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ORIGINAL ARTICLE

Mental health, pain and tiredness in adults born very preterm or with very low birthweight

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Abstract

Aim: Adults born preterm have increased risk of mental health problems and other neurodevelopmental conditions. We aimed to investigate associations of mental health with pain and tiredness in adults born very preterm (VP; <32 weeks) or very low birthweight (VLBW; <1500 g) and at term, and whether these associations are influenced by physical activity.

Methods: As part of an EU Horizon 2020 project, individual participant data from six prospective cohort studies were harmonised for 617 VP/VLBW and 1122 term-born participants. Mental health was assessed by the Achenbach System of Empirically

Abbreviations: ASR, Adult Self-Report; AYLS, Arvo Ylppö Longitudinal Study; BLS, Bavarian Longitudinal Study; CI, confidence interval; ESTER, Preterm Birth and Early Life Programming of Adult Health and Disease Study; HeSVA, Helsinki Study of Very Low Birth Weight Adults; NTNU, Norwegian University of Science and Technology; RECAP Preterm, Research on European Children and Adults Born Preterm; VLBW, very low birth weight; VP, very preterm.

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Based Assessment Adult Self-Report. Pain and tiredness were harmonised based on specific items from self-reported questionnaires. Associations between mental health and pain or tiredness were explored by linear regression.

Results: An increase in the mental health scales internalising, externalising and total problems was associated with increased pain and tiredness in the preterm and term group alike. Results were maintained when adjusting for physical activity.

Conclusion: The findings indicate that associations between mental health, pain and tiredness in adults are independent of gestation or birthweight. Future research should explore other potential mechanisms that may underlie the increased risk of mental health problems in the preterm population.

1 | INTRODUCTION

Preterm birth is associated with an increased risk of adverse health outcomes into adulthood, comprising mental health, neurodevelopmental and physical conditions.[1] The adverse mental health profile in adults born very preterm (VP; <32 weeks of gestation) or with very low birthweight (VLBW; <1500 g) is characterised by more internalising (i.e. anxious/depressive symptoms), inattention and avoidant personality problems,[2,3] alongside fewer externalising problems, such as rule-breaking, intrusive and antisocial personality problems than term-born peers.[2] Studies on how these mental health problems relate to other health outcomes are sparse in adults born VP.

In the general population, mental health problems, pain, fatigue and tiredness are common conditions, and studies suggest that a bidirectional relationship exists between mental health disorders and pain[4] and fatigue.[5] Preterm birth may pose an increased risk of experiencing pain later in life,[6,7] possibly due to early pain and stressful events altering pain modulating systems.[8] Even though children and adolescents born VP may have more sleep problems than term-born peers,[9] fatigue or tiredness has not been studied in preterm populations. In contrast, adults born VP report similar or lower vitality than their term-born peers,[10] but the relationship between mental health and tiredness or vitality within adults born VP/VLBW has not been studied.

Physical activity has been associated with improved mental health and well-being among adolescents, regardless of gestational age.[11] In the general population, being physically active may reduce reports of pain and improve sleep.[12,13] Thus, the level of physical activity undertaken could affect any association between mental health problems and reported pain or tiredness. Adults born with VLBW report to exercise less frequently than adults born at term.[14] Hence, the possible reciprocal influence between mental health, pain, tiredness and physical activity in adults born VP/VLBW is complex and unknown. Each of these factors can be a target for intervention with the potential to promote health.

In this study, we aimed to investigate associations between mental health and pain or tiredness in adults born VP/VLBW compared with adults born at term and whether these associations were influenced by physical activity.

Key Notes

- More mental health problems were associated with increased pain and tiredness independent of gestation or birthweight.
- Physical activity did not affect the associations between mental health, pain and tiredness.
- Future research should explore other potential mechanisms that may underlie the increased risk of mental health problems in the preterm population.

