Table of Contents

Supplementary Table 1. ………………………………………………………………………………………………………………………………………………………… in .xlsx format (external)

***Supplementary Table 2.* ………………………………………………………………………………………………………………………………………….…….……… *in .xlsx format (external)***

[Supplementary Table 3. 2](#_Toc188481363)

[Supplementary Table 4. 3](#_Toc188481364)

[Supplementary Table 5. 12](#_Toc188481365)

[Supplementary Table 6. 13](#_Toc188481366)

[Supplementary Table 7. 14](#_Toc188481367)

[Supplementary Table 8. 16](#_Toc188481368)

[Supplementary Table 9. 18](#_Toc188481369)

[Supplementary Table 10. 20](#_Toc188481370)

[Supplementary Table 11. 22](#_Toc188481371)

[Supplementary Table 12. 24](#_Toc188481372)

[Supplementary Table 13. 26](#_Toc188481373)

[Supplementary Table 14. 28](#_Toc188481374)

[Supplementary Table 15. 30](#_Toc188481375)

**Supplementary Table 3.** Genome-wide association study (GWAS) data used for computing polygenic scores within the target UK Biobank sample.

Abbreviations: PMID, PubMed ID; N, sample size; BMI, body mass index; CAD, coronary artery disease; T2DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; 2hGlu, glucose levels 2 hours after an oral glucose challenge; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; TG, triglycerides.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **GWAS disease/trait** | **Authors** | **Year** | **PMID** | **N cases** | **N controls** | **tot N** |
| BMI | Locke et al. | 2015 | 25673413 | - | - | 209,521 |
| CAD | Nikpay | 2015 | 26343387 | 60,801 | 123,504 | 184,305 |
| T2DM | Scott | 2017 | 28566273 | 26,676 | 132,532 | 159208 |
| FPG | Lagou et al. | 2021 | 33402679 | - | - | 140,595 |
| 2hGlu | Saxena et al. | 2010 | 20081857 | - | - | 15,234 |
| HbA1c | Wheeler et al. | 2017 | 28898252 | - | - | 123,665 |
| HDL | Graham et al. | 2021 | 34887591 | - | - | 1,654,960 |
| HOMA-IR | Dupuis et al. | 2010 | 20081858 | - | - | 37,037 |
| LDL | Graham et al. | 2021 | 34887591 | - | - | 1,654,960 |
| TG | Graham et al. | 2021 | 34887591 | - | - | 1,654,960 |

**Supplementary Table 4.** Overview of analytical variables sourced from UK Biobank data. This table reports the variables selected for analysis, the corresponding UK Biobank field ID or source of information, the original and used coding schemes, and the types of variables as categorized for statistical analysis.

Abbreviations: BMI, body mass index; CVDs, cardiovascular diseases; IR, insulin resistance; MetS, metabolic syndrome; N, number of; NA, not available or missing value; NAFLD, non-alcoholic steatohepatitis liver disease; PCOS, polycystic ovary syndrome; SARI, serotonin antagonist and reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; T2DM, type 2 diabetes mellitus; TCA, tricyclic antidepressants. UK educational qualifications includes: ‘College/University’ degree, which covers undergraduate (Bachelor’s degrees) and postgraduate degrees (Master’s and Doctoral degrees); ‘A/AS levels’ (Advanced/Advanced Subsidiary levels), qualifications typically pursued by students aged 16 to 18 as a preparatory step for university or vocational training; ‘GCSEs’ (General Certificate of Secondary Education), the primary set of exams taken by students at the end of compulsory education around age 16, replacing the historical ‘O levels’ (Ordinary Levels) and ‘CSEs’ (Certificate of Secondary Education, a non-academic track phased out in 1988 alongside O Levels); ‘NVQ’ (National Vocational Qualifications), ‘HND’ (Higher National Diploma), and ‘HNC’ (Higher National Certificate), which are vocational qualifications offered post-secondary education to provide practical skills and training in various fields.

| **Variable** | **Field ID or source of information used** | **Original coding** | **Used coding** | **Type of variable** |
| --- | --- | --- | --- | --- |
| Depression age at first diagnosis | 34: year of birth  Primary care diagnostic records (first diagnostic event) | Years  Dates | Number (age in years) | Continuous |
| Townsend deprivation index | 22189 | Number | Number | Continuous |
| Average household income | 738 | 1=Less than 18,000  2=18,000 to 30,999  3=31,000 to 51,999  4=52,000 to 100,000  5=Greater than 100,000  -1=Do not know  -3=Prefer not to answer | 1=Less than 18,000  2=18,000 to 30,999  3=31,000 to 51,999  4=Greater than 52,000  -1=NA  -3=NA | Categorical (factor) |
| N days/week of moderate physical activity | 884 | from 0 to 7  -1=Do not know  -3=Prefer not to answer | from 0 to 7  -1= NA  -3=NA | Integer, days/week |
| Education qualifications | 6138 | 1=College or University  2=A levels/AS levels or equivalent  3=O levels/GCSEs or equivalent  4=CSEs or equivalent  5=NVQ or HND or HNC or equivalent  6=Other professional qualifications  -7=None of the above  -3=Prefer not to answer | 1=College/University  2=A/AS levels  3=O levels/GCSEs/CSEs  4=NVQ/HND/  HNC/other professional qualifications  5=none of the above  -3=NA | Categorical (factor) |
| Neuroticism score | 20127 | from 0 to 12 | from 0 to 12 | Integer |
| Alcohol intake frequency | 1558 | 1=Daily or almost daily 2=Three or four times a week  3=Once or twice a week  4=One to three times a  month  5=Special occasions only  6=Never  -3=Prefer not to answer | 1=Daily or almost daily 2=Three or four times a week  3=Once or twice a week  4=One to three times a  Month/Special occasions only  5=Never  -3=NA | Categorical (factor) |
| BMI | 21001 | Kg/m2 | Kg/m2 | Continuous |
| Follow-up duration | Primary care diagnostic/prescription records, based on first and last diagnosis/prescription event | Dates | Number (years) | Continuous |
| Mean age during follow-up | 34: year of birth  Primary care diagnostic/prescription records, based on first and last diagnosis/prescription event | Years  Dates | Number (average age in years in the period between the first and last diagnosis/prescription event) | Continuous |
| N SARI prescriptions | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes | Number | Continuous |
| N SNRI prescriptions | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes | Number | Continuous |
| N SSRI prescriptions | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes | Number | Continuous |
| N tetracyclic antidepressant prescriptions | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes | Number | Continuous |
| N TCA prescriptions | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes | Number | Continuous |
| N antidepressant classes ever used | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes | Number | Continuous |
| N antidepressant switches | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes | Number | Continuous |
| Overall treatment time | Primary care records, based on intervals between dates of antidepressant prescriptions (excluding time windows ≥14 weeks) | Dates | Number (weeks) | Continuous |
| N depression diagnostic records | Primary care records, based on data extracted in a previous work (PMID 33753889) | Diagnosis codes | Number | Continuous |
| N antidepressant prescription records (including both antidepressant prescriptions and antidepressants with antipsychotic add-on prescriptions) | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes | Number | Continuous |
| N depression diagnostic records/N follow-up years | Primary care records, based on data extracted in a previous work (PMID 33753889); Primary care diagnostic/prescription records, based on first and last diagnosis/prescription event | Diagnosis codes  Dates | Number (years) | Continuous |
| N antidepressant prescription records (including both antidepressant prescriptions and antidepressants with antipsychotic add-on prescriptions)/N follow-up years | Primary care records, based on data extracted in a previous work (PMID 33753889); Primary care diagnostic/prescription records, based on first and last diagnosis/prescription event | Prescription codes  Dates | Number | Continuous |
| Sex | 31 | 1=Male  0=Female | 1=Male  0=Female | Binary |
| Ethnicity | 21000 | 1=White  1001=British  1002=Irish  1003=Any other white background  2=Mixed  2001=White and Black Caribbean  2002=White and Black African  2003=White and Asian  2004=Any other mixed background  3=Asian or Asian British  3001=Indian  3002=Pakistani  3003=Bangladeshi  3004=Any other Asian background  4=Black or Black British  4001=Caribbean  4002=African  4003=Any other Black background  5=Chinese  6=Other ethnic group  -1=Do not know  -3=Prefer not to answer | 1=European  1001=European  1002=European  1003=European  2=Mixed  2001=Mixed  2002=Mixed  2003=Mixed  2004=Mixed  3=Asian  3001=Asian  3002=Asian  3003=Asian  3004=Asian  4=African  4001=Mixed  4002=African  4003=African  5=Asian  6=Other  -1=NA  -3=NA | Categorical (factor) |
| Loneliness | 2020 | 1=Yes  0=No  -1=Do not know  -3=Prefer not to answer | 1=Yes  0=No  -1=NA  -3=NA | Binary |
| Long-standing illness, disability or infirmity | 2188 | 1=Yes  0=No  -1=Do not know  -3=Prefer not to answer | 1=Yes  0=No  -1=NA  -3=NA | Binary |
| Smoking status | 20116 | -3=Prefer not to answer  0=Never  1=Previous  2=Current | -3=NA  0=Never  1=Previous/Current | Binary |
| Irritability | 1940 | 1=Yes  0=No  -1=Do not know  -3=Prefer not to answer | 1=Yes  0=No  -1=NA  -3=NA | Binary |
| Nervous feelings | 1970 | 1=Yes  0=No  -1=Do not know  -3=Prefer not to answer | 1=Yes  0=No  -1=NA  -3=NA | Binary |
| Worrier/anxious feelings | 1980 | 1=Yes  0=No  -1=Do not know  -3=Prefer not to answer | 1=Yes  0=No  -1=NA  -3=NA | Binary |
| Tense/'highly strung' | 1990 | 1=Yes  0=No  -1=Do not know  -3=Prefer not to answer | 1=Yes  0=No  -1=NA  -3=NA | Binary |
| Guilty feelings | 2030 | 1=Yes  0=No  -1=Do not know  -3=Prefer not to answer | 1=Yes  0=No  -1=NA  -3=NA | Binary |
| Risk-taking | 2040 | 1=Yes  0=No  -1=Do not know  -3=Prefer not to answer | 1=Yes  0=No  -1=NA  -3=NA | Binary |
| General happiness | 20458 | -818=Prefer not to answer  -121=Do not know  1=Extremely happy  2=Very happy  3=Moderately happy  4=Moderately unhappy  5=Very unhappy  6=Extremely unhappy | 818=NA  -121=NA  1=Extremely happy, Very happy, Moderately happy  0=Moderately unhappy, Very unhappy, Extremely unhappy | Binary |
| Belief that own life is meaningful | 20460 | -818=Prefer not to answer  -121=Do not know  1=Not at all  2=A little  3=A moderate amount  4=Very much  5=An extreme amount | -818=NA  -121=NA  1=A moderate amount, Very much, An extreme amount  0 Not at all, A little | Binary |
| Recent feelings of inadequacy | 20507 | -818=Prefer not to answer  1=Not at all  2=Several days  3=More than half the days  4=Nearly every day | -818=NA  0=Not at all  1=Several days, More than half the days, Nearly every day | Binary |
| Recent trouble concentrating on things | 20508 | -818=Prefer not to answer  1=Not at all  2=Several days  3=More than half the days  4=Nearly every day | -818=NA  0=Not at all  1=Several days, More than half the days, Nearly every day | Binary |
| Miserableness | 1930 | 1=Yes  0=No  -1=Do not know  -3=Prefer not to answer | 1=Yes  0=No  -1=NA  -3=NA | Binary |
| Sensitivity/hurt feelings | 1950 | 1=Yes  0=No  -1=Do not know  -3=Prefer not to answer | 1=Yes  0=No  -1=NA  -3=NA | Binary |
| Fed-up feelings | 1960 | 1=Yes  0=No  -1=Do not know  -3=Prefer not to answer | 1=Yes  0=No  -1=NA  -3=NA | Binary |
| Worry too long after embarrassment | 2000 | 1=Yes  0=No  -1=Do not know  -3=Prefer not to answer | 1=Yes  0=No  -1=NA  -3=NA | Binary |
| Ever SARI prescriptions | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes | 1=Yes  0=No | Binary |
| Ever SNRI prescriptions | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes | 1=Yes  0=No | Binary |
| Ever SSRI prescriptions | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes | 1=Yes  0=No | Binary |
| Ever tetracyclic antidepressant prescriptions | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes | 1=Yes  0=No | Binary |
| Ever TCA prescriptions | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes | 1=Yes  0=No | Binary |
| Treatment resistance | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes  Dates | 1=Yes  0=No | Binary |
| Treatment non-response | Primary care records, based on data extracted in a previous work (PMID 33753889) | Prescription codes  Dates | 1=Yes  0=No | Binary |
| Major depressive disorder | Primary care records, based on data extracted in a previous work (PMID 33753889) | Diagnosis/prescription codes | 1=Yes  0=No | Binary |
| Bipolar disorder | Primary care records, based on data extracted in a previous work (PMID 33753889) | Diagnosis codes | 1=Yes  0=No | Binary |
| Psychotic disorder | Primary care records, based on data extracted in a previous work (PMID 33753889) | Diagnosis codes | 1=Yes  0=No | Binary |
| Substance use disorder | Primary care records, based on data extracted in a previous work (PMID 33753889) | Diagnosis codes | 0=no  1=yes | Binary |
| Any IR-related condition | Primary care records, based on IR-related conditions status | 1=Yes  0=No | 1=Yes  0=No | Binary |
| CAD | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| Cerebral ischemia | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| Cushing’s syndrome | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| CVDs | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| Dyslipidaemia | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| Familiar dyslipidaemia | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| Gestational diabetes | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| Gestational hypertension | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| Hypertension | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| MetS | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| NAFLD | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| Obesity/overweight | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| PCOS | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| Prediabetes | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| Rare IR-related conditions | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |
| T2DM | Primary care records, based on diagnostic records | Diagnosis codes (see Supplementary Tables 1-2) | 1=Yes  0=No | Binary |

