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Association between polygenic liability to depression and lifetime depression in at-risk adolescents

Enda M. Byrne^{1✉}, Nathan A. Gillespie², Jake M. Najman³, Anjali K. Henders⁴, Brittany L. Mitchell⁵, Dominic Dwyer^{6,7}, Simon Hartmann⁸, Blake S. Cavve⁹, G. Paul Amminger^{6,7}, Scott Clark⁸, Caroline Gao^{6,7}, Ashleigh Lin⁹, Lianne Schmaal^{6,7}, Andrew Thompson^{6,7}, Stephen J. Wood^{6,7,10,11}, J.T.W. Wigman¹², Alison R. Yung^{6,7,13}, Sarah E. Medland¹⁴, Jacob J. Crouse¹⁴, Jan Scott^{15,16}, James G. Scott^{1,5,17}, Gail M. Williams³, Barnaby Nelson^{6,7}, Nicholas G. Martin¹⁴, Ian B. Hickie¹⁴, Naomi R. Wray^{4,18} and Christel M. Middeldorp^{1,17,19,20,21}

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Internalising symptoms including depression, anxiety and somatic symptoms in adolescence are common. They can be transient, but they can also persist and progress to major depressive disorder (MDD). Polygenic risk scores for major depression (MD-PGS) may help identify which symptomatic adolescents are at greatest risk of later disorder. In a mega-analysis of two longitudinal population-based cohorts from Brisbane, Australia, we investigated whether polygenic liability to depression improves risk stratification among adolescents with elevated internalising symptoms. Internalising symptoms were assessed at age 14, lifetime MDD was assessed in young adulthood using the Composite International Diagnostic Interview, and MD-PGS were generated using summary statistics from the latest Psychiatric Genomics Consortium major depression genome-wide association study, excluding Australian cohorts. Analyses focused on comparisons between individuals in the top decile of risk and those in the remaining 90% of each cohort. A total of 302 cases with lifetime MDD and 1693 controls were included. Compared with adolescents outside the highest decile of internalising symptoms, those in the top decile at age 14 had a more than two-fold increased odds of lifetime MDD (OR = 2.56, 95% CI 1.92–3.49, $p = 5.4 \times 10^{-10}$). Individuals in the top decile of MD-PGS also showed increased odds of lifetime MDD compared with the remaining 90% (OR = 3.45, 95% CI 2.53–4.71, $p = 4.4 \times 10^{-15}$). Adolescents who were simultaneously in the top decile of both internalising symptoms and MD-PGS had an approximately eight-fold increased odds of lifetime MDD compared with individuals outside the top decile for both risk factors (OR = 8.58, 95% CI 4.04–18.26, $p = 1.2 \times 10^{-5}$). These findings indicate that polygenic risk scores for depression may have particular clinical utility for stratifying risk among adolescents already presenting with elevated internalising symptoms, identifying a subgroup at very high risk for later major depressive disorder.

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INTRODUCTION

As psychiatric disorders are substantially heritable, polygenic risk scores (PGS) that aggregate information from thousands of genetic variants to index an individual's genetic liability are of increasing interest as potential tools in psychiatry that can be combined with clinical information [1] to help stratify risk for mental health outcomes and increase the accuracy of diagnosis [2–4]. Clinicians commonly assess family history of mental health problems but many patients will not have a family history and

individuals can be at high genetic risk without having a family history of a psychiatric disorder [5]. Therefore, assessment of genetic risk that goes beyond family history may have value in identifying those most at risk of poor outcomes.

As not all the variation in risk in the population is attributable to genetics, PGS will never be fully predictive of whether someone will meet diagnostic criteria for a psychiatric disorder. However, a potential utility of PGS may lie in helping to identify who among those exhibiting symptoms is at risk of developing a disorder or

¹Child Health Research Centre, The University of Queensland, Brisbane, Australia. ²Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA. ³School of Public Health, The University of Queensland, Brisbane, Australia. ⁴Institute for Molecular Bioscience, The University of Queensland, Brisbane, Australia. ⁵QIMR Berghofer Medical Research Institute, Brisbane, Australia. ⁶Orygen, Melbourne, Australia. ⁷Centre for Youth Mental Health, The University of Melbourne, Melbourne, Australia. ⁸Adelaide Medical School, Discipline of Psychiatry, The University of Adelaide, Adelaide, Australia. ⁹Telethon Kids Institute, The University of Western Australia, Perth, Australia. ¹⁰Institute for Mental Health, University of Birmingham, Birmingham, UK. ¹¹Centre for Human Brain Health, University of Birmingham, Birmingham, UK. ¹²Department of Psychiatry, Interdisciplinary Center for Psychopathology and Emotion Regulation, University of Groningen, University Medical Center Groningen, Groningen, Netherlands. ¹³Institute for Mental and Physical Health and Clinical Translation (IMPACT), Deakin University, Melbourne, Australia. ¹⁴Youth Mental and Technology Health Team, Brain & Mind Centre, The University of Sydney, Camperdown, Australia. ¹⁵Department of Academic Psychiatry, Institute of Neuroscience, Newcastle University, Newcastle, England. ¹⁶Université de Paris, Paris, France. ¹⁷Child and Youth Mental Health Service, Children's Health Queensland Hospital and Health Service, Brisbane, Australia. ¹⁸Queensland Brain Institute, The University of Queensland, Brisbane, Australia. ¹⁹Department of Child and Adolescent Psychiatry and Psychology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands. ²⁰Department of Research and Quality of Care, Arkin Institute for Mental Health, Amsterdam, Netherlands. ²¹Levvel, Academic Centre for Child and Adolescent Psychiatry, Amsterdam, The Netherlands. ✉email: enda.byrne@uq.edu.au

