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## Supplementary Tables

### Supplementary Table S1: Previous MR Studies of Micronutrient Exposures in Depression

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Exposure | Study | Outcome Sample | Exposure Sample Size | Outcome Sample Size | MR Method | SNPs | Results (OR or beta; (95% confidence intervals)[[1]](#footnote-1) |
| Vitamin D | Michaelsson 20181 | Psychiatric Genomics Consortium (PGC) | 79,366 | 173,005 | Two-sample | 6 | 0.98 (0.93, 1.03) p=0.44[[2]](#footnote-2) |
| Milaneschi 20192 | Netherlands Study of Depression and Anxiety (NESDA) | 2,013 | 2,047 | One-sample | 6 | 0.94 (0.84, 1.06) p=0.34 |
| PGC | 79,366 | 480,359 | Two -sample | 6 | 0.97 (0.88, 1.07)[[3]](#footnote-3) p=0.50 |
| Mulugeta 20203 | PGC | 79,366 | 331,677 | Two sample | 6 | 0.97 per 50% increase in vit D (0.91, 1.04) |
| UK Biobank (UKBB) | 79,366 | 251,962 | Two sample | 6 | 0.97 per 50% increase (0.90, 1.05) |
| Libuda 20194 | UKBB Depressive Symptoms | 79,366 | 161,460 | Two sample | 6 | 0.025 (-0.05, 0.10) p=0.52 |
| UKBB Depression | 79,366 | 322,580 | Two-sample | 6 | 0.98 (0.96, 1.00) p=0.10 |
| Revez 20205 | PGC | 417,580 | 807,553 | Two-sample | 240 | 0.98 (0.96, 1.00) p=0.03b |
| B12 | Mollehave 2017 6 | Health 2006 & Inter 99 | 4,126 | 4,126 | One-sample | 12 | 0.96 (0.52, 1.79) p=0.91 |
| Folate | Health 2006 & Inter 99 | 3,942 | 3,942 | One-sample | 2 | 1.18 (0.18, 7.66) p=0.86 |
| Homocysteine | Yu 2022 | PGC | 44,147 | 42,455 | Two-sample | 13 | 0.95 (0.88, 1.00) p=0.12 |
|  |  |  |  |  |  |  |  |
| Calcium | Cheng 20197 | Chinese Women through CONVERGE consortium | 39,400 | 10,640 | Two-sample | 6 | 0.92 (0.67, 1.28) p=0.63 |
| Magnesium | 15,366 | 3 | 1.19 (0.22, 6.61) p=0.84 |
| Iron | 48,972 | 9 | 0.98 (0.91, 1.05) p=0.60 |
| Zinc | 2,603 | 2 | 0.99 (0.95, 1.03) p=0.66 |

### Supplementary Table S2: Characteristics of the PGC MDD GWAS

Summary statistics from thePsychiatric Genomics Consortium MDD GWAS published in 20198 were used as the primary outcome sample. This GWAS is a meta-analysis of the three largest independent GWASs of MDD to date, including 246,363 cases and 561,190 controls. 23andMe Participants provided informed consent and participated in the research online, under a protocol approved by the external AAHRPP-accredited IRB, Ethical & Independent Review Services (E&I Review). For full details of the methods used for genotyping in each cohort, please refer to the original publications.

|  |  |  |  |
| --- | --- | --- | --- |
| **Author** | **Sample** | **N** | **MDD categorisation** |
| Hyde et al9 | 23andMe discovery cohort/307k | 75,607 cases  231,747 controls | Self-report clinical diagnosis |
| Howard et al8 | UK Biobank | 127,552 cases  233,763 controls | Self-reported help seeking for problems with nerves, anxiety, tension, or depression |
| Wray et al10 | Total sample (five cohorts) | 43,204 cases  95,680 controls | See below for details. Individual cohort numbers below are prior to exclusion of 23andMe\_307k and prior release of UK Biobank data (N=4,381) |
| PGC 29 | 16,823 cases  25,632 controls | Structured diagnostic interviews from 29 samples as described in Wray et al.10 |
| deCODE | 1,980 cases  9,536 controls | National inpatient electronic records |
| GenScotland | 997 cases  6,358 controls | Structured diagnostic interview |
| GERA | 7,162 cases  38,307 controls | Kaiser Permanenta Northern California Electronic Medical records (1995-2013) |
| iPSYCH | 18,629 cases  17,841 controls | National inpatient electronic records |

