Supplement 1.

***UK Biobank cohort and definition of criterion for depression and anxiety***

The genotype data from 488,377 participants was obtained from the UK Biobank under UKB application 46478 (http://www.ukbiobank.ac.uk/about-biobank-uk/). The UK Biobank project is a large-scale prospective cohort study with deep genetic and health information from half a million UK participants since 2006, aged between 40 and 69 at recruitment (Bycroft et al., 2018). We have excluded the non-European subjects of UK Biobank in this study. The genotype data of the UK Biobank was restricted to only ‘white British’ based on self-reported ethnicity (UK Biobank field ID: 21000) in this study. Genotyping was performed using two similar genotyping arrays (UK BiLEVE Axiom Array and UK Biobank Axiom Array). Quality control (QC), imputation and post-imputation cleaning were performed centrally by the UK Biobank. In addition to routine quality checks approaches carried out during the process of sample retrieval, DNA extraction and genotype calling, specifically designed QC pipeline based on principal component analysis (PCA) was used to account for ethnically diverse population structure in both marker-based QC and sample-based QC (Bycroft et al., 2018). Marker-based QC was performed by using statistical tests designed primarily to check for consistency of genotype calling across experimental factors to identify poor quality markers. Single-nucleotide variants (SNPs) with calling rate < 98.5%, minor allele frequency (MAF) < 0.01 were removed. Samples with calling rate < 98.0% and mismatch between inferred sex and self-reported sex were removed. Imputation was carried out using the Haplotype Reference Consortium (HRC) reference panel and the IMPUTE4 software (https://jmarchini.org/software/) (Howie, Donnelly, & Marchini, 2009). Genotypes that were not directly assayed on this panel were then imputed with the UK 10K and the 1000 Genomes phase 3 reference panel. The genetically related subjects were excluded using the KING software (Manichaikul et al., 2010). Details regarding the UK Biobank's genotyping, QC and imputation can be found in the published study (Bycroft et al., 2018).

Two common psychiatric disorders were analyzed in this study, including depression (based on self-reported depression and the Patient Health Questionnaire (PHQ-9) scores) and anxiety (based on self-reported anxiety and the generalized anxiety disorder-7 (GAD-7) scores). Criteria for the diagnoses of depression and anxiety were derived from the definition of Davis et al (Davis et al., 2019).

For depression, the present study included 119,637 participants (66,703 females, 56.24 ± 7.61 years) having Patient Health Questionnaire (PHQ-9) data, and 121,191 participants (58,043 self-reported depression patients and 63,148 controls, 56.47 ± 7.65 years) having self-reported depression status data.

PHQ-9 (Kroenke, Spitzer, Williams, & Löwe, 2010) is a diagnostic algorithm to make a probable diagnosis of depression as a continuous measure with a total score (0-27), focusing on nine depressive symptoms and signs (as detailed below in UK Biobank: Little interest or pleasure in doing things 20514, Feeling down, depressed, or hopeless 20510, Trouble sleeping 20517, Feeling tired 20519, Poor appetite or overeating 20511, Feeling bad about yourself 20507, Trouble concentrating 20508, Moving or speaking slowly or fidgety or restless 20518, Thoughts that you would be better off dead 20513). The PHQ-9 score is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of 'not at all', 'several days', 'more than half the days', and 'nearly every day', respectively, and adding together the scores for the nine questions. However, the 9 symptom scores in the UK biobank range from 1 to 4. So we reduced the 9 symptom scores in UK biobank by 1 point and then added them up to in line with the score for each item in PHQ-9.

According to the previous study (Davis et al., 2019), the self-reported depression patients were defined by the code 1286 (denoting depression) from UK Biobank data field 20002 (Non-cancer illness code, self-reported), code 3 (denoting Probable Recurrent major depression (severe)), 4 (denoting Probable Recurrent major depression (moderate)) or 5 (denoting Single Probable major depression episode) from UK Biobank data field 20126 (Bipolar and major depression status) and code 11 (denoting depression) from UK Biobank data field 20544 (Mental health problems ever diagnosed by a professional).

