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Nineteen and Up study (19Up): understanding pathways to mental health disorders in young Australian twins

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ABSTRACT

Purpose The Nineteen and Up study (19Up) assessed a range of mental health and behavioural problems and associated risk factors in a genetically informative Australian cohort of young adult twins and their non-twin siblings. As such, 19Up enables detailed investigation of genetic and environmental pathways to mental illness and substance misuse within the Brisbane Longitudinal Twin Sample (BLTS).

Participants Twins and their non-twin siblings from Queensland, Australia; mostly from European ancestry. Data were collected between 2009 and 2016 on 2773 participants (age range 18–38, 57.8% female, 372 complete monozygotic pairs, 493 dizygotic pairs, 640 non-twin siblings, 403 singleton twins).

Findings to date A structured clinical assessment (Composite International Diagnostic Interview) was used to collect lifetime prevalence of diagnostic statistical manual (4th edition) (DSM-IV) diagnoses of major depressive disorder, (hypo)mania, social anxiety, cannabis use disorder, alcohol use disorder, panic disorder and psychotic symptoms. Here, we further describe the comorbidities and ages of onset for these mental disorders. Notably, two-thirds of the sample reported one or more lifetime mental disorder. In addition, the 19Up study assessed general health, drug use, work activity, education level, personality, migraine/headaches, suicidal thoughts, attention deficit hyperactivity disorder (ADHD) symptomatology, sleep–wake patterns, romantic preferences, friendships, familial environment, stress, anorexia and bulimia as well as baldness, acne, asthma, endometriosis, joint flexibility and internet use. The overlap with previous waves of the BLTS means that 84% of the 19Up participants are genotyped, 36% imaged using multimodal MRI and most have been assessed for psychological symptoms at up to four time points. Furthermore, IQ is available for 57%, parental report of ADHD symptomatology for 100% and electroencephalography for 30%.

Future plans The 19Up study complements a phenotypically rich, longitudinal collection of environmental and psychological risk factors. Future publications will explore hypotheses related to disease onset and development across the waves of the cohort. A follow-up study at 25+years is ongoing.

Strengths and limitations of this study

- Large sample size (n=2773; 369 monozygotic and 494 dizygotic twin pairs): provides statistical power (>0.8) to detect heritability >0.25, shared environment influences >0.2 and a genetic correlation >0.3 (when heritability for both phenotypes >20%).
- Well-characterised lifetime psychiatric diagnoses and substance use (DSM-IV abuse and dependence criteria, for a wide variety of licit and illicit substances, including non-medical use of over-the-counter and prescription substances).
- Rich biological samples: hair sample (cortisol) and longitudinal blood samples (vitamin D, antibodies, metabolites, gene expression, genome-wide association study (GWAS)).
- Longitudinal design: most participants have been assessed at 12, 14, 16 and 21 years. Repeated observations within 19Up, to study scores and diagnoses stability and reliability.
- Multimodal imaging: 36% of participants underwent structural and functional MRI and diffusion tensor imaging (DTI).

INTRODUCTION

Between 2009 and 2016, the Nineteen Up Study (19Up: Mapping neurobiological changes across mental health stages, see[1] for study protocol) assessed a range of mental health and behavioural problems and associated risk factors in a genetically informative Australian population sample of young adult twins and their non-twin siblings. These individuals are part of the ongoing Brisbane Longitudinal Twin Study (BLTS, or Brisbane Adolescent Twin Study: BATS,[1 2] which began in 1992 when twins were recruited from primary and secondary schools in the greater Brisbane area via media appeals and by word of mouth. A key strength of 19Up is the ability to link

twin data with a phenotypically rich, longitudinal collection of environmental and psychological risk factors including personality, psychiatric phenotypes and diagnostic outcomes, neurobiological correlates such as brain imaging and genome-wide association data (figure 1). As such, 19Up enables detailed investigation of the genetic and environmental pathways to mental illness as well as substance use and misuse.

The 19Up study complements and extends earlier BLTS and BATS studies conducted during adolescence (figure 1)[3–12] by providing a detailed assessment of mental health and substance use and misuse at a young adult age. The study was organised around collecting lifetime diagnoses of substance misuse and common mood disorders, but also a wide range of behavioural and subclinical assessments, as well as updates on phenotypes previously collected in the BLTS (figure 1). Finally, the 19Up data collection was also designed to contribute to twin and genetic consortia in psychiatry, personality and brain imaging. We hope that the description of the full sample below will assist future publications and encourage further collaborations making use of the rich 19Up data (see 'Collaboration' section).

Cohort description

Data were collected in three waves (NU1, NU2, NU3) between February 2009 and June 2016 (figure 2). Initially, mental health scores were collected via an online survey (NU1, n=373), which was replaced in September 2010 by a more detailed online questionnaire complemented by a Computer-Assisted Telephone Interview (CATI) of the Composite International Diagnostic Interview (CIDI[13]) (NU2, n=665). Beginning 1 July 2012, the online survey and CATI instruments were then merged into a unique, more economical online protocol, divided into three sections (see table 1 and figure 2). Ascertainment began with the oldest BLTS adult twins and their non-twin siblings in order to obtain data from individuals who had passed through the peak age range for the onset for substance use disorders, anxiety and mood disorders.[14–17]

The NU1 questionnaire assessed general health, mental health symptomatology (Somatic and Psychological Health Report: SPHERE-12,[18–21] KESSLER-6[22]), use of alcohol, nicotine,[23] cannabis and other substances including the non-medical use of prescriptions substances; migraine and headaches, inattention (The Strengths and Weaknesses of ADHD symptoms and Normal behaviour rating scale: SWAN)[24] and baldness (online supplementary file 2). The following waves (NU2 and 3) also included structured clinical assessment (CIDI),[13] self-reported symptoms of mania (Altman Self-Rating Mania Scale[25]), suicidal thoughts, sleep quality and sleep–wake patterns (Pittsburgh Sleep Quality Index[26] and Insomnia Severity Index[27]) and general demographics, where participants were asked about their work activity/occupation, level of education, quality of friendships, familial environment (Parental Bonding Instrument[28]) and exposure to adversity (List of Threatening Experiences[29–31]). Finally, sections of the NU2 and 3 questionnaires also assessed personality,[32–34] acne, asthma, anorexia, bulimia, endometriosis, joint flexibility, romantic preferences and internet use (online supplementary file 2, figure 1, see also ref.[1]).

We used the CIDI[13] to identify lifetime DSM-IV diagnoses of major depressive disorder (MDD), mania, social anxiety, cannabis dependence, alcohol dependence and panic disorder (with and without agoraphobia), basic epidemiology of ecstasy and methamphetamine use, as well as psychotic symptoms. These narrow DSM diagnoses can be used for collaborations with consortia and have served to extract an MDD case–control sample for the ENIGMA-MDD consortium,[35 36] with a tight control of the comorbidities present in the sample.

