Genetic and Environmental Contribution to the Co-Occurrence of Endocrine-Metabolic Disorders and Depression: A Nationwide Swedish Study of Siblings

Marica Leone, Ph.D., Ralf Kuja-Halkola, Ph.D., Amy Leval, Ph.D., Agnieszka Butwicka, M.D., Ph.D., Jakob Skov, M.D., Ph.D., Ruyue Zhang, Ph.D., Shengxin Liu, M.Sc., Henrik Larsson, Ph.D., Sarah E. Bergen, Ph.D.

Objective: Depression is common in individuals with endocrine-metabolic disorders and vice versa, and a better understanding of the underlying factors contributing to the comorbidity of these disorders is needed. This study investigated the familial coaggregation of depression and endocrine-metabolic disorders and estimated the contribution of genetic and environmental factors to their co-occurrence.

Methods: This population-based cohort study included 2.2 million individuals born in Sweden between 1973 and 1996, with follow-up through 2013. Participants were linked to their biological parents, allowing identification of full siblings, maternal half siblings, and paternal half siblings. Diagnoses of depression and endocrine-metabolic conditions were investigated, with the latter grouped into autoimmune disorders (autoimmune hypothyroidism, Graves' disease, and type 1 diabetes) and non-autoimmune disorders (type 2 diabetes, obesity, and polycystic ovary syndrome). Logistic regression and Cox regression were used to estimate the associations between endocrine-metabolic disorders and depression within the same individual and across siblings. Quantitative genetic modeling was performed to investigate the relative contribution of genetic and environmental influences.

Results: Individuals with endocrine-metabolic disorders had a significantly higher risk of depression, with odds ratios ranging from 1.43 (95% CI=1.30, 1.57) for Graves' disease to 3.48 (95% CI=3.25, 3.72) for type 2 diabetes. Increased risks extended to full and half siblings. These correlations were mainly explained by shared genetic influences for non-autoimmune conditions, and by nonshared environmental factors for autoimmune disorders, especially for type 1 diabetes.

Conclusions: These findings provide phenotypic and etiological insights into the co-occurrence of depression and various endocrine-metabolic conditions, which could guide future research aiming at identifying pathophysiological mechanisms and intervention targets.

Am J Psychiatry 2022; 179:824–832; doi: 10.1176/appi.ajp.21090954

Depression and endocrine and metabolic disorders are major causes of disability and mortality, representing a growing public health concern at the global level (1–3). Several studies have established elevated co-occurrence of depression and endocrine-metabolic diseases, including thyroid gland disorders, type 1 diabetes (T1D), type 2 diabetes (T2D), obesity, and polycystic ovary syndrome (PCOS) (4–8). A bidirectional relationship has been reported between depression and obesity, as well as between depression and T2D, where one disorder increases the risk of subsequent development of the other and vice versa. However, other studies examining the bidirectional phenotypic causation hypothesis have reported mixed results (6, 9, 10).

Several biological, psychological, and behavioral factors have been proposed to influence the associations between these conditions, acting as mediating mechanisms in the causal relationships between depression and endocrine-metabolic diseases, and/or as common underlying factors affecting the risks of these conditions. Shared genetic influences could represent some of these common origins contributing to the development of such co-occurring disorders. This is known as genetic pleiotropy, when certain conditions or traits share genetic risk variants conferring a disposition for both disorders or traits in the same individual. Studies of families and twins have shown that genetic factors explain ~40% of the phenotypic variation in liability for depression (11), ~40% for obesity (12), 81% for T1D (13), 72% for T2D (14), between 38% and 71% for PCOS (15), and ~60% for both Hashimoto's thyroiditis and Graves' disease (13). Growing evidence suggests genetic overlap between depression and some endocrine-metabolic disorders, in

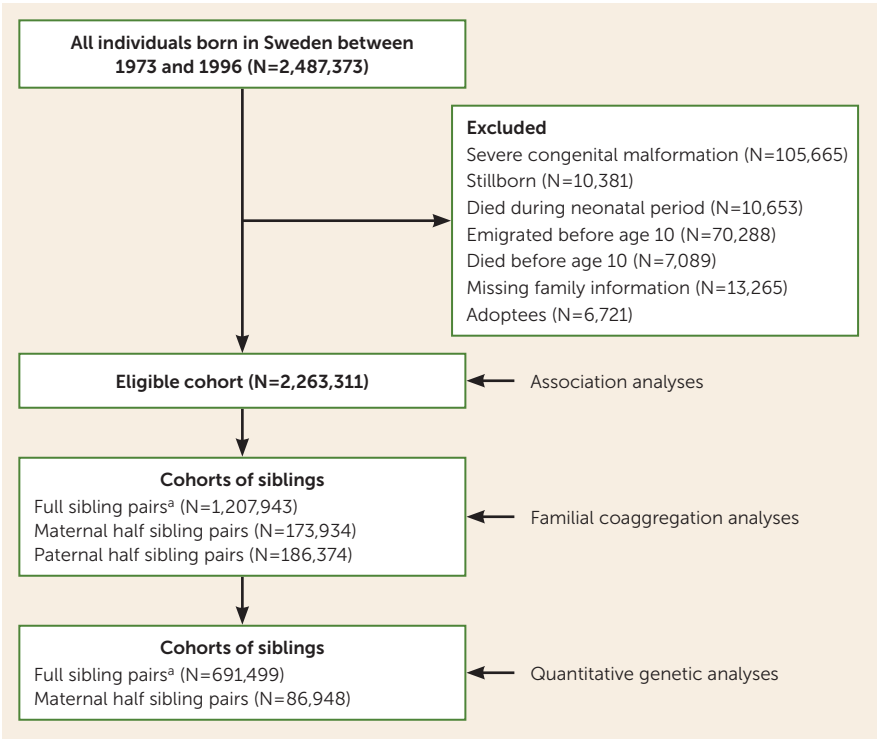
See related feature: **Editorial** *by Dr. Jespersen and colleagues (p. 788)*

