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Association between cognition and the retinal microvasculature in 11-year old children born preterm or at term

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ABSTRACT

Background: Retinal microvessels can be visualized non-invasively and mirror the status of the cerebral microvasculature.
Aims: To investigate whether in young children born prematurely or at term cognitive performance is related to retinal microvascular traits.
Study design, subjects: In 93 prematurely born infants (birth weight < 1000 g) and 87 controls born at term, we measured head circumference (HC) and determined intelligence quotient (IQ) by combining matrix reasoning and spatial span (Wechsler Non-Verbal test, Dutch version) and post-processed retinal photographs using Singapore I Vessel Assessment software (version 3.6).
Outcome measures, results: Compared with controls, cases had smaller HC (51.7 *vs* 53.4 cm; $p < 0.001$), lower IQ (93.9 *vs* 109.2; $p < 0.001$), smaller retinal arteriolar (CRAE; 162.7 *vs* 174.0 µm; $p < 0.001$) and venular (CRVE; 234.9 *vs* 242.8 µm; $p = 0.003$) diameters and CRAE/CRVE ratio (0.69 *vs* 0.72; $p = 0.001$). A 1-SD decrease in CRAE was associated with smaller HC (-0.53 cm; $p < 0.001$) and lower total IQ (-3.74; $p < 0.001$), matrix reasoning (-1.77; $p = 0.004$) and spatial span (-2.03; $p = 0.002$). These associations persisted after adjustment for sex and age and risk factors for cognitive impairment, including blood pressure, body mass index and parental educational attainment.
Conclusions: HC, total IQ, matrix reasoning and spatial span decrease with smaller retinal arteriolar diameter. Our findings suggest that maldevelopment of the cerebral microcirculation, as mirrored by the retinal microvasculature, has lasting effects on the growth of the brain and cognitive performance of prematurely born children.

1. Introduction

The micro- and macrovasculature undergo extensive, organ-specific perinatal maturation [1,2]. In 1989, the British epidemiologist David Barker suggested that intrauterine growth retardation, low birth weight, and premature birth predispose to cardiovascular disease later in life, including hypertension and coronary heart disease [1]. Around the same time, Brenner proposed that children at the lower end of the nephron endowment spectrum, *i.e.* children with low birth weight (growth restriction in term infants, preterm or both), have the highest risk for developing accelerated nephron loss and hypertension [2]. We designed the PREMATCH case-control study (Prematurity as Predictor of Children's Cardiovascular-Renal Health) to phenotype the micro- and macrocirculation of children born prematurely with extremely low

Abbreviations: CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; HC, head circumference; IQ, intelligence quotient

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birth weight (ELBW, below 1000 g) or delivered at term [3]. We previously demonstrated that at 11 years, ELBW children, compared with those born at term, had higher blood pressure, a 5- to 9-fold higher risk of prehypertension or hypertension, and smaller kidney size with lower glomerular filtration rate as estimated from the serum cystatin C level [4]. These findings are in line with the hypotheses proposed by Barker [1] and Brenner [2].

In addition to the kidney, the cerebral microcirculation requires extensive maturation in the perinatal period [5,6]. Several studies describe poorer cognitive performance [7–15] or narrower retinal arterioles [16] in 2- to 9-year old children born prematurely. The retinal microvessels can be visualized and quantified non-invasively and share embryogenetic and physiological characteristics with cerebral microvasculature [5]. To our knowledge, no previous study investigated whether there is association of head circumference or cognitive performance with retinal microcirculatory properties in prematurely born children, suggesting that a persistent microvascular deficit might contribute to the maldevelopment of the brain and poorer cognition. In our current study, we tested this hypothesis in 11-year old children born with ELBW or delivered at term, while accounting for blood pressure and other factors with possible impact on cognition.

2. Methods

2.1. Study participants

The study was conducted in accordance with the Helsinki declaration for investigations in human subjects [17]. The Ethics Committee of the University Hospitals approved the study. Based on good clinical practice guidelines and national legislation, parents or custodians provided written informed consent and the children informed assent. The study was registered at ClinicalTrials.gov (NCT02147457). We recruited cases from a cohort of 140 children born between 2000 and 2005, who survived after having been born with a birth weight of < 1000 g and after a gestation ranging from 23 to 33 weeks [3]. Of 140 invited children, 93 participated (66.4%). The 87 controls were either friends of the cases (n = 41) or recruited at an elementary school close to the examination center (n = 46) [3]. We excluded 10 participants from analysis, because retinal imaging was of poor quality (7 cases), or because their IQ levels were > 3 SDs lower than the group mean among cases (n = 2) or controls (n = 1). Thus, the number of children statistically analyzed included 84 cases and 86 controls.

