Supplementary Materials

Assessing the validity of a self-reported clinical diagnosis of schizophrenia.

Grace E Woolway; Sophie E Legge; Amy Lynham; Sophie E Smart; Leon Hubbard; Ellie R Daniel; Antonio F Pardiñas; Valentina Escott-Price; Michael C O'Donovan; Michael J Owen; Ian R Jones; James TR Walters.

Table of Contents

Supplementary Table 1: UK Biobank schizophrenia diagnosis definition	2
Supplementary Table 2: PPVs for psychosis in the clinically-ascertained sample	2
Supplementary Table 3: Diagnoses of participants who did not receive a schizophrenia or SA-D research diagnosis	.3
Supplementary Table 4. Predictive values for self-reported schizophrenia and medical record diagnosis of schizophrenia or other psychotic disorders	.3
Supplementary Table 5: Diagnosis variables used for self-reported, research interview, and medical record diagnosis groups	.4
Supplementary Table 6: Number of other psychotic and mood admissions by primary and secondary schizophrenia admission groups	.4
Supplementary Table 7: Other admission diagnoses by primary and secondary schizophrenia admission groups	.4
Supplementary Figure 1: NCMH self-reported diagnoses	5
Supplementary Figure 2: Self-reported diagnoses in UK Biobank's mental health questionnaire	6
Supplementary Figure 3: Principal components 1-6 by array	7
Supplementary Figure 4: Diagnosis endorsements and schizophrenia PRS	8
Supplementary Figure 5: Hospital admissions for schizophrenia and schizophrenia PRS	8
Supplementary Figure 6: Schizophrenia PRS and primary and secondary admission groups	9
Supplementary Note 1: PPV/NPV prevalence adjustment	9

UK Biobank schizophrenia diagnosis	Field ID
Medical record	l diagnosis
Primary care diagnosis	130875 (codes 30/31)
Hospital admission	130875/130885 (codes 40/41)
- Primary hospital admission	41202
 Secondary hospital admission 	41204
Death records	130875 (codes 20/21)
Self-report d	liagnosis
Mental health questionnaire	20544 (code 2)
Verbal self-report	20002 (code 1289)

Supplementary Table 1: UK Biobank schizophrenia diagnosis definition

The UK Biobank field identifiers used to create the schizophrenia diagnosis in UK Biobank.

Supplementary Table 2: PPVs for psychosis in the clinically-ascertained sample

Self-report method	Research diagnosis	Total number of participants who self- report psychosis (without schizophrenia/bipolar)	PSY self- report & SZ* research diagnosis	PSY self- report & non-SZ research diagnosis	PPV
	Schizophrenia		33	84	0.28
Lifetime clinical	Schizophrenia/SA-D		58	59	0.50
diagnosis	Schizophrenia/SA-	117	71	46	0.61
	D/other psychotic				
	disorders				
	Schizophrenia		25	69	0.27
Current clinical	Schizophrenia/SA-D		45	49	0.48
diagnosis	Schizophrenia/SA-	94	58	36	0.62
uldgilosis	D/other psychotic				
	disorders				
	Schizophrenia		22	29	0.43
Darticipant	Schizophrenia/SA-D		27	24	0.53
Participant	Schizophrenia/SA-	51	33	18	0.65
opinion	D/other psychotic				
	disorders				

Positive predictive values (PPV) for individuals who self-reported psychosis (without also reporting schizophrenia or bipolar disorder) in NCMH. Columns represent the self-reported method, the research interview diagnoses, total number of participants, and the number of individuals who had a (i) psychosis (- bipolar/schizophrenia) self-report and subsequent schizophrenia (plus SA-D/other psychotic disorders) research diagnosis, (ii) psychosis (- bipolar/schizophrenia) self-report and non-schizophrenia research diagnosis, and PPV. PPV, positive predictive value; SZ, schizophrenia; SA-D, schizoaffective disorder depressive-type. * Schizophrenia, schizophrenia/SA-D, and Schizophrenia/SA-D/other psychotic disorders combinations tested.

