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ORIGINAL RESEARCH

The Distribution and Influence Factors of Non-Invasive Tear Film Break-Up Time in Children

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Objective: To explore the distribution and influence factors of non-invasive tear film break-up time (NIBUT) in children.

Methods: This is a hospital-based cross-sectional study. Spherical equivalent error (SER) was measured with cycloplegia. NIBUT was measured by an ocular surface integrated analyzer.

Results: A total of 1269 children (1269 eyes) were included in this study. Participants' median age was 11 (range 6–18) years. 47.1% (598/1269) of participants were boys. The median NIBUT of myopic children and non-myopic children were 9.9 seconds (s) (Interquartile range, IQR: 6.4 to 16.1) and 10.9 s (IQR: 8.8 to 17.9), respectively, which was statistically significant ($p = 0.004$). In myopic children, 49.9% (573/1148) were able to achieve NIBUT of 10 s or more, compared to 67.8% (82/121) in non-myopic children, which was statistically significant ($p < 0.001$). There were 41 (3.57%) children in the myopic group and none (0%) in the non-myopic group with dry eye disease ($p = 0.028$). There was a positive correlation between NIBUT and age: NIBUT = 9.256 + 0.352*Age. 71.8% (824/1148) of myopic children used electronic products almost every day, compared to 37.2% (45/121) of non-myopic children, which was statistically significant ($p < 0.001$).

Conclusion: The NIBUT of myopic children was significantly shorter than that of non-myopic children. Children with myopia are more likely to have dry eyes. NIBUT increases with age. High frequency of electronic product use may be an important cause to NIBUT shortening in children.

Keywords: Tear film break-up time, dry eye, Myopia, ocular surface, children

Introduction

Previous studies have reported an association between myopia and dry eye disease (DED), which the risk of DED increases with the severity of myopia.[1,2] The reported prevalence of DED in the whole population is less than 10%,[3,4] while in myopic population, this number rises up to 45.39%.[5] Maychuk DY[6] et al reported similar findings. Meanwhile, the proportion of the global myopic population is increasing year by year, and is expected to reach more than 50% by 2050.[7] In China, the prevalence of myopia is more serious. In recent years, the number of myopia patients has shown a spurt of growth, there are more than 400 million people with myopia in China.[8]

The increased risk of DED in myopic patients is closely related to a variety of factors. First of all, myopic patients often use their eyes at close range for a long time, such as reading and using electronic products. Secondly, some myopic patients may have poor eye permeability due to improper wearing of glasses or contact lenses, which further aggravates dry eye symptoms.

Tear film is important for maintaining ocular surface health. Decreased tear film break-up time (BUT) is considered as part of the diagnostic criteria for DED.[9,10] BUT measurement, especially non-invasive BUT (NIBUT) measurement,

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could be an easy and economically friendly way for DED monitoring,[10–12] without damage to tear film stability compared with sodium fluorescein.[13,14] The measurement of NIBUT is completed by a high-resolution color camera, which can accurately record the tiny details of tear film changes. The whole process is non-contact, and the BUT is automatically measured, and the duration and position are recorded.

As far as we know, the distribution of NIBUT characteristics in children, especially in myopic children, and its influence factors have not been reported in detail, which is the purpose of this study.

Materials and Methods

Settings and Study Design

This was a hospital-based cross-sectional study. Participants complaint of blurred vision were recruited at Beijing Tongren Hospital (Beijing, China) between January 1, 2023, and July 30, 2023. The present study was approved by the Ethics Committee, Beijing Tongren Hospital, Capital Medical University and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects and/or their legal guardian.

Participants

Participants Were Selected Based on the Following Considerations

Inclusion criteria (1) Age, 6–18 years old; (2) Able to cooperate with NIBUT measurement, ocular surface disease index (OSDI) questionnaire measurement. (3) The cycloplegic SER measurement was completed.

Exclusion criteria (1) Worn contact lenses such as orthokeratology lenses in recent two weeks; (2) Had diabetes, rheumatoid arthritis, sjogren's syndrome or hyperthyroidism that affecting tear secretion; (3) Use of medications that have an effect on tear secretion (except artificial tears) in the last two weeks; (4) Had a history of eye trauma, ocular surgery (including refractive surgery) or infectious eye diseases.

