Electronic Supplementary Materials

An atlas on risk factors for type 2 diabetes: a wide-angled Mendelian randomisation study

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**ESM Method**

**The review of risk factors in observational study**

Database: PubMed  
Time: Until January 10, 2020  
In total, 1360 papers  
Search strategy: (((((((Meta-Analysis[Publication Type]) OR meta-analysis[Title/Abstract]) OR meta analysis[Title/Abstract]) OR meta-analyses[Title/Abstract]) OR meta analyses[Title/Abstract]) OR Systematic Review[Publication Type]) OR systematic review[Title/Abstract])) AND ((Risk Factors[MeSH Terms]) OR risk factor[Title/Abstract])) AND (((Diabetes Mellitus, Type 2[MeSH Terms]) OR type 2 diabetes[Title/Abstract]) OR type 2 diabetes mellitus[Title/Abstract]))

We firstly deleted all replicates with the same study materials. Since we aimed to pinpoint the possible risk factors for type 2 diabetes (not a quantitative meta-analysis), we merely screened the title and abstract of the studies. The studies with the same topic were included once regardless of used materials (study base). Results from this review are presented below:

| Health status               | Nutrition                  | Lifestyle                     | Internal biomarker                          | Socioeconomic status and other factors                        |
|-----------------------------|----------------------------|-------------------------------|---------------------------------------------|--------------------------------------------------------------|
| Hidradenitis suppurativa    | Diet quality               | Coffee consumption            | Aldose reductase                            | Education                                                   |
| Obstructive sleep apnea     | Diet pattern               | Tea consumption               | Fasting glucose                             | Income                                                      |
| Polycystic ovary syndrome   | Dietary energy density     | Alcohol consumption           | Intercellular adhesion molecule-1           | Occupation (long work hours, job strain, workplace bullying and violence, shift work) |
| Alzheimer's disease         | Fatty acid consumption     | Smoking                       | High-mobility group A1                     | Exposure to air pollution                                   |
| Asthma                      | Protein consumption        | Smokeless tobacco (snus)      | Transforming growth factor-β1               | Exposure to environmental chemicals (organochlorine pollutants, arsenic, cadmium, mercury, phthalates and bisphenol A) |
| Psoriasis                   | Isoflavones & Flavonoids consumption | Daytime napping               | Thyroid-stimulating hormone & free thyroxine | Sun exposure                                                |
| Psoriatic arthritis         | Cholesterol consumption    | Sleep (duration & short sleep)| Triglycerides                              | Residential proximity to major roadways                     |
| Osteoarthritis              | Fibre consumption          | Circadian                     | High-density lipoprotein cholesterol       | Adverse childhood experience                               |
| Giant cell arteritis        | Polyphenols consumption    | Breakfast skipping            | Low-density lipoprotein cholesterol        | Food insecurity                                             |
| Dupuytren disease           | Insulinotropic amino acids consumption | Physical activity          | Total cholesterol                           | Cardiovascular drugs (Statin therapy)                       |
| Non-alcoholic Fatty Liver Disease | Peptides consumption   | Areca-nut chewing             | Serum alanine aminotransferase             | Depression treatment & Antipsychotics                        |
| Medical Condition                          | Dietary or Nutritional Factors | Biomarkers/Factors |
|------------------------------------------|-------------------------------|--------------------|
| Atopic dermatitis                        | Fructose consumption          | Intermittent fasting |
| Chronic toxoplasmosis                    | Sucrose consumption           |                    |
| Hypertriglyceridemia waist               | Resveratrol consumption       | Inflammation biomarker |
| Thyroid function                         | Antioxidants consumption      | TNF                |
| Bullous skin diseases                    | Potato consumption            | IL-1β              |
| Inflammatory bowel disease               | Yoghurt consumption           | C-reactive protein |
| Rheumatoid arthritis                     | Egg consumption               | IL-6               |
| Systemic autoimmune disorders            | Vegetable consumption (citrus and cruciferous) | IL-18 |
| Allergic rhinitis                        | Soy consumption               | IL-10              |
| Food allergies                           | Diary consumption             | Platelet mean volume, distribution width and count |
| Microalbuminuria                         | Pasta consumption             |                    |
| Microvascular dysfunction                | Nut consumption               | Sex-related factor |
| Acanthosis nigricans                     | Fried-food consumption        | Menopause          |
| Periodontitis                            | White rice consumption        | Age at menarche    |
| Gestational diabetes                     | Beverages consumption         | Premature ovarian insufficiency |
| Depression                               | Branched-chain amino acids    | Testosterone level  |
| Stress                                   | Homocysteine                  | Parity             |
| Anxiety                                  | Beta-carotene levels          | Steroid sex hormones |
| Anorexia nervosa                         | Folate (vitamin B9)           | Sex hormone-binding globulin |
| Schizophrenia                            | Vitamin B12                   | Breastfeeding      |
| Bipolar disorder                         | Vitamin C                     |                    |
| Insomnia                                 | 25-hydroxyvitamin D           |                    |
| Bulimia nervosa                          | Vitamin E                     |                    |
| Spousal diabetes status                  |                               |                    |
| Hepatitis C Virus infection              |                               |                    |
| Laparoscopic sleeve gastrectomy          |                               |                    |
| Bariatric surgery                        |                               |                    |
| Chronic toxoplasmosis                    |                               |                    |
| Hypertriglyceridemia waist               |                               |                    |
| Thyroid function                         |                               |                    |
| Bullous skin diseases                    |                               |                    |
| Inflammatory bowel disease               |                               |                    |
| Rheumatoid arthritis                     |                               |                    |
| Systemic autoimmune disorders            |                               |                    |
| Allergic rhinitis                        |                               |                    |
| Food allergies                           |                               |                    |
| Microalbuminuria                         |                               |                    |
| Microvascular dysfunction                |                               |                    |
| Acanthosis nigricans                     |                               |                    |
| Periodontitis                            |                               |                    |
| Gestational diabetes                     |                               |                    |
| Depression                               |                               |                    |
| Stress                                   |                               |                    |
| Anxiety                                  |                               |                    |
| Anorexia nervosa                         |                               |                    |
| Schizophrenia                            |                               |                    |
| Bipolar disorder                         |                               |                    |
| Insomnia                                 |                               |                    |
| Bulimia nervosa                          |                               |                    |
### Table

| Binge eating disorder          | Phylloquinone (vitamin K1) | Height       |
|-------------------------------|---------------------------|--------------|
| Systolic blood pressure       | Vitamin K2                | Hip circumference |
| ABO and Rh blood groups       | Arsenic                   | Waist circumference |
| Preterm birth                 | Calcium                   | Waist-to-hip ratio |
| Cardiorespiratory fitness     | Iron                      | Weight change |
| Telomere length               | Magnesium                 | Favourable adiposity |
| Resting heart rate            | Potassium                 | Childhood BMI |
|                               | Selenium                  | Leptin levels |
|                               | Zinc                      | Weight loss  |

### Review of Mendelian randomization studies

Database: PubMed  
Time: Until January 10, 2020  
In total, 238 papers  

Search strategy: (((((Mendelian randomization[Title/Abstract]) OR Mendelian randomisation[Title/Abstract]) OR instrumental variable causal inference[Title/Abstract]) OR causal inference using instrumental variable[Title/Abstract]) OR causal inference using genetic variants[Title/Abstract])) AND (((Diabetes Mellitus, Type 2[MeSH Terms]) OR type 2 diabetes mellitus[Title/Abstract]) OR type 2 diabetes[Title/Abstract])

There was no replicated MR study on the same topic. We screened all titles and abstracts of included studies. We then extracted data (data in ESM Table 1) by reading the whole text (all included studies at the stage of screening were studies included finally). The detailed information on included studies is shown in ESM Table 1.
## ESM Table 1. Published Mendelian randomisation studies of possible risk factors for type 2 diabetes

