**Appendix S1.** List of neurological conditions recorded in the UK Biobank dataset (self-reported by participants; from data fields 6150, 20001 and 20002).

Brain cancer/primary malignant tumour

Brain haemorrhage

Brain/intracranial abscess

Cerebral aneurysm

Cerebral palsy

Chronic/degenerative neurological problem

Dementia/Alzheimer's disease/cognitive impairment

Encephalitis

Epilepsy

Head injury

Infection of nervous system

Ischaemic stroke

Meningeal cancer/malignant meningioma

Meningioma (benign)

Meningitis

Motor neurone disease

Multiple sclerosis

Neurological injury/trauma

Neuroma (benign)

Other demyelinating condition

Other neurological problem

Parkinson's disease

Spina bifida

Stroke

Subarachnoid haemorrhage

Subdural haematoma

Transient ischaemic attack

**Appendix S2.** List of psychotropic medications recorded in the UK Biobank dataset (self-reported by participants; from data field 20003).

| **Mood stabiliser** | **Anti-depressant (SSRI)** | **Anti-depressant** **(other)** | **Anti-psychotic** **(traditional)** | **Anti-psychotic** **(2nd generation)** | **Sedative/hypnotic** |
| --- | --- | --- | --- | --- | --- |
| lithium productPriadel (lithium)Camcolit (lithium)sodium valproateEpilim (sodium valproate)Depakote (semisodium valproate)valproic acid carbamazepine productcarbamazepineTegretol (carbamazepine)Teril (carbamazepine)Teril retard (carbamazepine)Timonil retard (carbamazepine)Epimaz (carbamazepine) | paroxetineSeroxat (paroxetine)fluoxetineProzac (fluoxetine)citalopramCipramil (citalopram) escitalopramCipralex (escitalopram)sertralineLustral (sertraline) fluvoxamine | mirtazapineZispin (mirtazapine)duloxetineCymbalta (duloxetine)Yentreve (duloxetine) venlafaxineEfexor (venlafaxine)amitriptylineElavil (amitriptyline) Tryptizol (amitriptyline)Lentizol (amitriptyline) amitriptyline+perphenazineTriptafen (amitriptyline+perphenazine)amitriptyline+chlordiazepoxideLimbitrol 10 (amitriptyline+chlordiazepoxide)Limbitrol-5 (amitriptyline+chlordiazepoxide)phenelzinemaoi - phenelzineNardil (phenelzine)moclobemideManerix (moclobemide)imipramineTofranil (imipramine)trimipramineSurmontil (trimipramine)dothiepindosulepinProthiaden (dosulepin)Thaden (dosulepin)clomipramineAnafranil (clomipramine)lofepramineGamanil (lofepramine)Lomont (lofepramine)mianserinBolvidon (mianserin)Norval (mianserin) | chlorpromazinecpz - chlorpromazineLargactil (chlorpromazine) haloperidolHaldol (haloperidol)Serenace (haloperidol) fluphenazine decanoatefluphenazineModecate (fluphenazine) Moditen tablet (fluphenazine) Moditen enanthate (fluphenazine)flupentixolFlupenthixol (flupentixol)Depixol (flupentixol)Fluanxol (flupentixol)zuclopenthixolClopixol (zuclopenthixol) loxapineLoxapac (loxapine)droperidol Droleptan (droperidol)trifluoperazineStelazine (trifluoperazine) thioridazineMelleril (thioridazine) | quetiapineSeroquel (quetiapine) risperidoneRisperdal (risperidone) olanzapineZyprexa (olanzapine)aripiprazoleAbilify (aripiprazole) amisulprideSolian (amisulpride)clozapine Clozaril (clozapine) | diazepamdiazepam productValium tablet (diazepam)Valium syrup (diazepam)Valium supp (diazepam)temazepamNormison (temazepam)Euhypnos (temazepam)zopicloneZimovane (zopiclone) zaleplonSonata (zaleplon)zolpidemStilnoct (zolpidem) nitrazepamMogadon (nitrazepam)Nitrados (nitrazepam)Remnos (nitrazepam)Somnite (nitrazepam)Noctesed (nitrazepam)Surem (nitrazepam)Unisomnia (nitrazepam)flunitrazepamRohypnol (flunitrazepam)triazolamHalcion (triazolam) |

**Methods S1.** Detailed description of the cognitive assessments.

Five cognitive measures were administered via computerised touchscreen interface:

* Reasoning

Thirteen questions were presented sequentially via touchscreen on a self-paced basis with an overall time limit of two minutes. Responses were selected from a multiple-choice array. Any questions not attempted during the two-minute time limit were scored as zero. The score for analysis was an unweighted total from 0 to 13 (UK Biobank data field 20016, known as the ‘fluid intelligence’ test), with higher scores indicating better performance.