### Supplementary Table S3: Studies contributing data for micronutrient GWASs with PGC MDD sample overlap

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Group** | **Exposure** | **Measure** | **Author** | **Population** | **Study** | **Cohort contributes data to PGC** | **N** |
| Water soluble Vitamins | Vitamin B6 | Serum B6 | Tanaka11 | Italy | InCHIANTI | No | 1178 |
|  |  |  |  | Italy | Progetto Nutrizione | No | 686 |
|  |  |  |  |  |  |  |  |
|  | Vitamin B9 | Serum Folate | Grarup12 | Iceland | Icelandic | No | 20,717 |
|  |  |  |  | Denmark | Inter-99 | No | 5,624 |
|  |  |  |  | Denmark | Health 2006 | No | 2,804 |
|  |  |  |  |  |  |  |  |
|  |  | Serum Homocysteine | Van Meurs13 | Italy | InCHIANTI | No | 1,208 |
|  |  |  |  | USA | Baltimore Longitudinal Study of Aging | No | 638 |
|  |  |  |  | USA/ UK | Nurse’s Health Study | No | 1,658 |
|  |  |  |  | USA | Women’s Genome Health Study |  | 13,974 |
|  |  |  |  | Netherlands | Rotterdam Study I | Yes | 3,414 |
|  |  |  |  | Netherlands | Rotterdam Study II | Yes | 1,868 |
|  |  |  |  | UK | TwinsUK cohort | No | 1,172 |
|  |  |  |  | Switzerland | CoLaus cohort | Yes | 5,434 |
|  |  |  |  | USA | Cardiovascular Health Study | No | 3,980 |
|  |  |  |  | USA | Framingham Heart Study | No | 10,251\* |
|  |  |  |  | Netherlands | Nijemen Medical Study | No | 550 |
|  |  |  |  |  |  |  |  |
|  | Vitamin B12 | Serum B12 | Grarup12 | Icelandic | Icelandic | No | 25,960 |
|  |  |  |  | Danish | Inter-99 | No | 5,481 |
|  |  |  |  | Danish | Health 2006 | No | 2,812 |
|  |  |  |  |  |  |  |  |
|  | Vitamin C | Plasma Vitamin C | Zheng 2021 | UK | Fenland | No | 10,771 |
|  |  |  |  | UK | EPIC-Norfolk | No | 16,756 |
|  |  |  |  | France, Italy, Spain, UK, Netherlands, Germany, Sweden, Denmark | EPIC-InterAct | No | 16,841 |
|  |  |  |  | As above | EPIC-CVD | No | 7,650 |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| Fat soluble Vitamins | Vitamin A | Serum Retinol | Mondul14 | Finland | Alpha-Tocopherol, Beta Carotene Cancer Prevention (ATBC) Study | No | 4,014 |
|  |  |  |  | USA | Prostate, Lung, Colorectal and Ovarian Cancer Screening trial | No | 992 |
|  |  |  |  | UK | Nurses Health Study (NHS) | No | 2772 |
|  |  |  |  | Italy | InCHIANTI | No | 1,124 |
|  |  |  |  |  |  |  |  |
|  |  | Beta Carotene | Ferrucci15 | Italy | InCHIANTI | No | 1,191 |
|  |  |  |  | USA | Women’s Health and Aging Study | No | 615 |
|  |  |  |  | USA | ATBC Study | No | 2,136 |
|  |  |  |  |  |  |  |  |
|  | Vitamin D | Serum 25(OH)D | Jiang16 | UK | 1958 British Birth Cohort | No | 4,985 |
|  |  |  |  | USA | The Cardiovascular Health Study | No | 1,791 |
|  |  |  |  | USA | The Framingham Heart Study | No | 5,654 |
|  |  |  |  | Sweden | The Gothenburg Osteoporosis and Obesity Determinants Study | No | 921 |
|  |  |  |  | USA | The Health, Aging, Body Composition Study | No | 1,558 |
|  |  |  |  | USA | The Indiana Women cohort | No | 567 |
|  |  |  |  | Finland | The North Finland Birth Cohort 1966 | No | 4,604 |
|  |  |  |  | USA | The Old Order Amish Study | No | 330 |
|  |  |  |  | Netherlands | The Rotterdam Study | Yes | 1,237 |
|  |  |  |  | UK | Twins UK | No | 5,135 |
|  |  |  |  | Finland | ATBC | No | 1,372 |
|  |  |  |  | USA | PLCO | No | 1,315 |
|  |  |  |  | USA | Atherosclerosis Risk in Communities (ARIC) | No | 8,124 |
|  |  |  |  | Germany | AtheroGene | No | 1,062 |
|  |  |  |  | Netherlands | B-vitamins for the Prevention of Osteoporotic Fractures (BPROOF) | No | 2,525 |
|  |  |  |  | USA | Epidemiology of Diabetes Interventions and Complications (EDIC) | No | 1,094 |
|  |  |  |  | Finland | Case- Control Study for  Metabolic Syndrome  (GENMETS) | No | 1,641 |
|  |  |  |  | Finland | The Helsinki Birth Cohort Study (HBCS) | No | 917 |
|  |  |  |  | USA | Coronary Heart Disease Case - Control Study nested within NHS and HPFS (HPFS\_CHD) | No | 1,245 |
|  |  |  |  | Italy | The Invecchiare in Chianti Study (InChianti) | No | 1,094 |
|  |  |  |  | Germany | Cooperative Health Research in the Region Augsburg (KORA) | Yes (controls) | 1,805 |
|  |  |  |  | Netherlands | Leiden Longevity Study (LLS) | No | 2,265 |
|  |  |  |  | Germany | Ludwigshafen Risk and Cardiovascular Health Study (LURIC) | No | 2,846 |
|  |  |  |  | USA | Multi -Ethnic Study of Atherosclerosis (MESA) | No | 2,240 |
|  |  |  |  | Netherlands | Nijmegen Biomedische Studie | No | 2,610 |
|  |  |  |  | UK/ USA | Breast Cancer Case-Control Study nestled in NHS | No | 870 |
|  |  |  |  | UK/ USA | Type II diabetes Case-Control Study nested within NHS | No | 724 |
|  |  |  |  | Scotland | The Orkney Complex Disease Study (ORCADES) | No | 847 |
|  |  |  |  | Scotland, Ireland and the Netherlands | Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) | No | 4,871 |
|  |  |  |  | Netherlands | Rotterdam Study I& II | Yes | 8,313 |
|  |  |  |  | Germany | The Study of Health in Pomerania (SHIP) | Yes | 1,655 |
|  | 2 |  |  | UK | The Scottish Colorectal Cancer Study | No | 1,165 |
|  |  |  |  | Finland | Cardiovascular risk in Young Finns Study | No | 1,984 |
|  |  |  |  | Sweden | Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) | No | 989 |
|  |  |  |  | Sweden | Uppsala Longitudinal Study of Adult Men (ULSAM) | No | 1,124 |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| Macrominerals | Calcium | Serum Calcium | O'Seaghadha17 | Iceland | Age Gene/Environment Susceptibility (AGES) | No | 1949 |
|  |  |  |  | USA | ARIC | No | 9049 |
|  |  |  |  | USA | Baltimore Study of Aging (BLSA) | No | 719 |
|  |  |  |  | USA | CHS | No | 1802 |
|  |  |  |  | Switzerland | CoLaus | Yes | 5411 |
|  |  |  |  | Croatia | CROATIA-Korcula | No | 880 |
|  |  |  |  | Croatia | CROATIA-Split | No | 488 |
|  |  |  |  | Croatia | CROATIA-Vis | No | 910 |
|  |  |  |  | USA | FHS | No | 2853 |
|  |  |  |  |  | HABC | No | 1554 |
|  |  |  |  | Italy | InCHIANTI | No | 1204 |
|  |  |  |  | UK | LBC1936 | No | 993 |
|  |  |  |  | UK | LOLIPOP EW A | No | 589 |
|  |  |  |  | UK | LOLIPOP EW P | No | 652 |
|  |  |  |  | UK | LOLIPOP EW610 | No | 927 |
|  |  |  |  | Sardinia | OGP Talana | No | 1039 |
|  |  |  |  | UK | ORCADES | No | 877 |
|  |  |  |  | Netherlands | Rotterdam Study | No | 3436 |
|  |  |  |  | Germany | SHIP | Yes | 4068 |
|  |  |  |  | UK | British Genetics of Hypertension Study (BRIGHT) | No | 1855 |
|  |  |  |  | Switzerland | Bus Santé | No | 4670 |
|  |  |  |  | Italy | INGI-Carlantino | No | 499 |
|  |  |  |  | Italy | INGI-FVG | No | 1432 |
|  |  |  |  | Italy | INGI-CILENTO | No | 1147 |
|  |  |  |  | Germany | Cooperative Health Research in the Region of Augsburg (KORA) F3 | Yes (controls) | 1640 |
|  |  |  |  | Germany | KORA F4 | Yes (controls) | 1809 |
|  |  |  |  | Germany | LURIC Study | No | 2927 |
|  |  |  |  | Sweden | the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) | No | 945 |
|  |  |  |  | Germany | SHIP-Trend | Yes | 986 |
|  |  |  |  | UK | TwinsUK |  | 3965 |
|  |  |  |  |  |  |  |  |
|  | Magnesium | Serum Magnesium | Meyer18 | USA | ARIC | No | 8,122 |
|  |  |  |  | USA | FHS | No | 2,866 |
|  |  |  |  | Netherlands | RS | Yes | 4,378 |
|  |  |  |  |  |  |  |  |
|  | Phosphate | Serum Phosphorus | Kestenbaum19 | USA | CHS | No | 2,337 |
|  |  |  |  | USA | ARIC | No | 8,122 |
|  |  |  |  | USA | FHS | No | 2,865 |
|  |  |  |  | Netherlands | RS | Yes | 3,516 |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| Microminerals | Iron | Serum Iron & Ferritin | Benyamin20 | Australia | Queensland Institute of medical research (QIMR) | Yes | 11,692 |
|  |  |  |  | Estonia | Estonian Genome Project | No | 893 |
|  |  |  |  | Italy | Val Borbera Study | No | 1,659 |
|  |  |  |  | Netherlands | Nijmegen Biomedical Study | No | 1,791 |
|  |  |  |  | UK | UK Blood Services Common Controls Panel | Yes (controls) | 2,419 |
|  |  |  |  | Italy | Micros/ Eurac | No | 1,218 |
|  |  |  |  | Netherlands | ERF/ Rotterdam | Yes | 871 |
|  |  |  |  | Germany | Kora F3/ F4 | Yes (controls) | 3,443 |
|  |  |  |  | Australia | Busselton Health Study | No | 877 |
|  |  |  |  | Estonia | Estonian Genome Project | No | 1,017 |
|  |  |  |  | Italy | InCHIANTI | No | 1,206 |
|  |  |  |  | Sardinia | SardiNIA study of Aging | No | 4,694 |
|  |  |  |  | Switzerland | CoLaus | Yes | 5,419 |
|  |  |  |  | Netherlands | Prevention of Renal and Vascular Endstage Disease (PREVEND) | No | 3,644 |
|  |  |  |  | UK | Fenland | No | 1,402 |
|  |  |  |  | France, Italy, Spain, UK, Netherlands, Germany, Sweden, Denmark | INTERACT | No | 9,294 |
|  |  |  |  |  |  |  |  |
|  | Copper | Erythrocyte Copper | Evans21 | Australia | QIMR | Yes | 2,603 |
|  |  |  |  |  |  |  |  |
|  | Manganese | Serum Manganese | Ng22 | Sweden | PIVUS | No | 949 |
|  | Selenium | Serum Selenium | Evans21 | Australia | QIMR | Yes | 2,603 |
|  |  |  |  | UK | Avon Longitudinal Study of Parents and Children (ALSPAC) | No | 2,874 |
|  | Zinc | Erythrocyte Zinc | Evans21 | Australia | QIMR | Yes | 2,603 |
|  |  |  |  |  |  |  |  |

