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ORIGINAL RESEARCH

Medical and neurobehavioural phenotypes in carriers of X-linked ichthyosis-associated genetic deletions in the UK Biobank

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ABSTRACT

Background X-linked ichthyosis (XLI) is an uncommon dermatological condition resulting from a deficiency of the enzyme steroid sulfatase (STS), often caused by X-linked deletions spanning *STS*. Some medical comorbidities have been identified in XLI cases, but small samples of relatively young patients has limited this. *STS* is highly expressed in subcortical brain structures, and males with XLI and female deletion carriers appear at increased risk of developmental/mood disorders and associated traits; the neurocognitive basis of these findings has not been examined.

Methods Using the UK Biobank resource, comprising participants aged 40–69 years recruited from the general UK population, we compared multiple medical/neurobehavioural phenotypes in males (n=86) and females (n=312) carrying genetic deletions spanning *STS* (0.8–2.5 Mb) (cases) to male (n=190 577) and female (n=277 862) non-carrier controls.

Results We identified an elevated rate of atrial fibrillation/flutter in male deletion carriers (10.5% vs 2.7% in male controls, Benjamini-Hochberg corrected p=0.009), and increased rates of mental distress (p=0.003), irritability (p<0.001) and depressive-anxiety traits (p<0.05) in male deletion carriers relative to male controls completing the Mental Health Questionnaire. While academic attainment was unaffected, male and female deletion carriers exhibited impaired performance on the Fluid Intelligence Test (Cohen's $d \leq 0.05$, corrected p<0.1). Neuroanatomical analysis in female deletion carriers indicated reduced right putamen and left nucleus accumbens volumes (Cohen's $d \leq 0.26$, corrected p<0.1).

Conclusion Adult males with XLI disease-causing deletions are apparently at increased risk of cardiac arrhythmias and self-reported mood problems; altered basal ganglia structure may underlie altered function and XLI-associated psychiatric/behavioural phenotypes. These results provide information for genetic counselling of deletion-carrying individuals and reinforce the need for multidisciplinary medical care.

INTRODUCTION

X-linked ichthyosis (XLI (OMIM: 308100)) is an uncommon dermatological condition characterised by the presence of large dark-brown scales,¹ although much milder skin phenotypes have been reported²; it occurs due to deficiency of the enzyme steroid sulfatase (STS), encoded by the X-linked *STS* gene (OMIM: 300747). *STS* cleaves sulfate

groups from steroid hormones (eg, dehydroepiandrosterone sulfate (DHEAS)) altering their solubility/activity; the XLI-associated skin phenotype arises from cholesterol sulfate accumulation in the stratum corneum. 80–90% of XLI cases are caused by complete/partial deletion of *STS*, with remaining cases attributable to *STS* point mutation(s); the typical deletion (~1.5 Mb) encompasses *STS* and a small number of adjacent genes.³ In ~85% of cases, the mutation is transmitted from unaffected (or mildly affected) carrier mothers, and in the remainder it occurs de novo during parental gametogenesis.⁴

Several extracutaneous comorbidities have been reported in individuals possessing XLI-associated mutations: a) benign corneal opacities affect ~10%–50% of males with XLI and ~25% of female carriers,¹ b) ~20% of males with XLI have cryptorchidism; an associated risk of testicular germ cell cancer is less clear and supported by a few case reports^{1 5} and c) delayed/prolonged labour affects ~60% of female carriers.^{1 6} Occasional comorbidities include: pyloric hypertrophy, congenital defect of the abdominal wall, acute lymphoblastic leukaemia, bilateral periventricular nodular heterotopia and end-stage renal failure.¹ Rare, larger genetic deletions which can include *NLGN4X* and *KAL* are associated with a number of neurological conditions such as epilepsy, intellectual disability, autism and anosmia, and contiguous gene syndromes including Rud, Conradi and Kallman syndromes.^{1 3} To date, samples of patients with XLI and carrier females have been relatively small/superficially phenotyped, and larger-scale studies may reveal hitherto unappreciated comorbidities with implications for morbidity/mortality.

STS is expressed in the developing and adult human brain (with highest expression in subcortical structures^{7 8}) and may therefore influence neurodevelopment. Boys with XLI are at elevated risk of developing attention deficit hyperactivity disorder (ADHD) and motor problems,^{3 9 10} and also potentially early onset psychosis.¹¹ We have previously shown that males with XLI exhibit higher rates of inattention, impulsivity (but not motor impulsivity), mood problems, disruptive behaviour and autism-related traits, and are more likely to be diagnosed with developmental conditions (including ADHD/autism) and mood disorders, when compared with males from the general population.¹² A study of

female carriers revealed a comparable suite of behavioural differences from control subjects, together with an increased likelihood of postpartum depression.⁶ The pattern of behavioural phenotypes seen in males with XLI/carrier females overlaps with that seen in STS-deficient mice,^{13–17} and may therefore be largely ascribed to biological effects of STS deficiency rather than ascertainment or socialisation effects. Previous behavioural phenotyping approaches in XLI have been suboptimal: a) survey-based studies did not collect genetic data and so could not objectively confirm or define *STS* deletion carrier status, and these studies may theoretically have elicited responses from more severely affected individuals inflating risk estimates, b) only relatively early age points have been assessed (average age <45 years) and c) studies have had either no control group, or no contemporaneously recruited control group. No study has yet investigated the cognitive or neurobiological basis of behavioural phenotypes in XLI. To address these limitations/knowledge gaps, here we use the power of the UK Biobank, a large, accessible resource comprising extensively phenotyped and genotyped members of the population of the UK,¹⁸ to compare medical/medication history, objective/self-reported behavioural/mental health measures, cognition and subcortical neuroanatomy between males and females carrying deletions most commonly seen in XLI and sex-matched non-carrier controls.

METHODS

Participants

Participants were individuals (aged 40–69 years) recruited under UK Biobank informed consent procedures between 2006–2010, for which anonymised genotype/phenotype data were available.¹⁹

CNV calling

Anonymised genotype data were downloaded as raw (CEL) files from the UK Biobank website,¹⁹ stored on a secure Linux server and analysed with UNIX-based commands. Affymetrix Power Tools (APT) software²⁰ was used to generate normalised signal intensity data, genotype calls and confidences. This argument incorporated genotypic sex data downloaded from the UK Biobank website, and compared with sex data generated through PennCNV-Affy software.²¹ Approximately 750 000 biallelic markers were analysed through PennCNV-Affy to process cluster plots. Canonical genotype clusters, Log R ratios and B allele frequencies were generated to complete the PennCNV recommended process for CNV calls. Individuals with deletions of 0.8–2.5 Mb spanning *STS* were identified, with calls and coordinates based on the GRCh37/hg19 genome build; this range was selected to reflect the majority of XLI cases, to facilitate robust CNV calling, and to exclude individuals with multiple complex medical issues arising from large contiguous gene deletions. Following QC, CNV data were available for a total of 468 837 individuals.

Measures

Hospital diagnoses according to the International Statistical Classification of Diseases and Related Health Problems Revision-10 (ICD-10),²² self-reported non-cancer illnesses, relevant questions from the Mental Health Questionnaire (MHQ)²³ and medication history were analysed. Highest levels of academic qualification and key performance measures on seven cognitive tasks (transformed and converted to z-scores as described previously²⁴) were also analysed: number of incorrect matches on the Pairs Matching Test (episodic memory), mean time to correctly identify matches in the Reaction Time Task (simple processing

speed), total number of correct answers in the 13-question Fluid Intelligence Test (reasoning/problem-solving),²⁵ maximum number of digits remembered in the ‘Digit Span’ task (numeric working memory), number of correct substitutions in a Symbol Digit Substitution Test (complex processing speed) and time to complete two variants of the Trail Making Task (visual attention). Brain images were acquired using Siemens Skyra 3T scanners in UK Biobank’s imaging centres in Cheadle and Newcastle, UK using identical acquisition protocols²⁶; T1-weighted brain images were processed using automated methods implemented in FreeSurfer²⁷ to obtain volumetric estimates for eight right and left subcortical regions.

Statistics

Data were analysed using SPSS V.25.0 (IBM). As male and female deletion phenotypes could differ in magnitude and/or nature, two comparisons were performed: male deletion carriers versus male non-carriers, and female deletion carriers versus female non-carriers. Across the overall sample for each cognitive/neuroimaging measure, outlying values >2.2 times the IQR below the first quartile, or above the third quartile, were excluded.²⁸ Categorical data were analysed using χ^2 test (continuity-adjusted for 2×2 analyses)/Fisher’s exact test, with ORs and 95% CIs presented as a measure of effect size. Normally distributed data were compared using unpaired t-test. Ordinal/non-normally distributed data, and small datasets (<30 participants), were compared using Mann-Whitney U test, with Cohen’s d presented as a measure of effect size.²⁹ For cognitive analyses with sample sizes >30, hierarchical linear regression controlling for age was performed.²⁴ Data are presented as median values (with 95% CIs) or mean±SE of the mean. Two-sided p values <0.05 were regarded as nominally significant, with p values <0.1 after Benjamini-Hochberg adjustment³⁰ regarded as surviving correction for multiple comparisons.

RESULTS

Identification and characterisation of deletion cases

We identified 86 male and 312 female deletion carriers, and 190 577 male and 277 862 female non-carriers, giving deletion rates of ~1/2200 in males and ~1/890 in females. The mean deletion size was 1.60±0.01 Mb from ChrX:6 487 716–8 087 815, encompassing the *PUDP/HDHD1* (OMIM: 306480), *STS*, *VCX* (OMIM: 300229) and *PNPLA4* (OMIM: 300102) genes and the *MIR4767* microRNA. Male deletion subjects did not differ significantly from male controls in terms of age (58.0±0.8 vs 57.1±0.02 years, respectively, $t[190\ 606]=-0.999$, $p=0.318$); the ages of female deletion subjects and female controls were also equivalent (56.3±0.5 vs 56.7±0.02 years, respectively, $t[228\ 024]=0.736$, $p=0.461$).

ICD-10 diagnoses

Nine ICD-10 unique descriptive codes were present in >2500 males overall and >2.5% of male deletion subjects, of which two were significantly more common in male deletion carriers than in control males (online supplementary table 1): ‘atrial fibrillation/flutter’ (10.5% vs 2.7%, OR 4.2 (95% CI 2.1 to 8.3), $p=0.001$) and ‘skin of other and unspecified parts of face’ (5.8% vs 1.5%, OR 4.0 (95% CI 1.6 to 9.9), $p=0.01$); while these p values would not survive stringent multiple comparison testing taking into account all possible ICD-10 codes, they did survive multiple comparison testing across the nine aforementioned codes (corrected $p=0.009$ and 0.045, respectively). Ten ICD-10 unique descriptive codes were present in >2500

females overall and >2.5% of female deletion subjects, none of which were significantly more common in deletion than control subjects (online supplementary table 2). Diagnosis rates of developmental and mood/anxiety disorders did not differ between male and female deletion and control subjects, although baseline rates of each were very low across groups (<0.5%) (online supplementary tables 3 and 4).

Self-reported non-cancer illnesses

We compared rates of self-reported non-cancer physical/mental illnesses of interest based on the ICD-10 findings above, or previous literature, across groups (online supplementary tables 5 and 6). Compared with male controls, male deletion cases reported a significantly higher prevalence of blistering/desquamating skin disorder (4.7% vs 0.2%, OR 28.6 (95% CI 10.4 to 78.4), corrected $p < 0.020$) and allergy/hypersensitivity/anaphylaxis (4.7% vs 0.5%, OR 9.1 (95% CI 3.3 to 24.9), corrected $p = 0.020$), and a nominally significantly increased rate of heart arrhythmia (3.5% vs 0.6%, OR 5.9 (95% CI 1.9 to 18.6), $p = 0.016$), atrial flutter (1.2% vs 0.0%, OR 31.1 (95% CI 4.3 to 226.6), $p = 0.032$) and eczema/dermatitis (7.0% vs 2.7%, OR 2.7 (95% CI 1.2 to 6.2), $p = 0.028$). Two conditions related to those previously reported in males with XLI were not reported significantly more frequently in male deletion carriers than male controls: ‘undescended testicle’ (0.0% vs 0.1%, $p > 0.99$) and ‘cataract’ (3.5% vs 1.6%, OR 2.3 (95% CI 0.7 to 7.2), $p = 0.15$). No non-cancer illnesses we assessed were reported significantly more frequently in female deletion than female control subjects.

