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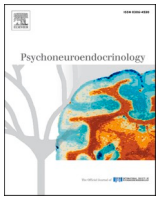

Weighing poor immunometabolic health in relatives for severity of affective symptoms: A study of patients with depressive and anxiety disorders and their siblings

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ABSTRACT

Background: Affective (i.e. depressive and anxiety) disorders often co-occur with immunometabolic diseases and related biological pathways. Although many large population-based and meta-analytic studies have confirmed this link in community and clinical samples, studies in at-risk samples of siblings of persons with affective disorders are lacking. Furthermore, this somatic-mental co-occurrence may be partially explained by familial clustering of the conditions. First, we examined whether the association between a wide range of immunometabolic diseases and related biomarker based risk-profiles with psychological symptoms replicates in at-risk siblings of probands with affective disorders. Second, leveraging on a sibling-pair design, we disentangled and quantified the effect of probands' immunometabolic health on siblings' psychological symptoms and on the association between immunometabolic health and these symptoms in siblings.

Methods: The sample included 636 participants (M_{age} = 49.7; 62.4% female) from 256 families, each including a proband with lifetime depressive and/or anxiety disorders and at least one of their sibling(s) (N = 380 proband-sibling pairs). Immunometabolic health included cardiometabolic and inflammatory diseases, body mass index (BMI), and composite metabolic (based on the five metabolic syndrome components) and inflammatory (based on interleukin-6 and C-reactive protein) biomarker indices. Overall affective symptoms and specific atypical, energy-related depressive symptoms were derived from self-report questionnaires. Mixed-effects analyses were used to model familial clustering.

Results: In siblings, inflammatory disease (γ = 0.25, p = 0.013), higher BMI (γ = 0.10, p = 0.033) and metabolic index (γ = 0.28, p < 0.001) were associated with higher affective symptoms, with stronger associations for atypical, energy-related depressive symptoms (additionally associated with cardiometabolic disease; γ = 0.56, p = 0.048). Immunometabolic health in probands was not independently associated with psychological symptoms in siblings nor did it moderate the association between immunometabolic health and psychological symptoms estimated in siblings.

Conclusions: Our findings demonstrate that the link between later life immunometabolic health and psychological symptoms is consistently present also in adult siblings at high risk for affective disorders. Familial clustering did not appear to have a substantial impact on this association. Instead, individual lifestyle, rather than familial factors, may have a relatively higher impact in the clustering of later life immunometabolic conditions with psychological symptoms in at-risk adult individuals. Furthermore, results highlighted the importance of focusing on specific depression profiles when investigating the overlap with immunometabolic health.

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1. Introduction

Affective (i.e. depressive and anxiety) disorders are among the leading causes of disability and high mortality risk worldwide (James et al., 2018). Their high disease burden is not only due to psychological suffering but also because of associated poorer somatic health (Otte et al., 2016), in particular poorer immunometabolic health (Gold et al., 2020). Indeed, affective disorders often co-occur with chronic somatic illnesses such as cardiometabolic (e.g. cardiovascular disease, diabetes mellitus) and inflammatory disease (e.g. rheumatoid arthritis, inflammatory bowel disease), an association that is likely bidirectional (Batelaan et al., 2016; Gold et al., 2020; Ng et al., 2022; Penninx and Lange, 2018). One potential explanation for this somatic-mental co-occurrence is shared underlying metabolic (e.g. dyslipidemia, hypertension, hyperglycemia) and inflammatory dysregulations (e.g. higher levels of C-reactive protein [CRP] and interleukin-6 [IL-6]) (Gold et al., 2020; Haapakoski et al., 2015; Pan et al., 2012; Penninx and Lange, 2018). Increasing evidence exists that the association of affective disorders with immunometabolic diseases and markers of related biological pathways are stronger for certain depressed clinical profiles, in particular those expressing atypical symptoms reflecting altered energy intake/expenditure balance (i.e. increased appetite/weight, hypersomnia, leaden paralysis, and low energy; Milaneschi et al., 2020, 2019). Thus far, many large population-based and meta-analytic studies have confirmed the association between poor immunometabolic health and (certain profiles of) affective symptoms within community (Howren et al., 2009; Leone et al., 2022; Smith et al., 2018; Valkanova and Ebmeier, 2013) and clinical samples of patients with affective disorders (Chae et al., 2023; Valkanova and Ebmeier, 2013), including some of our own studies (Lamers et al., 2020, 2019, 2018, 2013; Milaneschi et al., 2021b). However, an important research question to be answered is whether the association between immunometabolic health and affective symptoms is consistently present also in at-risk samples of siblings of persons with affective disorders, which thus far has been less studied (e.g. de Kluiver et al., 2020; Vaccarino et al., 2008).

Affective disorders and immunometabolic diseases show a familial clustering pattern, characterized by the fact that physical and behavioral traits tend to co-occur more frequently among close family members. The familial clustering of features may emerge as the combined effect of shared genetics and non-genetics (e.g. household environment) between family members. These two major sources of resemblance between family members may be expressed in biological (e.g. inflammatory reactivity) or behavioral pathways (e.g. learned poor dietary habits and sedentariness) potentially influencing the development of both affective disorders and immunometabolic diseases. In particular siblings, which often grow up in the same household and are often age peers, tend to share similarities in life course trajectories due to their reciprocal influence on each other as compared with other family ties (Her et al., 2021). Previous studies have shown moderate resemblance between siblings for affective symptoms (Moskvina et al., 2008; Stallings et al., 1997; van Sprang et al., 2021) and moderate to large resemblance for immunometabolic diseases (e.g. cardiovascular disease; Akbarzadeh et al., 2022; Kuo et al., 2017; van Hecke et al., 2017) and biomarkers (e.g. high-density lipoprotein [HDL]-cholesterol; Feng et al., 2008; Neijts et al., 2013; Santos et al., 2013). A significant cross-trait association between affective symptoms and immunometabolic diseases in siblings may be due to shared genetics, as supported by significant genetic correlations (range r_G: 0.11–0.26; Grotzinger et al., 2022; Wang et al., 2022; Wray et al., 2018) and shared markers of biological pathways between immunometabolic diseases and affective disorders (Howard et al., 2019), and/or shared unhealthy behaviors predisposing to immunometabolic diseases and affective disorders, such as physical inactivity (Khandaker et al., 2020). This familial clustering may partially explain the association between affective disorders and immunometabolic diseases.