| Exposure                        | Outcome GWAS                              | PMID          | Year | SNPs | Cases   | Controls | OR    | 95% CI          | Unit                | Largest T2DM GWAS |
|---------------------------------|-------------------------------------------|---------------|------|------|---------|----------|-------|-----------------|---------------------|--------------------|
| **Health status**               |                                            |               |      |      |         |          |       |                 |                     |                    |
| Systolic blood pressure         | Morris AP et al, 2012                     | 27702834      | 2017 | 28   | 37293   | 125686   | 1.02  | 1.01-1.03       | 1 mmHg              | NO                 |
| Telomere length                 | Morris AP et al, 2012                     | 28241208      | 2017 | 11   | 10415   | 53655    | 1     | 0.84-1.20       | SD                  | NO                 |
| Resting heart rate              | Mahajan A et al, 2018                     | 31648709      | 2019 | Genetic score | 74124   | 824006   | 1.12  | 1.11-1.12       | 10 beats/min         | YES                |
| **Nutritional factor**          |                                            |               |      |      |         |          |       |                 |                     |                    |
| α-Linolenic acid                | Mahajan A et al, 2018                     | 31690987      | 2019 | 1    | 74124   | 824006   | 0.93  | 0.90-0.96       | SD                  | YES                |
| Eicosapentaenoic acid           | Mahajan A et al, 2018                     | 31690987      | 2019 | 2    | 74124   | 824006   | 1.08  | 1.03-1.12       | SD                  | YES                |
| Docosapentaenoic acid           | Mahajan A et al, 2018                     | 31690987      | 2019 | 2    | 74124   | 824006   | 1.04  | 1.02-1.07       | SD                  | YES                |
| Docosahexaenoic acid            | Mahajan A et al, 2018                     | 31690987      | 2019 | 1    | 74124   | 824006   | 1.04  | 0.94-1.15       | SD                  | YES                |
| Linoleic acid                   | Mahajan A et al, 2018                     | 31690987      | 2019 | 3    | 74124   | 824006   | 0.96  | 0.94-0.98       | SD                  | YES                |
| Arachidonic acid                | Mahajan A et al, 2018                     | 31690987      | 2019 | 2    | 74124   | 824006   | 1.03  | 1.02-1.05       | SD                  | YES                |
| Palmitoleic acid                | Mahajan A et al, 2018                     | 31690987      | 2019 | 4    | 74124   | 824006   | 0.86  | 0.81-0.91       | SD                  | YES                |
| Oleic acid                      | Mahajan A et al, 2018                     | 31690987      | 2019 | 1    | 74124   | 824006   | 0.87  | 0.81-0.93       | SD                  | YES                |
| Palmitic acid                   | Mahajan A et al, 2018                     | 31690987      | 2019 | 1    | 74124   | 824006   | 0.98  | 0.87-1.09       | SD                  | YES                |
| Stearic acid                    | Mahajan A et al, 2018                     | 31690987      | 2019 | 3    | 74124   | 824006   | 1.09  | 1.09-1.15       | SD                  | YES                |
| Dairy product intake            | Vissers LET et al, 2019 (EPIC-InterAct)   | 30728219      | 2019 | 1    | 9686   | 12134    | 0.99  | 0.93-1.05       | 15 g/day             | NO                 |
| Isoleucine                      | Lotta LA et al, 2016 (Morris AP et al, 2013+EPIC-InterAct+UK Biobank) | 27898682      | 2016 | 4    | 47877   | 267694   | 1.44  | 1.26-1.65       | SD                  | NO                 |
| Leucine                         | Morris AP et al, 2013+EPIC-InterAct+UK Biobank | 27898682      | 2016 | 1    | 47877   | 267694   | 1.85  | 1.41-2.42       | SD                  | NO                 |
| Valine                          | Huang T et al, 2013 (17 studies)          | 24320691      | 2013 | 1    | 4011    | 4303     | 1.29  | 1.09-1.51       | 5 µmol/L            | NO                 |
| Homocysteine                    | Morris AP et al, 2012                     | 26664883      | 2015 | Genetic score | 34840   | 114981   | 1.09  | 0.92-1.30       | SD                  | NO                 |
| Homocysteine                    | Zeggini E et al, 2008                     | 19662379      | 2009 | 1    | 4549    | 5579     | 0.98  | 0.91-1.04       | 0.27 SD              | NO                 |
| 25-hydroxyvitamin D             | Mahajan A et al, 2018                     | 31548248      | 2019 | 7    | 74124   | 824006   | 0.94  | 0.88-0.99       | SD                  | YES                |
| Beta-carotene levels            | Mahajan A et al, 2018                     | 31548248      | 2019 | 7    | 74124   | 824006   | 0.94  | 0.88-0.99       | SD                  | YES                |
| Vitamin B12                     | Zeggini E et al, 2008                     | 19662379      | 2009 | 1    | 4549    | 5579     | 0.98  | 0.91-1.04       | 0.27 SD              | NO                 |
| Phylloquinone (vitamin K1)      | Morris AP et al, 2012+UK Biobank          | 30352877      | 2019 | 4    | 69647   | 551336   | 0.93  | 0.89-0.97       | 1 ln(mmol/L)         | NO                 |
| Alpha-tocopherol                | Mahajan A et al, 2018                     | 31548248      | 2019 | 6    | 74124   | 824006   | 1.05  | 0.85-1.28       | SD                  | YES                |
| Magnesium                       | Yarmolinsky J et al, 2018 (Morris AP et al, 2013+EPIC-InterAct+UK Biobank) | 30759836      | 2019 | 10   | 62892   | 596424   | 0.89  | 0.81-0.98       | per-unit            | NO                 |
| Selenium                        | Yarmolinsky J et al, 2018 (Morris AP et al, 2013+EPIC-InterAct+UK Biobank) | 29788239      | 2018 | 4    | 49266   | 249906   | 1.18  | 0.97-1.43       | 114 µg/L            | NO                 |
| Zinc                            | Xue A et al, 2018                         | 30759836      | 2019 | 2    | 62892   | 596424   | 1.01  | 0.92-1.12       | per-unit            | NO                 |
| **Lifestyle factor**            |                                            |               |      |      |         |          |       |                 |                     |                    |
| Coffee consumption a            | Morris AP et al, 2012                     | 27845333      | 2016 | 9    | 34840   | 114981   | 1.02  | 0.76-1.36       | cups of regular-type coffee/day | NO                 |
| Smoking initiation              | Mahajan A et al, 2018                     | 31852999      | 2019 | 377  | 74124   | 824006   | 1.28  | 1.20-1.37       | NA                  | YES                |
| Sleep duration                  | Scott RA et al, 2017                      | 30508554      | 2019 | 68   | 26676   | 132532   | 0.85  | 0.64-1.13       | NA                  | NO                 |
| Grip strength | Mahajan A et al, 2018 | 30798333 | 2019 | 130 | 74124 | 824006 | 0.72 | 0.51-1.01 | SD | YES |
|---------------|----------------------|----------|------|-----|-------|--------|------|-----------|----|-----|
| **Inflammatory factor** | | | | | | | | | |
| IL-1 receptor antagonist | Voight BF et al, 2010+Morris AP et al, 2012+EPIC-InterAct | 25726324 | 2015 | 2 | 18715 | 61691 | 0.99 | 0.97-1.10 | 0.22SD | NO |
| IL-6 receptor | IL6 MR consortium (40 studies) | 22421340 | 2012 | 1 | 12895 | 86807 | 0.97 | 0.94-1.00 | 15 mg/mL | NO |
| C-reactive protein | Morris AP et al, 2012 (stage 1) | 29753585 | 2018 | 15 | 12171 | 56862 | 1.15 | 0.93-1.42 | 1 ln(mg/L) | NO |
| C-reactive protein | Morris AP et al, 2012 (stage 1) | 30619477 | 2018 | 4 | 12171 | 56862 | 1.11 | 1.06-1.17 | NA | NO |
| IL-18 | Morris AP et al, 2012 | 31024619 | 2019 | 8 (correlated) | 26488 | 83964 | 1.14 | 1.03-1.26 | SD | NO |
| **Internal biomarker** | | | | | | | | | |
| Waist | | | | | | | | | |
| Birthweight | | | | | | | | | |
| Visceral fat mass (women) | | | | | | | | | |
| Obesity | | | | | | | | | |
| Sex hormone binding globulin | | | | | | | | | |
| Age at menarche | Scott RA et al, 2017 | 31614369 | 2020 | 118 | 26676 | 132532 | 0.83 | 0.78-0.88 | 1 year | NO |
| Testosterone | UK Biobank | medRxiv | 2019 | 81 | 11079 | 146152 | 1.07 | 0.80-1.43 | 0.1 nmol/L | NO |
| Sex hormone binding globulin | DIAGRAM Consortium, et al, 2014 | 26050255 | 2015 | 11 | 41439 | 103870 | 0.83 | 0.76-0.91 | SD | NO |
| **Hormone-related factor** | | | | | | | | | |
| **Obesity-related factor** | | | | | | | | | |
| Lean body mass (men) | Mahajan A et al, 2018 | 30798333 | 2019 | 313 | 37358 | 428483 | 0.94 | 0.88-1.01 | SD | YES |
| Lean body mass (women) | Mahajan A et al, 2018 | 30798333 | 2019 | 311 | 36766 | 395523 | 0.91 | 0.84-0.99 | SD | YES |
| Visceral fat mass (men) | UK Biobank | 31501611 | 2011 | 44 | 10002 | 150830 | 2.50 | 1.98-3.14 | 1 kg increase | NO |
| Visceral fat mass (women) | UK Biobank | 31501611 | 2011 | 44 | 4670 | 154511 | 7.34 | 4.48-12.0 | 1 kg increase | NO |
| Birthweight | Morris AP et al, 2012 | 31539074 | 2011 | 7 | 34840 | 114918 | 2.79 | 1.90-4.20 | SD | NO |
| BMI | UK Biobank | 31821322 | 2019 | 57 | 13982 | 273412 | 1.31 | 1.11-1.53 | 1 kg/m² | NO |
| Serum adiponectin | Voight BF et al, 2010 | 23833345 | 2013 | 4 | 15960 | 64731 | 1.06 | 0.84-1.33 | SD | NO |
| Waist-to-hip ratio adj for BMI | Morris AP et al, 2012 | 28196256 | 2017 | 48 | 40530 | 221277 | 1.77 | 1.57-2.00 | SD | NO |
| IGFBP-3 | Morris AP et al, 2012 | 31235487 | 2019 | 6 | 12171 | 56862 | 1.26 | 1.11-1.43 | SD | NO |
| Childhood BMI | Morris AP et al, 2012 | 29483184 | 2018 | 15 | 34840 | 114981 | 1.83 | 1.46-2.30 | SD | NO |

