Journal of Developmental Origins of Health and Disease

www.cambridge.org/doh

Original Article

Cite this article: Li J-R, Tsai S-J, Bai Y-M, Hsu J-W, Huang K-L, Su T-P, Li C-T, Lin W-C, Chen T-J, Pan T-L, and Chen M-H. (2021) Cardiometabolic disease risk among siblings of patients with major depressive disorder. *Journal of Developmental Origins of Health and Disease* **12**: 530–535. doi: 10.1017/S2040174420000860

Received: 20 April 2020
Revised: 4 July 2020
Accepted: 18 August 2020
First published online: 14 September 2020

Keywords:
Unaffected siblings; major depressive disorder; metabolic disorder; cerebrocardiovascular diseases

Address for correspondence: Mu-Hong Chen, MD, PhD, Department of Psychiatry, No. 201, Shih-Pai Road, Sec. 2, 11217, Taipei, Taiwan. Tel.: 886-2-28344012; Fax: 886-2-28344012. Email: kremer7119@gmail.com
Tai-Long Pan, PhD, School of Traditional Chinese Medicine, Chang Gung University, Taoyuan, Taiwan. Tel.: 886-2-28344012; Fax: 886-2-28344012. Email: pan@mail.cgu.edu.tw

CAMBRIDGE UNIVERSITY PRESS

Cardiometabolic disease risk among siblings of patients with major depressive disorder

Jia-Ru Li[1], Shih-Jen Tsai[1,2], Ya-Mei Bai[1,2], Ju-Wei Hsu[1,2], Kai-Lin Huang[1,2], Tung-Ping Su[1,2,3], Cheng-Ta Li[1,2], Wei-Chen Lin[1,2], Tzeng-Ji Chen[4,5], Tai-Long Pan[6,7,8] and Mu-Hong Chen[1,2]

[1]Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan; [2]Department of Psychiatry, College of Medicine, National Yang-Ming University, Taipei, Taiwan; [3]Department of Psychiatry, Cheng Hsin General Hospital, Taipei, Taiwan; [4]Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [5]Institute of Hospital and Health Care Administration, National Yang-Ming University, Taipei, Taiwan; [6]School of Traditional Chinese Medicine, Chang Gung University, Taoyuan, Taiwan; [7]Research Center for Industry of Human Ecology, Chang Gung University of Science and Technology, Taoyuan, Taiwan and [8]Liver Research Center, Division of Hepatology, Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Taoyuan, Taiwan

Abstract

Studies have suggested an association between metabolic and cerebrocardiovascular diseases and major depressive disorder (MDD). However, the risk of metabolic and cerebrocardiovascular diseases in the unaffected siblings of patients with MDD remains uncertain. Using the Taiwan National Health Insurance Research Database, 22,438 unaffected siblings of patients with MDD and 89,752 age-/sex-matched controls were selected and followed up from 1996 to the end of 2011. Individuals who developed metabolic and cerebrocardiovascular diseases during the follow-up period were identified. Compared with the controls, the unaffected siblings of patients with MDD had a higher prevalence of metabolic diseases, such as hypertension (5.0% vs. 4.5%, $p = 0.007$), dyslipidemia (5.6% vs. 4.8%, $p < 0.001$), and obesity (1.7% vs. 1.5%, $p = 0.028$), and cerebrocardiovascular diseases, such as ischemic stroke (0.6% vs. 0.4%, $p < 0.005$) and ischemic heart disease (2.1% vs. 1.7%, $p < 0.001$). Logistic regression analyses revealed that the unaffected siblings of patients with MDD were more likely to develop hypertension, dyslipidemia, ischemic stroke, and ischemic heart diseases during the follow-up period than the controls. Our study revealed a familial coaggregation between MDD and metabolic and cerebrocardiovascular diseases. Additional studies are required to investigate the shared pathophysiology of MDD and metabolic and cerebrocardiovascular diseases.

