Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Neurodevelopmental outcome of preterm twins at 5 years of age

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BACKGROUND: Twins are considered to be at an increased risk for perinatal mortality and morbidities, but it is unclear whether preterm twins are at an increased risk for poor developmental outcomes when compared to preterm singletons. Our aim was to compare the neurodevelopmental outcome of preterm twins vs singletons at 5 years of age.

METHODS: Very low birth weight and very low gestational age infants (twins $n = 66$, singletons $n = 157$) were recruited as a part of the PIPARI project in the Turku University Hospital, covering a regional population. Cognitive development, neuropsychological performance, and neurodevelopmental impairments (including cerebral palsy, hearing deficit, visual impairment, and intellectual disability) were evaluated at 5 years of age.

RESULTS: Twins and singletons had otherwise similar perinatal background factors, except for the higher proportion of preterm rupture of membranes in singletons. Twins had cognitive and neuropsychological outcomes that were otherwise comparable with singletons, but they had a slightly lower verbal intelligence quotient (estimate −5.81, 95% CI −11.14 to −0.48, $p = 0.03$). Being a twin was not a risk for neurodevelopmental impairments.

CONCLUSIONS: Our study shows that, contrary to a common hypothesis, the overall neurodevelopment of very preterm twins does not significantly differ from that of preterm singletons.

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INTRODUCTION

Twins are considered to be at an increased risk for perinatal mortality and morbidities such as neurodevelopmental impairments (NDIs), cerebral palsy (CP), impaired cognitive development, and neuropsychological difficulties when compared with singletons.[1–9] Monochorionic twins are thought to be at the greatest risk for a suboptimal outcome.[10–13] Selective intrauterine growth restriction, twin-to-twin transfusion syndrome, being the second-born twin, and intrauterine death of the twin sibling have all been suggested as risk factors for NDIs and increased mortality and morbidities.[4,14–19] A large part of twin-related risks may be explained by prematurity, and it is unclear whether preterm born twins are at an increased risk for poor outcomes when compared to other preterm infants. In Finland, 30% of very low birth weight (≤1500 g) (VLBW) or very low gestational age (<32 weeks of gestation) (VLGA) infants born in 2014 were from twin pregnancies.[20]

Three previous studies have evaluated the effects of being a twin on the risk of NDIs, including cognitive impairment, CP, and sensory impairments. They showed comparable outcomes in twins and singletons. Manuck et al.[21] studied a sample of preterm infants born before 34 weeks of gestation ($n = 1771$, twins $n = 302$) at the age of 2 years, Gnanendran et al.[22] extremely preterm infants ($n = 1473$, twins $n = 392$) born between 1998 and 2004 at the age of 2–3 years, and Eras et al.[23] VLGA infants ($n = 370$, twins $n = 159$) born between 2008 and 2009 at the corrected age of 12–18 months. Also lower mortality[3,24] has been observed in preterm twins than in age-matched singletons, with the exception of extremely preterm infants.[2,14,25]

Cognitive outcome of preterm twins has been evaluated in a study by Bodeau-Livinec et al.,[5] and they found in a large study sample ($n = 2773$) of VLGA infants born in 1997 that twins had slightly lower cognitive scores but no difference with respect to severe deficiencies at 5 years of age compared with singletons. On the other hand, Einaudi et al.[26] found a comparable cognitive outcome at the age of 4 years in a group of VLGA twins ($n = 23$) and singletons ($n = 31$) born between 1997 and 2000. Similarly, Kyriadikou et al.[27] found no difference in the cognitive outcomes at 24 months of age in 24 twins and 24 singletons born <34 weeks of gestation between 2008 and 2010.

Neuropsychological outcome of preterm twins compared with singletons has been evaluated only in few studies. Iannone et al.[9] showed in 86 preterm twins and 86 preterm singletons born at 27–36 weeks of gestation between 1991 and 1997 that twins had an increased risk for later neuropsychological disorders at 6–12 years of age. Raz et al.[28] found a modest twin disadvantage on language and visual processing tasks in 77 twins and 144 singletons born <34 weeks of gestation between 1996 and 2001. Hajnal et al.[29] had similar findings in VLBW twins vs singletons at the age of 2 years born between 1992 and 1994 ($n = 114$).

Overall, the literature concerning the outcome of preterm twins compared with singletons born at similar gestational age is