**Supplementary Table 5**. Distribution of patients with MDD having or not IR-related conditions in the whole sample and in the subsamples stratified based on the temporal order of diagnosis of MDD relative to IR-related conditions.

Abbreviations: IR, insulin resistance; MDD-after-IR, patients with MDD onset following any IR-related diagnosis; MDD-before-IR, patients with MDD onset before any IR-related diagnosis; CVDs, cardiovascular diseases; PCOS, polycystic ovary syndrome; MetS, metabolic syndrome; NAFLD, non-alcoholic steatohepatitis liver disease; T2DM, type 2 diabetes mellitus.

Note: Counts of IR-related conditions in the subsamples stratified by the timing of MDD onset (MDD-after-IR and MDD-before-IR) may not sum to the total in the whole MDD sample due to data exclusion of entries with placeholder or implausible diagnosis dates (e.g., 01/01/1901, 02/02/1902, 03/03/1903, 07/07/2037), as per data cleaning protocols.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Whole MDD sample** | | **MDD-after-IR** | **MDD-before-IR** |
| **Variable** | **No** | **Yes** | **Yes** | **Yes** |
| Any IR-related condition | 14,856 | 16,063 | 6,357 | 9,483 |
| CAD | 28,469 | 2,450 | 1,270 | 1,164 |
| Cerebral ischemia | 29,616 | 1,303 | 627 | 656 |
| Cushing’s syndrome | 30,904 | 15 | 9 | 6 |
| CVDs | 27,269 | 3,650 | 1,795 | 1,818 |
| Dyslipidaemia | 29,918 | 1,001 | 372 | 617 |
| Familiar dyslipidaemia | 28,959 | 1,960 | 905 | 1,034 |
| Gestational diabetes | 30,860 | 59 | 42 | 16 |
| Gestational hypertension | 30,847 | 72 | 61 | 11 |
| Hypertension | 21,420 | 9,499 | 4,168 | 5,164 |
| MetS | 30,896 | 23 | 10 | 13 |
| NAFLD | 30,173 | 746 | 251 | 489 |
| Obesity/overweight | 25,676 | 5,243 | 2,483 | 2,714 |
| PCOS | 30,840 | 79 | 59 | 19 |
| Prediabetes | 29,013 | 1,906 | 684 | 1,206 |
| Rare IR-related conditions | 30,817 | 102 | 39 | 61 |
| T2DM | 27,827 | 3,092 | 1,572 | 1,492 |

**Supplementary Table 6.** Differences in socio-demographic and clinical characteristics between patients with MDD not having a lifetime history of any IR-related condition (IR-) and patients with MDD having a history of any IR-related condition (IR+). This table reports non-significant findings, with statistical comparisons performed using Student’s two-sample t-tests and Pearson’s Chi-square tests for continuous and categorical variables, as appropriate.

Abbreviations: IR, insulin resistance-related conditions; SD, standard deviation; SARI, serotonin antagonist and reuptake inhibitors.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **IR-** | **IR+** | **Test statistic** | **p-value** |
| Belief that own life is meaningful, prop. yes/no | 0.85/0.15 | 0.83/0.17 | χ² = 6.097 | 0.014 |
| General happiness, prop. yes/no | 0.87/0.13 | 0.84/0.16 | χ² = 9.354 | 0.002 |
| Guilty feelings, prop. yes/no | 0.47/0.53 | 0.45/0.55 | χ² = 9.171 | 0.002 |
| Irritability, prop. yes/no | 0.42/0.58 | 0.42/0.58 | χ² = 0.003 | 0.953 |
| Miserableness, prop. yes/no | 0.7/0.3 | 0.7/0.3 | χ² = 0.977 | 0.323 |
| N depression diagnostic records, mean (SD) | 3.75 (5.92) | 3.6 (5.59) | t = 2.32 | 0.020 |
| N SARI prescriptions, mean (SD) | 0.89 (8.42) | 1.25 (10.54) | t = -3.29 | 0.001 |
| Nervous feelings, prop. yes/no | 0.39/0.61 | 0.38/0.62 | χ² = 0.619 | 0.431 |
| Neuroticism score, mean (SD) | 6.43 (3.33) | 6.47 (3.36) | t = -1.08 | 0.280 |
| Recent feelings of inadequacy, prop. yes/no | 0.39/0.61 | 0.4/0.6 | χ² = 1.442 | 0.230 |
| Risk-taking, prop. yes/no | 0.26/0.74 | 0.27/0.73 | χ² = 2.276 | 0.131 |
| Sensitivity/hurt feelings, prop. yes/no | 0.73/0.27 | 0.72/0.28 | χ² = 5.649 | 0.017 |
| Tense/'highly strung', prop. yes/no | 0.33/0.67 | 0.34/0.66 | χ² = 3.292 | 0.070 |
| Worrier/anxious feelings, prop. yes/no | 0.75/0.25 | 0.75/0.25 | χ² = 0.354 | 0.552 |
| Worry too long after embarrassment, prop. yes/no | 0.62/0.38 | 0.6/0.4 | χ² = 10.464 | 0.001 |

**Supplementary Table 7.** Differences in socio-demographic and clinical characteristics between patients with MDD not having a lifetime history of any IR-related condition (IR-) and patients with MDD onset preceding any IR-related diagnosis (MDD-before-IR). Student’s two-sample t-tests and Pearson’s Chi-square tests were used for continuous and categorical variables, as appropriate.

\*\*Statistically significant after Bonferroni correction.

