Associations of Birth Weight With Ocular Biometry, Refraction, and Glaucomatous Endophenotypes: The Australian Twins Eye Study

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• PURPOSE: To examine the relationship of birth weight with ocular measures in a Caucasian twin population.

• DESIGN: Cross-sectional study of 1498 twins (308 monozygotic and 441 dizygotic pairs) aged between 5 to 80 years participating in the Australian Twins Eye Study.

• METHODS: All participants underwent ophthalmic examination including bilateral cycloplegic autorefraction, keratometry, interpupillary distance (IPD), central corneal thickness, intraocular pressure (IOP), and retinal photography. Birth weight and gestation were obtained from a self-administered questionnaire. A subset of the twins also participated in the Tasmanian Infant Health Study (288) and the Childhood Blood Pressure Study (184), which collected data on birth parameters allowing for verification of data. Linear mixed models were used for the main analysis.

• RESULTS: Both the within-pair (β_w 0.27, 95% confidence interval [CI] 0.15, 0.38 mm per kg increase in birth weight, $P < .001$) and between-pair associations (β_B 0.22, 95% CI 0.08, 0.35, $P = .002$) of birth weight with axial length were significant and of similar magnitude (difference in effect, $P = .56$), after adjusting for relevant confounders. In contrast, birth weight was negatively associated with corneal curvature (β_w −0.82, 95% CI −1.09, −0.55 diopters per kg increase; β_B −0.69, 95% CI −0.98, −0.41, both $P < .001$). These associations remained significant within dizygotic and monozygotic pairs. Refraction, anterior chamber depth, IPD, IOP, and optic disc parameters are unrelated to birth weight.

• CONCLUSIONS: Consistent with previous studies in singleton children, lower birth weight is associated with shorter axial length and more curved corneas in this twin study. This also adds new insights into the emmetropization process. (Am J Ophthalmol 2010;xx:xxx. © 2010 by Elsevier Inc. All rights reserved.)

FETAL ORIGINS OF ADULT DISEASE HAS BEEN AN AREA of active research in the past 2 decades.[1,2] Many epidemiologic studies have shown that lower birth weight, shorter birth length, and smaller head circumference, regarded as markers for impaired intrauterine development, are associated with increased risk or earlier onset of cardiovascular diseases, hypertension, and diabetes.[1] Furthermore, new research has produced preliminary evidence that intrauterine environment may also have long-lasting impact on the development of ocular dimensions and retinal microcirculation. For example, recent population-based studies reported that smaller birth size such as low birth weight was associated with ocular traits such as shorter axial length,[3,4] narrower vitreous chamber,[3] more curved corneas,[3,4] larger cup-to-disc ratio,[5] and narrower retinal arteriolar caliber.[6] However, birth size seems to have little long-term effect on refractive error such as myopia.[3,4] Importantly, these investigations suggest that adverse intrauterine growth may confer increased future risk of diseases specifically affecting the eye (eg, glaucomatous optic neuropathy)[5] as well as other parts of the body.[1,2]

To date, limited population-based studies have explored the relationship between birth parameters and ocular measures.[3,5] Moreover, it is still unknown whether any potential associations between birth parameters and ocular measures are confounded by shared genes or shared environmental factors (eg, maternal nutrition) that affect both birth size and the development of ocular parameters. Within-pair analysis in a twin population offers an opportunity to disentangle these effects,[6,7] and we are unaware of any previous study examining this.

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The purpose of this report is therefore to investigate the relationship between birth weight and a range of ocular measures (ocular biometry, refraction, and glaucoma-related endophenotypes) in a large Caucasian twin population.

METHODS

• **STUDY POPULATION:** The Australian Twins Eye Study (ATES), involving 2235 twins and nontwin siblings, was designed to investigate the relative influence of genetic and environmental factors on a variety of ocular traits related to glaucoma. The study design and details of sample recruitment are described elsewhere.[8] In brief, the study population comprising predominantly Caucasian twins were ascertained from the Tasmanian Infant Health Study (TIHS) cohort,[9] the Brisbane Adolescent Twin Study,[6,10] and the Australia Twin Registry;[11] through media appeal; and from a school-recruitment approach during the period 2000 to 2008. All twins and their nontwin siblings in the ATES answered a standardized questionnaire providing details of sociodemographic and medical information and underwent a thorough ophthalmic examination.

