Comparisons of Refractive Errors Between Twins and Singletons in Chinese School-Age Samples

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Studies have reported that refractive errors are associated with premature births. As twins have higher prevalence of prematurity than singletons, it is important to assess similarity of the prevalence of refractive errors in twins and singletons for proper interpretations and generalizations of the findings from twin studies. We compared refractive errors and diopter hours between 561 pairs of twins and 3757 singletons who are representative of school-age children (7–15 years) residing in an urban area of southern China. We found that the means and variances of the continuous measurement of spherical equivalent refractive error and diopter hours were not significantly different between twins and singletons. Although the prevalence of myopia was comparable between twins and singletons, that of hyperopia and astigmatism was slightly but significantly higher in twins than in singletons. These results are inconsistent with those of adult studies that showed no differences in refractive errors between twins and singletons. Given that the sample size of twins is relatively small and that this study is the first to demonstrate minor differences in refractive errors between twins and singletons, future replications are necessary to determine whether the slightly higher prevalence of refractive errors in twins than in singletons found in this study was due to a sampling error or to the developmental delay often observed in twins in childhood.

Keywords: refractive errors, Chinese, twin, eye, myopia, hyperopia

Refractive errors refer to the disturbance in the balance of changes in the overall eye size and refractive components, especially the cornea and the lens (Troilo, 1992). Refractive errors have been classified as one of the five leading causes of visual impairment and blindness worldwide (Pararajasegaram, 1999). The most common refractive errors include myopia, hyperopia and astigmatism. The incidence of these refractive errors is rapidly increasing worldwide, and is currently a major public health concern (Saw et al., 1996; Tay et al., 1992). The prevalence of refractive errors is also known to vary considerably in different ethnic groups, with Asians generally showing higher prevalence than Caucasians (Saw et al., 1996).

To understand genetic and environmental etiologies of refractive errors, a number of twin studies have been undertaken. These studies have shown strong genetic influences and low shared environmental influences on refractive errors, with heritability estimates being approximately 50 to 90% (Dirani et al., 2006). Although twin studies provide valuable information about genetic and environmental influences on variations of complex traits and diseases, whether the findings from twin studies can be extrapolated to the general population is an issue that needs to be tested with empirical data.

It is well documented that twins are generally born 3 to 4 weeks prematurely and are substantially smaller than singletons born at similar gestational age. The intrauterine period is a time of rapid ocular growth, with reports suggesting significant relationships of refractive components with both birthweight and gestational age (O'Connor et al., 2007). As compared to full-term infants, preterm infants have been shown to have more spherical lenses, shorter axial lengths (Fledelius, 1992), and smaller corneas (Donzis et al., 1985), which makes preterm infants more vulnerable to the development of refractive errors and ocular diseases. A number of studies undertaken on the basis of singletons have shown that the prevalence of myopia, hyperopia, and astigmatism is higher among those born preterm than those born full-term (O'Connor et al., 2006; O'Connor et al., 2007).

Although twins are generally at a greater risk for the development of refractive errors than singletons,

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studies that compare the prevalence of refractive errors between twins and singletons have rarely been conducted. Recently, two studies (Dirani et al., 2008; Hammond et al., 2001) examined the prevalence of refractive errors in twins as part of their heritability estimations, and compared the prevalence of refractive errors in their twins with that in singletons on the basis of the published data. Although they were not able to directly match twins and singletons in terms of the sampling method, testing protocols or ages of the subjects, the authors concluded that the prevalence of refractive errors might be generally similar in twins and singletons. However, studies using well-matched samples are necessary to determine the comparability of the prevalence of refractive errors between twins and singletons. Furthermore, as the samples of the two studies were all from adult twins, it remains unknown whether similar results can be obtained from children and adolescent subjects. Given that the prevalence of refractive errors, particularly that of myopia, differs significantly with age, it is also important to examine children to make definitive conclusions about the similarity/difference of the prevalence of refractive errors in twins and singletons.

Although indoor near-work activities have been shown to explain only a small proportion of the total variance of refractive errors, they have been demonstrated to be risk factors for the development of myopia and other refractive errors (Ip et al., 2008; Mutti et al., 2002). In this study, we compared refractive errors (myopia, hyperopia, astigmatism, and a continuous measure of refractive error) and indoor near-work activities (dioptic hours) between school-age twins and singletons residing in the urban area of southern China. This study has three methodological strengths. First, twins and singletons were recruited from the same socioeconomic region using the same population-based sampling method. Second, twins and singletons were matched in terms of age. Finally, eye examinations for both twin and singleton samples were carried out by the same research group on the basis of the same study protocol.