### Supplementary Table S4: Micronutrient instruments used in analyses

SNP lists used in primary analyses are listed for each micronutrient; N = sample size; Chr = Chromosome P = p value for association; SNPs were mapped to genes using the GWAS catalog metadata or derived from original publications. Details of gene function were obtained from the National Library of Medicine (NLM) Gene database (<https://www.ncbi.nlm.nih.gov/gene/>). Genes encoding proteins directly related to the metabolism of each micronutrient (defined as processes related to micronutrient uptake, synthesis, transport, or degradation) were included in ‘functional’ sensitivity analyses and postfixed with an asterix\* in the gene column. Where the description given on the NLM Gene database did not clearly specify a physiological function with direct relevance to the metabolism of the specified micronutrient, biological pathways for the gene were cross-checked with the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway resource (<https://www.kegg.jp/kegg/>).23 Additional SNPs included in cIVW methods available on request from authors, or through the IEU Open GWAS <https://gwas.mrcieu.ac.uk>; GWAS id from the IEU Open GWAS is given in brackets: Vitamin D (*ebi-a-GCST005367*), copper (*ieu-a-1073*), selenium (*ieu-a-1077*) and zinc (*ieu-a-1079*).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Micronutrient | GWAS | N | SNP | P | Chr | gene |  | Function of gene with respect to micronutrient |
| Vitamin A (serum retinol) | Mondul 2011 | 9302 | rs10882272 | 6.51E-15 | 10 | RBP4\* | Retinol binding protein 4 | Encodes retinol binding protein, which delivers retinol from the liver stores to the peripheral tissues |
|  | 9302 | rs1667255 | 6.35E-14 | 18 | TTR\* | Transthyretin | Encodes transthyretin, which transports thyroid hormones in the plasma and cerebrospinal fluid. It is also involved in the transport of retinol (vitamin A) in the plasma by associating with retinol-binding protein. |
| Vitamin A (beta carotene) | Ferrucci 2009 | 3881 | rs6564851 | 1.6E-24 | 16 | BCO1\* | Beta-carotene oxygenase 1 | The protein encoded by this gene is a key enzyme in beta-carotene metabolism to vitamin A. It catalyzes the oxidative cleavage of beta,beta-carotene into two retinal molecules |
| Vitamin B6 | Tanaka 2009 | 1,864 | rs4654748 | 8.30E-18 | 1 | ALPL | Alkaline Phophatase | This gene encodes a member of the alkaline phosphatase family of proteins. The product of this gene is a membrane bound glycosylated enzyme that is not expressed in any particular tissue and is, therefore, referred to as the tissue-nonspecific form of the enzyme |
| Folate | Grarup 2013 | 37,465 | rs652197 | 1.40E-12 | 11 | FOLR3\* | Folate receptor gamma | Encodes a member of the folate receptor family of proteins, which mediate the delivery of 5-methylhydroolate to interior of cells |
|  |  | 37,337 | rs1801133 | 9.50E-53 | 1 | MTHFR\* | Methylenetetrahydrofolate reductase | Encodes a protein that catalyses the conversion of 5,10,methylenetetrahydrofolate to 5-methyltetrahydrofolate |
| Homocysteine | Van Meurs 2013 | 44,147 | rs1801133 | 4.34E-104 | 1 | MTHFR | Methylenetetrahydrofolate reductase | Catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a co-substrate for homocysteine remethylation to methionine |
|  |  |  | rs2275565 | 1.96E-10 | 1 | MTR | 5-methyltetrahydrofolate-homocysteine methyltransferase | Catalyzes the remethylation of homocysteine to methionine |
|  |  |  | rs9369898 | 2.17E-10 | 6 | MMUT | Methylmalonyl-CoA mutase | A vitamin B12-dependent enzyme which catalyzes the isomerization of methylmalonyl-CoA to succinyl-CoA |
|  |  |  | rs7130284 | 1.88E-20 | 11 | NOX4 | NADPH oxidase 4 | An oxygen sensor that catalyzes the reduction of molecular oxygen to various reactive oxygen species. |
|  |  |  | rs154657 | 1.74E-43 | 16 | DPEP1 | Dipeptidase 1 | Kidney membrane enzyme that hydrolyzes a variety of dipeptides and is implicated in renal metabolism of glutathione and its conjugates |
|  |  |  | rs234709 | 3.90E-24 | 21 | CBS | Cystathione beta-synthase | Catalyzes the conversion of homocysteine to cystathionine, the first step in the trans-sulfuration pathway |
|  |  |  | rs548987 | 1.12E-08 | 6 | SLC17A3 | Solute carrier family 17, member 3 | The protein encoded by this gene is a voltage-driven transporter that excretes intracellular urate and organic anions from the blood into renal tubule cells. |
|  |  |  | rs42648 | 1.97E-08 | 7 | GTBP10 | GTP binding protein 1 | Small G proteins, such as GTPBP10, act as molecular switches that play crucial roles in the regulation of fundamental cellular processes such as protein synthesis, nuclear transport, membrane trafficking, and signal transduction |
|  |  |  | rs1801222 | 8.43E-10 | 10 | CUBN | Cubilin | A receptor for intrinsic factor-vitamin B12 complexes |
|  |  |  | rs2251468 | 1.28E-12 | 12 | HNF1A | HNF homeobox A | A transcription factor required for the expression of several liver-specific genes |
|  |  |  | rs838133 | 7.48E-09 | 19 | FUT2 | Fucosyltransferase 2 | This gene is one of two encoding the galactoside 2-L-fucosyltransferase enzyme. The encoded protein is important for the final step in the soluble ABO blood group antigen synthesis pathway. It is also involved in cell-cell interaction, cell surface expression, and cell proliferation. |
|  |  |  | rs12780845 | 7.80E-10 | 10 | CUBN | Cubilin | A receptor for intrinsic factor-vitamin B12 complexes |
| Vitamin B12 | Grarup 2013 | 45,575 | rs2336573 | 8.40E-59 | 19 | CD320\* | CD320 molecule | This gene encodes the transcobalamin receptor that is expressed at the cell surface. It mediates the cellular uptake of transcobalamin bound cobalamin (vitamin B12). |
|  | 45,575 | rs1131603 | 4.90E-49 | 22 | TCN2\* | Transcobalamin 2 | This gene encodes a member of the vitamin B12-binding protein family. This plasma protein binds cobalamin and mediates the transport of cobalamin into cells. |
|  | 45,571 | rs3742801 | 1.70E-13 | 14 | ABCD4\* | ATP binding cassette subfamily D member 4 | The protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. Lysosomal membrane protein that transports cobalamin (Vitamin B12) from the lysosomal lumen to the cytosol in an ATP-dependent manner |
|  | 45,576 | rs2270655 | 2.20E-13 | 4 | MMAA\* | Metabolism of cobalamin associated A | Involved in translocation of vitamin B-12 into the mitochondria |
|  | 45,576 | rs34324219 | 1.10E-111 | 11 | TCN1\* | Transcobalamin 1 | This gene encodes a member of the vitamin B12-binding protein family, which facilitates the transport of cobalamin into cells. |
|  | 45,575 | rs7788053 | 1.70E-10 | 19 | FUT6 | Fucosyltransferase 6 | The protein encoded by this gene is a Golgi stack membrane protein |
|  | 45,568 | rs602662 | 2.40E-139 | 19 | FUT2 | Fucosyltransferase 2 | As above |
|  | 45,576 | rs1801222 | 3.30E-75 | 10 | CUBN\* | Cubilin | Cubilin (CUBN) acts as a receptor for intrinsic factor-vitamin B12 complexes. Cubulin is located within the epithelium of intestine and kidney. |
|  | 45,576 | rs41281112 | 8.90E-35 | 13 | CLYBL\* | Citramalyl-CoA lyase | Enables (S)-citramalyl-CoA lyase activity; magnesium ion binding activity; and malate synthase activity. Involved in protein homotrimerization and regulation of cobalamin metabolic process. |
|  | 45,574 | rs1141321 | 3.60E-26 | 6 | MMUT | Methylmalonyl-CoA mutase | Vitamin B-12 dependent enzyme |
| Vitamin C | Zheng 2021 | 52,018 | rs6693447 | 6.25E-10 | 1 | RER1 | Rhodopsin enhancer region | A conserved regulatory region upstream of the rhodopsin (RHO) gene, thought to bind retina-specific transcription factors |
|  |  |  | rs13028225 | 2.38E-30 | 2 | SLC23A3 | Solute carrier family 23 member 3 | Predicted to enable transmembrane transporter activity. |
|  |  |  | rs33972313 | 4.61E-90 | 5 | SLC23A1\* | Solute carrier family 23 member 1 | Encodes one of the two sodium-dependent vitamin C transporters used to transport vitamin C into the body and its distribution to organs |
|  |  |  | rs10051765 | 3.64E-09 | 5 | RGS14 | Regulator of G protein signalling | Encodes a member of the regulator of G-protein signaling family |
|  |  |  | rs7740812 | 1.88E-09 | 6 | GSTA5 | Glutathione S-transferase alpha 5 | Encodes glutathione S-transferase (GST)-α5, which catalyzes the conjugation of reduced glutathiones and a variety of electrophiles |
|  |  |  | rs174547 | 3.84E-08 | 11 | FADS1 | Fatty acid Desaturase 1 | Encodes fatty acid desaturase enzyme. |
