Self-Reported Mental Health Problems Among Adults Born Preterm: A Meta-analysis

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abstract

CONTEXT: Preterm birth increases the risk for mental disorders in adulthood, yet findings on self-reported or subclinical mental health problems are mixed.

OBJECTIVE: To study self-reported mental health problems among adults born preterm at very low birth weight (VLBW; ≤1500 g) compared with term controls in an individual participant data meta-analysis.

DATA SOURCES: Adults Born Preterm International Collaboration.

STUDY SELECTION: Studies that compared self-reported mental health problems using the Achenbach Young Adult Self Report or Adult Self Report between adults born preterm at VLBW (n = 747) and at term (n = 1512).

DATA EXTRACTION: We obtained individual participant data from 6 study cohorts and compared preterm and control groups by mixed random coefficient linear and Tobit regression.

RESULTS: Adults born preterm reported more internalizing (pooled β = .06; 95% confidence interval .01 to .11) and avoidant personality problems (.11; .05 to .17), and less externalizing (–.10; –.15 to –.06), rule breaking (–.10; –.15 to –.05), intrusive behavior (–.14; –.19 to –.09), and antisocial personality problems (–.09; –.14 to –.04) than controls. Group differences did not systematically vary by sex, intrauterine growth pattern, neurosensory impairments, or study cohort.

LIMITATIONS: Exclusively self-reported data are not confirmed by alternative data sources.

CONCLUSIONS: Self-reports of adults born preterm at VLBW reveal a heightened risk for internalizing problems and socially avoidant personality traits together with a lowered risk for externalizing problem types. Our findings support the view that preterm birth constitutes an early vulnerability factor with long-term consequences on the individual into adulthood.

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Preterm birth (<37 completed weeks of gestation) occurs in 1 in every 10 deliveries worldwide, amounting to 15 million births per year.[1] Preterm birth is among the current leading causes of perinatal mortality and morbidity.[2] The health risks associated with preterm birth extend across the life span, including risks for cognitive impairment[3,4] and aging-related illnesses such as cardiometabolic diseases.[5] In addition, individuals born preterm are at an increased risk for severe mental disorders.[6,7] Both those with severe and subclinical mental health problems are at a highly increased risk for adverse financial and social outcomes in adulthood.[8] Hence, it is important not only to investigate whether individuals born preterm are at an increased risk for diagnosed mental disorders but also self-reported subclinical mental health problems.

We are aware of only a few studies that have to date examined self-reported mental health in adults born preterm. These studies have resulted in mixed findings. Compared with young adults born at term (≥37 completed weeks of gestation), those born preterm at very (VLBW; ≤1500 g) or extremely low birth weight (ELBW; ≤1000 g) reported more internalizing problems, such as symptoms of anxiety and depression,[9–11] and reduced social functioning,[10,11] but equal levels of externalizing problems, such as aggression, fighting, or breaking rules,[9,10,12] and total behavior problems.[9,12] Less externalizing problems have been found in adults born at VLBW and/or <32 weeks of gestation compared with peers from general population[13] and in adults born at ELBW and/or <28 weeks of gestation compared with term controls.[14] In some studies, these differences have varied by sex[12,13] or have been characteristic only of preterms born small-for-gestational age (SGA).[10,15,16]

All of these studies have been conducted in relatively small samples. This has resulted in limited statistical power, which has been further compromised when analyzing men and women and those born SGA or appropriate-for-gestational age (AGA) separately, increasing the risk of chance findings. We report here the results of a meta-analysis combining individual-level data from 6 cohorts of adults born preterm at VLBW and their peers born at term within the Adults Born Preterm International Collaboration (APIC). The aim of the study was to investigate whether self-reported mental health problems of adults born preterm at VLBW differ from adults born at term. We expected the preterm group to report more internalizing problems and less or equal levels of externalizing problems. The sample size allows additional examination of group differences by sex or by the pattern of intrauterine growth restriction as reflected in SGA and AGA births. The APIC cohorts included in this meta-analysis are from different countries and regions allowing us to additionally examine whether variations in findings arise from cross-cultural differences. A previous meta-analysis on childhood mental health problems has pointed to universal differences in the mental health problems between children born preterm and term.[17] However, these differences varied by country in terms of magnitude.[17]

METHODS

Study Selection

APIC is an international research network aimed at studying health and well-being of adults born preterm through individual participant and aggregate data meta-analyses across multiple cohorts. On the basis of research literature and inquiries within the APIC network, we contacted research groups whom we knew to have followed up a cohort of adults born preterm at VLBW or ELBW. We required each cohort to have its own control group born at term and data on mental health problems collected using the Achenbach Adult Self-Report (ASR)[18] or the Achenbach Young Adult Self-Report (YASR).[19] To confirm that all eligible cohorts were included, we additionally conducted a systematic literature search on PubMed for articles published between January 1, 1975, and May 5, 2014 (Fig 1). As keywords, we used the following search terms: ("very low birth weight" or "extremely low birth weight") and "adult*" and ("psychopathology" or "mental health" or "psychiatric"). We screened for original English-language research articles to identify relevant study cohorts.

Of the included cohorts, those with published data on ASR or YASR were the McMaster cohort[10] from Canada (born 1977–1982), the Trondheim cohort[9] from Norway (born 1986–1988), and the Cleveland cohort[12] from the United States (born 1977–1979). Cohorts with unpublished data were the Helsinki Study of Very Low Birth Weight Adults[4] (HeSVA; born 1978–1985) and the Preterm Birth and Early Life Programming of Adult Health and Disease Study[20] (ESTER; born 1985–1989) from Finland and the Bavarian Longitudinal Study[21] (BLS; born 1985–1986) from Germany. Ethical approvals were provided by local ethics committees of the separate cohort studies. All participants gave their informed consent. We requested data on the original ASR and YASR raw scores, perinatal information, and other important covariates from all the participating cohorts. Data were harmonized to compute commensurate variables and pooled across the cohorts. All data were deidentified before pooling.