A total of 288 children participating in the ATES were recruited from the TIHS, which examined sudden infant death syndrome in infants during the years 1988 to 1995.[9] Among these children, 184 multiplets (born between 1991 and 1993) also participated in the Childhood Blood Pressure Study that examined cardiovascular diseases in 1999.[12]

Of the total population of 2235 twin individuals, we excluded 269 nontwin siblings, triplets, and twins with missing zygosity data; 349 persons who had no birth weight information; and an additional 119 single twins, leaving 1498 twin individuals with known zygosity and birth weight, comprising 308 monozygotic (MZ) and 441 dizygotic (DZ) twin pairs for this analysis.

• **BIRTH PARAMETERS ASSESSMENT:** We collected information on birth weight, birth order, and gestation duration for all participants in the ATES from a detailed self-administered questionnaire. Two hundred eighty-eight of the twins also had data relating to birth weight, birth length, head circumference, and gestational age extracted from medical birth records as part of their involvement in the TIHS, details of which have been published elsewhere.[6] Briefly, last menstrual period was used to estimate gestational duration. These data provided a means by which the self-reported birth parameters in the ATES could be validated.

Reliability assessment of 283 individuals with both birth weight and gestational age data in the ATES and the TIHS showed very high agreement between the 2 studies, with an intraclass correlation coefficient of 0.978 (95% confidence interval [CI], 0.972–0.982) for birth weight, and 0.992 (0.990-0.994) for gestational age. Low birth weight was defined as <2500 g. Prematurity was defined as <37 weeks gestation duration.[13]

TABLE 1. Characteristics of Monozygotic and Dizygotic Twin Pairs[a]

Characteristic	MZ Twins (n = 616; 308 Pairs)	DZ Twins (n = 882; 441 Pairs)	*P* Value[c]
Demographic factors			
Age, years[a]	19.0	17.0	<.001
Male gender, %	31.2	46.4	<.001
Birth parameters			
Birth weight, kg	2.4	2.5	<.001
Low birth weight, %	54.4	41.7	<.001
Small for gestational age, %	18.6	13.8	.16
Birth length, cm[a,b]	47.0	47.0	.03
Head circumference, cm[a,b]	33.0	33.0	.002
Prematurity, %	42.2	35.5	.004
Anthropometric measures			
Height, m	1.6	1.7	.19
Body mass index, kg/m^2	22.8	21.8	.57

DZ = dizygotic; MZ = monozygotic.
[a]Data show crude means (or median where indicated with %.
[b]Data available for only 50 MZ and 75 DZ twin pairs.
[c]$P < .05$, represents statistically significant difference in means or proportions, adjusted for age and gender, except for age and male gender, and rank sum test for birth length and head circumference.

• **MEASUREMENT OF OPTIC DISC PARAMETERS:** All twins and nontwin siblings had 10-degree stereoscopic optic disc–centered photographs taken (Nidek fundus camera 3-Dx/F; Nidek, Gamagori, Japan) after pupil dilation with tropicamide 1% or cyclopentolate 1% (for children). All fundus photographs were digitalized at high resolution (2102 × 1435 pixels, 2900 dpi, 36-bit color) using a Nikon CoolScan scanner (Nikon Corp, Tokyo, Japan).

Assessments of optic disc parameters, including optic disc, cup, and rim area, were performed by 2 trained graders using a standardized grading program.[14] Re-measurement of 50 randomly selected retinal photographs 3 months apart showed high intragrader reproducibility, with intraclass correlation coefficient (95% CI) of 0.94 (0.87-0.98) for optic disc area. The intergrader reliability was assessed in 73 randomly selected retinal images, and interclass correlation coefficient (95% CI) was 0.75 (0.67–0.86) for optic disc area.

