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Multidisciplinary and neuroimaging findings in preterm born very low birthweight individuals from birth to 28 years of age: A systematic review of a Norwegian prospective cohort study

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Abstract

Background: Children born preterm with very low birthweight (VLBW) face long-lasting neurodevelopmental challenges, where multidisciplinary assessments are warranted. The International Classification of Functioning, Disability and Health (ICF) provides a framework for understanding and conceptualising these outcomes.

Objectives: We aimed to review clinical and neuroimaging findings from birth to adulthood in a Norwegian cohort of individuals born preterm with VLBW (gestational age <37 weeks, birthweight ≤1500 g) within the framework of ICF.

Data Sources: We searched PubMed and Embase for articles reporting results of the Norwegian University of Science and Technology (NTNU) Low Birth Weight in a Lifetime Perspective study.

Study Selection and Data Extraction: We included original articles reporting proportions of adverse outcomes, mean group differences, risk factors or associations between outcomes. Data were extracted according to ICF's two-level classification. Body functions and structures comprised outcomes of brain structures, cognition, mental health, vision, pain and physical health. Activities and participation comprised motor skills, general and social functioning, education, employment, and health-related quality of life.

Synthesis: We performed a qualitative synthesis of included articles. Where mean (SD) was reported, we calculated group differences in SD units.

Results: Fifty-eight publications were included. Within body functions and structures, increased prevalence of brain structure pathology, lower cognitive performance, mental health problems, visual and physical health impairments through childhood, adolescence and young adulthood were reported among preterm VLBW participants compared with controls. Within activities and participation, motor problems, lower general and social functioning, and lower academic attainment were found. Perinatal factors were associated with several outcomes, and longitudinal findings suggested persistent consequences of being born preterm with VLBW.

Conclusions: Being born preterm with VLBW has long-term influences on body functions and structures, activities and participation. The ICF is appropriate for assessing general

domains of functioning and guiding the management of individuals born preterm with VLBW.

KEYWORDS
cognition, magnetic resonance imaging, mental health, motor skills, social functioning, very low birthweight

1 | BACKGROUND

Children born preterm with very low birthweight (VLBW) may face a spectrum of challenges.[1] As the preterm brain is vulnerable to injury and developmental disturbances,[2] the risk of later neurodevelopmental problems is substantial.[3] This may include adverse cognitive abilities,[4] mental health,[5,6] cardiometabolic[7] and respiratory outcomes,[8] motor skills,[9–11] social functioning,[12] and educational attainment.[13] With this broad range of possible adverse outcomes, multidisciplinary assessments are warranted. The first generations that survived following improvements in neonatal care of preterm birth in the 1980s are entering mid-adulthood, and there is increasing evidence that the various developmental problems may continue into adulthood.[14,15]

The International Classification of Functioning, Disability and Health (ICF) of the World Health Organization provides a scientific basis for understanding health and health-related states, outcomes and determinants, and changes in health functioning.[16] This model brings forth a framework for better conceptualising the wide-ranging functional outcomes of preterm birth and the factors affecting them.[1] Within the ICF, a person's health functioning is multi-dimensionally related to body functions and structures, activities and participation, and personal and environmental factors. While body functions and structures refer to physiological functions of body systems and the anatomical parts of the body, activities concern the execution of tasks or actions, and participation involvement in a life situation.[16]

The Norwegian University of Science and Technology Low Birth Weight in a Lifetime Perspective (NTNU LBW Life) study was the first to examine the brain in a cohort of preterm children with magnetic resonance imaging (MRI).[17] Furthermore, this prospective cohort study adopted a multidisciplinary approach that enables the long-term consequences of VLBW to be reviewed using the ICF model. In this systematic review, we present a qualitative synthesis of neuroimaging findings and clinical outcomes reported from the NTNU LBW Life study in childhood, adolescence and early adulthood. Within the framework of ICF, this systematic review aimed to describe (1) proportions of adverse outcomes in individuals born preterm with VLBW, (2) mean group differences in outcomes compared with those born at term, and (3) risk factors for adverse outcomes and associations between outcomes.

Synopsis

Study question

Using the International Classification of Functioning, Disability and Health framework, what are the rates of adverse outcomes and mean group differences from infancy to adulthood for those born preterm with VLBW and term in a Norwegian cohort?

What's already known

Being born preterm with VLBW involves a high risk for neurodevelopmental difficulties that may continue into early adulthood.

What this study adds

Multidisciplinary and neuroimaging findings in a well-defined study population from birth to 28 years of age show that being born preterm with VLBW has persistent influences on brain, cognition, mental health, vision, pain, physical health, motor skills, general and social functioning, education and employment, and health-related quality of life representing various components of the International Classification of Functioning, Disability and Health.

2 | METHODS

2.1 | Data sources

A literature search was carried out by the first author (KAIE) in PubMed and Embase in collaboration with the Head librarian at the NTNU University Library. Relevant MeSH terms, Emtree terms and keywords were combined with the site of the study or authors AMB and JS who initiated the study, and MSI and KAIE, leading follow-ups in adolescence and young adulthood. The full search strategy is documented in Table S1.

2.2 | Study selection and data extraction

Inclusion criteria were original peer-reviewed articles published in English reporting results of the VLBW cohort from Trondheim, Norway, born in 1986–1988, in terms of proportions of adverse outcomes, mean values of outcomes compared with controls, risk factors for adverse outcomes or associations between outcomes. Exclusion criteria were systematic reviews or meta-analyses, conference abstracts, editorials, letters and commentaries. KAIE and KADA screened titles and abstracts separately for eligibility. Disagreements were resolved by a discussion between the two reviewers. Next, full text of all included articles was assessed, and key characteristics were extracted, i.e. age at follow-up, aims, methods, reported outcomes, risk factors and associations.

2.3 | Synthesis

A qualitative synthesis of included articles was performed. Several articles presented outcomes within more than one domain or component of the ICF. If more than one article reported the same outcome, we used the results based on the larger sample. Where mean and standard deviation (SD) were given, we calculated group differences in SD units.

We grouped articles by their main outcome according to the two-level classification of the ICF (Table S2).[16] The ICF has two parts, each with two components. Part 1 concerns functioning and disability, with the components of *Body functions and structures* and *Activities and participation*. Part 2 concerns contextual factors with the components of *Environmental factors* and *Personal factors*.[16] Each component consists of various domains. Within *Body functions and structures*, we included outcomes of the brain as a structure of the nervous system and outcomes of cognition and mental health according to the mental functions chapter.[16] We included outcomes of vision and pain according to the chapter on sensory functions and pain, and outcomes of physical health according to chapters on cardiovascular and respiratory systems, and metabolic and endocrine systems, and neuromusculoskeletal and movement-related functions. Within *Activities and participation*, we included outcomes of motor skills according to the mobility chapter, physical activity as self-care, outcomes of general and social functioning according to chapters on general tasks and demands, and interpersonal interactions and relationships. We further included outcomes of education and employment according to the major life areas chapter.[16] Health-related quality of life was classified according to the community, social and civic life chapter and the other chapters of *Activities and participation*, as this is an overarching concept.[18]

We included birthweight, gestational age, perinatal morbidity, i.e. Apgar scores, days to regain birthweight, intraventricular haemorrhage, days on mechanical ventilation and days spent in the neonatal intensive care unit, and sex as *Personal factors* that relate to the individual.[16] Parental socioeconomic status (SES) and parental mental health were included as *Environmental factors*, which refer to all aspects of the external or extrinsic world that form the context of an individual's life and have an impact on that person's functioning.[16]

2.4 | Ethics approval

The NTNU LBW Life study was approved by the Regional Committee for Medical and Health Research Ethics of Central Norway (78–00, 4.2005.2605 and 2013/636).[19]

3 | RESULTS

The search resulted in 735 unique records (Figure 1), whereof 58 articles were eligible for this review, published between 1992 and 2019. Twenty-one articles gave proportions of adverse outcomes, 38 reported mean values compared with controls and 50 reported risk factors or associations between outcomes (Table S3). Forty-nine articles reported main outcomes within *Body functions and structures* and 9 articles within *Activities and participation* (Figure 2).

The NTNU LBW Life study included a preterm born VLBW group, defined by a birthweight ≤1500 g, admitted to the neonatal intensive care unit at St. Olavs Hospital, Trondheim, in 1986–88. A term born control group with birthweight ≥10th percentile adjusted for gestational age, sex and parity, was born to mothers in a 10% random sample of pregnant women residing in the Trondheim area in 1986–88.[19] Eligible for follow-up were 86 of 121 VLBW infants, and 118 of 120 control infants, as 33 VLBW infants died in the neonatal period, and two infants in each group were excluded due to having a diagnosis of a syndrome or congenital anomaly.[19] In the initial follow-ups in childhood, only the 1988 VLBW birth cohort was examined, later supplemented with the 1986 and 1987 VLBW birth cohorts for assessment in adolescence and young adult age.[19] Clinical assessment tools and different qualitative and quantitative MRI modalities used in the included articles are presented in Table 1.