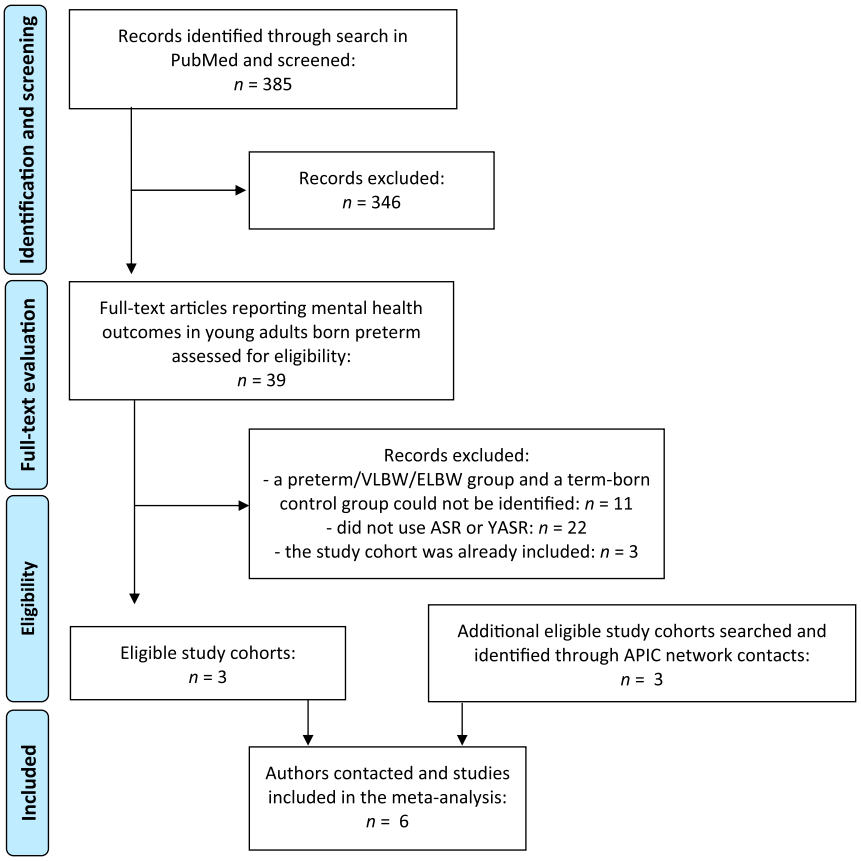

FIGURE 1
PRISMA Flow diagram depicting the search process to identify study cohorts eligible for the pooled analysis.

Participants

The study groups consisted of altogether 747 adults born preterm at VLBW and 1512 controls born at term (preterm and control groups, respectively) at ages 19 to 29 years. In the McMaster cohort, the preterm participants were all born at ELBW, whereas preterm groups in other cohorts included also those with a birth weight between 1000 and 1500 g. All cohorts were regional, and the control and preterm groups within each cohort were born during the same time period. The control groups in the original cohorts were frequency matched to the preterm group for sex (HeSVA, McMaster, BLS), age (HeSVA, Cleveland, McMaster), birth hospital (HeSVA), and family socioeconomic status (McMaster, BLS).[4,10,12,21] The original ESTER study design comprised 2 preterm groups (<34 and 34–37 weeks), 2 pregnancy complication groups (hypertension-spectrum pregnancy disorders and gestational diabetes), and a term-born control group. The Trondheim cohort originally included a VLBW group, a term-born SGA group defined by the 10th percentile according to Norwegian growth curves,[9] and a term-born control group not born SGA. Independent of the original study design of each cohort, we used unified criteria to form groups: all those born preterm at VLBW were included in the preterm group and all term-born participants in the control group. Thus, there is overrepresentation of offspring exposed to pregnancy complications (ESTER; 334 of 703 term controls) and SGA births (Trondheim) in the control group. However, only 1 of those defined as SGA according to regional criteria in the Trondheim cohort was SGA according to a uniform criterion[22] used in this meta-analysis. Data on exact length of gestation were not available for term controls in the McMaster[10] and Cleveland[12,23] cohorts.

Measures

Gestational Length and Birth Weight

Gestational length in weeks + days and birth weight in grams were derived from hospital records. Because of dissimilar national standards used in previous publications, we calculated birth weight in relation to gestational age SD scores based on uniform criteria for both sexes separately.[22] SGA was defined as birth weight for gestational age less than or equal to −2 SD and AGA as birth weight for gestational age greater than −2 SD and less than +2 SD. SGA and AGA status could not be calculated for controls in the McMaster and Cleveland cohorts.

Mental Health Problems

Mental health problems during the previous 6 months were self-reported in adulthood using the ASR[18] (HeSVA, Trondheim, ESTER) or YASR[19] (Cleveland, McMaster, BLS). The ASR is composed of 123 and YASR of 116 items that are self-rated on a scale from 0 (not true) to 2 (very or often true).

The Ratings to Scores software by ASEBA[24] was used to compute raw scores and T scores for scales according to the ASR form for both the ASR and YASR data. Thus, all scale scores across the study cohorts are based on the same items independent of the form version that was originally used.