2 | METHODS

2.1 | Study design

This study was part of the EU Horizon 2020 Research on European Children and Adults Born Preterm (RECAP Preterm) Consortium (RECAP website). We also searched for available cohorts in the Adults Born Preterm International Collaboration and the meta-analysis of Pyhälä and colleagues from 2017.[2] Six prospective cohort studies with available data on mental health, pain and tiredness in adulthood were identified; the Arvo Ylppö Longitudinal Study (AYLS, Finland),[15] the Bavarian Longitudinal Study (BLS, Germany),[16] the EPICure Study (United Kingdom and Ireland),[17] the Preterm Birth and Early Life Programming of Adult Health and Disease Study (ESTER, Finland),[18] the Helsinki Study of Very Low Birth Weight Adults (HeSVA, Finland)[19] and the Norwegian University of Science and Technology Low Birth Weight in a Lifetime Perspective study (NTNU Low Birth Weight Life, Norway).[20] Data from all six birth cohort studies were encrypted and transferred to NTNU. All studies had received country-specific ethical approval, with participants providing written informed consent. All adhered to the Declaration of Helsinki. This study was approved

by the Regional Committee for Medical and Health Research Ethics in Central Norway (2018/310).

2.2 | Study participants

Independent of the original study designs of the cohorts (Table 1), we defined the preterm group and the term comparison group across cohorts as VP (<32 weeks of gestation) and/or VLBW (<1500 g) and term-born (≥37 weeks of gestation). EPICure only included individuals born before week 26 in the preterm group. All participants with data on mental health, pain and tiredness were included. The study sample comprised 1739 participants: 617 born VP/VLBW and 1122 born at term, with participation rates ranging from 33.1% to 74.6% in the various cohorts. VP/VLBW non-participants had lower birthweight and gestational age, while a higher proportion of both VP/VLBW and term-born non-participants had low parental education level and neurosensory impairments (data not shown).

2.3 | Background characteristics

Background characteristics included individual-level information on demographic and perinatal characteristics, such as birthweight, gestational age, sex, parental education, age at mental health assessment and neurosensory impairment assessed in childhood (defined as visual/hearing/cognitive impairment and/or non-ambulatory cerebral palsy). Parental education was harmonised according to the International Standard Classification of Education into low (level 0–2), medium (3–5) and high (6–8).[21]

2.4 | Outcome measures

An overview of the measures used to assess mental health, pain and tiredness in each cohort is given in Supplemental Table S1.

2.4.1 | Mental health

The primary outcome was self-reported mental health problems in adulthood during the previous 6 months assessed by the Achenbach System of Empirically Based Assessment, Adult Self-Report (ASR) or Young ASR (the BLS cohort).[22] The ASR comprises 120 problem items (scored 0–2) yielding eight syndrome scales. Raw scores of the composite scales internalising problems (range 0–78; comprising the syndrome scales anxious/depressed, withdrawn and somatic complaints), externalising problems (range 0–70; comprising the syndrome scales aggressive behaviour, rule-breaking behaviour and intrusive) and total problems (range 0–240; a sum of all items and syndrome scales, also including the scales thought problems and attention problems that are not part of internalising or externalising problems. The ASR and Young ASR have high

TABLE 1 Summary of the background information of the cohorts included in this study.

Cohort	Country	Scale	Birth year	Initial eligibility criteria of the preterm group	Recruitment of the control group	Participants[a]/eligible *n* (%)		Age[a]
						VP/VLBW	Term-born	
AYLS	Finland	Regional	1985–86	GA < 37 week	Neonatal period	30/68 (44.1)	314/584 (53.8)	26 years
BLS	Germany	Regional	1985–86	VP/VLBW	Neonatal period	233/411 (56.8)	226/308 (73.4)	26 years
EPICure	UK and Ireland	National	1995	GA < 26 week	Childhood (data on GA or birthweight NA)	116/306 (37.9)	62/149 (41.6)	19 years
ESTER	Finland	Regional	1985–89	GA < 37 week	Pregnancy (ESTER NFBC) and adulthood (ESTER non-NFBC)	69/NA	328/NA	23 years
HeSVA	Finland	Regional	1978–85	VLBW≤1500 g	Adulthood (term-born SGA excl.)	111/254 (43.7)	104/314 (33.1)	22 years
NTNU LBW Life	Norway	Regional	1986–88	VLBW≤1500 g	Infancy (term-born SGA excl.)	58/82 (70.7)	88/118 (74.6)	26 years