3.1 | Outcomes of body functions and structures

3.1.1 | Brain

There were consistent findings of brain structure pathology from 1–6 years,[20] where the proportions ranged from 29.6% for focal white matter lesions to 77.7% for more diffuse white matter deviations in the VLBW group.[17,21] At 15 years, the proportion with brain structure pathology was substantially higher (Figure 3),[22] and cortical surface area and brain structure volume smaller in the VLBW compared with the control group (Table 2).[23] Also at 20 years, volumes were smaller in the VLBW group.[24] Cortical thickness and surface area decreased correspondingly in both groups from 15 to 20 years.[25] White matter integrity was poorer in the corpus callosum, thalamus, cingulum, internal capsule, occipital white matter and the major white matter tracts in the VLBW group at 15[26] and 20 years.[27]

3.1.2 | Cognition

At 5, 14 and 19 years, full IQ, verbal and performance IQ were lower in the VLBW compared with the control group (Table 2).[19,28–30] An IQ <1SD of the control group mean was seen in about half of the VLBW participants, and IQ <70 was found only in the VLBW group (Figure 3).[28] Poor performance (<2SD) on at least one attention or executive function test was found in three of four VLBW participants at 14 years.[29] Visual-motor integration was poorer at 14[30] and 19 years[31] compared with controls. Memory, attention and executive function test scores were lower in the VLBW than in the control group at 19 years.[32,33]

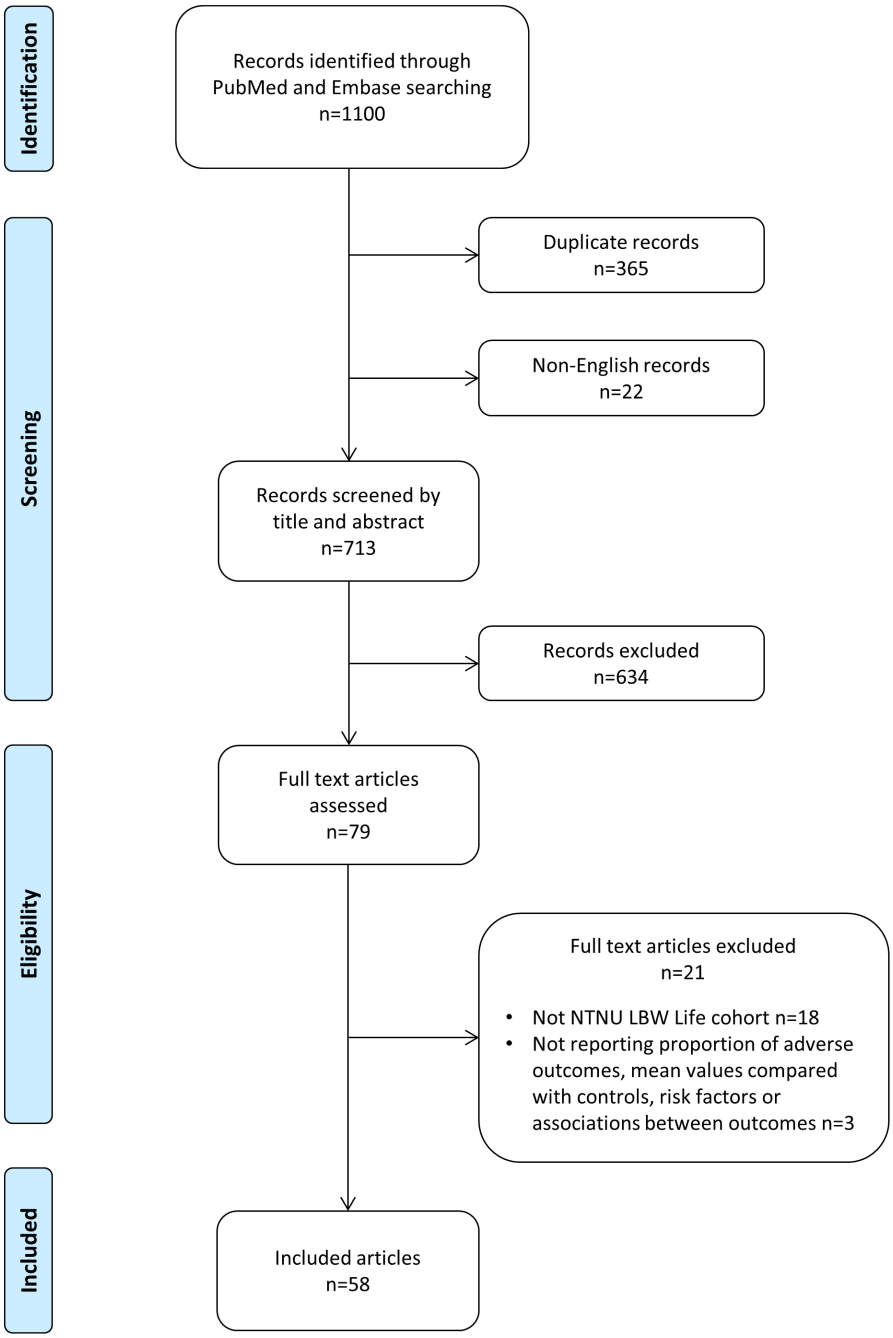

FIGURE 1 Flowchart for selection of articles from the NTNU Low Birth Weight in a Lifetime Perspective study. Abbreviations: NTNU LBW Life, Norwegian University of Science and Technology Low Birth Weight in a Lifetime Perspective study

3.1.3 | Mental health

Using structured clinical interviews, the proportion of psychiatric disorders was higher in the VLBW group at 14,[34] 19[35] and 26 years[36] compared with the control group (Figure 3). High psychiatric morbidity increased from 14 to 19 years[37] and further to 26 years.[36] Anxiety disorders were most prevalent across the ages,[34–36] and mood disorders and body dysmorphic disorder were also present at 26 years.[36] On screening questionnaires, more mental health problems in the VLBW group were reported by mothers and teachers at 14 years (Table 2),[38] and more internalising problems among VLBW participants compared with controls by self-report at 19 years.[39] At 26 years, a higher proportion reported borderline/clinical mental health problems in the VLBW than in the control group (Figure 3).[19] Higher attention screening scores were reported by teachers at 14 years for the VLBW compared with the control group,[34] and attention deficit hyperactivity disorder was diagnosed more often at 19 years.[35] Screening for autism spectrum traits showed a higher parent-reported sum score at 14 years,[34] and self-reported autism spectrum quotient scores were higher at 19[39] and 26 years[19] compared with controls (Table 2 and Figure 3).

3.1.4 | Vision

Near and distance visual acuity were poorer among VLBW participants at 14 years compared with controls (Table 2).[40] A higher

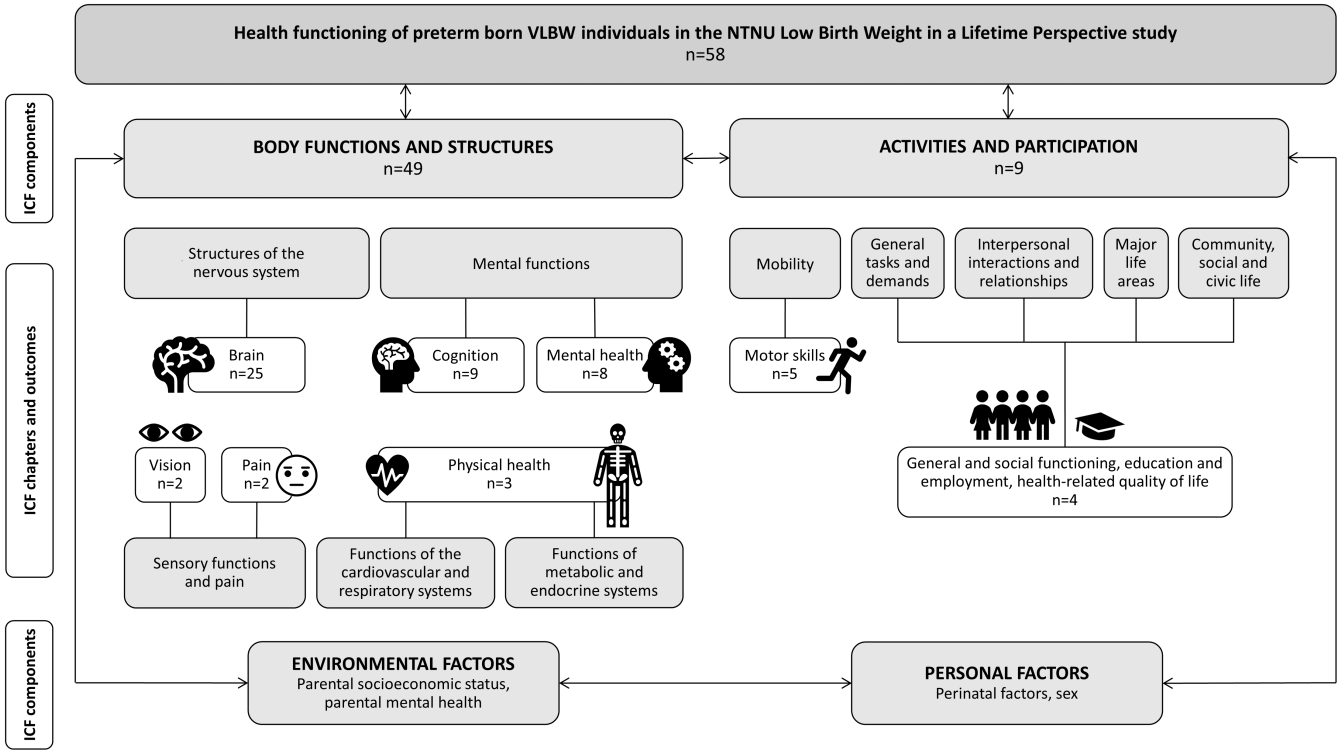

FIGURE 2 Main outcomes reported in articles of the NTNU Low Birth Weight in a Lifetime Perspective study according to the International Classification of Functioning, Disability and Health. Abbreviations: ICF, International Classification of Functioning, Disability and Health; NTNU, Norwegian University of Science and Technology; VLBW, very low birthweight

proportion of VLBW adolescents than controls had poor distance visual acuity and abnormal contrast sensitivity (Figure 3).[40] Poor stereopsis and convergence, latent or manifest strabismus and nystagmus were all more frequent in the VLBW than in the control group.[41] None of the children had received treatment for retinopathy of prematurity.[40]

3.1.5 | Pain

More VLBW participants reported moderate to very severe pain in the past four weeks compared with controls at 19 and 26 years.[42] The prevalence did not increase between these two ages, [42] neither did the prevalence of chronic pain from 26 to 28 years.[43]

3.1.6 | Physical health

The VLBW adolescents were shorter and lighter than controls, but their body mass index did not differ.[44,45] Examination of pulmonary function and cardiorespiratory fitness at 18 years showed that forced expiratory volume and maximal oxygen uptake were lower, and systolic blood pressure higher, in the VLBW group compared with controls.[45] At 26 years, both systolic and diastolic blood pressure were higher in the VLBW group (Table 2).[46] At this age, the proportions of VLBW participants with osteopenia and osteoporosis were higher than among controls (Figure 3).[47] Mean bone mineral content and density[47] and insulin sensitivity were lower, while HbA1c and insulin resistance were higher in the VLBW group.[46]