|  |  |  | rs117885456 | 1.70E-11 | 12 | SNRPF | small nuclear ribonucleoprotein polypeptide F | Unclear relevance to vitamin C metabolism |
|  |  |  | rs2559850 | 6.30E-20 | 12 | CHPT1 | Choline phosphotransferase 1 | Enables diacylglycerol cholinephosphotransferase activity. |
|  |  |  | rs10136000 | 1.33E-08 | 14 | AKT1 | AKT serine/threonine kinase 1 | Encodes AKT serine-thronine protein kinase family. |
|  |  |  | rs56738967 | 7.62E-10 | 16 | MAF | MAF bZIP transcription factor | The protein encoded by this gene is a DNA-binding, leucine zipper-containing transcription factor |
| Vitamin D | Jiang 2018 | 42,274 | rs3755967 | 4.74e-343 | 4 | GC\* | GC vitamin binding protein | The protein encoded by this gene binds to vitamin D and its plasma metabolites and transports them to target tissues. |
|  |  |  | rs10741657 | 2.05E-46 | 11 | CYP2R1\* | Cytochrome P450 family 2 subfamily R member 1 | Encodes and enzyme that catalyzes vitamin D into the active form |
|  |  |  | rs12785878 | 3.8E-62 | 11 | NADSYN1/DHCR7\* | Cytochrome P450 family 2 subfamily R member 1 | This enzyme is a microsomal vitamin D hydroxylase that converts vitamin D into the active ligand for the vitamin D receptor. |
|  |  |  | rs10745742 | 1.88E-14 | 12 | AMDHD1 | amidohydrolase domain containing 1 | Predicted to enable imidazolonepropionase activity. Predicted to be involved in histidine catabolic process. |
|  |  |  | rs8018720 | 4.72E-09 | 14 | SEC23A | SEC23 homolog A | Encodes a protein found in the ribosome-free transitional face of the endoplasmic reticulum (ER) and associated vesicles. |
|  |  |  | rs17216707 | 8.14E-23 | 20 | CYP24A1\* | Cytochrome p450 family 24 subfamily A member 1 | Mitochondrial protein that initiates the degradation of the physiologically active form (hormonal form) of vitamin D, playing a role in calcium and vitamin D homeostasis |
| Calcium | O'Seaghada 2013 | 61,054 | rs1801725 | 8.90E-86 | 3 | CASR\* | Calcium sensing receptor | Encodes a membrane G coupled calcium sensing receptor that senses small changes in calcium and maintains homeostasis through intracellular signalling pathways and parathyroid hormone secretion |
|  |  | 60,958 | rs780094 | 1.30E-10 | 2 | GCKR | Glucokinase regulator | Encodes glucokinase regulator, which plays a role in glucose homeostasis, but has multiple metabolic roles including of liver enzymes, amino acids and serum albumin |
|  |  | 60,040 | rs10491003 | 4.80E-09 | 10 | GATA3 | GATA binding protein 3 | GATA3 encodes a transcription factor involved in parathyroid gland development, therefore calcium homeostasis |
|  |  | 61,011 | rs7481584 | 1.20E-10 | 11 | CARS1 | Cysteinyl-tRNA synthetase | Encodes a cysteinyl-tRNA synthetase. Variants in this region lead to Beckwith-Wiedmann syndrome, associated with hypocalcemia and hypercalciuria |
|  |  | 60,928 | rs7336933 | 9.10E-10 | 13 | DGKH/KIAA0564 | Diacylglycerol kinase eta | Encodes diacylglycerol kinase eta, which is involved in regulating intracellular diacylglycerol and phophatidic acid. Variants in this gene have been associated with bipolar disorder |
|  |  | 60,966 | rs1570669 | 9.10E-12 | 20 | CYP24A1 | Cytochrome p450 family 24 subfamily A member 1 | Mitochondrial protein that initiates the degradation of the physiologically active form (hormonal form) of vitamin D, playing a role in calcium and vitamin D homeostasis |
|  |  |  |  |  |  |  |  |  |
| Copper | Evans 2013 | 2,603 | rs1175550 | 5.03E-10 | 1 | SMIM1 | small integral membrane protein 1 | Encodes a protein involved in red blood cell formation |
|  |  |  | rs2769264 | 2.63E-20 | 1 | SELENBP1 | selenium binding protein 1 | Encodes selenium binding protein. Uncertain role in copper metabolism |
| Ferritin | Benyamin 2014 | 48,972 | rs1800562 | 1.54E-38 | 6 | HFE | Homeostatic iron regulator | Encodes a protein that regulates iron absorption. Hereditary haemochromatosis is a recessive disorder resulting from defects in this gene |
|  |  |  | rs855791 | 1.38E-14 | 22 | TMPRSS6 | Transmembrane serine protease 6 | The protein encoded by this gene is a type II transmembrane serine proteinase that is found attached to the cell surface. |
|  |  |  | rs744653 | 8.37E-19 | 2 | SLC40A1 | Solute carrier family 40 member 1 | SLC40A1 is a cell membrane protein involved in iron export from duodenal epithelial cells. Defects in SLC40A1 are a cause of hemochromatosis type 4 |
|  |  |  | rs651007 | 1.31E-08 | 9 | ABO | alpha 1-3-galactosyltransferase | Encodes proteins related to ABO blood system |
|  |  |  | rs411988 | 1.59E-10 | 17 | TEX14 | Testis expressed 14, intracellular bridge forming factor | Encodes protein necessary for intercellular bridges in germ cells, which are required for spermatogenesis. Unclear relevance for iron homeostasis. |
| Iron | Benyamin 2014 | 48,972 | rs1800562 | 2.72E-97 | 6 | HFE\* | Homeostatic iron regulator | As above |
|  |  |  | rs1799945 | 1.10E-81 | 6 | HFE\* | Homeostatic iron regulator | As above |
|  |  |  | rs855791 | 1.32E-139 | 22 | TMPRSS6 | Transmembrane serine protease 6 | As above |
|  |  |  | rs8177240 | 6.65E-20 | 3 | TF\* | Transferrin | As above |
|  |  |  | rs7385804 | 1.36E-18 | 7 | TFR2\* | Transferrin receptor 2 | As above |
| Magnesium | Meyer 2010 | 15,366 | rs4072037 | 2.01E-36 | 1 | MUC1 | Mucin 1, cell surface associated | Unclear relevance for magnesium homeostasis. Involved in forming protective mucous barriers on epithelial surfaces, and have a role in intracellular signaling |
|  |  |  | rs13146355 | 6.27E-13 | 4 | SHROOM3 | Shroom family member 3 | Encodes protein that may regulate cell types in certain tissues. Involved in neural tube closure |
|  |  |  | rs11144134 | 8.21E-15 | 9 | TRPM6\* | Transient receptor potential cation channel subfamily M member 6 | Encodes a TRP ion channel subunit which mediates magnesium reuptake in kidneys |
|  |  |  | rs3925584 | 5.20E-16 | 11 | DCDC5 | doublecortin domain containing 5 | Unclear relevance for magnesium physiology |
|  |  |  | rs448378 | 1.25E-08 | 3 | MDS1 | Myelodysplasia syndrome 1 | Unclear relevance for magnesium physiology |
| Manganese | Ng 2015 | 949 | rs1776029 | 2.17E-14 | 1 | SLC30A10\* | Solute carrier family 30 member 10 | This gene plays a critical role in manganese transport and is induced by manganese in the liver |
|  |  |  | rs13107325 | 5.08E-11 | 4 | SLC39A8\* | Solute carrier family 39 member 8 | Encodes a protein found in plasma membrane and mitochondria involved in the cellular transport of zinc and manganese |
| Phosphorus | Kestenbaum 2010 | 21,726 | rs1697421 | 3.47E-16 | 1 | ALPL\* | Alkaline Phosphatase | Encodes a membrane bound enzyme that hydrolyses pyrophosphate into phosphate in cells. Rare mutations in this gene linked to hypophophatasia with failure to mineralize teeth and bone |
|  |  |  | rs17265703 | 6.26E-08 | 3 | CSTA | Cystatin A | Unclear relevance |
|  |  |  | rs9469578 | 5.15E-10 | 6 | IHPK3 | Inositol hexakisphosphate kinase 3 | Encodes a protein that belongs to the inositol phosphokinase (IPK) family. This protein is likely responsible for the conversion of inositol hexakisphosphate (InsP6) to diphosphoinositol pentakisphosphate (InsP7/PP-InsP5). |
|  |  |  | rs947583 | 2.19E-09 | 6 | PDE7B | Phosphodiesterase 7B | Hydrolyzes cAMP, which regulates many important physiological processes. May be involved in the control of cAMP-mediated neural activity and cAMP metabolism in the brain. Gene variants appear associated with Dyslexia |
|  |  |  | rs2970818 | 4.04E-08 | 12 | FGF6 | Fibroblast growth factor 6 | Plays an important role in the regulation of cell proliferation, cell differentiation, angiogenesis and myogenesis, and is required for normal muscle regeneration |
| Selenium | Evans 2013 | 2,603 | rs921943 | 9.40E-28 | 5 | DMGDH/ BHMT2 | Dimethylglycine dehydrogenase/ betaine-homocysteine S-methyltransferase 2 | Exact relevance to selenium status unclear. DMGDH encodes enzymes involved in choline catabolism. BHMT2 is one of two methyl transferases that can catalyze the transfer of the methyl group from betaine to homocysteine. |
|  |  |  |  |  |  |  |  |  |
| Zinc | Evans 2013 | 2603 | rs1532423 | 6.40E-12 | 8 | CA1 | Carbonic anhydrase 1 | Carbonic Anhydrases are a large family of zinc containing enzymes that catalyse the reversible hydration of carbon dioxide |
|  |  |  | rs2120019 | 1.55E-18 | 15 | PPCDC | Phosphopantothenoylcysteine decarboxylase | Protein coding gene involved in biosynthesis of coenzyme A (CoA) from vitamin B5, involved in multiple metabolic processes. |