For the control group of depression, after excluding participants with self-reported depression and depression single episode defined in Davis et al. study (Davis et al., 2019), we selected the participants who did not endorse depression and screened negative on PHQ or composite international diagnostic interview (CIDI) (Kessler, Andrews, Mroczek, Ustun, & Wittchen, 1998; Kroenke et al., 2010). According to CIDI (Kessler et al., 1998), core depression symptoms were defined by the UK Biobank data field 20446 and 20441. We chose the participants who response “NO” to the question “Have you ever had a time in your life when you felt sad, blue, or depressed for two weeks or more in a row?” or “Have you ever had a time in your life lasting two weeks or more when you lost interest in most things like hobbies, work, or activities that usually give you pleasure?” as non-depressed patients. More precisely, participants whose PHQ score ≤5 and did not have core symptoms were selected.

For anxiety, this study consisted 120,202 participants (67,010 females, 56.23 ± 7.61 years) having the GAD-7 data, and 107,947 participants (21,713 self-reported anxiety patients and 86,234 controls, 56.49 ± 7.57 years) having self-reported anxiety status data.

GAD-7 (Kroenke et al., 2010) is a classification algorithm to screen for and measure anxiety severity with scores ranging from 0 to 21, focusing on seven anxious symptoms and signs (as detailed below in UK Biobank: Feeling nervous, anxious or on edge 20506, Not being able to stop or control worrying 20509, Worrying too much about different things 20520, Trouble relaxing 20515, Being so restless that it is hard to sit still 20516, Becoming easily annoyed or irritable 20505, Feeling afraid as if something awful might happen 20512).The GAD-7 score is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of 'not at all', 'several days', 'more than half the days', and 'nearly every day', respectively, and adding together the scores for the seven questions. Score of 5 is taken as the cut-off point for mild anxiety. But the 7 symptom scores in the UK biobank range from 1 to 4. In order to in line with the score for each item in GAD, we reduced the 7 symptom scores in UK biobank by 1 point and then added them up.

According to the previous study (Davis et al., 2019), self-reported anxiety patients were defined by code 1287 (denoting anxiety/panic attacks) from UK Biobank data field 20002 (Non-cancer illness code, self-reported) and code 15 (denoting anxiety, nerves or generalized anxiety disorder) from UK Biobank data field data field 20544 (Mental health problems ever diagnosed by a professional).

For control group of anxiety, after excluding participants with self-reported anxiety and anxiety symptoms defined in Davis et al. study (Davis et al., 2019), we collected the participants who screened negative on GAD (GAD scores <5) (Kessler et al., 1998; Kroenke et al., 2010).

***UKB field corresponding to the definition of depression and anxiety***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Section A: present and past depression.** | | | | |
| **PHQ score:** | | | | |
| 1. **20514** 2. **20510** 3. **20534** 4. **20519** 5. **20511** 6. **20507** 7. **20508** 8. **20518** 9. **20513** | Over the last 2 weeks, how often have you been bothered by any of the following problems?  a. Little interest or pleasure in doing things  b. Feeling down, depressed, or hopeless  c. Trouble falling or staying asleep, or  sleeping too much  d. Feeling tired or having little energy  e. Poor appetite or overeating  f. Feeling bad about yourself or that you  are a failure or have let yourself or your  family down  g. Trouble concentrating on things, such  as reading the newspaper or watching  television  h. Moving or speaking so slowly that other  people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual  i. Thoughts that you would be better off  dead or of hurting yourself in some way | | [Select one from the following for each of the statements]  - 01 Not at all  - 02 Several days  - 03 More than half the days  - 04 Nearly every day  - DA Prefer not to answer | |
| **Depressive symptoms:** | | | | | |
| **20446** | | Have you ever had a time in your life when you felt sad, blue, or depressed for two weeks or more in a row? | | [Select one from]  - 01 Yes  - 00 No  - DA Prefer not to answer | |
| **20441** | | Have you ever had a time in your life lasting two weeks or more when you lost interest in most things like hobbies, work, or activities that usually give you pleasure? | | [Select one from]  - 01 Yes  - 00 No  - DA Prefer not to answer | |