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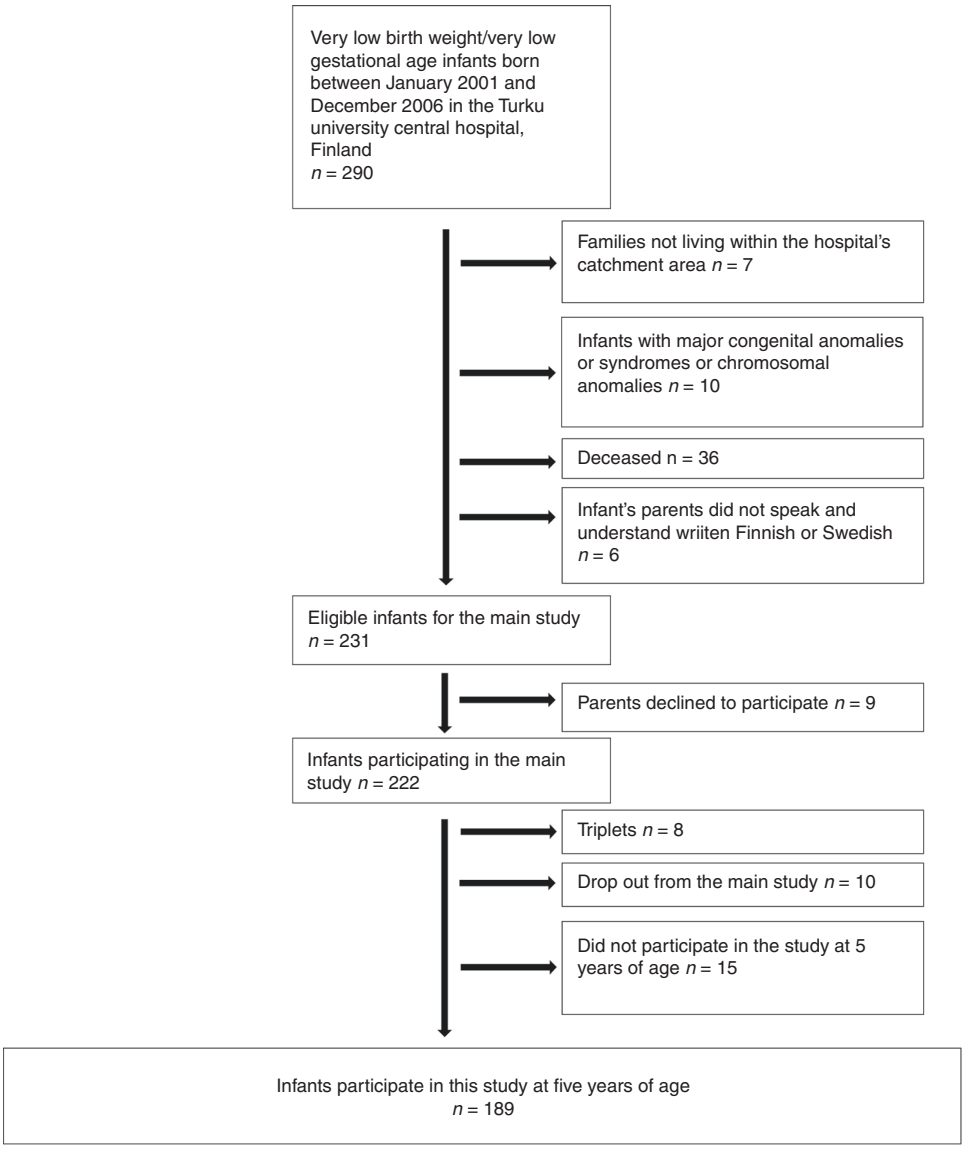

Fig. 1 Flow chart of the study population.

inconsistent and the methodologies and time points for evaluation in the studies are variable.

The aim of this study was to compare the neurodevelopmental outcomes of VLGA or VLBW twins and singletons and the associated risk factors at 5 years of age. We aimed to test whether the hypothesis that being a twin is a risk factor for poor neurodevelopmental outcome is still valid in preterm infants.

METHODS

Patient population

This study is part of the multidisciplinary PIPARI project (Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age). The initial inclusion criteria were: (1) the infant was born between 2001 and 2006 in the Turku University Hospital, Finland; (2) the birth weight was ≤1500 g or the gestational age <32 weeks; (3) the parents lived in the Turku region and spoke and understood written Finnish or Swedish. Infants with major congenital anomalies or syndromes or chromosomal anomalies were excluded ($n = 10$). In the present study, we also excluded triplets ($n = 10$, 2 of whom died). A total of 231 infants were eligible and 222 participated in the main PIPARI study (Fig. 1). From the 222 infants, 197 (88%) participated in the follow-up at 5 years of age. After exclusion of the triplets, 189 twins and singletons formed the final study population for this study. In addition, in this part of the study we also used the information about those infants who died ($n = 36$, 2 of whom were triplets and thus not included in this particular study). Parental consent was obtained after providing verbal and written information. The present study design was approved by the Ethical Committee of the Hospital District of Southwest Finland in June 2001.

The clinical data and information on maternal education were collected as part of the PIPARI protocol (Table 1). Gestational age was estimated based on ultrasonography during the first half of pregnancy. In addition, chorionicity was determined based on the presence of the lambda sign. Brain magnetic resonance imaging was performed at term age and classified as normal, minor pathology, or major pathology.[30] The characteristics of the drop outs ($n = 25$) are shown in Appendix 1.

Developmental assessment

Neurological status at 2 years of corrected age was assessed by a trained physician and a physiotherapist using the Hammersmith

Table 1. Characteristics of the study group shown separately for twins and singletons.

