High myopia and its associated factors in JPHC-NEXT Eye Study: a cross-sectional observational study

CURRENT STATUS: POSTED

Kiwako Mori
Keio University School of Medicine

Toshihide Kurihara
Keio University School of Medicine

kurihara@z8.keio.jp
Corresponding Author
ORCiD: https://orcid.org/0000-0002-5457-2720

Miki Uchino
keio University School of Medicine

Hidemasa Torii
Keio University School of Medicine

Motoko Kawashima
Keio University School of Medicine

Mariko Sasaki
Keio University School of Medicine

Yoko Ozawa
Keio University School of Medicine

Kazumasa Yamagishi
University of Tsukuba

Hiroyasu Iso
Osaka University

Norie Sawada
National Cancer Center

Shoichiro Tsugane
National Cancer Center
Abstract

Background
The increasing prevalence of high myopia has already been noted. It is important to know the factors associated with high myopia to prevent complications. In the present study, we investigated the epidemiological characteristics of high myopia and determine its related factors among a Japanese adult population.

Methods
JPHC-NEXT Eye Study was performed in Chikusei-city, located in a rural area in mid-east Japan in 2013-2015. A cross-sectional observational analysis was conducted to investigate prevalence and related factors of high myopia through this study. A total of 6,101 participants aged ≥40 years who have no history of ocular surgeries were included in this study. High myopia was defined as a spherical equivalent refraction of ≤ -6.00 diopters (D) based on the American Academy of Ophthalmology. Potential high myopia-related factors included intraocular pressure (IOP), corneal structure, corneal endothelial cell density, age, height, body mass index, heart rate, blood pressure, glutamic-oxaloacetic transaminase (GOT), glutamate pyruvate transaminase (GPT), gamma-glutamyl transpeptidase (GGTP), total cholesterol (T cholesterol), triglyceride, high-density lipoprotein cholesterol (HDL cholesterol), low-density lipoprotein cholesterol (LDL cholesterol), blood glucose (glucose), Hemoglobin A1c (HbA1c), creatinine, and current history of systemic and ocular disorders. The odds ratios of high myopia associated with these factors were estimated using the logistic regression models adjusted for the associated factors.

Results
The prevalence of high myopia was 3.8% among the men and 5.9% among the women with a significant difference. Age was inversely associated with high myopia. We also found a positive association between IOP and high myopia. Other factors were not associated with high myopia for either men or women.

Conclusions
In this community-based sample, age was inversely, and IOP was positively associated with high
myopia in both the men and the women.

Background
Myopia is one of the most prevalent conditions of the eye. It causes visual impairment in both children and adults that is usually correctable by optical aids such as glasses and contact lenses. High myopia is generally determined as -6.00 diopters (D) or less in refraction and axial lengths of 26.5 mm and more by the American Academy of Ophthalmology.[1] High myopia is associated with progressive and excessive elongation of the eyeball, which results in various funduscopic changes in the posterior fundus, and increases the risk of pathologic myopia, which may cause irreversible vision loss such as glaucoma, retinal detachment, and macular degeneration.[2] High myopia is a major cause of blindness in many countries[3], and the prevalence of myopia and high myopia is expected to increase globally from 2000 to 2050.[4] Thus, it is important to manage myopia progression and to prevent myopia-related ocular complications and vision loss the approximately 1 billion people with high myopia.[4]

Over the past few decades, some studies have provided information on the prevalence and risk factors for myopia, including genetic predisposition and environmental factors such as extended near work, less exercise, and luck of outdoor activities.[5] [6] [7] However, the etiology of myopia remains unclear. The length of indoor or outdoor activities[8-10], ethnicity[11], vitamins[12], diabetes[13], reading habits[14], body stature[15], lifestyles[15] and light environment[16] [17] [18] were suggested as associated factors for the progression of myopia.

Human lifestyles are rapidly changing. The factors that may affect the progression of myopia are essential to understand to find countermeasures for myopia. Community-based, population-based research is a reliable way to elucidate the associated factors. In order to elicit the high myopia associated factors, it was thought to be important to eliminate biases and prejudices as much as possible. We established this study to screen all the possible factors which were available in the collected data and personal information without manipulation. In addition, this study targeted adult population as subjects. Pathological myopia, which is usually preceded by high myopia and seen mostly in adults, is theoretically thought to be originated from myopia in children. To know possible
associated factors for high myopia in adults is considered to be a crucial key to render solutions to diminish the number of future high or pathological myopia in children.

We conducted the JPHC-NEXT Eye Study, an ancillary study of the Japan Public Health Center-Based Prospective Study for the Next Generation (JPHC-NEXT), to examine the prevalence of refractive status of the participants and factors associated with high myopia in Chikusei, a rural city in mid-east Japan. To our knowledge, this is the first large community-based study to determine the factors associated with high myopia.

Methods

Study design and participants

JPHC-NEXT Eye Study was performed in two regions, Saku-city and Chikusei-city. The subjects of this study are participants of annual checkups who aged 40 years or more in Chikusei-city, and a total of 7,098 subject who had taken ocular examination between 2013 and 2015 were included in this study. Out of them, 997 participants who had undergone ocular surgeries were excluded, because their refraction may have changed after the procedures. In the end, 6,101 participants aged from 40 to 93 years (86.0%) were included in this analysis (Fig 1). This study followed the tenets of the World Medical Association’s Declaration of Helsinki. The study protocol was approved by the Institutional Review Boards of Keio University, Osaka University, the University of Tsukuba, and the National Cancer Center. Written informed consent was obtained from all of the participants.