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having symptoms persist over time. One such instance is the onset of internalising symptoms in adolescence. Adolescence is a time of physical change often accompanied by changes in mood and increases in internalising problems. Internalising symptoms in adolescence are predictive of poor mental health in adulthood [6, 7]. A previous analysis in the Mater-University Study of Pregnancy (MUSP) cohort found that high internalising symptoms at age 14 were predictive of lifetime depressive disorders at age 21 [8]. However, some young people experience transient internalising symptoms during adolescence that resolve, whereas for others, symptoms will persist or intensify leading to a diagnosis of Major Depressive Disorder (MDD) or an anxiety disorder, the two most common psychiatric disorders [9]. Given the increasing rates of mental health problems in young people, youth mental health services are under increased strain and in some cases have long waiting lists for treatment. More accurate stratification of risk can help in prioritising resources for those most at risk of poor outcomes [10]. Information on genetic risk may be valuable in identifying who among adolescents who report high internalising symptoms is at risk of developing a depressive disorder.

The PGS for Major Depression (MD-PGS) derived from the largest published genome-wide association study (GWAS) to date was found to explain ~5.7% of the variance in liability to depression in independent cohorts [11]. The estimated odds ratio (OR) of depression per SD of MD-PGS was on average 1.57 across all cohorts and the OR for being a case in the tenth compared to the first decile was 4.92. Furthermore, risk did not increase linearly by decile. Those in the highest decile had substantially increased risk - consistent with the polygenic model of inheritance [12]. Similar results have been found for prediction of schizophrenia using PGS [13–15], indicating those in the highest decile of genetic risk have a disproportionate liability. In addition to predicting depression liability, the MD-PGS is associated with more severe depression including higher levels of recurrence [16, 17], earlier age of onset [16–18] and persistence of depression from adolescence into adulthood [19]. Evidence is accumulating that high MD-PGS is associated with poorer trajectories of illness among young people experiencing symptoms and incorporating it into clinical practice may lead to earlier intervention for those most at risk of persistent symptoms. It is likely that the most utility for clinicians will come from knowing whether a young person falls within the upper percentile of genetic risk. This may help to inform early intervention strategies, guide closer monitoring, anticipate potential trajectories and tailor therapeutic approaches accordingly.

While it is established that internalising symptoms in adolescence and MD-PGS are associated with risk of depressive disorders, to date there have been few studies evaluating how both of these risk factors together can predict risk.

In this study, we use data from two longitudinal cohort studies in Brisbane, Australia to evaluate to what extent the MD-PGS is associated with internalising symptoms in adolescence and lifetime MDD in young adulthood, and how combining information on internalising symptoms during adolescence and genetic risk can predict lifetime MDD at follow-up.

METHODS

Mater-university study of pregnancy

The Mater-University Study of Pregnancy (MUSP) is a longitudinal multigenerational cohort study in Brisbane, Australia. Full details of the recruitment and assessments are given elsewhere [20]. Briefly, expectant mothers attending their first obstetric appointment at the Mater Hospital were approached for participation in the study between 1981 and 1983. A total of 6753 women who gave birth were recruited into the study. A 5-year follow-up of the mothers ($n = 4843$) was conducted which included questions about their child's behaviour. A further follow-up was conducted at 14 years for mothers ($n = 5181$) and children ($n = 5166$). Further follow-ups were performed 27 years after the initial study for mothers ($n = 3501$)

and 30 years for their offspring ($n = 2474$). The 30-year follow-up occurred between 2011 and 2014.

Measures

At the 14-year follow-up, both mothers and offspring participated. Psychopathology of the offspring was measured using the Youth Self Report (YSR; self-report) [21], from which an overall broad internalising scale was extracted. We defined those scoring above the 90th percentile on the internalising scale as "cases", as described in previous studies and controls as those in the lowest nine deciles [22]. This allowed direct comparison with the polygenic risk score, for which the top decile was also evaluated.

Lifetime diagnosis for MDD was assessed in the offspring using the Composite International Diagnostic Interview (CIDI), a commonly used structured interview to assess diagnoses according to the *Diagnostic and Statistical Manual (Version 4)* [DSM IV] criteria at the 30-year follow up. A lifetime diagnosis of MDD at age 30 was the primary outcome variable which we aimed to predict using the adolescent symptom data and MD-PGS.

Family history was defined by a maternal depression or anxiety diagnosis as assessed at the 27-year follow-up when mothers were administered the CIDI or via self-report at the 5-year or 14-year follow-up. No data on paternal or sibling mental health were available.

Participants were divided into either low or middle/high income households according to whether the maternal-reported household income at the 14-year follow-up was categorised as $\geq$ / $<$ \$20,800AUD per annum, which distinguished between low and middle/high income households. We evaluated whether there were differences in the proportion of low-income households by regressing binary income status at age 14 against participation in the age 30 follow-up and contributing a biological sample.

Genotyping

Offspring were approached at the 30-year follow up to provide a blood sample for genotyping. A total of 1771 participants consented for the genetic arm of the study, of whom 1306 were genotyped on the Illumina PsychChip v 1.0. Prior to imputation, single nucleotide polymorphisms (SNPs) with $>5\%$ missingness, $<1\%$ minor allele frequency or deviation from Hardy-Weinberg Equilibrium ($p < 10^{-6}$) were removed. SNPs where the strand was ambiguous were also removed. To assess genetic ancestry, the data were combined with the populations from the 1000 Genomes Project Version 5. A set of SNPs in linkage equilibrium was generated using PLINK, principal components analysis was conducted and projected on to the first two principal components of the 1000 Genomes populations. Any sample more than 3 standard deviations from the bivariate mean of the European populations were considered to be non-European. A total of 4 non-European samples were identified and due to the small number, excluded from the analysis. The data were phased using MaCH and imputed to the 1000 Genomes Project Version 5 using minimac3. A further round of quality control to remove low quality and low frequency SNPs was performed. After QC, there were a total of 1256 unrelated individuals of European ancestry available for analysis.