* Reaction time

This test was based on a ‘Snap’-style computer game, in which participants were asked to press a button with their dominant hand as quickly as possible each time a matching pair of symbols was presented on-screen. Twelve pairs of symbols were presented in total. The score for analysis was the mean time (in milliseconds) to press the button, derived from all trials in which a matching pair occurred (UK Biobank data field 20023). Higher scores indicate slower (i.e. worse) performance.

* Numeric memory

A string of numbers was presented on-screen, and after a brief delay participants were asked to enter it from memory, in reverse order, via a numeric keypad. Each string was presented on screen for a period of 2000ms, plus an additional 500ms multiplied by the string length. A delay of 3000ms occurred between clearing the screen and activating the response keypad. All participants began with a string length of two, and successive strings increased by one, up to a maximum string length of 12. The test was discontinued after five successive incorrect responses at a string length of two, or after two successive incorrect responses at string lengths of three or more. The score for analysis was the maximum string length recalled correctly (UK Biobank data field 4282), with higher scores indicating better performance. This task was phased out before recruitment ended for reasons of time, yielding a smaller sample size than for the other cognitive measures.

* Pairs matching

Pairs of symbols were presented on-screen in a random array. Participants were asked to memorise the position of as many matching pairs as possible. The cards were then turned face down on the screen and participants were asked to touch as many pairs as possible in the fewest tries. The score for analysis was the number of errors made while attempting to select the pairs, with a higher score indicating worse performance. Two trials of this task were administered, one with three pairs of symbols and one with six pairs. Because of a ceiling effect on the three-pair trial, only the score on the six-pair trial of the test was analysed in the present study (UK Biobank data field 399.0.2).

* Prospective memory

The following instruction appeared on the touchscreen: “At the end of the games we will show you four coloured symbols and ask you to touch the blue square. However, to test your memory, we want you to actually touch the orange circle instead”. After a delay during which participants underwent the other cognitive tasks described above, a screen appeared showing four coloured shapes with the instruction to touch the blue square. If the participant touched the orange circle, their response was recorded as ‘correct on first attempt’. If they touched the blue square, they were given a prompt on-screen to try to recall what the original instruction was, and asked to respond again. If they correctly selected the orange circle after receiving this prompt, their response was recorded as ‘correct on second attempt’. All other responses were recorded as incorrect. For the present analyses, data were dichotomised as either ‘correct on first attempt’ or not (derived from UK Biobank data field 20018).

**Methods S2.** Statistical analysis.

Townsend index scores were categorised into quintiles based on frequency to facilitate comparisons across groups on the descriptive and unadjusted analyses; quintile 1 represents the least deprived and quintile 5 the most deprived areas. The characteristics and cognitive performance of each group were summarised using percentages, means and medians, as appropriate, and were compared using one-way ANOVA or the Kruskal-Wallis test for continuous data, and the Pearson *χ*2 test for categorical data. Bivariate associations between cognitive scores and other characteristics were tested using Pearson *χ*2 tests, Pearson or Spearman correlation tests, *t*-tests, or Mann-Whitney *U*-tests, depending on the type and distribution of the variables; standardised effect sizes are reported as Pearson’s *r*, Spearman’s *ρ*, risk ratios (RR), or *η*2. A natural log transformation was applied to normalise the reaction time data, but where results were similar between raw and transformed data, the former are reported for ease of interpretation.

