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Psychiatric disorders in individuals born very preterm / very low-birth weight: An individual participant data (IPD) meta-analysis

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ABSTRACT

Background: Data on psychiatric disorders in survivors born very preterm (VP; <32 weeks) or very low birthweight (VLBW; <1500 g) are sparse. We compared rates of psychiatric diagnoses between VP/VLBW and term-born, normal birthweight (term/NBW) control participants.

Methods: This individual participant data (IPD) meta-analysis pooled data from eligible groups in the Adults born Preterm International Collaboration (APIC). Inclusion criteria included: 1) VP/VLBW group (birth weight <1500 g and/or gestational age <32 weeks), 2) normal birth weight/term-born control group (birth weight >2499 g and/or gestational age ≥37 weeks), and 3) structured measure of psychiatric diagnoses using DSM or ICD criteria. Diagnoses of interest were Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Anxiety Disorder, Mood Disorder, Disruptive Behaviour Disorder (DBD), Eating Disorder, and Psychotic Disorder. A systematic search for eligible studies was conducted (PROSPERO Registration Number 47555).

Findings: Data were obtained from 10 studies (1385 VP/VLBW participants, 1780 controls), using a range of instruments and approaches to assigning diagnoses. Those born VP/VLBW had ten times higher odds of meeting criteria for ASD (odds ratio [OR] 10·6, 95% confidence interval [CI] 2·50, 44·7), five times higher odds of meeting criteria for ADHD (OR 5·42, 95% CI 3·10, 9·46), twice the odds of meeting criteria for Anxiety Disorder (OR 1·91, 95% CI 1·36, 2·69), and 1·5 times the odds of meeting criteria for Mood Disorder (OR 1·51, 95% CI 1·08, 2·12) than controls. This pattern of findings was consistent within age (<18 years vs. ≥18 years) and sex subgroups.

Interpretation: Our data suggests that individuals born VP/VLBW might have higher odds of meeting criteria for certain psychiatric disorders through childhood and into adulthood than term/NBW controls. Further research is needed to corroborate our results and identify factors associated with psychiatric disorders in individuals born VP/VLBW.

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Research in context

Evidence before this study

Children born very preterm and/or very low birth weight (VP/VLBW) are considered at increased risk for behavioural problems compared with children born at term and/or normal birth weight (term/NBW), however the increased odds for psychiatric disorders is less clear. We searched Pubmed and Scopus up to May 2020 using the terms “preterm born” AND "psychiatric diagnosis", “very low birth weight” AND “psychiatric diagnosis”, "preterm born" OR “very low birth weight” combined with each disorder “Autism”, “Depression”, “Anxiety” and “ADHD” (Attention-Deficit/Hyperactivity Disorder), “Eating Disorder”, and “Psychosis”. The ten studies we found that compared survivors born VP/VLBW to same aged term/NBW peers regarding psychiatric diagnoses using structured psychiatric measures had limited statistical power for low prevalence psychiatric disorders.

Added value of this study

This individual participant data meta-analysis suggests that individuals born VP/VLBW might have higher odds of meeting criteria for Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, and Anxiety Disorder than term/NBW controls.

Implications of all the available evidence

While surveillance programs for individuals born VP/VLBW rarely continue beyond early childhood and focus on cognitive and motor outcomes, our findings suggest that monitoring mental health across development in these high-risk individuals might be beneficial. Further studies are required to corroborate our findings.

1. Introduction

Very preterm birth (VP; <32 weeks' gestational age) and very low birth weight (VLBW; <1500 g) are associated with an increased risk of neurodevelopmental disabilities. [1-3] There is also evidence that VP/VLBW survivors are at greater risk of receiving a psychiatric diagnosis than individuals born at term in childhood.[4, 5] However, some psychiatric disorders do not overtly manifest until adolescence or adulthood, [6] and their consequences can be debilitating. [7]

Questionnaires are commonly used to assess mental health problems in VP/VLBW cohorts, from which studies have found increased levels of inattention, anxiety and depression. [4,8] Such questionnaires assess symptoms based on respondents' perceptions, and although clinically significant symptoms can be identified using cut-off scores, they are not diagnostic.

Psychiatric disorders among VP/VLBW individuals have been examined using population-based data linkage approaches, with studies reporting increased rates of Autism Spectrum Disorder (ASD), Schizophrenia and mental health hospitalization compared with term-born peers. [9-11] While population-based data linkage provides excellent statistical power, the data are limited to what has been captured, mild cases are under-reported, and inter-clinician reliability for diagnosing psychiatric disorders is not high. [12] Furthermore, psychiatric diagnosis may be greater in individuals born VP/VLBW given their increased surveillance. [10]

