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Research paper

Sociodemographic, lifestyle and clinical characteristics of energy-related depression symptoms: A pooled analysis of 13,965 depressed cases in 8 Dutch cohorts

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ABSTRACT

Background: In a substantial subgroup of depressed patients, atypical, energy-related depression symptoms (e.g. increased appetite/weight, hypersomnia, loss of energy) tend to cluster with immuno-metabolic dysregulations (e.g. increased BMI and inflammatory markers). This clustering is proposed to reflect a more homogeneous depression pathology. This study examines to what extent energy-related symptoms are associated and share sociodemographic, lifestyle and clinical characteristics.

Methods: Data were available from 13,965 participants from eight Dutch cohorts with DSM-5 lifetime major depression assessed by the Lifetime Depression Assessment Self-report (LIDAS) questionnaire. Information on four energy-related depression symptoms were extracted: energy loss, increased appetite, increased weight, and hypersomnia. Tetrachoric correlations between these symptoms, and associations of these symptoms with sociodemographic (sex, age, education), lifestyle (physical activity, BMI, smoking) and clinical characteristics (age of onset, episode duration, history, treatment and recency, and self-reported comorbidity) were computed.

Results: Correlations between energy-related symptoms were overall higher than those with other depression symptoms and varied from 0.90 (increased appetite vs increased weight) to 0.11 (increased appetite vs energy

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loss). All energy-related symptoms were strongly associated with higher BMI and a more severe clinical profile. Patients with increased appetite were more often smokers, and only patients with increased appetite or weight more often had a self-reported diagnosis of PTSD (OR = 1.17, p = 2.91E-08) and eating disorder (OR = 1.40, p = 4.08E-17).

Conclusions: The symptom-specific associations may have consequences for a profile integrating these symptoms, which can be used to reflect immuno-metabolic depression. They indicate the need to study immuno-metabolic depression at individual symptom resolution as a starting point.

1. Introduction

Depression is a highly heterogeneous disease with very diverse symptom profiles and many contributing biological mechanisms (Penninx et al., 2013). Around two-thirds of patients benefit from current depression treatments, which are mostly based on a one size fits all approach (Gaynes et al., 2009). Success rates of depression treatment are therefore likely to be improved by a personalized care approach: identifying clinically meaningful subgroups of patients with more homogeneous depression pathology to tailor treatment accordingly (Trivedi, 2016).

Accumulating evidence over the past decade shows that a subgroup of depressed patients exhibits a combination of immune-inflammatory and metabolic dysregulations (e.g. dysregulated levels of leptin, insulin, and other metabolic and inflammatory markers) and particular symptoms that belong to the DSM atypical specifier (reviewed in Milaneschi et al., 2020). The atypical depression subtype is defined in the DSM by the presence of mood reactivity plus two or more of the following symptoms: hypersomnia, increased appetite/weight, leaden paralysis and interpersonal rejection sensitivity. Dysregulated immuno-metabolic markers have not been generically related to all symptoms belonging to the DSM atypical specifier, but rather associate with a unique symptom profile including only those reflecting altered energy homeostasis (hypersomnia, increased appetite/weight, leaden paralysis, loss of energy) (Lamers et al., 2020). Patients endorsing these energy-related symptoms have a differential genetic (Milaneschi et al., 2017b) and neurobiological (Simmons et al., 2020) profile. These patients are hypothesized to represent an immuno-metabolic form of depression and to benefit most from treatments that impact on relevant immuno-metabolic pathways (e.g. exercise or dietary interventions) (Milaneschi et al., 2020; Vreijling et al., 2021). Symptoms belonging to this hypothesized immune-metabolic depression dimension overlap not only with atypical depression, but also partly with various other concepts such as bipolar disorder (Łojko et al., 2015) and seasonal affective disorder (Rosenthal et al., 1984).

While the concept of immuno-metabolic depression is relatively new, a great deal of previous epidemiological research focused on depression with atypical, energy-related features defined by the presence of hypersomnia, hyperphagia, or both. It is now well established that patients with these symptoms share several characteristics. For example, they are more often female, younger at the time of their first episode and more likely to have recurrent episodes and a severe depression course than those without (any of) these symptoms (Blanco et al., 2011). Other common characteristics are: comorbid anxiety and bipolar I disorder, higher rates of family history of depression, increased risk for suicide and mental health-care utilization (Matza et al., 2003; Lee et al., 2009). Recent results from a large community study from the UK Biobank cohort supported those of previous studies and additionally showed that depression with hypersomnia and weight gain was associated with smoking, obesity and lower physical activity (Brailean et al., 2019).

There is no consensus yet about which symptoms most optimally reflect immune-metabolic depression, and to what extent a symptom profile integrating these symptoms can be used for this. The current study makes further steps in resolving this by studying the co-occurrence and the shared or unique associations of energy-related depressive symptoms, including hypersomnia, weight gain, increased appetite and loss of energy, with sociodemographic, lifestyle, and clinical data. To our knowledge, no study thus far examined on a large scale the co-occurrence and correlates of individual energy-related symptoms. Furthermore, the field is limited by widely used depression scales not disaggregating opposite symptoms (e.g. appetite increase vs decrease), which however may have different correlates (Milaneschi et al., 2021; Moriarity et al., 2021).

