of depression.

### Depressive subtypes

The subtypes previously identified in this cohort by LCA were used. For a detailed description we refer to Veltman et al., (2017). In short, ten depressive symptoms 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 & Peters 1998). Three subtypes were identified: a severe atypical subtype (prevalence 15.0%), characterized by increased appetite and weight; a severe melancholic subtype (prevalence 38.4%), characterized by decreased appetite and weight; and a moderate severe subtype (prevalence 46.5%), characterized by lower symptom severity on all items. The subtypes are labelled "severe atypical", "severe melancholic", and "moderate severe" subtype, respectively. Although these labels resemble specific DSM specifiers, we do not intend to refer to these DSM specifiers. These labels were chosen to facilitate comparisons with previous studies (e.g. Lamers et al., 2013).

## Biological measures

### *Inflammatory measures*

Inflammatory markers included C-reactive protein (CRP), interleukin-6 (IL-6), and neutrophil gelatinase-associated lipocalin (NGAL). Fasting blood samples were obtained in the morning between 8 and 9 am after an overnight fast and kept frozen at  $-80^{\circ}\text{C}$ . High-sensitivity plasma levels of CRP were measured in duplicate by an immunoturbidimetric assay (Tina-quant CRPHS, Roche Diagnostics, Mannheim, Germany). Plasma IL-6 levels were measured in duplicate by a high sensitivity ELISA (PeliKine Compact™ ELISA, Sanquin, Amsterdam, The Netherlands). Intra- and inter-assay coefficients of variation were 2% and 2% for CRP, and 8% and 12% for IL-6, respectively. Plasma NGAL levels, an inflammatory marker earlier associated with late-life depression (Naudé et al., 2013) were quantified via a constructed sandwich ELISA, with the absorbance being determined at 492nm and 620nm using an ELISA reader (Asys UVM 340, Biochrom, Cambridge, UK). The inter- and intra-assay coefficients of variation were 2% and 5%, respectively. For a detailed explanation we refer to Naudé et al., (2013). Persons with a CRP value above ten ( $N=33$ ) were excluded, as this indicates a current inflammatory process as part of a somatic disease, which may interfere with a putative biological mechanism associated with a certain depressive subtype.

### *Cortisol*

Respondents were instructed to collect saliva samples at home on two consecutive days shortly after the interview at baseline. Instructions concerning saliva sampling prohibited eating, drinking tea or coffee or brushing teeth within 15 minutes before sampling. Furthermore, no dental work 24 hours prior to sampling was allowed. Saliva samples were obtained using Salivettes (Sarstedt, Germany) at six time points; at the time of awakening (T1), 30 minutes post-awakening (T2), 45 minutes post-awakening (T3), 60 minutes post-awakening (T4) and at 22:00 h (T5). The salivettes were restored in the tube labeled with date and time. After collecting all samples, the persons were asked to return the samples by post to the research center. After receipt, salivettes were centrifuged at 2000 g for ten minutes, aliquoted and stored at  $-80^{\circ}\text{C}$ . Cortisol analysis was performed by competitive electrochemiluminescence immunoassay (E170 Roche, Switzerland). The functional detection limit was 2.5 nmol/l and the intra- and inter-assay variability coefficients in the measuring range were less than 10%. A random selection of 22 assays were repeated if cortisol measures were high ( $> 60$  nmol/L); 19 high values remained high after reassessment and the mean of the values was used. Three high values became lower after reassessment and were reassessed for a second time. All three remained low and the mean of the two low values was used.

### *Cortisol awakening response*

From the four saliva samples taken within 1 h after awakening (T1 to T4), we calculated the area under the curve with respect to the increase (AUC<sub>i</sub>) and with respect to the ground (AUC<sub>g</sub>) using Pruessner's formulas (Pruessner et al., 2003). The AUC<sub>g</sub> is an estimate of the total cortisol secretion over the first hour after awakening, whereas the AUC<sub>i</sub> is a measure of the dynamics of the cortisol awakening response (CAR), more related to the sensitivity of the system, emphasizing changes over time after awakening (Edwards et al.,



2001; Fekedulegn et al., 2007; Schmidt-Reinwald et al., 1999). AUC<sub>i</sub> and AUC<sub>g</sub> could be calculated for all persons for whom all four morning samples were available (n=335). For those with 1 missing morning cortisol value (n=53) the missing value was imputed using linear regression analyses including information on the available three cortisol measures, sex, age, awakening time, and smoking status (see also Vreeburg et al., 2009a; Rhebergen et al., 2015). After imputation, AUCs could be calculated for 267 persons.