• **ZYGOSITY TESTING:** Blood or mouth swab samples were collected for DNA extraction in the ATES. Twin pair zygosity was confirmed by up to 12 highly polymorphic short tandem repeats (STR), with an accuracy of more than 99%.[15]

TABLE 2. . Correlation Between Ocular Outcomes With a Bonferroni Correction for Multiple Testing

	Axial Length (mm)	Anterior Chamber Depth (mm)	Corneal Curvature (diopters)	Central Corneal Thickness (μm)	Refractive Error (diopters)	Mean Intraocular Pressure (mm Hg)	Optic Disc Area (mm^2)	Optic Cup Area (mm^2)	Area Cup-to-Disc Ratio	IPD (mm)
Axial length (mm)	1.00									
Anterior chamber depth (mm)	.41[a]	1.00								
Corneal curvature (diopters)	−0.57[a]	.07	1.00							
Central corneal thickness (μm)	.06	−.02	−0.04	1.00						
Refractive error (diopters)	−0.16[b]	−0.31[a]	−0.43[a]	−0.09	1.00					
Mean intraocular pressure (mm Hg)	0	0	.04	.11	−0.05	1.00				
Optic disc area (mm^2)	.03	−0.18[a]	−0.25[a]	.03	.16[b]	−0.09	1.00			
Optic cup area (mm^2)	.12	−0.08	−0.20[a]	0	.09	.03	.61[a]	1.00		
Area cup-to-disc ratio	.13	−0.03	−0.14[b]	0	.05	.07	.37[a]	.95[a]	1.00	
IPD measure (mm)	.30[a]	.04	−0.30[a]	−0.04	.07	.05	.10	.13[b]	.14[b]	1.00

IPD = interpupillary distance.
[a]$P < .001$; [b]$.05 > P > .001$ (all other data, $P > .05$).

• **MEASUREMENT OF OCULAR BIOMETRY AND OTHER VARIABLES:** Participants underwent a comprehensive ophthalmic examination.[8] Postcycloplegic interpupillary distance (IPD) measure, central keratometry, and refractive errors for both eyes were measured using a Humphery-598 automatic refractor (Carl Zeiss Meditec, Inc, Miami, Florida, USA) after pupil dilation. To assess refraction status, spherical equivalents were calculated using the standard formula of the algebraic sum of the value of the sphere and half the cylinder value (sphere + 0.5 cylinder).[16] After topical anesthesia, bilateral intraocular pressure (IOP) was measured for each participant using the TONO-PEN XL (Reichert Ophthalmic Instruments, Depew, New York, USA). Measurements of central corneal thickness were obtained from the average reading of the central cornea using the Pachymeter Tomey SP 2000 (Tomey Corp, Nagoya, Japan) or Pachmate DGH 55 (DGH Technology, Inc, Exton, Pennsylvania, USA). The intraocular lens (IOL) Master (Carl Zeiss, Oberkochen, Germany) was used to obtain ocular biometry (axial length, anterior chamber depth, and horizontal and vertical corneal curvature).

Data for current height and weight in the ATES were collected from a self-administered questionnaire. For younger twins with no height and weight data, we used 184 readings available in the concurrent child blood pressure study,[17] which measured child height in centimeters using a wall-mounted measuring tape and weight in kilograms using a digital scale (SECA, model 782 2321009; Vogel & Halke, Hamburg, Germany). Body mass index (BMI) was calculated as kg/m^2.

• **STATISTICAL ANALYSIS:** A range of ocular measures including axial length, anterior chamber depth, corneal curvature, IPD measure (postcycloplegic), and glaucoma-related endophenotypes such as central corneal thickness, IOP, optic disc area, optic cup area, and optic cup-to-disc ratio were outcomes of interest and were all analyzed as continuous variables. Refraction was measured as spherical equivalent and was analyzed both as a continuous and a categorical trait (1 for spherical equivalent ≥ median and 0 for those < median). Spearman correlations between eye outcomes were obtained with Bonferonni adjustment for multiple comparisons.[18]

Standard linear regression was performed with "twins as individuals," initially controlling for age at examination and gender.[19] Logistic regression was performed for categorical outcome such as refractive error. Multivariable linear regression models were then constructed for those ocular outcomes with a significant association in the age-gender-adjusted linear models ($P < .05$) (for more details, see Supplemental Material at AJO.com).

The main form of analysis was then conducted by using linear mixed regression models, treating each twin pair as a cluster to account for the correlated nature of the data.[19] This model provided estimates of both within-pair (β_w) and between-pair (β_B) associations. Stratified analysis by zygosity was also performed using linear mixed models. Covariates included in the model were based on statistical and biological consideration of confounding.

We also investigated the associations of birth weight with ocular biometry in preterm twins using multivariable linear regression, accounting for family structure. Finally, we investigated the potential interaction of risk factors with gender. Where interactions were statistically significant ($P < .01$), stratified analyses were performed.