Data of Dutch population-based and clinical cohorts from the BIObanks Netherlands Internet Collaboration (BIONIC) within the Biobanking and BioMolecular resources Research Infrastructure (BBMRI) were analyzed, allowing us to study depression symptoms at a large scale and symptom diversity. BIONIC is an established overarching data infrastructure assembling data from several large Dutch studies with the aim to increase, via rapid phenotyping, the number of cases with lifetime major depressive disorder (MDD) and controls within studies with GWAS data. BIONIC developed the Lifetime Depression Assessment Self-report (LIDAS) based on the short Composite International Diagnostic Interview (CIDI), containing items on the DSM-5 criteria for MDD. The LIDAS also includes items on sociodemographic, lifestyle clinical characteristics, and medication use (Bot et al., 2017; Fedko et al., 2020). In the BIONIC subsample with lifetime MDD identified with the LIDAS, this study describes correlations among energy-related symptoms, as well as between these and other depression symptoms, and associations between energy-related symptoms and sociodemographic (sex, age, education), lifestyle (physical activity, body mass index, smoking) and clinical characteristics (age of onset, episode duration, history, treatment and recency, and self-reported diagnoses of other psychiatric disorders).

2. Methods

2.1. Sample

The total sample that filled in the LIDAS questionnaire consisted of 75,183 participants from eight Dutch cohorts: 45,822 from Lifelines (Scholtens et al., 2015), 21,787 from the Netherlands Twin Register (NTR) (Ligthart et al., 2019), 1215 from TRacking Adolescents' Individual Lives Survey (TRAILS) – population cohort and clinical cohort – (Oldehinkel et al., 2015), 1540 from Nijmegen Biomedical Study (NBS) (Galesloot et al., 2017), 924 from Nutrition Questionnaires plus (NQ-plus) (Brouwer-Brolsma et al., 2018), 226 from Erasmus Rucphen Family (ERF) (Henneman et al., 2008), 918 from The Hoorn Diabetes Care System cohort and the Hoorn studies (Van Der Heijden et al., 2017; Rutters et al., 2018), and 2751 from the Doetinchem Study (Picavet et al., 2017). Lifelines and NTR recruited families; these cohorts consisted of 7582 and 3641 unique families, respectively. The TRAILS cohorts were designed to investigate the determinants of mental health and social development in adolescents; therefore, the participants are younger compared to the other cohorts. The Hoorn Diabetes Care System cohort consisted solely of participants with type 2 diabetes and The Hoorn Studies were oversampled with participants with (pre-)diabetes for this study, and were combined in one Diabetes study cohort. Lifelines, NBS, NQ-plus, ERF, and the Doetinchem Study are population-based cohorts.

2.2. Measures

The online Lifetime Depression Assessment Self-report (LIDAS) (Bot et al., 2017; Fedko et al., 2020) contains questions regarding the two core symptoms for DSM-5 based depression diagnosis (answered with yes/no): depressed mood and loss of interest ('did you ever have a period of at least two weeks with this symptom') and other depressive symptoms (answered with yes/no): decreased functioning, increased appetite, decreased appetite, increases weight, decreased weight, hypersomnia (i.e. sleeping more than usual on a daily basis), energy loss, depressed mood, loss of interest, concentration problems, suicidal thoughts, worthlessness, trouble sleeping, psychomotor agitation and psychomotor retardation ('during the period of two weeks when you experienced depressed mood or loss of interest, did you experience this symptom'). Missing values for the questions regarding the depressive symptoms were set to 'no' (maximally 41 (0.3 %) missing per symptom). These were summarized into the DSM-5 criteria for MDD: decreased functioning, depressed mood, loss of interest, appetite or weight change, change in sleeping behavior, loss of energy, concentration problems, suicidal thoughts, psychomotor changes, worthlessness (yes/no). For the 75183 participants that filled in the LIDAS, the presence of lifetime MDD was determined according to the DSM-5 criteria. Previous research has shown that lifetime MDD classification assessed by the LIDAS questionnaire yields an adequate performance (sensitivity and specificity 85 % respectively 80 % compared to classification with Composite International Diagnostic Interview (CIDI)) (Bot et al., 2017). There were 13965 participants classified as lifetime MDD cases which were included in our analyses.

The survey also included questions regarding sociodemographic and lifestyle characteristics, namely sex, age, level of education, physical activity, body mass index (BMI) and smoking status. Education was dichotomized as low/medium and high (i.e. those with higher professional education/(pre-)university education). Smoking status (current smoker, former smoker, no smoker) was redefined as current smoking status (yes/no). Moderate to vigorous physical activity (MVPA) in leisure time was categorized from 1 (no MVPA) to 5 (MVPA >4 times per week). Clinical characteristics of MDD were also assessed by the LIDAS: age of first onset, duration of longest episode, presence of episode in last year (yes/no), recurrent depression (i.e. a history of two or more episodes) (yes/no). Furthermore, presence of a self-reported lifetime diagnosis of various psychiatric disorders was assessed including bipolar disorder, schizophrenia, eating disorder, anxiety disorder, panic disorder, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), phobia, attention deficit hyperactivity disorder (AD(*H*)D), personality disorder or alcohol addiction, as well as information on possible undergone treatments, such as antidepressant medication, psychotherapy, online intervention, running therapy and light therapy.

We distinguished two depressive symptom profiles: 'energy-related' (four items; increased appetite, increased weight, hypersomnia, energy loss, based on earlier observations that these are the symptoms linked to immune-metabolic depression) (Milaneschi et al., 2020), and 'non-energy-related' (ten items; depressed mood, loss of interest, concentration problems, suicidal thoughts, worthlessness, trouble sleeping, decreased appetite, decreased weight, psychomotor agitation and psychomotor retardation). The energy-related depressive symptom profile (ERS) score and non-energy-related depressive symptom (non-ERS) score were computed as the sum of the respective symptoms, divided by the total number of symptoms in the profile. The higher the ERS score, the more energy-related symptoms are present. The ERS score can therefore be considered a measure of energy-related symptom severity. The non-ERS score, however, is used only for comparison with the ERS score in order to examine whether associations are specific for the energy-related symptoms.