Abbreviations: AYLS, Arvo Ylppö Longitudinal Study; BLS, Bavarian Longitudinal Study; ESTER, The ESTER Preterm Birth Study; excl, excluded; GA, gestational age; HeSVA, Helsinki Study of Very Low Birth Weight Adults; NA, not available; NFBC, Northern Finland Birth Cohort (a part of ESTER participants were recruited from NFBC); NTNU LBW Life, Norwegian University of Science and Technology Low Birth Weight in a Lifetime Perspective; VP/VLBW, very preterm (<32 weeks of gestation)/very low birth weight (<1500 g).

[a]Participants with mental health assessment.

validity and reliability, and there is a high correlation for internalising ($r=0.99$), externalising ($r=0.97$) and total problems ($r=0.99$) between the two versions.[22]

2.4.2 | Pain

The cohort studies used various self-report questionnaires to measure pain. For AYLS, ESTER and HeSVA, the participants were asked whether they had aches or pains in different body parts during the past 6 months. Only items reflecting musculoskeletal pain were included for harmonisation. For BLS, EPICure and NTNU Low Birth Weight Life, the participants were asked for the severity of pain or discomfort during the past 4 weeks. The items were harmonised into any pain (coded 1) and no pain (coded 0) (Supplemental Table S1).

2.4.3 | Tiredness

Tiredness was measured by two items from different questionnaires. For AYLS, EPICure, ESTER and HeSVA, the item 'I get tired' (during the past month) from the Behavior Rating Inventory of Executive Function–Adult version[23] with scores 0=never, 1=sometimes and 2=often was used as it is. For BLS and NTNU Low Birth Weight Life, we harmonised the item 'Did you have a lot of energy' (during the past 4 weeks) from the Short Form-12[24] (BLS) and Short Form-36[25] (NTNU Low Birth Weight Life) into tiredness 0–2 (Supplemental Table S1). Comparison of the two items showed similar distribution of the categories after harmonisation.

2.4.4 | Physical activity

Self-reported physical activity was assessed in adulthood by one or several questions related to the duration and frequency of leisure-time physical activity and was harmonised across cohorts. We defined moderate to vigorous physical activity as hours per week corresponding to an intensity of >3 metabolic equivalents.[26] The BLS and EPICure cohorts did not collect data on physical activity.

2.5 | Statistical analyses

Individual participant data were analysed. We used linear regression with mental health scales (internalising, externalising and total problems) one at a time as dependent variables, and pain (or tiredness), group (VP/VLBW vs. term-born), cohort, age, sex and pain (or tiredness) x group as main independent variables. The interaction terms were added to test whether the associations between mental health and pain or tiredness differed in VP/VLBW and term-born participants. Pain was a dichotomous variable: no pain and pain. Tiredness was a three-category variable: never, sometimes and often, with never tired as the reference category. We adjusted for parental education as a plausible confounder in separate analyses. We also performed analyses with physical activity as a covariate in the model to investigate whether physical activity influenced the association between mental health and pain or tiredness.

The normality of residuals was judged by visual inspection of Q–Q plots. Due to some deviations from normality, we used bootstrapping with 2000 bootstrap samples and the bias-corrected and accelerated (BC_a) method. Ninety-five per cent confidence intervals (CIs) are reported where relevant, and a two-sided p-value <0.05 was considered statistically significant. SPSS 26.0 was used for data analyses.

3 | RESULTS

Background characteristics are shown in Table 2 for the total sample, and the same information for each cohort is shown in Supplemental Table S2. Parental education level was lower in the VP/VLBW than in the term-born group.

