Mental Health Outcomes of Adults Born Very Preterm or with Very Low Birth Weight: A systematic review

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Abstract

Preterm birth research is poised to explore the mental health of adults born very preterm(VP;<32^{+0} weeks gestational age) and/or very low birth weight(VLBW; <1500g) through individual participant data meta-analyses, but first the previous evidence needs to be understood. We systematically reviewed and assessed the quality of the evidence from VP/VLBW studies with mental health symptoms or disorders appearing in adulthood, excluding childhood onset disorders. Participants (≥18 years, born >1970) included VP/VLBW individuals with controls born at term(≥37^{+0} weeks) or with normal birth weight(NBW; ≥2500g). Thirteen studies were included. Studies consistently showed an increased risk for psychotropic medication use for VP/VLBW adults in comparison to NBW/term controls, but whether VP/VLBW adults have an increased risk for mental health disorders or symptoms appearing in adulthood remains uncertain. The quality of the evidence was moderate (65.8%) to high (34.2%). Further research in larger samples is needed.
Keywords: European Union, EU, Horizon 2020, RECAP, PremLife, Preterm, Premature, very low birth weight, VLBW, very preterm, VP, review, mental disorder, psychiatric disorder, depression, anxiety, bipolar, eating disorder, schizophrenia, externalizing, internalizing, psychiatric diagnosis

Rationale (A)

Globally, 10.6% of all births are preterm (<37 weeks of gestation), equating to 14.8 million live preterm births annually—a statistic which has increased since 2000[1]. In light of the continued global prevalence, and in conjunction with a now critical mass of preterm born adults who survived following the modern neonatal medicine era (post 1970)[2–4], research has begun to unravel the long-term consequences of preterm birth. Facilitated by the maturation of preterm birth study cohorts, the literature now provides significant evidence of developmental adversities across the lifespan[5–9]. However, findings are mixed on whether or not individuals born preterm have increased risk of developmental problems or disorders. In part, mixed results may be due to the limited number of individuals born preterm at different gestational ages in existing cohort studies, preventing more gestational age specific analyses, as well as the ability to control for other macro and micro level factors, which may contribute to risk or resiliency in certain groups.

Those Very Preterm (VP; $<32^{+0}$ weeks' gestation), constitute 15.3% of preterm births globally each year [1]. VP born individuals have been reported to have mean birth weight of 1810 (males) and 1750 (females) grams (g) at 31 completed weeks' gestation, decreasing approximately to 1500 g by week 30[10]. Hence, very low birth weight (VLBW; <1500g) is often synonymously used for exploring outcomes of VP born individuals. VP and VLBW born individuals have increased risks for physical and mental health adversities across the lifespan [5] corresponding to a significant economic burden in health and social care costs [11]. Mental health adversities, highlighted by high quality Nordic register studies, show VP born adults have increased risks for psychiatric hospitalization, nonaffective psychosis, depressive disorder, bipolar affective disorder, autism

spectrum disorders, attention-deficit/hyperactivity disorders, major/minor psychiatric diagnoses and eating disorders [12–16] across the lifespan. However, these findings do not differentiate the outcomes of adults from adolescents.

Three international projects RECAP Preterm[17], PremLife[18], and APIC (Adults Born Preterm International Collaboration)[19] are currently consolidating datasets from preterm birth cohort studies to afford gestational age specific meta-analyses of long term outcomes, which will allow for further adult preterm risk and resiliency research and for aggregate-data and individual participant data (IPD) meta-analyses. Accordingly, understanding the pre-existing evidence on mental health outcomes in VP/VLBW born adults, as well as discerning the quality of such evidence is a crucial and timely step for research. To our knowledge, no systematic reviews have focused on mental health outcomes of VP/VLBW born individuals that can have their onset in adulthood (≥18 years), namely on mood, anxiety, substance use, personality and schizophrenia spectrum disorders, nor has the overall quality of the existing evidence been assessed. Hence, this systematic review sought to crystalize the evidence on VP/VLBW born mental health outcomes appearing in adulthood and to explore the limitations and strengths of previous research as a way forward for the future. Disorders that by diagnostic definition have childhood onset, including psychological development disorders (e.g. autism spectrum disorders), behavioral and emotional disorders of childhood onset (e.g. attention-deficit/hyperactivity disorder), and intellectual development disorders were excluded.

Methods(A)

Inclusion criteria (B)

Any longitudinal case-control studies, cohort studies, registry studies, meta-analyses and Randomized Controlled Trials with gestational age or birth weight as the exposure and mental health outcomes assessed in adulthood were eligible for inclusion. There were no language restrictions.

Participants(B)

Study participants included VP or VLBW participants, as well as participants classified as Extremely Preterm (EP; $<28^{+0}$ weeks of gestation) or Extremely Low Birth Weight (ELBW; <1000 g). The controls included participants born at term ($\geq 37^{+0}$ weeks of gestation) or participants born with Normal Birth Weight (NBW; ≥2500 g). All participants were 18 years of age or older.

Exposure(B)

Exposure variables included VP birth status or VLBW defined in accordance with the WHO [20] and obtained from medical records or from medical birth registry data.