3.1.7 | Neuromusculoskeletal and movement-related functions

At 14 years of age, 11% of the participating VLBW adolescents had cerebral palsy compared with none of the controls (Figure 3).[44]

3.2 | Outcomes of activities and participation

3.2.1 | Motor skills

Proportions of motor problems were higher (Figure 3) and scores on the standardised motor tests poorer (Table 2) in the VLBW than in the control group at 1, 5 and 14 years.[44,48] This was evident in both total test scores and subscores of manual dexterity, ball skills and balance scores at 14[44] and 23 years.[49] Motor problems at 14 years were predicted by low motor scores at 1 and 5 years,[48] and the proportion of participants with motor problems did not change between 14 and 23 years.[49] Scores on the Grooved Pegboard with both dominant and non-dominant hand were poorer in VLBW

TABLE 1 Clinical assessment tools and neuroimaging modalities used in articles of the NTNU Low Birth Weight in a Lifetime Perspective study according to the International Classification of Functioning, Disability and Health

	Body functions and structures					Activities and participation	
Age at follow-up	Brain	Cognition	Mental health	Sensory functions (vision) and pain	Physical health	Motor skills	General and social functioning, HRQoL
1 year	MRI 1.5T[a], Touwen neurological examination[17]	BSID MDI, DDST Language and Personal/Social[54]			Head circumference, weight[58]	BSID PDI, DDST Fine and Gross motor[54]	
5–6 years	MRI 1.5T[a], Touwen neurological examination[21]	WPPSI-R[21]				Subscales of PDMS[21]	
14–15 years	MRI 1.5T[b],[22,23] DTI, voxel-wise statistical analysis,[26] MRS[81]	Subtests of WISC-III, Knox Cube, CPT, Stroop, WCST, TMT A & B,[29] VMI-IV,[30] dichotic listening[66]	KSADS, ADHD-R, ASSQ,[34] ASEBA CBCL/TRF/YSR, SDQ[38]	Visual acuity, contrast sensitivity,[40] strabismus, convergence, accommodation, stereopsis, nystagmus, saccades, smooth pursuit[41]	Head circumference, height, weight[44]	Movement ABC,[44] GP,[50] Inter- and intramodal matching task [82]	CHQ-CF, CHQ-PF, SCL-90-R,[52] CGAS,[34] PBI[52]
18–20 years	MRI 1.5T[b], FreeSurfer, DTI, TBSS[27]	WAIS-III,[28] BRIEF-A,[83] CPT, Design and Verbal Fluency, TMT 1–5, PASAT, Tower, Stroop,[33] VMI-V,[31] WMS-III[32]	KSADS, ADHD-R,[35] ASEBA ASR, AQ[39]		Head circumference, height, weight, waist circumference, skinfold thickness, blood pressure[c], flow-mediated dilatation of brachial artery, spirometry, maximal oxygen uptake[45]		CGAS,[35] SPPA-R, SF-36[39]
23 years	MRI 3T[d], FreeSurfer, DTI,[67] fMRI,[56] EEG[e84]	Adapted Not X-CPT for fMRI,[56] adapted cued go/no-go task for EEG[84]	ASEBA ASR, BDI[53]		Head circumference, height, weight[49]	Movement ABC-2, GP, TMT 5, HiMAT[49]	SF-36[53]

(Continues)

TABLE 1 (Continued)

	Body functions and structures					Activities and participation	
Age at follow-up	Brain	Cognition	Mental health	Sensory functions (vision) and pain	Physical health	Motor skills	General and social functioning, HRQoL
26–28 years	MRI 3T[f], FreeSurfer, DTI, TRACULA[85]		M.I.N.I. Plus,[36] ASEBA ASR, AQ, PDI-21[19]	Self-report of pain,[42,43] quantitative sensory testing[43]	Height, weight, waist and hip circumference, skinfold thickness, blood pressure[c,46] DXA[g,47] glucose metabolites, lipid profile[46]		GAF[36]

Abbreviations: ADHD-R, Attention Deficit Hyperactivity Disorder Rating Scale—Fourth edition; AQ, autism spectrum quotient; ASEBA, Achenbach System of Empirically Based Assessment; ASR, Adult Self-Report; ASSQ, Autism Spectrum Screening Questionnaire; BDI, Beck Depression Inventory; BRIEF-A, Behaviour Rating Inventory of Executive Function—Adult version; BSID, Bayley Scales of Infant Development; CBCL, Child Behaviour Checklist; CF, Child Form; CGAS, Children's Global Assessment Scale; CHQ, Child Health Questionnaire; CPT, Conners Continuous Performance Test; DDST, Denver Developmental Screening Test; DTI, diffusion tensor imaging; DXA, dual x-ray absorptiometry; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; GAF, Global Assessment of Functioning; GP, Grooved Pegboard; HiMAT, High-Level Mobility Assessment Tool; HRQoL, health-related quality of life; KSADS, Kiddie Schedule for Affective Disorders and Schizophrenia; M.I.N.I. Plus, Mini-International Neuropsychiatric Interview; MDI, Mental Development Index; Movement ABC-2, Movement Assessment Battery for Children—Second edition; Movement ABC, Movement Assessment Battery for Children; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NTNU, Norwegian University of Science and Technology; PASAT, Paced Auditory Serial Addition Test; PBI, Parental Bonding Instrument; PDI-21, The 21-item Peters et al. Delusions Inventory; PDI, Psychomotor Development Index; PDMS, Peabody Developmental Motor Scales; PF, Parent Form; SCL-90-R, Symptom Checklist-90-Revised; SDQ, Strengths and Difficulties Questionnaire; SF-36, Short Form 36 Health Survey; SPPA-R, Self-Perception Profile for Adolescents—Revised; Stroop, Stroop Color and Word Test; TBSS, Tract-based spatial statistics; TMT, Trail Making Test; TRACULA, TRActs Constrained by UnderLying Anatomy; TRF, Teacher Report Form; VMI-IV, Beery-Buktenica Developmental Test of Visual-Motor Integration—Fourth edition; VMI-V, Beery-Buktenica Developmental Test of Visual-Motor Integration— Fifth edition; WAIS-III, Wechsler Adult Intelligence Scale—Third edition; WCST, Wisconsin Card Sorting Test; WISC-III, Wechsler Intelligence Scale for Children—Third edition; WMS-III, Wechsler Memory Scale—Third edition; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence—Revised; YSR, Youth Self-Report.

[a]Phillips Gyroscan S 15.

[b]Siemens Magneton Symphony Sonata.

[c]Criticare 507N.

[d]Siemens Trio.

[e]21-channel Mitsar EEG system.

[f]Siemens Skyra.

[g]Hologic Discovery A S/N 83817.

adolescents[50] and young adults.[49] At 23 years, the VLBW participants also had poorer performance in more advanced gross motor skills.[49]

3.2.2 | Physical activity

At 26 years, VLBW participants reported less physical activity and exercise intensity than controls (Table 2).[46]

3.2.3 | General and social functioning

At 14 years, the odds of having suboptimal general functioning, i.e. scores <80 on the Children's Global Assessment Scale, were almost eight times increased in the VLBW compared with the control group,[34] and the odds of being bullied were six times increased.[51] Scores of general functioning were lower at 14, 19 and 26 years (Table 2).[34–36]

The VLBW adolescents and their mothers reported lower social competence at 14 years[38] and lower friends score at 19 years[39] compared with controls. At this age, they also reported lower self-esteem for athletic competence.[39]

3.2.4 | Education and employment

At 14 years, one-third of the VLBW adolescents received special educational services at school and lower scores for academic performance were reported by the adolescents themselves, their mothers and teachers.[38] Almost half of the 19-year-old VLBW participants, twice as many as the controls, were in vocational education and training instead

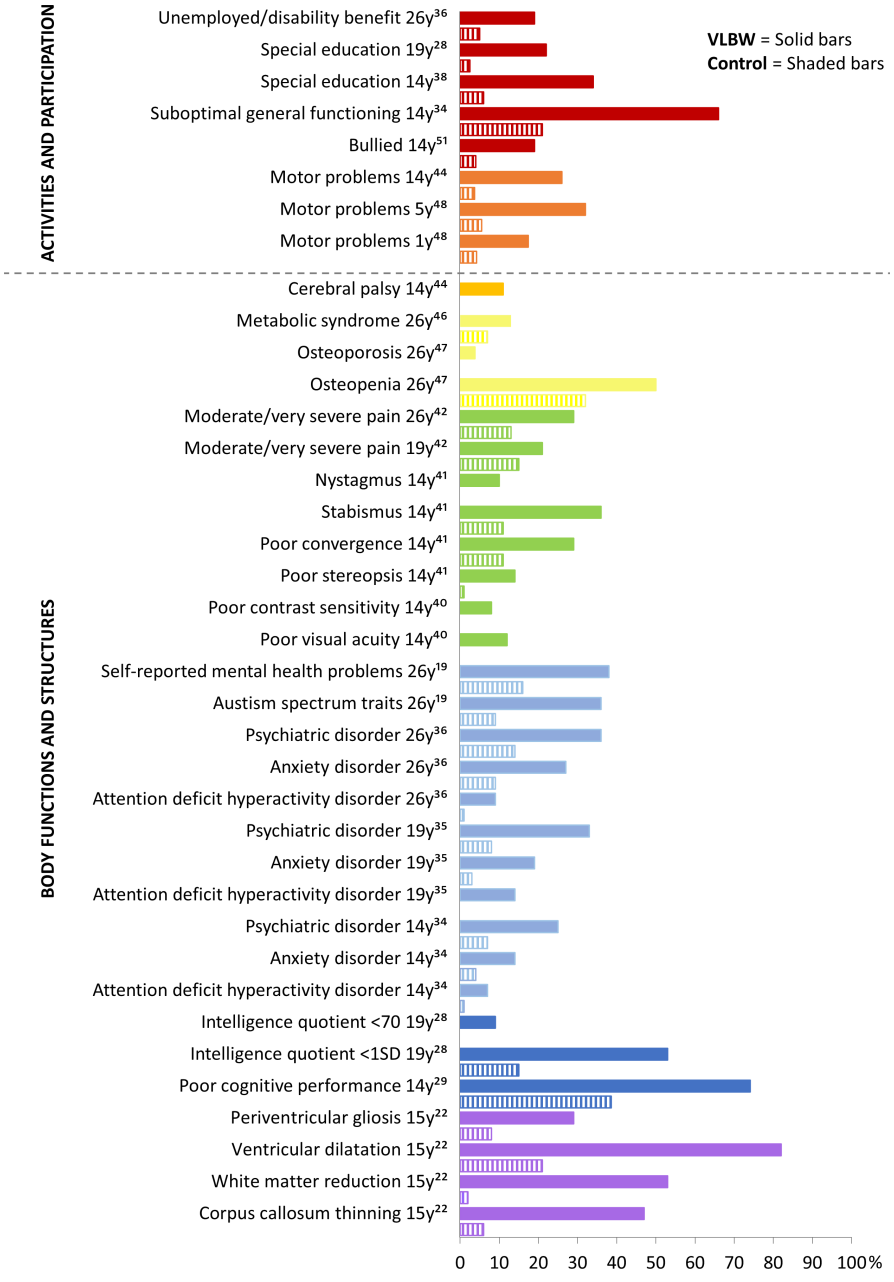

FIGURE 3 Proportions of adverse outcomes reported in articles of the NTNU Low Birth Weight in a Lifetime Perspective study in the VLBW (solid bars) and control group (shaded bars) according to the International Classification of Functioning, Disability and Health. Abbreviations: NTNU, Norwegian University of Science and Technology; SD, standard deviation; VLBW, very low birthweight