In addition, we derived alternative diagnoses of depressive, manic and hypomanic episodes that focus on the core diagnostic criteria (criteria A and B of the DSM) and do not enforce the DSM-IV exclusions related to substance use, putative cause of the disorder (eg, bereavement in depression) or hierarchy of DSM disorders (see online supplementary file 1). These represent broader definitions of the disorders, with greater rates of (co) morbidity and will be preferred for future studies of psychiatric trajectories in the BLTS (see online supplementary file 1 for more details about the clinical syndrome definitions).

Of the 4156 individuals invited to participate in the study, 67% of the twins and non-twin siblings provided complete data. Overall, females were slightly over-represented among the 19Up respondents: comprising 50.5% (95% CI 48.9 to 52.1) of the invited population but 57.8% (55.9 to 59.6) of the actual ascertained participants (table 1). Across the last two waves (NU2 and 3), 2773 twins and non-twin siblings completed the demographic and CIDI questionnaires (mean age=26.1, SD=4.1, range 18–38, 57.8% female, 369 complete monozygotic pairs, 494 dizygotic pairs). Due to the ascertainment strategy employed, participants who completed the telephone interview (NU2) were significantly older than participants who completed the online survey (mean age 27.4 (range=20.6–38.6) vs 25.7 (range=18.7–38.3), t=11.6, P=2.2E-16) but the sex ratio was comparable across the two waves: 58.2% vs 57.6%, χ^2=0.035, P=0.85 (table 1). The mean age of participants in NU1 was 24.7 (range=18.4–30.4) with a sex ratio of 62.9%. Ethnically, the cohort reflects the population structure of families with twins in Queensland at the time of recruitment, with a majority of participants of European ancestry and minorities of predominantly Asian ancestry.[1]

Non-twin participants were on average older than their twin siblings (26.9 vs 25.8, t=5.70, P=1.5e-8) and were more likely to be married (26.2% vs 20.0%, χ^2=14.5, P=0.0057) with children (22.3% vs 17.1%, χ^2=8.66, P=0.0033), but twins and non-twins siblings did not differ in education level (χ^2=2.2, df=7, P=0.94) or sex ratio (χ^2=0.017, P=0.89).

All participants had been invited to complete previous BLTS[1 2] studies (figure 1). Height, weight, personality,

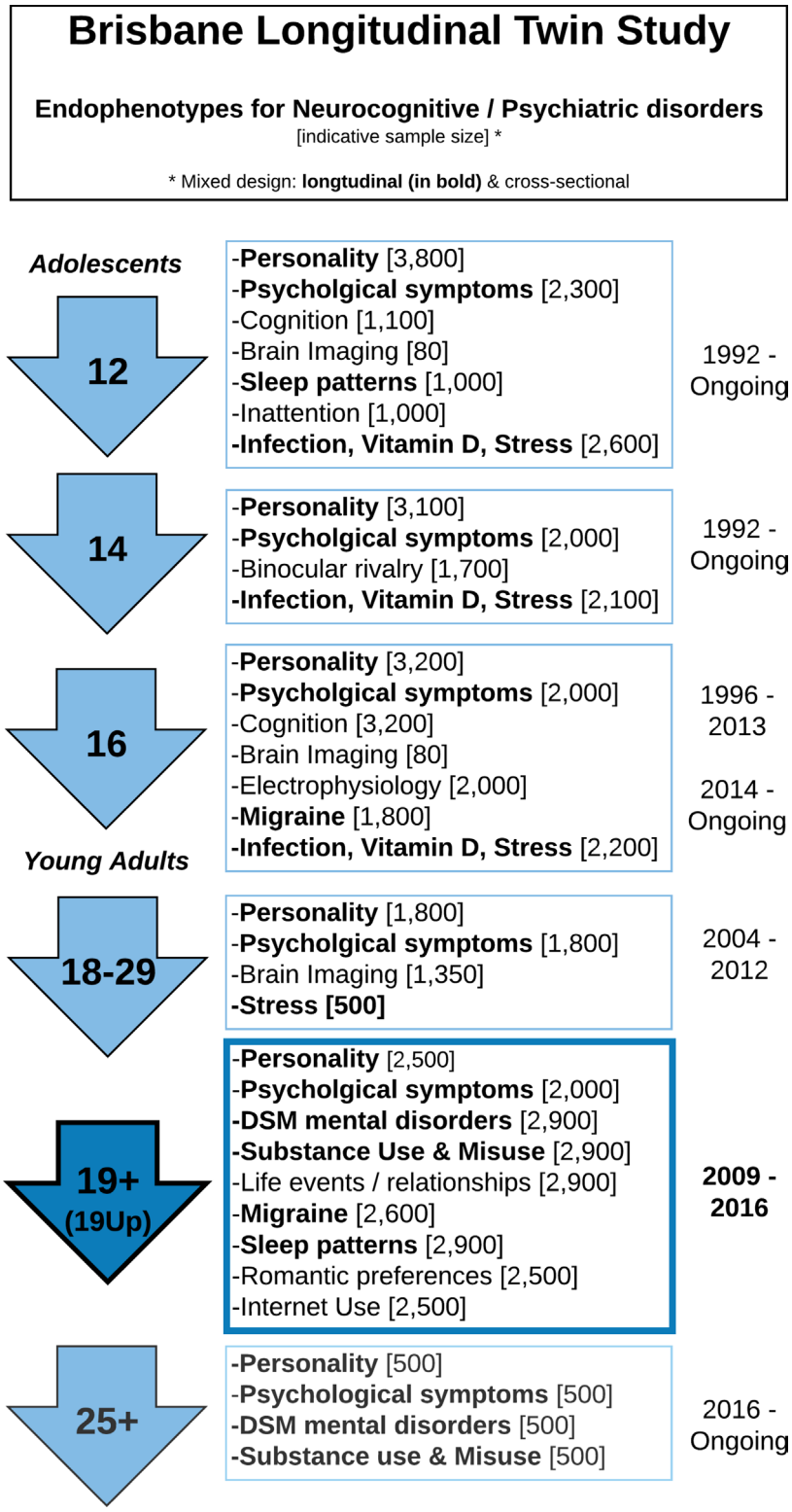

Figure 1 Summary of the Brisbane Longitudinal Twin Sample data collection. Longitudinal: vitamin D; infections (antibodies); neuroticism junior Eysenck personality questionnaire (JEPQ) neuroticism-extraversion-openness inventory (NEO); psychiatric signs (SPHERE). Cross-sectional: hair cortisol; cognition (verbal, performance IQ, working memory, information processing); binocular rivalry (rivalry rate); brain imaging (multimodal MRI); substance use (alcohol, tobacco, recreational drugs); sleep patterns (actigraphy); psychiatric diagnoses (Composite International Diagnostic Interview); life events/social support/ relationships (eg, early home environment, family relationships, traumatic events, socioeconomic factors). *Sample size in only indicative as many of the early waves are still recruiting new participants. Phenotypes in bold are collected longitudinally, other are cross-sectional.