Mental Health Questionnaire

Twenty-one male deletion and 95 female deletion carriers completed the MHQ, together with 58 855 male controls and 76 439 female controls. Male deletion carriers reported a significantly higher likelihood of having suffered mental distress preventing usual activities compared with male controls (57% vs 26%, OR 3.8 (95% CI 1.6 to 9.0), $p = 0.003$), but not a greater likelihood of having sought or received help for mental distress; female deletion carriers did not differ significantly from female controls on these measures (table 1). Mental health diagnoses reported in at least one male or female deletion carrier did not differ in frequency between deletion carriers and controls (table 1). No male or female deletion carriers reported having been diagnosed with any of the following conditions: schizophrenia/other psychotic disorder, personality disorder, mania/

bipolar disorder, bulimia nervosa, psychological overeating/binge eating, autism spectrum conditions, anorexia nervosa, agoraphobia or ADHD, and none of these conditions differed in frequency between deletion carriers and control subjects ($p > 0.99$).

Responses to the remaining questions of the MHQ are presented in online supplementary tables 7 and 8. Male deletion carriers were more likely than male controls to have experienced ‘recent easy annoyance or irritability’ ($p < 0.001$) or to have ‘ever experienced a period of extreme irritability’ ($p = 0.031$), and female deletion carriers were more likely than female controls to have experienced the former ($p = 0.018$) ($d \leq 0.02$). Male deletion carriers were significantly more likely than male controls to have experienced ‘prolonged feelings of sadness or depression’, ‘prolonged loss of interest in normal activities’ (OR 3.9 (95% CI 1.4 to 10.6), $p = 0.009$ and OR 3.5 (95% CI 1.5 to 8.6), $p = 0.006$, respectively) and ‘recent restlessness’ ($p = 0.008$, $d = 0.012$); we found weaker evidence for male deletion carriers being more affected than male controls by recent depression-related traits including: ‘feelings of inadequacy’ ($p = 0.039$), ‘trouble concentrating on things’ ($p = 0.011$), ‘thoughts of suicide and self-harm’ ($p = 0.024$) and ‘lack of interest or pleasure in doing things’ ($p = 0.015$) ($d < 0.015$). There was a nominally significantly increased prevalence of some anxiety-related traits in male deletion carriers relative to male controls, notably ‘ever feeling worried, tense or anxious for most of a month or longer’ (OR 2.8 (95% CI 1.2 to 6.7), $p = 0.027$). Male deletion carriers did not differ from male controls with respect to traumatic event exposure, unusual/psychotic experiences, most aspects of alcohol use, cannabis use or happiness/well-being measures. Female deletion carriers differed from controls on some responses ($0.01 < p < 0.05$); notably, the former group were more likely to have experienced a period of mania/excitability (OR 2.5 (95% CI 1.2 to 5.1), $p = 0.02$). Interestingly, both male and female deletion carriers reported consuming less alcohol than controls on a typical drinking day ($p = 0.013$ and $p = 0.033$, respectively, $d \leq 0.02$).

Medications

We found no difference in prescription rates for medications commonly used to treat heart arrhythmias (listed in online supplementary table 9) between male deletion carriers and male controls: male deletion (6/86, 7.0%) versus male controls (16 590/190 577, 8.7%) ($\chi^2_{(1)} = 0.142$, $p = 0.706$). Nor did we

Table 1 Frequency of mental distress, help-seeking behaviour and psychiatric illness in male and female deletion carriers and controls completing the mental health questionnaire

Measure	Male control	Male deletion	Statistical analysis	Female control	Female deletion	Statistical analysis
Ever suffered mental distress preventing usual activities? (Yes/No)	15 068 (26%)/42 882 (74%)	12 (57%)/9 (43%)	$\chi^2_{(1)} = 9.02$, $p = 0.003$	29 250/46 323	30/63	$\chi^2_{(1)} = 1.37$, $p = 0.242$
Ever sought or received help for mental distress? (Yes/No)	17 522/41 137	7/14	$\chi^2_{(1)} = 0.01$, $p = 0.914$	35 122/41 035	39/56	$\chi^2_{(1)} = 0.786$, $p = 0.375$
Social anxiety or social phobia (Yes/No)	756/58 099	0/21	$P > 0.99$	892/75 547	1/94	$P > 0.99$
Phobia (other than social or agoraphobia) (Yes/No)	576/58 279	1/20	$P = 0.187$	1256/75 183	2/93	$P = 0.671$
Panic attacks (Yes/No)	2266/56 589	1/20	$P = 0.562$	5197/71 242	6/89	$\chi^2_{(1)} = 0.000$, $p > 0.99$
Obsessive compulsive disorder (Yes/No)	329/58 526	1/20	$P = 0.111$	508/75 931	0/95	$P > 0.99$
Depression (Yes/No)	9188/49 667	6/15	$P = 0.125$	19587/56 852	24/71	$\chi^2_{(1)} = 0.000$, $p > 0.99$
Anxiety, nerves or generalised anxiety disorder (Yes/No)	6287/52 568	3/18	$P = 0.486$	12889/63 550	16/79	$\chi^2_{(1)} = 0.000$, $p > 0.99$

Table 2 Highest academic qualification achieved by male and female deletion carriers and controls

Highest academic qualification	Male control (n=1 80 071)	Male deletion (n=78)	Statistical analysis	Female control (n=2 12 817)	Female deletion (n=290)	Statistical analysis
College/University degree	62 371 (35%)	18 (23%)	P=0.083	67 798 (32%)	84 (29%)	$\chi^2_{(5)}=3.995, p=0.550$
A/AS Levels	19 794 (11%)	13 (17%)		27 229 (13%)	37 (13%)	
O Levels/GCSEs	36 430 (20%)	21 (27%)		55 181 (26%)	75 (26%)	
CSEs	10 424 (6%)	2 (2%)		12 550 (6%)	24 (8%)	
NVQ/HND/HNC	17 684 (10%)	6 (8%)		10 100 (4%)	12 (4%)	
None	33 368 (18%)	18 (23%)		39 959 (19%)	58 (20%)	

find any evidence for differential prescription of medications commonly used to treat ADHD-related symptoms (online supplementary table 9): male deletion (0/86, 0%) versus male controls (14/190 577, 0%) ($p>0.99$) and female deletion (0/312, 0%) versus female controls (11/227 862, 0%) ($p>0.99$). Finally, we found no evidence that prescription rates of medications used to treat mood symptoms (online supplementary table 9) differed across groups: male deletion (5/86, 5.8%) versus male controls (9419/190 577, 4.9%) ($p=0.617$) and female deletion (31/312, 9.9%) versus female controls (21 008/227 862, 9.2%) ($\chi^2_{(1)}=0.115, p=0.735$).

Academic qualifications and cognitive function

Neither male deletion, nor female deletion, carriers differed from their respective controls with respect to highest academic

qualification achieved (table 2). Male deletion subjects (57.5 ± 0.8 years) and female deletion subjects (56.3 ± 0.45 years) were compared with a subset of closely age-matched male (55–60 years, mean: 57.7 ± 0.01 years) and female (55–60 years, mean: 57.7 ± 0.01 years) control subjects on the cognitive tests. On average, male deletion carriers performed more poorly than male controls across all tasks, exhibiting significantly slower reaction times in the Reaction Time Test ($B=0.217\pm 0.101, \beta=0.010, p=0.032$), and providing significantly fewer correct answers in the Fluid Intelligence Test ($B=-0.465\pm 0.190, \beta=-0.021, p=0.014$); however, only the latter difference reached significance after correcting for multiple testing (corrected $p=0.098$) (table 3). Female deletion carriers only demonstrated significantly different (worse) performance from female controls on the Fluid Intelligence Test (corrected $p<0.0063, d=0.054$) (table 3).

Table 3 Performance on key measures of seven cognitive tasks by male and female deletion carriers and controls

Cognitive task	Control group	Deletion group	Statistical comparison	Benjamini-Hochberg corrected p value
<i>Male participants</i>				
Pairs Matching Test (total number of errors)	-0.11 (-0.11 to -0.11) (n=42 990)	0.25 (-0.11 to 0.54) (n=86)	$B=0.202\pm 0.112, \beta=0.009, p=0.071$	0.166
Reaction Time Test	-0.19 (-0.19 to -0.18) (n=42 626)	-0.025 (-0.19 to 0.265) (n=86)	$B=0.217\pm 0.101, \beta=0.010, p=0.032$	0.112
Fluid Intelligence Test (total number of correct answers)	0.40 (-0.07 to 0.40) (n=13 072)	-0.07 (-0.55 to 0.40) (n=31)	$B=-0.465\pm 0.190, \beta=-0.021, p=0.014$	0.098
Digit Span Test (maximum number of digits remembered)	0.21 (0.21 to 0.21) (n=4195)	0.21 (-0.165 to 0.97) (n=10)	$U=18 543.5, p=0.512$	0.563
Symbol Digit Substitution Test (number of correct substitutions)	0.05 (0.05 to 0.05) (n=11 664)	-0.35 (-0.838 to 0.345) (n=13)	$U=63 851, p=0.323$	0.452
Trail Making Test A (time to completion)	-0.19 (-0.22 to -0.17) (n=10 580)	-0.04 (-0.43 to 1.07) (n=14)	$U=58 547, p=0.175$	0.306
Trail Making Test B (time to completion)	-0.11 (-0.13 to -0.10) (n=10 588)	0.125 (-0.53 to 0.44) (n=14)	$U=67 499, p=0.563$	0.563
<i>Female participants</i>				
Pairs Matching Test (total number of errors)	-0.11 (-0.11 to -0.11) (n=54 151)	0.25 (-0.11 to 0.25) (n=312)	$B=0.105\pm 0.057, \beta=0.008, p=0.067$	0.235
Reaction Time Test	0.01 (0.01 to 0.01) (n=53 692)	-0.10 (-0.24 to 0.0495) (n=309)	$B=-0.0202\pm 0.052, \beta=-0.002, p=0.697$	0.835
Fluid Intelligence Test (total number of correct answers)	-0.07 (-0.07 to -0.07) (n=16 615) (mean: 0.05 ± 0.0074)	-0.07 (-0.55 to -0.07) (n=103) (mean: -0.31 ± 0.0972)	$B=-0.352\pm 0.096, \beta=-0.028, p<0.001$	<0.0063
Digit Span Test (maximum number of digits remembered)	0.21 (0.21 to 0.21) (n=5386)	0.21 (-0.54 to 0.59) (n=36)	$B=0.058\pm 0.160, \beta=0.005, p=0.716$	0.835
Symbol Digit Substitution Test (number of correct substitutions)	0.05 (0.05 to 0.05) (n=15 163)	0.15 (-0.25 to 0.54) (n=64)	$B=-0.063\pm 0.114, \beta=-0.004, p=0.581$	0.835
Trail Making Test A (time to completion)	-0.02 (-0.04 to 0.00) (n=13 179)	0.015 (-0.28 to 0.29) (n=58)	$B=0.020\pm 0.126, \beta=0.001, p=0.875$	0.875
Trail Making Test B (time to completion)	0.01 (-0.01 to 0.03) (n=13 206)	0.08 (-0.17 to 0.385) (n=58)	$B=0.123\pm 0.121, \beta=0.009, p=0.307$	0.716

Data are presented as median z-scores with 95% confidence limits.