One way to estimate the relevance of familial clustering is to examine cross-trait associations between affective psychopathology and poor immunometabolic health in siblings using a sibling-pair design. In such a design, it possible to disentangle and estimate the relevance of co-siblings' somatic and mental health in the association between affective disorders and immunometabolic conditions. Previously, we have found evidence for cross-trait associations between the presence of psychosocial risk factors (e.g. low income, childhood trauma) in one sibling and affective symptoms in their co-sibling (van Sprang et al., 2023). However, whether poor immunometabolic health in co-siblings is relevant for siblings' affective symptomats – on top of or in combination with siblings' own immunometabolic health – remains largely unknown. For instance, obese siblings may reinforce each other's unhealthy lifestyle (Christakis and Fowler, 2007; Ragelienė and Grønhøj, 2020), which in turn has been found to be a predisposing factor for affective psychopathology (Khandaker et al., 2020).

Only few studies have examined such cross-trait associations with regard to indicators of poor immunometabolic health and affective psychopathology within a sibling-pair design, with mixed results. For instance, while some studies showed that high risk for vascular disease (Kendler et al., 2009), angina (i.e. a risk indicator for coronary heart disease; van Hecke et al., 2017), obesity, diabetes mellitus (Leone et al., 2022), and asthma (Brew et al., 2018) in one sibling was associated with affective psychopathology in their co-sibling, others found no such associations (i.e. for cardiovascular disease; van Hecke et al., 2017). Also, in one of our own recent studies, we found no evidence for cross-trait associations between individual metabolic/inflammatory biomarkers and depressive symptom profiles within sibling pairs (de Kluiver et al., 2020). In the present study, we extend this work by examining the *added relevance* of co-siblings' poor immunometabolic health on siblings' affective symptoms, on top of or in combination with siblings' own immunometabolic health. Furthermore, rather than limiting the analyses to individual biomarkers, we investigated poor immunometabolic health more extensively, by including composite biomarker-based risk profiles and evaluating a wide array of immunometabolic disease outcomes. Importantly, none of the previous studies, including our own, adjusted cross-trait associations between co-siblings' somatic health and siblings' mental health for both co-siblings' mental health and siblings' somatic health (de Kluiver et al., 2020; Kendler et al., 2009; Leone et al., 2022) or only for either co-siblings' mental health (Brew et al., 2018) or siblings' somatic health (van Hecke et al., 2017). In the present study, cross-trait association between co-sibling somatic health and sibling mental health will be adjusted for both co-sibling mental health and sibling somatic health. The degree of impact of these adjustments (i.e. indexing the average familial levels of psychological and biological traits) on the association estimates may provide an indication on the relevance of familial clustering on the relationships examined.

Overall, the present study had two overarching aims addressed in three sequential steps. As a first aim (Step 1), we examined whether the association of a broad range of cardiometabolic/inflammatory diseases and related biomarker-based risk profiles with overall affective symptoms and with specific atypical, energy-related depressive symptoms replicates in an at-risk sample of siblings of persons with lifetime depressive and/or anxiety disorders (hereafter referred to as 'probands'). As a second aim, we were particularly interested in disentangling and quantifying the effect of familial clustering on this association. To this end, we used a sibling-pair design to study the effect of probands' immunometabolic health on siblings' psychological symptoms, over-and-above siblings' own immunometabolic health (Step 2), and on the association between immunometabolic health and psychological symptoms estimated in siblings (Step 3).

2. Materials and methods

The present study is a substudy of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study (2004-present) investigating the long-term course and consequences of

depressive (i.e. major depressive disorder and dysthymia) and anxiety disorders (i.e. generalized anxiety disorder, panic disorder with or without agoraphobia, social phobia, and agoraphobia only). A detailed description of the NESDA study design and sampling procedure has been reported elsewhere (Penninx et al., 2021). In short, the NESDA baseline sample consisted of 2981 participants aged 18–65 years, including 2319 persons with a lifetime affective (i.e. depressive and/or anxiety) disorder diagnosis and 652 healthy controls. Participants were assessed in face-to-face interviews at baseline, and 2-, 4-, 6-, and 9-year follow-up. Assessments included a diagnostic interview to assess the presence of DSM-IV-TR affective disorders (confirmed using the Composite Interview Diagnostic Instrument, lifetime version 2.1; Wittchen, 1994), a medical examination, and several questionnaires on symptom severity, other clinical characteristics, and lifestyle. Participants were excluded if they had a self-reported clinically overt diagnosis of psychiatric disorders other than affective disorders (such as, for instance, a psychotic disorder, obsessive compulsive disorder, bipolar disorder or severe addiction disorder), and they were not fluent in Dutch. The NESDA study protocol was approved by the ethical committee of participating universities, and all respondents provided written informed consent.

2.1. Study sample

During the 9-year follow-up (2014–2017), full-biological siblings of NESDA participants with a lifetime affective disorder (i.e. 'probands') were additionally recruited for the NESDA family study to investigate the development of psychopathology, biopsychosocial functioning, and health (behavior) within the family context. A detailed description of the sampling procedure and inclusion criteria of the NESDA family study has been provided elsewhere (van Sprang et al., 2021). For the present study, we selected all 636 participants from the NESDA family study. Participants were from 256 families, each including a lifetime affected proband and at least one of their siblings. A total of 380 siblings, related to 256 probands, participated ($N = 380$ proband-sibling pairs). Of the total of 256 families, 34.4% included more than one proband-sibling pair (van Sprang et al., 2021). The present study used data for probands assessed at the 9-year follow-up of NESDA, at the time of recruitment and assessment of siblings.

See **Fig. A1** in Supplementary materials **A** in the Appendix for an inclusion flowchart of probands and siblings into the NESDA family study. Probands were included if they (i) had an affective disorder diagnosis (i.e. current, in between two waves, or earlier in life before baseline) on at least two NESDA waves to ensure that there was at least some psychiatric burden, (ii) participated at the 9-year follow-up face-to-face interview and in at least three out of four face-to-face interviews prior to the 9-year follow-up, and (iii) had genetic data available. Full-biological siblings of probands were included if they (i) were currently living in the Netherlands, (ii) were aged between 18 and 78 years, and (iii) consented to participate in the 9-year follow-up face-to-face interview.