Confounders/Covariates (B)

We considered all covariates and confounders for eligibility and no exclusions were made based on these. However, we used predefined covariates for the quality of evidence assessment. Familial genetic confounding adjusted for via twin or sibling study design was the key covariate. Additionally, maternal age or parity, family/childhood socioeconomic status (SES; indexed by parental education, occupation or income), parental mental health, neonatal complications (perinatal asphyxia and birth traumas, neonatal hypoglycemia, neonatal respiratory disorders, low apgar scores, factors leading to NICU admission, brain injury), participant age/birth year and participant sex were considered important.

Outcomes(B)

Outcomes included diagnoses of mental health disorders or symptoms in adulthood. These included any outcome for mood disorders, depression, bipolar disorder, anxiety, internalizing symptoms or externalizing symptoms.

Since the review sought to elucidate mental health disorders appearing in adulthood, disorders defined with onset in childhood by the International Classification of Diseases, Tenth Revision (ICD-10)[21] i.e. Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD), were out of the scope of this review.

Timing(B)

Only birth cohort and register studies including individuals born after 1970 were included, to account for the major changes in neonatal care.

Setting(B)

The study settings could be either hospital(s) or population based study groups.

Exclusion Criteria(B)

Study exclusion criteria included self-reported gestational age or birth weight of VP/VLBW groups, and study designs i.e. qualitative studies, poster sessions, conference abstracts, letters to the editor, reviews and retrospective studies. Additionally, any cohorts born before 1970 and studies with participants below the age of 18 years were excluded. Duplicate studies reporting the same outcome measure for the same cohort or population at the same follow-up time point were also excluded. In which case, the report with the largest sample size at that particular time point was considered the most relevant. In the case of the same results being reported by an individual cohort study and in an aggregate data or IPD meta-analysis, the meta-analysis was included if all of the studies in the meta-analysis met the inclusion criteria and the individual studies were excluded.

Search & Study Selection(B)

Systematic search strategies were applied in PubMed, Web of Science and PROQUEST from inception to October 2019. Studies identified from grey literature were also included. The search

strategies are provided in Supplementary material A.1. All duplicate studies were removed. Study inclusion and exclusion were determined by the predefined criteria set out above. Study selection occurred in two rounds. First, title and abstract review for relevance; second, full-text review to determine final inclusion.

See PRISMA flow diagram for more details (Figure 1).

PRISMA FLOW DIAGRAM HERE

Data Extraction(B)

The reviewers extracted pre-specified study characteristics, i.e. cohort name, sample size, exposure and outcome definitions, covariates, year of birth, location, age at assessment and study results from each study, using a uniform template.

Quality of Evidence Assessment(B)

Two reviewers (RR and MLP) independently assessed quality of evidence for all included studies using the Newcastle-Ottawa Scale (NOS) using pre-specified 'acceptable' criteria for each domain. The NOS assesses studies based on three domains: Selection, Comparability, and Outcome. Studies could receive up to nine stars, four stars in the 'Selection' for 1) Representativeness of the exposed cohort, 2) Selection of the non-exposed cohort, 3) Ascertainment of the exposure, and 4) Demonstration that the outcome of interest was not present at the start of the study exposure. Studies could receive another two stars for 'Comparability' for

5) Comparability of cohorts based on the design or analysis, and 6) Study controls for at least 3 additional risk factors. The final three stars for the 'Outcome' domain were awarded on the bases of 7) Assessment of outcome, 8) Was follow-up long enough for outcomes to occur, and 9) Adequacy of follow up of cohorts. The acceptable criteria used by both assessors for each item is reported in Supplementary Table B.2. If the assessors disagreed, then a consensus was reached with a third assessor (KH). Studies with ≥7 were rated as 'High' quality, studies with 4-6 received a 'Moderate' quality rating, and studies with <4 stars received a 'poor' quality rating. See Supplementary Table B.2 NOS Quality of Evidence Acceptable Criteria.

Results(A)

Summary of Included Studies (B)

Thirteen studies met the inclusion criteria, with data from eight cohorts and two national register studies. The included studies comprise cohorts from Australia (Royal Women's Hospital), Canada (McMaster), Finland (Helsinki Study of Very Low Birth Weight Adults, HeSVA), Germany (Bavarian Longitudinal Study, BLS), New Zealand (NZ VLBW), Norway (Trondheim), UK and the Republic of Ireland (EPICure), and USA (Cleveland) and populations from Sweden (Swedish MBR) and Norway (Norwegian MBR). The birth years range from 1977-1995 with follow-up ages ranging from 18-35 years in the included studies. Studies reported outcomes for any mental disorder, and total problems and related symptoms (n=10), mood, depression, bipolar and anxiety disorders, and internalizing problems and related symptoms (n=12), substance use disorders, and externalizing problems and related symptoms (n=7), eating disorders and symptoms (n=3),

schizophrenia spectrum disorders and symptoms (n=3), and psychiatric medication use (n=3). Four studies reported exposures as EP or VP, while 10 studies reported exposures as ELBW or VLBW. Two studies indicated the control exposure as NBW, while 11 studies used term birth as the control exposure, and two studies defined the controls as NBW term born individuals. See Table 1 for included studies by outcome and publication year. Table 1 also shows the method of the outcome measurement.

INSERT TABLE OF INCLUDED STUDIES HERE

Any mental disorder and total problems and related symptoms (B)

Two studies with participants aged 26-35 years reported an increased risk of any mental disorder, measured by structured clinical interviews, in VLBW/ELBW adults compared to term-born/NBW controls[22,23]. In contrast, one study showed no significant difference in the risk of any mental disorder, also identified from a structured clinical interview, between 24-29-year-old VLBW and NBW participants [24].