Abbreviations: IR, insulin resistance-related conditions; SD, standard deviation; BMI, body mass index; SARI, serotonin antagonist and reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants. UK educational qualifications includes: ‘College/University’ degree, which covers undergraduate (Bachelor’s degrees) and postgraduate degrees (Master’s and Doctoral degrees); ‘A/AS levels’ (Advanced/Advanced Subsidiary levels), qualifications typically pursued by students aged 16 to 18 as a preparatory step for university or vocational training; ‘GCSEs’ (General Certificate of Secondary Education), the primary set of exams taken by students at the end of compulsory education around age 16, replacing the historical ‘O levels’ (Ordinary Levels) and ‘CSEs’ (Certificate of Secondary Education, a non-academic track phased out in 1988 alongside O Levels); ‘NVQ’ (National Vocational Qualifications), ‘HND’ (Higher National Diploma), and ‘HNC’ (Higher National Certificate), which are vocational qualifications offered post-secondary education to provide practical skills and training in various fields.

| **Variable** | **IR-** | **MDD-before-IR** | **Test statistic** | **p-value** |
| --- | --- | --- | --- | --- |
| Alcohol intake frequency, N (%) | Daily or almost daily=2,593 (0.17)  Three or four times a week=3,107 (0.21)  Once or twice a week=3,991 (0.27)  One to three times a  month/Special occasions only=3,896 (0.26)  Never=1,236 (0.08) | Daily or almost daily=2,502 (0.16)  Three or four times a week=2,752 (0.17)  Once or twice a week=3,875 (0.24)  One to three times a  month/Special occasions only=4,943 (0.31)  Never=1,941 (0.12) | χ² = 148.161 | 5.04e-31\*\* |
| Average household income, N (%) | <18,000£=3,316 (0.22)  18,000-30,999£=3,283 (0.22)  31,000-51,999£=3,481 (0.23)  >52,000£=2,751 (0.18) | <18,000£=5,080 (0.32)  18,000-30,999£=3,701 (0.23)  31,000-51,999£=2,775 (0.17)  >52,000£=1,777 (0.11) | χ² = 433.65 | 1.14e-93\*\* |
| Belief that own life is meaningful, prop. yes/no | 0.85/0.15 | 0.83/0.17 | χ² = 3.036 | 0.081 |
| BMI (kg/m²), mean (SD) | 26.21 (4.16) | 29.58 (5.38) | t = -51.65 | <5e-324\*\* |
| Age at first depression diagnosis (years), mean (SD) | 46.29 (11.13) | 44.74 (11.15) | t = 10.59 | 4.00e-26\*\* |
| Education qualifications, N (%) | College/University=4603 (0.31)  A/AS levels=1,821 (0.12)  O levels/GCSEs/CSEs=4,444 (0.30)  NVQ/HND/  HNC/other professional qualifications=1,631 (0.11)  none of the above=2,192 (0.15) | College/University=3,554 (0.22)  A/AS levels=1,530 (0.09)  O levels/GCSEs/CSEs=4,323 (0.27)  NVQ/HND/  HNC/other professional qualifications=2,151 (0.13)  none of the above=4,252 (0.26) | χ² = 537.405 | 5.43e-115\*\* |
| Ever SARI prescriptions, prop. yes/no | 0.06/0.94 | 0.07/0.93 | χ² = 35.73 | 2.27e-09\*\* |
| Ever SNRI prescriptions, prop. yes/no | 0.13/0.87 | 0.16/0.84 | χ² = 63.806 | 1.37e-15\*\* |
| Ever SSRI prescriptions, prop. yes/no | 0.86/0.14 | 0.81/0.19 | χ² = 110.496 | 7.63e-26\*\* |
| Ever TCA prescriptions, prop. yes/no | 0.5/0.5 | 0.62/0.38 | χ² = 328.997 | 1.59e-73\*\* |
| Ever tetracyclic antidepressant prescriptions, prop. yes/no | 0.13/0.87 | 0.15/0.85 | χ² = 12.479 | 4.11e-04\*\* |
| Fed-up feelings, prop. yes/no | 0.64/0.36 | 0.67/0.33 | χ² = 12.456 | 4.17e-04\*\* |
| Follow-up duration (years), mean (SD) | 38.34 (13.11) | 41.82 (13.52) | t = -19.83 | 1.16e-86\*\* |
| General happiness, prop. yes/no | 0.87/0.13 | 0.84/0.16 | χ² = 5.954 | 0.015 |
| Guilty feelings, prop. yes/no | 0.47/0.53 | 0.47/0.53 | χ² = 0.072 | 0.789 |
| Irritability, prop. yes/no | 0.42/0.58 | 0.42/0.58 | χ² = 0 | 0.986 |
| Loneliness, prop. yes/no | 0.35/0.65 | 0.38/0.62 | χ² = 21.214 | 4.11e-06\*\* |
| Long-standing illness, disability or infirmity, prop. yes/no | 0.35/0.65 | 0.54/0.46 | χ² = 760.167 | 2.47e-167\*\* |
| Mean age during follow-up (years), mean (SD) | 53.54 (8.21) | 58.33 (7.7) | t = -46.1 | <5e-324\*\* |
| Miserableness, prop. yes/no | 0.7/0.3 | 0.71/0.29 | χ² = 3.652 | 0.056 |
| N antidepressant classes ever used, mean (SD) | 1.71 (0.88) | 1.86 (0.98) | t = -12.32 | 9.96e-35\*\* |
| N antidepressant prescription records, mean (SD) | 41.86 (59.28) | 58.94 (73.41) | t = -19.05 | 4.53e-80\*\* |
| N antidepressant prescription records/follow-up years, mean (SD) | 1.26 (1.92) | 1.62 (2.26) | t = -13.01 | 1.59e-38\*\* |
| N antidepressant switches, mean (SD) | 1.77 (2.36) | 2.21 (2.86) | t = -12.35 | 7.19e-35\*\* |
| N days/week of moderate physical activity, mean (SD) | 3.6 (2.37) | 3.49 (2.43) | t = 3.23 | 0.001 |
| N depression diagnostic records, mean (SD) | 3.75 (5.92) | 4.13 (6.35) | t = -4.66 | 3.21e-06\*\* |
| N depression diagnostic records/follow-up years, mean (SD) | 0.11 (0.23) | 0.11 (0.18) | t = 0.98 | 0.329 |
| N SARI prescriptions, mean (SD) | 0.89 (8.42) | 1.3 (10.41) | t = -3.24 | 0.001 |
| N SNRI prescriptions, mean (SD) | 3.4 (21.44) | 5.45 (24.47) | t = -6.68 | 2.38e-11\*\* |
| N SSRI prescriptions, mean (SD) | 26.41 (39.23) | 32.06 (47.99) | t = -9.6 | 9.40e-22\*\* |
| N TCA prescriptions, mean (SD) | 8.79 (26.29) | 16.48 (39.62) | t = -16.7 | 4.83e-62\*\* |
| N tetracyclic antidepressant prescriptions, mean (SD) | 1.91 (12.79) | 2.89 (15.44) | t = -5.14 | 2.73e-07\*\* |
| Nervous feelings, prop. yes/no | 0.39/0.61 | 0.4/0.6 | χ² = 3.472 | 0.062 |
| Neuroticism score, mean (SD) | 6.43 (3.33) | 6.61 (3.33) | t = -3.61 | 3.06e-04\*\* |
| Overall treatment time (weeks), mean (SD) | 184.05 (229.77) | 250.84 (277.64) | t = -19.54 | 3.86e-84\*\* |
| Recent feelings of inadequacy, prop. yes/no | 0.39/0.61 | 0.38/0.62 | χ² = 0.263 | 0.608 |
| Recent trouble concentrating on things, prop. yes/no | 0.36/0.64 | 0.38/0.62 | χ² = 1.943 | 0.163 |
| Risk-taking, prop. yes/no | 0.26/0.74 | 0.27/0.73 | χ² = 1.346 | 0.246 |
| Sensitivity/hurt feelings, prop. yes/no | 0.73/0.27 | 0.74/0.26 | χ² = 0.674 | 0.412 |
| Sex (M/F, proportion) | 0.26/0.74 | 0.34/0.66 | χ² = 159.812 | 1.24e-36\*\* |
| Smoking status, prop. yes/no | 0.47/0.53 | 0.52/0.48 | χ² = 62.699 | 2.41e-15\*\* |
| Tense/’highly strung’, prop. yes/no | 0.33/0.67 | 0.35/0.65 | χ² = 8.518 | 0.004 |
| Townsend deprivation index, mean (SD) | -1.27 (3.03) | -0.87 (3.2) | t = -9.58 | 1.07e-21\*\* |
| Treatment non-response, prop. yes/no | 0.2/0.8 | 0.26/0.74 | χ² = 123.468 | 1.10e-28\*\* |
| Treatment resistance, prop. yes/no | 0.08/0.92 | 0.13/0.87 | χ² = 125.998 | 3.08e-29\*\* |
| Worrier/anxious feelings, prop. yes/no | 0.75/0.25 | 0.76/0.24 | χ² = 3.403 | 0.065 |
| Worry too long after embarrassment, prop. yes/no | 0.62/0.38 | 0.62/0.38 | χ² = 0.245 | 0.620 |

**Supplementary Table 8.** Differences in socio-demographic and clinical characteristics between patients with MDD not having a lifetime history of any IR-related condition (IR-) and patients with MDD onset following any IR-related diagnosis (MDD-after-IR). Student’s two-sample t-tests and Pearson’s Chi-square tests were used for continuous and categorical variables, as appropriate.

\*\*Statistically significant after Bonferroni correction.

