**Supplementary Table 1. Sociodemographic differences between persons with atypical**

**depression versus depression with typical neurovegetative symptoms**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Atypical Depression** | | **Typical Depression** | |  |  |
|  |  | N=2,305 |  | N=12,660 |  |  |  |
|  |  | **n** | **%** | **n** | **%** | **OR (95% CI)** | **P value** |
| Age | 45to54  55to64  65to74  75Plus | 625  1,051  585  44 | 27.1  45.6  25.4  1.9 | 2,324  5,002  4,757  577 | 18.4  39.5  37.6  4.6 | Ref  0.78(0.70-0.87)  0.45(0.40-0.51)  0.28(0.21-0.39) | P < 0.001  P < 0.001  P < 0.001 |
| Gender | Female  Male | 1,732  573 | 75.1  24.9 | 9,575  3,085 | 75.6  24.4 | Ref  1.03(0.92-1.14) | P = 0.61 |
| Education | None  Other(vocational)  Secondary school  A level  Degree | 113  89  705  397  974 | 5.0  3.9  31.0  17.4  42.8 | 794  700  3,895  1,768  5,378 | 6.3  5.6  31.1  14.1  42.9 | Ref  0.89(0.66-1.20)  1.27(1.03-1.57)  1.57(1.26-1.98)  1.27(1.03-1.57) | P = 0.45  P < 0.01  P < 0.001  P < 0.05 |
| Income | <£18,000  £18,000-30,000  £30,000-52,000  £52,000-100,000  >£100,000 | 442  511  597  457  94 | 21.0  24.3  28.4  21.8  4.5 | 1,944  2,798  3,270  2,709  733 | 17.0  24.4  28.6  23.7  6.4 | Ref  0.80(0.69-0.92)  0.80(0.70-0.92)  0.74(0.64-0.85)  0.56(0.44-0.71) | P < 0.01  P < 0.01  P < 0.001  P < 0.001 |
| House ownership | Rent social  Rent private  Own mortgage  Own outright | 197  120  1,078  839 | 8.8  5.4  48.3  37.6 | 474  366  5,483  6,062 | 3.8  3.0  44.3  49.0 | Ref  0.78(0.61-1.02)  0.47(0.39-0.56)  0.33(0.27-0.40) | P = 0.07  P < 0.001  P < 0.001 |

*Note:* Atypical depression is defined as meeting the DSM-V criteria for MDD and reporting symptoms of hypersomnia and weight gain; depression with typical neurovegetative symptoms is defined as meeting the DSM-V criteria for MDD and reporting symptoms of hyposomnia and weight loss.

**Supplementary Table 2. Differences in depression age of onset, severity, recurrence, episode duration, and help seeking between persons with atypical depression versus depression with typical neurovegetative symptoms**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Atypical Depression** | | **Typical Depression** | |  |  |
| N=2,305 | | N=12,660 |  |  |  |
|  | **N** | **Mean (SD)** | **N** | **Mean (SD)** | **OR (95% CI)** | **P value** |
| Age depression onset | 2,120 | 31.9(14.5) | 12,051 | 36.1(14.1) | 0.99 (0.99-0.99) | P < 0.001 |
|  | **N** | **%** | **N** | **%** | **OR (95% CI)** | **P value** |
| Severe depression | 910 | 39.5 | 3,090 | 24.4 | 1.89 (1.72-2.08) | P < 0.001 |
| Recurrent depression | 1,583 | 74.9 | 6,786 | 55.8 | 2.26 (2.04-2.52) | P < 0.001 |
| Duration of worst episode |  |  |  |  |  |  |
| <1 month | 76 | 3.3 | 654 | 5.2 | Ref |  |
| 1 to 3 months | 436 | 19.0 | 3,347 | 26.6 | 1.14(0.88-1.46) | P < 0.05 |
| 3 to 6 months | 440 | 19.2 | 2,693 | 21.4 | 1.43(1.10-1.85) | P < 0.001 |
| 6 to 12 months | 434 | 18.9 | 2,600 | 20.7 | 1.47(1.14-1.91) | P < 0.001 |
| 1 to 2 years | 352 | 15.4 | 1,864 | 14.8 | 1.74(1.33-2.27) | P < 0.001 |
| >2 years | 554 | 24.2 | 1,410 | 11.2 | 3.56(2.74-4.61) | P < 0.001 |
| Help seeking for depression | 2,076 | 90.1 | 10,387 | 82.2 | 1.94(1.67-2.25) | P < 0.001 |