Descriptive statistics for ASR, pain, tiredness and physical activity in the total sample are shown in Table 3, while the same information for each cohort is shown in Supplemental Table S3. Box plots visualising the ASR scores for the two groups in each category of pain and tiredness are presented in Figure 1.

The results from the linear regression analyses are shown in Table 4. Overall, an increase in the internalising, externalising and total problems score was associated with more pain and tiredness in both groups. The beta values for internalising problems and tiredness tended to be higher in the VP/VLBW group than in the term-born group (tiredness sometimes: 5.4 (CI:4.2–6.8) vs. 4.0 (CI:3.1–4.9), tiredness often: 15.9 (CI:13.6–18.2 vs. 13.7 (CI:12.1–15.4)). However, there were no between-group differences in the associations between mental health and pain or tiredness, indicated by the lack of significant interaction effects. Adjusting for parental education did not change the results (data not shown).

When we added physical activity as a covariate in the linear regression analyses, BLS and EPICure were excluded from the analyses as detailed above. Results from linear regression analyses unadjusted and adjusted for physical activity are shown in Supplemental Table S4. The beta values were unchanged after adjusting for physical activity, showing that physical activity did not influence the associations between mental health problems and pain or tiredness in either the VP/VLBW or the term-born comparison group.

4 | DISCUSSION

In this study from the EU Horizon 2020 project RECAP Preterm with data from six European cohort studies, more mental health problems were associated with increased pain and tiredness. The associations

TABLE 2 Background characteristics of the VP/VLBW and term-born group.

	n	VP/VLBW		*n*	Term-born	
Birthweight (g), mean (SD)	617	1188	(365)	1059	3556	(482)
Gestational age (week), mean (SD)	617	29.0	(3.1)	1060	39.8	(1.2)
Female sex, *n* (%)	617	314	(50.9)	1121	626	(55.8)
Neurosensory impairment, *n* (%)	567	92	(14.9)	1031	6	(0.5)
Parental education level, *n* (%)	593			1103		
Low (ISCED 0–2)		69	(11.6)		93	(8.4)
Middle (ISCED 3–5)		371	(62.6)		541	(49.0)
High (ISCED 6–8)		153	(25.8)		469	(42.5)
Age at assessment (year), mean (SD)	617	23.9	(3.0)	1122	24.5	(2.1)

Abbreviations: ISCED, International Standard Classification of Education; Neurosensory impairment, visual impairment, hearing impairment, cerebral palsy, and/or cognitive disability (IQ < 70); SD, standard deviation; VP/VLBW, very preterm (<32 completed weeks)/very low birth weight (<1500 g).

TABLE 3 Descriptive statistics for outcome variables in the VP/VLBW and term-born group.

Outcome variables	*n*	VP/VLBW		*n*	Term-born	
Internalising problems, mean (SD)	617	11.8	(10.8)	1122	9.4	(9.2)
Externalising problems, mean (SD)	617	6.5	(6.7)	1122	7.4	(6.5)
Total problems, mean (SD)	617	33.7	(26.0)	1122	31.6	(23.0)
Pain (yes), *n* (%)	601	285	(47.4)	1063	704	(66.2)
Tiredness, *n* (%)	598			1102		
Never		169	(28.3)		222	(20.1)
Sometimes		301	(50.3)		687	(62.3)
Often		128	(21.4)		193	(17.5)
Physical activity (h/week), mean (SD)	262	4.0	(3.6)	813	6.5	(2.8)

Abbreviations: h, hours; SD, standard deviation; VP/VLBW, very preterm (<32 completed weeks)/very low birth weight (<1500 g).

did not differ between adults born VP/VLBW and at term, and being more physically active did not influence any of the associations.