The scales yielded 3 sum scales measuring internalizing, externalizing, and total problems; 8 syndrome scales measuring anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive

behavior, rule-breaking behavior, and intrusive behavior; and 6 *Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition* (*DSM-IV*)-oriented scales measuring depressive, anxiety, somatic, avoidant personality, attention deficit/hyperactivity, and antisocial personality problems; and 1 scale measuring critical items (a clinician-based sum of items referring to problems clinicians may typically be particularly concerned about).[18]

Covariates

Covariates included sex, age at testing, and as a proxy of socioeconomic position of the childhood family, the highest education of either parent at participant's birth (Cleveland, BLS), childhood (McMaster), and adolescence (Trondheim) as reported by the parent(s) and in adulthood as reported by the participant (HeSVA, ESTER). Parental education was classified into lower secondary or less, higher secondary education, lower tertiary education, or higher tertiary education. An additional category was used for missing values. Information on singleton/multiple birth was extracted from hospital records. Neurosensory impairments were determined as cerebral palsy, severe hearing or visual deficit, or IQ <70. Data on cerebral palsy, hearing deficit, or visual deficit were based on clinical assessments in childhood (HeSVA, Cleveland, McMaster, Trondheim, BLS), and/or self-reports in adulthood (HeSVA, ESTER). Data on estimated IQ were available from clinical assessments in childhood (McMaster), or adulthood (HeSVA, Trondheim, BLS).

Statistical Analyses

We conducted a 2-step individual participant data random-effects meta-regression analysis in which analyses were first run separately for each cohort, and the results from the individual cohorts were then combined in a meta-analysis. We used T scores of the scales as outcome measures. First, we tested whether those born preterm differed from term controls on the sum scales (internalizing, externalizing, and total problems) by using multiple linear regression models. We then tested whether the groups differed in the syndrome, *DSM-IV*-oriented, and critical items scales by using Tobit regressions. Tobit models are designed to estimate linear relationships between variables when there exists either left or right censoring in the outcome variable. Pooled effects and 95% confidence intervals (CIs) were then computed using the random-effects method with DerSimonian and Laird technique.[25] In all meta-analyses, between-study heterogeneity was tested using the Cochran's Q statistic and quantified by the I^2 value. Low heterogeneity was defined as an I^2 value of 0% to 25%, moderate heterogeneity as an I^2 of 25% to 75%, and high heterogeneity as an I^2 of 75% to 100%. We reran the 2-step meta-analyses by restricting the preterm group to ELBW births and compared them with the term controls. All analyses were adjusted for sex, age at assessment, parental education, multiple birth, and neurosensory impairments. Analyses contrasting the preterm and term groups were subsequently rerun after excluding individuals with neurosensory impairments (199 preterms and 21 controls). We also examined whether the group differences varied by sex, and if those born preterm differed in mental health problems according to SGA or AGA birth weight. All statistical analyses were performed with Stata, version 14.0 (StataCorp, College Station, TX).

RESULTS

Characteristics of the preterms and controls are in Table 1. Supplemental Figure 5 shows the unadjusted T scores for the mental health problems for preterms (Panel A) and for controls (Panel B) in each cohort.

Differences in Mental Health Problems Between Preterms and Controls

In the pooled individual participant data meta-analyses, preterms reported more internalizing problems ($P = .02$) and less externalizing problems ($P < .001$) than controls (Fig 2). On the syndrome scales, preterms reported less rule-breaking behavior and intrusive behavior (Fig 3), and on the *DSM-IV*-oriented scales, they reported more avoidant personality and fewer antisocial personality problems (Fig 4) than controls (Ps < .001). No statistical heterogeneity existed between the study cohorts in these analyses (I^2 < 27.0% in all analyses, Ps > .23) (Fig 2–4). When we excluded individuals with neurosensory impairments from the analyses, the significant findings remained virtually identical (pooled meta-analysis Ps < .005; data not shown), except for 2: in the pooled meta-analysis the difference between preterms and controls on internalizing problems became nonsignificant ($P = .052$), and the previously marginally significant difference in the withdrawn problems, with preterms reporting higher levels, became significant ($P = .01$).

When we restricted the comparisons to those preterms who were born at ELBW, they reported fewer externalizing problems than term-born controls (pooled β = –0.07; 95% CI = –0.14 to –0.01, $P = .04$) (Supplemental Table 2). There was no significant heterogeneity between the study cohorts in this analysis ($I^2 = 36.6\%$, $P > .13$) and no other significant differences between the groups (Ps > .07).

TABLE 1 Characteristics of the Group Born Preterm at VLBW (≤1500 g) or ELBW (≤1000 g) and of the Group of Term Controls as Pooled Across Study Cohorts and by Each Individual Study Cohort

