Polygenicity of Comorbid Depression in Multiple Sclerosis

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Abstract (n=350 words; max 350 words)

**Background:** Depression is common in multiple sclerosis (MS); and is associated with faster disability progression. The etiology of comorbid depression in MS remains poorly understood. Identification of individuals with a high risk for depression, via polygenic scores (PGS), may facilitate earlier identification. Previous genetic studies of depression considered depression as a primary disorder, not a comorbidity, and thus findings may not generalize to MS. Body mass index (BMI) is a risk factor for both MS and depression and its association may highlight differences in depression in MS. To improve the understanding of comorbid depression in MS, we will investigate PGS in people with MS, with the hypothesis that higher depression PGS is associated with increased odds for comorbid depression in MS.

**Methods:** Samples from three sources (Canada, UK Biobank, and the United States) were used. Individuals were grouped into cases (MS/comorbid depression) and compared to three control groups: MS/no depression, depression/no immune disease, and healthy persons. We employed three depression definitions: lifetime clinical diagnoses, self-reported diagnoses, and depressive symptoms. The PGS were tested in association with depression using regression.

**Results:** 106,682 individuals of European genetic ancestry were used: Canada \(n=370; 213\) with MS), UK Biobank \(n=105,734; 1,390\) MS), and USA \(n=578\) MS). Meta-analyses revealed individuals with MS and depression had a higher depression PGS compared to both MS without depression (odds ratio range per standard deviation [SD]: 1.29-1.38, \(P<0.05\)) and healthy controls (odds ratio range per SD: 1.49-1.53, \(P<0.025\)), regardless of the definition applied and when sex-stratified. The BMI PGS was associated with depressive symptoms \((P\leq.001)\). The depression PGS did not differ between depression occurring as a comorbid condition with MS or as the primary condition (odds ratio range per SD: 1.03-1.13, all \(P>0.05\)).

**Discussion:** Higher depression genetic burden was associated with ~30-40% increased odds of depression in European genetic ancestry participants with MS compared to those without depression and was no different compared to those with depression and no comorbid immune disease. This study paves the way for further investigations into the possible use of PGS for assessing psychiatric disorder risk in MS and its application to non-European genetic ancestries.
Introduction

Persons with multiple sclerosis (MS) are at high risk for depression (incidence rate ratio: 2.41, 95% confidence interval [CI]: 2.21-2.64).\(^1\) A retrospective cohort study of 2,312 people with MS found significantly greater annual disability progression, as measured by Expanded Disability Status Scale (EDSS) over 10 years in those with a mood or anxiety disorder (beta=0.28, \(P=0.0002\)).\(^2\) The effect of depression on mortality in MS is greater than the association of either MS or depression alone (attributable proportion: 13-14%).\(^3\) Despite the adverse effects of depression in MS, it remains under-diagnosed and under-treated.\(^4\) Therefore, an unmet need is the identification of individuals with a high risk for depression to potentially facilitate earlier screening or treatment.

The reasons for the co-occurrence of MS and depression are incompletely understood. Risk factors for depression in MS include increasing disability,\(^5\) disease course,\(^5\) and obesity.\(^6\) Another factor associated with modulating risk for depression is genetic variation. Genetic variation can stratify individuals with respect to disease risk, including for depression.\(^7\) Many common health conditions, including depression, are polygenic, meaning many genes underpin their pathophysiology. Genetic or polygenic scores (PGS) capture polygenicity and are the number of inherited common variants, weighted by their effects. PGS have been investigated in people with MS, most often as the MS disease risk PGS in connection with brain imaging outcomes\(^8,9\), including a recent study that found modest associations between the MS PGS and changes in brain volume in European subjects with MS.\(^9\) Whereas, the depression PGS was not associated with self-reported depression in 184 MS European subjects with depression.\(^10\)

Outside MS, a genome-wide meta-analysis of 246,363 depression cases found individuals in the top depression PGS decile had 3.5-fold higher odds of depression (\(P=1.68\times10^{-8}\)), compared to those in the first decile.\(^11\) This genome-wide association study (GWAS) of depression did not assess depression as a comorbidity and thus findings may not generalize to individuals of European genetic ancestry with other primary conditions such as MS. A separate GWAS of depression specifically in MS did not identify any significant variants associated with depression relative to MS, but the sample size included only 182 cases of depression.\(^12\)
There are limited studies that have directly assessed whether the depression PGS is associated with depression in MS, especially using gold standard assessments of major depressive disorder (MDD). Thus, we aimed to determine whether the depression PGS is associated with comorbid depression in MS compared to: MS and no comorbid depression, depression not comorbid with an immune disease, and healthy controls. Given that obesity is a risk factor for MS and depression, we also considered PGS for body mass index (BMI). We sought to answer our research question using samples from Canada, the United Kingdom, and the United States to enhance precision and generalizability of our findings. We hypothesized that higher depression PGS is associated with increased odds for comorbid depression in MS.

