Supplementary material

eMethods

Genotyping, quality control, and imputation

Samples were genotyped on the Illumina Global Screening Array SNP (version 2) at the Genome Québec Innovation Centre (McGill University). Samples passing quality control were imputed (reference panel: Haplotype Reference Consortium, r1.1)[1] on the Michigan Imputation Service.[2] We removed imputed variants with a low minor allele frequency (<0.01) and INFO score <0.9, with 6,628,937 variants for analyses. UK samples were genotyped using the Affymetrix UK Biobank Axiom Array, with genotype data available for 487,410 participants following central quality control and imputation (reference panel: Haplotype Reference Consortium, r1.1) like the Canadian samples, with full details reported previously.[3] We filtered imputed data for low minor allele frequency (<0.01) and INFO score <0.6, with 9,709,770 variants remaining. USA samples were genotyped using HumanOmni1-Quad chip array at the Translational Genomics Research Institute, Arizona, with genotype data available for self-reported white participants following quality control and imputation (reference panel: TOPMed). Imputed data were filtered for low minor allele frequency (<0.01) and INFO score <0.7, with 8,810,353 variants remaining. To determine genetic ancestry, we performed principal components analysis in PLINK (v1.9) 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.[4,5] We excluded any samples that were further than three standard deviations from the 1000 Genomes European superpopulation reference on principal components 1 or 2.[5] After removing the non-European genetic ancestry participants, the principal components were regenerated and were used as covariates.

PGS Computation

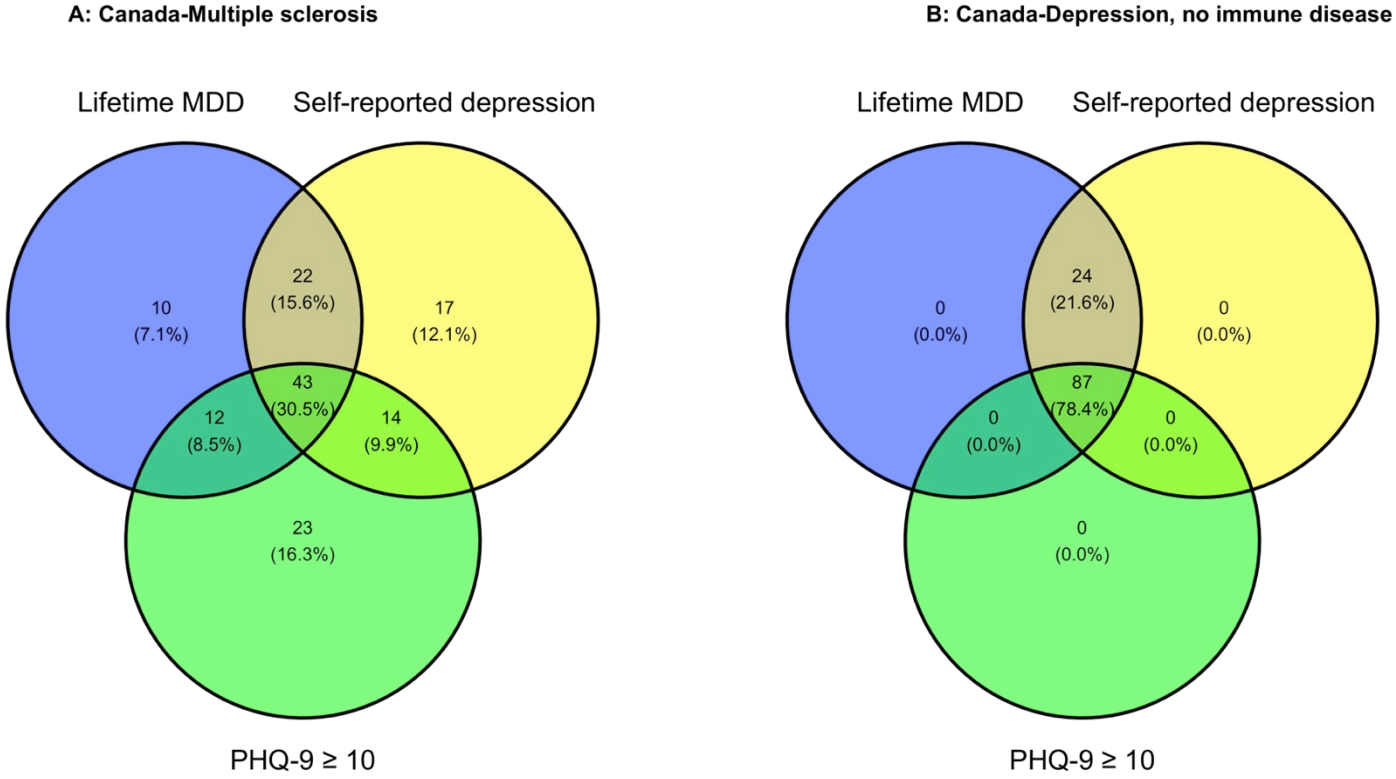
PGS were generated as the sum of the risk allele scores, weighted by their effects from the discovery GWAS.[6] For the Canadian and USA samples, we performed linkage disequilibrium clumping (r^2<0.1 in 1-Mb window) on any overlapping SNPs with the 1000 Genomes Project European samples for the reference. PGS were calculated using PLINK (v1.9) for different scores based on 8 different p-value thresholds ($p \leq 5\times10^{-8}$, $p \leq 1\times10^{-5}$, $p \leq 1\times10^{-3}$, $p \leq 0.01$, $p \leq 0.05$, $p \leq 0.1$, $p \leq 0.5$, and $p \leq 1$). We computed the variance in outcome [Nagelkerke's pseudo-R^2 [7]] explained by the depression PGS as the difference in R^2 from a logistic model including the depression PGS and a baseline model with genetic ancestry principal components (***eTable 2***) to determine which p-value threshold to include in our modelling. For the UKB, we removed any UKB samples from the existing summary statistics as this would inflate the results and PGS were computed using the SbayesR module in GCTB.[8] We standardized all PGS to a mean of 0 (standard deviation, SD=1).