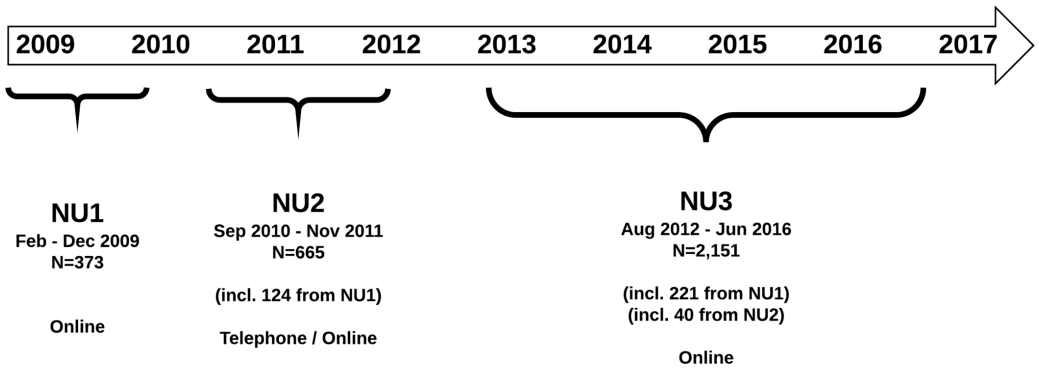

Figure 2 Timeline of the Nineteen and Up study data collection. Because of the changes in protocols, participants from NU1 were all reapproached to complete the following NU2 or NU3 waves. The vast majority (92%) then completed NU2 or NU3. Despite an interval of several years, these data provide an opportunity to examine test–retest reliability of scores or compare collection methods (eg, self-report online vs telephone interview). In addition to providing insight into the validity of the measures, these data are important for twin modelling as the stability of a phenotype or diagnosis sets an upper limit for the heritability.

psychiatric signs, sleep patterns, migraine and blood samples (haematological and immunological measures: eg, antibodies markers of infections, vitamin D) were collected longitudinally in the BLTS, with up to five time points for some phenotypes (figure 1). In addition, genome-wide single nucleotide polymorphism (SNP) genotypes are currently available for 84% (n=2324) of the 19Up participants. These data have been imputed

Table 1 Demographics of the final sample and detail by wave

	Total*	NU1	NU2	NU3
N invited	4156†	841†	2240†	3374†
% females (95% CI)	50.5% (48.9 to 52.1)	54.8% (51.4 to 58.2)	50.4% (48.3 to 52.4)	49.7% (48.0 to 51.4)
N completed (response rate)	2773 (67%)	373 (44%)	665 (30%)	2151 (64%)
Mean age (SD) (range)	26.1 (4.1) (18.7–38.6)	24.7 (3.3) (18.4–30.4)	27.4 (2.9) (20.6–38.6)	25.7 (4.3) (18.7–38.3)
% females (95% CI)	57.8% (55.9 to 59.6)	62.9% (57.7 to 67.8)	58.2% (54.3 to 62.0)	57.6% (55.4 to 60.0)
Marital status % (n)		NA‡		
Married	21.6% (599)		28.1% (187)	19.4% (418)
Separated	1.0% (28)		0.9% (6)	1.1% (23)
Divorced	1.0% (28)		1.4% (9)	0.9% (20)
Widowed	0.1% (3)			0.1% (3)
Never married	76.3% (2115)		69.6% (463)	78.4% (1687)
Have children % (95% CI)	18.3% (16.9 to 19.8)	NA‡	22.1% (19.0 to 25.5)	17.3% (15.7 to 19.0)
Highest education level§ % (n)		NA‡		
No formal education	0.0% (1)		0.0% (0)	0.05% (1)
Primary school	0.0% (0)		0.0% (0)	0.0% (0)
Junior secondary school	1.8% (51)		1.5% (10)	2.1% (45)
Senior secondary school	16.2% (449)		14.4% (96)	16.9% (364)
Certificate or diploma	24.3% (675)		29.3% (195)	23.2% (498)
Degree	44.7% (1239)		39.5% (263)	45.7% (983)
Postgraduate diploma, masters, PhD	12.8% (354)		15.2% (101)	11.9% (256)
Don't know/prefer not to answer	0.1% (4)		0.0% (0)	0.18% (4)

*NU1 data is in part reported in ref.,[1] but not included in the total sample or used in this analysis as most of the participants (345 out of 373: 92%) later completed NU2 or NU3.
†4156 unique individuals were invited to participate in the 19Up, but some were invited in several waves. Participants invited in NU1 were all reinvited in NU2. They were also invited as part of NU3 if they had not completed NU2 and not refused to be recontacted. Forty participants of NU2 also completed NU3.
‡Succinct demographics for NU1 were collected as part of a different study on political views and economical games and different questions were used.
§Participants were asked about their highest level of education (completed or partially completed) at the time of questionnaire.
19Up, Nineteen and Up study.

and quality controlled (see ref.[1] for details) using state-of-the-art procedures,[37–40] which allow combining data from different arrays, and currently represent a more cost-effective approach to study complex human traits than whole-genome sequencing (at current prices).[41]

Multimodal brain MRI was collected cross-sectionally and is available for 987 (36%) of the 19Up respondents (see ref.[42] for all details). Further assessments during adolescence are available for part of 19Up: cognition (available for 56.8% of the sample), parental report of ADHD symptomatology (100%), binocular rivalry (19.6%) and electroencephalography (30.4%) (see refs.[2 4 7 43] for details about these waves). Finally, a follow-up study of all 19Up participants has been funded and is currently ongoing (expected mean age at follow-up 25).