2.2. Clinical measurements

Blood pressure was the average of three consecutive auscultatory readings obtained according to European guidelines [18] with a standard mercury sphygmomanometer after the children had rested in sitting position for at least 5 min. Body weight was measured, using the Omron Karada Scan HBF511 (Omron Health Care, Kyoto, Japan) and body height by a wall–mounted ruler. Body mass index was weight in kilograms divided by height in meters squared. We converted the anthropometric measurements to Z–scores based on Flemish growth charts [19]. Retinopathy of prematurity was staged as described elsewhere [20].

2.3. Visual acuity

Technicians tested the visual acuity (clearness of vision, *i.e.* spatial resolution of the visual processing system) of participants through the non–invasive adapted Snellen chart (Medical Workshop, Groningen, The Netherlands) at six meters for the left and right eye separately, using one–eye blinding glasses. This test was performed without visual aids. Visual acuity was expressed in decimals based on adaptive Snellen charts. Calculations were done in logMAR (log Minimum Angle Resolution). Normal visual acuity is defined as a detailed vision at six meters expressed as 6/6 or 20/20 or 1.00 in decimals or 0.00 logMAR [21,22]. Impaired visual acuity was defined as < 0.50 [21]. For statistical analysis, a vision of < 0.1 was artificially set at 0.1.

2.4. Retinal imaging

Participants were asked to refrain from exercise or caffeinated beverages for at least 6 h before retinal imaging. We applied a non-mydriatic approach in a dimly lit room to obtain retinal photographs, one image per eye in each participant, with the Canon Cr-DGi retinal visualization system combined with the Canon D-50 digital camera (Canon Inc., Medical Equipment Group, Utsunomiya, Japan). We determined the central retinal arteriolar (CRAE) and venular (CRVE) equivalent, which represent the retinal arteriolar and venular diameters. We used the validated computer-assisted program SIVA (Singapore I Vessel Assessment, version 3.6, Singapore Eye Research Institute, Singapore) based on formulae published by Parr [23] and Hubbard [24]. The software returns average vessel diameters according to the revised Knudtson formula [25]. The arteriole-to-venule diameter ratio (AVR) was CRAE divided by CRVE. Intra–observer variability (F.-F.W.) and inter–observer (Z.-Y.Z. and F.-F.W.) variability were assessed from repeated measurements in 30 children, using intraclass correlation coefficients [26]. For the intra-observer repeatability, the correlation coefficients were 0.98 for CRAE, 0.99 for CRVE and 0.98 for AVR and for inter-observer reproducibility they were 0.94, 0.93 and 0.87, respectively [26].

2.5. Neurocognitive performance

In cases and controls, neurocognitive performance was investigated by the Wechsler Non–Verbal test, Dutch version (Pearson, The Netherlands). Matrix reasoning and spatial span were assessed to estimate the intelligence quotient (IQ) equivalent (*i.e.* total score) [27]. To score parental education, we applied a standardized questionnaire and recoded the International Standard Classification of Education Scale [28] into 4 levels ranging from low (1) to high (4) education [29].

2.6. Statistical analysis

For database management and statistical analysis, we used SAS software, version 9.4 (SAS Institute, Cary, NC). We applied Shapiro-Wilk test to test normality of distributions. For comparison of means, we used a t-test or Wilcoxon-Mann-Whitney test depending on the distribution and for comparison of proportions the $\chi 2$-statistic, respectively. Statistical significance was a two-sided significance level of 0.05. While accounting for the stratification in cases and controls, we applied linear regression to test the association of head circumference, total IQ, matrix reasoning and spatial span with the retinal traits, first unadjusted and next with adjustments applied for sex, age and body mass index. Models with IQ as outcome were additionally adjusted for mean arterial pressure. In fully adjusted models we also accounted for paternal and maternal educational attainment. A missing value of visual acuity in 1 case was replaced by the cases' mean.