2.2. Measurements

All measurements, which included psychological symptoms, indicators of poor immunometabolic health, and sociodemographics, were similarly assessed in both probands and their siblings.

2.2.1. Psychological symptoms

Past week severity and number of symptoms was measured with the 30-item self-report version of the Inventory of Depressive Symptomatology (IDS; Rush et al., 1996) for depression and with the 21-item Beck Anxiety Inventory (BAI; Beck et al., 1988) for anxiety. The IDS and the BAI showed good psychometric properties in previous studies (Beck et al., 1988; Osman et al., 2002; Rush et al., 1996; Trivedi et al., 2004) and excellent internal consistency in the present sample (IDS: $\alpha = 0.87$; BAI: $\alpha = 0.91$). Given their partial content overlap and large correlation ($r = 0.71$; van Sprang et al., 2023), IDS and BAI scores were standardized and averaged into an overall IDS/BAI score to reflect number and current severity of overall affective symptoms. The use of standardized and averaged symptom severity scores including the IDS and the BAI is in line with earlier work (Solis et al., 2021; van Sprang et al., 2023). Consistent with previous studies (Lamers et al., 2020; Milaneschi et al., 2021a), we derived an atypical, energy-related depressive symptom profile by summing up 5 IDS items: increased appetite, increased weight, hypersomnia, leaden paralysis and low energy. This led to a sum-score ranging from 0 to 15. The 5 IDS items showed a Chronbach's α of 0.67. However, since this parameter is highly dependent on the number of items, we estimated the mean inter-item correlation as suggested for instrument with limited set of items. The result of 0.28 indicated a satisfactory level of homogeneity (Briggs and Cheek, 1986). In the analyses, psychological symptoms measured in siblings were used as outcome variables, whereas psychological symptoms measured in probands were used as covariates to take into account familial clustering of psychopathology.

2.2.2. Indicators of poor immunometabolic health

Indicators of poor immunometabolic health measured in siblings and the same indicators of poor immunometabolic health measured in probands were used as explanatory variables in the analyses.

2.2.2.1. Chronic somatic disease. Cardiometabolic disease was defined as the presence of (i) a self-reported clinical diagnosis of heart/cardiac disease, stroke, transient ischemic attack, aortic aneurysm, atherosclerosis/narrowing or hardening of arteries/claudication, pulmonary embolism/blood clot, deep vein thrombosis, phlebitis, chronic venous insufficiency, or angioplasty and/or (ii) use of anti-diabetic medication (Anatomical Therapeutic Chemical [ATC] code: A10) or statins (ATC codes: C10AA, C10B). In addition, hypertension was included in the definition of cardiometabolic disease only when the clinical self-reported diagnosis was verified by anti-hypertensive medication use (ATC codes: C03, C07, C08, C09).

Inflammatory disease was defined as the presence of (i) a self-reported clinical diagnosis of rheumatoid arthritis, inflammatory respiratory (i.e. asthma, chronic bronchitis, pulmonary emphysema) and bowel diseases (i.e. Crohn's disease, colitis ulcerosa, diverticulitis), ulcers, liver cirrhosis, systemic lupus erythematosus, hepatitis, multiple sclerosis, or other autoimmune diseases and/or (ii) use of non-steroidal anti-inflammatory medication, including anti-inflammatory and anti-rheumatic preparations (ACT code: M01A), corticosteroids (ACT code: M01B), and aminosalicylic acid and similar agents (ATC code: A07EC).

2.2.2.2. Metabolic and inflammatory biomarkers. As part of the medical examination, body mass index (BMI) and single metabolic biomarkers (i.e. waist circumference, systolic blood pressure, glucose level, triglyceride level, HDL-cholesterol level) were analyzed as continuous measures. BMI was calculated as weight in kg divided by height in m^2. Waist circumference was measured with a measuring tape at the central point between the lowest front rib and pelvic edge (i.e. the highest front point of the pelvis) on light clothing. BMI and waist circumference values of pregnant women were excluded from the present analyses. Blood pressure was measured twice during supine rest on the right arm using the Omron M4-I HEM 752 A, and averaged over the two measurements. Glucose, triglyceride, and HDL-cholesterol levels were determined from fasting morning blood plasma using standardized laboratory methods. In line with previous studies (Lamers et al., 2020; Licht et al., 2010), systolic blood pressure, glucose, triglyceride, and HDL-cholesterol levels were adjusted for relevant medication use to take into account the known impact that medications have on these biomarker levels: for systolic blood pressure, 10 mm Hg was added for anti-hypertensive medication use; for glucose, 7.0 mmol/l (126 mg/dl) was assigned in case of anti-diabetic medication use and having glucose levels < 7.0

mmol/l; for triglycerides, 0.67 mmol/l was added for fibrate use (ATC code: C10AB) and 0.19 mmol/l was added for nicotinic acid use (ATC codes: C10AD, C10BA01); for HDL-cholesterol, 0.10 mmol/l was subtracted for fibrate use and 0.15 mmol/l was subtracted for nicotinic acid use. HDL-cholesterol scores were reversed, since lower values are indicative of higher risk.

Inflammatory biomarkers (i.e. IL-6, CRP) were determined from fasting morning blood plasma. IL-6 was measured in duplicate by a high-sensitivity solid-phase enzyme-linked immunosorbent assay (ELISA; Human IL-6 Quantikine HS kit, R&D Systems, Minneapolis, MN, USA), which has a lower detection limit of 0.08 pg/ml and a sensitivity range of 0.016–0.110 pg/ml for IL-6. Plasma levels of CRP were measured in duplicate by a high-sensitivity particle enhanced immunoturbidimetric assay (CRPHS, Roche Diagnostics, Indianapolis, IN, USA), which has a lower detection limit of 0.15 mg/l and a sensitivity of 0.3 mg/l for CRP. All participants had IL-6 and CRP levels above the lower detection limits and, as such, all values could be included in the analyses. Intra- and inter-assay coefficients of variation for the kits have been reported elsewhere (Lamers et al., 2020).