Screening examination

The screening included ophthalmic examinations (refraction, intraocular pressure, central corneal thickness, and corneal endothelium density), measurement of height (HT), weight (WT), blood pressure, serum laboratory data including glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), gamma-glutamyl transpeptidase (GGTP), total cholesterol (T cholesterol), fasting triglyceride (triglycerides), high density lipoprotein (HDL cholesterol), low density lipoprotein (LDL cholesterol), fasting blood glucose (glucose), hemoglobin A1c (HbA1c), and creatinine, and a history of systemic and ocular disorders. Serum T cholesterol, triglycerides, HDL cholesterol, LDL cholesterol,
HbA1c, GGTP and creatinine were measured by visible absorption spectrometry. Serum glucose, GOT, and GPT were measured using ultraviolet absorption spectrometry. Blood pressure was measured two times and the second reading was adopted. Refractive status and intraocular pressure (IOP) were measured using an auto refractometer (Tonoref II, Nidek, Gamagori, Japan). Central corneal thickness and corneal endothelium density were measured by using a specular-type pachymeter (Specular microscope XIII, Konan, Nishinomiya, Japan).

Information on past medical history

Information on histories of hypertension, diabetes and dyslipidemia was collected through face-to-face interview at the baseline survey. Likewise, inquiry about smoking history and alcohol history as well as histories of ocular disease and its surgery were also performed.

Definitive Examination

The spherical equivalent refraction (SEq) was calculated from the refraction using the following formula: the full spherical power plus half of the cylindrical power. Initially, the mean values of the SEq of the right eyes and the left eyes were compared in the entire population of the current study. There was no significant difference in the median SEq between the right eyes and the left eyes (-0.13 vs -0.00 (D), p=0.10). Thus, we used the SEq of the right eyes to evaluate the refractive status in this study. A high myopia was defined as SEq of -6.00 D or less based on the American Academy of Ophthalmology criteria.[1]

Statistical Analysis

Statistical analyses were performed using IBM SPSS statistics version 23 (IBM, Armonk, NY, USA). Differences across the groups were tested using an analysis of (co)variance or the chi-square test. Student’s t-test was used for independent variables showing normal distribution, and nonparametric tests such as Mann-Whitney’s U test were applied to TG, GLU, SEq, IOP, corneal radius, central corneal thickness, and corneal endothelial cell number. To analyze the relationships of alcohol intake and
smoking history with high myopia, Fisher's exact probability test and logistic analysis were performed. Age and multivariable adjusted OR and 95% CI of the high myopia according to the quartiles of each risk factor were calculated sex-specifically using logistic regression models. The multivariate models included age, height, body mass index, systolic blood pressure (SBP), triglycerides, HDL cholesterol, LDL cholesterol, HbA1c, IOP, and central corneal thickness. The linear trend of ORs across the quartiles were tested by using the continuous variables of the explanatory variables. A p value of less than 0.05 was considered statistically significant.

**Results**

**Participants**

The prevalence of high myopia in the current study was 5.0%, 3.8% in men and 5.9% in women. High myopia was more prevalent among women than men (p<0.001). According to the age distribution, the prevalence of high myopia in the 40s, 50s, 60s, 70s, 80s, and 90s was 10.6%, 8.8%, 3.5%, 2.0%, 1.2%, and 0.0%, respectively (Fig 2). The median SEq of the right eyes in total was -0.13 D ranging from -23.13 D to +10.25 D, with 1st quartile -1.38 and 3rd quartile +0.88 D. In the men, the median SEq was -0.13 D ranging from -18.88 D to +10.25 D, with 1st quartile -1.25 and 3rd quartile +0.88 D. In the women, the median SEq was -0.13 D ranging from -23.13 D to +6.88 D, with 1st quartile -1.63 and 3rd quartile +0.88 D. The median SEq of the right eye was not significantly different between genders (p=0.52).

**Associations between systemic factors and high myopia**

We evaluated the associations between systemic factors and high myopia (Table 1). The mean age for the high myopia group was significantly lower than non-high myopia group (55.7±10.5 vs 62.8±10.3 years, p<0.001). The peak of the high myopia prevalence by age was from 40 to 49 years (6.2% among the men and 13.0% among the women). The mean height for the high myopia group was significantly higher than others (158.8±8.0 vs 157.5±8.7 cm, p=0.009). A similar difference was also found in the age and heights of men and women, respectively (Table 1). No significant difference between the high myopia group and non-high myopia group was observed in weight, waist, and
diastolic blood pressure. Among the laboratory data, T cholesterol, triglycerides, and LDL cholesterol were significantly different between the two groups in men. Glucose and HbA1c were significantly different between the two groups in the women. Regarding the relationship between alcohol intake and high myopia, ORs for high myopia and alcohol intake history were 1.166 (95%CI 0.371-3.662) in the men and 0.900 (95%CI 0.467-1.732) in the women. ORs for high myopia and tobacco use history were 0.598 (95%CI 0.340-1.051) in the men and 0.967 (95%CI 0.593-1.577) in the women (S1 Table).