3. Results

3.1. Characteristics of study participants

Table 1 lists the characteristics of 84 cases and 86 controls. The number of girls was similar among cases and controls (43 [51.2%] *vs* 44 [51.2%]; p = 0.99). There were no differences in age and body mass index between cases and controls ($p \geq 0.057$; Table 1). Compared with controls, cases were 3.96 cm (95% confidence interval [CI], −6.83 to −1.08; p = 0.007) shorter, 3.84 kg (CI, −6.73 to −0.95; p = 0.009) lighter and had 1.71 cm (CI, 0.95 to 6.73; p = 0.009) smaller head circumference. The corresponding differences for body height, weight,

Table 1
Characteristics of cases and controls.

Characteristics	Cases (n = 84)	Controls (n = 86)	p-value
Anthropometric measurement			
Age (years)	11.2 (10.9 to 11.5)	10.9 (10.6 to 11.1)	0.064
Body height (cm)	145.4 (143.4 to 147.3)	149.3 (147.2 to 151.5)	0.007
Z-score for height	−0.34 (−0.53 to −0.16)	0.58 (0.36 to 0.80)	< 0.001
Body weight (kg)	36.7 (34.6 to 38.8)	40.5 (38.5 to 42.6)	0.009
Z-score for weight	−0.44 (−0.65 to −0.22)	0.33 (0.15 to 0.52)	< 0.001
Body mass index (kg/m2)	17.1 (16.5 to 17.8)	18.0 (17.4 to 18.5)	0.057
Z-score for body mass index	−0.36 (−0.61 to −0.12)	0.02 (−0.18 to 0.22)	0.014
Head circumference (cm)	51.7 (51.3 to 52.1)	53.4 (53.1 to 53.8)	< 0.001
Z-score for head circumference	−1.06 (−1.30 to −0.83)	0.06 (−0.14 to 0.26)	< 0.001
Blood pressure			
Systolic (mm Hg)	112.8 (110.7 to 115.0)	105.3 (103.5 to 107.1)	< 0.001
Diastolic (mm Hg)	67.6 (66.2 to 69.0)	64.1 (62.7 to 65.4)	< 0.001
Mean (mm Hg)	82.7 (81.4 to 84.0)	77.8 (76.6 to 79.0)	< 0.001
Visual acuity			
Right eye	0.69 (0.61 to 0.76)	0.92 (0.86 to 0.98)	< 0.001
Left eye	0.68 (0.60 to 0.76)	0.95 (0.89 to 1.01)	< 0.001
Retinal phenotypes			
Central arteriolar diameter (μm)	162.7 (160.0 to 165.4)	174.0 (171.5 to 176.5)	< 0.001
Central venular diameter (μm)	234.9 (231.0 to 238.8)	242.8 (239.2 to 246.4)	0.003
Arteriole-to-venule ratio	0.69 (0.68 to 0.70)	0.72 (0.71 to 0.73)	0.001
Cognitive outcomes			
Total IQ	93.9 (91.4 to 96.4)	109.2 (106.4 to 112.1)	< 0.001
Matrix reasoning	47.5 (46.1 to 49.0)	53.3 (51.6 to 55.0)	< 0.001
Spatial span	46.2 (44.5 to 47.9)	56.1 (54.2 to 58.1)	< 0.001

Values are mean (95% confidence interval). Z-scores were based on Flemish growth charts (reference [19]). Head circumference was unavailable in 14 cases and 8 controls.