In line with previous work (e.g. Lamers et al., 2020), two indices were constructed from the individual biomarkers: (i) a metabolic index, an overall measure of metabolic syndrome reflecting a composite cardiometabolic risk profile and (ii) an inflammatory index, an overall measure of low-grade systemic inflammation. For the metabolic index, glucose and triglyceride measures were $\log_e$-transformed and then all five metabolic biomarkers were standardized and averaged into an overall measure. For blood pressure, only systolic blood pressure was included in the metabolic index. The inflammatory index was calculated by $\log_e$-transforming, standardizing, and averaging IL-6 and CRP measures.

2.2.3. Sociodemographics

Potentially confounding sociodemographic variables included age (in years), sex, years of education, and current smoking status (yes/no), which were included in the analyses as covariates.

2.3. Statistical analyses

Analyses were conducted in R (version 4.1.2; R Core Team, 2021) using the *gamlj*-package (version 2.6.2; Gallucci, 2019). Data were analyzed using mixed-effects regression analyses, with a random intercept of 'Family-ID' to account for within-family clustering (34.4% of families included more than one proband-sibling pair; van Sprang et al., 2021).

As a benchmark, intraclass correlations (ICC) were calculated to examine the degree (i.e. 'small': ICC $<$ 0.15; 'medium': 0.15 $\leq$ ICC $<$ 0.3; 'large': ICC $\geq$ 0.3; Bliese, 2000; James, 1982) of resemblance in psychological symptoms and immunometabolic health indicators among probands and siblings (N = 636). ICCs were obtained from unconditional means models (linear for continuous data; logistic for dichotomous data), which were adjusted for age, sex, years of education, and current smoking status to reduce residual error (Shoukri et al., 2013). A detailed description of the calculation of ICC estimates and 95% confidence intervals (CI) can be found in Supplementary materials **A** in the Appendix.

Then, associations between outcomes in sibling (i.e. symptom severity of overall affective symptoms and specific atypical, energy-related depressive symptoms) and explanatory variables in siblings and probands (i.e. BMI, cardiometabolic disease, inflammatory disease, metabolic index, inflammatory index) were estimated among proband-sibling pairs (N = 380). All models were adjusted for proband symptom severity (i.e. to rule out the possibility that associations were due to familial clustering of psychopathology) as well as for proband and sibling age, sex, education, and current smoking status.[1] Analyses were divided in three main steps, using separate analytical models for each of the 5 indicators of poor immunometabolic health. In Step 1, indicators of poor immunometabolic health measured in siblings were included as explanatory variables. In Step 2, the same indicators of poor immunometabolic health measured in probands were added to Step 1 models in order to examine the potential independent contribution of proband immunometabolic health to sibling psychological symptoms. By adjusting effects of proband immunometabolic health for sibling immunometabolic health, potential associations of proband immunometabolic health with sibling psychological symptoms could not simply be explained by within-sibling comorbidity between poor immunometabolic health and psychopathology. In Step 3, sibling $\times$ proband indicator interaction terms were added to Step 2 models for each to evaluate whether the association between an indicator of poor immunometabolic health and symptom severity in siblings was moderated by the presence/degree of this indicator in probands. For instance, a significant sibling $\times$ proband interaction for BMI would indicate that the strength of the link between BMI and psychological symptoms in the sibling is increased (in case of a positive interaction) or reduced (in case of a negative interaction) when the proband (also) has a relatively high BMI. Analyses were repeated for individual components of metabolic and inflammatory index. In addition, analyses were repeated after excluding participants with a CRP level $>$ 10 mg/l, as such high CRP levels might be indicative of current infection (Nehring and Patel, 2019), although not necessarily (Mac Giollabhui et al., 2020).

Statistical tests were two-sided and considered to be statistically significant at $p < 0.05$. Proband-sibling pairs with missing data on a variable were deleted listwise from the analyses including that variable. To provide more insight into the size of the effect of familial clustering (i.e. also taking into account indicators of poor immunometabolic health in probands), percentages of additional explained variance (ΔR^2) were reported for indicators showing a significant proband main effect in Step 2 or a significant sibling $\times$ proband interaction in Step 3, as compared to Step 1. In line with recommendations by Nakagawa et al. (2017) for R^2 in mixed-effects models, both marginal (i.e. additional variance explained by fixed effects) and conditional ΔR^2 (i.e. additional variance explained by both fixed and random effects) were reported. The R code is available on the Open Science Framework (https://osf.io/g6e74/) to reproduce all analyses.

3. Results

The mean age of the sample was 49.7 years (SD = 13.2, range 20–78), mean years of education was 13.3%, and 62.4% were female. Sample characteristics for probands and siblings separately can be found in Table 1. Missing data on study variables was small (see **Table A.1** in Supplementary materials **A** in the Appendix). Of the 380 siblings, 191 (50.3%) had a lifetime depressive and/or anxiety disorder, while 189 (49.7%) had no lifetime disorders. Fig. 1 shows the covariate-adjusted ICCs of psychological symptoms and immunometabolic health indicators. The majority of indicators consistently showed comparable ranges of small to medium ICCs (ICC range: 0.14–0.25), with 18–21% of the variance in psychological symptoms and 14–25% of the variance in immunometabolic health explained by familial clustering. ICCs for individual components of metabolic and inflammatory index can be found in **Fig. B.1** of Supplementary materials **B** in the Appendix.

Associations of indicators of poor immunometabolic health in siblings and probands with overall affective symptoms in siblings are

[1] Cross-trait associations between siblings of psychosocial risk factors such as age, sex, education, and current smoking status with affective psychopathology have been studied previously in the same sample (van Sprang et al., 2023).

Table 1
Sample characteristics of probands and siblings.