eAppendix

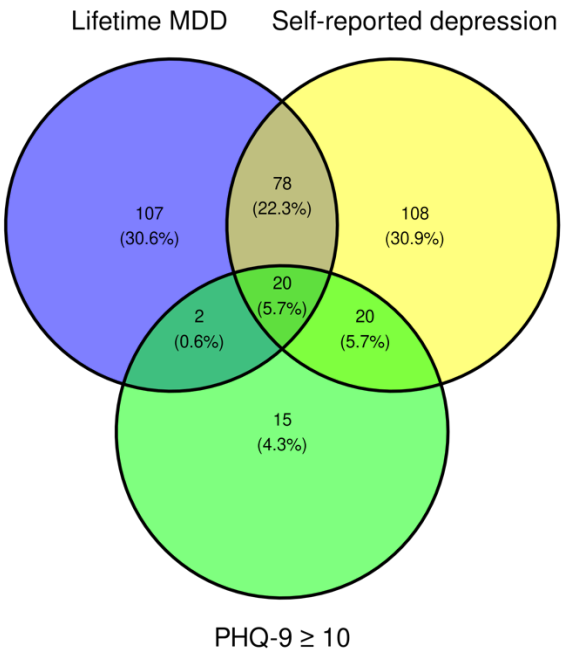
Recommendations for improving inclusivity in clinical trials and research in general.

Under-representation is prevalent across MS (and other disease areas) clinical trials[9] and more generally in research.[10] Bodicoat *et al* (2021) performed a rapid review of and made recommendations on ways of promoting inclusivity in clinical trials and more generally for clinical research.[11] From 72 eligible articles on inclusivity in clinical trials, the authors found that the barriers often were unique by population and that a multi-faceted approach would be essential to improving inclusion. Bodicoat *et al* made 15 recommendations which included 6 broad areas of types of strategies: (1) research staff, (2) communication, (3) community, (4) education, (5) feasibility or identification and (6) outcomes. For research staff, this would include providing cultural competency training. Regarding communications, including more inclusive means of communication, like video calling, or offering extended office hours and personalizing communication whereby the individual to be recruited is seen as an individual and not a 'research subject'. Establishing an advisory panel that is specific to the community such that voices of under-served groups are heard. More inclusive education involves providing more transparent and more readily available information about the study. Ensuring that the study criteria are not inadvertently excluding groups of individuals that are under-served ("feasibility"). Last, regarding outcomes, specifically, sex and gender identity, it is important to collect both sex at birth and gender identity. These recommendations are poised to be highly relevant to improve representation in clinical trials within MS as well as the general MS research realm.