Abbreviations: IR, insulin resistance-related conditions; SD, standard deviation; BMI, body mass index; SARI, serotonin antagonist and reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants. UK educational qualifications includes: ‘College/University’ degree, which covers undergraduate (Bachelor’s degrees) and postgraduate degrees (Master’s and Doctoral degrees); ‘A/AS levels’ (Advanced/Advanced Subsidiary levels), qualifications typically pursued by students aged 16 to 18 as a preparatory step for university or vocational training; ‘GCSEs’ (General Certificate of Secondary Education), the primary set of exams taken by students at the end of compulsory education around age 16, replacing the historical ‘O levels’ (Ordinary Levels) and ‘CSEs’ (Certificate of Secondary Education, a non-academic track phased out in 1988 alongside O Levels); ‘NVQ’ (National Vocational Qualifications), ‘HND’ (Higher National Diploma), and ‘HNC’ (Higher National Certificate), which are vocational qualifications offered post-secondary education to provide practical skills and training in various fields.

| **Variable** | **IR-** | **MDD-after-IR** | **Test statistic** | **p-value** |
| --- | --- | --- | --- | --- |
| Alcohol intake frequency, N (%) | Daily or almost daily=2,593 (0.17)  Three or four times a week=3,107 (0.21)  Once or twice a week=3,991 (0.27)  One to three times a  month/Special occasions only=3,896 (0.26)  Never=1,236 (0.08) | Daily or almost daily=987 (0.15)  Three or four times a week=1,004 (0.16)  Once or twice a week=1,529 (0.24)  One to three times a  month/Special occasions only=1,988 (0.31)  Never=831 (0.13) | χ² = 227.70 | 4.12e-48\*\* |
| Average household income, N (%) | <18,000£=3,316 (0.22)  18,000-30,999£=3,283 (0.22)  31,000-51,999£=3,481 (0.23)  >52,000£=2,751 (0.18) | <18,000£=2,097 (0.33)  18,000-30,999£=1,436 (0.23)  31,000-51,999£=1,035 (0.16)  >52,000£=684 (0.11) | χ² = 472.54 | 4.26e-102\*\* |
| Belief that own life is meaningful, prop. yes/no | 0.85/0.15 | 0.82/0.18 | χ² = 5.115 | 0.024 |
| BMI (kg/m²), mean (SD) | 26.21 (4.16) | 31 (6.12) | t = -56.8 | <5e-324\*\* |
| Age at first depression diagnosis (years), mean (SD) | 46.29 (11.13) | 56.5 (9.26) | t = -69.08 | <5e-324\*\* |
| Education qualifications, N (%) | College/University=4,603 (0.31)  A/AS levels=1,821 (0.12)  O levels/GCSEs/CSEs= 4,444 (0.30)  NVQ/HND/  HNC/other professional qualifications= 1,631 (0.11)  none of the above= 2,192 (0.15) | College/University=1,313 (0.21)  A/AS levels=581 (0.10)  O levels/GCSEs/CSEs=1,691 (0.26)  NVQ/HND/  HNC/other professional qualifications=852 (0.13)  none of the above=1,818 (0.29) | χ² = 700.43 | 2.81e-150\*\* |
| Ever SARI prescriptions, prop. yes/no | 0.06/0.94 | 0.06/0.94 | χ² = 1.104 | 0.293 |
| Ever SNRI prescriptions, prop. yes/no | 0.13/0.87 | 0.13/0.87 | χ² = 0.017 | 0.897 |
| Ever SSRI prescriptions, prop. yes/no | 0.86/0.14 | 0.88/0.12 | χ² = 18.397 | 1.79e-05\*\* |
| Ever TCA prescriptions, prop. yes/no | 0.5/0.5 | 0.53/0.47 | χ² = 14.961 | 1.10e-04\*\* |
| Ever tetracyclic antidepressant prescriptions, prop. yes/no | 0.13/0.87 | 0.17/0.83 | χ² = 43.454 | 4.34e-11\*\* |
| Fed-up feelings, prop. yes/no | 0.64/0.36 | 0.68/0.32 | χ² = 18.479 | 1.72e-05\*\* |
| Follow-up duration (years), mean (SD) | 38.34 (13.11) | 39.44 (14.04) | t = -5.32 | 1.08e-07\*\* |
| General happiness, prop. yes/no | 0.87/0.13 | 0.84/0.16 | χ² = 5.93 | 0.015 |
| Guilty feelings, prop. yes/no | 0.47/0.53 | 0.43/0.57 | χ² = 28.444 | 9.64e-08\*\* |
| Irritability, prop. yes/no | 0.42/0.58 | 0.42/0.58 | χ² = 0.012 | 0.911 |
| Loneliness, prop. yes/no | 0.35/0.65 | 0.38/0.62 | χ² = 11.729 | 6.15e-04\*\* |
| Long-standing illness, disability or infirmity, prop. yes/no | 0.35/0.65 | 0.61/0.39 | χ² = 1109.539 | 2.79e-243\*\* |
| Mean age during follow-up (years), mean (SD) | 53.54 (8.21) | 58.73 (7.8) | t = -43.62 | <5e-324\*\* |
| Miserableness, prop. yes/no | 0.7/0.3 | 0.69/0.31 | χ² = 0.216 | 0.642 |
| N antidepressant classes ever used, mean (SD) | 1.71 (0.88) | 1.8 (0.89) | t = -6.4 | 1.65e-10\*\* |
| N antidepressant prescription records, mean (SD) | 41.86 (59.28) | 52.2 (68.93) | t = -10.43 | 2.46e-25\*\* |
| N antidepressant prescription records/follow-up years, mean (SD) | 1.26 (1.92) | 1.55 (2.34) | t = -8.78 | 1.85e-18\*\* |
| N antidepressant switches, mean (SD) | 1.77 (2.36) | 1.88 (2.34) | t = -3.07 | 0.002 |
| N days/week of moderate physical activity, mean (SD) | 3.6 (2.37) | 3.39 (2.44) | t = 5.48 | 4.48e-08\*\* |
| N depression diagnostic records, mean (SD) | 3.75 (5.92) | 2.82 (4.08) | t = 13.21 | 1.16e-39\*\* |
| N depression diagnostic records/follow-up years, mean (SD) | 0.11 (0.23) | 0.08 (0.13) | t = 13.23 | 8.42e-40\*\* |
| N SARI prescriptions, mean (SD) | 0.89 (8.42) | 1.15 (10.63) | t = -1.7 | 0.089 |
| N SNRI prescriptions, mean (SD) | 3.4 (21.44) | 3.86 (23.41) | t = -1.33 | 0.183 |
| N SSRI prescriptions, mean (SD) | 26.41 (39.23) | 31.5 (43.52) | t = -8.03 | 1.07e-15\*\* |
| N TCA prescriptions, mean (SD) | 8.79 (26.29) | 12.15 (34.2) | t = -6.98 | 3.04e-12\*\* |
| N tetracyclic antidepressant prescriptions, mean (SD) | 1.91 (12.79) | 3.22 (16.24) | t = -5.69 | 1.27e-08\*\* |
| Nervous feelings, prop. yes/no | 0.39/0.61 | 0.36/0.64 | χ² = 16.601 | 4.61e-05\*\* |
| Neuroticism score, mean (SD) | 6.43 (3.33) | 6.27 (3.4) | t = 2.71 | 0.007 |
| Overall treatment time (weeks), mean (SD) | 184.05 (229.77) | 213.59 (235.49) | t = -8.43 | 3.80e-17\*\* |
| Recent feelings of inadequacy, prop. yes/no | 0.39/0.61 | 0.44/0.56 | χ² = 10.104 | 0.001 |
| Recent trouble concentrating on things, prop. yes/no | 0.36/0.64 | 0.44/0.56 | χ² = 22.628 | 1.97e-06\*\* |
| Risk-taking, prop. yes/no | 0.26/0.74 | 0.27/0.73 | χ² = 2.48 | 0.115 |
| Sensitivity/hurt feelings, prop. yes/no | 0.73/0.27 | 0.69/0.31 | χ² = 32.644 | 1.11e-08\*\* |
| Sex (M/F, proportion) | 0.26/0.74 | 0.41/0.59 | χ² = 459.144 | 7.38e-102\*\* |
| Smoking status, prop. yes/no | 0.47/0.53 | 0.53/0.47 | χ² = 64.19 | 1.13e-15\*\* |
| Tense/’highly strung’, prop. yes/no | 0.33/0.67 | 0.33/0.67 | χ² = 0.082 | 0.774 |
| Townsend deprivation index, mean (SD) | -1.27 (3.03) | -0.55 (3.27) | t = -14.88 | 1.25e-49\*\* |
| Treatment non-response, prop. yes/no | 0.2/0.8 | 0.23/0.77 | χ² = 20.168 | 7.09e-06\*\* |
| Treatment resistance, prop. yes/no | 0.08/0.92 | 0.11/0.89 | χ² = 26.1 | 3.24e-07\*\* |
| Worrier/anxious feelings, prop. yes/no | 0.75/0.25 | 0.73/0.27 | χ² = 12.73 | 3.60e-04\*\* |
| Worry too long after embarrassment, prop. yes/no | 0.62/0.38 | 0.57/0.43 | χ² = 43.63 | 3.97e-11\*\* |

**Supplementary Table 9.** Results of one-way Analysis of Variance (ANOVA) comparing socio-demographic and clinical variables across three groups: (1) patients with MDD not having a lifetime history of any insulin resistance-related condition (IR-), (2) patients diagnosed with MDD after the onset of any insulin resistance-related condition (MDD-after-IR), (3) patients diagnosed with MDD before the onset of any insulin resistance-related condition (MDD-before-IR). Post hoc Tukey’s Honestly Significant Difference (HSD) p-values for group comparisons are included to facilitate understanding of pairwise differences between groups (significant for p-values<0.05).

\*\*Statistically significant ANOVA result after Bonferroni correction.