	Probands $N = 256$	Siblings $N = 380$
Sociodemographics		
Age (years), *M* (*SD*)	48.52 (13.10)	50.46 (13.25)
Female sex, %	73.4	55.0
Education (years), *M* (*SD*)	13.42 (2.99)	13.17 (3.22)
Current smoking status, %	20.3	24.3
Immunometabolic health		
BMI (kg/m^2), *M* (*SD*)	26.11 (4.94)	25.88 (4.66)
Cardiometabolic disease, %	25.4	22.7
Inflammatory disease, %	22.7	25.3
Waist circumference (cm), *M* (*SD*)	91.48 (14.23)	92.96 (13.33)
Systolic blood pressure (mmHg), *M* (*SD*)	134.77 (20.23)	142.30 (22.05)
Fasting plasma glucose level (mmol/L), *M* (*SD*)	5.49 (0.93)	5.56 (1.03)
Triglyceride level (mmol/L), *M* (*SD*)	1.29 (0.91)	1.29 (0.92)
HDL-cholesterol level (mmol/L), *M* (*SD*)	1.60 (0.46)	1.56 (0.46)
IL-6 level (pg/ml), *M* (*SD*)	1.36 (2.32)	1.25 (2.47)
CRP level (mg/L), *M* (*SD*)	2.63 (5.06)	2.51 (4.39)
Medication use		
Fibrates or nicotine acid use, %	0.4	0.0
Statin use, %	9.0	9.5
Anti-diabetic medication use, %	5.5	4.7
Anti-hypertensive medication use, %	20.3	16.3
Non-steroidal anti-inflammatory medication use, %	5.9	3.4
Mental health		
Current depressive symptom severity, *M* (*SD*)	16.45 (10.49)	13.15 (9.72)
Current anxiety symptom severity, *M* (*SD*)	9.22 (8.11)	5.72 (6.09)
Current atypical, energy-related depressive symptom severity, *M* (*SD*)	2.79 (2.54)	2.04 (2.23)
Current (past 12-month) affective disorder diagnosis, %	37.5	26.8
Lifetime affective disorder diagnosis, %	100.0	50.3

Note: Sample sizes vary slightly due to marginally missing data on immunometabolic health indicators (see **Table A.1** in Supplementary materials **A** in the Appendix). *M* = mean; *SD* = standard deviation; BMI = Body Mass Index; HDL = High-Density Lipoprotein; IL-6 = interleukin-6; CRP = C-reactive protein; affective = depressive and/or anxiety.

reported in Table 2. Analyses with individual-level sibling indicators only (Table 2, Step 1) showed that higher BMI ($\gamma = 0.10$, $p = 0.033$), inflammatory disease ($\gamma = 0.25$, $p = 0.013$), and higher metabolic index ($\gamma = 0.28$, $p < 0.001$) were associated with more severe affective symptoms. In order to investigate the importance of weighing indicators of poor immunometabolic health within a family context, we then added as additional explanatory variables the same indicators assessed in probands in Step 2 and the sibling × proband indicator interaction terms in Step 3. No significant proband main effects (all $p > 0.13$; Table 2, Step 2) or sibling × proband interactions (all $p > 0.15$; Table 2, Step 3) were found for any of the indicators of poor immunometabolic health.

When focusing on more specific atypical, energy-related symptoms (Table 3), associations of poor immunometabolic health indicators increased in strength. Consistent with the findings for outcome of overall affective symptoms in sibling, analyses with individual-level sibling indicators only (Table 3, Step 1) showed that higher BMI ($\gamma = 0.58$, $p < 0.001$), inflammatory disease ($\gamma = 0.59$, $p = 0.023$), and higher metabolic index ($\gamma = 0.85$, $p < 0.001$) were associated with higher atypical, energy-related symptoms in sibling. In addition to these indicators, a significant positive association with atypical, energy-related symptoms in sibling was found for cardiometabolic disease ($\gamma = 0.56$, $p = 0.048$). When adding the same indicators assessed in probands as additional explanatory variables in Step 2 (Table 3), an independent negative association of proband cardiometabolic disease was found ($\gamma = -0.59$, $p = 0.046$, $\Delta R^2_{marginal} = 1.0\%$, $\Delta R^2_{conditional} = 0.001\%$). Of note, while its direction and effect size were similar, the association between proband cardiometabolic disease and sibling atypical, energy-related symptoms did not reach statistical significance ($\gamma = -0.54$, $p = 0.068$) when sibling cardiometabolic disease was not controlled for. No significant sibling × proband interactions were found for any of the indicators of poor immunometabolic health (all $p > 0.19$; Table 3, Step 3).

Repeating analyses for individual components of metabolic and inflammatory index as explanatory variables showed a similar pattern of results (full model results can be found in Supplementary materials B in the Appendix): as compared to outcome of overall affective symptoms in siblings (**Table B.1**), associations of individual biomarkers with outcome of specific atypical, energy-related symptoms (**Table B.2**) were stronger and there was no consistent added effect of also taking into account individual biomarkers in probands, on top of (Step 2) or in combination with (Step 3) those in siblings. In addition, rerunning analyses after excluding participants with a CRP level > 10 mg/l (i.e. 11 siblings in Step 1 and 20 proband-sibling pairs in Step 2 and Step 3) did not substantially change results (results not shown), indicating that (the lack of) cross-trait associations between probands and siblings were unlikely to be influenced by current acute infections. Furthermore, results remained unchanged when rerunning analyses after excluding pregnant participants (i.e. 1 sibling in Step 1 and 7 proband-sibling pairs in Step 2 and Step 3; results not shown), indicating that associations of individual (or based on) biomarkers other than BMI and waist circumference with psychological symptoms were unlikely to be influenced by current pregnancy.

