The prevalence of myopia is increasing globally and has reached pandemic levels. Initial estimates, based on current data and comparable United Nations population statistics, predict that myopia will affect 50% (4949 million) of the world’s population by 2050. The prevalence of myopia is highest in Asia Pacific and will affect 50% (4949 million) of the world’s population by 2050, according to the United Nations. Myopia in its early stages is very closely associated with growth, so it would seem plausible that deficits in nutritional intake and status could play a role in its development and progression. A number of observational studies have shown serum trace elements, such as zinc and copper, to be lower in myopic children/adolescents when compared with controls in parts of Asia. It is likely, however, that a combination of influences is responsible for determining refractive status and not one factor acting in isolation.

Diet is an important environmental and lifestyle factor that has been studied in many eye diseases. Myopia in its early stages is very closely associated with growth, so it would seem plausible that deficits in nutritional intake and status could play a role in its development and progression. A number of observational studies have shown serum trace elements, such as zinc and copper, to be lower in myopic children/adolescents when compared with controls in parts of Asia. It is likely, however, that a combination of influences is responsible for determining refractive status and not one factor acting in isolation.

Diet is an important environmental and lifestyle factor that has been studied in many eye diseases. Myopia in its early stages is very closely associated with growth, so it would seem plausible that deficits in nutritional intake and status could play a role in its development and progression. A number of observational studies have shown serum trace elements, such as zinc and copper, to be lower in myopic children/adolescents when compared with controls in parts of Asia. It is likely, however, that a combination of influences is responsible for determining refractive status and not one factor acting in isolation.
an array of structural and electrophysiological ocular manifestations. In fact, zinc is an integral element required for the structure and activity of many metalloenzymes and plays an important role in vitamin A metabolism. This role is potentially of interest in myopia given that retinoic acid, a metabolite of vitamin A, is thought to be an important molecular signal in regulating eye size and scleral extracellular matrix metabolism. Zinc is also a fundamental part of zinc finger DNA-binding proteins and assists in transcriptional processes and gene expression, in addition to having an important antioxidant role. Hence, there are numerous pathways by which zinc deficiency could contribute to the development and progression of myopia.

Although there is preliminary evidence to support a relationship between zinc and myopia, those findings are specific to Asia and cannot be readily extrapolated to other populations for numerous reasons. Dietary habits, for example, are subject to regional variation due to cultural and agricultural/ecological differences. Such variation is likely to create differences in zinc intake and bioavailability across regions. In addition, the prevalence of myopia is much higher in Asia than in other regions, suggesting the presence of ethnic or constitutional susceptibilities, which may not prevail in other regions. There is therefore a need for similar investigations in a Western population.

There are currently no population-based studies of which we are aware that have specifically explored or reported on the relationship between dietary zinc intake and myopia. The National Health and Nutrition Examination Study is a program of studies designed to assess the health and nutritional status of adults and children in the United States. In the National Health and Nutrition Examination Study 2007 to 2008 cycle, data relating to dietary and supplement-based zinc intake and data on refractive error were simultaneously collected (refractive data have not been collected in more recent cycles). The aim of this study therefore is to test the hypothesis that low zinc intake may be associated with myopia in the U.S. population using a subsample of children/adolescents from the National Health and Nutrition Examination Study 2007 to 2008.

METHODS

Data Collection and Study Population

A nationally representative sample of noninstitutionalized U.S. civilians was selected by using a complex, stratified, multistage sample design. The National Health and Nutrition Examination Study is an ongoing 2-year cycle of studies, in which data are collected by household interview or physical examination in mobile examination centers. The studies are administered by the National Center for Health Statistics at the Centers for Disease Control and Prevention. The study protocol was approved by the National Center for Health Statistics Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants. Additional information on the study design and methods is provided elsewhere.