Abbreviations: BMI, body mass index; MDD, major depressive disorder; SARI, serotonin antagonist and reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; HSD, honestly significant difference; IR, insulin resistance-related conditions.

| **Variable** | **IR-,**  **mean (SD)** | **MDD-after-IR,**  **mean (SD)** | **MDD-before-IR,**  **mean (SD)** | **F-statistic** | **p-value (F)** | **Tukey’s HSD p-value: Group 1 vs.**  **Group 2** | **Tukey’s HSD p-value: Group 1 vs.**  **Group 3** | **Tukey’s HSD p-value: Group 2 vs.**  **Group 3** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Mean age during follow-up (years) | 53.54 (8.21) | 58.73 (7.8) | 58.33 (7.7) | 1,480.013 | <5e-324\*\* | <0.05 | <0.05 | <0.05 |
| Follow-up duration (years) | 38.34 (13.11) | 39.44 (14.04) | 41.82 (13.52) | 195.495 | 4.30e-85\*\* | <0.05 | <0.05 | <0.05 |
| Townsend deprivation index | -1.27 (3.03) | -0.55 (3.27) | -0.87 (3.2) | 126.522 | 1.90e-55\*\* | <0.05 | <0.05 | <0.05 |
| N days/week of moderate physical activity | 3.6 (2.37) | 3.39 (2.44) | 3.49 (2.43) | 16.296 | 8.45e-08\*\* | <0.05 | <0.05 | <0.05 |
| BMI (kg/m²) | 26.21 (4.16) | 31 (6.12) | 29.58 (5.38) | 2,506.994 | <5e-324\*\* | <0.05 | <0.05 | <0.05 |
| N antidepressant classes ever used | 1.71 (0.88) | 1.8 (0.89) | 1.86 (0.98) | 82.367 | 2.11e-36\*\* | <0.05 | <0.05 | <0.05 |
| N antidepressant switches | 1.77 (2.36) | 1.88 (2.34) | 2.21 (2.86) | 87.402 | 1.41e-38\*\* | <0.05 | <0.05 | <0.05 |
| Overall treatment time, weeks | 184.05 (229.77) | 213.59 (235.49) | 250.84 (277.64) | 212.694 | 1.83e-92\*\* | <0.05 | <0.05 | <0.05 |
| N depression diagnostic records | 3.75 (5.92) | 2.82 (4.08) | 4.13 (6.35) | 102.083 | 6.50e-45\*\* | <0.05 | <0.05 | <0.05 |
| Age at depression onset | 46.29 (11.13) | 56.5 (9.26) | 44.74 (11.15) | 2,597.303 | <5e-324\*\* | <0.05 | <0.05 | <0.05 |
| N SARI prescriptions | 0.89 (8.42) | 1.15 (10.63) | 1.3 (10.41) | 5.656 | 0.004 | 0.175 | <0.05 | 0.565 |
| N SNRI prescriptions | 3.4 (21.44) | 3.86 (23.41) | 5.45 (24.47) | 23.926 | 4.14e-11\*\* | 0.377 | <0.05 | <0.05 |
| N SSRI prescriptions | 26.41 (39.23) | 31.5 (43.52) | 32.06 (47.99) | 61.316 | 2.65e-27\*\* | <0.05 | <0.05 | 0.701 |
| N tetracyclic antidepressant prescriptions | 1.91 (12.79) | 3.22 (16.24) | 2.89 (15.44) | 23.710 | 5.14e-11\*\* | <0.05 | <0.05 | 0.34 |
| N TCA prescriptions | 8.79 (26.29) | 12.15 (34.2) | 16.48 (39.62) | 161.522 | 1.65e-70\*\* | <0.05 | <0.05 | <0.05 |
| N antidepressant prescription records | 41.86 (59.28) | 52.2 (68.93) | 58.94 (73.41) | 202.176 | 5.88e-88\*\* | <0.05 | <0.05 | <0.05 |
| N depression records/follow-up years | 0.11 (0.23) | 0.08 (0.13) | 0.11 (0.18) | 64.864 | 7.75e-29\*\* | <0.05 | 0.577 | <0.05 |
| N antidepressant prescription records/follow-up years | 1.26 (1.92) | 1.55 (2.34) | 1.62 (2.26) | 98.367 | 2.61e-43\*\* | <0.05 | <0.05 | 0.088 |

**Supplementary Table 10.** Association between lifetime insulin resistance-related diagnoses and depression treatment outcomes in the UK Biobank cohort, after adjusting for relevant covariates. R² values are provided to assess the proportion of phenotypic variance explained by the full model. The Hosmer-Lemeshow χ² test and its corresponding p-value to evaluate the goodness of fit of logistic regression models (p-values>0.05 suggests that the model fits the data well).

\*\* Statistically significant after Bonferroni correction (alpha=0.05/(27 predictors\*3 outcomes)=0.0006.

Abbreviations: OR, odds ratio; CIs, confidence intervals; IR, insulin resistance; TRD, treatment-resistant depression; CVDs, cardiovascular diseases; PCOS, polycystic ovary syndrome; MetS, metabolic syndrome; NAFLD, non-alcoholic steatohepatitis liver disease; T2DM, type 2 diabetes mellitus.

1. Treatment-resistant depression outcome

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Predictor** | **OR (95% CIs)** | **P-value** | **Nagelkerke's R²** | **Hosmer-Lemeshow χ²** | **Hosmer-Lemeshow p-value** |
| Any IR-related condition | 1.5 (1.38-1.64) | 1.66e-20\*\* | 0.019 | 9.741 | 0.284 |
| CAD | 1.4 (1.21-1.61) | 3.51e-06\*\* | 0.014 | 8.053 | 0.428 |
| Cerebral ischemia | 1.19 (0.98-1.43) | 0.076 | 0.013 | 19.553 | 0.012 |
| Cushing's syndrome | 4.75 (1.57-14.36) | 0.006 | 0.013 | 14.899 | 0.061 |
| CVDs | 1.34 (1.18-1.51) | 2.51e-06\*\* | 0.015 | 9.876 | 0.274 |
| Dyslipidaemia | 0.93 (0.74-1.17) | 0.553 | 0.013 | 16.954 | 0.031 |
| Familiar dyslipidaemia | 1.23 (1.05-1.43) | 0.012 | 0.013 | 15.213 | 0.055 |
| Gestational diabetes | 0.99 (0.35-2.81) | 0.989 | 0.013 | 14.076 | 0.080 |
| Gestational hypertension | 0.75 (0.3-1.89) | 0.548 | 0.013 | 14.125 | 0.079 |
| Hypertension | 1.25 (1.14-1.36) | 8.34e-07\*\* | 0.015 | 7.861 | 0.447 |
| MetS | 1.89 (0.63-5.63) | 0.253 | 0.013 | 15.353 | 0.053 |
| NAFLD | 1.43 (1.13-1.8) | 0.003 | 0.014 | 14.651 | 0.066 |
| Obesity/overweight | 1.41 (1.28-1.56) | 1.99e-11\*\* | 0.016 | 7.855 | 0.448 |
| PCOS | 2.32 (1.25-4.29) | 0.008 | 0.013 | 14.987 | 0.059 |
| Prediabetes | 1.47 (1.26-1.7) | 4.57e-07\*\* | 0.015 | 15.394 | 0.052 |
| Rare IR-related conditions | 2.11 (1.26-3.55) | 0.005 | 0.014 | 12.898 | 0.115 |
| T2DM | 1.6 (1.42-1.81) | 6.02e-14\*\* | 0.017 | 9.605 | 0.294 |

1. Antidepressant non-response outcome

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Predictor** | **OR (95% CIs)** | **p-value** | **Nagelkerke's R²** | **Hosmer-Lemeshow χ²** | **Hosmer-Lemeshow p-value** |
| Any IR-related condition | 1.36 (1.28-1.44) | 5.32e-22\*\* | 0.019 | 5.385 | 0.716 |
| CAD | 1.22 (1.09-1.36) | 3.58e-04\*\* | 0.015 | 7.867 | 0.447 |
| Cerebral ischemia | 1.21 (1.05-1.39) | 0.009 | 0.014 | 11.593 | 0.170 |
| Cushing's syndrome | 1.8 (0.6-5.4) | 0.297 | 0.014 | 9.178 | 0.327 |
| CVDs | 1.2 (1.1-1.32) | 9.37e-05\*\* | 0.015 | 13.236 | 0.104 |
| Dyslipidaemia | 1.02 (0.87-1.2) | 0.796 | 0.014 | 9.581 | 0.296 |
| Familiar dyslipidaemia | 1.15 (1.02-1.29) | 0.023 | 0.014 | 7.633 | 0.470 |
| Gestational diabetes | 1.45 (0.74-2.87) | 0.282 | 0.014 | 9.160 | 0.329 |
| Gestational hypertension | 0.74 (0.38-1.42) | 0.360 | 0.014 | 12.274 | 0.139 |
| Hypertension | 1.18 (1.1-1.26) | 7.75e-07\*\* | 0.015 | 10.091 | 0.259 |
| MetS | 2.78 (1.19-6.49) | 0.018 | 0.014 | 11.327 | 0.184 |
| NAFLD | 1.35 (1.13-1.61) | 0.001 | 0.015 | 14.069 | 0.080 |
| Obesity/overweight | 1.34 (1.24-1.44) | 8.55e-14\*\* | 0.017 | 11.440 | 0.178 |
| PCOS | 1.13 (0.64-1.99) | 0.682 | 0.014 | 10.727 | 0.218 |
| Prediabetes | 1.4 (1.25-1.57) | 7.33e-09\*\* | 0.016 | 9.089 | 0.335 |
| Rare IR-related conditions | 1.65 (1.07-2.57) | 0.025 | 0.014 | 11.402 | 0.180 |
| T2DM | 1.38 (1.25-1.52) | 8.56e-11\*\* | 0.016 | 13.185 | 0.106 |

1. Overall treatment time (weeks) outcome

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictor** | **β (SE)** | **p-value** | **R²** |
| Any IR-related condition | 50.51 (3.26) | 8.80e-54\*\* | 0.035 |
| CAD | 38.28 (6) | 1.85e-10\*\* | 0.027 |
| Cerebral ischemia | 17.46 (7.79) | 0.025 | 0.026 |
| Cushing's syndrome | 39.53 (66.39) | 0.552 | 0.026 |
| CVDs | 31 (5.04) | 7.70e-10\*\* | 0.027 |
| Dyslipidaemia | 19.06 (8.83) | 0.031 | 0.026 |
| Familiar dyslipidaemia | 30.11 (6.5) | 3.66e-06\*\* | 0.026 |
| Gestational diabetes | 43.41 (38.88) | 0.264 | 0.026 |
| Gestational hypertension | 21.24 (32.4) | 0.512 | 0.026 |
| Hypertension | 33.5 (3.5) | 1.10e-21\*\* | 0.029 |
| MetS | 128.59 (52.96) | 0.015 | 0.026 |
| NAFLD | 61.36 (10.15) | 1.52e-09\*\* | 0.027 |
| Obesity/overweight | 36.81 (4.21) | 2.34e-18\*\* | 0.028 |
| PCOS | 14.17 (30.66) | 0.644 | 0.026 |
| Prediabetes | 45.19 (6.55) | 5.37e-12\*\* | 0.027 |
| Rare IR-related conditions | 45 (25.93) | 0.083 | 0.026 |
| T2DM | 63.57 (5.41) | 8.61e-32\*\* | 0.031 |

**Supplementary Table 11.** Association between insulin resistance-related conditions diagnosed after MDD onset and depression treatment outcomes in the UK Biobank cohort, after adjusting for relevant covariates.