Materials and Methods

Participants

Twins

Twin participants in the present study were drawn from the Guangzhou Twin Eye Study (GTES). Details of the study population and methodology of the GTES were published elsewhere (He et al., 2006). In brief, the GTES is a population-based twin study established in 2005 to investigate genetic and environmental etiologies of ocular diseases and related traits. In the GTES, twins were identified using an official Household Registry of Guangzhou and verified by a door-to-door survey in Guangzhou city. In 2006, a total of 580 twin pairs aged from 7 to 15 years living in two districts (Liwan and Yuexiu) near the Zhongshan Ophthalmic Center participated in the baseline study. The response rate of the baseline study was 82.3%. Of 580 pairs, 19 pairs of twins whose data were unusable because of either pathological eye condition or unsatisfactory pupillary dilation for cycloplegic refraction were excluded from the analysis. The final twin sample included 561 pairs of twins consisting of 357 MZ and 204 DZ pairs. The higher participation rate of MZ than DZ twins in the sample may reflect lower DZ than MZ twin birth rates in East Asians (Hur & Kwon, 2005). The mean age of the twin sample was 10.8 years (*SD* = 2.6) and 49% of the twins were female.

Zygosity of all same-sex twin pairs was determined by 16 DNA markers (PowerPlex 16 system, Promega, Madison, USA) (Tomsey et al. 2001) at the forensic medical department of Sun Yat-sen University.

Singletons

Singletons in the present study were drawn from the participants of the Refractive Error Study in Children (RESC; Negrel et al., 2000). The RESC is a series of population-based surveys of refractive errors and visual impairments conducted in children from different ethnic groups living in various environments of the world. As part of the RESC survey, eye examination data were collected from school-age children (5–15 years) residing in the Liwan district of Guangzhou city between October, 2002, and January, 2003. The Liwan district was chosen for the RESC survey because its residents were representative of the population in urban area of southern China in terms of demographic and socioeconomic characteristics. A total of 5053 children living in 4814 households were solicited for participation in the RESC survey through a door-to-door survey. Of 5053 children, 4364 underwent eye examinations, giving a response rate of 86.4%. Further details of the Guangzhou sample of the RESC survey were described by He et al. (2004). Of 4364 children, 566 subjects who were 5 or 6 years old, and 41 children whose data were unusable either because of temporary machine malfunction or unsatisfactory pupillary dilation, were excluded from the analysis. Thus, the final singleton sample used for this analysis included 3757 children aged from 7 to 15 years with a mean of 11.2 years (*SD* = 2.5). Fifty-one per cent of the sample were female.

Measures

Refractive Errors

Four measures of refractive errors were used in the present study: A continuous measure of spherical equivalent (SE) and categorical measures of myopia, hyperopia and astigmatism. Both the GTES and RESC studies used the same protocol to examine these refractive errors. Cycloplegia was induced for each eye, with 2 drops of 1% cyclopentolate (1% Cyclogyl, Alcon Labs, Fort Wroth, Texas) instilled 5 minutes apart. After an additional 15 minutes pupil dilatation, cycloplegia was evaluated and considered complete if light reflex was absent. Otherwise, a third drop was administered after 20 minutes. Autorefractometers (for twins: KR8800, Topcon Corp, Tokyo, Japan; for singletons: ARK-30; Nidek Corp.) were used to obtain refraction measures and keratometry readings. Results for each eye were converted into their SE (half the amount of cylinder plus the spherical component) as diopters (D). Because results derived from the right and left eyes were similar (spearman correlation coefficient for SE between the right and left eye = 0.93 for both twins and singletons), only data of the right eye were used. Myopia was defined as SE of less than or equal to –0.50D, hyperopia defined as SE of +2.00D or more, and astigmatism as SE of +0.75D or more.

Diopter Hours

An interviewer-administered questionnaire was used to collect detailed information about demographic characteristics and near work activities for twins and singletons. Near work activity questions used in the present study primarily refer to indoor activities, including the number of hours per day spent on reading, using computer, watching television, and playing video games separately on weekdays and weekends. The average weighted number of hours per day for each type of near work activity was generated from the formula: hours per weekday × 5/7 + hours per weekend × 2/7. Diopter hours were then calculated as follows: (3 × the average weighted number of hours per day spent reading) + (2 × the average weighted number of hours per day spent on computer or playing video games) + (1 × the average weighted number of hours per day spent watching television; Zadnik et al., 1994).