Definition of Dry Eye

According to the 2016 consensus report by the Asia Dry Eye Society,[10] the diagnosis of dry eye disease (DED) should meet the following two conditions: Patients have subjective symptoms of ocular surface and OSDI score>12;[15] Average NIBUT<10 seconds.

Outcomes and Measurements

OSDI Questionnaire

The OSDI questionnaire includes 12 questions, and each question is scored according to the frequency of occurrence. 0 is zero; 1. Sometimes; 2. About half of the time; 3. Frequent occurrence; 4 is continuous occurrence. Final OSDI score = sum of all scores x100/(number of questions x 4). The total score ranges from 0 to 48.

NIBUT Measurement

The new generation Oculus Ocular Surface integrated analyzer (Manufactured by Oculus, Germany) was used to complete the measurement of NIBUT. The focus center of the device was directed to the apex of the cornea. Software built into the device automatically records the average NIBUT.

Statistical Analysis

The Shapiro–Wilk test is used to test the normality of a continuous variable such as NIBUT. Median value, inter-quartile range (IQR), together with the reference interval (2.5% to 97.5% quantile) were used for statistical description of NIBUT. Frequency and percentage were used for statistical description of categorical variables such as sex. Wilcoxon rank sum test was used for comparison on continuous variables that were not normally distributed. Chi-square test was used for comparison on categorical variables when total expected frequency is 40 or above, and no single expected frequency is less than 1, otherwise Fisher exact test would be used. SER≤-0.5D in any eye would be defined as myopia. If both eyes were myopic or neither eye was myopic, one eye was randomly selected for data analysis. If one eye was myopic, that the single myopic eye was used and the patient was categorized in the "myopic" group as opposed to the 'non-myopic

group'. Analysis was done using the open-source R program (https://www.r-project.org/, version 4.2.0). The significance level was 0.05, two-tailed.

Results

Participants Recruitment and Selection

Participants were recruited consecutively between January 1, 2023, and July 30, 2023. Initially, 1395 children complaint of blurred vision was assessed for eligibility, 126 were excluded. In detail, 32 were over 18 years old, 71 did not complete the NIBUT measurement, 23 did not complete cycloplegic SER measurement. Finally, a total of 1269 children (1269 eyes) were included in this study.

Participants Characteristics

The median age was 11 (range: 6–18) years. Boys accounts for 47.1% (598/1269). The median OSDI score was 2 (IQR:0 to 5). The median IOP was 17 (IQR: 15 to 18.5) mmHg. The median SER were −1.875 D (IQR: −2.875 D to −1.25 D, range: −5.75 D to 1.25 D). 68.2% (865/1269) participants used electronic product almost everyday, while only 7.3% (93/1269) used them less frequently (<15 times/month). The details of characteristics of included participants were shown in Table 1.

NIBUT Distribution

Participants' NIBUT ranged from 3.7s to 25.7s (Figure 1A), and the median level was 10.1 s (IQR: 6.8 to 16.3). The median NIBUT of non-myopic children and myopic children were 10.9 s (IQR: 8.8 to 17.9) and 9.9 s (IQR: 6.4 to 16.1), respectively (Table 1), which was statistically significant (p = 0.004). Compared with non-myopic children, the NIBUT of myopic children was significantly shorter (Figure 1B). The distribution of NIBUT of boys and girls showed no significant difference (Figure 1C). NIBUT increases with age (Figure 1D).

10.7% (136/1269) participants had a NIBUT of <5 s, 37.7% (478/1269) had a NIBUT between 5s-10s, 39.7% (504/1269) had a NIBUT between 10 s to 20 s, 11.9% (151/1269) had a NIBUT ≥20 s. In myopic children, 49.9% (573/1148) were able to achieve NIBUT of 10 s or more, compared to 67.8% (82/121) in non-myopic children, which was statistically significant (p < 0.001) (Table 2). Specifically, for those whose NIBUT was <10 s, 3.57% (41/1148) children in the myopic group and 0% in the non-myopic group had an OSDI score of >12.