4. Discussion

The present study investigated associations of a broad range of

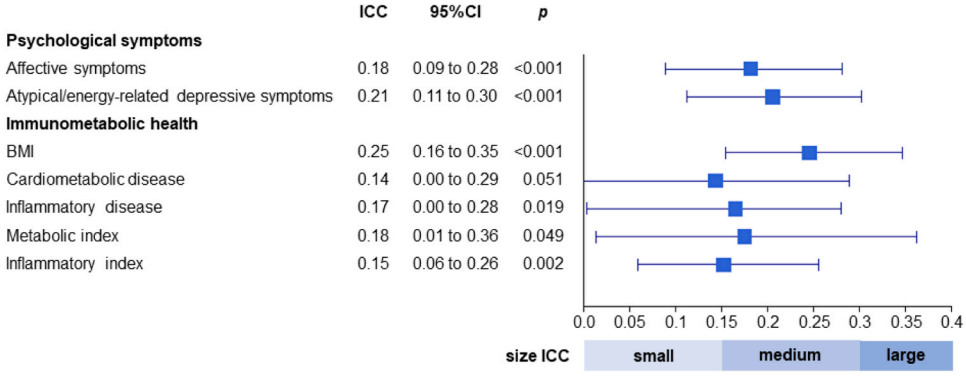

Fig. 1. The degree of proband-sibling resemblance in psychological symptoms and immunometabolic health, as reflected by covariate-adjusted (i.e. age, sex, years of education, current smoking status) intraclass correlations (ICC). Higher values indicate a higher degree of resemblance among probands and siblings from the same family ('small': ICC < 0.15, 'medium': 0.15 ≤ ICC < 0.3, and 'large': ICC ≥ 0.3; Bliese, 2000; James, 1982). Note that these analyses included all probands and siblings as singletons ($N = 636$) and not as proband-sibling pairs. A detailed description of the calculation of ICC estimates, 95% confidence intervals, and derived *p*-values testing whether estimates were significantly larger than zero can be found in Supplementary materials A in the Appendix. ICCs for individual components of metabolic and inflammatory index can be found in Fig. B.1 in Supplementary materials B in the Appendix. 95% CI = 95% confidence interval; BMI = Body Mass Index.

Table 2
Associations between immunometabolic health indicators and overall affective symptoms in the sibling (Step 1), and the independent (Step 2) and moderation effect (Step 3) of immunometabolic health in the proband ($N = 380$ proband-sibling pairs).

	Step 1			Step 2			Step 3		
Immunometabolic health indicators	γ	SE_γ	p	γ	SE_γ	p	γ	SE_γ	p
BMI									
sibling	**0.10**	**0.04**	**0.033**	**0.10**	**0.05**	**0.033**			
proband				-0.01	0.05	0.836			
sibling × proband interaction							0.003	0.002	0.166
Cardiometabolic disease									
sibling	0.15	0.11	0.172	0.16	0.11	0.141			
proband				-0.17	0.11	0.137			
sibling × proband interaction							-0.04	0.22	0.875
Inflammatory disease									
sibling	**0.25**	**0.10**	**0.013**	**0.25**	**0.10**	**0.014**			
proband				0.004	0.11	0.973			
sibling × proband interaction							0.16	0.23	0.482
Metabolic index									
sibling	**0.28**	**0.08**	**< 0.001**	**0.28**	**0.08**	**< 0.001**			
proband				-0.01	0.08	0.894			
sibling × proband interaction							-0.06	0.10	0.525
Inflammatory index									
sibling	-0.08	0.06	0.142	-0.08	0.06	0.159			
proband				-0.02	0.06	0.759			
sibling × proband interaction							-0.09	0.06	0.156

Note: Estimates (γ) and standard errors were retrieved from linear mixed-effects models with a random intercept of 'Family-ID' to account for within-family clustering: Step 1 (sibling individual-level associations), Step 2 (sibling and proband individual-level associations), and Step 3 (sibling × proband interactions). All models were adjusted for proband and sibling age, sex, education, and current smoking status and proband overall affective symptoms. Significant associations ($p < .05$) are presented in bold. Sample sizes vary slightly due to marginally missing data on immunometabolic health indicators (see **Table A.1** in Supplementary materials **A** in the Appendix). Results for individual components of metabolic and inflammatory index can be found in **Table B.1** in Supplementary materials **B** in the Appendix. SE_γ = standard error of γ.

Table 3
Associations between immunometabolic health indicators and specific atypical, energy-related depressive symptoms in the sibling (Step 1), and the independent (Step 2) and moderation effect (Step 3) of immunometabolic health in the proband ($N = 380$ proband-sibling pairs).

	Step 1			Step 2			Step 3		
Immunometabolic health indicators	γ	SE_γ	p	γ	SE_γ	p	γ	SE_γ	p
BMI									
sibling	**0.58**	**0.11**	**< 0.001**	**0.62**	**0.11**	**< 0.001**			
proband				-0.24	0.12	0.057			
sibling × proband interaction							0.002	0.005	0.644
Cardiometabolic disease									
sibling	**0.56**	**0.28**	**0.048**	**0.61**	**0.28**	**0.033**			
proband				**-0.59**	**0.29**	**0.046**			
sibling × proband interaction							-0.29	0.57	0.613
Inflammatory disease									
sibling	**0.59**	**0.26**	**0.023**	**0.64**	**0.26**	**0.015**			
proband				-0.40	0.29	0.172			
sibling × proband interaction							0.46	0.59	0.443
Metabolic index									
sibling	**0.85**	**0.20**	**< 0.001**	**0.92**	**0.20**	**< 0.001**			
proband				-0.34	0.22	0.121			
sibling × proband interaction							-0.33	0.25	0.192
Inflammatory index									
sibling	0.05	0.14	0.719	0.08	0.14	0.544			
proband				-0.26	0.15	0.086			
sibling × proband interaction							-0.09	0.16	0.563

Note: Estimates (γ) and standard errors were retrieved from linear mixed-effects models with a random intercept of 'Family-ID' to account for within-family clustering: Step 1 (sibling individual-level associations), Step 2 (sibling and proband individual-level associations), and Step 3 (sibling × proband interactions). All models were adjusted for proband and sibling age, sex, education, and current smoking status and proband specific atypical, energy-related depressive symptoms. Significant associations ($p < .05$) are presented in bold. Sample sizes vary slightly due to marginally missing data on immunometabolic health indicators (see **Table A.1** in Supplementary materials **A** in the Appendix). Results for individual components of metabolic and inflammatory index can be found in **Table B.2** in Supplementary materials **B** in the Appendix. SE_γ = standard error of γ.

cardiometabolic (such as diabetes mellitus, cardiovascular disease, stroke, and hypertension) and inflammatory diseases (such as rheumatoid arthritis and inflammatory respiratory/bowel disease) and related biomarker-based risk profiles with overall affective symptoms and with specific atypical, energy-related depressive symptoms. First, we examined whether these associations replicate in an at-risk sample of siblings of probands with lifetime affective disorders. Second, we used a sibling-pair design in order to disentangle and quantify the effect of familial clustering on these associations. Specifically, we studied the unique contribution of probands' immunometabolic health on siblings' psychological symptoms.