Statistical Analysis

Because both SE and diopter hours were significantly correlated with age, we divided the total samples into three age groups: 7–9 years, 10–12 years, and 13–15 years. Comparisons of the mean, variance and the prevalence for each variable were performed between MZ and DZ twins and between twins and singletons for each age group as well as for the total sample. We also examined birth order effects within twin pairs (i.e., the difference between the first- and the second-born twins). However, only 1 of 19 comparisons yielded a statistically significant difference, suggesting that the effects of birth order on refractive errors and diopter hours are minimal (data not shown). We compared continuous variables (SE and diopter hours) and categorical variables (myopia, hyperopia, and astigmatism) separately using different statistical procedures.

Continuous variables. As the distribution of SE was skewed and kurtotic, a Box/Cox transformation (Blackie & Harris, 1997) of the data was made to achieve normal distributions. The diopter hours were approximately normally distributed. We used Mx (Neale et al., 2003) to perform genetic model-fitting analysis. Mx calculates twice the negative log-likelihood (–2*LL*) of the data. To test the equality of means and variances between groups, we examined the difference in –2*LL* between the full and reduced model. In the full model, the means and variances of two groups were set to vary, whereas in the reduced model they were constrained to be equal. The difference in –2*LL* is Chi-square distributed with degrees of freedom equal to the difference in degrees of freedom. Thus, a significant change in Chi-square between the full and reduced model would suggest that the reduction is not acceptable, whereas a non-significant change in Chi-square would indicate that the reduced model is better than the full model.

Categorical variables. To compare the prevalence of myopia, hyperopia, and astigmatism between MZ and DZ twins and between twins and singletons for each age group as well as for the total sample, we computed odds ratios using the generalized estimating equation (GEE) modeling implemented in the Stata Statistical Software (Release 8.0, Stata Corporation, 2003). The GEE model in Stata takes account of dependence between the two members of a twin pair.

Results

Refractive Errors

Spherical Equivalent

Figure 1 shows the graphic presentation of the distributions of SE for the first-born twins and singletons broken down by age.

Refractive errors progressed with age in both twins and singletons. Overall, the distributions of the SE were similar in the first-born twins and singletons. Observations made from Figure 1 were confirmed by model-fitting analyses (Table 1). When we equated the means and variances of SE across MZ and DZ twins (Model 1) and across twins and singletons (Model 2) from the full model, no significant change in –2*LL* occurred in any of the age groups. These results suggest that the means and variances of the continuous measure of SE are similar in twins and singletons as well as in the two types of twins in school-age children.

Myopia, Hyperopia and Astigmatism

Table 2 presents the prevalence of myopia, hyperopia, and astigmatism in three age groups as well as in the total sample for twins and singletons.

While the prevalence of astigmatism did not show significant age effects in either twins or singletons, the prevalence of myopia increased with age and that of hyperopia decreased with age in both twins and singletons. The prevalence of myopia for MZ and DZ twins and for singletons in the total sample were 42.0%, 41.2%, and 42.7% respectively, suggesting marked similarity in the prevalence between twins and singletons as well as between the two types of twins. None of the comparisons of the prevalence in myopia in Table 2 attained a statistical significance.

The prevalence of hyperopia was not significantly different between MZ and DZ twins in any of the three age groups or in the total sample. However, twins had slightly but consistently higher prevalence

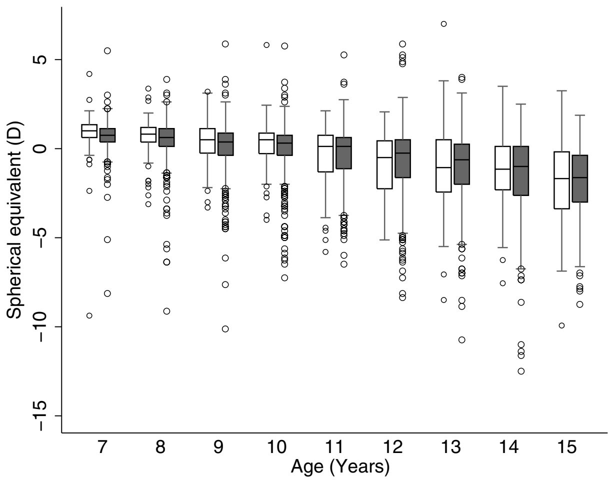

Figure 1

Distributions of spherical equivalent refractive error in the right eye for the first-born twins (white boxes) and singletons (grey boxes) by age, as measured with cycloplegic refraction. Each box represents the interquartile range (25th to the 75th percentiles). The solid line in the box represents the median value and the whiskers indicate ±1.5 times interquartile range.

