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Article

Twenty-Five and Up (25Up) Study: A New Wave of the Brisbane Longitudinal Twin Study

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Abstract

The aim of the 25 and Up (25Up) study was to assess a wide range of psychological and behavioral risk factors behind mental illness in a large cohort of Australian twins and their non-twin siblings. Participants had already been studied longitudinally from the age of 12 and most recently in the 19Up study (mean age = 26.1 years, SD = 4.1, range = 20–39). This subsequent wave follows up these twins several years later in life (mean age = 29.7 years, SD = 2.2, range = 22–44). The resulting data set enables additional detailed investigations of genetic pathways underlying psychiatric illnesses in the Brisbane Longitudinal Twin Study (BLTS). Data were collected between 2016 and 2018 from 2540 twins and their non-twin siblings (59% female, including 341 monozygotic complete twin-pairs, 415 dizygotic complete pairs and 1028 non-twin siblings and singletons). Participants were from South-East Queensland, Australia, and the sample was of predominantly European ancestry. The 25Up study collected information on 20 different mental disorders, including depression, anxiety, substance use, psychosis, bipolar and attention-deficit hyper-activity disorder, as well as general demographic information such as occupation, education level, number of children, self-perceived IQ and household environment. In this article, we describe the prevalence, comorbidities and age of onset for all 20 examined disorders. The 25Up study also assessed general and physical health, including physical activity, sleep patterns, eating behaviors, baldness, acne, migraines and allergies, as well as psychosocial items such as suicidality, perceived stress, loneliness, aggression, sleep–wake cycle, sexual identity and preferences, technology and internet use, traumatic life events, gambling and cyberbullying. In addition, 25Up assessed female health traits such as morning sickness, breastfeeding and endometriosis. Furthermore, given that the 25Up study is an extension of previous BLTS studies, 86% of participants have already been genotyped. This rich resource will enable the assessment of epidemiological risk factors, as well as the heritability and genetic correlations of mental conditions.

Keywords: Mental health; cohort study; longitudinal; genetics

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The Twenty-Five Up Study (25Up: Can we predict who will develop mental disorders? A long-term study of adolescent twins) ran from 2016 to 2018 and assessed a wide range of mental health and behavioral disorders in a young Australian cohort consisting of twins and their non-twin siblings. This study is an extension of its predecessor, the 19Up study, and the Brisbane Longitudinal Twin Study (BLTS; Couvy-Duchesne et al., 2018; Gillespie et al., 2013), which examined mental health and alcohol and substance use (Gillespie et al., 2009) in a large sample of young twin adults (mean age = 26.1, range = 19.7–38.6). 25Up aimed to assess individuals who were slightly older than those in 19Up, with the similar overall aim of collecting data that will help shed light on the risk factors and pathways involved in the development of affective disorders. These studies represent a large collection of a wide array of phenotypic data, including psychological and environmental variables of relevance for mental health and disorders. Some of these include personality dimensions and psychological symptoms, mental disorders that meet the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed., *DSM-5*; American Psychiatric Association, 2013) and five diagnostic criteria: alcohol and substance use and misuse, migraine, sleep behaviour, as well as neurobiological correlates (neuroimaging) and genome-wide genotyping (Figure 1). Notably, the mean age increase between the individuals participating in the 19Up and 25Up studies was 3.6 years (Supplementary Figure 1).

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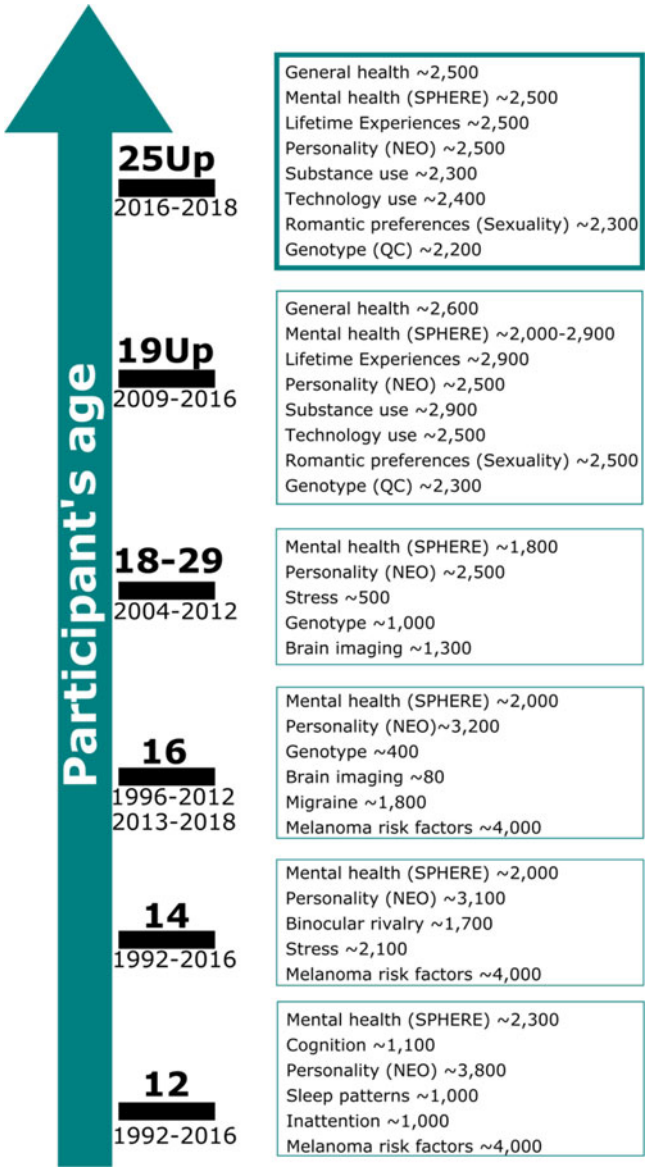

