

Myopia and Cognitive Performance: Results From the Gutenberg Health Study

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PURPOSE. To analyze the association between myopia and cognitive performance.

METHODS. A cohort of the population-based Gutenberg Health Study included 3819 eligible enrollees between 40 and 79 years. We used the Tower of London (TOL) test to assess cognitive performance. Myopia was defined as a spherical equivalent (SE) ≤ -0.5 diopters (D) via noncycloplegic autorefractometry. We conducted linear mixed models with the SE as the dependent variable and the age, sex, duration of education, and TOL score as covariates.

RESULTS. Complete data were available for 3452 participants (90.4%). The mean TOL score was 14.0 ± 3.9 in the myopes versus 12.9 ± 4.0 in the nonmyopes ($P < 0.001$). The mean TOL score increased with the magnitude of myopia: it was 13.9 ± 3.9 in low (less than -3 D); 14.2 ± 3.7 in moderate (between -3 and -6 D); and 14.6 ± 3.5 in high myopia (-6 D and greater; $P < 0.001$). Both the duration of education and cognitive performance were correlated with the magnitude of myopia ($r = -0.21$, $P < 0.001$ and $r = -0.15$, $P < 0.001$, respectively). In a linear mixed model, the duration of education significantly predicted myopia ($\beta = -0.14$; $t = -7.55$; $P < 0.001$), whereas cognitive performance did not ($\beta = -0.017$; $t = -1.26$; $P = 0.207$). There was a significant effect of age on the SE ($\beta = 0.049$; $t = 9.89$; $P < 0.001$).

CONCLUSIONS. When regarded separately, cognitive performance is linked to myopia. However, duration of education, which may be directly related to the risk factors for myopia, is more directly and strongly related to myopia than is cognitive performance. Cognitive ability may be associated with myopia primarily through its impact on level of education.

Keywords: myopia, cognitive performance, educational level, populations-based study, epidemiology

The development of myopia is a complex process with several risk factors identified to date. There are considerable differences in the prevalence and severity of myopia in various regions of the world and different ethnicities.¹ Significant changes in myopia prevalence have been identified within the same population during previous decades with increases in myopia.^{2,3} Shortsightedness has a substantial medical impact on the individuals affected, as well as a considerable economic burden to society. Severe myopia is a major cause of visual impairment worldwide as a result of associated ocular comorbidities, particularly rhegmatogenous retinal detachment, myopic macular degeneration, premature cataract, and glaucoma.¹

Both genetic and environmental factors have been demonstrated to play some role in the pathogenesis of myopia.⁴⁻⁷ To date, the documented contribution of genetic variation on phenotypic variation in refractive error is relatively small.^{1,5,7} The current best estimates of the explanatory power of

identified associated SNPs in adult populations is less than 10%. Guggenheim and colleagues⁸ reported that common SNPs explained approximately 35% of the variation in refractive error in a pediatric cohort. Nevertheless, it has to be noted that the estimate of 35% is based on some contestable assumptions when the raw figure was 25%. It should also be noted that the Avon Longitudinal Study of Parents and Children (ALSPAC) area is a relatively stable, well-educated and affluent area, and therefore variation in educational factors may be limited. This would reduce the explanatory power of environmental variables, and enhance the explanatory power of genetic variables. Compared with a broader population sample such as that of the GHS, ALSPAC may give higher estimates of genetic contributions.

Findings from The International Consortium for the Refractive Error and Myopia (CREAM) and 23andMe studies showed that loci associated with adult population variations in refractive error are of small effect.⁸⁻¹⁰ When considering that the



prevalence of myopia has changed so fast, only environmental and social factors can explain the changes that have taken place. A study of Inuit people on the northern Alaska in 1969 showed the following: Of adults who had grown up in isolated communities, only 2 of 131 had myopia. However, more than half of their children and grandchildren were shortsighted.¹¹

Several environmental factors have been linked to the prevalence and magnitude of myopia, including near-work and outdoor activity during childhood and adolescence, educational level and residence (urban versus rural).¹ In a previous study, we reported school education and postschool professional education were highly associated with the prevalence and severity of myopia.⁵ Other studies have demonstrated a potential link between myopia and intelligence.¹²⁻¹⁴ Saw et al.¹⁵ assessed the association between the intelligence quotient (IQ) measured with the nonverbal Raven Standard Progressive Matrix test and myopia in children and concluded that nonverbal IQ may be a stronger risk factor for myopia compared with books read per week. Furthermore, the Singapore Cohort Study of the Risk factors for Myopia has reported on academic results, finding them similar in explanatory power to IQ: school grades, as possible indicators of either cumulative engagement in near-work activity or intelligence, were positively associated with myopia in Singapore children.¹⁶