Characteristics	Twins, $n = 66$	Singletons, $n = 157$	p
Died, *n* (%)	9 (14)	25 (16)	0.84
Male, *n* (%)	35 (53)	93 (58)	0.56
Caesarean section, *n* (%)	34 (52)	97 (62)	0.18
Antenatal steroid, *n* (%)	63 (95)	137 (87)	0.09
PROM[a]	8 (12)	45 (29)	0.01
Pre-eclampsia	15 (23)	39 (25)	0.17
Maternal hypertension	4 (6)	12 (8)	1.00
Maternal diabetes	0 (0)	3 (2)	0.56
Gestational diabetes	5 (8)	8 (5)	0.53
Clinical chorioamnionitis	3 (5)	10 (6)	0.76
Gestational age (weeks)[b]	$28^{6/7}$ ($2^{4/7}$) [23, 34]	$28^{3/7}$ (3) [23, $35^{6/7}$]	0.45
Birth weight (g)[b]	1103 (307) [390, 1820]	1075 (338) [384, 2025]	0.57
Birth weight *z*-score[b]	−1.4 (1.5) [−4.1, 1.8]	−1.3 (1.5) [−4.9, 3.4]	0.83
Birth weight *z*-score <−2.0, *n* (%)	26 (39)	55 (35)	0.75
Maternal education[c], *n* (%)			0.40
≤9 years	7 (12)	13 (10)	
9–12 years	11 (19)	37 (29)	
>12 years	39 (68)	79 (61)	
Neonatal septicaemia	2 (3)	1 (1)	0.21
Days in mechanical ventilation[b]	11 (14) [1, 59]	8 (17.2) [0, 173]	0.12
Brain pathology in brain MRI at term age[d]			0.08
Normal	24 (45)	77 (63)	
Minor	11 (21)	16 (13)	
Major	18 (34)	29 (24)	
First born twin, *n* (%)	30 (45)		
Monochorionic twin, *n* (%)	13 (20)		
Intrauterine death of co-twin, *n* (%)	4 (6)		
Birth weight discordance >20%, *n* (%)	9 (13)		
Fetoscopic laser photocoagulation, *n*	0 (0)		

[a]Premature rupture of the membranes (PROM) >18 h before delivery
[b]Data are presented as means, (standard deviations), and [min, max]
[c]Data available for 130 of the singletons and 56 of the twins
[d]Data available for 122 of the singletons and 53 of the twins

Infant Neurological Examination.[31] The diagnosis of CP, including the grading of severity by Gross Motor Function Classification System,[32] was ascertained by one pediatric neurologist (L.H.) at 2 years of corrected age after a systematic clinical follow-up. Vision and hearing were assessed by an ophthalmologist and audiologist, respectively, as a part of the clinical follow-up. Severe hearing impairment was defined as a hearing loss requiring amplification in at least one ear. Severe visual impairment was defined as a visual acuity <0.3 or blindness.

Cognitive assessments were conducted by a trained psychologist. Cognitive development at 5 years of chronological age (−1 week to 2 months) was evaluated using a short form of the Wechsler Preschool and Primary Scale of Intelligence—Revised (WPPSI-R).[33] The subtests Information, Sentences, Arithmetic, Block Design, Geometric Design and Picture Completion were included, and the full-scale intelligence quotient (FSIQ), verbal intelligence quotient (VIQ), and performance intelligence quotient (PIQ) were estimated (mean = 100, standard deviation = 15). A quotient of ≥85 was considered normal intelligence, a quotient of 70–84 was considered slightly below normal, and a quotient of ≤69 was considered significantly below normal intelligence.

Neuropsychological performance of the Finnish speaking preterm infants at 5 years of chronological age (−1 week to 2 months) was evaluated by a trained psychologist. Eleven subtests from the standardized, Finnish version of the NEPSY II,[34,35] were used to evaluate attention (Auditory Attention and Visual Attention), executive functioning (Inhibition), memory functions (Narrative Memory, Memory of Design, and Word List Interference), visuomotor and visuospatial functions (Visuomotor Precision and Design Copy), and language (Speeded Naming, Comprehension of Instructions, and Phonological Processing). Standard scores were based on the results of a control group of healthy term-born children (mean = 10, standard deviation = 3).[36] A standard score of eight or above was considered as average performance, six or seven as slightly below average, and five or below as significantly below average.[35,36]

A child was classified as having NDI if she or he had a diagnosis of CP, a hearing deficit, a visual impairment, or a FSIQ <70.

Statistical analyses

The association between the continuous outcome variables (FSIQ, VIQ, PIQ, and the NEPSY II subtests) and twin or singleton status was studied using mixed-effects models, controlling for the use of antenatal steroids, gestational age, mode of birth, birth weight *z*-score, gender, and the length of maternal education, with >12 years as the reference category. Gestational age and birth weight

z-score were continuous variables and the use of antenatal steroids, mode of birth, gender, and the length of maternal education were categorical variables. The covariates were chosen a priori based on clinical judgment and previous literature. The association between the composite outcome of NDI or death and twin or singleton status was studied using a generalized linear mixed model, controlling for the same variables. In order to take into consideration the correlation of observations among twins, family was included in all models as a random effect. Additional analyses were performed including only children born ≤32 gestational weeks.

The association between the continuous outcome variables (FSIQ, VIQ, PIQ, and the NEPSY II subtests) and monochorionic and dichorionic twins was studied using mixed-effects models while controlling for variables (being a first born twin, birth weight discordance >20% between the twins, the use of antenatal steroids, gestational age, mode of birth, birth weight *z*-score, gender, and the length of maternal education, with >12 years as the reference category), which were chosen for the model if they were statistically significant (p value <0.1) in univariate analysis. Family was included as a random effect. Intrauterine death of the co-twin was not included in the analyses as there were only four cases in the study population. The covariates were chosen a priori based on clinical judgment and previous literature. The association between the composite outcome of NDI or death and monochorionic and dichorionic twins was studied using a generalized linear mixed model, controlling for variables as described above. Additional analysis including only children born ≤32 gestational weeks were performed with same methods.

