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Visual-motor integration and fine motor skills in children born extremely preterm: associations with neonatal brain volumes

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Abstract

Objectives

This exploratory study aimed to investigate associations between neonatal brain volumes and visual-motor integration (VMI) and fine motor skills in children born EPT when they reached 6.5 years of age.

Setting

Prospective population-based cohort study in Stockholm, Sweden, during three years.

Participants

All children born before gestational age 27 weeks 2004-2007 in Stockholm, without major morbidities and impairments, and who underwent magnetic resonance imaging at term-equivalent age.

Main outcome measures

Brain volumes were calculated using morphometric analyses in regions known to be involved in VMI and fine motor functions. VMI was assessed with The Beery-Buktenica Developmental Test of Visual-Motor Integration - Sixth Edition and fine motor skills were assessed with the manual dexterity subtest from the Movement Assessment Battery for Children-Second Edition, at 6.5 years. Associations between the brain volumes and VMI and fine motor skills were evaluated using partial correlation, adjusted for total cerebral parenchyma and sex.

Results

Out of 107 children born at gestational age <27 weeks, 83 were assessed at 6.5 years and 66/83 were without major brain lesions or cerebral palsy and included in the analyses. A representative subsample underwent morphometric analyses: automatic segmentation (n=34) and atlas-based segmentation (n=26). The precentral

gyrus was associated with both VMI (r=0.54, p=0.007) and fine motor skills (r=0.54, p=0.01). Associations were also seen between fine motor skills and the volume of the cerebellum (r=0.42, p=0.02), brainstem (r=0.47, p=0.008) and grey matter (r=-0.38, p=0.04).

Conclusions

Neonatal brain volumes in areas known to be involved in VMI and fine motor skills were associated with scores for these two functions when children born EPT without major brain lesions or cerebral palsy were evaluated at 6.5 years of age. Establishing clear associations between early brain volume alterations and later VMI and/or fine motor skills could make early interventions possible.

Strengths and limitations of this study

- This was a robust population-based cohort study design that used advanced magnetic resonance imaging techniques and established assessment tools
- It studied visual-motor integration and fine motor skills in extremely preterm born children at 6.5 years, which is an important age for Swedish school children
- Although we had to exclude numerous children from the morphometric analyses, due to strict data quality criteria, the sample was representative of the cohort
- We were unable to include a control group of children born at term in the analyses

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Competing interests: None

Introduction

Visual-motor function is an important cross-modal ability that involves the integration of visual function and perception, eye-hand coordination, fine motor skills and visual-motor integration (VMI) [1]. Studies have shown that VMI can predict a child´s future hand-writing skills [2-4] and academic performance in reading, writing and mathematics [5]. Evaluating VMI performance is therefore an important component of the test batteries that are used to detect children who risk school problems. Fine motor skills are a fundamental component of hand and visual-motor function, which also

contributes to school performance[6]. Several reports have shown that children born preterm have poor VMI and motor function [7 8-10] and it is well known that this group of children risk poor school performance and learning disabilities [11-13].

Although problems with VMI can stem from any of the underlying abilities listed above, when VMI and motor abilities have been investigated together, and perceptual and general cognitive abilities have been held constant, children with lower general motor scores are seen to have lower VMI scores [14]. Children born very low birth weight show a similar pattern [15]: VMI showing stronger relationships with motor ability than with visual perception, suggesting that motor skills and manual fine motor skills in particular, are crucial components underlying VMI. On the other hand, visual perceptual deficits in children born EPT are well documented [7] and their role in VMI should not be underestimated. Therefore, an inductive exploration of brain areas associated with VMI is a useful approach, especially when investigating potentially atypical brain development trajectories[16].

It is largely unknown how the developmental alterations of the brain affect VMI and fine motor skills in children born preterm. However, we have previously reported that neonatal brain volumes are affected in preterm infants [17], and other researchers have shown that these alterations in preterm brain volumes persist until at least early childhood [18]. Volumetric alterations in the brain have also been associated with neurodevelopmental outcomes in preterm born children [19 20]. However, the relationship between volume alterations in the brains of children born extremely (EPT), at less than 27 weeks of gestation, and VMI and fine motor skills at school age remains largely unexplored. We hypothesized that early brain volume alterations would be related to later VMI and fine motor skills in such children. To explore these possible associations, we used atlas-based and automatic segmentation to measure

the brain volumes at term-equivalent age, and carried out a clinical evaluation of VMI and fine motor skills at the age of 6.5 years.

Methods

Study population

The study population was a sub-cohort of the Extremely Preterm Infants in Sweden Study (EXPRESS) cohort. EXPRESS was a prospective national population-based cohort study which invited all children born in Sweden at a gestational age (GA) of less than 27 weeks over a three-year period to take part in clinical follow ups at 2.5 and 6.5 years of age[21 22]. The present study included 107 children born in Stockholm between January 1 2004 and March 31 2007, without chromosomal aberrations, congenital malformations or infections, who had undergone magnetic resonance imaging (MRI) of the brain at term equivalent age.

Gestational age was assessed by maternal ultrasound at around a GA of 18 weeks and perinatal and neonatal data were prospectively collected from the children´s medical records. Cranial ultrasound was performed on a regular basis during the neonatal period up to a GA of 40 weeks, according to our clinical routine. Children were excluded from the analyses in the present study if they had major brain lesions defined as intraventricular hemorrhage, periventricular leukomalacia, severe white matter score according to Inder [23] or hydrocephalus, or cerebral palsy (CP) as defined by the Surveillance of Cerebral Palsy in Europe Working Group [24]. All children had been screened for retinopathy of prematurity and evidence-based treatment had been administered [25].

The study was approved by the local ethics committee in Stockholm and the parents of all the children gave their written, informed consent before the study.

Assessment at 6.5 years of age

Visual-motor integration was assessed using the Beery-Buktenica Developmental Test of Visual-Motor Integration - sixth edition [26]. This test consists of 30 geometrical shapes that the child is asked to copy with a pen and paper and it is terminated when three figures in a row have been incorrectly copied. The drawings are examined and acceptable approximations of the model drawings are each given one point. The raw score is the total number of correct drawings and this is then transformed to an age-corrected standard score. Standard scores were used in the analyses in this study. The normative mean score is 100 with a standard deviation (SD) of 15.

Fine motor skills were assessed with the manual dexterity subtest of the Movement Assessment Battery for Children – Second edition (M-ABC-2) which measures unimanual speed, bimanual coordination and unimanual spatial accuracy [27]. Age-adjusted standard scores were used for the analyses. The reference mean score is 10 with a standard deviation of 3, and scores below 7 indicate definitive or borderline motor problems.

Binocular visual acuity was measured with habitual correction at three meters with the Lea Hyvärinen chart [28]. Visual impairment was defined as a visual acuity of less than 0.33 in the better eye.

MRI data acquisition and processing

All the children were scanned using a Philips Intera 1.5 Tesla MRI system (Philips International, Amsterdam, The Netherlands) at term equivalent age. A sagittal T1-weighted turbo spin echo sequence, an axial inversion recovery sequence and an axial T2-weighted sequence were run. The three-dimensional T1-weighted images were acquired with an echo time of 4.6 msec, a repetition time of 40 msec, a flip angle of 30°, a voxel size of 0.7 × 0.7 × 0.1 mm and a field of view of 180mm. The MRI protocol has previously been reported [29]. Quality assurance was considered

important in order to obtain accurate data, even though this meant that we were left with a relatively small sample size. The imaging data was checked for quality, based on a visual inspection of the raw data sets, and the reasons for low imaging quality are presented in **Figure 1.**

Atlas based segmentation

The brain was divided into 90 anatomical regions, by adapting an automated anatomical labelling neonatal atlas [30], as previously described [17]. Briefly, the intensity image that generated the neonatal atlas was registered to the T1-weighted image of each infant, then the generated deformation field was used to transform the label map with 90 regions from the atlas space to the subject space. A visual inspection was performed for each subject and each step.

We selected brain regions that had been previously described as being in the networks that mediate VMI and fine motor skills, namely the visual, salience, sensory motor and default mode networks [31-33]. We also considered the subcortical regions: pallidum, putamen, caudate and thalamus. The volume of each brain region was determined by adding together the volumes of their components.

Automatic segmentation

We first performed automatic segmentation of brain tissues (T1-weighted images) using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm), running on MATLAB version 7.5 (MathWorks, Natick, Massachusetts, USA). This process focused on specific neonatal priors, including grey matter, white matter, cerebrospinal fluid, deep grey matter, the cerebellum and brainstem, which have previously been described in detail [34 35]. We then applied a Diffeomorphic Anatomical Registration Through an Exponential Lie algebra algorithm (DARTEL) to improve the inter-subject registration [36]. Finally, all the images were modulated. The Easy Volume Toolbox [37] was used to

extract the global brain tissue volumes from the segmented, normalized and modulated images of each child.