All analyses were performed for the right eye (except for IOP, where the average of right and left eye measurements was used because of variation of the measurement) using STATA 11.0 (Stata Corp, College Station, Texas, USA).

TABLE 3. Overall Associations of Ocular Measures With Birth Weight

Ocular Measures[a]	Birth Weight, kg (n)					
	<2.5 (703)	2.5–2.9 (506)	3.0–3.4 (239)	3.5–3.7 (36)	≥3.8 (14)	*P* Value[b]
Axial length (mm)	23.13 (0.03)	23.19 (0.04)	23.36 (0.06)	23.38 (0.15)	23.19 (0.25)	.002
Corneal curvature (diopters)	43.87 (0.06)	43.69 (0.07)	43.16 (0.10)	42.90 (0.25)	42.86 (0.41)	<.001
Central corneal thickness (μm)	544.82 (1.41)	544.39 (1.66)	543.80 (2.39)	536.12 (6.03)	546.74 (10.60)	.42
IPD measure (mm)	60.24 (0.16)	60.51 (0.19)	61.05 (0.27)	61.45 (0.74)	62.01 (1.20)	.002
Mean IOP (mm Hg)	16.00 (0.11)	15.93 (0.13)	15.82 (0.19)	16.68 (0.50)	15.11 (0.83)	.66
Optic disc area (mm^2)	2.05 (0.02)	2.05 (0.02)	2.10 (0.03)	2.23 (0.08)	2.15 (0.13)	.03
Optic cup area (mm^2)	0.43 (0.01)	0.44 (0.02)	0.45 (0.02)	0.51 (0.06)	0.59 (0.09)	.16
Area cup-to-disc ratio	0.20 (0.01)	0.20 (0.01)	0.20 (0.02)	0.22 (0.02)	0.27 (0.04)	.44

IOP = intraocular pressure; IPD = interpupillary distance.

[a]Mean (standard error) for ocular biometry and glaucomatous endophenotypes, adjusted for age and gender.

[b]*P* value for trend, adjusted for age and gender derived from linear regression.

TABLE 4. Associations Between Birth Weight and Axial Length in the Entire Sample of Twins and by Zygosity[a]

Parameter	Mean (95% CI) Change in Axial Length (mm) per kg Increase in Birth Weight[b]					
	MZ+DZ (n = 1498)	*P* Value	MZ (n = 616; 308 Pairs)	*P* Value	DZ (n = 882; 441 Pairs)	*P* Value
β_c	0.25 (0.16, 0.34)	<.001	0.25 (0.14, 0.37)	<.001	0.25 (0.13, 0.38)	<.001
β_w	0.27 (0.15, 0.38)	<.001	0.30 (0.16, 0.44)	<.001	0.27 (0.11, 0.43)	.001
β_B	0.22 (0.08, 0.35)	.002	0.16 (−0.04, 0.36)	.11	0.23 (0.05, 0.41)	.01
Test for difference[c]	—	.56	—	.26	—	.77

β_c = common (twins as individuals) regression coefficient; β_w = within-pair regression coefficient; β_B = between-pair regression coefficient; DZ = dizygotic; MZ = monozygotic.

[a]Linear mixed regression models were used. Twins were treated as individuals but the models accounted for clustering within a pair and allowed for different correlations in monozygotic and dizygotic pairs.

[b]CI denotes confidence interval. Adjusted for age, gender, spherical equivalent, gestational age.

[c]Data show the likelihood ratio test for the heterogeneity of the between- and within-pair effects.

(See the online Supplemental Material at AJO.com for more details of the statistical analysis.)

RESULTS

SELECTED CHARACTERISTICS INCLUDING DEMOGRAPHIC information, birth parameters, and anthropometric measures of the study sample stratified by zygosity are shown in Table 1. The median age of the whole study sample was 17 years (range, 5-80 years). MZ twins (n = 616; 308 pairs) were more likely to be female and older, and a higher proportion were of low birth weight, small for gestational age, and premature than DZ twins (n = 882; 441 pairs). MZ and DZ twins had the same median birth length of 47 cm, although MZ twins had a slightly greater but significantly different range (33–51 weeks and 38–53 weeks, respectively, $P = .03$). Similarly, the median head circumference of 33 cm was the same in both twin types, but the range was significantly larger in DZ twins (27–36 cm) compared to MZ twins (23–37 cm) ($P = .002$).