2.3. Statistical methods

The prevalence of the fourteen symptoms within the lifetime depression cases was determined within each cohort and in the pooled cohorts. Second, the correlations between the non-core symptoms of depression were computed using correlations for ordinal variables, i.e. tetrachoric correlations using the *cor_auto* function from the R package *qgraph* (Epskamp et al., 2012). The core symptoms depressed mood and loss of interest were excluded since these where part of the MDD selection criteria and therefore collider bias would have been introduced when computing correlations. Third, associations between energy-related symptoms were described by creating a four-way cross-classification table. Fourth, the associations between the depression symptoms (the four energy-related symptoms, the ERS score and the non-ERS score) and the sociodemographic, lifestyle and clinical characteristics were investigated using either regression models (TRAILS, NBS, NQplus, ERF, Hoorn studies, Doetinchem study) or generalized estimating equations (GEE) models accounting for familial clustering (NTR, Lifelines). By design, there are many families contained in Lifelines and NTR, which can create underlying correlation structures in the data. Therefore, we implemented GEE models with family ID as clustering variable for these two cohorts using the GEE function from the GEE library in the R programming environment. Symptoms, ERS and non-ERS scores were used as predictor, and characteristics as outcome. Linear (GEE/regression) models were conducted for continuous outcomes and logistic (GEE/regression) models for categorical outcomes. All continuous variables were standardized prior to the analyses, and the models were adjusted for sex and age. The models with sex or age as outcome were not adjusted for sex or age, respectively. Cases with missing values for the outcome of a model were not included in this respective model. Due to data-related privacy reasons, we were not able to combine the data from Lifelines and the other seven cohorts. Therefore, the results from the analyses (the above mentioned correlations and associations between symptoms and characteristics) were obtained for each of the eight cohorts separately and combined with meta-analyses using the *rmeta* package (metacor function for correlations; meta.summaries function for GEE models) in the R programming environment. Fixed effect meta-analyses, assuming homogeneity between the samples, were conducted to compute summary estimates from the coefficients and standard errors from the eight cohorts. Heterogeneity tests were performed (STable 1), showing that out of the 319 meta-analyses only six showed significant heterogeneity, justifying fixed effect meta-analysis. For the symptom level analysis, the linear and GEE models were also applied with an additional correction for the individual non-energy-related symptoms. The analysis for the ERS score was repeated while correcting for the non-ERS score. After meta-analysing results from the eight cohorts, all *p*-values obtained from the meta-analysis were together adjusted for multiple testing, and the significance level was set at FDR < 0.05.

3. Results

3.1. Sample characteristics

From the 75183 participants that filled in the LIDAS questionnaire, there were 13965 lifetime depression cases included in the analysis (Table 1), of whom 71 % percent were female and the average age was 48.0 years (sd 13.8). The average age of onset of depression was 31.0 (sd 13.5) years, and the duration of the longest depressed episode was on average 20 weeks (sd 42.7). The majority of the participants (56 %) had experienced multiple depressed episodes in their lifetime, and approximately 36 % had an episode in the last year. An overview of sample characteristics for each cohort is shown in STable 2.

Table 1
Characteristics of the total sample of lifetime depression cases.

	Total sample $N = 13,965$	
Female (N, %)	9897	70.9 %
Age in years (mean, sd)	48.0	13.8
High level of education (N, %)	7788	55.8 %
BMI in kg/m^2 (mean, sd)	25.7	4.7
Current smoker (N, %)	2215	15.9 %
Physical activity (N, %) - none	3142	22.5 %
- 1x per week	3834	27.5 %
- 2x per week	3533	25.3 %
- 3x per week	2047	14.7 %
- ≥4x per week	1397	10.0 %
Multiple depressed episodes in lifetime (N, %)	7857	56.3 %
Depressed episode last year (N, %)	5038	36.1 %
Duration longest depressed episode in weeks (mean, sd)	20.6	42.7
Age of onset in years (mean, sd)	31.0	13.5

3.2. Depressive symptoms prevalence and intercorrelations

The prevalence of the fourteen depression symptoms among the lifetime depression cases is shown in Fig. 1. Besides the high prevalence of the core symptoms, depressed mood (89.6 %) and loss of interest (87.7 %), we observed a high prevalence (>80 %) of concentration problems (97.7 %), worthlessness (81.6 %) and energy loss (96.8 %). Besides energy loss, the other energy-related depressive symptoms had a prevalence of 21.7 % (increased appetite), 12.6 % (increased weight) and 43.2 % (hypersomnia). The prevalence did not deviate much between the cohorts for the majority of the symptoms, although some symptoms showed larger inter-cohort differences. For example, the TRAILS population showed high prevalence of worthlessness, decreased appetite and hypersomnia relative to the other studies. This may be due to the young age (mean 24.3 years) of this sample, by design, in comparison to the other cohorts (range mean age 41.8–65.3, STable 2).