*a* Effect estimation was based on instrumental variables excluding body mass index-related SNPs. OR of type 2 diabetes was 1.20 (95% CI, 1.00, 1.42) based on all genome-wide significant SNPs for coffee consumption. *b* Only one SNP was associated with IGFBP-3 at the genome-wide significance level. The link of medRxiv is: https://www.medrxiv.org/content/10.1101/19005132v1.
### ESM Table 2. Information of the data sources for exposures included in this Mendelian randomisation study

| Risk factor                        | PMID          | Year  | Cases   | Controls | Population | SNP* | SNPs excluded due to LD | Unit       |
|-----------------------------------|---------------|-------|---------|----------|------------|------|------------------------|------------|
| **Somatic health status**         |               |       |         |          |            |      |                        |            |
| Asthma                            | 29273806      | 2018  | 19,954  | 107,715  | European   | 16   | 1                      | Events     |
| Atopic dermatitis                 | 26482879      | 2015  | 18,900  | 84,166   | European   | 21   | 0                      | Events     |
| Dupuytren disease                 | 28866342      | 2017  | 4041    | 8251     | European   | 25   | 0                      | Events     |
| Giant cell arteritis              | 28041642      | 2017  | 2134    | 9125     | European   | 3    | 0                      | Events     |
| Hyperthyroidism                   | 30367059      | 2018  | 3340    | 49,983   | European   | 8    | 0                      | Events     |
| Hypothyroidism                    | 30367059      | 2018  | 1840    | 49,983   | European   | 8    | 0                      | Events     |
| Microalbuminuria                  | 30220432      | 2018  | 382,500 | NA       | European   | 33   | 0                      | SD         |
| Microvascular dysfunction         | 26343387      | 2015  | 60,801  | 123,504  | Mix        | 44   | 1                      | Events     |
| Osteoarthritis                    | 29559693      | 2018  | 30,727  | 297,191  | European   | 8    | 0                      | Events     |
| Periodontitis                     | 29346566      | 2017  | 1030    | 9,471    | European   | 2    | 0                      | Events     |
| Polycystic ovary syndrome         | 30566500      | 2018  | 10,074  | 103,164  | European   | 14   | 0                      | Events     |
| Rheumatoid arthritis              | 24390342      | 2014  | 18,136  | 49,724   | European   | 8    | 0                      | Events     |
| Systolic blood pressure           | 30224653      | 2018  | >1 million | NA     | Mix        | 229  | 11                     | mmHg       |
| Telomere length                   | 28241208      | 2017  | 9,190   | NA       | European   | 16   | 6                      | SD         |
| **Mental health status**          |               |       |         |          |            |      |                        |            |
| Anorexia nervosa                  | 31308545      | 2019  | 16,992  | 55,525   | European   | 8    | 0                      | Events     |
| Lifetime anxiety disorder         | BioRxiv       | 2019  | 25,453  | 58,113   | European   | 5    | 0                      | Events     |
| Post-traumatic stress disorder    | 31594949      | 2019  | 23,212  | 151,447  | European   | 2    | 0                      | Events     |
| Schizophrenia                     | 29483656      | 2018  | 11,260  | 24,542   | European   | 143  | 17                     | Events     |
| **Nutritional factor & Internal biomarker** | | | | | | | |
| Homocysteine                      | 23824729      | 2013  | 44,147  | NA       | European   | 18   | 4                      | SD         |
| Isoleucine                        | 27898682      | 2016  | 16,596  | NA       | European   | 5    | 0                      | SD         |
| Leucine                           | 27898682      | 2016  | 16,597  | NA       | European   | 1    | 0                      | SD         |
| Valine                            | 27898682      | 2016  | 16,598  | NA       | European   | 1    | 0                      | SD         |
| β-carotene (precursor to vitamin A) | 19185284     | 2009  | 3941    | NA       | European   | 1    | 0                      | 0.27 SD    |
| Retinol (vitamin A)               | 21878437      | 2011  | 5006    | NA       | European   | 2    | 0                      | ln(ug/L)   |
| Vitamin B6                        | 19303062      | 2009  | 18,640  | NA       | European   | 1    | 0                      | SD         |
| Folate (vitamin B9)               | 23754956      | 2013  | 37,341  | NA       | Mix        | 3    | 1                      | SD         |
| Vitamin B12                       | 23754956      | 2013  | 45,576  | NA       | Mix        | 15   | 1                      | SD         |
| Vitamin C                         | 20519558      | 2010  | 15,087  | NA       | European   | 1    | 0                      | SD         |
| Vitamin E                         | 21729881      | 2011  | 5006    | NA       | European   | 3    | 0                      | ln(ng/mL)  |
| Copper                            | 23720494      | 2013  | 2603    | NA       | European   | 2    | 0                      | NA         |
| Iron                              | 25352340      | 2014  | 48,972  | NA       | European   | 5    | 0                      | SD         |
| Magnesium                         | 20700443      | 2010  | 15,366  | NA       | European   | 6    | 0                      | SD         |
| Potassium (urinary)               | 31409800      | 2019  | 446,238 | NA       | European   | 13   | 0                      | mmol/L     |
| Sodium (urinary)                  | 31409800      | 2019  | 446,237 | NA       | European   | 50   | 3                      | mmol/L     |
|                                | Year | Value 1  | Value 2  | Value 3  | Value 4  | Value 5  | Unit  |
|--------------------------------|------|----------|----------|----------|----------|----------|-------|
| Selenium                       | 2019 | 9639     | NA       | European | 4        | 2        | NA    |
| Zinc                           | 2013 | 2603     | NA       | European | 3        | 0        | NA    |
| Thyroid-stimulating hormone    | 2018 | 72 167   | NA       | European | 61       | 14       | SD    |
| Free thyroxine                 | 2018 | 72 167   | NA       | European | 31       | 7        | SD    |
| High-density lipoprotein cholesterol | 2013 | 188 577  | NA       | Mix       | 71       | 0        | SD    |
| Low-density lipoprotein cholesterol | 2013 | 188 577  | NA       | Mix       | 58       | 0        | SD    |
| Total cholesterol              | 2013 | 188 577  | NA       | Mix       | 74       | 0        | SD    |
| Total triglyceride             | 2013 | 188 577  | NA       | Mix       | 40       | 0        | SD    |
| Alanine aminotransferase       | 2011 | 61 089   | NA       | Mix       | 4        | 0        | per 100% change |
| Alkaline phosphatase           | 2011 | 61 091   | NA       | Mix       | 14       | 0        | per 100% change |
| γ-glutamyl transferase         | 2011 | 61 092   | NA       | Mix       | 26       | 0        | per 100% change |
| Serum uric acid                | 2019 | 288 649  | NA       | European | 123      | 26       | 1 mg/mL |
| Serum ferritin                 | 2014 | 48 972   | NA       | European | 8        | 0        | SD    |
| Fetuin-A levels               | 2015 | 2734     | NA       | European | 1        | 0        | SD    |
| Lipoprotein(a)                 | 2009 | 15 937   | NA       | European | 2        | 0        | SD    |
| Bilirubin levels               | 2019 | 39 261   | NA       | European | 10       | 0        | 1 mg/dL |
| Alanine                        | 2016 | 22 569   | NA       | European | 1        | 0        | SD    |
| Phenyllalanine                 | 2016 | 22 660   | NA       | European | 2        | 0        | SD    |
| Tyrosine                       | 2016 | 24 918   | NA       | European | 1        | 0        | SD    |
| Haemoglobin                    | 2012 | 135 367  | NA       | Mix       | 27       | 1        | 1 g/dl |
| Inflammatory factor            |      |          |          |          |          |          |       |
| TNF                            | 2016 | 30 912   | NA       | European | 4        | 1        | ln(mg/L) |
| C-reactive protein             | 2018 | 204 402  | NA       | European | 58       | 0        | ln(mg/L) |
| IgE                            | 2012 | 6819     | NA       | European | 3        | 0        | ln(mg/L) |
| IL-1 receptor antagonist       | 2014 | 2160     | NA       | European | 2        | 0        | 0.22 SD |
| IL-2 receptor subunit α        | 2017 | 8293     | NA       | European | 1        | 0        | SD    |
| IL-6 receptor subunit α        | 2018 | 3301     | NA       | European | 1        | 0        | NA    |
| IL-16                           | 2017 | 3483     | NA       | European | 1        | 0        | SD    |
| IL-17                           | 2017 | 7760     | NA       | European | 1        | 0        | SD    |
| IL-18                           | 2017 | 3636     | NA       | European | 3        | 0        | SD    |
| Mean platelet volume           | 2016 | 164 454  | NA       | European | 294      | 75       | SD    |
| Platelet count                 | 2016 | 166 066  | NA       | European | 287      | 80       | SD    |
| Platelet distribution width    | 2016 | 164 433  | NA       | European | 206      | 66       | SD    |
| Plateletcrit                   | 2016 | 164 339  | NA       | European | 272      | 85       | SD    |
| Lifestyle and sleep-related factor |  |          |          |          |          |          |       |
| Alcohol consumption            | 2019 | 941 280  | NA       | European | 99       | 16       | Drinks/week |
| Coffee consumption             | 2019 | 375 833  | NA       | European | 14       | 2        | 50% increase |
| Caffeine intake                | 2011 | 47 341   | NA       | European | 2        | 0        | Cubic-root transformed mg/d |
| Breakfast skipping             | 2019 | 193 860  | NA       | European | 6        | 0        | NA    |
| Lifetime smoking               | 2019 | 462 690  | NA       | European | 126      | 0        | SD    |
| Daytime napping                | 2019 | 452 071  | NA       | European | 37       | 1        | Daytime sleepiness |
| Measure                                 | Study ID | Year | Value 1   | Value 2   | Value 3   | Ethnicity   | Events | Notes |
|----------------------------------------|----------|------|-----------|-----------|-----------|-------------|--------|-------|
| Sleep duration                         | 30846698 | 2019 | 446 118   | NA        | 78        | European    | 5      | Hours/day |
| Short sleep (<7 hours)                 | 30846698 | 2019 | 106 192   | 305 742   | European  | 27          | 2      | Events |
| Long sleep (>9 hours)                  | 30846698 | 2019 | 34 184    | 305 742   | European  | 8           | 0      | Events |
| Apnoea-hypopnea index                  | 31786426 | 2019 | 1786      | NA        | Mix       | 2           | 0      | Events/hour |
| Insomnia                               | 30804565 | 2019 | 397 972   | 933 038   | European  | 248         | 40     | Events |
| Morningness                            | 30696823 | 2019 | 372 765   | 278 530   | European  | 351         | 32     | Events |
| Restless leg syndrome                  | 29029846 | 2017 | 15 126    | 95 725    | European  | 20          | 0      | Events |
| Moderate to vigorous physical activity  | 29899525 | 2018 | 377 234   | NA        | European  | 9           | 0      | SD    |
| Vigorous physical activity             | 29899525 | 2018 | 98 060    | 162 995   | European  | 5           | 0      | ≥3 vs 0 days/week |
| Strenuous sports or other exercises    | 29899525 | 2018 | 124 842   | 225 650   | European  | 6           | 0      | ≥2–3 vs 0 days/week |
| Accelerometry                          | 29899525 | 2018 | 91084     | NA        | European  | 2           | 0      |       |
| Sex-hormone related factor & sex hormone |          |      |           |           |           |             |        |       |
| Age at menarche                        | 28436984 | 2017 | 370 000   | NA        | Mix       | 389         | 0      | 1 year |
| Age at menopause                       | 26414677 | 2015 | 70 000    | NA        | European  | 42          | 0      | 1 year |
| Testosterone levels                    | 32042192 | 2018 | 425 097   | NA        | European  | 239         | 0      | SD    |
| Sex hormone binding globulin           | 32042192 | 2020 | 425 097   | NA        | European  | 659         | 0      | SD    |
| Oestradiol levels                      | 29325096 | 2018 | 11 097    | NA        | European  | 2           | 0      | 1 pg/mL |
| Obesity-related factor & education     |          |      |           |           |           |             |        | 1 milli-gravities |
| Birthweight                            | 23202124 | 2013 | 69 308    | NA        | European  | 7           | 0      | 0.1kg |
| Childhood BMI                          | 26604143 | 2016 | 35 668    | NA        | Mix       | 15          | 0      | SD    |
| Adulthood BMI                          | 30124842 | 2018 | 700 000   | NA        | European  | 941         | 280    | SD    |
| Adulthood height                       | 30124842 | 2018 | 700 000   | NA        | European  | 3290        | 1574   | SD    |
| Body fat percentage                    | 30305743 | 2018 | 500 000   | NA        | European  | 370         | 0      | SD    |
| Visceral fat mass                      | 31501611 | 2019 | 400 000   | NA        | European  | 44          | 7      | 1 kilogram |
| Adiponectin levels                     | 22479202 | 2012 | 45 891    | NA        | Mix       | 17          | 4      | µg/mL |
| Leptin levels                          | 26833098 | 2016 | 52 140    | NA        | European  | 5           | 0      | ln(µg/mL) |
| Education                              | 30038396 | 2018 | 1 131 881 | NA        | European  | 1271        | 475    | SD    |