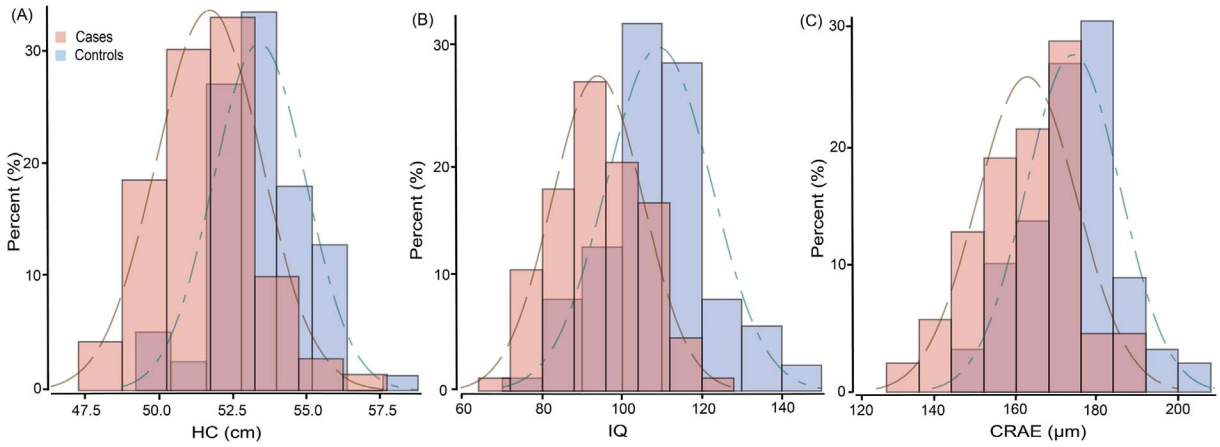

Fig. 1. Frequency distributions of head circumference (A) total IQ (B) and central retinal arterial equivalent (C) in cases and controls. The red and blue histograms represent cases and controls, respectively. HC, head circumference; IQ, total intelligence quotient; CRAE, central retinal arteriolar equivalent. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

body mass index and head circumference derived from *Z*-scores were −0.92 (CI, −1.21 to −0.64; $p < 0.001$), −0.77 (CI, −1.06 to −0.49; $p < 0.001$), −0.39 (CI, −0.70 to −0.08; $p = 0.014$) and −1.13 (CI, −1.44 to −0.82; $p < 0.001$), respectively. Systolic and diastolic blood pressure were 7.5 (CI, 4.8 to 10.3; $p < 0.001$) and 3.6 (CI, 1.7 to 5.5; $p < 0.001$) mm Hg higher in cases than controls (Table 1). Compared with controls (Table 1 and Fig. 1), cases had lower levels of total IQ (93.9 *vs* 109.2; $p < 0.001$), matrix reasoning (47.5 *vs* 53.3; $p < 0.001$) and spatial span (46.2 *vs* 56.1; $p < 0.001$). Paternal educational levels were equally distributed among cases and controls (low 6.1 *vs* 2.4%; medium-low 46.3 *vs* 49.4%; medium-high 23.2 *vs* 32.5% and high 22.0 *vs* 15.7%; $p = 0.23$) as well as maternal educational levels (low 7.3 *vs* 1.2%; medium-low 42.2 *vs* 38.6%; medium-high 35.4 *vs* 44.6% and high 17.1 *vs* 14.5%; $p = 0.22$). Girls had a smaller head circumference than boys (52.2 *vs* 53.0 cm; $p = 0.012$). However, there were no differences between girls and boys in matrix reasoning (50.4 *vs* 50.5; $p = 0.97$), spatial span (50.4 *vs* 52.1 $p = 0.28$) or IQ (100.8 *vs* 102.5; $p = 0.45$). Table 2 provides additional information on the perinatal and postnatal characteristics of the 84 cases. Retinopathy of prematurity stage 3 or higher was present in 13 (15.5%) cases and treated with laser therapy in all.

3.2. Retinal phenotypes

Visual acuity was not normally distributed. It was lower in cases than controls (Table 1): right eye, 0.69 *vs* 0.92 ($p < 0.001$) and left eye, 0.68 *vs* 0.95 ($p < 0.001$). In all children combined, central retinal arteriolar and venular equivalent and their ratio were averaged (± SD) 168.4 ± 13.3 μm, 238.9 ± 17.7 μm and 0.71 ± 0.05. Cases compared with controls (Fig. 1 and Table 1) had lower central retinal

Table 2
Characteristics of 84 cases.