The main strength of this study is the large sample size combining individual participant data across six population-based cohort studies in Europe, increasing the power and generalisability of the results. Furthermore, groups were defined by uniform criteria across the cohorts, and participants were assessed at a similar age in young adulthood. To avoid potential confounding effects, we adjusted for cohort, age, sex and parental education. Our results may be representative for high-income countries and infants born at the limit of viability at the time of recruitment. Participants in five cohorts were born VP/VLBW from 1978 to 1988 before the so-called surfactant era, while the youngest cohort (EPICure) only included infants born before week 26 in 1995. Thus, there is a slight overrepresentation of participants born extremely preterm. However, despite that pre- and neonatal care improved greatly after the 1990s and increased the survival of the most immature infants, neurodevelopmental and cognitive outcomes have remained relatively stable.[27,28] Hence, long-term outcomes of extremely preterm births after these improvements in pre- and neonatal care may be comparable to VP/VLBW births before the surfactant era. There is a small underrepresentation of individuals born small for gestational age in the term-born group, since they were excluded in the HeSVA and NTNU Low Birth Weight Life cohorts. Cohort studies are prone to selective drop-out, and non-participant analyses in our study indicated that the most vulnerable participants were lost to follow-up in both the VP/VLBW and term-born group, and data were therefore not missing at random. This may have contributed to less variability in our data, possibly reducing the strength of the associations between mental health, pain and tiredness. Nevertheless, the validity of regression models has been shown to be marginally affected by selection bias in cohort studies.[29]

Mental health was assessed by the same self-report tool across all cohorts. Pain was measured during the past 6 months in three cohorts and during the past 4 weeks in three cohorts. The first yields a higher percentage of pain, and the last a lower percentage of pain, however, this was the same for both groups. Based on the accessible questionnaires, it was unfortunately not possible to distinguish between acute and chronic pain. For tiredness, we harmonised two items from different questionnaires since the same questionnaire was not available for all cohorts. Still, the distribution of the three response categories was similar after harmonisation. We do not have information about the types of physical activity reported. However, all cohorts focused on duration, frequency and intensity, and we