*Note:* Models are adjusted for age and gender

**Supplementary Table 3. Differences in lifestyle factors and adverse life events between persons with atypical depression versus depression with typical neurovegetative symptoms**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Atypical Depression** | | **Typical Depression** | |  |  |
|  |  | N=2,305 |  | N=12,660 |  |  |  |
| ***Lifestyle factors*** |  | **n** | **%** | **n** | **%** | **OR (95% CI)** | **P value** |
| Smoking | Never  Ever | 1,117 | 48.7 | 5,962 | 47.2 | Ref  1.11(1.01-1.21) | P < 0.05 |
| Social isolation | No  Yes | 293 | 12.9 | 1,233 | 9.8 | Ref  1.37(1.20-1.58) | P < 0.001 |
| Loneliness | No  Yes | 223 | 10.1 | 668 | 5.4 | Ref  1.74(1.50-2.01) | P < 0.001 |
| Moderate physical activity | No  Yes | 1,312 | 56.9 | 8,244 | 65.1 | Ref  0.80(0.74-0.88) | P < 0.001 |
| ***Childhood adversities*** | |  |  |  |  |  |  |
| Felt loved | Yes  No | 378 | 16.5 | 1,311 | 10.4 | Ref  1.66 (1.46-1.88) | P < 0.001 |
| Felt hated | No  Yes | 645 | 28.1 | 2,205 | 17.5 | Ref  1.72(1.55-1.91) | P < 0.001 |
| Physical abuse | No  Yes | 449 | 19.6 | 1,762 | 13.9 | Ref  1.40(1.25-1.57) | P < 0.001 |
| Sexual abuse | No  Yes | 251 | 11.2 | 971 | 7.8 | Ref  1.42(1.22-1.65) | P < 0.001 |
| Had someone to take to doctor when needed as a child | Yes  No | 263 | 11.5 | 1,021 | 8.1 | Ref  1.50(1.-1.73) | P < 0.001 |
| ***Adulthood adversities*** | |  |  |  |  |  |  |
| Been in confiding relationship | Yes  No | 450 | 19.9 | 1,799 | 14.5 | Ref  1.47(1.31-1.65) | P < 0.001 |
| Physical violence by (ex)partner | No  Yes | 394 | 17.2 | 1,641 | 13.0 | Ref  1.33(1.18-1.50) | P < 0.001 |
| Belittlement by (ex)partner | No  Yes | 837 | 36.5 | 3,562 | 28.2 | Ref  1.41(1.28-1.55) | P < 0.001 |
| Non-consensual sexual interference by (ex)partner | No  Yes | 201 | 8.8 | 744 | 5.9 | Ref  1.49(1.26-1.75) | P < 0.001 |
| Unable to pay rent or mortgage | No  Yes | 317 | 13.9 | 1,226 | 9.8 | Ref  1.46(1.28-1.67) | P < 0.001 |
| ***Catastrophic trauma*** | No  Yes | 1,562 | 67.8 | 7,232 | 57.1 | Ref  1.56(1.42-1.71) | P < 0.001 |

*Note*: Models are adjusted for age and gender. Catastrophic trauma is defined being attacked, mugged, robbed,

exposed to violent crime, sexual assault, serious accidents, life-threatening illness, combat or war, violent death.

**Supplementary Table 4. Differences in psychiatric and physical comorbidities between persons with atypical depression versus depression with typical neurovegetative symptoms**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Atypical Depression** | | | | **Typical Depression** | | | |  | |  | |
|  | N=2,305 | |  | | N=12,660 | |  | |  | |  | |
| ***Probable psychiatric diagnoses based on self-reported symptoms*** | | | | | |  | |  | |  | |
|  | **n** | | **%** | | **n** | | **%** | | **OR (95% CI)** | | **P value** | |
| Wider Bipolar | 166 | | 7.4 | | 536 | | 4.3 | | 1.66(1.39-2.00) | | P < 0.001 | |
| Bipolar I | 118 | | 5.3 | | 324 | | 2.6 | | 1.94(1.56-2.42) | | P < 0.001 | |
| Bipolar II | 38 | | 1.7 | | 154 | | 1.2 | | 1.32(1.92-1.89) | | P = 0.13 | |
| GAD | 754 | | 60.2 | | 2,884 | | 45.9 | | 1.70(1.50-1.93) | | P < 0.001 | |
| PTSD | 717 | | 31.3 | | 1,970 | | 15.6 | | 2.28(2.06-2.53) | | P < 0.001 | |
| ***Self-reported psychiatric diagnoses*** | |  | |  | |  | |  | |  | |
| Schizophrenia | 14 | | 0.6 | | 25 | | 0.2 | | 2.79(1.43-5.44) | | P < 0.01 | |
| Other psychosis | 50 | | 2.2 | | 140 | | 1.1 | | 1.90(1.37-2.65) | | P < 0.001 | |
| Panic attacks | 413 | | 17.9 | | 1,663 | | 13.1 | | 1.43(1.27-1.61) | | P < 0.001 | |
| Agoraphobia | 40 | | 1.7 | | 119 | | 0.9 | | 1.93(1.34-2.79) | | P < 0.001 | |
| Social phobia | 135 | | 5.9 | | 338 | | 2.7 | | 2.12(1.72-2.61) | | P < 0.001 | |
| Any other phobia | 83 | | 3.6 | | 263 | | 2.1 | | 1.81(1.41-2.33) | | P < 0.001 | |
| OCD | 75 | | 3.3 | | 164 | | 1.3 | | 2.32(1.76-3.07) | | P < 0.001 | |
| Anorexia nervosa | 18 | | 0.8 | | 243 | | 1.9 | | 0.38(0.23-0.61) | | P < 0.001 | |
| Bulimia nervosa | 24 | | 1.0 | | 105 | | 0.8 | | 1.02(0.65-1.61) | | P = 0.90 | |
| Binge-eating | 116 | | 5.0 | | 64 | | 0.5 | | 10.06(7.36-13.75) | | P < 0.001 | |
| ADHD | 10 | | 0.4 | | 19 | | 0.2 | | 2.65(1.22-5.77) | | P < 0.05 | |
| Autism spectrum disorder | 16 | | 0.7 | | 21 | | 0.2 | | 3.43(1.77-6.64) | | P < 0.001 | |
| Personality disorder | 27 | | 1.2 | | 88 | | 0.7 | | 1.49(0.96-2.31) | | P = 0.07 | |
| Any addiction | 360 | | 16.3 | | 1,222 | | 9.9 | | 1.65(1.45-1.88) | | P < 0.001 | |
| Substance Dependence | 232 | | 10.7 | | 759 | | 6.00 | | 1.65(1.41-1.93) | | P < 0.001 | |
| Alcohol Dependence | 61 | | 2.7 | | 178 | | 1.4 | | 1.79(1.32-2.42) | | P < 0.001 | |
| Self-harm | 385 | | 16.8 | | 1,397 | | 11.1 | | 1.47(1.30-1.67) | | P < 0.001 | |
| Suicidal intention among | 219 | | 59.5 | | 801 | | 59.8 | | 1.04(0.82-1.32) | | P = 0.21 | |
| self-harmers |  | |  | |  | |  | |  | |  | |
| ***Physical comorbidities*** |  | |  | |  | |  | |  | |  | |
| Any long-standing illness | 1,169 | | 50.7 | | 4,032 | | 32.5 | | 2.46(2.25-2.70) | | P < 0.001 | |
| CVD | 650 | | 28.3 | | 2,608 | | 20.6 | | 1.92(1.72-2.13) | | P < 0.001 | |
| Metabolic syndrome | 194 | | 8.4 | | 401 | | 3.2 | | 3.48(2.90-4.18) | | P < 0.001 | |
| Body Mass Index (kg/m2) |  | |  | |  | |  | |  | |  | |
| *Normal (< 18.5)* | 334 | | 14.5 | | 5,909 | | 46.8 | | Ref. | |  | |
| *Underweight (18.5–24.9)* | 3 | | 0.1 | | 116 | | 0.9 | | 0.44(0.14-1.40) | | P = 0.16 | |
| *Overweight (25.0–29.9)* | 834 | | 36.2 | | 4,614 | | 36.5 | | 3.58(3.13-4.10) | | P < 0.001 | |
| *Obese (>30)* | 1,131 | | 49.1 | | 1,998 | | 15.8 | | 11.34(9.91-12.99) | | P <0.001 | |