Table 4 Volumes of eight subcortical brain regions (right and left hemisphere) in male and female deletion carriers and controls

Hemisphere	Subcortical region	Volume in control female subjects (cm ³) (n=415)	Volume in female deletion subjects (cm ³) (n=14)	Statistical comparison Mann-Whitney U value, p value	Benjamini-Hochberg corrected p value
Left	Lateral ventricle	7.62 (7.08 to 8.06)	9.32 (7.50 to 11.18)	2038, 0.059	0.189
	Thalamus	7.15 (7.05 to 7.25)	7.17 (6.19 to 7.53)	2582.5, 0.480	0.640
	Caudate	3.20 (3.17 to 3.24)	3.15 (2.91 to 3.21)	2347, 0.226	0.452
	Putamen	4.84 (4.78 to 4.90)	4.44 (3.82 to 4.99)	1912, 0.030	0.120
	Pallidum	1.23 (1.19 to 1.25)	1.15 (0.99 to 1.25)	2168.5, 0.106	0.283
	Hippocampus	4.10 (4.05 to 4.15)	4.08 (3.79 to 4.51)	2823, 0.857	0.914
	Amygdala	1.48 (1.45 to 1.50)	1.47 (1.30 to 1.57)	2676.5, 0.617	0.705
	Nucleus accumbens	0.52 (0.50 to 0.53)	0.44 (0.40 to 0.49)	1668, 0.007	0.072
Right	Lateral ventricle	7.17 (6.83 to 7.64)	8.57 (7.48 to 10.58)	2257, 0.159	0.363
	Thalamus	6.28 (6.25 to 6.35)	6.11 (5.83 to 6.70)	2537, 0.420	0.611
	Caudate	3.30 (3.26 to 3.36)	3.21 (3.04 to 3.44)	2462, 0.338	0.541
	Putamen	4.64 (4.58 to 4.71)	4.31 (3.88 to 4.63)	1713, 0.009	0.072
	Pallidum	1.40 (1.39 to 1.42)	1.31 (1.16 to 1.40)	1816.5, 0.019	0.101
	Hippocampus	4.23 (4.20 to 4.27)	4.19 (3.97 to 4.60)	2903, 0.997	0.997
	Amygdala	1.53 (1.51 to 1.55)	1.46 (1.37 to 1.76)	2635, 0.554	0.682
	Nucleus accumbens	0.54 (0.53 to 0.55)	0.50 (0.45 to 0.60)	2460, 0.329	0.541

Data are presented as median values with 95% confidence limits.

Subcortical neuroanatomy

Neuroimaging data were available for only two male deletion carriers hence analysis was limited to a comparison between female deletion carriers (n=14) and a subset of female controls (n=415) matched as closely as possible for handedness, scanning centre, age at scanning (61.2±2.9 vs 61.0±0.04 years, respectively, $t[4.0]=-0.060$, $p=0.955$), and intracranial volume (1396±39 vs 1399±4 cm³, respectively, $t[13.2]=0.074$, $p=0.942$). Four subcortical brain regions were nominally significantly smaller in deletion than control subjects (left and right putamen, right pallidum and left nucleus accumbens); two of these comparisons (right putamen and left nucleus accumbens) survived correction for multiple testing (corrected $p=0.072$, $d=0.254$ and $d=0.264$, respectively), while a third almost did (right pallidum, corrected $p=0.101$, $d=0.232$) (table 4).

DISCUSSION

We aimed to refine and extend the list of medical and neuro-behavioural phenotypes linked to XLI-associated genetic mutations using an approach arguably less prone to confounding than those undertaken previously. The prevalence of the mutation-of-interest in our sample was ~1/890 females, a figure consistent with published estimates of 1/750–1200 based on prenatal screening data and mutation transmission rates.^{6 31} The prevalence of the mutation among males in our sample was ~1/2200, a figure slightly lower than the ~1/1500 estimate arising from prenatal screening in North American populations.^{32 33} Although the lower prevalence in our sample could reflect geographical genetic differences, it more likely reflects an ascertainment bias whereby some males with XLI-associated genetic deletions are not recruited into the UK Biobank; this could be due, in part, to psychological characteristics of this group.³⁴ Our experimental strategy meant that individuals with small deletions or point mutations within *STS* would have been included in the non-deletion carrier ‘control’ group; however, the inclusion of these rare individuals would have negligible effects on the overall group score, and would likely act to reduce the magnitude of between-group effects.

Unsurprisingly, the prevalence of relevant skin phenotypes based on ICD-10 and self-report diagnostic data was significantly higher in male deletion carriers relative to non-carriers. However, <6% of male deletion carriers reported a relevant diagnosis, implying that older STS-deficient individuals are only rarely being diagnosed with XLI. This may be because the dermatological manifestations of the condition are frequently mild with only more severe and/or visible cases recognised, and some cases could have been misdiagnosed as eczema/dermatitis.³⁵ Within male deletion subjects, we found no evidence for increased rates of phenotypes most closely related to those previously suggested to be elevated in individuals with XLI (testicular maldescent and cataracts); given reliable existing data on an association between XLI and cryptorchidism in paediatric patients,¹ the lack of association with testicular maldescent observed currently may be explained by an unwillingness or inability of older participants to self-report this condition.

We identified one robust novel medical phenotype, atrial fibrillation/flutter, presenting more commonly in male deletion carriers (10.5%) than in controls (2.7%); importantly, the prevalence rate of atrial fibrillation/flutter in our controls is comparable with that observed in epidemiological studies across Europe and the USA (2%–3%).³⁶ Possible mechanism(s) underlying the relationship between XLI-associated mutations and heart arrhythmia are manifold and might be investigated in experimentally tractable systems. It is noteworthy that XLI impacts on circulating DHEAS levels,^{37 38} which have repeatedly been linked to atrial fibrillation in older men,^{39–41} and that paroxysmal supraventricular tachycardia has been noted in a young boy with XLI.⁴² DHEAS may feasibly influence atrial fibrillation through conversion to biologically active androgens and oestrogens, via vascular remodelling, or through its anti-inflammatory action.⁴⁰ It is also of interest that microarray analysis has implicated reduced triadin expression in STS-deficient mouse tissues⁴³ as, in man, the absence of cardiac triadin is associated with increased risk of arrhythmia.^{44 45} Although prescription rates for medication used to treat heart arrhythmias did not differ across groups, this might be explained by the fact that these medications are used to treat other conditions.

We found no evidence that male or female deletion carriers differed from their respective controls in terms of rates of psychiatric/neurological diagnoses, and prescription rates for medications used to treat ADHD and mood disorders were equivalent across groups. However, these findings should be viewed in light of low levels of psychopathology within the UK Biobank sample,¹⁸ and in particular, the very low baseline rate of developmental disorder diagnoses. MHQ analysis revealed that both male and female deletion carrier groups were affected by higher rates of irritability than their respective controls, an observation in line with our previous findings,^{6,12} and with elevated levels of aggression in STS-deficient mice.^{16,46} Male deletion carriers were more likely than male controls to report experiencing psychological distress and a variety of depressive and anxiety-related symptoms, and mood symptoms may be under-recognised within this group. The increased rate of depressive and anxiety-related traits in male deletion carriers is unlikely to be due to increased exposure to traumatic events, but may feasibly be related to having to live with a potentially stigmatising, lifelong skin condition; however, the fact that STS-deficient mice exhibit anxiety-related traits¹⁶ suggests that biological influences contribute. Female deletion carriers showed some evidence for differences in mood symptoms from controls, but these differences were smaller in magnitude and less consistent in pattern/direction than those observed for males, in accordance with the idea that female deletion carriers exhibit milder phenotypes than male deletion carriers.

Given data suggesting increased rates of ADHD^{3,9,10} and inattention in male¹² and female⁶ deletion carriers, and attentional abnormalities in STS-deficient mice,¹⁷ we anticipated group differences on attentionally demanding cognitive tasks. Although we did find some evidence that male deletion carriers exhibited slower reaction times than male controls on a simple stimulus-response task (consistent with impaired attention, reduced motor impulsivity and/or slower processing speed), the two groups did not differ on the Trail Making Tasks. This lack of effect could be explained by low power. We did find evidence across both male and female deletion groups for poorer performance on the Fluid Intelligence Task, taxing multiple high-level cognitive skills; this performance deficit did not translate into impairments in academic performance.

We examined, for the first time, the effects of XLI-associated genetic mutations on neuroanatomy, although only in female carriers. Our analyses provide preliminary evidence for reduced right putamen and pallidum volume, and left accumbens volume, but no other subcortical structural changes, in deletion carriers relative to controls. We argue that these specific structural differences are genuine, and could partially explain effects on disorder risk/cognition/behaviour: a) STS is highly expressed in the basal ganglia during human neurodevelopment⁸ and adult STS-deficient male mice exhibit substantially altered striatal neurochemistry,⁴⁷ b) reduced volume of the putamen/nucleus accumbens is observed in idiopathic autism⁴⁸ and ADHD⁴⁹ cases (with reduced pallidum volume also seen in the former), c) adult basal ganglia volumes correlate with aspects of intelligence⁵⁰ and this structure mediates attention/distractibility.⁵¹ Future functional neuroimaging studies in male and female deletion carriers might examine the extent to which the structure, function and neurochemistry of the basal ganglia correlates with behavioural and cognitive measures. As basal ganglia serotonergic (5-HT) function mediates attention, impulsivity and mood phenotypes (notably via 5-HT_{2A} and 5-HT_{2C} receptors)^{52,53} and is altered in STS-deficient mice,⁴⁷ a particular focus on this system may be warranted.

In summary, this study has highlighted a novel medical phenotype coupled with XLI-associated mutations, has confirmed an

excess of depression and anxiety-related traits in male carriers, and has, for the first time, identified cognitive and neuroanatomical correlates of these genetic differences. Our findings indicate that individuals with XLI might benefit from multidisciplinary clinical care from dermatologists, psychiatrists, and cardiologists, and should lead to improved genetic counselling for patients and their families.

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Supplementary Table 1. ICD-10 medical diagnoses in male deletion carriers and male controls.

UK Biobank diagnosis code	ICD-10 descriptive code	Male controls affected	Male controls unaffected	Male deletion carriers affected	Male deletion carriers unaffected	Prevalence in male controls	Prevalence in male deletion carriers	Statistics	Benjamini- Hochberg corrected p- value (FDR<0.1)
1429	Skin of other and unspecified parts of face	2880	187697	5	81	1.5	5.8	p=0.01	0.045
1522	Malignant neoplasm of prostate	5192	185385	3	83	2.7	3.5	p=0.51	0.653
3704	Cataract, unspecified	5573	185004	3	83	2.9	3.5	p=0.742	0.742
4231	Atrial fibrillation and flutter	5193	185384	9	77	2.7	10.5	p=0.001	0.009
5004	Unilateral or unspecified inguinal hernia, without obstruction or gangrene	13031	177546	4	82	6.8	4.7	$\chi^2[1]=0.348,$ p=0.555	0.653
5058	Non-infective gastro-enteritis and colitis, unspecified	3930	186647	3	83	2.1	3.5	p=0.262	0.59
5078	Diverticular disease of large intestine without perforation or abscess	5645	184932	5	81	3.0	5.8	p=0.112	0.336
12318	Other and unspecified abdominal pain	4614	185963	3	83	2.4	3.5	p=0.467	0.653
12388	Unspecified haematuria	7459	183118	4	82	3.9	4.7	p=0.581	0.653

Supplementary Table 2. ICD-10 medical diagnoses in female deletion carriers and female controls.

UK Biobank diagnosis code	ICD-10 descriptive code	Female controls affected	Female controls unaffected	Female deletion carriers affected	Female deletion carriers unaffected	Prevalence in female controls	Prevalence in female deletion carriers	Statistics	Benjamini-Hochberg corrected p-value (FDR<0.1)
1945	Leiomyoma of uterus, unspecified	5357	222505	9	303	2.4	2.9	$\chi^2[1]=0.189$, $p=0.664$	1.000
3401	Carpal tunnel syndrome	6662	221200	9	303	2.9	2.9	$\chi^2[1]=0.000$, $p>0.99$	1.000
3704	Cataract, unspecified	7141	220721	13	299	3.1	4.2	$\chi^2[1]=0.781$, $p=0.377$	1.000
4429	Varicose veins of lower extremities without ulcer or inflammation	6948	220914	8	304	3.0	2.6	$\chi^2[1]=0.111$, $p=0.739$	1.000
5029	Diaphragmatic hernia without obstruction or gangrene	6265	221597	12	300	2.7	3.8	$\chi^2[1]=1.021$, $p=0.312$	1.000
5058	Non-infective gastro-enteritis and colitis, unspecified	6536	221326	9	303	2.9	2.9	$\chi^2[1]=0.000$, $p>0.99$	1.000
6570	Gonarthrosis, unspecified	5379	222483	9	303	2.4	2.9	$\chi^2[1]=0.179$, $p=0.673$	1.000
10640	Postmenopausal bleeding	7099	220763	11	301	3.1	3.5	$\chi^2[1]=0.064$, $p=0.800$	1.000
12318	Other and unspecified abdominal pain	8539	219323	11	301	3.7	3.5	$\chi^2[1]=0.003$, $p=0.955$	1.000
12461	Headache	3294	224568	8	304	1.4	2.6	$p=0.097$	0.970
1429	Skin of other and unspecified parts of face	2804	225058	1	311	1.2	0.3	$p=0.196$	-
4231	Atrial fibrillation and flutter	2551	225311	3	309	1.1	1.0	$p>0.99$	-

Supplementary Table 3. ICD-10 mental health diagnoses in male deletion carriers and male controls.