Some VP/VLBW cohort studies have used structured psychiatric interviews to examine the odds of meeting criteria for psychiatric disorders compared with term controls. Such studies are rare and have limited statistical power for low prevalence psychiatric disorders. [13] Meta-analyses have reported that individuals born VP/VLBW are more likely to meet diagnostic criteria for ASD and Attention Deficit Hyperactivity Disorder (ADHD) than those born at term,[14,15] and some, but not all, cohort studies have noted elevated rates of Anxiety and Mood disorders. [16-19]

Meta-analyses summarize the evidence in the literature, but they use summary estimates and have limited capacity to differentiate effects based on subject characteristics (e.g., sex and age at assessment). In contrast, individual participant data (IPD) meta-analyses pool subject data across studies to address limitations relating to traditional meta-analyses while maximizing statistical power. In this study, the Adults born Preterm International Collaboration (APIC) pooled data from studies that assessed diagnostic criteria for psychiatric disorders, with the aim of determining the odds of meeting criteria in individuals born VP/VLBW compared with term/normal birth weight (NBW) peers. We were particularly interested in ADHD, ASD, and Anxiety and Mood disorders, and investigated whether the odds of meeting criteria for psychiatric disorders differed by sex and age at assessment (<18 years vs. ≥18 years). [20-26]

2. Methods

This IPD meta-analysis was conducted by APIC, comprising international research groups with longitudinal data on VP/VLBW cohorts, with a focus on adult outcomes. APIC groups with eligible cohorts were invited to participate. In addition, we performed a systematic search for eligible cohorts. The proposed IPD meta-analysis was registered at International Prospective Register of Systematic Reviews PROSPERO (Registration Number 47555).

2.1. Systematic Search

We searched for eligible studies following PRISMA guidelines and using Pubmed and Scopus databases. Search terms included a combination of keywords: “preterm born” AND "psychiatric diagnosis", “very low birth weight” AND “psychiatric diagnosis”, "preterm born" OR “very low birth weight” combined with each disorder “Autism”, “Depression”, “Anxiety” and “ADHD” (Attention-Deficit/Hyperactivity Disorder), “Eating Disorder”, “Psychosis” without data limit. Inclusion criteria were: 1) birth weight <1500 g and/or gestational age <32 weeks, 2) normal birth weight (>2499 g) and term-born (≥37 weeks) control group, and 3) assessment of meeting criteria for any psychiatric diagnosis based on structured measures using DSM or ICD criteria. Selective cohorts (e.g., randomized controlled trials) were excluded. There was no restriction for age at time of psychiatric interview, year of birth, or publication date. The screening was conducted independently by two reviewers (DM and MA), and the assessment of each manuscript by DM with uncertainty resolved by discussion with a third reviewer (PA). For cohorts with data at different ages in the same participants, all timepoints were analyzed where possible.

The search was originally completed in 2016 and updated in May 2020, resulting in a total of 3143 papers, with abstracts of 1874 papers evaluated in relation to inclusion criteria (see Figure 1). Forty-one articles were identified as possibly meeting the inclusion criteria. These articles were retrieved, and the full text reviewed by DM. When there was uncertainty regarding eligibility, consensus was reached between DM and PA. Ten studies (from 9 cohorts) met inclusion criteria, with 8 of the 9 co-