Findings to date

Among the full DSM-IV diagnostic criteria, social anxiety and MDD were the most prevalent diagnoses (both at 17.5%, n=486), followed by panic disorder without agoraphobia (1.5%, n=42) and panic disorder with agoraphobia (0.9%, n=24). In addition, 14.3% (n=397) of the respondents reported a past panic attack and 0.5% (n=14) qualified for a manic episode (table 2). Lifetime prevalence of mental disorders were slightly increased when the lower threshold of cases meeting DSM-IV clinical criteria (A and

Table 2 Prevalence of DSM-IV diagnoses in the 19Up study

	Total prevalence % (95% CI)	Prevalence males % (95% CI)	Prevalence females % (95% CI)	P values males versus females	Prevalence NU2 % (95% CI)	Prevalence NU3 % (95% CI)	P values NU2 versus NU3
Affective disorders							
MDD	17.5% (16.1 to 19.0)	13.8% (11.9 to 15.9)	20.3% (18.3 to 22.3)	**1.06E-05**	15.2% (12.6 to 18.2)	18.3% (16.6 to 20.0)	0.078
Social anxiety	17.5% (16.1 to 19.0)	13.2% (11.3 to 15.3)	20.7% (18.8 to 22.8)	**3.2E-07**	16.2% (13.6 to 19.3)	17.9% (16.3 to 19.7)	0.35
Panic disorder (with agoraphobia)	0.9% (0.57 to 1.3)	0.3% (0.1 to 0.8)	1.3% (0.8 to 2.0)	5.9E-3*†	1.1% (0.5 to 2.3)	0.8% (0.5 to 1.3)	0.72
Panic disorder (without agoraphobia)	1.5% (1.1 to 2.1)	0.9% (0.4 to 1.6)	2.0% (1.4 to 2.8)	0.023†	1.7% (0.9 to 3.0)	1.5% (1.0 to 2.1)	0.88
Panic attack	14.3% (13.0 to 15.7)	9.2% (7.6 to 11.0)	18.1% (16.3 to 20.1)	**4.5E-11**	15.6% (13.0 to 18.7)	13.9% (12.5 to 15.5)	0.29
Manic episode	0.5% (0.3 to 0.9)	0.7% (0.3 to 1.4)	0.4% (0.2 to 0.9)	0.39	0.6% (0.2 to 1.6)	0.5% (0.2 to 0.9)	0.93*
Substance use							
Lifetime use of any drug‡	57.8% (56.0 to 59.7)	63.2% (60.4 to 66.0)	53.9% (51.4 to 56.4)	**1.0E-06**	62.3% (58.4 to 65.9)	56.5% (54.3 to 58.6)	9.4E-3†
Cannabis abuse	11.6% (10.5 to 12.9	17.0% (14.9 to 19.3)	7.7% (6.44 to 9.11)	**5.6E-14**	15.3% (12.7 to 18.4)	10.4% (9.2 to 11.8)	**7.5E-4**
Cannabis dependence	6.8% (5.9 to 7.8)	9.8% (8.2 to 11.7)	4.6% (3.7 to 5.8)	**1.1E-07**	10.7% (8.5 to 13.3)	5.6% (4.7 to 6.7)	**8.9E-06**
Alcohol abuse	33.8% (32.1 to 35.6)	40.2% (37.4 to 43.1)	29.2% (27.0 to 31.5)	**2.1E-09**	36.7% (33.0 to 40.5)	32.9% (30.9 to 35)	0.081
Alcohol dependence	28.0% (26.3 to 29.7)	35.4% (32.7 to 38.2)	22.6% (20.6 to 24.7)	**1.66E-13**	32.8% (29.2 to 36.5)	26.5% (24.6 to 28.4)	**0.0019**
Core diagnostic criteria							
Depression	25.8% (24.2 to 27.5)	20.3% (18.1 to 22.8)	29.8% (27.6 to 32.1)	**2.7E-08**	25.1% (21.9 to 28.6)	26% (24.2 to 27.9)	0.68
Hypomania	6.3% (5.5 to 7.3)	6.3% (5.0 to 7.8)	6.4% (5.3 to 7.7)	0.97	5.7% (4.1 to 7.8)	6.5% (5.5 to 7.7)	0.52
Mania	2.0% (1.5 to 2.6)	2.1% (1.4 to 3.1)	2.0% (1.4 to 2.8)	1	1.1% (0.5 to 2.3)	2.3% (1.7 to 3.1)	0.06
N	2773	1170	1603		665	2151	

Significant P values after multiple testing correction are highlighted in bold. Analyses performed using a χ^2 test (1 degree of freedom) unless stated. Cells report prevalence % (95% CI).
*Fisher's exact test used.
†Would not survive multiple testing correction of 0.05/22=0.0022.
‡Illicit drug or non-medical use of prescription drug. Participants are asked specifically about cocaine, amphetamine-type stimulants, inhalants, sedatives or sleeping pills, hallucinogens, opioids, party drugs (ecstasy, ketamine, GHB), over-the-counter/prescription pain killers and analgesics for non-medical purposes, over-the-counter/prescription stimulants for non-medical purposes, or other.
19Up, Nineteen and Up study; MDD, major depressive disorder.

Table 3 Prevalence of psychotic symptoms

	Total prevalence	Prevalence males	Prevalence females	P values males versus females	Prevalence NU2	Prevalence NU3	P values NU2 versus NU3
Psychotic symptoms in the last 12 months	2.7% (2.2 to 3.4)	2.9% (2.1 to 4.1)	2.6% (1.9 to 3.5)	0.66	2.4% (1.4 to 4.0)	2.8% (2.2 to 3.6)	0.68
Lifetime presence of any psychotic symptoms*	7.1% (6.2 to 8.1)	7.4% (6.0 to 9.1)	6.8% (5.6 to 8.2)	0.57	7.8% (6.0 to 10.2)	6.8% (5.8 to 8.0)	0.44
Visual hallucinations	3.9% (3.2 to 4.7)	3.6% (2.6 to 4.9)	4.1% (3.2 to 5.2)	0.60	4.2% (2.8 to 6.1)	3.8% (3.0 to 4.7)	0.73
Auditory hallucinations	3.3% (2.7 to 4.0)	3.9% (2.9 to 5.3)	2.8% (2.1 to 3.8)	0.13	3.3% (2.1 to 5.1)	3.3% (2.6 to 4.2)	1.0
Delusions: thought insertion and thought broadcasting	0.4% (0.21 to 0.73)	0.6% (0.26 to 1.3)	0.3% (0.1 to 0.6)	0.22†	0.6% (0.2 to 1.7)	0.3% (0.2 to 0.7)	0.30†
Delusions: 'made' feelings and impulses	0.3% (0.2 to 0.6)	0.3% (0.1 to 0.9)	0.3% (0.1 to 0.7)	1†	0.6% (0.2 to 1.6)	0.2% (0.1 to 0.6)	0.23†
Delusions of reference	1.1% (0.7 to 1.5)	1.5% (0.9 to 2.4)	0.7% (0.4 to 1.3)	0.11	2.0% (1.1 to 3.4)	0.7% (0.5 to 1.3)	0.015‡
Delusions of persecution	0.9% (0.6 to 1.3)	0.9% (0.5 to 1.7)	0.9% (0.5 to 1.6)	0.98	1.1% (0.5 to 2.3)	0.9% (0.5 to 1.4)	0.81
N	2773	1170	1603		665	2151	

Cells report prevalence % (95% CI). P values calculated using a χ^2 test unless stated otherwise.
*Includes any of the psychotic symptoms.
†Fisher's exact test used.
‡Would not survive multiple testing correction of 0.05/16=0.0031.