Univariate associations between categorical variables were studied using the chi-square test, and in the case of continuous variables, *t* test was used.

Statistical analyses were carried out using a 9.4 version of SAS Institute Inc. (Cary, NC) for Windows, and p values of <0.05 were considered to be statistically significant.

RESULTS

NDI or death

Of the 223 otherwise eligible infants, 34 (15%) died before the age of 5 years. Of these, 6 infants died during the delivery, 10 died within the first day of life, 14 died during the first week of life, 3 died during the first month of life, and 1 died at the age of 4 months. NDI was found in 14 (7%) of the surviving 189 study patients. Altogether, 48 (22%) of the 223 study patients had NDI or died. From these 48 children, 14 were twins (21% of the twins) and 34 were singletons (22% of the singletons). The total number of children with CP was nine and four children had a hearing impairment. None of the children had a visual impairment. The assessment of the FSIQ was performed successfully in 11/14 infants with NDI and was found to be <70 in 4 children. The risk for composite outcome of NDI or death was similar for twins and singletons in univariate and multivariate analyses (estimate 0.59, 95% confidence interval (CI) −0.80 to 1.98, $p = 0.39$). Of the background variables, the use of antenatal corticosteroids ($p = 0.01$) and higher gestational age ($p = 0.04$) reduced the risk of NDI or death. We performed post hoc analyses for the study patients born ≤32 weeks of gestation ($n = 159$). The results remained similar (Appendix 2).

Cognitive development

Of the 189 children included in the study, 178 (94%) participated in the assessment of cognitive development at 5 years of age. Table 2 shows the distribution of the children based on their FSIQ,

Table 2. Cognitive development (WPPSI-R) and neuropsychological performance (NEPSY II) at 5 years of age in twins and singletons.

	Data available, *n* (%)	Data missing, *n* (%)		Data available, *n* (%)	Data missing, *n* (%)		*p*
WPPSI-R	Twin, $n = 57$						
				Singleton, $n = 132$			
FSIQ $n = 174$	52 (91)	5 (9)	99.5 (18.8) [39, 140]	122 (92)	10 (8)	100.4 (15.0) [64, 133]	0.74
VIQ $n = 178$	54 (95)	3 (5)	99.9 (15.4) [58, 129]	124 (94)	8 (6)	103.8 (14.9) [39, 130]	0.21
PIQ $n = 177$	53 (93)	4 (7)	99.6 (18.0) [43, 136]	124 (94)	8 (6)	96.5 (16.5) [39, 139]	0.35
NEPSY II	Twin $n = 57$						
				Singleton $n = 122$			
Auditory Attention $n = 152$	47 (82)	10 (18)	8.9 (2.2) [1, 12]	105 (86)	17 (14)	8.7 (3.5) [1. 19]	0.52
Visual Attention $n = 167$	54 (95)	3 (5)	8.4 (2.7) [1, 13]	113 (93)	9 (7)	8.5 (2.2) [4, 14]	0.72
Inhibition $n = 160$	51 (89)	6 (11)	9.1 (3.1) [4, 14]	109 (89)	13 (11)	8.5 (3.2) [1, 15]	0.26
Narrative Memory $n = 165$	51 (89)	6 (11)	9.0 (2.6) [1, 15]	114 (93)	8 (7)	9.8 (2.8) [4, 19]	0.14
Memory of Design $n = 166$	51 (89)	6 (11)	8.1 (2.7) [1, 13]	115 (94)	7 (6)	7.9 (3.1) [1, 19]	0.80
Word List Interference $n = 163$	52 (91)	5 (9)	8.5 (4.1) [1, 15]	111 (91)	11 (9)	8.1 (3.7) [1, 15]	0.50
Visuomotor Precision $n = 171$	55 (96)	2 (4)	8.0 (3.0) [3, 17]	116 (95)	6 (5)	7.9 (3.4) [3, 18]	0.56
Design Copy $n = 157$	49 (86)	8 (14)	9.1 (3.2) [1, 15]	108 (89)	14 (11)	8.0 (3.3) [1, 12]	0.06
Speeded Naming $n = 160$	51 (89)	6 (11)	9.2 (2.8) [1, 17]	109 (89)	13 (11)	8.6 (2.8) [1, 17]	0.20
Comprehension of Instructions $n = 173$	57 (100)	0 (0)	9.2 (3.6) [1, 19]	116 (95)	6 (5)	8.9 (2.7) [1, 15]	0.62
Phonological Processing $n = 174$	57 (100)	0 (0)	8.7 (2.3) [5, 13]	117 (96)	5 (4)	8.9 (2.7) [1, 15]	0.73

Data are presented as means, (standard deviations) and [min, max]
WPPSI-R Wechsler Preschool and Primary Scale of Intelligence—Revised, *FSIQ* full-scale intelligence quotient, *VIQ* verbal intelligence quotient, *PIQ* performance intelligence quotient

Table 3. Cognitive development (WPPSI-R) of very low birth weight/very low gestational age twins at 5 years of age compared with singletons.