*Note:* Models are adjusted for age and gender

Supplementary Table 5. Tetrachoric correlations between individual depressive symptoms among persons with lifetime probable MDD

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Weight gain | Hypersomnia | Weight loss | Hyposomnia | Concentration | Tiredness | Interest loss | Sadness | Worthlessness | Death thoughts |
| Weight gain | 1.00 |  |  |  |  |  |  |  |  |  |
| Hypersomnia | 0.20\*\*\* | 1.00 |  |  |  |  |  |  |  |  |
| Weight loss | N/A | -0.20\*\*\* | 1.00 |  |  |  |  |  |  |  |
| Hyposomnia | 0.06\*\*\* | N/A | -0.14\*\*\* | 1.00 |  |  |  |  |  |  |
| Concentration | -0.04\* | 0.07\*\*\* | -0.04\* | -0.09\*\*\* | 1.00 |  |  |  |  |  |
| Tiredness | 0.21\*\*\* | 0.34\*\*\* | -0.18\*\*\* | 0.01 | 0.22\*\*\* | 1.00 |  |  |  |  |
| Interest loss | 0.06\*\*\* | 0.26\*\*\* | -0.08\*\*\* | 0.04\*\* | 0.07\*\*\* | 0.13\*\*\* | 1.00 |  |  |  |
| Sadness | -0.08\*\* | 0.02 | -0.06\* | -0.02 | 0.01 | -0.13\* | N/A | 1.00 |  |  |
| Worthlessness | 0.13\*\*\* | 0.20\*\*\* | -0.16\*\*\* | 0.02\* | 0.15\*\*\* | 0.09\*\*\* | 0.17\*\*\* | 0.21\*\*\* | 1.00 |  |
| Death thoughts | 0.01 | 0.04\*\*\* | 0.02\* | -0.08\*\*\* | 0.01 | -0.08\*\*\* | 0.03\* | 0.07\*\* | 0.14\*\*\* | 1.00 |

\* p < 0.05; \*\* p < 0.01; \*\*\*p < 0.001; the correlation between sadness and interest loss could not be computed because there are no depressed persons with a score of zero on both sadness and interest loss given that the MDD criteria require the presence of at least one of the two symptoms.

