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Depression profilers and immuno-metabolic dysregulation: Longitudinal results from the NESDA study

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ABSTRACT

Background: Major depressive disorder (MDD) is linked to higher cardio-metabolic comorbidity that may in part be due to the low-grade inflammation and poorer metabolic health observed in MDD. Heterogeneity of MDD is however large, and immune-inflammatory and metabolic dysregulation is present in only part of the MDD cases. We examined the associations of four depression dimensional profilers (atypical energy-related symptom dimension, melancholic symptom dimension, childhood trauma severity, and anxious distress symptom dimension) with immuno-metabolic outcomes, both cross-sectionally and longitudinally.

Methods: Three waves covering a 6-year follow-up (> 7000 observations) of the Netherlands Study of Depression and Anxiety (NESDA) were used. Depression profilers were based on the Inventory of Depressive Symptomatology, the Beck Anxiety Inventory, and the Childhood Trauma index. An inflammatory index (based on IL-6 and CRP), a metabolic syndrome index (based on the five metabolic syndrome components), and a combination of these two indices were constructed. Mixed models were used for cross-sectional and longitudinal models, controlling for covariates.

Results: Of the four depression profilers, only the atypical, energy-related symptom dimension showed robust associations with higher scores on the inflammatory, metabolic syndrome and combined inflammatory-metabolic indexes cross-sectionally, as well as at follow-up. The melancholic symptom dimension was associated with lower scores on the metabolic syndrome index both cross-sectionally and longitudinally.

Conclusion: The atypical energy-related symptom dimension was linked to poorer immune-inflammatory and metabolic health, while the melancholic symptom dimension was linked to relatively better metabolic health. Persons with high atypical energy-related symptom burden, representing an immuno-metabolic depression, may be the most important group to target in prevention programs for cardiometabolic disease, and may benefit most from treatments targeting immuno-metabolic pathways.

1. Introduction

Major depressive disorder (MDD) is one of the leading causes of disability in today's society (GBD Disease and Injury Incidence and Prevalence Collaborators, 2018, 2017; Vos et al., 2016), both in developed and developing countries. A relatively early age of onset and the often chronic course of depression contribute to this high disability. Besides disability arising from depression, patients also have an increased risk of developing somatic comorbidities such as diabetes mellitus, stroke, hypertension, and cardiovascular disease, adding to their burden of disease and increasing mortality risk (Otte et al., 2016). Understanding the mechanisms underlying this comorbidity is important to reduce the disease burden of depression and its comorbidities, via prevention and early interventions.

Poorer lifestyle (e.g. smoking, alcohol use, unhealthy diet, physical inactivity) in depressed patients is a likely contributing factor to the increased somatic comorbidity in depression. Yet, in studies controlling for differences in lifestyle an independent effect of depression is still observed, indicating that lifestyle factors do not fully explain the association between depression and somatic disease (Penninx, 2017).

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Another explanation lies in the pathophysiology of depression. For instance, metabolic and immune-inflammatory dysregulations observed in depression constitute risk factors for diabetes and cardiovascular disease as well (Milaneschi et al., 2020; Otte et al., 2016). These dysregulations include increased levels of inflammatory markers indicating low-grade inflammation, higher rates of metabolic syndrome and obesity, insulin and leptin resistance, and more dyslipidemia. However, meta-analyses on these dysregulations show relatively small effect sizes and high statistical heterogeneity (Cao et al., 2018; Howren et al., 2009; Jung et al., 2017; Kan et al., 2013; Köhler et al., 2017; Milaneschi et al., 2020; Pan et al., 2012; Vancampfort et al., 2014). Several reasons could be causing these. Small pooled effect sizes could simply reflect the fact that depression is a multifactorial disorder, with small contributions of a large number of aspecific (peripheral) markers or processes that are altered in many other non-communicable diseases as well, but could also be the result of large heterogeneity in effect size across studies. Statistical heterogeneity could arise from differences in the design of and measurements used in studies, but could reflect differences in the samples studied as well, including those caused by the clinical heterogeneity of MDD itself.

Not all persons with depression present with immune or metabolic dysregulations. There is increasing evidence that only certain subgroups of patients exhibit these (Osimo et al., 2019). Several studies have for instance shown that persons presenting with atypical symptom profiles are more likely to have immune-inflammatory and metabolic dysregulation (Glaus et al., 2014, 2013; Hickman et al., 2014; Lamers et al., 2016b, 2013); this association seems particularly driven by the symptoms reflecting altered energy intake/expenditure balance: increased appetite and other energy-related symptoms such as weight gain, hypersomnia, fatigue and leaden paralysis (Alshehri et al., 2019; Lamers et al., 2018; Milaneschi et al., 2015; Simmons et al., 2018). The clustering of these atypical, energy-related symptoms gives rise to a dimensional symptom profile that our group labeled “immuno-metabolic depression” (IMD) (Lamers et al., 2019, 2018; Milaneschi et al., 2020) which we hypothesize is specifically linked to immune-metabolic dysregulation. But other depression characteristics and forms have also been reported to be linked to immune-inflammatory or metabolic dysregulation. For example, melancholic forms of depression have also been linked in a few studies, but not in all, to increased levels of inflammatory markers compared to controls or to non-melancholic depression (Yang et al., 2018). Depression with co-morbid anxiety disorder or with substantial anxiety features (as for instance defined by the DSM-5 anxious distress specifier) has also been found to be associated with increased innate cytokine production capacity, although not with basal levels of inflammatory markers, (Gaspersz et al., 2017) and higher monocyte count (Shim et al., 2016). Anxiety disorders themselves and anxiety symptoms too have been linked to metabolic syndrome (Hiles et al., 2016; Tang et al., 2017). Moreover, a meta-analysis on childhood trauma showed that persons with childhood trauma had higher levels of inflammatory markers than persons without childhood trauma (Baumeister et al., 2015), and there is mounting evidence that adversity early in life is linked to poorer cardiometabolic health outcomes (Suglia et al., 2018). As childhood trauma is often present in depression, high childhood trauma levels could constitute another depression characteristic that is linked to immuno-metabolic dysregulations.