Background variable	WPPSI-R		
	FSIQ, $n = 162$	VIQ, $n = 165$	PIQ, $n = 165$
Twins	(−2.30) [−8.49 to 3.90] 0.47	**(−5.73)** **[−11.17 to −0.29]** **0.04**	(1.23) [−5.28 to 7.75] 0.71
Antenatal steroids not given	(−7.19) [−21.11 to 6.73] 0.31	**(−11.86)** **[−23.16 to −0.56]** **0.04**	**(−14.77)** **[-28.12 to −1.41]** **0.03**
Vaginal delivery	(1.98) [−3.70 to 7.66] 0.49	(3.46) [−1.56 to 8.47] 0.17	(0.72) [−5.24 to 6.68] 0.81
Male gender	**(−4.95)** **[−9.88 to −0.02]** **0.05**	(0.64) [−3.76 to 5.05] 0.77	**(−10.24)** **[−15.33 to −5.16]** **<0.001**
Increase in birth weight *z*-score	(−1.75) [−3.69 to 0.20] 0.08	(−0.65) [−2.45 to 1.15] 0.47	(−1.56) [−3.52 to 0.51] 0.14
Increase in gestational age (days)	(0.19) [−1.06 to 1.44] 0.76	(1.02) [−0.06 to 2.10] 0.06	(0.42) [−0.84 to 1.68] 0.51
Maternal education[a]			
≤9 years	(−7.42) [−16.41 to 1.57] 0.09	**(−11.24)** **[−19.23 to −3.325** **0.006**	(0.24) [−9.22 to 9.71] 0.96
9–12 years	**(−7.26)** **[−13.49 to −1.03]** **0.02**	**(−8.56)** **[−14.10 to −3.03]** **0.003**	(−4.31) [−10.83 to 2.22] 0.19

Results from the analyses controlling for the use of antenatal steroids, gestational age, mode of birth, birth weight *z*-score, gender, and the length of maternal education. Results are given as (mean difference estimate), [95% confidence interval], and *p* value. Results with statistical significance are in bold
WPPSI-R Wechsler Preschool and Primary Scale of Intelligence—Revised, *FSIQ* full-scale intelligence quotient, *VIQ* verbal intelligence quotient, *PIQ* performance intelligence quotient
[a]More than 12 years is used as the reference category

VIQ, and PIQ in the WPPSI-R. The cognitive outcome between twins and singletons did not differ significantly in univariate analyses. The results from the mixed effect models are shown in Table 3. Twins were found to be at an increased risk for lower VIQ but not for lower FSIQ or PIQ. Associations of the background variables with cognitive development are shown in Table 3. Lack of antenatal steroids was associated with lower VIQ and PIQ, male gender was associated with lower PIQ and FSIQ, and shorter maternal education associated with lower PIQ and FSIQ. Mode of the delivery, birth weight *z*-score, and gestational age did not associate with cognitive outcome. We performed post hoc analyses for the study patients born ≤32 weeks of gestation ($n = 148$). The results remained otherwise similar, but the difference in VIQ disappeared (Appendix 2).

Neuropsychological functions

Neuropsychological functions were assessed in 174 (92%) of the 189 study patients at 5 years of age. Swedish speaking children ($n = 10$) were not included in the analyses concerning NEPSY II, as the NEPSY II results are not fully comparable to those of Finnish speaking children. Table 2 shows the distribution of the participants based on the NEPSY II subtests. The neuropsychological performance of twins and singletons did not differ significantly in univariate or multivariate analyses. The results from the mixed-effects models are shown in Table 4. Associations between the background variables and neuropsychological development are shown in Table 4. Lack of antenatal steroids associated with poorer performance in Narrative Memory and Design Copy subtests, male gender with poorer performance in Auditory Attention, Visuomotor Precision, and Design Copy subtests, increase in gestational age in better performance in Auditory Attention, Visuomotor Precision, and Phonological Processing subtests, and shorter maternal education with poorer performance in Auditory Attention, Word List Interference, Speeded Naming, and Comprehension of Instructions subtest. Mode of delivery and birth weight *z*-score did not associate with neuropsychological outcome. We performed post hoc analyses for the study patients born ≤32 weeks of gestation ($n = 152$). The results remained similar (Appendix 2).

Effect of chorionicity

Of the 66 twins in our study population, 57 (86%) were alive and participated in the evaluations at 5 years of age. Out of all twins, 13 (20%) were from monochorionic pregnancies. Of the 66 twins, 14 (21%) suffered from NDI or died. Chorionicity did not affect the risk of composite outcome of NDI or death in univariate or in multivariate analyses (estimate −0.63, 95% CI −3.49 to 2.24, $p = 0.68$). Chorionicity was not associated with the cognitive outcome or neuropsychological performance of these preterm twins in either univariate or multivariate analyses (Table 5). We performed post hoc analyses for the twins born ≤32 weeks of gestation ($n = 60$). The results remained otherwise similar, but monochorionicity was associated with better performance on the Narrative Memory subtest of the NEPSY II (estimate 2.23, 95% CI 0.44–4.02, $p = 0.02$) (Appendix 3).