Associated between ocular features and high myopia

Associations between ocular features and high myopia were also evaluated (Table1). The median IOP was significantly higher for the high myopia group than the others (14.30 vs 13.30 mmHg, p<0.001). A similar difference was found in the median IOP of the men or women, respectively. A significant difference was also observed in the median corneal radius between the high myopia group and the others (7.62 vs 7.64 mm, p=0.024). However, no significant difference was found in the median corneal radius of the men and women, respectively. There was no significant difference in central corneal thickness and corneal endothelial cell number between the two groups.

IOP and age associated with high myopia

A multivariable logistic regression analysis was performed to identify the factors associated with high myopia (Table 2). The ORs adjusted for multivariable factors were significant for age and IOP in the men and the women. In men, the values were as follows: the ORs adjusted with other factors for high myopia in each age group were 40-58 years (OR 1), 59-65 years (OR 0.44, 95%CI 0.22-0.89), 66-70 years (OR 0.43, 95%CI 0.20-0.93), and no younger than 71 years (OR 0.48, 95%CI 0.22-1.06, p for trend 0.049). The ORs adjusted with other factors for high myopia in the groups of IOP were ≤11.2 mmHg (OR 1), 11.3-13.2 mmHg (OR 3.34, 95%CI 0.93-12.00), 13.3-15.2 mmHg (OR 5.18, 95%CI 1.49-18.04), and ≥15.3 mmHg (OR 7.73, 95%CI 2.24-26.77), respectively (p for trend<0.001).

In women, the values were as follows: the ORs adjusted with other factors for high myopia in each age group were 40-54 years (OR 1), 55-62 years (OR 0.57, 95%CI 0.36-0.90), 63-68 years (OR 0.35,
95% CI 0.21-0.59), and no younger than 69 years (OR 0.21, 95% CI 0.11-0.41) (p for trend <0.001).

The ORs adjusted with other factors in each IOP group were ≤11.6 mmHg (OR 1), 11.7-13.6 mmHg (OR 2.23, 95% CI 1.23-4.05), 13.7-15.6 mmHg (OR 2.25, 95% CI 1.21-4.16), and ≥15.7 mmHg (OR 2.33, 95% CI 1.24-4.37), respectively (p for trend 0.023). In summary, as the age increases, the OR decreases, and as the IOP increases, the OR increases in both men and women.

Discussion

This community-based study showed the prevalence of high myopia and associated factors including physical, ocular and demographic factors among adult Japanese for the first time. The factors associated with myopia were widely investigated as we analyzed biochemistry tests, blood pressure, height, body weight, habit of smoking, alcohol intake, past medical history, and present diseases. In this current study, we found that high myopia is more prevalent in women, younger age, and it has higher IOP.

High myopia affects approximately 1-4% of adults aged ≥40 years, and its prevalence was higher in some studies of East Asian adults and adolescents.[19-26] Our findings showed that the prevalence of high myopia was 5.0%, which was no less than the generally affected rates, although Chikusei-city is in a rural area where its prevalence has usually been lower compared to urban areas.[23] In our study, the high myopia rate in the older population was relatively low and the younger generation had a higher prevalence of high myopia, which may be reflect cohort effects. Although the reason for this cohort effects is unknown, the prevalence of high myopia could be expected to increase in future.

Some previous studies reported the relationship of height[27-29] and BMI[15, 30-32] with myopia; however, we did not find such association. A possible reason for this discrepancy is confounding; the previous reports did not adjust for age and any other confounding factors. In fact, BMI and height were shown to be associated with high myopia in unadjusted models, and adjustment for age resulted in the elimination of this significance in our study, presumably because age is a strong predisposing factor for BMI and height reflecting cohort effects.

As for the other laboratory factors, there was no significant difference. A few studies suggested that hyperglycemia and hyperlipidemia led to myopic shift, whereas other studies revealed that the
refractive shift was more likely hyperopic with hypoglycemia.[33-36] Further analysis is needed to elucidate the influence of metabolic shift.

In terms of alcohol intake and smoking history, both factors did not show any associations with high myopia according to our results. Also, liver functions, represented by GOT, GPT, and GGTP, did not show any relationship to high myopia. Previous reports also found that there were no significant trends observed between smoking and refractive errors.[37]

The percentage of high myopia in men and women was 3.8% and 5.9%, respectively, indicating significant gender difference. It has been reported that female sex had a predisposition of high myopia.[38] Likewise, female sex was proven to be high risk for myopic complications usually caused by high myopia.[39] Hyman L et al. reported that female sex is independently associated with faster myopic progression.[40] Although there have been no reports describing causal relationship between gender and high myopia.

The mean IOP linearly increased parallel to the myopic progression. It has been reported that IOP was associated with central corneal thickness, age, and blood pressure.[41, 42] Even after adjustment for these factors, we still found that high IOP was significantly associated with high myopia while there are conflicting evidences regarding relationship of high myopia and IOP.[43-45]

This study has several limitations. First, since this was a cross-sectional study, the causal relationships cannot be determined. Second, some known risk factors of myopia such as natural guardians, near work, outdoor activities, and academic backgrounds were unavailable in this study. Moreover, neither measuring of the axial length nor lens examinations has been performed. With respect to the lenses, factors of cataracts remain to be considered. We also should consider environmental differences across generations which might have affected the result of associations of age with high myopia.

As discussed, the factors associated with high myopia were undetermined. This study did not suggest that height, BMI, blood glucose, hypocholesteremia, liver dysfunction, kidney dysfunction, smoking, and alcohol intake were associated with high myopia, whereas women, young age and high IOP were found to be related to high myopia. Meanwhile, high IOP and young age were found to be risk factors
for high myopia, which may indicate the path for future studies concerning myopia control.