than that of singletons in all three age groups as well as in the total sample, although the difference attained a statistical significance only in the total sample.

The results for astigmatism were similar to those for hyperopia. No significant difference was found between MZ and DZ twins. However, in all three age groups as well as for the total sample, twins showed slightly but consistently higher prevalence of astigmatism as compared to singletons, although the statistically significant difference was only found in the total sample. This may be due to that only the total sample has sufficient statistical power to detect such a small difference.

Diopter Hours

Figure 2 shows the distributions of diopter hours for the first-born twins and singletons broken down by age. The mean of diopter hours increased with age in both twins and singletons. The distributions of diopter hours were generally similar among the first-born twins and singletons.

The results of the model-fitting for diopter hours (Table 1) were consistent with the observations made from Figure 2. Constraining the means and variances for diopter hours to be equal across MZ and DZ twins from the full model yielded no significant change in $-2LL$ for any of the three age groups or for the total sample (Model 1). When we equated the means and variances across twins and singletons, however, two (the mean for the age group 7–9 and the variance for the age group 13–15) of eight comparisons produced significant differences in $-2LL$ (Model 2). In the 7- to 9-year-old group, twins had lower diopter hours than singletons, while singletons had higher variance than twins in the 13- to 15-year-old group. However, the effect size (the standardized mean difference between groups divided by the common

Table 1

Model-Fitting Results for Spherical Equivalent and Diopter Hours

		Full Model		Model 1 (MZ = DZ)		Model 2 (Twins = Singletons)	
Measure		*−2LL*	*df*	*Δ−2LL(3df)*	*p*	*Δ−2LL(4df)*	*p*
SEt							
7–9 years	Mean	3947.1	1502	5.26	0.15	5.32	0.26
	Variance	3947.1	1502	0.69	0.88	1.16	0.88
10–12 years	Mean	4494.3	1649	1.98	0.58	3.80	0.43
	Variance	4494.3	1649	2.98	0.39	3.46	0.48
13–15 years	Mean	4319.6	1689	2.28	0.66	0.04	0.98
	Variance	4319.6	1689	1.08	0.78	5.96	0.20
Total	Mean	12653.9	4865	5.79	0.12	7.23	0.12
	Variance	12653.9	4865	2.42	0.49	2.54	0.64
Diopter hours							
7–9 years	Mean	6026.3	1223	1.63	0.65	12.64	0.01
	Variance	6026.3	1223	7.45	0.06	9.18	0.06
10–12 years	Mean	6534.2	1318	1.11	0.78	3.15	0.53
	Variance	6534.2	1318	0.84	0.84	6.07	0.19
13–15 years	Mean	6974.5	1396	6.88	0.08	7.21	0.13
	Variance	6974.5	1396	0.42	0.94	13.93	0.01
Total	Mean	19551.0	3962	5.33	0.15	6.42	0.17
	Variance	19551.0	3962	0.48	0.92	2.03	0.73

Note: SEt = spherical equivalent data after Box/Cox transformation.

Table 2

The Prevalence Rates (%) of Myopia, Hyperopia, and Astigmatism and Their 95% CIs for MZ and DZ Twins and Singletons†