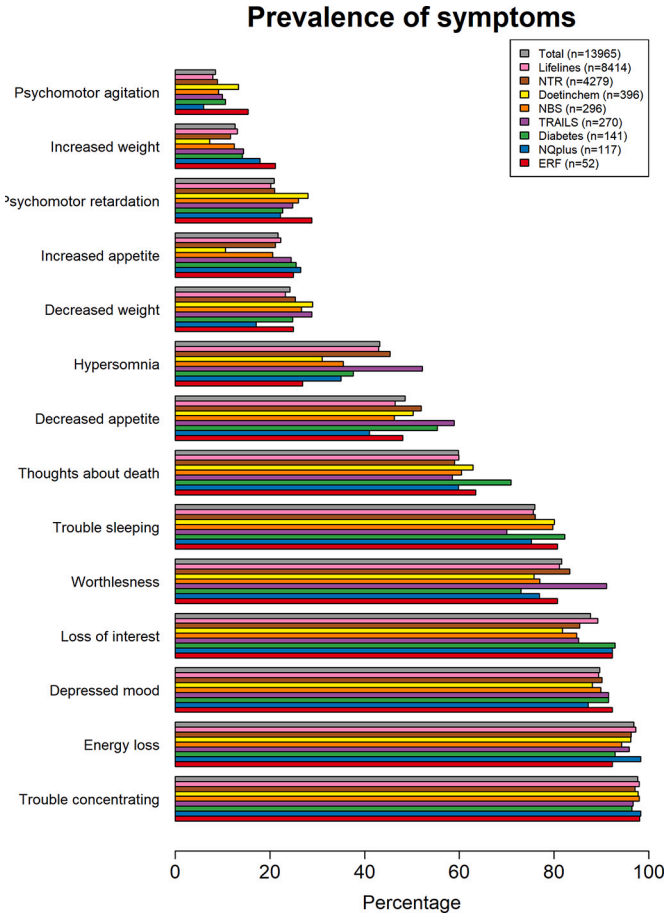

Fig. 1. Prevalence of the fourteen depressive symptoms, in the pooled sample (first bar) and in the individual cohorts (see legend).

We investigated the associations between the symptoms via tetrachoric correlations (Fig. 2). There were many significant correlations (see STable 3 for adjusted *p*-values). Here, we mention the correlations that were significantly different from zero (adjusted p-value <0.05) and larger than ±0.1. Increased appetite and increased weight were most strongly associated with each other ($r = 0.90$), and with hypersomnia (respectively $r = 0.15$; $r = 0.17$), energy loss (r = 0.15; $r = 0.11$), but also worthlessness (r = 0.17; $r = 0.14$). Increased weight was also correlated with thoughts about death (r = 0.11). The correlation between hypersomnia and energy loss ($r = 0.25$) was higher than the correlation of other symptoms with hypersomnia or energy loss. Hypersomnia was also significantly correlated with psychomotor retardation (r = 0.15) and decreased weight ($r = -0.16$). Energy loss was also significantly correlated with psychomotor retardation (r = 0.17), trouble concentrating ($r = 0.23$) and thoughts about death ($r = -0.15$). Of the participants reporting increased appetite, approximately 50 % also reported increased weight (1575/3029) and hypersomnia (1540/3029). Of those reporting hypersomnia (1540/6034), about 25 % also reported increased appetite and 15 % reported increased weight (926/6034). Increased appetite/weight and hypersomnia showed large overlap with energy loss (STable 4a). With regards to the distribution of the ERS score, most participants reported one (6138/14096) or two (5207/14096) out of four symptoms (Stable 4b).

3.3. Sociodemographic characteristics

Next, we focused on the characterization of the four energy-related depressive symptoms and the ERS score, in terms of sociodemographic, lifestyle and clinical characteristics. Participants with increased appetite (OR = 1.24, $p = 8.91E-25$), increased weight (OR = 1.15, $p = 8.31E-12$) and energy loss (OR = 1.11, $p = 1.46E-09$) were more often female than participants without this symptom, while hypersomnia was not associated with sex (Fig. 3). Furthermore, increased appetite (beta = −0.08, $p = 1.64E-24$), increased weight (beta = −0.02, $p = 3.73E-03$) and hypersomnia (beta = −0.13, $p = 1.10E-55$) were related to lower age. Participants endorsing increased appetite (OR = 0.91, $p = 2.48E-07$), increased weight (OR = 0.90, $p = 6.09E-09$), or energy loss (OR = 0.96, $p = 2.58E-02$) had a significantly lower level of education. Almost all significant associations between the four energy-related depressive symptoms and the sociodemographic characteristics remained after correcting for the non-energy-related depressive symptoms (STable 5). The ERS score was significantly associated with being female (OR = 1.19, $p = 2.76E-18$), a lower level of education (OR = 0.90, $p = 2.14E-09$) and lower age (beta = −0.12, $p = 9.58E-50$). The non-ERS score was also associated with being female (OR = 1.09, $p = 4.58E-06$) and a lower level of education (OR = 0.86, $p = 1.43E-17$). The associations between the ERS score and the sociodemographic characteristics remained significant after correction for the non-ERS score (STable 5).

3.4. Lifestyle characteristics

Increased appetite (but not increased weight) was associated with being a non-smoker (OR = 0.88, $p = 1.08E-07$), while participants with hypersomnia were significantly more often smokers (OR = 1.12, $p = 1.62E-06$). Hypersomnia (beta = −0.04, $p = 2.27E-06$) and energy loss (beta = −0.02, $p = 2.03E-02$) were associated with lower physical activity. All energy-related depressive symptoms were strongly associated with higher BMI. After correcting for non-energy-related depressive symptoms, only the association between increased appetite and smoking did not remain significant (STable 5). The ERS score was only significantly associated with higher BMI (beta = 0.30, $p = 3.16E-265$) and this association remained significant after correction for the non-ERS score.