Characteristics	Values
Perinatal characteristics, n (%)	
Tocolysis	25 (29.8)
Pre-eclampsia	26 (30.9)
Chorioamnionitis	4 (4.8)
Antenatal lung maturation	75 (89.3)
Premature rupture of membranes	16 (19.0)
Postnatal characteristics	
Gestational age (weeks)	27.5 (25.0 to 31.0)
Birth weight (g)	799.3 (525.0 to 990.0)
Ventilation (days)	11.5 (0 to 35)
Oxygen need (days)	36.6 (1.0 to 103.0)
Ibuprofen, n (%)	39 (46.4)
Postnatal steroids, n (%)	42 (50.0)
Retinopathy of prematurity ≥3, n (%)	13 (15.5)
Intraventricular hemorrhage, n (%)	18 (21.4)

Values are mean (95% confidence interval) or n (%). To accelerate antenatal lung maturation, mothers received intramuscular betamethasone on two consecutive days.

arteriolar equivalent (−11.3 µm; CI, −15.0 to −7.7; $p < 0.001$), central retinal venular equivalent (−7.9 µm; CI, −13.1 to −2.6; $p = 0.003$) and arteriole-to-venule ratio (−0.03; CI, −0.04 to −0.01; $p = 0.001$).

3.3. Association with the retinal microcirculation

Fig. 1 shows the overlap in the distributions of head circumference, IQ and central retinal arteriolar equivalent in cases and controls. In unadjusted models including all children, head circumference ($r = 0.29$; $p < 0.001$) and total IQ ($r = 0.26$; $p < 0.001$) increased with central retinal arteriolar equivalent. As shown in Fig. 2, total IQ ($p = 0.011$) and matrix reasoning ($p = 0.016$) increased with central retinal arteriolar equivalent independent of mean arterial pressure with a similar trend for spatial span ($p = 0.059$).

In unadjusted models including all children (Table 3), a 1–SD decrement in the central retinal arteriolar equivalent was associated with a 0.53 cm ($p < 0.001$) smaller head circumference. With adjustments applied for sex, age and body mass index, this estimate became 0.57 cm ($p < 0.001$) and with additional adjustment for parental educational attainment 0.58 cm ($p < 0.001$; Table 3 and Fig. 3). Associations of head circumference with the arteriole-to-venule ratio mirrored those of central retinal arteriolar equivalent (Table 3). Results using the *Z*-score for head circumference were confirmatory.

In unadjusted models (Table 3), a 1–SD decrement in the central retinal arteriolar equivalent was associated with lower total IQ, matrix reasoning and spatial span. The estimates were −3.74 ($p < 0.001$), −1.77 ($p = 0.004$) and −2.03 ($p = 0.002$), respectively. With adjustments applied for sex, age, body mass index and mean arterial pressure, estimates became −3.20 ($p = 0.007$), −1.54 ($p = 0.029$) and −1.72 ($p = 0.018$), respectively. A 1–SD decrease in arteriole-to-venule ratio was significantly associated with lower IQ (−3.29; $p = 0.002$), matrix reasoning (−2.04; $p = 0.001$) and spatial span (−1.32, $p = 0.053$) in unadjusted models. The corresponding estimates in adjusted models were −2.89 ($p = 0.013$), −1.97 ($p = 0.004$) and −0.99 ($p = 0.19$). Fully adjusted models additionally accounted for maternal and paternal educational attainment and produced confirmatory results (Table 3 and Fig. 3). None of the associations of head circumference, total IQ, matrix reasoning or spatial span with the central retinal venular equivalent reached significance in unadjusted or adjusted models.

4. Discussion

To the best of our knowledge, our study is the first that assessed the multivariable-adjusted associations of head circumference and cognitive performance with retinal microvascular traits in children born prematurely or delivered at term. The key findings can be summarized as follows: (i) compared with those born at term, former ELBW infants at 11 years had smaller head circumference and narrower retinal arteriolar and venular diameters and a smaller arteriole-to-venule ratio; (ii) former ELBW children performed less than children born at term in tests of total IQ, matrix reasoning, and spatial span; (iii) and with adjustments applied for risk factors for cognitive impairment, including mean arterial pressure, body mass index and parental educational attainment, total IQ, matrix reasoning and spatial span remained positively correlated with the central retinal arteriolar equivalent and arteriole-to-venule ratio. Previous studies did not detect sex differences in latent general and broad cognitive abilities, which is line with our current findings [30,31].