Conclusions
In conclusion, this epidemiological study performed in a Japanese rural area revealed significant results: being women, young and having high IOP were factors associated with high myopia, while height, BMI, cholesterol level, glucose level, and other considered possible risk factors for high myopia in previous studies, were not associated with prevalence of myopia.

Abbreviations

| Abbreviation | Description                            |
|--------------|----------------------------------------|
| HT           | height                                 |
| BMI          | body mass index                        |
| WT           | body weight                            |
| HR           | heart rate                             |
| SBP          | systolic blood pressure                |
| DBP          | diastolic blood pressure               |
| GOT          | glutamic-oxaloacetic transaminase      |
| GPT          | glutamate pyruvate transaminase        |
| GGTP         | gamma-glutamyl transpeptidase          |
| T CHOL       | total cholesterol                      |
| TG           | triglyceride                           |
| HDL CHOL     | high-density lipoprotein cholesterol   |
| LDL CHOL     | low-density lipoprotein cholesterol    |
| HbA1c        | Hemoglobin A1c                         |
| GLU          | glucose                                |
| IOP          | intraocular pressure                   |

Declarations

**Ethics approval and consent to participate**

This study followed the tenets of the World Medical Association’s Declaration of Helsinki. The study protocol was approved by the Institutional Review Boards of Keio University, Osaka University, the
University of Tsukuba, and the National Cancer Center. Written informed consent was obtained from all of the participants.

**Consent for publication**

Consent for publication was obtained from each person partaking in this study in written consent forms.

**Availability of data and materials**

All data generated or analysed during this study are included in this published article and its supplementary information.

**Competing Interests statement**

The authors declare that they have no competing interests.

**Funding:**

Toshihide Kurihara:
Specified contribution from Keio University

Kenya Yuki:
JSPS KAKENHI Grant Number JP16K11271
Specified contribution from Keio University
2015 Novartis Research Grant
Kazuo Tsubota:
Specified contribution from Keio University

Shoichiro Tsugane
National Cancer Center Research and Development Fund

Authors’ contributions

KM, TK, MU, HT, MK, MS, YO, KY, HI, NS, ST, KY and KT participated in the design of the study. KM, UM, MK, KY, NS and KY collected and analyzed the data. All authors interpreted the data. KM wrote the article. TK, UM, KY, NS and KY critically revised the article. HI, ST and KT reviewed the literature. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Ikuno Y, Ohji M: High Myopia and the Vitreoretina; Complications. In: Retina (Philadelphia, Pa). Volume 3, 5 edn. Edited by Ryan SJ. Los Angeles, CA: ELSEVIER; 2013: 1912-1919.

2. Wong TY, Ferreira A, Hughes R, Carter G, Mitchell P: Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review. American journal of ophthalmology 2014, 157(1):9-25.e12.

3. Hsu WM, Cheng CY, Liu JH, Tsai SY, Chou P: Prevalence and causes of visual impairment in an elderly Chinese population in Taiwan: the Shihpai Eye
Study. Ophthalmology 2004, 111(1):62-69.

4. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, Wong TY, Naduvilath TJ, Resnikoff S: Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. Ophthalmology 2016, 123(5):1036-1042.

5. Goldschmidt E, Jacobsen N: Genetic and environmental effects on myopia development and progression. Eye (London, England) 2014, 28(2):126-133.

6. Dirani M, Chamberlain M, Shekar SN, Islam AF, Garoufalis P, Chen CY, Guymer RH, Baird PN: Heritability of refractive error and ocular biometrics: the Genes in Myopia (GEM) twin study. Investigative ophthalmology & visual science 2006, 47(11):4756-4761.

7. Ramessur R, Williams KM, Hammond CJ: Risk factors for myopia in a discordant monozygotic twin study. Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists) 2015, 35(6):643-651.

8. Rose KA, Morgan IG, Smith W, Burlutsky G, Mitchell P, Saw SM: Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney. Archives of ophthalmology (Chicago, Ill : 1960) 2008, 126(4):527-530.

9. Wu PC, Tsai CL, Wu HL, Yang YH, Kuo HK: Outdoor activity during class recess reduces myopia onset and progression in school children. Ophthalmology 2013, 120(5):1080-1085.

10. He M, Xiang F, Zeng Y, Mai J, Chen Q, Zhang J, Smith W, Rose K, Morgan IG: Effect of Time Spent Outdoors at School on the Development of Myopia Among Children in China: A Randomized Clinical Trial. JAMA 2015, 314(11):1142-1148.

11. Rudnicka AR, Owen CG, Nightingale CM, Cook DG, Whincup PH: Ethnic differences in the prevalence of myopia and ocular biometry in 10- and 11-year-old
children: the Child Heart and Health Study in England (CHASE). Investigative ophthalmology & visual science 2010, 51(12):6270-6276.

12. Tideman JW, Polling JR, Voortman T, Jaddoe VW, Uitterlinden AG, Hofman A, Vingerling JR, Franco OH, Klaver CC: Low serum vitamin D is associated with axial length and risk of myopia in young children. Eur J Epidemiol 2016, 31(5):491-499.

13. Galvis V, Lopez-Jaramillo P, Tello A, Castellanos-Castellanos YA, Camacho PA, Cohen DD, Gomez-Arbelaez D, Merayo-Lloves J: Is myopia another clinical manifestation of insulin resistance? Med Hypotheses 2016, 90:32-40.

