Nutritional Factors and Myopia: An Analysis of National Health and Nutrition Examination Survey Data

Elise N. Harb, OD, PhD, FAAO[1]* and Christine F. Wildsoet, OD, PhD, FAAO[1]

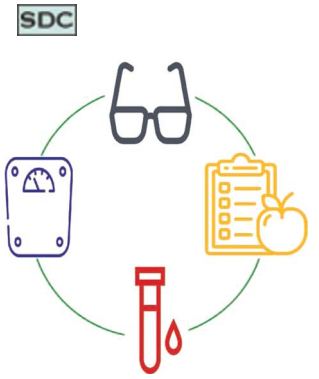
SIGNIFICANCE: The rise in the prevalence of myopia, a significant worldwide public health concern, has been too rapid to be explained by genetic factors alone and thus suggests environmental influences.

PURPOSE: Relatively little attention has been paid to the possible role of nutrition in myopia. The availability of the large National Health and Nutrition Examination Survey data set, which includes results from vision examinations, offers the opportunity to investigate the relationship between several nutrition-related factors, including body metrics, and the presence and magnitude of myopia.

METHODS: Cross-sectional survey data sets with vision examination, demographic, body metrics, and nutritional data, collected as part of the National Health and Nutrition Examination Survey over the years of 2003 to 2008, were extracted for analysis. Based on already published basic and epidemiological studies, the following parameters were selected for study: body height and body mass index, demographics, serum vitamin D and glucose/insulin levels, and caffeine intake, using multivariable models and objectively measured refractive errors as the main outcome measure.

RESULTS: Data from a total of 6855 ethnically diverse Americans aged 12 to 25 years were analyzed. In final multivariate models, female sex and age were the most significant factors related to myopia status and refractive error. In general, neither body metrics (body mass index) nor nutritional factors (serum vitamin D, glucose levels, and caffeine intake) were found to be associated with refractive error or myopia status; however, increased insulin levels were related to increased odds of having myopia.

CONCLUSIONS: These largely negative findings suggest that other environmental factors, such as those related to the visual environment, may contribute more to the development and/or progression of myopia and would argue for continued research in these areas in support of more evidence-based myopia clinical management.



Author Affiliations:
[1]University of California at Berkeley School of Optometry, Berkeley, California
*harbe@berkeley.edu

Optom Vis Sci 2021;98:458–468. doi:10.1097/OPX.0000000000001694

Supplemental Digital Content: *Direct URL links are provided within the text.*

Myopia has seen a rapid rise in its prevalence worldwide over the last generation, such that half of the world's population is expected to be myopic by 2050.[1] Myopia carries a significant economic burden (approximately US $268 billion)[2] and a sight-threatening ocular disease burden.[3] Although genetic factors play a role in the development of myopia,[4–8] they cannot explain the rapid increase in myopia prevalence.

Several environmental factors have been implicated in the development and progression of myopia, with significant research directed at the possible role of near work[9] and, more recently, of reduced time outdoors (discussed hereinafter[10]) as risk factors. However, in both cases, no general agreement has been reached on key contributing factors, and the etiology of myopia will likely prove to be multifactorial in nature. For example, early epidemiological studies of myopia noted an apparent link between the advent of formalized classroom education and the development of myopia in Inuit populations.[11,12] However, during this period of increasing Western influence, diets also underwent significant modification.[13,14]

Overall, there has been limited investigation into the role of nutritional factors in myopia. In one early observational report, diets of high glycemic load were described as a risk factor for myopia by Cordain et al.,[13] who speculated that hyperinsulinemia might modify scleral growth factors, as a possible underlying mechanism. However, in apparent contradiction of this hypothesis, a cross-sectional study of Singaporean children (aged 7 to 9 years)[15] found that children with shorter stature and increased body mass index had less myopic refractions, assuming body mass index reflects glycemic load. Nonetheless, studies using animal models of myopia have provided evidence linking insulin with enhanced eye growth[16] and also for protective effects of both caffeine and one of its metabolites, 7-methylxanthine, against myopia development,[17–19] with choroidal and scleral targets as possible sites of action in the latter case.[17]

Significant attention has been paid recently to the protection afforded by outdoor exposure against myopia development, with four randomized controlled trials involving Asian schoolchildren reporting generally positive benefit from increased outdoor recess time.[20–23] Although there is ongoing debate regarding the role of outdoor high light intensities,[24–27] it is also important to note that exposure to sunlight and serum vitamin D levels are highly positively correlated. Nonetheless, although two relevant large cohort studies found an association between serum vitamin D levels and refractive error,[28,29] their authors reached diverging interpretations of their results with respect to the role of low serum vitamin D levels as a risk factor for myopia development, with one group noting the likely confounding effect of time outdoors on vitamin D serum levels,[29] which is consistent with observations from a previous genome-wide association study.[30]

The availability of the large U.S. National Health and Nutrition Examination Survey data set allowed for further investigation of

the relationship between various nutritional and body metric factors and the presence and magnitude of myopia, which describes the scope of the study reported here. The National Health and Nutrition Examination Survey comprises a series of ongoing studies, which was initiated in 1960 by the U.S. Centers for Disease Control and Prevention, and aims to investigate the health and nutritional status of children and adults across the United States through the collection of data concerning demographic, socioeconomic, and health-related variables (via physiological and laboratory measurements).

METHODS

Participant Cohort

The study reported here was limited to participants during study years 2003 to 2008. Because refractive error data were available only for participants 12 years or older, the current analyses were also limited to participants aged 12 to 25 years, with the upper limit taking into account the possibility of late-onset myopia.[31–33] Both univariate and multivariate analyses were applied to extracted data. Initially, participants with available refractive error data were extracted (n = 6855) if they met the inclusion criteria of not having either previous refractive surgery (n = 18) or the possibility of corneal disease, as indicated by keratometric readings of more than 50 D (n = 21). Given that corneal power is, on average, approximately 48 to 50 D in full-term human infants[34,35] and only decreases with age,[36,37] cornea with 50 D or more in the steeper meridian was used as a potential biomarker for corneal disorders and used as a basis for excluding participants.

The demographic features (age, sex, ethnicity) of this final participant cohort (n = 6855) are summarized in Table 1. In the case of univariate analyses, participants with available refractive error data and factor(s) of interest were included, with the sample size varying accordingly, as indicated hereinafter. However, only participants with complete data sets (n = 1974 [29%]) were used in multivariate analyses. Importantly, a sensitivity analysis demonstrated that participants with complete versus incomplete data sets had similar ethnicity distributions (<3% difference in all ethnicity categories), range of refractive errors (+8.5 to –17.625 vs. +6.00 to –20.25 D), mean spherical equivalent refractive error (mean difference, 0.009 D), and proportion of participants with myopia (<0.3% difference). None of these differences were statistically significant (all comparisons, $P > .05$).

TABLE 1. Summary of participant demographic characteristics, expressed in terms of number and percentage of participant cohort, in those participants aged 12 to 25 years with available refractive error data

Participant characteristics	Total (n = 6855)
Female sex	3430 (50.04%)
Ethnicity	
Non-Hispanic White	2131 (31.09%)
Non-Hispanic Black	2112 (30.81%)
Mexican American	1942 (28.33%)
Other Hispanic	375 (5.47%)
Multiethnic/other	295 (4.30%)

The mean (standard deviation) age of the participant cohort was 17.05 (3.63) years.

All study sampling methods pertaining to the National Health and Nutrition Examination Survey data set have been described elsewhere.[38] All study methods followed the tenets of the Declaration of Helsinki and were approved by the National Center for Health Statistics Research Ethics Board, and informed consent was documented before participant participation. Note also that data collection is limited to National Health and Nutrition Examination Survey–trained health technicians, as a quality control measure. Pertinent to the analyses reported here, open-source data were extracted and used for analysis as described hereinafter.