Class of disorder	Subclass of disorder	UK Biobank diagnosis code	ICD-10 descriptive code	Male controls affected	Male controls unaffected	Male deletion carriers affected	Male deletion carriers unaffected	Prevalence in male controls	Prevalence in male deletion carriers	P-value
Developmental disorders	Autism-related disorders	3210	Childhood autism							
		3121	Atypical autism							
		3123	Other childhood disintegrative disorder	20	190557	0	86	0.0	0.0	>0.99
		3125	Asperger's syndrome							
		3126	Other pervasive developmental disorders							
		3127	Pervasive developmental disorder, unspecified							
		3131	Disturbance of activity and attention							
	Hyperkinetic disorder	3132	Hyperkinetic conduct disorder	0	190577	0	86	0.0	0.0	>0.99
		3133	Other hyperkinetic disorders							
		3134	Hyperkinetic disorder, unspecified							
		3136	Conduct disorder confined to the family context							
	Conduct disorders	3137	Unsocialised conduct disorder							
		3138	Socialised conduct disorder							
		3139	Oppositional defiant disorder							
		3140	Other conduct disorders	2	190575	0	86	0.0	0.0	>0.99
		3141	Conduct disorder, unspecified							
		3143	Depressive conduct disorder							
		3144	Other mixed disorders of conduct and emotions							
		3145	Mixed disorder of conduct and emotions, unspecified							
	Dyslexia and alexia	12446	Dyslexia and alexia	0	190577	0	86	0.0	0.0	>0.99
	Schizophrenia	2864	Paranoid schizophrenia							
		2865	Hebephrenic schizophrenia							
		2866	Catatonic schizophrenia							
		2867	Undifferentiated schizophrenia							
		2868	Postschizophrenic depression	175	190402	0	86	0.1	0.0	>0.99
		2869	Residual schizophrenia							
		2870	Simple schizophrenia							
		2871	Other schizophrenia							
2872		Schizophrenia, unspecified								
2873	Schizotypal disorder									

Mood and anxiety disorders

Mania/bipolar disorder	2895	Hypomania								
	2896	Mania without psychotic symptoms								
	2897	Mania with psychotic symptoms								
	2898	Other manic episodes								
	2899	Manic episode, unspecified								
	2901	Bipolar affective disorder, current episode hypomanic								
	2902	Bipolar affective disorder, current episode manic without psychotic symptoms								
	2903	Bipolar affective disorder, current episode manic with psychotic symptoms	214	190363	0	86	0.1	0.0	>0.99	
	2904	Bipolar affective disorder, current episode mild or moderate depression								
	2905	Bipolar affective disorder, current episode severe depression without psychotic symptoms								
	2906	Bipolar affective disorder, current episode severe depression with psychotic symptoms								
	2907	Bipolar affective disorder, current episode mixed								
	2908	Bipolar affective disorder, currently in remission								
	2909	Other bipolar affective disorders								
	2910	Bipolar affective disorder, unspecified								
	Depressive disorder	2912	Mild depressive episode							
		2913	Moderate depressive episode							
		2914	Severe depressive episode without psychotic symptoms							
		2915	Severe depressive episode with psychotic symptoms							
		2916	Other depressive episodes							
		2917	Depressive episode, unspecified							
		2919	Recurrent depressive disorder, current episode mild	587	189990	0	86	0.3	0.0	>0.99
		2920	Recurrent depressive disorder, current episode moderate							
		2921	Recurrent depressive disorder, current episode severe without psychotic symptoms							
		2922	Recurrent depressive disorder, current episode severe with psychotic symptoms							
		2923	Recurrent depressive disorder, currently in remission							
		2924	Other recurrent depressive disorders							
		2925	Recurrent depressive disorder, unspecified							
		2937	Agoraphobia							

Anxiety disorder

2938	Social phobias							
2939	Specific (isolated) phobias							
2940	Other phobic anxiety disorders							
2941	Phobic anxiety disorder, unspecified							
2943	Panic disorder [episodic paroxysmal anxiety]	236	190341	0	86	0.1	0.0	>0.99
2944	Generalised anxiety disorder							
2945	Mixed anxiety and depressive disorder							
2946	Other mixed anxiety disorders							
2947	Other specified anxiety disorders							
2948	Anxiety disorder, unspecified							

Obsessive Compulsive Disorder

2950	Predominantly obsessional thoughts or ruminations							
2951	Predominantly compulsive acts [obsessional rituals]							
2952	Mixed obsessional thoughts and acts	19	190558	0	86	0.0	0.0	>0.99
2953	Other obsessive-compulsive disorders							
2954	Obsessive-compulsive disorder, unspecified							

Supplementary Table 4. ICD-10 mental health diagnoses in female deletion carriers and female controls.

		UK Biobank diagnosis code	ICD-10 descriptive code	Female controls affected	Female controls unaffected	Female deletion carriers affected	Female deletion carriers unaffected	Prevalence in female controls	Prevalence in female deletion carriers	P-value
Developmental disorders	Autism-related disorders	3210	Childhood autism							
		3121	Atypical autism							
		3123	Other childhood disintegrative disorder	20	227842	0	312	0.0	0.0	>0.99
		3125	Asperger's syndrome							
		3126	Other pervasive developmental disorders							
		3127	Pervasive developmental disorder, unspecified							
		3131	Disturbance of activity and attention							
	Hyperkinetic disorder	3132	Hyperkinetic conduct disorder	0	227862	0	312	0.0	0.0	>0.99
		3133	Other hyperkinetic disorders							
		3134	Hyperkinetic disorder, unspecified							
		3136	Conduct disorder confined to the family context							
	Conduct disorders	3137	Unsocialised conduct disorder							
		3138	Socialised conduct disorder							
		3139	Oppositional defiant disorder							
		3140	Other conduct disorders	0	227862	0	312	0.0	0.0	>0.99
		3141	Conduct disorder, unspecified							
		3143	Depressive conduct disorder							
		3144	Other mixed disorders of conduct and emotions							
		3145	Mixed disorder of conduct and emotions, unspecified							
	Dyslexia and alexia	12446	Dyslexia and alexia	2	227860	0	312	0.0	0.0	>0.99
	Schizophrenia	2864	Paranoid schizophrenia							
		2865	Hebephrenic schizophrenia							
		2866	Catatonic schizophrenia							
2867		Undifferentiated schizophrenia								
2868		Postschizophrenic depression	87	227775	0	312	0.0	0.0	>0.99	
2869		Residual schizophrenia								
2870		Simple schizophrenia								
2871		Other schizophrenia								
2872		Schizophrenia, unspecified								
2873		Schizotypal disorder								

Mood and anxiety disorders

Mania/bipolar disorder

2895	Hypomania							
2896	Mania without psychotic symptoms							
2897	Mania with psychotic symptoms							
2898	Other manic episodes							
2899	Manic episode, unspecified							
2901	Bipolar affective disorder, current episode hypomanic							
2902	Bipolar affective disorder, current episode manic without psychotic symptoms							
2903	Bipolar affective disorder, current episode manic with psychotic symptoms	346	227516	0	312	0.2	0.0	>0.99
2904	Bipolar affective disorder, current episode mild or moderate depression							
2905	Bipolar affective disorder, current episode severe depression without psychotic symptoms							
2906	Bipolar affective disorder, current episode severe depression with psychotic symptoms							
2907	Bipolar affective disorder, current episode mixed							
2908	Bipolar affective disorder, currently in remission							
2909	Other bipolar affective disorders							
2910	Bipolar affective disorder, unspecified							
2912	Mild depressive episode							
2913	Moderate depressive episode							
2914	Severe depressive episode without psychotic symptoms							
2915	Severe depressive episode with psychotic symptoms							
2916	Other depressive episodes							
2917	Depressive episode, unspecified							
2919	Recurrent depressive disorder, current episode mild	759	227103	1	311	0.3	0.3	>0.99
2920	Recurrent depressive disorder, current episode moderate							
2921	Recurrent depressive disorder, current episode severe without psychotic symptoms							
2922	Recurrent depressive disorder, current episode severe with psychotic symptoms							
2923	Recurrent depressive disorder, currently in remission							
2924	Other recurrent depressive disorders							
2925	Recurrent depressive disorder, unspecified							

Anxiety disorder	2937	Agoraphobia							
	2938	Social phobias							
	2939	Specific (isolated) phobias							
	2940	Other phobic anxiety disorders							
	2941	Phobic anxiety disorder, unspecified							
	2943	Panic disorder [episodic paroxysmal anxiety]	365	227497	1	311	0.2	0.3	0.394
	2944	Generalised anxiety disorder							
	2945	Mixed anxiety and depressive disorder							
	2946	Other mixed anxiety disorders							
	2947	Other specified anxiety disorders							
Obsessive Compulsive Disorder	2948	Anxiety disorder, unspecified							
	2950	Predominantly obsessional thoughts or ruminations							
	2951	Predominantly compulsive acts [obsessional rituals]							
	2952	Mixed obsessional thoughts and acts	14	227848	0	312	0.0	0.0	>0.99
	2953	Other obsessive-compulsive disorders							
	2954	Obsessive-compulsive disorder, unspecified							

Supplementary Table 5. Non-cancer illnesses in male deletion carriers and male controls.

Body system	UK Biobank non-cancer illness code	Non-cancer illness	Male controls affected	Male controls unaffected	Male deletion carriers affected	Male deletion carriers unaffected	Prevalence in male controls	Prevalence in male deletion carriers	P-value	Benjamini-Hochberg corrected p-value (FDR<0.1)
Heart and cardiovascular	1066	Heart/cardiac problem	688	189889	0	86	0.4	0.0	>0.99	>0.99
	1077	Heart arrhythmia	1167	189410	3	83	0.6	3.5	0.016	0.208
	1471	Atrial fibrillation	2355	188222	1	85	1.2	1.2	>0.99	>0.99
	1483	Atrial flutter	72	190505	1	85	0.0	1.2	0.032	0.250
	1485	Irregular heartbeat	412	190165	0	86	0.2	0.0	>0.99	>0.99
Reproductive	1214	Testicular problems (not cancer)	593	189984	0	86	0.3	0.0	>0.99	>0.99
	1404	Male infertility	27	190550	0	86	0.0	0.0	>0.99	>0.99
	1679	Undescended testicle	188	190389	0	86	0.1	0.0	>0.99	>0.99
Thyroid	1224	Thyroid problem (not cancer)	164	190413	0	86	0.1	0.0	>0.99	>0.99
	1225	Hyperthyroidism	586	189991	0	86	0.3	0.0	>0.99	>0.99
	1226	Hypothyroidism	3085	187492	1	85	1.6	1.2	>0.99	>0.99
Eye	1278	Cataract	2993	187584	3	83	1.6	3.5	0.154	0.858
Immune system	1374	Allergy/hypersensitivity/anaphylaxis	1015	189562	4	82	0.5	4.7	0.001	0.020
Skin	1452	Eczema/dermatitis	5108	185469	6	80	2.7	7.0	0.028	0.250
	1453	Psoriasis	2628	187949	1	85	1.4	1.2	>0.99	>0.99
	1454	Blistering/desquamating skin disorder	325	190252	4	82	0.2	4.7	<0.001	<0.020
Nervous										