The brisbane longitudinal twin study

The Brisbane Longitudinal Twin Study (BLTS) is a longitudinal study of twins and their siblings recruited from high schools in the Greater Brisbane Area that began in 1992 [23]. Twins were recruited at ages 12 and 14 for studies on the development of melanocytic naevi via media appeals and by word of mouth. In this study, to ensure comparability of the results between MUSP and the BLTS, we utilise data from the twins when they were aged 13–15. A total of 1913 participants from 915 families were assessed for depressive symptoms at age 14.

Twins and their siblings were invited to the Nineteen and Up (19Up) study. The primary focus of this longitudinal study was to elucidate pathways to onset of common mental disorders and substance abuse from adolescence to young adulthood. 19Up was conducted between 2009 and 2016 [24]. A total of 2773 twins and their siblings aged between 18 and 38 years participated.

Measures

Depressive symptoms in the adolescent twins were assessed using a shortened version of the Somatic and Psychological Health Report (SPHERE-12) [25]. The SPHERE is a self-report questionnaire developed

from existing self-report and diagnostic instruments designed for screening for common mental disorders in general practice. The individual items and scoring of the SPHERE-12 are shown in the Supplementary Note. A previous study using these data found that item response scores derived from the SPHERE assessed during adolescence were predictive of meeting criteria for mental disorders in adulthood [26]. As in the MUSP study, we evaluated the predictive ability of the overall SPHERE scale as well as evaluating the risk of those scoring above the 90th percentile compared to those with scores below the 90th percentile. The 90th percentile corresponds to a score of 9 or more on the SPHERE-12. As the scale consists of discrete values, this score captures the top 13% of the distribution of SPHERE scores. A positive screen on the SPHERE-12 requires a score of 5 (at least 2 on the PSYCH-6 scale and 3 on the SOMA-6 scale) and so the 90th percentile is more stringent.

The 19Up study was conducted in three waves. The second and third waves included an online version of the CIDI from which lifetime diagnosis of MDD could be obtained. Therefore, diagnostic information was not available for all participants in 19Up. Cases were participants who met the DSM-V criteria for lifetime MDD according to the CIDI. Controls were those who did not meet criteria for lifetime MDD or an anxiety disorder. No information on family history was available in 19Up. Parental income was not directly assessed. Socioeconomic status at age 14 was derived from parental self-reported occupation. Occupations were mapped to the Australian Socioeconomic Index (SEI) 2006 (AUSEI06) occupational status scale [27] as previously described [28]. For each individual, AUSEI06 was ascertained for each parent, and childhood status for each twin pair was set to the maximum of their maternal and paternal values. To evaluate whether there was bias in retention in BLTS between the age 14 visit and the 19Up study, logistic regression was conducted with participation in 19Up as the dependent variable, and SEI scores at age 14 as the independent variable. Attrition bias was also assessed by evaluating whether those who were assessed at age 14 and participated in 19Up ($n = 787$) had lower MD-PGS than those who did not participate in 19Up.

Genotyping

The genotyping has been described in detail elsewhere [23]. Briefly, twins and their siblings were genotyped on the Illumina 610k chip. The same quality control filters as used in MUSP were applied prior to imputation to the 1000 Genomes Project data phase 3 version 5 using the University of Michigan imputation server [29]. A further set of quality controls were applied to remove poorly imputed SNPs. Using principal components analysis, a total of 24 individuals were identified as being of non-European (primarily Asian) ancestry and were excluded from the analysis.

Polygenic risk scores

The initial SNP weights were drawn from the summary statistics of a meta-analysis of cohorts in the most recent Psychiatric Genomics Consortium Major Depression (MD) genome-wide association study (GWAS), with all Australian cohorts excluded to avoid sample overlap. The summary statistics were generated from 510,763 cases and 3,346,858 controls. SBayesRC [30], a Bayesian method that reweights SNP effects from summary statistics while accounting for linkage disequilibrium (LD) and functional annotations in the genome was used to generate the posterior weights. A pre-computed eigen-decomposition dataset from LD matrices generated using 20,000 unrelated participants of European ancestry from the UK Biobank was downloaded from the GCTB website (<https://gctbhub.cloud.edu.au/software/gctb>) and used to model LD. After imputing missing SNPs in the GWAS summary statistics, a total of 6,079,492 SNPs with minor allele frequency > 0.01 were included in the analysis.

The $-score$ function in PLINK version 1.9 [31] was used to generate the PGS from the posterior SNP weights. PGS were standardised to the sample mean and standard deviation of the individual cohorts prior to analysis. Individuals in each cohort were split into deciles according to PGS.