Fig. 1. Summary of the BLTS data collection. Longitudinal: vitamin D; infections (antibodies); neuroticism junior Eysenck personality questionnaire (JEPQ) Neuroticism–Extraversion–Openness inventory (NEO); psychiatric signs (SPHERE). Cross-sectional: hair cortisol; cognition (verbal, performance IQ, working memory, and information processing); binocular rivalry (rivalry rate); brain imaging (multimodal magnetic resonance imaging); substance use (alcohol, tobacco, and recreational drugs); sleep patterns (actigraphy); psychiatric diagnoses (Composite International Diagnostic Interview); life events/social support/relationships (e.g. early home environment, family relationships, traumatic events, socioeconomic factors). Note: Sample size is only indicative as some of the waves are still recruiting new participants. Figure adapted from Couvy-Duchesne et al. (2018) and Gillespie et al. (2013).

The 25Up study was structured so as to collect further psychological, behavioral and subclinical assessments, with the aim of using these to understand the factors involved in the development and progression of mental health disorders from late teenage years to early adulthood. This new wave of the BLTS will allow us to gain insight into the genetic basis of behavioral phenotypes, mental health and comorbidities. Finally, as with the 19Up study, data collection was also designed to contribute to twin and genetic consortia in psychiatry, personality and behavior genetics. The aim of the present article is to describe the key characteristics of the cohort and give examples of important themes (e.g. comorbidity and primacy of onset in dual diagnoses) that can be examined in future in more detailed analyses of the cohort data, and also to highlight the opportunities for new collaborations that could make use of the rich 25Up data set.

Methods

Study Contact

Between February 2016 and October 2018, 3785 individuals were approached via email to participate in the 25Up study, which entailed a detailed, three-part, self-report online survey (TFU1, TFU2, and TFU3). There was a 67.1% response rate (2540 individuals) for completing the first part of the survey (TFU1) and a 62% response rate (2343 individuals) for completing all three parts of the survey (TFU1, TFU2, and TU3). Follow-up was conducted by a phone call 1–2 weeks after the initial contact email. Supplementary Figure 2 depicts the variation in participant response.

Part 1 of the survey (TFU1, $N = 2540$) assessed general health, medical and treatment history as well as lifetime diagnoses. TFU2 ($N = 2484$) expanded on TFU1, assessing other physical characteristics such as baldness, skin tone and acne, as well as a multitude of conditions and behavioral characteristics. TFU3 ($N = 2343$) was the final part of the survey, containing questions addressing sexual identity, quality of romantic relationships, sexual and romantic preferences. For further information regarding the specific items addressed in each section, the instruments used to assess these items and number of participants answering each section, refer to Table 1.

Statistical Analyses

In this study, we focus on describing the prevalence, risk factors (i.e. age and sex), comorbidity and primacy of onset of self-reported mental health variables. A study assessing specific diagnoses using the relevant questionnaires is outside the scope of this cohort description. Age and sex effects were assessed by means of logistic regression modeling in Python using the statsmodels module. The variables of interest were included as covariates and their significance was assessed using Wald tests.

Disorder Clustering and Comorbidity Analysis

All pairwise tetrachoric correlations (ρ) were calculated using *R* (3.1.1) and the *psych* package (v1.4.3). Briefly, the presence or absence of a disorder was coded as a binary vector, and all disorders were compared by computing their tetrachoric correlation coefficient. Next, a hierarchical clustering was performed using Ward's minimum intracluster variance objective function (Ward, 1963) with a distance metric calculated as $1 - \rho$. Mixed-effects logistic regressions were used to calculate the increase in risk on a second disorder given the occurrence of a given disorder. The function *glmer* from the R library *lme* was used, including age and sex as fixed effects, and the family ID as grouping factor for the random effects variance–covariance structure. For each pair of disorders, one was modeled as an outcome variable, while the other one was used as a predictor. The *p*-values of the association of one disorder with another were subjected to a Bonferroni multiple testing correction.

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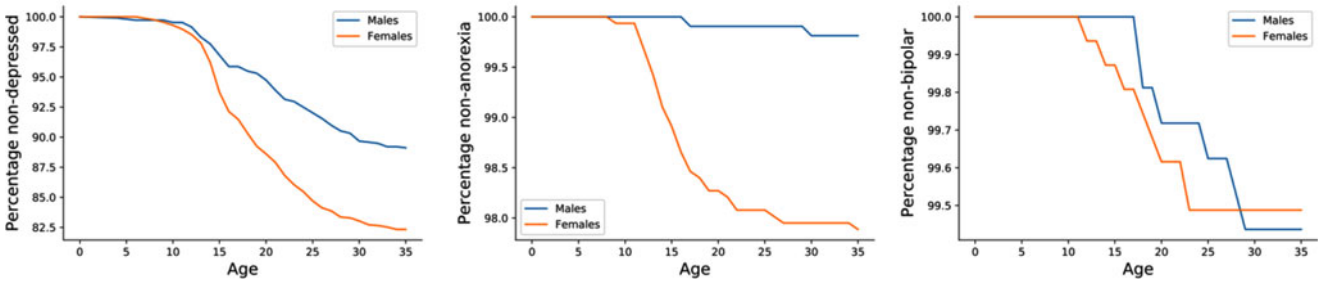

Fig. 2. Kaplan–Meier curves stratified by sex. Kaplan–Meier curves depict the self-reported age of onset for three disorders (depression, anorexia and bipolar disorder, respectively) in the 25Up cohort.