### Supplementary Table S5: Heterogeneity Statistics for MR analyses

Heterogeneity statistics for each MR analysis is given below: number of SNPs in analysis (nSNPs); percentage of variance explained in exposure for primary analyses (R2), mean F statistic (mFc); I2 statistic (I2), Cochran’s Q, Rucker’s Q and Egger intercept, with p values in brackets.

clumping threshold (r2, either 0.001 for traditional analyses, and 0.2 for correlated analyses). As none of the analyses had SNPs removed after Steiger filtering, the results are equivalent.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  | **MAJOR DEPRESSIVE DISORDER** | | |  | **RECURRENT DEPRESSION** | | |
|  |  | **nSNPs** | **R2** | **r2** | **mFc** | **I2** |  | **Cochrans Q (p)** | **Ruckers Q (p)** | **Egger Int (p)** |  | **Cochrans.Q.p.** | **Ruckers.Q.p.** | **Egger.Intercept..p.** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Water Soluble Vitamins | **Vitamin B6** | 1 | 1.5% | NA | 27 | NaN |  | NA (NA) | NA (NA) | NA (NA) |  | NA (NA) | NA (NA) | NA (NA) |
| **Vitamin B9** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Folate* | 2 | 0.6% | 0.001 | 620 | 0.94 |  | NA (NA) | NA (NA) | NA (NA) |  | NA (NA) | NA (NA) | NA (NA) |
| *Homocysteine* | 12 | 2.8% | 0.001 | 101 | 0.99 |  | 29 (0.003) | 28 (0.002) | -0.002 (0.70) |  | 13 (0.32) | 12 (0.26) | -0.004 (0.81) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Vitamin B12** | 9 | 5.4% | 0.001 | 192 | 0.98 |  | 17 (0.03) | 17 (0.02) | 0.0028 (0.73) |  | 10 (0.25) | 7 (0.47) | 0.03 (0.1) |
| *Functional* | *7* | 3.7% | 0.001 | 159 | 0.98 |  | 16 (0.01) | 16 (0.01) | 0.005 (0.69) |  | 7 (0.28) | 3 (0.76) | 0.04 (0.08) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **VitaminC** | 11 | 1.8% | 0.001 | 85 | 0.97 |  | 21 (0.02) | 14 (0.12) | 0.008 (0.06) |  | 20 (0.026) | 20 (0.016) | 1.3e-05 (1) |
| *Functional* | *1* | 0.8% | NA | 400 | NaN |  | NA (NA) | NA (NA) | NA (NA) |  | NA (NA) | NA (NA) | NA (NA) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fat soluble vitamins | ***Vitamin A*** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Retinol* | 2 | 0.1% | 0.001 | 56 | 0.99 |  | NA (NA) | NA (NA) | NA (NA) |  | NA (NA) | NA (NA) | NA (NA) |
| *Beta carotene* | 1 | 1.1% | 0.001 | 99 | NaN |  | NA (NA) | NA (NA) | NA (NA) |  | NA (NA) | NA (NA) | NA (NA) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Vitamin D** | 6 | 3.6% | 0.001 | 169 | 0.98 |  | 2 (0.8) | 2 (0.68) | -0.0003 (0.95) |  | 2 (0.79) | 2 (0.68) | 0.004 (0.79) |
| *Functional* | *4* | 3.4% | 0.001 | 234 | 0.99 |  | 2 (0.54) | 2 (0.38) | -0.003 (0.69) |  | 1 (0.69) | 1 (0.5) | -0.006 (0.8) |
| *Correlated* | *29* |  | 0.2 | 296 |  |  | 44 (0.03) | 31 (0.27) | 1.01 (<0.001) |  | 35 (0.16) | 35 (0.14) | 1 (0.47) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Macrominerals | **Serum Calcium** | 7 | 0.2% | 0.001 |  | 74 | 0.96 |  | 23 (0.001) | 18 (0.003) | -0.01 (0.27) |  | 9 (0.17) | 8 (0.14) | 0.01 (0.52) |
| *Functional* | *1* | 0.1% | 0.001 |  | 315 | NaN |  | NA (NA) | NA (NA) | NA (NA) |  | NA (NA) | NA (NA) | NA (NA) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Magnesium** | 5 | 2.2% | 0.001 |  | 60 | 0.9 |  | 9 (0.07) | 5 (0.14) | -0.01 (0.27) |  | 7 (0.15) | 4 (0.24) | -0.04 (0.27) |
| *Functional* | *1* | 0.4% | NA |  | 121 | NaN |  | NA (NA) | NA (NA) | NA (NA) |  | NA (NA) | NA (NA) | NA (NA) |
| *Correlated* | *7* |  | 0.2 |  | 48 |  |  | 10 (0.15) | 9 (0.11) | 0.99 (0.56) |  | 7 (0.31) | 5 (0.42) | 0.96 (0.14) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Phosphate** | 5 | 1.2% | 0.001 |  | 40 | 0.98 |  | 4 (0.44) | 4 (0.29) | -0.003 (0.87) |  | 4 (0.45) | 4 (0.32) | -0.02 (0.75) |
| *Functional* | *1* | 0.4% | 0.2 |  | 67 | NaN |  | NA (NA) | NA (NA) | NA (NA) |  | NA (NA) | NA (NA) | NA (NA) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Microminerals | **Copper** | 2 | 5.3% | 0.001 |  | 62 | 0.99 |  | NA (NA) | NA (NA) | NA (NA) |  | NA (NA) | NA (NA) | NA (NA) |
|  |  |  | 0.2 |  | 378 |  |  | 4 (0.66) | 4 (0.54) | 1 (0.98) |  | 4 (0.64) | 4 (0.59) | 0.98 (0.46) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Ferritin** | 6 | 1.2% | 0.001 |  | 69 | 0.98 |  | 5 (0.41) | 2 (0.67) | 0.01 (0.18) |  | 4 (0.57) | 4 (0.42) | 0.001 (0.94) |
| *Correlated* | *6* |  | 0.2 |  | 41 |  |  | 5 (0.37) | 4 (0.47) | 1.01 (0.18) |  | 4 (0.51) | 4 (0.37) | 1 (0.81) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Iron** | 4 | 3.3% | 0.001 |  | 315 | 1 |  | 4 (0.22) | 4 (0.13) | -0.003 (0.70) |  | 1 (0.72) | 0 (0.79) | -0.02 (0.45) |
| *Functional* | *4* | 2.6% | 0.001 |  | 237 | 1 |  | 4 (0.28) | 3 (0.18) | -0.003 (0.67) |  | 1 (0.82) | 1 (0.77) | -0.01 (0.60) |
| *Correlated* | *31* |  | 0.2 |  | 140 |  |  | 101 (<0.001) | 101 (7.5e-10) | 1 (0.79) |  | 34 (0.29) | 34 (0.25) | 1 (0.72) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Manganese** | 2 | 11.0% | 0.001 |  | 50 | 0.81 |  | NA (NA) | NA (NA) | NA (NA) |  | NA (NA) | NA (NA) | NA (NA) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Selenium** | 1 | 2.5% | NA |  | 119 | NaN |  | NA (NA) | NA (NA) | NA (NA) |  | NA (NA) | NA (NA) | NA (NA) |
| *Correlated* | *7* |  | 0.2 |  | 109 |  |  | 4 (0.55) | 1 (0.85) | 1.02 (0.10) |  | 3 (0.63) | 3 (0.55) | 1.03 (0.54) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Zinc** | 2 | 4.2% | 0.001 |  | 61 | 0.99 |  | NA (NA) | NA (NA) | NA (NA) |  | NA (NA) | NA (NA) | NA (NA) |
| *Correlated* | *7* |  | 0.2 |  | 225 |  |  | 16 (0.01) | 15 (0.01) | 1 (0.59) |  | 7 (0.32) | 5 (0.43) | 0.98 (0.14) |

### Supplementary Table S6: Table containing SEIVW/SEcIVW ratios for relevant micronutrients.

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Major Depressive Disorder  (n=430,775)  SEIVW  /SEcIVW | Recurrent Depression  (n= 80,933)  SEIVW  /SEcIVW |
|  |  |  |  |
| Vitamin D |  | 1.59 | 2.36 |
| Iron |  | 1.58 | 2.03 |
| Ferritin |  | 1.31 | 0.96 |
| Magnesium |  | 1.13 | 1.44 |
| Copper |  | 2.63 | 3.06 |
| Selenium |  | 2.32 | 2.63 |
| Zinc |  | 1.16 | 3.38 |
|  |  |  |  |

The table below provides ratios of standard errors for each micronutrient/ outcome set. MR estimates derived using correlated MR methods should not be ‘strikingly more precise’ than the estimates derived using uncorrelated variants.24 Correlated MR estimates with standard errors 2-3 times smaller than the estimate using non-correlated instruments should be checked carefully. In particular, as estimates are highly dependent on the LD matrix, this must reflect the population ancestry of the exposure/ outcome GWAS samples.24 The harmonized exposure/ outcome alleles also need to be aligned with the alleles in the LD matrix as this can also bias results. Although the precision for several of the analyses was much higher than for the uncorrelated analyses, the consistency between effect estimates between traditional and correlated MR is reassuring.