Supplementary Table 3: Diagnoses of participants who did not receive a schizophrenia or SA-D research diagnosis

DSM 4 Diagnosis	Number of participants
Alcohol induced psychosis	2
Bipolar disorder type 1	8
Brief psychotic disorder	2
Cyclothymia	2
Delusional disorder	1
Major depressive disorder recurrent	5
Major depressive disorder single episode	1
Psychosis not otherwise specified	8
Psychotic depression	4
Schizoaffective bipolar type	15
Substance induced psychotic disorder	2
Unknown	1

DSM 4 diagnoses of participants who self-reported schizophrenia and did not receive a SCAN-based research interview diagnosis of schizophrenia or schizoaffective disorder depressive type (SA-D) (n=51).

Supplementary Table 4. Predictive values for self-reported schizophrenia and medical record diagnosis of schizophrenia or other psychotic disorders.

	Medical record schizophrenia /other psychotic disorders Yes	Medical record schizophrenia /other psychotic disorders No	
Self-reported schizophrenia Yes	491	124	PPV*: 0.772
Self-reported schizophrenia No	1853	332852	NPV*: 0.995
	Sensitivity: 0.209	Specificity: 0.9996	

Positive predictive values (PPV), negative predictive values (NPV), sensitivity and specificity of individuals who self-reported schizophrenia either verbally to a nurse on the initial assessment or on the mental health questionnaire and had a medical record diagnosis of schizophrenia or other psychotic disorders. Other psychotic disorders include codes corresponding to schizotypal disorder, persistent delusional disorders, acute and transient psychotic disorders, induced delusional disorder, schizoaffective disorders, other nonorganic psychosis and unspecified nonorganic psychosis. * Adjusted values based on point prevalence (unadjusted PPV = 0.798374, unadjusted NPV = 0.9944638).

Supplementary Table 5: Diagnosis variables used for self-reported, research interview, and medical record diagnosis groups.

Array	Number of CardiffCOGS cases	Number of NCMH cases	Number of NCMH controls
GSA	0	981	484
OmniExpress	632	0	0
PsychArray	0	562	265

Number of participants by OmniExpress/PsychArray/GSA array platforms in the genetic subset.

Supplementary Table 6: Number of other psychotic and mood admissions by primary and secondary schizophrenia admission groups

	UK Biobank field ID	Primary schizophrenia admission (0) (N=209)	Secondary schizophrenia admission only (1) (N=459)
Other psychotic related diagnosis	130877, 130879, 130881, 130885, 130887, 130889	64 (31%)	115 (25%)
Mood diagnosis	130891:130903	73 (35%)	164 (36%)

The number (and percentage) of other psychotic related diagnoses and mood diagnoses of participants who had a primary admission of schizophrenia and a secondary admission of schizophrenia. Diagnoses were assigned based on a hospital admission code (40) or hospital admission and other sources code (41).

(See <u>https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=2405</u> for further details).

Supplementary Table 7: Other admission diagnoses by primary and secondary schizophrenia admission groups

	UK Biobank field ID	Primary schizophrenia admission (0) (N=93)	Secondary schizophrenia admission only (1) (N=233)
Delirium	130847	2 (2%)	25 (11%)
Cognitive disorders	130837:130843	3 (3%)	15 (6%)
Substance disorders	130855:130873	12 (13%)	28 (12%)
Anxiety related disorders	130905:130911	16 (17%)	44 (19%)
Other psychiatric diagnosis	130913:130991	15 (16%)	32 (14%)

Table 7 shows the number (and percentage) of other mental health diagnoses of participants who did not have either a psychotic related diagnosis or a mood diagnosis by primary and secondary admission groups. Diagnoses were assigned based on a hospital admission code (40) or hospital admission and other sources code (41).

(See <u>https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=2405</u> for further details).