Of the background variables, increase in gestational age was associated with lower risk of composite outcome of NDI or death ($p = 0.03$) and better performance in Visuomotor Precision subtest in the NEPSY II (estimate 0.36, 95% CI 0.004 to 9.71, $p = 0.05$). Being the first-born twin was associated with poorer

Table 4. Neuropsychological performance (NEPSY II) of very low birth weight/very low gestational age twins at 5 years of age compared with singletons.

Background variable	NEPSY II										
	Auditory Attention, $n = 149$	Visual Attention, $n = 164$	Inhibition, $n = 156$	Narrative Memory, $n = 161$	Memory of Design, $n = 162$	Word List Interference, $n = 159$	Visuomotor Precision, $n = 167$	Design Copy, $n = 153$	Speeded Naming, $n = 157$	Comprehension of Instructions, $n = 169$	Phonological Processing, $n = 170$
Twins	(−0.16) [−1.39 to 1.07] 0.80	(−0.09) [−0.88 to 0.70] 0.82	(0.56) [−0.58 to 1.70] 0.33	(−0.97) [−1.97 to 0.084] 0.06	(0.17) [−0.93 to 1.27] 0.76	(0.17) [−1.21 to 1.56] 0.80	(−0.02) [−1.21 to 1.16] 0.97	(0.81) [−0.35 to 1.97] 0.17	(0.46) [−0.58 to 1.50] 0.38	(0.11) [−0.93 to 1.14] 0.84	(−0.33) [−1.24 to 0.58] 0.47
Antenatal steroids not given	(−1.10) [−4.28 to 2.08] 0.49	(0.90) [−1.03 to 2.84] 0.36	(−0.16) [−3.12 to 2.80] 0.91	**(−2.43) [−4.67 to −0.19] 0.03**	(−0.08) [−2.54 to 2.37] 0.95	(−1.15) [−4.50 to 2.19] 0.50	(−1.48) [−4.22 to 1.26] 0.29	**(−3.33) [−5.96 to −0.71] 0.01**	(−0.21) [−2.76 to 2.35] 0.87	(−1.22) [−3.62 to 1.19] 0.32	(−0.79) [−2.87 to 1.30] 0.46
Vaginal delivery	(0.10) [−1.01 to 1.20] 0.86	(−0.01) [−0.79 to 0.77] 0.98	(−0.40) [−1.48 to 0.68] 0.47	(−0.71) [−1.65 to 0.23] 0.14	(−0.28) [−1.32 to 0.75] 0.59	(−0.01) [−1.34 to 1.32] 0.98	(−0.31) [−1.41 to 0.79] 0.58	(−0.44) [−1.54 to 0.67] 0.44	(0.23) [−0.75 to 1.21] 0.64	(0.21) [−0.79 to 1.201] 0.68	(0.16) [−0.70 to 1.03] 0.71
Male gender	**(−1.11) [−2.14 to −0.07] 0.04**	(−0.62) [−1.38 to 0.13] 0.11	(−0.41) [−1.44 to 0.62] 0.43	(−0.01) [−0.91 to 0.89] 0.98	(−0.87) [−1.85 to 0.12] 0.09	(−0.18) [−1.45 to 1.09] 0.78	**(−1.53) [−2.54 to −0.52] 0.003**	**(−1.45) [−2.52 to −0.38] 0.008**	(0.13) [−0.78 to 1.08] 0.75	(−0.27) [−1.21 to 0.67] 0.57	(−0.28) [−1.10 to 0.55] 0.51
Increase in birth weight *z*-score	(−0.14) [−0.29 to 0.58] 0.52	(−0.13) [−0.44 to 0.18] 0.41	(−0.002) [−0.43 to 0.43] 0.99	(−0.06) [−0.42 to 0.31] 0.76	(−0.13) [−0.54 to 0.28] 0.53	(0.03) [−0.49 to 0.55] 0.91	(0.11) [−0.30 to 0.53] 0.60	(−0.15) [−0.59 to 0.29] 0.51	(0.02) [−0.37 to 0.41] 0.92	(−0.01) [−0.40 to 0.38] 0.96	(−0.08) [−0.42 to 0.25] 0.62
Increase in gestational age (days)	**(0.30) [0.04 to 0.55] 0.02**	(−0.08) [−0.26 to 0.10] 0.40	(−0.07) [−0.32 to 0.18] 0.60	(−0.07) [−0.14 to 0.29] 0.50	(−0.16) [−0.39 to 0.07] 0.17	(0.16) [−0.15 to 0.46] 0.31	**(0.36) [0.12 to 0.59] 0.004**	(0.07) [−0.18 to 0.33] 0.56	(0.09) [−0.13 to 0.31] 0.43	(0.12) [−0.10 to 0.35] 0.28	**(0.22) [0.03 to 0.41] 0.02**
Maternal education[a]											
≤9 years	(−0.28) [−2.08 to 1.51] 0.76	(−0.79) [−1.97 to 0.39] 0.19	(−0.31) [−1.96 to 1.34] 0.71	(−0.69) [−2.16 to 0.78] 0.35	(−0.69) [−2.27 to 0.90] 0.39	**(−2.31) [−4.35 to −0.26] 0.03**	(−0.85) [−2.52 to 0.82] 0.32	(0.80) [−0.87 to 2.47] 0.35	(−0.61) [−2.14 to 0.91] 0.43	**(−2.37) [−3.88 to −0.86] 0.002**	(−0.57) [−1.89 to 0.75] 0.39
9–12 years	**(−1.73) [−2.9 to −0.52] 0.005**	(−0.84) [−1.71 to 0.04] 0.06	(−0.80) [−2.00 to 0.39] 0.19	(−0.59) [−1.63 to 0.44] 0.26	(0.14) [−1.00 to 1.28] 0.81	(−1.01) [−2.47 to 0.44] 0.17	(−0.60) [−1.82 to 0.62] 0.33	(−0.24) [−1.47 to 1.00] 0.71	**(−1.51) [−2.58 to −0.43] 0.007**	(−1.08) [−2.19 to 0.02] 0.05	(−0.09) [−1.05 to 0.87] 0.85