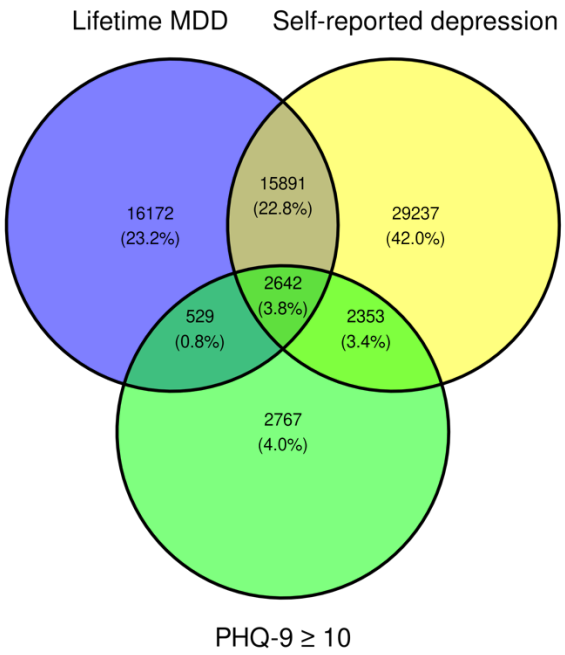
eFigure 1 Overlap in the three definitions of depression used in the (A-B) Canadian and (C-D) UK Biobank (UKB) samples. MDD: major depressive disorder.



C: UKB-Multiple sclerosis



D: UKB-Depression, no immune disease



eTable 1: List of conditions and corresponding ICD-10 codes and survey question number for use in defining healthy controls in UKB and Canada samples.

Condition	ICD-10 code (UKB)	Baseline survey data fields (UKB)
High cholesterol (hyperlipidemia)	E780, E782, E784, E785[12]	1473
High blood pressure (hypertension)	I10–I13, I15[12]	1065, 1072
Heart trouble (such as angina, congestive heart failure, or coronary artery disease, myocardial infarction)	I20–I25[12]	1066, 1074
Disease of arteries in the legs (Peripheral vascular disease)	I70, I73.8, I73.9[13]	1067, 1087, 1088
Asthma, emphysema, chronic bronchitis, or chronic obstructive pulmonary disease	J45, J46, J43, J40-J42, J42	1111, 1472, 1113, 1112
Diabetes mellitus (type 1/type 2)	E10, E11	1220[14]; 1222 (type 1), 1223 (type 2)
Cancer of the breast/colon/lung/skin or others	C0-C33, C34, C45-C49, C51-C60, C62-C97	2453
Migraine	G43	1265[15]
Thyroid disease	E2, E3, E05, E06	1226, 1225, 1428
Lupus (systemic lupus erythematosus)	M32	1381
Degenerative arthritis (osteoarthritis)	M15, M16, M17, M18, M19, M47	1465[16]
Osteoporosis	M80, M81, M82	1309
Fibromyalgia	M79.7	1542
Kidney disease	N10-N19[17]	1192, 1193, 1194, 1405
Peptic ulcer disease, gastroesophageal reflux disease (GERD)	K25 (peptic ulcer) K21 (GERD)	1400, 1138
Liver problems (e.g. cirrhosis, Hepatitis B, Hepatitis C, Fatty Liver)	K70-K77	1158, 1579, 1580
Irritable bowel syndrome	K58	1154
Epilepsy (seizure disorder)	G40, G41[12]	1264
Depression	F32–F34[12]	1286
Anxiety disorder	F40, F41[12]	1287
Bipolar disorder	F31[18]	1291
Schizophrenia	F20	1289
Other psychiatric disorders (substance use, ADHD, eating disorders, personality disorders)	F10-F19 (-F17), K70, F50, F60, F90	1408, 1409, 1410, 1604, 1470
Immune diseases: inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, celiac, psoriasis, Sjogren's	K50, K51[12], G35, M5, M6, K90, L40, M35	1461, 1261, 1464, 1456, 1453, 1382
Brain injury (concussions or other trauma)	S02, S06, S09[19]	1266
Polycystic ovarian syndrome	E28	1350