Table 1 Comparison on Demographic Information and Ocular Parameters Between Myopic and Non-Myopic Group

	Overall ***N=1269***	**Non-Myopic** ***N=121***	**Myopic** ***N=1148***	**p**
Age (years)	11 [9;13]	11 [9;14]	11 [9;13]	0.506
Gender:				0.215
Girls	671 (52.9%)	57 (47.1%)	614 (53.5%)	
Boys	598 (47.1%)	64 (52.9%)	534 (46.5%)	
OSDI (Score)	2 [0;5]	2 [1;6]	2 [0;5]	0.561
NIBUT (seconds)	10.1 [6.8;16.3]	10.9 [8.8;17.9]	9.9 [6.4;16.1]	0.004
IOP (mmHg)	17.0 [15.0;18.5]	17.0 [15.0;19.0]	17.0 [15.0;18.5]	0.716
Flat corneal curvature (D)	42.8 [41.8;43.8]	42.6 [41.5;43.5]	42.8 [41.8;43.8]	0.180
Steep corneal curvature (D)	43.4 [42.2;44.5]	43.0 [41.9;44.6]	43.5 [42.2;44.5]	0.196
Frequency of electronic product use				<0.001
Every day or nearly	865 (68.2%)	45 (37.2%)	824 (71.8%)	
>15 times/month	311 (24.5%)	52 (43.0%)	269 (23.4%)	
0–15 times/month	93 (7.3%)	24 (19.8%)	55 (4.8%)	

Note: NIBUT=Non-invasive tear break-up time. OSDI=ocular surface disease index. IOP=intraocular pressure.