**Methods and Procedures**

**Study design and samples**

We used samples from three existing studies from Canada, the United Kingdom, and the United States to generate a case-control study design.

**Canada**

The Canadian Institutes of Health Research Team on Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease is a prospective 3-year longitudinal study of immune-mediated inflammatory diseases. As previously reported, participants residing in Manitoba, Canada were recruited between November 2014 and July 2016. Cohorts included participants with MS, a lifetime history of depression disorders but no chronic immune disease, or healthy controls. Multiple recruitment methods were used including poster placement in hospitals, private medical clinics, and educational institutions. For the MS cohort, recruitment included in-person or telephone calls or mailouts to patients from community-based and tertiary care clinics. Blood samples were collected in addition to sociodemographic and clinical data. Participants were ≥18 years of age and had to be sufficiently proficient in English to complete questionnaires.
United Kingdom

The UK Biobank (UKB) is a population-based cohort of >500,000 individuals aged 37-73 years from the UK who were recruited 2006-2010.\textsuperscript{15} Participants were invited to answer touchscreen questionnaires at an assessment centre, which contained sections about diseases and was followed by a research nurse-led interview for further details regarding the diseases reported. In addition, linked hospital admission records using international classification of diseases (ICD)-version 10 codes were utilized to identify diagnoses from hospitals. Of the original cohort, \~158,000 individuals completed a web-based mental health questionnaire, which included the Composite International Diagnostic Interview-Short Form (CIDI-SF).\textsuperscript{16} Blood samples were collected. From this cohort, we selected individuals who had MS, had a lifetime history of depression but no immune disease, or healthy controls.

USA

The CombiRx trial (ClinicalTrial.gov: NCT00211887) was a 3-arm, randomized, multi-center, Phase-III trial of combination MS disease-modifying therapies (interferon-\textbeta\textsubscript{1a} and glatiramer acetate vs. either agent alone).\textsuperscript{17} Criteria for the study included neurologist-confirmed MS, with \geq2 relapses in the prior 3 years; aged 18-60 years, EDSS=0-6 and no relapses in the 30 days prior to screening and randomization. Those completing the 3-year core study were invited to the extension which included an additional 4 years (total of 7 years of follow-up). Blood samples were collected. The USA samples were utilized only for comparing comorbid depression in MS to MS without depression, given this was a MS clinical trial sample.

Participant definitions and measures

We employed four groups of participants: (1) MS and depression (cases), (2) MS and no depression (control), (3) depression and no immune disease (control), and (4) healthy (control).

To increase sample size, which is of importance in genetic studies, we included data from three different studies. When retrospectively combining data from multiple sources, a common issue is the phenotypes were assessed differently. We harmonized the depression phenotypes between the studies, which included comparing a gold standard depression measure
(Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, SCID-DSM-IV) in the Canadian sample with that of a comparable version in the UKB sample which combined ICD-10 diagnoses and the CIDI-SF. We then expanded this definition to include a self-reported measure of depression and another related, but different construct: depressive symptoms (PHQ-9). We had one measure of depression in the USA sample, which was self-reported depression.

**Canada**

Cases were defined as those with neurologist-confirmed MS and depression. Depression was defined three ways: (1) lifetime depression was assessed using the gold standard SCID-DSM-IV,

(2) self-reported depression diagnosed by a doctor, which was derived from a questionnaire validated for use in MS, and (3) Baseline Patient Health Questionnaire-9 (PHQ-9), a validated 9-item self-reported tool that assesses depressive symptom severity over the previous two weeks, with a total score of 0 to 27. We used a validated PHQ-9 cut-off for the presence of at least moderate depressive symptoms (PHQ-9 ≥ 10).

Three control groups were defined: persons with MS and no comorbid depression; depression without a comorbid immune disease and healthy controls. Depression not comorbid with an immune disease was defined the same as for depression in individuals with MS. Immune diseases that were excluded from this group (eTable 1). Healthy controls were excluded for: any chronic medical condition (eTable 1), known cognitive impairment, any positive response to the SCID-DSM-IV screening questions for depressive/anxiety disorders, any head injury associated with loss of consciousness or amnesia, or chronic medication use with the exceptions (contraceptives, hormone replacement therapy, transient antibiotic use, or multivitamins).