Seven cohorts with participants aged 19-29 years reported total problem scores with self-reported symptoms scales. Six of these studies were included in an IPD meta-analysis [25], which found no differences in self-reported total problem scores between 18-28-year-old VP/VLBW and term participants. However, one study [26] which was included in the IPD meta-analysis at a younger age (20 years), reported that VLBW participants had significantly higher total problem scores than term born appropriate for gestational age (AGA) controls in a follow-up at an older age (26 years)[26]. Furthermore, the EPICure cohort, which was not included in the meta-analysis, also

reported a significantly higher total difficulties score in 19-year-old EP individuals compared with term controls[27].

Mood, depression, bipolar and anxiety disorders and internalizing problems and related symptoms (B)

Two studies showed that the risk of mood disorders [22,28] and one showed that the risk of depression[24] in a structured clinical interview were higher in 26-29-year-old VLBW/VP participants compared to term/NBW controls. However, one of these studies reported that the group difference in mood disorders was not significant when accounting for multiple testing[28].

In contrast, three studies in 22-35-year-old participants [23,29,30] found no differences in the risk of major depressive disorder or self-reported depression diagnosis between VLBW/ELBW and term controls, and one study which focused on bipolar disorder did not test the differences because of small number of cases. However, in one of these studies [29] self-reported depression diagnosis was more frequent among VLBW small for gestational age (SGA) participants and less frequent among VLBW appropriate for gestational age (AGA) participants than among term born controls.

One study [22] reported an increased risk of anxiety disorders in a structured clinical interview at age 26 years. Whereas, five other studies which measured anxiety disorders also via structured clinical interview reported no differences for VLBW/ELBW/VP compared to term controls in any anxiety disorder [24,28,30], Generalized Anxiety Disorder (GAD), panic disorder, social phobia or obsessive-compulsive disorders [22,23]. However, one of these studies was not able to pursue

testing differences in agoraphobia, social phobia, specific phobia, panic, obsessive compulsive and post-traumatic stress disorders between VLBW and term born controls because of lack or small number of cases[22].

The APIC IPD meta-analysis[25]found an increased risk of self-reported internalizing symptoms for VP/VLBW participants, and for subscales, including avoidant personality problems[25], but found no differences in its withdrawn, somatic complaints and anxious/depressive subscales. One study included in the IPD meta-analysis at 20 years, also reported increased internalizing symptoms and the withdrawn behavior and somatic complaints subscale scores later at 26 years, but did not report differences in a subscale measuring depressive/anxiety symptoms [26]. One other study also reported significantly increased emotional symptoms in EP participants compared to term controls at age 19 [27].

With regard to depressive symptoms, one study reported that VLBW adults scored higher than NBW controls at age 24-29 years [24]. However, one study reported that the depressive symptoms scores were higher for those born VLBW and SGA and lower for those born VLBW and AGA than for term controls at the age of 18-27 years [29]. Yet, another study [31] found no differences in depressive symptoms scores between VLBW participants and term born controls. One study reported no differences for anxiety, phobic anxiety and obsessive compulsive disorder symptoms in VLBW participants compared to NBW controls[24].

Substance use disorders, and externalizing problems and related symptoms(B)

Three studies[22–24] reported no differences in risk of substance use disorder between VLBW/ELBW participants compared to NBW/term controls at age 24-36 years. One of the studies[22] also reported separately no differences for alcohol or drug dependencies.

One IPD meta-analysis[25] found a decreased risk for externalizing symptoms and for scales measuring rule-breaking, intrusive and antisocial personality problems in VLBW/EP participants compared with term born controls. In contrast, the Trondheim study included in the meta-analysis at age 20, reported significantly increased externalizing problems in the VLBW participants compared to term born controls in a later follow-up at age 26, but found no difference in subscales measuring aggressive or rule-breaking behavior [26]). One study found no differences in conduct problems between ELBW and term-born participants at age 19 [27].

Eating disorders and related symptoms(B)

Three studies assessed eating disorders, or symptoms thereof, in VLBW born adults [22,24,32]. One study[22] found no cases with eating disorders in either the VLBW or term groups, another study[24] found no differences between VLBW participants and NBW controls in eating disorders, while another study [32] found a decreased risk of eating disorder symptoms in VLBW adults compared to term born controls at age 18-27 years.

Schizophrenia spectrum disorders and related symptoms(B)

Only three studies, two from the same cohort, assessed schizophrenia spectrum disorders or their symptoms [22,24,26]. One study reported no differences between VLBW and NBW controls in psychotic and bipolar disorders, measured with a clinical interview, as one clinical entity, or in psychoticism or paranoid ideation symptoms at age 24-29 years [24]. In the other study, differences in psychotic disorders could not be examined because of small number of cases[22], but individuals born VLBW had significantly more frequent delusion inventory scores above the clinical cutoff than term-born peers at age 26 years[26], although there were no difference in continuous delusion scores.

Psychotropic medication use(B)

Two large scale population-based studies [33,34] on psychotropic medication use with prescription register data from the Nordic countries reported an increased risk of being prescribed any psychotropic medications in both VP and EP participants compared to term born controls at age 24-35 years.