### Supplementary Table S7: Heterogeneity analyses for reverse MR analyses

Heterogeneity statistics for reverse MR analyses, in which MDD is treated as the exposure, and the micronutrient as the outcome. Results on the left are prior to Steiger filtering, with the results on the right after Steiger filtering. The clumping threshold for traditional analyses (r2) is 0.001, but for cIVW this is relaxed to 0.2. The columns include number of SNPs in analysis (nSNPs); mean F statistic (mFc); percentage of variance explained in exposure (R2), I2 statistic (I2), Cochran’s Q, Rucker’s Q and Egger intercept, with p values in brackets. For cEgger analyses, obly intercept p values are given in the R readout, and hence the intercept value is not included.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Unfiltered** | | |  | |  | |  | |  | |  | |  | | **Steiger** | | **Filtered** | |  | |  | |
| **Outcome** | **r2** | **nSNPs** | **mFc** | **R2** | **I2** | | **Cochrans Q(p)** | | **Ruckers Q(p)** | | **Int (p)** | | **nSNPs** | | **mFc** | | **R2** | | **I2** | | **Cochrans Q(p)** | | **Ruckers Q(p)** | | **Int (p)** | |
|  |  |  |  |  |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |
| **Vitamin D** | <0.001 | 66 | 45 | *1.8%* | 0.98 | | 156 (0.002) | | 156 (0.002) | | -6E-04 (0.77) | | 53 | | 47 | | *1.5%* | | 0.98 | | 37(0.94) | | 37(0.93) | | 0.001 (0.55) | |
|  | <0.2 | 110 | 43 | *2.9%* | 0.98 | | 189 (3E-6) | | 188 (3E-6) | | (0.41) | | 91 | | 44 | | *2.4%* | | 0.98 | | 103 (0.17) | | 102 (0.2) | | (0.47) | |
|  |  |  |  |  |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |
| **Magnesium** | <0.001 | 42 | 45 | *1.20%* | 0.98 | | 41(0.47) | | 40(0.47) | | -0.01(0.32) | | 26 | | 44 | | 0.70% | | 0.98 | | 5(1) | | 5(1) | | 0.01 (0.65) | |
|  | <0.2 | 60 | 43 | 1.60% | 0.98 | | 73 (0.1) | | 72 (0.1) | | (0.31) | | 36 | | 43 | | 0.9 | | 0.98 | | 8 (1) | | 8 (1) | | (0.91) | |
|  |  |  |  |  |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |
| **Copper** | <0.001 | 66 | 45 | 1.8% | 0.98 | | 50(0.92) | | 50(0.91) | | -0.003 (0.90) | | 15 | | 43 | | 0.4% | | 0.98 | | 0(1) | | 0(1) | | -0.02 (0.78) | |
|  | <0.2 | 110 | 43 | 2.90% | 0.98 | | 143 (0.02) | | 141 (0.02) | | (0.02) | | 27 | | 41 | | 0.70% | | 0.98 | | 1(1) | | 1(1) | | (0.79) | |
|  |  |  |  |  |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |
| **Iron** | <0.001 | 64 | 46 | 1.8% | 0.98 | | 57(0.65) | | 57(0.67) | | -0.01 (0.21) | | 46 | | 45 | | 1.3% | | 0.98 | | 17(1) | | 17(1) | | 0.004 (0.74) | |
|  | <0.2 | 107 | 43 | 2.8% | 0.98 | | 165 (2E-4) | | 163 (3E-4) | | (0.15) | | 71 | | 43 | | 1.9% | | 0.98 | | 29 (1) | | 29 (1) | | (0.75) | |
|  |  |  |  |  |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |
| **Ferritin** | <0.001 | 64 | 46 | 1.8% | 0.98 | | 56(0.71) | | 52(0.81) | | -0.02 (0.04) | | 48 | | 45 | | 1.3% | | 0.98 | | 11(1) | | 11(1) | | -0.004 (0.67) | |
|  | <0.2 | 104 | 43 | 2.70% | 0.98 | | 157 (5E-4) | | 145 (0.004) | | (0.001) | | 67 | | 43 | | 1.80% | | 0.98 | | 19(1) | | 19(1) | | (0.87) | |
|  |  |  |  |  |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  | |
| **Selenium** | <0.001 | 66 | 45 | *1.8%* | 0.98 | | 66 (0.45) | | 65 (0.44) | | -0.023 (0.34) | | 18 | | 45 | | 0.5% | | 0.98 | | 1 (1) | | 1 (1) | | -0.01 (0.85) | |
|  | <0.2 | 110 | 43 | 2.9% | 0.98 | | 172 (1E-4) | | 170 (4E-4) | | (0.18) | | 29 | | 44 | | 0.8% | | 0.98 | | 1 (1) | | 1 (1) | | (0.98) | |

**Supplementary Material**

### Supplementary Material S1: Supplementary Methods

#### 

#### Calculating variance (r2)

Variance explained in the exposure was calculated for each SNP using the formula:

2 x beta2x EAF x (1-EAF) / (2 x beta2 x EAF x (1-EAF) + SE2 x 2 x N x EAF x (1-EAF))

Where beta is the effect size of the SNP on the exposure, and SE is the corresponding standard error, EAF is the effect allele frequency and N is the sample size of the exposure GWAS. The variance for each SNP in the instrument was summed to provide the total variance overall for that instrument set.

For analyses using depression as an exposure (ie reverse MR), we used the TwoSampleMR package to approximate the R-squared statistic using the “get\_r\_from\_lor” function, with prevalence set at 10%. This result was squared to get the approximate r2.

#### 

#### Calculating F Statistics

F-statistics for each exposure were calculated using the formula:

F= (Σ r2/nSNP)/ ((1-Σ r2)/(N-nSNP-1))

Where Σ r2 is the sum of the variance explained in the exposure for each SNP, nSNP is the number of SNPs and N is the sample size of the exposure GWAS

### Supplementary Material S2: Individual Micronutrient MR plots

For each exposure, the following plots are shown:

i) Scatter plot showing how MR estimates compare between MR methods.

ii) Funnel plot depicting instrumental variable precision. The log(odds ratios) of each IV is plotted on the x-axis (βIV) against instrument strength on the y axis (1/ SEIV). Asymmetry may suggest directional pleiotropy.

iii) Forest plot showing individual SNP ratio estimates (SNP-outcome estimate / SNP-exposure estimate), and

iv) Leave one out plot showing inverse variance weighted (IVW) estimates after omitting each SNP

#### Water Soluble Vitamins

##### Serum Folate and Major Depressive Disorder (N=430,775)

A graph with a line and a point

Description automatically generated with medium confidenceA graph of a method

Description automatically generatedA graph with a red line

Description automatically generatedA grid of white squares

Description automatically generated

##### Serum Folate and Recurrent Depression (N= 80,933)

#### A graph with a line Description automatically generatedA graph with a line Description automatically generated

#### A graph with a red line Description automatically generatedA grid of white squares Description automatically generated

##### Serum homocysteine and Major Depressive Disorder (N=430,775)

A graph with lines and dots

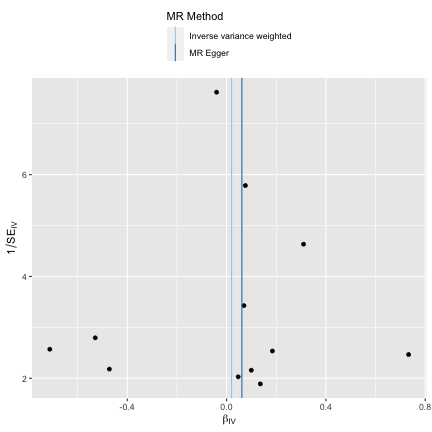
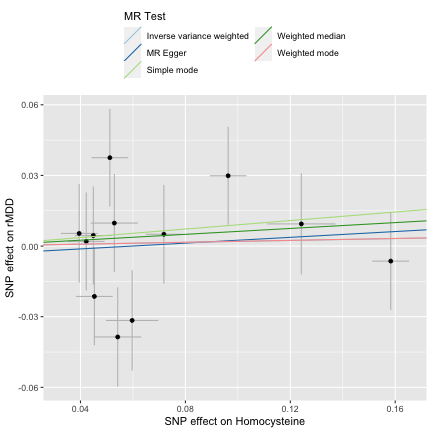
Description automatically generatedA graph with black dots and numbers