Table 1. Variables examined in the different surveys of the 25Up study

TFU1	Instrument	Approximate *N*
Demographics	Young and Well Cooperative Research Centre (YAW CRC)	2540
General health and well-being	QIMR 16Up	682–2535
Puberty	Perceived pubertal timing (Cance et al., 2012)	1310–2476
Cognition	Self-perceived	2481
Medical history	National Comorbidity Survey (NCS) screener	1949
Morning sickness	Nausea and Vomiting of Pregnancy (NVP) Short form	1777
Breast feeding	NVP short form	550
Pregnancy-related depression	screen	300–655
Mental health	Global Assessment of Functioning (GAF)	2489
Mental health	NCS Screener	2489
Mental health	Treatment history	874
Alcohol/substances	Treatment history	843
Family mental health	YAW CRC	2379
Lifetime experiences — anxiety disorders	NCS screener	2455
Panic disorder	NCS screener	2493
Social phobia	NCS screener	1563
Specific phobia	NCS screener	2493
Separation anxiety disorder	NCS screener	2370
Major Depressive Disorder (MDD)	NCS screener	2500
Mania–hypomania	NCS screener	2445
Irritable depression	NCS screener	2488
Oppositional defiance disorder	NCS screener	2487
Conduct disorder	NCS screener	2513
ADHD	NCS screener	2298
Intermitent explosive disorder	NCS screener	2512
Current mental health	BMRI	2536
Current mental health	Kessler 10	2538
Day functioning	Composite International Diagnostic Interview (CIDI)	2529
Personality	NEO TIPI Scale	2536
Hypo mania screener	Five-item self-report	2402
Psychosis screener	Self-rated scale based on CIDI	2513
Functional impairment	GAF	1442
Functional impairment	Social and Occupational Functioning Assessment Scale	1442
Suicidality	Self-harm/past month/lifetime	2531
Alcohol or other substance misuse	From QIMR 16Up	2369
Physical health and activity schedule	Australian Bureau of Statistics National Survey	2200
Sleep–wake cycle	BMRI from 19Up	2489
Eating behaviors	YAW CRC	2465
Body image	YAW CRC	2534
Relationships and social networking	QIMR 16Up	2514
TFU2	**Instrument**	**Approximate N**
Demographics being a twin	NA	2141
Physical phenotypes — Part 1	HWB	1490
Physical phenotypes — Part 2	HWB	2468
Migraines	HWB	2434
Migraines — females	HWB	566
Asthma eczema allergies	HWB	2403
Endometriosis	HWB	1497

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Table 1. (*Continued*)

TFU1	Instrument	Approximate *N*
Physical Phenotypes — Part 3	HWB	2449
Current mental health	Perceived stress scale	2464
Current mental health	Borderline, autism and loneliness (PAI/BOR and SRS)	2460
Current mental health	Adult ADHD Self-Report	2440
Current mental health	Buss Perry Aggression Questionnaire	2432
Sleep–wake cycle	Pittsburgh Sleep Quality Assessment)	2424
Sleep apnea screen	Maislin et al., 1995	2348
Caffeine and general sleep questions	NA	2413
Sleep–wake cycle	Insomnia Severity Index	2379
Eating behavior and anorexia nervosa	From QIMR 16Up	2394
Social networking and relationships	PBI	2321
Social networking and relationships	Kessler perceived social support	2241
Stressful life events	List of threatening experiences	2301
Technology use	YAW CRC	2405
Games and gambling	Problem gambling severity index	1942
Cyberbullying and sexting	NA	2160
TFU3	**Instrument**	**Approximate N**
Demographics	NA	2331
Romantic preferences	Designed by Zietsch (from 19Up)	2324
Romantic preferences	Fluid gender identity based on Multi-GIQ (Joel et al., 2014)	2295
Romantic preferences — females	Contraceptives	1430
SNR-disgust	Three domain disgust scale	2280
Sociosexuality	NA	2290
Self-rated physical attractiveness	NA	2286
Attraction	NA	2254
Relationships	NA	1736
Partner section	Cognition and self-report IQ, education level, SPHERE, height and weight and eye color	9

Note: TFU1, TFU2 and TFU3 refer to the three parts of the online questionnaire. Approximate *N* represents the average of not null respondents for representative (not follow-up) questions of each section.

Power Analysis

Phenotype simulations (of continuous traits) and power analyses were performed using the powerFun, MASS and OpenMx R libraries. Multivariate data were simulated using the mvrnorm function specifying a variance–covariance structure determined by a linear combination of varying values for the additive genetic (A) and common environmental (C) components. The sample sizes of these simulated distributions were identical to the number of twin-pairs available in the 25Up cohort. OpenMx was used to fit an ACE model to the simulated data. The significance of the A and C variance components was assessed using a log likelihood ratio test (the mxCompare function of OpenMx) comparing the full model to a model only including the other two components (e.g. ACE vs. CE). This procedure was repeated 100 times, and power was estimated by counting the number of iterations in which the studied component was rejected. A similar procedure was used to simulate and assess the power to detect a genetic correlation. Two phenotypes were simulated with a specified underlying genetic correlation, and a bivariate ACE model was used to assess the significance of the genetic correlation. The results are available in the Supplementary Figure 3.