In keeping with our current observations, several studies described poorer cognitive performance in 2- to 9-year old children born prematurely [7–15]. For instance, Anderson and colleagues determined the cognitive outcome of 298 ELBW (< 1000 g) or very preterm infants (< 28 weeks of gestation) born in 1990s compared with 262 normal birth weight controls. At 8 years, cases had lower full-scale IQ than

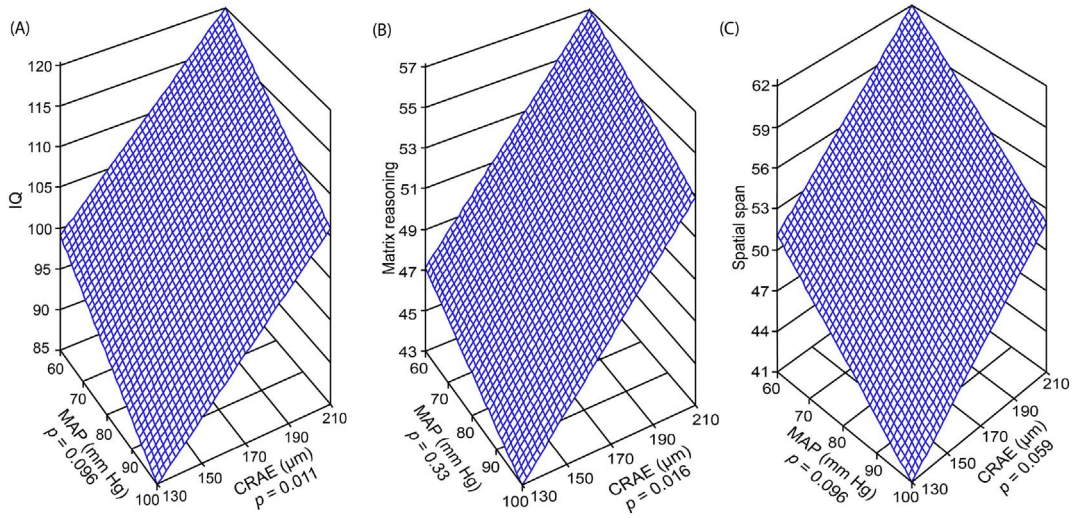

Fig. 2. Associations of indices of IQ with mean arterial pressure and central retinal arteriolar equivalent. The plane shows the independent associations of full scale IQ (A), matrix reasoning IQ (B) and spatial processing IQ (C) with mean arterial pressure (MAP) and central retinal arteriolar equivalent (CRAE).

Table 3
Association of head circumference and cognitive performance with retinal traits.

Phenotype model	Head circumference (n = 148)		Cognitive performance (n = 170)		
	Absolute value	Z-score	Total IQ	Matrix reasoning	Spatial span
CRAE					
Unadjusted	−0.53 (−0.78 to −0.28)***	−0.37 (−0.51 to −0.22)***	−3.74 (−5.73 to −1.75)***	−1.77 (−2.95 to −0.58)**	−2.03 (−3.28 to −0.78)**
Adjusted	−0.57 (−0.79 to −0.35)***	−0.35 (−0.48 to −0.22)***	−3.20 (−5.50 to −0.90)**	−1.54 (−2.92 to −0.16)*	−1.72 (−3.14 to −0.30)*
Fully adjusted	−0.58 (−0.81 to −0.36)***	−0.36 (−0.49 to −0.23)***	−3.18 (−5.58 to −0.78)**	−1.69 (−3.06 to −0.32)*	−1.55 (−3.03 to −0.07)*
AVR					
Unadjusted	−0.35 (−0.61 to −0.09)**	−0.20 (−0.36 to −0.04)*	−3.29 (−5.36 to −1.22)**	−2.04 (−3.28 to −0.80)**	−1.32 (−2.67 to 0.02)
Adjusted	−0.44 (−0.71 to −0.18)***	−0.26 (−0.42 to −0.10)**	−2.89 (−5.16 to −0.63)*	−1.97 (−3.28 to −0.66)**	−0.99 (−2.49 to 0.50)
Fully adjusted	−0.41 (−0.68 to −0.14)**	−0.24 (−0.41 to −0.08)**	−2.57 (−4.96 to −0.17)*	−1.83 (−3.20 to −0.46)**	−0.81 (−2.38 to 0.76)

Abbreviations: CRAE, central retinal arteriolar equivalent; AVR, arteriole-to-venule ratio. Effect size (95% confidence interval) express the difference associated with a 1-SD decrease in CRAE or AVR. All models are adjusted for sex, age and body mass index. Adjusted models with cognitive performance as outcome also include mean arterial pressure as covariable. Fully adjusted models additionally accounted for parental educational level, but because of unavailability of this information only include 165 participants (82 cases and 83 controls). Head circumference was available in 70 cases and 78 controls.