Databases

The vision database includes noncycloplegic objective autorefractor (Nidek ARK-760; NIDEK Co., Ltd., Gamagori, Aichi, Japan) measurements. Recorded refractive errors (median of three repeated measures) were included in analyses only when a confidence rating of at least 5 (scale from 1 to 9) was achieved at the time of measurement. The mean (standard deviation) confidence rating of the refraction data used in our analyses was 8.86 (0.43). For use in analyses, spherical equivalent refractive errors (i.e., average of the refractions in two principal meridians) were calculated from the data for the right eyes of all included participants, and spherical equivalent refractive errors of –0.75 D or worse were classified as myopic. This more conservative definition of myopia was used to avoid misclassification of myopia, given that cyclopegic agents were not used in measuring refractive errors.

To monitor childhood growth and weight gain, the National Health and Nutrition Examination Survey collected a series of body metrics, including body mass index (in kilograms per meter squared) and standing height (in centimeters). From the National Health and Nutrition Examination Survey laboratory database, several nutritional factors were extracted for use in analyses. Total 25-hydroxyvitamin D levels (in nanomoles per liter) were measured in collected samples using a standardized liquid chromatography–tandem mass spectrometry method. Fasting (for at least 9 hours) plasma glucose (hexokinase method; in millimoles per liter) and serum insulin (enzyme-linked immunosorbent assay method; in picomoles per liter) were obtained for participants 12 years or older attending morning study visits as part of an ongoing effort by the National Health and Nutrition Examination Survey to estimate the prevalence of diabetes in the United States. Information about caffeine intake was extracted from dietary interviews performed as part of the "What We Eat in America" initiative. Using a validated U.S. Department of Agriculture survey method, participants were interviewed initially in person during a study visit and subsequently by telephone (3 to 10 days after the in-person interview, but not on the same day of the week). During both interviews, participants were encouraged to make use of a set of measuring guides (e.g., glasses/mugs, bowls, drink boxes and bottles, household spoons, and measuring cups and spoons) to more accurately estimate the amounts of foods and liquids consumed. For the purpose of the current study, estimates of daily caffeine intake (in milligrams) from each of the two interviews were averaged for each participant.

Data Analyses

The National Health and Nutrition Examination Survey analytical guidelines for 1999 to 2010 are available at www.cdc.gov/nchs/data/series/sr_02/sr02_161.pdf. Analyses were performed using Stata 14.2 (StataCorp, College Station, TX). Statistical analyses (χ^2 or Kruskal-Wallis) were performed to investigate the

relationships between refractive errors and demographic and nutritional factors. Multivariable logistic and linear regression models were also created using myopia status (presence/absence) and magnitude of myopia (spherical equivalent refractive error) as outcome variables. The inclusion of covariates in the final models was hypothesis-driven, and collinearity was evaluated across all covariates. Ethnicity was included through the use of dummy variables, and interaction terms were included in the final models if their coefficients differed significantly from zero, as determined by the Wald test. An α value of 0.05 was used in all data analyses as an indicator of statistical significance. Summary statistics are reported as means, including standard deviations and/or 95% confidence intervals, unless indicated otherwise.

RESULTS

Demographic Factors and Myopia Status

Participant refractive error ranged from +8.5 D of hyperopia to –20.25 D of myopia, with a mean of low myopia (–0.86 ± 1.90 D). Approximately 35% (35.3%) of the cohort were myopic, with the mean spherical equivalent refractive error of this subgroup being –2.66 ± 2.05 D. The mean spherical equivalent refractive error of the remaining nonmyopic participants was 0.12 ± 0.74 D. Although there was a statistically significant increase in spherical equivalent refractive error with increasing participant age ($P = .001$), the difference across age groups was small, although extreme myopia outliers existed in all age groups (Fig. 1). Investigation into the possible influences of these outliers (DFBETA model diagnostics) found no meaningful effects for any age group. Both sex and ethnicity seemed to influence spherical equivalent refractive error (Fig. 2), although differences did not always reach statistical significance. Specifically, female participants were more likely to be myopic compared with male participants (37.8 vs. 32.8%, $P < .0001$), and they also had a significantly greater magnitude of myopia compared with male participants (–2.78 ± 2.04 vs. –2.54 ± 2.06 D, $P = .0002$). In relation to ethnicity, except for the multiethnic/other group, which was on average more myopic (–1.38 ± 2.31 D), the other ethnic groups had similar mean refractive errors (range, –0.75 to –0.89 D). Nonetheless, there were significant differences between these groups (based on ANOVA testing), both in terms of mean spherical equivalent refractive error ($P = .0001$) and in the proportion of myopic participants ($P < .0001$), with Blacks having the lowest (33.1%) and the other/multiethnic group having the highest (46.1%) values. Of those with myopia, mean spherical equivalent refractive errors also differed significantly with ethnicity ($P = .001$), with Mexican Americans having the least myopic spherical equivalent refractive error (–2.48 ± 1.86 D) and the other/multiethnic group having the highest (–3.15 ± 2.21 D).

Body Metrics and Nutritional Factors and Myopia Status

Body Metrics

Summary statistics for all body metric and nutritional factors, partitioned by participant demographic characteristics, including age (stratified into 12- to 18- and 19- to 25-year age groups), are shown in Appendix Table A1, available at http://links.lww.com/OPX/A484, and described in more detail hereinafter. The relationships between each nutritional and body metric factor and age, stratified by ethnicity and myopia status, are illustrated in Fig. 3. Because the distributions for nutritional and body metric factors (except for standing height) proved to be quite skewed, significant

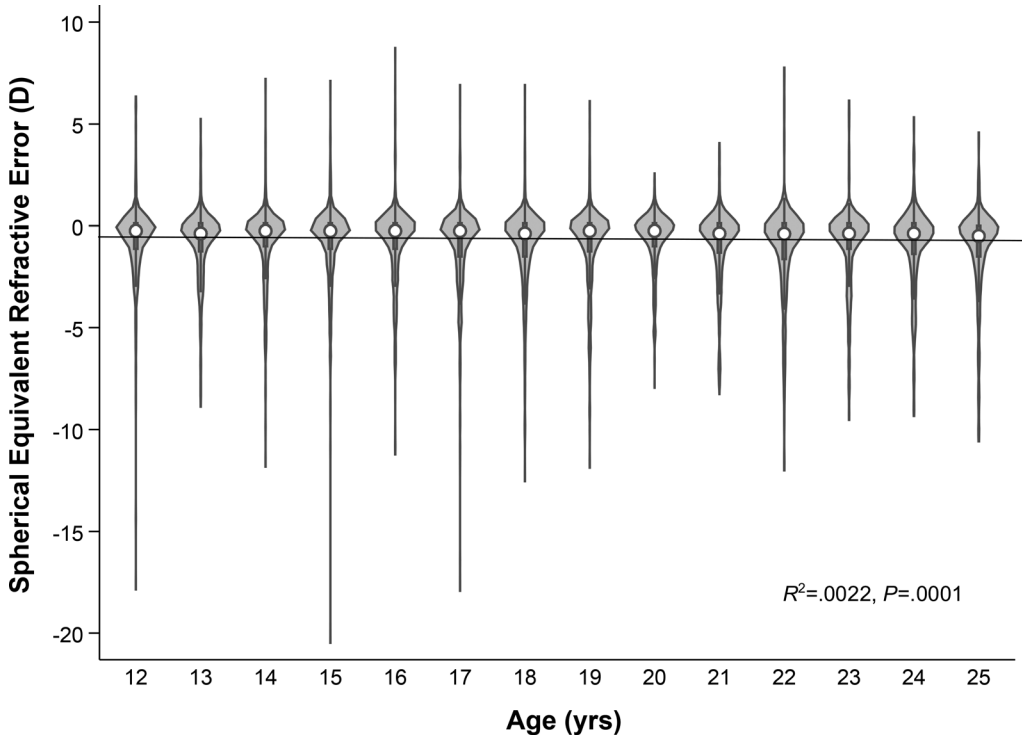


FIGURE 1. Violin plot showing the significant relationship between spherical equivalent refractive error and age for the participant cohort.