Supplementary Figure 1: NCMH self-reported diagnoses

Has a doctor or health professional ever told you that you have any of the following diagnoses? (tick all that apply)

	Attention Deficit Hyperactivity Disorder (ADHD)
Π	Autism
	Asperger's or other Autism Spectrum Disorder (e.g. Pervasive Developmental Disorder)
	Dyslexia
	Dyspraxia
	Conduct Disorder
	Oppositional Defiant Disorder (ODD)
	Tic Disorders
	Tourette's Disorder
	Intellectual Disability (ID) / Learning Disability (LD)
	Depression
	Bipolar Disorder / Manic Depression
	Mania / Hypomania
	Schizoaffective Disorder
	Psychosis
	Schizophrenia
	Postnatal Psychosis / Puerperal Psychosis
	Postnatal Depression
	Anorexia
	Bulimia
	Obsessive Compulsive Disorder (OCD)
	Agoraphobia
	Panic Disorder
	Phobias
	Anxiety
	Borderline Personality Disorder
	Other Personality Disorder
	Post-Traumatic Stress Disorder (PTSD)
	Alzheimer's Disease
	Other dementia
	Alcohol Abuse / Misuse
	Other substance Abuse / Misuse (please specify)
	Genetic Syndrome (e.g. VCFS) (please specify)
	Self-harm or suicide attempts
Ш	Other (please specify) Page 10

List of mental health diagnoses given to participants to choose from in NCMH cohort.

Supplementary Figure 2: Self-reported diagnoses in UK Biobank's mental health questionnaire