\*\* Statistically significant after Bonferroni correction (alpha=0.05/(27 predictors\*3 outcomes)=0.0006.

Abbreviations: OR, odds ratio; CIs, confidence intervals; R², proportion of phenotypic variance in the outcome explained by the full model; IR, insulin resistance; TRD, treatment-resistant depression; CVDs, cardiovascular diseases; PCOS, polycystic ovary syndrome; MetS, metabolic syndrome; NAFLD, non-alcoholic steatohepatitis liver disease; T2DM, type 2 diabetes mellitus.

1. Treatment-resistant depression outcome

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Predictor** | **OR (95% CIs)** | **p-value** | **Nagelkerke’s R²** | **Hosmer-Lemeshow χ²** | **Hosmer-Lemeshow p-value** |
| Any IR-related condition | 1.63 (1.48-1.79) | 9.13e-24\*\* | 0.022 | 10.729 | 0.218 |
| CAD | 1.46 (1.23-1.73) | 1.26e-05\*\* | 0.014 | 14.793 | 0.063 |
| Cerebral ischemia | 1.22 (0.97-1.53) | 0.084 | 0.013 | 19.003 | 0.015 |
| Cushing’s syndrome | 8.85 (2.18-35.92) | 0.002 | 0.014 | 14.332 | 0.074 |
| CVDs | 1.38 (1.2-1.59) | 7.91e-06\*\* | 0.014 | 13.548 | 0.094 |
| Dyslipidaemia | 1.1 (0.86-1.41) | 0.463 | 0.013 | 15.448 | 0.051 |
| Familiar dyslipidaemia | 1.37 (1.14-1.65) | 8.51e-04 | 0.014 | 13.479 | 0.096 |
| Gestational diabetes | 0.96 (0.12-7.62) | 0.967 | 0.013 | 13.257 | 0.103 |
| Gestational hypertension | - | - | - | - | - |
| Hypertension | 1.36 (1.23-1.5) | 3.00e-09\*\* | 0.017 | 4.721 | 0.787 |
| MetS | 1.85 (0.53-6.5) | 0.336 | 0.013 | 16.847 | 0.032 |
| NAFLD | 1.46 (1.14-1.87) | 0.002 | 0.014 | 17.864 | 0.022 |
| Obesity/overweight | 1.52 (1.35-1.72) | 3.29e-12\*\* | 0.017 | 7.122 | 0.524 |
| PCOS | 3.59 (1.27-10.16) | 0.016 | 0.013 | 18.392 | 0.018 |
| Prediabetes | 1.56 (1.33-1.82) | 2.45e-08\*\* | 0.016 | 17.602 | 0.024 |
| Rare IR-related conditions | 2.4 (1.32-4.36) | 0.004 | 0.014 | 14.675 | 0.066 |
| T2DM | 1.8 (1.57-2.07) | 2.57e-17\*\* | 0.019 | 10.515 | 0.231 |

1. Antidepressant non-response outcome

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Predictor** | **OR (95% CIs)** | **p-value** | **Nagelkerke’s R²** | **Hosmer-Lemeshow χ²** | **Hosmer-Lemeshow p-value** |
| Any IR-related condition | 1.45 (1.35-1.55) | 1.80e-25\*\* | 0.022 | 4.774 | 0.781 |
| CAD | 1.29 (1.13-1.47) | 1.42e-04\*\* | 0.015 | 12.508 | 0.130 |
| Cerebral ischemia | 1.25 (1.06-1.48) | 0.008 | 0.015 | 15.314 | 0.053 |
| Cushing’s syndrome | 3.39 (0.84-13.65) | 0.086 | 0.014 | 10.911 | 0.207 |
| CVDs | 1.25 (1.12-1.4) | 5.26e-05\*\* | 0.015 | 11.301 | 0.185 |
| Dyslipidaemia | 1.1 (0.91-1.32) | 0.329 | 0.014 | 10.034 | 0.263 |
| Familiar dyslipidaemia | 1.2 (1.04-1.38) | 0.014 | 0.014 | 8.933 | 0.348 |
| Gestational diabetes | 2.32 (0.65-8.3) | 0.197 | 0.014 | 8.177 | 0.416 |
| Gestational hypertension | 0.87 (0.18-4.14) | 0.864 | 0.014 | 11.736 | 0.163 |
| Hypertension | 1.29 (1.19-1.39) | 9.12e-11\*\* | 0.017 | 8.547 | 0.382 |
| MetS | 3.01 (1.15-7.88) | 0.025 | 0.014 | 11.403 | 0.180 |
| NAFLD | 1.37 (1.13-1.66) | 0.001 | 0.015 | 13.667 | 0.091 |
| Obesity/overweight | 1.42 (1.3-1.56) | 4.30e-14\*\* | 0.017 | 9.069 | 0.337 |
| PCOS | 1.25 (0.45-3.5) | 0.670 | 0.014 | 10.734 | 0.217 |
| Prediabetes | 1.44 (1.28-1.63) | 3.70e-09\*\* | 0.016 | 16.680 | 0.034 |
| Rare IR-related conditions | 1.88 (1.13-3.14) | 0.016 | 0.014 | 9.667 | 0.289 |
| T2DM | 1.5 (1.35-1.68) | 3.27e-13\*\* | 0.017 | 6.207 | 0.624 |

1. Overall treatment time (weeks) outcome

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictor** | **β (SE)** | **p-value** | **R²** |
| Any IR-related condition | 64.02 (3.76) | 1.27e-64\*\* | 0.039 |
| CAD | 45.04 (7.33) | 8.16e-10\*\* | 0.027 |
| Cerebral ischemia | 28.15 (9.37) | 0.003 | 0.026 |
| Cushing’s syndrome | 60.93 (87.81) | 0.488 | 0.026 |
| CVDs | 37.25 (6.03) | 6.53e-10\*\* | 0.028 |
| Dyslipidaemia | 33.43 (10.17) | 0.001 | 0.026 |
| Familiar dyslipidaemia | 49.44 (7.96) | 5.30e-10\*\* | 0.027 |
| Gestational diabetes | 65.84 (78.57) | 0.402 | 0.026 |
| Gestational hypertension | 84.49 (78.55) | 0.282 | 0.026 |
| Hypertension | 45.93 (4.18) | 5.31e-28\*\* | 0.032 |
| MetS | 162.62 (60.24) | 0.007 | 0.026 |
| NAFLD | 71.6 (10.8) | 3.41e-11\*\* | 0.027 |
| Obesity/overweight | 54.75 (5.17) | 3.51e-26\*\* | 0.029 |
| PCOS | 36.75 (57.03) | 0.519 | 0.026 |
| Prediabetes | 56.52 (6.98) | 5.90e-16\*\* | 0.028 |
| Rare IR-related conditions | 45.14 (30.84) | 0.143 | 0.026 |
| T2DM | 84.25 (6.28) | 7.31e-41\*\* | 0.033 |

**Supplementary Table 12.** Association between pre-existing insulin resistance-related conditions diagnosed prior to MDD onset, and depression treatment outcomes in the UK Biobank cohort, after adjusting for relevant covariates.

\*\* Statistically significant after Bonferroni correction (alpha=0.05/(27 predictors\*3 outcomes)=0.0006.

Abbreviations: OR, odds ratio; CIs, confidence intervals; R², proportion of phenotypic variance in the outcome explained by the full model; IR, insulin resistance; TRD, treatment-resistant depression; CVDs, cardiovascular diseases; PCOS, polycystic ovary syndrome; MetS, metabolic syndrome; NAFLD, non-alcoholic steatohepatitis liver disease; T2DM, type 2 diabetes mellitus.

1. Treatment-resistant depression outcome

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Predictor** | **OR (95% CIs)** | **p-value** | **Nagelkerke’s R²** | **Hosmer-Lemeshow χ²** | **Hosmer-Lemeshow p-value** |
| Any IR-related condition | 1.26 (1.12-1.41) | 1.02e-04\*\* | 0.016 | 7.024 | 0.534 |
| CAD | 1.29 (1.03-1.63) | 0.028 | 0.014 | 12.805 | 0.119 |
| Cerebral ischemia | 1 (0.7-1.43) | 0.996 | 0.013 | 15.666 | 0.047 |
| Cushing’s syndrome | 1.63 (0.19-14.17) | 0.659 | 0.013 | 15.856 | 0.044 |
| CVDs | 1.2 (0.99-1.47) | 0.068 | 0.014 | 3.391 | 0.908 |
| Dyslipidaemia | 0.35 (0.17-0.72) | 0.004 | 0.014 | 11.459 | 0.177 |
| Familiar dyslipidaemia | 0.98 (0.73-1.3) | 0.877 | 0.013 | 8.749 | 0.364 |
| Gestational diabetes | 1.08 (0.32-3.59) | 0.905 | 0.013 | 13.739 | 0.089 |
| Gestational hypertension | 0.91 (0.36-2.31) | 0.846 | 0.013 | 16.693 | 0.033 |
| Hypertension | 1.01 (0.88-1.16) | 0.883 | 0.016 | 4.831 | 0.775 |
| MetS | 3.75 (0.33-42.21) | 0.285 | 0.013 | 16.745 | 0.033 |
| NAFLD | 1.24 (0.61-2.5) | 0.553 | 0.014 | 14.861 | 0.062 |
| Obesity/overweight | 1.23 (1.05-1.44) | 0.012 | 0.013 | 11.180 | 0.192 |
| PCOS | 1.93 (0.89-4.18) | 0.094 | 0.013 | 15.151 | 0.056 |
| Prediabetes | 0.9 (0.55-1.46) | 0.665 | 0.013 | 14.860 | 0.062 |
| Rare IR-related conditions | 1.55 (0.53-4.53) | 0.420 | 0.013 | 15.895 | 0.044 |
| T2DM | 1.03 (0.8-1.33) | 0.830 | 0.013 | 12.391 | 0.135 |