Depression, which is characterized by sadness, loss of interest, anhedonia, lack of appetite, feelings of guilt, low self-esteem or self-worth, sleep disturbance, feelings of tiredness, and poor concentration, is one of the commonest mental disorders worldwide and is estimated to affect over 300 million people globally.[1] Moreover, it affects the individual's well-being and ability to perform socially defined roles and tasks.[2] The global point prevalence rate was 4.7% (4.4%–5.0%), and the pooled annual incidence was 3.0% (2.4%–3.8%).[3] Although the pathophysiology of major depressive disorder (MDD) remains unclear, a number of factors, including biogenic amine deficiency, neurogenesis, genetic, environmental, immunologic, and endocrine factors, were suggested to be associated with MDD development.[4]

In addition, depression has been associated with shortened life expectancy and impaired quality of life.[5,6] Mortality risk over relatively short periods could be attributed to unnatural causes of death, including suicide and unintentional injuries.[7,8] By contrast, mortality risk over longer periods may be due to chronic physical conditions associated with depression, such as cerebrocardiovascular diseases and metabolic disorders.[7,8] Indeed, evidence confirmed the elevated risks of cerebrocardiovascular and metabolic diseases among patients with MDD.[9–11] Similarly, other psychiatric disorders, including schizophrenia or bipolar disorder, were also found to have higher risks of metabolic and cerebrocardiovascular diseases.[12–14]

Researchers further assessed whether individuals, especially the first-degree relatives (i.e., siblings), at increased familial risk of psychiatry disorders, may have elevated rates of cerebrocardiovascular or metabolic diseases.[15–21] Toma *et al.* revealed that cardiovascular risk score based on the sum of the presence of diabetes, hypertension, obesity, dyslipidemia, stroke, angina, and myocardial infarction was highest among adolescents with bipolar disorder having familial bipolar disorder, intermediate among adolescents with bipolar disorder having no familial bipolar disorder and lowest in healthy comparisons without bipolar disorder and familial bipolar disorder.[17] Sobczak *et al.* found the healthy first-degree relatives of patients with bipolar disorder were prone to having increased level of omega-6 polyunsaturated fatty acids and lower level of

high-density lipoprotein cholesterol.[18] Mannie *et al.* demonstrated that the individuals with a family history of depressive disorder had elevated systolic blood pressure and diminished insulin sensitivity compared with those without family history.[20] The major limitations of the aforementioned studies included small sample size, cross-sectional study design, and only inclusion of young subjects that may limit the generalizability.

In the current study, using the Taiwan National Health Insurance Research Database (NHIRD), with a large sample size and longitudinal study design, we investigated the risks of metabolic diseases, namely type 2 diabetes mellitus, hypertension, and dyslipidemia, and the risks of cerebrocardiovascular diseases, namely stroke and ischemic heart disease, among the unaffected siblings of patients with MDD. We hypothesized that the unaffected siblings of patients with MDD have an increased risk of subsequent metabolic and cerebrocardiovascular diseases during the follow-up period compared with the controls.

Methods

Data source

Taiwan National Health Research Institute audits and releases the Taiwan NHIRD for scientific and study purposes. Individual medical records included in the NHIRD are anonymous to protect patient privacy. Comprehensive information on insured individuals is included in the database, including demographic data, dates of clinical visits, disease diagnoses, and medical interventions. In this study, using each resident's unique personal identification number, all of the information was linked. Subsequently, following the method of Kuo *et al.* and Cheng *et al.*, family kinships in the NHIRD were used for genealogy reconstruction.[22,23] The diagnostic codes used were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in many epidemiologic studies in Taiwan.[23–26]

Inclusion criteria for the unaffected siblings of patients with MDD and the control group

Individuals who were born before 1990 and had the siblings with MDD (ICD-9-CM codes: 296.2x, 296.3x) but had no personal diagnosis of severe mental disorders (ICD-9-CM codes: 295, 296, 297) at any time were enrolled as the study group. The age-, sex-, income-, level-of-urbanization-and birth-time-matched (1:4) control group was randomly identified after eliminating the study cases, those who had been given a diagnosis of severe mental disorders at any time, and those with any sibling with severe mental disorders. The study and control groups were included and followed from 1996 to the end of 2011. The occurrence of metabolic (type 2 diabetes, hypertension, dyslipidemia, obesity) and cerebrocardiovascular (stroke, ischemic heart diseases) diseases was identified during the follow-up period. Metabolic and cerebrocardiovascular diseases were diagnosed by board-certified physicians. Level of urbanization (level 1 to level 5; level 1: most urbanized region; level 5: least urbanized region) was also assessed for our study.[27] This study was approved by the Institutional Review Board of Taipei Veterans General Hospital.