**Supplementary Table 6: Question and Answer Format of the UK Biobank Mental Health Questionnaire**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** |  | **Question Asked** | **Possible Answers** | |
| ***Sociodemographic factors*** | |  |  |  |
|  |  |  |  | |
| **Age** |  | Please confirm your month & year of | mm yyyy | |
|  |  | birth |  |  |
| **Gender** |  | Please confirm your sex | 0 | = Female |
|  |  |  | 1 | = Male |
|  |  |  |  |  |
| **Education** |  | Which of the following qualifications | 0 | = None of the above |
|  |  | do you have? | 1 | = Other |
|  |  |  | 2 | = GCSE |
|  |  |  | 3 | = A Level |
|  |  |  | 4 | = Degree |
|  |  |  |  |  |
| **Income** |  | What is the average total income | 0 | = <£18,000 |
|  |  | before tax received by your household? | 1 | = £18,000-30,000 |
|  |  |  | 2 | = £30,000-52,000 |
|  |  |  | 3 | = £52,000-100,000 |
|  |  |  | 4 | = >£100,000 |
|  |  |  | UN = Do not know | |
|  |  |  | DA = Prefer not to answer | |
|  |  |  |  | |
| **House ownership** |  | Do you own or rent the | 1= Rent social | |
|  |  | accommodation that you live in? | 2 | = Rent private |
|  |  |  | 3 | = Own mortgage |
|  |  |  | 4 | = Own outright |
|  |  |  | UN = Do not know | |
|  |  |  | DA = Prefer not to answer | |
| ***Risk factors and life events*** | |  |  |  |
|  | |  |  |  |
| **Smoking** |  | Do you smoke tobacco now? (i.e., | 0 | = No |
|  |  | during the baseline UKB assessments) | 1 | = Yes, on most or all days |
|  |  |  | 2 | = Only occasionally |
|  |  |  | 3 | = Prefer not to answer |
|  |  | In the past, how often have you | 0 | = I have never smoked |
|  |  | smoked tobacco? | 1 | = Just tried once or twice |
|  |  |  | 2 | = Smoked occasionally |
|  |  |  | 3 | = Smoked on most or all days |
|  |  |  | 4 | = Prefer not to answer |
|  |  |  | A binary variable was derived for | |
|  |  |  | smoking status: | |
|  |  |  | 0 | = Never smoked, if current smoker = 0 |
|  |  |  | and past smoker < 2; | |
|  |  |  | 1 | = Ever smoker, if current smoker = 1 |
|  |  |  | and/or past smoker > 1 | |
|  |  |  |  | |
| **Moderate physical** |  | In a typical week, on how many days | A binary variable was generated: | |
| **activity** |  | did you do 10 minutes of moderate | 1 | = 10 minutes of moderate physical |
|  |  | physical activities like carrying light | activities at least 3 days a week; | |
|  |  | loads, cycling at normal pace? (do not | 0 | = 10 minutes of moderate physical |
|  |  | include walking) | activities less than 3 days a week; | |
|  |  |  |  |  |

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| --- | --- | --- | --- |
| **Social isolation** | (1) “Including yourself, how many | 1 point for living alone | |
|  | people are living together in your |  |  |
|  | household? Include those who usually |  |  |
|  | live in the house such as students living |  |  |
|  | away from home during term time, |  |  |
|  | partners in the armed forces or |  |  |
|  | professions such as pilots”; |  |  |
|  | (2) “How often do you visit friends or | 1 point for friends and family visit less | |
|  | family or have them visit you? | than once a month | |
|  | (3) “Which of the following | 1 point for no participation in social | |
|  | [leisure/social activities] do you engage | activities at least weekly | |
|  | in once a week or more often?”. |  |  |
|  |  | Total score 0=3 | |
|  |  | A binary variable was derived: | |
|  |  | 0 | = no social isolation, if total score ≤ 1 |
|  |  | 1 | = social isolation, if total score ≥ 2 |
| **Loneliness** | (1) “Do you often feel lonely?” | 0 | = No |
|  |  | 1 | = Yes |
|  | (2) “How often are you able to confide | 0 | = almost daily to once every few |
|  | in someone close to you?” | months | |
|  |  | 1 | = never or almost never |
|  | Elovainio, M., C. Hakulinen, et al. | A binary variable was derived. | |
|  | "Contribution of risk factors to excess | Lonely|: total score = 2 | |
|  | mortality in isolated and lonely | Not lonely|: total score < 2 | |
|  | individuals: an analysis of data from |  |  |
|  | the UK Biobank cohort study." The |  |  |
|  | Lancet Public Health **2**: e260-e266. |  |  |
|  |  |  |  |
| **Childhood adverse** | Includes 1 question from each domain | 0 | = Never true |
| **events** | of the Childhood Trauma | 1 | = Rarely true |
|  | Questionnaire. | 2 | = Sometimes true |
|  |  | 3 | = Often |
|  | *Walker, E. A., et al. (1999). "Adult* | 4 | = Very often true |
|  | *health status of women with histories of* | DA = Prefer not to answer | |
|  | *childhood abuse and neglect." The* |  |  |
|  | *American Journal of Medicine* ***107****(4):* | Binary variables were derived based on | |
|  | *332-339* | the following thresholds: | |
|  |  | 20489 Felt loved as a child < 2 | |
|  |  | OR | |
|  |  | 20488 Physically abused by family as a | |
|  |  | child ≥2 | |
|  |  | OR | |
|  |  | 20487 Felt hated by family member as a | |
|  |  | child ≥2 | |
|  |  | OR | |
|  |  | 20490 Sexually molested as a child ≥2 | |
|  |  | OR | |
|  |  | 20491 Someone to take to doctor when | |
|  |  | needed as a child < 3 | |
|  |  |  |  |
| **Adult adverse events** | Based on answers to the five questions | 0 | = Never true |
|  | of Adult Trauma Screen (written for | 1 | = Rarely true |
|  | this questionnaire). | 2 | = Sometimes true |