1. Antidepressant non-response outcome

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Predictor** | **OR (95% CIs)** | **p-value** | **Nagelkerke’s R²** | **Hosmer-Lemeshow χ²** | **Hosmer-Lemeshow p-value** |
| Any IR-related condition | 1.19 (1.1-1.29) | 3.85e-05\*\* | 0.016 | 6.040 | 0.643 |
| CAD | 1.12 (0.94-1.34) | 0.210 | 0.014 | 10.894 | 0.208 |
| Cerebral ischemia | 1.04 (0.8-1.35) | 0.770 | 0.014 | 8.777 | 0.361 |
| Cushing’s syndrome | 0.61 (0.07-5.23) | 0.648 | 0.014 | 9.622 | 0.293 |
| CVDs | 1.09 (0.94-1.27) | 0.261 | 0.014 | 8.651 | 0.373 |
| Dyslipidaemia | 0.75 (0.52-1.08) | 0.122 | 0.014 | 14.859 | 0.062 |
| Familiar dyslipidaemia | 1.05 (0.86-1.29) | 0.640 | 0.014 | 12.324 | 0.137 |
| Gestational diabetes | 1.32 (0.58-3.01) | 0.503 | 0.014 | 10.328 | 0.243 |
| Gestational hypertension | 0.71 (0.34-1.47) | 0.356 | 0.014 | 10.727 | 0.218 |
| Hypertension | 0.99 (0.9-1.09) | 0.799 | 0.016 | 11.977 | 0.152 |
| MetS | 5.91 (0.53-65.77) | 0.148 | 0.014 | 15.794 | 0.045 |
| NAFLD | 1.13 (0.66-1.94) | 0.656 | 0.014 | 11.843 | 0.158 |
| Obesity/overweight | 1.2 (1.07-1.36) | 0.002 | 0.014 | 5.684 | 0.683 |
| PCOS | 1.11 (0.56-2.19) | 0.774 | 0.014 | 11.350 | 0.183 |
| Prediabetes | 1.12 (0.8-1.56) | 0.505 | 0.014 | 8.648 | 0.373 |
| Rare IR-related conditions | 1.24 (0.52-2.97) | 0.625 | 0.014 | 10.584 | 0.226 |
| T2DM | 1.04 (0.86-1.25) | 0.693 | 0.014 | 4.925 | 0.766 |

1. Overall treatment time (weeks) outcome

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictor** | **β (SE)** | **p-value** | **R²** |
| Any IR-related condition | 26.37 (4.07) | 9.62e-11\*\* | 0.030 |
| CAD | 22.33 (9.6) | 0.020 | 0.025 |
| Cerebral ischemia | -10.72 (13.81) | 0.438 | 0.025 |
| Cushing’s syndrome | 10.88 (101.37) | 0.915 | 0.026 |
| CVDs | 13.8 (8.09) | 0.088 | 0.025 |
| Dyslipidaemia | -39.3 (18.18) | 0.031 | 0.026 |
| Familiar dyslipidaemia | -3.54 (10.83) | 0.744 | 0.026 |
| Gestational diabetes | 44.02 (46.21) | 0.341 | 0.026 |
| Gestational hypertension | 8.34 (35.54) | 0.814 | 0.026 |
| Hypertension | 9.07 (4.97) | 0.068 | 0.029 |
| MetS | -70.09 (143.34) | 0.625 | 0.026 |
| NAFLD | -16.34 (29.42) | 0.579 | 0.026 |
| Obesity/overweight | 7.41 (6.47) | 0.252 | 0.026 |
| PCOS | 9.25 (36.7) | 0.801 | 0.026 |
| Prediabetes | -39.71 (17.83) | 0.026 | 0.026 |
| Rare IR-related conditions | 50.27 (48.71) | 0.302 | 0.025 |
| T2DM | 6.22 (9.71) | 0.521 | 0.025 |

**Supplementary Table 13.** Association between polygenic scores (PGSs) for insulin resistance-related conditions and depression treatment outcomes in the UK Biobank cohort, after adjusting for relevant covariates. R² and PGS-R² values are provided to assess the proportion of phenotypic variance explained either by the full model including covariates or the model including only PGS, respectively. The Hosmer-Lemeshow χ² test and its corresponding p-value to evaluate the goodness of fit of logistic regression models (p-values>0.05 suggests that the model fits the data well).

\*\* Statistically significant after Bonferroni correction (alpha=0.05/(28 predictors\*3 outcomes)=0.0006

Abbreviations: OR, odds ratio; CIs, confidence intervals; BMI, body mass index; CAD, coronary artery disease; T2DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; 2hGlu, glucose levels 2 hours after an oral glucose challenge; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; TG, triglycerides; PGS, polygenic score; TRD, treatment-resistant depression.

1. Treatment-resistant depression outcome

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Predictor** | **OR (95% CIs)** | **p-value** | **Nagelkerke's R²** | **Nagelkerke's PGS-R²** | **Hosmer-Lemeshow χ²** | **Hosmer-Lemeshow p-value** |
| BMI | 1.04 (1-1.09) | 0.040 | 0.019 | 2.96e-04 | 4.246 | 0.834 |
| CAD | 1.02 (0.98-1.06) | 0.272 | 0.019 | 8.48e-05 | 6.384 | 0.604 |
| T2DM | 1.01 (0.97-1.06) | 0.504 | 0.019 | 3.13e-05 | 7.577 | 0.476 |
| FPG | 0.97 (0.93-1.01) | 0.107 | 0.019 | 1.82e-04 | 10.641 | 0.223 |
| 2hGlu | 1 (0.96-1.04) | 0.950 | 0.019 | 2.73e-07 | 6.574 | 0.583 |
| HbA1c | 1 (0.96-1.04) | 0.838 | 0.019 | 2.95e-06 | 7.361 | 0.498 |
| HDL | 1 (0.96-1.05) | 0.841 | 0.019 | 2.83e-06 | 7.729 | 0.460 |
| HOMA-IR | 1 (0.96-1.04) | 0.938 | 0.019 | 4.27e-07 | 5.385 | 0.716 |
| LDL | 0.98 (0.94-1.02) | 0.372 | 0.019 | 5.59e-05 | 11.714 | 0.164 |
| TG | 1.05 (1.01-1.1) | 0.015 | 0.019 | 4.15e-04 | 8.209 | 0.413 |

1. Antidepressant non-response outcome

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Predictor** | **OR (95% CIs)** | **p-value** | **Nagelkerke's R²** | **Nagelkerke's PGS-R²** | **Hosmer-Lemeshow χ²** | **Hosmer-Lemeshow p-value** |
| BMI | 1.02 (0.99-1.05) | 0.117 | 0.022 | 1.30e-04 | 10.172 | 0.253 |
| CAD | 1.01 (0.98-1.04) | 0.368 | 0.022 | 4.28e-05 | 5.541 | 0.699 |
| T2DM | 0.99 (0.97-1.02) | 0.723 | 0.021 | 6.64e-06 | 8.791 | 0.360 |
| FPG | 0.98 (0.95-1.01) | 0.234 | 0.022 | 7.51e-05 | 15.466 | 0.051 |
| 2hGlu | 1 (0.97-1.03) | 0.960 | 0.021 | 1.32e-07 | 7.135 | 0.522 |
| HbA1c | 1 (0.97-1.03) | 0.860 | 0.021 | 1.65e-06 | 7.019 | 0.535 |
| HDL | 0.99 (0.96-1.02) | 0.382 | 0.021 | 4.04e-05 | 7.163 | 0.519 |
| HOMA-IR | 1.01 (0.98-1.04) | 0.473 | 0.021 | 2.73e-05 | 8.906 | 0.350 |
| LDL | 1 (0.97-1.02) | 0.740 | 0.021 | 5.81e-06 | 5.952 | 0.653 |
| TG | 1.02 (0.99-1.05) | 0.152 | 0.022 | 1.09e-04 | 5.061 | 0.751 |

1. Overall treatment time (weeks) outcome

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Predictor** | **β (SE)** | **p-value** | **R²** | **PGS-R²** |
| BMI | -1.08 (1.56) | 0.489 | 0.031 | 1.81e-05 |
| CAD | 3.39 (1.56) | 0.030 | 0.031 | 1.79e-04 |
| T2DM | -0.7 (1.58) | 0.659 | 0.031 | 7.35e-06 |
| FPG | -1.81 (1.55) | 0.245 | 0.031 | 5.10e-05 |
| 2hGlu | -0.18 (1.66) | 0.914 | 0.031 | 4.43e-07 |
| HbA1c | -0.82 (1.58) | 0.604 | 0.031 | 1.02e-05 |
| HDL | -3.43 (1.55) | 0.027 | 0.031 | 1.84e-04 |
| HOMA-IR | 1.02 (1.58) | 0.518 | 0.031 | 1.57e-05 |
| LDL | -1.81 (1.55) | 0.244 | 0.031 | 5.13e-05 |
| TG | 3.89 (1.57) | 0.014 | 0.031 | 2.30e-04 |

**Supplementary Table 14.** Association between polygenic scores (PGSs) for insulin resistance (IR)-related conditions and depression treatment outcomes in the UK Biobank cohort, stratified to include patients with MDD with no lifetime history of IR-related conditions and those who developed IR-related conditions following the onset of MDD. The analyses were adjusted for relevant covariates.