As with myopia, it has proven to be difficult to identify genes for cognitive ability or educational attainment. Currently, identified SNPs account for less than 5% of variance.¹⁷⁻¹⁹ In a study by Benyamin et al.,²⁰ no individual SNPs were detected with genome-wide significance, but aggregate effects of common SNPs explained 22% to 46% of phenotypic variation in childhood intelligence. A paper by Plomin and Deary²¹ attempts to explain the increase in heritability of intelligence with age in terms of a genetic amplification hypothesis. But it is also possible that the influence of family environmental factors increases with age, and that this translates into an increasingly high twin study heritability, which increasingly over-estimates the genetic contribution in the broader population.

The level of education is associated with cognitive ability^{22,23}; thus, we raised the question as to whether cognitive ability is a better predictor of myopia compared with educational level. Therefore, we conducted this study to analyze the association between myopia and cognitive performance in an adult Caucasian cohort.

MATERIALS AND METHODS

The Gutenberg Health Study (GHS) is a population-based, prospective, observational cohort study in the Rhine-Main Region in Midwestern Germany with 15,010 participants and a follow-up after 5 years. The study population was randomly selected from the governmental registry offices and equally stratified by sex and area of residence (rural or urban) for each decade of age. According to the state law of Rhineland-Palatinate, it is mandatory for every individual to register his or her personal and residential data in Germany. Participants were contacted by letter and invited for the baseline examination. The response rate was approximately 60% for the first 5000 participants (Wild P, unpublished observations, 2015). Additional details regarding the study have been published.^{24,25} The 5-year follow-up examination of the entire cohort was initiated in April 2012. The assessment of cognitive ability (Tower of London [TOL] test²⁶) was added to the study protocol in April 2012.

In the present investigation, data from a follow-up cohort of 3819 subjects enrolled in the GHS between April 2012 and December 2013 were evaluated. The age range was 40 to 79.

We excluded participants with a history of refractive or cataract surgery. The sample of GHS was drawn in three similar waves to allow subsample analyses after the inclusion of 5000 participants (A2 cohort). After a 5-year follow-up, all participants were invited to visit the study center for the follow-up. The sample of 3819 in our study represents all in whom refractive data and TOL results are available in the 5-year follow-up sample of the A2-cohort.

All participants underwent a thorough ophthalmologic examination of 25 minutes duration, which followed standard operating procedures and included a medical history of eye diseases, noncycloplegic autorefractometry and visual acuity testing (Humphrey Automated Refractor/Keratometer [HARK] 599 with an integrated Snellen eye chart; Carl Zeiss Meditec AG, Jena, Germany). We calculated the spherical equivalent (SE) by adding the spherical correction value and half the cylinder value, and we used the mean of both eyes for analysis, with the exception of the linear mixed models. When the data from one eye were missing, we used the SE of the other eye. Myopia was defined as an SE ≤ -0.5 diopters (D).

The study protocol and study documents were approved by the local ethics committee of the Medical Chamber of Rhineland-Palatinate, Germany (reference no. 837.020.07; original vote: March 22, 2007, latest update: October 20, 2015). Written informed consent was obtained from each subject after explanation of the nature and possible consequences of the study. This research adhered to the tenets of the Declaration of Helsinki.

Cognitive Performance

The TOL test, Freiburg version²⁶ was used for the assessment of cognitive functioning. The test measures planning ability²⁷ and is defined as a test of complex executive functions. Planning is a form of problem solving and denotes the mental conception and evaluation of behavioral sequences and associated outcomes prior to their actual execution.²⁸ Consequently, the TOL performance is clearly linked to fluid intelligence²⁹ and strongly coupled with prefrontal functioning.^{26,30}

The TOL test is referred to as a disc-transfer paradigm, in which planning is required for an efficient transformation of a given start state into a desired goal state within the minimum number of moves. The classic version of the TOL consists of three differentially colored balls placed on three vertical rods of different heights, which may hold a maximum of one, two, or three balls, respectively (for an overview on other versions and variants, see Ref. 31; Fig. 1).