Results from the analyses controlling for the use of antenatal steroids, gestational age, mode of birth, birth weight z-score, gender, and the length of maternal education. Results are given as (mean difference estimate), [95% confidence interval], and *p* value. Results with statistical significance are in bold

[a]More than 12 years is used as the reference category

Table 5. Cognitive development (WPPSI-R) and neuropsychological performance (NEPSY II) of very low birth weight/very low gestational age monochorionic twins at 5 years of age compared with dichorionic twins.

Outcome measures	Monochorionic vs dichorionic twin
WPPSI-R	
FSIQ, $n = 52$	(0.16) [−12.14 to 12.46] 0.98
VIQ, $n = 54$	(−1.05) [−11.15 to 9.05] 0.84
PIQ, $n = 53$	(1.57) [−10.41 to 13.55] 0.79
NEPSY II	
Auditory Attention, $n = 47$	(−0.88) [−2.46 to 0.69] 0.27
Visual Attention, $n = 53$	(−1.13) [−2.89 to 0.62] 0.20
Inhibition, $n = 50$	(−0.41) [−2.47 to 1.65] 0.69
Narrative Memory, $n = 49$	(1.43) [−0.34 to 3.21] 0.11
Memory of Design, $n = 50$	(−0.76) [−2.78 to 1.25] 0.45
Word List Interference, $n = 51$	(−0.77) [−3.58 to 2.03] 0.64
Visuomotor Precision, $n = 54$	(−0.66) [−2.70 to 1.39] 0.52
Design Copy, $n = 49$	(−0.73) [−2.97 to 1.51] 0.51
Speeded Naming, $n = 50$	(−1.31) [−3.24 to 0.63] 0.18
Comprehension of Instructions, $n = 56$	(0.32) [−2.06 to 2.87] 0.79
Phonological Processing, $n = 56$	(0.23) [−1.33 to 1.78] 0.77

Results from the analyses controlling for the effects of being a first born twin, birth weight discordance >20% between the twins, the use of antenatal steroids, gestational age, mode of birth, birth weight *z*-score, gender, and the length of maternal education. Results are given as (mean difference estimate), [95% confidence interval], and *p* value. None of the results are statistically significant

WPPSI-R Wechsler Preschool and Primary Scale of Intelligence—Revised, *FSIQ* full-scale intelligence quotient, *VIQ* verbal intelligence quotient, *PIQ* performance intelligence quotient

performance in the Speeded Naming (estimate −2.15, 95% CI −3.62 to −0.68, $p = 0.005$) and Visual Attention (estimate −1.54, 95% CI −2.91 to −0.16, $p = 0.03$) subtests of the NEPSY II. In addition, lower maternal education associated with poorer performance on the Word List Interference (<9 years education: estimate −4.50, 95% CI −8.02 to −0.97, $p = 0.01$), Narrative Memory (<9 years education: estimate −3.06, 95% CI −5.18 to −0.93, $p = 0.006$), and Inhibition (9–12 years education: estimate −2.66, 95% CI −4.75 to −0.56, $p = 0.01$) subtests of the NEPSY II.

DISCUSSION

This study evaluated the neurodevelopmental outcome of preterm twins at 5 years of age compared with preterm singletons in a cohort of VLBW/VLGA children. We found that twins, in general, have comparable outcomes with singletons in terms of cognitive development, neuropsychological performance, and neurosensory morbidities and mortality.

While twins in general are thought to be at an increased risk for CP, cognitive delay, and mortality,[4,6,7] the literature concerning preterm twins is inconsistent. While the risks seen in twins are partly explained by the high rate of prematurity associated with multiple pregnancies, it is not known whether being a twin, in itself, poses a risk for the prematurely born infant. In one previous study with a large cohort (twin $n = 1376$, singleton $n = 7630$) of extremely low birth weight children, twins were found to be at an increased risk for NDI or death when compared with singletons.[8] However, our study of VLBW/VLGA children did not find any associations between NDI or death and being a twin. The same finding has also been made by three large study groups of VLGA[28,29] and VLBW[5] cohorts. Only Bodeau-Livinec et al.[5] reported the proportion of monochorionic twins in the sample but concluded that it did not affect the outcome of the twins. Hajnal et al.[29] compared two cohorts of VLBW infants born in different decades (born in 1983–85 and 1992–94). They found a clear improvement in the outcomes (mortality, CP, developmental delay) of preterm twins in contrast to no improvement in singletons, suggesting that improved perinatal follow-up of twin pregnancies and care of twins has led to better survival rates and outcomes for preterm twins.