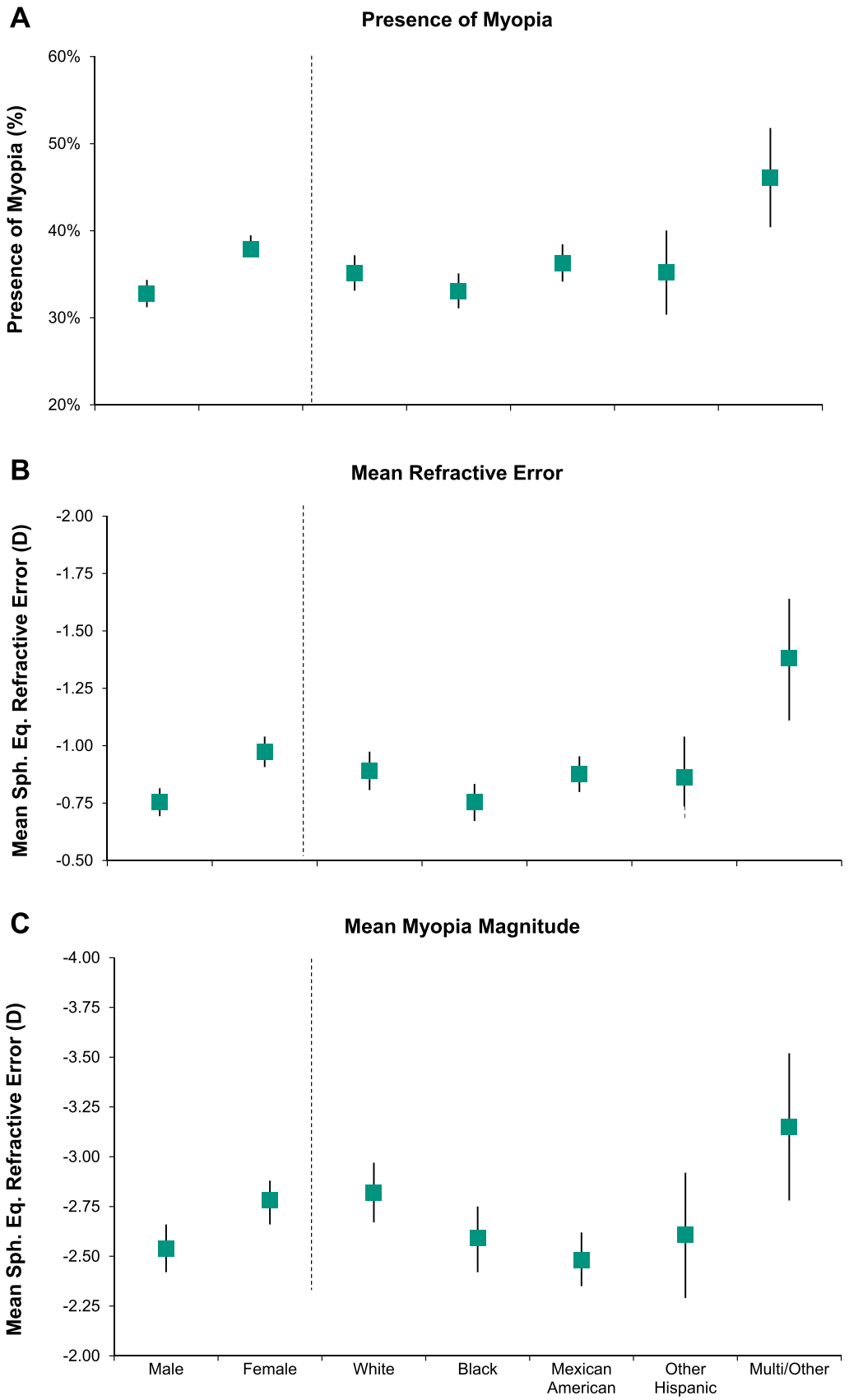


FIGURE 2. Myopia presence (percent of cohort; A) and spherical equivalent refractive error (D) for all participants (B) and for myopic participants (C), segregated by sex and ethnicity in all cases. Data presented as means with 95% confidence intervals.

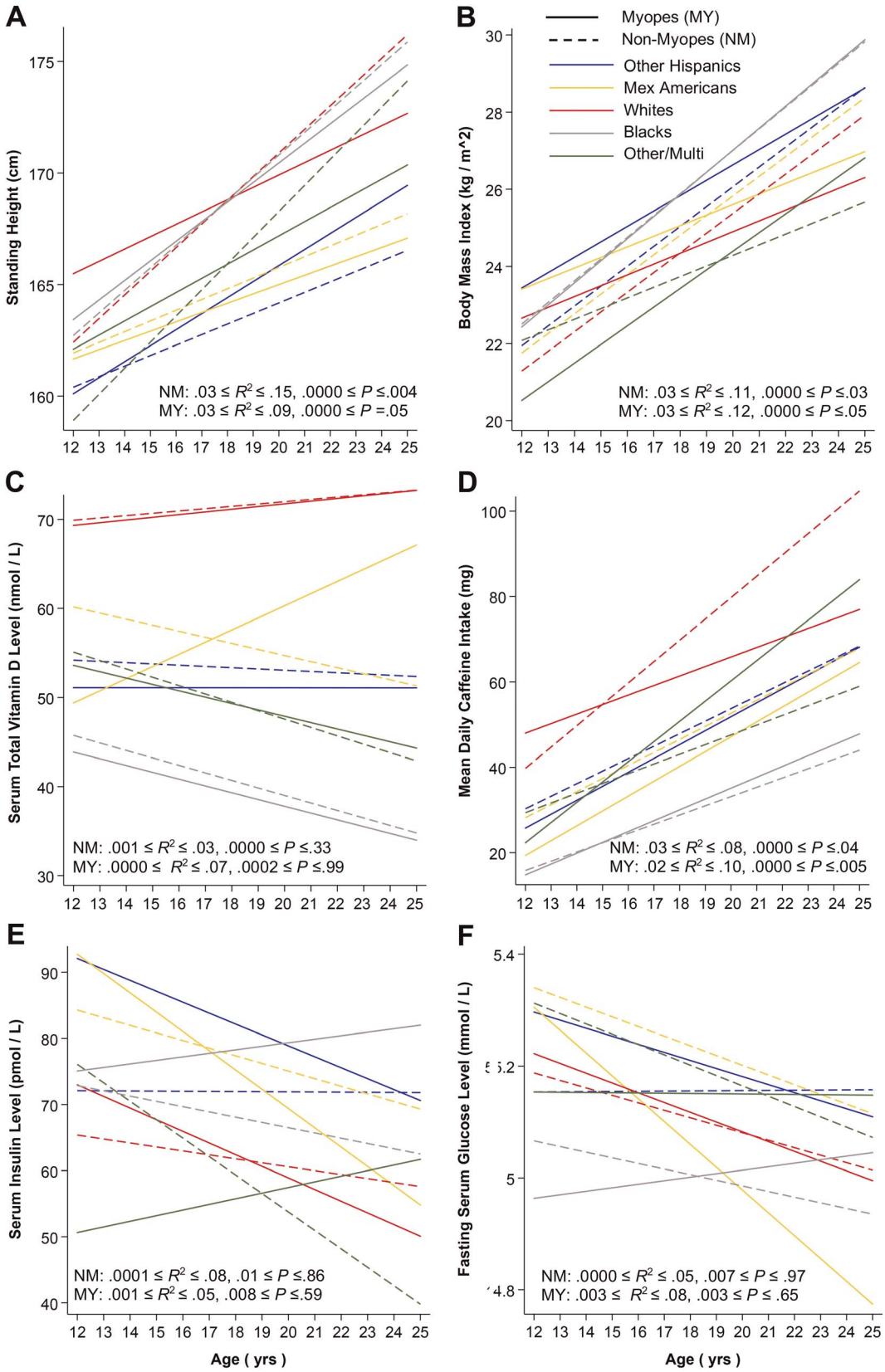


FIGURE 3. Plots of standing body height (A), body mass index (B), vitamin D level (C), caffeine intake (D), fasting serum insulin level (E), and fasting serum glucose level (F) against age, stratified by ethnicity group and myopia status. Results of correlation analyses for myopic and nonmyopic subgroups are also shown.