14. Hsu CC, Huang N, Lin PY, Tsai DC, Tsai CY, Woung LC, Liu CJ: Prevalence and risk factors for myopia in second-grade primary school children in Taipei: A population-based study. J Chin Med Assoc 2016, 79(11):625-632.

15. Terasaki H, Yamashita T, Yoshihara N, Kii Y, Sakamoto T: Association of lifestyle and body structure to ocular axial length in Japanese elementary school children. BMC ophthalmology 2017, 17(1):123.

16. Torii H, Ohnuma K, Kurihara T, Tsubota K, Negishi K: Violet Light Transmission is Related to Myopia Progression in Adult High Myopia. Scientific reports 2017, 7(1):14523.

17. Torii H, Kurihara T, Seko Y, Negishi K, Ohnuma K, Inaba T, Kawashima M, Jiang X, Kondo S, Miyauchi M et al: Violet Light Exposure Can Be a Preventive Strategy Against Myopia Progression. EBioMedicine 2017, 15:210-219.

18. Karouta C, Ashby RS: Correlation between light levels and the development of deprivation myopia. Investigative ophthalmology & visual science 2014, 56(1):299-309.

19. Tarczy-Hornoch K, Ying-Lai M, Varma R: Myopic refractive error in adult Latinos:
the Los Angeles Latino Eye Study. *Investigative ophthalmology & visual science* 2006, **47**(5):1845-1852.

20. Pan CW, Wong TY, Lavanya R, Wu RY, Zheng YF, Lin XY, Mitchell P, Aung T, Saw SM: Prevalence and risk factors for refractive errors in Indians: the Singapore Indian Eye Study (SINDI). *Investigative ophthalmology & visual science* 2011, **52**(6):3166-3173.

21. Saw SM, Gazzard G, Koh D, Farook M, Widjaja D, Lee J, Tan DT: Prevalence rates of refractive errors in Sumatra, Indonesia. *Investigative ophthalmology & visual science* 2002, **43**(10):3174-3180.

22. Ezelum C, Razavi H, Sivasubramaniam S, Gilbert CE, Murthy GV, Entekume G, Abubakar T: Refractive error in Nigerian adults: prevalence, type, and spectacle coverage. *Investigative ophthalmology & visual science* 2011, **52**(8):5449-5456.

23. Xu L, Li J, Cui T, Hu A, Fan G, Zhang R, Yang H, Sun B, Jonas JB: Refractive error in urban and rural adult Chinese in Beijing. *Ophthalmology* 2005, **112**(10):1676-1683.

24. Liang YB, Wong TY, Sun LP, Tao QS, Wang JJ, Yang XH, Xiong Y, Wang NL, Friedman DS: Refractive errors in a rural Chinese adult population the Handan eye study. *Ophthalmology* 2009, **116**(11):2119-2127.

25. Wong TY, Foster PJ, Hee J, Ng TP, Tielsch JM, Chew SJ, Johnson GJ, Seah SK: Prevalence and risk factors for refractive errors in adult Chinese in Singapore. *Investigative ophthalmology & visual science* 2000, **41**(9):2486-2494.

26. Wang TJ, Chiang TH, Wang TH, Lin LL, Shih YF: Changes of the ocular refraction among freshmen in National Taiwan University between 1988 and 2005. *Eye (London, England)* 2009, **23**(5):1168-1169.
27. Gardiner PA: The relation of myopia to growth. Lancet (London, England) 1954, 266(6810):476-479.

28. Johansen EV: Simple myopia in schoolboys in relation to body height and weight. Acta ophthalmologica 1950, 28(3):355-361.

29. Rim TH, Kim SH, Lim KH, Kim HY, Baek SH: Body Stature as an Age-Dependent Risk Factor for Myopia in a South Korean Population. Seminars in ophthalmology 2017, 32(3):326-336.

30. Roy A, Kar M, Mandal D, Ray RS, Kar C: Variation of Axial Ocular Dimensions with Age, Sex, Height, BMI-and Their Relation to Refractive Status. Journal of clinical and diagnostic research : JCDR 2015, 9(1):Ac01-04.

31. Saw SM, Chua WH, Hong CY, Wu HM, Chia KS, Stone RA, Tan D: Height and its relationship to refraction and biometry parameters in Singapore Chinese children. Investigative ophthalmology & visual science 2002, 43(5):1408-1413.

32. Nangia V, Jonas JB, Matin A, Kulkarni M, Sinha A, Gupta R: Body height and ocular dimensions in the adult population in rural Central India. The Central India Eye and Medical Study. Graefes Arch Clin Exp Ophthalmol 2010, 248(11):1657-1666.

33. Fledelius HC, Fuchs J, Reck A: Refraction in diabetics during metabolic dysregulation, acute or chronic. With special reference to the diabetic myopia concept. Acta ophthalmologica 1990, 68(3):275-280.

34. Gwinup G, Villarreal A: Relationship of serum glucose concentration to changes in refraction. Diabetes 1976, 25(1):29-31.

35. Lim LS, Gazzard G, Low YL, Choo R, Tan DT, Tong L, Yin Wong T, Saw SM: Dietary factors, myopia, and axial dimensions in children. Ophthalmology 2010, 117(5):993-997.e994.
36. Edwards MH: **Do variations in normal nutrition play a role in the development of myopia?** *Optometry and vision science : official publication of the American Academy of Optometry* 1996, 73(10):638-643.