Statistical analyses

The analyses were carried out with SPSS for Windows, version 22.0 (SPSS Inc, Chicago, Illinois, USA) and the data were checked for normality, homogeneity and outliers. In order to compare the groups, we used the Student´s t-test and Mann Whitney U test for continuous variables and the chi-square test or Fisher´s exact test for categorical data, as appropriate. The associations between brain volumes, VMI scores and fine motor skills scores were explored using partial correlation. Total cerebral parenchyma (CPAR) – the sum of the grey matter and white matter, excluding cerebrospinal fluid - was used as a covariate to control for generalized scaling effects. Because sex, GA at birth and the GA at the time of the scan have previously been shown to influence brain volume size in preterm children [38 39] we performed the analyses with different covariate pairs. First we used CPAR and GA at birth, then we used CPAR and the GA at scan and finally we used CPAR and sex. GA at birth and GA at scan did not influence the results, but sex did, so CPAR and sex were chosen as the covariates in the final model. There was one multivariate outlier which was identified by the Mahalanobis distance when we investigated the atlas segmentation data in relation to the fine motor skills scores, and this child was excluded from those analyses. Bonferroni's correction for multiple comparisons was not applied because of the exploratory nature of the study and the reduced sample size examined [40-42]. The level of significance was set at a two-sided p-value of <0.05.

Results

Study population

A summary of the study population is presented in **Figure 1** and their perinatal characteristics are presented in **Table 1.** At the time of the scan, the median (range) GA in the 66 children without major brain lesions or CP was 40.8 (39.1-45.3) weeks and for the assessment of VMI and fine motor skills it was 6 years 5 months (6 years 3 months - 7 years 2 months).

The subsample of 34 children with high-quality MRI scans was representative of the whole cohort with regard to their perinatal and neonatal characteristics, findings on structural MRI, gestational age at MRI, age at assessment at 6.5 years and mean VMI and fine motor score (**Supplementary Table 1**). During the atlas-based segmentation process, 8 subjects had co-registration failure, leaving 26 children in the final sample. These 26 children were also representative of the cohort of 66 children with regard to the above characteristics, except for days on mechanical ventilation, which was a median (range) of 3 (0-36) days for the sub-sample versus 10 (0-55) days for the other children (p=0.04) **(Supplementary Table 2).**

Assessment at 6.5 years of age

The mean (SD) VMI standard score for the 66 children without major brain lesions or CP was 93 (10), 7 points (0.5 SD) below the norm. The mean (SD) VMI scores for the 29 girls was higher than for the 37 boys: mean (SD) at 96 (10) versus 90 (8), respectively (p=0.02).

The mean (SD) fine motor skills score was 8 (3), which was 2 points (0.5 SD) below the norm, and there were no significant sex differences as the girls scored 8 (3) and the boys 7 (3) (p=0.16).

None of the children included in the study had a visual impairment.

Brain volumes and associations with VMI and fine motor skills

We identified a number of regions that demonstrated significant associations between brain volumes, VMI and fine motor skills scores. VMI performance showed a positive correlation with the volume of the precentral gyrus (partial r=0.54, p=0.007), whereas the fine motor skills scores showed a positive correlation with the volumes of the precentral gyrus (partial r = 0.54, p=0.01), the cerebellum (partial r = 0.42, p=0.02) and the brainstem (partial r = 0.47 p=0.008) and a negative correlation with cortical grey matter volume (partial r = -0.38, p=0.04) (**Figure 2**). All the correlation analyses can be found in **Supplementary Table 3**.

Discussion

In this study, the associations between brain volumes at term equivalent age and VMI and fine motor skills at 6.5 years in children born EPT without major brain lesions or CP were explored in regions of the brain previously reported to be involved in those functions. The volume of the precentral gyrus showed a positive correlation with both VMI and fine motor skills, and the volumes of the cerebellum and the brainstem correlated positively to fine motor skills. Total cortical grey matter volume showed a negative correlation with fine motor skills.

The group scores for the children included in this study were below the test norms on both VMI and fine motor skills, which was in line with previous studies where children born preterm have consistently shown poorer VMI performance and fine motor skills compared to children born at term[7 43]. However, the lower group performance is still considered to be within low average range. Within this relatively well-functioning group of children born EPT, we found a small, but statistically significant, difference between the sexes with regards to VMI performance, with girls outperforming boys. Sex differences in VMI performance have consistently been reported in children born

preterm [7] and MRI studies of children born preterm have revealed differences between the sexes in brain volumes and the microstructure of the brain [38 44 45], indicating altered early development of the brain in boys born preterm. This indicates that the brain of preterm born boys develops in an altered way compared to preterm born girls, affecting both the structure and the function of the brain.

Cerebellar underdevelopment, with reductions in cerebellar volume, and sustained white matter injuries in children born preterm, have been suggested as possible mechanisms for poor visuo-motor function [46 9 33], although many neural networks comprised of other neural structures have also been proposed to be involved in VMI including the visual, motor, sensory, salience and default mode networks, the subcortical regions and the brain stem [47 48]. Even though this study is the first, to our knowledge, to explore the associations between brain volumes at term equivalent age and VMI at 6.5 years in a cohort of children born EPT, there have been previous reports of associations between brain volumes and VMI performance in more mature preterm children. In these reports, positive correlations were seen between the growth rate of the caudate and the thalamus during the neonatal period and VMI scores at 4 years of age [31], and between thalamic and cerebellar white matter volumes and VMI scores at 15 years of age [32]. We did not find these associations in our cohort and this finding was in line with a previous study that evaluated 8-year-old children born preterm [49]. One explanation for these different results could be individual childhood growth trajectories and different gestational ages in the various study cohorts. Additional studies using inductive (exploration) and deductive (hypotheses-driven) approaches will be useful in determining the relationships between VMI and neural structure.

VMI performance is dependent on fine motor skills. And, fine motor skills have been shown to be a facilitator of visuo-motor function even though the causality of this mediation is not known [46]. The present study revealed positive correlations between better fine motor skills and larger volumes of the precentral gyrus, the cerebellum and the brainstem - motor areas of the brain that have been reported to be involved in fine motor skills [50]. The precentral gyrus, which is located in the frontal lobe, is the origin of the corticospinal tracts known to affect motor functions. A smaller precentral gyrus could, therefore, be expected to be correlated with reduced motor performance and also to diminished VMI performance, in line with our findings, since fine motor skills have been shown to be a mediator of visuo-motor function, even though the cause of this mediation is not known [46]. Both the cerebellum and the brain stem are important for fine motor skills and VMI, as well as for other tasks that rely on the motor system [47], and our results support their important role in this cross-modal function. In addition, the cerebellum has long been known to be involved in movement modulation, balance and coordination, and there is now evidence that it is also important for a number of cognitive functions, including visuospatial attention [51]. Finally, cerebellar growth has been shown to relate to visual perception at school age in children born very preterm [52] and specific sub-regional volumes of the cerebellum have been shown to be related to VMI and influenced by other perinatal factors, such as pain and infections[52]. Taken together, the literature suggests that neurocorrelates for fine motor skills are important for VMI performance as well, whether the neurocorrelates are contributing to VMI performance directly, or indirectly, through fine motor skills. The current findings suggest that the brain growth of the precentral gyrus, cerebellum and brainstem have already altered during the neonatal period and that this affects functions such as VMI and fine motor skills.

We were surprised to find a negative correlation between cortical grey matter volume and fine motor skills in our cohort, despite the fact that Keunen et al reported a similar finding. Those authors also reported an inverse relationship between cortical grey matter volume and fine motor function when children who were born preterm reached 2.5 years [20]. Measuring the cortical grey volume depends on the segmentation methods used to separate grey matter from the cerebellum which could make the classifying cortical grey matter volume imprecise. It is also possible that atypical patterns of brain development play a role in the grey matter volume and fine motor skills relationship, in the preterm brain [16].

A strength of this study is its population-based prospective cohort study design. The study focused on children born EPT without major brain lesions, which meant that our cohort was relatively healthy. This was reflected in their average range performances on both the VMI and the fine motor skills tests, with a mean of only -0.5 SD below the norms, which is higher than previously reported in preterm populations. This study also has several limitations. We had to exclude many children from the morphometric analyses, due to the strict criteria for data quality, and this was a reflection of the well-known difficulties in processing neonatal MRI images in children born EPT. This left us with a relatively small sample size, although the children with morphometric data were largely representative of the whole cohort. Visual-motor integration was assessed with the main Beerys VMI test, but did not include the supplementary tests of visual perception and motor coordination which could have enabled us to distinguish between visual perception and fine motor function with regard to the VMI function. Finally, we were not able to include a control group of children born at term.