Statistical analysis

For between-group comparisons, the F test was used for continuous variables and Pearson's X^2 test for nominal variables, where appropriate. After adjusting for demographic data (age, sex, income, and level of urbanization), logistic regression models were used to investigate the odds ratios (OR) of subsequent metabolic diseases (type 2 diabetes, hypertension, dyslipidemia, obesity) between study and control cohorts. Logistic regression models with the additional adjustment of metabolic diseases were performed to assess the likelihoods of subsequent cerebrocardiovascular diseases (stroke, ischemic heart disease) between study and control groups. In addition, logistic regression analyses stratified by sex were also examined to clarify the role of sex in the risks of subsequent metabolic and cerebrocardiovascular diseases. A 2-tailed p-value of less than 0.05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 19 software (SPSS Inc.) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC).

Results

The demographic characteristics and prevalence of metabolic and cerebrocardiovascular diseases of the study sample were listed in Table 1. In all, 22,438 unaffected siblings of patients with MDD and 89,752 controls were enrolled in our study, with an average age of 32.81 ± 8.22 years. The unaffected siblings of patients with MDD had the higher prevalence of metabolic diseases, such as hypertension (5.0% vs. 4.5%, $p = 0.007$), dyslipidemia (5.6% vs. 4.8%, $p < 0.001$), obesity (1.7% vs. 1.5%, $p = 0.028$), and cerebrocardiovascular diseases, such as ischemic heart disease (2.1% vs. 1.7%, $p < 0.001$), any stroke (1.3% vs. 1.1%, $p = 0.006$), and ischemic stroke (0.6% vs. 0.4%, $p = 0.005$) compared with the controls (Table 1).

Logistic regression analyses with an adjustment of demographic data (age, sex, level of urbanization, and income) found that the unaffected siblings of patients with MDD were more likely to have hypertension (OR: 1.12, 95% CI: 1.04–1.21), dyslipidemia (OR: 1.21, 95% CI: 1.13–1.29), and obesity (OR: 1.14, 95% CI: 1.01–1.27) later in life compared with the controls (Table 2). Further analyses with additional adjustment of metabolic diseases found that the unaffected siblings of patients with MDD had increased risks of developing any stroke (OR: 1.18, 95% CI: 1.03–1.35), ischemic stroke (OR: 1.30, 95% CI: 1.06–1.60), and ischemic heart disease (OR: 1.21, 95% CI: 1.08–1.36) during the follow-up period compared with the control group (Table 3). Subanalyses stratified by sex reported that brothers of patients with MDD had the elevated risks of developing hypertension (OR: 1.16, 95% CI: 1.06–1.26), dyslipidemia (OR: 1.22, 95% CI: 1.12–1.33), ischemic stroke (OR: 1.33, 95% CI: 1.03–1.71), and ischemic heart disease (OR: 1.20, 95% CI: 1.04–1.40) compared with the controls; sisters of patients with MDD were prone to developing dyslipidemia (OR: 1.18, 95% CI: 1.05–1.32), type 2 diabetes (OR: 1.20, 95% CI: 1.04–1.38), obesity (OR: 1.16, 95% CI: 1.00–1.34), and ischemia heart disease (OR: 1.23, 95% CI: 1.02–1.48) (Tables 2 and 3).

Discussion

Our findings supported the study hypothesis that the unaffected siblings of patients with MDD exhibit a higher prevalence of subsequent metabolic and cerebrovascular diseases, especially dyslipidemia, ischemic stroke, and ischemic heart disease compared with the controls. In addition, the unaffected sisters of patients with MDD were more likely to develop type 2 diabetes later in life compared with the controls.

https://doi.org/10.1017/S2040174420000860 Published online by Cambridge University Press

Table 1. Demographic data and prevalence of the metabolic and cerebrocardiovascular disorders among the siblings of patients with major depression and controls