NA, not available; PMID, PubMed ID; SD indicates standard deviation; SNP, single-nucleotide polymorphism
All biomarkers were measured in serum or blood levels, except for sodium and potassium in urinary levels.
Source for Lifetime anxiety disorder: https://www.biorxiv.org/content/10.1101/203844v2.full
*Not all these SNPs were included in the MR analyses because some were not associated with the exposure at the genome-wide significance level (p<5×10⁻⁸), were in linkage disequilibrium, or not available in the type 2 diabetes dataset.
| Exposure                        | PubMed ID  | Definition                                                                                                                                                                                                                                                                                                                                 |
|--------------------------------|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Somatic health status          |            |                                                                                                                                                                                                                                                                                                                                          |
| Asthma                         | 29273806   | The definition of asthma was based on physicians’ diagnoses and/or standardized questionnaires.                                                                                                                                                                                                                                         |
| Atopic dermatitis              | 26482879   | Clinical diagnosis                                                                                                                                                                                                                                                                                                                         |
| Dupuytren disease              | 28886342   | The affected case subjects were individuals who had undergone surgical treatment for their disease. The diagnosis of GCA was established according to the 1990 American College of Rheumatology classification criteria for this disease. In addition, the diagnosis was subsequently confirmed by either a biopsy of the temporal artery (89.83%) or arterial imaging (10.17%) consistent with GCA. |
| Giant cell arteritis            | 28041642   | The diagnosis of GCA was established according to the 1990 American College of Rheumatology classification criteria for this disease. In addition, the diagnosis was subsequently confirmed by either a biopsy of the temporal artery (89.83%) or arterial imaging (10.17%) consistent with GCA. |
| Hypothyroidism                 | 30367059   | Hypothyroidism cases with TSH below the reference range                                                                                                                                                                                                                                                                                   |
| Hyperthyroidism                | 30367059   | Hypothyroidism cases with TSH levels above the cohort-specific reference range                                                                                                                                                                                                                                                                                                     |
| Microalbuminuria               | 30220432   | The mean SBP and DBP values from two automated or two manual blood pressure measurements                                                                                                                                                                                                                                              |
| Polycystic ovary syndrome      | 30566500   | Cases were diagnosed with PCOS based on NIH or Rotterdam Criteria or by self-report.                                                                                                                                                                                                                                                      |
| Rheumatoid arthritis           | 24390342   | All RA cases fulfilled the 1987 criteria of the American College of Rheumatology for RA diagnosis or were diagnosed with RA by a professional rheumatologist.                                                                                                                                                                              |
| Systolic blood pressure        | 30224653   | The mean SBP and DBP values from two automated or two manual blood pressure measurements                                                                                                                                                                                                                                               |
| Telomere length                | 28241208   | LTL measurement was performed by Southern blot analysis of the terminal restriction fragments, generated by the restriction enzymes *Hinf*I and *Rsa*I after verification of DNA integrity.                                                                                                                                                   |
| Mental health status           |            |                                                                                                                                                                                                                                                                                                                                          |
| Anorexia nervosa               | 31308545   | Case definitions established a lifetime diagnosis of anorexia nervosa via hospital or register records, structured clinical interviews, or online questionnaires based on standardized criteria (Diagnostic and Statistical Manual of Mental Disorders (DSM) III-R, DSM-IV, International Classification of Diseases (ICD) 8, ICD-9 or ICD-10), whereas in the UK Biobank, cases self-reported a diagnosis of anorexia nervosa. Cases met one of two definitions. First was self-reporting a lifetime professional diagnosis of one of the core five anxiety disorders, (generalised anxiety disorder, social phobia, panic disorder, agoraphobia or specific phobia; n=21 108). Further case was defined as meeting criteria for a likely lifetime diagnosis of DSM-IV generalised anxiety disorder based on anxiety questions from the Composite International Diagnostic Interview (CIDI) Short-form questionnaire. PTSD assessment was based either on lifetime (where possible) or current PTSD (i.e. including participants with a potential lifetime PTSD diagnosis as controls), and PTSD diagnosis was established using various instruments and different versions of the DSM (DSM-III-R, DSM-IV, DSM-5). |
| Lifetime anxiety disorder      | BioRxiv    | Case definitions established a lifetime diagnosis of anorexia nervosa via hospital or register records, structured clinical interviews, or online questionnaires based on standardized criteria (Diagnostic and Statistical Manual of Mental Disorders (DSM) III-R, DSM-IV, International Classification of Diseases (ICD) 8, ICD-9 or ICD-10), whereas in the UK Biobank, cases self-reported a diagnosis of anorexia nervosa. Cases met one of two definitions. First was self-reporting a lifetime professional diagnosis of one of the core five anxiety disorders, (generalised anxiety disorder, social phobia, panic disorder, agoraphobia or specific phobia; n=21 108). Further case was defined as meeting criteria for a likely lifetime diagnosis of DSM-IV generalised anxiety disorder based on anxiety questions from the Composite International Diagnostic Interview (CIDI) Short-form questionnaire. PTSD assessment was based either on lifetime (where possible) or current PTSD (i.e. including participants with a potential lifetime PTSD diagnosis as controls), and PTSD diagnosis was established using various instruments and different versions of the DSM (DSM-III-R, DSM-IV, DSM-5). |
| Post-traumatic stress disorder | 31594949   | Case definitions established a lifetime diagnosis of anorexia nervosa via hospital or register records, structured clinical interviews, or online questionnaires based on standardized criteria (Diagnostic and Statistical Manual of Mental Disorders (DSM) III-R, DSM-IV, International Classification of Diseases (ICD) 8, ICD-9 or ICD-10), whereas in the UK Biobank, cases self-reported a diagnosis of anorexia nervosa. Cases met one of two definitions. First was self-reporting a lifetime professional diagnosis of one of the core five anxiety disorders, (generalised anxiety disorder, social phobia, panic disorder, agoraphobia or specific phobia; n=21 108). Further case was defined as meeting criteria for a likely lifetime diagnosis of DSM-IV generalised anxiety disorder based on anxiety questions from the Composite International Diagnostic Interview (CIDI) Short-form questionnaire. PTSD assessment was based either on lifetime (where possible) or current PTSD (i.e. including participants with a potential lifetime PTSD diagnosis as controls), and PTSD diagnosis was established using various instruments and different versions of the DSM (DSM-III-R, DSM-IV, DSM-5). |
| Schizophrenia                  | 29483656   | Unknown                                                                                                                                                                                                                                                                       |
| Nutritional factor & Internal biomarker                                      | Code       |
|---------------------------------------------------------------------------|------------|
| Homocysteine                                                              | 23824729   |
| Isoleucine                                                                | 27898682   |
| Leucine                                                                   | 27898682   |
| Valine                                                                    | 27898682   |
| β-carotenoit                                                               | 19185284   |
| Retinol (vitamin A)                                                       | 21878437   |
| Vitamin B6                                                                | 19303062   |
| Folate (vitamin B9)                                                       | 23754956   |
| Vitamin B12                                                               | 23754956   |
| Vitamin C                                                                 | 20519558   |
| Vitamin E                                                                 | 21729881   |
| Copper                                                                    | 23720494   |
| Iron                                                                       | 25352340   |
| Magnesium                                                                 | 20700443   |
| Potassium (urinary)                                                       | 31409800   |
| Sodium (urinary)                                                          | 31409800   |
| Selenium                                                                  | 30972295   |
| Zinc                                                                       | 23720494   |
| Thyroid-stimulating hormone                                               | 30367059   |
| Free thyroxine                                                            | 30367059   |
| High-density lipoprotein cholesterol                                      | 24097068   |
| Low-density lipoprotein cholesterol                                       | 24097068   |
| Total cholesterol                                                         | 24097068   |
| Total triglyceride                                                        | 24097068   |
| Alanine aminotransferase                                                  | 22001757   |
| Alkaline phosphatase                                                      | 22001757   |
| γ-glutamyl transferase                                                     | 22001757   |
| Serum uric acid                                                           | 31578528   |
| Serum ferritin                                                            | 25352340   |