Conclusion

In summary, this study found positive correlations between VMI performance, fine

motor skills and brain volumes at term-equivalent age in regions that were already known to be involved in these functions. To our knowledge, this is the first study to examine the relationship between neonatal brain volumes and VMI and fine motor skills at the age of 6.5 years in a population-based cohort of children born EPT. Further studies including larger sample sizes are needed to confirm our results, to explore the relationships between the underlying visual and motor modalities and VMI in greater depth, and to examine the potential use of early regional brain volumes as imaging biomarkers related to VMI and fine motor skills. Since it has been reported that early interventions can improve VMI in general school populations [53] as well as in children born preterm [54] , a possibility of early identification of children at risk could diminish the impact of preterm birth on these functions.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from the parents of all individual participants included in the study.

Author's contributions:

J Bolk designed the study, collected data, performed analyses, interpreted the data, drafted and revised the manuscript and approved the final version.

N Padilla designed the study, collected data, performed analyses, interpreted the data, revised the manuscript and approved the final version.

L Broström collected data, interpreted data, revised the manuscript and approved the final version.

L Forsman collected data, interpreted data, revised the manuscript and approved the final version.

K Hellgren collected data, interpreted data, revised the manuscript and approved the final version.

U Åden designed the study, collected data, interpreted the data, revised the manuscript and approved the final version

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Abbreviations: *Cerebral palsy (CP), Sum of grey and white matter excluding cerebrospinal fluid (CPAR), Extremely Preterm Born (EPT), Gestational age (GA), Magnetic Resonance Imaging (MRI), Movement Assessement Battery for Children-2 (M-ABC), Standard Deviation (SD), Visual-motor integration (VMI)*

Data sharing statement: Any requests for data sharing should be addressed to author U.Å.

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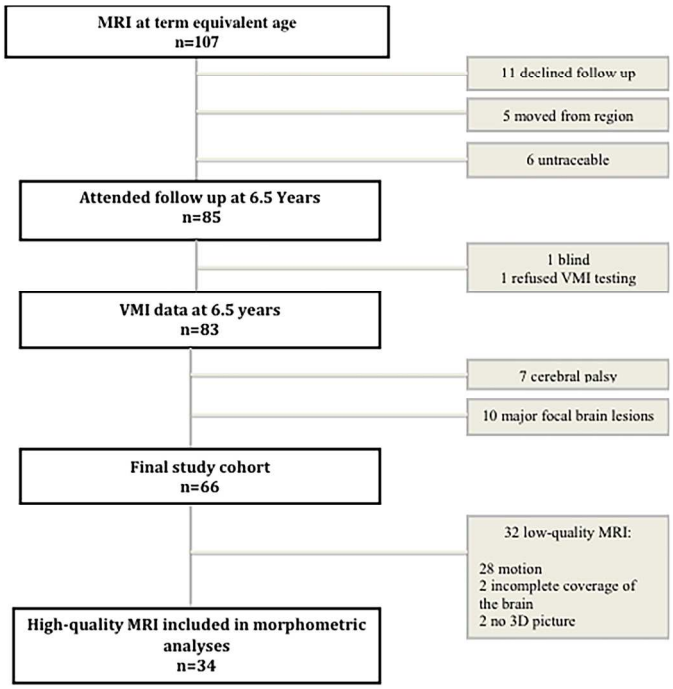

Figure 1. Study population

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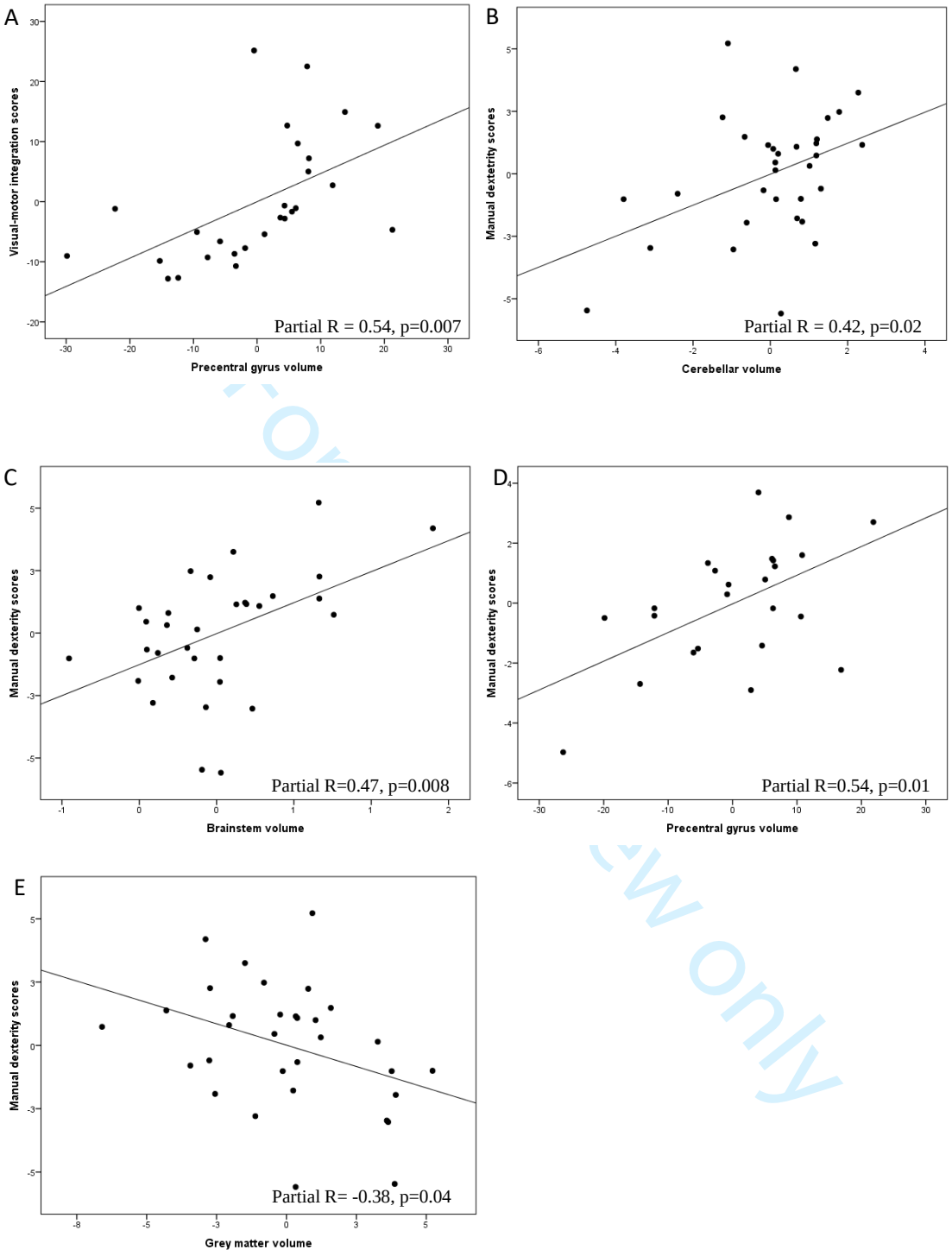

Figure 2. Illustrations of partial correlations between neonatal brain volumes, visual-motor integration and fine motor skills (assessed by manual dexterity scores on the Movement Assessment Battery for Children-2) at 6.5 years of age, using plots of residuals. Analyses are adjusted for total cerebral parenchyma (grey matter plus white matter) and sex. (A) Correlations between the volume of the precentral gyrus and visual-motor integration scores. (B-E) Correlations between the volumes of the cerebellum, brainstem, precentral gyrus, grey matter and fine motor skills.

Table 1. Characteristics of the 66 children born at gestational age below 27 weeks and without major brain lesions or cerebral palsy (n = 66)

Gestational age at birth, weeks, median (range)	25.6 (23.4-26.6)
Birth weight, grams, mean (SD)	839 (152)
Gender, girls/boys	29/37
Small for gestational age, n (%)	4 (6)
Prenatal steroids, n (%)	60 (91)
Premature Rupture of the Membranes, n (%)	19 (29)
Cesarean section, n (%)	32 (48)
Sepsis, n (%)	51 (77)
Days of mechanical ventilation, median (range)	7 (0-55)
Postnatal steroids, n (%)	11 (17)
Bronchopulmonary dysplasia, oxygen at 36 weeks, n (%)	26 (39)
Necrotizing Enterocolitis, n (%)	6 (9)
Patent Ductus Arteriosus, ligation, n (%)	20 (30)
Laser treatment for Retinopathy of Prematurity, n (%)	8 (12)
Intraventricular hemorrhage grade I-II, n (%)	23 (35)

SD = Standard Deviation,. n = number. Sepsis was defined as positive blood culture or clinical picture of sepsis in association with elevated C-reactive protein or leukocyte count. Data on small for gestational age was missing for four children.