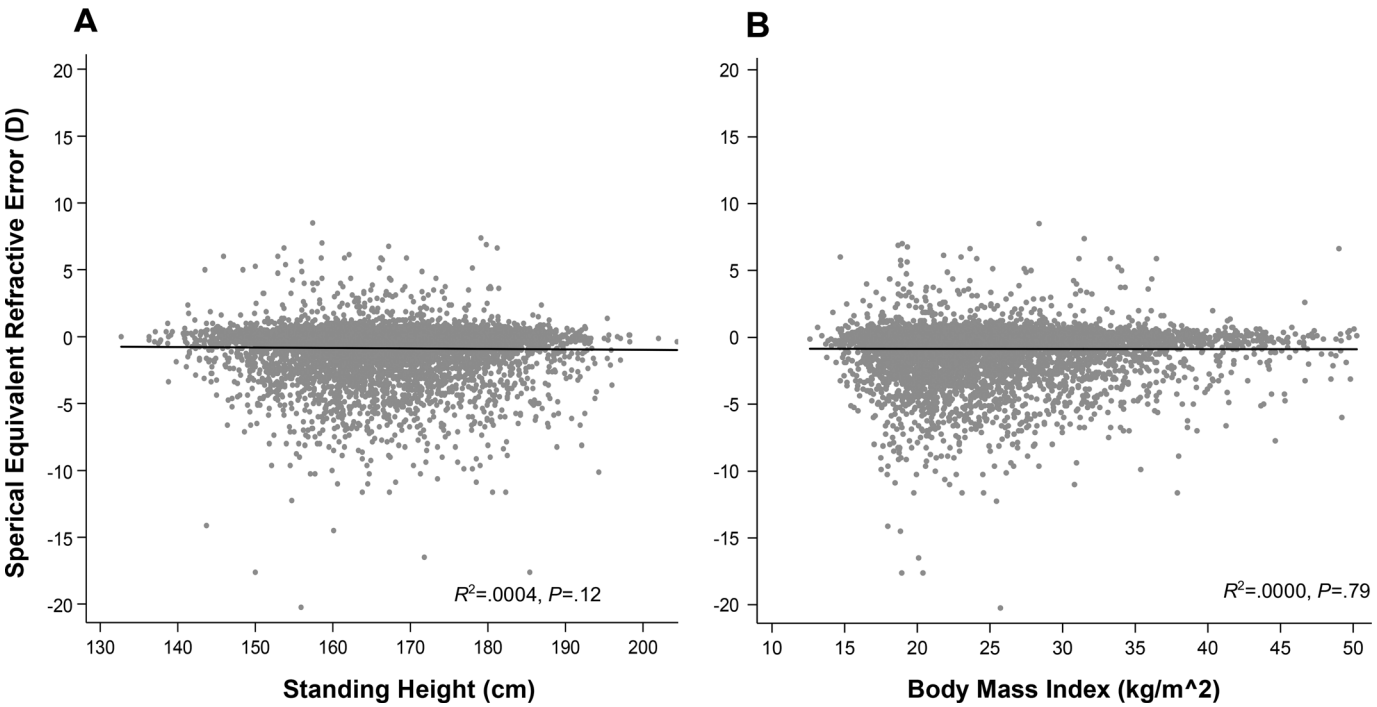


FIGURE 4. Plots of spherical equivalent refractive error (D) against standing body height (A) and body mass index (B). No significant correlation between either of the body metrics and spherical equivalent refractive error was observed.

outliers were identified for each factor via the interquartile range method (outlier identified as falling outside the lower and/or upper fences in a box-and-whisker plot) and removed from analyses. For any given factor, this method removed between 0.12% (vitamin D) and 2.67% (serum insulin) of the data. Nonetheless, no significant differences were identified in a sensitivity analysis performed to determine if the removal of outliers influenced the results of linear regression analyses for the respective nutritional/body metric factors.

The average height and body mass index of participants who had both refractive error and body metric data (n = 6764, 99%) were 166.18 ± 10.35 cm and 24.78 ± 6.53 kg/m^2, respectively. Notably, the latter value is just outside the range for overweight, as defined by the U.S. Centers for Disease Control and Prevention (25.0 to <30 kg/m^2; www.cdc.gov). Female participants had significantly higher body mass indexes compared with male participants (25.02 ± 6.34 vs. 24.19 ± 5.81 kg/m^2, P = .0001) and were significantly shorter than male participants (160.95 ± 7.03 vs. 171.38 ± 10.52 cm, P < .0001). Ethnicity also significantly influenced height (P < .0001) and body mass index (P < .0001). In relation to height, Whites were the tallest (168.43 ± 10.29 cm) and Mexican Americans were the shortest (162.93 ± 9.52 cm). In relation to body mass index, Blacks had the highest values (25.40 ± 7.37 kg/m^2) and the other/multiethnic group had the lowest values (23.32 ± 5.83 kg/m^2). As expected, both body mass index and height significantly increased with age, regardless of ethnicity or myopia status, except for height in Mexican American myopes (Figs. 3A, B). However, neither height nor body mass index was significantly correlated with spherical equivalent refractive error (Figs. 4A, B, both $R^2 \leq 0.0004$ and $P \geq .12$).

Nutritional Factors

A total of 4838 participants (71%) had both serum vitamin D and refractive error data. The mean serum vitamin D level for these participants was 54.78 ± 22.11 nmol/L, with a large percentage (~48%) classifiable as deficient in vitamin D, as defined by the Vitamin D Council (<50 nmol/L; www.vitamindcouncil.org). On average, female participants had a small but significant decrease in serum vitamin D levels compared with male participants (54.08 ± 23.44 vs. 55.20 ± 19.89 nmol/L, P < .0001). There were also significant ethnicity-related differences (Fig. 3C; P < .0001), with Blacks having the lowest levels (41.45 ± 16.01 nmol/L) and Whites having the highest (71.28 ± 22.02 nmol/L). Myopic and nonmyopic groups had similar serum vitamin D levels (54.13 ± 21.58 vs. 54.92 ± 21.84 nmol/L, P = .23), as also reflected in the nonsignificant correlation between serum vitamin D levels and spherical equivalent refractive errors for this cohort overall (Fig. 5A; R^2 = 0.0002, P = .32).

For participants who had both caffeine intake and refractive error data (n = 5864, 86%), the mean daily caffeine intake was 44.07 ± 53.60 mg and increased significantly with age, regardless of ethnicity or myopia status, as might be expected (Fig. 3D; all, $P \leq .04$). Overall, male participants had significantly higher caffeine intake compared with female participants (47.14 ± 56.78 vs. 41.17 ± 50.25 mg, P = .006). There were also significant ethnicity-related differences in caffeine intake (P < .0001), with Blacks having the lowest intake (25.83 ± 38.32 mg) and Whites having the highest (64.30 ± 64.48 mg). However, there was no significant difference in the mean caffeine intake of myopic and nonmyopic participants (43.02 ± 52.64 vs. 44.64 ± 54.11 mg, respectively; P = .27) and no significant correlation between caffeine intake and spherical equivalent refractive error for this cohort overall (Fig. 5B, R^2 = 0.0000, P = .93).