In the GHS, the participants were individually tested in a quiet air-conditioned room. The overall duration of the test session was limited to 20 minutes. To facilitate handling of the computerized task especially for older and inexperienced participants, individuals were tested with a touchscreen display, which has been proven highly feasible for studies with elderly subjects. The problem set of TOL consisted of an optimized selection of four-, five-, and six-move problems (eight problems each) that represent a monotonic increase of problem difficulty.²⁶ For the analysis of the global planning performance, a TOL score was computed by summing the number of problems that were solved in the minimum number of moves.

Assessment of Level of Education

The level of education was determined via a questionnaire. In the initial step, we took into account each individual's highest level achieved in school and the postschool professional education.⁵ We subsequently calculated the "total years of education" as the sum of school and postschool professional education years.

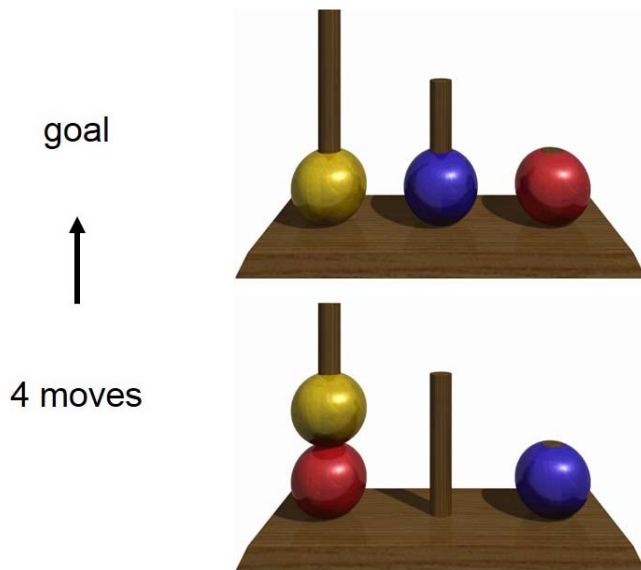


FIGURE 1. Tower of London test. Example for a task with four moves to reach the goal figure. Participants are instructed to transform the start state in the lower half of the screen into the goal state in the upper half on the screen following three rules: (1) only one ball may be moved at a time; (2) a ball cannot be moved when another ball is lying on top of it; and (3) three balls may be placed on the tallest peg, two balls on the middle peg, and one ball on the shortest peg.

Statistical Analyses

Our central data management unit performed quality controls for all data and checked for completeness and correctness using predefined algorithms and quality/plausibility controls. We conducted all analyses using statistical software (PASW statistics 21; SPSS, Inc., Chicago, IL, USA). Spearman correlation coefficients were calculated for the TOL score, total years of education, and SE. We used the Jonckheere-Terpstra test for univariate analyses between the TOL score and categorical variables. We also applied linear mixed models, in which we included both eye measurements individually instead of their mean value, age, sex, and either the variable “total years of education” (sum of school and postschool education years), or the TOL score in two subsequent models, and finally both variables in the same model. For the linear mixed models we used both eyes ($n = 6904$) to be able to adjust for the dependency of both eyes within one individual. All P values correspond to 2-tailed tests. This investigation comprises an explorative study; thus, no adjustments were made for multiple comparisons. As a result of the substantial number of tests applied in this study, P values must be interpreted with caution and in connection with effect estimates.

RESULTS

Of the 3819 participants, data regarding refraction, the cognition test and the educational level were available in 3452 participants (90.4%). Of these participants, 1399 participants (40.5%) were myopic. The study sample characteristics are presented in Table 1.

Refractive Error and Cognitive Performance

A higher cognitive performance was identified in the myopes: the mean TOL score was 14.0 ± 3.9 in the myopes versus 12.9 ± 4.0 in the nonmyopes ($P < 0.001$). The mean TOL score increased with the magnitude of shortsightedness (Fig. 2): it

TABLE 1. Study Sample Characteristics

Group	Total	Men	Women
n (%)	3452 (100)	1770 (51.3)	1682 (48.7)
Age, y, mean \pm SD	59.5 ± 10.7	59.9 ± 10.7	59.0 ± 10.7
SE (mean of both eyes), mean \pm SD, D	-0.43 ± 2.6	-0.48 ± 2.6	-0.40 ± 2.5
Myopia (SE ≤ -0.5), n (%)	1399 (40.5)	726 (41.0)	673 (40.0)
TOL score, mean \pm SD	13.3 ± 4.0	13.9 ± 3.9	12.8 ± 3.9
Total education, y, mean \pm SD	13.7 ± 2.7	14.0 ± 2.7	13.3 ± 2.7

was 13.9 ± 3.9 in low (less than -3 D), 14.2 ± 3.7 in moderate (between -3 and -6 D); and 14.6 ± 3.5 in high (-6 D and greater) myopia ($P < 0.001$). Cognitive performance according to the TOL score was correlated with the magnitude of myopia ($r = -0.17$, $P < 0.001$).