One additional study has reported that self-reported antidepressant medication use is higher among VLBW participants born SGA than among term born controls, with no difference between all VLBW adults compared to controls at age 18-27 years[29].

Table of Excluded Studies(B)

All studies excluded after full-text review are listed in the Table of Excluded Studies, along with a brief indication of the reason for exclusion. See Supplementary Table B.1 Excluded Studies.

Quality of Evidence Assessment(B)

As several studies reported multiple outcomes of varying quality, studies were rated individually by outcome. Hence, some studies have multiple quality ratings depending on the number of outcomes. Due to the systematic review study inclusion criteria, 0 studies were judged to have poor quality, 25 study outcomes were rated to have moderate quality(65.8%), and 13 were rated as high(34.2%). Notably, none of the included studies accounted for all of the important, pre-specified covariates, namely genetic confounding, which could have been addressed for instance using a sibling or twin study design. Although, several studies did adjust for some of the predefined key covariates such as sex(n=10), age/birth year(n=9), and SES/parental education (n=13), while parental mental health(n=2), neonatal complications i.e. brain injury (n=1), or parity(n=1) were accounted for in far less studies. Hence, the comparability of the study findings downgraded the results in all studies. In spite of this, overall, we judged the quality of evidence for all outcome domains to be moderate to high quality. See Table 1 Summary of Main Findings for Included Studies and the Supplementary Table B.2 NOS Quality of Evidence Acceptable Criteria for more details.

Discussion(A)

Summary of Evidence(B)

Our review found that the odds of any psychotropic medication use, derived from nationwide registers in two population-based studies, was 1.3[33] to 2.1-times [34]higher for VP adults, and in one cohort study self-reported antidepressant medication use was 4.0-times higher for VLBW adults born SGA than for term controls [29]. However, our review suggests, that the evidence on whether VP/VLBW adults have higher risk of mental health disorders appearing in adulthood than term/NBW controls and whether they differ in the symptoms of these disorders, remain uncertain [22–34]. Although, the findings lack consensus, it may not be for the lack of quality in the evidence in the studies we reviewed, as the studies were overall moderate to high quality, with none rated as poor quality. However, it does suggests the need for larger study samples.

Of the three studies that tested the risk of any mental health disorder, a significantly higher risk for VP/VLBW adults in comparison to NBW/term controls was reported in two, while in one this risk was not significant. Of the six studies that tested the risk of mood disorders, three reported a significantly higher risk for any mood/depressive disorder, while three reported that the risk for depressive/major depressive disorder was not significant. Of the five studies that tested the risk of anxiety disorders, one reported a significantly higher risk for any anxiety disorder, three reported that this risk was not significant, and one reported that the risk for GAD, social phobia, panic or obsessive-compulsive disorders was not significant. Three studies focused on substance use disorders and found no significant elevation in the risk, and the two studies that focused on eating and schizophrenia spectrum disorders reported no significant elevation in the risk. Moreover, in one of the studies, which suggested that the risk for any mood disorder was higher, the differences between VP/VLBW and term/NBW controls were no longer significant when accounting for

multiple testing. As well as in four studies, which focused on depressive, bipolar, panic disorders, agoraphobia, social phobia, specific phobia, GAD, OCD, PTSD, eating, schizophrenia spectrum disorders, VP/VLBW and term/NBW comparisons could not be performed because the number of cases in the VP/VLBW and/or in NBW/term control groups were small or zero.

Of the studies that tested differences between VP/VLBW adults and term controls in symptoms of mental disorders, significant differences in total, internalizing and/or externalizing problems were reported in nine, while no differences were reported in three. Among these studies is an IPD meta-analysis of six cohort studies. It reported no differences between VP/VLBW adults and NBW/term controls in total problems, and higher levels of internalizing and lower levels of externalizing problems for VP/VLBW adults than for NBW/term controls. Furthermore, one study reported that VP/VLBW adult showed higher levels of clinically relevant schizophrenia spectrum disorder symptoms than NBW/term controls, one reported no such differences, and one additional study reported that VP/VLBW adults displayed lower levels of eating disorder symptoms than NBW/term controls.

While this mixed pattern of findings in relation to mental health disorders appearing in adulthood and their symptoms is in contrast with the two population-based studies showing increased risk of any psychotropic medication use for VP/VLBW adults, the major reason for this discrepancy appears to relate to differences in sample sizes. While the two population-based samples included 980 and 3670 VP adults and 243283 and 588410 term controls, respectively, in all but two individual cohort studies focusing on mental health disorders and symptoms were the VP/VLBW and/or NBW/term control group sizes less than 100. The IPD meta-analysis included 747

VP/VLBW and 1512 term controls. Hence, these findings suggest that before any firm conclusions about longer-term mental health outcomes of VP/VLBW adults can be made, much larger individual cohort studies than those conducted thus far and aggregate-data and IPD meta-analyses are urgently needed. In favor of this view are the five large, population-wide studies of over 4.6 million VP/VLBW adults and NBW/term controls, which have demonstrated an increased risk of a host of mental health disorders for VP/VLBW born adults [12,13,16,35,36], which however did not differentiate the outcomes for adults from adolescents.