TABLE 2 Mean values (SD) of outcomes reported in articles of the NTNU Low Birth Weight in a Lifetime Perspective study according to the International Classification of Functioning, Disability and Health

	Number (% male)		Age in years (SD)			Mean (SD)				
Citation	VLBW	Control	VLBW	Control	Outcome	VLBW		Control		SD difference
Body functions and structures										
Brain										
Martinussen et al. 2005[23]	50 (52)	58 (38)	15.2 (0.6)	15.5 (0.5)	Cortical surface area right hemisphere (cm^2)	815	(96)	885	(81)	−0.86
					Cortical surface area left hemisphere (cm^2)	814	(96)	879	(81)	−0.80
					Cortical thickness right hemisphere (mm)	2.13	(0.09)	2.16	(0.09)	−0.33
					Cortical thickness left hemisphere (mm)	2.13	(0.09)	2.17	(0.09)	−0.44
					Cortical volume right hemisphere (cm^3)	173	(21)	191	(20)	−0.90
					Cortical volume left hemisphere (cm^3)	174	(22)	190	(20)	−0.80
Martinussen et al. 2009[30]	50 (52)	57 (39)	15.2 (0.6)	15.5 (0.5)	Total intracranial volume (cm^3)	1470	(163)	1548	(118)	−0.66
					Cerebral grey matter volume (cm^3)	592	(70)	626	(56)	−0.61
					Cerebral white matter volume (cm^3)	380	(64)	413	(43)	−0.77
					Hippocampus volume (cm^3)	7.7	(0.9)	8.3	(0.8)	−0.75
					Amygdale volume (cm^3)	3.3	(0.4)	3.5	(0.3)	−0.67
					Thalamus volume (cm^3)	16	(2.3)	19	(1.5)	−2.00
					Cerebellar grey matter volume (cm^3)	118	(13)	124	(11)	−0.55
					Cerebellar white matter volume (cm^3)	22	(3.6)	25	(3.0)	−1.00
Skranes et al. 2012[50]	49 (51)	58 (40)	15.1 (0.6)	15.3 (0.5)	Thickness entorhinal cortex left hemisphere (mm)	2.39	(0.27)	2.63	(0.28)	−0.86
					Thickness entorhinal cortex right hemisphere (mm)	2.36	(0.29)	2.56	(0.34)	−0.59
Botellero et al. 2016[69]	44 (41)	60 (42)	19 years 7 months	19 years 8 months	Cerebellar white matter (ml)	26.60	(4.03)	29.83	(3.10)	−1.04
			(7 months)	(6 months)	Cerebellar grey matter (ml)	96.59	(11.14)	103.57	(8.85)	−0.79
Botellero et al. 2017[70]	44 (41)	60 (42)	19 years 7 months	19 years 8 months	Cingulum (ml)	20.64	(3.16)	23.07	(2.79)	−0.87
			(7 months)	(6 months)	Frontal cortex (ml)	117.39	(28.83)	190.93	(16.94)	−4.34
					Insula (ml)	12.79	(2.25)	13.83	(1.39)	−0.75
					Occipital cortex (ml)	46.79	(6.66)	49.08	(4.52)	−0.51
					Parietal cortex (ml)	110.68	(14.41)	124.54	(11.04)	−1.26
					Temporal cortex (ml)	107.64	(16.65)	120.15	(11.65)	−1.07
					Thalamus (ml)	13.24	(1.81)	15.30	(1.32)	−1.56
					Subcortical grey matter (ml)	44.12	(5.03)	48.22	(3.96)	−1.04

TABLE 2 (Continued)

Citation	Number (% male)		Age in years (SD)		Outcome	Mean (SD)				SD difference
	VLBW	Control	VLBW	Control		VLBW		Control		
Vangberg et al. 2006[26]	34 (47)	47 (38)	15.2 (0.7)	15.5 (0.5)	FA Posterior limb of internal capsule left hemisphere	0.28	(0.03)	0.31	(0.02)	−1.50
					FA Posterior limb of internal capsule right hemisphere	0.36	(0.07)	0.46	(0.05)	−2.00
					FA Thalamus left hemisphere	0.27	(0.04)	0.32	(0.03)	−1.67
					FA Thalamus right hemisphere	0.28	(0.04)	0.34	(0.03)	−2.00
					FA Cingulum left hemisphere	0.36	(0.08)	0.48	(0.07)	−1.71
					FA Cingulum right hemisphere	0.46	(0.08)	0.56	(0.05)	−2.00
					FA Corpus callosum (splenium) left hemisphere	0.44	(0.12)	0.57	(0.07)	−1.86
					FA Corpus callosum (splenium) right hemisphere	0.57	(0.10)	0.69	(0.06)	−2.00
					FA Corpus callosum (genu) left hemisphere	0.60	(0.07)	0.64	(0.06)	−0.67
					FA Corpus callosum (genu) right hemisphere	0.54	(0.07)	0.59	(0.05)	−1.00
					FA Occipital white matter left hemisphere	0.40	(0.07)	0.46	(0.05)	−1.20
					FA Occipital white matter right hemisphere	0.42	(0.07)	0.47	(0.06)	−0.83
					FA Superior longitudinal fasciculus left hemisphere	0.26	(0.04)	0.32	(0.06)	−1.00
					FA Superior longitudinal fasciculus right hemisphere	0.28	(0.06)	0.35	(0.06)	−1.17
					FA Arcuate fasciculus left hemisphere	0.27	(0.06)	0.35	(0.07)	−1.14
					FA Arcuate fasciculus right hemisphere	0.34	(0.06)	0.39	(0.05)	−1.00
Eikenes et al. 2011[27]	49 (41)	59 (37)	20.2 (0.8)	20.3 (0.5)	FA Corpus callosum (genu) left hemisphere	0.64	(0.06)	0.66	(0.04)	−0.50
					FA Corpus callosum (genu) right hemisphere	0.64	(0.07)	0.67	(0.05)	−0.60
					FA Corpus callosum (splenium) left hemisphere	0.74	(0.07)	0.78	(0.03)	−1.33
					FA Corpus callosum (splenium) right hemisphere	0.72	(0.07)	0.76	(0.02)	−2.00
					FA Corpus callosum (body)	0.64	(0.06)	0.68	(0.04)	−1.00
					FA External capsule left hemisphere	0.35	(0.03)	0.37	(0.03)	−0.67
					FA External capsule right hemisphere	0.36	(0.03)	0.38	(0.02)	−1.00
					FA Superior longitudinal fasciculus left hemisphere	0.34	(0.02)	0.38	(0.02)	−2.00
					FA Superior longitudinal fasciculus right hemisphere	0.35	(0.03)	0.38	(0.03)	−1.00
					FA Fornix body	0.31	(0.07)	0.37	(0.04)	−1.50
					FA Fornix left hemisphere	0.39	(0.03)	0.42	(0.02)	−1.50
					FA Fornix right hemisphere	0.40	(0.03)	0.43	(0.02)	−1.50
					FA Cingulum left hemisphere	0.30	(0.06)	0.34	(0.05)	−0.80
					FA Cingulum right hemisphere	0.29	(0.05)	0.32	(0.05)	−0.60

(Continues)

TABLE 2 (Continued)