	Siblings of patients with major depression ($n = 22,438$)	Controls ($n = 89,752$)	p-Value
Age (years, SD)	32.81 (8.22)	32.81 (8.22)	0.992
Sex (n, %)			1.000
Male	11,223 (50.0)	44,892 (50.0)	
Female	11,215 (50.0)	44,860 (50.0)	
Prevalence of metabolic disorders			
Hypertension (n, %)	1112 (5.0)	4047 (4.5)	**0.007**
Age at diagnosis (years, SD)	38.22 (11.91)	38.54 (11.98)	0.420
Dyslipidemia (n, %)	1260 (5.6)	4299 (4.8)	**<0.001**
Age at diagnosis (years, SD)	36.29 (11.63)	36.10 (11.91)	0.609
Type 2 diabetes (n, %)	596 (2.7)	2253 (2.5)	0.217
Age at diagnosis (years, SD)	36.02 (12.83)	36.68 (12.57)	0.253
Obesity (n, %)	389 (1.7)	1371 (1.5)	**0.028**
Age at diagnosis (years, SD)	27.63 (9.41)	27.04 (8.78)	0.247
Prevalence of cerebrocardiovascular disorders			
Any stroke (n, %)	289 (1.3)	963 (1.1)	**0.006**
Age at diagnosis (years, SD)	35.47 (14.61)	35.82 (15.67)	0.740
Ischemic stroke (n, %)	133 (0.6)	400 (0.4)	**0.005**
Age at diagnosis (years, SD)	43.20 (14.21)	42.84 (14.32)	0.804
Hemorrhagic stroke (n, %)	82 (0.4)	349 (0.4)	0.669
Age at diagnosis (years, SD)	27.70 (12.73)	29.02 (14.63)	0.451
Ischemic heart disease (n, %)	467 (2.1)	1506 (1.7)	**<0.001**
Age at diagnosis (years, SD)	38.55 (13.47)	40.10 (13.43)	**0.028**
Level of urbanization (n, %)			1.000
1 (most urbanized)	6373 (28.4)	25,492 (28.4)	
2	7897 (35.2)	31,588 (35.2)	
3	3072 (13.7)	12,288 (13.7)	
4	2142 (9.5)	8568 (9.5)	
5 (most rural)	2954 (13.2)	11,816 (13.2)	
Income-related insured amount (n, %)			1.000
≤15,840 NTD/month	6527 (29.1)	26,108 (29.1)	
15,841–25,000NTD/month	7583 (33.8)	30,332 (33.8)	
≥25,001NTD/month	8328 (37.1)	33,312 (37.1)	

NTD: new Taiwan dollar; SD: standard deviation.

Table 2. Logistic regression analyses of the metabolic disorders among the siblings of patients with major depression and controls[a]

	Hypertension (OR, 95% CI)	Dyslipidemia (OR, 95% CI)	Type 2 diabetes (OR, 95% CI)	Obesity (OR, 95% CI)
Siblings of patients with major depression	**1.12 (1.04–1.21)**	**1.21 (1.13–1.29)**	1.06 (0.97–1.17)	**1.14 (1.01–1.27)**
Brothers of patients with major depression	**1.16 (1.06–1.26)**	**1.22 (1.12–1.33)**	0.97 (0.86–1.11)	1.10 (0.91–1.33)
Sisters of patients with major depression	1.03 (0.90–1.19)	**1.18 (1.05–1.32)**	**1.20 (1.04–1.38)**	**1.16 (1.00–1.34)**

OR: Odds ratio; CI: Confidence interval.**Bold** type means the statistical significance.
[a]Adjusted for demographic data.

https://doi.org/10.1017/S2040174420000860 Published online by Cambridge University Press

Table 3. Logistic regression analyses of the cerebrocardiovascular disorders among the siblings of patients with major depression and controls[a]

	Any stroke (OR, 95% CI)	Ischemic stroke (OR, 95% CI)	Hemorrhagic stroke (OR, 95% CI)	Ischemic heart disease (OR, 95% CI)
Siblings of patients with major depression	**1.18 (1.03–1.35)**	**1.30 (1.06–1.60)**	0.93 (0.73–1.19)	**1.21 (1.08–1.36)**
Brothers of patients with major depression	1.18 (0.99–1.41)	**1.33 (1.03–1.71)**	0.99 (0.73–1.34)	**1.20 (1.04–1.40)**
Sisters of patients with major depression	1.17 (0.94–1.45)	1.25 (0.88–1.78)	0.84 (0.56–1.26)	**1.23 (1.02–1.48)**

OR: Odds ratio; CI: Confidence interval. **Bold** type means the statistical significance.
[a]Adjusted for demographic data and metabolic diseases.