Characteristic		Preterm VLBW/ELBW	Control	*P* for Preterm Versus Control
		n (%)/Mean (SD)	*n* (%)/Mean (SD)	
Participants	All	747	1512	
	HeSVA	108 (50.7)	105 (49.3)	
	Cleveland	241 (51.0)	232 (49.0)	
	McMaster	142 (51.6)	133 (48.4)	
	Trondheim	42 (25.1)	125 (74.9)	
	ESTER	46 (6.1)	703 (93.9)	
	BLS	168 (44.0)	214 (56.0)	
Age at assessment, y	All	22.9 (2.7)	23.1 (2.3)	.14
	HeSVA	24.6 (2.1)	24.6 (2.2)	.89
	Cleveland	20.2 (0.5)[a]	20.1 (0.5)[a]	.05
	McMaster	23.3 (1.2)	23.7 (1.0)[b]	.004
	Trondheim	19.6 (0.8)	19.7 (0.7)	.64
	ESTER	23.0 (1.4)	23.4 (1.2)	.07
	BLS	26.3 (0.6)	26.3 (0.6)	.74
Men	All	335 (44.8)	710 (47.0)	.34
	HeSVA	48 (44.4)	45 (42.9)	.82
	Cleveland	116 (48.1)	108 (46.6)	.73
	McMaster	62 (43.7)	60 (45.1)	.81
	Trondheim	19 (45.2)	54 (43.2)	.82
	ESTER	13 (28.3)	342 (48.6)	.007
	BLS	77 (45.8)	101 (47.2)	.79
Gestational length, wk	All	29.7 (2.6)	39.8 (1.3)[c]	<.001
	HeSVA	29.3 (2.4)	40.1 (1.1)	<.001
	Cleveland	30.1 (2.3)	NA; all ≥37	NA
	McMaster	27.5 (2.3)	NA	NA
	Trondheim	29.0 (2.3)	39.7 (1.2)	<.001
	ESTER	30.5 (2.3)	39.8 (1.3)[c]	<.001
	BLS	31.0 (2.4)	40.1 (1.2)	<.001
Birth weight (g)	All	1120 (243)	3501 (517)	<.001
	HeSVA	1137 (218)	3609 (489)	<.001
	Cleveland	1180 (219)	NA	NA
	McMaster	840 (125)	3388 (481)	<.001
	Trondheim	1238 (191)	3361 (547)	<.001
	ESTER	1258 (198)	3573 (526)	<.001
	BLS	1193 (216)	3360 (446)	<.001
ELBW	All	289 (38.7)	NA	NA
	HeSVA	30 (27.8)	0 (0.0)	NA
	Cleveland	63 (26.1)	NA	NA
	McMaster	142 (100.0)	0 (0.0)	NA
	Trondheim	6 (14.3)	0 (0.0)	NA
	ESTER	8 (17.4)	0 (0.0)	NA
	BLS	40 (23.8)	0 (0.0)	NA
SGA[d]	All	97 (13.0)	9 (0.8)[e]	<.001
	HeSVA	9 (8.3)	0 (0.0)	.003
	Cleveland	28 (11.6)	NA	NA
	McMaster	15 (10.6)	NA	NA
	Trondheim	2 (4.8)	1 (0.8)[f]	.10
	ESTER	3 (6.5)	4 (0.6)[g]	<.001
	BLS	40 (23.8)	4 (1.9)	<.001
Multiple birth	All	147 (19.7)[h]	14 (0.9)	<.001
	HeSVA	17 (15.7)	0 (0.0)	<.001
	Cleveland	43 (17.8)	NA	NA
	McMaster	14 (9.9)[h]	NA	NA
	Trondheim	9 (21.4)	0 (0.0)	<.001
	ESTER	13 (28.3)	7 (1.0)	<.001
	BLS	51 (30.4)	7 (3.3)	<.001
Neurosensory impairments	All	119 (15.9)	21 (1.4)	<.001
	HeSVA	9 (8.3)	1 (1.0)	.01
	Cleveland	20 (4.2)	0 (0.0)	<.001
	McMaster	47 (33.1)	10 (7.5)	<.001

TABLE 1 Continued

Characteristic		Preterm VLBW/ELBW	Control	*P* for Preterm Versus Control
		n (%)/Mean (SD)	*n* (%)/Mean (SD)	
	Trondheim	2 (4.8)	1 (0.8)	.09
	ESTER	6 (13.0)	8 (1.1)	<.001
	BLS	35 (20.8)	1 (0.5)	<.001
Highest parental education				
Lower secondary or less	All	152 (20.3)	181 (12.0)	<.001
	HeSVA	11 (10.2)	6 (5.7)	.23
	Cleveland	50 (20.7)	34 (14.7)	.08
	McMaster	22 (15.5)	19 (14.3)	.78
	Trondheim	19 (45.2)	31 (24.8)	.01
	ESTER	4 (8.7)	55 (7.8)	.83
	BLS	46 (27.4)	36 (16.8)	.01
Higher secondary	All	260 (34.8)	668 (44.2)	<.001
	HeSVA	21 (19.4)	18 (17.1)	.66
	Cleveland	97 (40.2)	81 (34.9)	.23
	McMaster	38 (26.8)	31 (23.3)	.51
	Trondheim	2 (4.8)	18 (14.4)	.10
	ESTER	26 (56.5)	411 (58.5)	.80
	BLS	76 (45.2)	109 (50.9)	.27
Lower tertiary	All	174 (23.3)	305 (20.2)	.09
	HeSVA	40 (37.0)	35 (33.3)	.57
	Cleveland	74 (30.7)	90 (38.8)	.07
	McMaster	36 (25.4)	42 (31.6)	.25
	Trondheim	7 (16.7)	29 (23.2)	.37
	ESTER	5 (10.9)	91 (12.9)	.68
	BLS	12 (7.1)	18 (8.4)	.65
Higher tertiary	All	124 (16.6)	311 (20.6)	.02
	HeSVA	34 (31.5)	46 (43.8)	.06
	Cleveland	3 (1.2)	10 (4.3)	.04
	McMaster	35 (24.6)	37 (27.8)	.55
	Trondheim	10 (23.8)	27 (21.6)	.77
	ESTER	11 (23.9)	140 (19.9)	.51
	BLS	31 (18.5)	51 (23.8)	.20
Not known/missing	All	37 (5.0)	47 (3.1)	.03
	HeSVA	2 (1.9)	0 (0.0)	.16
	Cleveland	17 (7.1)	17 (7.3)	.91
	McMaster	11 (7.7)	4 (3.0)	.08
	Trondheim	4 (9.5)	20 (16.0)	.30
	ESTER	0 (0.0)	6 (0.9)	.53
	BLS	3 (1.8)	0 (0.0)	.05

NA, not available.
[a] Fifteen missing (data imputed with cohort-specific mean value in analyses).
[b] Two missing (data imputed with cohort-specific mean value in analyses).
[c] Seven missing.
[d] According to Olsen et al growth standards[25]; birth weight for sex and gestational length less than or equal to –2 SD.
[e] Ten missing.
[f] One missing.
[g] Nine missing.
[h] Three missing.