This list of conditions is those that were excluded to define the Canadian healthy control group using self-reported questionnaires. In addition to define the control group with depression and no immune disease, we used the list of immune diseases here.

eTable 2: Variance explained in depression outcome by the polygenic score as measured by Nagelkerke pseudo-R^2.

	Depression PGS			Body mass index PGS		
P-value threshold	**Canada**	**USA**	**UKB**	**Canada**	**USA**	**UKB**
p≤5e-8	**4.16***	0.10	N/A	0.77	0.06	N/A
p≤1e-5	1.63	1.00	N/A	0.53	0.46	N/A
p≤1e-3	0.11	2.36	N/A	0.60	**0.81**	N/A
p≤0.01	0.03	4.09	N/A	0.48	0.54	N/A
p≤0.05	1.56	4.09	N/A	0.64	0.48	N/A
p≤0.1	2.92	4.65	N/A	0.66	0.44	N/A
p≤0.5	2.37	4.69	N/A	0.83	0.42	N/A
p≤1	2.38	**4.72**	N/A	**0.85**	0.39	N/A
SBayesR	N/A	N/A	**1.36**	N/A	N/A	**4.4e-05**

Outcome used: lifetime major depressive disorder diagnosis using SCID-DSM IV in multiple sclerosis (Canada), self-reported depression in multiple sclerosis (USA), lifetime major depressive disorder using CIDI-SF or ICD-10 (UKB). R^2 expressed as a percentage (%). Bolded represents the highest pseudo-R^2 per PGS, per study site; and thus the selected p-value threshold for analyses.

eTable 3: Multivariable logistic regression analyses investigating the association between the depression polygenic score with multiple sclerosis (MS) and comorbid depression and (A) MS and no comorbid depression or (B) depression and no comorbid immune disease.

	A: MS-depression (case) compared to MS-no depression (control)				**B: MS-depression (case) compared to Depression-no immune disease (control)**		
Outcome	**Canada**	**UKB**	**USA**	**Meta-Analysis**	**Canada**	**UKB**	**Meta-Analysis**
Lifetime major depressive disorder	1.38 (1.03-1.85), 0.03	1.36 (1.17-1.59), <.001	N/A	1.36 (1.19-1.56), <.001, I^2=0%	1.05 (0.78-1.43), 0.7	1.15 (0.99-1.31), 0.06	1.13 (0.99-1.29), 0.06; I^2=38.5%
Self-reported depression	1.35 (1.01-1.78), 0.04	1.17 (1.01-1.36), 0.03	1.46 (1.21-1.74), <.001	1.29 (1.16-1.44), <.001, I^2=41.0%[a]	1.02 (0.76-1.36), 0.8	1.04 (0.90-1.19), 0.6	1.03 (0.91-1.17), 0.6; I^2=0%[a]
PHQ-9 ≥ 10	1.37 (1.01-1.85), 0.04	1.39 (1.03-1.89), 0.03	N/A	1.38 (1.11-1.71), 0.003, I^2=0%	1.09 (0.81-1.46), 0.5	1.07 (0.81-1.31), 0.6	1.08 (0.88-1.32), 0.5; I^2=43.2%

The information in this table is the same as what is represented in Figure 1. Each depression measure is assessed as a separate model includes the polygenic scores for depression and body mass index, the first 5 genetic ancestry principal components, age, and sex. The results for the body mass index polygenic score are in Table 3. Data represented as: odds ratio, (95%CI), P-value, I^2 (for meta-analyses). Bolded p-value indicates P≤0.05. [a]Random-effect inverse-variance weighted model, whereas others used a fixed-effect.

eTable 4: Number of participants included in meta-analyses.