Homocysteine was measured in each cohort by using one of the following methods: isotope-dilution liquid chromatography–tandem mass spectrometry, gas chromatography–coupled mass spectrometry, HPLC, or enzymatic, immune, or chemiluminescence.

Blood samples were measured via high-performance liquid chromatography.

Serum alpha-tocopherol levels were measured by high-performance liquid chromatography, with a coefficient of variation (CV) of 2.2%. Gamma-tocopherol was not measured at study baseline.

Sodium and potassium concentrations in stored urine samples were measured by the ion selective electrode method (potentiometric method) using Beckman Coulter AU5400, UK Ltd.

Blood lipid levels were typically measured after >8 h of fasting. Individuals known to be on lipid-lowering medication were excluded when possible. LDL cholesterol levels were directly measured in ten studies (24% of total study individuals) and were estimated using the Friedewald formula41 in the remaining studies.

NMR spectroscopy on serum samples from 2,269 LOLIPOP and 4,247 NFBC1966 participants with genome-wide data to investigate the relationships of the identified loci with lipoprotein and intermediary metabolism.

The laboratory methods were used to measure serum urate.

Clinically and readily measurable
| Table 1: Biobank Biomarkers | Measurement Method and Units |
|-----------------------------|-------------------------------|
| Fetuin-A levels             | Plasma concentrations were measured by enzyme-linked immunosorbent assays (Human Fetuin-A ELISA; BioVendor) in the laboratory of Professor Pischon, Molecular Epidemiology Group, Max Delbrück Center for Molecular Medicine (MDC), Berlin-Buch, Germany. |
| Lipoprotein(a)              | Lp(a) lipoprotein was measured by means of one latex-enhanced immunoturbidimetric assay (Immuno) in samples from case subjects that had been obtained in study clinics. In addition, Lp(a) lipoprotein was measured in a random subgroup of case subjects and control subjects with the use of a second latex-enhanced immunoturbidimetric assay (Randox Laboratories) on an ADVIA 1800 autoanalyzer (Siemens). |
| Bilirubin levels            | Serum total bilirubin levels (both direct and indirect bilirubin) were measured through automated biochemical profiling, and the unit of bilirubin concentration was milligram per deciliter. |
| Alanine                     | The quantitative high-throughput NMR metabolomics platform, used to quantify human blood metabolites, was applied. |
| Phenylalanine               | The quantitative high-throughput NMR metabolomics platform, used to quantify human blood metabolites, was applied. |
| Tyrosine                    | The quantitative high-throughput NMR metabolomics platform, used to quantify human blood metabolites, was applied. |
| Hemoglobin                  | The quantitative high-throughput NMR metabolomics platform, used to quantify human blood metabolites, was applied. |
| Inflammatory factor         | Each study typically collected venous blood samples from their participants frozen as either serum or plasma and stored below -80°C until the time of measurement. Serum or plasma levels of TNF-α were measured using various types of immunoassays and expressed as pg/ml. Serum CRP in mg/L by was measured using standard laboratory techniques and transformed the values by natural log. |
| TNF                         | Total IgE concentrations were measured with the FEIA CAP system (Pharmacia, Freiburg, Germany). |
| C-reactive protein          | IL-1 receptor antagonist serum concentrations were measured using the Quantikine ELISA Kit (R&D Systems, Wiesbaden, Germany). |
| IgE                         | A total of 48 cytokines were measured by using Bio-Rad’s premixed Bio-Plex Pro Human Cytokine 27-plex Assay and 21-plex Assay, and Bio-Plex 200 reader with Bio-Plex 6.0 software. A multiplexed, aptamer-based approach (SOMAscan assay) was used to measure the relative concentrations of 3,622 plasma proteins or protein complexes assayed using 4,034 modified aptamers. |
| IL-1 receptor antagonist    | A total of 48 cytokines were measured by using Bio-Rad’s premixed Bio-Plex Pro Human Cytokine 27-plex Assay and 21-plex Assay, and Bio-Plex 200 reader with Bio-Plex 6.0 software. |
| IL-2 receptor subunit α     | Full blood counts were measured in UK Biobank and INTERVAL study participants using clinical hematology analyzers at the centralized processing laboratory of UK Biocenter (Stockport, UK). |
| IL-6 receptor subunit α     | Full blood counts were measured in UK Biobank and INTERVAL study participants using clinical hematology analyzers at the centralized processing laboratory of UK Biocenter (Stockport, UK). |
| IL-16                       | Full blood counts were measured in UK Biobank and INTERVAL study participants using clinical hematology analyzers at the centralized processing laboratory of UK Biocenter (Stockport, UK). |
| IL-17                       | Full blood counts were measured in UK Biobank and INTERVAL study participants using clinical hematology analyzers at the centralized processing laboratory of UK Biocenter (Stockport, UK). |
| IL-18                       | Full blood counts were measured in UK Biobank and INTERVAL study participants using clinical hematology analyzers at the centralized processing laboratory of UK Biocenter (Stockport, UK). |
| Mean platelet volume        | Questionnaire survey, drinks per week |
| Platelet count              | Coffee intake was collected using a 24-hour recall questionnaire (Oxford WebQ) in a subset of UK Biobank participants. Researchers used the mean intake from participants who completed at least two dietary recalls. Intake was assessed using a validated semi-quantitative food frequency questionnaire (FFQ). For each item, participants were asked how often, on average, they had consumed a specified amount of each beverage or food over the past year. The participants could choose from nine frequency categories (never, 1–3 per month, 1 per week, 2–4 per week, 5–6 per week, 1 per day, 2–3 per day, 4–5 per day and 6 or more per day). Intakes of nutrients |
| Platelet distribution width | Caffeine intake was collected using a 24-hour recall questionnaire (Oxford WebQ) in a subset of UK Biobank participants. Researchers used the mean intake from participants who completed at least two dietary recalls. Intake was assessed using a validated semi-quantitative food frequency questionnaire (FFQ). For each item, participants were asked how often, on average, they had consumed a specified amount of each beverage or food over the past year. The participants could choose from nine frequency categories (never, 1–3 per month, 1 per week, 2–4 per week, 5–6 per week, 1 per day, 2–3 per day, 4–5 per day and 6 or more per day). Intakes of nutrients |
| Plateletcrit                | Caffeine intake was collected using a 24-hour recall questionnaire (Oxford WebQ) in a subset of UK Biobank participants. Researchers used the mean intake from participants who completed at least two dietary recalls. Intake was assessed using a validated semi-quantitative food frequency questionnaire (FFQ). For each item, participants were asked how often, on average, they had consumed a specified amount of each beverage or food over the past year. The participants could choose from nine frequency categories (never, 1–3 per month, 1 per week, 2–4 per week, 5–6 per week, 1 per day, 2–3 per day, 4–5 per day and 6 or more per day). Intakes of nutrients |
and caffeine were calculated using US Department of Agriculture food composition sources. In these calculations, researchers assumed that the content of caffeine was 137 mg per cup of coffee, 47 mg per cup of tea, 46 mg per can or bottle of cola or other caffeinated carbonated beverage, and 7 mg per 1 oz serving of chocolate candy. Researchers assessed the total intake of caffeine by summing the caffeine content for the specified amount of each food multiplied by a weight proportional to the frequency of its use.

The breakfast cereal–skipping data from 24-h recalls from the UK Biobank

Smoking measures available in the UK Biobank were self-reported and collected at initial assessment. They included: smoking status, age at initiation in years, age at cessation in years and number of cigarettes smoked per day. The lifetime smoking index was constructed based on the method outlined by Leffondrè, Abrahamowicz, Xiao, and Siemiatyck (2006).

Self-reported daytime sleepiness was ascertained in the UK Biobank using the question “How likely are you to dose off or fall asleep during the daytime when you don’t mean to? (e.g. when working, reading or driving)” with the response options of “Never/rarely”, “sometimes”, “often”, “all of the time”, “do not know”, and “prefer not to answer”. Participants reporting “do not know” and “prefer not to answer” were set to missing. Other responses were coded continuously as 1 to 4 corresponding to the severity of daytime sleepiness.

Participants were asked: About how many hours sleep do you get in every 24 h? (please include naps), with responses in hour increments. Sleep duration was treated as a continuous variable and also categorized as either short (6 h or less), normal (7 or 8 h), or long (9 h or more) sleep duration. Extreme responses of less than 3 h or more than 18 h were excluded and Do not know or Prefer not to answer responses were set to missing. Participants who self-reported any sleep medication (see Supplementary Method 1) were excluded.