* $p \leq 0.05$, significance of the associations.

** $p \leq 0.01$, significance of the associations.

*** $p \leq 0.001$, significance of the associations.

normal controls with a difference averaging 9.4 (CI, 6.7–12.1) [8]. Subsequently, the same research group reported that preterm children had significant executive dysfunction compared with their healthy controls [9]. Marlow and colleagues assessed cognitive performance at a median age of 6.3 years in 241 prematurely born children (≤25 weeks of gestation) and 160 classmates born at term. Each preterm child had also been evaluated at 30 months of age. By using reference norms, cognitive impairment, defined as results > 2 SDs below the mean, was present in 21% of the prematurely born children, as compared with 1% in the standardized data. This proportion rose to 41% when compared with classmates. The mean difference in overall cognitive ability between cases and controls was 24 (CI, 20 to 27) [10]. Among children with severe disability at 30 months of age, 86% still had moderate-to-severe disability at 6 years of age, confirming as observed in our current study the lasting influence of prematurity [10]. Along similar lines, of 441 extremely preterm infants (< 27 weeks) who had received active perinatal care in Sweden, 30.4% had mild disability, 20.2% had moderate disability, and 13.4% had severe disability. Only 3% of the controls had moderate to severe disability [15].

Head circumference reflects fetal brain growth [32]. Several previous studies correlated IQ with anatomical brain characteristics in children born prematurely [33–36]. A meta-analysis of fifteen studies [35] included 818 very preterm/very low birthweight children and 450 term-born peers. Effect sizes were determined for each study and expressed as the difference between very preterm/very low birth weight children and controls divided by the pooled standard deviation of the two group. Compared with controls, very preterm/very low birthweight children had smaller brain volumes amounting to 0.58 (CI, −0.73 to −0.43; $p < 0.001$) for the total brain, to 0.53 (CI, −0.67 to −0.40; $p < 0.001$) for white matter, to 0.62 (CI, −0.76 to −0.48; $p < 0.001$) for grey matter and to 0.74 (CI, −0.92 to −0.56; $p < 0.001$) for the cerebellum. Reduced brain volume were associated with decreased general cognitive functioning [35]. Other studies [37–39] noted associations of psychological, neurocognitive or behavioral function or school performance with brain volumes in adolescents born prematurely. In keeping with the aforementioned reports [7,37–40], in our current study, we correlated cognitive performance with an anatomical index, *i.e.* the diameter of the retinal microvessels and showed a positive multivariable-adjusted correlation.

That prematurely born children have narrower retinal arterioles than term children is well established [16,41], but to our knowledge no previous study reported on the correlation between cognitive performance and the retinal arteriolar diameters. In a population-based cohort study, retinal arteriolar calibers were measured from digitized retinal photographs in 4122 6-year old children. After adjustment for image grader, sex, age of the child, maternal lifestyle and sociodemographic confounders, children born at < 34 weeks and at 34–37 weeks of gestation, compared with children born at term, had narrower retinal arteriolar caliber with SD scores amounting to −0.46 (CI, −0.77 to −0.15) and −0.24 (CI, −0.42 to −0.05), respectively [16]. In the Cardiovascular Risk in Young Finns Study [41], children aged 3–18 years were randomly selected from five Finnish University cities. At age 34–49 years, with adjustments applied for sex, age, employment, marital status and smoking, premature compared with term