Do Differences in Mental Health Problems Between Preterm and Controls Vary by Sex?

Sex × preterm versus control interactions were significant in the analyses of intrusive behavior ($P = .02$) and avoidant personality problems ($P = .03$). In the separate meta-analyses for men and women, both preterm men (β = –.02; 95% CI = –.04 to –.00; $P = .03$) and women (β = –.10; 95% CI = –.17 to –.03; $P = .005$) reported fewer problems on intrusive behaviors than controls. Furthermore, both preterm men (β = .02; 95% CI = .00 to .04; $P = .02$) and women (β = .18; 95% CI = .11 to .25; $P < .001$) reported more avoidant personality problems than controls. However, the differences between preterms and controls were more pronounced in women.

Do Differences in Mental Health Problems in the Preterm Group Vary by SGA and AGA Birth?

Finally, we examined whether those born preterm at SGA and AGA differed from each other in mental health problems. The SGA group reported fewer thought problems

than the AGA group (β = −3.00; 95% CI = −4.45 to −1.55; *P* < .001). Otherwise these groups were similar (*P*s > .05; data not shown).

DISCUSSION

Our study is the first individual participant data meta-analysis of self-reported mental health problems in young adults born preterm. Our sizable sample of 747 adults born preterm at VLBW and of 1512 term controls represent data from 6 longitudinal birth cohort studies from 5 countries. We found that those born preterm at VLBW reported more internalizing and avoidant personality problems and fewer externalizing, rule-breaking, intrusive, and antisocial personality problems than term controls. When the analyses were restricted to the smallest of preterms, those born preterm at ELBW reported fewer externalizing problems than controls. Cohort heterogeneity was not significant in any of these analyses. Findings are thus not explained by differences in cultural or region-specific origins of the cohorts. Differences between preterms and controls were not accounted for by the participant's age, sex, multiple birth, parental education, or neurosensory impairments. Additional sensitivity analyses excluding individuals with neurosensory impairments did not alter the main findings substantially.

Our findings suggest that there is a universal phenotype of mental health problems in adults born preterm characterized by internalizing and avoidant personality problems. This indicates that adults born VLBW may worry more; be more anxious, shy, and withdrawn; and lack self-confidence in social relationships. These findings are in partial agreement with individual studies on self-reported mental health problems in adults born preterm showing more internalizing and social problems

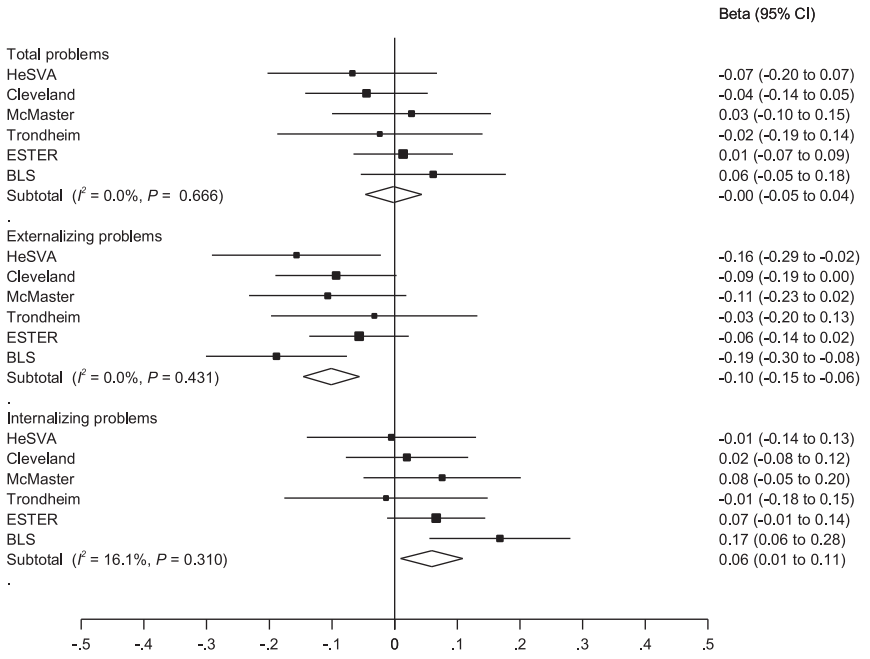

FIGURE 2

Associations between preterm birth at VLBW or ELBW and self-reported total, externalizing and internalizing problems in adulthood. The black boxes and corresponding numbers represent betas and reflect mean differences between the preterm group born at VLBW or ELBW and the term control group in T score units adjusted for sex, age at follow-up in adulthood, multiple birth, parental education and neurosensory impairments, and error bars and corresponding numbers show 95% CI. The size of the black box indicates the weight (%) of the individual value in the overall meta-analysis.

but less consistent findings on externalizing problems.[9,10,12–14] Previous studies on personality traits have also shown more withdrawal, social avoidance, and anxiousness[26,27] and less extraversion, hostility, and assertiveness[28–30] in VLBW adults. Furthermore, these behavioral characteristics of VLBW adults are reflected in their reports of less risk-taking behavior and fewer romantic partners.[16,27,31] Our results are also in partial agreement with childhood meta-analyses that have demonstrated more internalizing and attention problems but mixed findings on externalizing problems.[32,33] Thus, our findings suggest that problems in internalizing and social behaviors may persist into adulthood. The absence of self-reported attention problems in preterm-born adults in our meta-analysis may reflect a change in the symptom manifestation from childhood to adulthood. However, speculation on developmental change should be treated with caution because the age-dependent decline in attention-deficit/hyperactivity disorder (ADHD) problems seems to be even greater in the general population,[21] and different measures and/or informants have been used to measure symptomatology in childhood and in adulthood.