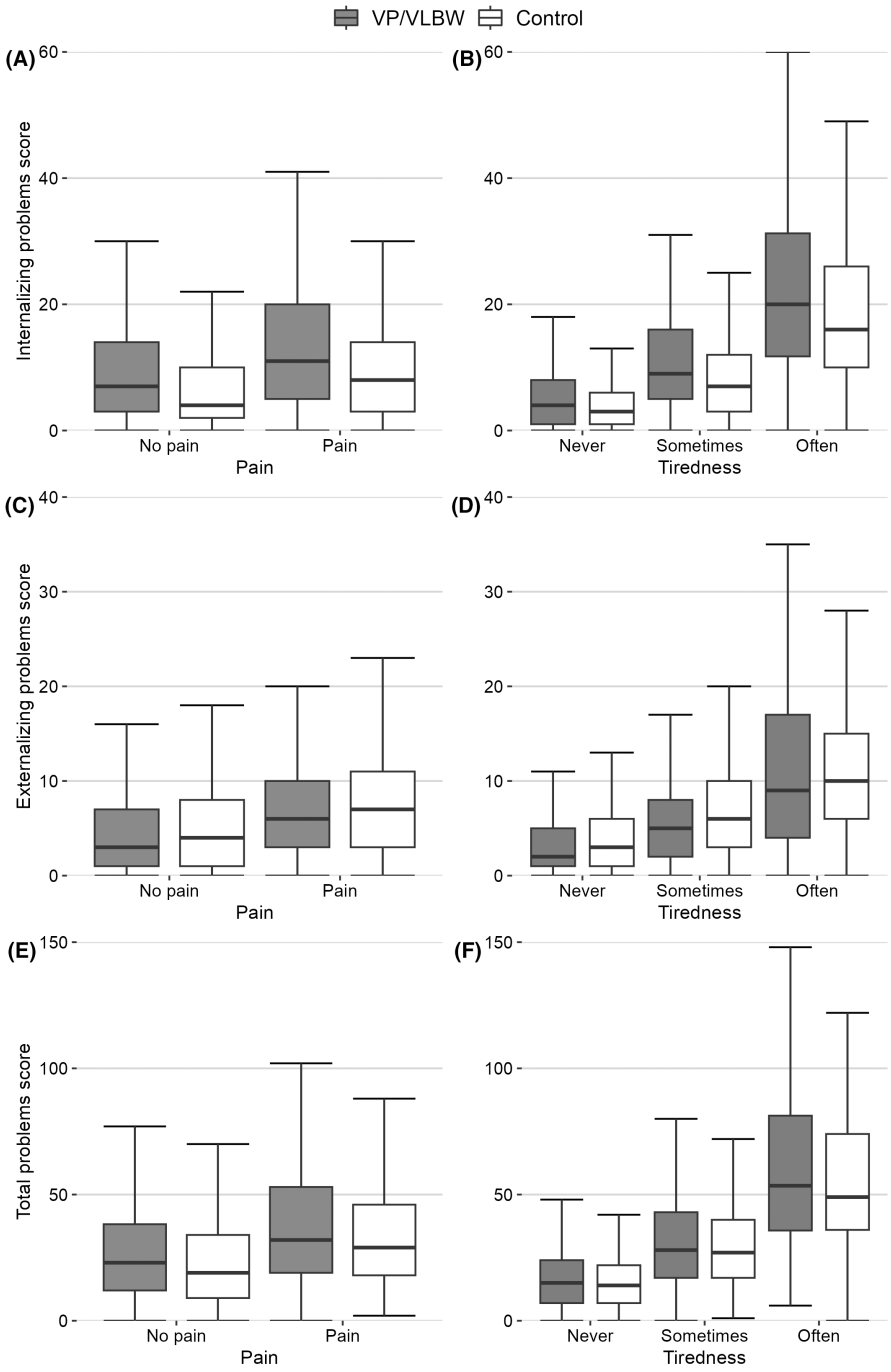

FIGURE 1 Box plots visualising the mental health scores (internalising, externalising and total problems) for each category of pain (A, C, E) and tiredness (B, D, F) in the very preterm/very low birthweight (VP/VLBW; <32 weeks of gestation/<1500 g) and term-born control group. Boxes extend from the 25th to the 75th percentile, horizontal lines denote the median, and vertical lines denote the largest and smallest values that are not outliers.

used a cut-off value of three metabolic equivalents, allowing us to create a uniform variable.

The relationship between mental health and pain or tiredness has not been explored in preterm populations. However, several studies based on the general population have shown an association between mood disorders and pain,[4,30,31] and between psychiatric symptoms and fatigue or lack of energy,[5] which is in line with our findings. As preterm birth is associated with altered activity in the hypothalamic–pituitary–adrenal axis,[32–34] the associations between mental health problems, pain and tiredness could have been expected to be stronger in adults born VP/VLBW than at term. However, studies showing an association between stress-related adult disease and dysfunction in the hypothalamic–pituitary–adrenal axis have focused on more severe and long-term pain and tiredness, such as chronic pain and fatigue.[35] Hooten and colleagues have found shared neural mechanisms and brain alterations in regions responsible for emotional processing for patients with chronic pain and mental disorders.[4] It might be that investigating associations between mental health and chronic pain or fatigue could have resulted in differences between adults born preterm and at term. On the other hand, there could be similar mechanisms underlying these associations, regardless of gestational age and birthweight.

Although physical activity can be beneficial for both mental health status, pain and tiredness,[11–13] we did not find that physical activity affected the relationship between these measures. As we used self-reported moderate to vigorous physical activity, we

TABLE 4 Linear regression models showing the association between mental health and pain or tiredness in the VP/VLBW and term-born group.