particular obesity (16), T2D (17), and PCOS (4). This finding has been supported by a number of studies using molecular genetic data (18–20), while other investigations failed to replicate some of these results (21, 22). The inconsistency in evidence is likely due to differences in disorder measurements, depression heterogeneity, and methodological approaches.

A greater understanding of the possible risk factors shared between these conditions is needed in order to elucidate potentially modifiable targets that could lead to tailored treatment strategies for individuals with co-occurring depression and different endocrine-metabolic disorders. Longitudinal population-based research using clinical diagnoses could help enlighten the etiological underpinnings of these conditions.

We investigated the familial coaggregation of clinically diagnosed depression and endocrine-metabolic disorders to test for the presence of shared familial liability, and we estimated the genetic and environmental contributions to the co-occurrence of these conditions using quantitative genetic modeling.

FIGURE 1. Flow diagram of the study population



[a] Excluding monozygotic twin pairs.

METHODS

Study Population

We conducted an observational cohort study using nationwide Swedish registers linked by unique personal identity numbers (23). The cohort selection process is illustrated in Figure 1. All individuals born in Sweden between 1973 and 1996 were identified from the Medical Birth Register (24). Demographic information was obtained from the Total Population Register (25), Cause of Death Register (26), and Multi-Generation Register (27). We excluded children with severe congenital malformations, stillbirths, and neonatal deaths. We further excluded individuals who emigrated or died before age 10, had missing information regarding their biological parents, or were adopted. The final cohort consisted of 2,263,311 individuals who were followed up from birth until emigration, death, or December 31, 2013, whichever occurred first. Each individual was linked to their biological parents to create three cohorts of siblings: full siblings, maternal half siblings, and paternal half siblings (see Table S1 in the online supplement). Monozygotic twins were excluded from the sibling analyses because their genetic sharing is higher than that of other full siblings. This study necessitated no informed consent and was approved by the Regional Ethical Review Board in Stockholm (2013/862-31/5).

Assessment of Endocrine-Metabolic Disorders and Depression

We used information from the National Patient Register (28), which reached full nationwide coverage for hospitalizations in 1987 and 80% coverage for outpatient diagnoses in 2001, coded according to ICD-8, ICD-9, and ICD-10. We investigated endocrine-metabolic disorders diagnosed during the follow-up period, grouping these into autoimmune disorders (autoimmune hypothyroidism, Graves' disease, and T1D) and non-autoimmune disorders (T2D, obesity, and PCOS), including the first-time diagnosis for each disease, irrespective of prior endocrine-metabolic disorders. Because PCOS affects only women, only females were included in the analyses investigating this disorder. Depression cases were defined as individuals who received a depression diagnosis during the follow-up. A complete list of all ICD codes included in this study is provided in Tables S2 and S3 in the online supplement.

STATISTICAL ANALYSIS

Association and Familial Coaggregation Analyses

We used logistic regression and Cox proportional hazards regression models to evaluate the association between endocrine-metabolic disorders and depression, comparing unadjusted (logistic regression) and adjusted (Cox regression) estimates for follow-up time. For the logistic regression, we coded exposures (endocrine-metabolic disorders) and

outcome (depression) as lifetime diagnoses (0 or 1 for absence or presence, respectively), and estimated odds ratios with 95% confidence intervals. In the Cox models, we computed hazard ratios and 95% confidence intervals, using attained age as the underlying timescale (i.e., we compared individuals of the same age) and time-varying exposure—where an individual was considered unexposed until the first observed diagnosis of the exposure condition, and exposed afterward. Since Cox regression takes into account time at diagnosis, we compared models in which the exposure was an endocrine-metabolic disease with models in which the exposure was depression, to explore whether the order of these diagnoses influences the associations.

First, we compared the risk of depression in individuals with and without endocrine-metabolic disorders in the full cohort. Then we evaluated familial coaggregation patterns of these disorders, analyzing full siblings, maternal half siblings, and paternal half siblings separately, comparing the risk of the outcome disorder in individuals with a sibling with and without the exposure disorder. If an association between two disorders is observed in the index person, and if the association exists but is lower in the full-sibling sample, this indicates that shared familial liability contributes to the phenotypic association between these conditions. Further comparison of different types of siblings can point to the source of familial liability (genetic or environmental). Full siblings share on average 50% of their segregating genes, whereas half siblings share 25%. Full and maternal half siblings tend to share environmental factors to a greater extent than paternal half siblings, as they had a similar prenatal environment and often reside predominantly with their mothers after parental separation (29). Thus, a greater association among full siblings compared with maternal half siblings suggests that genetic factors may be of importance, whereas a greater association in maternal compared with paternal half siblings indicates shared environmental contributions.