Data from the National Health and Nutrition Examination Study cycle 2007 to 2008, the most recent cycle with concurrent measures of vision and dietary zinc, were used in this analysis. In total, 10,149 individuals participated in the National Health and Nutrition Examination Study 2007 to 2008. Among those, all participants aged 12 to 19 years (n = 1156) were selected for this study. This age range was selected to prioritize the analysis of dietary intake during school-going years, the period during which myopia most frequently develops. Of these 1156 participants, 61 had missing refractive error data and were excluded. No reason was provided for the missing data. Analysis of the demographic profile of the participants with missing refractive error data reveals that the missing data seem to be randomly spread across sex, socioeconomic, and ethnic groups. In addition, participants with severe eye infection or incomplete, missing, or unreliable data for 24-hour recall nutrient intake were excluded (Fig. 1). Finally, 1095 participants were found to be eligible for inclusion in the analysis.

Participant Data and Measurements

All participants underwent automated objective refraction/keratometric evaluation on both eyes, carried out by trained health technicians. Participants’ refractive error and corneal curvature were measured three times, without cycloplegia, using the Nidek Autorefractor Model ARK-760 instrument (Nidek Co. Ltd., Tokyo, Japan). Refraction measurements were converted into spherical equivalent refraction, calculated as the spherical value plus half of the astigmatic value. Myopia was defined by spherical equivalent refraction of ≤−1.00 D because of the absence of cycloplegia in the method.

Demographic information including age, sex, ethnicity (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other race), and family income were obtained from in-person household interviews. Body measurements such as height (in centimeters), weight (in kilograms), and waist circumference (in centimeters) were taken during physical examinations in the mobile examination center. Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. Physical activity levels were categorized using the Global Physical Activity Questionnaire. Moderate physical activity was categorized as “yes” if participants engaged in any moderate-intensity sports, fitness, or recreational activities that cause a small increase in breathing or heart rate for at least 10 minutes continuously, such as brisk walking, cycling, and swimming.

Copyright © American Academy of Optometry. Unauthorized reproduction of this article is prohibited.
Dietary and Supplemental Intake Assessment

Dietary intake was assessed using two 24-hour dietary recall interviews. Dietary intake data were used to estimate the types and amounts of foods and beverages (including all types of water) consumed during the 24-hour period before the interview (midnight to midnight) and to estimate intakes of energy, nutrients, and other food components from those food and beverages. The first dietary interview was administered in a private setting in the mobile examination center, and the second interview was conducted by telephone over the following 3 to 10 days. During the interviews, a multiple-pass protocol was used. Interviewers used a predefined script incorporated into the dietary recall system to ensure consistency in administration of the interviews. Nutrient intakes were calculated using the U.S. Department of Agriculture Food and Nutrient Databases for dietary analysis. In this study, these dietary recall data were used to calculate total daily energy intake and total nutrient intake of zinc and copper from food and beverages. Copper intake was included because of the known antagonistic effect of zinc intake on copper absorption. The 24-hour dietary supplement questionnaire was administered after the 24-hour dietary recall using a similar protocol. Information on all vitamins, minerals, herbs, and nonprescription antacids that were consumed during a 24-hour period was obtained. Total nutrient intake from food and beverages was summed with total intake from supplements to calculate total nutrient intake of zinc and copper.

Statistical Analysis

All statistical analyses were performed using SAS procedure (version 9.4; SAS Institute, Inc., Cary, NC) to reflect the complex sampling design and sampling weights of the National Health and Nutrition Examination Study and to provide nationally representative prevalence estimates. Participants’ characteristics were described using means and standard errors for continuous variables, and numbers and percentages for categorical variables according to spherical equivalent. For analyses of continuous and categorical variables, t tests and design-adjusted Rao-Scott Pearson-type $\chi^2$ tests, respectively, were used. Total nutrient intakes were presented as median with interquartile range.

To estimate the relationship between total zinc and total copper intake with the health outcome of myopia, the National Cancer Institute method was used. This method was first used to estimate usual intake of zinc and copper from 24-hour dietary recall interviews. The two primary challenges of dietary data are measurement error adjustment and positively skewed data. Regression calibration and Box-Cox transformation were used to overcome these (the National Cancer Institute method uses adaptive Gaussian quadratic), and 24-hour recall data were replaced with a predictor of true intake of total zinc and total copper using 24-hour recall data and age and sex as covariates to aid estimates. This predictor of usual intake was then used to analyze zinc and copper as potential independent variables of myopia in the health outcome model. This mixed-effects method was implemented using SAS macros MIXTRAN, DISTRIB, and INDIVINT V1.1. These macros were downloaded at https://epi.grants.cancer.gov/diet/usualintakes/macros_single.html#ver1.