Self-report questionnaires captured the following at baseline: sex, date of birth, annual household income, highest level of education attained (high school or lower: elementary school, junior high school, high school diploma/GED vs. above high school: college, technical/trade, university), years of education, and smoking history. To facilitate harmonization, we categorized: annual household income (Canadian dollars: <$50,000,
≥$50,000, or “declined”), educational attainment (high school or below, above high school) and ever-smokers (lifetime smoked ≥100 cigarettes). A research assistant measured weight and height for BMI (kg/m²).

UK

We defined people with MS using ≥2: primary or secondary hospital admission code (ICD-10: G35), lifetime baseline self-reported condition (data-field 20002: 1261) or lifetime self-reported MS disease modifying therapy (any of: interferon-beta/interferon beta-1b 1a/avonex/betaferon, glatiramer/copaxone). Newer MS disease modifying therapies were not included given the recruitment period predated their availability.

Like the Canadian sample, cases were defined as persons with MS and comorbid depression. We defined lifetime depression using the presence of either primary or secondary hospital admission codes for depression (ICD-10: F32/F33) or CIDI-SF based MDD. We also included lifetime baseline self-reported condition (Data-Field 20002: 1286) and a baseline PHQ-9 measure which was also dichotomized to define moderate depressive symptoms (PHQ-9≥10). Three control groups were defined: persons with MS and no comorbid depression; depression not comorbid with an immune disease and healthy controls. Depression that was not comorbid with an immune disease was defined in the same manner as depression in those with MS (ICD-10/CIDI-SF, self-report depression or using the PHQ-9) and immune diseases were excluded (eTable 1). Healthy controls were defined like the Canadian by excluding chronic conditions using hospital admission codes or self-reported conditions (eTable 1).

Self-report questionnaires captured the following at baseline: sex, age, BMI, annual household income (converted from 1 British Pounds [GBP] to 1.61 Canadian Dollars [CAD], and into: <$50,000, ≥$50,000, or “declined”), highest education achieved ([high school or lower]: A levels/AS levels or equivalent, Certificate of Secondary Education or equivalent, O levels/General Certificate of Secondary Education or equivalent vs. [Above high school]: National Vocational Qualification or Higher National Diploma or higher National Certificate or equivalent, College or University degree, Other professional qualifications e.g.: nursing, teaching vs. [Other]), and years of education. Ever-smokers were defined as current or ever tobacco smoking on most days or occasionally.
Participants had neurologist-confirmed MS. Depression comorbidity was assessed in a self-reported manner using medical history (at trial enrollment) and the use of concomitant medications (enrollment and follow-up). The following were captured at the clinical trial enrolment visit: sex, age, BMI, highest level of education attained (high school/above high school), and smoking history (ever/never).

**Genotyping, quality control, and imputation**

Further details of the genotyping, quality control and imputation can be found in the eMethods. Genotype data was available on 445 Canadian and 599 USA participants. There was genotype data available for 487,410 UK participants following central quality control and imputation. To determine genetic ancestry, we performed principal components analysis in PLINK using the 1000 Genomes phase 3 v5 data as the reference (N=2,493 unrelated individuals, by “Superpopulation”: 659 African, 347 Admixed, 504 East Asian, 503 Europeans, 480 South Asian) along with our study data. We excluded any samples that were further than three standard deviations from the 1000 Genomes European superpopulation reference on principal components 1 or 2 (N removed: 75 Canada; 27 700 UKB; 21 USA). After removing the non-European genetic ancestry participants, the principal components were regenerated without the reference data and were used as covariates.

**PGS generation**

Details are available in the eMethods (eTable 2) but briefly, polygenic scores were calculated using summary statistics from recent GWAS’ for depression and BMI. PGS were generated as the sum of the risk allele scores, weighted by their effects from the discovery GWAS and standardized to a mean of 0 (standard deviation, SD=1).
Statistical analyses

We described the three samples regarding their characteristics using either the median (interquartile range, IQR), mean (standard deviation, SD) or frequency (percent, %).

To test whether PGS was associated with depression or depressive symptoms in MS, we used multivariable logistic regression (binary outcome) or linear regression (continuous outcome for PHQ-9 scores). We report the results as odds ratios (OR) for logistic models or beta estimate (linear models) per 1-SD increase in PGS. We included the following covariates into the models: age (continuous), sex, and first five genetic ancestry principal components. We compared those with MS-comorbid depression (case) to: (1) MS-no comorbid depression, (2) depression-no comorbid immune disease, and (3) healthy controls in each sample. The summary results for each comparison were then meta-analysed across samples using a fixed-effect inverse-variance weighted model, when between study heterogeneity \(I^2\) was ≤50%, or random-effect \(I^2>50\%\) inverse-variance weighted model.\(^{25}\) Given the association of BMI with MS and depression, we also considered baseline BMI in place of PGS in our analyses comparing MS-depression and MS-no depression and depression-no immune disease. Lastly, given males with MS experience higher relative rates of depression than females with MS,\(^{26}\) we performed sex-stratified analyses comparing MS-depression (case) to MS-no comorbid depression.