We also examined differences in findings by sex, and if in the preterm group those born SGA and AGA differed from each other. In both men and women, less intrusive behavior problems and more avoidant personality problems were more characteristic of preterms than of controls, but the group differences were more pronounced among women. Furthermore, preterms born SGA reported less thought problems than those born AGA. These specific associations have not been reported before, although elevated risk of depressive,[15] internalizing,[10] and ADHD[16,34] problems for preterms born SGA, and internalizing

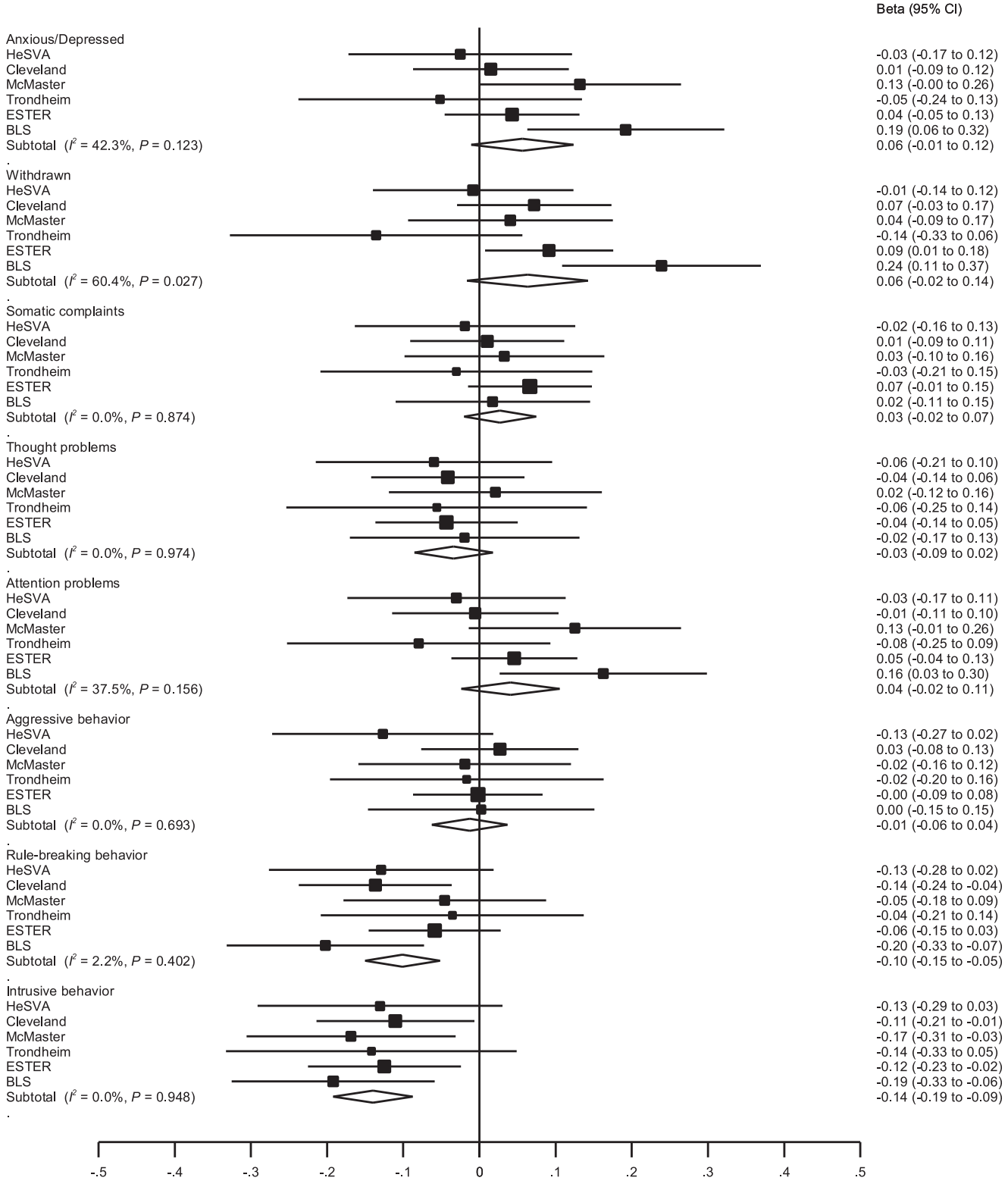

FIGURE 3

Associations between preterm birth at VLBW or ELBW and mental health problems on the ASR syndrome scales in adulthood. The black boxes and corresponding numbers represent betas and reflect mean differences between the preterm group born at VLBW or ELBW and the term control group in T score units adjusted for sex, age at follow-up in adulthood, multiple birth, parental education and neurosensory impairments, and error bars and corresponding numbers show 95% CI. The size of the black box indicates the weight (%) of the individual value in the overall meta-analysis.