The usual intakes of nutrient zinc and copper were divided into quartiles and treated as an explanatory variable for myopia in simple and multiple logistic regression, with quartile 1 as the reference category. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, ethnicity, family income, body mass index, recreational activity, copper, and total energy intake (in kilocalories per day). Tests for linear trends were conducted using regression with a median value of each category of the analyzed exposure as a single ordinal variable. To further explore the relationship between usual intake of zinc and myopia, we performed multivariate linear regression on the association between total zinc intake and spherical equivalent refractive error in the myopic population. All reported probabilities were two sided, with $P < .05$ considered statistically significant.

RESULTS

The demographic, anthropometric, and dietary intake characteristics of study participants according to refractive status are reported in Table 1. Of the 1095 participants, 30% were myopic ($\leq −1.00$ D). Spherical equivalent refractive error in the right and left eyes was highly correlated (Pearson correlation = 0.87, $P < .001$). Therefore, only data for the right eyes are presented.

As expected, there was a significant difference in spherical equivalent between the myopic and nonmyopic participant groups ($P < .001$). There were, however, no significant differences in demographic (sex, age, ethnicity, family income) or anthropometric (height, weight, and waist circumference) characteristics between myopic and nonmyopic participants ($P > .05$ for all). Similarly, no significant difference was found in body mass index or frequency of regular physical activity between myopes and nonmyopes; however, $P$ values of .06 and .06, respectively, were noted.

The median daily total zinc, copper, and energy intakes of participants with myopia were not significantly different from those without myopia.

The association between total zinc and copper intakes and myopia in simple and multiple logistic regression models is presented in Table 2. The simple odds ratio with 95% confidence intervals indicated that total zinc and copper intakes were not associated with myopia. The lack of association persisted after initial adjustment for age and sex and after additional adjustment for body mass index, ethnicity, family income, recreational activity, copper, and total daily energy intake in multivariate analysis. The multivariate-adjusted odds ratios (95% confidence intervals) for myopia were 0.88 (0.59 to 1.30; $P = .57$) and 1.19 (0.68 to 2.08; $P = .18$) in the highest versus lowest quartile of zinc and copper intakes, respectively. Similarly, the copper-to-zinc ratio was not associated with risk of myopia (odds ratio, 1.06 (0.65 to 1.71); $P = .29$).

The results of multiple linear regression are shown in Table 3. Spherical equivalent refractive error was not significantly associated with total zinc intake in the myopic group in either the simple model, or after adjustment for age and sex in model 1 ($P = .14$), or after subsequent adjustment for body mass index, ethnicity, family income, recreational activity, copper intake, and total daily energy intake in model 2 ($P = .13$).

All analyses were repeated for data in the previous cycle, National Health and Nutrition Examination Study 2005 to 2006, to confirm our findings herein. Similar statistical analysis (as outlined previously) was performed on eligible subjects aged 12 to 19 years ($n = 1936$). The median (interquartile range) intakes of zinc were 10.26 (8.98) mg/d in nonmyopes and 10.67 (8.95) mg/d in myopes ($P = .51$; supplement-based zinc intake data were not included in this earlier cycle because the collection method differed from that of 2007 to 2008). The multivariate-adjusted odds ratio (95% confidence interval)
for myopia was 0.75 (0.44 to 1.24; \( P = .56 \)) in the highest versus lowest quartile of zinc intake.

**DISCUSSION**

We found no significant association between dietary zinc intake and myopia in U.S. children/adolescents aged 12 to 19 years after adjustment for potential confounders. To our knowledge, this is the first study to explore the association between total zinc intake and myopia in children/adolescents using nationally representative data.