#### *Diurnal slope*

Diurnal slope was calculated by subtraction of the evening sample (T5) from the sample at awakening (T1) resulting in the decline in cortisol levels during the day. Due to missing samples at T1 or T5, diurnal slope could be calculated for 400 persons.

#### **Covariates and descriptive variables**

Subtypes 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 1-year comorbid anxiety disorder, both assessed by the CIDI, and severity of depressive symptoms as assessed with the 30-item Inventory of Depressive Symptomatology (IDS) (Rush et al., 1996). Cognitive functioning was measured with the Mini Mental State Examination (MMSE) (Folstein et al., 1975).

Physical health indicators included smoking status; pain using the number of pain locations (range 0-7) listed in the Chronic Graded Pain scale (Von Korff 1992); presence of metabolic syndrome as assessed according to the adjusted Adult Treatment Panel (ATP III) criteria (Expert panel, 2001); body mass index (BMI); presence of cardiovascular disease as assessed by self-report of coronary disease, angina pectoris, heart failure or a history of stroke, and supported by appropriate medication use or being currently under treatment by a physician; and the use of non-steroidal anti-inflammatory drugs (NSAIDs) (ATC-code N02BA01), non-selective monoamine reuptake inhibitors (N06AA), selective serotonin reuptake inhibitors (N06AB), non-selective monoamine oxidase inhibitors (N06AF), monoamine oxidase A inhibitors (N06AG), or other antidepressants (N06AX). Daily alcohol use was measured with the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993). Number of chronic diseases was measured by using the LASA Questionnaire (Kriegsman et al., 1996). Previous literature demonstrates that a great variety of characteristics may act as putative confounders in the association between biomarkers and depression subtypes. However, in our previous studies (Veltman et al., 2017; Rhebergen et al., 2015), we examined the association of a wide variety of psychosocial characteristics with depression subtypes and putative confounders of HPA-axis functioning, respectively, in the NESDO-cohort. Characteristics that previously did not cause the estimate for subtypes or cortisol measures in regression analyses to change more than 10% were not considered as putative confounders in the current paper.

### Statistical analysis

All analyses were performed in SPSS, version 21.0. First, levels of inflammatory markers and cortisol parameters were compared across groups using analyses of variance. In case of non-normal distributions, biological measures were natural log-transformed. If non-normality prevailed despite transformation, Kruskal-Wallis tests were performed.

Next, multinomial regression analyses were conducted, with depression subtypes as outcome. Analyses were adjusted for putative confounders, determined through adding all putative confounders separately to the model. Putative confounders were added to the final model if they caused the estimate for subtypes in regression analyses to change more than 10%. Despite not reaching the 10% threshold, severity was added as a putative confounder too, in line with earlier research that found biology measures and severity of depression to be correlated (Vreeburg et al., 2009b; Knorr et al., 2010; Lamers et al., 2013; Rhebergen et al., 2015).

### Results

**Table 1** shows the sociodemographic and clinical characteristics of the different subtypes of depression, with differences in distribution of sex, age, depression severity and onset, and comorbid anxiety. In addition, metabolic syndrome and BMI were higher in atypical depression, whereas the presence of heart disease was lower in the melancholic subtype.

Inflammatory markers and cortisol parameters across depression subtypes did not differ significantly in univariate analyses (**Table 1**). In addition, in the and fully adjusted regression models, no significant associations were found between inflammatory markers or cortisol parameters and depression subtypes (see **table 2**). Post-hoc we explored whether results would differ if we included cases with a CRP level >10, but no subtype differences were found with this approach either. Since we had a considerable number of missing values, we did post-hoc analyses on an imputed data set, exploring whether the lack of significance could be explained by missingness. Multiple imputation was used for missingness on both inflammation (CRP, NGAL, IL-6) and cortisol (AUC<sub>G</sub>, AUC<sub>I</sub>, diurnal slope), using all covariates and variables as used in the regression models, generating five data sets. However, this did not give different results (data available upon request).

## Discussion

This study aimed to examine differences in inflammatory markers and cortisol parameters in empirically derived subtypes of depression in older adults. Bivariate and multivariate analyses did not yield differences between atypical, melancholic and moderate severe forms of depression, neither for inflammatory markers nor cortisol parameters.