37. Saw SM, Chia KS, Lindstrom JM, Tan DT, Stone RA: **Childhood myopia and parental smoking.** *The British journal of ophthalmology* 2004, 88(7):934-937.

38. Mo Y, Wang MF, Zhou LL: **Risk factor analysis of 167 patients with high myopia.** *International journal of ophthalmology* 2010, 3(1):80-82.

39. Asakuma T, Yasuda M, Ninomiya T, Noda Y, Arakawa S, Hashimoto S, Ohno-Matsui K, Kiyohara Y, Ishibashi T: **Prevalence and risk factors for myopic retinopathy in a Japanese population: the Hisayama Study.** *Ophthalmology* 2012, 119(9):1760-1765.

40. Hyman L, Gwiazda J, Hussein M, Norton TT, Wang Y, Marsh-Tootle W, Everett D: **Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial.** *Archives of ophthalmology (Chicago, Ill : 1960)* 2005, 123(7):977-987.

41. Wong TT, Wong TY, Foster PJ, Crowston JG, Fong CW, Aung T: **The relationship of intraocular pressure with age, systolic blood pressure, and central corneal thickness in an asian population.** *Investigative ophthalmology & visual science* 2009, 50(9):4097-4102.

42. Wang D, Huang W, Li Y, Zheng Y, Foster PJ, Congdon N, He M: **Intraocular pressure, central corneal thickness, and glaucoma in chinese adults: the liwan eye study.** *American journal of ophthalmology* 2011, 152(3):454-462.e451.

43. David R, Zangwill LM, Tessler Z, Yassur Y: **The correlation between intraocular pressure and refractive status.** *Archives of ophthalmology (Chicago, Ill : 1960)* 1985, 103(12):1812-1815.
Lee AJ, Saw SM, Gazzard G, Cheng A, Tan DT: *Intraocular pressure associations with refractive error and axial length in children.* The British journal of ophthalmology 2004, 88(1):5-7.

Han X, Yang T, Zhang J, Yu S, Guo X, Yan W, Hu Y, He M: *Longitudinal changes in intraocular pressure and association with systemic factors and refractive error: Lingtou Eye Cohort Study.* BMJ open 2018, 8(2):e019416.

### Tables

Table 1: The association between systemic and ocular features and high myopia

| Variables                  | Non high myopia | High myopia | P value |
|----------------------------|-----------------|-------------|---------|
| Men                        |                 |             |         |
| Age                        | 64.2±10.4       | 58.7±11.2   | <0.001  |
| HT                         | 164.8±6.5       | 166.7±6.4   | 0.007   |
| BMI                        | 23.8±3.1        | 24.3±4.2    | 0.169   |
| HR                         | 62.6±13.7       | 63.4±14.5   | 0.666   |
| SBP                        | 128.6±17.1      | 129.4±17.9  | 0.684   |
| DBP                        | 76.8±11.6       | 78.5±12.4   | 0.176   |
| GOT                        | 26.4±58.1       | 23.6±8.0    | 0.677   |
| GPT                        | 24.7±47.3       | 24.9±12.1   | 0.972   |
| GGTP                       | 46.3±58.7       | 40.0±24.2   | 0.374   |
| T CHOL                     | 119.3±33.7      | 209.3±31.3  | 0.003   |
| TG                         | 105.0†          | 117.0†      | 0.023†  |
| HDL CHOL                   | 57.0±14.5       | 56.4±13.7   | 0.733   |
| LDL CHOL                   | 121.0±30.7      | 129.7±29.9  | 0.020   |
| GLU                        | 99.0†           | 99.0†       | 0.597†  |
| HbA1c                      | 5.8±0.8         | 5.7±0.5     | 0.215   |
| Creatinine                 | 0.9±0.3         | 0.9±0.1     | 0.733   |
| IOP                        | 13.3†           | 15.0†       | <0.001† |
| Corneal radius             | 7.7†            | 7.7†        | 0.198†  |
| Central corneal thickness  | 556.0†          | 565.0†      | 0.391†  |
| Corneal endothelial cell number | 2793.0†     | 2789.5†     | 0.538†  |
### Women

| Variable         | High                  | Non                  | OR 1 | 95% CI   | P value |
|------------------|-----------------------|----------------------|------|----------|---------|
| Age              | 61.8±10.2             | 54.4±9.9             | <0.001 |
| HT               | 152.5±6.2             | 155.4±5.9            | 0.001 |
| BMI              | 22.8±3.5              | 22.2±3.9             | 0.012 |
| HR               | 64.6±13.4             | 64.6±15.0            | 0.964 |
| SBP              | 122.1±17.5            | 117.4±18.2           | <0.001 |
| DBP              | 72.7±11.3             | 71.9±13.2            | 0.358 |
| GOT              | 22.5±9.2              | 21.5±8.5             | 0.168 |
| GPT              | 19.0±11.7             | 18.7±12.9            | 0.815 |
| GGTP             | 25.4±26.2             | 25.6±23.2            | 0.920 |
| T CHOL           | 216.4±35.1            | 214.6±36.4           | 0.461 |
| TG               | 90.0†                 | 83.0†                | 0.076†† |
| HDL CHOL         | 67.3±15.1             | 69.2±14.4            | 0.117 |
| LDL CHOL         | 130.6±31.8            | 131.3±32.5           | 0.783 |
| GLU              | 95.0†                 | 91.0†                | <0.001†† |
| HbA1c            | 5.8±0.6               | 5.6±0.5              | 0.011 |
| Creatinine       | 0.6±0.1               | 0.6±0.1              | 0.235 |
| IOP              | 13.7†                 | 14.0†                | 0.038†† |
| Corneal radius   | 7.6†                  | 7.6†                 | 0.327†† |
| Central corneal thickness | 551.0†    | 553.5†              | 0.159†† |
| Corneal endothelial cell number | 2740.0†  | 2725.0†              | 0.159†† |