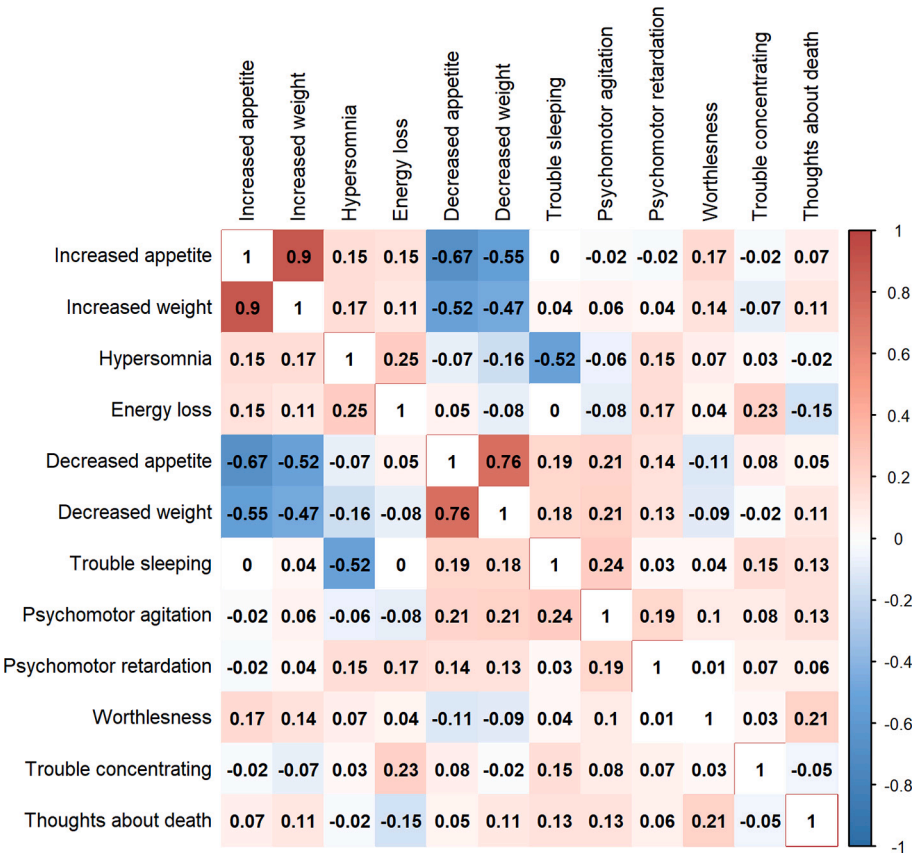

Fig. 2. Correlations between the twelve non-core symptoms. The color-coded size of the correlations is given in case the corresponding correlation is significant (adj. $p < 0.05$), otherwise the respective field is blank.

No significant association between the ERS score and physical activity or smoking was found. The non-ERS score was associated with being a smoker (OR = 1.32, p = 1.65E-31), and decreased BMI (beta = −0.05, p = 3.88E-08).

3.5. Clinical depression characteristics

Participants with increased appetite (OR = 1.23, p = 8.01E-32), increased weight (OR = 1.20, p = 1.36E-25), or energy loss (OR = 1.06, p = 3.96E-03) significantly more often had an episode in the past year, while participants with hypersomnia (OR = 0.91, p = 6.82E-08) less often had an episode in the past year (Fig. 4). Increased appetite (OR = 1.30, p = 3.70E-47), increased weight (OR = 1.21, p = 7.08E-25) and energy loss (OR = 1.08, p = 2.82E-06), but not hypersomnia, were also related to having recurrent episodes. Increased appetite, increased weight and hypersomnia, but not energy loss, were associated with longer duration of the episodes (beta = 0.02, p = 9.15E-03; beta = 0.05, p = 1.67E-09; beta = 0.05, p = 7.63E-09) and lower age of onset (beta = −0.07, p = 7.33E-20; beta = −0.05, p = 6.34E-13; beta = −0.05, p = 1.36E-13). After the correction for the non-energy-related depressive symptoms, all significant associations remained, except for the association between hypersomnia and the presence of an episode in the past year, and between increased appetite and duration of the longest episode (STable 5).

The ERS score was associated with having recurrent episodes (OR = 1.23, p = 6.55E-32), a longer duration of the episodes (beta = 0.06, p = 4.56E-11), the presence of an episode in the past year (OR = 1.14, p = 6.37E-13), and lower age of onset (beta = −0.08, p = 2.15E-26). The non-ERS score was also associated with these clinical markers, with similar ORs as the ERS score, with the exception of the episode duration (beta = 0.20, p = 3.32E-136, Fig. 4 and STable 5). After adjusting for the non-ERS score all associations between the ERS score and the clinical characteristics remained significant.

3.6. Self-reported diagnoses of other psychiatric disorders

Increased appetite and increased weight (but not hypersomnia) were associated with a higher likelihood to have self-reported eating disorder (respectively OR = 1.40, p = 4.08E-16; OR = 1.41, p = 5.48E-23), PTSD (OR = 1.17, p = 2.91E-08; OR = 1.20, p = 1.56E-12), personality disorder (OR = 1.26, p = 1.21E-09; OR = 1.21, p = 3.68E-07), and ADHD (OR = 1.10, p = 1.15E-02; OR = 1.16, p = 5.53E-05, Sup. Fig. 1). Furthermore, increased appetite, increased weight and hypersomnia were related to self-reported bipolar disorder (OR = 1.15, p = 1.36E-02; OR = 1.22, p = 1.40E-04; OR = 1.22, p = 1.43E-03) and panic disorder (OR = 1.07, p = 2.27E-02; OR = 1.08, p = 7.36E-03; OR = 1.09, p = 3.59E-03). The associations between the ERS score and the other self-reported psychiatric disorders were all significant, except for OCD and phobia. The non-ERS score was also associated with all the other self-reported diagnoses, with higher ORs as the ERS score (Sup. Fig. 1 and STable 5). After additional correction, all associations remained significant.