There are some limitations to the existing literature on dimensions or subtypes of depression and immune-inflammatory and metabolic dysregulation. First, only a limited number of studies are available, and makes that meta-analyses can only draw tentative conclusions (Yang et al., 2018). Second, most of these studies are cross-sectional; longitudinal studies evaluating depression subtypes and immune-inflammatory (Glaus et al., 2018) or metabolic dysregulation (Lasserre et al., 2016, 2014; Polanka et al., 2017) that can shed light on temporal associations are scarce. Third, studies often limit themselves to a single dimension or subtype of depression, collapsing everyone not belonging to that particular subtype in the comparison case group. As a result, this comparison group is an umbrella for several other subtypes, which hampers comparison to studies evaluating different dimensions or subtypes. Evaluation of various depression characteristics simultaneously could help prioritize those types that seem most important in the associations with inflammation and metabolic dysregulations. The fourth issue with depression dimensions and subtype research is that is still very much leans on the binary approach of classification in a research era where the importance of dimensional thinking (e.g. RDoc) is growing(Insel et al., 2010). The knowledge that binary depression subtypes are often overlapping, as shown in various studies (Arnow et al., 2015; Glaus et al., 2018) and share a large part of their genetic liability (Milaneschi et al., 2017), calls for the use of dimensional profilers for various subtypes rather than using binary groups. As patients can of course score high on multiple dimensional profilers, and as childhood trauma could lead to specific symptom profiles, it is important to examine correlations between profilers.

The aim of the current study was to evaluate cross-sectional and longitudinal associations between four depression dimensional profilers (atypical, energy-related symptom dimension; melancholic dimension; childhood trauma index; and anxious distress dimension) with measures of inflammatory and metabolic dysregulations, using three waves of data from the Netherlands Study of Depression and Anxiety (NESDA). Analyses were done in the entire sample as well as in the subset of current depression cases and correlations between profilers were examined.

2. Methods

2.1. Sample

NESDA is a longitudinal cohort study on the course and consequences of depression (Penninx et al., 2008). At baseline n = 2981 persons with and without depressive (MDD or dysthymia) or anxiety (general anxiety disorder, panic disorder, agoraphobia, social phobia) disorders (confirmed by the Composite International Diagnostic Interview (CIDI, version 2.1)) were included from the community, primary care, and secondary care settings between 2003 and 2007. Exclusion criteria were: not speaking Dutch or having a severe psychiatric disorder. The assessment included a diagnostic interview to assess the presence of depressive and anxiety disorders, a medical exam, and several questionnaires on symptom severity, other clinical characteristics and lifestyle. For the current study, we used the baseline data, 2 and 6-year follow-up in which inflammatory markers were assessed. All participants signed informed consent and the study was approved by the Medical Ethics Committee of the participating universities.

For the current study, we selected the following persons. For cross-sectional analyses, we selected per wave, all participants who had valid values on all four dimensional profilers and at least one of the outcomes available. For longitudinal analyses, participants needed to have all four dimensional profilers at baseline and at least one outcome available at follow-up. This resulted in 2882 participants being included from baseline, n = 2241 from the 2-year follow-up and n = 1955 from the 6-year follow-up, leading to a total of 7078 observations.

3. Depression assessment and depression subtypes

Major depressive episodes were assessed with the Composite International Diagnostic Interview (CIDI, version 2.1) (Wittchen, 1994), conducted by trained research staff. Current depression was defined by the presence of a DSM-IV MDD diagnosis in the past six months.

Four dimensional depression profilers were created. Density plots for each profiler are presented in Fig. 1 as well as the items used in each profiler. For the atypical, energy-related symptom dimension and melancholic symptom dimension, a sum score was made based on items from the 30-item self-report version of the Inventory of Depressive Symptomatology (IDS) (Rush et al., 1996). For the atypical, energy-