Separate univariate regression models were constructed to investigate the relationship between mood disorder category and each of the five cognitive measures, followed by a series of multivariate models with additional covariates added sequentially. In each regression model, the dependent variable was the cognitive measure. The independent variable was mood disorder category, which was entered as a categorical variable, with the control group as the reference value. The type of regression model used depended on the nature and distribution of the cognitive data and the need to address any violation of model assumptions. For reasoning, reaction time and numeric memory, linear regression models were used, with bootstrapped standard errors to minimise the effect of non-normal residuals and heteroscedasticity; results are presented as unstandardised coefficients with 95% confidence intervals (CI). The distribution of the pairs matching data was found to be significantly positively skewed and leptokurtic, but a log transformation was not advisable due to the presence of zero-values in the data. Instead, a negative binomial regression model was used (results presented as incidence rate ratios [IRR] with 95% CI). Performance on the prospective memory test was coded dichotomously, with 1 representing ‘correct on first attempt’ and 0 representing other outcomes (including correct on second attempt and incorrect), and a logistic regression model was applied; results are presented as odds ratios (OR) with 95% CI.

The first multivariate model (Model 1) adjusted for age and gender. Model 2 also included current smoking status (smoker versus non), alcohol use (daily/almost daily versus other) and psychotropic medication (yes/no). Current depressive symptoms score was added in Model 3. Models 4i and 4ii added degree (yes/no) or Townsend score, respectively, to Model 3; these were added separately at this stage in order to allow separate investigation of their effects, because they are often conflated. Model 5 was the fully adjusted model and included all the covariates in Model 3 plus degree and Townsend score.

The presence of statistically significant interactions between the mood disorder category variable and other covariates (age group [decade], gender, degree, psychotropic medication) was tested by applying the likelihood ratio test to model estimations with and without an interaction term. Where this indicated presence of a significant interaction across the cognitive variables, stratified analyses were then carried out to investigate the differential effect of the covariate on the regression results.

Analyses were repeated using a narrower control group comprising only participants with no mood disorder, for the purpose of comparison. Repeat analyses were also conducted which were restricted to only those participants who provided complete data on all the covariates (and therefore could be entered in to the final model), in order to explore the potential effect of missing data across successive adjusted models.

**Results S1.** Association between cognitive performance and other variables.

* Age

Older age was associated with worse performance on all cognitive tests: reasoning *r*=-0.051; reaction time *ρ*=0.321; numeric memory *r*=-0.118; pairs matching *ρ*=0.145; prospective memory *r*=-0.103 (all *p*<0.001).

* Gender

Men scored slightly better than women on all tests (reasoning *r*=0.058; reaction time *r*=0.085; numeric memory *r*=0.088; prospective memory risk ratio [RR]=1.02; all *p*<0.001) except the pairs matching task, on which women performed marginally better (*r*=0.008, *p*=0.004).

* Deprivation

Slightly better performance was seen on all tests in participants with less deprived Townsend scores: reasoning *ρ*=-0.121; reaction time *ρ*=0.042; numeric memory *ρ*=-0.063; pairs matching *ρ*=0.011; prospective memory *r*=-0.097 (all *p<*0.001).

* Education

Having a degree was associated with better cognitive performance: reasoning *r*=0.307; reaction time *r*=0.089; numeric memory *r*=0.169; pairs matching *r*=0.045; prospective memory RR=1.11 (all *p*<0.001).

* Smoking

There were differences in performance (*p*<0.001) associated with smoking status on all tests except numeric memory. Current smokers showed relatively lower performance on reasoning (mean [SD]: current 5.67 [2.17], former 6.11 [2.11], never 6.07 [2.17]) and prospective memory (% correct on first attempt: current 74.9, former 78.5, never 77.1) but relatively better performance on pairs matching (error score mean [SD]: current 3.87 [3.26], former 4.04 [3.25], never 4.04 [3.41]). Former smokers had the slowest reaction time (median [25th, 75th percentile]: current 543 [484, 622], former 547 [488, 621], never 542 [481, 620]).