	Multiple sclerosis-depression (case) compared to multiple sclerosis-no depression (control)			**Multiple sclerosis-depression (case) compared to depression-no immune disease (control)**			**Multiple sclerosis-depression (case) compared to Healthy (control)**		
Outcome	**Total**	**Case**	**Control**	**Total**	**Case**	**Control**	**Total**	**Case**	**Control**
1. Lifetime major depressive disorder	1,603	294	1,309	35,639	294	35,345	54,561	294	54,267
2. Self-reported depression	2,181	664	1,517	50,556	322	50,234	54,589	322	54,267
3. PHQ-9	807	149	658	8,547	149	8,398	54,416	149	54,267

eTable 5: Correlation between measured BMI and BMI PGS in each sample, by participant group.

	Multiple sclerosis						
	[1] Comorbid self-reported depression	**[2] No comorbid self-reported depression**	**[3] Self-reported depression, no immune disease**	**[4] Healthy controls**	**Z-statistic; P-value [1] vs. [2]**	**Z-statistic; P-value [1] vs. [3]**	**Z-statistic; P-value [1] vs. [4]**
Canada	0.25 (0.05, 0.43), 0.01	0.35 (0.18, 0.51), <.001	0.27 (0.10, 0.43), 0.003	0.11 (-0.11, -0.38), 0.2	-0.79, 0.4	-0.15, 0.9	0.8, 0.4
UKB	0.14 (-0.01, 0.28), 0.06	0.15 (0.10, 0.20), <.001	0.21 (0.20, 0.22), <.001	0.18 (0.17, 0.19), <.001	-0.14, 0.8	-0.15, 0.9	-0.61, 0.5
USA	0.22 (0.11, 0.31), <.001	0.31 (0.19, 0.42), <.001	N/A	N/A	-1.13, 0.3	N/A	N/A

Presented as: r, (95% confidence interval), p-value.

eTable 6: Investigating the association between the baseline body mass index (BMI, kg/m^2) with multiple sclerosis (MS) and comorbid depression and (A) MS and no comorbid depression or (B) depression and no comorbid immune disease.

	A: MS-depression (case) compared to MS-no depression (control)				**B: MS-depression (case) compared to Depression-no immune disease (control)**		
Outcome	**Canada**	**UKB**	**USA**	**Meta-Analysis**	**Canada**	**UKB**	**Meta-Analysis**
Lifetime MDD	1.04 (1.00-1.08), 0.051	1.03 (1.01-1.06), **0.02**	N/A	1.03 (1.01-1.05), **0.01**, 0%	0.97 (0.95-1.01), 0.2	0.99 (0.97-1.03), 0.9	0.98 (0.96-1.00). 0.1, 50%[a]
Self-reported depression	1.03 (0.99-1.08), 0.06	1.04 (1.01-1.06), **0.003**	1.00 (0.98-1.03), 0.7	1.02 (0.99-1.05), 0.052, 66%[a]	0.97 (0.94-1.01), 0.1	0.99 (0.97-1.02), 0.6	0.98 (0.97-1.00). 0.1, 50%[a]
PHQ-9 ≥ 10	1.05 (1.01-1.10), **0.01**	1.00 (0.95-1.06), 0.98	N/A	1.00 (1.00-1.06), 0.2, 45.9%	0.98 (0.94-1.01), 0.2	0.94 (0.89-0.99), **0.03**	0.96 (0.94-1.00), 0.2, 18.8%

MDD: Major depressive disorder.

Each depression measure is assessed as a separate model includes the baseline BMI, age, and sex. Data represented as: odds ratio, (95%CI), P-value, I^2 (for meta-analyses). Bolded p-value indicates P≤0.05. [a]Random-effect inverse-variance weighted model, whereas others used a fixed-effect.

eTable 7: Sex-stratified multivariable logistic regression investigating the association between the baseline BMI (kg/m^2) with multiple sclerosis (MS) and comorbid depression and MS and no comorbid depression.