system	1243	Psychological/psychiatric problem	167	190410	0	86	0.1	0.0	>0.99	>0.99
	1258	Chronic/degenerative neurological problem	66	190511	0	86	0.0	0.0	>0.99	>0.99
	1259	Motor neurone disease	34	190543	0	86	0.0	0.0	>0.99	>0.99
	1261	Multiple sclerosis	387	190190	0	86	0.2	0.0	>0.99	>0.99
	1262	Parkinson's Disease	485	190092	0	86	0.3	0.0	>0.99	>0.99
	1263	Dementia/Alzheimer's/cognitive impairment	65	190512	0	86	0.0	0.0	>0.99	>0.99
	1264	Epilepsy	1709	188868	1	85	0.9	1.2	0.539	>0.99
	1265	Migraine	2894	187683	2	84	1.5	2.3	0.376	>0.99
	1286	Depression	8541	182036	2	84	4.5	2.3	0.595	>0.99
	1287	Anxiety/panic attacks	2120	188457	3	83	1.1	3.5	0.072	0.468
	1288	Nervous breakdown	275	190302	0	86	0.1	0.0	>0.99	>0.99
	1289	Schizophrenia	304	190273	0	86	0.2	0.0	>0.99	>0.99
	1290	Deliberate self-harm/suicide	82	190495	0	86	0.0	0.0	>0.99	>0.99
	1291	Mania/bipolar disorder	508	190069	0	86	0.3	0.0	>0.99	>0.99
	1408	Alcohol dependency	460	190117	0	86	0.2	0.0	>0.99	>0.99
	1409	Opioid dependency	20	190557	0	86	0.0	0.0	>0.99	>0.99
	1410	Other substance abuse	34	190543	0	86	0.0	0.0	>0.99	>0.99
	1469	Posttraumatic Stress Disorder	145	190432	0	86	0.1	0.0	>0.99	>0.99
	1470	Anorexia/bulimia	15	190562	0	86	0.0	0.0	>0.99	>0.99
	1531	Postnatal depression	1	190576	0	86	0.0	0.0	>0.99	>0.99
	1614	Stress	267	190310	0	86	0.1	0.0	>0.99	>0.99
	1615	Obsessive Compulsive Disorder	49	190528	0	86	0.0	0.0	>0.99	>0.99
	1616	Insomnia	119	190458	0	86	0.1	0.0	>0.99	>0.99

Supplementary Table 6. Non-cancer illnesses in female deletion carriers and female controls.

Body system	UK Biobank non-cancer illness code	Non-cancer illness	Female controls affected	Female controls unaffected	Female deletion carriers affected	Female deletion carriers unaffected	Prevalence in female controls	Prevalence in female deletion carriers	P-value	Benjamini-Hochberg corrected p-value (FDR<0.1)
Heart and cardiovascular	1066	Heart/cardiac problem	666	227196	2	310	0.3	0.6	0.232	>0.99
	1077	Heart arrythmia	1147	226715	2	310	0.5	0.6	0.673	>0.99
	1471	Atrial fibrillation	1084	226778	0	312	0.5	0.0	0.412	>0.99
	1483	Atrial flutter	26	227836	0	312	0.0	0.0	>0.99	>0.99
	1485	Irregular heartbeat	389	227473	0	312	0.2	0.0	>0.99	>0.99
Reproductive	1402	Endometriosis	3556	224306	1	311	1.6	0.3	0.102	>0.99
	1403	Female infertility	516	227346	1	311	0.2	0.3	0.507	>0.99
Thyroid	1224	Thyroid problem (not cancer)	946	226916	1	311	0.4	0.3	>0.99	>0.99
	1225	Hyperthyroidism	2695	225167	5	307	1.2	1.6	0.426	>0.99
	1226	Hypothyroidism	17905	209957	23	289	7.9	7.4	$\chi^2[1]=0.046, p=0.831$	>0.99
Eye	1278	Cataract	3921	223941	6	306	1.7	1.9	$\chi^2[1]=0.003, p=0.955$	>0.99
Immune system	1374	Allergy/hypersensitivity/anaphylaxis	2035	225827	1	311	0.9	0.3	0.536	>0.99
Hair	1667	Alopecia/hair loss	66	227796	0	312	0.0	0.0	>0.99	>0.99
Skin	1452	Eczema/dermatitis	6257	221605	9	303	2.7	2.9	$\chi^2[1]=0.000, p>0.99$	>0.99
	1453	Psoriasis	2323	225539	6	306	1.0	1.9	0.143	>0.99
	1454	Blistering/desquamating skin disorder	336	227526	0	312	0.1	0.0	>0.99	>0.99
Nervous system	1243	Psychological/psychiatric problem	219	227643	0	312	0.1	0.0	>0.99	>0.99
	1258	Chronic/degenerative neurological problem	81	227781	0	312	0.0	0.0	>0.99	>0.99

1259	Motor neurone disease	14	227848	0	312	0.0	0.0	>0.99	>0.99
1261	Multiple sclerosis	1135	226727	3	309	0.5	1.0	0.205	>0.99
1262	Parkinson's Disease	283	227579	1	311	0.1	0.3	0.322	>0.99
1263	Dementia/Alzheimer's/cognitive impairment	51	227811	0	312	0.0	0.0	>0.99	>0.99
1264	Epilepsy	1775	226087	3	309	0.8	1.0	0.526	>0.99
1265	Migraine	10083	217779	7	305	4.4	2.2	$\chi^2[1]=3.011, p=0.083$	>0.99
1286	Depression	16496	211366	27	285	7.2	8.7	$\chi^2[1]=0.729, p=0.393$	>0.99
1287	Anxiety/panic attacks	3959	223903	6	306	1.7	1.9	$\chi^2[1]=0.001, p=0.973$	>0.99
1288	Nervous breakdown	366	227496	0	312	0.2	0.0	>0.99	>0.99
1289	Schizophrenia	147	227715	0	312	0.1	0.0	>0.99	>0.99
1290	Deliberate self-harm/suicide	110	227752	0	312	0.0	0.0	>0.99	>0.99
1291	Mania/bipolar disorder	657	227205	1	311	0.3	0.3	0.594	>0.99
1408	Alcohol dependency	177	227685	0	312	0.1	0.0	>0.99	>0.99
1409	Opioid dependency	5	227857	0	312	0.0	0.0	>0.99	>0.99
1410	Other substance abuse	14	227848	0	312	0.0	0.0	>0.99	>0.99
1469	Posttraumatic Stress Disorder	150	227712	0	312	0.1	0.0	>0.99	>0.99
1470	Anorexia/bulimia	314	227548	0	312	0.1	0.0	>0.99	>0.99
1531	Postnatal depression	401	227461	0	312	0.2	0.0	>0.99	>0.99
1614	Stress	374	227488	2	310	0.2	0.6	0.094	>0.99
1615	Obsessive Compulsive Disorder	48	227814	0	312	0.0	0.0	>0.99	>0.99
1616	Insomnia	296	227566	0	312	0.1	0.0	>0.99	>0.99

Supplementary Table 7. Mental Health Questionnaire (MHQ) responses in male deletion carriers and male controls.

Depression

<i>Dual answer questions</i>	Male control	Male deletion	Statistics
Ever had prolonged feelings of sadness or depression? (Yes/No)	25669(44%)/33052(56%)	15(75%)/5(25%)	$\chi^2[1]=6.733, p=0.009$
Ever had prolonged loss of interest in normal activities? (Yes/No)	18460(31%)/40257(69%)	13(62%)/8(38%)	$\chi^2[1]=7.680, p=0.006$
Depression possibly related to stressful or traumatic event (Yes/No)	17354/9770	10/6	$\chi^2[1]=0.000, p>0.99$
Feelings of tiredness during worst episode of depression (Yes/No)	18384/5915	12/3	$p>0.99$
Did your sleep change? (Yes/No)	17353/6075	12/4	$p>0.99$
Trouble falling asleep (Yes/No)	13225/4128	8/4	$p=0.496$
Sleeping too much (Yes/No)	3417/13936	3/9	$p=0.714$
Waking too early (Yes/No)	13086/4267	8/4	$p=0.505$
Difficulty concentrating during worst depression (Yes/No)	18463/6009	15/1	$p=0.141$
Feelings of worthlessness during worst episode of depression (Yes/No)	12321/13251	11/5	$\chi^2[1]=1.948, p=0.163$
Thoughts of death during worst depression (Yes/No)	11891/13902	5/10	$\chi^2[1]=0.537, p=0.464$
Depression possibly related to childbirth (Yes/No)	-	-	-
Professional informed about depression (Yes/No)	15373/11745	8/8	$\chi^2[1]=0.083, p=0.774$
Substances taken for depression (unprescribed)(Yes/No)	1236/57619	1/20	$p=0.360$
Substances taken for depression (prescribed)(Yes/No)	9914/48941	5/16	$p=0.382$
Substances taken for depression (drugs or alcohol)(Yes/No)	4566/54289	2/19	$p=0.676$
Talking therapies (Yes/No)	9046/49809	5/16	$p=0.356$
Other non-drug therapies (e.g. yoga) (Yes/No)	2334/56521	2/19	$p=0.202$
<i>Multiple answer questions</i>			
Trouble falling or staying asleep, or sleeping too much (1: not at all-4:nearly every day)	1.74±0.006	2.07±0.267	$U=519025.5, p=0.153$
Recent feelings of inadequacy (1: not at all-4:nearly every day)	1.34±0.005	1.57±0.228	$U=511192, p=0.039$
Recent trouble concentrating on things (1: not at all-4:nearly every day)	1.33±0.005	1.57±0.228	$U=487101, p=0.011$
Recent feelings of depression (1: not at all-4:nearly every day)	1.36±0.005	1.64±0.248	$U=519805.5, p=0.072$
Recent poor appetite or overeating (1: not at all-4:nearly every day)	1.28±0.005	1.36±0.225	$U=582574.5, p=0.450$
Recent thoughts of suicide or self-harm (1: not at all-4:nearly every day)	1.10±0.003	1.29±0.221	$U=552023.5, p=0.024$
Recent lack of interest or pleasure in doing things (1: not at all-4:nearly every day)	1.34±0.005	1.57±0.228	$U=490482.5, p=0.015$
Recent changes in speed/amount of moving or speaking (1: not at all-4:nearly every day)	1.11±0.003	1.36±0.225	$U=561630, p=0.069$
Recent feelings of tiredness or low energy (1: not at all-4:nearly every day)	1.76±0.006	2.00±0.234	$U=499865.5, p=0.196$
Fraction of day affected during worst episode of depression (1:less than half the day-4:all day long)	2.76±0.007	2.93±0.245	$U=177823.5, p=0.614$
Frequency of depressed days during worst episode of depression (1:less often-3:every day)	2.23±0.004	2.21±0.214	$U=180055.5, p=0.510$

Weight change during worst episode of depression (0: stayed about the same or was on a diet, 1:gained weight, 2:lost weight, 3:both gained and lost weight)	0:12603, 1:3055, 2:5651, 3:1175	0:13, 1:2, 2:1, 3:0	p=0.213
Duration of worst depression (1:less than a month-6:over two years)	2.88±0.011	3.07±0.438	U=201796, p=0.660
Impact on normal roles during worst episode of depression (0:not at all-3:a lot)	1.95±0.006	2.00±0.234	U=215475.5, p=0.949
Age at first episode of depression (yrs)	39.29±0.104	37.71±4.876	U=185977.5, p=0.659
Age at last episode of depression (yrs)	49.30±0.091	55.21±2.689	U=145534, p=0.188
Lifetime number of depressed periods	145.17±2.420	287.79±124.757	U=147693.5, p=0.072

Mania

Dual answer questions

Manifestations of mania (more talkative than usual) (Yes/No)	2896/55959	2/19	p=0.277
Manifestations of mania (more restless than usual)(Yes/No)	6607/52248	5/16	p=0.079
Manifestations of mania (my thoughts were racing)(Yes/No)	5337/53518	4/17	p=0.117
Manifestations of mania (needed less sleep than usual)(Yes/No)	1978/56877	2/19	p=0.156
Manifestations of mania (more creative than usual)(Yes/No)	1902/56953	0/21	p>0.99
Manifestations of mania (was easily distracted)(Yes/No)	4551/54304	4/17	p=0.074
Manifestations of mania (was more confident than usual)(Yes/No)	1992/56863	0/21	p>0.99
Manifestations of mania (was more active than usual)(Yes/No)	3019/55836	3/18	p=0.090
Ever had a period of mania/excitability? (Yes/No)	2814/54385	1/20	p>0.99
Ever had a period of extreme irritability? (Yes/No)	14245(25%)/43013(75%)	10(48%)/11(52%)	$\chi^2[1]=4.654, p=0.031$
Severity of problems due to mania or irritability (No problems/caused problems)	8987/4173	4/5	p=0.153