* Alcohol

Participants who never consume alcohol obtained the poorest scores on all tests (all *p*<0.001):

* + Reasoning *η*2 0.034;
	+ Reaction time in ms, median (25th, 75th percentile): Never 570 (504, 660); special occasions 559 (496, 640); 1-3 times p/month 539 (480, 617); 1-2 times p/week 539 (480, 617); 3-4 times p/week 535 (480, 610); daily/almost daily 539 (481, 613);
	+ Numeric memory *η*2 0.015;
	+ Pairs matching errors, median (25th, 75th percentile): Never 4 (2, 6); special occasions 3 (2, 6); each other group 3 (2, 5);
	+ Prospective memory % correct on first attempt: Never 64.4; special occasions 69.7; 1-3 times p/month 78.3; 1-2 times p/week 77.4; 3-4 times p/week 81.2; daily/almost daily 81.8.
* Psychotropic medication

Consumption of any psychotropic medication was weakly associated with poorer performance: reasoning *r*=-0.038; reaction time *r*=0.036; numeric memory *r*=-0.041; pairs matching *r*=0.016; prospective memory RR=0.93 (all *p*<0.001).

* Current depressive symptoms

Higher current depressive symptom scores were associated with slightly worse performance on all tests except pairs matching: reasoning *ρ*=-0.056; reaction time *r*=0.016; numeric memory *ρ*=-0.034; prospective memory *r*=-0.037 (all *p*<0.001).

* Neuroticism

Higher neuroticism scores were similarly associated with slightly poorer performance: reasoning *r*=-0.059; reaction time *ρ*=0.011; numeric memory *r*=-0.043; pairs matching *ρ*=0.017; prospective memory *r*=-0.036 (all *p*<0.001).

**Figure S1.** Sample composition.

a. Participants self-reported one or more neurological conditions which can potentially affect cognitive performance (see Appendix S1 for full list).