Limitations & Strengths(B)

The limitations of this systematic review stem largely from the limitations in the current body of evidence. A key limitation in all included studies comes from a lack of control for familial genetic confounding, accountable for through sibling and twin study designs. Furthermore, the small sample sizes in most studies limits the generalizability of the findings, the limited statistical power increasing the likelihood of both false positive and false negative findings, as well as limiting the exploration of outcomes with lower prevalence rates and exploration of important covariates, confounders, and moderators. The lack of uniform adjustment for important covariates across studies, such as a genetic confounding, childhood SES, parental mental health, neonatal complications, parity, participant age, and sex, further reduces the comparability of the findings. Furthermore, three cohorts retrospectively recruited controls[23,25,27]and did not clearly report if their gestational age or birthweight was verified. Hence, these cohorts may have used retrospective

self-reports which are prone to bias. It is also important to note that although we excluded duplicate publications of the same outcome at the same age from the same cohort, most of the included cohorts provided multiple outcomes, either at a different time point or with a different measure. Therefore, a large portion of the findings reported in this review come from a select group of cohorts. Many of the studies also have used self-reports of mental health, not gold standard diagnostic interviews, precluding inferences to diagnosed disorders.

Our review focused on mental health outcomes appearing in adulthood. While we excluded the mental disorders, which have childhood onset by definition, some of the included disorders with possible adulthood onset (e.g. anxiety disorders) also may have had their onset in childhood or adolescence[37]. Mental disorders and psychiatric symptoms show both homotypic and heterotypic continuity from childhood to adulthood, with childhood internalizing and externalizing problems predicting both internalizing and externalizing disorders and their symptoms in adulthood [27,37–40]. Such continuity is present also in EP children: the EPICure study, showed clinically significant total psychiatric problems at age 2.5 years predicted increased total psychiatric problems at ages 6, 11, 16 and 19 years[27]. A study from the McMaster cohort also shows a lack of normative age-related decline in internalizing problems from adolescence to adulthood in individuals born ELBW[41]. .Furthermore in the EPICure study the effects of EP on psychiatric symptoms on the SDQ stayed similar from childhood to young adulthood[27], and previous studies show similar effects of VP/VLBW on ADHD and ASD across childhood, and adolescence and young adulthood ages [42–44]. Hence, while we included only studies assessing mental health phenotypes after 18 years of age, we do not know at which age these mental health

disorders or symptoms had begun. This limits the conclusions that can be made of our findings being specific to adult age.

Moreover, the literature is almost devoid of large-scale studies focusing on VP or VLBW adult mental health, especially those that report results stratified by age or birth year. Although, a handful of large Nordic register studies [12,13,16,35,36] have analyzed mental health across the lifespan by gestational age and birth weight, the studies did not report the findings separately by age, birth year, or time of diagnosis. In parallel, the majority of the participants in the included studies were born in the late 1970s and 1980s, and only one study included participants born in the 1990s [27]. In light of the continuous improvements in neonatal medicine [45,46], the adult mental health findings in our review, may not be generalizable to more modern born preterm adults, although more modern childhood and adolescent studies also show high frequencies of neurodevelopmental disabilities [47], psychiatric symptoms [48] , ASD [49] and ADHD [50,51]. Therefore, neonatal medicine improvements may not necessarily translate to improvements in lifespan mental health of those surviving after VP/VLBW births as the risks related to these births remain. Meta-analytic evidence shows that ELBW birth predicts similarly increased parent and teacher-rated internalizing and externalizing problems, conduct disorders and ADHD problems in childhood in cohorts born before 1990s and in cohorts born since 1990 [9]. In addition, with a special focus on VP or VLBW born adult mental health, the findings of this review are not generalizable to broader preterm or low birth weight populations. However, Nordic register studies suggest dose-response effects of gestation length on psychotropic medication use and mental health disorders [12,13,33,34], with the highest risks observed among individual born EP, but with increased risks of the psychiatric phenotypes observed across the degrees of prematurity[12]. Finally, in a letter

to the editor, the EPICure study[52] (excluded for publication type), found EP did not predict offspring depression or anxiety disorders or ASR total or externalizing problems or its subscale scores at age 19 years. EP was associated with increased internalizing problems and its subscale scores, but only associations with anxiety problems remained significant after corrections for multiple testing. Small sample size and high attrition were factors limiting the generalizability of these findings[52]. The contradictory findings further suggests the need for larger scale studies in order to clarify effects observed in different preterm subgroups.

Implications(B)

Our study has several important implications. While the data on mental health outcomes appearing in adulthood of VP/VLBW individuals remain limited and the pattern of findings between the different studies is mixed, the studies included in this systematic review encourage harmonizing and pooling data for aggregate-data and IPD meta-analyses using standardized measures and definitions. This will have several advantages over the individual studies that can help in overcoming the previous study limitations. These include increased statistical power to study rarer outcomes and to increase generalizability of the findings, and to study gestational age specific associations as well as identify factors fostering resiliency. This systematic review also points to the importance to follow-up the existing preterm cohorts as they age, to study if any mental health adversities extend to middle- or older-adulthood and to disorders that peak later in life e.g. Schizophrenia.