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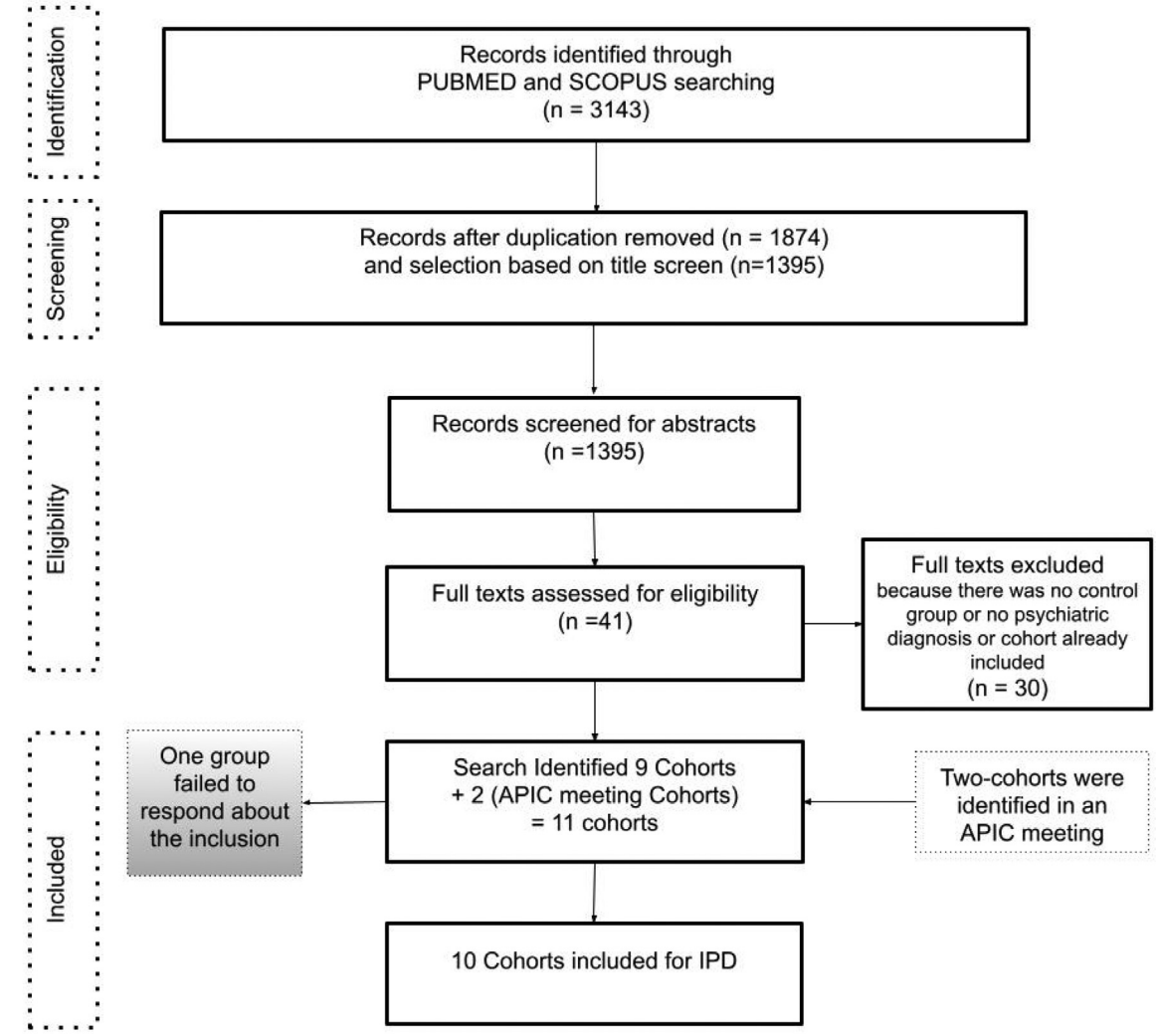

Figure 1. Systematic search flow diagram.
APIC – Adults Born Preterm International Collaboration
IPD – Individual Participant Data Meta-analysis

horts from APIC groups. Groups were invited to participate, with all groups agreeing except one which did not respond. Two additional eligible cohorts were identified at an APIC meeting. In summary, there were 10 cohorts from 8 countries including Australia (n=2), [16, 19] United States, [27] United Kingdom (n=2), [18, 28] Norway, [29-31] Canada, [32] Germany, [17] Finland, [33] and New Zealand. [34]

2.2. Ethics and Governance

This project was approved by Melbourne's Royal Children's Hospital Human Research Ethics Committee (HREC38098). Participating groups (n=10) obtained ethical permission to share data, and completed a research data sharing agreement to transfer non-identifiable individual level data.

2.3. Data Requested

Groups were requested to provide perinatal data (e.g., gestational age, birth weight, sex), socio-demographic data (e.g., maternal educational level), age at assessment, IQ, and research-assigned psychiatric diagnoses for each participant. Individuals with genetic syndromes or major malformations that affected neurodevelopment were excluded. Psychiatric disorders were classified into broad categories: ADHD (any, inattentive, hyperactive/impulsive, and combined subtypes), ASD, Anxiety Disorders, Mood Disorders, Disruptive Behaviour Disorders (DBD, i.e., Conduct Disorder, Oppositional Defiant Disorder), Eating Disorders, and Psychotic Disorders. Studies used different structured psychiatric measures and approaches to assign diagnoses (see Table 1), and number of participants with data varied across diagnoses.

2.4. Data Analysis

Data were analyzed using Stata SE 16.1. Proportions of participants who met diagnostic criteria were compared between VP/VLBW and term/NBW groups using generalized linear mixed models in a one-step approach. VP/VLBW and term/NBW groups were compared by inclusion of a fixed effect for group in the models. For each dependent variable, we considered both a random in-

Table 1
Description of studies included in IPD meta-analysis.