Non high myopia: SEq >-6D, High myopia: SEq ≤-6D

†: Median

††: Mann-Whitney U test

HT = height, BMI = body mass index, HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, GOT = glutamic-oxaloacetic transaminase, GPT = glutamate pyruvate transaminase, GGTP = gamma-glutamyl transpeptidase, T CHOL = total cholesterol, TG = triglyceride, HDL CHOL= high-density lipoprotein cholesterol, LDL CHOL = low-density lipoprotein cholesterol, GLU = glucose, HbA1c = Hemoglobin A1c, IOP = intraocular pressure

---

**Table 2** Logistic regression analysis to identify factors associated with high myopia

| High myo | Non high | OR 1 | 95% CI   | P value | OR 2 |
|----------|----------|------|----------|---------|------|
|        | pia (number) | myo (number) |
|--------|--------------|--------------|
| Men    |              |              |
| Age    | -58          | 43 / 552     | 1 | 1 |
|        | 59-65        | 21 / 574     | 0.47 (0.2 - 0.80) | 0.44 (0.75 - 2) |
|        | 66-70        | 13 / 523     | 0.32 (0.1 - 0.60) | 0.43 (0.70 - 0) |
|        | 71-          | 15 / 686     | 0.28 (0.1 - 0.51) | 0.48 (0.54 - 1) |
| p for trend |            |              | <0.01 |
| HT     | -160         | 16 / 589     | 1 | 1 |
|        | 161-164      | 15 / 537     | 0.92 (0.4 - 1.89) | 0.95 (0.47 - 4) |
|        | 165-168      | 24 / 563     | 1.20 (0.6 - 2.33) | 1.42 (0.13 - 2) |
|        | 169-         | 37 / 646     | 1.27 (0.6 - 2.44) | 1.65 (0.59 - 3) |
| p for trend |            |              | 0.343 |
| BMI    | -21.6        | 20 / 577     | 1 | 1 |
|        | 21.7-23.5    | 26 / 571     | 1.28 (0.7 - 2.32) | 1.41 (0.03 - 6) |
|        | 23.6-25.6    | 17 / 583     | 0.84 (0.4 - 1.63) | 0.96 (0.35 - 0) |
|        | 25.7-        | 28 / 586     | 1.24 (0.6 - 2.23) | 1.07 (0.87 - 9) |
| p for trend |            |              | 0.750 |
| SBP    | -116         | 22 / 572     | 1 | 1 |
|        | 117-127      | 19 / 560     | 1.04 (0.5 - 1.94) | 0.61 (0.51 - 8) |
|        | 128-138      | 28 / 567     | 1.64 (0.9 - 2.92) | 0.98 (0.12 - 8) |
|        | 139-         | 22 / 619     | 1.26 (0.6 - 2.34) | 0.83 (0.80 - 3) |
| p for trend |            |              | 0.304 |
| TG     | -73          | 7 / 508      | 1 | 1 |
|        | 74-105       | 20 / 521     | 2.77 (1.1 - 6.61) | 2.93 (1.57 - 4) |
|        | 106-149      | 22 / 505     | 3.18 (1.3 - 7.52) | 3.10 (1.43 - 9) |
|        | 150-         | 22 / 522     | 2.76 (1.1 - 6.54) | 2.79 (1.62 - 1) |
| p for trend |            |              | 0.041 |
| HDL CHOL | -46         | 19 / 501     | 1 | 1 |
|        | 47-          | 15 / 515     | 0.77 (0.3 - 1.53) | 0.78 (0.54 - 1) |
|                | OR 1 | 95%CI             | P value |
|----------------|------|------------------|---------|
| LDL CHOL       | 1.01 | (0.5 - 1.93)     | 0.99    |
|                | 0.87 | (0.4 - 1.69)     | 1.14    |
| p for trend    |      | 0.824            |         |
| HbA1c          |       |                  |         |
| -5.3           | 0.95 | (0.4 - 1.95)     | 0.84    |
| 5.4-5.5        | 0.91 | (0.4 - 1.83)     | 0.75    |
| 5.6-5.9        | 1.08 | (0.5 - 2.23)     | 0.83    |
| p for trend    |      | 0.998            |         |
| IOP            |       |                  |         |
| -11.2          | 2.35 | (0.9 - 5.95)     | 3.34    |
| 11.3-13.2      | 2.81 | (1.1 - 7.01)     | 5.18    |
| 13.3-15.2      | 4.85 | (2.0 - 11.6)     | 7.73    |
| p for trend    |      | <0.01            |         |
| Central corneal thickness |       |                  |         |
| -531           | 1.07 | (0.5 - 2.09)     | 0.93    |
| 532-556        | 1.26 | (0.6 - 2.40)     | 1.05    |
| 557-583        | 1.50 | (0.8 - 2.77)     | 1.01    |
| p for trend    |      | 0.145            |         |