Multiple answer questions

Longest period of mania or irritability (1: less than 24hrs-3: a week or more)	1.86±0.007	2.13±0.350	U=45749, p=0.396
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Anxiety

Dual answer questions

Ever felt worried, tense or anxious for most of a month or longer (Yes/No)	11828(21%)/44247(79%)	9(43%)/12(57%)	$p=0.027$
Ever worried more than most people would in similar situation (Yes/No)	10750/39424	7/10	p=0.069
Stronger worrying (than other people) during period of worst anxiety (Yes/No)	8585/1581	6/1	p>0.99
Worried most days during period of worst anxiety (Yes/No)	12058/2097	8/1	p>0.99

Number of things worried about during worst period of anxiety (One thing/More than one thing)	6743/7534	2/6	p=0.295
Difficulty stopping worrying during worst period of anxiety (Yes/No)	13174/1095	7/1	p=0.472
Multiple worries during worst period of anxiety (Yes/No)	10070/4067	7/2	p>0.99
Tense, sore or aching muscles during worse period of anxiety (Yes/No)	4173(31%)/9314(69%)	6(75%)/2(25%)	p=0.013
Difficulty concentrating during worst period of anxiety (Yes/No)	10560/3599	9/0	p=0.124
More irritable than usual during worst period of anxiety (Yes/No)	9967/3686	8/1	p=0.460
Restless during period of worst anxiety (Yes/No)	8577/5227	4/4	p=0.487
Keyed up or on edge during worst period of anxiety (Yes/No)	10917/3139	8/1	p=0.694
Frequent trouble falling or staying asleep during worst period of anxiety (Yes/No)	10850(76%)/3464(24%)	4(44%)/5(56%)	p=0.043
Easily tired during worst period of anxiety (Yes/No)	8955/4786	6/3	p>0.99
Professional informed about anxiety (Yes/No)	8376/6254	5/4	p>0.99
Substances taken for anxiety (unprescribed)(Yes/No)	901/57954	1/20	p=0.277
Substances taken for anxiety (prescribed)(Yes/No)	5748/53107	4/17	p=0.143
Substances taken for anxiety (drugs or alcohol) (Yes/No)	3191/55664	2/19	p=0.317
Activities undertaken to treat anxiety (talking therapies)(Yes/No)	5495/53360	3/18	p=0.440
Activities undertaken to treat anxiety (other therapeutic activities e.g. yoga)(Yes/No)	1657/57198	1/20	p=0.451

Multiple answer questions

Recent easy annoyance or irritability (1: not at all-4:nearly every day)	1.31±0.002	1.86±0.210	U=405199, p<0.001
Recent feelings of nervousness or anxiety (1: not at all-4:nearly every day)	1.28±0.002	1.62±0.234	U=536245, p=0.159
Recent inability to stop or control worrying (1: not at all-4:nearly every day)	1.23±0.002	1.48±0.178	U=517872.5, p=0.058
Recent feelings of foreboding (1: not at all-4:nearly every day)	1.16±0.002	1.33±0.174	U=571941, p=0.330
Recent trouble relaxing (1: not at all-4:nearly every day)	1.31±0.003	1.52±0.178	U=524358.5, p=0.109
Recent restlessness (1: not at all-4:nearly every day)	1.14±0.002	1.38±0.161	U=506824.5, p=0.008
Recent worrying too much about different things (1: not at all-4:nearly every day)	1.31±0.003	1.62±0.212	U=522739, p=0.112
Longest period spent worried or anxious (months)	158±3	563±172	U=26962.5, p=0.010
Frequency of inability to stop worrying during worst period of anxiety (0:Never-3:Often)	2.19±0.006	2.56±0.176	U=49519.5, p=0.165
Frequency of difficulty controlling worry during worst period of anxiety (0:Never-3:Often)	2.19±0.006	2.56±0.176	U=55332.5, p=0.380
Impact on normal roles during worst period of anxiety (0: Not at all-3: A lot)	1.89±0.008	2.22±0.222	U=54027.5, p=0.319

Additions

Ever addicted to any substance or behaviour (Yes/No)	4080/54067	1/19	p>0.99
Ever addicted to alcohol (Yes/No)	1755/2025	1/0	p=0.464
Ongoing addiction to alcohol (Yes/No)	756/974	1/0	p=0.437
Ever physically dependent on alcohol (Yes/No)	551/1132	0/1	p>0.99
Ever addicted to prescription or over-the-counter medication (Yes/No)	466/3566	0/1	p>0.99
Ever addicted to illicit or recreational drugs (Yes/No)	358/3662	0/1	p>0.99
Ever addicted to a behaviour or miscellaneous	1176/2833	1/0	p=0.294
Ongoing behavioural or miscellaneous addiction (Yes/No)	524/630	1/0	p=0.455

Alcohol use

Frequency of drinking alcohol (0: Never-4: 4 or more times a week)	2.87±0.005	2.90±0.194	U=588100.5, p=0.697
Amount of alcohol drunk on a typical drinking day (1: 1-2 units-5: 10 or more units)	2.11±0.005	1.52±0.190	U=407457, p=0.013
Frequency of consuming 6 or more units of alcohol (1: Never-5: daily or almost daily)	2.29±0.005	2.24±0.275	U=574833.5, p=0.931
Frequency of inability to cease drinking in last year (1: Never-5: daily or almost daily)	1.18±0.003	1.00±0.000	U=251328, p=0.203
Frequency of failure to fulfil normal expectations due to drinking alcohol in last year (1: Never-5: daily or almost daily)	1.09±0.002	1.14±0.097	U=262675, p=0.364
Frequency of needing morning drink of alcohol after heavy drinking session in last year (1: Never-5: daily or almost daily)	1.01±0.001	1.00±0.000	U=279118, p=0.759
Frequency of feeling guilt or remorse after drinking alcohol in last year (1: Never-5: daily or almost daily)	1.25±0.003	1.07±0.071	U=251369, p=0.303
Frequency of memory loss due to drinking alcohol in the last year (1: Never-5: daily or almost daily)	1.18±0.003	1.07±0.071	U=260994.5, p=0.449
Ever been injured or injured someone else through drinking alcohol (0: No, 1:Yes, but not in last year, 2:Yes, during the last year)	0:55282, 1:3206, 2:321	0:20, 1:1, 2:0	p>0.99
Ever had known person concerned about, or recommend reduction of, alcohol consumption (0: No, 1:Yes, but not in last year, 2:Yes, during the last year)	0:50820, 1:4072, 2:3847	0:19, 1:1, 2:1	p>0.99
Age when known person last commented about drinking habits (yrs)	51.3±0.2	67.0±0.0	U=464, p=0.196

Cannabis use

Ever taken cannabis (0:No, 1:1-2 times, 2:3-10 times, 3:11-100 times, 4: more than 100 times)	0.52±0.004	0.14±0.101	U=517372.5, p=0.092
Maximum frequency of taking cannabis (1:Less than once a month, 2:once a month or more but not every week, 3:once a week or more, but not every day, 4:Every day)	1.70±0.008	1.00±0.000	U=9036, p=0.293
Age when last took cannabis (yrs)	33.2±0.1	23.0±2.0	U=8252, p=0.279

Unusual and psychotic experiences

Dual answer questions

Ever seen an unreal vision (Yes/No)	1562/56684	1/20	p=0.435
Ever heard an unreal voice (Yes/No)	914/57657	0/21	p>0.99
Ever believed in unreal communications or signs (Yes/No)	406/58263	0/21	p>0.99
Ever believed in unreal conspiracy against self (Yes/No)	539/58134	0/21	p>0.99
Ever talked to a health professional about unusual or psychotic experiences (Yes/No)	603/1965	0/1	p>0.99
Ever prescribed medication for unusual or psychotic experiences (Yes/No)	332/2232	0/1	p>0.99

Multiple answer questions

Number of times seen an unreal vision	33.1±1.9	192.0±0.0	U=103, p=0.134
Number of times heard an unreal voice	69.5±3.9	-	-
Number of times believed in unreal communications or signs	75.1±5.4	-	-
Number of times believed in unreal conspiracy against self	29.7±1.8	-	-
Frequency of unusual or psychotic experiences in last year (0:Not at all-4: Nearly every day or daily)	0.54±0.020	0.00±0.000	U=896.5, p=0.516
Age when first had unusual or psychotic experience (yrs)	35.9±0.5	15.0±0.0	U=341.5, p=0.236
Distress caused by unusual or psychotic experiences (0:Not distressing at all-4: Very distressing)	1.47±0.026	0.00±0.000	U=328, p=0.186

Traumatic events

Felt loved as a child (0:Never true-4: Very often true)	3.23±0.004	3.05±0.288	U=603250.5, p=0.863
Someone to take to doctor when needed as a child (0:Never true-4: Very often true)	3.76±0.003	3.90±0.066	U=479201.5, 0.459
Been in a confiding relationship as an adult (0:Never true-4: Very often true)	3.00±0.005	3.19±0.245	U=570132, p=0.613
Able to pay rent/mortgage as an adult (0:Never true-4: Very often true)	3.74±0.003	3.86±0.104	U=590821, p=0.676
Been in serious accident believed to be life-threatening (0:Never, 1:Yes, but not in last 12 months, 2:Yes, within the last 12 months)	0:50989, 1:7578, 2:209	0:20, 1:1, 2:0	p=0.545
Been involved in combat or exposed to war zone (0:Never, 1:Yes, but not in last 12 months, 2:Yes, within the last 12 months)	0:55263, 1:3429, 2:63	0:20, 1:1, 2:0	p>0.99
Diagnosed with life-threatening illness (0:Never, 1:Yes, but not in last 12 months, 2:Yes, within the last 12 months)	0:48114, 1:9006, 2:1547	0:15, 1:6, 2:0	p=0.215
Victim of physically violent crime (0:Never, 1:Yes, but not in last 12 months, 2:Yes, within the last 12 months)	0:44349, 1:14083, 2:335	0:15, 1:6, 2:0	p=0.657
Witnessed sudden violent death (0:Never, 1:Yes, but not in last 12 months, 2:Yes, within the last 12 months)	0:47486, 1:10851, 2:417	0:19, 1:2, 2:0	p=0.487
Avoided activities or situations because of previous stressful experience in past month (0:Not at all-4:Extremely)	0.23±0.003	0.38±0.201	U=571980.5, p=0.367
Repeated disturbing thoughts of stressful experience in past month (0:Not at all-4:Extremely)	0.31±0.003	0.62±0.234	U=541898.5, p=0.186
Felt very upset when reminded of stressful experience in past month (0:Not at all-4:Extremely)	0.38±0.003	0.71±0.260	U=544289, p=0.235
Felt irritable or had angry outbursts in past month (0:Not at all-4:Extremely)	0.57±0.005	1.20±0.389	U=78051, p=0.078

Felt distant from other people in past month (0:Not at all-4:Extremely)	0.64±0.006	0.30±0.153	U=91915, p=0.328
Happiness and subjective wellbeing			
General happiness (1:Extremely happy-6:Extremely unhappy)	2.40±0.003	2.62±0.212	U=545238, p=0.326
General happiness with own health (1:Extremely happy-6:Extremely unhappy)	2.63±0.004	2.81±0.281	U=566695, p=0.491
Belief that own life is meaningful (1:Not at all-5:an extreme amount)	3.69±0.003	3.48±0.245	U=556178.5, p=0.518

Supplementary Table 8. Mental Health Questionnaire (MHQ) responses in female deletion carriers and female controls.