Center	Years of birth	VP-VLBW/control n/n	Males VP-VLBW/control n/n	Attrition VP-VLBW/control %	VP-VLBW only	Age assessed	Interview measure	Psychiatric outcomes assessed						
								ADHD	ASD	Anxiety Disorder	Mood Disorder	DBD	Eating Disorder	Psychosis
McMaster, Canada[32]	1977-82	84/89	31/36	50% / 62%	Mean 24.0	mean 32.0	MINI-Plus (self)	Y		Y	Y			
UCHL, UK [28]	1979-84	165/105	82/59	46% / NA	28.9/1229	18.4	CIS-R (self)			Y	Y			
Helsinki, Finland[33]	1985-86	21/734	11/345	52% overall	29.5/1232	25.5 years	M-CIDI (self)			Y	Y			
Bavaria, Germany[17]	1985-86	200/190	106/92	51% / 64%	30.4/1319	26.0	DIA-X/M-CIDI (self)			Y	Y		Y	
NTNU, Norway[29-31]	1986-88	69/92*	35/40*	60% / 64%	28.8/1177	14.2 19.7	K-SADS, (self and parent)	Y†	Y	Y	Y	Y	Y	Y
VICS, Australia[16]	1991-92	207/149	92/62	72% / 60%	26.7/892	18.2	SCID, ChIPS (self)	Y		Y	Y		Y	Y
EPICure, UK[18]	1995	219/152	101/64	71% / 69%	24.9/746	10.9	DAWBA (parent & teacher)	Y	Y	Y	Y	Y		
Canterbury, NZ[34]	1998-2000	102/107	51/56	96% / 98%	27.8/1051	9.0	DAWBA (parent)	Y	Y	Y	Y	Y	Y	Y
Cleveland, USA[27]	2001-04	140/108*	66/51*	75% / NA	25.9/820	5.9 6.9 7.8	ChIPS (Parent)	Y		Y	Y	Y	Y	Y
VIBeS, Australia[19]	2001-04	177/60	94/31	78% / 85%	27.5/975	7.5	DAWBA (parent)	Y	Y	Y	Y	Y		

ADHD=Attention Deficit-Hyperactivity Disorder; ASD=Autism Spectrum Disorder; BW=birthweight (g); ChIPS=Children's Interview for Psychiatric Syndromes; CIS-R=Clinical Interview Schedule-Revised; DAWBA=Development and Well Being Assessment; DBD=Disruptive Behavior Disorder; DIA-X/M-CIDI=Munich Composite International Diagnostic Interview; DISC-IV=Diagnostic Interview Schedule for Children-IV; GA=gestational age (weeks); K-SADS= Schedule for Affective Disorders and Schizophrenia for School-age Children; MINI-Plus=Mini-International Neuropsychiatric Interview, Plus; NA – Not available; NTNU= Norwegian University of Science and Technology; SCID= Structured Clinical Interview for DSM-IV; UCHL=University College Hospital London; VIBeS=Victorian Infant Brain Studies; VICS=Victorian Infant Collaborative Study Group; VLBW=very low birthweight; VP=very preterm; Y=yes; data are n/n for each group respectively unless otherwise specified.

* based on participants with data from at least one assessment

† no ADHD subtypes. Studies listed in chronological order by years of birth

tercept model (including a random effect for study site) as well as a random intercept and slope model (by adding a second random effect to allow for different relationships between VP/VLBW and control groups among different study sites) and compared models using a likelihood ratio test. Given no substantial increase in model fit with the random intercept and slope model for any of the outcomes, the simpler random intercept only models are reported as the primary results. Where participants had been assessed on multiple occasions, we maximized the amount of data by adding a second random effect for study participant. Where models would not converge, we used the oldest timepoint an individual participant was assessed and a random effect for study participant was not required. Models were repeated adjusting for age at assessment and sex, and including interactions of group with age and sex. We reported independent effects of age at assessment (as a continuous variable) and sex for each diagnosis, adjusting for group. As we had *a priori* interest in group distinctions within adults and children separately and within the sexes separately, analyses were repeated for age (<18 years vs ≥18 or more years) and sex subgroups. As a sensitivity analysis, we repeated the main group comparisons excluding adult participants who had an IQ <70 (n=27 VP/VLBW; n=4 controls). Study quality was assessed independently by three reviewers (MA, DM, PA) according to the Newcastle Ottawa Scale (NOS), with high quality studies categorised by scores ≥ 7, moderate risk categorised by scores of 5 to 6, and high risk categorized by scores ≤ 4. Two reviewers (MA, DM) had no involvement with any of the pooled studies, while the third reviewer had involvement in two of the pooled studies.

2.5. Role of the Funding Source

Funders had no role in study design, data collection, analysis, interpretation, or manuscript preparation. PA, DM & LD had full access to the pooled data and take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author takes responsibility for the decision to submit for publication.

3. Results

Data from 10 eligible cohorts from eight countries were pooled, totaling 1385 VP/VLBW and 1780 term/NBW participants (Table 1). Years of birth ranged from 1977 to 2004, mean age at assessment varied from 6 to 32 years, and VP/VLBW cohorts differed in mean gestational age (range: 24·9 – 30·4 weeks) and birthweight (range: 746 – 1319 g) (Table 1).

The number of studies, participants, and observations differed between psychiatric diagnoses, being largest for Anxiety Disorder and Mood Disorder, for which ten studies contributed data, and lowest for ASD and Psychotic Disorder, where four studies contributed data (Table 2). Odds of meeting diagnostic criteria were highest for ADHD, Anxiety and Mood disorders, and lowest for Psychotic and Eating disorders (Table 2). Compared with controls, there was strong evidence that individuals born VP/VLBW were more likely to meet criteria for ADHD (any, Inattentive and Combined subtypes), ASD, and Anxiety and Mood disorders, before and after adjusting for age at diagnosis and sex (Table 2, Supplementary Table 1). No conclusions were altered when excluding adult participants with an IQ <70 (Supplementary Table 2).