	MZ		DZ		Twins in total		Singleton		Odds ratio (95% CI)			
Characteristic	Prevalence	*n*	Prevalence	*n*	Prevalence	*n*	Prevalence	*n*	$OR_{DZ\text{-}MZ}$	$p_{DZ\text{-}MZ}$	$OR_{T\text{-}S}$	$p_{T\text{-}S}$
Myopia												
7–9	20.1 (15.3, 25.0)	54/268	17.1 (10.8, 23.5)	24/140	19.1 (15.3, 22.9)	78/408	16.4 (14.2, 18.5)	181/1107	0.82 (0.43, 1.57)	0.55	0.83 (0.59, 1.17)	0.29
10–12	40.4 (34.0, 46.8)	93/230	44.5 (36.4, 52.7)	65/146	42.0 (37.0, 47.0)	158/376	40.7 (38.0, 43.4)	523/1286	1.18 (0.70, 1.99)	0.53	0.95 (0.73, 1.24)	0.71
13–15	70.8 (64.7, 76.9)	153/216	64.8 (56.2, 73.4)	79/122	68.6 (63.7, 73.6)	232/338	66.0 (63.5, 68.5)	900/1364	0.76 (0.42, 1.38)	0.36	0.88 (0.65, 1.19)	0.41
All	42.0 (38.4, 45.6)	300/714	41.2 (36.4, 46.9)	168/408	41.7 (38.8, 44.6)	468/1122	42.7 (41.1, 44.3)	1604/3757	0.96 (0.71, 1.32)	0.83	1.04 (0.89, 1.22)	0.59
Hyperopia												
7–9	6.7 (3.7, 9.7)	18/268	5.7 (1.8, 9.6)	8/140	6.4 (4.0, 8.8)	26/408	5.1 (3.8, 6.5)	57/1107	0.84 (0.30, 2.33)	0.74	0.78 (0.45, 1.34)	0.37
10–12	6.5 (3.3, 9.7)	15/230	4.1 (0.9, 7.3)	6/146	5.6 (3.3, 7.9)	21/376	3.3 (2.4, 4.3)	43/1286	0.61 (0.20, 1.92)	0.40	0.58 (0.32, 1.09)	0.09
13–15	3.2 (0.9, 5.6)	7/216	4.1 (0.5, 7.7)	5/122	3.6 (1.6, 5.5)	12/338	1.9 (1.2, 2.6)	26/1364	1.28 (0.30, 5.42)	0.74	0.52 (0.24, 1.15)	0.11
All	5.6 (3.9, 7.3)	40/714	4.7 (2.6, 6,7)	19/408	5.3 (4.0, 6.6)	59/1122	3.3 (2.8, 3.9)	126/3757	0.82 (0.42, 1.60)	0.57	0.61 (0.43, 0.88)	0.01
Astigmatism												
7–9	47.0 (41.0, 53.0)	126/268	42.1 (33.9, 50.4)	59/140	45.3 (40.5, 50.2)	185/408	41.6 (38.7, 44.6)	461/1107	0.82 (0.50, 1.35)	0.44	0.86 (0.66, 1.12)	0.27
10–12	43.9 (37.5, 50.4)	101/230	52.1 (43.9, 60.3)	76/146	47.1 (42.0, 52.1)	177/376	41.3 (38.6, 44.0)	531/1286	1.39 (0.85, 2.26)	0.19	0.79 (0.61, 1.02)	0.07
13–15	45.8 (39.1, 52.5)	99/216	51.6 (42.6, 60.6)	63/122	47.9 (42.6, 53.3)	162/338	43.9 (41.3, 46.6)	599/1364	1.26 (0.74, 2.17)	0.40	0.85 (0.65, 1.11)	0.24
All	45.7 (42.0, 49.3)	326/714	48.5 (43.7, 53.4)	198/408	46.7 (43.8, 49.6)	524/1122	42.3 (40.8, 43.9)	1591/3757	1.12 (0.84, 1.50)	0.44	0.84 (0.72, 0.97)	0.02

Note: † 95%CI are in parenthesis. Generalized estimating equation models take account of the nonindependence of twin subjects.

standard deviation) of difference for diopter hours in the 7- to 9-year-old group was only 0.22, suggesting that the magnitude of the difference for diopter hours between twins and singletons is small if the difference existed. Taken together, these findings indicate that diopter hours are generally comparable between twins and singletons as well as between MZ and DZ twins.

Discussion

In the past 2 decades, there have been growing interests of using twin studies to understand genetic and environmental factors as well as to localize genes for refractive errors. However, given the ocular damages that preterm neonates have often shown, it is important to assess whether the prevalence of refractive errors is similar in twins and singletons for proper interpretations and generalizations of the findings from twin studies. To our knowledge, the present study is the first to compare the prevalence of refractive errors in relatively well-matched population-based samples of school-age twins and singletons.