**Table S1.** Regression models for the association between lifetime mood disorder features and cognitive performance.

|  | **Unadjusted** | **Model 1**a | **Model 2**b | **Model 3**c | **Model 4i**d | **Model 4ii**e | **Model 5**f |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Coefficient****(95% CI)** | ***p*** | **Coefficient****(95% CI)** | ***p*** | **Coefficient****(95% CI)** | ***p*** | **Coefficient****(95% CI)** | ***p*** | **Coefficient (95% CI)** | ***p*** | **Coefficient (95% CI)** | ***p*** | **Coefficient (95% CI)** | ***p*** |
| **Reasoning score**g | n = 139 140 |  | n = 139 140 |  | n = 137 377 |  | n = 126 796 |  | n = 126 000 |  | n = 126 584 |  | n = 125 789 |  |
| Single episode major depression | 0.27(0.23, 0.31) | <.001 | 0.30(0.25, 0.34) | <.001 | 0.31(0.27, 0.36) | <.001 | 0.31(0.26, 0.35) | <.001 | 0.27(0.23, 0.32) | <.001 | 0.30(0.25, 0.35) | <.001 | 0.26(0.22, 0.31) | <.001 |
| Recurrent major depression (moderate) | 0.08(0.05, 0.12) | <.001 | 0.11(0.08, 0.14) | <.001 | 0.16(0.12, 0.20) | <.001 | 0.26(0.22, 0.29) | <.001 | 0.22(0.19, 0.26) | <.001 | 0.25(0.21, 0.30) | <.001 | 0.22(0.18, 0.26) | <.001 |
| Recurrent major depression (severe) | -0.12(-0.17, -0.07) | <.001 | -0.12(-0.17, -0.06) | <.001 | 0.01(-0.04, 0.05) | .758 | 0.18(0.12, 0.23) | <.001 | 0.09(0.03, 0.14) | .002 | 0.21(0.15, 0.27) | <.001 | 0.12(0.07, 0.17) | <.001 |
| Bipolar disorder | -0.27-0.38, -0.17) | <.001 | -0.32(-0.41, -0.22) | <.001 | -0.18(-0.32, -0.04) | .012 | 0.04(-0.08, 0.17) | .488 | -0.03(-0.13, 0.08) | .625 | 0.11(-0.02, 0.23) | .087 | 0.04(-0.06, 0.13) | .442 |
| **Reaction time (ms)**g | n = 142 335 |  | n = 142 335 |  | n = 140 501 |  | n = 129 242 |  | n = 128 320 |  | n = 129 025 |  | n = 128 104 |  |
| Single episode major depression | -6.59(-9.41, -3.77) | <.001 | -6.21(-8.56, -3.87) | <.001 | -6.80(-9.18, -4.42) | <.001 | -6.09(-8.94, -3.23) | <.001 | -5.76(-8.82, -2.69) | <.001 | -5.78(-8.28, -3.28) | <.001 | -5.47(-8.19, -2.75) | <.001 |
| Recurrent major depression (moderate) | -4.96(-7.11, -2.81) | <.001 | -1.85(-3.95, 0.25) | .084 | -3.92(-6.10, -1.73) | <.001 | -6.70(-9.00, -4.41) | <.001 | -6.28(-8.29, -4.26) | <.001 | -6.64(-8.62, -4.66) | <.001 | -6.24(-8.29, -4.20) | <.001 |
| Recurrent major depression (severe) | 4.12(1.52, 6.72) | .002 | 8.48(5.13, 11.83) | <.001 | 3.55(0.39, 6.71) | .028 | -0.51(-3.08, 2.07) | .700 | 0.32(-2.78, 3.41) | .842 | -1.64(-4.23, 0.96) | .216 | -0.82(-3.39, 1.75) | .530 |
| Bipolar disorder | 2.37(-5.28, 10.02) | .543 | 13.93(7.17, 20.70) | <.001 | 8.67(1.91, 15.44) | .012 | 3.48(-2.53, 9.49) | .257 | 4.06(-0.83, 8.95) | .104 | 1.15(-5.43, 7.72) | .733 | 1.70(-5.11, 8.51) | .625 |
| **Numeric memory score**g | n = 42 245h |  | n = 42 245h |  | n = 41 580h |  | n = 38 426h |  | n = 38 151h |  | n = 38 325h |  | n = 38 051h |  |
| Single episode major depression | 0.07 (0.01, 0.13) | .015 | 0.08(0.03, 0.13) | .001 | 0.09(0.03, 0.16) | .003 | 0.09(0.03, 0.15) | .002 | 0.07(0.02, 0.13) | .009 | 0.09(0.04, 0.14) | <.001 | 0.07 (0.02, 0.12) | .004 |
| Recurrent major depression (moderate) | 0.00 (-0.04, 0.04) | .868 | 0.01(-0.03, 0.05) | .644 | 0.04(-0.00, 0.08) | .054 | 0.07(0.02, 0.12) | .003 | 0.06(0.02, 0.10) | .006 | 0.08(0.04, 0.11) | <.001 | 0.06 (0.02, 0.11) | .004 |
| Recurrent major depression (severe) | -0.08 (-0.14, -0.02) | .006 | -0.09(-0.15, -0.03) | .002 | -0.03(-0.10, 0.04) | .364 | 0.04(-0.02, 0.11) | .175 | 0.01(-0.04, 0.06) | .687 | 0.05(-0.02, 0.12) | .126 | 0.02 (-0.04, 0.08) | .505 |
| Bipolar disorder | -0.10 (-0.26, 0.07) | .267 | -0.15(-0.29, -0.01) | .035 | -0.06(-0.19, 0.07) | .354 | 0.04(-0.12, 0.21) | .596 | 0.01(-0.14, 0.16) | .860 | 0.07(-0.08, 0.22) | .383 | 0.03 (-0.10, 0.16) | .606 |