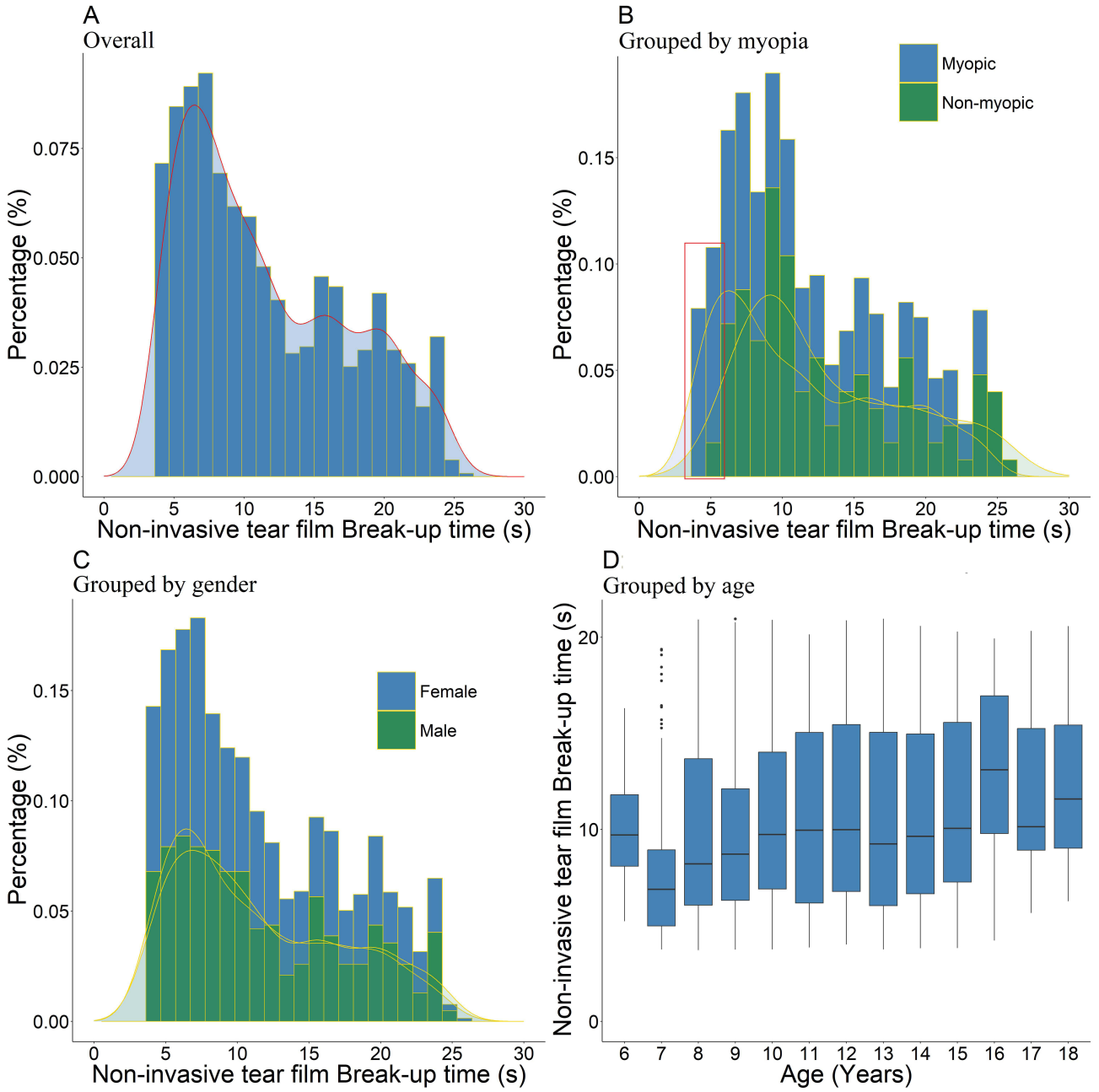

Figure 1 Characteristics of tear film break-up time of included participants (**A**). Distribution of tear film break-up time of all included children. (**B**). Distribution of tear film break-up time in myopic and non-myopic children. (**C**). Distribution of tear film break-up time in boys and girls. (**D**). Distribution of tear film break-up time in children of different ages.

The median levels of NIBUT of children at 6–18 age were 9.4 s (IQR: 7.4 to 12.3), 6.9 s (IQR: 4.8 to 9.0), 8.5 s (IQR: 6.2 to 16.0), 9.1 s (IQR: 6.3 to 13.7), 10.2 s (IQR: 6.9 to 15.9), 10.9 s (IQR: 6.7 to 16.8), 10.3 s (IQR: 6.8 to 16.4), 9.3 s (IQR: 6.1 to 15.4), 11.0 s (IQR: 6.6 to 18.0), 11.0 s (IQR: 7.5 to 18.8), 14.6 s (IQR: 10.7 to 19.9), 14.2 s (IQR: 9.6 to 18.6), and 12.6 s (IQR: 11.1 to 16.6), respectively (Table 3).

The Association Between NIBUT and Age

In the total participants, NIBUT has a positive correlation with age, NIBUT = 9.389+0.355*Age ($p < 0.001$), as shown in line plot (Figure 2A). In boys, NIBUT has a positive correlation with age, NIBUT = 8.772+0.491*Age ($p < 0.001$); In girls, NIBUT has a positive correlation with age, NIBUT = 10.024+0.220*Age ($p < 0.001$) (Figure 2B). In myopic

Table 2 Subgroup Analysis on Non-Invasive Tear Break-Up Time Myopic and Non-Myopic Group

	Overall ***N=1269***	**Non-Myopic** ***N=121***	**Myopic** ***N=1148***	**p**
NIBUT				0.002
≥20s	151(11.9%)	18 (14.8%)	133 (11.6%)	
10s-20s	504(39.7%)	64 (52.9%)	440 (38.3%)	
5s-10s	478(37.7%)	33 (27.3%)	445 (38.8%)	
<5s	136(10.7%)	6 (5.0%)	130 (11.3%)	

Note: NIBUT: non-invasive tear break-up time.

Table 3 The Distribution of Non-Invasive Tear Break-Up Time of Myopic Children at Different Age

Age (Years)	**N**	**Median (IQR)**
6	N = 26	9.4 (7.4, 12.3)
7	N = 73	6.9 (4.8, 9.0)
8	N = 115	8.5 (6.2, 16.0)
9	N = 128	9.1 (6.3, 13.7)
10	N = 156	10.2 (6.9, 15.9)
11	N = 156	10.9 (6.7, 16.8)
12	N = 148	10.3 (6.8, 16.4)
13	N = 120	9.3 (6.1, 15.4)
14	N = 88	11.0 (6.6, 18.0)
15	N = 46	11.0 (7.5, 18.8)
16	N = 28	14.6 (10.7, 19.9)
17	N = 42	14.2 (9.6, 18.6)
18	N = 22	12.6 (11.1, 16.6)

Abbreviation: IQR: Inter-quartile range.

children, NIBUT has a positive correlation with age, NIBUT = 9.256+0.352*Age ($p < 0.001$); In non-myopic children, NIBUT has a positive correlation with age, NIBUT = 10.899+0.350*Age ($p < 0.001$) (Figure 2C).