biobank^{*} Thoughts and feelings

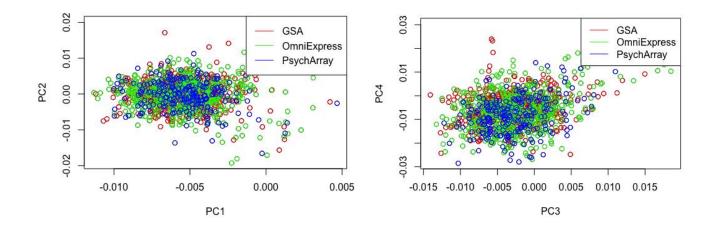
Diagnoses

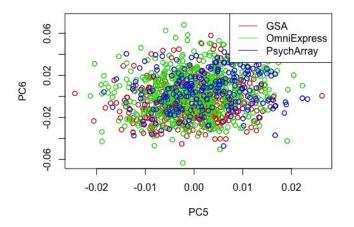
A4 Have you been diagnosed with one or more of the following mental health problems by a professional, even if you don't have it currently? (tick all that apply): Anorexia nervosa Bulimia nervosa Psychological over-eating or binge-eating Schizophrenia Any other type of psychosis or psychotic illness A personality disorder Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD) None of the above Prefer not to answer Back without saving Save/Continue	more of the following mental health Bullimia nervosa problems by a professional, even if you Psychological over-eating or binge-eating don't have it currently? (tick all that apply): Psychological over-eating or binge-eating By professional we mean: any doctor, nurse or person with specialist training (such as a psychologist or therapist). Please include disorders even if you did not need treatment for them or if you did not agree with the diagnosis. Any other type of psychosis or psychotic illness A personality disorder Autism, Asperger's or autistic spectrum disorder Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD) None of the above Prefer not to answer			
problems by a professional, even if you Builfilla flervosa group on the specialist currently? (tick all that apply): Psychological over-eating or binge-eating By professional we mean: any doctor, nurse or person with specialist training (such as a psychologist or therapist). Please include disorders even if you did not need treatment for them or if you did not agree with the diagnosis. Any other type of psychosis or psychotic illness A personality disorder Autism, Asperger's or autistic spectrum disorder Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD) None of the above Prefer not to answer Prefer not to answer	problems by a professional, even if you Builtman nervosa Psychological over-eating or binge-eating Schizophrenia Schizophrenia Any other type of psychosis or psychotic illness A personality disorder Autism, Asperger's or autistic spectrum disorder Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD) None of the above Prefer not to answer PROGRESS:	, ,	Anorexia nervosa	
don't have it currently? (tick all that apply): Psychological over-eating or binge-eating By professional we mean: any doctor, nurse or person with specialist training (such as a psychologist or therapist). Please include disorders even if you did not need treatment for them or if you did not agree with the diagnosis. Any other type of psychosis or psychotic illness A personality disorder A utism, Asperger's or autistic spectrum disorder Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD) None of the above Prefer not to answer Prefers not to answer	don't have it currently? (tick all that apply): Psychological over-eating or binge-eating By professional we mean: any doctor, nurse or person with specialist training (such as a psychologist or therapist). Please include disorders even if you did not need treatment for them or if you did not agree with the diagnosis. Any other type of psychosis or psychotic illness A personality disorder A utism, Asperger's or autistic spectrum disorder Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD) None of the above Prefer not to answer Prefer not to answer		Bulimia nervosa	
person with specialist training (such as a psychologist or therapist). Please include disorders even if you did not need treatment for them or if you did not agree with the diagnosis. Any other type of psychosis or psychotic illness A personality disorder Autism, Asperger's or autistic spectrum disorder Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD) None of the above Prefer not to answer Back without saving Save/Continue	 person with specialist training (such as a psychologist or therapist). Please include disorders even if you did not need treatment for them or if you did not agree with the diagnosis. A personality disorder A utism, Asperger's or autistic spectrum disorder Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD) None of the above Prefer not to answer 		Psychological over-eating or binge-eating	
psychologist or therapist). Please include Any other type of psycholic liness disorders even if you did not need treatment for A personality disorder http://disorder.org/lines/l	psychologist or therapist). Please include Any other type of psycholic linness disorders even if you did not need treatment for A personality disorder them or if you did not agree with the diagnosis. A tutism, Asperger's or autistic spectrum disorder Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD) None of the above Prefer not to answer Save/Continue		C Schizophrenia	
disorders even if you did not need treatment for them or if you did not agree with the diagnosis. A personality disorder Autism, Asperger's or autistic spectrum disorder Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD) Vone of the above Prefer not to answer Back without saving Save/Continue Progress: Progress: Progress: Progress:	disorders even if you did not need treatment for them or if you did not agree with the diagnosis. A personality disorder Autism, Asperger's or autistic spectrum disorder Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD) Vone of the above Prefer not to answer Back without saving Save/Continue Progress:		Any other type of psychosis or psychotic illness	
Back without saving Save/Continue	Back without saving Save/Continue		A personality disorder	
disorder (ADD/ADHD) None of the above Prefer not to answer	disorder (ADD/ADHD) None of the above Prefer not to answer Save/Continue PROGRESS:	them or if you did not agree with the diagnosis.	Autism, Asperger's or autistic spectrum disorder	
Progress: Progress:	Back without saving Save/Continue PROGRESS:			
Back without saving Save/Continue PROGRESS:	Back without saving Save/Continue		☑ None of the above	
Progress:	Progress:		Prefer not to answer	
Improving the health of future general	Improving the health of future generat	Progress:		
			Improving the health of future of	generat
		· · · ·		
		biobank Thou	ights and feelings	
biobank [*] Thoughts and feelings	oiobank [*] Thoughts and feelings			
piobank [*] Thoughts and feelings	oiobank [*] Thoughts and feelings	Diagnoses		
Diobank [*] Thoughts and feelings				
Diobank ^{**} Thoughts and feelings				