The mean serum glucose and insulin levels for those participants who also had refractive error data (n = 2895, 42%) were

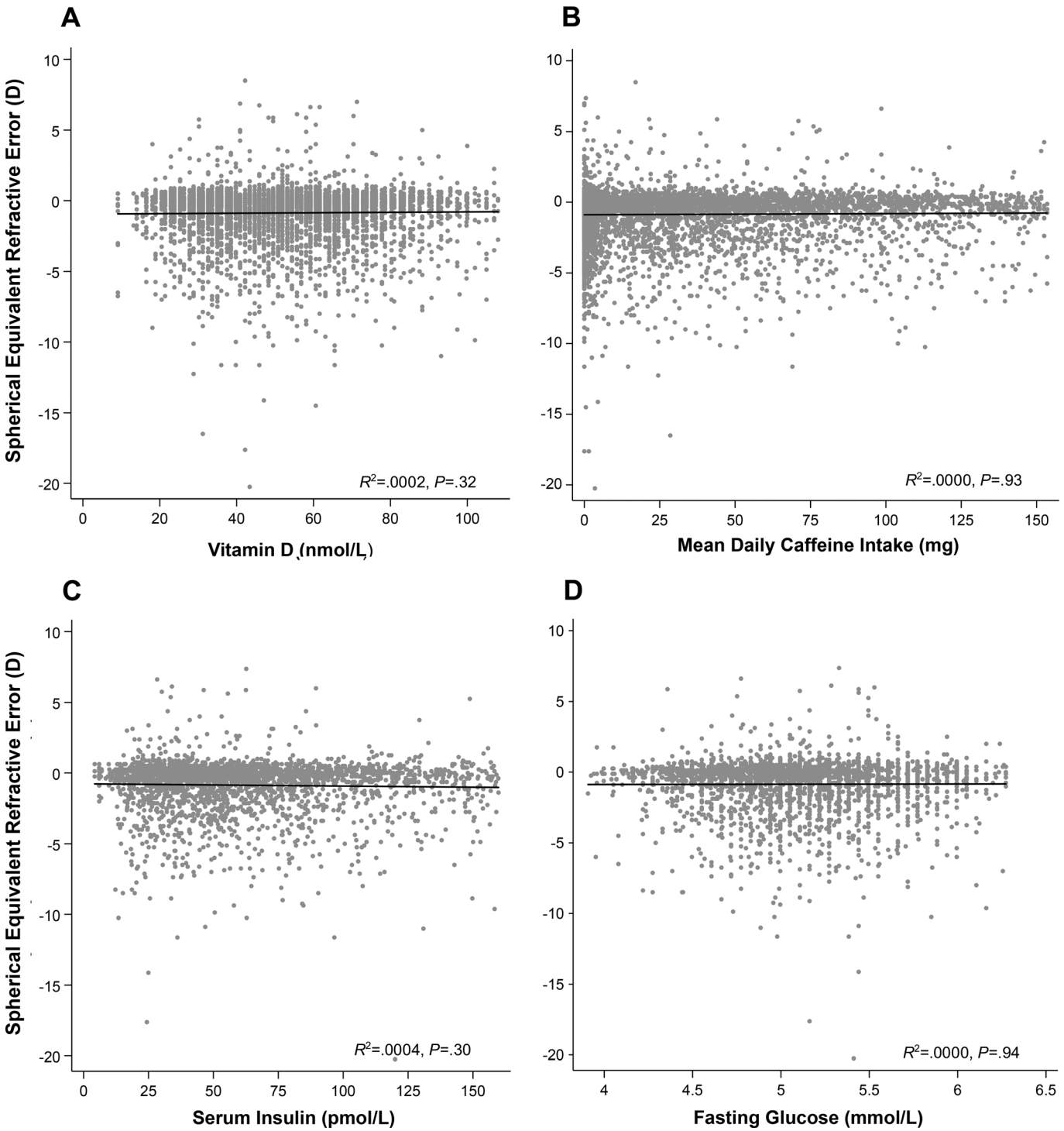


FIGURE 5. Plots of spherical equivalent refractive error (D) and serum vitamin D level (A), caffeine intake (B), fasting serum insulin level (C), and fasting serum glucose level (D). No significant correlation between any of the nutritional factors and spherical equivalent refractive error was observed.

5.10 ± 5.10 mmol/L and 70.20 ± 48.29 pmol/L, respectively. In general, there was no effect of age on insulin or glucose levels, regardless of ethnicity or myopia status, except for an observation in White participants as shown in Figs. 3E, F. Male participants had significantly higher glucose levels than did female participants (5.22 ± 0.45 vs. 4.97 ± 0.46 mmol/L, $P < .00001$), but lower insulin levels (64.89 ± 48.87 vs. 76.04 ± 49.17 pmol/L, $P < .00001$). Glucose levels varied significantly with ethnicity ($P < .0001$), with Blacks having the lowest levels (5.00 ± 0.45 mmol/L) compared with all other ethnic groups, who had similar glucose levels (5.11 [White] to 5.19 [other/multiethnic] mmol/L). Insulin levels also showed significant ethnicity-related differences ($P < .0001$), with the other/multiethnic group having the lowest levels (60.43 ± 39.89 pmol/L) and other Hispanics having the highest

TABLE 2. Results generated from multivariate models, with adjustment for demographic, nutritional, and body metric factors in those participants with complete data sets (n = 1974)

	Mean refractive error (D)		Presence of myopia	
	Coefficient (95% CI)	*P*	Odds ratio (95% CI)	*P*
Female sex	–0.20 (–0.380 to –0.015)	**.03**	1.27 (1.040 to 1.545)	**.02**
Age (per 1-y increase)	–0.04 (–0.063 to –0.008)	**.01**	1.03 (1.002 to 1.064)	**.04**
Ethnicity				
Non-Hispanic White	Reference		Reference	
Non-Hispanic Black	0.11 (–0.162 to 0.379)	.43	0.81 (0.605 to 1.088)	.16
Mexican American	0.11 (–0.132 to 0.350)	.37	0.84 (0.650 to 1.095)	.20
Other Hispanic	0.17 (–0.322 to 0.655)	.50	0.77 (0.452 to 1.324)	.35
Multiethnic/other	–0.41 (–0.862 to 0.051)	.08	1.13 (0.700 to 1.837)	.61
Total vitamin D (per 1-nmol/L increase)	0.002 (–0.002 to 0.007)	.33	1.00 (0.992 to 1.002)	.30
Daily caffeine intake (per 1-mg increase)	–0.0008 (–0.0009 to 0.0026)	.34	1.00 (0.997 to 1.000)	.16
Fasting glucose (per 1-mmol/L increase)	–0.07 (–0.272 to 0.138)	.52	1.05 (0.840 to 1.309)	.67
Insulin (per 1-pmol/L increase)	–0.0005 (–0.0028 to 0.0019)	.70	1.003 (1.000 to 1.005)	**.04**
Body mass index (per 1-kg/cm^2 increase)	0.002 (–0.017 to 0.020)	.84	0.99 (0.971 to 1.010)	.35

Statistically significant effects are shown in bold. Body height was removed from models because of collinearity with age and body mass index. CI = confidence interval.

(77.27 ± 53.61 pmol/L). There was no statistically significant difference in glucose levels between myopic and nonmyopic participants ($P = .81$), although insulin levels were significantly higher in myopic participants ($P = .01$). However, neither glucose levels nor insulin levels proved to be significantly correlated with spherical equivalent refractive error (Figs. 5C, D; both $R^2 \leq 0.004$, $P \geq .30$).