The statistical significance level was set at \(P\leq0.05\). We did not impute missing data (other than the genetic data). Analyses were performed using \(R\) (v.4.1.2) with the following packages: \textit{tidyverse}, \textit{data.table}, \textit{metafor}, and \textit{cowplot}.

Data availability

Individual participant data collected for the USA samples cannot be shared but access may be granted via authorization from the Executive Committee. The Canadian dataset cannot be shared because some participants did not agree to data sharing. An application to access UK data is available via the UK Biobank. Analyses code is available: https://github.com/kkowalec/ms-depression.
Standard Protocol Approvals, Registrations, and Patient Consents

The Canadian study was approved by the University of Manitoba Health Research Ethics Board and Shared Health/Winnipeg Regional Health Authority and all patients provided informed consent. Participants in the USA study provided informed consent and ethical approval was granted by the respective collecting institution. The UK Biobank had obtained informed consent from all participants included in this study, with the study originally approved from the Karolinska Institutet Ethics Committee.

Results

We included a total of 106,682 European genetic ancestry samples from three countries or sources: Canada n=370 (213 MS, 57%), UKB n=105,734 (1,390 MS, 0.8%), and USA n=578 (100% MS) (Table 1). Persons with MS from the USA sample were younger and reported lower rates of smoking, compared to the persons with MS in the Canadian and UKB samples (Table 1). The UKB sample is a population-based study, and as such had lower rates of depression, compared to the Canadian and USA samples, with the rates of comorbid depression in people with MS, depending on the definition, ranging from 40.8%-45.1% (Canada), 14.7-16.3% (UKB) and 56.8% (USA) (data not shown). The rate of self-reported depression was similar between the two samples collected from MS clinics and clinical trial settings (Canada: 45.1%; USA: 56.8%). The overlap between the three measures of depression varied, with 30.5% (Canada) participants with MS having comorbid depression as defined by all three measures (eFigure 1), whereas 5.7% of the UKB MS population had depression as defined by all definitions.

Using any of the three depression definitions, meta-analyses revealed persons with MS and comorbid depression had a significantly higher depression genetic burden compared to both MS-no depression (OR per 1-SD increase in PGS: 1.29-1.38, Figure 1, eTables 3 and 4) and healthy controls (OR per 1-SD increase in PGS: 1.49-1.53, Table 2). The effect sizes were similar regardless of the measure used to define depression. Genetic variation associated with BMI was not significantly associated with MS-depression compared to either MS-no depression nor to healthy controls (Table 3). In the Canadian sample, the BMI PGS was significantly associated with self-reported depression and moderate depressive symptoms in MS (Table 3). Given the
lack of any association between the BMI PGS and comorbid depression in the meta-analyses, to ensure BMI PGS was associated with measured BMI in our samples, we did find a strong correlation between BMI and BMI PGS in all samples used (eTable 5). We repeated the primary analyses using baseline BMI, instead of BMI PGS, and again found no overall effect in association with depression in MS (eTables 6 and 7).

We then compared the depression PGS between MS-depression to depression not comorbid with an immune disease. The meta-analyses showed the depression genetic burden in MS with comorbid depression was not significantly different from that of depression without a comorbid immune disease (Figure 1). The BMI PGS was also not significantly associated with MS-depression compared to depression without a comorbid immune disease (Table 3), apart from self-reported depression and moderate depressive symptoms in the Canadian sample (Table 3).

We utilized a continuous outcome (PHQ-9) to define current depressive symptoms in the Canadian and UKB samples (eTable 8). In the meta-analysis, higher cumulative genetic burden for depression and BMI were associated with current depressive symptoms (depression PGS Beta=0.28, BMI PGS Beta=0.13, both $P \leq .001$, eTable 8). We stratified these analyses by BMI category and by sex, with the meta-analytic effects and standard errors in a similar size and direction to that of the unstratified meta-analysis.

We stratified the MS-depression compared to MS-no depression analyses by sex (Table 4, eTables 9 and 10). We observed similar proportions of males and females in each sample by depression measure (eTable 9). The stratified meta-analyses revealed similar results to the unstratified (Table 4). The BMI PGS was not associated with any depression definition in the sex-stratified meta-analysis models (eTable 10).

**Discussion**

We used a large sample of ~106,000 individuals, predominantly from the UK, including 2,181 people with MS, from three countries to confirm our hypothesis that the depression PGS is associated with comorbid depression in MS. We found that a 1-SD increase in the depression PGS is associated with ~30-40% increased odds for depression in persons with MS. We also
found the PGS for depression had a similar association with depression among individuals with MS and in those without a comorbid immune disease.