Citation	Number (% male)		Age in years (SD)		Outcome	Mean (SD)				SD difference
	VLBW	Control	VLBW	Control		VLBW		Control		
Hollund et al. 2018[67]	31 (35)	31 (42)	22.5 (0.7)	22.7 (0.7)	FA CST Noncrossing fibres dominant hand area	0.575	(0.038)	0.589	(0.030)	−0.47
					FA CST Crossing fibres dominant hand area	0.430	(0.040)	0.413	(0.030)	0.57
					FA CST Noncrossing fibres nondominant hand area	0.572	(0.037)	0.596	(0.037)	−0.65
					FA CST Crossing fibres nondominant hand area	0.440	(0.039)	0.423	(0.025)	0.68
					FA CST Noncrossing fibres dominant foot area	0.584	(0.039)	0.600	(0.033)	−0.48
					FA CST Crossing fibres dominant foot area	0.459	(0.045)	0.443	(0.030)	0.53
					FA CST Noncrossing fibres nondominant foot area	0.587	(0.040)	0.609	(0.031)	−0.71
					FA CST Crossing fibres nondominant foot area	0.468	(0.043)	0.442	(0.026)	1.00
					FA CST Noncrossing fibres dominant premotor area	0.552	(0.040)	0.568	(0.031)	−0.52
					FA CST Crossing fibres dominant premotor area	0.428	(0.027)	0.418	(0.024)	0.42
					FA CST Noncrossing fibres nondominant premotor area	0.544	(0.033)	0.544	(0.042)	0.00
					FA CST Crossing fibres nondominant premotor area	0.434	(0.025)	0.424	(0.019)	0.53
					FA CC Noncrossing fibres motor area	0.448	(0.049)	0.469	(0.039)	−0.54
					FA CC Crossing fibres motor area	0.492	(0.042)	0.499	(0.284)	−0.02
					FA CC Noncrossing fibres premotor area	0.495	(0.030)	0.495	(0.037)	0.00
					FA CC Crossing fibres premotor area	0.444	(0.034)	0.488	(0.032)	−1.38
Cognition										
Lærum et al. 2019[19]	21 (n/r)	75 (n/r)	5 (n/r)	5 (n/r)	Full scale IQ	94.9	(16.6)	108.0	(12.7)	−1.03
Kulseng et al. 2006[29]	54 (n/r)	83 (n/r)	14.1 (0.3)	14.2 (0.3)	Knox Cube (trial 1)	12.8	(2.3)	13.9	(2.0)	−0.55
					Knox Cube (trial 2)	12.1	(2.5)	13.6	(1.9)	−0.79
					CPT Hit reaction time	355.9	(74.5)	328.4	(46.5)	0.59
					Stroop Color names	21.9	(13.5)	18.3	(3.3)	1.09
					Stroop Colors of rectangles	30.0	(13.8)	23.9	(4.5)	1.36
					Stroop Interference	58.7	(24.9)	50.5	(11.4)	0.72
					TMT A	19.1	(7.8)	15.4	(6.1)	0.61
					TMT B	46.7	(22.0)	31.9	(18.6)	0.80
					WCST Errors of preservation	18.7	(11.5)	12.3	(8.1)	0.79
					WCST Nonperseverative errors	23.9	(15.7)	14.8	(10.2)	0.89
					Estimated total IQ (2 subtests)	86.4	(19.9)	97.1	(14.3)	−0.75

TABLE 2 (Continued)

Citation	Number (% male)		Age in years (SD)		Outcome	Mean (SD)				SD difference
	VLBW	Control	VLBW	Control		VLBW		Control		
Martinussen et al. 2009[30]	50 (52)	57 (39)	15.2 (0.6)	15.5 (0.5)	Estimated verbal IQ	82	(19)	93	(16)	−0.69
					Estimated performance IQ	81	(28)	101	(19)	−1.05
					VMI-IV	20	(4)	23	(3)	−1.00
					VMI-IV motor coordination	21	(3)	24	(2)	−1.50
					VMI-IV visual perception	23	(4)	25	(3)	−0.67
Løhaugen et al. 2010[28]	55 (55)	81 (52)	19 years 2 months	19 years 2 months	Full scale IQ	88	(13)	101	(12)	−1.08
			(11 months)	(8 months)	Verbal IQ	87	(11)	98	(12)	−0.92
					Performance IQ	91	(16)	104	(12)	−1.08
Sripada et al. 2015[31]	47 (43)	56 (38)	19.7 (0.9)	19.7 (0.6)	VMI-V	24.6	(3.6)	26.7	(2.4)	−0.87
					VMI-V Motor coordination	27.4	(2.7)	29.2	(1.8)	−1.00
					VMI-V Visual perception	27.6	(2.0)	27.9	(2.3)	−0.13
Aasen et al. 2016[84]	30 (40)	33 (45)	22.0 (0.8)	22.1 (0.8)	Adapted cued go/no-go task Reaction time	355.8	(44.2)	348.0	(40.9)	0.19
					Adapted cued go/no-go task SD of reaction time	81.44	(24.4)	75.58	(21.4)	0.27
					Adapted cued go/no-go task Omission	3.40	(4.3)	1.42	(1.6)	1.24
					Adapted cued go/no-go task Commission	0.87	(1.5)	0.64	(1.0)	0.23
Mental health										
Indredavik et al. 2004[34]	56 (54)	83 (42)	14.1 (0.3)	14.2 (0.3)	ADHD-R Attention score (teacher-report)	7.1	(6.0)	3.8	(5.9)	0.56
					ADHD-R Hyperactivity score (teacher-report)	2.7	(4.4)	2.1	(4.4)	0.14
					ADHD-R Total score (teacher-report)	9.8	(9.0)	5.9	(10.0)	0.39
					ASSQ Sum score	5.5	(5.9)	2.0	(2.7)	1.30
Indredavik et al. 2005[38]	56 (54)	83 (42)	14.1 (n/r)	14.2 (n/r)	ASEBA YSR Internalising problems	6.9	(5.5)	7.3	(5.9)	−0.07
					ASEBA YSR Externalising problems	7.4	(4.8)	8.2	(5.6)	−0.14
					ASEBA YSR Total problems	23.8	(15.0)	24.9	(15.6)	−0.07
					ASEBA CBCL Internalising problems (mother-report)	6.2	(6.0)	3.3	(3.7)	0.78
					ASEBA CBCL Externalising problems (mother-report)	5.5	(8.4)	2.4	(2.9)	1.07
					ASEBA CBCL Total problems (mother-report)	19.2	(16.3)	8.7	(8.3)	1.27
					ASEBA TRF Internalising problems	7.3	(7.2)	2.9	(3.3)	1.33
					ASEBA TRF Externalising problems	4.2	(5.8)	3.7	(7.2)	0.07
					ASEBA TRF Total problems	22.1	(18.0)	12.3	(16.9)	0.58
					SDQ Total difficulties (self-report)	8.1	(5.0)	7.5	(4.9)	0.12
					SDQ Total difficulties (mother-report)	8.6	(6.5)	3.4	(2.9)	1.79
					SDQ Total difficulties (teacher-report)	7.1	(4.9)	4.1	(4.2)	0.71

(Continues)

TABLE 2 (Continued)

Citation	Number (% male)		Age in years (SD)		Outcome	Mean (SD)				SD difference
	VLBW	Control	VLBW	Control		VLBW		Control		
Lund et al. 2012[39]	43 (40)	74 (42)	19.5 (0.6)	19.7 (0.5)	ASEBA ASR Internalising problems	11.6	(10.7)	7.4	(7.3)	0.58
					ASEBA ASR Externalising problems	7.7	(6.1)	6.7	(5.9)	0.17
					ASEBA ASR Total problems	35.5	(24.4)	27.8	(20.8)	0.37
					AQ Total score	15.4	(4.6)	13.1	(5.1)	0.45
Husby et al. 2016[53]	35 (40)	37 (41)	22.5 (0.7)	22.7 (0.6)	ASEBA ASR Critical items	4.6	(3.4)	2.8	(2.7)	0.67
					ASEBA ASR Internalising problems	12.9	(9.4)	8.6	(7.7)	0.56
					ASEBA ASR Externalising problems	8.3	(6.0)	6.6	(5.7)	0.30
					ASEBA ASR Total problems	38.6	(21.7)	29.0	(18.6)	0.52
Lærum et al. 2019[19]	61 (54)	88 (43)	26.4 (0.7)	26.5 (0.5)	ASEBA ASR Critical items	3.3	(3.5)	1.8	(2.0)	0.75
					ASEBA ASR Internalising problems	11.8	(10.8)	7.1	(6.7)	0.70
					ASEBA ASR Externalising problems	6.8	(6.6)	3.9	(4.0)	0.73
					ASEBA ASR Total problems	34.0	(24.5)	21.6	(17.4)	0.71
					AQ Sum score	15.5	(6.3)	12.3	(5.3)	0.60
					PDI-21 Grand Total	15.7	(21.2)	11.3	(16.5)	0.27
Vision										
Lindqvist et al. 2007[40]	51 (55)	77 (42)	14.5 (0.4)	14.6 (0.5)	Distance visual acuity (best correction), both eyes	1.17	(0.27)	1.30	(0.19)	−0.68
					Near visual acuity (best correction), both eyes	0.91	(0.27)	1.02	(0.24)	−0.46
Pain										
Iversen et al. 2018[43]	51 (49)	86 (44)	28.3 (range 27.3–29.9)	28.5 (range 27.6–29.7)	Upper cool detection threshold (°C)	1.3	(0.5)	1.4	(0.7)	−0.14
					Lower cool detection threshold (°C)	2.6	(1.5)	2.5	(1.0)	0.10
					Upper warmth detection threshold (°C)	2.5	(1.0)	2.3	(0.8)	0.25
					Lower warmth detection threshold (°C)	5.5	(3.1)	5.1	(2.6)	0.15
					Upper cold pain threshold (°C)	17.0	(8.1)	18.1	(7.9)	−0.14
					Lower cold pain threshold (°C)	19.4	(7.6)	20.2	(7.8)	−0.10
					Upper heat pain threshold (°C)	12.8	(3.7)	13.4	(3.5)	−0.17
					Lower heat pain threshold (°C)	14.1	(3.2)	14.1	(2.7)	0.00
					Upper pressure pain threshold (kPa)	949	(231)	985	(215)	−0.17
					Lower pressure pain threshold (kPa)	719	(229)	751	(203)	−0.16
Physical health										
Evensen et al. 2004[44]	54 (54)	83 (42)	14.1 (0.3)	14.2 (0.3)	Head circumference (cm)	54.3	(1.9)	55.9	(1.5)	−1.07
					Height (cm)	161	(9.3)	167	(7.6)	−0.79
					Weight (kg)	49.9	(12.1)	56.8	(10.7)	−0.64
					Body mass index (kg/m^2)	19.1	(3.9)	20.2	(3.0)	−0.37

TABLE 2 (Continued)