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|  |  |  |  |
| --- | --- | --- | --- |
|  |  | 3 | = Often |
|  |  | 4 | = Very often true |
|  |  | DA = Prefer not to answer | |
|  |  | Binary variables were derived based on | |
|  |  | the following thresholds: | |
|  |  | 20522 Been in a confiding relationship as | |
|  |  | an adult < 2 | |
|  |  | 20523 Physical violence by partner or ex- | |
|  |  | partner as an adult ≥ 2 | |
|  |  | 20521 Belittlement by partner or ex- | |
|  |  | partner as an adult ≥2 | |
|  |  | 20524 Sexual interference by partner or | |
|  |  | ex-partner without consent as an adult ≥2 | |
|  |  | 20525 Able to pay rent/mortgage < 3 | |
|  |  |  |  |
| **Catastrophic trauma** | In your life, have you: | Endorsed one or more events from | |
|  | a) Been a victim of a sexual assault, | checklist | |
|  | whether by a stranger or someone you |  |  |
|  | knew? | 0 | = Never |
|  | b) Been attacked, mugged, robbed, or | 1 | = Yes, but not in the last 12 months |
|  | been the victim of a physically violent | 2 | = Yes, within the last 12 months |
|  | crime? | DA = Prefer not to answer | |
|  | c) Been in a serious accident that you |  |  |
|  | believed to be life-threatening at the | A binary variable was derived | |
|  | time? | 0 | = Never |
|  | d) Witnessed a sudden violent death | 1 | = Ever (experienced 1 or several |
|  | (eg. murder, suicide, aftermath of an | catastrophic events within the last 12 | |
|  | accident)? | months or before) | |
|  | e) Been diagnosed with a life- |  |  |
|  | threatening illness? |  |  |
|  | f) Been involved in combat or exposed |  |  |
|  | to a war-zone (either in the military or |  |  |
|  | as a civilian)? |  |  |
|  |  |  |  |
| ***Depression Features*** |  |  |  |
|  |  |  |  |
| **Depression age of onset** | Regarding times in your life when you | Record years of age when first felt this | |
|  | have had feelings of depression or loss | way | |
|  | of interest: | UN = Do not know | |
|  | About how old were you the FIRST | DA = Prefer not to answer | |
|  | time you had a period of two weeks |  |  |
|  | like this? (Whether or not you received |  |  |
|  | any help for it.) |  |  |
|  |  |  | |
| **Severe depression** | Meets criteria for a lifetime diagnosis | A binary variable was derived: | |
|  | of MDD (see Depression Ever below) | 1 | = severe MDD |
|  | and reports all 8/8 symptoms of | 0 | = non-severe MDD |
|  | depression assessed with CIDI-SF and |  |  |
|  | reports a lot of impairment. |  |  |
|  |  |  | |
| **Recurrent depression** | Regarding times in your life when you | Text box for number. | |
|  | have had feelings of depression or loss | 1 | = single depression episode |
|  | of interest: | 2 and above = recurrent depression | |
|  | How many periods did you have in | episodes | |
|  | your life lasting two or more weeks |  |  |
|  | where you felt like this? |  |  |
|  |  |  |  |
| **Depression duration** | Please think of the two-week period in | 1 | = less than a month |
|  | your life when your feelings of | 2 | = between one and three months |

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|  |  |  |  |
| --- | --- | --- | --- |
|  | depression or loss of interest were | 3 | = over three months, but less than six |
|  | worst. About how long did you feel | months | |
|  | this way? | 4 | = over six months, but less than 12 |
|  |  | months | |
|  |  | 5 | = one to two years |
|  |  | 6 | = over two years |
| **Help seeking for** | Regarding times in your life when you | 0 | = No |
| **depression** | have had feelings of depression or loss | 1 | = Yes |
|  | of interest: | UN = Do not know | |
|  | Did you ever tell a professional about | DA = Prefer not to answer | |
|  | these problems (medical doctor, |  |  |
|  | psychologist, social worker, counsellor, |  |  |
|  | nurse, clergy, or other helping |  |  |
|  | professional) |  |  |
|  |  |  |  |
| ***Psychiatric comorbidities based on self-reported diagnoses*** | |  |  |
|  |  |  |  |
| **Clinical diagnoses** | Have you been diagnosed with one or | [Select up to seven from] | |
| **based on self–reports** | more of the following mental health | 0 | = None of the above |
| **(A)** | problems by a professional, even if you | 1 | = Depression |
|  | don’t have it currently? (tick all that | 2 | = Mania, hypomania, bipolar or manic- |
|  | apply): | depression | |
|  |  | 3 | = Anxiety, nerves or generalized |
|  | By professional we mean: any doctor, | anxiety disorder | |
|  | nurse or person with specialist training | 4 | = Social anxiety or social phobia |
|  | (such as a psychologist or therapist). | 5 | = Agoraphobia |
|  |  | 6 | = Any other phobia (e.g. disabling fear |
|  | Please include disorders even if you | of heights or spiders | |
|  | did not need treatment for them or if | 7 | = Panic attacks |
|  | you did not agree with the diagnosis | 8 | = Obsessive compulsive disorder |
|  |  | (OCD) | |
|  |  | DA = Prefer not to answer | |
|  |  |  | |
| **Clinical diagnoses** | Have you been diagnosed with one or | [Select up to eight from] | |
| **based on self–reports** | more of the following~~;~~ mental health | 0 | = None of the above |
| **(B)** | problems by a professional, even if you | 1 | = Anorexia nervosa |
|  | don’t have it currently? (tick all that | 2 | = Bulimia nervosa |
|  | apply): | 3 | = Psychological over-eating or binge- |
|  |  | eating | |
|  | By professional we mean: any doctor, | 4 | = Schizophrenia |
|  | nurse or person with specialist training | 5 | = Any other type of psychosis or |
|  | (such as a psychologist or therapist). | psychotic illness | |
|  | Please include disorders even if you | 6 | = A personality disorder |
|  | did not need treatment for them or if | 7 | = Autism, Asperger’s or autistic |
|  | you did not agree with the diagnosis. | spectrum disorder | |
|  |  | 8 | = Attention deficit or attention deficit |
|  |  | and hyperactivity disorder (ADD/ADHD) | |
|  |  | DA = Prefer not to answer | |
|  |  |  |  |
| **Any addiction** | Have you ever been addicted to or | 1 | = Yes |
|  | dependent on one or more things, | 0 | = No |
|  | including substances (not | UN = Do not know | |
|  | cigarettes/coffee) or behaviors (such as | DA = Prefer not to answer | |
|  | gambling)? |  |  |
|  |  |  |  |
| **Substance Dependence:** | Have you been addicted to or | 1 | = Yes |
|  | dependent on prescription or over-the- | 0 | = No |
|  | counter medication? | UN = Do not know | |
|  |  | DA = Prefer not to answer | |
|  | Have you been addicted to illicit or | 1 | = Yes |
|  | recreational drugs? | 0 | = No |