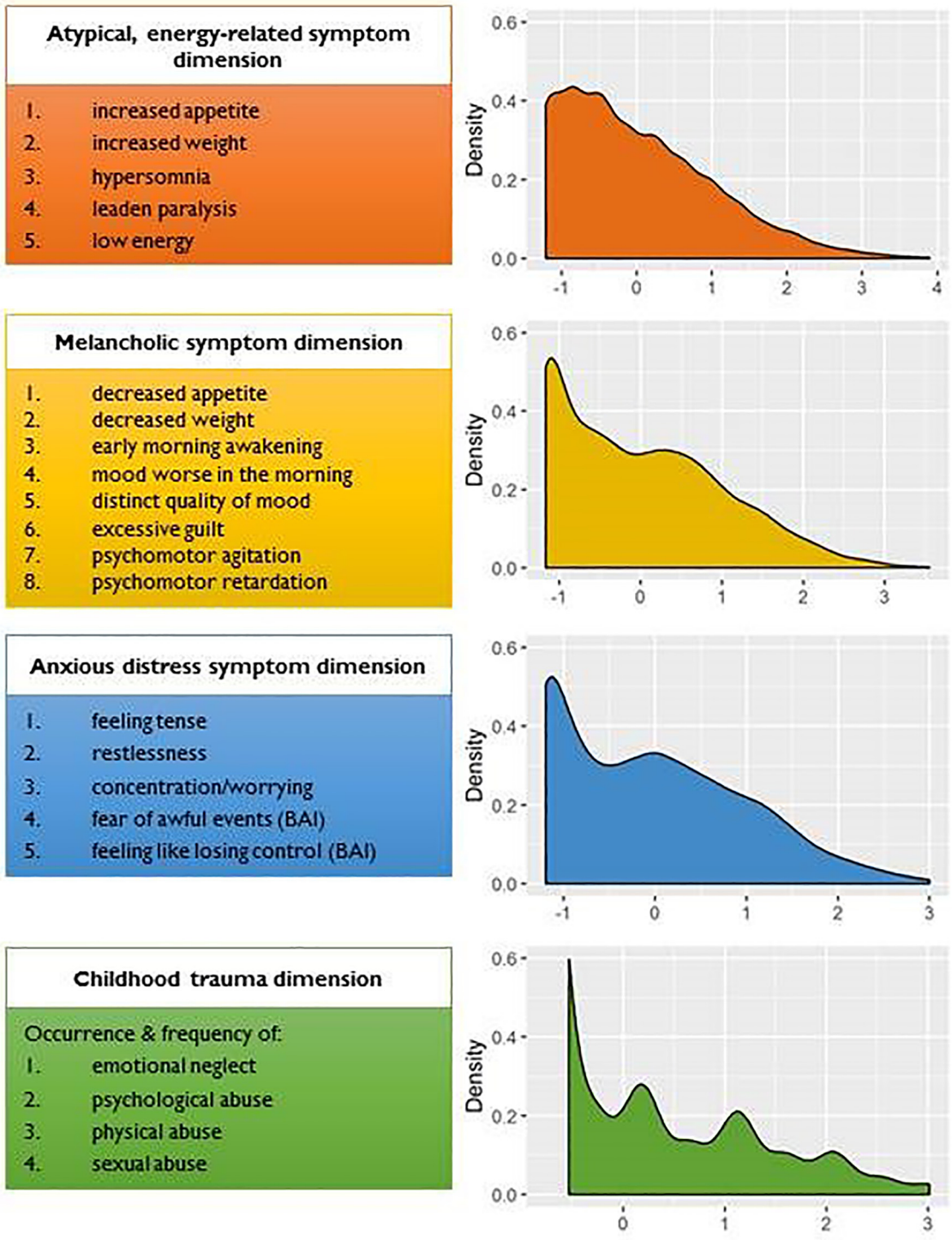

Fig. 1. Overview of dimensional profilers and density plots of standardized profilers at baseline.

related symptom dimension, we summed the 5 items we consider as belonging to the immuno-metabolic depression (IMD) domain, based on previous findings on individual symptoms with immuno-metabolic dysregulation (Milaneschi et al., 2020). It included the following items: increased appetite, increased weight, hypersomnia, leaden paralysis and low energy, and ranges from 0 to 15. For melancholic features, we summed all 8 melancholic features in the IDS (Khan et al., 2006) being: diurnal variation (mood worse in the morning), early morning awakening, distinct quality of mood, excessive guilt, decreased appetite, decreased weight, psychomotor agitation and psychomotor retardation. This led to a score ranging from 0 to 24.

An anxious distress specifier (ADS) dimension was constructed using three items from the IDS and two items of the Beck Anxiety Inventory (BAI) (Beck et al., 1988) that matched with the five criteria for the DSM-5 anxious distress specifier (see also (Gaspersz et al., 2016)). The sum of these 5 items (IDS items feeling tense, restlessness, concentration/worrying, and BAI items fear of awful events, feeling like losing control) resulted in a score ranging from 0 to 15. The presence of childhood trauma was determined using the Childhood trauma index (CTI) (De Graaf et al., 2002) that incorporates the occurrence and

frequency of four types of abuse before age 16 (emotional neglect, psychological abuse, physical abuse, and sexual abuse) on a scale from 0 to 8. While we realize that CT is a risk factor more so than a true dimensional symptom score, as this has found to be linked to immune-metabolic measures, we did include this profiler as well. For the sake of readability we use the term dimensional profiler here as well. All four dimensional depression profilers were standardized.

4. Inflammatory and metabolic markers

Inflammatory markers were determined from fasting morning blood plasma at baseline, 2 and 6-year follow-up. Plasma levels of CRP at baseline were measured in duplicate by an in-house high-sensitivity enzyme-linked immunosorbent assay (ELISA) based on purified protein and polyclonal anti-CRP antibodies (Dako, Glostrup, Denmark). The lower detection limit of CRP is 0.1 mg/L and the sensitivity is 0.05 mg/L. Intra- and inter-assay coefficients of variation were 5% and 10%, respectively. Plasma levels of CRP in the follow-up waves were measured in duplicate by a high-sensitivity particle enhanced immunoturbidimetric assay (CRPHS, Roche Diagnostics, Indianapolis, IN, USA). The lower detection limit of CRP in this kit is 0.15 mg/L and the sensitivity is 0.3 mg/L. Intra- and inter-assay coefficients of variation were as follows. Intra-assay: 2-yr FU 5%; 6-yr FU 7%; Inter-assay 2-yr FU 4%; 6-yr FU 9%. Plasma IL-6 levels at baseline were measured in duplicate by a high-sensitivity ELISA (PeliKine CompactTM ELISA, Sanquin, Amsterdam, the Netherlands). The lower detection limit of IL-6 is 0.35 pg/ml and the sensitivity is 0.10 pg/ml. Intra- and inter-assay coefficients of variation were 8% and 12%, respectively. At the 2- and 6-year follow-up, IL-6 was measured in duplicate by a high-sensitivity solid-phase ELISA (Human IL-6 Quantikine HS kit, R&D Systems, Minneapolis, MN, USA). The lower detection limit of IL-6 in this kit is 0.08 pg/ml and the sensitivity range is 0.016–0.110 pg/ml. Intra- and inter-assay coefficients of variation were 7.8% and 7.2%, respectively.