Results

Cohort Description

Of the 3785 individuals invited to participate in the study, 62% of the twins and non-twin siblings provided complete data. Overall, females were slightly over-represented among the 25Up respondents, comprising 52% of the invited population but 59.5% of actual ascertained participants (Table 2). Survey completion rates were high and, of the participants who had completed TFU1, 2484 (97.8%) completed the second section of the survey (TFU2), and 2343 (92.2%) completed the third part (TFU3). Females tended to complete all sections of the survey more often than males, with 95.3% of females completing all three parts compared to 87.7% of males. The greatest dropout for men was between completing Part 2 (96.3%) and Part 3 (87.7%) of the survey. The mean age of all participants was 29.7 (SD = 4.2, range = 22–44; Supplementary Figure 2), consisting of 341 complete monozygotic pairs, 415 dizygotic pairs, 125 MZ singletons, 269 DZ singletons and 634 siblings. Twins and non-twin siblings did not differ in maximum educational attainment level ($p = .57$), but nontwin individuals were older (30.5 vs. 29.4, $p = .001$), more likely to be married (62% vs. 55%, $p = .001$) and less likely to have children compared with co-twins (49.6% vs. 57.5%, $p = .001$). Ethnically, the cohort reflects the population structure of families with twins in Queensland at the time of recruitment, with a majority of participants having European ancestry and minorities of predominantly Asian ancestry (Gillespie et al., 2013).

All participants had been invited to complete previous BLTS (Gillespie et al., 2013; Wright & Martin, 2004) studies (Figure 1). Therefore, variables such as height, weight, personality, psychiatric signs, sleep patterns, migraine and blood samples (hematological and immunological measures: e.g. antibodies markers of infections, vitamin D) were collected longitudinally in the BLTS, with up to five time points for some phenotypes (Figure 1). A noteworthy example is the assessment of personality traits using the Neuroticism–Extraversion–Openness (NEO) Personality Inventory-related scales (Costa & McRae, 1992). Although some cohorts present different versions of the NEO (due to updates and study design changes), the overall constructs measured should remain highly isomorphic,

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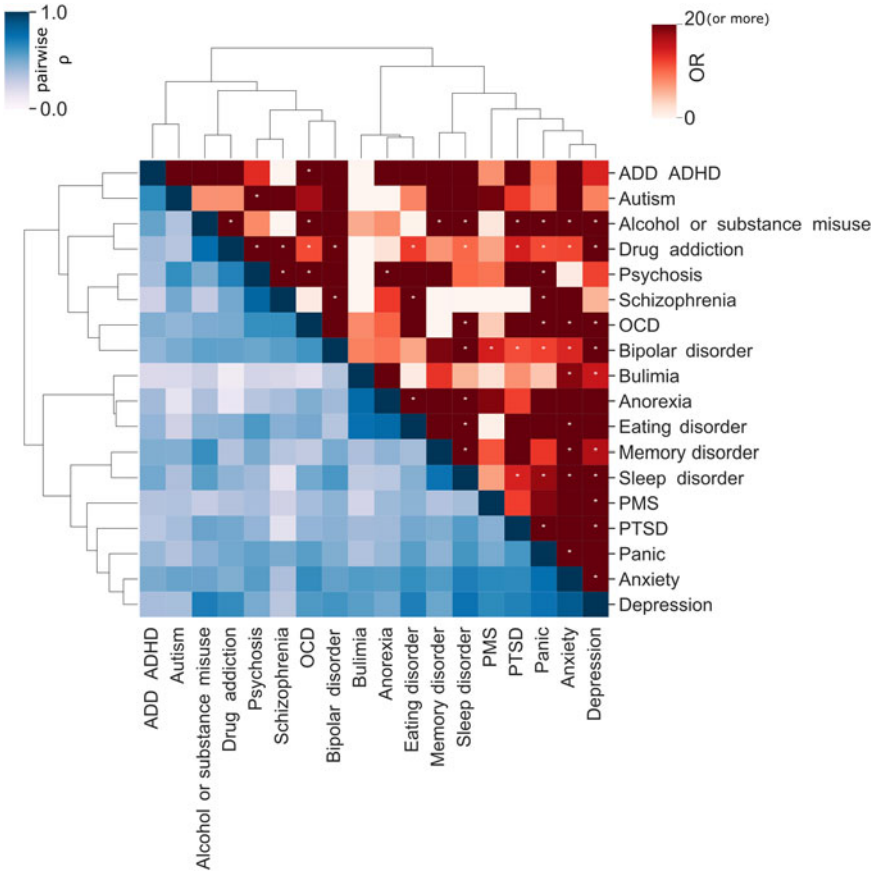

Fig. 3. Disorder comorbidity within the 25Up study. Lower triangle depicts a hierarchical clustering (Ward's method) of the disorders based on their self-reported lifetime co-occurrence (tetrachoric correlations). Upper triangle portrays lifetime comorbidity odds ratio (ordered based on the clustering of the lower triangle). Note: $^{*}p < .05$ after multiple testing correction ($\alpha < .000146$).