In the present study, we found that depression polygenicity plays a role in comorbid depression in MS and did not change based on sex, nor when compared to depression occurring as the primary disease. A similar increase in the hazard (~30%) for hospital-based depression diagnosis was identified in a Danish study of 34,573 individuals from the general population, when depression occurred as a comorbidity of Alzheimer’s disease, and to that of ~7,000 moderate-severe major depressive disorder cases. Our study also provides evidence of a biological basis of depression for people with MS, whereas previous studies have identified conflicting associations between family history of depression and the occurrence of depression in MS.

Our current study utilizes a direct measure of genetic variation of depression, as opposed to family history which captures genetic and environmental influences. Further understanding of the biological basis of depression in people with MS could be uncovered by either candidate gene studies or by a GWAS of depression specifically in those with MS. However, candidate gene studies in depression, in general, have not largely been supported and a GWAS of depression including N<200 participants with depression and MS yielded no genome-wide significant findings.

The effect size of the association between depression PGS and comorbid depression in MS from our study did not largely differ based on whether depression was assessed either as a lifetime or current condition, or using ICD diagnostic codes, psychiatric interview, or depressive symptoms. The most recent large scale GWAS of depression, which was used here to compute the PGS in the Canada and USA cohorts, included >240,000 cases of depression collected from a variety of sources, including those ascertained from clinics and the broader group of self-declared affected individuals. A study including 12,106 individuals with major depressive disorder found similarly that the effect of the depression PGS did not vary depending on the depression definition. A study specifically in MS also found that the same depression PGS used in this study was not associated with the development of self-reported depression (hazard ratio=1.04, 95%CI=0.99-1.08, P=0.063), but included a much smaller number of depression cases (N=184, 20.1%).
BMI is a known risk factor for the development of both MS\textsuperscript{13} and depression.\textsuperscript{34} We found that BMI polygenicity was not significantly associated with comorbid depression in MS, compared to any of the control groups, nor in the sex-stratified models, potentially due to the low variance explained by the BMI PGS. However, our meta-analyses showed that a 1-SD increase in the BMI PGS was associated with increasing depressive symptoms (as measured by the PHQ-9) and when stratified by BMI category. Outside the field of MS, a Generation Scotland study including 13,921 individuals found that the BMI PGS was not associated with a lifetime SCID diagnosis of depression, although it was associated with increasing psychological distress.\textsuperscript{35} BMI-increasing genetic variation might be associated with increasing depressive symptoms but not a clinical lifetime diagnosis of depression in MS. We previously demonstrated in those with an immune disease, including MS, rheumatoid arthritis, or inflammatory bowel disease, that a 1-SD increase in the BMI genetic burden, had 2.31 greater odds of high depressive symptoms, whereas those without an immune disease did not show this association.\textsuperscript{36} Along with the current study, our results collectively point to possible differences in depressive symptoms compared to meeting a disorder definition. In addition, clinical subtypes of depression, such as atypical depression, are known to be differentially associated with BMI genetic variation\textsuperscript{37} and future studies including subtypes of depression in MS may help with addressing this area further.

In terms of understanding the development of depression in MS, large administrative health data studies have shown that the rate of depression is elevated in the 5 years prior to MS diagnosis\textsuperscript{38} but Mendelian randomization studies have shown that depression is not causally linked to MS.\textsuperscript{13} The reason for their co-occurrence might therefore be related to chance, improved detection due to increased health service use, or due to genetic or environmental risks. Obesity is a shared risk factor between depression and MS, which here we found to be associated with depressive symptoms in MS, although other common risk factors, such as smoking may also be explored in future work. The etiology of depression in MS may be heterogeneous. In some individuals with MS, depression may also occur secondary to structural changes in the brain.\textsuperscript{39}
Our findings may have clinical relevance for people with newly diagnosed MS as they could be screened for their risk of depression using the depression PGS, and offered counselling or pharmacological therapies early, as preventative medicine. Preventative strategies, such as cognitive behavioral and problem-solving therapy, for depression to reduce its burden has shown success in targeted groups, including in newly diagnosed epilepsy. Screening for depression using PGS has not yet been effective, but in subgroups, for e.g., in people with MS, where the base rate of depression is higher than the general population, theoretically, depression screening using PGS may prove useful. It could also allow health care to be more proactive, e.g., harmless interventions such as mental health literacy training might be appropriate for a high-risk group (i.e., with a high depression PGS) who have not yet become depressed. This might also be a better way to encourage earlier intervention than formal screening. The identification of depression in MS is often complicated by the presence of somatic symptoms (e.g., fatigue, difficulty sleeping) that are characteristic of both depression and MS. Additional tools for identification of depression, such as the depression PGS, may prove useful in these scenarios.