While the current evidence is still limited, any longer-term mental health adversity following VP/VLBW birth will multiply the economic costs, especially given the high economic costs of mental health disorders for both the individual and the respective family. Besides mental health problems, VP/VLBW itself is the root of various direct (e.g. additional hospitalization) and indirect costs (e.g. labor market adjustments of the parents, more parenting time), which families and the respective preterm born individual have to bear. For example, using data from England and Wales in 2006 it has been estimated that the total cost of preterm birth to public sector was £2.946 billion (US $4.567 billion) and the incremental cost per VP child in comparison to term child surviving to 18 years was £61781 (US $95760) [11] . However, the costs depend on the actual development on the health care system and supply and hence are likely to differ from country to country. The same is true for the costs of mental health. The OECD estimates the costs of mental health problems at around 600 billion euro. This implies costs of ranging from two to more than five percent of the annual GDP in EU countries[53].

Conclusions(B)

To our knowledge, this is the first systematic review focused on mental health outcomes appearing adults born VP or VLBW. The review provides a systematic, critical assessment of the quality of the evidence performed independently by two researchers, highlighting the key areas for improvement in future studies. Our systematic review found consistent, moderate to high quality evidence that VP or VLBW born adults are at an increased risk for any psychotropic medication use, while in regards to their higher risk for mental health disorders appearing in adulthood and their symptoms the moderate to high quality evidence is mixed. The limitations in the current

evidence signal a need for more high quality, large scale VP studies accounting for important covariates, through aggregate-data and/or IPD meta-analysis and register based studies.

Acknowledgements(B)

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Practice Points

Adult mental health outcomes of individuals born VP/VLBW:

- Lacks systematic reviews and assessment of the quality of evidence of the studies
- Studies with moderate to high quality evidence
- Use of psychotropic medication is higher, but evidence in regards to increased risk of mental disorders appearing in adulthood and symptoms remains uncertain.

Research Directions

Adult mental health outcomes of individuals born VP/VLBW:

- Pooling and harmonizing data of exiting cohorts for aggregate-data and individual participant data meta-analyses and new large-scale studies to allow sufficient power for gestational age specific, year of birth- and age- stratified analyses and to allow studying outcomes with lower prevalence rates.
- Extending follow-up of the preterm cohorts into middle- and older adulthood
- Identification of sex-specificity and factors that foster resiliency

REFERENCES

[1] Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. The Lancet Global Health 2019;7:e37–46. https://doi.org/10.1016/S2214-109X(18)30451-0.

[2] Berrington JE, Hearn RI, Bythell M, Wright C, David Embleton N. Deaths in Preterm Infants: Changing Pathology Over 2 Decades NEC Necrotizing enterocolitis PMS Perinatal Mortality Survey 2012. https://doi.org/10.1016/j.jpeds.2011.06.046.

[3] Field DJ, Dorling JS, Manktelow BN, Draper ES. Survival of extremely premature babies in a geographically defined population: Prospective cohort study of 1994-9 compared with 2000-5. BMJ 2008;336:1221–3. https://doi.org/10.1136/bmj.39555.670718.BE.

[4] Institute of Medicine (US) Roundtable on Environmental Health Sciences R and M, Mattison DR, Wilson S, Coussens C, Gilbert D. Preterm Birth and Its Consequences 2003.

[5] Raju TNK, Buist AS, Blaisdell CJ, Moxey-Mims M, Saigal S. Adults born preterm: a review of general health and system-specific outcomes. Acta Paediatrica 2017;106:1409–37. https://doi.org/10.1111/apa.13880.

[6] Wolke D, Johnson S, Mendonça M. The Life Course Consequences of Very Preterm Birth 2019. https://doi.org/10.1146/annurev-devpsych-121318.

[7] Baumann N, Bartmann P, Wolke D. Health-related quality of life into adulthood after very preterm birth. Pediatrics 2016;137. https://doi.org/10.1542/peds.2015-3148.

[8] Nielsen TM, Pedersen M v., Milidou I, Glavind J, Henriksen TB. Long-term cognition and behavior in children born at early term gestation: A systematic review. Acta Obstetricia et Gynecologica Scandinavica 2019;98:1227–34. https://doi.org/10.1111/aogs.13644.

[9] Mathewson KJ, Chow CHT, Dobson KG, Pope EI, Schmidt LA, van Lieshout RJ. Mental health of extremely low birth weight survivors: A systematic review and meta-analysis. Psychological Bulletin 2017;143:347–83. https://doi.org/10.1037/bul0000091.

[10] SKJAERVEN R, GJESSING HK, BAKKETEIG LS. Birthweight by gestational age in Norway. Acta Obstetricia et Gynecologica Scandinavica 2000;79:440–9. https://doi.org/10.1034/j.1600-0412.2000.079006440.x.

[11] Mangham LJ, Petrou S, Doyle LW, Draper ES, Marlow N. The cost of preterm birth throughout childhood in England and Wales. Pediatrics 2009;123:e312–27. https://doi.org/10.1542/peds.2008-1827.

[12] Nosarti C, Reichenberg A, Murray RM, Cnattingius S, Lambe MP, Yin L, et al. Preterm Birth and Psychiatric Disorders in Young Adult Life. ARCH GEN PSYCHIATRY 2AD:1–8. https://doi.org/10.1001/archgenpsychiatry.2011.1374.

[13] D'Onofrio BM, Class QA, Rickert ME, Larsson H, Långström N, Lichtenstein P. Preterm birth and mortality and morbidity: a population-based quasi-experimental study. JAMA Psychiatry 2013;70:1231–40. https://doi.org/10.1001/jamapsychiatry.2013.2107.