Depression

Dual answer questions

	Female control	Female deletion	Statistics
Ever had prolonged feelings of sadness or depression? (Yes/No)	48061/28148	61/33	$\chi^2[1]=0.068$, $p=0.795$
Ever had prolonged loss of interest in normal activities? (Yes/No)	34628/41541	46/48	$\chi^2[1]=0.328$, $p=0.567$
Depression possibly related to stressful or traumatic event (Yes/No)	38341/10536	46/15	$\chi^2[1]=0.176$, $p=0.674$
Feelings of tiredness during worst episode of depression (Yes/No)	37680/6401	53/8	$\chi^2[1]=0.017$, $p=0.897$
Did your sleep change? (Yes/No)	34919/7056	47/8	$\chi^2[1]=0.0072$, $p=0.788$
Trouble falling asleep (Yes/No)	26474/8445	33/14	$\chi^2[1]=0.527$, $p=0.468$
Sleeping too much (Yes/No)	7305/27614	15/32	$\chi^2[1]=2.796$, $p=0.094$
Waking too early (Yes/No)	26601(76%)/8318(24%)	29(62%)/18(38%)	$\chi^2[1]=4.650$, $p=0.031$
Difficulty concentrating during worst depression (Yes/No)	34573/8215	47/11	$\chi^2[1]=0.000$, $p>0.99$
Feelings of worthlessness during worst episode of depression (Yes/No)	23734/21821	32/29	$\chi^2[1]=0.000$, $p>0.99$
Thoughts of death during worst depression (Yes/No)	25425/20559	29/30	$\chi^2[1]=0.667$, $p=0.414$
Depression possibly related to childbirth (Yes/No)	5592/38405	4/50	$\chi^2[1]=0.931$, $p=0.335$
Professional informed about depression (Yes/No)	33629/15198	36/24	$\chi^2[1]=1.806$, $p=0.179$
Substances taken for depression (unprescribed)(Yes/No)	3433/73006	4/91	$p>0.99$
Substances taken for depression (prescribed)(Yes/No)	22619/53820	25/70	$\chi^2[1]=0.344$, $p=0.558$
Substances taken for depression (drugs or alcohol)(Yes/No)	5131/71308	5/90	$\chi^2[1]=0.129$, $p=0.720$
Talking therapies (Yes/No)	20634/55805	17/78	$\chi^2[1]=3.539$, $p=0.060$
Other non-drug therapies (e.g. yoga) (Yes/No)	8083/68356	5/90	$\chi^2[1]=2.298$, $p=0.130$

Multiple answer questions

Trouble falling or staying asleep, or sleeping too much (1: not at all-4:nearly every day)	1.91±0.005	1.94±0.138	U=3619934, $p=0.988$
Recent feelings of inadequacy (1: not at all-4:nearly every day)	1.36±0.004	1.33±0.098	U=3554178.5, $p=0.716$
Recent trouble concentrating on things (1: not at all-4:nearly every day)	1.30±0.003	1.38±0.092	U=3434322.5, $p=0.190$
Recent feelings of depression (1: not at all-4:nearly every day)	1.36±0.003	1.40±0.096	U=3385837, $p=0.230$
Recent poor appetite or overeating (1: not at all-4:nearly every day)	1.40±0.004	1.37±0.106	U=3612522.5, $p=0.943$
Recent thoughts of suicide or self-harm (1: not at all-4:nearly every day)	1.07±0.002	1.10±0.063	U=3556579, $p=0.549$
Recent lack of interest or pleasure in doing things (1: not at all-4:nearly every day)	1.31±0.003	1.48±0.118	U=3351972.5, $p=0.070$
Recent changes in speed/amount of moving or speaking (1: not at all-4:nearly every day)	1.10±0.002	1.13±0.055	U=3530409, $p=0.287$
Recent feelings of tiredness or low energy (1: not at all-4:nearly every day)	1.82±0.005	2.00±0.135	U=3187494.5, $p=0.026$
Fraction of day affected during worst episode of depression (1:less than half the day-4:all day long)	2.94±0.005	2.94±0.136	U=1332636, $p=0.458$

Frequency of depressed days during worst episode of depression (1:less often-3:every day)	2.39±0.003 0:13555(32%), 1:8175(19%), 2:17686(42%), 3:2935(7%)	2.29±0.088 0:23(38%), 1:18(30%), 2:16(27%), 3:3(5%)	U=1348177.5, p=0.281
Weight change during worst episode of depression (0: stayed about the same or was on a diet, 1:gained weight, 2:lost weight, 3:both gained and lost weight)			p=0.046
Duration of worst depression (1:less than a month-6:over two years)	3.16±0.008	3.40±0.229	U=1319400, p=0.232
Impact on normal roles during worst episode of depression (0:not at all-3:a lot)	1.96±0.005	2.06±0.130	U=1392219, p=0.240
Age at first episode of depression (yrs)	36.46±0.076	36.60±2.014	U=1271678.5, p=0.903
Age at last episode of depression (yrs)	49.75±0.066	50.52±2.003	U=1218252.5, p=0.478
Lifetime number of depressed periods	127.43±1.708	136.71±47.624	U=1373136, p=0.834

Mania

Dual answer questions

Manifestations of mania (more talkative than usual) (Yes/No)	3418/73021	5/90	p=0.618
Manifestations of mania (more restless than usual)(Yes/No)	8175/68264	11/84	$\chi^2[1]=0.013$, p=0.910
Manifestations of mania (my thoughts were racing)(Yes/No)	6868/69571	9/86	$\chi^2[1]=0.000$, p>0.99
Manifestations of mania (needed less sleep than usual)(Yes/No)	2446/73993	3/92	p>0.99
Manifestations of mania (more creative than usual)(Yes/No)	1629/74810	3/92	p=0.459
Manifestations of mania (was easily distracted)(Yes/No)	6050/70389	9/86	$\chi^2[1]=0.139$, p=0.710
Manifestations of mania (was more confident than usual)(Yes/No)	1788/74651	2/93	p>0.99
Manifestations of mania (was more active than usual)(Yes/No)	3560/72879	6/89	p=0.457
Ever had a period of mania/excitability? (Yes/No)	2699(4%)/72286(96%)	8(9%)/86(91%)	p=0.020
Ever had a period of extreme irritability? (Yes/No)	19708/54139	28/64	$\chi^2[1]=0.482$, p=0.488
Severity of problems due to mania or irritability (No problems/caused problems)	12387/4893	17/7	$\chi^2[1]=0.000$, p>0.99

Multiple answer questions

Longest period of mania or irritability (1: less than 24hrs-3: a week or more)	1.87±0.006	1.96±0.146	U=226797, p=0.504
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Anxiety

Dual answer questions

Ever felt worried, tense or anxious for most of a month or longer (Yes/No)	21663/48664	29/58	$\chi^2[1]=0.156$, $p=0.693$
Ever worried more than most people would in similar situation (Yes/No)	18547/44811	24/58	$\chi^2[1]=0.000$, $p>0.99$
Stronger worrying (than other people) during period of worst anxiety (Yes/No)	15018/3472	20/6	$p=0.614$
Worried most days during period of worst anxiety (Yes/No)	23462/2607	30/4	$p=0.772$
Number of things worried about during worst period of anxiety (One thing/More than one thing)	11030/15252	14/19	$\chi^2[1]=0.000$, $p>0.99$
Difficulty stopping worrying during worst period of anxiety (Yes/No)	25033/1270	31/3	$p=0.225$
Multiple worries during worst period of anxiety (Yes/No)	20153/5710	22/12	$\chi^2[1]=2.721$, $p=0.099$
Tense, sore or aching muscles during worse period of anxiety (Yes/No)	10714/13835	17/15	$\chi^2[1]=0.814$, $p=0.367$
Difficulty concentrating during worst period of anxiety (Yes/No)	19580/6073	28/7	$\chi^2[1]=0.097$, $p=0.755$
More irritable than usual during worst period of anxiety (Yes/No)	17422/7083	29/4	$\chi^2[1]=3.739$, $p=0.053$
Restless during period of worst anxiety (Yes/No)	14721/10128	24/10	$\chi^2[1]=1.371$, $p=0.242$
Keyed up or on edge during worst period of anxiety (Yes/No)	20731/4966	26/7	$\chi^2[1]=0.003$, $p=0.957$
Frequent trouble falling or staying asleep during worst period of anxiety (Yes/No)	22484/3855	27/7	$p=0.329$
Easily tired during worst period of anxiety (Yes/No)	19085/6157	26/9	$\chi^2[1]=0.000$, $p>0.99$
Professional informed about anxiety (Yes/No)	16979/9893	19/16	$\chi^2[1]=0.838$, $p=0.360$
Substances taken for anxiety (unprescribed)(Yes/No)	2501(3%)/73938(97%)	7(7%)/88(93%)	$p=0.037$
Substances taken for anxiety (prescribed)(Yes/No)	11511/64928	13/82	$\chi^2[1]=0.053$, $p=0.817$
Substances taken for anxiety (drugs or alcohol) (Yes/No)	3964/72475	4/91	$p>0.99$
Activities undertaken to treat anxiety (talking therapies)(Yes/No)	11601/64838	11/84	$\chi^2[1]=0.695$, $p=0.404$
Activities undertaken to treat anxiety (other therapeutic activities e.g. yoga)(Yes/No)	5843/70596	3/92	$\chi^2[1]=2.108$, $p=0.147$

Multiple answer questions

Recent easy annoyance or irritability (1: not at all-4:nearly every day)	1.34±0.002	1.44±0.061	$U=3213617$, $p=0.018$
Recent feelings of nervousness or anxiety (1: not at all-4:nearly every day)	1.41±0.002	1.42±0.073	$U=3594330$, $p=0.913$
Recent inability to stop or control worrying (1: not at all-4:nearly every day)	1.37±0.002	1.51±0.087	$U=3308660$, $p=0.113$
Recent feelings of foreboding (1: not at all-4:nearly every day)	1.26±0.002	1.34±0.069	$U=3340145$, $p=0.118$
Recent trouble relaxing (1: not at all-4:nearly every day)	1.43±0.003	1.52±0.086	$U=3477052$, $p=0.428$
Recent restlessness (1: not at all-4:nearly every day)	1.17±0.002	1.25±0.060	$U=3380896$, $p=0.059$
Recent worrying too much about different things (1: not at all-4:nearly every day)	1.47±0.003	1.53±0.090	$U=3545082$, $p=0.872$
Longest period spent worried or anxious (months)	190±2	164±63	$U=289967.5$, $p=0.471$
Frequency of inability to stop worrying during worst period of anxiety (0:Never-3:Often)	2.32±0.004	2.40±0.131	$U=428042$, $p=0.328$

Frequency of difficulty controlling worry during worst period of anxiety (0:Never-3:Often)	2.35±0.004	2.49±0.126	U=406215, p=0.138
Impact on normal roles during worst period of anxiety (0: Not at all-3: A lot)	1.84±0.006	2.20±0.152	U=371698, p=0.022

Addictions

Ever addicted to any substance or behaviour (Yes/No)	3820/71829	3/91	p=0.634
Ever addicted to alcohol (Yes/No)	1340/2213	2/1	p=0.561
Ongoing addiction to alcohol (Yes/No)	579/741	1/1	p>0.99
Ever physically dependent on alcohol (Yes/No)	279/997	0/2	p>0.99
Ever addicted to prescription or over-the-counter medication (Yes/No)	670/3093	1/2	p=0.445
Ever addicted to illicit or recreational drugs (Yes/No)	217/3579	0/3	p>0.99
Ever addicted to a behaviour or miscellaneous	643/3145	1/2	p=0.428
Ongoing behavioural or miscellaneous addiction (Yes/No)	327/302	1/0	p>0.99

Alcohol use

Frequency of drinking alcohol (0: Never-4: 4 or more times a week)	2.43±0.005	2.31±0.136	U=3429009.5, p=0.345
Amount of alcohol drunk on a typical drinking day (1: 1-2 units-5: 10 or more units)	1.60±0.003	1.44±0.092	U=2542520, p=0.033
Frequency of consuming 6 or more units of alcohol (1: Never-5: daily or almost daily)	1.69±0.004	1.56±0.102	U=2758770, p=0.304
Frequency of inability to cease drinking in last year (1: Never-5: daily or almost daily)	1.22±0.004	1.06±0.056	U=556594.5, p=0.076
Frequency of failure to fulfil normal expectations due to drinking alcohol in last year (1: Never-5: daily or almost daily)	1.08±0.002	1.03±0.028	U=594290.5, p=0.341
Frequency of needing morning drink of alcohol after heavy drinking session in last year (1: Never-5: daily or almost daily)	1.01±0.001	1.06±0.056	U=604122, p=0.012
Frequency of feeling guilt or remorse after drinking alcohol in last year (1: Never-5: daily or almost daily)	1.33±0.004	1.11±0.053	U=544904, p=0.090
Frequency of memory loss due to drinking alcohol in the last year (1: Never-5: daily or almost daily)	1.17±0.003	1.14±0.099	U=573224, p=0.200
Ever been injured or injured someone else through drinking alcohol (0: No, 1:Yes, but not in last year, 2:Yes, during the last year)	0:74194, 1:1897, 2:302	0:93, 1:2, 2:0	p>0.99
Ever had known person concerned about, or recommend reduction of, alcohol consumption (0: No, 1:Yes, but not in last year, 2:Yes, during the last year)	0:72584, 1:2059, 2:1695	0:90, 1:3, 2:2	p=0.865
Age when known person last commented about drinking habits (yrs)	50.1±0.3	47.3±10.7	U=2607, p=0.908