The strengths of this study include a large sample size, inclusion of different countries and multiple definitions of depression. This provides replication and evidence of generalizability in terms of the depression PGS and its application to European cohorts of people with MS. Although our study had multiple definitions of depression, we did not have depression subtype information, which may have proven helpful in identifying heterogeneity between depression occurring as a comorbid condition rather than the primary condition. The inclusion of the UKB as a sample in our study represents a strength due to its comprehensiveness and size. However, the UKB is also limited by a “healthy volunteer” selection bias, whereby individuals that volunteered for the UKB are more health-conscious than non-participants. This likely led to the lower rates of depression in the UKB sample compared to our clinical samples from Canada and the USA. In this study, we did not aim to generate prevalence or incidence rates of depression, but rather, examine the association between a genetic exposure (depression PGS) with depression, and we were able to generate widely generalizable results between three international samples. Including additional measures of external validity, such as external
samples or additional phenotype measures, along with the UKB has been noted to be important when performing research studies using UKB data. Some findings did not replicate between samples, including a significant association between BMI PGS with either self-reported depression or moderate depressive symptoms in MS, and may require a larger sample from individuals with MS. Future areas of research to further unravel the heterogeneity of depression in MS could include information on the treatment of depression and clinical features or depression subtype information.

Another limitation was that our findings are only generalizable to those of European genetic ancestry. The decision to select individuals only of European genetic ancestry is supported by empirical evidence, including differences in allele frequencies, linkage disequilibrium, and causal effect sizes between populations, which results in risk prediction of diseases to vary by population. A recent GWAS of depression in those of East Asian genetic ancestry found none of the European genetic ancestry depression loci to be significant, with similar findings in an African American study. Subsequently, applying the depression GWAS results from a European population to a non-European population would result in low transferability and a reduction in the PGS predictive power. There are methods available for computing trans-ancestry PGS (e.g., PRS-CSx), but our study had a limited number of non-European genetic ancestry samples (e.g. East Asian or African) to apply these methods. Collectively, this highlights the need for future collection of samples to include more diverse populations with extensive data collection (e.g., to identify depression and MS) and may include the Million Veterans Program or the All of Us Research Program. However, each of these biobanks would individually have small numbers of people with MS; thus, specific targeted collection may be necessary. It is also important to further develop other aspects of the ‘genetic discovery pipeline’ including biobanks with coverage on entire populations (for e.g., using samples from newborn screening programs as is done in Australia), genotyping arrays and imputation panels with better multi-ancestry coverage. Aside from genetic studies, under-representation is often prevalent across MS research, including a lack of diversity in clinical trials and other research studies. This could be improved by implementing a multi-faceted approach to address barriers like
healthcare distrust, invest in the enrolment in underrepresented regions and using inclusivity tools such as Dynamic Consents. Additional recommendations are available in the eAppendix.

We found that a one standard deviation increase in the depression genetic burden was associated with ~30-40% increased odds of depression in European genetic ancestry participants with MS, irrespective of the depression definition, compared to both MS with no comorbid depression and healthy controls. MS and comorbid depression had a similar genetic burden of depression compared to those with depression and no comorbid immune disease. Future studies replicating this association in a large cohort of non-European genetic ancestry is imperative. In conclusion, although PGS are not currently used in clinic for assessing risk of depression, our findings indicate that future studies are warranted to determine whether depression PGS testing in subgroups, such as people with MS, may be more appropriate when the base rate of depression is higher, allowing more precise approaches to management of depression to those groups.