|  | **IRR****(95% CI)** | ***p*** | **IRR****(95% CI)** | ***p*** | **IRR****(95% CI)** | ***p*** | **IRR****(95% CI)** | ***p*** | **IRR****(95% CI)** | ***p*** | **IRR****(95% CI)** | ***p*** | **IRR****(95% CI)** | ***p*** |
| **Pairs matching (errors)**i | n = 143 828 |  | n = 143 828 |  | n = 141 964 |  | n = 130 413 |  | n = 129 446 |  | n = 130 195 |  | n = 129 229 |  |
| Single episode major depression | 0.97 (0.95, 0.98) | <.001 | 0.98 (0.96, 0.99) | .008 | 0.97 (0.95, 0.99) | .002 | 0.97 (0.95, 0.99) | .004 | 0.97 (0.96, 0.99) | .007 | 0.97 (0.96, 0.99) | .005 | 0.98 (0.96, 0.99) | .009 |
| Recurrent major depression (moderate) | 0.98 (0.97, 0.99) | .023 | 1.01 (0.99, 1.02) | .452 | 1.00 (0.99, 1.02) | .852 | 0.99 (0.98, 1.01) | .259 | 0.99 (0.98, 1.01) | .385 | 0.99 (0.98, 1.01) | .301 | 0.99 (0.98, 1.01) | .428 |
| Recurrent major depression (severe) | 1.04 (1.02, 1.06) | <.001 | 1.06 (1.04, 1.08) | <.001 | 1.05 (1.03, 1.07) | <.001 | 1.03 (1.01, 1.05) | .001 | 1.04 (1.02, 1.06) | <.001 | 1.03 (1.01, 1.05) | .002 | 1.03 (1.02, 1.05) | <.001 |
| Bipolar disorder | 1.04 (0.99, 1.08) | .085 | 1.08 (1.04, 1.12) | <.001 | 1.07 (1.03, 1.11) | .001 | 1.04 (0.99, 1.08) | .076 | 1.04 (1.00, 1.09) | .045 | 1.03 (0.99, 1.07) | .148 | 1.04 (0.99, 1.08) | .095 |
|  | **OR****(95% CI)** | ***p*** | **OR****(95% CI)** | ***p*** | **OR****(95% CI)** | ***p*** | **OR****(95% CI)** | ***p*** | **OR****(95% CI)** | ***p*** | **OR****(95% CI)** | ***p*** | **OR****(95% CI)** | ***p*** |
| **Prospective memory (correct 1st attempt)**j | n = 143 136 |  | n = 143 136 |  | n = 141 288 |  | n = 129 885 |  | n = 128 944 |  | n = 129 667 |  | n = 128 727 |  |
| Control group (reference) | 1 | - | 1 | - | 1 | - | 1 | - | 1 | - | 1 | - | 1 | - |
| Single episode major depression | 1.39 (1.31, 1.48) | <.001 | 1.38(1.30, 1.47) | <.001 | 1.41(1.32, 1.50) | <.001 | 1.41(1.32, 1.50) | <.001 | 1.38(1.29, 1.47) | <.001 | 1.40(1.31, 1.49) | <.001 | 1.37 (1.28, 1.47) | <.001 |
| Recurrent major depression (moderate) | 1.15 (1.10, 1.20) | <.001 | 1.12(1.07, 1.17) | <.001 | 1.17(1.12, 1.22) | <.001 | 1.27(1.21, 1.33) | <.001 | 1.25(1.19, 1.31) | <.001 | 1.26(1.20, 1.32) | <.001 | 1.25 (1.19, 1.31) | <.001 |
| Recurrent major depression (severe) | 0.91 (0.87, 0.96) | <.001 | 0.88(0.83, 0.93) | <.001 | 0.97(0.92, 1.02) | .261 | 1.12(1.05, 1.18) | <.001 | 1.08(1.02, 1.15) | .012 | 1.15(1.08, 1.22) | <.001 | 1.11 (1.05, 1.18) | .001 |
| Bipolar disorder | 0.84 (0.75, 0.94) | .003 | 0.77(0.68, 0.86) | <.001 | 0.86(0.76, 0.96) | .010 | 1.01(0.89, 1.14) | .915 | 0.98(0.86, 1.12) | .781 | 1.07(0.94, 1.22) | .293 | 1.05 (0.92, 1.19) | .501 |

CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio.

a. Adjusted for age, gender.

b. Adjusted for age, gender, current smoker, alcohol daily/almost daily, on psychotropic medication.

c. Adjusted for age, gender, current smoker, alcohol daily/almost daily, on psychotropic medication, current depressive symptoms score.

d. Adjusted for age, gender, current smoker, alcohol daily/almost daily, on psychotropic medication, current depressive symptoms score, has a degree.

e. Adjusted for age, gender, current smoker, alcohol daily/almost daily, on psychotropic medication, current depressive symptoms score, Townsend score.

f. Adjusted for age, gender, current smoker, alcohol daily/almost daily, on psychotropic medication, current depressive symptoms score, has a degree, Townsend score.

g. Linear regression with bootstrapped standard errors; omitted reference group was the control group.

h. The Numeric Memory task was removed from the baseline battery before recruitment ended, yielding smaller possible sample sizes than for the other cognitive measures.

i. Negative binomial regression; omitted reference group was the control group.

j. Logistic regression.