Non high myopia: SEq >-6D, High myopia: SEq ≤-6D
OR 1: Adjusted by age
OR 2: Adjusted by age, HT, BMI, SBP, TG, HDL CHOL, LDL CHOL, HbA1c, IOP and central corneal thickness
HT = height, BMI = body mass index, SBP = systolic blood pressure, TG = triglyceride, HDL CHOL = high-density lipoprotein cholesterol, LDL CHOL = low-density lipoprotein cholesterol, HbA1c = Hemoglobin A1c, IOP = intraocular pressure
| Age  | pia (number) | myo (number) | p for trend |
|------|--------------|--------------|-------------|
| 55-62 | 54 / 763     | 0.50 (0.3 - 0.70) | 0.57 (0.54) |
| 63-68 | 34 / 947     | 0.25 (0.1 - 0.37) | 0.35 (0.70) |
| 69-   | 15 / 884     | 0.12 (0.0 - 0.20) | 0.21 (0.69) |
|       |              |              | <0.0 (0.0)  |
|       |              |              | 01          |
|       |              |              | 0.056       |
|       |              |              | 0.020       |
|       |              |              | 0.411       |
|       |              |              | 0.548       |
|       |              |              | 1.37 (1.39) |

Women

| Age  | pia (number) | myo (number) | p for trend |
|------|--------------|--------------|-------------|
| 55-62 | 54 / 763     | 0.50 (0.3 - 0.70) | 0.57 (0.54) |
| 63-68 | 34 / 947     | 0.25 (0.1 - 0.37) | 0.35 (0.70) |
| 69-   | 15 / 884     | 0.12 (0.0 - 0.20) | 0.21 (0.69) |
|       |              |              | <0.0 (0.0)  |
|       |              |              | 01          |
|       |              |              | 0.056       |
|       |              |              | 0.020       |
|       |              |              | 0.411       |
|       |              |              | 0.548       |
|       |              |              | 1.37 (1.39) |
|                |     |     |     |     |     |
|----------------|-----|-----|-----|-----|-----|
|                | 66- | 75  | 76- | 44  | 1.32 (0.8 - 2.13) |
|                |     |     |     |     | 1.25 (1.4) |
| p for trend    |     |     |     |     | 0.617 |
| LDL CHOL       | -107| 38  | 707 | 1   | 1   |
|                | 108 | 30  | 752 | 0.86 (0.5 - 1.40) |
|                | 127 |     |     | 1.07 (1.4) |
|                | 128 | 57  | 735 | 1.63 (1.0 - 2.52) |
|                | 149 |     |     | 2.07 (1.8) |
|                | 150 | 37  | 769 | 0.95 (0.5 - 1.52) |
|                |     |     |     | 1.27 (1.3) |
| p for trend    |     |     |     |     | 0.497 |
| HbA1c          | -5.4| 54  | 722 | 1   | 1   |
|                | 5.5 | 49  | 715 | 1.22 (0.8 - 1.83) |
|                | 5.6 |     |     | 1.29 (1.4) |
|                | 5.7 | 25  | 678 | 0.79 (0.4 - 1.31) |
|                | 5.8 |     |     | 0.85 (1.3) |
|                | 5.9 | 34  | 848 | 0.91 (0.5 - 1.46) |
|                |     |     |     | 1.03 (1.4) |
| p for trend    |     |     |     |     | 0.435 |
| IOP            | -11.6| 26 | 697 | 1   | 1   |
|                | 11.7| 55  | 867 | 1.54 (0.9 - 2.50) |
|                | 13.6|     |     | 2.23 (2.7) |
|                | 13.7| 61  | 806 | 1.84 (1.1 - 2.96) |
|                | 15.6|     |     | 2.25 (2.7) |
|                | 15.7| 56  | 840 | 1.52 (0.9 - 2.46) |
|                |     |     |     | 2.33 (2.7) |
| p for trend    |     |     |     |     | 0.109 |
| Central corneal thickness | -524 | 54 | 812 | 1   | 1   |
|                | 525 | 44  | 790 | 0.77 (0.5 - 1.17) |
|                | 550 |     |     | 0.83 (1.2) |
|                | 551 | 42  | 803 | 0.72 (0.4 - 1.09) |
|                | 557 |     |     | 0.70 (1.1) |
|                | 575 | 60  | 799 | 0.99 (0.6 - 1.46) |
|                |     |     |     | 0.92 (1.3) |
| p for trend    |     |     |     |     | 0.953 |

Non high myopia: SEq >-6D, High myopia: SEq ≤-6D
OR 1: Adjusted by age
OR 2: Adjusted by age, HT, BMI, SBP, TG, HDL CHOL, LDL CHOL, HbA1c, IOP and central corneal thickness
HT = height, BMI = body mass index, SBP = systolic blood pressure, TG = triglyceride, HDL CHOL = high-density lipoprotein, LDL CHOL = low-density lipoprotein cholesterol, HbA1c = Hemoglobin A1c, IOP = intraocular pressure

Figures
Study flow chart of this study. The number of participants who were 40 years old and over was 7098. Of them, 5987 participants were defined as the subjects after excluding, 997 participants who had a history of ocular surgery, and 114 participants who did not have refractive indices of their right eye.
Distribution of spherical equivalent refraction in Chikusei-city. (a) The distribution map shows the spherical equivalent refraction of the right eye in the subjects. (b) Spherical equivalent refraction of the right eye in the men subjects. (c) Spherical equivalent refraction of the right eye in the women subjects.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
CHIKUSEI MORI et al Supporting Information BMC Ophthalmol.docx