	VP/VLBW ($n = 617$)		Term-born ($n = 1121$)		
	β	(95% CI)	β	(95% CI)	p-value (group*predictor)
Internalising problems					
Pain[a]	3.2	(1.6-4.9)	3.1	(1.9–4.2)	0.916
Tiredness[b] (sometimes)	5.4	(4.2–6.8)	4.0	(3.1–4.9)	0.066
Tiredness[b] (often)	15.9	(13.6–18.2)	13.7	(12.1–15.4)	0.150
Externalising problems					
Pain[a]	2.0	(0.9–3.0)	1.9	(1.1–2.7)	0.923
Tiredness[b] (sometimes)	2.0	(1.1–2.8)	2.7	(1.9–3.5)	0.179
Tiredness[b] (often)	7.2	(5.6–8.8)	6.8	(5.6–8.1)	0.724
Total problems					
Pain[a]	8.6	(4.8-12.4)	9.1	(6.2–11.8)	0.830
Tiredness[b] (sometimes)	13.2	(10.1–16.7)	12.7	(10.3–15.1)	0.777
Tiredness[b] (often)	40.3	(34.9–45.9)	34.8	(30.9–39.1)	0.120

Note: Regression coefficient β for pain and tiredness, in linear regression with mental health scales (internalising, externalising and total problems) one at a time as dependent variables, and pain (or tiredness), group, cohort, age, sex and pain (or tiredness) x group as independent variables. Pain was a dichotomous variable: no pain and pain. Tiredness was a three-category variable: never, sometimes and often, with never tired as reference category. Higher β indicates increased mental health problems. p-values for group*predictor indicate between-group differences for associations between mental health and pain or tiredness.

Abbreviations: CI, confidence interval; VP/VLBW, very preterm (<32 weeks of gestation)/very low birth weight (<1500 g).

[a]Data missing for 16 VP/VLBW and 59 term-born participants.

[b]Data missing for 19 VP/VLBW and 20 term-born participants.

do not know if physical activity measured by accelerometry, or other types and intensities of leisure-time activities would yield a different result. Alternatively, physical activity might contribute equally to mental health, pain and tiredness, thereby not affecting the association.

4.1 | Clinical implications

For clinicians, our findings emphasise the importance of exploring the co-occurrence of mental health problems, pain and tiredness to better understand and provide targeted help to the individual. Future studies should evaluate more severe pain and tiredness (such as chronic pain and fatigue) and explore potential neural mechanisms underlying the associations with mental health in preterm and term populations. Future studies may also investigate how distinct types and intensities of physical activity affect long-term outcome and well-being in adults born preterm.

5 | CONCLUSION

The study suggests that mental health problems are associated with pain and tiredness in adults, whether born VP/VLBW or at term. We found that physical activity did not weaken these associations. Future research should explore other potential mechanisms that may underlie the increased risk of mental health problems in the preterm population.

AUTHOR CONTRIBUTIONS

Ingrid Marie Husby Hollund: Data curation; formal analysis; funding acquisition; investigation; methodology; visualization; writing – original draft. **Kristina Anna Djupvik Aakvik:** Data curation; formal analysis; investigation; methodology; writing – review and editing. **Silje Dahl Benum:** Formal analysis; investigation; methodology; visualization; writing – review and editing. **Sigrid Hegna Ingvaldsen:** Investigation; methodology; visualization; writing – review and editing. **Stian Lydersen:** Formal analysis; supervision; writing – review and editing. **Marjaana Tikanmäki:** Data curation; investigation; writing – review and editing. **Petteri Hovi:** Data curation; investigation; writing – review and editing. **Katri Räikkönen:** Data curation; investigation; writing – review and editing. **Eero Kajantie:** Data curation; investigation; methodology; writing – review and editing. **Samantha J Johnson:** Data curation; investigation; writing – review and editing. **Neil Marlow:** Data curation; investigation; writing – review and editing. **Nicole Baumann:** Data curation; investigation; writing – review and editing. **Dieter Wolke:** Data curation; investigation; writing – review and editing. **Marit S. Indredavik:** Conceptualization; data curation; funding acquisition; investigation; methodology; project administration; supervision; writing – review and editing. **Kari Anne I. Evensen:** Conceptualization; data curation; formal analysis; funding

acquisition; investigation; methodology; project administration; supervision; writing – original draft.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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