Table 2 shows the correlations among various ocular measures. All the optic disc parameters including disc area, cup area, and cup-to-disc area ratio were significantly correlated ($P < .001$). Axial length and horizontal corneal curvature were among those most highly correlated outcomes ($r = -0.57$, $P < .001$). There were moderately strong correlations between axial length and anterior chamber depth, IPD measure, anterior chamber depth and refractive error, horizontal corneal curvature and refractive error ($r > 0.3$, $P < .001$). However, two other correlations including those between axial length and refractive error and that between axial length and central corneal thickness were weak and nonsignificant.

Axial length, corneal curvature (horizontal), IPD, central corneal thickness, mean IOP, and optic disc and cup area were approximately normally distributed in the study population, with the mean (SD) being 23.20 (0.88) mm, 43.68 (1.54) diopters (D), 60.55 (3.94) mm, 544.29 (35.09) μm, 15.95 (2.98) mm Hg, 2.06 (0.43) mm^2, and 0.44 (0.31) mm^2, respectively. The distribution of refractive error was peaked (Kurtosis 18.79) and skewed to the

TABLE 5. Associations Between Birth Weight and Corneal Curvature in the Entire Sample of Twins and by Zygosity[a]

Parameter	Mean (95% CI) Change in Corneal Curvature (Diopters) per kg Increase in Birth Weight[b]					
	MZ + DZ (n = 1498)	*P* Value	MZ (n = 616; 308 Pairs)	*P* Value	DZ (n = 882; 441 Pairs)	*P* Value
β_c	−0.76 (−0.95, −0.56)	<.001	−0.78 (−1.05, −0.51)	<.001	−0.71 (−0.99, −0.44)	<.001
β_w	−0.82 (−1.09, −0.55)	<.001	−0.78 (−1.13, −0.44)	<.001	−0.86 (−1.24, −0.48)	<.001
β_B	−0.69 (−0.98, −0.41)	<.001	−0.78 (−1.20, −0.35)	<.001	−0.56 (−0.94, −0.19)	.003
Test for difference[c]	—	.53	—	.99	—	.26

β_c = common (twins as individuals) regression coefficient; β_w = within-pair regression coefficient; β_B = between-pair regression coefficient; DZ = dizygotic; MZ = monozygotic.

[a]Linear mixed regression models were used. Twins were treated as individuals but the models accounted for clustering within a pair and allowed for different correlations in monozygotic and dizygotic pairs.

[b]CI denotes confidence interval. Adjusted for age, gender, current height, and gestational age.

[c]Data show the likelihood ratio test for the heterogeneity of the between- and within-pair effects.

left (skewness −2.22) and the median in the right eye was 0 D (range, −16.50–6.38). The distribution of anterior chamber depth was peaked (Kurtosis 9.49) and slightly skewed to the left (skewness −1.65) and the median in the right eye was 3.65 mm (range, 1.65–4.46).

Using standard linear regression with each twin treated as an individual, Table 3 shows the associations between birth weight and ocular measures after controlling for age and gender. Birth weight was significantly associated with both axial length and corneal curvature (both horizontal and vertical) in this model. However, no significant relationship between birth weight and central corneal thickness was observed, nor between birth weight and other ocular measures including IPD, mean IOP, optic cup area, or optic cup-to-disc area ratio. Birth weight was only marginally significantly associated with optic disc area ($P < .03$), but this association did not persist in further adjustment for other confounders. Neither anterior chamber depth nor refractive error was related to birth weight ($P = .49$ and $P = .18$, respectively, data not shown).

Table 4 presents the results from the linear mixed regression models for the associations between birth weight and axial length fitted for the whole sample of twins (MZ + DZ) and separately by zygosity (MZ or DZ). Both the within-pair (β_w 0.27, 95% CI 0.15, 0.38) and between-pair (β_B 0.22, 95% CI 0.08, 0.35) associations of birth weight with axial length were significant and of a similar magnitude, after adjusting for age, gender, spherical equivalent, and gestational age. These associations remained significant even after adjustment for current height (β_w 0.28, 95% CI 0.15, 0.28; β_B 0.20, 95% CI 0.05, 0.34) given current height may be associated with axial length.[20] This implies that the association between lower birth weight and shorter axial length was not merely attributable to people with lower birth weight growing up to be shorter in stature.