Many studies to date have established the link between poor

immunometabolic health and psychological symptoms within community (Howren et al., 2009; Leone et al., 2022; Smith et al., 2018; Valkanova and Ebmeier, 2013) and clinical samples of patients with affective disorders (Chae et al., 2023; Valkanova and Ebmeier, 2013). Also within the entire NESDA cohort, several immunometabolic biomarkers and BMI were found to be associated to (certain profiles of) affective symptoms, both cross-sectionally (Lamers et al., 2018, 2013; Milaneschi et al., 2021b) and longitudinally (Lamers et al., 2020, 2019). Importantly, the present study showed that this association is also mirrored within the NESDA family study of adult individuals at high risk for affective disorders: siblings of persons with lifetime affective disorders with immunometabolic diseases or commonly related metabolic dysregulations (i.e. higher BMI and metabolic syndrome index) had more psychological symptoms. This is in line with findings from two previous studies in at-risk samples of siblings of persons with affective disorders (de Kluiver et al., 2020; Vaccarino et al., 2008) and is consistent with previous meta-analytic evidence showing that patients with cardiometabolic disease and more metabolic dysregulations have an increased risk for depression as compared to controls (Valkanova and Ebmeier, 2013). Rather than focusing on isolated immunometabolic illnesses or biomarkers, we confirmed associations for a broad range of robust immunometabolic disease indicators and composite risk profiles based on individual biomarkers. This is especially relevant given that risks related to immunometabolic illness extend to a wide variety of psychopathology, indicating that their underlying mechanisms are most likely general, rather than disease-specific (Penninx and Lange, 2018). Moreover, the present study extends previous literature by showing that inflammatory diseases were related to higher symptoms – a relation that has been understudied to date: in contrast to cardiometabolic disease (Ghaemmohamadi et al., 2018; González-Castro et al., 2021; Mitchell et al., 2017; Rotella and Mannucci, 2013; Valkanova and Ebmeier, 2013; Yuan et al., 2019), large-scale meta-analytic studies on the increased risk for affective psychopathology in relation to inflammatory disease are lacking (with the exception of a few specific individual diseases, including rheumatoid arthritis, asthma, and pulmonary emphysema; Ng et al., 2022; Ye et al., 2021; Zhang et al., 2011).

While the present paper showed that inflammatory *diseases* were associated with more psychological symptoms, no association was found for inflammatory *index*. This may be explained by the fact that the inflammatory index is indicative of low-grade systemic inflammation, which is not necessarily the case in (active) inflammatory disease, for which substantially higher levels of inflammatory biomarkers would be expected. There are a lot of mechanisms that impact on low-grade systemic inflammation, which in itself is a complex pathway with many involved cytokines other than IL-6 and CRP. As such, the inflammatory index may pick up a much broader mechanism than only pointing towards inflammatory disease. Another possible reason is that we studied associations within in a high-risk sample of siblings of lifetime affected probands (of which 50.3% have a lifetime affective disorder themselves) with an already relatively elevated inflammation as what could be expected for healthy subjects. This reasoning is in line with previous meta-analytic evidence suggesting that inflammatory biomarker elevations in depression may not be due to an inflamed subgroup, but rather due to a continuous distribution of inflammatory biomarkers in depressed individuals, which is more homogeneous (shifted towards higher values) than in non-depressed individuals (Osimo et al., 2020).

In accordance with previous findings in (older) adult samples (Akbarzadeh et al., 2022; Feng et al., 2008; Kuo et al., 2017; Neijts et al., 2013; Santos et al., 2013; van Hecke et al., 2017), our findings confirm that, to a certain extent, immunometabolic diseases and related dysregulations cluster within families at high risk for affective disorders. The consistent mild to moderate proband-sibling resemblance across immunometabolic health features indicates that siblings of lifetime affected probands may (have) experience(d) similar adversities, but that substantial individual differences exist between siblings from the same family. Although admittedly speculative, this certain degree of clustering in immunometabolic health features between siblings from the same at-risk family may be expressed in shared biological (e.g. increased inflammatory reactivity) or behavioral pathways (e.g. learned poor dietary habits, sedentary behaviors, and unhealthy lifestyle features such as smoking or hazardous alcohol use) between siblings that have potentially influenced the development of both immunometabolic and mental health problems.

We were particularly interested in the relevance of familial clustering in the association between immunometabolic health and psychological symptoms. The associations of immunometabolic diseases and related dysregulations in siblings were not substantially affected by adjustment for immunometabolic and mental health status of probands. More importantly, there was limited evidence that the presence of poor immunometabolic health in the proband had a unique contribution for psychological symptoms in the sibling, over-and-above or in combination with siblings' own individual immunometabolic health. Overall, this suggest that familial clustering does not have a substantial impact on the cross-trait association between later life immunometabolic health and psychological symptoms in at-risk adult subjects. The mild to moderate proband-sibling resemblance in immunometabolic health (ICC range: 0.14–0.25) is comparable to what we have previously found in the same sample for psychosocial risk factors (ICCs range: 0.11–0.32; van Sprang et al., 2021). Nevertheless, we found very limited evidence for an added effect of proband risk over-and-above a sibling's individual risk for most indicators of poor immunometabolic health, while in another previous study in the same sample we showed that psychosocial risk factors in the proband were associated with affective symptoms in siblings, controlling for siblings' psychosocial risk factors (van Sprang et al., 2023). One possible reason for this difference in findings may be that psychosocial risk factors (e.g. early life adversity, low education/income) have their origin in the early family environment with strong long-term effect on both family members throughout the life span. Poor immunometabolic health on the other hand generally manifests in later adult life, in which individual factors (e.g., individual unhealthy lifestyle) may have a larger impact as compared to shared familial factors (Plomin, 2011; Plomin and Daniels, 1987). Large pedigree-based studies (Huider et al., 2021) showed that there is detectable but very small genetic covariance between, for instance major depressive disorder and traits such as BMI ($r_G = 0.08$) and obesity ($r_G = 0.16$). As such, it is conceivable that cross-sibling associations between immunometabolic health and psychological symptoms would be difficult to detect within the NESDA family study sample that has a relatively old age (i.e. mean age of approximately 50 years).