Table 2. Demographics of the 25Up cohort

	Total	Females	Males
Completed Part 1 (TFU1)	2540 (100.0%)	1523 (100.0%)	1017 (100.0%)
Completed Part 2 (TFU2)	2484 (97.8%)	1505 (98.8%)	979 (96.3%)
Completed Part 3 (TFU3)	2343 (92.2%)	1451 (95.3%)	892 (87.7%)
Age (*SD*; range)	29.7 (4.2; 22–44]	29.4 (4.3; 22–44)	29.9 (4.2; 22–41)
Single	679 (26.7%)	393 (25.8%)	286 (28.1%)
Married	1502 (59.1%)	916 (60.1%)	586 (57.6%)
Relationship	296 (11.7%)	175 (11.5%)	121 (11.9%)
Separated but married	35 (1.4%)	22 (1.4%)	13 (1.3%)
Divorced	23 (0.9%)	12 (0.8%)	11 (1.1%)
Widowed	0 (0.0%)	0 (0.0%)	0 (0.0%)
No formal education	10 (0.4%)	6 (0.4%)	4 (0.4%)
Primary school	0 (0.0%)	0 (0.0%)	0 (0.0%)
Junior high school	36 (1.4%)	10 (0.7%)	26 (2.6%)
Senior high school	259 (10.2%)	156 (10.2%)	103 (10.1%)
Certificate or diploma	679 (26.7%)	358 (23.5%)	321 (31.6%)
Degree	1,054 (41.5%)	680 (44.6%)	374 (36.8%)
Postgraduate diploma, masters or PhD	500 (19.7%)	312 (20.5%)	188 (18.5%)

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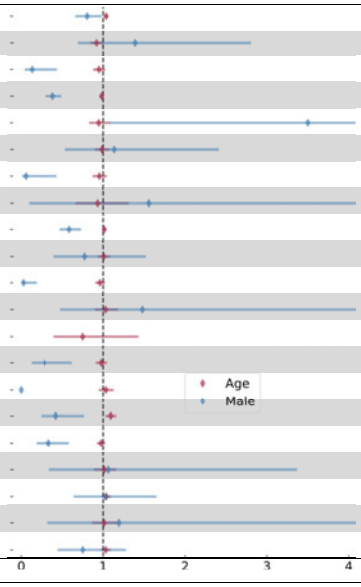
Table 3. Lifetime prevalence of self-reported mental health disorders in the 25Up study

	N	Prevalence (%)*	Male Prevalence (%)	Female Prevalence (%)	OR —95%C.I.—	Sex pvalue	Age pvalue
AnyMHP	519	20.6	18.6	21.7		**0.030**	**0.002**
ADD ADHD	32	1.3	1.5	1.1		0.360	0.060
Anorexia	37	1.5	0.3	2.2		**0.001**	0.190
Anxiety	402	16.0	8.9	20.5		**0.000**	0.140
Autism	13	0.5	0.9	0.3		**0.040**	0.410
Bipolar Disorder	28	1.1	1.2	1.1		0.740	0.730
Bulimia	27	1.1	0.1	1.7		**0.005**	0.310
Conduct Disorder	2	0.1	0.1	0.1		0.750	0.690
Depression	436	17.3	12.9	20.0		**0.000**	0.290
Drug addiction	38	1.5	1.3	1.6		0.460	0.840
Eating disorder	57	2.3	0.1	3.7		**0.000**	0.210
Memory disorder	12	0.5	0.6	0.4		0.500	0.650
Narcolepsy	1	0.0	0.1	0.0		1.000	0.380
OCD	45	1.8	0.7	2.5		**0.002**	0.510
PMS	28	1.1	0.0	1.8		1.000	0.460
PTSD	61	2.4	1.4	3.1		**0.005**	**0.004**
Panic	83	3.3	1.5	4.5		**0.000**	0.330
Psychosis	12	0.5	0.5	0.5		0.920	0.830
SUD	73	2.9	3.0	2.8		0.910	0.190
Schizophrenia	9	0.4	0.4	0.3		0.790	0.880
Sleep disorder	63	2.5	2.2	2.7		0.290	0.290



Nominally significant P values are highlighted in bold. Analyses were performed by using a logistic regression accounting simultaneously for the effects of sex (females as a reference) and age. OR - odds ratio, C.I.- 95% confidence intervals. MHP- mental health problem. ADD/ADHD- Attention deficit disorder/Attention deficit and hypercativity disorder. OCD- obsessive compulsive disorder. PMS - premenstrual syndrome. PTSD - post traumatic stress disorder. SUD- Alcohol and substance misuse. , MHP- mental health problem. *Prevalences calculated based only on not null values (participants that responded to the section (N=2516)

as we would expect with biometrical phenotypes (such as height) and other behavioral instruments such as the Somatic and Psychological HEalth REport (SPHERE; Hickie et al., 2001) (also used to assess mental health on most of the BLTS). In addition, genome-wide single nucleotide polymorphism genotypes are currently available for 86% ($N = 2205$) of participants.