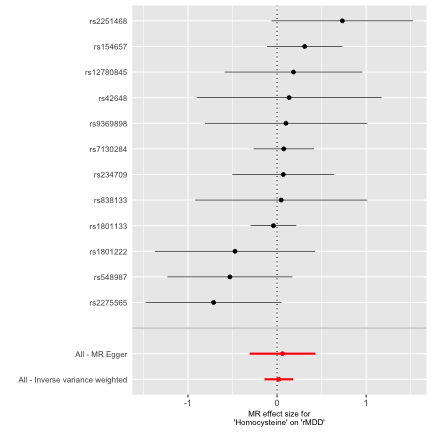
Description automatically generatedA graph with black and red lines

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Description automatically generated with medium confidence

##### Serum Homocysteine and Recurrent Depression (N= 80,933)



A graph with black and red lines

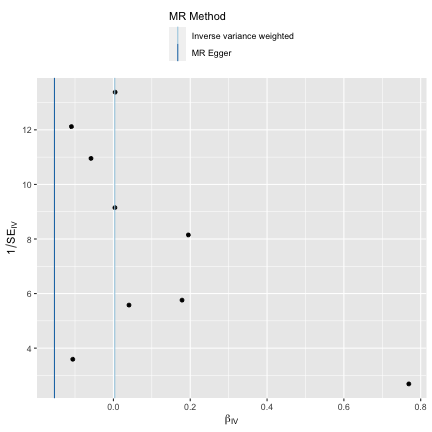
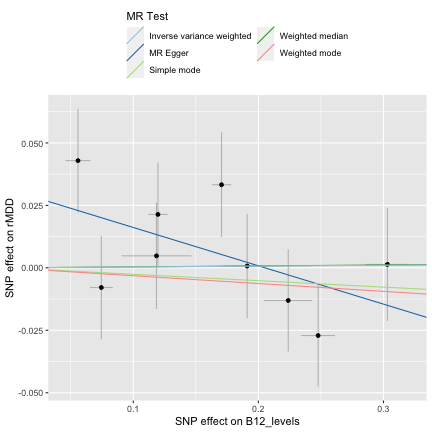
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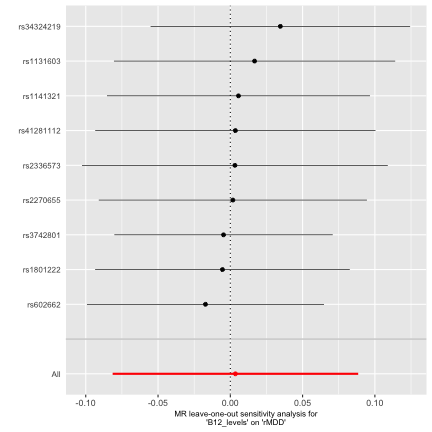
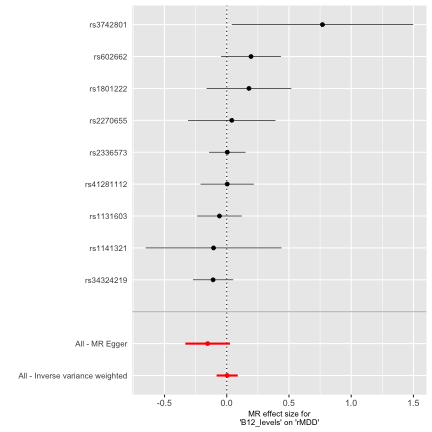
##### Serum B12 and Major Depressive Disorder (N=430,775)

#### A graph of a graph with lines and numbers Description automatically generated with medium confidenceA graph with black dots Description automatically generated

#### A graph with black and red lines Description automatically generatedA graph with black and red lines Description automatically generated

##### Serum B12 and Recurrent Depression (N= 80,933)

**

**

##### Vitamin C and Major Depressive Disorder (N=430,775)

A graph with lines and numbers

Description automatically generatedA graph with black dots

Description automatically generated

A graph with black and red lines

Description automatically generatedA graph with black and red lines

Description automatically generated

##### Vitamin C and Recurrent Depression (N= 80,933)

A graph with lines and numbers

Description automatically generatedA graph with black dots

Description automatically generated

A graph with black and red lines

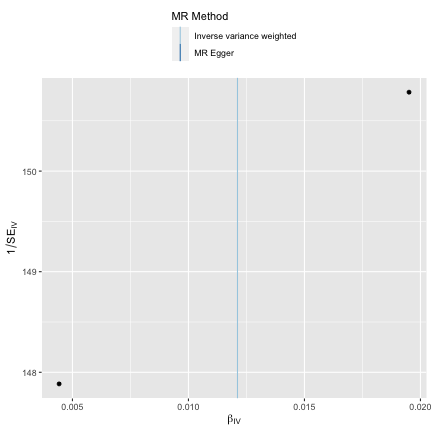
Description automatically generatedA graph with lines and dots

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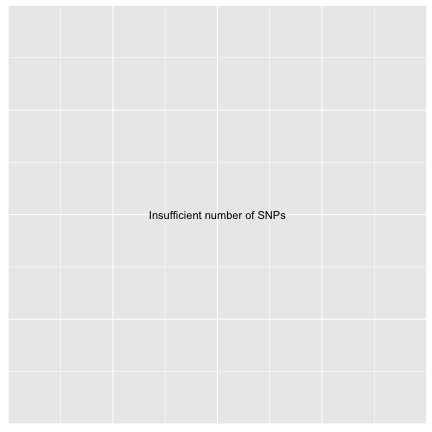
#### Fat Soluble Vitamins

##### Serum Retinol and Major Depressive Disorder (N=430,775)

A graph with a line

Description automatically generated

A graph with a red line

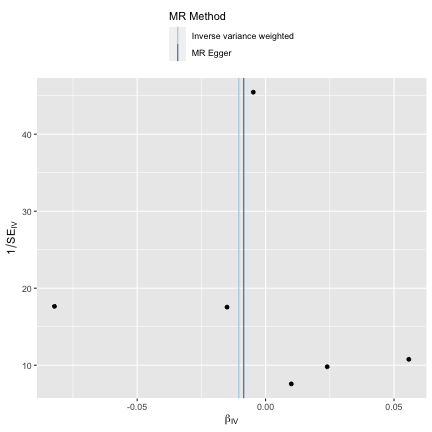
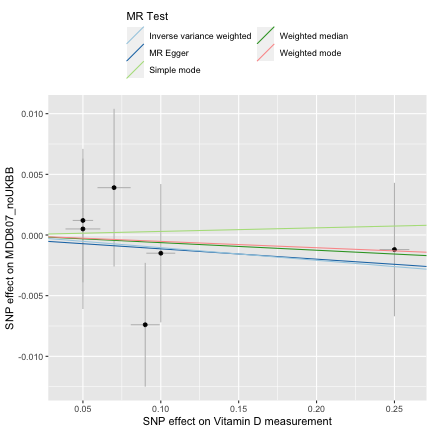
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##### Serum Retinol and Recurrent Depression (N= 80,933)

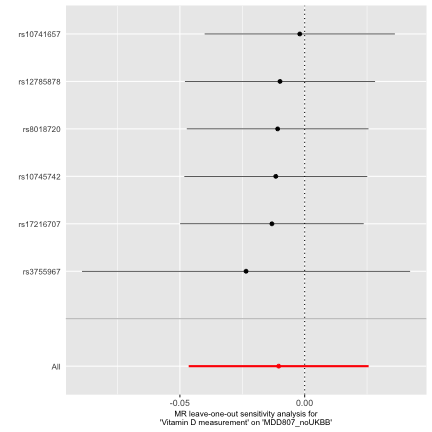
#### A graph with a line in the center Description automatically generatedA graph with numbers and lines Description automatically generated

#### A graph with a red line Description automatically generatedA grid of white squares Description automatically generated