Although several studies have examined inflammation parameters and cortisol measures in the older depressed population before (Belvederi Murri et al., 2014; Martinez et al., 2016), this has not been done using data-driven subtypes. In younger adults these parameters have been examined within subtypes before. The results of our study differ from several studies done in younger adults, demonstrating a correlation between subtypes of depression and both inflammatory markers (Rothermundt et al., 2001; Lamers et al., 2013) and cortisol parameters (Nelson and Davis 1997; Gold and Chrousos 2002; Stetler and Miller 2011; Lamers et al., 2013). Studies on biological parameters and depression subtypes in older persons are scant. One study found an overall immunometabolic downregulation in older depressed persons, except for DSM-defined atypical depression (Vogelzangs et al., 2014). Another study found that late-life depression is correlated with NGAL, but only in patients with visceral obesity (Marijnissen et al., 2014), or in patients with recurring MDD (Naudé et al., 2013). Within our study, the atypical subtype is characterised by a higher mean BMI, but no significant correlation between this subtype and NGAL was found, nor an overall immunometabolic downregulation in our melancholic and moderately severe subtypes. Hence, the scarce previous findings could not be replicated. Next, a meta-analysis found a positive correlation between cortisol measures and late-life depression, especially morning cortisol, but again effects were small, and information on cortisol levels in depression subtypes was lacking (Belvederi Murri et al., 2014). In contrast with our hypothesis, we could not demonstrate an association between cortisol levels and depression subtypes, but due to the lack of studies in older adults on depression subtypes and cortisol, comparisons with other studies are hampered.

Since depression is believed to be a heterogeneous disorder, with different pathophysiological processes leading to different symptom complexes, we expected that subtyping late-life depression would give more consistent results, similar to findings in younger adults (Lamers et al., 2013). However, while depression subtypes in older adults mimic subtypes in younger adults (Hybels et al., 2011; Veltman et al., 2017), our study failed to show a similar, consistent correlation between depressive subtypes and biological measurements. These findings suggest that the pathogenesis of depression in older adults may be more difficult to disentangle than that of depression in younger adults. Possibly both (patho)physiological processes involved in aging and/or the presence of somatic comorbidities and corresponding medication use may impact on biomarkers, and, hence, blur any association between depression subtypes and inflammatory and cortisol measures. Insight into depression in the older population is of paramount importance in order to improve diagnosis, treatment, and prediction of prognosis. However, we think that the current biological parameters, being involved in a vast array of processes in both aging and disease, are not specific enough and therefore insufficient to demonstrate the pathophysiological processes underlying depression in older age.

### Limitations

A limitation of this study is the missing data of cortisol measures for several subjects, and to a lesser extent inflammatory measures, decreasing the cohort size and thereby the power. However, results did not become significant after imputation analysis either (data available upon request). Another limitation is the lack of information regarding the duration of the current depressive episode.

### Conclusion

To conclude, this study is the first to examine putative underlying pathophysiological mechanisms of previously identified, data-driven subtypes of depression, in a large cohort of older adults. No significant differences in inflammation markers and cortisol parameters across subtypes were observed. To date, studies on biological disturbances in depressed older adults consistently report inconsistent results, suggesting that the currently used biological parameters may be involved in both aging and disease processes, muddling insight in the pathogenesis of late-life depression.

### Funding/acknowledgment:

FL has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement No. PCIG12-GA-2012-334065.

The infrastructure for the NESDO study (<http://nesdo.amstad.nl>) is funded through the Fonds NutsOhra (project 0701-065), Stichting tot Steun VCVGZ, NARSAD The Brain and Behaviour Research Fund (grant ID 41080), and the participating universities and mental health care organizations (VU University Medical Center, Leiden University Medical Center, University Medical Center Groningen, UMC St Radboud, and GGZ inGeest, GG Net, GGZ Nijmegen and Parnassia).