Increasing age at assessment was associated with lower odds of meeting criteria for ADHD-Combined subtype, but higher odds for Mood and Eating disorders across all participants, adjusting for sex and group (Table 3). Males had higher odds of meeting criteria for ADHD (any, Hyperactive and Combined subtypes) and ASD than females, but lower odds for Anxiety and Mood disorders across all participants, adjusting for age at assessment and group (Table 3).

Table 2
Results from one-stage IPD meta-analyses for psychiatric diagnoses comparing VP/VLBW with control groups.

Psychiatric Diagnosis	N cohorts	N individuals	N observations	VP/VLBW	Control	Unadjusted		Adjusted*	
						OR (95% CI)	P value	OR (95% CI)	P value
ADHD	7	1704	2267	18·8% (237/1259)	8·4% (85/1008)	5·42 (3·10, 9·46)	<0·001	5·30 (3·05, 9.20)	<0.001
-Inattentive	6	1541	1997	8·1% (93/1146)	4·0% (34/851)	2·83 (1·63, 4·93)	<0·001	2·86 (1·64, 4.98)	<0.001
-Hyperactive	6	1543	1999	3·4% (39/1147)	2·9% (25/852)	1·32 (0·67, 2·61)	0·42	1·36 (0·69, 2·68)	0·38
-Combined	6	1543	1999	8·2% (94/1147)	2·9% (25/852)	5·43 (2·43, 12·1)	<0·001	5·22 (2·27, 12·0)	<0·001
ASD	4	933	933	5·6% (28/542)	0·5% (2/391)	10·6 (2·50, 44·7)	0·001	10·3 (2·41, 43·6)†	0·002†
Anxiety	10	3145	3708	16·2% (270/1665)	11·4% (232/2043)	1·91 (1·36, 2·69)	<0·001	1·97 (1·39, 2·78)	<0·001
Mood	10	3143	3705	7·6% (126/1664)	7·3% (150/2041)	1·51 (1·08, 2·12)	0·02	1·55 (1·10, 2·19)	0·011
DBD	5	1227	1792	2·6% (26/1007)	2·2% (17/785)	1·28 (0·58, 2·82)	0·54	1·28 (0·58, 2·82)	0·55
Eating Disorder	5	1365	1930	1·0% (10/1019)	1·4% (13/911)	0·69 (0·28, 1·73)	0·43	0·77 (0·21, 2·78)	0·69
Psychotic Disorder	4	975	1538	0·2% (2/818)	0·6% (4/720)	0·44 (0·05, 4·08)	0·47	0·37 (0·04, 3·82)	0·41

ADHD=Attention Deficit-Hyperactivity Disorder; ASD=Autism Spectrum Disorder (ASD); CI=confidence interval; DBD=Disruptive Behaviour Disorder; OR=odds ratio; VP=very preterm; VLBW=very low birthweight.
* adjusted for age at assessment and sex;
† model run without random effect for study participant as none were assessed for ASD on more than one occasion

Table 3
Independent associations of age at assessment and male sex with psychiatric diagnosis.

Psychiatric Diagnosis	Age at assessment	P-Value	Male sex	P-Value	Interaction P-values	
	OR per year (95% CI)		OR (95% CI)		Age x group	Sex x group
ADHD	0·97 (0·89, 1·04)	0·38	2·43 (1·52, 3·89)	<0·001	0·89	0·92
– Inattentive	1·04 (0·98, 1·11)	0·23	1·54 (0·96, 2·48)	0·08	0·40	0·73
– Hyperactive	0·85 (0·68, 1·05)	0·12	2·46 (1·25, 4·87)	0·009	0·21	0·07
– Combined	0·82 (0·74, 0·92)	<0·001	2·07 (1·05, 4·09)	0·037	0·45	0·38
ASD	0·98 (0·78, 1·22)	0·84	2·47 (1·11, 5·51)	0·027	0·34	*
Anxiety	1·02 (0·95, 1·09)	0·34	0·42 (0·30, 0·58)	<0·001	0·92	0·57
Mood	1·11 (1·04, 1·18)	0·001	0·55 (0·40, 0·76)	<0·001	0·96	0·49
Disruptive Behavior Disorder	1·03 (0·74, 1·43)	0·85	1·91 (0·84, 4·38)	0·12	0·50	0·52
Eating Disorder	1·39 (1·07, 1·81)	0·014	0·02 (0·0004, 0·68)	0·031	0·27	†
Psychotic Disorder	0·92 (0·73, 1·16)	0·50	4·59 (0·33, 64·4)	0·26	0·54	‡

Results from multivariable one-stage IPD meta-analyses, adjusted for group. ADHD=Attention Deficit-Hyperactivity Disorder; ASD=Autism Spectrum Disorder; CI=confidence interval; IPD=individual participant data; OR=odds ratio;
* unable to calculate because no female controls with ASD
† unable to calculate because no male controls with eating disorder
‡ unable to calculate because no preterm females with psychotic disorder

Table 4
One-stage IPD meta-analyses for psychiatric diagnoses comparing VP/VLBW with control groups, within age subgroups.