Within-cohort analysis

A series of univariate and multivariable logistic regression analyses were conducted within each cohort separately. The association between internalising symptoms at age 14 and the MD-PGS in each cohort was evaluated. The association between the MD-PGS and lifetime MDD in adulthood both per standard deviation of MD-PGS and by decile was then estimated. In BLTS, we evaluated the association between MD-PGS and lifetime MDD in the entire 19Up cohort and then in the subset who had been screened with the SPHERE at age 14. We further compared the top

decile of internalising at age 14 compared to those in the lowest nine deciles and similarly for the top decile of MD-PGS as predictors of lifetime MDD. Next internalising symptoms at age 14 and MD-PGS and maternal history of depression or anxiety (in MUSP only) were evaluated as predictors of lifetime MDD at age 30 both independently and in a joint model. To investigate collinearity between high internalising, high MD-PGS and family history, the variance inflation factor of each variable in the multiple regression was estimated using the “car” package in R. Lastly, the association of both high internalising symptoms and high MD-PGS, as measured by comparing those in the top decile of both variables to those with neither high internalising nor high PGS, with lifetime MD was evaluated. We further evaluated to what extent changing the cut-off of high MD-PGS to include the top 15% or top 20% of risk affected the results. All analyses included sex and the first 10 genetic principal components to account for potential population stratification as covariates. Primary analyses were conducted using the glm function in R v4.1.3. To account for relatedness between twins in the BLTS, a linear mixed model which included a kinship matrix as a random effect was fit in GCTA [32]. A mega-analysis of the two cohorts was then conducted.

Mega-analysis

A mega-analysis of the two cohorts was conducted to evaluate associations between lifetime MDD and (i) the top decile of MD-PGS versus the remaining 90%, (ii) the top decile of internalising symptoms versus the remaining 90%, and (iii) the combined presence of both high genetic risk and high internalising symptoms.

RESULTS

MUSP

Descriptive statistics for demographic and outcome variables both in the entire cohort of offspring assessed at age 14, those assessed at the age 30 follow-up, and the subset of participants who were included in the genetic analysis are shown in Table 1. Participants from low-income families were significantly less likely ($OR = 0.69$, $CI (0.58 - 0.81)$, $p = 8.7 \times 10^{-6}$) to have participated in the age 30 follow-up and provided DNA. However, both the mean score on the YSR internalising scale ($\beta = 0.65$, $SE = 0.25$, $p = 8.9 \times 10^{-3}$) and the proportion of participants classified as a case were higher in those who were genotyped.

A total of 1208 participants had data on internalising symptoms at age 14 and lifetime depression at age 30 and passed genotyping QC. Of these, there were 244 (21%) who met lifetime criteria for MDD at the 30-year follow-up and 964 who were controls. The mean age at interview was 29 years (range 28 - 32 years).

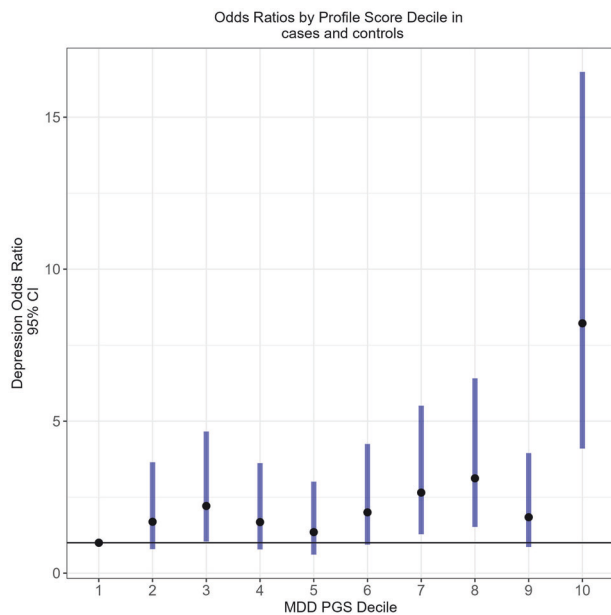
The MD-PGS was significantly associated with internalising scores at age 14 ($\beta = 0.63$ per SD of PGS, $SE = 0.21$, $p = 4.03 \times 10^{-3}$). Lifetime MDD at age 30 was associated with the MD-PGS ($OR = 1.66$ per standard deviation (95% $CI = 1.43 - 1.92$), $p = 8.3 \times 10^{-9}$). We further sought to evaluate how the association with lifetime MDD varied by decile of MD-PGS by comparing risk in each of the top 9 deciles compared to the lowest decile of risk. The results are shown in Fig. 1 and Supplementary Table 1. The prevalence of MDD in the lowest MD-PGS decile was 9.9% (12 cases and 109 controls).

With the exception of the 9th decile, all deciles from the 7th onwards were associated with significantly increased risk of MDD compared to the lowest decile. Those in the top decile have an 8-fold increased risk of MDD compared to those in the lowest decile ($OR = 8.22 (4.10 - 16.49)$; $p = 3.04 \times 10^{-9}$). Compared to the remaining 90% of the cohort, those in the top decile for risk have an approximate 4-fold increase in odds compared to the remaining 90% ($OR = 4.39 (2.97 - 6.48)$; $p = 9.8 \times 10^{-14}$). Those in the top 20% of the MD-PGS distribution have a 2.27-fold increase in risk compared to the bottom 80%.

We then evaluated the association between lifetime MDD and internalising scores measured at age 14. Being in the top decile of internalising scores on the YSR at age 14 was predictive of lifetime MDD with an approximate 2-fold increase in odds compared to the remaining 90% of the study sample ($OR = 2.29 (1.59 - 3.30)$;

Table 1. Descriptive information for the Mater-University Study of Pregnancy (MUSP) and Brisbane Longitudinal Twin Study (BLTS) for the entire cohort at age 14 and those followed up in adulthood.