There were three main findings in this study. First, the means and variances of the continuous measure of refractive errors were similar in twins and singletons as well as across MZ and DZ twins. Second, the prevalence of myopia, hyperopia, and astigmatism was very similar across MZ and DZ twins. However, there was some indication that the prevalence of hyperopia and astigmatism was slightly higher in twins than in singletons, although the prevalence of myopia was comparable in twins and singletons. Finally, diopter hours were generally similar in twins and singletons as well as in the two types of twins.

Tomozzoli et al. (2003) compared the ophthalmic examinations in preschooler twins and triplets and singletons (8 to 54 months of age) who were born prematurely and found no significant differences in the prevalence of refraction errors between multiples and singletons, although the rates of various eye morbidity and refractive defects were high in the premature children irrespective of multiple birth status. Based on these results, the authors concluded that multiple gestations added no extra risk beyond that due to prematurity. Several researchers have argued that although subtle to severe refractive errors are common among infants born prematurely, these refractive defects can be reduced during early childhood through

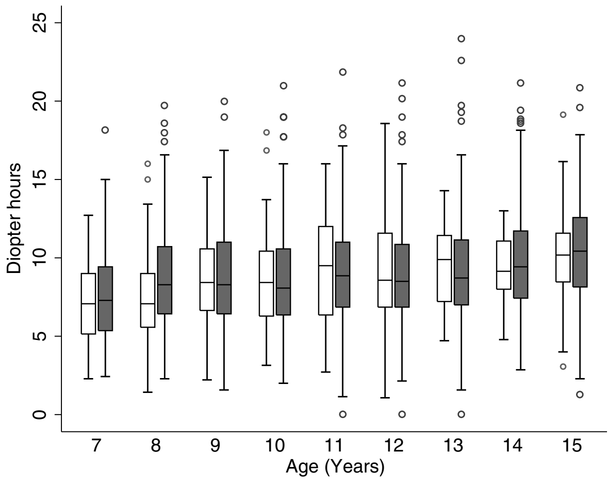

Figure 2

Distributions of diopter hours for the first-born twins (white boxes) and singletons (grey boxes) by age. Each box represents the interquartile range (25th to the 75th percentiles). The solid line in the box represents the mean and the whiskers indicate ±1.5 times interquartile range.

the process of emmetropisation (Grosvenor, 1998; Saw et al., 2004).

Our data in Table 2 show that the prevalence of myopia, hyperopia, and astigmatism tends to be slightly but consistently higher in twins than in singletons. These results support the findings of the Tomozzoli et al. study (2003) showing that as a consequence of prematurity, twins at birth have somewhat higher prevalence of refractive errors, as compared to singletons born at term. However, given the two adult twin studies mentioned earlier (Dirani et al., 2008; Hammond et al., 2001) showing no differences of the prevalence of myopia, hyperopia, and astigmatism between twins and singletons in adulthood, most of the refractive defects found in twins at birth are likely to disappear over time through the postnatal catch-up growth.

In our analyses, the mean and variance of the continuous measurement of the transformed SE refractive error was not significantly different between twins and singletons, while the prevalence of the categorical measures of refractive errors showed some differences. It may be that minor differences between twins and singletons existed at the tails of the raw data of the SE refractive error. But the Box/Cox transformation of the continuous data may have eliminated these minor differences and consequently, twins and singletons did not appear significantly different in the continuous measurement of the SE refractive error. Taken together, our study suggests that differences in the prevalence of various refractive errors between school-age twins and singletons are minimal, if they existed, and unlikely to influence interpretations and generalizations of the findings from twin studies to the population at large.

Although the information of near work activities is not comprehensive without outdoor activities assessment, our analysis of diopter hours suggests that the indoor near-work activity level relevant to the development of refractive errors is largely similar in twins and singletons as well as in MZ and DZ twins. In the youngest group (7–9 years), twins showed somewhat lower level of diopter hours than that of singletons. However, this difference is likely to be a chance finding resulting from multiple comparisons, given that the size of the difference was small and that the difference appeared only in the eight year old children.

Twins in our study were drawn from residents of the two districts, Liwan and its neighborhood, Yuexiu, whereas singletons were drawn from residents of the Liwan district only. We added Yuexiu district to increase our twin sample. As socioeconomic characteristics of these two districts were very similar, it is unlikely that the Yuexiu sample influenced the results of our study substantially. However, to better understand the similarity/difference of the prevalence of refractive errors in childhood and adolescence, there is a clear need for future comparison studies using larger and better-matched twin and singleton samples.

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