Multivariable Modeling

Results for all multivariate models are summarized in Table 2. An initial linear regression multivariate model was created to identify the factors associated with participant refractive error (spherical equivalent refractive error). Given the collinearity of participant age and body mass index with height and the fact that height was not related to myopia status in univariate analysis, height was not included in our final models. In addition, age was standardized by centering the variable on the mean age of the cohort (17.05 years). Although no significant associations between either ethnicity or any of the nutritional factors and spherical equivalent refractive error were identified, the relationship between sex, age, and spherical equivalent refractive error proved to be statistically significant, with female participants having more myopic spherical equivalent refractive errors than male participants (by –0.20 D [–0.380 to –0.015], $P = .03$) and older participants having more myopic spherical equivalent refractive error (–0.04 D [–0.063 to –0.008] more myopia per 1-year increase in age; $P = .01$). Although not significant, participants in the multiethnic/other ethnicity group were also, on average, slightly more myopic compared with Whites (by –0.41 D [–0.862 to 0.051], $P = .08$). We also explored potential nonlinear effects of age by including age^2 in our model; however, no increase in significance was found when all other model covariates were considered (combined age effect $P = .16$).

For participant myopia status, sex showed a significant effect such that the odds of having myopia were significantly greater for female than male participants (odds ratio, 1.27 [1.040 to 1.545]; $P = .02$). Although ethnicity had no significant effect, older age was significantly associated with greater odds of having myopia (odds ratio, 1.03 [1.002 to 1.064]; $P = .04$). In relation to body metrics and nutritional factor, only increased insulin levels were associated with significantly increased odds of having myopia (odds ratio, 1.003 [1.0002 to 1.005]; $P = .04$).

Additional linear regression modeling was undertaken using the data from those participants who were both myopic and had data for all other variables (n = 703), with specific interest in associations between the magnitude of myopia and demographic, body metrics, and nutritional factors (data not shown). Although female participants had more myopic spherical equivalent refractive errors than did male participants on average (by –0.19 D), this difference was not statistically significant ($P = .26$). Older myopic participants also tended to be more myopic than younger participants, although this effect of age was also neither statistically nor clinically significant (–0.03 D more per 1-year increase in age; $P = .24$). In relation to ethnicity, the largest difference was between myopes in the other/mixed compared with White groups (by –0.66 D), although this was not statistically significant ($P = .10$). None of the body metric and nutritional factors proved to have predictive value as determinants of the magnitude of myopia (all, $P > .20$).

DISCUSSION

To our knowledge, the current study represents one of only three studies to exploit the National Health and Nutrition Examination Survey database as a resource for investigating environmental contributions to the development of myopia,[39–41] with one of the other studies also investigating nutritional but not body metric factors.[40,41] The analyses used in our study revealed more female participants to be affected by myopia than male participants overall (12- to 25-year cohort: 38 vs. 33%). Female participants were also found

to have more myopic refractive errors and a greater odds of having myopia, as were older participants. Although univariate analyses identified ethnicity-related differences in mean spherical equivalent refractive errors and participant myopia, there was no significant association with either the presence of myopia or its magnitude, after controlling for other participant factors. In general, none of the nutritional factors examined (serum vitamin D, plasma glucose, and caffeine intake) proved to be significantly related to the presence of myopia in this participant cohort, although participants with increased insulin levels had a significantly increased odds of being myopic.

In relation to the influence of body metrics and consistent with the results of the current analysis, a number of population-based studies across the globe have reported relationships between increased eye length and/or myopia in taller individuals.[15,42–48] Although these studies have generally involved older cohorts (≥40 years of age) with likely stable refractive errors, two Asian studies involving children (aged 7 to 9 years) provide exceptions.[15,48] In one study involving Taiwanese children[48] and another population-based study involving Chinese adults,[49] height was found to be positively associated with longer eyes but not with myopia, with the likely explanation for this apparent discrepancy lying in the other structural differences found in the eyes of taller individuals, namely, deeper anterior chambers, thinner lenses, and flatter corneas. The latter findings are also generally consistent with sex differences identified in a systematic review of ocular biometry data, which found male participants to have longer eyes (by ~0.50 mm), flatter corneas (by ~0.50 D), and deeper anterior chamber depths (by ~0.16 mm) compared with female participants, except for those male participants of Asian ethnicity who had steeper corneas than did female participants.[50] Further challenging the relevance of body metrics to myopia is a large Israeli cohort study (N = 106,926) of conscripted male participants aged 17 to 19 years in which no relationship between myopia and either body height or mass index was found.[51]

As noted earlier and consistent with our results, Cordain et al.[13] proposed a link between hyperinsulinemia with myopia development. Other studies have also reported links between diabetics and myopia.[52,53] However, that lenticular changes offer an explanation for the increased prevalence in myopia in diabetic individuals is supported by results from a later, small study by some of the same researchers.[54] Nonetheless, that the glycemic profiles of populations worldwide might explain observed increases in myopia prevalence figures was suggested by the authors of a recent review of related epidemiological literature, which included speculation on possible mechanisms by which insulin could promote ocular growth.[55] However, evidence for the latter from studies involving animal models is equivocal; although insulin was found to promote myopia development in a few studies involving chicks, the pattern of axial elongation was atypical in that anterior segment changes contributed most to the overall increases in eye length.[16,56]

Because increased time spent outdoors is recognized to be protective against myopia[21,23,57,58] and also tightly tied linked to serum levels of vitamin D, there has been interest in whether vitamin D alone might be protective. A number of related hypotheses concerning how low serum vitamin D levels could increase the risk of myopia have been proposed, including upregulation of scleral extracellular remodeling and synergistic interaction with retinoic acid, a recognized ocular growth regulator.[59] However, consistent with results of the current study, four large cohort studies, including one National Health and Nutrition Examination Survey cohort analysis, failed to establish a link between low level of vitamin D and myopia.[28,29,40,60] Furthermore, in the current study, Blacks had the lowest serum levels of vitamin D, as has been reported in previous studies,[61] yet Blacks also had the lowest proportion of myopes (35%; 1% below the average), with similar findings contained in other reports.[62–64] A recent study that used Mendelian randomization to investigate the role of low serum vitamin D levels in myopia development, without the confounding effect of outdoor activity, also found no evidence of a causal relationship.[30] Interestingly, a study in tree shrews involving experimentally induced myopia also failed to demonstrate a positive benefit from vitamin D_3 supplementation, although control animals were not deficient (Siegwart JT, Jr., et al. IOVS 2011;52: E-Abstract 6298).[65]

A number of recent animal model studies have yielded strong supporting data for the potential therapeutic benefits of caffeine and one of its metabolites, 7-methylxanthine, a nonselective adenosine receptor antagonist.[17–19] These results are also consistent with a relative reduction in axial elongation and myopia progression observed with oral 7-methylxanthine in an earlier pediatric clinical trial in Denmark.[66] Longer-term clinical trials are ongoing in Denmark, the only country to have approved oral 7-methylxanthine tablets for myopia control to date. Unfortunately, analyses reported here were necessarily limited to the National Health and Nutrition Examination Survey–based data covering caffeine intake, as data covering caffeine metabolites in urine are only available from 2009, when refractive error measurements were discontinued. Related to other nutritional factors, to our knowledge, there have only been two other systematic analyses of this open-access National Health and Nutrition Examination Survey data set with respect to myopia development and/or progression and nutritional factors to date.[40,41] One of these studies examined the association of total zinc intake and myopia in National Health and Nutrition Examination Survey participants aged 12 to 19 years and found no association.[41]

The large ethnically diverse National Health and Nutrition Examination Survey participant cohort combined with the analyses used in the current study represents its major strengths, with the availability of objective refractive error data representing an additional strength, given that axial length data were not available. In addition, that all measurements were performed in a standardized way by trained technicians, according to well-defined protocols, across all National Health and Nutrition Examination Survey sites, adds further value to this data set. Nonetheless, there are several limitations to consider, the most significant of which relates to the ethnic categories used during the study years analyzed. Given the high prevalence of myopia in Asian populations, both in Asian countries and in the United States, the lack of an "Asian" category represents a major limitation. Nonetheless, the fact that the other/mixed ethnic category, albeit small, had the highest proportion of myopes (46%; 11% more than the cohort average) and who were also relatively more myopic (–3.15 D; 0.67 D more than the myopic cohort average) likely reflects the fact that Asian participants were included in this ethnic category. In addition, it is important to note that the refractive error data were limited to children 12 years or older, after the typical age at onset of childhood myopia and as reflected in the presence of myopia in many of the participants in our study cohort. This may in part explain why age, which has been shown to influence refractive error in many other studies,[62,66–68] proved to be of only borderline statistical significance in our multivariate modeling. In addition, the nutritional data captured from adolescents are likely to be different from those

representing younger children. Finally, although it is important to disentangle the likely confounding effects of outdoor activity when considering the relationship between serum vitamin D levels and myopia, neither comprehensive measures of outdoor activity nor season of data collection is available in this data set, and only minimal data concerning sunlight exposure are available.