3.7. Treatment

Participants with energy-related depressive symptoms were more likely to have had past treatment and more likely to have had antidepressant medication or psychotherapy in the past (Sup. Fig. 2). The association with antidepressant medication was strongest in patients with hypersomnia (OR = 1.20, p = 5.33E-24), while the strength of the associations with psychotherapy did not differ much between the symptoms. Increased appetite, increased weight and hypersomnia were

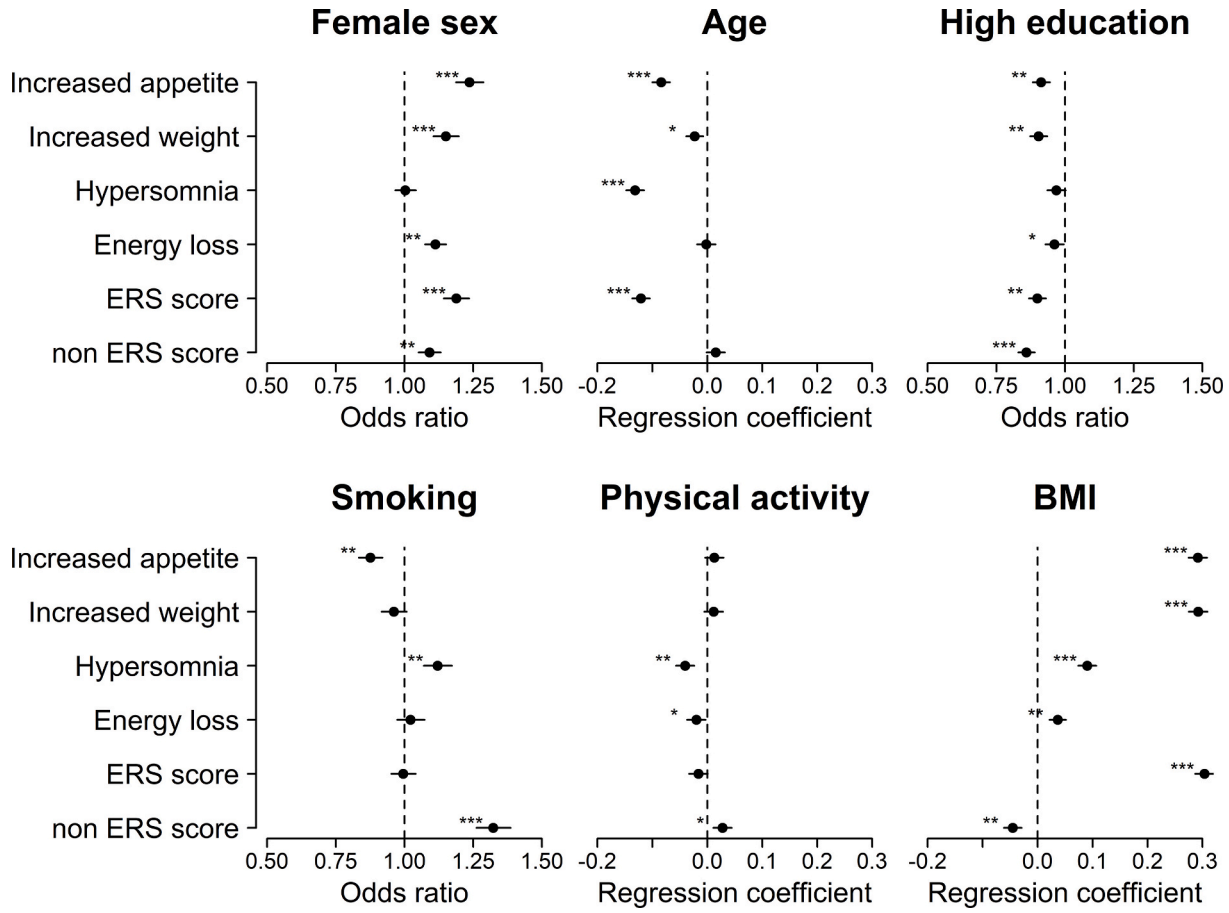

Fig. 3. Results from the pooled analysis of associations between the energy-related depressive symptoms and the sociodemographic and lifestyle characteristics (adjusted for age and sex). For dichotomous and continuous response variables the 95 % confidence interval of the odds ratio respectively regression coefficient is given. ERS score: the energy-related depressive symptom score. Non-ERS score: the non-energy-related depressive symptom score. * adj. *p*-value <0.05, ** adj. p-value <1E-05, *** adj. p-value <1E-10.