Educational Level and Cognitive Performance

Overall, 22 (0.6%) persons never graduated from school, and 1466 (37.9%); 950 (24.9%); 377 (9.9%); and 1013 (26.5%) graduated after 9, 10, 12 and 13 years, respectively. Regarding postschool education, 251 (6.6%) had no professional training, whereas 1811 (47.4%) went to primary and 629 (16.5% [$n = 629$]) to secondary vocational schools, and 1096 (28.7%) had a university degree. An association was identified between the performance in the TOL and the level of education: the total years of education were associated with increased cognitive performance ($r = 0.28$; $P < 0.001$). Furthermore, a correlation was identified between the total years of education and the magnitude of myopia ($r = -0.23$, $P < 0.001$).

Multivariable Analyses

The score of TOL with the potential confounders of age and sex, as well as the total years of education were included in a linear mixed model with the SEs of the left and the right eye as the dependent variables.

The results of the linear mixed model expanded the associations identified in the correlational analyses. When

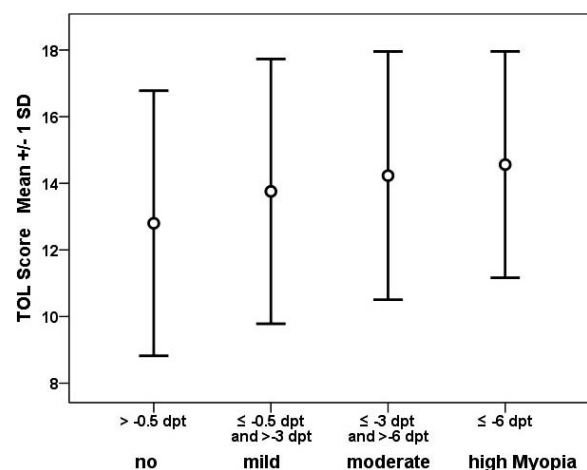


FIGURE 2. Association between the TOL score and the magnitude of myopia. Error bars (with mean \pm 1 SD). The mean TOL score increased with the magnitude of shortsightedness: it was 13.9 ± 3.9 in low (less than -3 D); 14.2 ± 3.7 in moderate (between -3 and -6 D); and 14.6 ± 3.5 in high (-6 D and greater) myopia ($P < 0.001$).

TABLE 2. Multivariable Analysis

Independent Variables	β	<i>T</i>	<i>P</i> Value	95% CI
Age	0.056	13.266	<0.001	0.048 to 0.064
Sex*	0.076	0.909	0.364	-0.088 to 0.239
TOL score	-0.026	-2.210	0.027	-0.048 to -0.003
Constant	-3.463			

A linear mixed model was used to calculate the effects of age, sex, and TOL score on the SE.

* Reference: male.

age, sex, and the TOL score were included in the model (Table 2), associations between age ($\beta = 0.056$; $P < 0.001$) and the TOL score ($\beta = -0.026$; $P = 0.027$) with the magnitude of myopia were found. When the TOL score was replaced by the total years of education (Table 3), age ($\beta = 0.051$; $P < 0.001$) and total years of education ($\beta = -0.143$; $P < 0.001$) were associated with magnitude of myopia. Table 4 summarizes the multivariable model with all four variables and indicates that the years of education ($\beta = -0.14$; $P < 0.001$) and age ($\beta = 0.049$; $P < 0.001$) were significantly associated with the magnitude of myopia; however, no significant effect was identified for cognitive performance ($\beta = -0.017$, $P = 0.207$) or sex ($\beta = -0.009$; $P = 0.925$).