Our findings differ from those of previously published observational studies that have suggested that there may be an association between low zinc intake and status and myopia. A recent study by Fedor et al.\(^\text{15}\) on participants aged 7 to 17 years found the average serum zinc concentration in patients with myopia (0.865 ± 0.221 mg/L) to be significantly lower than that in controls (1.054 ± 0.174 mg/L). In contrast to our study, a significantly higher copper/zinc ratio was also found in myopic participants compared with controls (1.196 ± 0.45 vs. 0.992 ± 0.203), indicating possible disruption of antioxidant defenses. The sample size was limited (n = 121), however, and only moderate to high myopes were included in the study (spherical equivalent, \( \leq -3 \) D), with the myopic group having a particularly high mean spherical equivalent of \(-7.31 \) D.\(^\text{15}\)

An examination of serum micronutrient levels (zinc, iron, copper, magnesium, manganese, and lead) involving 120 myopic primary school students was also carried out in Dongguan, China. Serum levels of zinc and iron were found to be significantly lower in myopes than in controls, whereas there was no significant difference in other trace elements measured.\(^\text{13}\)

---

**TABLE 1.** Demographic, anthropometric, and dietary intake characteristics of study participants according to refractive status

|                      | Nonmyope, SER > –1.00 D | Myope, SER ≤ –1.00 D | \( P \) |
|----------------------|--------------------------|----------------------|------|
| Subjects, no. (%)    | 767 (70.0)               | 328 (30.0)           |      |
| Sex, no. (%)         |                          |                      |      |
| Male                 | 417 (51.5)               | 159 (49.2)           |      |
| Female               | 350 (48.5)               | 169 (50.7)           | .57  |
| Age, mean ± SE (y)   | 15.4 ± 0.1               | 15.6 ± 0.2           | .44  |
| Ethnicity, no. (%)   |                          |                      |      |
| Mexican American     | 162 (10.3)               | 98 (14.7)            |      |
| Other Hispanic       | 109 (6.6)                | 42 (6.6)             |      |
| Non-Hispanic white   | 257 (63.2)               | 92 (57.7)            |      |
| Non-Hispanic black   | 208 (15.1)               | 79 (13.8)            |      |
| Other race           | 31 (4.6)                 | 17 (7.0)             | .29  |
| Ocular examination, mean ± SE |                |                      |      |
| Spherical equivalent | +0.07 ± 0.0               | –3.17 ± 0.2           | <.001|
| Systemic evaluation, mean ± SE |            |                      |      |
| Height (cm)          | 1.66 ± 0.6               | 1.67 ± 0.8           | .46  |
| Weight (kg)          | 64.5 ± 0.9               | 67.6 ± 1.5           | .08  |
| Body mass index (kg/m²) | 23.2 ± 0.3           | 24.1 ± 0.5           | .06  |
| Waist (cm)           | 80.2 ± 0.7               | 83.0 ± 1.4           | .07  |
| Recreational activity, no. (%) |            |                      |      |
| Yes                  | 486 (67.1)               | 190 (61.0)           |      |
| No                   | 268 (32.8)               | 130 (38.9)           | .06  |
| Family income, no. (%) |                      |                      |      |
| 1 (low)              | 123 (11.8)               | 44 (9.1)             |      |
| 2                    | 221 (22.7)               | 79 (19.0)            |      |
| 3                    | 161 (22.4)               | 72 (17.6)            |      |
| 4 (high)             | 253 (43.2)               | 126 (54.1)           | .17  |
| Daily component intake, median (interquartile range) |            |                      |      |
| Total energy (kcal)  | 1936 (1255.4)            | 1927.4 (1282.7)      | .67  |
| Total zinc (mg)      | 11.1 (10.8)              | 10.8 (10.2)          | .11  |
| Total copper (mg)    | 1.07 (0.9)               | 1.05 (0.9)           | .83  |
| Zinc-to-copper ratio | 9.7 (5.04)               | 9.2 (5.1)            | .24  |

Data are presented as mean ± SE, number (percent), or median (interquartile range). SER = spherical equivalent refractive error.