As part of the medical examination, all indicators for metabolic syndrome were assessed including fasting glucose, HDL cholesterol, triglycerides, blood pressure and waist circumference at each wave. Waist circumference was measured with a measuring tape at the central point between the lowest front rib and the highest front point of the pelvis on light clothing. HDL cholesterol, triglycerides, and glucose were determined using routine standardized laboratory methods. Blood pressure was measured twice during supine rest on the right arm with the Omron M4-I, HEM 752A, and was averaged over the two measurements. Continuous measures of HDL-cholesterol, triglycerides, glucose and blood pressure were adjusted for medication as previously described (Grundy et al., 2005; Licht et al., 2010). For HDL-cholesterol 0.10 mmol/l was subtracted for use of fibrates (C10AB) and 0.15 mmol/l was subtracted for use of nicotinic acid (C10AD, C10BA01); for triglycerides 0.67 mmol/l was added for use of fibrates and 0.19 mmol/l was added for use of nicotinic acid use. For glucose, a value of 7.0 mmol/liter (126 mg/dl) was assigned for persons using anti-diabetic medication and having glucose levels less than 7.0 mmol/liter. For systolic blood pressure, 10 mm Hg was added for persons using anti-hypertensive medication.

As outcome measures in the current study, we constructed three indices 1) an inflammation index, 2) a metabolic index and 3) a combined inflammatory-metabolic index. The inflammation index was based on CRP and IL-6 measures that were first log_e transformed, then standardized, and the mean of the two was used as inflammation index. Persons with CRP $>$ 10 mg/L, indicative of acute infection or an active autoimmune disorder, were excluded from the index. For the metabolic index, triglycerides were log_e transformed and then all metabolic syndrome components were standardized. Because low rather than high values of HDL are a risk factor, HDL scores were reversed after standardization. For blood pressure, only systolic blood pressure was included. A mean of the five standardized variables was used as metabolic index. Lastly, the combined index was made by taking the sum of the inflammatory and metabolic indices. Similar indices have been used before for inflammation and metabolic syndrome (Gaspersz et al., 2017; Vogelzangs et al., 2016).

5. Covariates

Sociodemographic variables were sex, age and years of education at baseline. Other covariates were assessed at all waves and included current smoking (yes/no), number of alcoholic drinks per week as assessed with the AUDIT (Babor et al., 1989), and number of chronic diseases for which a person received treatment based on a self-report list of 20 common chronic diseases (including: asthma, chronic bronchitis or pulmonary emphysema, heart diseases or infarct, diabetes, stroke or CVA, arthritis or arthrosis, rheumatic complaints, tumor or malignant tumor, high blood pressure, stomach or intestinal ulcer, intestinal diseases, liver disease or cirrhosis, epilepsy, and thyroid gland disease). Medication use was assessed by drug container inspection of drugs used in the past month. All medication was coded according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification. We made a variable for use of anti-inflammatory medication (ATC codes: M01A, M01B, A07EB, A07EC, No/Yes), drugs used in diabetes (ATC code A10) and a variable for statins (ATC codes: C10AA, C10B, No/Yes). Body mass index (BMI, weight in kg divided by height in m^2), was added to the model of the inflammation index only in a second step. The reason for this is that BMI may be part of the underlying mechanism explaining associations between depression characteristics and immuno-metabolic measures (Horn et al., 2018). From this perspective, BMI would be a mediator and not a confounder. The reason for not correcting for BMI in the models of metabolic syndrome and combined index is that BMI is highly correlated with waist circumference, which was part of the metabolic and combined index. As in a previous report on this dataset, antidepressants did not impact on the results in sensitivity analyses (Lamers et al., 2019), we did not include them here.

6. Statistical analyses

We first described characteristics per wave using descriptive statistics and calculated Pearson's correlation between baseline profilers, and between the baseline inflammatory and metabolic syndrome indices. To evaluate the cross-sectional associations between depression characteristics and the outcomes, we combined the three data waves in one single analysis, thus using all available data to maximize the dataset for analysis. We used linear mixed models with wave as a repeated effect, patient ID as within-subject effect and using an unstructured correlation matrix. Models were corrected for wave and all (wave-specific) covariates, except for BMI. BMI was added in a second model but only for the inflammation index outcome. We analyzed each profiler in a separate model and subsequently ran a multivariable model with all four profilers. Analyses were repeated in a subset of current MDD cases.

Longitudinal models to evaluate associations of baseline depression profilers on indices at 2 and 6-year were also run with linear mixed models with wave as a repeated effect, patient ID as within-subject effect and using an unstructured correlation matrix. Time-by-subtype interactions were tested, and if not statistically significant, removed from the longitudinal models. All baseline covariates were included, except for BMI that was only added in a second step to the inflammation index models. Again, in a subset of current MDD cases only, we also modeled all four predictors simultaneously in one model. All analyses were conducted in SPSS (version 24, IBM) and using $p < 0.05$.

7. Results

Sample characteristics across the three waves are reported in Table 1. At baseline, the mean age was 41.9 years (SD 13.1) and 66.4%

Table 1
Sample characteristics across three waves.