PsychiatricDiagnosis	Age <18 years				Age >=18 years†			
	VP/VLBW	Control	OR (95% CI)	P-value	VP/VLBW	Control	OR (95% CI)	P-value
ADHD	20·1% (202/1005)	9·9% (76/764)	5·17 (2·77, 9·65)	<0·001	13·8% (35/254)	3·7% (9/244)	3·94 (1·84, 8·46)	0·001
-Inattentive	7·4% (70/942)	4·1% (28/683)	2·48 (1·34, 4·59)	0·004	11·3% (23/204)	3·6% (6/168)	3·43 (1·36, 8·64)	0·009
-Hyperactive	4·0% (38/942)	3·5% (9/481)	0·79 (0·31, 2·01)	0·62*	0·5% (1/205)	0·6% (1/169)	0·82 (0·05, 13·3)	0·89
-Combined	9·4% (89/942)	3·4% (23/683)	6·01 (2·52, 14·3)	<0·001	2·4% (5/205)	1·2% (2/169)	1·75 (0·33, 9·27)	0·51
ASD	5·2% (28/542)	0·5% (2/391)	10·6 (2·50, 44·71)	0·02	‡-	-		
Anxiety	14·0% (154/1100)	9·9% (78/788)	2·23 (1·33, 3·76)	0·003	20·5% (116/565)	12·3% (154/1255)	1·44 (1·05, 1·97)	0·025
Mood	3·6% (40/1099)	2·3% (18/786)	1·79 (0·98, 3·29)	0·06	15·2% (86/565)	10·5% (132/1255)	1·42 (0·996, 2·03)	0·053
DBD	2·6% (25/956)	2·4% (17/710)	1·20 (0·53, 2·72)	0·66	2·0% (1/50)	0·0% (0/75)	NC	
Eating Disorder	0·2% (1/647)	0·0% (0/566)	NC		2·4% (9/371)	3·8% (13/345)	0·63 (0·27, 1·50)	0·30
Psychotic Disorder	0·3% (2/647)	0·5% (3/565)	0·66 (0·06, 7·49)	0·74	0·0% (0/171)	0·6% (1/155)	NC	

ADHD=Attention Deficit-Hyperactivity Disorder; ASD=Autism Spectrum Disorder (ASD); CI=confidence interval; DBD=Disruptive Behavior Disorder; IPD=individual participant data; NC=not calculable: OR=odds ratio.
* model allowing for multiple observations from individual participants would not converge so data restricted to one observation obtained at the latest age only
† no participants assessed more than once at 18 years or older and hence model does not require random effect for participant
‡ no observations for ASD and age >=18 years

There was little evidence for group interactions with either age at assessment or sex for any diagnoses (Table 3).

Among younger individuals (<18 years at assessment), those born VP/VLBW had higher odds for meeting criteria for ADHD (any, Inattentive, Combined subtypes), ASD and Anxiety Disorder compared with controls, and there was weak evidence for higher odds of Mood Disorder (Table 4). Within the older subgroup, individuals born VP/VLBW had higher odds of meeting criteria for ADHD (any, Inattentive subtype) and Anxiety Disorder, and there was weak evidence for higher odds of Mood Disorder (Table 4).

VP/VLBW females had higher odds of meeting criteria for ADHD (any, Inattentive, Combined subtypes) and Anxiety Disorder than control females, and there was weak evidence for higher odds of Mood Disorder (Table 5). VP/VLBW males were at higher risk for meeting criteria for ADHD (any, Inattentive, Combined subtypes), and for ASD and Anxiety Disorder than control males (Table 5).

In general, included studies were of high quality (see Supplementary Table 3), utilising representative cohorts and blinded assessment. Retention was lower in adult follow-up studies compared with child follow-up studies (not shown).

Table 5
One-stage IPD meta-analyses for psychiatric diagnoses comparing VP/VLBW with control groups, within sex subgroups.