NIBUT also shows a significant association with SER, NIBUT = 12.033 + 0.219*SER ($p = 0.046$) (Figure 2D). There were 41 (3.57%) children in the myopia group and none (0%) in the non-myopia group with DED ($p = 0.028$).

Use of Electronic Products

71.8% (824/1148) of the myopic children used electronic products almost every day, compared to 37.2% (45/121) of the non-myopic children, which was statistically significant ($p < 0.001$).

Discussion

The present study aims at exploring the characteristics of NIBUT in myopic children and their difference with non-myopic children. The main findings are: 1) The NIBUT of myopic children is significantly shorter than that of non-myopic children. 2) High frequency of electronic product use may be an important cause to NIBUT shortening in children. 3) Children with myopia are more likely to have DED. 4) NIBUT increases with age.

It is reported that children in Asia tend to have shorter NIBUT.[14] Our study found similar findings. It goes without saying that the median NIBUT level for myopic children is only 9.9 s, and even for non-myopic children, the median NIBUT level is only 10.9 s. What we are more concerned about is why NIBUT in myopic children is shorter than that in non-myopic children, and the proportion of children with DED is higher, the reasons may be multifaceted. In general, there is no direct evidence of a causal relationship between myopia and DED, but people with myopia do tend to have

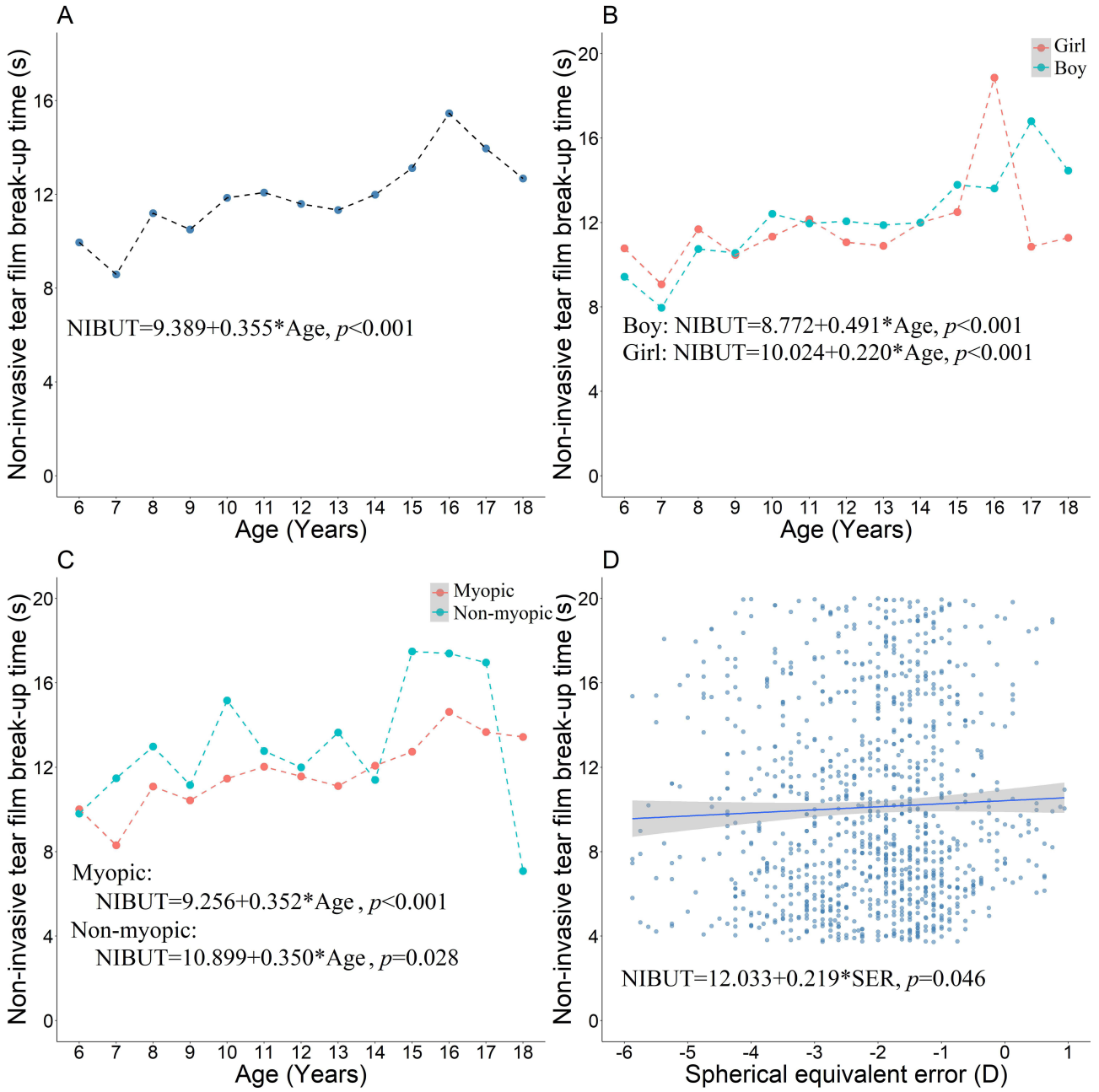

Figure 2 Influence factors of tear film break-up time. (**A**). Association between tear film break-up time and age in all included children. (**B**). Association between tear film break-up time and age in myopic and non-myopic children (**C**). Association between tear film break-up time and age in boys and girls. (**D**). Association between tear film break-up time and spherical equivalent error in all included children. The asterisk represents multiplication.

poor ocular surface conditions. As myopic patients often overuse electronic products (video display terminals, VDT), which is a common risk factor for DED.[14,16,17] The blink frequency is reported to be significantly reduced upon using VDT,[18] and the secretion of the meibomian gland cannot be discharged normally, which reduces the stability of tear film and causes DED.[19] Similarly, a significant decrease in NIBUT was found after four hours of cell phone use.