	Baseline n = 2882	2-yr follow-up n = 2241	6-yr follow-up n = 1955
Demographics (Baseline)			
Age, mean (SD)	41.9 (13.1)	42.4 (13.2)	42.4 (13.1)
Female, N (%)	1914 (66.4)	1461 (65.2)	1280 (65.5)
Years education, Mean (SD)	12.2 (3.3)	12.3 (3.3)	12.5 (3.2)
Health & lifestyle			
Current smoker, N (%)	1098 (38.1)	694 (31.0)	535 (27.4)
BMI, mean (SD)*	25.6 (4.9)	25.8 (4.9)	26.1 (5.0)
No of disease under treatment, median (IQR)*	0 (0–1)	0 (0–1)	0 (0–1)
No of Alcoholic drinks/wk, median (IQR)*	3.7 (0.2–8.7)	3.7 (0.2–8.7)	3.7 (0.2–8.2)
Anti-inflammatory med use, N (%)	129 (4.5)	123 (5.5)	99 (5.1)
Statin use, N (%)	196 (6.8)	171 (7.6)	201 (10.3)
Diabetic drug use, N (%)	92 (3.2)	92 (4.1)	87 (4.5)
Clinical characteristics			
Current MDD, n (%)	1067 (37.0)	497 (22.2)	308 (15.8)
Current Anxiety disorder, n (%)	1254 (43.5)	614 (27.4)	375 (19.2)
Depression dimensional profilers			
Atypical, energy-related symptom dimension, median (IQR)	3 (1–5)	2 (1–4)	2 (1–4)
Melancholic symptom dimension, median (IQR)	4 (1–7)	2 (0–5)	2 (0–4)
Childhood trauma index dimension, median (IQR)	0 (0–3)	0 (0–3)	0 (0–2)
Anxious distress symptom dimension, median (IQR)	4 (1–6)	2 (0–4)	1 (0–4)

MDD major depressive disorder; IM immuno-metabolic; SD standard deviation; IQR interquartile range.
*Missings imputed with within-person mean or Wave mean.

was female. At baseline, 37% of the sample had a current depression, which decreased in the 2 and 6-year waves to 22.2% and 15.8%, respectively (Table 1). Correlations at baseline between the four profilers and between the outcomes are presented in Fig. 2 and ranged from 0.26 to 0.73 between the dimensional profilers and from 0.35 to 0.85 between the outcome indices.

7.1. Cross-sectional associations

When combining and analyzing the three waves simultaneously on the cross-sectional associations between depression profilers and immuno-metabolic indices (n = 2875, $n_{observations}$ = 7078), both in the univariable and multivariable models, the atypical, energy-related symptom dimension was associated with higher values of the outcomes (multivariable $B(se)_{inflammation\ index} = 0.067\ (0.011)$, $B(se)_{MetSyn\ index} = 0.062\ (0.006)$, $B(se)_{combined\ index} = 0.121(0.014)$, all p-values < 0.0001, Table 2). The melancholic symptom dimension was negatively associated with the metabolic syndrome index both in the univariable and multivariable models (multivariable B(se) = −0.031 (0.007), p = < 0.0001). In the multivariable model, the anxious distress symptom dimension, in addition, showed a negative association with the inflammation index (B(se) = −0.031 (0.013), p = 0.02). There were no significant interactions between the profilers and wave, except for the melancholic symptom dimension in the metabolic syndrome index model, indicating differences in the association across waves. Examination of the results revealed that the negative estimate for the association between the melancholic symptom dimension and the metabolic syndrome index was strongest in the baseline wave, with estimates becoming smaller in the follow-up waves (not tabulated).

In the analyses of the subset of current MDD cases, the pattern of results remained comparable albeit with slightly higher estimates than in analyses of the entire sample. In the univariable model, the childhood trauma dimension showed a significant association with the inflammatory index (B(se) = 0.037 (0.018), p = 0.046), which was no longer statistically significant in the multivariable model (p = 0.06) although it should be noted that the estimate did not change much. No significant interactions between profilers and wave were observed, indicating that associations were consistent across waves.

When additionally adjusting the models for the inflammation index outcome with BMI, the atypical, energy-related symptom dimension remained statistically significant in the entire sample but with a much smaller effect estimate (multivariable model B(se) = 0.024 (0.010), p = 0.02), which was no longer associated in the MDD subset (data not shown).

7.2. Longitudinal associations

Longitudinal analyses evaluating the association between baseline depression characteristic and inflammation and metabolic indices at follow-up revealed that again, the atypical, energy-related symptom dimension was significantly associated with the three outcomes at follow-up in both univariable and multivariable models (multivariable $B(se)_{inflammation\ index} = 0.091\ (0.017)$, $B(se)_{MetSyn\ index} = 0.095\ (0.014)$, $B(se)_{combined\ index} = 0.185\ (0.026)$, all p-values < 0.0001, Table 3). The melancholic symptom dimension, in addition, was negatively

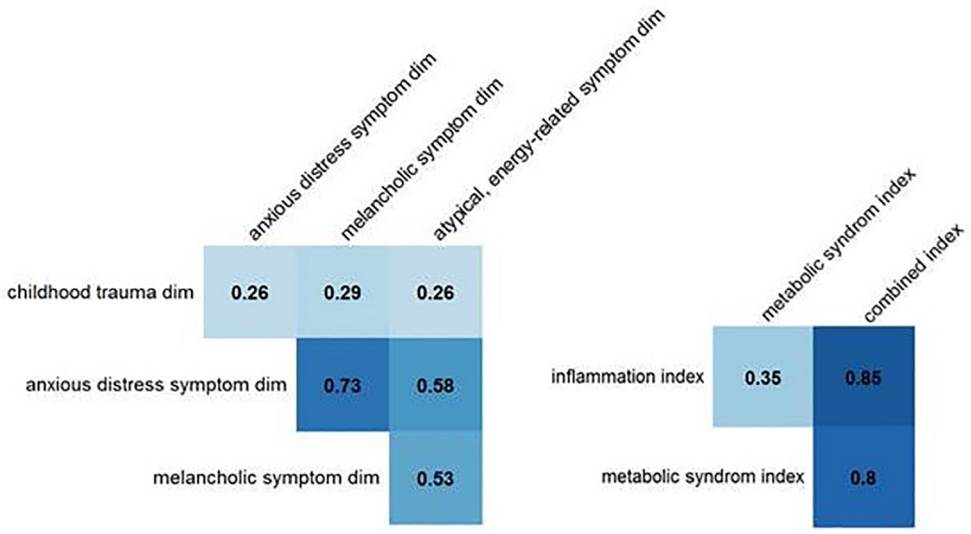

Fig. 2. Pearson correlations between dimensional profilers and between indices at baseline.