http://links.lww.com/WNL/C885
References


Figure Legend

**Figure 1** Multivariable logistic regression analyses investigating the association between the depression polygenic score with multiple sclerosis (MS) and comorbid depression compared with (A) MS and no depression or (B) depression with no comorbid immune disease. Each depression definition is assessed as a separate model including the polygenic scores for depression and BMI, the first 5 genetic ancestry principal components, age, and sex. BMI polygenic score results are reported in Table 3. Data represented as: odds ratio and 95%CI. Random-effect inverse-variance weighted model was used for self-reported depression (Heterogeneity A: $I^2=41.0\%$, B: $I^2=0\%$), whereas the other meta-analytic results used a fixed-effect model (Heterogeneity-Lifetime major depressive disorder A: $I^2=0\%$, B: $I^2=38.5\%$; PHQ-9 $\geq 10$ A: $I^2=0\%$; B: $I^2=43.2\%$). This figure visualises the content of eTable 3.
Table 1 Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>Canada, n=370</th>
<th>UKB, n=105,734</th>
<th>USA, n=578</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MS, depression</td>
<td>MS, no depression</td>
<td>Depression, no immune disease</td>
</tr>
<tr>
<td>N</td>
<td>96 (25.9)</td>
<td>117 (31.6)</td>
<td>111 (30)</td>
</tr>
<tr>
<td>Socio-demographic and general health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>80 (83.3)</td>
<td>94 (80.3)</td>
<td>89 (80.2)</td>
</tr>
<tr>
<td>Age, y</td>
<td>51.0 (11.9)</td>
<td>51.8 (13.2)</td>
<td>46.4 (13.4)</td>
</tr>
<tr>
<td>Highest education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ High school</td>
<td>39 (40.6)</td>
<td>33 (28.2)</td>
<td>31 (27.9)</td>
</tr>
<tr>
<td>&gt; High school</td>
<td>55 (57.3)</td>
<td>80 (68.4)</td>
<td>75 (67.6)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.1)</td>
<td>4 (3.4)</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Declined</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.7 (2.4)</td>
<td>14.6 (2.8)</td>
<td>14.8 (2.9)</td>
</tr>
<tr>
<td>Income (SCAD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; $50,000</td>
<td>31 (32.3)</td>
<td>37 (31.6)</td>
<td>49 (44.1)</td>
</tr>
<tr>
<td>≥ $50,000</td>
<td>55 (57.3)</td>
<td>66 (56.4)</td>
<td>53 (47.7)</td>
</tr>
<tr>
<td>Declined</td>
<td>10 (10.4)</td>
<td>14 (12)</td>
<td>9 (8.1)</td>
</tr>
<tr>
<td>Ever-smoker</td>
<td>63 (65.6)</td>
<td>61 (52.1)</td>
<td>52 (46.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.8 (8.5)</td>
<td>27.9 (6.2)</td>
<td>31.4 (8.5)</td>
</tr>
<tr>
<td>Overweight</td>
<td>33 (34.4)</td>
<td>39 (33.3)</td>
<td>21 (18.9)</td>
</tr>
<tr>
<td>Obese</td>
<td>34 (35.4)</td>
<td>33 (28.2)</td>
<td>58 (52.3)</td>
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<tr>
<td>Mental health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime MDD</td>
<td>65 (67.7)</td>
<td>22 (18.8)</td>
<td>111 (100)</td>
</tr>
<tr>
<td>Self-reported MDD</td>
<td>96 (100)</td>
<td>0</td>
<td>111 (100)</td>
</tr>
<tr>
<td>PHQ-9 score</td>
<td>9.9 (5.8)</td>
<td>5.1 (4.7)</td>
<td>13.2 (6.5)</td>
</tr>
<tr>
<td>PHQ-9 ≥ 10</td>
<td>57 (59.4)</td>
<td>35 (29.9)</td>
<td>97 (78.4)</td>
</tr>
<tr>
<td>PHQ-9 ≥ 15</td>
<td>45 (46.9)</td>
<td>20 (17.1)</td>
<td>77 (69.4)</td>
</tr>
<tr>
<td>Genetic factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD-PGS</td>
<td>0.08 (0.9)</td>
<td>-0.2 (1.1)</td>
<td>0.09 (1.1)</td>
</tr>
<tr>
<td>BMI-PGS</td>
<td>0.03 (0.9)</td>
<td>-0.23 (0.9)</td>
<td>-0.18 (0.9)</td>
</tr>
</tbody>
</table>

Categorical variables reported as n (%) and continuous measures reported as mean (SD). Depression as a participant category is defined using self-reported depression for all samples. *Missing n=72 (12.5%). †For UKB, the denominator for the PHQ-9 measure is n=134 multiple sclerosis-self reported depression, n=252 multiple sclerosis-no self-reported depression, n=31,393 depression, n= 12,619 healthy.

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Table 2: Multivariable logistic regression analyses investigating the association between the polygenic scores for depression and body mass index with multiple sclerosis and comorbid depression compared to healthy controls

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canada</th>
<th>UKB</th>
<th>Meta-Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Depression PGS</td>
<td>Body mass index PGS</td>
<td>Depression PGS</td>
</tr>
<tr>
<td>Lifetime MDD</td>
<td>1.96 (1.22-3.17); 0.005</td>
<td>1.46 (0.95-2.23); 0.08</td>
<td>1.49 (1.29-1.72); &lt;.001</td>
</tr>
<tr>
<td>Self-reported depression</td>
<td>1.92 (1.21-3.04); 0.005</td>
<td>1.64 (1.04-2.59); 0.03</td>
<td>1.31 (1.15-1.51); &lt;.001</td>
</tr>
<tr>
<td>PHQ-9 ≥ 10</td>
<td>1.83 (1.16-2.91); 0.009</td>
<td>1.63 (1.04-2.54); 0.03</td>
<td>1.39 (1.07-1.83); 0.02</td>
</tr>
</tbody>
</table>

MDD: Major depressive disorder. PGS: Polygenic risk score.