	Females				Males			
Diagnosis	VP/VLBW	Control	OR (95% CI)	P-value	VP/VLBW	Control	OR (95% CI)	P-value
ADHD	15·4% (103/671)	6·2% (34/551)	5·87 (2·40, 14·3)	<0·001	22·8% (134/588)	11·2% (51/457)	4·96 (2·46, 10·0)	<0·001
-Inattentive	7·0% (43/613)	3·5% (16/642)	2·41 (1·17, 4·98)	0·017	9·4% (50/533)	4·6% (18/389)	3·24 (1·40, 7·51)	0·006
-Hyperactive	2·9% (18/613)	1·1% (5/462)	3·42 (0·96, 12·2)	0·06	3·9% (21/534)	5·1% (20/390)	0·83 (0·36, 1·89)	0·65
-Combined	6·2% (38/613)	2·8% (13/462)	2·67* (1·06, 6·73)	0·037	10·5% (56/534)	3·1% (12/390)	5·55 (2·23, 13·8)	<0·001
ASD	3·1% (9/270)	0% (0/208)	NC		7·0% (19/272)	1·1% (2/183)	6·86 (1·57, 30·0)	0·011
Anxiety	19·4% (168/868)	14·3% (155/1087)	1·81 (1·13, 2·91)	0·014	12·8% (102/797)	8·1% (77/956)	2·27 (1·30, 3·94)	0·004
Mood	8·9% (77/867)	9·3% (101/1086)	1·46 (0·99, 2,15)	0·06	6·1% (49/797)	5·1% (49/955)	1·64 (0·95, 2·85)	0·08
DBD	1·1% (11/523)	1·4% (6/420)	1·44* (0·52, 3·99)	0·48	3·1% (15/484)	3·0% (11/365)	1·11 (0·28, 4·52)	0·88
Eating Disorder	1·7% (9/532)	2·7% (13/488)	0·67 (0·28, 1·62)	0·38	0·2% (1/487)	0% (0/423)	NC	
Psychotic Disorder	0% (0/438)	0·5% (2/389)	NC		0·5% (2/380)	0·6% (2/331)	0·87 (0·12, 6·21)	0·89

ADHD=Attention Deficit-Hyperactivity Disorder; ASD=Autism Spectrum Disorder (ASD); CI=confidence interval; DBD=Disruptive Behavior Disorder; IPD=individual participant data; NC=not calculable; OR=odds ratio.
* model would not converge so analysis restricted just to those with data at latest age

4. Discussion

This IPD meta-analysis of psychiatric diagnoses found that individuals born VP/VLBW had ten times higher odds of meeting criteria for ASD, five times higher odds of meeting criteria for ADHD, twice the odds of meeting criteria for Anxiety Disorder, and 1.5 times the odds for a Mood Disorder than individuals born term/NBW. This pattern of results generally persisted within age and sex subgroups. Our findings provide support for a "preterm behavioral phenotype;"[4] a proposal that preterm birth is associated with symptoms of inattention, anxiety and social difficulties which represent core components of ADHD, ASD and Anxiety Disorder.

The odds of receiving an ADHD diagnosis is reported to be 3 times higher in the VP population. [14] Results from our pooled cohort provide further confirmation of the increased odds for ADHD in the VP/VLBW group. Our study shows the increase in meeting criteria for ADHD persists into adulthood, albeit at lower rates than observed in childhood. Consistent with epidemiological studies, [26] males were more likely than females to meet criteria in our combined VP and term group, but VP/VLBW males and females both had approximately 5 times the odds of meeting criteria for ADHD compared with term counterparts. The inattentive subtype is reported to be more common than the hyperactive and combined subtypes in individuals born VP/VLBW, [16, 18, 35] which is what we found in adulthood but not childhood. The implications of ADHD can be widespread; for example, children born VP/VLBW who have ADHD experience more educational difficulties than those without ADHD. [36]

In our VP/VLBW cohort the proportion who met criteria for ASD was 5·6%, similar to 7% reported in a meta-analysis of children born preterm. [15] The proportion who met criteria for ASD in our controls was 0·5%, slightly lower than 0·8% estimated in the general population. [37] ASD diagnosis increases with decreasing GA at birth, [38, 39] but we chose not to investigate associations with gestational age (or birthweight) because of divergent gestational ages of participants across the different cohorts (Table 1). Criteria for ASD was more commonly met in boys (Table 5), but not exclusively, being present in 3·1% of VP/VLBW girls. Given the lack of long-term longitudinal studies, the stability of ASD diagnosis and rate in adulthood in this population is unknown. While the prevalence of ASD is low, a considerable proportion of VP/VLBW children exhibit functionally important symptoms associated with ASD without meeting the clinical criteria. [38, 40]

Preterm individuals have been reported to be 3 times more likely to meet criteria for Anxiety or Depression. [41] While the rate of Anxiety and Mood disorders was high in our VP/VLBW cohort, the rate of these disorders in the term/NBW group was also substantial. After adjustment, our VP/VLBW group had twice the odds of meeting criteria for Anxiety Disorder and 1.5 times the odds of meeting criteria for Mood Disorder compared with the term/NBW group. Anxiety and Mood disorders were more common in females, and Mood Disorder increased with age, consistent with previous research. [20, 21, 25] VP/VLBW children (<18 years) had 2·2 times the odds of meeting criteria for Anxiety Disorder than term/NBW children, but the odds decreased to 1·4 in adulthood (≥ 18 years). For Mood Disorder, the rate was low in childhood for both groups, and substantially higher in adulthood. The increased odds for both Anxiety and Mood disorders were comparable for VP/VLBW compared with controls in males and females separately. In summary, Anxiety and Mood disorders are common psychiatric disorders in the general population, but the rate is marginally higher in VP/VLBW individuals.