There are few previous studies comparing the cognitive outcome of prematurely born twins and singletons. Hajnal et al.[29] and Kyriakidou et al.[27] found similar cognitive outcomes in preterm twins and singletons in their small patient samples. The proportion of monochorionic twins was not reported. Bodeau-Livinec et al.[5] showed slightly lower cognitive performance in twins in a large sample of VLGA infants. Chorionicity did not affect the outcome in this study, which had 39.1% monochorionic twins. Iannone et al.[9] found more language and learning difficulties in twins at school age in a study sample with 44% monochorionic twins. In a recently published large cohort study, twins ($n = 245$) and singletons ($n = 568$) born before 28 weeks of gestation performed similarly in cognitive and neuropsychological testing at 10 years of age.[37] Overall, according to literature, being a twin poses no major risk for severe cognitive deficits. Thus our finding of a similar general cognitive level in twins and singletons at 5 years of age is in accordance with previous studies. The difference in verbal performance between twins and singletons in our study was modest and unlikely to be of major clinical importance. It is also possible that twins, regardless of gestational age, may have different language development, which could lead to poorer verbal performance than that of singletons.[23,37] Explanations may be related to, for example, the unique verbal interaction between twin pairs ("private language") or more limited interaction time with parents in twins compared with singletons.[38–40]

Neuropsychological performance can be affected in preterm infants despite a normal cognitive level. The neuropsychological functions of preterm twins have not been widely studied before. Raz et al.[23] found that preterm twins, 90% of which were born from dichorionic pregnancy, were at a modest disadvantage regarding language functions and visual processing at pre-school age. Iannone et al.[9] evaluated the self-regulatory processes of the preterm twins at six to 12 years of age through clinical observation in addition to cognitive evaluation but found no significant difference between twins and singletons. In addition, Einaudi et al.[26] found VLGA twins and singletons to have comparable outcomes on neuropsychological screening at four to seven years of age. They found birth weight discordance and chorionicity to be the only perinatal risk factors for poor outcome. Despite different assessment methods, similar neuropsychological functioning was found in preterm twins and singletons in our study as well as in previous literature.

Monochorionicity exposes the developing fetus to an increased risk of mortality and morbidities.[10–13] One potential complication is twin-to-twin transfusion syndrome, which only occurs in monochorionic twin pregnancies. The intrauterine demise of one fetus may also cause problems to the survivor due to shared blood flow. Several twin studies have not taken into account the effects of chorionicity on the outcome, with a few exceptions. Hack et al.[17] evaluated the outcome of twins at 22 months of corrected age in a cohort that also included full-term twins. They found no significant differences in the incidence of CP or in the neurodevelopmental outcomes between dichorionic and uncomplicated monochorionic twins, with the exception of higher incidence of mildly delayed development of hearing and language in monochorionic twins. Kawamura et al.[41] and Bodeau-Livinec

et al.[5] did not find monochorionicity to increase the risk of death, CP, or developmental delay in VLBW/VLGA infants. To our knowledge, the role of chorionicity on the neuropsychological outcomes of preterm twins has previously only been evaluated in two small studies.[26,28] Einaudi et al.[26] showed, in univariate analyses, that monochorionic twins have a higher incidence of low non-verbal performance and more learning disabilities. On the other hand, Raz et al.[28] found monochorionic twins to have comparable neuropsychological functioning compared with dichorionic twins. In both of these studies, the number of monochorionic twins was small, which might explain the contradictory results. In our study sample, the outcome at 5 years of age did not differ between monochorionic and dichorionic twins. However, it should be noted that the number of monochorionic twins in our study was too small to draw any definite conclusions.

The perinatal care of preterm infants, as well as twins and higher multiples, has developed greatly in recent years. In a recent study with a large cohort of VLGA triplets, there were no significant differences in the incidence of mortality and major neonatal morbidities with this high-risk patient group and age-matched singletons.[42] Also a clear improvement in outcome (mortality, CP, developmental delay) has been seen earlier in VLBW twins born in different decades (1983–85 and 1992–94).[26] There is also a trend seen in the literature review that the publications from the past decade are less likely to find twins to be in a risk for poor developmental outcome when compared with singletons. These findings suggest that improved perinatal follow-up and care of twins and higher multiples might have led to better survival rates and outcomes for preterm multiples. This might be a potential explanation why we were unable to find significant differences in the outcome of preterm twins and singletons.

A limitation of our study is the rather small number of patients, which causes a risk of coincidental findings or missing some true associations. This is especially true for the subgroup analyses. Another limitation is that some psychological evaluations could not be completed owing to, for example, lack of cooperation or attention difficulties, resulting in missing data. This is a potential source of bias in our study, as the children whose test results are missing are likely to be ones with poor outcomes.

According to our findings, it seems that VLBW/VLGA twins have no major additional neurodevelopmental risks when compared with VLBW/VLGA singletons at 5 years of age. The preterm twins did not have any developmental advantage in comparison with singletons either. Altogether, the outcomes of the twins were comparable with the outcomes of the singletons.

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AUTHOR CONTRIBUTIONS

M.Y.: Took part in the design of the study and statistical analyses and interpretation of data and drafted the initial manuscript. L.H., A.L., E.E. and L.L.: Took part in the design of the study and statistical analyses and interpretation of data and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ADDITIONAL INFORMATION

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