Studies have found an association between the family history of severe mental disorders and cardiometabolic diseases. Huang *et al.* reported an increased risk of type 2 diabetes among the unaffected siblings of patients with schizophrenia.[21] Mannie *et al.* assessed the cardiometabolic conditions between healthy controls and young people who had no personal history of depression but had a family history of depressive illness and demonstrated that those with a family history of depression had elevated systolic blood pressure and arterial stiffness and diminished insulin sensitivity compared with the controls.[20] They suggested that young people who had a family history of depression were more likely to have an altered cardiovascular risk profile in young adulthood even if depressive symptoms were absent, which may be due to the common risk factors between MDD and cardiometabolic diseases.

Our findings of the increased likelihoods of metabolic and cerebrocardiovascular diseases in the unaffected siblings of patients with MDD were in agreement with those of Mannie *et al.*[20] The genetic liability, common environmental factors, and epigenetic interactions may contribute to the familial coaggregation of MDD and metabolic and cerebrocardiovascular diseases.[28–31] The hypothesis of a genetic overlap between depression and metabolic and cerebrocardiovascular diseases has been supported by studies describing coshared genetics and possible risk gene pathway.[32,33] For instance, the 12q chromosome has been linked to depression, hypertension, dyslipidemia, obesity, stroke, and ischemic heart disease.[34–37] Amare *et al.* reviewed 24 cardiovascular and metabolic disease genes implicated in depression, bipolar disorder, or both and found that BDNF, CREB1, GNAS, and POMC played crucial roles in the pathophysiology of both cardiometabolic diseases and mood disorders.[33] Thus, at least one or a few genes or gene variants across these loci may explain the pleiotropic or comorbid linkage of the aforementioned phenotypes.

The pathophysiology underlying the association between depression vulnerability and cardiometabolic diseases is unknown. Lower central serotonergic responsivity, a biomarker of depression vulnerability, has been suggested to be associated with cardiometabolic risks and carotid artery atherosclerosis.[38,39] Muldoon *et al.* revealed that lower central serotonergic responsivity was associated with obesity, dyslipidemia, higher systolic and diastolic blood pressure, greater insulin resistance, and less physical activity.[38] Muldoon *et al.* further reported that a 1 standard deviation lower prolactin response was associated with the greater intima-media thickness of carotid artery and found that the metabolic syndrome mediated, but did not fully account for, the association between lower central serotonergic responsivity and greater intima-media thickness.[39] Beyond the serotonergic hypothesis of depression vulnerability and cardiometabolic risks, the dysregulated hypothalamic–pituitary–adrenal (HPA) axis may play a crucial role in this relationship.[40] Mannie *et al.* compared 49 young people who had not been depressed themselves but who had a family history of MDD with a group of 55 participants who had no personal and family history of depression and demonstrated that at-risk young people had a higher level of waking salivary cortisol than the comparison subjects on both workdays and nonworkdays.[40] Previous studies have suggested that an alteration of HPA axis, such as cortisol hypersecretion, was significantly related to the risks of metabolic and cardiovascular diseases.[41–43]

The role of sex in the risk of metabolic and cerebrocardiovascular diseases between study and control groups was another interesting finding in our study. Block *et al.* suggested that younger female patients with MDD were more likely to have metabolic diseases than those without MDD, and they further found that age may extenuate this association.[44] Gil *et al.* found a significant relationship of depressive symptoms with elevated glucose levels in women and with obesity in men.[45] Furthermore, depressive symptoms were considered to be associated with metabolic diseases among Japanese urban men.[46] Alemany *et al.* hypothesized that metabolic disease is a maturity-onset disease, and levels of androgens and estrogens could account for differences between the sexes and delayed manifestation of metabolic syndrome by counterbalancing the pathogenetic force of glucocorticoids toward metabolic syndrome.[47] The fluctuations of sex hormones that flag reproductive events in women may affect metabolic and neurochemical pathways that are linked to both MDD and metabolic and cerebrocardiovascular diseases.[48] Additional studies are required to investigate the effect of sex on metabolic and cerebrocardiovascular diseases between patients with MDD and their relatives.