Findings to Date

The 25Up study has collected information on 20 different psychiatric or affective disorders (see Table 3) and a range of lifestyle, health and behavioural traits (Table 1). Overall, ~20% of the participants self-reported a lifetime major mental health problem affecting their everyday life. This estimate is consistent with estimates for the Australian population (Department of Health, 2009). Among the disorders examined, general anxiety (16%, $N = 402$) and depression (17.3%, $N = 436$) were the most prevalent diagnoses. Following these, panic, substance use, sleep, and post traumatic stress disorders (PTSD) had the highest prevalence in the 25Up cohort (3.3%, 2.9%, 2.5% and 2.4%, respectively; Table 3).

Sex Differences

The differences in response rates and fallout rates between males and females motivated the assessment of whether *self-reported* lifetime prevalence of mental health problems was associated with sex in this cohort. Both depression and general anxiety were far more prevalent in females than males (11.6% vs. 5%, $p < .001$ and 15.3% vs. 3.4%, $p < .001$, respectively). PTSD, obsessive-compulsive disorder (OCD), panic disorder, general eating disorders and bulimia and anorexia showed significant sex effects, all having a higher prevalence in females (Table 3). In addition, PTSD was the only disorder to show a nominally significant increased prevalence with age ($p = .006$), although this did not survive correcting for multiple testing, but would be consistent with a higher probability for the occurrence of a traumatic event as time passes. No other differences reached statistical significance in this cohort (Table 3).

Age of Onset

The age of onset of the examined self-reported phenotypes (disorders) was not significantly different between males and females. In the case of depression, females had a slightly earlier age of onset (18.8 years vs. 20.5 years, $p \leq .001$; Figure 2 and Supplementary Figure 4). The youngest mean age of onset was for autistic spectrum disorders, including Asperger syndrome (mean = 5.5 years, SD = 6.5), while the oldest mean age of onset recorded in this cohort was for psychosis (mean = 24.4 years, SD = 5.9). Age of onset estimates was not available for alcohol dependence and misuse as only the age at alcohol drinking initiation (mean = 16.0 years) was collected. Notably, the mean age of onset of anorexia, bulimia and eating disorders were all during adolescence (~16 years), while the mean age of onset for other disorders was mostly around young adulthood (Table 4 and Supplementary Figure 4).

Disorder Comorbidity

There is a known overlap between affective, anxiety and substance use disorders (Kessler et al., 1996; Merikangas et al., 1996; Regier et al., 1990). Within the 25Up study, evidence of the relationships between the 20 disorders was observed through hierarchical clustering. Self-reported history of psychosis and schizophrenia

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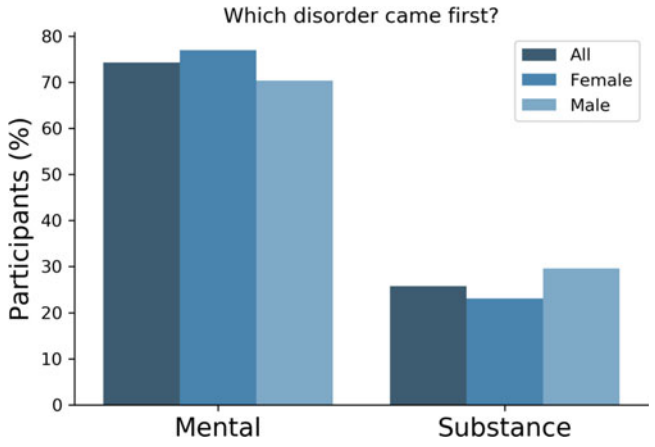

Fig. 4. Most participants reported a mental disorder prior to substance abuse. Bar plots depicting the number of participants reporting precedence of either a mental or a substance abuse disorder. Only participants that reported both type of conditions responded to this question ($n = 66$).

clustered together, as did anorexia, bulimia and eating disorders. Additional clusters were attention deficit and hypercativity disorder (ADHD) and autism, as well as depression, anxiety, PTSD and panic disorder (Figure 3). In order to quantify the increased risk of a condition, given the presence of a second condition (while correcting for the effects of age, sex and relatedness), we used a mixed-effects logistic regression approach (see Methods). All significant associations between the disorders studied were positive while none of the negative associations (i.e. decreased risk) reached statistical significance. Individuals who were rated as positive for an alcohol and other substance misuse were more likely to score positive for memory disorder and depression ($p < .05$ after multiple testing correction). Furthermore, a significant risk increase was also detected between psychosis and schizophrenia and between depression and a variety of other comorbid disorders, including PTSD, sleep disorder and premenstrual syndrome (PMS) among others (Figure 3). Interestingly, of those participants (both males and females) reporting substance misuse ~50% reported also having another mental health disorder, the majority reported that the substance abuse disorder followed the mental condition (Figure 4).

The 25Up Cohort Will Enable Longitudinal Analyses

The unique strength of the 25Up study is that it is the latest wave in a longitudinal study spanning more than 20 years. This allows for unparalleled analysis of the dynamic nature of mental health variables as individuals progress through adolescence and into young adulthood. For example, when comparing the lifetime prevalence of self-reported psychotic symptoms (CIDI Psychosis Screener; Scott et al., 2006) in the previous 19Up cohort to those in 25Up, we found that, as expected, the prevalence for most symptoms has increased in the 25Up. However, there were instances where the lifetime prevalence decreased in the 25Up cohort, pointing to possible recall bias. Nonetheless, with those that increased, the increase was heterogeneous, that is, the prevalence of some symptoms did not change significantly, whereas others doubled (Figure 5). The extent to which this heterogeneity is caused by recall bias or other factors might be studied in the future. Notably, the BLTS includes several potential isomorphic instruments (such as depression and personality) that will enable genetic and environmental longitudinal analyses.