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|  |  |  |  |
| --- | --- | --- | --- |
|  |  | UN = Do not know | |
|  |  | DA = Prefer not to answer | |
|  |  | *Note:* Substance dependence is a | |
|  |  | subcategory of any addiction | |
|  |  |  |  |
| **Alcohol Dependence:** | Have you been physically dependent | 1 | = Yes |
|  | on alcohol? | 0 | = No |
|  | This means experiencing withdrawal | UN = Do not know | |
|  | symptoms, such as sweating, shaking | DA = Prefer not to answer | |
|  | and nausea, if you didn’t drink. |  |  |
|  |  | *Note:* Alcohol dependence is a | |
|  |  | subcategory of substance dependence | |
|  |  |  |  |
| **Self-harm behaviours** | Have you contemplated harming | 0 | = No |
|  | yourself (for example by cutting, | 1 | = Yes, once |
|  | biting, hitting yourself or taking an | 2 | = Yes, more than once |
|  | overdose)? | DA = Prefer not to answer | |
|  | Have you deliberately harmed yourself, | 0 | = No |
|  | whether or not you meant to end your | 1 | = Yes |
|  | life? | DA = Prefer not to answer | |
|  |  |  |  |
| **Self-harm with suicide** | Have you harmed yourself with the | 0 | = No |
| **attempt** | intention to end your life? | 1 | = Yes |
|  |  | DA = Prefer not to answer | |
|  |  |  |  |
| ***Physical comorbidities*** |  |  |  |
|  |  |  |  |
| **Long-standing illness** | Do you have any long-standing illness, | 0 | = No |
|  | disability or infirmity? | 1 | = Yes |
|  |  | UN = Do not know | |
|  |  | DA = Prefer not to answer | |
|  |  |  |  |
| **Metabolic syndrome** | Participants were classified as having |  |  |
|  | metabolic syndrome if: |  |  |
|  | - Their waist circumference was: |  |  |
|  | ≥ 102 cm for males and |  |  |
|  | ≥ 88 cm for females; |  |  |
|  | - They had any two of the |  |  |
|  | following: diabetes, hypertension, |  |  |
|  | hypercholesterolemia. |  |  |
|  |  |  |  |
| **Diabetes** | **Q1:** Has a doctor ever told you that | 0 | = No |
|  | you have diabetes? | 1 | = Yes |
|  |  | UN = Do not know | |
|  |  | DA = Prefer not to answer | |
|  | **Q2:** Do you regularly take any of the | 1 | = cholesterol lowering medication |
|  | following medications? (you can select | 2 | = blood pressure medication |
|  | more than one answer) | 3 | = insulin |
|  |  | UN = Do not know | |
|  |  | DA = Prefer not to answer | |
|  |  | Participants were considered as diabetes | |
|  |  | cases if they answered | |
|  |  | Q1 = 1 and/or Q2 = 3. | |