[20] Besides, myopic children often have visual fatigue, which is closely related to DED.[21] On the one hand, visual fatigue often causes the occurrence and development of chronic eye inflammation, which then causes and aggravates DED. On the other hand, visual fatigue causes increased blinking in children,[14] which affects the stability of tear film and promotes the occurrence of dry eye. Nowadays, myopia is becoming a global issue, it is estimated that by 2050 there will be nearly 5 billion myopic people worldwide.[7] The problem of myopia is particularly serious in Asia. In China, the myopia rate

reaches 52.7% in middle school and 80.61% in high school.[22] And there is a trend of increasing year by year, the rising rate of myopia may also indirectly lead to the prevalence of dry eyes.

Our study also reveals a positive correlation between NIBUT and age. Specifically, with one year increase, the NIBUT increase 0.352 s in myopic children and 0.350 s in non-myopic children. Meanwhile among adults, the trend is reversed.[23,24]

Conclusion

In summary, the NIBUT of myopic children is significantly shorter than that of the non-myopic children, the frequency of electronic products using may be the risk factor of NIBUT shortening. Age is an influence factor of NIBUT, NIBUT in children shows a positive correlation with age.

The strength of this study includes a large sample size, and covers a wide range of ages. The limitation of this study lies in that other confirmation examinations of dry eye like Schirmer I test was not performed, and there may be some deviation in the diagnosis of dry eye. Besides, there were few patients in the non-myopic group, although we achieved a power of 0.843, which means it is enough to detect the difference in NIBUT between the non-myopic group and myopic group. However, when describing the NIBUT characteristics of non-myopic groups, their representativeness is limited.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

All experimental protocols were approved by the Ethics Committee, Beijing Tongren Hospital, Capital Medical University. The present study was approved by the Ethics Committee, Beijing Tongren Hospital, Capital Medical University and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects and/or their legal guardian.

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Disclosure

The authors report no conflicts of interest in this work.

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