[14] Hertz CL, Mathiasen R, Hansen BM, Mortensen EL, Greisen G. Personality in Adults Who Were Born Very Preterm. PloS One 2013;8:e66881. https://doi.org/10.1371/journal.pone.0066881.

[15] Cnattingius S, Hultman CM, Dahl M, Sparén P. Very preterm birth, birth trauma, and the risk of anorexia nervosa among girls. Archives of General Psychiatry 1999;56:634–8. https://doi.org/10.1001/archpsyc.56.7.634.
[16] Abel KM, Wicks S, Susser ES, Dalman C, Pedersen MG, Mortensen PB, et al. Birth Weight, Schizophrenia, and Adult Mental Disorder. Archives of General Psychiatry 2010;67:923. https://doi.org/10.1001/archgenpsychiatry.2010.100.
[17] Research on European Children and Adults born Preterm(RECAP) n.d. https://recap-preterm.eu/ (accessed March 11, 2020).
[18] Premlife Project n.d. https://warwick.ac.uk/fac/sci/psych/research/lifespan/premlife/ (accessed March 11, 2020).
[19] APIC – – Adults Born Preterm International Collaboration n.d. http://www.apic-preterm.org/ (accessed March 15, 2020).
[20] Preterm birth n.d. https://www.who.int/news-room/fact-sheets/detail/preterm-birth (accessed March 11, 2020).
[21] ICD-10 Version:2016 n.d. https://icd.who.int/browse10/2016/en (accessed March 18, 2020).
[22] Laerum AMW, Reitan SK, Evensen KAI, Lydersen S, Brubakk A-M, Skranes J, et al. Psychiatric Disorders and General Functioning in Low Birth Weight Adults: A Longitudinal Study. Pediatrics 2017;139. https://doi.org/10.1542/peds.2016-2135.
[23] van Lieshout RJ, Boyle MH, Saigal S, Morrison K, Schmidt LA. Mental health of extremely low birth weight survivors in their 30s. Pediatrics 2015;135:452–9. https://doi.org/10.1542/peds.2014-3143.
[24] Westrupp EM, Northam E, Doyle LW, Callanan C, Anderson PJ. Adult psychiatric outcomes of very low birth weight survivors. The Australian and New Zealand Journal of Psychiatry 2011;45:1069–77. https://doi.org/10.3109/00048674.2011.620561.
[25] Pyhala R, Wolford E, Kautiainen H, Andersson S, Bartmann P, Baumann N, et al. Self-Reported Mental Health Problems Among Adults Born Preterm: A Meta-analysis. Pediatrics 2017;139. https://doi.org/10.1542/peds.2016-2690.
[26] Laerum AMW, Reitan SK, Evensen KAI, Lydersen S, Brubakk A-M, Skranes J, et al. Psychiatric symptoms and risk factors in adults born preterm with very low birthweight or born small for gestational age at term. Bmc Psychiatry 2019;19. https://doi.org/10.1186/s12888-019-2202-8.
[27] Linsell L, Johnson S, Wolke D, Morris J, Kurinczuk JJ, Marlow N. Trajectories of behavior, attention, social and emotional problems from childhood to early adulthood following extremely preterm birth: a prospective cohort study. European Child & Adolescent Psychiatry 2019;28:531–42. https://doi.org/10.1007/s00787-018-1219-8.
[28] Jaekel J, Baumann N, Bartmann P, Wolke D. Mood and anxiety disorders in very preterm/very low–birth weight individuals from 6 to 26 years. Journal of Child Psychology and Psychiatry 2018;59:88–95. https://doi.org/10.1111/jcpp.12787.
[29] Raikkonen K, Pesonen A-K, Heinonen K, Kajantie E, Hovi P, Jarvenpaa A-L, et al. Depression in young adults with very low birth weight. Archives of General Psychiatry 2008;65:290–6. https://doi.org/10.1001/archgenpsychiatry.2007.40.