Supplementary Table 1. Characteristics of the children born at gestational age<27 weeks with or without high quality MRI

	High quality MRI n=34	**Low quality MRI n=32**	***p***
Gestational age at birth, weeks, median (range)	25.85 (23.4-26.6)	25.45 (23.4-26.6)	0.16
Birth weight, grams, mean (SD)	857 (154)	820 (47)	0.33
Gender, girls/boys, n	15/19	14/18	1.00
Small for gestational age, n	1	3	0.35
Prenatal steroids, n	32	28	0.42
Premature rupture of the membranes, n	10	9	1.00
Cesarean section, n	16	16	1.00
Sepsis, n	24	27	0.24
Days of mechanical ventilation, median (range)	3 (0-37)	11 (0-55)	**0.04**
Postnatal steroids, n	4	7	0.33
Bronchopulmonary Dysplasia, oxygen at 36 weeks, n	12	14	0.62
Necrotizing enterocolitis, n	1	5	0.10
Patent ductus arteriosus, ligation, n	9	11	0.60
Laser treatment for retinopathy of prematurity , n	2	6	0.14
Intraventricular hemorrhage grade I-II, n	10	13	0.44
Mild white matter abnormality, n	18	12	0.09
Gestational age at MRI, weeks, median (range)	40.79 (39.14-45.28)	40.28 (39.14-43.28)	0.08
Age at 6.5 year assessment, months, median (range)	77.20 (75.29-80.18)	77.23 (76.03-86.33)	0.59
VMI standard score, mean (SD)	94 (10)	91 (9)	0.20
M-ABC-2 manual dexterity score, mean (SD)	8 (2)	7 (3)	0.68

All children were without cerebral palsy, focal brain lesions or severe white matter abnormalities. SD = Standard deviation, MRI = Magnetic Resonance Imaging, VMI=Visual-motor integration, M-ABC-2=Movement Assessment Battery for Children-2

Supplementary Table 2. Characteristics of the children born at gestational age <27 weeks with and without atlas segmentation data.

	Atlas segmentation data n=26	**No atlas segmentation data n=40**	*p*
Gestational age at birth, weeks, median (range)	26.85 (23.4-26.6)	25.50 (23.4-26.6)	0.28
Birth weight, grams, mean (SD)	874 (153)	817 (146)	0.13
Gender, girls/boys	13/13	16	0.46
Small for gestational age, n	0	4	0.15
Prenatal steroids, n	25/26	35	0.39
Premature rupture of the membranes, n	7	12	1.00
Cesarean Section, n	10	22	0.22
Sepsis, n	17	34	0.08
Days of mechanical ventilation, median (range)	3 (0-36)	10 (0-55)	0.04
Postnatal steroids, n	3	8	0.51
Bronchopulmonary Dysplasia, oxygen at 36 weeks, n	10	16	1.00
Necrotizing enterocolitis, n	0	6	0.07
Patent ductus arteriosus, ligation, n	7	13	0.79
Laser treatment for retinopathy of prematurity , n	1	7	0.13
Intraventricular hemorrhage grade I-II, n	7	16	0.30
Mild white matter abnormality, n	16	14	0.09
Gestational age at MRI, weeks, median (range)	40.93 (39.71-43.28)	40.36 (39.14-45.28)	0.18
Age at 6.5 year assessment, months, median (range)	77.16 (75.29-80.20)	77.23 (76.03-86.33)	0.21
VMI standard score, mean (SD)	91.69 (14.14)	89.82 (11.71)	0.87

M-ABC-2 manual dexterity score, mean (SD)	7 (2)	8 (3)	0.38

All children were without cerebral palsy, focal brain lesions or severe white matter abnormalities.

SD = Standard deviation, MRI = Magnetic Resonance Imaging, VMI=Visual-motor integration, M-ABC-2=Movement Assessment Battery for Children-2

Supplementary Table 3. Correlations between brain volumes at term equivalent age, visual-motor integration and fine motor skills scores a 6.5 years in children born at GA <27 weeks.

Brain region	**Visual-motor integration**		**Fine motor skills**	
	Correlation coefficient (partial r)	**p**	**Correlation coefficient (partial r)**	**p**
Grey matter	0.05	0.77	-0.38	**0.04**
White matter	-0.33	0.07	0.11	0.57
Deep grey matter	0.02	0.93	0.05	0.79
Cerebellum	0.24	0.19	0.42	**0.02**
Brain stem	0.08	0.66	0.47	**0.008**
Frontal lobe	-0.11	0.61	-0.19	0.40
Temporal lobe	-0.10	0.63	-0.12	0.61
Parietal lobe	-0.33	0.12	-0.22	0.32
Occipital lobe	0.18	0.40	0.26	0.24
Central Region	0.35	0.09	0.30	0.17
Networks				
Visual network				
Superior occipital gyrus	0.23	0.28	0.39	0.07
Middle occipital gyrus	0.12	0.59	0.06	0.78
Inferior occipital gyrus	-0.26	0.22	-0.21	0.35
Calcarine cortex	-0.24	0.27	-0.01	0.97
Cuneus	0.27	0.20	0.20	0.37
Lingual gyrus	-0.13	0.54	-0.01	0.67
Motor network				
Precentral gyrus	0.54	**0.007**	0.54	**0.01**
Frontal medial	0.005	0.99	-0.05	0.83
Supplementary motor area	-0.03	0.89	-0.19	0.40
Sensory network				
Postcentral gyrus	0.07	0.75	0.17	0.45
Salience network				
Insula	-0.001	0.99	-0.08	0.73
Anterior cingulate gyrus	0.09	0.67	0.10	0.65
Thalamus	-0.04	0.87	0.11	0.62
Amygdala	-0.16	0.45	-0.23	0.31
Default mode network				
Precuneus	-0.26	0.22	-0.05	0.84
Angular_gyrus	0.26	0.21	-0.17	0.45
Hippocampus	-0.08	0.72	-0.11	0.63
Subcortical regions				
Subcortical grey matter, total	-0.10	0.63	-0.04	0.86
Pallidum	0.01	0.99	0.07	0.76

Caudate	-0.04	0.85	-0.09	0.70
Putamen	-0.26	0.23	0.06	0.79

All children are without cerebral palsy or major brain lesions. Results from Pearson´s partial correlation, adjusted for total cerebral parenchyma (total cortical grey and white matter) and sex. Central region = precentral and postcentral gyri, rolandic operculum bilaterally.

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Visual-motor integration and fine motor skills at 6.5 years of age and associations with neonatal brain volumes in children born extremely preterm in Sweden: population-based cohort study

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Visual-motor integration and fine motor skills at 6.5 years of age and associations with neonatal brain volumes in children born extremely preterm in Sweden: population-based cohort study

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Abstract

Objectives

This exploratory study aimed to investigate associations between neonatal brain volumes and visual-motor integration (VMI) and fine motor skills in children born EPT when they reached 6.5 years of age.

Setting

Prospective population-based cohort study in Stockholm, Sweden, during three years.

Participants

All children born before gestational age 27 weeks 2004-2007 in Stockholm, without major morbidities and impairments, and who underwent magnetic resonance imaging at term-equivalent age.

Main outcome measures

Brain volumes were calculated using morphometric analyses in regions known to be involved in VMI and fine motor functions. VMI was assessed with The Beery-Buktenica Developmental Test of Visual-Motor Integration - Sixth Edition and fine motor skills were assessed with the manual dexterity subtest from the Movement Assessment Battery for Children-Second Edition, at 6.5 years. Associations between the brain volumes and VMI and fine motor skills were evaluated using partial correlation, adjusted for total cerebral parenchyma and sex.

Results

Out of 107 children born at gestational age <27 weeks, 83 were assessed at 6.5 years and 66/83 were without major brain lesions or cerebral palsy and included in the analyses. A representative subsample underwent morphometric analyses: automatic segmentation (n=34) and atlas-based segmentation (n=26). The precentral gyrus was associated with both VMI (r=0.54, p=0.007) and fine motor skills (r=0.54, p=0.01). Associations were also seen between fine motor skills and the volume of the cerebellum (r=0.42, p=0.02), brainstem (r=0.47, p=0.008) and grey matter (r=-0.38, p=0.04).

Conclusions

Neonatal brain volumes in areas known to be involved in VMI and fine motor skills were associated with scores for these two functions when children born EPT without major brain lesions or cerebral palsy were evaluated at 6.5 years of age. Establishing clear associations between early brain volume alterations and later VMI and/or fine motor skills could make early interventions possible.