CONCLUSIONS AND CLINICAL RELEVANCE

The key risk factors related to myopia development and/or progression remain to be identified and are very likely multifactorial. However, clinicians are frequently called on to make recommendations about behavioral modifications that might reduce myopia development and progression. Although sex and age seem to be most closely tied to the presence and magnitude of myopia, the results presented here suggest that insulin levels may also be an important factor. No other nutritional or body metric factors seem to be closely tied to the presence or magnitude of myopia. These largely negative findings suggest that other environmental factors, such as those related to the visual environment, may contribute more to the development and/or progression of myopia and would argue for continued research in these areas in support of more evidence-based myopia clinical management.

ARTICLE INFORMATION

Supplemental Digital Content: Appendix Table A1. Summary statistics (mean ± standard deviation) for participants with available body metric and nutritional factors data, stratified by sex and age group, is available at http://links.lww.com/OPX/A484.

Submitted: October 8, 2019

Accepted: February 19, 2021

Funding/Support: National Eye Institute (K12 EY017269).

Conflict of Interest Disclosure: None of the authors have reported a financial conflict of interest.

Author Contributions: Conceptualization: ENH; Data Curation: ENH; Formal Analysis: ENH; Funding Acquisition: ENH; Investigation: ENH; Methodology: ENH; Resources: CFW; Supervision: CFW; Writing – Original Draft: ENH; Writing – Review & Editing: ENH, CFW.

REFERENCES

1. Holden BA, Fricke TR, Wilson DA, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. Ophthalmology 2016;123:1036–42.

2. Smith TST, Frick KD, Holden BA, et al. Potential Lost Productivity Resulting from the Global Burden of Uncorrected Refractive Error. Bull World Health Organ 2009;87:431–7.

3. Flitcroft DI. The Complex Interactions of Retinal, Optical and Environmental Factors in Myopia Aetiology. Prog Retin Eye Res 2012;31:622–60.

4. Dirani M, Chamberlain M, Garoufalis P, et al. Refractive Errors in Twin Studies. Twin Res Hum Genet 2006;9:566–72.

5. Fan Q, Verhoeven VJ, Wojciechowski R, et al. Meta-analysis of Gene-environment–wide Association Scans Accounting for Education Level Identifies Additional Loci for Refractive Error. Nat Commun 2016;7:11008.

6. Wojciechowski R, Hysi PG. Focusing in on the Complex Genetics of Myopia. PLoS Genet 2013;9:2–5.

7. Chen Y, Wang W, Han X, et al. What Twin Studies Have Taught Us about Myopia. Asia Pac J Ophthalmol (Phila) 2016;5:411–4.

8. Sherwin JC, Mackey DA. Update on the Epidemiology and Genetics of Myopic Refractive Error. Expert Rev Ophthalmol 2013;8:63–87.

9. Huang HM, Chang DST, Wu PC. The Association between Near Work Activities and Myopia in Children—A Systematic Review and Meta-analysis. PLoS One 2015;10:e0140419.

10. Xiong S, Sankaridurg P, Naduvilath T, et al. Time Spent in Outdoor Activities in Relation to Myopia Prevention and Control: A Meta-analysis and Systematic Review. Acta Ophthalmol 2017;95:551–66.

11. Young FA, Leary GA, Baldwin WR, et al. The Transmission of Refractive Errors within Eskimo Families. Optom Vis Sci 1969;46:676–85.

12. Morgan RW, Munro M. Refractive Problems in Northern Natives. Can J Ophthalmol 1973;8:226–8.

13. Cordain L, Eaton SB, Miller JB, et al. An Evolutionary Analysis of the Aetiology and Pathogenesis of Juvenile-onset Myopia. Acta Ophthalmol Scand 2002;80:125–35.

14. Cordain L, Watkins BA, Sebastian A, et al. Origins and Evolution of the Western Diet: Health Implications for the 21st Century. Am J Clin Nutr 2005;81:341–54.

15. Saw SM, Chua WH, Hong CY, et al. Height and Its Relationship to Refraction and Biometry Parameters in Singapore Chinese Children. Invest Ophthalmol Vis Sci 2002;43:1408–13.

16. Zhu X, Wallman J. Opposite Effects of Glucagon and Insulin on Compensation for Spectacle Lenses in Chicks. Invest Ophthalmol Vis Sci 2009;50:24–36.

17. Trier K, Olsen EB, Kobayashi T, et al. Biochemical and Ultrastructural Changes in Rabbit Sclera After Treatment with 7-methylxanthine, Theobromine, Acetazolamide, or L-ornithine. Br J Ophthalmol 1999;83:1370–5.

18. Nie HH, Huo LJ, Yang X, et al. Effects of 7-methylxanthine on Form-deprivation Myopia in Pigmented Rabbits. Int J Ophthalmol 2012;5:133–7.

19. Hung LF, Arumugam B, Ostrin L, et al. The Adenosine Receptor Antagonist, 7-methylxanthine, Alters Emmetropizing Responses in Infant Macaques. Invest Ophthalmol Vis Sci 2018;59:472–86.

20. Wu PC, Tsai CL, Hu CH, et al. Effects of Outdoor Activities on Myopia among Rural School Children in Taiwan. Ophthalmic Epidemiol 2010;17:338–42.

21. Jin JX, Hua WJ, Jiang X, et al. Effect of Outdoor Activity on Myopia Onset and Progression in School-aged Children in Northeast China: The Sujiatun Eye Care Study. BMC Ophthalmol 2015;15:73–84.

22. Guo Y, Liu LJ, Xu L, et al. Myopic Shift and Outdoor Activity among Primary School Children: One-year Follow-up Study in Beijing. PLoS One 2013;8:e75260.

23. Wu PCC, Chen CYCT, Lin KK, et al. Myopia Prevention and Outdoor Light Intensity in a School-based Cluster Randomized Trial. Ophthalmology 2018;125:1239–50.

24. Stone RA, Cohen Y, McGlinn AM, et al. Development of Experimental Myopia in Chicks in a Natural Environment. Invest Ophthalmol Vis Sci 2016;57:4779–89.

25. Vannas AE, Ying G-S, Stone RA, et al. Myopia and Natural Lighting Extremes: Risk Factors in Finnish Army Conscripts. Acta Ophthalmol Scand 2003;81:588–95.

26. Ashby RS, Schaeffel F. The Effect of Bright Light on Lens Compensation in Chicks. Invest Ophthalmol Vis Sci 2010;51:5247–53.

27. Read SA, Collins MJ, Vincent SJ. Light Exposure and Physical Activity in Myopic and Emmetropic Children. Optom Vis Sci 2014;91:330–41.

28. Choi JA, Han K, Park YM, et al. Low Serum 25-hydroxyvitamin D Is Associated with Myopia in Korean Adolescents. Invest Ophthalmol Vis Sci 2014;55:2041–7.