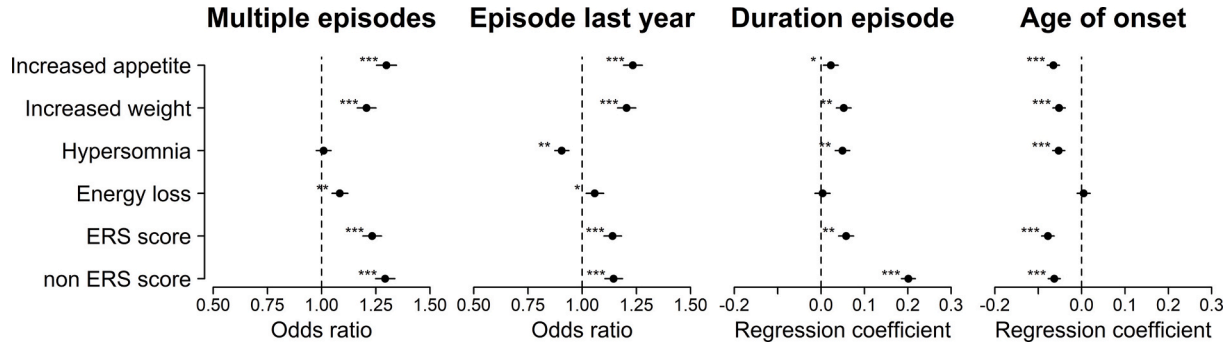

Fig. 4. Results from the pooled analysis of associations between the energy-related depressive symptoms and the clinical depression characteristics (adjusted for age and sex). For dichotomous and continuous response variables the 95 % confidence interval of the odds ratio respectively regression coefficient is given. ERS score: the energy-related depressive symptom score. Non-ERS score: the non-energy-related depressive symptom score. * adj. p-value <0.05, ** adj. p-value <1E-05, *** adj. p-value <1E-10.

associated with having undergone light therapy (OR = 1.19, $p = 5.87E-05$; OR = 1.19, $p = 1.47E-05$; OR = 1.34, $p = 1.18E-09$). In the model that included the non-energy-related depressive symptoms, these associations remained significant. The ERS score was associated with almost all treatment options, except running therapy. The associations of the ERS score with treatment were strongest for light therapy (OR = 1.36, $p = 1.77E-12$) and antidepressant medication (OR = 1.18, $p = 1.93E-21$). The non-ERS score was also associated with increased adherence of all treatments, with larger ORs as the ERS score (with the exception of light therapy, Sup Fig. 1 and STable 5). After additional correction, all associations between the ERS score and past treatments remained significant.

4. Discussion

In a large study of 13,965 adults with lifetime major depressive disorder from the Dutch population, this study extensively investigated associations between individual energy-related depressive symptoms

and their sociodemographic, lifestyle and clinical correlates. The energy-related depressive symptoms showed significant but low inter-correlations and partially shared characteristics. The notable differences in the characteristics of energy-related depressive symptoms indicate the potential value of studying depression subtypes at individual symptom resolution as a starting point.

Overall, we observed that energy-related symptoms were more strongly (and positively) correlated with each other than with other symptoms of depression. These positive correlations are in support of a profile integrating these symptoms: the strengths of these correlations help interpreting this profile. The relative low correlation ($r = 0.15$) between increased appetite and both hypersomnia and energy loss indicates that this profile reflects patients with relatively heterogeneous symptomatology. A similar observation was made in the symptom structure of seasonal affective disorder (Smetter et al., 2021). Two additional observations emerged. First, the associations between worthlessness and increased appetite/weight were relatively strong. Self-critical thinking, including thoughts of worthlessness and inadequacy, has been linked to both depression and disordered eating and is found to explain in part their relationship (Porter et al., 2018). A study comparing depressive symptoms between people with depressive and eating disorders found worthlessness to be more prominent among patients with eating disorders than depression (Voderholzer et al., 2019). Although worthlessness may not directly reflect altered energy homeostasis in the body, it could still contribute on a psychological or behavioral level, for instance via disordered eating, to the energy-related symptom burden. Second, psychomotor retardation showed relatively strong associations with hypersomnia and energy loss. This result fits with those of Lamers et al. (2018) demonstrating associations between psychomotor retardation and metabolic dysregulations (higher BMI, lower high-density lipoprotein cholesterol and higher triglycerides), possibly explained by lower physical activity.

A central finding to emerge from this study is that all energy-related depressive symptoms (and their profile) were consistently and most strongly positively associated with BMI. The positive associations with BMI were specific for the energy-related depressive symptoms: the non-ERS score showed a negative association with BMI. While this may seem self-evident, it should be remembered that these are not current symptoms, but that these symptoms have been reported to have occurred *in the context of a lifetime* episode of depression. BMI was the only characteristic studied here that showed this specific association with the ERS score that was not found for the non-ERS score. These results support epidemiological evidence that the association between depression and elevated BMI is most evident in patients with atypical depression (Silva et al., 2020), particularly driven by energy-related depressive symptoms (de Kluiver et al., 2020; Lamers et al., 2020; Milaneschi et al., 2020). The strongest associations with BMI were found for increased appetite and weight. This coincides with finding of shared genetic liability (measured with polygenic risk scores) for BMI and depression with increased appetite and/or weight specifically (Milaneschi et al., 2017b).