Strengths and limitations of this study

- This was a robust population-based cohort study design that used advanced magnetic resonance imaging techniques and established assessment tools
- It studied visual-motor integration and fine motor skills in extremely preterm born children at 6.5 years, which is an important age for Swedish school children
- Although we had to exclude numerous children from the morphometric analyses, due to strict data quality criteria, the sample was representative of the cohort
- We were unable to include a control group of children born at term in the analyses

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Competing interests: None

Introduction

Visual-motor function is an important cross-modal ability that involves the integration of visual function and perception, eye-hand coordination, fine motor skills and visual-motor integration (VMI) [1]. Studies have shown that VMI can predict a child´s future

hand-writing skills [2-4] and academic performance in reading, writing and mathematics [5]. Evaluating VMI performance is therefore an important component of the test batteries that are used to detect children who risk school problems. Fine motor skills are a fundamental component of hand and visual-motor function, which also contributes to school performance[6]. Several reports have shown that children born preterm have poor VMI and motor function [7 8-10] and it is well known that this group of children risk poor school performance and learning disabilities [11-13].

Although problems with VMI can stem from any of the underlying, contributing abilities listed above, when VMI and motor abilities have been investigated together, and perceptual and general cognitive abilities have been held constant, children with lower general motor scores are seen to have lower VMI scores [14]. Children born very low birth weight show a similar pattern [15]: VMI showing stronger relationships with motor ability than with visual perception, suggesting that motor skills and manual fine motor skills in particular, are crucial components underlying VMI. On the other hand, visual perceptual deficits in children born EPT are well documented [7] and their role in VMI should not be underestimated even though their contribution to VMI in children born EPT was not investigated in the present study. Therefore, a less-defined exploration of brain areas known to be associated with VMI is a useful approach, especially when investigating the neural associations of a multi-modal ability, in groups with potentially atypical brain development trajectories[16].

It is largely unknown how the developmental alterations of the brain affect VMI and fine motor skills in children born preterm. However, we have previously reported that neonatal brain volumes are affected in preterm infants [17], and other researchers have shown that these alterations in preterm brain volumes persist until at least early childhood [18]. Volumetric alterations in the brain have also been associated with

neurodevelopmental outcomes in preterm born children [19 20]. However, the relationship between volume alterations in the brains of children born extremely (EPT), at less than 27 weeks of gestation, and VMI and fine motor skills at school age remains largely unexplored.

It has been reported that several networks in the brain are involved in the mediation of VMI and fine motor skills - the visual, salience, sensory motor and default mode networks [21]. Previous studies in adolescents born preterm have indicated that volumes of the cerebellum and thalamus [22], superior temporal gyrus, insula, medial occipital lobe and temporal lobe [23] are associated to VMI scores. Also, a study looking at brain growth in preterm children reported that growth of the caudate and globus palldius could predict VMI scores [24].Based on these previous reports, we hypothesized that early brain volume alterations in these regions and networks in the brain would be related to later VMI and fine motor skills in Children born extremely preterm. We used an exploratory approachto investigate these possible associations, using two separate analyses to measure the brain volumes at term-equivalent age : atlas-based segmentation and automatic segmentation, and carried out a clinical evaluation of VMI and fine motor skills at the age of 6.5 years.

Methods

Study population

The study population was a sub-cohort of the Extremely Preterm Infants in Sweden Study (EXPRESS) cohort. EXPRESS was a prospective national population-based cohort study which invited all children born in Sweden at a gestational age (GA) of less than 27 weeks over a three-year period to take part in clinical follow ups at 2.5 and 6.5 years of age[25 26]. The present study included 107 children born in Stockholm

between January 1 2004 and March 31 2007, without chromosomal aberrations, congenital malformations or infections, who had undergone magnetic resonance imaging (MRI) of the brain at term equivalent age.

Gestational age was assessed by maternal ultrasound at around a GA of 18 weeks and perinatal and neonatal data were prospectively collected from the children´s medical records. Cranial ultrasound was performed on a regular basis during the neonatal period up to a GA of 40 weeks, according to our clinical routine. Children were excluded from the analyses in the present study if they had major brain lesions defined as intraventricular hemorrhage, periventricular leukomalacia, severe white matter score according to Inder [27] or hydrocephalus, or cerebral palsy (CP) as defined by the Surveillance of Cerebral Palsy in Europe Working Group [28]. All children had been screened for retinopathy of prematurity and evidence-based treatment had been administered [29].

The study was approved by the local ethics committees in Stockholm and Lund (Regionala etikprövningsnämnden in Stockholm, dnr 04-889/2, 2006/1217-32 and 2010/850-31/1; Regionala etikprövningsnämnden in Lund, dnr 42/2004, dnr 2009/9 and dnr 2016/104) and the parents of all the children gave their written, informed consent before the study.

Assessment at 6.5 years of age

Visual-motor integration was assessed using the Beery-Buktenica Developmental Test of Visual-Motor Integration - sixth edition [30]. This test consists of 30 geometrical shapes that the child is asked to copy with a pen and paper and it is terminated when three figures in a row have been incorrectly copied. The drawings are examined and acceptable approximations of the model drawings are each given one point. The raw score is the total number of correct drawings and this is then transformed to an age-

corrected standard score. Standard scores were used in the analyses in this study. The normative mean score is 100 with a standard deviation (SD) of 15.

Fine motor skills were assessed with the manual dexterity subtest of the Movement Assessment Battery for Children – Second edition (M-ABC-2) which measures unimanual speed, bimanual coordination and unimanual spatial accuracy [31]. Age-adjusted standard scores were used for the analyses. The reference mean score is 10 with a standard deviation of 3, and scores below 7 indicate definitive or borderline motor problems.

Binocular visual acuity was measured with habitual correction at three meters with the Lea Hyvärinen chart [32]. Visual impairment was defined as a visual acuity of less than 0.33 in the better eye.

MRI data acquisition and processing

All the children were scanned using a Philips Intera 1.5 Tesla MRI system (Philips International, Amsterdam, The Netherlands) at term equivalent age.. The child was fed before the scanning procedure and given a low dose of chloralhydrate (30 mg/kg) orally or rectally, as previously described **[33].** A sagittal T1-weighted turbo spin echo sequence, an axial inversion recovery sequence and an axial T2-weighted sequence were run. The three-dimensional T1-weighted images were acquired with an echo time of 4.6 msec, a repetition time of 40 msec, a flip angle of 30°, a voxel size of 0.7 × 0.7 × 0.1 mm and a field of view of 180mm. The MRI protocol has previously been reported [33]. Quality assurance was considered important in order to obtain accurate data, even though this meant that we were left with a relatively small sample size. The imaging data was checked for quality, based on a visual inspection of the raw data sets, and the reasons for low imaging quality are presented in **Figure 1.** MRI data went into two separate analyses, atlas based segmentation and automatic

segmentation; atlas-based segmentation to conduct the regional segmentation of specific regions [34] and automatic segmentation to extract the mean volumes of the grey matter white matter, cerebrospinal fluid, basal ganglia, brainstem and cerebellum [35].

Atlas based segmentation

The whole brain of the included infants was divided into 90 anatomical regions, by using the automated anatomical labelling neonatal atlas [34], as previously described [36]. Briefly, the intensity image that generated the neonatal atlas was registered to the T1-weighted image of each infant, then the generated deformation field was used to transform the label map with 90 regions from the atlas space to the subject space (Supplementary Figure 1). A visual inspection was performed for each subject and each step. The volume of each region was determined by using a proper script written in MATLAB selecting the region of interest via its voxel value.

We selected brain regions that had been previously described as being in the networks that mediate VMI and fine motor skills, namely the visual, salience, sensory motor and default mode networks [22-24]. We also considered the subcortical regions: pallidum, putamen, caudate and thalamus. The volume of each brain region was determined by adding together the volumes of their components.

Automatic segmentation

We first performed automatic segmentation of brain tissues (T1-weighted images) using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm), running on MATLAB version 7.5 (MathWorks, Natick, Massachusetts, USA). This process focused on specific neonatal priors, including grey matter, white matter, cerebrospinal fluid, deep grey matter, the cerebellum and brainstem, which have previously been described in detail [17 35]. We used the tissue class images created during segmentation to generate a

custom template to improve coregistration using Diffeomorphic Anatomical Registration Through an Exponential Lie algebra algorithm (DARTEL). [37]. After this step the images were modulated via SPM 8 software to improve the inter-subject registration.. The Easy Volume Toolbox [38] was used to extract the global brain tissue volumes from the segmented, normalized and modulated images of each child.