The within-pair association was of similar magnitude in DZ twins (β_w 0.30, 95% CI 0.16, 0.44) and MZ twins (β_w 0.27, 95% CI 0.11, 0.43). No significant differences of within-pair and between-pair effects were observed in the overall cohort, MZ and DZ twins as indicated by the likelihood ratio test, although the between-pair association became nonevident among DZ twins.

The results from the linear mixed regression models for the association between birth weight and corneal curvature in the whole sample of twins (MZ + DZ) and separately by zygosity (MZ or DZ) are shown in Table 5. Given that results for both horizontal and vertical corneal curvature were similar, only results for horizontal corneal curvature are presented. In contrast to the positive association between birth weight and axial length, lower birth weight was associated with higher corneal curvature. These results show consistent significant within-pair and between-pair associations after controlling for age, gender, current height, and gestational age (β_w −0.82, 95% CI −1.09, −0.55; β_B −0.69, 95% CI −0.98, −0.41) in the whole twin population, with similar magnitude. These significant associations persisted even in the stratified analyses by zygosity.

Birth weight was significantly associated with IPD in the whole sample, after adjusting for age, gender, current height, and gestational age (β 0.79, 95% CI 0.31, 1.26, $P = .001$). However, birth weight was not related to this facial parameter within twin pairs in the whole sample (β_w 0.35, 95% CI −0.33, 1.04, $P = .32$), although between-pair association remained evident (β_B 0.78, 95% CI 0.15, 1.40, $P = .01$). In the stratified analysis within MZ twins, birth weight was also not associated with IPD (β_w 0.28, 95% CI −0.54, 1.10, $P = .50$).

In this twin sample, we were also able to analyze birth weight relative to gestational age. After controlling for age, gender, and current height, twins who had larger birth weight for gestational age scores 6–8 ($\beta = 0.20$, 95% CI 0.03, 0.38; $\beta = 0.41$, 95% CI 0.16, 0.66; $\beta = 0.33$, 95% CI 0.11, 0.55, respectively) also had longer axial length than those with the birth weight for gestational age score 1, showing strong linear trend (P for trend < .001). Twin pairs who had larger birth weight for gestational age scores

also had flatter corneas than those with birth weight for gestational age score 1 (P for trend $< .001$). These trends persisted in the stratified analyses by zygosity.

There was no gender difference in the relationships between birth weight and any ocular biometry measures. The significant associations of lower birth weight with shorter axial length (β 0.23, 95% CI 0.07, 0.39, $P = .006$) and more curved corneas (β −0.62, 95% CI −0.94, −0.31, $P < .001$) remained in preterm twins (n = 555).

DISCUSSION

IN THIS COHORT COMPRISING 308 MZ AND 441 DZ TWIN pairs who participated in the ATES, we showed that twins with lower birth weight tended to have shorter axial length and more steeply curved corneas. These associations remained evident even in within-pair assessment of MZ twins, after adjusting for age, gender, gestational age, and other relevant confounders. The between-pair effect of the associations between lower birth weight and shorter axial length and more curved corneas were also significant and of similar magnitude to the within-pair effect. Our study thus supports the hypothesis that impaired fetal development has a long-term effect on ocular biometry measures, possibly linked to specific individual factors (eg, different fetal nutrient supply lines),[19] independent of possible determinants that would be constant across twin pairs (eg, maternal nutrition, general maternal health, and any other unmeasured shared factors across twin pairs). The within-pair associations of birth weight with axial length and corneal curvature were evident even among MZ twins alone, indicating that genetic differences in the inherited genome are unlikely to explain these associations.[21] These associations persisted in supplementary analyses of twins born prematurely, and remained significant when birth weight for gestational age was used as a parameter to assess the birth size effect that was independent of gestational age. However, birth weight was not related to anterior chamber depth, refraction status, IPD, and glaucomatous endophenotypes (eg, central corneal thickness, IOP, and optic disc measures) in this twin study.