\*\* Statistically significant after Bonferroni correction (alpha=0.05/(27 predictors\*3 outcomes)=0.0006

Abbreviations: OR, odds ratio; CIs, confidence intervals; R², proportion of phenotypic variance in the outcome explained by the full model; PGS-R², proportion of phenotypic variance in the outcome explained by individual PGSs; BMI, body mass index; CAD, coronary artery disease; T2DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; 2hGlu, glucose levels 2 hours after an oral glucose challenge; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; TG, triglycerides; PGS, polygenic score; TRD, treatment-resistant depression.

1. Treatment-resistant depression outcome

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Predictor** | **OR (95% CIs)** | **p-value** | **Nagelkerke’s R²** | **Nagelkerke’s PGS-R²** | **Hosmer-Lemeshow χ²** | **Hosmer-Lemeshow p-value** |
| BMI | 1.05 (1-1.1) | 0.053 | 0.022 | 3.32e-04 | 14.591 | 0.068 |
| CAD | 1.02 (0.98-1.07) | 0.348 | 0.022 | 7.81e-05 | 10.653 | 0.222 |
| T2DM | 1.02 (0.97-1.06) | 0.484 | 0.022 | 4.34e-05 | 7.529 | 0.481 |
| FPG | 0.95 (0.91-1) | 0.045 | 0.022 | 3.57e-04 | 7.628 | 0.471 |
| 2hGlu | 1 (0.96-1.05) | 0.854 | 0.022 | 3.02e-06 | 13.631 | 0.092 |
| HbA1c | 0.98 (0.93-1.02) | 0.362 | 0.022 | 7.37e-05 | 12.754 | 0.121 |
| HDL | 1.01 (0.96-1.05) | 0.803 | 0.022 | 5.50e-06 | 13.395 | 0.099 |
| HOMA-IR | 1 (0.96-1.05) | 0.889 | 0.022 | 1.72e-06 | 13.345 | 0.101 |
| LDL | 0.99 (0.94-1.03) | 0.580 | 0.022 | 2.71e-05 | 11.537 | 0.173 |
| TG | 1.05 (1-1.1) | 0.033 | 0.022 | 4.02e-04 | 6.948 | 0.542 |

1. Antidepressant non-response outcome

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Predictor** | **OR (95% CIs)** | **p-value** | **Nagelkerke’s R²** | **Nagelkerke’s PGS-R²** | **Hosmer-Lemeshow χ²** | **Hosmer-Lemeshow p-value** |
| BMI | 1.03 (0.99-1.06) | 0.116 | 0.025 | 1.65e-04 | 5.465 | 0.707 |
| CAD | 1.02 (0.99-1.06) | 0.204 | 0.025 | 1.07e-04 | 1.651 | 0.990 |
| T2DM | 0.99 (0.95-1.02) | 0.444 | 0.024 | 3.89e-05 | 1.683 | 0.989 |
| FPG | 0.98 (0.94-1.01) | 0.161 | 0.025 | 1.31e-04 | 6.802 | 0.558 |
| 2hGlu | 1.01 (0.98-1.05) | 0.532 | 0.024 | 2.59e-05 | 2.807 | 0.946 |
| HbA1c | 0.99 (0.96-1.03) | 0.631 | 0.024 | 1.53e-05 | 2.126 | 0.977 |
| HDL | 0.99 (0.96-1.03) | 0.660 | 0.024 | 1.29e-05 | 2.214 | 0.974 |
| HOMA-IR | 1.01 (0.97-1.04) | 0.738 | 0.024 | 7.45e-06 | 3.050 | 0.931 |
| LDL | 0.99 (0.96-1.03) | 0.705 | 0.024 | 9.52e-06 | 3.542 | 0.896 |
| TG | 1.02 (0.98-1.05) | 0.382 | 0.024 | 5.08e-05 | 2.905 | 0.940 |

1. Overall treatment time (weeks) outcome

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Predictor** | **β (SE)** | **p-value** | **R²** | **PGS-R²** |
| BMI | -0.93 (1.78) | 0.602 | 0.032 | 1.28e-05 |
| CAD | 2.8 (1.77) | 0.113 | 0.032 | 1.18e-04 |
| T2DM | -1.69 (1.8) | 0.346 | 0.032 | 4.19e-05 |
| FPG | -1.49 (1.76) | 0.397 | 0.032 | 3.39e-05 |
| 2hGlu | -0.51 (1.89) | 0.788 | 0.032 | 3.42e-06 |
| HbA1c | -1.16 (1.79) | 0.517 | 0.032 | 1.99e-05 |
| HDL | -3.19 (1.76) | 0.070 | 0.032 | 1.56e-04 |
| HOMA-IR | 0.88 (1.79) | 0.622 | 0.032 | 1.15e-05 |
| LDL | -2.32 (1.76) | 0.188 | 0.032 | 8.21e-05 |
| TG | 2.83 (1.79) | 0.113 | 0.032 | 1.19e-04 |

**Supplementary Table 15.** Association between polygenic scores (PGSs) for insulin resistance (IR)-related conditions and depression treatment outcomes in the UK Biobank cohort, stratified to include patients with MDD with no lifetime history of IR-related conditions and those who developed IR-related conditions before the onset of MDD. The analyses were adjusted for relevant covariates.

\*\* Statistically significant after Bonferroni correction (alpha=0.05/(27 predictors\*3 outcomes)=0.0006

Abbreviations: OR, odds ratio; CIs, confidence intervals; R², proportion of phenotypic variance in the outcome explained by the full model; PGS-R², proportion of phenotypic variance in the outcome explained by individual PGSs; BMI, body mass index; CAD, coronary artery disease; T2DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; 2hGlu, glucose levels 2 hours after an oral glucose challenge; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; TG, triglycerides; PGS, polygenic score; TRD, treatment-resistant depression.

1. Treatment-resistant depression outcome

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Predictor** | **OR (95% CIs)** | **p-value** | **Nagelkerke’s R²** | **Nagelkerke’s PGS-R²** | **Hosmer-Lemeshow χ²** | **Hosmer-Lemeshow p-value** |
| BMI | 1.05 (1-1.11) | 0.044 | 0.024 | 4.36e-04 | 2.468 | 0.963 |
| CAD | 1.02 (0.96-1.07) | 0.548 | 0.024 | 3.89e-05 | 2.197 | 0.974 |
| T2DM | 1.04 (0.99-1.09) | 0.150 | 0.024 | 2.23e-04 | 3.596 | 0.892 |
| FPG | 0.97 (0.92-1.02) | 0.206 | 0.024 | 1.73e-04 | 3.759 | 0.878 |
| 2hGlu | 0.98 (0.93-1.04) | 0.496 | 0.024 | 4.99e-05 | 4.602 | 0.799 |
| HbA1c | 0.99 (0.94-1.05) | 0.829 | 0.024 | 5.05e-06 | 2.978 | 0.936 |
| HDL | 1 (0.95-1.05) | 0.900 | 0.024 | 1.71e-06 | 2.191 | 0.975 |
| HOMA-IR | 1 (0.95-1.06) | 0.920 | 0.024 | 1.10e-06 | 1.997 | 0.981 |
| LDL | 0.97 (0.92-1.02) | 0.225 | 0.024 | 1.58e-04 | 3.194 | 0.922 |
| TG | 1.07 (1.01-1.12) | 0.014 | 0.025 | 6.46e-04 | 2.756 | 0.949 |

1. Antidepressant non-response outcome

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Predictor** | **OR (95% CIs)** | **p-value** | **Nagelkerke’s R²** | **Nagelkerke’s PGS-R²** | **Hosmer-Lemeshow χ²** | **Hosmer-Lemeshow p-value** |
| BMI | 1.02 (0.98-1.06) | 0.261 | 0.026 | 9.90e-05 | 6.394 | 0.603 |
| CAD | 0.99 (0.96-1.03) | 0.634 | 0.026 | 1.78e-05 | 12.980 | 0.113 |
| T2DM | 1.01 (0.97-1.04) | 0.763 | 0.026 | 7.13e-06 | 7.979 | 0.436 |
| FPG | 0.99 (0.95-1.03) | 0.552 | 0.026 | 2.77e-05 | 13.480 | 0.096 |
| 2hGlu | 1.01 (0.97-1.05) | 0.511 | 0.026 | 3.40e-05 | 9.067 | 0.337 |
| HbA1c | 1.01 (0.97-1.05) | 0.674 | 0.026 | 1.39e-05 | 11.456 | 0.177 |
| HDL | 0.98 (0.95-1.02) | 0.302 | 0.026 | 8.38e-05 | 11.069 | 0.198 |
| HOMA-IR | 1.01 (0.97-1.05) | 0.539 | 0.026 | 2.97e-05 | 9.657 | 0.290 |
| LDL | 0.99 (0.95-1.02) | 0.501 | 0.026 | 3.54e-05 | 8.640 | 0.374 |
| TG | 1.02 (0.99-1.06) | 0.219 | 0.026 | 1.18e-04 | 8.472 | 0.389 |

1. Overall treatment time (weeks) outcome

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Predictor** | **β (SE)** | **p-value** | **R²** | **PGS-R²** |
| BMI | -2.19 (1.75) | 0.210 | 0.035 | 8.63e-05 |
| CAD | 2.33 (1.76) | 0.186 | 0.035 | 9.61e-05 |
| T2DM | -2.13 (1.78) | 0.233 | 0.035 | 7.84e-05 |
| FPG | -1.48 (1.76) | 0.400 | 0.035 | 3.89e-05 |
| 2hGlu | -0.43 (1.89) | 0.818 | 0.035 | 2.91e-06 |
| HbA1c | -1.53 (1.78) | 0.390 | 0.035 | 4.06e-05 |
| HDL | -3.35 (1.75) | 0.055 | 0.035 | 2.03e-04 |
| HOMA-IR | -1.45 (1.79) | 0.418 | 0.035 | 3.60e-05 |
| LDL | -1.25 (1.74) | 0.473 | 0.035 | 2.84e-05 |
| TG | 4.38 (1.77) | 0.014 | 0.035 | 3.35e-04 |