Table 2
Cross-sectional association between depression profilers and inflammatory and metabolic indices over three waves in entire sample and in current MDD cases only (n = 2875, $n_{observations}$ = 7078).

	Inflammation index		Metabolic Syndrome index		Combined inflammatory & metabolic syndrome Index	
ENTIRE SAMPLE *Univariable*	B (se)	p-value	B (se)	p-value	B (se)	p-value
Atypical, energy-related symptom dimension	0.051 (0.009)	< **0.0001**	0.050 (0.005)	< **0.0001**	0.097 (0.012)	< **0.0001**
Melancholic symptom dimension	−0.002 (0.009)	0.87	−0.014 (0.005)	**0.009**	−0.015 (0.012)	0.24
Childhood trauma index dimension	0.020 (0.012)	0.095	0.016 (0.009)	0.09	0.034 (0.018)	0.052
Anxious distress symptom dimension	−0.004 (0.010)	0.64	0.000 (0.006)	0.97	−0.001 (0.013)	0.92
Multivariable						
Atypical, energy-related symptom dimension	0.067 (0.011)	< **0.0001**	0.062 (0.006)	< **0.0001**	0.121 (0.014)	< **0.0001**
Melancholic symptom dimension	−0.010 (0.013)	0.44	−0.031 (0.007)	< **0.0001**	−0.043 (0.016)	**0.008**
Childhood trauma index dimension	0.014 (0.012)	0.24	0.011 (0.009)	0.23	−0.025 (0.018)	0.17
Anxious distress symptom dimension	−0.031 (0.013)	**0.02**	−0.006 (0.007)	0.40	−0.029 (0.017)	0.10
CURRENT MDD CASES ONLY *Univariable*	B (se)	p-value	B (se)	p-value	B (se)	p-value
Atypical, energy-related symptom dimension	0.070 (0.017)	< **0.0001**	0.079 (0.011)	< **0.0001**	0.137 (0.025)	< **0.0001**
Melancholic symptom dimension	0.002 (0.018)	0.89	−0.017 (0.012)	0.14	−0.008 (0.024)	0.73
Childhood trauma index dimension	0.037 (0.018)	**0.046**	0.012 (0.013)	0.36	0.034 (0.018)	0.052
Anxious distress symptom dimension	−0.008 (0.018)	0.66	0.002 (0.012)	0.88	0.006 (0.025)	0.81
Multivariable						
Atypical, energy-related symptom dimension	0.079 (0.018)	< **0.0001**	0.088 (0.012)	< **0.0001**	0.150 (0.025)	< **0.0001**
Melancholic symptom dimension	−0.001 (0.022)	0.98	−0.035 (0.014)	**0.012**	−0.034 (0.030)	0.25
Childhood trauma index dimension	0.034 (0.018)	0.06	0.010 (0.013)	0.46	0.044 (0.027)	0.095
Anxious distress symptom dimension	−0.039 (0.023)	0.09	−0.008 (0.015)	0.60	−0.029 (0.031)	0.35

Dimensional profilers are standardized. Model adjusted for Wave, age, sex and years of education, number of chronic diseases under treatment, anti-inflammatory medication use, statin use, antidiabetic drug use, smoking status, and alcohol intake. SE standard error; CI confidence interval.

associated with the metabolic syndrome index (multivariable B (se) = −0.057 (0.016), p = 0.001). Childhood trauma and ASD dimensions were not associated with the indices at follow-up (p > 0.05). No significant time by profiler interactions were observed, except for the melancholic symptom dimension in the model of the metabolic syndrome index, where persons with higher values of the profiler showed a larger increase over time in metabolic syndrome index score between 2 and 6-year follow-up than persons with lower scores on the melancholic symptom dimension.

In the MDD case analyses, a similar pattern of results was yet again found with the atypical, energy-related symptom dimension being associated with the outcomes (multivariable $B(se)_{inflammation\ index}$ = 0.110 (0.025), $B(se)_{MetSyn\ index}$ = 0.099 (0.020), $B(se)_{combined\ index}$ = 0.204 (0.037), all p-values < 0.0001). None of the other profilers was associated with the indices at follow-up (all p-values > 0.05). No significant profiler by time interactions were observed indicating that

Table 3
Longitudinal associations between baseline profilers and inflammation and metabolic index at follow-up.