	Canada		UKB		USA		Meta-Analysis	
Outcome	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
Lifetime MDD	1.04 (1.01-1.09), **0.03**	0.99 (0.89-1.10), 0.8	1.03 (0.99-1.06), 0.054	1.05 (0.97-1.14), 0.2	N/A	N/A	1.03 (1.00-1.05), 0.5, 0%	1.03 (0.96-1.10), 0.4, 0%
Self-reported depression	1.05 (1.01-1.09), **0.02**	0.95 (0.85-1.06), 0.6	1.05 (1.02-1.08), **<.001**	0.97 (0.89-1.06), 0.5	1.00 (0.97-1.02), 0.9	1.02 (0.97-1.09), 0.3	1.02 (1.00-1.03), 0.5, 80%[a]	0.99 (0.95-1.04), 0.4, 0%
PHQ-9 ≥ 10	1.04 (0.99-1.09), 0.06	1.12 (0.99-1.27), 0.06	1.03 (0.97-1.10), 0.3	0.90 (0.74-1.10), 0.3	N/A	N/A	1.03 (1.00-1.07), 0.6, 0%	1.06 (0.81-1.23), 0.5, 72%[a]

MDD: Major depressive disorder.

Each depression measure is assessed as a separate model includes the baseline BMI, age, and sex. Data represented as: odds ratio, (95%CI), P-value, I^2 (for meta-analyses). Bolded p-value indicates P≤0.05. [a]Random-effect inverse-variance weighted model, whereas others used a fixed-effect.

eTable 8: Linear regression analyses investigating the association between the polygenic scores for depression and body mass index with baseline depressive symptoms in the Canadian and UKB samples.

	Canada					UKB					Meta-analysis				
	All	Stratified by BMI		Stratified by sex		All	Stratified by BMI		Stratified by sex		All	Stratified by BMI		Stratified by sex	
		Normal	Over-weight	Female	Male		Normal	Over-weight	Female	Male		Normal	Over-weight	Female	Male
Depression PGS	0.76 (0.30), **0.01**	0.98 (0.42), **0.02**	0.70 (0.42), 0.09	0.55 (0.35), 0.1	1.38 (0.7), 0.051	0.28 (0.02) **<.001**	0.22 (0.04), **<.001**	0.31 (0.04), <.**001**	0.32 (0.04), <.**001**	0.22 (0.04), <.**001**	0.28 (0.03), **<.001**, I^2=60.7%	0.22 (0.03), **<.001**, I^2=69.1%	0.31 (0.04), **<.001**, I^2=0%	0.32 (0.04), **<.001**, I^2=0%	0.22 (0.04), **<.001**, I^2=63.5%
Body mass index PGS	0.76 (0.32), **0.01**	-0.47 (0.48), 0.3	0.67 (0.45), 0.1	0.74 (0.4), 0.051	1.07 (0.8), 0.2	0.21 (0.03) **<.001**	-0.01 (0.03), 0.75	0.12 (0.03), **<.001**	0.13 (0.03), **<.001**	0.12 (0.04), **0.002**	0.13 (0.03), **<.001**, I^2=74.7%	-0.01 (0.03), 0.7, I^2=0%	0.13 (0.04), <.**001,** I^2=30.9%	0.13 (0.03), **<.001,** I^2=57.3%	0.11 (0.04), **0.002**, I^2=29.7%
Disease group: Multiple sclerosis	6.3 (0.92), **<.001**	5.4 (1.1), **<.001**	6.3 (1.3), **<.001**	6.2 (1.1), **<.001**	6.1 (1.6), <.**001**	4.0 (0.05) **<.001**	3.0 (0.3), **<.001**	3.7 (0.3), <.**001**	3.4 (0.3), **<.001**	3.5 (0.4), <.**001**	3.6 (0.2), <.**001**, I^2=88.7%	3.2 (0.3), <.**001**, I^2=77.5%	3.9 (0.3), **<.001**, I^2=72.6%	3.5 (0.3), **<.001**, I^2=83.6%	3.6 (0.5), **<.001**, I^2=58.8%
Disease group: Depression	11.4 (0.98), **<.001**	11.4 (1.3), **<.001**	11.2 (1.5), <.**001**	11.4 (1.2), **<.001**	12.5 (1.8), **<.001**	3.5 (0.2), **<.001**	3.3 (0.07), <.**001**	4.4 (0.07), **<.001**	3.9 (0.07), <.**001**	4.2 (0.08), <.**001**	4.1 (0.05), <.**001,** I^2=98.2%	3.3 (0.07), <.**001,** I^2=97.4%	4.4 (0.07), **<.001**, I^2=95.2%	3.9 (0.07), **<.001,** I^2=97.4%	4.3 (0.08), **<.001**, I^2=95.2%