Citation	Number (% male)		Age in years (SD)		Outcome	Mean (SD)				SD difference
	VLBW	Control	VLBW	Control		VLBW		Control		
Husby et al. 2013[49]	36 (42)	37 (41)	22.5 (0.7)	22.7 (0.6)	Head circumference (cm)	56.0	(1.8)	57.4	(1.7)	−0.82
					Height (cm)	168.8	(9.4)	173.2	(10.7)	−0.41
					Weight (kg)	66.6	(14.0)	73.5	(15.7)	−0.44
					Body mass index (kg/m^2)	23.3	(4.2)	24.4	(3.8)	−0.29
Balasuriya et al. 2018[46]	55 (49)	75 (47)	26.4 (0.6)	26.5 (0.4)	Weight (kg)	72.8	(16.2)	75.9	(15.4)	−0.20
					Body mass index (kg/m^2)	24.7	(5.1)	24.6	(4.3)	0.02
					Waist circumference (cm)	86.2	(12.0)	84.9	(11.2)	0.12
					Body fat (%)	25.0	(9.2)	23.8	(7.8)	0.15
					Systolic blood pressure (mmHg)	125.7	(13.3)	119.3	(12.3)	0.52
					Diastolic blood pressure (mmHg)	71.9	(7.6)	68.6	(7.1)	0.46
					Fasting glucose mmol/L	5.00	(0.44)	4.92	(0.39)	0.21
					HbA1c (%)	5.21	(0.26)	5.09	(0.27)	0.44
					Insulin sensitivity (HOMA2-IS)	70.9	(25.9)	86.0	(35.4)	−0.43
					Total cholesterol	4.24	(0.85)	4.17	(0.81)	0.09
					Metabolic syndrome score	186	(17)	179	(17)	0.41
Activities and participation										
Motor skills										
Evensen et al. 2009[48]	23 (52); 25 (64)	71 (45); 73 (47)	12.3 months (0.3 months); 5.8 (0.3)	13.3 months (0.6 months); 5.3 (0.3)	BSID PDI 1 years	100.3	(17.5)	108.9	(12.0)	−0.72
					PDMS Eye/hand coordination 5 years	79.0	(5.6)	80.7	(3.3)	−0.52
					PDMS Balance 5 years	56.8	(5.4)	59.1	(4.3)	−0.53
					PDMS Locomotor 5 years	100.6	(11.5)	105.9	(5.4)	−0.98
Evensen et al. 2004[44]	54 (54)	83 (42)	14.1 (0.3)	14.2 (0.3)	Movement ABC Manual dexterity	2.5	(2.9)	1.2	(1.6)	0.81
					Movement ABC Ball skills	2.7	(2.5)	1.6	(1.9)	0.58
					Movement ABC Static/dynamic balance	5.7	(4.0)	3.5	(2.9)	0.76
					Movement ABC Total score	11.0	(7.8)	6.3	(4.4)	1.07
Skranes et al. 2012[50]	49 (51)	58 (40)	14.2 (0.3)	14.2 (0.3)	GP Dominant hand (s)	79.8	(48)	65.1	(8)	1.84
					GP Nondominant hand (s)	89.7	(43)	73.5	(11)	1.47

(Continues)

TABLE 2 (Continued)

Citation	Number (% male)		Age in years (SD)		Outcome	Mean (SD)				SD difference
	VLBW	Control	VLBW	Control		VLBW		Control		
Husby et al. 2013[49]	36 (42)	37 (41)	22.5 (0.7)	22.7 (0.6)	GP Dominant hand (s)	70.7	(19.0)	62.2	(9.5)	0.89
					GP Nondominant hand (s)	80.6	(35.1)	68.3	(10.6)	1.16
					TMT 5 Motor speed (s)	28.6	(10.8)	19.9	(5.6)	1.55
					Movement ABC-2 Manual dexterity	24.5	(8.6)	28.2	(5.4)	−0.69
					Movement ABC-2 Aiming and catching	17.1	(5.0)	19.3	(4.6)	−0.48
					Movement ABC-2 Balance	28.1	(9.4)	32.6	(3.9)	−1.15
					Movement ABC-2 Total score	69.7	(20.2)	80.2	(8.7)	−1.21
					HiMAT 8-item score	26.0	(6.1)	29.3	(2.5)	−1.32
					HiMAT Total score	44.9	(7.9)	49.6	(3.4)	−1.38
Physical activity										
Balasuriya et al. 2018[46]	55 (49)	75 (47)	26.4 (0.6)	26.5 (0.4)	Daily physical activity (min)	18	(22)	29	(26)	−0.42
					Average exercise intensity (Borg's rating scale)	13.0	(6.4)	15.0	(4.9)	−0.41
General and social functioning										
Indredavik et al. 2004[34]	56 (54)	83 (42)	14.1 (0.3)	14.2 (0.3)	CGAS score	72.8	(16.5)	85.3	(8.2)	−1.52
Lund et al. 2011[35]	44 (39)	75 (43)	19.5 (0.6)	19.7 (0.5)	CGAS score	76	(14)	86	(8)	−1.25
Lærum et al. 2017[36]	44 (48)	81 (47)	26.3 (0.7)	26.5 (0.5)	GAF Function score	78.5	(18.4)	87.4	(8.7)	−1.02
					GAF Symptom score	79.3	(16.1)	86.4	(10.3)	−0.69
Indredavik et al. 2005[38]	56 (54)	83 (42)	14.1 (n/r)	14.2 (n/r)	ASEBA YSR Social	6.3	(1.8)	7.5	(1.4)	−0.86
					ASEBA CBCL Social (mother-report)	6.0	(2.2)	7.3	(1.5)	−0.87
Lund et al. 2012[39]	43 (40)	74 (42)	19.5 (0.6)	19.7 (0.5)	SPPA-R Athletic competence	2.3	(0.7)	2.8	(0.6)	−0.83
					SPPA-R Physical appearance	2.8	(0.8)	2.8	(0.7)	0.00
					SPPA-R Social acceptance	3.4	(0.5)	3.5	(0.4)	−0.25
					SPPA-R Romantic appeal	2.7	(0.6)	2.9	(0.5)	−0.40
					SPPA-R Close friends	3.4	(0.6)	3.6	(0.4)	−0.50
					SPPA-R Global self-worth	3.1	(0.8)	3.1	(0.5)	0.00
					ASEBA ASR Friends	10.3	(1.7)	11.1	(1.1)	−0.73
Husby et al. 2016[53]	35 (40)	37 (41)	22.5 (0.7)	22.7 (0.6)	ASEBA ASR Friends	10.0	(2.1)	10.8	(1.4)	−0.57
Education										
Indredavik et al. 2005[38]	56 (54)	83 (42)	14.1 (n/r)	14.2 (n/r)	ASEBA YSR Academic performance	1.7	(0.6)	2.2	(0.4)	−1.25
					ASEBA CBCL Academic performance (mother-report)	1.8	(0.7)	2.2	(0.4)	−1.00
					ASEBA TRF Academic performance	2.8	(0.8)	3.3	(0.6)	−0.83

TABLE 2 (Continued)

Citation	Number (% male)		Age in years (SD)		Outcome	Mean (SD)				SD difference
	VLBW	Control	VLBW	Control		VLBW		Control		
Lund et al. 2012[39]	43 (40)	74 (42)	19.5 (0.6)	19.7 (0.5)	SPPA-R School competence	2.9	(0.6)	3.0	(0.6)	−0.17
Health-related quality of life										
Indredavik et al. 2005[52]	56 (54)	83 (42)	14.1 (0.3)	14.2 (0.3)	CHQ-CF Global health	77.6	(21.3)	82.0	(17.9)	−0.25
					CHQ-PF Global health	81.8	(15.5)	86.7	(17.1)	−0.29
					CHQ-PF Physical health sum	48.2	(13.4)	50.2	(9.4)	−0.21
					CHQ-PF Psychosocial health sum	40.2	(17.0)	50.8	(7.6)	−1.39
Lund et al. 2012[39]	43 (40)	74 (42)	19.5 (0.6)	19.7 (0.5)	SF-36 Physical functioning	90.2	(20.4)	95.5	(10.1)	−0.52
					SF-36 Role-physical	89.0	(19.1)	91.1	(22.2)	−0.09
					SF-36 Bodily pain	80.2	(22.6)	80.2	(22.5)	0.00
					SF-36 Social functioning	91.0	(12.6)	92.6	(13.1)	−0.12
					SF-36 Role emotional	87.6	(24.2)	90.9	(23.7)	−0.14
					SF-36 Vitality	50.1	(19.1)	56.2	(14.2)	−0.43
					SF-36 General health	79.3	(17.8)	78.7	(19.8)	0.03
					SF-36 Mental health	73.6	(15.0)	79.2	(11.9)	−0.47
Husby et al. 2016[53]	35 (40)	37 (41)	22.5 (0.7)	22.7 (0.6)	SF-36 Physical functioning	90.4	(13.6)	96.6	(5.9)	−1.05
					SF-36 Role-physical	80.0	(30.8)	96.4	(10.7)	−1.53
					SF-36 Bodily pain	68.7	(28.3)	82.0	(18.3)	−0.73
					SF-36 Social functioning	86.1	(16.5)	94.3	(13.3)	−0.62
					SF-36 Role emotional	78.1	(33.3)	95.2	(20.0)	−0.86
					SF-36 Vitality	49.2	(14.2)	54.9	(13.2)	−0.43
					SF-36 General health	72.1	(18.9)	66.8	(20.0)	0.27
					SF-36 Mental health	70.6	(16.8)	77.4	(13.2)	−0.52
					SF-36 Physical component summary	47.8	(5.9)	51.2	(4.1)	−0.83
					SF-36 Mental component summary	45.2	(8.4)	49.7	(6.4)	−0.70

Abbreviations: ADHD-R, Attention Deficit Hyperactivity Disorder Rating Scale—Fourth edition; AQ, autism spectrum quotient; ASEBA, Achenbach System of Empirically Based Assessment; ASR, Adult Self-Report; ASSQ, Autism Spectrum Screening Questionnaire; BSID, Bayley Scales of Infant Development; CBCL, child behaviour checklist; CC, corpus callosum; CF, child form; CGAS, Children's Global Assessment Scale; CHQ, Child Health Questionnaire; CPT, Conners Continuous Performance Test; CST, corticospinal tract; FA, fractional anisotropy; GAF: Global Assessment of Functioning; GP, Grooved Pegboard; HiMAT, High-Level Mobility Assessment Tool; IQ, intelligence quotient; Movement ABC, Movement Assessment Battery for Children; Movement ABC-2, Movement Assessment Battery for Children—Second edition; n/r, no report; NTNU, Norwegian University of Science and Technology; PDI, Psychomotor Development Index; PDI-21, Peters et al. Delusions Inventory; PDMS, Peabody Developmental Motor Scales; PF, Parent Form; SD, standard deviation; SDQ, Strengths and Difficulties Questionnaire; SF-36, Short Form 36 Health Survey; SPPA-R, Self-Perception Profile for Adolescents—Revised; Stroop, Stroop Color and Word Test; TMT, Trail Making Test; TRF, Teacher Report Form; VLBW, very low birthweight; VMI-IV, Berry-Buktenica Developmental Test of Visual-Motor Integration—Fourth edition; VMI-V, Beery-Buktenica Developmental Test of Visual-Motor Integration—Fifth edition; WCST, Wisconsin Card Sorting Test; YSR, Youth Self-Report.