			Offspring participants at 14 year follow-up (<i>n</i> = 5166)	Offspring participants at 30 year follow-up (<i>n</i> = 2322)	Offspring with depression and genetic data (<i>n</i> = 1208)
MUSP	Sex	Males	2656	928	475
		Females	3478	1394	751
	Years Education (mean)				13.33
	Family Income (%)	Low	20.9	17.4	16.5
		Medium/ High	79.1	82.6	83.5
	YSR internalising score (mean; range)		13.55 (0 - 51)	14.27 (0 - 51)	14.45 (0 - 51)
	YSR case	Yes	474 (9.2%)	260 (11.2%)	132 (11.0%)
		No	4692 (90.8%)	2062 (88.8%)	1076 (89.0%)
	BLTS				
			Age 14 SPHERE measurement (<i>n</i> = 1913)	19Up study (<i>n</i> = 941)	Genetic Data (<i>n</i> = 934)
	Sex	Male	918	396	392
		Female	995	545	542
	SPHERE score (mean; range)		4.15 (0 - 24)	4.08 (0 - 24)	4.09 (0 - 24)
	SPHERE cases (score $\geq$ 9)	Yes	253 (13.2)	109 (11.5%)	109 (11.6%)
		No	1660 (86.8)	832 (88.5)	825 (88.6%)
	Australian Socioeconomic Index Score		60.48 (7.21 - 100)	61.46 (12.4 - 100)	62.11 (12.4 - 100)

**Fig. 1** Odds ratios for lifetime MDD at age 30 for each decile of PGS compared to the lowest decile in MUSP cohort.

$p = 6.9 \times 10^{-05}$). The odds associated with high PGS was comparable to that of having a maternal history of anxiety or depression ($OR = 2.58$ ($1.94 - 3.43$) $p = 3.6 \times 10^{-11}$). As polygenic risk may be associated with both maternal family history and internalising scores, we fit a multiple regression model to evaluate the association of all variables together with lifetime MDD. The

estimated effect sizes of all the predictors were slightly attenuated however, there remained significant evidence of independent associations with the outcome when adjusting for the effect of the other (Table 2). The variance inflation factor for each of the variables was 1.00 indicating minimal collinearity.

Given the independent associations of high internalising scores in adolescence and high MD-PGS with lifetime MDD, we sought to investigate the risk of MDD for those individuals who were in the top 10% both for the YSR internalising scale and for the MD-PGS. Only 23 individuals (2% of the sample) were in the top decile for both variables. Compared to those who are not in the top decile of internalising symptoms and PGS, the odds of meeting criteria for MDD was >8-fold ($OR = 8.93$ ($3.69 - 21.58$); 1.1×10^{-06}). Among these individuals, the prevalence of MDD was 65%. This compared with a prevalence of MDD of 49% in those in the top decile of PGS only and 36% in those in the top decile of internalising symptoms only. As the number of individuals in the high-risk group with both high internalising and high PGS was small, we investigated how relaxing the PGS threshold to include those in the top 15% and top 20% respectively affected the odds of diagnosis. This led to a slight attenuation of the odds ratios but the odds of having a diagnosis remained high for those with both high internalising and PGS.

BLTS

A total of 2291 participants (59.1% female) from 1123 families completed the CIDI in the 19Up and passed genotyping QC. The mean age at interview was 26.03 (range = 18.66 – 38.64). A total of 440 individuals who met DSM-5 criteria for MDD and 1496 controls were included in 19Up. A total of 170 MDD cases and 617 controls from the 19Up study were screened using the SPHERE at age 14 (Table 1). There was no evidence of differences in family SEI at age 14 in those who enrolled in 19Up compared to those who

Table 2. Association of internalising symptoms in childhood and adolescence and polygenic risk scores for MDD with lifetime MDD in MUSP and BLTS.

Mater University Study of Pregnancy (MUSP)			Univariate logistic regression		Multivariable logistic regression	
Predictor	N with risk factor (Proportion with lifetime depression)	N without risk factor (Proportion with lifetime depression)	OR	P-value	OR	P-value
Top 10% YSR Internalising Age 14	132 (0.36)	1076 (0.18)	2.29 (1.59 – 3.30)	6.9 x 10E-05	1.95 (1.29 – 2.97)	1.4 x 10E-03
Top 10% MD-PGS	116 (0.49)	1092 (0.17)	4.39 (2.97 – 6.48)	9.8 x 10E-14	4.18 (2.74 – 6.20)	1.3 x 10E-11
Maternal Depression/Anxiety	501 (0.29)	701 (0.14)	2.58 (1.94 – 3.43)	3.6 x 10E-11	2.32 (1.71 – 3.12)	3.8 x 10E-08
Top 10% in YSR Internalising and MD-PGS	23 (0.65)	983 (0.16)	8.93 (3.69 – 21.58)	1.1 x 10E-06		
Top 10% YSR Internalising and top 15% MD-PGS	29 (0.62)	926 (0.16)	7.53 (3.46 – 16.37)	3.5 x 10E-07		
Top 10% YSR Internalising and top 20% MD-PGS	36 (0.52)	873 (0.16)	5.20 (2.64 – 10.42)	2.1 x 10E-06		
Brisbane Longitudinal Twin Study (BLTS)						
Top 10% SPHERE Age 14	85 (0.40)	702 (0.26)	2.69 (1.67 – 4.34)	1.6 x 10E-05	2.31 (1.46 – 3.70)	3.8 x 10E-04
Top 10% MD-PGS	67 (0.34)	720 (0.20)	2.26 (1.31 – 3.90)	3.4 x 10E-03	1.91 (1.14 – 3.14)	1.4 x 10E-02
Top 10% SPHERE and MD-PGS	7 (0.57)	642 (0.18)	5.62 (1.22 – 25.96)	2.7 x 10E-02		
Top 10% SPHERE and top 15% MD-PGS	11 (0.45)	607 (0.18)	3.99 (1.17 – 13.61)	2.6 x 10E-02		
Top 10% SPHERE and top 20% MD-PGS	21 (0.38)	582 (0.18)	3.04 (1.20 – 7.68)	1.3 x 10E-02		

did not ($p = 0.11$). Similarly, there was no evidence that those who participated in 19Up had lower MD-PGS than those who were had a SPHERE measurement at age 14 but did not participate (Odds Ratio of participation in 19Up = 0.97 per SD of MD-PGS (CI = 0.94 – 1.13), $p = 0.46$). The mean SPHERE score at age 14 of those who participated in 19Up was not significantly different from the entire cohort at age 14 (Table 1), although a smaller proportion of those at follow-up met the criteria for being a case.