B) was applied: 25.8% (n=715) for MDD, 6.3% (n=175) for hypomania and 2.0% (n=56) for mania.

Over half (57.8%, n=1604) of the samples reported illicit substance use including the non-medical use of over-the-counter and prescription substances (table 2). Among the substance use disorders, DSM-IV diagnoses of lifetime alcohol abuse (Alc-ab) and dependence (Alc-dep) were the most prevalent at 33.8% (n=938) and 28.0% (n=776), respectively. In comparison, lifetime prevalence of cannabis abuse (can-ab) and dependence (can-dep) were 11.6% (n=322) and 6.8% (n=189, table 2).

Among participants, 7.1% (n=196) had experienced one or more psychotic symptoms in their lifetime (table 3). Visual hallucinations were the most common, occurring in 3.9% (n=107) of the sample, followed by auditory hallucinations (3.3%, n=91), while delusions were rare (thoughts insertion and thought broadcasting: 0.4% (n=11) 'made' feelings and impulses: 0.3% (n=9), delusions of references: 1.1% (n=29) and delusions of persecution: 0.9% (n=25)).

The prevalence for (DSM-IV) mood disorders was higher in females than males (table 2). For example, females were almost 1.5-fold as likely than males to meet criteria for MDD (DSM-IV narrow diagnosis: 20.3% F, 13.8% M, χ^2=14.2, P=1.6E-4; broad criteria: 29.8% F, 20.3% M, χ^2=30.9, P=2.7E-8) and social anxiety (20.7% F, 13.2% M, χ^2=26.4, P=3.2E-7). Panic disorder was at least three times more prevalent in females than males (with agoraphobia 1.3% F, 0.3% M, χ^2=7.6, P=5.9E-3, without agoraphobia 2.0% F, 0.1% M, χ^2=5.2, P=0.02). Similarly, panic attack(s) were more common in females than males (18.1% F 9.2% M, χ^2=43.4, P=4.5E-11). No significant sex differences were observed in the prevalence of manic episode or psychotic symptoms (table 2).

Substance use disorders were more common in males (can-ab: 17.0% M, 7.7% F, χ^2=56.5, P=5.6E-14; can-dep: 9.8% M, 4.6% F, χ^2=28.1, P=1.1E-7; Alc-ab: 40.2% M, 29.2% F, χ^2=35.9, P=2.1E-9; Alc-dep: 35.4% M, 22.6% F, χ^2=54.3, P=1.7E-13). Use of any illegal drug (including the non-medical use of over-the-counter and prescription substances) was also significantly higher in males compared with females (63.2% M, 53.9% F, χ^2=23.8, P=1.0E-6, table 2). For Alc-dep the prevalence was higher in the CATI (NU2) compared with online (NU3) participants (table 2, online supplementary file 1), which could be partly explained by the older age of the NU2 sample compared with the NU3 participants (table 1).

Ages of onset was comparable across sexes for all DSM-IV diagnoses, but it varied substantially across disorders (ie, 11.5 years for social anxiety, 18.5 years for panic disorder and around 20 years for MDD and can-dep; table 4). Age of onset was not available for alcohol dependence as only the age at initiation (16.0 years) was collected. The mean ages of onset for manic episode, panic attack and psychotic symptoms were 19.6, 17.6 and 15.7 years, respectively.

The lifetime prevalence reported above highlights how common mental disorders may be in an unselect sample of young Australian adult twins. Together with the large sample size of the present study and the longitudinal detailed phenotyping, the 19Up study is suited to identifying early markers of mental health risk and shed light on the pathways to psychiatric disorders.

DISCUSSION

Prevalence of MDD (DSM-IV) in 19Up was higher than that reported by the 2007 National Survey of Mental Health and Wellbeing (7%)[44] the WHO World Mental Health Surveys (12.8%)[45] or in a large adolescent cohort from the USA[46] while comparable prevalence have been reported in New Zealand[47 48] and in Australian women.[49] These results highlight that if overall MDD is a common condition in high-income countries[47] its

Table 4 Differences in the age of onset for males and females

	Mean age of onset (SD)	Mean age of onset males (SD)	Mean age of onset females (SD)	P values males versus females
Manic episode	19.6 (5.0)	19.2 (5.4)	20.0 (5.6)	0.87
First psychotic symptom	15.7 (6.4)	15.0 (6.4)	16.2 (6.3)	0.21
Major depressive disorder	20.6 (5.1)	21.3 (5.4)	20.3 (5.0)	0.038
Social anxiety	11.6 (5.0)	11.3 (4.7)	11.7 (5.1)	0.42
Cannabis abuse	19.7 (3.1)	19.8 (3.0)	19.6 (3.2)	0.65
Cannabis dependence	19.8 (3.0)	20. 0 (2.9)	19.6 (3.0)	0.39
Cannabis initiation	17.7 (4.1)	17.5 (2.8)	17.9 (4.9)	0.05
Alcohol initiation	16.0 (1.8)	15.8 (1.8)	16.1 (1.8)	**1.20E-05**
Panic attack	17.6 (5.5)	16.8 (5.9)	17.9 (5.3)	0.11
Panic disorder with or without agoraphobia	18.7 (5.7)	20.4 (5.0)	18.3 (5.9)	0.22

Age of onset was not collected for alcohol abuse, dependence and use disorder. We reported age at first drink (initiation), age at first intoxication and age of 'regular use' (one drink a month for 6 months) have also been collected.
After multiple testing correction are shown in bold.

observed prevalence depends on the age of the respondent. Similarly, the younger age of participants in the 19Up study likely explains the younger mean age of onset for MDD compared with published research.[50 51] Our lifetime prevalence for social anxiety was higher than that previously reported in Australia,[49 52] New Zealand[48] and the USA,[53] but similar to the prevalence in a separate sample of Australian twins.[54] Age of onset for social anxiety in the 19Up study was comparable to previous reports.[48 50 51]

The prevalence of panic disorder without agoraphobia has been reported to be between 2.3% and 10.9%,[46 48 53 55] higher than our findings (1.5%). Published prevalences of panic disorder with agoraphobia are also higher than in our study (1.1%–3.8%[53 55] vs. 0.9%), which could be due to our limited age range.