All possible combinations of sibling pairs were identified, with each individual contributing at least once as an index person and once as a sibling. The analyses were adjusted for sex and birth year to account for differences in disorder prevalence between sexes and over the study period. We used a cluster robust (sandwich) estimator for standard error calculation, clustered by family, to account for nonindependence of family data (30). A p value <0.05 was considered statistically significant. Additionally, to adjust for multiple testing, we report a Bonferroni-corrected significance level of $p<0.005$, accounting for the 11 main analyses. Data management was performed using SAS, version 9.4.6 (SAS Institute, Cary, N.C.), and analyses were performed using R, version 4.0.3 (R Foundation for Statistical Computing, Vienna).

Sensitivity Analyses

We conducted several sensitivity analyses. First, we restricted the study population to individuals born between 1987 and 1996 (rather than 1973–1996) to minimize loss of early diagnoses for the oldest individuals in the main cohort due to the fact that inpatient information from the National Patient Register reached nationwide coverage in 1987. Second, because females have a twofold increased risk of depression compared with males (31), we conducted analyses stratified by sex of the outcome person to investigate differences between sexes. Finally, we performed analyses stratified by parental educational attainment as an indicator of socioeconomic status, defined as low (primary school and lower and upper secondary school) or high (≥1 year of university), using information from the Longitudinal Integration Database for Health Insurance and Labor Market Studies (32).

Quantitative Genetic Analyses

Quantitative genetic modeling was used to estimate the contribution of genetic, shared, and nonshared environmental factors to the familial liability and to evaluate the genetic and environmental correlations across disorders (33). In these analyses, full and maternal half sibling pairs were included. Within each family, we selected only one pair of siblings (the oldest, for a longer follow-up time) to avoid dependency between sibling pairs from the same family and to increase the precision of the estimates, resulting in 691,499 full sibling pairs and 86,948 maternal half sibling pairs (for PCOS, only female individuals were included: 211,178 full sibling pairs and 29,418 maternal half sibling pairs). Given the low prevalence of Graves' disease in the sibling cohorts, this disorder was not included in the quantitative genetic analyses. Because diagnoses were treated as binary variables, we used a liability threshold framework, where disease risks were assumed to represent an underlying normal distribution of liability and the risk was above an estimated threshold if the disease was observed and below the threshold if no disease was observed (33). Correlations between these assumed normally distributed liabilities are referred to as tetrachoric correlations. We specified additive genetic (A), shared environmental (C; nongenetic factors that make siblings in a pair similar), and nonshared environmental (E; unique environmental components making siblings dissimilar) factors as sources of variance and covariance between depression and endocrine-metabolic disorders. The following assumptions were made: A factors correlate at 0.50 for full siblings and 0.25 for half siblings, as they share 50% and 25% of their cosegregating genes, respectively; C factors correlate at 1 for both full and maternal half siblings; E factors correlate at 0 across all siblings. For each combination of depression and endocrine-metabolic disorders, we fitted bivariate models that included A, C, and E components (ACE model). Because the prevalence of disorders tends to differ in nuclear families and extended families, prevalence rates were allowed to vary across full and half siblings (34). Analyses were adjusted for sex and birth year of both the index person and the sibling (except for PCOS analysis, where no sex adjustment was made) and were performed in OpenMx (35) using weighted least squares. More details on the model are

provided in the supplementary methods section in the online supplement.

RESULTS

The demographic and clinical characteristics of the study population are summarized in Table 1. A total of 2,263,311 individuals (48.8% female) were followed up for a median of 27 years (IQR=22, 34). The prevalence of depression was 5.2% during the observed period (N=118,051; 63.0% female), and it was generally consistent across advancing birth years. The mean age at first recorded inpatient or outpatient diagnosis of depression was 23 years for both sexes, with the majority of individuals receiving their first diagnosis between ages 17 and 30, reflecting a lower risk of depression in childhood as well as limited follow-up for the youngest participants in the study cohort. Individuals with depression appear to have a higher prevalence of endocrine-metabolic disorders than individuals without depression (see Table S4 in the online supplement for sex-specific prevalence), particularly of autoimmune hypothyroidism and obesity. The prevalences of all conditions among sibling cohorts are reported in Tables S5–S7 in the online supplement.

Association and Familial Coaggregation Analyses

Associations between endocrine-metabolic disorders and depression, and their familial coaggregation, are shown in Figure 2. Compared to the general population, individuals diagnosed with endocrine-metabolic disorders had statistically significantly increased risk of depression (for exposure to any autoimmune disease, odds ratio=2.05, 95% CI=1.99, 2.12; for exposure to any non-autoimmune disease, odds ratio=2.33, 95% CI=2.28, 2.39). The strongest associations were observed for exposure to T2D (odds ratio=3.48, 95% CI=3.25, 3.72), obesity (odds ratio=2.44, 95% CI=2.37, 2.50), and autoimmune hypothyroidism (odds ratio=2.34, 95% CI=2.25, 2.44). The risk of depression was considerably lower but present in full siblings of individuals with endocrine-metabolic disorders compared with full siblings of individuals without endocrine-metabolic disorders (odds ratios ranged from 1.15 [95% CI=1.02, 1.29] for exposure to Graves' disease to 1.53 [95% CI=1.37, 1.69] for exposure to T2D). Associations between depression and T2D, obesity, autoimmune hypothyroidism, and PCOS were higher in full siblings compared to maternal half siblings, suggesting genetic influences on each disorder. In contrast, no difference in depression risk was observed between full, maternal half, and paternal half siblings of individuals with T1D, potentially indicating that unique environmental factors may underlie the association between the two disorders. Finally, the magnitude of odds ratios observed between maternal and paternal half siblings was overall comparable, suggesting a weak role of shared environmental factors in explaining these associations.