PGS: Polygenic score.

The outcome in all models is the baseline PHQ-9 measure. The exposures include all factors listed in addition to the first 5 genetic ancestry principal components, age, and sex. For the disease group, the reference category is the healthy controls. Bolded p-value indicates P≤0.05. No evidence of interaction between MS and the PGS: Interaction terms: Full model interaction terms (beta, p-value): Depression PGS*MS (1.07, 0.3), Depression PGS*depression (0.35, 0.9), BMI PGS*MS (1.34, 0.2), BMI PGS*Depression (-0.08, 0.9). BMI-stratified model interaction terms: Depression PGS*MS (Normal weight: 1.09, 0.2; Overweight: 1.9, 0.6), Depression PGS*Depression (Normal weight: -0.13, 0.5; Overweight: 1.2, 0.8).

eTable 9: Number of females and males included in sex-stratified regression.

	Canada, *N*=213		**UKB, *N*=1,390[A]**		**USA, *N*=578**	
Outcome	**Female, *n*=174**	**Male, *n*=39**	**Female, *n*=1,015**	**Male, *n*=375**	**Female, *n*=417**	**Male, *n*=161**
Lifetime MDD	71 (40.8)	16 (41.0)	162 (15.9)	45 (12)	N/A	N/A
Self-reported depression	80 (46.0)	16 (41.0)	184 (18.1)	42 (11.2)	259 (59.7)	83 (49.4)
PHQ-9 ≥ 10	72 (41.4)	20 (51.3)	43 (14.5)	14 (15.7)	N/A	N/A
PHQ-9 score, mean	7.1 (5.6)	7.6 (6.4)	4.8 (4.9)	4.7 (4.9)	N/A	N/A

MDD: Major depressive disorder.

[A]For UKB, the denominator for the lifetime major depressive disorder and self-reported depression is N=1,390 multiple sclerosis. For the PHQ-9 measure, the denominator is N=297 females with multiple sclerosis, 89 males with multiple sclerosis.

eTable 10: Sex-stratified logistic regression investigating the association between the polygenic score for body mass index with multiple sclerosis and comorbid depression.

	Canada		UKB		USA		Meta-Analysis	
Outcome	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
Lifetime MDD	1.12 (0.76-1.63), 0.5	1.55 (0.61-3.9), 0.4	0.9 (0.75-1.07), 0.2	1.27 (0.93-1.7), 0.1	N/A	N/A	0.94 (0.80-1.10), 0.4, 2.7%	1.30 (0.96-1.76), 0.09, 0%
Self-reported depression	1.36, (0.94-1.97); 0.1	4.12 (1.01-16.9), **0.050**	0.97 (0.82-1.15), 0.8	1.08 (0.7-1.5), 0.6	1.15 (0.95-1.41), 0.06	1.39 (0.98-1.98), 0.06	1.08 (0.95-1.22), 0.2, 38.1%	1.26 (0.99-1.60), 0.06, 47.3%
PHQ-9 ≥ 10	1.16 (0.78-1.73), 0.5	5.23 (1.5-18.5), **0.01**	1.06 (0.75-1.47), 0.7	1.16 (0.6-2.22), 0.6	N/A	N/A	1.10 (0.85-1.42), 0.5, 0%	2.23 (0.52-9.62), 0.3, 76.9%[a]

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.