A3 Have you been diagnosed with one or Depression more of the following mental health Mania, hypomania, bipolar or manic-depression problems by a professional, even if you don't have it currently? (tick all that apply): Anxiety, nerves or generalized anxiety disorder Social anxiety or social phobia By professional we mean: any doctor, nurse or person with specialist training (such as a psychologist or therapist). Please include disorders even if you did not need treatment for them or if you did not agree with the diagnosis. Agoraphobia Any other phobia (eg disabling fear of heights or spiders) Panic attacks Obsessive compulsive disorder (OCD) None of the above Prefer not to answer Back without saving Save/Continue PROGRESS Improving the health of future generations

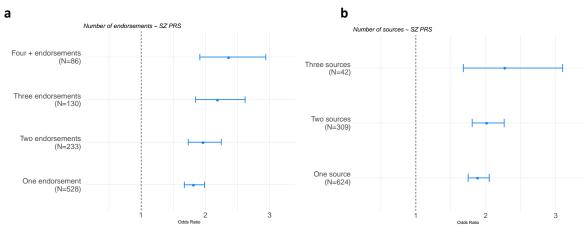
List of diagnoses participants can choose from in the mental health questionnaire (MHQ) in the UK Biobank.

Supplementary Figure 3: Principal components 1-6 by array





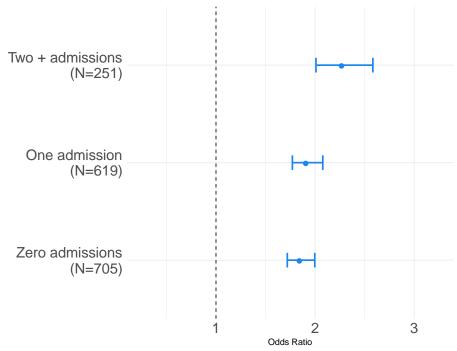
Principal component (PC) plots by each genotyping array (Infinium Global Screening Array (GSA), OmniExpress, PsychArray) to demonstrate any batch effects. The plots demonstrate that the distribution of individuals across PCs did not differ depending on which genotyping array was used.



Supplementary Figure 4: Diagnosis endorsements and schizophrenia PRS

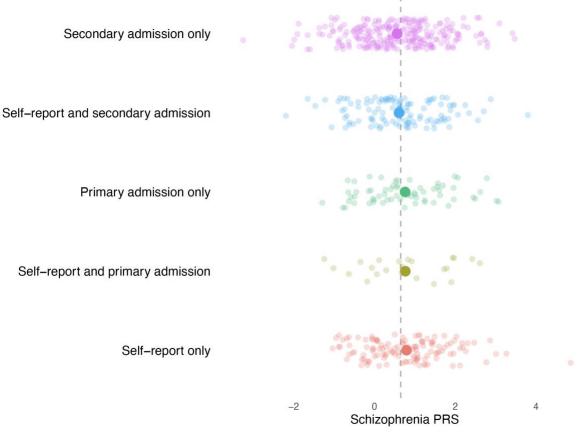
As participants' schizophrenia PRS increased, the number of times a diagnosis was reported increased. Figure 5a displays the number of endorsements (number of times a diagnosis is reported in UK Biobank). Figure 5b shows the same graph when concatenating all hospital admissions into one hospital endorsement.

Supplementary Figure 5: Hospital admissions for schizophrenia and schizophrenia PRS



As participants' schizophrenia PRS increases the odds of having an admission increases.

Supplementary Figure 6: Schizophrenia PRS and primary and secondary admission groups



Schizophrenia PRS by primary and secondary admission diagnoses, subdivided into those with only an admission code and those with both a self-report and admission code. The dotted line represents the mean schizophrenia polygenic risk score.

Supplementary Note 1: PPV/NPV prevalence adjustment

In the UK Biobank, predictive values were adjusted to the point prevalence of schizophrenia (0.6%). The following formulas were used to adjust the PPV and NPV:

PPV = (sensitivity x prevalence)/[(sensitivity x prevalence)+((1 - specificity) x (1 - prevalence))]

NPV = (specificity x (1 - prevalence))/[(specificity x (1 - prevalence))+((1 - sensitivity) x prevalence)]