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|  |  |  |  |
| --- | --- | --- | --- |
| **Hypertension** | **Q1:** Has a doctor ever told you that | 0 | = No |
|  | you have high blood pressure? | 1 | = Yes |
|  |  | UN = Do not know | |
|  |  | DA = Prefer not to answer | |
|  | **Q2:** Do you regularly take any of the | 1 | = cholesterol lowering medication |
|  | following medications? (you can select | 2 | = blood pressure medication |
|  | more than one answer) | 3 | = insulin |
|  |  | UN = Do not know | |
|  |  | DA = Prefer not to answer | |
|  |  | Participants were considered as | |
|  |  | hypertension cases if they answered | |
|  |  | Q1 = 1 and/or Q2 = 2. | |
|  |  |  |  |
| **Hypercholesterolemia** | **Q1:** Has a doctor ever told you that | 0 | = No |
|  | you have hypercholesterolemia | 1 | = Yes |
|  |  | UN = Do not know | |
|  | **Q2:** Do you regularly take any of the | DA = Prefer not to answer | |
|  | following medications? (you can select |  |  |
|  | more than one answer) | 1 | = cholesterol lowering medication |
|  |  | 2 | = blood pressure medication |
|  |  | 3 | = insulin |
|  |  | UN = Do not know | |
|  |  | DA = Prefer not to answer | |
|  |  | Participants were considered as | |
|  |  | hypertension cases if they answered | |
|  |  | Q1 = 1 and/or Q2 = 1. | |
|  |  |  |  |
| **Cardiovascular disease** | Has a doctor ever told you that you | 1 | = Heart attack |
|  | have had any of the following | 2 | = Angina |
|  | conditions? (You can select more than | 3 | = Stroke |
|  | one answer) | 4 | = High blood pressure |
|  |  | 0 | = None of the above |
|  |  | DA = Prefer not to answer | |
|  |  | A binary variable was derived: | |
|  |  | 0 | = None |
|  |  | 1 | = any of the above |
|  |  |  |  |

11

**Supplementary Table 7. Case and control criteria derived from the UK Biobank Mental Health Questionnaire**

|  |  |  |
| --- | --- | --- |
| **Disorder - case and control** | **Fields and codes** | **Notes and references** |
| **definitions** |  |  |
|  |  |  |
| **Case: Lifetime depression** | At least one core symptom of |  |
|  | depression, most or all of the day on | CIDI-SF (Composite International |
|  | most or all days for a two-week | Diagnostic Interview – Short Form), |
|  | period, with at least five depressive | depression module, lifetime version. |
|  | symptoms that represent a change | Scored based on DSM definition of |
|  | from usual occurring over the same | major depressive disorder |
|  | time-scale, with some or a lot of |  |
|  | impairment. | *Kessler RC, Andrews G, Mroczek D,* |
|  | Persistent sadness (20446) = Yes OR | *Ustun B, Wittchen HU (1998). The* |
|  | Loss of interest (20441) = Yes | *World Health Organization composite* |
|  | AND | *international diagnostic interview* |
|  | How much of day (20436) = Most of | *short‐form (CIDI‐SF). Int J Methods* |
|  | day or All day long | *Psychiatr Res, 7(4):171-85.* |
|  | AND |  |
|  | Did you feel this way (20439) = |  |
|  | Almost every day or Every day AND |  |
|  | Impairment (20440) = Somewhat or A |  |
|  | lot |  |
|  | AND |  |
|  | Total number of symptoms endorsed |  |
|  | (core and others) >= 5 |  |
|  | Persistent sadness (core) 20446; Loss |  |
|  | of interest (core) 20441; Tired or low |  |
|  | energy 20449; Gain or loss of weight |  |
|  | 20536 = Gain, Loss or Gain and loss; |  |
|  | Sleep change 20532; Trouble |  |
|  | concentrating 20435; Feeling |  |
|  | worthless 20450; Thinking about |  |
|  | death 20437 |  |
|  |  |  |
| **Control: Lifetime** | Not endorsing depression or screening | Case plus control plus subthreshold |
| **depression** | positive on PHQ or CIDI | should include all participants with |
|  | NOT (reported diagnosis of depression | valid responses. By excluding |
|  | 20544 or 20002) | subthreshold symptoms, we can be |
|  | AND | confident that this group has not |
|  | NOT Core symptoms from above | experienced a classical depressive |
|  | AND | episode |
|  | PHQ score ≤5 |  |
|  |  |  |
| **Case: Lifetime bipolar** | Ever manic/hyper or irritable, plus at | Case for depression is not required in |
| **disorder type I:** | least three other features (four if never | DSM-IV diagnostic criteria, but it is |
|  | manic/hyper), plus duration a week or | added here to improve the positive |
|  | more, plus symptoms caused | predictive value of the test (see text |
|  | significant problems. Requires also to | and references). This definition does |
|  | be case for depression ever. | not exclude antidepressant-induced |
|  | Case {depression ever} | mania. |
|  | AND |  |
|  | High/Hyper 20501 = 01 OR Irritable | *Cerimele et al. (2014). The prevalence* |
|  | 20502 = 01 | *of bipolar disorder in primary care* |
|  | AND | *samples: a systematic review, General* |
|  | Four features from: | *Hospital Psychiatry 36: 19-25* |
|  |  High/Hyper 20501; Active |  |
|  | 20548(01); Talkative | *Carvalho, A. F., Y. Takwoingi, et al.* |
|  | 20548(02); Less sleep | *(2015). "Screening for bipolar* |
|  | 20548(03); Creative/ideas | *spectrum disorders: a comprehensive* |
|  | 20548(04); Restless |  |
|  |  | 12 |