Cannabis use

Ever taken cannabis (0:No, 1:1-2 times, 2:3-10 times, 3:11-100 times, 4: more than 100 times)	0.35±0.003	0.25±0.062	U=3573919.5, p=0.720
Maximum frequency of taking cannabis (1:Less than once a month, 2:once a month or more but not every week, 3:once a week or more, but not every day, 4:Every day)	1.57±0.008	1.24±0.161	U=93387, p=0.092
Age when last took cannabis (yrs)	31.1±0.1	31.9±3.0	U=115429.5, p=0.744

Unusual and psychotic experiences*Dual answer questions*

Ever seen an unreal vision (Yes/No)	2692/72930	4/90	p=0.579
Ever heard an unreal voice (Yes/No)	1384/74696	2/93	p=0.692
Ever believed in unreal communications or signs (Yes/No)	530/75688	2/93	p=0.142
Ever believed in unreal conspiracy against self (Yes/No)	498/75783	1/94	p=0.464
Ever talked to a health professional about unusual or psychotic experiences (Yes/No)	777/3188	2/4	p=0.335
Ever prescribed medication for unusual or psychotic experiences (Yes/No)	388/3572	2/4	p=0.111

Multiple answer questions

Number of times seen an unreal vision	31.8±1.4	49.3±46.9	U=3719, p=0.518
Number of times heard an unreal voice	55.7±2.9	103.5±106.5	U=998.5, p=0.831
Number of times believed in unreal communications or signs	62.6±4.5	107.5±102.5	U=239, p=0.279
Number of times believed in unreal conspiracy against self	26.1±1.8	30.0±0.0	U=121.5, p=0.474
Frequency of unusual or psychotic experiences in last year (0:Not at all-4: Nearly every day or daily)	0.42±0.013	0.67±0.494	U=10899.5, p=0.638
Age when first had unusual or psychotic experience (yrs)	34.7±0.4	48.2±10.4	U=7062, p=0.182
Distress caused by unusual or psychotic experiences (0:Not distressing at all-4: Very distressing)	1.41±0.021	1.83±0.749	U=10298.5, p=0.606

Traumatic events

Felt loved as a child (0:Never true-4: Very often true)	3.24±0.004	3.32±0.095	U=3471803, p=0.457
Someone to take to doctor when needed as a child (0:Never true-4: Very often true)	3.73±0.003	3.85±0.043	U=3404766, p=0.243
Been in a confiding relationship as an adult (0:Never true-4: Very often true)	2.98±0.005	2.99±0.138	U=3338756.5, p=0.856
Able to pay rent/mortgage as an adult (0:Never true-4: Very often true)	3.70±0.003	3.61±0.100	U=3424319, p=0.570
Been in serious accident believed to be life-threatening (0:Never, 1:Yes, but not in last 12 months, 2:Yes, within the last 12 months)	0:71274, 1:4882, 2:174	0:83, 1:12, 2:0	p=0.060
Been involved in combat or exposed to war zone (0:Never, 1:Yes, but not in last 12 months, 2:Yes, within the last 12 months)	0:75355, 1:1002, 2:23 0:64635, 1:10067,	0:95, 1:0, 2:0	p=0.650
Diagnosed with life-threatening illness (0:Never, 1:Yes, but not in last 12 months, 2:Yes, within the last 12 months)	2:1371 0:65682, 1:10283,	0:78, 1:16, 2:0	p=0.293
Victim of physically violent crime (0:Never, 1:Yes, but not in last 12 months, 2:Yes, within the last 12 months)	2:283	0:81, 1:13, 2:0	p=0.916
Witnessed sudden violent death (0:Never, 1:Yes, but not in last 12 months, 2:Yes, within the last 12 months)	0:69572, 1:6424, 2:295	0:87, 1:8, 2:0	p>0.99
Avoided activities or situations because of previous stressful experience in past month (0:Not at all-4:Extremely)	0.34±0.003	0.52±0.094	U=3269628, p=0.026
Repeated disturbing thoughts of stressful experience in past month (0:Not at all-4:Extremely)	0.44±0.003	0.53±0.084	U=3361072, p=0.129

Felt very upset when reminded of stressful experience in past month (0:Not at all-4:Extremely)	0.62±0.003	0.76±0.097	U=3308762, p=0.099
Felt irritable or had angry outbursts in past month (0:Not at all-4:Extremely)	0.49±0.004	0.63±0.119	U=951869.5, p=0.217
Felt distant from other people in past month (0:Not at all-4:Extremely)	0.64±0.005	0.78±0.131	U=941187, p=0.179
Happiness and subjective wellbeing			
General happiness (1:Extremely happy-6:Extremely unhappy)	2.42±0.003	2.42±0.092	U=3560178, p=0.812
General happiness with own health (1:Extremely happy-6:Extremely unhappy)	2.63±0.003	2.59±0.087	U=3566806.5, p=0.795
Belief that own life is meaningful (1:Not at all-5:an extreme amount)	3.70±0.003	3.70±0.114	U=3317623, p=0.285

Supplementary Table 9. List of medications commonly used to treat heart arrythmia, ADHD-related symptoms and mood symptoms.

Drug type	Effect on symptoms	Biobank Code	Drug
Beta-blocker	Anti-arrhythmia	1140866738	atenolol
	Anti-arrhythmia	1141146126	atenolol+bendrofluazide
	Anti-arrhythmia	1141194810	atenolol+bendroflumethiazide
	Anti-arrhythmia	1141180778	atenolol+chlorthalidone
	Anti-arrhythmia	1141146124	atenolol+chlorthalidone
	Anti-arrhythmia	1141146128	atenolol+co-amilozide
	Anti-arrhythmia	1140860426	atenolol+nifedipine 50mg/20mg m/r capsule
	Anti-arrhythmia	1140879760	bisoprolol
	Anti-arrhythmia	1140864950	bisoprolol fumarate+hydrochlorothiazide 10mg/6.25mg tablet
	Anti-arrhythmia	1140879818	metoprolol
	Anti-arrhythmia	1140860308	metoprolol tartrate+chlorthalidone 100mg/12.5mg tablet
	Anti-arrhythmia	1140879854	sotalol
	Anti-arrhythmia	1140860332	sotalol hydrochloride+hydrochlorothiazide 80mg/12.5mg tablet
	Anti-arrhythmia	1140860404	metoprolol tartrate+hydrochlorothiazide 100mg/12.5mg tablet
Calcium channel blocker	Anti-arrhythmia	1140888510	verapamil
	Anti-arrhythmia	1140879806	diltiazem
	Anti-arrhythmia	1140926778	diltiazem hcl+hydrochlorothiazide 150mg/12.5mg m/r capsule
Cardiac glycoside	Anti-arrhythmia	2038459814	digoxin
	Anti-arrhythmia	1140865966	digoxin product
Sodium channel blocker	Anti-arrhythmia	1140888570	flecainide
Calcium and potassium channel blocker	Anti-arrhythmia	1140888502	amiodarone
	Reduction in inattention, hyperactivity and/or impulsive symptoms	1140867894	pemoline
	Reduction in inattention, hyperactivity and/or impulsive symptoms	1140917138	ritalin 10mg tablet
Centrally Acting Sympathomimetics	Reduction in inattention, hyperactivity and/or impulsive symptoms	1141199446	atomoxetine
	Reduction in inattention, hyperactivity and/or impulsive symptoms	1141180976	dexamfetamine
	Reduction in inattention, hyperactivity and/or impulsive symptoms	1140879680	dexamphetamine
Tricyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140867938	amitriptyline+chlorthalidone 12.5mg/5mg capsule

Monoamine Oxidase A Inhibitors Reversible	Antidepressant/treatment of mood symptoms	1140867920	moclobemide
Monoamine Oxidase A and B Inhibitors Irreversible	Antidepressant/treatment of mood symptoms	1140867914	tranylcypromine
Selective Serotonin Reuptake Inhibitors	Antidepressant/treatment of mood symptoms	1140867888	paroxetine
Selective Serotonin Reuptake Inhibitors	Antidepressant/treatment of mood symptoms	1140867878	sertraline
Monoamine Oxidase A and B Inhibitors Irreversible	Antidepressant/treatment of mood symptoms	1140867856	isocarboxazid
	Antidepressant/treatment of mood symptoms	1140867852	nardil 15mg tablet
Monoamine Oxidase A and B Inhibitors Irreversible	Antidepressant/treatment of mood symptoms	1140867850	phenelzine
Tricyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140867818	nortriptyline
	Antidepressant/treatment of mood symptoms	1140867812	norval 10mg tablet
Tetracyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140867774	amoxapine
Tricyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140867756	trimipramine
Tricyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140867726	lofepramine
Tricyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140867640	doxepin
Tricyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140867632	dothapax 25mg capsule
Tricyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140867624	prothiaden 25mg capsule
	Antidepressant/treatment of mood symptoms	1140856074	butriptyline
Tricyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140909806	dosulepin
Monoamine Oxidase A and B Inhibitors Irreversible	Antidepressant/treatment of mood symptoms	1140910504	maoi - isocarboxazid
Monoamine Oxidase A and B Inhibitors Irreversible	Antidepressant/treatment of mood symptoms	1140910704	maoi - phenelzine
Monoamine Oxidase A and B Inhibitors Irreversible	Antidepressant/treatment of mood symptoms	1140910820	maoi - tranylcypromine
Serotonin and Noradrenaline Reuptake Inhibitors	Antidepressant/treatment of mood symptoms	1140916282	venlafaxine
	Antidepressant/treatment of mood symptoms	1140917460	nefazodone
Selective Serotonin Reuptake Inhibitors	Antidepressant/treatment of mood symptoms	1140921600	citalopram
Noradrenaline Reuptake Inhibitors	Antidepressant/treatment	1141151978	reboxetine

	of mood symptoms		
Tetracyclic Antidepressants	Antidepressant/treatment of mood symptoms	1141152732	mirtazapine
Serotonin and Noradrenaline Reuptake Inhibitors	Antidepressant/treatment of mood symptoms	1141176854	bupropion
Selective Serotonin Reuptake Inhibitors	Antidepressant/treatment of mood symptoms	1141180212	escitalopram
Serotonin and Noradrenaline Reuptake Inhibitors	Antidepressant/treatment of mood symptoms	1141200564	duloxetine
Serotonin Uptake Inhibitors	Antidepressant/treatment of mood symptoms	1140882244	molipaxin 50mg capsule
Serotonin Receptor Agonists	Antidepressant/treatment of mood symptoms	1140879730	buspirone
Monoamine Oxidase B Inhibitors	Antidepressant/treatment of mood symptoms	1140879668	selegiline
Serotonin Uptake Inhibitors	Antidepressant/treatment of mood symptoms	1140879634	trazodone
Tricyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140879632	protriptyline
Tricyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140879630	imipramine
	Antidepressant/treatment of mood symptoms	1140879628	dothiepin
	Antidepressant/treatment of mood symptoms	1140879624	desipramine
Tricyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140879620	clomipramine
Tricyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140879616	amitriptyline
Tetracyclic Antidepressants	Antidepressant/treatment of mood symptoms	1140879556	mianserin
Selective Serotonin Reuptake Inhibitors	Antidepressant/treatment of mood symptoms	1140879544	fluvoxamine
Selective Serotonin Reuptake Inhibitors	Antidepressant/treatment of mood symptoms	1140879540	fluoxetine