The AHI was defined as the total number of apneas and hypopneas per hour of sleep. The delta-AHI is the increase/decrease of AHI across eight years as shown in the formula below: delta-AHI = AHI follow-up – AHI baseline OSA was defined according to AHI. Researchers elected to define OSA as AHI ≥ 15 events/hour, a cutoff point that presents more solid evidence of associated outcomes. Individuals with incident OSA were those with an AHI < 15/h at baseline, which presented an AHI ≥ 15h at follow-up. Individuals that did not develop OSA (controls) were those with an AHI ≤ 15h at both baseline and follow-up studies.

Insomnia complaints were measured using questionnaire data; an independent sample (the Netherlands Sleep Register)12, which gives access to similar question data, as well as clinical interviews assessing insomnia disorder, was used to validate the specific questions so that they were good proxies of insomnia disorder. Responses to two identical questions (“Are you naturally a night person or a morning person?”) were used to define the dichotomous morning person phenotype in the 23andMe cohort, with one question having a wider selection of neutral options. For the first instance, the possible answers were “Night owl”, “Early bird” and “Neither”, and for the second “Night person”, “Morning person”, “Neither”, “It depends” and “I’m not sure”. Individuals with discordant or neutral responses to both were excluded. For those with one neutral and one non-neutral response, their non-neutral response was used to define their phenotype. Morning people were coded as 1 (cases; N = 120,478) and evening people were coded as 0 (controls; N = 127,622). The UK Biobank collected a single self-reported measure of Chronotype (“Morning/evening person (chronotype)”; data-field 1180). Participants were prompted to answer the question “Do you consider yourself to be?” with one of six possible answers: “Definitely a ‘morning’ person”, “More a ‘morning’ than ‘evening’ person”, “More an ‘evening’ than a ‘morning’ person”, “Definitely an ‘evening’ person”, “Do not know” or “Prefer not to answer”, which we coded as 2, 1, −1, −2, 0 and missing, respectively.
| Restless leg syndrome | 29029846 |
|-----------------------|----------|
| People with restless legs syndrome were recruited in specialist outpatient clinics for movement disorders and in sleep units. Restless legs syndrome was diagnosed in face-to-face interviews by an expert neurologist, based on the International Restless Legs Syndrome Study Group diagnostic criteria. |

| Moderate to vigorous physical activity | 29899525 |
|--------------------------------------|----------|
| Moderate-to-vigorous PA (MVPA) was calculated by taking the sum of total minutes/week of MPA multiplied by four and the total number of VPA minutes/week multiplied by eight, corresponding to their metabolic equivalents. In the last 4 weeks did you spend any time doing the following?" and follow-up questions assessing the frequency and typical duration of “strenuous sports” and of “other exercises”. The possible responses to the initial question were: ‘walking for pleasure’, ‘other exercises’, ‘strenuous sports’, ‘light DIY’, ‘heavy DIY’, ‘none of the above’, and ‘prefer not to answer’. Researchers identified individuals spending 2–3 days/week or more doing strenuous sports or other exercises (SSOE), for a duration of 15–30 min or greater. For vigorous PA (VPA), participants were asked: “In a typical WEEK, how many days did you do 10 min or more of vigorous physical activity? (These are activities that make you sweat or breathe hard such as fast cycling, aerobics, heavy lifting)”. For each of these questions, those who indicated 1 or more such days were then asked “How many minutes did you usually spend doing moderate/vigorous activities on a typical DAY”. Participants were asked to include activities performed for work, leisure, travel and around the house. We excluded individuals who selected “prefer not to answer” or “do not know” on the above questions, those reporting not being able to walk, and individuals reporting more than 16 h of either MPA or VPA per day. Those reporting >3 h/day of VPA or MPA were recorded to 3 h, as recommended. |

| Strenuous sports or other exercises | 29899525 |
|------------------------------------|----------|

| Vigorous physical activity | 29899525 |
|---------------------------|----------|

| Sex-related factor |
|--------------------|
| Age at menarche | 28436984 |
| Age at menopause | 26414677 |
| Testosterone levels | 32042192 |
| Sex hormone binding globulin | 32042192 |
| Estradiol levels | 29325096 |

| Obesity-related factor & education |
|-----------------------------------|
| Birthweight | 23202124 |
| Childhood BMI | 26604143 |
| Adulthood BMI | 30124842 |
| Adulthood height | 30124842 |
| Body fat percentage | 30305743 |

Body composition estimation by impedance measurement.
Two UKBB subcohorts were constructed: one training dataset with VAT mass measured by DXA (instance 2; $n = 5,109$), to which the prediction models were calibrated; and one application dataset (instances 0 and 1; $n = 502,638$), in which VAT mass was predicted using the calibrated prediction models.

| Visceral fat mass | 31501611 | Adiponectin levels were measured using ELISA or RIA methods. |
|------------------|----------|-------------------------------------------------------------|
| Adiponectin levels | 22479202 | Circulating levels of leptin                                 |
| Leptin levels     | 26833098 |                                                             |
## ESM Table 4. Power estimation

| Effect size (odds ratio) | 0.001 | 0.005 | 0.01  | 0.02  | 0.05  | 0.10  | 0.15  | 0.2   |
|--------------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| 0.1                      | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  |
| 0.3                      | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  |
| 0.5                      | 0.99  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  |
| 0.7                      | 0.72  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  |
| 0.8                      | 0.39  | 0.96  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  |
| 0.9                      | 0.13  | 0.46  | 0.75  | 0.96  | 1.00  | 1.00  | 1.00  | 1.00  |
| 1.1                      | 0.13  | 0.45  | 0.73  | 0.96  | 1.00  | 1.00  | 1.00  | 1.00  |
| 1.2                      | 0.39  | 0.95  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  |
| 1.3                      | 0.68  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  |
| 1.5                      | 0.98  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  |
| 1.7                      | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  |
| 1.9                      | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  |
| 2.0                      | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  |
| 3.0                      | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  | 1.00  |

The power estimation was based on 74124 type 2 diabetes cases and 824006 controls and we assumed type 1 error rate as 0.05. The webtool power calculator: [https://shiny.cnsgenomics.com/mRnd/](https://shiny.cnsgenomics.com/mRnd/).
### ESM Table 5. False discovery rate adjusted $p$ values for all tested associations using DIAGRAM consortium