Statistical analyses

The analyses were carried out with SPSS for Windows, version 22.0 (SPSS Inc, Chicago, Illinois, USA) and the data were checked for normality, homogeneity and outliers. In order to compare the groups, we used the Student´s t-test and Mann Whitney U test for continuous variables and the chi-square test or Fisher´s exact test for categorical data, as appropriate. The associations between brain volumes, VMI scores and fine motor skills scores were explored using partial correlation. Total cerebral parenchyma (CPAR) – the sum of the grey matter and white matter, excluding cerebrospinal fluid - was used as a covariate to control for generalized scaling effects. Because sex, GA at birth and the GA at the time of the scan have previously been shown to influence brain volume size in preterm children [39 40] we performed the analyses with different covariate pairs. First we used CPAR and GA at birth, then we used CPAR and the GA at scan and finally we used CPAR and sex. GA at birth and GA at scan did not influence the results, but sex did, so CPAR and sex were chosen as the covariates in the final model. There was one multivariate outlier which was identified by the Mahalanobis distance when we investigated the atlas segmentation data in relation to the fine motor skills scores, and this child was excluded from those analyses. Bonferroni's correction for multiple comparisons was not applied because of the exploratory nature of the study and the reduced sample size examined [41-43]. The level of significance was set at a two-sided p-value of <0.05.

Results

Study population

A summary of the study population is presented in **Figure 1** and their perinatal characteristics are presented in **Table 1.**

Table 1. Characteristics of the 66 children born at gestational age below 27 weeks and without major brain lesions or cerebral palsy (n = 66)

Gestational age at birth, weeks, median (range)	25.6 (23.4-26.6)
Birth weight, grams, mean (SD)	839 (152)
Gender, girls/boys	29/37
Small for gestational age, n (%)	4 (6)
Prenatal steroids, n (%)	60 (91)
Premature Rupture of the Membranes, n (%)	19 (29)
Cesarean section, n (%)	32 (48)
Sepsis, n (%)	51 (77)
Days of mechanical ventilation, median (range)	7 (0-55)
Postnatal steroids, n (%)	11 (17)
Bronchopulmonary dysplasia, oxygen at 36 weeks, n (%)	26 (39)
Necrotizing Enterocolitis, n (%)	6 (9)
Patent Ductus Arteriosus, ligation, n (%)	20 (30)
Laser treatment for Retinopathy of Prematurity, n (%)	8 (12)
Intraventricular hemorrhage grade I-II, n (%)	23 (35)

SD = Standard Deviation,. n = number. Sepsis was defined as positive blood culture or clinical picture of sepsis in association with elevated C-reactive protein or leukocyte count. Data on small for gestational age was missing for four children.

At the time of the scan, the median (range) GA in the 66 children without major brain lesions or CP was 40.8 (39.1-45.3) weeks and for the assessment of VMI and fine motor skills it was 6 years 5 months (6 years 3 months - 7 years 2 months).

The subsample of 34 children with high-quality MRI scans was representative of the whole cohort with regard to their perinatal and neonatal characteristics, findings on structural MRI, gestational age at MRI, age at assessment at 6.5 years and mean VMI and fine motor score (**Supplementary Table 1**). During the atlas-based segmentation process, 8 subjects had co-registration failure, leaving 26 children in the final sample. These 26 children were also representative of the cohort of 66 children with regard to the above characteristics, except for days on mechanical ventilation, which was a median (range) of 3 (0-36) days for the sub-sample versus 10 (0-55) days for the other children (p=0.04) **(Supplementary Table 2).**

Assessment at 6.5 years of age

The mean (SD) VMI standard score for the 66 children without major brain lesions or CP was 93 (10), 7 points (0.5 SD) below the norm. The mean (SD) VMI scores for the 29 girls was higher than for the 37 boys: mean (SD) at 96 (10) versus 90 (8), respectively (p=0.02).

The mean (SD) fine motor skills score was 8 (3), which was 2 points (0.5 SD) below the norm, and there were no significant sex differences as the girls scored 8 (3) and the boys 7 (3) (p=0.16).

None of the children included in the study had a visual impairment.

Brain volumes and associations with VMI and fine motor skills

We identified a number of regions that demonstrated significant associations

between brain volumes, VMI and fine motor skills scores. VMI performance showed a positive correlation with the volume of the precentral gyrus (partial r=0.54, p=0.007), whereas the fine motor skills scores showed a positive correlation with the volumes of the precentral gyrus (partial r = 0.54, p=0.01), the cerebellum (partial r = 0.42, p=0.02) and the brainstem (partial r = 0.47 p=0.008) and a negative correlation with cortical grey matter volume (partial r = -0.38, p=0.04) (**Figure 2**). All the correlation analyses can be found in **Supplementary Table 3**.

Discussion

In this exploratory study, the associations between brain volumes at term equivalent age and VMI and fine motor skills at 6.5 years in children born EPT without major brain lesions or CP were explored in regions of the brain previously reported to be involved in those functions. The volume of the precentral gyrus showed a positive correlation with both VMI and fine motor skills, and the volumes of the cerebellum and the brainstem correlated positively to fine motor skills. Total cortical grey matter volume showed a negative correlation with fine motor skills.

The group scores for the children included in this study were below the test norms on both VMI and fine motor skills, which was in line with previous studies where children born preterm have consistently shown poorer VMI performance and fine motor skills compared to children born at term[7 44]. However, the lower group performance is still considered to be within low average range. Within this relatively well-functioning group of children born EPT, we found a small, but statistically significant, difference between the sexes with regards to VMI performance, with girls outperforming boys. Sex differences in VMI performance have consistently been reported in children born preterm [7] and MRI studies of children born preterm have revealed differences between the sexes in brain volumes and the microstructure of the brain [39 45 46],

indicating altered early development of the brain in boys born preterm. This indicates that the brain of preterm born boys develops in an altered way compared to preterm born girls, affecting both the structure and the function of the brain.

Cerebellar underdevelopment, with reductions in cerebellar volume, and sustained white matter injuries in children born preterm, have been suggested as possible mechanisms for poor visuo-motor function [47 9 23], although many neural networks comprised of other neural structures have also been proposed to be involved in VMI including the visual, motor, sensory, salience and default mode networks, the subcortical regions and the brain stem [21 48]. Even though this study is the first, to our knowledge, to explore the associations between brain volumes at term equivalent age and VMI at 6.5 years in a cohort of children born EPT, there have been previous reports of associations between brain volumes and VMI performance in more mature preterm children. In these reports, positive correlations were seen between the growth rate of the caudate and the thalamus during the neonatal period and VMI scores at 4 years of age [24], and between thalamic and cerebellar white matter volumes and VMI scores at 15 years of age [22]. We did not find these associations in our cohort and this finding was in line with a previous study that evaluated 8-year-old children born preterm [49]. One explanation for these different results could be individual childhood growth trajectories and different gestational ages in the various study cohorts. Additional studies using inductive (exploration) and deductive (hypotheses-driven) approaches will be useful in determining the relationships between VMI and neural structure.

VMI performance is dependent on fine motor skills. And, fine motor skills have been shown to be a facilitator of visuo-motor function even though the causality of this mediation is not known [47]. The present study revealed positive correlations between

better fine motor skills and larger volumes of the precentral gyrus, the cerebellum and the brainstem - motor areas of the brain that have been reported to be involved in fine motor skills [50]. The precentral gyrus, which is located in the frontal lobe, is the origin of the corticospinal tracts known to affect motor functions. A smaller precentral gyrus could, therefore, be expected to be correlated with reduced motor performance and also to diminished VMI performance, in line with our findings, since fine motor skills have been shown to be a mediator of visuo-motor function, even though the cause of this mediation is not known [47]. Both the cerebellum and the brain stem are important for fine motor skills and VMI, as well as for other tasks that rely on the motor system [48], and our results support their important role in this cross-modal function. In addition, the cerebellum has long been known to be involved in movement modulation, balance and coordination, and there is now evidence that it is also important for a number of cognitive functions, including visuospatial attention [51]. Finally, cerebellar growth has been shown to relate to visual perception at school age in children born very preterm [52] and specific sub-regional volumes of the cerebellum have been shown to be related to VMI and influenced by other perinatal factors, such as pain and infections[52]. Taken together, the literature suggests that neurocorrelates for fine motor skills are important for VMI performance as well, whether the neurocorrelates are contributing to VMI performance directly, or indirectly, through fine motor skills. The current findings suggest that the brain growth of the precentral gyrus, cerebellum and brainstem have already altered during the neonatal period and that this affects functions such as VMI and fine motor skills.

We were surprised to find a negative correlation between cortical grey matter volume and fine motor skills in our cohort, despite the fact that Keunen et al reported a similar finding. Those authors also reported an inverse relationship between cortical

grey matter volume and fine motor function when children who were born preterm reached 2.5 years [20]. Measuring the cortical grey volume depends on the segmentation methods used to separate grey matter from the cerebellum which could make the classifying cortical grey matter volume imprecise. It is also possible that atypical patterns of brain development play a role in the grey matter volume and fine motor skills relationship, in the preterm brain [16].