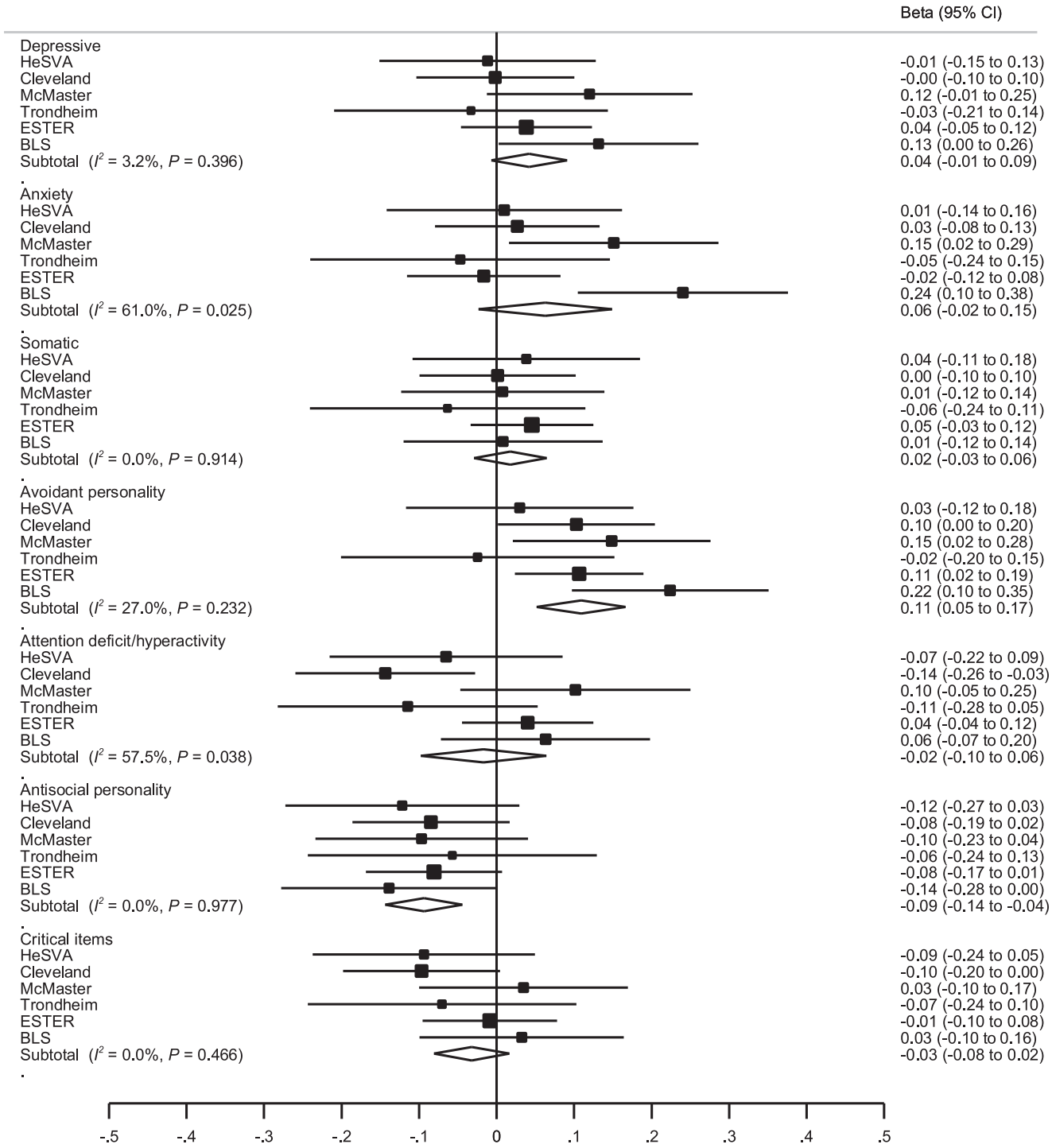

FIGURE 4

Associations between preterm birth at VLBW or ELBW and mental health problems on the ASR *DSM-IV*-oriented scales and critical items in adulthood. The black boxes and corresponding numbers represent betas and reflect mean differences between the preterm group born at VLBW or ELBW and the term control group in T score units adjusted for sex, age at follow-up in adulthood, multiple birth, parental education and neurosensory impairments, and error bars and corresponding numbers show 95% CI. The size of the black box indicates the weight (%) of the individual value in the overall meta-analysis.

problems for preterm women[12] have been reported. The inconsistent pattern of previous studies and the current meta-analysis may arise from different sample sizes or different definitions of SGA. It is also noteworthy that previous meta-analyses in preterm children have not studied whether there are differences in mental health problems between the sexes, or between those born SGA or AGA.[32,33]

Apart from studies using self-reports of mental health, nationwide registry studies have demonstrated an increased risk for a range of manifest psychiatric disorders, including nonaffective psychotic disorders and bipolar affective disorders, depressive disorders, ADHD, and autism[6,7] in adults born preterm. Other studies using structured psychiatric interviews have also found an increased risk for depression and anxiety disorders[11,35,36] and ADHD[34,36] and a lower risk for substance-use disorders[34] in adulthood. Childhood studies, which have indicated increased risks for attention and internalizing problems,[32,33] as well as externalizing problems,[32] have used parent- or teacher-reports.