**Depression single episode:**

|  |  |  |
| --- | --- | --- |
|  | Please think of the two-week period in your life when your feelings of depression or loss of interest were worst: |  |
| **20447** | Did this worst period start within two months of the death of someone close to you or after a stressful or traumatic event in your life? | [Select one from]  - 01 Yes  - 00 No  -DA Prefer not to answer |
| **20436 (Fraction of day affected)** | How much of the day did these feelings usually last? | - 04 All day long  - 03 Most of the day  - 02 About half of the day  - 01 Less than half of the day  - NA Do not know  - DA Prefer not to answer |
| **20439 (Frequency of depressed days)** | Did you feel this way | - 03 Every day  - 02 Almost every day  - 01 Less often  - NA Do not know  - DA Prefer not to answer |
| **20449** | Did you feel more tired out or low on energy than is usual for you? | - 01 Yes  - 00 No  - NA Do not know  - DA Prefer not to answer |
| **20536** | Did you gain or lose weight without trying, or did you stay about the same weight? | - 01 Gained weight  - 02 Lost weight  -03 Both gained and lost some weight during the episode  - 00 Stayed about the same or was on a diet  - NA Do not know  - DA Prefer not to answer |
| **20532** | Did your sleep change? | - 01 Yes  - 00 No  - NA Do not know  - DA Prefer not to answer |
| **a) 20533**  **b) 20535**  **c) 20534** | Was that:  a Trouble falling asleep  b Waking too early  c Sleeping too much | [Three questions grouped together, each with forced choice]  - 01 Yes  - 00 No |
| **20435** | Did you have a lot more trouble concentrating than usual? | - 01 Yes  - 00 No  - NA Do not know  - DA Prefer not to answer |
| **20450** | People sometimes feel down on themselves, no good, worthless. Did you feel this way? | - 01 Yes  - 00 No  - NA Do not know  - DA Prefer not to answer |
| **20437** | Did you think a lot about death – either your own, someone else’s or death in general? | - 01 Yes  - 00 No  - UN Do not know  - DA Prefer not to answer |
| **20438 (Duration of worst depression)** | About how long altogether did you feel this way? Count the time before, during and after the worst two weeks. | - 01 Less than a month  - 02 Between one and three months  - 03 Over three months, but less than six months  - 04 Over six months, but less than 12 months  - 05 One to two years  - 06 Over two years  - DA Prefer not to answer |
| **20440** | Think about your roles at the time of this episode, including study / employment, childcare and housework, leisure pursuits. How much did these problems interfere with your life or activities? | - 03 A lot  - 02 Somewhat  - 01 A little  - 00 Not at all  - DA Prefer not to answer |
|  | Regarding times in your life when you have had feelings of depression or loss of interest: |  |
| **20442** | How many periods did you have in your life lasting two or more weeks where you felt like this? | - 01 One  - 02 Several  - DA Prefer not to answer |
| **20442** | Enter number | Abox1: Integer box 2 – 999  Abox1 & “number of times”  OR  - 01 Too many to count / One episode ran into the next. |
| **20433** | About how old were you the FIRST time you had a period of two weeks like this? (Whether or not you received any help for it.) | Abox2: Integer box 2 to current age  Abox2 & “years of age when first felt this way”  OR  - UN Do not know  OR  - DA Prefer not to answer |
| **20445** | Did this episode occur within months of giving birth? Or has it been suggested you had post-natal depression? | - 01 Yes  - 00 No  - NA Not applicable  - UN Do not know  - DA Prefer not to answer |
| **20434** | About how old were you the LAST time you had a period of two weeks like this? (Whether or not you received any help for it) | Abox3: Integer box 2 to current age  Abox3 & “years of age when last felt this way”  Or  - UN Don’t know  Or  - DA Prefer not to answer |
| **20448** | Did you ever tell a professional about these problems (medical doctor, psychologist, social worker, counsellor, nurse, clergy, or other helping professional)? | - 01 Yes  - 00 No  - UN Do not know  - DA Prefer not to answer |
| **20546** | Did you ever try the following for these problems? (tick all that apply) | [Select up to three]  - 01 Medication prescribed to you (for at least two weeks)  - 02 Unprescribed medication  (more than once)  - 03 Drugs or alcohol (more than once)  - 00 None of the above  - DA Prefer not to say |
| **20547** | Did you ever try talking therapies for these problems, or other structured activities you regard as therapeutic? Include only those you attended more than once. | [Select up to two]  - 01 Talking therapies, such as psychotherapy, counselling, group therapy or CBT  - 02 Other therapeutic activities such as mindfulness, yoga or art classes  - 00 None of the above  - DA Prefer not to answer |
| **Section B: generalized anxiety disorder** | | |
| **GAD-7** | | |