The outcome is multiple sclerosis-depression (case) compared to healthy controls. Each depression measure is assessed as a separate model and includes the polygenic scores for depression and BMI, the first 5 genetic ancestry principal components, age, and sex. Data represented as: odds ratio (95%CI); P-value. I² (for meta-analyses). Bolded p-value indicates P≤0.05. aRandom-effect inverse-variance weighted model, whereas others used a fixed-effect.
Table 3: Multivariable logistic regression analyses investigating the association between the body mass index (BMI) polygenic score with multiple sclerosis (MS) and comorbid depression and (A) MS and no comorbid depression or (B) depression and no comorbid immune disease

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canada</th>
<th>UKB</th>
<th>USA</th>
<th>Meta-Analysis</th>
<th>Canada</th>
<th>UKB</th>
<th>Meta-Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime MDD</td>
<td>1.17 (0.84-1.66), 0.4</td>
<td>0.98 (0.84-1.14), 0.7</td>
<td>N/A</td>
<td>1.01 (0.88-1.16), 0.9, 0%</td>
<td>1.28 (0.93-1.78), 0.2</td>
<td>0.96 (0.84-1.11), 0.6</td>
<td>1.07 (0.82-1.39), 0.6, 59.3%a</td>
</tr>
<tr>
<td>Self-reported depression</td>
<td>1.46 (1.04-2.06), <strong>0.02</strong></td>
<td>1.00 (0.86-1.16), 0.9</td>
<td>1.18 (0.99-1.41), 0.051</td>
<td>1.16 (0.96-1.40), 0.1, 61.5%a</td>
<td>1.47 (1.05-2.05), <strong>0.02</strong></td>
<td>1.02 (0.89-1.16), 0.7</td>
<td>1.18 (0.84-1.67), 0.3, 74.0%a</td>
</tr>
<tr>
<td>PHQ-9 ≥ 10</td>
<td>1.45 (1.02-2.08), <strong>0.04</strong></td>
<td>1.04 (0.78-1.38), 0.7</td>
<td>N/A</td>
<td>1.21 (0.87-1.67), 0.2, 51.1%a</td>
<td>1.45 (1.01-2.09), <strong>0.04</strong></td>
<td>0.96 (0.73-1.24), 0.7</td>
<td>1.16 (0.77-1.75), 0.4, 70.6%a</td>
</tr>
</tbody>
</table>

MDD: Major depressive disorder.

Each depression measure is assessed as a separate model includes the polygenic scores for depression and BMI, the first 5 genetic ancestry principal components, age, and sex. The results for the depression polygenic score are in Fig. 1 and Table S3. Data represented as: odds ratio, (95%CI), P-value, I² (for meta-analyses). Bolded p-value indicates P≤0.05. *Random-effect inverse-variance weighted model, whereas others used a fixed-effect.
### Table 4: Sex-stratified multivariable logistic regression investigating the association between the polygenic score for depression and multiple sclerosis and comorbid depression

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canada</th>
<th>UKB</th>
<th>USA</th>
<th>Meta-Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Lifetime MDD</td>
<td>1.41 (1.01-1.95), 0.04</td>
<td>1.38 (0.67-2.83), 0.4</td>
<td>1.39 (1.17-1.65), &lt;0.001</td>
<td>1.22 (0.86-1.73), 0.2</td>
</tr>
<tr>
<td>Self-reported depression</td>
<td>1.37 (0.99-1.89), 0.051</td>
<td>1.10 (0.44-2.74), 0.8</td>
<td>1.22 (1.03-1.44), 0.01</td>
<td>1.01 (0.7-1.4), 0.9</td>
</tr>
<tr>
<td>PHQ-9 ≥ 10</td>
<td>1.28 (0.91-1.81), 0.15</td>
<td>2.25 (0.98-5.2), 0.054</td>
<td>1.70 (1.19-2.48), 0.004</td>
<td>0.67 (0.31-1.36), 0.2</td>
</tr>
</tbody>
</table>

MDD: Major depressive disorder.

The outcome is multiple sclerosis-depression (case) compared to multiple sclerosis-no depression (control) in females or males. Each depression measure is assessed as a separate model and includes the polygenic scores for depression and BMI, the first 5 genetic ancestry principal components, and age. Bolded p-value indicates P≤0.05.
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Kaarina Kowalc, Kathryn C Fitzgerald, Amber Salter, et al.
Neurology published online June 8, 2023
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