The MD-PGS was significantly associated with SPHERE score at age 14 ($\beta = 0.35$ per SD, SE = 0.13, $p = 6.6 \times 10^{-03}$). The MD-PGS was also significantly associated with lifetime MDD in the whole 19Up cohort (OR = 1.59 per SD (1.29 – 1.62), $p = 4.1 \times 10^{-08}$). The association by decile of polygenic risk is shown in Fig. 2. The odds ratio in the highest decile compared to the lowest was 4.57 (2.66 – 7.84) $p = 3.24 \times 10^{-08}$ (Fig. 2, Supplementary Table 2).

Being in the top decile of SPHERE scores at age 14 was associated with increased risk for lifetime MDD (OR = 2.69 (1.67 – 4.34), $p = 1.63 \times 10^{-05}$) (Table 2). Those in the top decile of MD-PGS had a similarly increased risk (OR = 2.26 (1.31 – 3.90), $p = 3.40 \times 10^{-03}$) compared to those in the lowest nine deciles. When both the SPHERE and PGS predictors were fit together in the same model, the odds ratios were slightly attenuated but remained significant (Table 2). There were only 7 individuals who were in the top decile of symptoms and MD-PGS. For this group, the odds of MDD were 5.62 (1.22 – 25.96) $p = 2.7 \times 10^{-02}$. A total of 4 out of 7 (57%) of these individuals had lifetime depression. This compared to a prevalence of 40% (34 cases and 51 controls) in those in the top decile of the SPHERE and 34.0% (23 cases and 44 controls) in the top decile of MD-PGS. The lifetime prevalence

of MDD in those outside of both the top decile of symptoms and the PGS was 17.0%.

Mega-analysis

The results of the mega-analysis of the two cohorts were similar to those from the individual cohorts however with smaller confidence intervals due to the increased sample size (Fig. 3, Table 3). The odds of MDD associated with being in the top decile of internalising at age 14 was 2.56 (CI = 1.92 – 3.49, $p = 5.4 \times 10^{-10}$). For the top decile of MD-PGS, the OR was 3.45 (CI = 2.43 – 4.71, $p = 4.4 \times 10^{-15}$).

Individuals with high internalising and high PGS had an 8-fold increased risk of lifetime MDD compared to those with neither high internalising nor high PGS (OR = 8.58 (4.04 – 18.26), $p = 1.2 \times 10^{-15}$). Using a threshold of top 15% led to a slight attenuation in the odds ratio (OR = 6.69 (3.53 – 12.75), $p = 5.7 \times 10^{-09}$). For those in the top 10% of adolescent internalising and top 20% of MD-PGS, the odds ratio was 4.51 (CI = 2.63–7.72, $p = 4.0 \times 10^{-08}$).

DISCUSSION

This study examined how polygenic risk for depression (MD-PGS) and internalising symptoms in adolescence jointly predict lifetime major depressive disorder (MDD) in early adulthood. Using two longitudinal Australian cohorts, we found that both high MD-PGS and elevated internalising symptoms at age 14 were independently associated with increased risk of lifetime MDD. Importantly, individuals in the top decile for both risk factors had an eight-fold higher likelihood of meeting diagnostic criteria compared to those without elevated genetic or symptom risk.

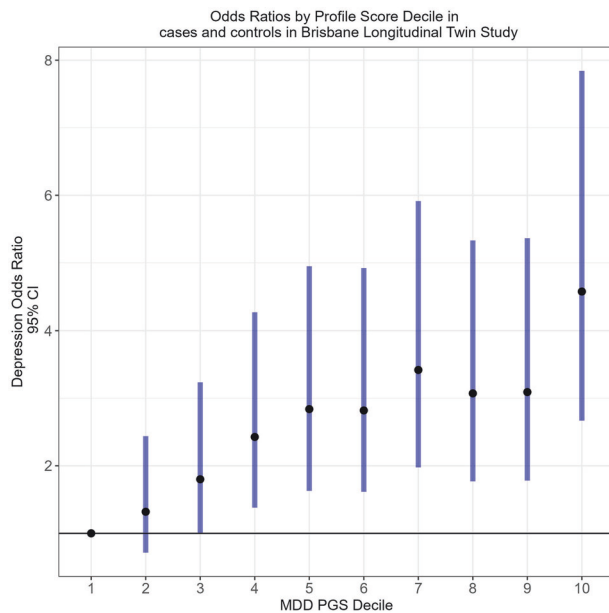


Fig. 2 Odds ratios for lifetime MDD in young adulthood for each decile of PGS compared to the lowest decile in the BLTS cohort.