| 1. **20506** 2. **20509** 3. **20520** 4. **20515** 5. **20516** 6. **20505** 7. **20512** | Over the last 2 weeks, how often have you been bothered by any of the following problems?  a) Feeling nervous, anxious or on edge  b) Not being able to stop or control worrying  c) Worrying too much about different things  d) Trouble relaxing  e) Being so restless that it is hard to sit still  f) Becoming easily annoyed or irritable  g) Feeling afraid as if something awful might happen  [7 questions on one screen in grid] | [Select one from the following for each of the statements]  - 01 Not at all  - 02 Several days  - 03 More than half the days  - 04 Nearly every day  - DA Prefer not to answer |
| **GAD ever** | | |
| **20421** | Have you ever had a period lasting one month or longer when most of the time you felt worried, tense, or anxious? | - 01 Yes  - 00 No  - UN Do not know  - DA Prefer not to answer |
| **20420** | What is the longest period of time that this kind of worrying has ever continued? | Bbox2: Integer 0-99  Bbox1: Integer 0-11  Bbox02 & “year(s) and” & Bbox01 & “month(s)”  OR  - 03 All my life / as long as I can remember |
| **20425** | People differ a lot in how much they worry about things. Did you ever have a time when you worried a lot more than most people would in your situation? | - 01 Yes  - 00 No  - UN Do not know  - DA Prefer not to answer |
|  | Please think of the period in your life when you have felt worried, tense, anxious, or more worried than most people would in your situation. This could be in the past, or it could be continuing now. |  |
| **20542** | During that period, was your worry stronger than in other people? | - 01 Yes  - 00 No  - UN Do not know  - DA Prefer not to answer |
| **20538** | Did you worry most days? | - 01 Yes  - 00 No  - UN Do not know  - DA Prefer not to answer |
| **20543** | Did you usually worry about one particular thing, such as your job security or the failing health of a loved one, or more than one thing? | - 01 One thing  - 02 More than one thing  - UN Do not know  - DA Prefer not to answer |
| **20541** | Did you find it difficult to stop worrying? | - 01 Yes  - 00 No  - UN Do not know  - DA Prefer not to answer |
| **20540** | Did you ever have different worries on your mind at the same time? | - 01 Yes  - 00 No  - UN Do not know  - DA Prefer not to answer |
| **20539** | How often was your worry so strong that you couldn’t put it out of your mind no matter how hard you tried? | - 03 Often  - 02 Sometimes  - 01 Rarely  - 00 Never  - UN Do not know  - DA Prefer not to answer |
| **20537** | How often did you find it difficult to control your worry? | - 03 Often  - 02 Sometimes  - 01 Rarely  - 00 Never  - UN Do not know  - DA Prefer not to answer |
| 1. **20426** 2. **20423** 3. **20429** 4. **20419** 5. **20422** 6. **20417** 7. **20427** | When you were worried or anxious, were you also:  a) Restless?  b) Keyed up or on edge?  c) Easily tired?  d) Having difficulty keeping your mind on what you were doing?  e) More irritable than usual?  f) Having tense, sore, or aching muscles?  g) Often having trouble falling or staying asleep?  [Seven questions on one screen] | Force choice:  - 01 Yes  - 02 No  - NA Do not know  For following options: |
|  | Regarding times in your life when you have felt worried, tense or anxious: |  |
| **20428** | Did you ever tell a professional about these problems (medical doctor, psychologist, social worker, counsellor, nurse, clergy, or other helping professional)? | - 01 Yes  - 00 No  - UN Do not know  - DA Prefer not to answer |
| **20549** | Did you ever use the following for the worry or the problems it caused? (tick all that apply):  Please include any treatments that you have already told us about under ‘depression’ if they were also for anxiety: | - 01 Medication prescribed to you (for at least two weeks)  - 02 Unprescribed medication  (more than once)  - 03 Drugs or alcohol (more than once)  - 00 None of the above  - DA Prefer not to say |
| **20550** | Did you ever try talking therapies for these problems, or other structured activities you regard as therapeutic? Include only those you attended more than once.  Please include any treatments that you have already told us about under “depression” if they were also for anxiety: | [Select up to two]  - 01 Talking therapies, such as psychotherapy, counselling, group therapy or CBT  -02 Other therapeutic activities such as mindfulness, yoga or art classes  - 00 None of the above  - DA Prefer not to answer |
| **20418** | Think about your roles at the time of this episode, including study / employment, childcare and housework, leisure pursuits. How much did these problems interfere with your life or activities? | [Choose one of]  - 03 A lot  - 02 Somewhat  - 01 A little  - 00 Not at all  - DA Prefer not to answer |

***References***

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