Overall, estimates were consistent when using Cox models, regardless of whether depression was modeled as the outcome or the exposure disorder (see Figure S1 in the online supplement).

Estimates, p values, and Bonferroni-corrected p values for all analyses are listed in Tables S8–S10 in the online supplement.

TABLE 1. Demographic and clinical characteristics of the study cohort

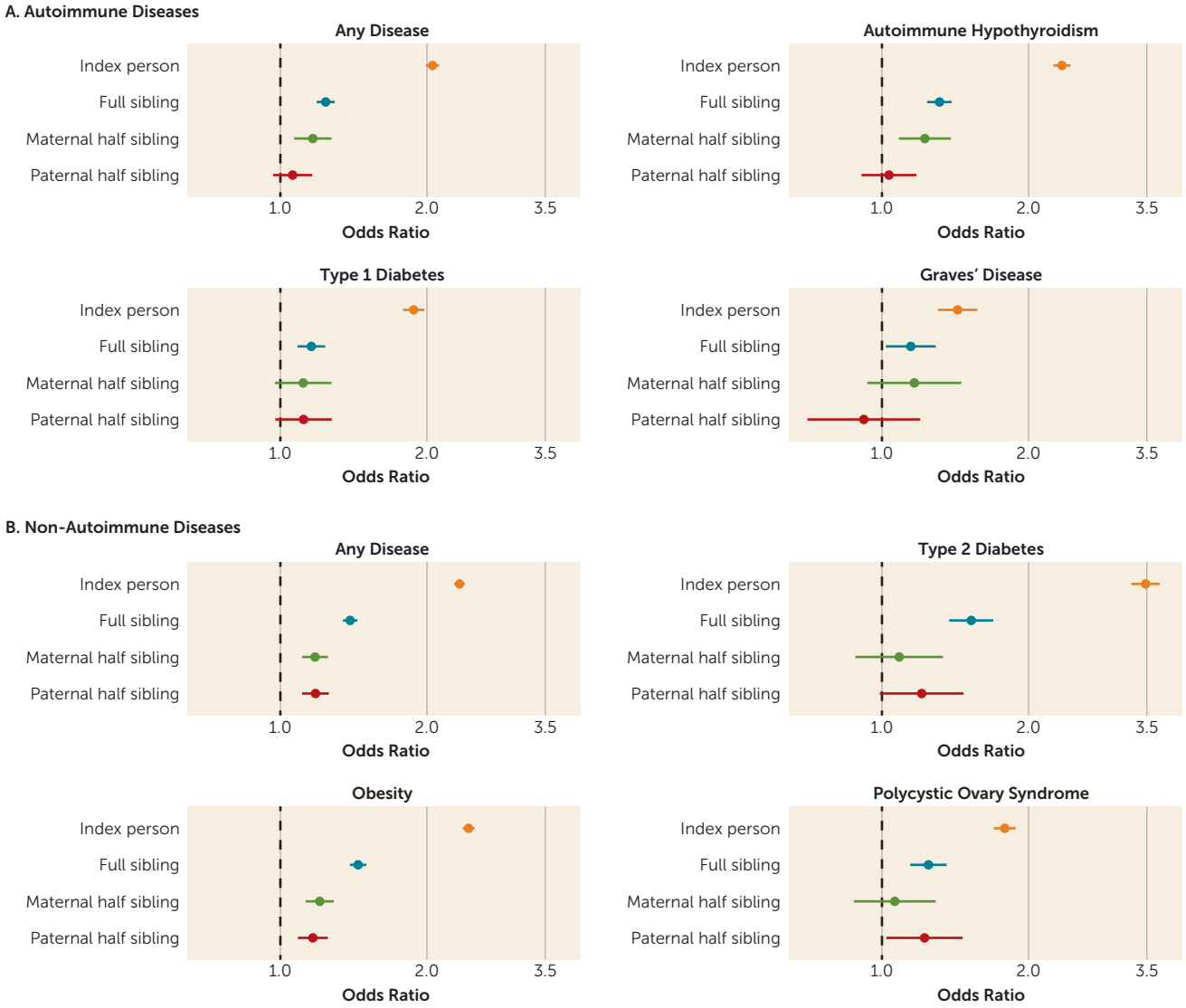
Measure	No Depression		Depression	
	N	%	N	%
Total cohort	2,145,260	94.8	118,051	5.2
Sex				
Female	1,030,975	48.1	74,326	63.0
Male	1,114,285	51.9	43,725	37.0
Birth year				
1973–1977	438,857	20.5	23,852	20.2
1978–1982	399,259	18.6	25,000	21.2
1983–1987	415,993	19.4	27,310	23.1
1988–1992	517,278	24.1	28,041	23.8
1993–1996	373,873	17.4	13,848	11.7
	Mean	SD	Mean	SD
Age (years) at first recorded diagnosis of depression				
Female			23.2	6.3
Male			23.8	6.3
	N	%	N	%
Age (years) at first recorded diagnosis of depression, by age group				
4–12			1,027	0.9
13–16			14,123	12.0
17–20			30,114	25.5
21–25			30,889	26.2
26–30			22,823	19.3
31–40			15,422	13.1
Endocrine and metabolic disorders				
Any autoimmune condition	37,733	1.8	4,720	4.0
Autoimmune hypothyroidism	17,993	0.8	2,892	2.4
Graves' diseases	4,951	0.2	489	0.4
Type 1 diabetes	17,507	0.8	1,737	1.5
Any non-autoimmune condition	55,925	2.6	8,080	6.8
Type 2 diabetes	5,431	0.3	1,049	0.9
Obesity	41,305	1.9	6,126	5.2
Polycystic ovary syndrome[a]	12,397	1.2	1,675	2.3

[a] When polycystic ovary syndrome was investigated, only female individuals were included (N=1,105,301, of whom 74,326 [6.7%] received a diagnosis of depression).