Consistent with previous research, the effect of MD-PGS was non-linear, with risk concentrated in the highest deciles rather than increasing uniformly across the distribution [11, 16]. This pattern underscores the clinical relevance of identifying individuals at the upper tail of genetic liability. Our findings suggest that combining genetic information with symptom profiles could substantially improve risk stratification, enabling earlier intervention for adolescents most likely to experience persistent or severe depression. [33]

These findings add to the growing body of literature showing that PGS derived from genetic studies of depression are associated with persistence and increase of depressive symptoms from adolescence into adulthood [34]. The potential utility of PGS in psychiatry is growing as genotyping becomes more affordable and widely integrated into healthcare. Similar approaches are already being adopted in other fields, such as cardiovascular disease and oncology [35,36]. As genome-wide association studies expand in sample size and in the scope of variants analysed, the predictive accuracy of MD-PGS will improve, and thresholds for clinical decision-making can be refined. For now, focusing on individuals in the highest risk percentiles offers a pragmatic strategy for translating genetic insights into practice. However, at present these thresholds are only relative to the cohorts in which the PGS are calculated. In the most recent major depression GWAS, for community cohorts the average odds ratio across cohorts of the top decile compared to the bottom decile was 4.92 [11]. The corresponding value in BLTS was similar ($OR = 4.57$), but for MUSP, it was larger ($OR = 8.16$), indicating that the PGS results in MUSP may be inflated relative to other cohorts. However, the results from the PGC GWAS studies of some other cohorts were higher than in MUSP. The high odds ratio of the PGS in MUSP could be due to sampling variation as the sample size is small relative to other cohorts in which PGS prediction has been conducted. However, there are few cohorts available with genetic data and mental health information in both adolescence and adulthood. For PGS to be used in clinical settings, population-based thresholds will need to be calibrated and standardised methods for generating PGS will be required [37].

The results presented here should be viewed in light of several limitations. Firstly, the longitudinal studies required volunteer

participation and individuals with severe mental health problems may have been less likely to participate initially and could have been lost to follow-up in subsequent waves of data collection, therefore introducing a possible sampling bias. We did not find evidence that those in the follow-up in either cohort were less likely to have internalising problems in adolescence. However, we did find that those from low-income households were less likely to participate in the 30-year follow-up in MUSP which may have biased the analysis. Furthermore, both cohorts had a sex ratio close to 1 at baseline, but in the follow up the ratio was closer to 1.5 women to men which may have inflated the prevalence rates. Secondly, while both longitudinal studies were conducted in the same city at similar times, differences in ascertainment and assessment may affect the comparability of the studies. MUSP recruited women giving birth at a hospital and potential participants were directly approached by the investigators. BLTS relied on parents of twins responding to media advertisements and so may be less representative of the general population. It is noteworthy that the odds ratio of the PGS was lower in BLTS compared to MUSP, which may be due to ascertainment or to the fact that the participants were on average younger when followed up and so some participants could still have a depressive episode before reaching age 30 that would not be assessed. Thirdly, because of the timing of the assessments we cannot know which participants already meet criteria for major depression at age 14 or prior to that. Diagnostic criteria for a major depressive episode were not assessed at age 14. There is a need for genetically informative longitudinal studies that assess mental health symptoms at more frequent timepoints and can assess incident depression. We evaluated the association of internalising scores at age 14 because this was when the follow-up of the MUSP sample occurred. It is possible that internalising symptoms measured at different ages may be more strongly associated with depression than those measured at age 14. Fourthly, in both cohorts the assessment of diagnostic criteria was through computerised versions of the CIDI, rather than by clinician interview. This may have led to higher prevalence rates. However, we do not expect this to inflate the PGS prediction.

Lastly, only individuals of European ancestry were included in the analyses. An important consideration for equity is that most current PGS are derived from European ancestry samples. Their predictive performance is substantially reduced in non-European populations, which risks exacerbating health disparities if these tools are implemented without adaptation. To ensure fairness and clinical utility across diverse populations, future research must prioritize the inclusion of underrepresented ancestries in genetic studies and employ methods for cross-ancestry calibration of PGS.

Despite these limitations, we found that in two Australian longitudinal cohorts, high MD-PGS is comparable in accuracy to high internalising in adolescence and family history in predicting risk for lifetime depression. Evaluating the MD-PGS in those exhibiting high levels of internalising symptoms can identify a subgroup at very high risk of meeting the clinical criteria for MDD. These findings suggest that polygenic risk for depression is an important factor to pursue in future risk prediction models, which will ultimately aid clinical decision-making.

DATA AVAILABILITY

The Brisbane Longitudinal Twin Study (BLTS) and Mater-University Study of Pregnancy (MUSP) datasets contain sensitive individual-level health and genetic information and are therefore not publicly available. Researchers wishing to access BLTS data should contact Professor Nicholas G. Martin. Researchers wishing to access MUSP data should contact Professor Jake M. Najman. Requests will be considered in accordance with participant consent, institutional policies, ethical approvals, and data governance requirements. Analysis scripts used in this study are available from the corresponding author upon reasonable request.