We consistently found stronger associations of immunometabolic health indicators with outcome of specific atypical, energy-related depressive symptoms than with outcome of overall affective symptoms, underscoring the clinical heterogeneity of depression. This is in line with previous results of us and others (Fried et al., 2020; Lamers et al., 2020, 2018; Simmons et al., 2020), showing that several inflammatory (i.e. CRP, IL-6, tumor necrosis factor α) and metabolic (i.e. fasting glucose, HDL-cholesterol, triglycerides, systolic blood pressure, waist circumference) biomarkers were specifically associated with atypical, energy-related symptoms, but not with melancholic symptoms. This underscores that metabolic/inflammatory dysregulations are not generically associated with affective symptomatology but map more consistently on atypical symptoms reflecting altered energy intake/expenditure balance. This atypical symptom dimension may therefore signal an immuno-metabolic form of depression (Milaneschi et al., 2020), that may explain the high co-morbidity of cardiometabolic and/or inflammatory diseases and depressive disorders. However, other researchers have emphasized that depression is even more heterogeneous and that we might need to go beyond (symptom profile) sum-scores and examine specific symptoms individually (Fried and Nesse, 2015; Lorenzo-Luaces et al., 2021). For instance, a recent study indicated that specifically symptoms related to fatigue and appetite, but not other symptoms, such as insomnia/hypersomnia were associated

with high inflammation (Moriarity et al., 2022). Overall, this underscores the need for future studies to explicitly study the clinical heterogeneity of depression.

Of note is that we did find one effect of familial clustering on siblings' atypical, energy-related symptoms: cardiometabolic disease in probands was unexpectedly associated with *decreased* symptoms in siblings. The direction of this effect is opposite to findings from the available sibling and twin studies showing that poor immunometabolic health in siblings *increased* psychopathology in co-siblings (Brew et al., 2018; Kendler et al., 2009; Leone et al., 2022; van Hecke et al., 2017). However, we only found this effect in relation to outcome of atypical, energy-related symptoms and not for any of the other tested immunometabolic health indicators. Moreover, given the genetic correlation between cardiometabolic disease and affective psychopathology (Grotzinger et al., 2022; Wang et al., 2022; Wray et al., 2018) and assuming that this genetic overlap is responsible for causing both conditions within the family, we may have (unintentionally) induced a spurious correlation (i.e. collider effect) between proband cardiometabolic disease and sibling symptomatology by adjusting for sibling cardiometabolic disease. This is supported by the finding that proband cardiometabolic disease was not associated with sibling symptomatology when sibling cardiometabolic disease was removed from the model. Thus, this result should be interpreted with caution.

A clear strength of the present study is the use of the sibling design, which allows to adequately study the effect of familial clustering by controlling for proband symptoms (excluding the possibility that effects were due to familial clustering of psychopathology) and sibling immunometabolic health (allowing to study the unique effect of proband immunometabolic health). Additionally, our sample had a relatively old age, which allows for the examination of siblings' more definite clinical profiles and interindividual discrepancies between siblings that emerged across the lifespan. However, the present study is not without limitations. First, as this study only used cross-sectional data, no conclusions can be drawn with regard to the direction of effects, especially since the association of poor immunometabolic health with affective symptoms is likely bidirectional (Batelaan et al., 2016; Gold et al., 2020; Ng et al., 2022; Penninx and Lange, 2018). Second, although this study used a relatively large clinically relevant sibling sample of 380 proband-sibling pairs, we may have had insufficient power for identifying interaction effects (Gelman et al., 2020). Third, self-report measures of psychological symptoms and chronic somatic diseases may have been confounded by participants' differential recall accuracy. However, we deem the impact low because previous studies have shown good performance of the self-reported IDS in capturing clinical diagnoses of depression (Drieling et al., 2007; Rush et al., 1996) and adequate accuracy of self-reported chronic somatic diseases (Kriegsman et al., 1996). Moreover, in the present study, self-reported presence of chronic somatic diseases was complemented with relevant medication use based on drug container observation to identify diseases that may have been missed by the self-report. Fourth, within the NESDA sibling study, no siblings of probands without a lifetime affective disorder were recruited as a control group. This is however important, as this would have provided a baseline against which cross-trait associations between siblings from at-risk families could have been compared (Maciejewski et al., 2018). As such, we were unable to test whether our findings could be generalized to the general adult population.

5. Conclusion

To conclude, the present study confirmed that a broad range of indicators of poor immunometabolic health are related to higher psychological symptoms also in at-risk adult siblings of probands with a lifetime affective disorder, with stronger effects for atypical, energy-related depressive symptoms than for overall affective symptoms. Although our findings confirmed that sibling resemblance of each immunometabolic health indicator was mild to moderate, we found limited evidence for a unique association of poor immunometabolic health in probands for siblings' affective symptoms. This suggests that in this specific sample of adult siblings from families at high risk for affective disorders, familial clustering does not have a substantial impact on the relationship between later-life immunometabolic alterations and psychological symptoms. Individual lifestyle factors offer an alternative explanation but future studies are needed to identify the exact mechanisms underlying the relationship.

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CRediT authorship contribution statement

B.W.J.H.P. developed the NESDA study concept and design. Together with B.W.J.H.P., B.M.E., and A.M.v.H. were closely involved in the design of the NESDA family study. E.D.v.S. prepared the data for the analyses. E.D.v.S. performed the data analysis and interpretation under supervision of D.F.M., B.W.J.H.P, and Y.M. E.D.v.S. drafted the manuscript, and Y.M., B.W.J.H.P., D.F.M., C.A.H., and E.J.G. provided critical revisions. All authors approved the final version of the paper for submission.

Declaration of Competing Interest

None.

Data Availability

The data that support the findings of this study are available via the website of NESDA (https://www.nesda.nl/pro-index/), which will be provided after handing in a data request. This paper was pre-registered on the Open Science Framework; here, the R code for the analyses can be found as well (https://osf.io/g6e74/).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106326.

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