Sensitivity Analyses

When restricting the study population to individuals born between 1987 and 1996 (rather than between 1973 and 1996), patterns of association were comparable to those observed when using the full cohort (see Figure S2 in the online supplement). Statistically significant sex differences were observed for exposure to autoimmune hypothyroidism (females: odds ratio=2.27, 95% CI=2.17, 2.37; males: odds

FIGURE 2. Association and familial coaggregation of depression and endocrine-metabolic disorders, grouped as autoimmune and non-autoimmune diseases[a]



[a] Error bars indicate 95% confidence intervals.

ratio=3.45, 95% CI=3.07, 3.88) and obesity (females: odds ratio=2.32, 95% CI=2.25, 2.40; males: odds ratio=3.02, 95% CI=2.85, 3.20) (see Figure S3 in the online supplement). Finally, parental educational attainment did not appear to influence the associations between endocrine-metabolic disorders and depression (see Figure S4 in the online supplement).

Quantitative Genetic Analyses

Heritability was estimated to be 39% in depression; approximately 70% in obesity, T1D, and T2D; 57% in autoimmune hypothyroidism; and 28% in PCOS (see Table S11 in the online supplement).

In agreement with the observed pattern of odds ratios of depression in individuals with and without endocrine-metabolic disorders, stronger phenotypic correlations were observed between depression and T2D (odds ratio=0.22, 95% CI=0.20, 0.23), obesity (odds ratio=0.19, 95% CI=0.18, 0.20), and autoimmune hypothyroidism (odds ratio=0.17, 95% CI=0.16, 0.18), with genetic factors explaining 74%, 56%, and 34% of these correlations, respectively, and unique environmental factors explaining 33%, 32%, and 53%, respectively (Figure 3). In contrast, we found little evidence of genetic influences underlying the correlation between depression and T1D, with nonshared environmental factors explaining 84% of the phenotypic correlation (odds ratio=0.11, 95% CI=0.10, 0.13). Finally, our results pointed to a weak shared environmental contribution to the co-occurrence of depression and all endocrine-metabolic disorders. Estimates (with 95% confidence intervals) of the phenotypic correlations and the bivariate heritability explained by A, C, and E are listed in Tables S12 and S13 in the online supplement. It is important to note that the confidence

FIGURE 3. Phenotypic correlations and bivariate heritability between depression and endocrine-metabolic disorders explained by additive genetic, shared, and nonshared environmental factors[a]

[a] Because no constraints on direction (positive or negative) of contribution of genetic, shared environmental, and nonshared environmental factors to covariance were imposed, some contributions may be in opposite directions compared to the others. However, the presented percentages add up to 100% when summing positive and negative contributions.

intervals for some of these estimates were particularly wide due to model optimization issues.

DISCUSSION

In this nationwide register-based study of 2,263,311 individuals, we explored the associations between endocrine-metabolic disorders and depression using two complementary designs: familial coaggregation analysis and quantitative genetic modeling. To our knowledge, this is the largest sibling study investigating these associations and the first study to quantify and decompose the correlations between depression and T1D into genetic and environmental etiologies.

In line with previous research, we showed that individuals with endocrine-metabolic disorders were at increased risk of depression compared with the general population, especially for exposure to T2D, obesity, and hyperthyroidism (2.3–3.5 times higher odds), with males displaying elevated relative risks for the latter two compared to females' relative risks. Full siblings of individuals with endocrine-metabolic disorders were also at higher risk of depression, suggesting that shared familial liability contributes to the co-occurrence of these conditions.

For the non-autoimmune endocrine-metabolic disorders (T2D, obesity, and PCOS), the shared familial liability was primarily due to genetics, with very small contributions from shared environmental factors, as suggested by the familial coaggregation analysis (i.e., the strongest associations with depression were found between full siblings, followed by maternal and paternal half siblings), and these findings were further supported by quantitative genetic modeling. Our results are consistent with previous studies suggesting shared genetic origins between depression and these conditions (4, 16, 17), which is also reflected in the shared mechanisms linking these disorders (36). For example, a number of common biological mechanisms have been proposed to explain the bidirectional depression-obesity link, including hyperactivation of the hypothalamic-pituitary-adrenal axis, immuno-inflammatory activation, and neuroendocrine system dysregulation (6). These biological pathways may act as

common underlying mechanisms influencing the liability to both depression and obesity, and/or as mediating factors in the causal link between the two conditions. Similar shared biological origins have been suggested to explain the bidirectional relationship between depression and T2D (10). Intuitively, associations between obesity, T2D, and PCOS have also been established, all displaying common metabolic abnormalities such as insulin resistance (37, 38). Overall, our findings suggest that similar etiologies for depression and comorbid obesity, T2D, and PCOS exist, and that family history may help identify risk factors for these co-occurring disorders. Furthermore, characterization and modification of upstream biomarkers of both depression and these non-autoimmune conditions could potentially prevent development of such chronic and debilitating illnesses. It is important to note that ~30% of the phenotypic correlation between depression and non-autoimmune endocrine-metabolic disorders was attributable to environmental influences not shared between siblings. Behavioral and psychosocial factors such as sedentary lifestyle, poor nutrition, and poor sleep hygiene may represent some of these risk factors, which are accessible and modifiable, and which should remain key targets for prevention strategies and treatments of both depression and these endocrine-metabolic disorders. Some antidepressants have also been shown to influence the risk of obesity and T2D, although inconsistency of the evidence highlights the need for further investigation of the causal role of antidepressants in the development of these conditions (10, 39).