This study had several limitations. First, the prevalence of cerebrocardiovascular disease and MDD may be underestimated because only those who sought medical help and consultation were enrolled. However, the diagnoses of metabolic and cerebrocardiovascular diseases were made by board-certified physicians. Therefore, the diagnostic validity was improved. In addition, the other clinical scenario of undetected or untreated depression and other psychiatric disorders in unaffected relatives may be also possible. Not only risks of metabolic and cerebrocardiovascular diseases but also risks of mental disorders should be closely monitored among unaffected relatives, such as siblings in current study. Second, the prevalence of metabolic and cerebrocardiovascular diseases rise with age. In current study, the lifetime prevalence of metabolic and cerebrocardiovascular diseases may be underestimated owing to the not-long-enough (15 years) follow-up duration. Future studies with a longer follow-up duration (>15 years) would be required to validate our findings. Third, some factors, such as environmental factors, personal lifestyle, education, occupation, and engagement in physical activity, were not available in the Taiwan NHIRD. Therefore, we could not examine the influence of these factors.

In conclusion, the unaffected siblings of patients with MDD had a slightly higher risk of subsequent hypertension, dyslipidemia, obesity, ischemic stroke, and ischemic heart disease later in life

https://doi.org/10.1017/S2040174420000860 Published online by Cambridge University Press

compared with the controls. The unaffected sisters of patients with MDD were more likely to develop type 2 diabetes later in life compared with the controls. Our study revealed a familial coaggregation between MDD and metabolic and cerebrocardiovascular diseases in a large sample. Our findings suggest that clinicians should pay more attention to the cardiometabolic health of the unaffected siblings of patients with MDD. Screening those siblings of patients with MDD to evaluate the risk of metabolic and cerebrocardiovascular diseases, even those siblings without MDD per se, may be a valuable strategy of risk stratification in public health. Additional studies are required to investigate the shared pathophysiology between MDD and cardiometabolic diseases.

Acknowledgements. We thank Mr I-Fan Hu for his friendship and support.

We thank Dr JRL, Prof TLP, and Dr MHC, who designed the study, wrote the protocol and manuscripts, Dr JWH, Dr YMB, Dr TPS, Dr CTL, Dr SJT, Dr KLH, and Dr WCL, who assisted with the preparation and proof-reading of the manuscript, and Dr YMB, Dr MHC, and Dr TJC, who provided the advices on statistical analysis.

Financial support. The study was supported by grant from Taipei Veterans General Hospital (V103E10-001, V104E10-002, V105E10-001-MY2-1, V105A-049, V106B-020, V107B-010, V107C-181) and Ministry of Science and Technology, Taiwan (107-2314-B-075-063-MY3, 108-2314-B-075-037). The funding source had no role in any process of our study.

Conflict of interest. None.

Ethical standards. None.