DISCUSSION

A higher cognitive ability was identified in myopes compared with nonmyopes, and the TOL score increased with the magnitude of myopia. We performed additional analyses to better understand the associations between cognitive performance, level of education, and the spherical equivalent. In the univariate analyses, a higher performance in the TOL was identified in the individuals who had spent more years in educational activities. As previously reported, myopia was associated with a higher level of education.⁵ In the multivariable analyses including age, sex and either the TOL score or the total years of education, both cognitive performance as well as total years of education (and age) were associated with the magnitude of myopia. Nevertheless, when both, the TOL score and the total years of education were included in the same multivariable model the effect of education stayed almost constant, whereas the effect of cognitive performance was attenuated and not statistically significant anymore. Therefore, in summary, the total years of education and age were significantly associated with the magnitude of myopia; however, no significant effects were identified for cognitive performance or sex. This finding indicates that with an increasing duration of education, the spherical equivalent became more myopic, whereas for higher cognitive performance, no association with myopia was identified. With respect to age, the results indicated that the older participants

TABLE 3. Multivariable Analysis

Independent Variables	β	<i>T</i>	<i>P</i> Value	95% CI
Age	0.051	11.304	<0.001	0.042 to 0.060
Sex*	0.010	0.101	0.919	-0.178 to 0.197
Total education, y	-0.143	-7.827	<0.001	-0.180 to -0.108
Constant	-1.499			

A linear mixed model was used to calculate the effects of age, sex, and total years of education on the SE.

* Reference: male.

TABLE 4. Multivariable Analysis

Independent Variables	β	<i>T</i>	<i>P</i> Value	95% CI
Age	0.049	9.89	<0.001	0.039 to 0.058
Sex*	-0.009	-0.094	0.925	-0.199 to 0.181
TOL score	-0.017	-1.26	0.207	-0.043 to 0.009
Total education, y	-0.14	-7.55	<0.001	-0.177 to -0.104
Constant	-1.17			

A linear mixed model was used to calculate the effects of age, sex, TOL score, and total years of education on the SE.

* Reference: male.

exhibited less myopia. This is in line with a recently published meta-analysis of population-based, cross-sectional studies from the European Eye Epidemiology (E3) Consortium which showed that the increase in the level of education in younger population did not fully explain the cohort effect of increasing myopia.³² It is noteworthy with regards to our study that cognitive decline in older people is a different issue compared to the cognitive trajectory in a population based sample and the observation merits further investigation. Regarding the paper by Williams and colleagues³² one has to keep in mind that the conclusion depended on the assumption that the demands of primary education did not change with age. In the oldest participants, the task of primary schools was to provide students with minimal numeracy and literacy, but in the post-WW2 period, the task had become to prepare children to go on to complete secondary and even postsecondary education, demanding higher standards. This generational effect rather than simply the effect of age has to be kept in mind when interpreting associations of age and education.

To the best of our knowledge, this is the first population-based study to concurrently assess the link between myopia and cognitive performance considering the educational level as a confounder.

Our findings suggest that duration of education, which may be directly related to the risk factors for myopia, such as near-work and time spent outdoors, and thus to the direct biological pathways for the control of eye growth, is a stronger predictor of myopia compared with cognitive ability. Consequently, cognitive ability, which may have a significant genetic component, appears to be less directly related to myopia and may be associated with myopia primarily through its impacts on level of education.

In a previous study, we demonstrated the link between school educational level and myopia.⁵ In these preceding analyses, single nucleotide polymorphisms (SNPs), which are known to have an impact on myopia, were included; however, they only marginally explained the additional variance. In the present analyses, the research focus differed with the addition of a cognitive parameter and the association with education persisted, which underlines its important role in myopia development. Recently, our group published that older age groups have a lower prevalence of myopia within the GHS cohort.³³ We confirmed the age dependency in the present study using multivariate analyses. It is implicit that some of this age difference may be a result of the increasing educational standards. Another fact to consider is that higher educational achievement is associated with more time spent doing near-work and potentially less time outdoors. Thus, a prolonged education as assessed in our study may be a summarizing surrogate of other risk factors associated with myopia, such as near-work activity and less time outdoors. We were unable to adjust for outdoor activity because this variable is not documented in the Gutenberg Health Study. It has been shown that increasing time spent outdoors may be a simple strategy

by which to reduce the risk of developing myopia and its progression in children and adolescents.³⁴ Therefore, by engaging in outdoor activity, young individuals may work against the increased risk by near-work.³⁵