| Risk factor                                         | Original $p$ value | Critical Value | Benjamini-Hochberg adjusted $p$ value | Significant using an FDR of 0.05? |
|-----------------------------------------------------|--------------------|----------------|---------------------------------------|----------------------------------|
| Adulthood BMI                                       | 1.40E-44           | 5.21E-04       | 1.34E-42                              | Yes                              |
| Alanine                                             | 6.50E-25           | 0.001          | 3.12E-23                              | Yes                              |
| Body fat percentage                                 | 3.40E-23           | 0.002          | 1.09E-21                              | Yes                              |
| Visceral fat mass                                    | 2.20E-20           | 0.002          | 5.28E-19                              | Yes                              |
| Sex hormone binding globulin                        | 9.39E-14           | 0.003          | 1.80E-12                              | Yes                              |
| Age at menarche                                      | 1.30E-12           | 0.003          | 2.08E-11                              | Yes                              |
| Systolic blood pressure                             | 2.10E-10           | 0.004          | 2.88E-09                              | Yes                              |
| Insomnia                                            | 1.00E-09           | 0.004          | 1.20E-08                              | Yes                              |
| Lifetime smoking                                    | 4.00E-08           | 0.005          | 4.27E-07                              | Yes                              |
| Isoleucine                                          | 8.73E-08           | 0.005          | 8.38E-07                              | Yes                              |
| Childhood body mass index                           | 3.40E-06           | 0.006          | 2.97E-05                              | Yes                              |
| Caffeine intake                                     | 1.00E-05           | 0.006          | 8.00E-05                              | Yes                              |
| Adulthood height                                    | 4.00E-04           | 0.007          | 0.003                                 | Yes                              |
| Leucine                                             | 0.001              | 0.007          | 0.007                                 | Yes                              |
| Valine                                              | 0.001              | 0.008          | 0.006                                 | Yes                              |
| Testosterone levels                                 | 0.002              | 0.008          | 0.012                                 | Yes                              |
| High-density lipoprotein cholesterol                | 0.002              | 0.009          | 0.011                                 | Yes                              |
| Birthweight                                         | 0.004              | 0.009          | 0.021                                 | Yes                              |
| Total cholesterol                                   | 0.005              | 0.010          | 0.025                                 | Yes                              |
| Alanine aminotransferase                            | 0.009              | 0.010          | 0.043                                 | Yes                              |
| Phenylalanine                                       | 0.015              | 0.011          | 0.069                                 | No                               |
| Coffee consumption                                  | 0.017              | 0.011          | 0.074                                 | No                               |
| Tyrosine                                            | 0.019              | 0.012          | 0.079                                 | No                               |
| IL-6 receptor subunit α                             | 0.021              | 0.013          | 0.084                                 | No                               |
| Sodium (urinary)                                    | 0.024              | 0.013          | 0.092                                 | No                               |
| Selenium                                            | 0.025              | 0.014          | 0.092                                 | No                               |
| IL-1 receptor antagonist                            | 0.034              | 0.014          | 0.121                                 | No                               |
| Folate (vitamin B9)                                 | 0.038              | 0.015          | 0.130                                 | No                               |
| Low-density lipoprotein cholesterol                 | 0.044              | 0.015          | 0.146                                 | No                               |
| Giant cell arteritis                                | 0.048              | 0.016          | 0.154                                 | No                               |
| Fetuin-A levels                                     | 0.049              | 0.016          | 0.152                                 | No                               |
| Periodontitis                                       | 0.054              | 0.017          | 0.162                                 | No                               |
| IL-16                                               | 0.056              | 0.017          | 0.163                                 | No                               |
| Iron                                                | 0.074              | 0.018          | 0.209                                 | No                               |
| Apnoea-hypopnea index                               | 0.081              | 0.018          | 0.222                                 | No                               |
| Free thyroxine                                      | 0.099              | 0.019          | 0.264                                 | No                               |
| Anorexia nervosa                                    | 0.100              | 0.019          | 0.259                                 | No                               |
| Condition                           | Value1  | Value2  | Value3  | Status  |
|------------------------------------|---------|---------|---------|---------|
| Lipoprotein(a)                     | 0.110   | 0.020   | 0.278   | No      |
| Breakfast skipping                 | 0.129   | 0.020   | 0.318   | No      |
| Circulating adiponectin            | 0.144   | 0.021   | 0.346   | No      |
| Polycystic ovary syndrome          | 0.145   | 0.021   | 0.340   | No      |
| Atopic dermatitis                  | 0.145   | 0.022   | 0.331   | No      |
| Vigorous physical activity         | 0.156   | 0.022   | 0.348   | No      |
| Tumour necrosis factor             | 0.164   | 0.023   | 0.358   | No      |
| IgE                                | 0.198   | 0.023   | 0.422   | No      |
| IL-2 receptor subunit α            | 0.203   | 0.024   | 0.424   | No      |
| Daytime napping                    | 0.205   | 0.024   | 0.419   | No      |
| Oestradiol levels                 | 0.210   | 0.025   | 0.420   | No      |
| Homocysteine                       | 0.225   | 0.026   | 0.441   | No      |
| Sleep duration                     | 0.234   | 0.026   | 0.449   | No      |
| Copper                             | 0.238   | 0.027   | 0.448   | No      |
| Microalbuminuria                   | 0.241   | 0.027   | 0.445   | No      |
| Short sleep (<7 h)                | 0.247   | 0.028   | 0.447   | No      |
| Plateletcrit                       | 0.273   | 0.028   | 0.485   | No      |
| Vitamin B6                         | 0.295   | 0.029   | 0.515   | No      |
| Strenuous sports or other exercises| 0.306   | 0.029   | 0.525   | No      |
| Age at menopause                   | 0.312   | 0.030   | 0.525   | No      |
| Mean platelet volume               | 0.317   | 0.030   | 0.525   | No      |
| Magnesium                          | 0.347   | 0.031   | 0.565   | No      |
| Dupuytren disease                  | 0.352   | 0.031   | 0.563   | No      |
| Osteoarthritis                     | 0.357   | 0.032   | 0.562   | No      |
| Post-traumatic stress disorder     | 0.360   | 0.032   | 0.557   | No      |
| Retinol (vitamin A)                | 0.364   | 0.033   | 0.555   | No      |
| β-carotenoid (precursor to vitamin A) | 0.382   | 0.033   | 0.573   | No      |
| Lifetime anxiety disorder          | 0.388   | 0.034   | 0.573   | No      |
| Long sleep (>9 h)                  | 0.389   | 0.034   | 0.566   | No      |
| Thyroid-stimulating hormone        | 0.396   | 0.035   | 0.567   | No      |
| Accelerometery                     | 0.408   | 0.035   | 5.79E-01| No      |
| Microvascular dysfunction          | 0.414   | 0.035   | 0.584   | No      |
| IL-17                              | 0.415   | 0.036   | 0.577   | No      |
| Potassium (urinary)                | 0.415   | 0.036   | 0.569   | No      |
| Vitamin E                          | 0.419   | 0.037   | 0.567   | No      |
| Bilirubin levels                   | 0.423   | 0.038   | 0.564   | No      |
| Restless leg syndrome              | 0.430   | 0.038   | 0.565   | No      |
| Alkaline phosphatase               | 0.469   | 0.039   | 0.608   | No      |
| Platelet count                     | 0.470   | 0.039   | 0.602   | No      |
| Rheumatoid arthritis               | 0.481   | 0.040   | 0.608   | No      |
| Telomere length                    | 0.495   | 0.040   | 0.617   | No      |
| Measure                              | Estimate | Std. Error | Lower CI | Upper CI | Adjusted for Multiple Testing |
|-------------------------------------|----------|------------|----------|----------|------------------------------|
| Moderate to vigorous physical activity | 0.525    | 0.041      | 0.646    | No       |
| Platelet distribution width         | 0.613    | 0.041      | 0.745    | No       |
| Alcohol consumption                 | 0.631    | 0.042      | 0.757    | No       |
| Serum ferritin                      | 0.634    | 0.042      | 0.751    | No       |
| Asthma                              | 0.647    | 0.043      | 0.757    | No       |
| Total triglyceride                  | 0.756    | 0.043      | 0.874    | No       |
| Vitamin B12                         | 0.762    | 0.044      | 0.871    | No       |
| Haemoglobin                         | 0.801    | 0.044      | 0.905    | No       |
| Hyperthyroidism                     | 0.820    | 0.045      | 0.915    | No       |
| Hypothyroidism                      | 0.821    | 0.045      | 0.906    | No       |
| C-reactive protein                  | 0.833    | 0.046      | 0.909    | No       |
| Serum uric acid                     | 0.876    | 0.046      | 0.945    | No       |
| Leptin levels                       | 0.877    | 0.047      | 0.935    | No       |
| γ-glutamyl transferase              | 0.897    | 0.047      | 0.946    | No       |
| Morningness                         | 0.910    | 0.048      | 0.950    | No       |
| Zinc                                | 0.923    | 0.048      | 0.953    | No       |
| Schizophrenia                       | 0.944    | 0.049      | 0.964    | No       |
| Vitamin C                           | 0.973    | 0.049      | 0.983    | No       |
| IL-18                               | 0.974    | 0.050      | 0.974    | No       |