References

1. Aleksandrova LR, Phillips AG, Wang YT. Antidepressant effects of ketamine and the roles of AMPA glutamate receptors and other mechanisms beyond NMDA receptor antagonism. *J Psychiatry Neurosci.* 2017; 42, 222–229.
2. Buist-Bouwman MA, De Graaf R, Vollebergh WA, Alonso J, Bruffaerts R, Ormel J. Functional disability of mental disorders and comparison with physical disorders: a study among the general population of six European countries. *Acta Psychiatr Scand.* 2006; 113, 492–500.
3. Ferrari AJ, Somerville AJ, Baxter AJ, *et al.* Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychol Med.* 2013; 43, 471–481.
4. Jesulola E, Micalos P, Baguley IJ. Understanding the pathophysiology of depression: from monoamines to the neurogenesis hypothesis model – are we there yet? *Behav Brain Res.* 2018; 341, 79–90.
5. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *Am J Psychiatry.* 2014; 171, 453–462.
6. O'Neil A, Stevenson CE, Williams ED, Mortimer D, Oldenburg B, Sanderson K. The health-related quality of life burden of co-morbid cardiovascular disease and major depressive disorder in Australia: findings from a population-based, cross-sectional study. *Qual Life Res.* 2013; 22, 37–44.
7. Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. *J Affect Disord.* 2002; 72, 227–236.
8. Gilman SE, Sucha E, Kingsbury M, Horton NJ, Murphy JM, Colman I. Depression and mortality in a longitudinal study: 1952–2011. *Cmaj.* 2017; 189, e1304–e1310.
9. Miettola J, Niskanen LK, Viinamäki H, Kumpusalo E. Metabolic syndrome is associated with self-perceived depression. *Scand J Prim Health Care.* 2008; 26, 203–210.
10. O'Connor C M, Gurbel PA, Serebruany VL. Depression and ischemic heart disease. *Am Heart J.* 2000; 140, 63–69.
11. Dong JY, Zhang YH, Tong J, Qin LQ. Depression and risk of stroke: a meta-analysis of prospective studies. *Stroke.* 2012; 43, 32–37.
12. Chen MH, Pan TL, Hsu JW, *et al.* Risk of type 2 diabetes in adolescents and young adults with attention-deficit/hyperactivity disorder: a nationwide longitudinal study. *J Clin Psychiatry.* 2018; 79.
13. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders – a systematic review and meta-analysis. *Schizophr Bull.* 2013; 39, 306–318.
14. Vancampfort D, Vansteelandt K, Correll CU, *et al.* Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. *Am J Psychiatry.* 2013; 170, 265–274.
15. Fernandez-Egea E, Bernardo M, Donner T, *et al.* Metabolic profile of antipsychotic-naive individuals with non-affective psychosis. *Br J Psychiatry.* 2009; 194, 434–438.
16. Koponen H, Vuononvirta J, Mäki P, *et al.* No difference in insulin resistance and lipid levels between controls and adolescent subjects who later develop psychosis. *Schizophr Res.* 2008; 104, 31–35.
17. Toma S, Fiksenbaum L, Omrin D, Goldstein BI. Elevated familial cardiovascular burden among adolescents with familial bipolar disorder. *Front Psychiatry.* 2019; 10, 8.
18. Sobczak S, Honig A, Christophe A, *et al.* Lower high-density lipoprotein cholesterol and increased omega-6 polyunsaturated fatty acids in first-degree relatives of bipolar patients. *Psychol Med.* 2004; 34, 103–112.
19. Dong C, Sanchez LE, Price RA. Relationship of obesity to depression: a family-based study. *Int J Obes Relat Metab Disord.* 2004; 28, 790–795.
20. Mannie ZN, Williams C, Diesch J, Steptoe A, Leeson P, Cowen PJ. Cardiovascular and metabolic risk profile in young people at familial risk of depression. *Br J Psychiatry.* 2013; 203, 18–23.
21. Huang MH, Chen MH, Huang KL, *et al.* Increased risk of type 2 diabetes among the siblings of patients with schizophrenia. *CNS Spectr.* 2019; 24, 453–459.
22. Kuo CF, Grainge MJ, Valdes AM, *et al.* Familial aggregation of systemic lupus erythematosus and coaggregation of autoimmune diseases in affected families. *JAMA Intern Med.* 2015; 175, 1518–1526.
23. Cheng CM, Chang WH, Chen MH, *et al.* Co-aggregation of major psychiatric disorders in individuals with first-degree relatives with schizophrenia: a nationwide population-based study. *Mol Psychiatry.* 2018; 23, 1756–1763.
24. Chen MH, Lan WH, Hsu JW, *et al.* Risk of developing type 2 diabetes in adolescents and young adults with autism spectrum disorder: a nationwide longitudinal study. *Diabetes Care.* 2016; 39, 788–793.
25. Chen MH, Pan TL, Li CT, *et al.* Risk of stroke among patients with post-traumatic stress disorder: nationwide longitudinal study. *Br J Psychiatry.* 2015; 206, 302–307.
26. Chen MH, Su TP, Chen YS, *et al.* Attention deficit hyperactivity disorder, tic disorder, and allergy: is there a link? A nationwide population-based study. *J Child Psychol Psychiatry.* 2013; 54, 545–551.
27. Liu CY, Hung YT, Chuang YL, Chen YJ, Weng WS, Liu JS. Incorporating development stratification of Taiwan townships into sampling design of large scale health interview survey. *J Health Manage.* 2006; 4, 1–22.
28. Natsuaki MN, Ge X, Leve LD, *et al.* Genetic liability, environment, and the development of fussiness in toddlers: the roles of maternal depression and parental responsiveness. *Dev Psychol.* 2010; 46, 1147–1158.
29. Liu L, Li Y, Tollefsbol TO. Gene-environment interactions and epigenetic basis of human diseases. *Curr Issues Mol Biol.* 2008; 10, 25–36.
30. Bornstein SR, Schuppenies A, Wong ML, Licinio J. Approaching the shared biology of obesity and depression: the stress axis as the locus of gene-environment interactions. *Mol Psychiatry.* 2006; 11, 892–902.
31. Della-Morte D, Guadagni F, Palmirotta R, *et al.* Genetics of ischemic stroke, stroke-related risk factors, stroke precursors and treatments. *Pharmacogenomics.* 2012; 13, 595–613.
32. McCaffery JM, Duan QL, Frasure-Smith N, *et al.* Genetic predictors of depressive symptoms in cardiac patients. *Am J Med Genet B Neuropsychiatr Genet.* 2009; 150b, 381–388.
33. Amare AT, Schubert KO, Klingler-Hoffmann M, Cohen-Woods S, Baune BT. The genetic overlap between mood disorders and cardiometabolic diseases: a systematic review of genome wide and candidate gene studies. *Transl Psychiatry.* 2017; 7, e1007.