29. Guggenheim JA, Williams C, Northstone K, et al. Does Vitamin D Mediate the Protective Effects of Time Outdoors on Myopia? Findings from a Prospective Birth Cohort. Invest Ophthalmol Vis Sci 2014;55:8550–8.

30. Cuellar-Partida G, Williams KM, Yazar S, et al. Genetically Low Vitamin D Concentrations and Myopic Refractive Error: A Mendelian Randomization Study. Int J Epidemiol 2017;46:1882–90.

31. Grosvenor T, Scott R. Comparison of Refractive Components in Youth-onset and Early Adult-onset Myopia. Optom Vis Sci 1991;68:204–9.

32. Rahi JS, Cumberland PM, Peckham CS. Myopia over the Lifecourse: Prevalence and Early Life Influences in the 1958 British Birth Cohort. Ophthalmology 2011;118:797–804.

33. McBrien NA, Millodot M. A Biometric Investigation of Late Onset Myopic Eyes. Acta Ophthalmol 1987;65:461–8.

34. Friling R, Weinberger D, Kremer I, et al. Keratometry Measurements in Preterm and Full Term Newborn Infants. Br J Ophthalmol 2004;88:8–10.

35. Isenberg SJ, Del Signore M, Chen A, et al. Corneal Topography of Neonates and Infants. Arch Ophthalmol 2004;122:1767–71.

36. Mutti DO, Mitchell GL, Jones LA, et al. Axial Growth and Changes in Lenticular and Corneal Power during Emmetropization in Infants. Invest Ophthalmol Vis Sci 2005;46:3074–80.

37. Ehlers N, Sørensen T, Bramsen T, et al. Central Corneal Thickness in Newborns and Children. Acta Ophthalmol 1976;54:285–90.

38. Centers for Disease Control and Prevention (CDC): National Center for Health Statistics. National Health and Nutrition Examination Study (NHANES). Available at: https://www.cdc.gov/nchs/nhanes/index.htm. Accessed March 26, 2021.

39. Migneron-Foisy V, Bouchard MF, Freeman EE, et al. Myopia and Exposure to Organophosphate and Pyrethroid Pesticides in the General United States Population. Invest Ophthalmol Vis Sci 2017;58:4915–24.

40. Chiang SY, Weng TH, Lin CM, et al. Ethnic Disparity in Prevalence and Associated Risk Factors of Myopia in Adolescents. J Formos Med Assoc 2020;119:134–43.

41. Burke N, Butler JS, Flitcroft I, et al. Association of Total Zinc Intake with Myopia in U.S. Children and Adolescents. Optom Vis Sci 2019;96:647–54.

42. Wang D, Ding X, Liu B, et al. Longitudinal Changes of Axial Length and Height Are Associated and Concomitant in Children. Invest Ophthalmol Vis Sci 2011;52:7949–53.

43. Zhang J, Hur YM, Huang W, et al. Shared Genetic Determinants of Axial Length and Height in Children: The Guangzhou Twin Eye Study. Arch Ophthalmol 2011;129:63–8.

44. Yin G, Wang YX, Zheng ZY, et al. Ocular Axial Length and Its Associations in Chinese: The Beijing Eye Study. PLoS One 2012;7:e43172.

45. Bikbov MM, Kazakbaeva GM, Gilmanshin TR, et al. Axial Length and Its Associations in a Russian Population: The Ural Eye and Medical Study. PLoS One 2019;14:e0211186.

46. Wu HM, Gupta A, Newland HS, et al. Association between Stature, Ocular Biometry and Refraction in an Adult Population in Rural Myanmar: The Meiktila Eye Study. Clin Exp Ophthalmol 2007;35:834–9.

47. Eysteinsson T, Jonasson F, Arnarsson Á, et al. Relationships between Ocular Dimensions and Adult Stature among Participants in the Reykjavik Eye Study. Acta Ophthalmol Scand 2005;83:734–8.

48. Huang CY, Hou CH, Lin KK, et al. Relationship of Lifestyle and Body Stature Growth with the Development of Myopia and Axial Length Elongation in Taiwanese Elementary School Children. Indian J Ophthalmol 2014;62:865–9.

49. Wong TY, Foster PJ, Johnson GJ, et al. The Relationship between Ocular Dimensions and Refraction with Adult Stature: The Tanjong Pagar Survey. Invest Ophthalmol Vis Sci 2001;42:1237–42.

50. Hoffer KJ, Savini G. Effect of Gender and Race on Ocular Biometry. Int Ophthalmol Clin 2017;57:137–42.

51. Rosner M, Laor A, Belkin M. Myopia and Stature: Findings in a Population of 106,926 Males. Eur J Ophthalmol 1995;5:1–6.

52. Fledelius HC. Myopia and Diabetes Mellitus with Special Reference to Adult-onset Myopia. Acta Ophthalmol 1986;64:33–8.

53. Sjolie AK, Goldschmidt E. Myopia in Insulin Treated Diabetes. Acta Ophthalmol 1985;63:89.

54. Goldschmidt E, Jacobsen N. Genetic and Environmental Effects on Myopia Development and Progression. Eye 2014;28:126–33.

55. Galvis V, López-Jaramillo P, Tello A, et al. Is Myopia Another Clinical Manifestation of Insulin Resistance? Med Hypotheses 2016;90:32–40.

56. Feldkaemper MP, Neacsu I, Schaeffel F. Insulin Acts as a Powerful Stimulator of Axial Myopia in Chicks. Invest Ophthalmol Vis Sci 2009;50:13–23.

57. Wu PC, Tsai CL, Wu HL, et al. Outdoor Activity during Class Recess Reduces Myopia Onset and Progression in School Children. Ophthalmology 2013;120:1080–5.

58. He M, Xiang F, Zeng Y, et al. Effect of Time Spent Outdoors at School on the Development of Myopia among Children in China a Randomized Clinical Trial. JAMA 2015;314:1142–8.

59. McFadden SA, Howlett MHC, Mertz JR. Retinoic Acid Signals the Direction of Ocular Elongation in the Guinea Pig Eye. Vision Res 2004;44:643–53.

60. Tideman JWL, Polling JR, Voortman T, et al. Low Serum Vitamin D Is Associated with Axial Length and Risk of Myopia in Young Children. Eur J Epidemiol 2016;31:491–9.

61. Harris SS. Vitamin D and African Americans. J Nutr 2006;136:1126–9.

62. Hyman L, Gwiazda J, Hussein M, et al. Relationship of Age, Sex, and Ethnicity with Myopia Progression and Axial Elongation in the Correction of Myopia Evaluation Trial. Arch Ophthalmol 2005;123:977–87.

63. Vitale S, Sperduto RD, Ferris FL. Increased Prevalence of Myopia in the United States between 1971–1972 and 1999–2004. Arch Ophthalmol 2009;127:1632–9.

64. Hashemi H, Fotouhi A, Yekta A, et al. Global and Regional Estimates of Prevalence of Refractive Errors: Systematic Review and Meta-analysis. J Curr Ophthalmol 2018;30:3–22.

65. Trier K, Munk Ribel-Madsen S, Cui D, et al. Systemic 7-methylxanthine in Retarding Axial Eye Growth and Myopia Progression: A 36-month Pilot Study. J Ocul Biol Dis Infor 2008;1:85–93.

66. Lee MW, Lee SE, Lim H-B, et al. Longitudinal Changes in Axial Length in High Myopia: A 4-year Prospective Study. Br J Ophthalmol 2020;104:600–3.

67. Parssinen O, Lyyra A. Myopia and Myopic Progression among School Children: A Three Year Follow-up Study. Invest Ophthalmol Vis Sci 1993;34:2794–802.

68. Zadnik K. The Glenn A. Fry Award Lecture (1995). Myopia Development in Childhood. Optom Vis Sci 1997;74:603–8.