##### Serum 25 (OH) Vitamin D and Major Depressive Disorder (N=430,775)

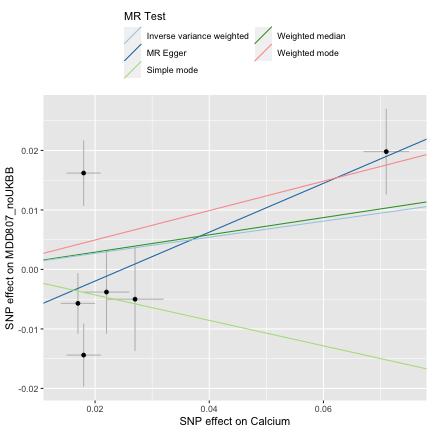


A graph with lines and dots

Description automatically generated

#### Macrominerals

##### Calcium and Major Depressive Disorder (N=430,775)

A graph of a method

Description automatically generated

A graph with lines and dots

Description automatically generatedA graph with black and red lines

Description automatically generated

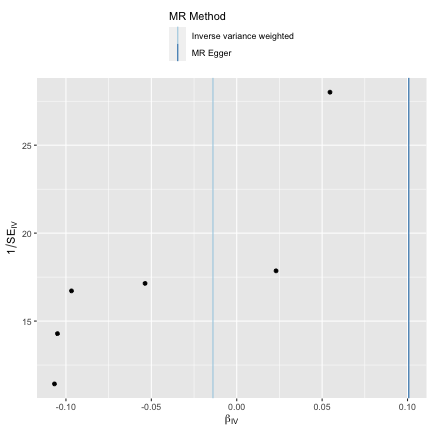
##### Calcium and Recurrent Depression (N= 80,933)

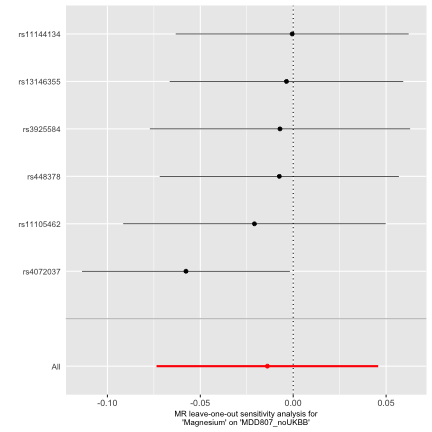
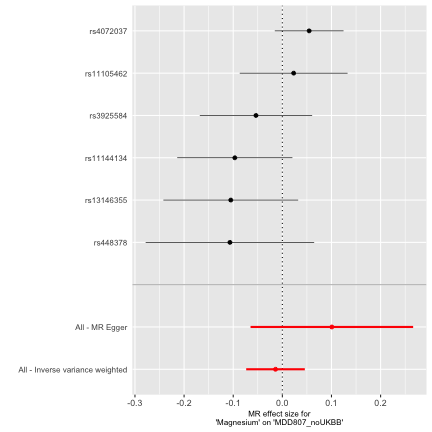
#### A graph with lines and numbers Description automatically generatedA graph with lines and numbers Description automatically generated

#### A graph with lines and numbers Description automatically generatedA graph with black and red lines Description automatically generated

##### Serum Magnesium and Major Depressive Disorder (N=430,775)

A graph of different colors and lines

Description automatically generated with medium confidence



##### Serum Magnesium and Recurrent Depression (N= 80,933)

A graph with lines and numbers

Description automatically generatedA graph of a graph

Description automatically generated

A graph with a red line

Description automatically generatedA graph with black and red lines

Description automatically generated

##### Phosphate and Major Depressive Disorder (N=430,775)

A graph with lines and numbers

Description automatically generatedA graph with numbers and lines

Description automatically generated

A graph with lines and dots

Description automatically generatedA graph with black and red lines

Description automatically generated

##### Phosphate and Recurrent Depression (N= 80,933)

A graph with lines and numbers

Description automatically generatedA graph with black dots and white squares

Description automatically generated

A graph with lines and dots

Description automatically generatedA graph with lines and dots

Description automatically generated

#### Microminerals

##### Serum Iron and Major Depressive Disorder (N=430,775)

A graph with different colored lines

Description automatically generatedA graph with numbers and lines

Description automatically generated

A graph with a red line

Description automatically generatedA graph with black and red lines

Description automatically generated

##### Serum Iron and Recurrent Depression (N= 80,933)

A graph of different colors and lines

Description automatically generated with medium confidenceA graph with black dots and white lines

Description automatically generated

A graph with a red line and black line

Description automatically generatedA graph with black and red lines

Description automatically generated

##### Serum Ferritin and Major Depressive Disorder (N=430,775)

A graph of a graph with different colored lines

Description automatically generated with medium confidenceA graph with black dots and numbers

Description automatically generated

A graph with lines and dots

Description automatically generatedA graph with black and red lines

Description automatically generated

##### Serum Ferritin and Recurrent Depression (N= 80,933)

A graph with lines and numbers

Description automatically generatedA graph of a method

Description automatically generated

A graph with lines and dots

Description automatically generatedA graph with black and red lines

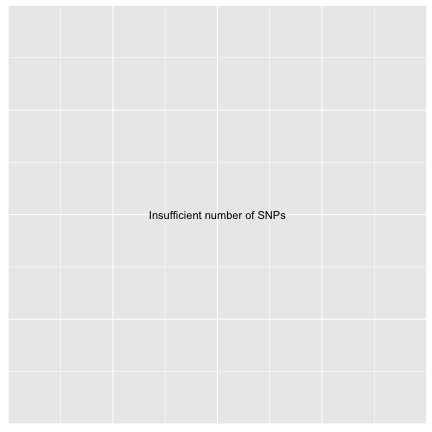
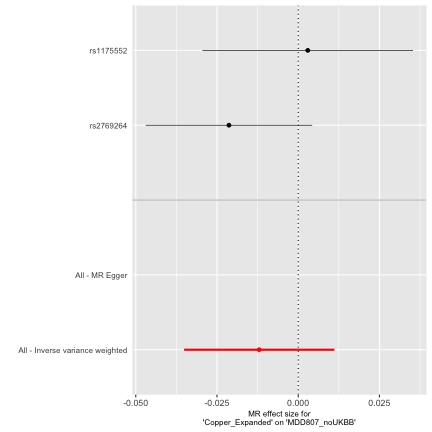
Description automatically generated

##### Erythrocyte Copper and Major Depressive Disorder (N=430,775)

A graph with a line

Description automatically generatedA graph of a method

Description automatically generated



##### Erythrocyte Copper and Recurrent Depression (N= 80,933)

#### A graph with a line and a line Description automatically generatedA graph with numbers and lines Description automatically generated

#### A graph with a red line Description automatically generatedA grid of white squares Description automatically generated

##### Serum Manganese and Major Depressive Disorder (N=430,775)

A graph with a line

Description automatically generatedA graph of a method

Description automatically generated

A graph with a red line

Description automatically generatedA grid of white squares

Description automatically generated

##### Serum Magnanese and Recurrent Depression (N= 80,933)

A graph with a line

Description automatically generatedA graph of a method

Description automatically generated

A graph with a red line

Description automatically generatedA grid of white squares

Description automatically generated

##### Serum Selenium and Major Depressive Disorder (N=430,775)

A graph with a line

Description automatically generatedA graph with numbers and letters

Description automatically generated

A graph with a red line

Description automatically generatedA grid of white squares

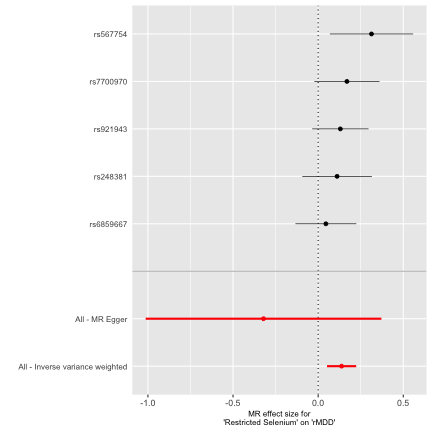
Description automatically generated

##### Serum Selenium and Recurrent Depression (N= 80,933)

A graph with lines and numbers

Description automatically generatedA graph with black dots

Description automatically generated

A graph with black and red lines

Description automatically generated

##### Erythrocyte Zinc and Major Depressive Disorder (N=430,775)

A graph with a line and a line

Description automatically generatedA graph with numbers and a white background

Description automatically generated with medium confidence

A graph with lines and dots

Description automatically generatedA grid of white squares

Description automatically generated

##### Erythrocyte Zinc and Recurrent Depression (N= 80,933)

A graph with a line

Description automatically generatedA graph with numbers and letters

Description automatically generated

A graph with lines and dots

Description automatically generatedA grid of white squares

Description automatically generated

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1. Results are given per SD change in exposure unless otherwise stated. p-values are included where in original publication [↑](#footnote-ref-1)
2. Original paper gives OR in terms of decrease in vitamin D levels, i.e., OR: 1.02 per SD decrease in vitamin D levels (95% confidence intervals: 0.97, 1.08) [↑](#footnote-ref-2)
3. Original paper gives OR in log odds ratio. OR converted from publication data: -0.02 (SE: 0.011) p=0.029 [↑](#footnote-ref-3)