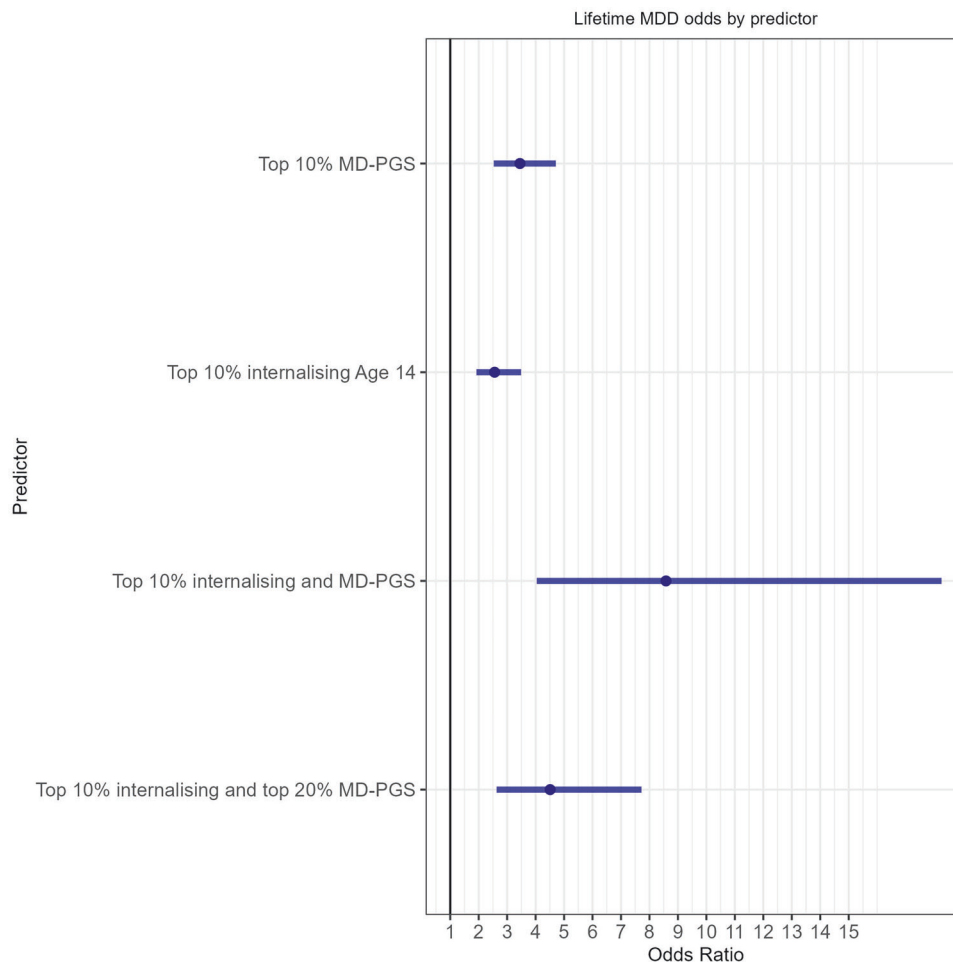


Fig. 3 Results of mega-analysis across cohorts comparing the odds associated with lifetime MDD for the top decile of internalising scores at age 14, the top decile of MDD polygenic risk, and both together.

Table 3. Mega-analysis results of predictors of lifetime depression in Brisbane Longitudinal Twin Study and Mater-University Study of Pregnancy.

Mega-Analysis	N with Risk Factor (Proportion with lifetime depression)	N without risk factor (Proportion with lifetime depression)	OR (Confidence Interval)	P-value
Top 10% internalising Age 14	217 (0.37)	1778 (0.19)	2.56 (1.92 - 3.49)	5.4 x 10E-10
Top 10% MD-PGS	183 (0.43)	1812 (0.20)	3.45 (2.53 - 4.71)	4.4 x 10E-15
Top 10% internalising and MD-PGS	30 (0.63)	1625 (0.17)	8.58 (4.04 - 18.26)	1.2 x 10E-05
Top 10% internalising and top 15% MD-PGS	40 (0.57)	1533 (0.17)	6.69 (3.53 - 12.75)	5.7 x 10E-09
Top 10% internalising and top 20% MD-PGS	57 (0.47)	1455 (0.17)	4.51 (2.63 - 7.72)	4.0 x 10E-08

CODE AVAILABILITY

Bash and R scripts used for analysis are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

EMB, NRW and CMM conceived the study. EMB performed the analyses and drafted the manuscript. NAG, AKH, BLM, SEM, JGS, GMW, IBH, NGM and NRW contributed to genetic data generation and quality control. NAG, JMN, AKH, JGS, GMW, NGM, SEM, JGS, IBH, contributed to cohort recruitment, data collection and study management. DD, SH, BSC, GPA, SC, CG, AL, LS, AT, SJW, JTWW, ARY, JJC, JS provided critical revisions and intellectual content. All authors contributed to interpretation of the findings, critically revised the manuscript, and approved the final version.

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COMPETING INTERESTS

Scott R Clark has participated in advisory and educational boards and received speaker's fees from Janssen- Cilag, Lundbeck, Otsuka, and Servier; research funding from Janssen-Cilag, Lundbeck, Otsuka, and Gilead; and data sharing from Viatrix Australia. Ian B Hickie has previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lilly, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management of anxiety and depression. He is the Chief Scientific Advisor to and a 3.2% equity shareholder in InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the \$30 M Australian Government-funded Project Synergy (2017–20) and to lead transformation of mental health services internationally through the use of innovative technologies.

ETHICAL CONSIDERATIONS

Ethical approval was obtained for the Brisbane Longitudinal Twin Study (BLTS) from the Human Research Ethics Committee at the Queensland Berghofer Institute of Medical Research (references: EC00278 and P1212). Participants gave informed

consent for providing DNA and for genetic analyses. The Mater-University of Queensland Study of Pregnancy (MUSP) aged 30 follow-up was approved by both the Mater Misericordiae Ltd. Human Research Ethics Committee (Ethical clearance # HREC/17/ MHS/135) and the University of Queensland Behavioural and Social Sciences Ethical Review Committee (Ethical clearances #2015001524 and #2018000111). Written informed consent was obtained from the MUSP mothers and their offspring, from the former when the offspring were aged 14 years, and from the latter when they were 21 years and 30 years old, by the ethics committees at the Mater Hospital and/or the University of Queensland approved each phase of the study. Approval for conducting genetic analysis was given by the University of Queensland Human Research Ethics Board on 18/03/2020.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41380-026-03917-5>.

Correspondence and requests for materials should be addressed to Enda M. Byrne.

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