A strength of this study is its population-based prospective cohort study design. The study focused on children born EPT without major brain lesions, which meant that our cohort was relatively healthy. This was reflected in their average range performances on both the VMI and the fine motor skills tests, with a mean of only -0.5 SD below the norms, which is higher than previously reported in preterm populations. This study also has several limitations. We had to exclude many children from the morphometric analyses, due to the strict criteria for data quality, and this was a reflection of the well-known difficulties in processing neonatal MRI images in children born EPT. This left us with a relatively small sample size, although the children with morphometric data were largely representative of the whole cohort. This was due to rigorous entry and data quality criteria, as well as implicit methodological difficulties related to the scanning of preterm infants. Scanning preterm neonates is considered a challenging task due to their immature physiology and anatomy. Patient motion may occur more often thus patient preparation and image protocols should be modified and be dedicated for neonates. To minimize this limitation the development of novel pulse sequences to increase the speed of image acquisition, and MRI coils tailored to the head size of the subject, would have the potential to further increase success [53] .

Segmentation of cerebral tissues at term-equivalent age in children who were born extremely preterm is challenging due to the characteristics of the developing preterm

brain. The segmentation can be limited in small structures of the brain since the volumes are smaller and there is also a lower signal-to-noise ratio in preterm children. To minimize this we used only high quality MRI. To guide segmentation we used a larger number of tissue probability maps from preterms [35]with an extraclass tissue map for background, to provide a better modelling of the cerebrospinal fluid and other non-brain voxels and also ta aid further tissue classification. Visual-motor integration was assessed with the main Beerys VMI test, but did not include the supplementary tests of visual perception and motor coordination which could have enabled us to distinguish between visual perception and fine motor function with regard to the VMI function. We did not adjust for any diagnosis of autism or ADHD, which are reported to be common in children born extremely preterm [54]and have been linked to altered brain development in preterms[36 55] Finally, we were not able to include a control group of children born at term.

Conclusion

In summary, this study found positive correlations between VMI performance, fine motor skills and brain volumes at term-equivalent age in regions that were already known to be involved in these functions. To our knowledge, this is the first study to examine the relationship between neonatal brain volumes and VMI and fine motor skills at the age of 6.5 years in a population-based cohort of children born EPT. Further studies including larger sample sizes are needed to confirm our results, to explore the relationships between the underlying visual and motor modalities and VMI in greater depth, and to examine the potential use of early regional brain volumes as imaging biomarkers related to VMI and fine motor skills. Since it has been reported that early interventions can improve VMI in general school populations

[56] as well as in children born preterm [57] , a possibility of early identification of children at risk could diminish the impact of preterm birth on these functions.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from the parents of all individual participants included in the study.

Author's contributions:

J Bolk designed the study, collected data, performed analyses, interpreted the data, drafted and revised the manuscript and approved the final version.

N Padilla designed the study, collected data, performed analyses, interpreted the data, revised the manuscript and approved the final version.

L Broström collected data, interpreted data, revised the manuscript and approved the final version.

L Forsman collected data, interpreted data, revised the manuscript and approved the final version.

K Hellgren collected data, interpreted data, revised the manuscript and approved the final version.

U Åden designed the study, collected data, interpreted the data, revised the manuscript and approved the final version

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Abbreviations: *Cerebral palsy (CP), Sum of grey and white matter excluding cerebrospinal fluid (CPAR), Extremely Preterm Born (EPT), Gestational age (GA), Magnetic Resonance Imaging (MRI), Movement Assessement Battery for Children-2 (M-ABC), Standard Deviation (SD), Visual-motor integration (VMI)*

Data sharing statement: Any requests for data sharing should be addressed to author U.Å.

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Figure 1. Study population

Figure 2. Illustrations of partial correlations between neonatal brain volumes, visual-motor integration and fine motor skills (assessed by manual dexterity scores on the Movement Assessment Battery for Children-2) at 6.5 years of age, using plots of residuals. Analyses are adjusted for total cerebral parenchyma (grey matter plus white matter) and sex. (A) Correlations between the volume of the precentral gyrus and visual-motor integration scores. (B-E) Correlations between the volumes of the cerebellum, brainstem, precentral gyrus, grey matter and fine motor skills. Results are presented without correction for multiple comparisons.

Supplementary Figure1. Atlas overlaid on the sagittal, coronal and axial T1-weighted images from a single preterm child. Individual anatomical regions are color coded.

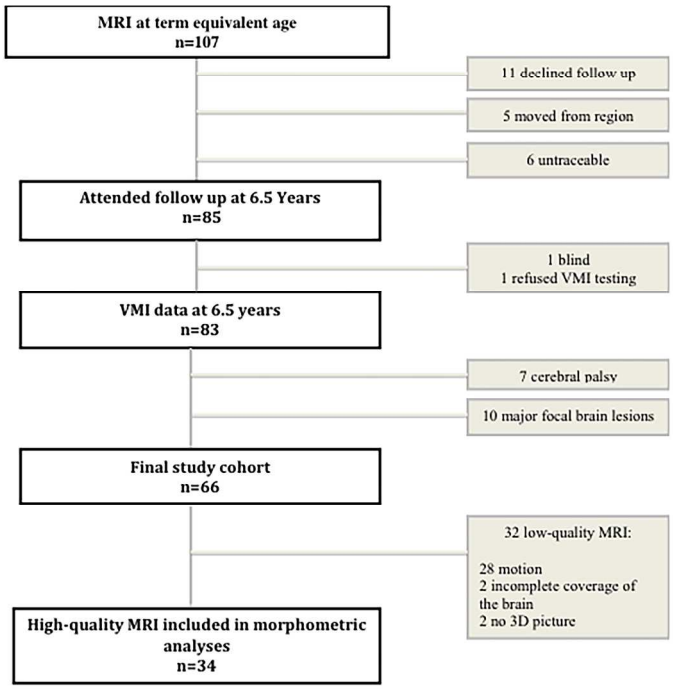


Figure 1. Study population

515x387mm (300 x 300 DPI)

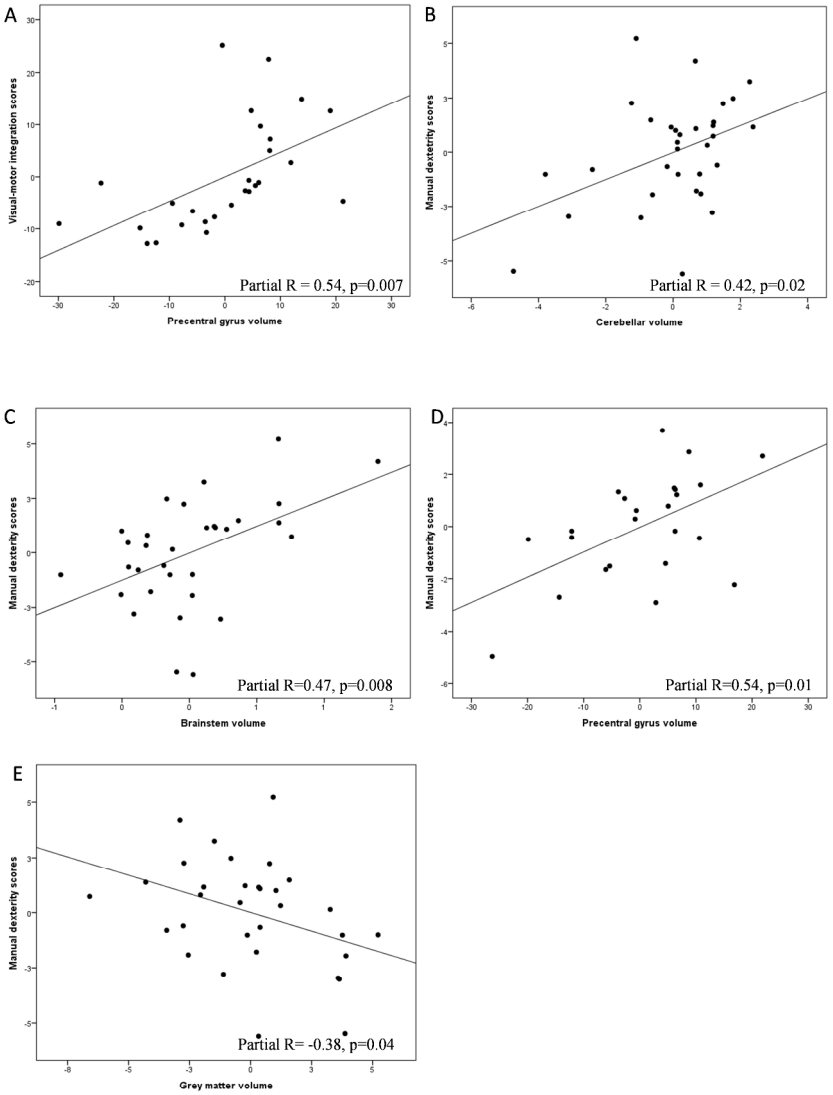
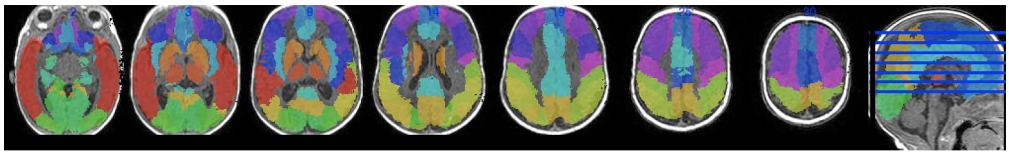