Population studies found between 5.4% and 6.2% of Australians meet criteria for cannabis abuse.[56 57] However, the prevalence has been reported higher (11.4%) within 25–44 years,[57] comparable to our results for can-ab/can-dep (11.6%/6.8%). In addition, we found 28.0% of those in 19Up were alcohol dependent (33.8% with alcohol abuse), consistent with previous publications,[53 58] despite differences in recruitment and age of the respondents. The differences with studies that reported lower prevalence of alcohol dependence in both Australia (3.8%)[57] and New Zealand (4%)[48] could be due to differences in data collection (face-to-face vs online), recruitment and demographics. Finally, prevalence of use of any illegal substance (and misuse of prescription drug) was comparable to previously available Australian data (57.8% compared with 51.2% in 20–29 years, 59.3% in 30–39).[48 59]

Prevalence of psychotic symptoms in the 19Up study (7.1%) matched results of the largest studies to date,[60 61] while other studies reported prevalence between 5.5%[62] and 11.7%.[63] Hallucinations were the most common symptom, as previously reported,[60] and the prevalence of specific symptoms was comparable to our results.[60 62 63] However, we found a younger mean age of onset for psychotic symptoms (15.7 years) than previous studies,[64] which could be attributed to the age range of the cohort.

Overall, the sex differences matched previous studies. Affective disorders were all more prevalent in women[46 48 54 65–67] while substance use disorders (and abuse or dependence) were more common in men.[16 46 48 59]

In our sample, comorbidities were widespread across the diagnoses (table 5, online supplementary file 3) consistent with previous epidemiological results[45 50 52 57 58 68–70] and explained in part by genetic correlations between psychiatric diagnoses.[71 72] About 60.4% of our sample met the criteria for at least one DSM-IV diagnosis in their lifetime, with 18.0% of these reporting a second lifetime diagnoses, 9.1% reporting three diagnoses and 6.8% reporting four or more lifetime diagnoses. When considering only the core symptoms of depression, core mania/hypomania and previous psychotic experiences, 31.9% of the sample reported at least one clinical syndrome (24.0% with exactly one clinical syndrome, 6.7% with two lifetime clinical syndrome and 1.2% with the three clinical syndromes).

Consistent with previous reports,[45 50 52 55] most mood disorders were significantly comorbid (table 5, online supplementary file 3) and the non-significant associations may be explained by the low prevalence of manic episodes and agoraphobia (yielding low statistical power). In addition, MDD was also associated with presence of psychotic symptoms, previously reported in an Australian sample[69] and in a worldwide mega-analysis.[70] An association between social anxiety and psychotic symptoms had also been reported[69 70] but did not reach significance in our study. Finally, panic attacks were associated with higher risk

Table 5 Proportion of people with one DSM-IV disorder (rows) who also have another disorder (columns)