However, mental health problems were self-reported in the current study. Therefore, direct comparisons with studies that have fused diagnoses of severe mental disorders from nationwide registries or that have used structured psychiatric interviews or parent- or teacher-reports are not fully justified. For example, psychotic disorders or autism are not comprehensively assessed in the ASR. It has been estimated that health care services use and expenditure is higher in the preterm group,[37] which may also lead to more sensitive diagnosing of psychiatric disorders among them. However, the partially discrepant study findings may also reflect the difference between categorical diagnostic approaches and dimensional self-assessments. Diagnoses represent severe mental disorders, whereas dimensional self-assessments also cover the subclinical symptoms. Thus, they supplement each other in adding understanding of mental health problems among adults born preterm. Hence, differences in the study findings may arise from the different source of obtaining information and different focus of instruments. In line with this, previous studies have demonstrated that parent ratings and in-depth psychiatric interviews assign more problems to preterm-born adults' mental health than their self-reports.[9,12,13,38]

Potential underlying mechanisms for our findings are multiple, including neurobiological, endocrinological, and psychosocial processes, which may individually affect or interact, resulting in the outcomes found in our meta-analysis.[39] Being born preterm affects brain development, causing reductions in total brain volume and disruptions in specific regional structures, structural connectome, and functional connectivity,[40–42] with neuroinflammation possibly contributing to the disruption of neural development.[43,44] Furthermore, potential abnormalities in brain development and function may directly be associated with behavioral, mental, and social problems,[45,46] or the association may be mediated by executive function problems.[47–50] In relation to endocrinological pathways, preterm birth, together with periods of treatment in the NICU, parental separation, and distress, may alter the hypothalamic-pituitary-adrenal axis functioning of the developing infant[51–55] and predispose preterm children to stress-related problems. Furthermore, there is increasing evidence that preterm children may more frequently be targets of peer victimization (bullying), which may as well contribute to emotional problems through increased psychosocial stress and marginalization.[39,56] In addition, although studies on parenting sensitivity with preterm children are varied,[57] prematurity may cause long-term challenges for the development of parent-child relationship that fosters the emotional and behavioral development of the child.[51,58] Naturally, genetic mechanisms cannot be ruled out either. However, at least part of the association between preterm birth and mental health problems is found to be independent of familial confounding.[7] Although sociodemographic factors have also been shown to differ between preterm and term populations[59] and to affect mental health outcomes,[60] our findings persisted after controlling for parental education.

Our study has limitations, including the lack of data on childhood or adolescent mental health, so we could not study continuity of mental health in preterm individuals in our meta-analysis. In addition, our findings from exclusively self-reported data should be confirmed by other assessment methods, including psychiatric diagnostic interviews and alternative data sources such as ratings by parents or spouses, given the previously demonstrated discrepancy between the self-report and parent assessments.[9,12,13,38] The several strengths of our study include the large sample size combining individual participant data across 6 cohorts. Yet although the direction of differences between ELBW and term controls was generally similar to differences we found between VLBW and term controls, the relatively low number of ELBWs in these cohorts may have restricted the power to detect statistically significant differences. We were able to gather comprehensive perinatal, childhood, and adulthood data, which enabled us to control for various confounders and analyze the results according to subgroups. An additional strength lies in the self-reported mental health problems scales that were comparable across cohorts.

CONCLUSIONS

According to our individual participant data meta-analysis across 6 cohorts from 5 countries,

self-reports of adults born preterm at VLBW reveal a characteristic preterm behavioral phenotype that includes a heightened risk for internalizing type of problems and avoidant personality problems in combination with a lowered risk for externalizing problem types. Our findings support the view that preterm birth constitutes an early vulnerability factor with long-term consequences on the individual into adulthood. This calls for increasing attention from school and health care professionals to recognize the preterm behavioral phenotype and the potential need for supportive measures. Research on preventive interventions is warranted to investigate whether these long-term effects can be attenuated.

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ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
AGA: appropriate for gestational age
APIC: Adults Born Preterm International Collaboration
ASR: Achenbach Adult Self-Report
BLS: Bavarian Longitudinal Study
CI: confidence interval
DSM-IV: Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition
ELBW: extremely low birth weight
ESTER: Preterm Birth and Early Life Programming of Adult Health and Disease Study
HeSVA: Helsinki Study of Very Low Birth Weight Adults
SGA: small for gestational age
VLBW: very low birth weight
YASR: Achenbach Young Adult Self-Report

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Dr Pyhälä and Mrs Wolford participated in planning the study concept and design, acquisition, statistical analysis and interpretation of data, drafting the manuscript, and critical revision of the manuscript; Dr Kautiainen participated in planning the study concept and design, was responsible for statistical analysis, and participated in data interpretation and critical revision of the manuscript; Ms Baumann and Drs Andersson, Bartmann, Brubakk, Evensen, Hovi, and Van Lieshout participated in planning the study concept and design, acquisition and interpretation of data, and critical revision of the manuscript; Dr Lahti participated in planning the study concept and design, statistical analysis, and interpretation of data and critical revision of the manuscript; Drs Saigal, Schmidt, Indredavik, and Wolke were responsible for planning 3 original cohort studies (McMaster, Trondheim, and Bavarian Longitudinal Study, respectively), supervised the study, and participated in planning the current study concept and design, in acquisition and interpretation of data and in critical revision of the manuscript; Dr Kajantie was responsible for planning 2 original cohort studies (Helsinki Study of Very Low Birth Weight Adults and Preterm Birth and Early Life Programming of Adult Health and Disease Study); supervised the study; obtained funding for the study; and participated in planning the current study concept and design, in acquisition and interpretation of data, and in critical revision of the manuscript; Dr Räikkönen was responsible for planning 2 original cohort studies (Helsinki Study of Very Low Birth Weight Adults and Preterm Birth and Early Life Programming of Adult Health and Disease Study); supervised the study; obtained funding for the study; and participated in planning the current study concept and design and in acquisition, statistical analysis and interpretation of data, drafting the manuscript, and critical revision of the manuscript; and all authors approved the final manuscript as submitted.

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