In contrast, the phenotypic correlations between depression and autoimmune endocrine-metabolic disorders (autoimmune hypothyroidism and T1D), while not high (0.17 and 0.11, respectively), were largely explained by nonshared environmental factors. This was especially relevant in the association between T1D and depression, for which no evidence of shared genetic influences emerged. Our results are in line with a previous study, which found a weak genetic contribution to the co-occurrence of depression and autoimmune disorders using cross-trait polygenic risk score analyses and linkage disequilibrium score regression (40).

This may reflect the existence of a direct link between these disorders via environmental mechanisms and/or causal environmental factors influencing the risk of both conditions. In accordance with emerging evidence, our study showed that although both T1D and T2D result in persistent hyperglycemia, their association with depression appeared to be driven by different underlying mechanisms. T1D usually has an earlier onset than T2D, with the potential to disrupt developmental processes during childhood and adolescence. Psychological mechanisms (e.g., parental stress and the burden of a lifelong disorder requiring a complex management regimen) as well as biological mechanisms (e.g., inflammation and cerebral damage) have been suggested to mediate the link between T1D and depression (7).

From the quantitative genetic analyses, negative genetic and environmental contributions were observed for some phenotypes, for which there may be a number of possible reasons. For example, it is possible for a parameter whose true value is zero to be negative due to sampling error, which is particularly likely in smaller samples (41). Another possibility is that such negative estimates actually reflect the underlying genetic or environmental mechanisms under investigation (42, 43), for example, genes that have opposite effects on two phenotypes, or full-sibling cross-disorder correlations that are larger than the phenotypic correlations. Replication studies with larger sample sizes are needed.

Parental education level did not appear to influence the association and familial coaggregation of depression and endocrine-metabolic disorders; moreover, these findings were consistent in the quantitative genetic analyses, where we observed only a weak contribution of environmental factors shared between siblings (e.g., parental academic performance) to the co-presentation of these disorders.

Findings from the familial coaggregation analyses were consistent when comparing logistic and Cox regression models, indicating that there was no major difference when modeling the explored diagnoses as lifetime conditions or when considering time to diagnosis. Furthermore, similar results were obtained when depression was modeled as the outcome condition or as the exposure condition, suggesting a possible bidirectionality between the investigated disorders, but also encouraging caution when using diagnosis ordering to infer causality, since diagnostic records do not provide definitive information about when health problems occurred.

This study enhances our understanding of co-occurring depression and endocrine-metabolic disorders, and it underscores the importance of screening for comorbid symptoms in individuals with these conditions, which may lead to risk identification and early detection of concomitant conditions, as well as promotion of appropriate prevention and intervention strategies. Thus, collaboration between psychiatrists and endocrinologists should be prioritized in an effort to comprehensively manage both psychiatric and somatic conditions. Moreover, we present evidence of stronger shared genetic influences between depression and T2D, obesity, and PCOS compared with autoimmune disorders, suggesting different etiologies for these comorbid conditions and the need for tailored treatment strategies for individuals with depression and different comorbid endocrine-metabolic conditions.

This study had several limitations. Depression and endocrine-metabolic disorders treated within primary care could not be captured, possibly limiting the generalizability of the findings to the more severe clinical cases, as well as to treatment-seeking individuals. Yet, diagnoses given to children and adolescents are well captured in the National Patient Register, as it is standard for these patients to be referred to specialist health care for these conditions.

Exposure to T1D and T2D could have been misclassified, since ICD-8 and ICD-9 did not distinguish between the two types. Nevertheless, we were able to minimize this issue by restricting T1D measures to individuals with a diagnosis of

diabetes before age 19, given that the majority (98%–99%) of Swedish children diagnosed with diabetes at 0–18 years of age have been shown to have T1D (44). Since the maximum age at the end of follow-up was 40 years, we could investigate only early-onset forms of T2D, autoimmune hypothyroidism, and Graves' disease, which could represent more heritable forms of these disorders and therefore may explain why we found stronger genetic contributions to these disorders compared to a previous study using linkage disequilibrium score regression (45). Similarly, we defined obesity using clinical diagnoses rather than BMI measures, potentially capturing a more serious form of the disorder, which could explain the increased heritability estimated in this study compared with previous research (45, 46). Moreover, depression heterogeneity could have hampered the results, since the explored associations are likely to vary in different subgroups of patients. Further research is needed to investigate the role of age at onset of depression, symptom profiles, severity, depression history, and other psychiatric comorbidities.

Given the low power in our quantitative genetic analyses, caution in interpretation of the genetic and environmental correlations is warranted, and replication studies with increased sample sizes are encouraged. Furthermore, one key assumption of quantitative genetic analyses is that there are no correlations or interactions between genes and environment (47). As a consequence, estimates may be biased if this assumption does not hold. Future research assessing gene-environment interplay will be important to gain further insights into the etiology of depression and endocrine-metabolic disorders.