	Inflammation index at FU		Metabolic Syndrome index at FU		Combined inflammatory & metabolic syndrome Index at FU	
ENTIRE SAMPLE *Univariable*	B (se)	p-value	B (se)	p-value	B (se)	p-value
Atypical, energy-related symptom dimension	0.076 (0.014)	< **0.0001**	0.063 (0.011)	< **0.0001**	0.144 (0.021)	< **0.0001**
Melancholic symptom dimension	0.025 (0.014)	0.07	−0.013 (0.011)	0.25	0.023 (0.021)	0.29
Childhood trauma index dimension	0.019 (0.014)	0.18	0.011 (0.011)	0.34	0.032 (0.021)	0.13
Anxious distress symptom dimension	0.024 (0.014)	0.099	0.006 (0.012)	0.63	0.037 (0.022)	0.09
Multivariable	B (se)	p-value	B (se)	p-value	B (se)	p-value
Atypical, energy-related symptom dimension	0.091 (0.017)	< **0.0001**	0.095 (0.014)	< **0.0001**	0.185 (0.026)	< **0.0001**
Melancholic symptom dimension	−0.003 (0.021)	0.87	−0.057 (0.016)	**0.001**	−0.051 (0.031)	0.10
Childhood trauma index dimension	0.005 (0.014)	0.71	0.007 (0.012)	0.56	0.013 (0.022)	0.55
Anxious distress symptom dimension	−0.026 (0.022)	0.22	−0.008 (0.017)	0.66	−0.032 (0.033)	0.33
CURRENT MDD CASES ONLY *Univariable*	B (se)	p-value	B (se)	p-value	B (se)	p-value
Atypical, energy-related symptom dimension	0.108 (0.023)	< **0.0001**	0.098 (0.018)	< **0.0001**	0.207 (0.035)	< **0.0001**
Melancholic symptom dimension	0.017 (0.025)	0.49	0.002 (0.020)	0.90	0.031 (0.038)	0.42
Childhood trauma index dimension	0.027 (0.021)	0.20	0.026 (0.017)	0.13	0.058 (0.032)	0.07
Anxious distress symptom dimension	0.036 (0.026)	0.16	0.038 (0.020)	0.07	0.089 (0.039)	**0.02**
Multivariable	B (se)	p-value	B (se)	p-value	B (se)	p-value
Atypical, energy-related symptom dimension	0.110 (0.025)	< **0.0001**	0.099 (0.020)	< **0.0001**	0.204 (0.037)	< **0.0001**
Melancholic symptom dimension	−0.018 (0.030)	0.55	−0.039 (0.024)	0.11	−0.053 (0.046)	0.25
Childhood trauma index dimension	0.023 (0.021)	0.28	0.022 (0.017)	0.19	0.049 (0.032)	0.12
Anxious distress symptom dimension	0.002 (0.032)	0.96	0.020 (0.026)	0.44	0.037 (0.049)	0.45

Dimensional profilers are standardized. Time by profiler interaction not significant and therefore omitted from models. Model adjusted for time, age, sex and years of education, number of chronic diseases under treatment, anti-inflammatory medication use, statin use, antidiabetic drug use, smoking status, and alcohol.

changes in outcomes between 2 and 6-year follow-up did not differ for different values of the profiler.

Correction of the inflammation index models for BMI at baseline reduced the effect estimates of the atypical, energy-related symptom dimension in the entire sample and in MDD cases, but both remained statistically significant (multivariable $B(se)_{entire\ sample}$0.035 (0.017), p = 0.03; $B(se)_{MDD\ cases}$ = 0.048 (0.024), p = 0.046).

8. Discussion

Using three waves of the NESDA study containing 2875 individuals and over 7000 observations, and evaluating multiple dimensional depression profilers simultaneously, we found a consistent pattern of the atypical, energy-related symptom dimension being associated both cross-sectionally with higher levels of the immuno-metabolic indices, as well as longitudinally with higher values of the indices at follow-up, indicating more inflammatory and metabolic dysregulations being present in persons with a higher atypical, energy-related symptom burden. In contrast, the melancholic symptom dimension was associated with lower values on the metabolic syndrome index in both cross-sectional and longitudinal analyses, and with lower values of the combined index in cross-sectional analyses, indicative of less metabolic dysregulations in those with more melancholic features.

The present findings confirm previous results of us and other groups showing that immuno-metabolic dysregulations map more consistently to “atypical” behavioral symptoms reflecting altered energy intake/expenditure balance such as increased appetite, weight gain, hypersomnia, fatigue, and leaden paralysis (Glaus et al., 2014; Hickman et al., 2014; Lamers et al., 2018, 2013; Simmons et al., 2018). Moreover, the longitudinal findings that atypical, energy-related symptoms are associated with higher levels of the indices at follow-up are in line with other longitudinal studies, findings that depression with atypical features was associated with higher BMI over time (Lamers et al., 2016a), a steeper increase over time in waist circumference and fasting glucose and higher incidence of metabolic syndrome (Lasserre et al., 2016), a higher incidence of obesity (Lasserre et al., 2014; Polanka et al., 2017). This symptom dimension may therefore indeed reflect an immuno-metabolic form of depression, that is at increased risk of developing co-morbid cardiovascular and metabolic disease over time.

For the melancholic symptom dimension, we found some indication of relatively less biological dysregulation, as indicated by negative associations with the metabolic and combined index in multivariable models of the entire sample. It has been previously observed that melancholic forms of depression are associated with a lower BMI and lower prevalence of metabolic syndrome (Lamers et al., 2010; Seppala et al., 2011; Silva et al., 2020). A previous meta-analysis on melancholic depression did not find conclusive evidence of a link to increased inflammatory markers, although the number of studies available was limited (Yang et al., 2018), and this study adds to this evidence. Thus, melancholic forms of depression – while linked to higher cortisol levels (Lamers et al., 2013; Stetler and Miller, 2011)– may not be linked to inflammatory and metabolic dysregulations. This may be counter-intuitive, as long-term elevation of glucocorticoids has been demonstrated to impact glucose and lipid metabolism. But our findings do not stand on their own: a large population-based cohort study previously only showed an increased incidence of metabolic syndrome and increases in glucose and waist circumference over time in atypical, but not in melancholic depression (Lasserre et al., 2016). In a study of late-life depression, melancholic depression was likewise associated with lower glucose levels as compared to non-depressed cases (Vogelzangs et al., 2014b). In line with this, in NESDA we earlier did not find any significant association between higher cortisol levels and inflammatory variables (Black et al., 2017). A possible explanation for these negative findings could be that other factors present in melancholic depression may counter the effects of increased cortisol on metabolic processes, for instance a lower appetite observed in melancholic cases may lead to lower energy (e.g., fat and carbohydrate) intake, subsequently lowering blood lipids and glucose. Another factor could be that HPA-axis dysregulation may normalize after a patient reaches remission, thus reducing somewhat the risk of lasting changes in lipid and glucose metabolism. Furthermore, interaction between these stress systems could also be hampered after prolonged dysregulation of one of the them. Previous results from NESDA indeed showed that strong intercorrelations between the autonomic nervous system and metabolic syndrome indicators but no significant association between these systems with HPA-axis functioning (Licht et al., 2010).