[30] Darlow BA, Horwood LJ, Pere-Bracken HM, Woodward LJ. Psychosocial outcomes of young adults born very low birth weight. Pediatrics 2013;132. https://doi.org/10.1542/peds.2013-2024.
[31] Husby IM, Stray KMT, Olsen A, Lydersen S, Indredavik MS, Brubakk AM, et al. Long-term follow-up of mental health, health-related quality of life and associations with motor skills in young adults born preterm with very low birth weight. Health and Quality of Life Outcomes 2016;14. https://doi.org/10.1186/s12955-016-0458-y.
[32] Wehkalampi K, Hovi P, Strang-Karlsson S, Räikkönen K, Pesonen AK, Heinonen K, et al. Reduced body size and shape-related symptoms in young adults born preterm with very low birth weight: Helsinki study of very low birth weight adults. Journal of Pediatrics 2010. https://doi.org/10.1016/j.jpeds.2010.02.045.
[33] Crump C, Winkleby MA, Sundquist K, Sundquist J. Preterm birth and psychiatric medication prescription in young adulthood: a Swedish national cohort study. International Journal of Epidemiology 2010;39:1522–30. https://doi.org/10.1093/ije/dyq103.
[34] Engeland A, Bjørge T, Klungsøyr K, Skurtveit S, Furu K. Preterm births and use of medication in early adulthood: a population-based registry study. Pharmacoepidemiology and Drug Safety 2017;26:742–51. https://doi.org/10.1002/pds.4174.
[35] Class QA, Rickert ME, Larsson H, Lichtenstein P, D'Onofrio BM. Fetal growth and psychiatric and socioeconomic problems: population-based sibling comparison. The British Journal of Psychiatry : The Journal of Mental Science 2014;205:355–61. https://doi.org/10.1192/bjp.bp.113.143693.
[36] Pettersson E, Larsson H, D'Onofrio B, Almqvist C, Lichtenstein P. Association of Fetal Growth with General and Specific Mental Health Conditions. JAMA Psychiatry 2019;76:536–43. https://doi.org/10.1001/jamapsychiatry.2018.4342.
[37] Jones PB. Adult mental health disorders and their age at onset. British Journal of Psychiatry 2013;202. https://doi.org/10.1192/bjp.bp.112.119164.
[38] Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. Archives of General Psychiatry 2009;66:764–72. https://doi.org/10.1001/archgenpsychiatry.2009.85.
[39] Loth AK, Drabick DAG, Leibenluft E, Hulvershorn LA. Do childhood externalizing disorders predict adult depression? A meta-analysis. Journal of Abnormal Child Psychology 2014;42:1103–13. https://doi.org/10.1007/s10802-014-9867-8.
[40] Meque I, Dachew BA, Maravilla JC, Salom C, Alati R. Externalizing and internalizing symptoms in childhood and adolescence and the risk of alcohol use disorders in young adulthood: A meta-analysis of longitudinal studies. Australian and New Zealand Journal of Psychiatry 2019;53:965–75. https://doi.org/10.1177/0004867419844308.
[41] van Lieshout RJ, Ferro MA, Schmidt LA, Boyle MH, Saigal S, Morrison KM, et al. Trajectories of psychopathology in extremely low birth weight survivors from early adolescence to adulthood: a 20-year longitudinal study. Journal of Child Psychology and Psychiatry and Allied Disciplines 2018;59:1192–200. https://doi.org/10.1111/jcpp.12909.

[42] Franz AP, Bolat GU, Bolat H, Matijasevich A, Santos IS, Silveira RC, et al. Attention-deficit/hyperactivity disorder and very preterm/very low birth weight: A meta-analysis. Pediatrics 2018;141. https://doi.org/10.1542/peds.2017-1645.

[43] Pyhala R, Hovi P, Lahti M, Sammallahti S, Lahti J, Heinonen K, et al. Very Low Birth Weight, Infant Growth, and Autism-Spectrum Traits in Adulthood. Pediatrics 2014;134:1075–83. https://doi.org/10.1542/peds.2014-1097.

[44] Agrawal S, Rao SC, Bulsara MK, Patole SK. Prevalence of autism spectrum disorder in preterm infants: A meta-Analysis. Pediatrics 2018;142. https://doi.org/10.1542/peds.2018-0134.

[45] Stoelhorst GMSJ, Rijken M, Martens SE, Brand R, den Ouden AL, Wit JM, et al. Changes in neonatology: Comparison of two cohorts of very preterm infants (Gestational Age <32 weeks): The Project On Preterm and Small for Gestational Age Infants 1983 and the Leiden Follow-up Project on Prematurity 1996-1997. Pediatrics 2005;115:396–405. https://doi.org/10.1542/peds.2004-1497.

[46] Horbar JD, Wright EC, Onstad L. Decreasing Mortality Associated With the Introduction of Surfactant Therapy: An Observational Study of Neonates Weighing 601 to 1300 Grams at Birth. Pediatrics 1993;92.

[47] Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. Pediatrics 2005;115:997–1003. https://doi.org/10.1542/peds.2004-0221.

[48] Vederhus BJ, Eide GE, Natvig GK, Markestad T, Graue M, Halvorsen T. Health-related quality of life and emotional and behavioral difficulties after extreme pretermbirth: Developmental trajectories. PeerJ 2015;2015. https://doi.org/10.7717/peerj.738.

[49] Verhaeghe L, Dereu M, Warreyn P, de Groote I, Vanhaesebrouck P, Roeyers H. Extremely Preterm Born Children at Very High Risk for Developing Autism Spectrum Disorder. Child Psychiatry and Human Development 2016;47:729–39. https://doi.org/10.1007/s10578-015-0606-3.

[50] Wilson-Ching M, Molloy CS, Anderson VA, Burnett A, Roberts G, Cheong JL y., et al. Attention Difficulties in a Contemporary Geographic Cohort of Adolescents Born Extremely Preterm/Extremely Low Birth Weight. Journal of the International Neuropsychological Society 2013;19:1097–108. https://doi.org/10.1017/S1355617713001057.

[51] Burnett A, Davey CG, Wood SJ, Wilson-Ching M, Molloy C, Cheong JLY, et al. Extremely preterm birth and adolescent mental health in a geographical cohort born in the 1990s. Psychological Medicine 2014;44:1533–44. https://doi.org/10.1017/S0033291713002158.

[52] Johnson S, O'Reilly H, Ni Y, Wolke D, Marlow N. Psychiatric Symptoms and Disorders in Extremely Preterm Young Adults at 19 Years of Age and Longitudinal Findings From Middle Childhood. Journal of the American Academy of Child and Adolescent Psychiatry 2019;58:820-826.e6. https://doi.org/10.1016/j.jaac.2019.02.020.

[53] OECD Health Division. Health at a Glance: Europe 2018. 2018. https://doi.org/10.1787/health_glance_eur-2018-en.