Table 4. Disorder age of onset in the 25Up study

Trait	Males	Females	*p*-value
ADD/ADHD	9.91 (3.2)	10.4 (6.09)	0.8
Anorexia	23.5 (6.5)	16.6 (5.1)	0.1
Anxiety	19.2 (6.7)	18.4 (6.4)	0.4
Autism/Asperger	4.0 (4.53)	8.5 (8.5)	0.5
Bipolar disorder	21.6 (5.5)	19.5 (4.3)	0.3
Bulimia	30.0 (0.0)	16.4 (2.2)	NA
Conduct disorder	6.0 (0.0)	11.0 (0.0)	NA
Depression	20.5 (6.6)	18.8 (5.6)	0.01
Drug addiction	18.1 (2.8)	18.5 (3.3)	0.7
Eating disorder	29.0 (0.0)	16.5 (4.1)	NAN
Memory disorder	19.5 (4.0)	22.8 (8.8)	0.6
Narcolepsy	NA	NA	NA
OCD	20.7 (4.5)	16.8 (6.6)	0.2
PMS	NA	17.5 (5.8)	NA
PTSD	22.8 (5.4)	22.5 (6.5)	0.9
Panic	22.2 (6.2)	19.7 (7.1)	0.2
Psychosis	23.8 (3.1)	24.8 (7.4)	0.8
Schizophrenia	19.7 (2.4)	20.8 (6.6)	0.8
Sleep disorder	21.8 (6.0)	20.9 (8.0)	0.7
Alcohol and substance misuse	20.0 (4.6)	18.6 (4.1)	0.2

Note: ADD/ADHD = attention deficit disorder/attention-deficit hyper-activity disorder; OCD = obsessive-compulsive disorder; PMS = premenstrual syndrome; PTSD = post traumatic stress disorder.

Discussion

Here we described the demographics and self-reported history of mental disorders in the 25Up cohort. Our findings are consistent with previous mental illness prevalence estimates in Australia (Lawrence et al., 2016; Liddell et al., 2016), and observations of women having a higher prevalence of PTSD (Galea et al., 2005; Gavranidou & Rosner, 2003), panic disorder (Crowe et al., 1983; Weissman et al., 1997) eating disorders (Mitchison & Hay, 2014), depression (Weissman & Klerman, 1977) and anxiety disorders (Bandelow & Michaelis, 2015). We detected a significant association between sex and OCD prevalence, an observation not previously made in adults (Karno et al., 1988; López-Solà et al., 2014), but only in individuals with an age of onset before or during adolescence (Grant, 2014). We also identified a nominal association of PTSD with age, although a plausible explanation of this effect could be related to a higher probability of a stressful event with age, but this association did not survive multiple testing corrections.

There is consistent evidence for a broad distinction between externalizing and internalizing disorders (Cosgrove et al., 2011; Krueger et al., 1998). Nonetheless, our findings suggest high levels of lifetime comorbidity between affective and substance use disorders. This is consistent with recent studies detecting a genetic overlap between psychological distress, somatic distress, affective disorders and substance use (Chang et al., 2018) and with the *self-medication hypothesis* suggesting substance misuse as a coping mechanism (Marshall, 1994; Myrick & Brady, 2003). Notably, we identified a high comorbidity between externalizing

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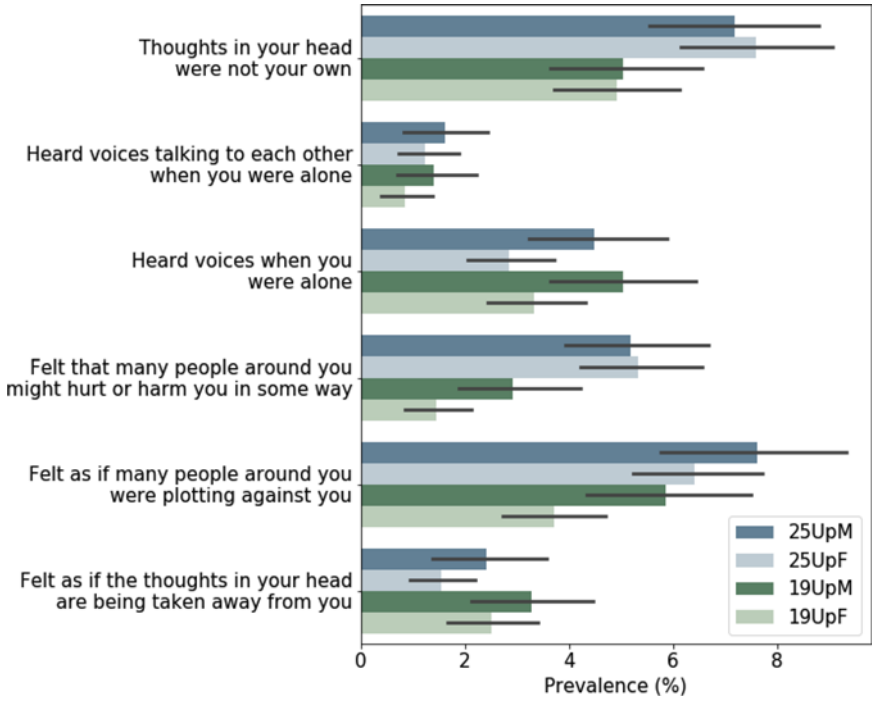