|  |  |  |
| --- | --- | --- |
|  | 20548(5); Confident | *meta-analysis of accuracy studies."* |
|  | 20548(55); Thoughts racing | *Journal of affective disorders* ***172****:* |
|  | 20548(7); Easily distracted | *337-346* |
|  | 20548(8) |  |
|  | AND |  |
|  | Duration 20492 = A week or more |  |
|  | AND |  |
|  | Symptoms caused problem 20493 = |  |
|  | yes |  |
|  |  |  |
| **Variant: Lifetime bipolar** | As above, without disruption from | There is less agreement over the |
| **type II:** | symptoms | definition of bipolar affective disorder |
|  | Case {depression ever} | type II. DSM-IV criteria require |
|  | AND | symptoms for four days or more. Here |
|  | High/Hyper 20501 = 01 OR Irritable | is one week, so could be predicted to |
|  | 20502 = 01 | miss some cases. |
|  | AND |  |
|  | Four features as above |  |
|  | AND |  |
|  | Duration 20492 = A week or more |  |
|  |  |  |
| **Control: Hypomania /** | NOT {hypomania/mania} AND NOT |  |
| **Mania** | {categorised bipolar on last UKB |  |
|  | categorisation 20126 = 1 or 2} AND |  |
|  | NOT {self-reported bipolar |  |
|  | 20544=10} |  |
|  |  |  |
| **Case: Lifetime GAD** | Excessive worrying about a number of | CIDI-SF (Composite International |
|  | issues, occurring most days for six | Diagnostic Interview – Short Form), |
|  | months and difficult to control, with | GAD module, lifetime version. Scored |
|  | three or more somatic symptoms and | based on DSM definition of GAD |
|  | functional impairment. |  |
|  | Worried tense of anxious (20421) = | *Kessler RC, Andrews G, Mroczek D,* |
|  | Yes | *Ustun B, Wittchen HU. The World* |
|  | AND | *Health Organization composite* |
|  | Duration (20420) >= 6 months or All | *international diagnostic interview* |
|  | my life | *short‐form (CIDI‐SF). Int J Methods* |
|  | AND | *Psychiatr Res. 1998;7(4):171-85.* |
|  | Most days (20538) = Yes |  |
|  | AND | *National Institute for Health and* |
|  | Excessive: More than most (20425) | *Clinical Excellence. Generalised* |
|  | OR Stronger than most (20542) | *anxiety disorder and panic disorder in* |
|  | AND | *adults: management. NICE Clinical* |
|  | Number of issues: More than one | *Guideline CG113 (available at* |
|  | thing (20543) OR Different worries | *https://www.nice.org.uk/guidance/cg1* |
|  | (20540) | *13) 2011* |
|  | AND |  |
|  | Difficult to control: Difficult to stop |  |
|  | worrying (20541) OR Couldn’t put it |  |
|  | out of mind (20539) OR Difficult to |  |
|  | control (20537) |  |
|  | AND |  |
|  | Functional impairment: Role |  |
|  | interference (20418) = Some or A lot |  |
|  | AND |  |
|  | 3 somatic symptoms out of: |  |
|  | Restless. 20426; Keyed up or |  |
|  | on edge. 20423; Easily tired. |  |
|  | 20429; Having difficulty |  |
|  | keeping your mind on what |  |
|  | you were doing. 20419; More |  |
|  |  | 13 |

|  |  |  |
| --- | --- | --- |
|  | irritable than usual. 20422; |  |
|  | Having tense, sore, or aching |  |
|  | muscles. 20417; Often having |  |
|  | trouble falling or staying |  |
|  | asleep. 20427 |  |
|  |  |  |
| **Control: Lifetime GAD** | Not meeting criteria for GAD ever nor | Excluding those that screen positive |
|  | scoring over low cut-off for GAD-7 | for mild anxiety means that there is |
|  | NOT case {GAD ever} | greater confidence that this group have |
|  | AND | not had anxiety disorder |
|  | GAD-7 score < 5 |  |
|  |  |  |
| **Case: Current PTSD** | Case: PCL-6 sum of scores ≥ 14 | Does not currently require catastrophic |
|  |  | trauma, but it refers to “stressful |
|  | Sum of scores on questions | event” in the text of the questions as |
|  | representing the core symptoms of | this is not an exhaustive list of |
|  | PTSD (scored 1-5) | possible traumatic events. |
|  | {[20497Repeated disturbing thoughts](http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20497) |  |
|  | [of stressful experience in past month](http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20497) | Using PHQ item for concentration, |
|  | [20498Felt very upset when reminded](http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20498) | scores out of 29 (conventionally |
|  | [of stressful experience in past month](http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20498) | scores out of 30), and will make it |
|  | [20495Avoided activities or situations](http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20495) | slightly harder to reach conventional |
|  | [because of previous stressful](http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20495) | threshold. |
|  | [experience in past month](http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20495) |  |
|  | [20496Felt distant from other people in](http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20496) | *Lang AJ, Stein MB (2005).An* |
|  | [past month](http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20496) | *abbreviated PTSD checklist for use as* |
|  | [20494Felt irritable or had angry](http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20494) | *a screening instrument in primary* |
|  | [outbursts in past month}](http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20494) | *care. Behaviour Research and* |
|  | + 20508 Trouble concentrating | *Therapy,43(5):585-94* |
|  | (scored 1-4) |  |
|  | (nb biobank coded 0-4, subtract 5 to |  |
|  | adjust) |  |
|  |  |  |
| **Control: Current PTSD** | PCL-6 sum of scores 13 or less. | *Note:* “Current” PTSD refers to |
|  |  | persons meeting the criteria for PTSD |
|  |  | when completing the MHQ |
|  |  | assessments. |
|  |  |  |