While some characteristics were present for all energy-related depressive symptoms (increased BMI, an overall more severe clinical profile), some were present for only one or two symptoms. We discuss here the contrast between hypersomnia and increased appetite or weight: due to the high prevalence (96.8 %) and therefore negligible variation among energy loss in our sample, contrasts between energy loss and the other three energy-related symptoms were of less interest. Being female, lower educational level, having recurrent depression and a recent episode, and self-reported PTSD, eating disorder and personality disorder were all associated with increased appetite or weight, but not with hypersomnia. Moreover, while persons with increased appetite were less likely to be smokers, persons with hypersomnia were more likely to be smokers. This variability has impact on the symptom profile integrating the energy-related depressive symptoms: for example, due to the non-consistent directions of effects, smoking was not associated with the ERS profile score. Despite this variability, the energy-related depressive symptoms studied here could still arise from a common aetiology and together represent a clinically meaningful symptom profile that belongs to an immuno-metabolic depression dimension, since the sociodemographic, lifestyle and clinical characteristics studied here may not be causal for the occurrence of immuno-metabolic depression. Therefore, it is important to assess whether there is also variability in biological correlates of energy-related depressive symptoms, closer to the core of immuno-metabolic depression pathology. Previous research using data from a large cohort study among patients with lifetime depression and/or anxiety has indeed shown that increased appetite, but not hypersomnia, is related to leptin dysregulation (Milaneschi et al., 2017a) and elevated levels of inflammatory biomarkers, such as CRP, TNF-alpha (Lamers et al., 2018). Additionally, a recent Mendelian randomization study found that increased BMI is causal for the development of increased appetite during depression, although there was no support for a causal link with hypersomnia (Pistis et al., 2021). Therefore, we strongly recommend close attention to the correlates of individual depressive symptoms, in particular in studies investigating biological mechanisms, before using symptom profiles integrating these symptoms.

Present findings partly confirm other associations between energy-related depressive symptoms and factors typically associated with atypical depression subtypes. Consistent with this literature, three out of four energy-related depressive symptoms, as well as the energy-related depressive symptom profile, were significantly related to female gender and younger age (Agosti and Stewart, 2001; Matza et al., 2003; Lee et al., 2009; Blanco et al., 2011; Brailean et al., 2019). Although previous analyses did not find an association with education (Agosti and Stewart, 2001; Matza et al., 2003), our results showed that, with the exception of hypersomnia, persons endorsing energy-related depressive symptoms have a lower educational level. Within UK Biobank, depression withboth hypersomnia and weight gain, has been associated with unhealthy behaviors such as smoking and low physical activity (Brailean et al., 2019). Here we replicated these findings only for hypersomnia, but not for weight gain, suggesting that hypersomnia may be the symptom driving these associations identified in UK Biobank.

Participants with energy-related depressive symptoms shared clinical characteristics indicative of a more severe illness course: they more often had recurrent, recent and longer episodes and a younger age of onset than patients that did not have these symptoms. Furthermore, they were more likely to self-report a lifetime diagnosis of eating disorder, PTSD, personality disorder and bipolar disorder. Similar characteristics have been observed across various operationalizations of depression with atypical, energy-related symptoms (Matza et al., 2003; Lee et al., 2009; Blanco et al., 2011; Brailean et al., 2019). These studies also indicated associations with higher help seeking rates, lifetime deprivation and adversity, medical comorbidities (e.g. cardiovascular disease, diabetes and hypertension) (Brailean et al., 2019), suicidal ideation and impaired functioning (Matza et al., 2003; Blanco et al., 2011). Future research may therefore expand the examination of atypical, energy-related depressive symptoms in psychiatric disorders related to depression, such as seasonal affective disorder or bipolar disorder, or somatic disorders characterized by immuno-metabolic dysregulations, such as obesity, cardiovascular diseases or diabetes.

The clinical characteristics of the energy-related depressive symptoms (profile) were also found for the non-ERS score, showing that these characteristics are not specific for depression with energy-related symptoms and also associated with other symptom domains of depression. Although in the present study significant correlations were found between the energy-related depressive symptoms and other, non-energy-related symptoms, the additional correction for the non-energy-related depressive symptoms showed that the identified characteristics of the energy-related symptoms were mostly independent of the presence of other depression symptoms. Comparable characteristics were observed for the ERS score, also after correcting for the non-ERS score (i.e., a proxy for depression severity, unrelated to the energy-

related symptoms), indicating that these findings cannot be attributed to depression severity.

Some limitations need to be considered whilst interpreting the findings. First, this was a cross-sectional study, and causal association cannot be determined. Second, the sample was restricted to the Dutch population and findings may not generalize to other countries. Third, the LIDAS is a lifetime assessment of MDD. The symptoms analyzed were those self-reported as occurring during the worst 2-week depressed period, which has its limitations due to recall biases. Nevertheless, the LIDAS has been shown to have adequate sensitivity and specificity for measuring lifetime MDD compared to CIDI MDD interviews (Bot et al., 2017). Finally, leaden paralysis was not assessed with the LIDAS, but is considered to additionally belong to the energy-related depressive symptom profile associated with immuno-metabolic depression. Strengths of the study include the large and diverse sample of adults and adolescents from both population-based and clinical cohorts, and the disaggregation of neurovegetative symptoms (appetite and sleep alterations) allowing us to specifically characterize persons with increased appetite and weight.

To conclude, among persons with lifetime depression from the Dutch population, this large-scale study confirmed some co-occurrence of energy-related depressive symptoms and established robust characteristics of these symptoms. While some characteristics were present for all energy-related depressive symptoms, such as BMI and most clinical variables, other characteristics were present for only two or three symptoms. For example, female gender, self-reported PTSD and personality disorder were associated with increased appetite but not with hypersomnia. Although it is still plausible that these symptoms arise from a common aetiology and share biological pathways, future work examining correlates of depressive symptoms at individual symptom resolution are needed.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.11.005.

Conflicts of interest

BP has received research funding (not related to the current paper) from Boehringer Ingelheim and Jansen Research.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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