A data-linkage study reported that VP individuals were 2·5 times more likely to be hospitalized for psychosis and 3·5 times more likely to be diagnosed for an Eating Disorder compared with term peers, although absolute rates were very low. [10] In our cohort there were also very low rates of meeting criteria for Psychotic and Eating disorders, and there was little evidence that the odds were higher in the VP/VLBW group compared with the term/NBW group. Our findings are consistent with a recent review examining mental health outcomes in adults born VP/VLBW. [13] Cohort studies have tended to report similar rates of DBD (conduct disorder and oppositional defiant disorder) in VP/VLBW and term/NBW children, [18, 19], supported by our analyses.

We did not examine co-morbidities as the pooled studies used different measures and diagnostic criteria. Furthermore, most of the studies adopted DSM-III or DSM-IV criteria, which unlike the DSM-V, do not allow for a dual diagnosis of ASD and ADHD. This is problematic given these two disorders often co-occur, [42] and are among the most common psychiatric disorders in VP/VLBW individuals. A next step in studying psychiatric disorders in the VP/VLBW population will be to better understand co-morbidities, which will be critical for devising assessment and management policies. Using a parent screening tool (Child Symptom Inventory-4), the ELGAN group reported 15% of extremely preterm 10-year-olds fulfilled criteria for one psychiatric disorder and, another 14% for two or more diagnoses. [43] Highlighting the importance of co-morbidities, poorer functional outcomes (ie. school functioning, quality of life) are related to increasing co-morbidities. [7, 44]

While we found increased odds of individuals meeting criteria for ADHD, ASD, Anxiety and Mood disorders in our VP group compared with term controls, only a small minority of individuals were assigned a diagnosis. Thus, families can be reassured that a diagnosis is relatively uncommon. Of course, individuals can exhibit important symptoms that warrant support without reaching the threshold for a diagnosis, and while the evidence is mixed, it is

reasonable to expect the proportion of individuals with subthreshold symptoms to be higher for the VP population. [17, 45, 46]

Our study is the first to pool individual, patient-level data from international cohorts to evaluate the risk of psychiatric disorders in individuals born VP/VLBW in comparison to term/NBW peers. This approach enhances statistical power to investigate risk in low prevalence conditions, and has the advantage of being able to adjust for potential confounders and assess specific risk factors such as age and sex. For some diagnoses such as Mood Disorder, our mixed models resulted in higher odds ratios than might be expected given the absolute frequencies of the pooled data. We used a one-stage approach which does not assess heterogeneity between studies. However, a two-stage approach for the more common diagnoses revealed no evidence for heterogeneity between studies. Our study had some limitations. The pooled studies used different instruments, diagnostic criteria, and approach to assigning diagnoses. As such, we focused on broad diagnostic categories (e.g. Anxiety Disorder, Mood Disorder, DBD), and could not examine rate of "any" psychiatric disorder or psychiatric co-morbidities. Furthermore, cohorts were from high income countries, and we reported on rates of individuals meeting diagnostic criteria based on standardized measures. Finally, data acquired from pooled studies did not include multiple birth status and as such allowance for clustering in the analyses was not possible.

Moving forward, we recommend that cohorts harmonize follow-up instruments, [47] so that future IPD meta-analyses can examine specific psychiatric disorders and co-morbidities. Future research should explore the role of other risk factors on psychiatric outcomes such as fetal growth restriction, cranial ultrasound abnormalities and infection. Finally, longitudinal studies are necessary as intermittent remission of psychiatric disorders can occur along with shifts in diagnoses across time. [48]

In conclusion, compared with individuals born at term/NBW, individuals born VP/VLBW had higher odds of meeting criteria for ADHD, ASD, and Anxiety and Mood disorders. We recommend further research to identify factors associated with psychiatric disorders in individuals born VP/VLBW, which will assist with the early identification and management of those at greatest risk.

5. Contributors

PA, DM, and LD developed the idea and study design. PA, DM, MA & LD were responsible for the statistical analyses performed and take responsibility for the integrity of the data and the accuracy of the data analysis. The manuscript was drafted by PA, DM and LD. All authors were involved in the acquisition, analysis, or interpretation of data, as well as the critical revision of the manuscript. All authors had full access to the data and approved the decision to submit for publications.

6. Data sharing

This individual participant data meta-analysis was possible due to the sharing of data from groups in the Adults born Preterm International Collaboration (APIC). In order to pool these cohorts, institutional data sharing agreements were needed. To access this data permission will be required from the participating research groups.

Declaration of Competing Interest

No declaration of interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101216.

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