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**Table 1.** Characteristics of stable subgroups (n=359)

	Total sample	Group 1, Severe atypical	Group 2, Severe melancholic	Group 3, Moderate severity	Overall P-value(df)
Prevalence	359 (100%)	54 (15.0%)	138 (38.4%)	167 (46.5%)	
<b>Sociodemographics</b>					
Sex, female, %	66.0	83.3	68.8	58.1	0.002(2)
Age, mean (SD), years	70.5(7.4)	68.3(6.7)	70.5(7.1)	71.5(7.7)	0.02(2)
Education, mean (SD), years	10.4(3.4)	11.0(3.7)	10.1(3.2)	10.4(3.4)	0.30(2)
<b>Clinical characteristics</b>					
Age onset, mean (SD) years	48.5(20.3)	41.7(20.7)	49.6(19.1)	49.9(20.8)	0.04(2)
Presence 1 year anxiety diagnosis, %	40.1	38.9	48.6	33.5	0.03(2)
Severity (IDS), mean (SD)	30.5(13.0)	32.2(11.8)	32.6(14.2)	28.0(11.8)	0.01(2)
MMSE score, median (IQR)	28.0(2)	28.0(2)	28.0(3)	28.0(2)	0.16(2)
<b>Physical health</b>					
Current smoking, %	27.0	31.5	26.5	26.5	0.75(2)
Chronic pain grade, median (IQR)	2.00(2)	2.00(3)	2.00(2)	2.00(2)	0.09(2)
Metabolic syndrome, %	44.0	63.0	35.5	44.9	0.003(2)
Body mass index, median (IQR)	26.3(4.4)	27.7(5.9)	25.3(5.7)	25.3(5.3)	<0.001(2)
Cardiovascular disease, %	17.8	24.1	10.1	22.2	0.01(2)
NSAID use, %	23.7	29.6	18.1	26.3	0.24(2)
Antidepressant use, %	72.1	63.0	81.9	67.1	0.02(2)
Alcohol # daily, median (IQR)	0.06(1.2)	0.03(1.2)	0.03(0.5)	0.15(1.2)	0.26(2)
# chronic diseases, mean (SD)	2.12(1.5)	2.44(1.5)	2.06(1.5)	2.07(1.4)	0.21(2)
<b>Inflammation markers</b>					
NGAL, mean (SD) <sup>a</sup>	63.8(29.5)	57.5(20.6)	66.7(37.4)	63.6(24.0)	0.59(2)
IL-6, median (IQR) <sup>b</sup>	0.52(1.48)	0.65(1.80)	0.47(1.32)	0.52(1.7)	0.63(2)
CRP, mean(SD)	2.3(1.9)	2.7(2.1)	2.1(1.8)	2.3(1.9)	0.18(2)
<b>Cortisol parameters</b>					
AUCg, mean (SD) <sup>a</sup>	20.0(9.8)	21.2(10.6)	20.4(9.8)	19.3(9.5)	0.49(2)
AUCi, median (IQR) <sup>b</sup>	-0.2(8.3)	-0.1(11.8)	0.6(8.8)	-0.2(8.3)	0.94(2)
Diurnal slope T5/ T1, mean (SD) <sup>a</sup>	13.6(11.0)	14.9(10.4)	13.8(12.0)	13.0(10.5)	0.56(2)

<sup>a</sup> Normal distribution was reached after natural log transformation. Untransformed means are presented.

<sup>b</sup> Despite transformation, no normal distribution was reached



**Table 2.** Odds Ratios and 95% CIs for inflammation markers (n=351) and cortisol parameters (n=294) across subtypes of depression in older adults

	Comparison of severe subtypes to moderate subtype (=reference)		Severe Atypical vs Severe Melancholic (=ref), OR (95% CI)
	Severe Atypical, OR (95% CI)	Severe Melancholic, OR (95% CI)	
NGAL <sup>a</sup>	0.83(0.58-1.20)	0.92(0.72-1.18)	0.83(0.58-1.20)
IL-6 <sup>a</sup>	1.06(0.80-1.42)	1.02(0.79-1.33)	1.04(0.80-1.34)
CRP <sup>a</sup>	1.17(0.85-1.62)	0.91(0.70-1.20)	1.29(0.92-1.80)
AUCg <sup>b</sup>	1.24(0.84-1.84)	1.13(0.85-1.51)	1.10(0.73-1.64)
AUCi <sup>b</sup>	0.88(0.60-1.31)	0.91(0.68-1.21)	0.97(0.65-1.46)
Diurnal slope <sup>b</sup>	1.30(0.92-2.08)	1.14(0.87-1.51)	1.21(0.80-1.83)

<sup>a</sup>Adjusted for gender, age, severity, use of antidepressants.

<sup>b</sup>Adjusted for gender, age, severity, smoking, amount of daylight, use of salicylic acid derivative.