TABLE 3 Risk factors for adverse outcomes and associations between outcomes in the preterm VLBW group reported in articles of the NTNU Low Birth Weight in a Lifetime Perspective study according to the International Classification of Functioning, Disability and Health

	Body functions and structures									
	Brain					Cognition				
	MRI pathology	Volume	Surface area	FA	MRS	DL	IQ	WMS-III	PASAT	Not X-CPT
Contextual factors										
Personal factors										
BW	1 year[54]	15 years[23,30] 20 years[24,32]	15 years[23] 20 years[55]	20 years[27]			19 years[28]	19 years[32]		
GA	1 year[54]	15 years[23] 20 years[26]	20 years[55]	20 years[27]						23 years[56]
Apgar score	1 year[54]								19 years[33]	
Days to BW regain		15 years[30]	15 years[23]							
IVH										
Days on ventilator	1 year[54]	20 years[24]	15 years[23]	20 years[27]				19 years[32]		
Days in NICU		20 years[24,32]	20 years[55]	20 years[27]			19 years[28]	19 years[32]		
Sex										
Environmental factors										
Parental SES										
Body functions and structures										
Brain										
MRI pathology	1–6 years[20]									
Volume		15–20 years[24]								
Surface area			15–20 years[25]							
Cognition										
BSID MDI	1 years[54]									
IQ	6 years[21]	15 years[23,30] 20 years[24]	15 years[23,50] 20 years[55,61]	15 years[59] 20 years[27]	15 years[60]	14 years[66]				23 years[56]
Attention										
Executive function			19 years[33]							
WCST	15 years[62]		15 years[23]	15 years[63]	15 years[60]					
WMS-III		20 years[32]								
Stroop	15 years[62]					14 years[66]				
TMT 2–4										
CPT						14 years[66]				
VMI-IV/V		15 years[30]	15 years[50] 20 years[31]	15 years[59] 20 years[31]	15 years[60]					
Mental health										
KSADS										
M.I.N.I. Plus										
ADHD-R	15 years[65]			15 years[59]		14 years[66]				
ASSQ										
ASEBA ASR										23 years[56]
Vision				15 years[64]						
Pain										

							Activities and participation				
	Mental health			Physical health			Motor skills		General and social functioning, HRQoL		
BRIEF-A	KSADS	ASEBA ASR	SDQ	Bone quality	BP/ Metabolic	Pain	PDMS	Movement ABC	Special education	Bullied	SF-36
	14 years[57]										
	14 years[57]	26 years[19]			26 years[46]						
	14 years[57]										
		26 years[19]									
		26 years[19]				28 years[43]					
		26 years[19]				28 years[43]					
					26 years[46]						
	19 years[35]	14 years[38]									
										14 years[51]	
									19 years[33]		
									19 years[33]		
19 years[83]											
19 years[83]											
	14-19 years[37]	14 years[38]	14 years[38]								
	14–19-26 years[36]										
										14 years[51]	
										14 years[51]	
								14 years[68]			
						19-26 years[42]					
						26-28 years[43]					

(Continues)

	Body functions and structures									
	Brain					Cognition				
	MRI pathology	Volume	Surface area	FA	MRS	DL	IQ	WMS-III	PASAT	Not X-CPT
Physical health										
Anthropometry		1-15 years[23]	1-15 years[23]				1-6 years[58]			
Metabolic syndrome										
Activities and participation										
Motor skills										
BSID PDI	1 years[54]									
DDST Gross	1 years[54]									
PDMS	6 years[21,58]									
GP			15 years[50]	15 years[59] 23 years[67]						
TMT 5										
Movement ABC				15 years[59] 23 years[67]						
HiMAT										
General and social functioning, HRQoL										
CGAS		15 years[69,70] 19 years[69,70]		15 years[59]	15 years[60]					
SF-36										

Abbreviations: ADHD-R, Attention Deficit Hyperactivity Disorder Rating Scale—Fourth edition; ASEBA, Achenbach System of Empirically Based Assessment; ASR, Adult Self-Report; ASSQ, Autism Spectrum Screening Questionnaire; BP, blood pressure; BRIEF-A, Behaviour Rating Inventory of Executive Function—Adult version; BSID, Bayley Scales of Infant Development; BW, birthweight; CGAS, Children's Global Assessment Scale; CPT, Conners Continuous Performance Test; DDST, Denver Developmental Screening Test; DL, dichotic listening; FA, fractional anisotropy; GA, gestational age; GP, Grooved Pegboard; HiMAT, High-Level Mobility Assessment Tool; HRQoL, health-related quality of life; IQ, intelligence quotient; IVH, intraventricular hemorrhage; KSADS, Kiddie Schedule for Affective Disorders and Schizophrenia; M.I.N.I. Plus, Mini-International Neuropsychiatric Interview; MDI, Mental Development Index; Movement ABC, Movement Assessment Battery for Children; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NICU, neonatal intensive care unit; NTNU, Norwegian University of Science and Technology; PASAT, Paced Auditory Serial Addition Test; PDI, Psychomotor Development Index; PDMS, Peabody Developmental Motor Scales; SDQ, Strengths and Difficulties Questionnaire; SES, socioeconomic status; SF-36, Short Form 36 Health Survey; Stroop, Stroop Color and Word Test; TMT, Trail Making Test; VLBW, very low birthweight; VMI-IV, Beery-Buktenica Developmental Test of Visual-Motor Integration—Fourth edition; VMI-V, Beery-Buktenica Developmental Test of Visual-Motor Integration—Fifth edition; WCST, Wisconsin Card Sorting Test; WMS-III, Wechsler Memory Scale—Third edition.

Grey shaded areas indicate significant associations.

of higher education.[28] At 26 years, fewer VLBW than control participants had completed high school and one-fifth of the VLBW participants were unemployed or received disability benefits (Figure 3).[36]

3.2.5 | Health-related quality of life

At 14 years, there were no group differences in self-reported global health, while the parents reported lower psychosocial health for the VLBW adolescents compared with controls.[52] At 19 years, the VLBW group reported poorer mental health-related quality of life.[39] Moreover, up to 23 years, both physical and mental health-related quality of life declined in the VLBW group.[53]

3.3 | Risk factors and associations between outcomes

3.3.1 | Personal and environmental factors

In the VLBW group, lower birthweight and/or gestational age were associated with brain structure pathology at 1 year,[54] smaller brain volumes[23,24,30,32] and cortical surface area[23,55] at 15 and 20 years and poorer white matter integrity at 20 years (Table 3).[27] Furthermore, lower birthweight and/or gestational age were associated with lower IQ at 19 years,[28] poorer performance on a functional MRI task of adaptive control at 23 years,[56] higher systolic and diastolic blood pressure and metabolic syndrome score at 26 years,[46] and more psychiatric

								Activities and participation				
	Mental health			Physical health				Motor skills		General and social functioning, HRQoL		
BRIEF-A	KSADS	ASEBA ASR	SDQ	Bone quality	BP/ Metabolic	Pain	PDMS	Movement ABC	Special education	Bullied	SF-36	
	0-14 years[57]			1-26 years[47] 26 years[46]			1-6 years[58]	14 years[44]				
								1-14 years[48]				
								5-14 years[48]				
											23 years[53]	
		23 years[53]									23 years[53]	
								14-23 years[49]		14 years[51]	23 years[53]	
											23 years[53]	
												20-23 years[5]

diagnoses and symptoms at 14[57] and 26 years.[19] Perinatal morbidity was associated with brain structure pathology at 1 year,[54] brain volumes at 15 years,[24,30,32] cortical surface area at 15[23] and 20 years,[55] white matter integrity at 20 years,[27] IQ[28] and neuropsychological test scores[33] at 19 years, psychiatric problems at 14 years,[57] self-reported mental health problems at 26 years,[19] and pain scores at 28 years.[43]

In the control group, more boys than girls had symptoms of attention deficit hyperactivity disorder,[34] attention and externalising problems,[38] but this was not the case in the VLBW group. At 26 years, VLBW males were shorter than control males,[47] while systolic and diastolic blood pressure were higher and lean body mass lower in VLBW females than in control females.[46]

At 14 years, adjustment for parental SES both increased and decreased the odds of having total mental health problems reported by mothers and fathers, respectively,[38] and at 19 years, decreased the odds for psychiatric morbidity.[35] Parents of VLBW adolescents experienced increased emotional burden, but they did not have more mental health problems than others.[52] Parental mental health was not associated with the VLBW participants having a psychiatric disorder at 26 years.[36]

3.3.2 | Body functions and structures

Smaller head circumference at 1 year was associated with smaller brain volume and surface area,[23] and psychiatric problems[57] at 14–15 years. Both smaller head circumference and lower body weight at 1 year were associated with lower IQ at 6 years.[58] Weight gain at 1 year correlated with bone mineral content and density at 26 years[47] and metabolic syndrome score were associated with bone mineral density at 26 years.[46]

Lower cognitive scores were associated with brain structure pathology at 1 year.[54] IQ was associated with brain structure pathology at 6 years,[21] brain volumes,[23,30] surface area,[23,50] white matter integrity[59] and spectroscopy findings[60] at 15 years, and brain volumes,[24] surface area[55,61] and white matter integrity[27] at 20 years. Furthermore, poorer performance on several neuropsychological tests was associated with brain structure pathology,[62] smaller brain volumes[30,32] and surface area,[31,33,50] poorer white matter integrity[31,59,63] and spectroscopy findings[60] at 15 and 20 years. Poorer white matter integrity of corpus callosum and frontal white matter areas were associated with lower visual acuity at 15 years.[64]