Fig. 5. Comparison of lifetime prevalence of any psychotic symptoms in the 19Up and 25Up cohort studies. Bar plots depict the prevalence and 95% confidence intervals (1000 bootstrap pseudo replications) of psychotic symptoms in the 19Up and 25Up cohorts stratified by sex. Results are depicted only for participants with available data for both data sets ($n = 2319$; M = males, F = females).

and internalizing disorders such as depression and substance misuse or OCD and attention deficit disorder (ADD)/ADHD. Furthermore, we detected expected comorbidity of co-occurring diseases and symptoms such as eating disorders and anorexia (Thornton et al., 2010), drug addiction and alcohol misuse, psychosis and schizophrenia (National Collaborating Centre for Mental Health 2014) and depression and anxiety (Gorman, 1996). Depression was the disorder with the highest comorbidity, having a significant association with around half of the conditions. Altogether, these observations are consistent with the high genetic correlation between psychiatric disorders and the overlap in diagnostic criteria (Anttila et al., 2018; Bulik-Sullivan et al., 2015). Furthermore, these findings suggest the self-reported lifetime of mental health conditions on the 25Up to be valid and reliable.

We also analyzed whether there were sex differences in the age of onset of psychiatric and substance abuse disorders. Our findings indicated a nominally significant difference in the age of onset of depression, which is consistent with previous observations on adolescents (Avenevoli et al., 2015). Notably, the mean age of onset of eating disorders was during adolescence, as previously reported (Hudson et al., 2007; Volpe et al., 2016).

Strengths and Limitations

The 25Up study represents a large effort to characterize and understand the genetic, environmental and behavioral factors associated with mental health in young adults transitioning from adolescence. More than 50 different mental health and lifestyle variables, such as technology use, sociosexuality and substance use, were assessed in (on average) ~2100 twins, making this a rich and valuable data set. The preceding work on the BLTS cohort has started to shed light onto the genetic and neurobiological etiology of substance abuse (Chang et al., 2018; Gillespie et al., 2018; Schmaal et al., 2016). We expect that this follow-up of the cohort will drive further cross-sectional and longitudinal genetic epidemiology studies of human behaviour and mental health.

The sample size of the 25Up study (341 complete monozygotic twin-pairs and 415 dizygotic pairs) should allow the detection of heritability estimates ≥30% and common environmental influences >30% with at least 80% power (Martin et al., 1978; Visscher et al., 2008). Furthermore, the 25Up cohort provides at least 80% power to detect genetic correlations as low as $r_g = .3$ (considering a heritability for each trait >20%) in line with cohorts with similar sizes and power simulations. The existence of longitudinal biometric and mental health data could enable novel family and epidemiological studies to be performed. The longitudinal nature of the BLTS has enabled the discovery that lifetime progression of self-reported psychotic symptoms is heterogeneous. Future studies assessing the genetic and environmental factors accounting for this heterogeneity across development could result in new intervention and prevention strategies.

Some limitations of the 25Up study must be noted. Although clinical, lifestyle and demographic variables were assessed through established instruments, they were obtained through online surveys and therefore all responses are subject to the possible biases and accuracy of self-report questionnaires. Notably, recall bias (e.g. not remembering a depressive episode) and subjectivity (e.g. when rating their physical and mental health) should be considered and corrected for, before conducting analyses and especially before comparing with other population-based studies. It is also important to note that all analyses presented in this article were based on self-reported lifetime medical history data and therefore are not necessarily in accordance with observations made when using other criteria, such as the *DSM*-5. Additionally, caution must be taken when trying to ascertain specific disorders from the instruments used in this study. For example, with schizophrenia, self-reported and CIDI-based ascertainment might not match the *DSM-5* diagnostic criteria.

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Furthermore, genetic and epidemiological analyses using the twins from the 25Up cohort will inevitably assume the cohort to be representative of the overall (age-matched) population. It is well documented that the liability to twinning has a genetic component (Mbarek et al., 2016; Painter et al., 2010) and could therefore be genetically correlated with other traits (Laisk et al., 2018). Moreover, environmental differences between twins and nontwins (such as twins being treated more similar than siblings) are also a possible source of bias. Nonetheless, both of these limitations can be circumvented by including the large number of siblings who are part of the 25Up cohort in the analyses.

Conclusion

The 25Up cohort represents a rich data set that will enable analyses of the epidemiology, heritability and genetic correlations of well-being and mental health variables. The overall prevalence of mental disorders and the prevalence rates for lifetime comorbidities were in line with previous studies. As an update of the BLTS, it represents a unique opportunity for longitudinal studies aiming at further understanding the etiology and heterogeneity underlying the progression of affective, mood and substance use disorders from young- to mid-adulthood. Here, we exemplified this by comparing item-level prevalence of psychotic items across the 19Up and 25Up cohorts, identifying a heterogeneous increase that might be explained by dynamic (age-dependent) genetic effects. Moreover, the inclusion of surveys focused on the usage of technological devices (e.g. internet and mobile phone usage) will enable unprecedented analysis of their relationship with mental health. We anticipate the 25Up cohort to be an attractive resource to boost collaboration, ultimately propelling scientific discovery.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/thg.2019.27.

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