Figure 2. Illustrations of partial correlations between neonatal brain volumes, visual-motor integration and fine motor skills (assessed by manual dexterity scores on the Movement Assessment Battery for Children-2) at 6.5 years of age, using plots of residuals. Analyses are adjusted for total cerebral parenchyma (grey matter plus white matter) and sex. (A) Correlations between the volume of the precentral gyrus and visual-motor integration scores. (B-E) Correlations between the volumes of the cerebellum, brainstem, precentral gyrus, grey matter and fine motor skills. Results are presented without correction for multiple comparisons.

335x421mm (300 x 300 DPI)



Supplementary Figure 1. Atlas overlaid on the sagittal, coronal and axial T1-weighted images from a single preterm child. Individual anatomical regions are color coded.

700x101mm (300 x 300 DPI)

Supplementary Table 1. Characteristics of the children born at gestational age<27 weeks with or without high quality MRI

	High quality MRI n=34	**Low quality MRI n=32**	***p***
Gestational age at birth, weeks, median (range)	25.85 (23.4-26.6)	25.45 (23.4-26.6)	0.16
Birth weight, grams, mean (SD)	857 (154)	820 (47)	0.33
Gender, girls/boys, n	15/19	14/18	1.00
Small for gestational age, n	1	3	0.35
Prenatal steroids, n	32	28	0.42
Premature rupture of the membranes, n	10	9	1.00
Cesarean section, n	16	16	1.00
Sepsis, n	24	27	0.24
Days of mechanical ventilation, median (range)	3 (0-37)	11 (0-55)	**0.04**
Postnatal steroids, n	4	7	0.33
Bronchopulmonary Dysplasia, oxygen at 36 weeks, n	12	14	0.62
Necrotizing enterocolitis, n	1	5	0.10
Patent ductus arteriosus, ligation, n	9	11	0.60
Laser treatment for retinopathy of prematurity , n	2	6	0.14
Intraventricular hemorrhage grade I-II, n	10	13	0.44
Mild white matter abnormality, n	18	12	0.09
Gestational age at MRI, weeks, median (range)	40.79 (39.14-45.28)	40.28 (39.14-43.28)	0.08
Age at 6.5 year assessment, months, median (range)	77.20 (75.29-80.18)	77.23 (76.03-86.33)	0.59
VMI standard score, mean (SD)	94 (10)	91 (9)	0.20
M-ABC-2 manual dexterity score, mean (SD)	8 (2)	7 (3)	0.68

All children were without cerebral palsy, focal brain lesions or severe white matter abnormalities. SD = Standard deviation, MRI = Magnetic Resonance Imaging, VMI=Visual-motor integration, M-ABC-2=Movement Assessment Battery for Children-2

Supplementary Table 2. Characteristics of the children born at gestational age <27 weeks with and without atlas segmentation data.

	Atlas segmentation data n=26	**No atlas segmentation data n=40**	*p*
Gestational age at birth, weeks, median (range)	26.85 (23.4-26.6)	25.50 (23.4-26.6)	0.28
Birth weight, grams, mean (SD)	874 (153)	817 (146)	0.13
Gender, girls/boys	13/13	16	0.46
Small for gestational age, n	0	4	0.15
Prenatal steroids, n	25/26	35	0.39
Premature rupture of the membranes, n	7	12	1.00
Cesarean Section, n	10	22	0.22
Sepsis, n	17	34	0.08
Days of mechanical ventilation, median (range)	3 (0-36)	10 (0-55)	0.04
Postnatal steroids, n	3	8	0.51
Bronchopulmonary Dysplasia, oxygen at 36 weeks, n	10	16	1.00
Necrotizing enterocolitis, n	0	6	0.07
Patent ductus arteriosus, ligation, n	7	13	0.79
Laser treatment for retinopathy of prematurity , n	1	7	0.13
Intraventricular hemorrhage grade I-II, n	7	16	0.30
Mild white matter abnormality, n	16	14	0.09
Gestational age at MRI, weeks, median (range)	40.93 (39.71-43.28)	40.36 (39.14-45.28)	0.18
Age at 6.5 year assessment, months, median (range)	77.16 (75.29-80.20)	77.23 (76.03-86.33)	0.21
VMI standard score, mean (SD)	91.69 (14.14)	89.82 (11.71)	0.87

M-ABC-2 manual dexterity score, mean (SD)	7 (2)	8 (3)	0.38

All children were without cerebral palsy, focal brain lesions or severe white matter abnormalities.

SD = Standard deviation, MRI = Magnetic Resonance Imaging, VMI=Visual-motor integration, M-ABC-2=Movement Assessment Battery for Children-2

Supplementary Table 3. Correlations between brain volumes at term equivalent age, visual-motor integration and fine motor skills scores a 6.5 years in children born at GA <27 weeks.

Brain region	**Visual-motor integration**		**Fine motor skills**	
	Correlation coefficient (partial r)	**p**	**Correlation coefficient (partial r)**	**p**
Grey matter	0.05	0.77	-0.38	**0.04**
White matter	-0.33	0.07	0.11	0.57
Deep grey matter	0.02	0.93	0.05	0.79
Cerebellum	0.24	0.19	0.42	**0.02**
Brain stem	0.08	0.66	0.47	**0.008**
Frontal lobe	-0.11	0.61	-0.19	0.40
Temporal lobe	-0.10	0.63	-0.12	0.61
Parietal lobe	-0.33	0.12	-0.22	0.32
Occipital lobe	0.18	0.40	0.26	0.24
Central Region	0.35	0.09	0.30	0.17
Networks				
Visual network				
Superior occipital gyrus	0.23	0.28	0.39	0.07
Middle occipital gyrus	0.12	0.59	0.06	0.78
Inferior occipital gyrus	-0.26	0.22	-0.21	0.35
Calcarine cortex	-0.24	0.27	-0.01	0.97
Cuneus	0.27	0.20	0.20	0.37
Lingual gyrus	-0.13	0.54	-0.01	0.67
Motor network				
Precentral gyrus	0.54	**0.007**	0.54	**0.01**
Frontal medial	0.005	0.99	-0.05	0.83
Supplementary motor area	-0.03	0.89	-0.19	0.40
Sensory network				
Postcentral gyrus	0.07	0.75	0.17	0.45
Salience network				
Insula	-0.001	0.99	-0.08	0.73
Anterior cingulate gyrus	0.09	0.67	0.10	0.65
Thalamus	-0.04	0.87	0.11	0.62
Amygdala	-0.16	0.45	-0.23	0.31
Default mode network				
Precuneus	-0.26	0.22	-0.05	0.84
Angular_gyrus	0.26	0.21	-0.17	0.45
Hippocampus	-0.08	0.72	-0.11	0.63
Subcortical regions				
Subcortical grey matter, total	-0.10	0.63	-0.04	0.86
Pallidum	0.01	0.99	0.07	0.76

Caudate	-0.04	0.85	-0.09	0.70
Putamen	-0.26	0.23	0.06	0.79

All children are without cerebral palsy or major brain lesions. Results from Pearson´s partial correlation, adjusted for total cerebral parenchyma (total cortical grey and white matter) and sex. Central region = precentral and postcentral gyri, rolandic operculum bilaterally. Results are presented without correction for multiple comparisons.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-11
Bias	9	Describe any efforts to address potential sources of bias	10-12
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10-11
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,12,Figure 1
		(b) Give reasons for non-participation at each stage	7, 12, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8,11
		(b) Indicate number of participants with missing data for each variable of interest	11, Figure 1
		(c) Summarise follow-up time (eg, average and total amount)	7, 12, Supplementary Table 1, Supplementary Table 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12 Figure 2
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplementary Table 1, Supplementary Table 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	11,12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17,18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3-4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.