Symptoms of attention deficit hyperactivity disorder were associated with brain structure pathology,[65] white matter integrity[59] and dichotic listening scores[66] at 14–15 years. At 23 years, self-reported anxiety problems and poorer mental health were associated with performance on a functional MRI task of adaptive control[56] and lower motor speed.[53]

3.3.3 | Activities and participation

Motor test scores were associated with brain structure pathology at 1[54] and 6 years,[21,58] surface area at 15 years,[50] and white matter integrity at 15[59] and 23 years.[67] Smaller head circumference and lower body weight at 1 year predicted lower motor scores at 6 years,[58] while higher weight in adolescence was associated with poorer

motor scores at 14 years.[44] Motor problems were partly explained by visual impairments at 14 years.[68]

General functioning was associated with white matter integrity[59] and spectroscopy findings at 15 years[60] and brain volumes at 15 and 19 years.[69,70] Special education was associated with lower scores on attention and executive function tests at 19 years.[33] Higher odds of being bullied were associated with low IQ, motor problems, symptoms of attention deficit hyperactivity disorder and autism spectrum traits at 14 years,[51] and health-related quality of life was associated with motor scores at 23 years.[53]

4 | COMMENT

4.1 | Principal findings

In this systematic review, we used the ICF framework to report neuroimaging findings and clinical outcomes of the NTNU LBW Life study from childhood through adolescence and into young adult age. Within *Body functions and structures*, we found that preterm born VLBW adolescents had an increased risk of abnormal cerebral MRI findings and poorer cognitive function, mental and physical health. Within *Activities and participation*, we have documented challenges in motor skills, general and social functioning, and education and employment, across adolescence and young adulthood, including declining health-related quality of life from adolescence through the twenties. Lower birthweight and gestational age, and perinatal morbidity were risk factors for adverse outcomes.

4.2 | Strengths of the study

The main strength of this systematic review is the synthesis of a prospective longitudinal multidisciplinary follow-up of a defined study population over three decades, assessing a broad spectrum of health. The literature search was carried out in two databases and records were screened independently by two authors, one without prior knowledge of the NTNU LBW Life study (KADA). Included articles were published in international peer-reviewed journals. Neuroimaging was performed with state-of-the-art methods, psychiatric diagnoses were set by clinicians using acknowledged semi-structured interviews, and standardised clinical assessment tools were age-appropriate and consistent with current recommendations.[71] The use of ICF as a framework developed to provide a broad perspective of health and interrelated functions,[16] draws attention to other aspects of functioning than just a narrow bodily perspective.

4.3 | Limitations of the data

Within the ICF, it may be difficult to separate outcomes and make them fit into components and domains. This is demonstrated in ICF linkage studies, where health-status measurements, such as the Short Form 36 Health Survey, may cover different ICF components.[18] Nevertheless, this approach brings attention to the biopsychosocial model of health[16] and the interrelationship of different outcomes.

The NTNU LBW Life study comprised a control group of non-small for gestational age (non-SGA) children, which may indicate a better functioning control group than the general population. However, the estimates of cognition, motor skills and psychiatric morbidity suggest that the control group is representative of the general population.[28,34,44] Other well-known birth cohort studies, such as the Helsinki Study of Very Low Birth Weight Adults, have also used a control group of non-SGA children.[72]

Loss to follow-up is inevitable in any long-term study, and follow-up rates of 50–80% have been suggested as acceptable in cohort studies.[73] As previous publications have documented that there were no differences in maternal and perinatal factors or clinical characteristics between participants and non-participants,[28,34,48] we consider the sample at each follow-up timepoint to be representative of the initial cohort. Although the relatively small cohort size is a limitation, the statistical power was sufficient to detect group differences with reliability.

4.4 | Interpretation

4.4.1 | Body functions and structures

The brain is extensively examined in preterm cohorts,[2] but longitudinal neuroimaging studies combined with clinical assessments from childhood into adulthood are few. The frequency of abnormal MRI findings was consistently higher in the preterm born VLBW group than in the term born control group across ages, and structural grey matter pathology and abnormal white matter connectivity were associated with cognitive and neuropsychological deficits, motor problems and symptoms of attention deficit hyperactivity disorder, indicating specific brain structure–function relationships.

The preterm born VLBW participants had about 13 points lower IQ than controls at 19 years. Using individual participant data of eight cohorts from two consortia (Research on European Children and Adults Born Preterm [RECAP Preterm] and Adults Born Preterm International Collaboration [APIC]), Eves et al.[4] found that very preterm/VLBW participants ($n = 1068$) had 0.78SD lower mean IQ scores than term-born participants ($n = 1067$) at mean age 24 years, equivalent to a difference of 12 IQ points. Further, our findings of poorer performance on several neuropsychological tests in adolescence and young adulthood are supported by a review of Saigal et al.[13] stating that cognitive deficits and problems with executive functioning persist to adulthood in very preterm survivors.

Increased psychiatric morbidity from 14 years to 19 and 26 years is in line with two comprehensive meta-analyses in the APIC consortium, showing long-term consequences of being born preterm

with VLBW into adulthood, especially internalising problems,[5] anxiety and mood disorders, attention deficit hyperactivity and autism spectrum disorders.[6] The increased risk of attention deficit hyperactivity disorder is also supported by a recent publication that includes register data from Finland.[74] A large multinational cohort study using data from several Nordic registers has documented an increased risk of autism spectrum disorder for each week of decreasing gestation from week 40 to week 24.[75]

Our finding of reduced expiratory airflow of the lungs is confirmed by a meta-analysis of individual participant data in the APIC consortium, where the mean difference was −0.78SD between the very preterm/VLBW (n = 935) and control participants (n = 722).[8] Also the blood pressure findings were confirmed by larger data in the APIC consortium, where systolic blood pressure was 3.4 mmHg higher in VLBW adults (n = 1571) compared with controls (n = 777), and even higher for females and those exposed to maternal pre-eclampsia.[7] Results on decreased bone mineral density[76] and increased insulin resistance[72] from the Finnish studies are also in line with the results from the NTNU LBW Life study.

4.4.2 | Activities and participation

Motor test scores were generally 1.0SD poorer in the preterm VLBW group across ages, which is consistent with a recent review.[9] A meta-analysis of studies using the Bayley Scales of Infant Development and the Movement Assessment Battery for Children found effect size differences of −0.88SD and − 0.65SD between children born very preterm/VLBW and controls.[10] Another meta-analysis found a 6-fold increase of motor problems in very preterm/VLBW children,[11] well in line with the estimate of the NTNU LBW Life study.

Measures of general and social functioning showed that several aspects of life were affected by preterm birth. In a broad overview of adult outcomes of very preterm/VLBW survivors, using data from both cohort and registry-linkage studies, the authors conclude that adults born preterm are more likely to remain single and that reproduction is diminished.[13] In a meta-analysis, adults born preterm were found to be less likely to experience romantic relationships, sexual intercourse, or to become parents, but the quality of relationships with partners and friends was not impaired.[77]

Educational level was consistently lower in the preterm born VLBW group than in the control group, which adds to the literature on adult functioning and societal consequences of being born preterm with VLBW. Saigal et al.[13] found that most studies reported lower educational attainment, lower income and higher requirements for social assistance, particularly among those with neurodevelopmental disabilities. Furthermore, self-reported health-related quality of life was lower for very preterm/VLBW individuals compared with full term counterparts,[13] whereas a systematic review of 18 studies of 15 cohorts reported no conclusive evidence of the lower health-related quality of life among very preterm/VLBW adults.[78]

4.4.3 | Underlying mechanisms

The broad spectrum of problems across various ICF domains, ranging from abnormal MRI findings, cognitive, mental and motor problems, to lower general and social functioning, and lower health-related quality of life, suggest a common aetiology that probably involves a combination of and an interplay between genetic, antenatal and postnatal risk factors.[79] Being born preterm with VLBW has major immediate and long-term consequences for immature organ systems, particularly the brain and lungs, causing neurodevelopmental problems and impaired cardiorespiratory function, which may persist to adulthood. Presently, emerging evidence suggests that perinatal inflammation causing white matter damage is likely to be a contributor to adverse neurodevelopmental outcomes, including cerebral palsy, cognitive impairment, attention deficit hyperactivity disorder and autism spectrum disorder.[80] However, a broad array of antecedents and correlates may be involved, ranging from maternal and foetal infections and postnatal morbidity to socioeconomic disadvantage and environmental exposures, with genetic polymorphism and epigenetic changes involved in the cascade of mechanisms.[80] The long-term follow-up provides a well-documented description of the preterm VLBW phenotype and its association to neuroimaging findings, to be examined in relation to such underlying aetiological factors.

4.4.4 | Clinical implications

A substantial part of the included articles addressed body functions and structures as their main outcome, although several publications reported more than one outcome and associations with domains within activities and participation. The combination of quantitative neuroimaging and multidisciplinary assessments gave the opportunity to investigate structure–function relationships in the preterm brain that had not been reported earlier. This has contributed to a better understanding of how aberrant early development of the preterm brain may have lasting functional consequences. However, activities and participation may be the most important outcomes for the individuals themselves. In this systematic review, we emphasise that being born preterm with VLBW may lead to a complexity of outcomes. Studies have traditionally focused on body functions and structures, and we encourage more research on outcomes within activities and participation. Similar to results in other studies,[3,4,9,10,12] lower birthweight and gestational age, and perinatal morbidity were associated with several adverse consequences and may be used to identify preterm born children most likely to experience problems in adulthood. The broad spectrum of outcomes across body functions and structures, and activities and participation brings an important message to clinicians; the diversity of challenges should be covered in multidisciplinary follow-up. An overall view in line with the ICF components may open for novel approaches in the management of preterm born VLBW individuals.

5 | CONCLUSIONS

This systematic review demonstrates the long-lasting complexity of challenges for preterm born VLBW individuals, involving the brain, cognition, mental and physical health, motor skills, general and social functioning, education and employment, as well as health-related quality of life. This preterm born cohort with VLBW, followed from birth to young adulthood, did not outgrow the biological risk, and the various domains of ICF were all affected. Importantly, some of these domains should be possible to influence through either intervention or adaptation and could therefore be a target for management, aiming to promote well-being and quality of life through the years of growth.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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SUPPORTING INFORMATION

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