When investigating the possible role of socioeconomic status, we performed our analyses across different parental education levels; given that academic performance has been shown to be moderately heritable and correlated with offspring education (48), there is a risk that adjusting for parental educational attainment could lead to biased estimates (e.g., by conditioning on a collider). Finally, although we found no evidence of a major effect of socioeconomic status in the explored associations, it is important to note that parental educational attainment may inadequately capture the complexity of socioeconomic status.

In summary, we presented convergent evidence from two methods, supporting knowledge from previous research on the comorbidity between depression and various endocrine-metabolic disorders and providing new insights into the etiological sources of their co-occurrence. We reported considerable shared genetic influences between depression and non-autoimmune endocrine-metabolic disorders, and limited common genetic factors between depression and autoimmune disorders, particularly T1D. Our results encourage clinical vigilance for co-presentation of endocrine-metabolic disorders and depression, providing a useful foundation for future research aimed at characterizing and targeting the underlying biological mechanisms and modifiable risk factors.

AUTHOR AND ARTICLE INFORMATION

Janssen Pharmaceutical Companies of Johnson & Johnson, Solna, Sweden (Leone, Leval); Department of Medical Epidemiology and Biostatistics (Leone, Kuja-Halkola, Leval, Butwicka, Zhang, Liu, Larsson, Bergen) and Department of Molecular Medicine and Surgery (Skov), Karolinska Institutet, Solna, Sweden; Child and Adolescent Psychiatry Stockholm, Stockholm Health Care Services, Region Stockholm, Sweden (Butwicka); Department of Child Psychiatry, Medical University of Warsaw, Warsaw (Butwicka); Department of Biostatistics and Translational Medicine, Medical University of Lodz, Lodz, Poland (Butwicka); Department of Medicine, Karlstad Central Hospital, Karlstad, Sweden (Skov); School of Medical Sciences, Örebro University, Örebro, Sweden (Larsson).

Send correspondence to Dr. Bergen (sbergen@gmail.com).

This study was funded by the European Union's Horizon 2020 Research and Innovation Programme under Marie Sklodowska-Curie grant agreement no. 721567.

Dr. Leone is an employee of Johnson & Johnson. Dr. Leval is an employee of and owns stock in Johnson & Johnson. Dr. Larsson has received research grants from Shire/Takeda; he has served as a speaker for Evolan Pharma, Medice, and Shire/Takeda; he has received sponsorship from Evolan Pharma and Shire/Takeda for a conference; and he is editor-in-chief of *JCPP Advances*. The other authors report no financial relationships with commercial interests.

Received September 27, 2021; revision received May 9, 2022; accepted June 27, 2022; published online September 21, 2022.

REFERENCES

1. World Health Organization: Depression and Other Common Mental Disorders: Global Health Estimates. Geneva, World Health Organization, 2017
2. Taylor PN, Albrecht D, Scholz A, et al: Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol 2018; 14: 301–316
3. Bhupathiraju SN, Hu FB: Epidemiology of obesity and diabetes and their cardiovascular complications. Circ Res 2016; 118:1723–1735
4. Cesta CE, Kuja-Halkola R, Lehto K, et al: Polycystic ovary syndrome, personality, and depression: a twin study. Psychoneuroendocrinology 2017; 85:63–68
5. Loh HH, Lim LL, Yee A, et al: Association between subclinical hypothyroidism and depression: an updated systematic review and meta-analysis. BMC Psychiatry 2019; 19:12
6. Milaneschi Y, Simmons WK, van Rossum EFC, et al: Depression and obesity: evidence of shared biological mechanisms. Mol Psychiatry 2019; 24:18–33
7. Moulton CD, Pickup JC, Ismail K: The link between depression and diabetes: the search for shared mechanisms. Lancet Diabetes Endocrinol 2015; 3:461–471
8. Siegmann E-M, Müller HHO, Luecke C, et al: Association of depression and anxiety disorders with autoimmune thyroiditis: a systematic review and meta-analysis. JAMA Psychiatry 2018; 75:577–584
9. Speed MS, Jefsen OH, Børglum AD, et al: Investigating the association between body fat and depression via Mendelian randomization. Transl Psychiatry 2019; 9:184
10. Bergmans RS, Rapp A, Kelly KM, et al: Understanding the relationship between type 2 diabetes and depression: lessons from genetically informative study designs. Diabet Med 2021; 38:e14399
11. Sullivan PF, Neale MC, Kendler KS: Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000; 157: 1552–1562
12. Robinson MR, English G, Moser G, et al: Genotype-covariate interaction effects and the heritability of adult body mass index. Nat Genet 2017; 49:1174–1181
13. Skov J, Eriksson D, Kuja-Halkola R, et al: Co-aggregation and heritability of organ-specific autoimmunity: a population-based twin study. Eur J Endocrinol 2020; 182:473–480