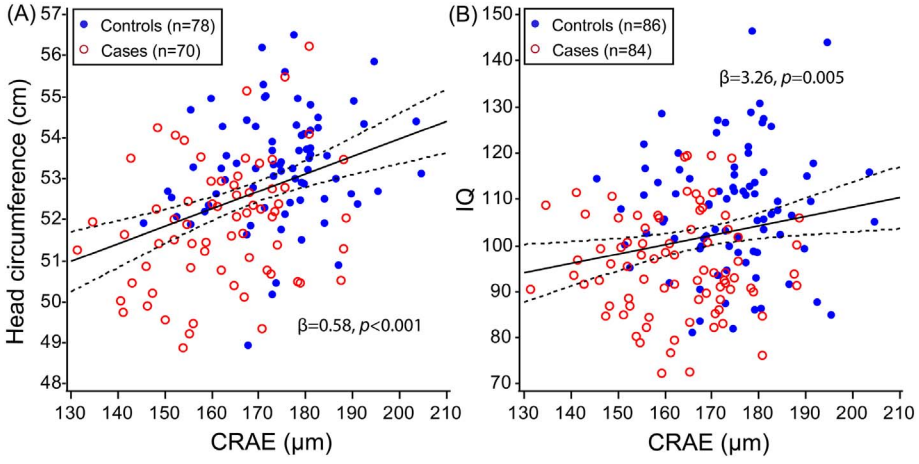

Fig. 3. Multivariable-adjusted associations of head circumference (A) and total IQ (B) with central retinal arteriolar equivalent (CRAE). The partial regression coefficients were standardized as in Table 3 and adjusted for sex, age, body mass index and parental educational level. The model for IQ was additionally adjusted for mean arterial pressure.

birth was associated with narrower retinal arteriolar diameters (19.9 *vs* 20.3 pixels; $p = 0.034$) [41]. In none of these studies [16,41], investigators described an association between cognitive performance and retinal arteriolar diameter. In our view two studies approached our current findings and support our interpretation [6,32]. Yau and colleagues observed associations between subclinical white matter pathology and retinal vessel alterations among obese adolescents with metabolic syndrome (mean age, 17.5 years) and suggested that subtle white matter pathology in adolescents with metabolic syndrome has a vascular origin [6]. In a longitudinal study of 58 preterm infants born after 30–32 weeks of gestation [32], head circumference was measured twice weekly from birth until discharge from the hospital up to 31 weeks later. The postnatal deficit in head circumference paralleled the degree of retinopathy of prematurity and in the authors' view was consistent with a disease process common to the brain and the eye [32].

Observational studies cannot ascertain mechanisms. However, some investigators hypothesized that retinal vascular abnormalities in children born preterm reflect generalized vascular changes [42], which provide an explanation of why preterm children appear to have an increased risk of cardiovascular disease later in life [42,43]. The retina shares similar embryological origin, anatomical features and physiological properties with the brain and hence offers a unique and accessible "window" to study the correlates and consequences of subclinical pathology [5,44]. While these concepts have been introduced into clinical research in adults in the fields of stroke and dementia [5,45], our literature search did not reveal any previous study linking cognitive performance in young children born prematurely or at term to the retinal microvasculature. Our findings suggest that the difference between cases and controls in head circumference, IQ, spatial span and matrix reasoning in 11-year old children results from microvascular maldevelopment or dysfunction in the perinatal period and in line with the literature is persistent from birth onwards [10,15,41]. In addition, our multivariable-adjusted analyses revealed that other risk factors for cognitive impairment, in particular high blood pressure, metabolic dysregulation as reflected by body mass index, and parental educational attainment were of minor influence compared with the maldevelopment or malfunction of the intracerebral microcirculation. Limitations of our current study are its cross-sectional case-control design, the absence of a longitudinal follow-up of cognitive performance from early childhood onwards, its relatively small sample size. The relatively small number of children with retinopathy of prematurity or intraventricular hemorrhage might explain the null association of cognitive performance at 11-years with these traits in unadjusted and multivariable-adjusted analyses. Furthermore, the control group in our study scored nearly 10 standard points above the age-expected mean based on the normative sample of the Wechsler Intelligence Scale for Children [46]. The high performance in the control group might have inflated the effect sizes in the comparison with the preterm group.

In conclusion, with adjustments applied for covariables of cognitive function, including sex, age, mean arterial pressure, body mass index and parental educational attainment, head circumference, total IQ, matrix reasoning and spatial span decreased with smaller retinal arteriolar diameter. Our findings suggest that maldevelopment of the cerebral microcirculation, as mirrored by the retinal microvasculature, has lasting effects on the cognitive performance of prematurely born children. The clinical corollary of our findings is that, in view of the lifelong lasting ramifications of premature birth on public health and education [12], the timely identification of those infants who are the largest risk for cognitive impairment and who may benefit from early intervention, should rise on the research agenda.

Conflict of interest statement

None of the authors declares a conflict of interest.

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Disclosures

None.

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