The current study, to our knowledge, is the first twin study to investigate the association of birth size with a range of ocular measures. Our study demonstrates that smaller birth size (eg, birth weight) is associated with shorter axial length and more curved corneas in twins, which is in line with the findings reported in 2 recent studies from singleton schoolchildren populations.[3,4] Our within-pair analysis in the present cohort extends these observations to twins and adds further insights into whether the associations of birth weight with ocular biometric structure found in previous studies in children are attributable to shared environment (eg, maternal factors), common genetic factors, or other pathways associated with twin individuals. Thus, our findings provide further insights into the recent studies performed in singleton schoolchildren populations, one in Singapore Chinese individuals (7–9 years)[3] and another in an ethnically diverse (predominately Caucasian) Australian population (6-year-olds).[4] Given that twins are more likely to be born prematurely than singletons and maternal factors associated with gestation duration may differ between twin and singleton pregnancies,[22] within-pair analysis (standardized with gestation duration) and using birth weight for gestational age for analysis thus add important evidence that these associations were independent of gestation length, suggesting that the findings from this twin study are applicable beyond twins with the gestation profile of this cohort.

Our twin study shows that birth weight appears to have little effect on refraction status, which is consistent with reports from the singleton pediatric populations,[3,4] providing strong evidence for the hypothesis that compensatory emmetropization occurs to maintain the optimal refractive power although impaired fetal growth may alter the ocular dimensions.[3,23] The finding that birth weight is not related to anterior chamber depth is well supported by the 2 recent studies from singleton schoolchildren populations.[3,4] The current twin study, however, adds no evidence that birth weight is associated with any optic disc dimensions such as area, or cup area, or cup-to-disc area ratio, and thus does not support the findings from a cross-sectional analysis from the Sydney Childhood Eye Study, which identified an association between smaller birth size (eg, lower birth weight, shorter birth length, and smaller head circumference) and decreased vertical disc diameter, increased cup diameter, and larger cup-to-disc ratio.[5] This discrepancy clearly implicates that future work is required in this area. Nevertheless, our finding is consistent with an animal study suggesting no long-term impact of fetal growth restriction on the diameter of ganglion cell axons in the optic nerve.[24]

In a 18-year follow-up study, which consisted of 302 children with birth weight less than 2000 g and 237 full-term controls (only 137 of 537 were followed for 18 years), low birth weight was found to permanently compromise the development of facial parameters such as IPD.[25] In contrast, our within-pair association of smaller birth weight with shorter IPD became nonsignificant, particularly within MZ twin pairs, indicating that this association may likely be confounded by some shared genetic factors.

Strengths of our study include its large sample of twins, the collection of extensive ocular measures, and the use of a standardized protocol to measure the optic disc parameters from digitized photographs. Findings from our study should be interpreted within the context of several potential limitations. First, residual confounding may partly explain some of the associations, particularly for the between-pair assessments. Our analyses also could not rule out the possibility that the within-pair birth weight and ocular biometry (eg, axial length, corneal curvature) associations observed may also reflect postnatal environmental

influences or later individual-specific epigenetic change. Second, birth parameters other than birth weight and gestational age (birth length and head circumference) were not available in the ATES. Although a subset of the twins also participated in the TIHS, which collected data on birth length and head circumference, the number is too small to allow meaningful analysis with sufficient statistical power. Third, the collection of variables such as birth weight and gestational age from self-administered questionnaires increases the likelihood of measurement error, and thus may have weakened, at least to some extent, any associations we observed. Nevertheless, reliability assessment of the data collected from self-administered questionnaires in the ATES and from medical birth records in the TIHS was fairly high. Fourth, this regression analysis does not provide full genetic analysis.[19] Fifth, proper information on chorion type was not available to assist our interpretation.[26,27] Finally, 54.5% of the twin participants (816/1498) were under 17 years in the current study, and a proportion of these children and adolescents who will eventually develop refractive error in adulthood may not be evident by this early stage.

Consistent with previous observations in 2 singleton school-aged children populations, lower birth weight is associated with shorter axial length and more curved corneas in this twin population. These findings reflect that fetus-specific factors rather than shared maternal or genetic factors may influence the long-term development of ocular dimensions. Refraction, anterior chamber depth, IPD, IOP, and optic disc parameters are unrelated to birth weight. Although they may not be directly applicable to clinical settings, findings from this twin study add to the growing literature that impaired fetal growth may have a long-lasting effect on ocular biometry, and that despite these major neonatal influences, emmetropization remains relatively stable during later years of life.

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SUPPLEMENTAL MATERIAL: EXPANDED METHODS

• **STATISTICAL ANALYSIS:** The first multivariable linear regression model was constructed for axial length, adjusted for age, gender, spherical equivalent, and gestational age. We also performed additional adjustment for current height. The second multivariable linear regression model was constructed for corneal curvature, adjusted for age, gender, current height, and gestational age. The third multivariable linear regression model was constructed for interpupillary distance, adjusted for age, gender, current height, and gestational age.