14. Willemsen G, Ward KJ, Bell CG, et al: The concordance and heritability of type 2 diabetes in 34,166 twin pairs from international twin registers: the Discordant Twin (DISCOTWIN) consortium. Twin Res Hum Genet 2015; 18:762–771
15. Vink JM, Sadrzadeh S, Lambalk CB, et al: Heritability of polycystic ovary syndrome in a Dutch twin-family study. J Clin Endocrinol Metab 2006; 91:2100–2104
16. Afari N, Noonan C, Goldberg J, et al: Depression and obesity: do shared genes explain the relationship? Depress Anxiety 2010; 27: 799–806
17. Kan C, Pedersen NL, Christensen K, et al: Genetic overlap between type 2 diabetes and depression in Swedish and Danish twin registries. Mol Psychiatry 2016; 21:903–909
18. Milaneschi Y, Lamers F, Peyrot WJ, et al: Genetic association of major depression with atypical features and obesity-related immunometabolic dysregulations. JAMA Psychiatry 2017; 74: 1214–1225
19. Hagenaars SP, Coleman JRI, Choi SW, et al: Genetic comorbidity between major depression and cardio-metabolic traits, stratified by age at onset of major depression. Am J Med Genet B Neuropsychiatr Genet 2020; 183:309–330
20. Day F, Karaderi T, Jones MR, et al: Large-scale genome-wide meta-analysis of polycystic ovary syndrome suggests shared genetic architecture for different diagnosis criteria. PLoS Genet 2018; 14: e1007813
21. Samaan Z, Garasia S, Gerstein HC, et al: Lack of association between type 2 diabetes and major depression: epidemiologic and genetic evidence in a multiethnic population. Transl Psychiatry 2015; 5:e618
22. Jiang X, Deng Q, Stener-Victorin E: Is there a shared genetic basis and causal relationship between polycystic ovary syndrome and psychiatric disorders: evidence from a comprehensive genetic analysis. Hum Reprod 2021; 36:2382–2391
23. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al: The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 2009; 24:659–667
24. Axelsson O: The Swedish medical birth register. Acta Obstet Gynecol Scand 2003; 82:491–492
25. Ludvigsson JF, Almqvist C, Bonamy A-KE, et al: Registers of the Swedish total population and their use in medical research. Eur J Epidemiol 2016; 31:125–136
26. Brooke HL, Talbäck M, Hörnblad J, et al: The Swedish cause of death register. Eur J Epidemiol 2017; 32:765–773
27. Ekbom A: The Swedish multi-generation register; in Methods in Biobanking. Heidelberg, Springer, 2011, pp 215–220
28. Ludvigsson JF, Andersson E, Ekbom A, et al: External review and validation of the Swedish national inpatient register. BMC Public Health 2011; 11:450
29. Statistics Sweden: Different families live in different ways: a survey on residence and support of children after a separation (Demographic Reports 2014:1). Stockholm, Statistics Sweden, 2014. https://www.scb.se/publication/23711
30. Williams RL: A note on robust variance estimation for cluster-correlated data. Biometrics 2000; 56:645–646
31. Kuehner C: Why is depression more common among women than among men? Lancet Psychiatry 2017; 4:146–158
32. Ludvigsson JF, Svedberg P, Olén O, et al: The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) and its use in medical research. Eur J Epidemiol 2019; 34: 423–437
33. Neale M, Cardon LR: Methodology for Genetic Studies of Twins and Families. Heidelberg, Springer Science and Business Media, 2013
34. Kuja-Halkola R, D'Onofrio BM, Larsson H, et al: Maternal smoking during pregnancy and adverse outcomes in offspring: genetic and environmental sources of covariance. Behav Genet 2014; 44: 456–467
35. Neale MC, Hunter MD, Pritikin JN, et al: OpenMx 2.0: extended structural equation and statistical modeling. Psychometrika 2016; 81:535–549
36. Howard DM, Adams MJ, Clarke T-K, et al: Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci 2019; 22:343–352
37. Naderpoor N, Shorakae S, Joham A, et al: Obesity and polycystic ovary syndrome. Minerva Endocrinol 2015; 40:37–51
38. Rubin KH, Glintborg D, Nybo M, et al: Development and risk factors of type 2 diabetes in a nationwide population of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2017; 102: 3848–3857
39. Lee SH, Paz-Filho G, Mastronardi C, et al: Is increased antidepressant exposure a contributory factor to the obesity pandemic? Transl Psychiatry 2016; 6:e759
40. Glanville KP, Coleman JRI, O'Reilly PF, et al: Investigating pleiotropy between depression and autoimmune diseases using the UK Biobank. Biol Psychiatry Glob Open Sci 2021; 1:48–58
41. Verhulst B, Prom-Wormley E, Keller M, et al: Type I error rates and parameter bias in multivariate behavioral genetic models. Behav Genet 2019; 49:99–111
42. Haldane JB: The negative heritability of neonatal jaundice. Ann Hum Genet 1996; 60:3–5
43. Steinsaltz D, Dahl A, Wachter KW: On negative heritability and negative estimates of heritability. Genetics 2020; 215:343–357
44. Zachrisson I, Tibell C, Bang P, et al: Prevalence of type 2 diabetes among known cases of diabetes aged 0–18 years in Sweden. J Pediatr Endocrinol Metab 2003; 16(S4):919–955
45. Bulik-Sullivan B, Finucane HK, Anttila V, et al: An atlas of genetic correlations across human diseases and traits. Nat Genet 2015; 47: 1236–1241
46. Huider F, Milaneschi Y, Van der Zee MD, et al: Major depressive disorder and lifestyle: correlated genetic effects in extended twin pedigrees. Genes 2021; 12:1509
47. Elston RC, Satagopan JM, et al: Statistical Human Genetics: Methods and Protocols. Heidelberg, Springer, 2012
48. Branigan AR, McCallum KJ, et al: Variation in the heritability of educational attainment: an international meta-analysis. Soc Forces 2013; 92:109–140