		MDD	Social anxiety	Cannabis abuse	Cannabis dependence	Alcohol abuse	Alcohol dependence	Panic with agora	Panic without agora	Panic attack	Manic episode	Psychotic symptoms	Any illegal substance use*
MDD	Cases	–	**33.7% (29.6 38.2)**	9.5% (7.1 to 12.5)	5.8% (3.9 to 8.3)	34.8% (30.6 to 39.2)	30% (26 to 34.4)	1.9% (0.9 to 3.6)	**4.3% (2.8 to 6.6)**	**31.1% (27 to 35.4)**	1% (0.4 to 2.5)	**11.3% (8.7 to 14.6)**	60.1% (55.6 to 64.4)
	Controls		**14.1% (12.7 to 15.6)**	12.1% (10.8 to 13.5)	7% (6 to 8.2)	33.6% (31.7 to 35.6)	27.5% (25.7 to 29.4)	0.7% (0.4 to 1.1)	**0.9% (0.6 to 1.4)**	**10.8% (9.5 to 12.1)**	0.4% (0.2 to 0.8)	**6.2% (5.2 to 7.2)**	57.4% (55.3 to 59.4)
	P values		**7.80E-25**	0.12	0.36	0.66	0.29	0.021	**7.70E-08**	**8.30E-31**	0.15	**8.60E-05**	0.29
Social anxiety	Cases	**33.7% (29.6 to 38.2)**	–	15.2% (12.2 to 18.8)	9.3% (6.9 to 12.3)	36.8% (32.6 to 41.3)	**34.2% (30.0 to 38.6)**	2.1% (1.0 to 3.9)	**4.1% (2.6 to 6.4)**	**30.5% (26.4 to 34.8)**	**1.6% (0.8 to 3.3)**	9.7% (7.3 to 12.7)	62.1% (57.6 to 66.4)
	Controls	**14.1% (12.7 to 15.6)**		10.8% (9.6 12.2)	6.3% (5.4 to 7.4)	33.2% (31.3 to 35.2)	**26.7% (24.9 to 28.5)**	0.6% (0.3 to 1.1)	**1.0% (0.6 to 1.5)**	**10.9% (9.7 to 12.3)**	**0.3% (0.1 to 0.6)**	6.5% (5.6 to 7.6)	56.9% (54.9 to 59)
	P values	**7.80E-25**		0.0078	0.024	0.14	**0.001**	0.0043	**6.90E-07**	**1.10E-28**	**3.8E-4**	0.018	0.039
Cannabis abuse	Cases	14.3% (10.7 to 18.7)	23.0% (18.6 to 28)	–	**50.0% (44.6 to 55.4)**	**71.7% (66.4 to 76.5)**	**60.2% (54.7 to 65.6)**	2.5% (1.2 to 5.0)	0.6% (0.1 to 2.5)	**21.7% (17.4 to 26.7)**	**1.9% (0.8 to 4.2)**	**12.4% (9.1 to 16.6)**	**98.1% (95.8 to 99.2)**
	Controls	18% (16.5 to 19.5)	16.8% (15.4 to 18.4)		**1.1% (0.8 1.7)**	**28.8% (27.1 to 30.7)**	**23.7% (22.1 to 25.5)**	0.7% (0.4 to 1.1)	1.6% (1.2 to 2.2)	**13.3% (12.0 to 14.8)**	**0.3% (0.2 to 0.7)**	**6.4% (5.4 to 7.4)**	**52.5% (50.6 to 54.5)**
	P values	0.12	0.0078		**6.0E-233**	**2.2E-52**	**2.0E-42**	0.0026	0.25	**7.50E-05**	**0.0012**	**0.00011**	**2.80E-54**
Cannabis dependence	Cases	14.8% (10.2 to 20.9)	23.8% (18.1 to 30.6)	**85.2% (79.1 89.8)**	–	**69.8% (62.7 to 76.2)**	**65.1% (57.8 71.8)**	2.6% (1.0 to 6.4)	0.5% (0.0 to 3.4)	**27.5% (21.4 34.6)**	**3.2% (1.3 to 7.1)**	**17.5% (12.5 to 23.8)**	**97.9% (94.3 to 99.3)**
	Controls	17.7% (16.3 to 19.3)	17.1% (15.6 to 18.6)	**6.2% (5.3 to 7.2)**		**31.2% (29.4 to 33)**	**25.3% (23.6 to 27)**	0.7% (0.5 to 1.2)	1.6% (1.2 to 2.2)	**13.4% (12.1 to 14.7)**	**0.3% (0.1 to 0.6)**	**6.3% (5.4 7.3)**	**54.9% (53.0 to 56.8)**
	P values	0.36	0.024	**6.0E-233**		**5.20E-27**	**1.50E-31**	0.02	0.4	**1.50E-07**	**1.30E-06**	**1.80E-08**	**1.80E-30**
Alcohol abuse	Cases	18.0% (15.6 to 20.7)	19.1% (16.6 to 21.8)	**24.6% (21.9 to 27.5)**	**14.1% (11.9 to 16.5)**	–	**63.3% (60.1 to 66.4)**	1.3% (0.7 to 2.3)	1.8% (1.1 to 2.9)	**17.4% (15.0 to 20.0)**	**1.2%(0.6 2.2)**	8.0% (6.4 to 10.0)	**82.3% (79.7 to 84.7)**
	Controls	17.3% (15.6 to 19.1)	16.7% (15.1 to 18.5)	**5.0% (4.0 to 6.1)**	**3.1% (2.4 to 4.0)**		**9.9% (8.6 to 11.4)**	0.7% (0.4 to 1.2)	1.4% (0.9 to 2.0)	**12.8% (11.3 to 14.4)**	**0.2%(0.0 0.5)**	6.6% (5.5 to 7.9)	**45.3% (43.0 to 47.7)**
	P values	0.66	0.14	**2.2E-52**	**5.2E-27**		**1.7E-192**	0.14	0.45	**0.0012**	**0.0011**	0.2	**2.8E-77**
Alcohol dependence	Cases	18.8% (16.2 to 21.8)	**21.4% (18.6 to 24.5)**	**25% (22.0 to 28.2)**	**15.9% (13.4 to 18.7)**	**76.5% (73.4 to 79.5)**	–	1.3% (0.7 to 2.4)	1.9% (1.1 to 3.2)	**19.3% (16.6 to 22.3)**	1.2% (0.6 to 2.3)	7.9% (6.1 to 10.0)	**83.1% (80.3 to 85.6)**
	Controls	17% (15.4 to 18.8)	**16% (14.5 to 17.7)**	**6.4%(5.4 to 7.6)**	**3.3% (2.6 to 4.2)**	**17.2% (15.6 to 19.0)**		0.7% (0.4 to 1.2)	1.4% (0.9 to 2.0)	**12.4% (11.0 to 13.9)**	0.3% (0.1 to 0.6)	6.8% (5.7 to 8.0)	**48% (45.8 to 50.2)**
	P values	0.29	**0.001**	**2.00E-42**	**1.50E-31**	**1.7E-192**		0.2	0.34	**3.50E-06**	0.0062	0.35	**4.90E-63**
Panic disorder with agoraphobia	Cases	37.5% (19.6 to 59.2)	41.7% (22.8 to 63.1)	33.3% (16.4 to 55.3)	20.8% (7.9 to 42.7)	50% (31.4 to 68.6)	41.7% (22.8 to 63.1)	–	NA	NA	4.2% (0.2 to 23.1)	4.2% (0.2 to 23.1)	75.0% (52.9 to 89.4)
	Controls	17.4% (16 to 18.8)	17.3% (15.9 to 18.8)	11.4% (10.3 to 12.7)	6.7% (5.8 to 7.7)	33.7% (31.9 to 35.5)	27.9% (26.2 to 29.6)		1.5% (1.1 to 2.1)	13.6% (12.3 to 14.9)	0.5% (0.3 to 0.8)	7.1% (6.2 to 8.1)	57.7% (55.8 to 59.5)
	P values	0.021	0.0043	0.0026	0.02	0.14	0.2		NA*	NA*	0.27	0.88	0.13
Panic disorder without agoraphobia	Cases	**50% (35.5 to 64.5)**	**47.6% (32.3 to 63.4)**	4.8% (0.8 to 17.4)	2.4% (0.1 to 14.1)	40.5% (26.0 to 56.7)	35.7% (22.0 to 52.0)	0%	–	100%	0%	19.0% (9.1 to 34.6)	66.7% (50.4 to 80)
	Controls	**17% (15.6 to 18.5)**	**17.1% (15.7 to 18.5)**	11.7% (10.5 to 13)	6.9% (6.0 to 7.9)	33.7% (32.0 to 35.5)	27.9% (26.2 to 29.6)	0.9% (0.6 to 1.3)		13% (11.8 to 14.3)	0.5% (0.3 to 0.9)	6.9% (6.0 to 7.9)	57.7% (55.8 to 59.6)
	P values	**7.70E-08**	**6.90E-07**	0.25	0.4	0.45	0.34	NA		NA	1†	0.006	0.31