We also used the Australian national birth weight percentiles by gestational age based on twin data[S1] to estimate birth weight for gestational age, which may allow an assessment of the relationship between birth weight and ocular measures that is independent of gestational age. Birth weight for gestational age was divided into 8 different percentile categories (≤5, >5 to 10, >10 to 25, >25 to 50, >50 to 75, >75 to 90, >90 to 95, and >95, corresponding to birth weight for gestational scores 1 to 8). Birth weight for gestational score under the 10th percentile was used to define small for gestational age and as a proxy for fetal growth restriction.

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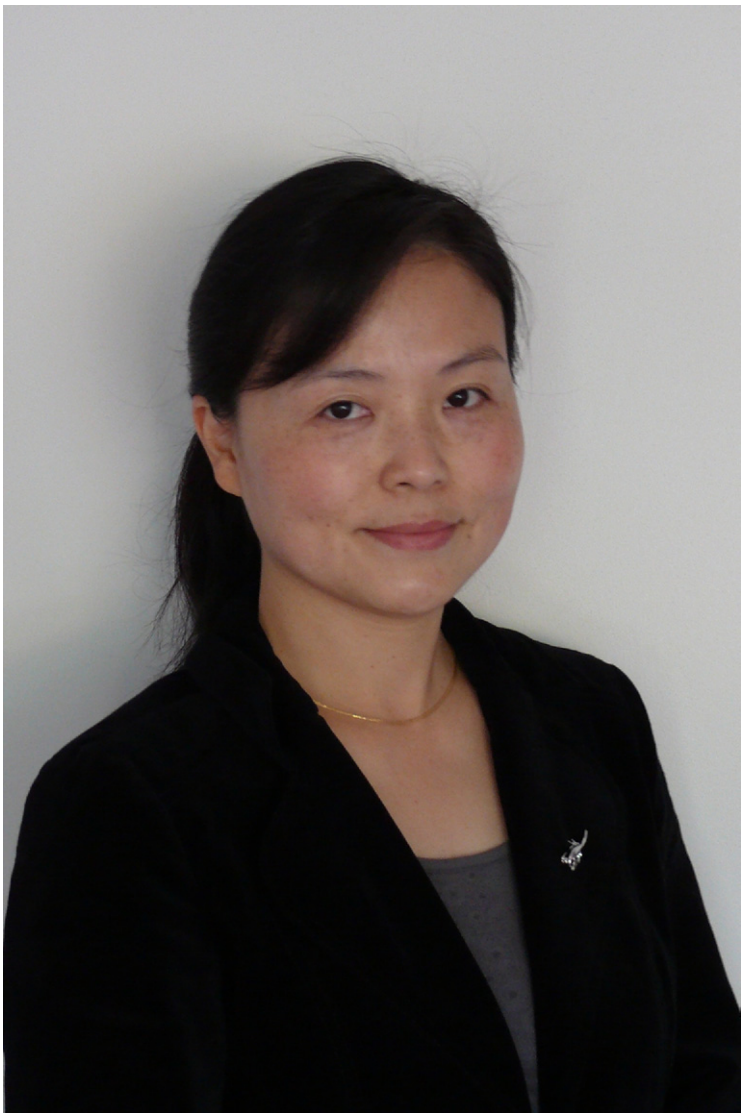

Biosketch

Cong Sun, MD, PhD, is currently a research fellow based at Murdoch Children's Research Institute, Melbourne, Australia. She received her medical degree from Nanjing University, following by a residency in ophthalmology. Dr Sun completed her MPH and then PhD at the University of Melbourne in 2010. Her PhD examined the genetic and environmental determinants of a novel marker for microvascular changes associated with systemic vascular diseases. Her research interests extend to cardiovascular epidemiology.

Biosketch

Professor Mackey has extensively studied large pedigrees with Leber Hereditary Optic Neuropathy. Creating one of the world's largest glaucoma biobanks, his Glaucoma Inheritance Study in Tasmania has helped define phenotype-genotype correlations in myocilin and other glaucoma genes. The Twins Eye Study in Tasmania and Brisbane is investigating the genetic environmental basis on ocular biometry related to glaucoma and myopia. He also leads the Norfolk Island Eye Study and the Western Australian Raine Eye Health Study.