When considering myopia and cognitive performance alone, we observed a significant association between both factors and, thus, confirm previous findings at first glance.^{12–14,36} However, after performing more detailed statistical analyses that combined several potential predictors for myopia, the impact of cognition clearly decreases in contrast to educational outcome. This indirect and weaker impact of cognition on myopia may have several reasons in contrast to previous findings that indicate strong positive associations. One difference is the age of the examined samples: the studies listed in the review of Verma and Verma¹⁴ addressed intelligence and myopia in children and adolescents between the ages 5 to 19.¹⁴ At the end of this age range, fluid intelligence is well developed and stable. School education, especially for academic degrees, will be completed a minimum of 3 years later and professional education even later. Thus, if intense near-work is the relevant factor for the association between educational outcome and myopia, it is likely not to unfold its full impact until the age of 19. As a consequence, it is not astonishing that years of schooling and intelligence weigh equally in the relationship with myopia in males aged 17 to 19 years as addressed in a previous study.¹² There are some reasons why our and previous studies cannot be compared directly. First, most studies included adolescents with the oldest age of 19 years (e.g., see Ref 12). In our cohort, participants are in the age range of 40 to 79 and their duration of education is thus completely assessed. Second, a difference can be found in the assessment of cognitive ability. Whereas we used an objective, reliable and construct-validated instrument with adequate psychometric properties, others used teacher-based school performance to assess cognitive functioning to further associate with myopia.³⁶ Third, other differences arose in the applied statistical methods. In the overall model we included both factors (cognitive function and duration of education) as equal predictors, whereas others covaried each of both factors when performing univariate analyses to myopia.¹³ In line with our results, analysis of educational level covarying for IQ explained more variance for myopia group than when IQ scores were covaried with educational level ($F = 65.04$ versus $F = 47.5$).¹³

Our findings are in contrast to the results published by Ong et al.³⁷ in a Malay Singapore cohort, who reported an increased likelihood of cognitive dysfunction in myopes aged 60 to 79 years. In addition to the age differences between the samples, another source for these incoherent results may be that the authors used the abbreviated mental test (AMT). The test is a simple, 10-item questionnaire used for dementia screening that cannot be compared with an elaborate neuropsychologic assessment of planning performance over a 20-minute period. Nevertheless, the observation merits further investigation.

The strengths of our study include: (1) its population-based design in the Midwestern part of Europe that included an age range from 40 to approximately 80 years; (2) a substantial number of participants from both rural and urban areas; (3) the consideration of both school and postschool professional training in our study cohort; and (4) assessment of cognitive performance using a psychometrical well-validated instrument that measures a homogeneous psychologic construct.

The study limitations that follow merit consideration. No data are available regarding outdoor activity. Thus, we could not adjust for this variable in our multivariable analyses. There may be some degree of overestimation of myopia, particularly in the younger age group, because the refraction was measured without cycloplegia.^{38,39} Moreover, the response rate is

approximately 60%. There may be a greater tendency toward less study participation in individuals with a low socioeconomic status because of the lack of interest or suspicion, as well as among highly educated individuals because of a potentially higher workload. We are unaware of the educational level of the individuals who refused to participate in the GHS. Both cognitive performance ($r = -0.15$) and educational status ($r = -0.21$) were associated with myopia in a bivariate model. In the multivariable regression analyses, the 95% confidence interval (CI) of the TOL estimate included zero. We therefore interpreted TOL scores as less relevant, being aware that this can also be a methodologic artifact. Our results may have been influenced by collider bias.⁴⁰ Our analysis only examines the relationship between myopia, education and one element of cognitive ability: The TOL test measures one aspect of cognitive ability, namely planning and problem solving. Maybe a test of verbal cognitive ability, for example, would have been more appropriate—or that more comprehensively all elements of cognitive ability/intelligence should have been considered before making any conclusions. We chose this test as it has been shown that the TOL is significantly related to visuospatial intelligence as measured with Raven Standard Progressive Matrix test,²⁹ and thus clearly captures fluid intelligence. Furthermore, the TOL is feasible within the setting of an epidemiologic study as the examination takes 20 minutes only and is independent of language, reading, and writing skills.

Based on our previous⁵ and present results, we conclude that educational years provide a better predictor of myopia compared with cognitive performance or SNPs. Our data do not allow testing to what extent educational outcomes depend on cognitive ability, and to what extent cognitive ability depends on education. Future studies should also test whether education has its effect of myopia via near-work or other parameters.

There is considerable variability in the prevalence and magnitude of myopia in studies from other continents; nevertheless, our findings suggest that the association between shortsightedness and education, irrespective of cognitive performance, may be nearly universal.^{5,13,41–47} Moreover, cognitive ability may be associated with myopia primarily through its impact on educational behavior.

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