Childhood trauma was previously found to be associated with higher inflammatory markers in a meta-analysis (Baumeister et al., 2015), and it is believed to be linked to many cardiometabolic outcomes (Suglia et al., 2018). Several small studies on childhood trauma in depression found IL-6 levels to be correlated with childhood trauma scores within cases, and higher IL-6 in MDD with childhood trauma versus controls (de Punder et al., 2018; Grosse et al., 2016; Müller et al., 2019; Munjiza et al., 2018; Pedrotti Moreira et al., 2018). In contrast, in the current study, the childhood trauma index was not linked to any of the outcomes. This could perhaps be explained by a relatively low number of persons with high scores on the childhood trauma index in the current study. We also did not observe strong associations between the anxious distress profiler and the outcomes, despite the fact that anxiety features are linked to poorer immuno-metabolic health as well (Hiles et al., 2016; Tang et al., 2017). It is however in line with our previous baseline findings that the anxious distress specifier dimensional score was not associated with basal levels of inflammation (Gaspersz et al., 2017). It should be noted that persons under treatment for PSTD were not included in the NESDA study, although a PSTD assessment at 4-year follow-up showed that the 5-year prevalence was 6.7% (Spinhoven et al., 2014b). As PTSD may develop after childhood trauma, the exclusion of PTSD cases at baseline in the sample could partially explain the lack of findings for childhood trauma.

When evaluating dimensions or subtypes of depression, stability of such dimensions or subtypes over time is a pre-requisite for being meaningful. We previously showed that symptom profiles tend to be fairly stable over time in this dataset, with on average 76% of depressed cases staying in the same symptom cluster after 2 years (Lamers et al., 2012), which is in line with other studies finding neurovegetative symptoms to be relatively stable(Nierenberg et al., 1996; Stunkard et al., 1990). As for childhood trauma, it was previously demonstrated within NESDA that that CTI scores showed adequate concordance with the Childhood trauma questionnaire collected four years after the baseline assessment (Spinhoven et al., 2014a).

Immuno-metabolic depression (IMD) is characterized by the clustering clustering of immuno-metabolic biological dysregulations and with atypical, behavioral symptoms reflecting altered energy intake/expenditure balance (increased appetite and other energy-related symptoms such as weight gain, hypersomnia, fatigue and leaden paralysis). It is is a new concept based on a decade of research into the heterogeneity of depression of our group and others; we recently explicated a full model of IMD in a review (Milaneschi et al., 2020). Being a novel concept, the validity of it needs to be further elucidated. The robust patterns of associations between atypical, energy-related symtpoms and poorer immuno-metabolic health however, is in line with the IMD model and adds evidence for the validity of the concept and IMD model, even though effect sizes may be small. Replication in independent datasets is needed, also including other implied metabolic markers, such as leptin, to help fully characterize IMD-linked immuno-metabolic dysregulation. Current longitudinal findings nevertheless imply that those with more atypical, energy-related symptoms linked to IMD are most at risk of developing cardio-metabolic disease. Persons with high atypical, energy related symptom burden could therefore benefit more than those with high melancholic symptom burden from programs aiming to prevent the onset of such somatic co-morbidity, such as weight loss, healthy eating, or exercise programs. Second,

treatment targeting immuno-metabolic pathways, such as anti-inflammatory medications, may be more beneficial to patients with higher atypical, energy-related symptom burden. Future treatment trials should enrich their samples with cases scoring high on these symptoms to evaluate the role of these symptoms in predicting treatment success, and thus inform personalized medicine initiatives. While elevated inflammatory markers have been linked to treatment resistant depression (Strawbridge et al., 2015; Vogelzangs et al., 2014a), it is yet to be investigated if atypical, energy-related depression symptoms play a major role in treatment-resistant depression. Controlled clinical trials assessing inflammatory markers are needed to establish such association.

This study had some limitations. Different kits for IL-6 and CRP were used for the baseline assays compared to the follow-up waves. Strengths of the study include the large and well-phenotyped sample making it possible to look at multiple profilers simultaneously. Potential bias introduced by loss-to-follow-up was handled by using linear mixed models which can account for missing data.

To conclude, this study found that atypical, energy-related symptoms of depression that are likely part of immuno-metabolic depression (IMD), were both cross-sectionally and longitudinally associated with poorer inflammatory and metabolic health, implying that this group is at highest risk of developing cardio-metabolic comorbidities over time. As none of the other profiles showed such robust patterns, this indicates that persons with high atypical, energy-related symptom burden may be the most important group to target in prevention programs for cardio-metabolic disease, and may benefit most from treatments targeting immuno-metabolic pathways. Future studies are needed to replicate findings and to study these symptoms as predictor of treatment response.

Declaration of Competing Interest

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