The False discovery rate estimation is based on the Benjamini-Hochberg method to identify which values remain significant at an FDR of choosing, when adjusting for multiple testing (https://tools.carbocation.com/FDR).
| Risk factor                        | Used SNPs | F  | I²a | IVW model 95% CI | Weighted median model 95% CI | MR-Egger 95% CI | p value for pleiotropy |
|-----------------------------------|-----------|----|-----|------------------|-----------------------------|-----------------|--------------------------|
| **Somatic health status**         |           |    |     | OR               | p value                     | OR             | p value                  |
| Anorexia nervosa                  | 8         | 53.8 | 66  | 0.92             | 0.84, 1.02                  | 0.100          | 0.493, 1.05, 0.97       | 0.074, 0.71, 0.02       | 0.352, 0.76, 0.002      |
| Lifetime anxiety disorder         | 5         | 42.6 | 83  | 1.05             | 0.94, 1.18                  | 0.388          | 0.002, 1.03, 1.12       | 0.493, 0.71, 0.02       | 0.352, 0.76, 0.002      |
| Post-traumatic stress disorder    | 2         | 34.4 | -   | 0.96             | 0.87, 1.05                  | 0.360          | -                        | -                        | -                        |
| Schizophrenia                     | 111       | 51.3 | 71  | 1.00             | 0.97, 1.04                  | 0.944          | 0.241, 0.97, 1.01       | 0.493, 0.71, 0.02       | 0.352, 0.76, 0.002      |
| **Mental health status**          |           |    |     | OR               | p value                     | OR             | p value                  |
| **Nutritional factor & internal biomarker** |           |    |     | OR               | p value                     | OR             | p value                  |
| β-carotene (precursor to vitamin A) | 1        | 98.6 | -   | -                | 0.96, 1.05                  | 0.382          | -                        | -                        | -                        |
| Retinol (vitamin A)               | 2         | 56.9 | -   | 1.15             | 0.85, 1.56                  | 0.364          | -                        | -                        | -                        |
| Vitamin B6                        | 1         | 26.8 | -   | 1.00             | 0.99, 1.00                  | 0.295          | -                        | -                        | -                        |
| Folate (vitamin B9)               | 2         | 83.7 | -   | 0.88             | 0.78, 0.99                  | 0.038          | -                        | -                        | -                        |
| Vitamin B12                       | 12        | 746.2 | 1  | 0.99             | 0.95, 1.04                  | 0.762          | 0.100, 0.95, 1.06       | 0.918, 0.98, 0.89       | 0.055, 0.654            |
| Vitamin C                         | 1         | 27.1 | -   | 1.00             | 0.99, 1.01                  | 0.973          | -                        | -                        | -                        |
| Vitamin E                         | 3         | 11.4 | 63  | 1.21             | 0.76, 1.93                  | 0.419          | 1.30, 0.80, 2.12        | 0.294, 1.01, 0.78       | 0.076, 0.101            |
| Copper                            | 2         | 62.7 | -   | 1.03             | 0.98, 1.07                  | 0.238          | -                        | -                        | -                        |
| Iron                              | 5         | 331.4 | 51  | 1.06             | 0.99, 1.13                  | 0.074          | 1.06, 1.00, 1.13        | 0.040, 1.14, 1.02       | 0.015, 0.116            |
| Magnesium                         | 6         | 58.8 | 75  | 1.08             | 0.92, 1.26                  | 0.347          | 1.09, 0.96, 1.24        | 0.165, 1.51, 1.00       | 0.048, 0.088            |
| Potassium (urinary)               | 13        | 44.1 | 71  | 0.71             | 0.32, 1.61                  | 0.415          | 0.75, 0.36, 1.54        | 0.429, 0.10, 0.00       | 0.374, 0.442            |
| Sodium (urinary)                  | 47        | 48.1 | 94  | 2.69             | 1.14, 6.34                  | 0.024          | 3.33, 2.11, 5.27        | 1.5E-7, 0.26, 0.01      | 0.446, 0.170            |
| Selenium                          | 2         | 81.1 | -   | 1.05             | 1.01, 1.10                  | 0.025          | -                        | -                        | -                        |
| Zinc                              | 2         | 59.7 | -   | 1.00             | 0.96, 1.04                  | 0.923          | -                        | -                        | -                        |
| Test                        | Median (range) | Median (range) |
|-----------------------------|----------------|----------------|
| Thyroid-stimulating hormone | 46 (28, 68)    | 90 (58, 115)   |
| Free thyroxine              | 23 (17, 31)    | 65 (29, 101)   |
| High-density lipoprotein cholesterol | 69 (59, 84) | 157 (145, 168) |
| Low-density lipoprotein cholesterol | 58 (51, 64) | 162 (116, 208) |
| Total cholesterol           | 74 (58, 99)    | 139 (112, 189) |
| Total triglyceride          | 40 (15, 33)    | 159 (112, 199) |
| Lipoprotein(a)              | 2 (1, 3)       | 575 (253, 1000) |
| Alanine aminotransferase    | 4 (2, 5)       | 104 (47, 185)  |
| Alkaline phosphatase        | 14 (6, 20)     | 71 (28, 167)   |
| γ-glutamyl transferase      | 26 (12, 42)    | 188 (91, 337)  |
| Serum uric acid             | 97 (38, 168)   | 154 (47, 247)  |
| Serum ferritin              | 8 (1, 16)      | 69 (13, 125)   |
| Fetal-A levels              | 1 (0.5, 2)     | 1331.8 (714.9, 2322) |
| Bilirubin levels            | 10 (5, 15)     | 190 (67, 323)  |
| Homocysteine                | 13 (6, 23)     | 89 (50, 159)   |
| Isoleucine                  | 4 (2, 5)       | 36.4 (1.2, 7.4) |
| Leucine                     | 1 (0.5, 2)     | 37.7 (1.2, 1.8) |
| Valine                      | 1 (0.5, 2)     | 54.3 (1.2, 1.8) |
| Alanine                     | 1 (0.5, 2)     | 100.0 (51.6, 58.2) |
| Phenylalanine               | 2 (1, 3)       | 72.7 (1.1, 3.1) |
| Tyrosine                    | 1 (0.5, 2)     | 100.0 (0.8, 0.9) |
| Haemoglobin                 | 19 (14, 25)    | 50.8 (8.7, 9.8) |
| Inflammatory factor         |                |                |
| Tumour necrosis factor      | 3 (1, 5)       | 33.8 (61, 76)  |
| C-reactive protein          | 57 (33, 83)    | 165.8 (96, 120) |
| IgE                         | 3 (2, 4)       | 80.6 (10, 110) |
| IL-1 receptor antagonist    | 2 (1, 4)       | 78.9 (3.1, 1.2) |
| IL-2 receptor subunit α     | 1 (0, 3)       | 164.2 (0.9, 4.1) |
| IL-6 receptor subunit α     | 1 (0, 3)       | 5040.4 (0.9, 100) |
| IL-16                       | 1 (0, 3)       | 133.1 (0.9, 1.0) |
| IL-17                       | 1 (0, 3)       | 40.4 (1.0, 1.5) |
| IL-18                       | 3 (1, 5)       | 80.3 (0, 1.0) |
| Mean platelet volume        | 284 (193, 374) | 234.7 (60, 542) |
| Platelet count              | 193 (134, 150) | 133.4 (82, 95) |
| Platelet distribution width | 134 (100, 165) | 150.5 (45, 450) |
| Plateleterit                | 173 (120, 200) | 120.6 (84, 96) |
| Lifestyle and sleep-related factor |            |                |
| Alcohol consumption         | 83 (67, 100)  | 78.7 (48, 100) |
### Coffee consumption
|          |          |          |          |          |          |          |          |          |          |          |
|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
|          | 12       | 159.5    | 94       | 1.59     | 1.09     | 2.32     | 0.017    | 1.29     | 1.15     | 1.46     | 1.8E-5   |
| Caffeine intake | 2       | 69.4     | -        | 1.17     | 1.09     | 1.25     | 1.0E-5   | -        | -        | -        | -        |
| Breakfast skipping | 6     | 39.0     | 81       | 1.72     | 0.85     | 3.46     | 0.129    | 2.34     | 1.41     | 3.89     | 0.001    |
| Lifetime smoking | 126    | 48.8     | 76       | 1.61     | 1.36     | 1.91     | 4.0E-8   | 1.52     | 1.30     | 1.78     | 6.0E-8   |
| Daytime napping | 35     | 42.6     | 87       | 1.77     | 0.73     | 4.24     | 0.205    | 2.23     | 1.22     | 4.09     | 0.009    |
| Sleep duration | 73      | 39.9     | 88       | 0.83     | 0.62     | 1.12     | 0.234    | 0.97     | 0.80     | 1.17     | 0.741    |
| Sleep vari   | 125     | 48.8     | 76       | 1.61     | 1.36     | 1.91     | 4.0E-8   | 1.52     | 1.30     | 1.78     | 6.0E-8   |
| Short sleep (<7 h) | 25  | 25.8     | 85       | 1.14     | 0.92     | 1.41     | 0.247    | 1.10     | 0.95     | 1.28     | 0.216    |
| Long sleep (>9 h) | 8     | 28.6     | 97       | 0.79     | 0.47     | 1.34     | 0.389    | 0.98     | 0.86     | 1.11     | 0.711    |

CI indicates confidence interval; IVW, inverse-variance weighted; OR, odds ratio;

* a \( I^2 \) indicates the heterogeneity among used SNPs for each exposure.

* b For traits with \( \geq 3 \) SNPs, the results were based on IVW model with random effects, and for traits with <3 SNPs, the results were based on IVW model with fixed effects.

* c Estimates were not available for traits with less than 3 SNPs.

* d \( P \) for the intercept in the MR-Egger regression.
ESM Table 7. Replication analyses using data from the FinnGen consortium for associations with $p<0.05$ in IVW analysis based on the DIAGRAM consortium

| Risk factor                        | $I^2$ | OR   | 95% CI       | $p$ value |
|-----------------------------------|-------|------|--------------|-----------|
| **Adulthood**                     |       |      |              |           |
| BMI                               | 51    | 1.46 | 1.35, 1.58   | 3.30E-20  |
| Visceral fat mass                 | 58    | 2.18 | 1.67, 2.85   | 1.21E-8   |
| Alanine                           | -     | 0.62 | 0.45, 0.87   | 0.006     |
| Body fat percentage               | 61    | 1.71 | 1.46, 2.02   | 9.61E-11  |
| Age at menarche                   | 31    | 0.88 | 0.83, 0.95   | 3.00E-4   |
| Insomnia                          | 32    | 1.17 | 1.10, 1.25   | 2.90E-6   |
| Systolic blood pressure           | 32    | 1.26 | 1.11, 1.43   | 4.80E-4   |
| Lifetime smoking                  | 15    | 1.19 | 0.93, 1.51   | 0.162     |
| Isoleucine                        | 45    | 1.23 | 0.91, 1.65   | 0.176     |
| Childhood BMI                     | 79    | 1.78 | 1.26, 2.51   | 0.001     |
| Caffeine intake                   | -     | 1.10 | 0.92, 1.32   | 0.283     |
| Birthweight                       | -     | 0.72 | 0.59, 0.88   | 1.58E-3   |
| Testosterone                      | -     | 0.79 | 0.62, 1.00   | 0.048     |
| SHBG adjusted for BMI             | -     | 0.61 | 0.51, 0.72   | 1.18E-8   |
| Valine                            | -     | 1.27 | 0.92, 1.77   | 0.148     |
| Leucine                           | -     | 1.34 | 0.90, 1.99   | 0.148     |
| HDL cholesterol                   | 72    | 0.77 | 0.65, 0.91   | 0.002     |
| Total cholesterol                 | 54    | 0.94 | 0.83, 1.07   | 0.351     |
| Adulthood height                  | 23    | 0.97 | 0.94, 1.00   | 0.039     |
| Alanine aminotransferase          | 0     | 1.01 | 0.99, 1.03   | 0.315     |
| Coffee consumption                | 33    | 1.50 | 1.13, 1.98   | 0.005     |
| Phenylalanine                     | -     | 1.43 | 0.95, 2.15   | 0.083     |
| Tyrosine                          | -     | 0.73 | 0.53, 1.02   | 0.066     |
| Sodium (urinary)                  | 66    | 2.75 | 1.07, 7.09   | 0.036     |
| IL-6 receptor subunit $\alpha$    | -     | 0.98 | 0.95, 1.01   | 0.148     |
| IL-1 receptor antagonist          | -     | 1.10 | 0.82, 1.49   | 0.522     |
| LDL cholesterol                   | 57    | 0.99 | 0.88, 1.13   | 0.957     |
| Giant cell arteritis              | 0     | 1.07 | 1.01, 1.13   | 0.015     |
| Fetuin-A levels                   | -     | 0.97 | 0.92, 1.03   | 0.276     |

CI indicates confidence interval; IVW, inverse-variance weighted; SHBG, sex hormone binding globulin; SNP, single nucleotide polymorphism.
ESM Fig 1. Rationale and key assumptions for Mendelian randomization study
ESM Fig 2. Scatterplot of the alcohol-associated single nucleotide polymorphisms (SNPs) with alcohol consumption (standard deviations of log-transformed drinks/week) and type 2 diabetes (T2D)

The solid line and shaded area represent the MR-Egger causal estimate with its 95% confidence interval, respectively.