34. Abkevich V, Camp NJ, Hensel CH, *et al*. Predisposition locus for major depression at chromosome 12q22–12q23.2. *Am J Hum Genet*. 2003; 73, 1271–1281.
35. Aberg K, Dai F, Sun G, *et al*. A genome-wide linkage scan identifies multiple chromosomal regions influencing serum lipid levels in the population on the Samoan islands. *J Lipid Res*. 2008; 49, 2169–2178.
36. Wilson SG, Adam G, Langdown M, *et al*. Linkage and potential association of obesity-related phenotypes with two genes on chromosome 12q24 in a female dizygous twin cohort. *Eur J Hum Genet*. 2006; 14, 340–348.
37. Sherva R, Miller MB, Pankow JS, *et al*. A whole-genome scan for stroke or myocardial infarction in family blood pressure program families. *Stroke*. 2008; 39, 1115–1120.
38. Muldoon MF, Mackey RH, Williams KV, Korytkowski MT, Flory JD, Manuck SB. Low central nervous system serotonergic responsivity is associated with the metabolic syndrome and physical inactivity. *J Clin Endocrinol Metab*. 2004; 89, 266–271.
39. Muldoon MF, Mackey RH, Sutton-Tyrrell K, Flory JD, Pollock BG, Manuck SB. Lower central serotonergic responsivity is associated with preclinical carotid artery atherosclerosis. *Stroke*. 2007; 38, 2228–2233.
40. Mannie ZN, Harmer CJ, Cowen PJ. Increased waking salivary cortisol levels in young people at familial risk of depression. *Am J Psychiatry*. 2007; 164, 617–621.
41. Vargas J, Junco M, Gomez C, Lajud N. Early life stress increases metabolic risk, HPA axis reactivity, and depressive-like behavior when combined with postweaning social isolation in rats. *PLoS One*. 2016; 11, e0162665.
42. Lemche E, Chaban OS, Lemche AV. Neuroendorine and epigentic mechanisms subserving autonomic imbalance and HPA dysfunction in the metabolic syndrome. *Front Neurosci*. 2016; 10, 142.
43. Burford NG, Webster NA, Cruz-Topete D. Hypothalamic-pituitary-adrenal axis modulation of glucocorticoids in the cardiovascular system. *Int J Mol Sci*. 2017; 18.
44. Block A, Schipf S, Van der Auwera S, *et al*. Sex- and age-specific associations between major depressive disorder and metabolic syndrome in two general population samples in Germany. *Nord J Psychiatry*. 2016; 70, 611–620.
45. Gil K, Radziłłowicz P, Zdrojewski T, *et al*. Relationship between the prevalence of depressive symptoms and metabolic syndrome: results of the SOPKARD project. *Kardiol Pol*. 2006; 64, 464–469.
46. Nishina M, Nishina K, Ohira T, Makino K, Iso H. Associations of psychological distress with metabolic syndrome among Japanese urban residents. *J Atheroscler Thromb*. 2011; 18, 396–402.
47. Alemany M. Do the interactions between glucocorticoids and sex hormones regulate the development of the metabolic syndrome? *Front Endocrinol*. 2012; 3, 27.
48. Soares CN, Zitek B. Reproductive hormone sensitivity and risk for depression across the female life cycle: a continuum of vulnerability? *J Psychiatry Neurosci*. 2008; 33, 331–343.

https://doi.org/10.1017/S2040174420000860 Published online by Cambridge University Press