Continued

Table 5 Continued

		MDD	Social anxiety	Cannabis abuse	Cannabis dependence	Alcohol abuse	Alcohol dependence	Panic with agora	Panic without agora	Panic attack	Manic episode	Psychotic symptoms	Any illegal substance use*
Panic attack	Cases	**38% (33.3 to 43)**	**37.3% (32.5 to 42.3)**	**17.6% (14.1 to 21.8)**	**13.1% (10 to 16.9)**	**41.1% (36.2 to 46.1)**	**37.8% (33.0 to 42.8)**	6.0% (4.0 to 9.0)	10.6% (7.8 to 14.1)	–	**2.3% (1.1 to 4.4)**	**15.6% (12.3 to 19.7)**	64.7% (59.8 to 69.4)
	Controls	**14.1% (12.7 to 15.6)**	**14.2% (12.9 to 15.7)**	**10.6% (9.4 to 11.9)**	**5.8% (4.9 to 6.8)**	**32.6% (30.7 to 34.6)**	**26.3% (24.6 to 28.2)**	NA	NA		**0.2% (0.1 to 0.5)**	**5.6% (4.8 to 6.7)**	56.7% (54.7 to 58.7)
	P values	**8.30E-31**	**1.10E-28**	**7.50E-05**	**1.50E-07**	**0.0012**	**3.50E-06**	NA*	NA*		**6.70E-07**	**1.50E-12**	0.0032
Manic episode	Cases	35.7% (14 to 64.4)	**57.1% (29.6 to 81.2)**	**42.9% (18.8 to 70.4)**	**42.9% (18.8 to 70.4)**	**78.6% (48.8 to 94.3)**	64.3% (35.6 to 86)	7.1% (0.4 to 35.8)	0.0%	**64.3% (35.6 to 86.0)**	–	7.1% (0.4 to 35.8)	78.6% (48.8 to 94.3)
	Controls	17.4% (16 to 18.9)	**17.3% (15.9 to 18.8)**	**11.5% (10.3 to 12.7)**	**6.6% (5.7 to 7.6)**	**33.6% (31.8 to 35.4)**	27.8% (26.1 to 29.5)	0.8% (0.5 to 1.3)	1.5% (1.1 to 2.1)	**14.1% (12.8 to 15.4)**		7.1% (6.2 to 8.1)	57.7% (55.9 to 59.6)
	P values	0.15	**0.00038**	**0.0012**	**1.30E-06**	**0.0011**	0.0062	0.27	1†	**6.70E-07**		1	0.19
Psychotic symptoms	Cases	**28.1%**[22 35]	24.0% (18.3 to 30.7)	**20.4% (15.1 to 26.9)**	**16.8% (12.0 to 23.0)**	38.3% (31.5 to 45.5)	31.1% (24.8 to 38.2)	0.5% (0.0 to 3.2)	4.1% (1.9 to 8.2)	**31.6% (25.3 to 38.7)**	0.5% (0.0 to 3.2)	–	65.3% (58.1 to 71.9)
	Controls	**16.7% (15.3 to 18.2)**	17% (15.6 to 18.6)	**10.9% (9.8 to 12.2)**	**6.1% (5.2 to 7.1)**	33.5% (31.7 to 35.4)	27.7% (26.0 to 29.5)	0.9% (0.6 to 1.4)	1.3% (0.9 to 1.9)	**13% (11.7 to 14.4)**	0.5% (0.3 to 0.9)		57.3% (55.3 to 59.2)
	P values	**8.60E-05**	0.018	**1.1E-4**	**1.8E-08**	0.2	0.35	0.88	0.006	**1.5E-12**	1		0.034
Any illegal substance use‡	Cases	18.2% (16.4 to 20.2)	18.8% (17.0 to 20.8)	**19.7% (17.8 to 21.8)**	**11.5% (10.0 to 13.2)**	**48.1% (45.7 to 50.6)**	**40.2% (37.8 to 42.7)**	1.1% (0.7 to 1.8)	1.7% (1.2 to 2.5)	16.0% (14.3 to 17.9)	0.7% (0.4 to 1.3)	8.0% (6.7 to 9.4)	–
	Controls	16.6% (14.5 to 18.9)	15.7% (13.7 to 18.0)	**0.5% (0.2 to 1.2)**	**0.3% (0.1 to 0.9)**	**14.2% (12.3 to 16.4)**	**11.2% (9.5 to 13.2)**	0.5% (0.2 to 1.2)	1.2% (0.7 to 2.1)	12.0% (10.2 to 14.0)	0.3% (0.1 to 0.8)	5.8% (4.6 to 7.4)	
	P values	0.29	0.039	**2.80E-54**	**1.80E-30**	**2.80E-77**	**4.90E-63**	0.13	0.31	0.0032	0.19	0.034	

Read rows first followed by columns, for example, of participants with MDD 33.5% also had social anxiety. Significant P -values after multiple testing correction (Bonferroni corrected, significance threshold: 0.05/24=1.7E-3) appear in bold.
*Diagnoses and criteria whose definitions mutually exclude each other (eg, panic attack required for a diagnosis of panic disorder).
†Fisher's exact test used.
‡Illicit drug or non-medical use of prescription drug. Include cocaine, amphetamine-type stimulants, inhalants, sedatives or sleeping pills, hallucinogens, opioids, party drugs (ecstasy, ketamine, GHB), over-the-counter/prescription pain killers and analgesics for non-medical purposes, Over-the-counter/prescription stimulants for non-medical purposes, or other.
MDD, major depressive disorder.

of all affective disorders, substance abuse, dependence and initiation, as well as psychotic symptoms, most of which were already reported using the DSM-IV classification.[55] Panic disorder, on the other hand, was only associated with increased risk of affective disorders and alcohol abuse/dependence in the 19Up study.[55 67]

Substance misuse and any drug use were, unsurprisingly,[57] highly comorbid (table 5, online supplementary file 3). Furthermore, alcohol and cannabis abuse and dependence were associated with higher risk of panic attacks[55] and manic episodes.[73] Finally, alcohol dependence was more likely to be reported by individuals with social anxiety,[74] while cannabis abuse and dependence were more common in individuals reporting psychotic symptoms.[70]

Strengths and limitations

The 19Up study is a major resource to study mental health and substance use in an Australian sample of young adults. The main strengths of the 19Up within the BLTS are

- Large sample size (n=2773; 369 monozygotic and 494 dizygotic twin pairs): Provides significant power (>0.8) to detect heritability >0.25, shared environment influences >0.2 and a genetic correlation >0.3 (when heritability for both phenotypes>20%).[75 76]
- Genotyping: The majority (84%) of the sample has been genotyped allowing GWAS studies,[77] SNP-based heritability estimation[75 78] and polygenic risk scores analyses.[79 80]
- Longitudinal design: Most participants have been assessed at 12, 14, 16 and 21 years.
- Well-characterised lifetime psychiatric and substance use, DSM-IV abuse and dependence criteria, for a wide variety of licit and illicit substances (including non-medical use of over-the-counter and prescription substances).
- Rich biological samples: Hair sample (cortisol, see ref.[81]) and longitudinal blood samples (vitamin D, antibodies, metabolites, gene expression, GWAS).
- Multimodal Imaging: 36% of participants underwent structural and functional MRI and DTI.
- Repeated observations within 19Up, to study scores and diagnoses stability and reliability.

A main limitation of the 19Up study is the relatively young age of the participants when estimating lifetime prevalence as some controls may develop a mental disorder after the time of assessment. However, it is expected that a later assessment will capture additional lifetime cases. The next wave of the BLTS, currently under way, should provide a further assessment of the twins' psychopathologies in adulthood. In addition, twins are not necessarily a random sample of the population as twinning is likely heritable[82] and could be associated to some traits of interest. However, we can compare twins and non-twin siblings in this sample to rule out any confounding effect of twinning. Another limitation is that the factors influencing the different participation rates in the different waves (or in the overall study) are largely unknown. This non-random sampling could limit making inference about the general BLTS sample or the general population. Finally, the fact the assessments of clinical diagnoses were completed using different instruments (phone or online) and outside of a clinical interview with a psychiatrist or psychologist may also be a limitation.

Here, we reported the demographics of the full 19Up sample and highlighted the high lifetime prevalence and comorbidities between psychiatric disorder present in an unselected sample of young Australian adult twins. This should allow future studies to use the rich BLTS data in order to shed light on the pathways to psychiatric disorders. Finally, we hope that publicising the 19Up study (and the BLTS) may lead to new collaborations.

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