---

www.optvissci.com Optom Vis Sci 2019; Vol 96(9) 650

Copyright © American Academy of Optometry. Unauthorized reproduction of this article is prohibited.
Another study investigating serum levels of zinc, copper, and selenium in 168 Chinese middle school students reported levels of all trace elements in the myopic group, which were much lower than the levels observed in the emmetropic group, whereas degree of myopia was negatively correlated with levels of serum zinc and copper.\textsuperscript{14} These findings were supported by Xie et al.,\textsuperscript{16} who reported significantly lower zinc and iron concentrations and higher copper concentrations in the serum of their myopic patients. Zinc was also negatively correlated with the degree of myopia in this study. Interestingly, and important to note, although serum zinc levels were found to be lower in myopic children/adolescents, no study found myopes to have zinc deficiency levels (<70 \( \mu \text{g/dL} \)).

There are numerous possible explanations for the conflicting findings reported herein. Study design and methodological differences need to be acknowledged, as our study only measured dietary zinc intake, and recently published evidence on National Health and Nutrition Examination Study data suggests that serum zinc concentration in the U.S. population is not related to dietary or supplemental zinc.\textsuperscript{28} Population-based differences also merit consideration, as most previous studies were carried out on Asian populations; thus, any study investigating dietary zinc intake in a white population might find different results.

### TABLE 2. Weighted odds ratio (95% confidence intervals) of myopia across quartiles of zinc intake, NHANES 2007 to 2008

| Intake cutoff        | Simple | Model 1 | Model 2 |
|----------------------|--------|---------|---------|
| Total zinc intake (mg/d) |        |         |         |
| Quartile 1 (low)     | <8.8   | 1 (ref) | 1 (ref) | 1 (ref) |
| Quartile 2           | 8.8 to <11.4 | 0.75 (0.41–1.37) | 0.75 (0.41–1.37) | 0.81 (0.41–1.60) |
| Quartile 3           | 11.4 to <14.2 | 0.71 (0.39–1.29) | 0.72 (0.38–1.35) | 0.69 (0.37–1.30) |
| Quartile 4 (high)    | ≥14.2  | 0.85 (0.60–1.21) | 0.86 (0.59–1.30) | 0.88 (0.59–1.3) |
| P-trend              | .55    | .69     | .58     |
| Total copper intake (mg/d) |        |         |         |
| Quartile 1 (low)     | <0.90  | 1 (ref) | 1 (ref) | 1 (ref) |
| Quartile 2           | 0.90 to <1.12 | 0.66 (0.37–1.17) | 0.66 (0.37–1.17) | 0.67 (0.35–1.32) |
| Quartile 3           | 1.12 to <1.38 | 0.97 (0.67–1.42) | 0.98 (0.67–1.43) | 1.12 (0.75–1.76) |
| Quartile 4 (high)    | ≥1.38  | 1.00 (0.67–1.48) | 1.00 (0.65–1.56) | 1.19 (0.68–2.08) |
| P-trend              | .36    | .34     | .18     |
| Zinc-to-copper ratio |        |         |         |
| Quartile 1 (low)     | <7.37  | 1 (ref) | 1 (ref) | 1 (ref) |
| Quartile 2           | 7.37 to <9.62 | 1.00 (0.75–1.33) | 0.98 (0.74–1.31) | 1.04 (0.95–1.39) |
| Quartile 3           | 9.62 to <12.47 | 0.73 (0.52–1.03) | 1.36 (0.97–1.90) | 1.34 (0.95–1.90) |
| Quartile 4 (high)    | ≥12.47 | 0.96 (0.62–1.49) | 1.03 (0.66–1.60) | 1.06 (0.65–1.71) |
| P-trend              | .35    | .36     | .29     |

Model 1 adjusted for age and sex. Model 2 adjusted for copper intake, age, sex, ethnicity, body mass index, family income, recreational activity, and daily energy intake (in kilocalories per day, continuous). NHANES = National Health and Nutrition Examination Survey; ref = reference.

### TABLE 3. Multiple linear regression analysis for the association between total zinc intake and SER in the myopic group (n = 328)

|                         | Simple model | Model 1 | Model 2 |
|-------------------------|--------------|---------|---------|
|                         | Estimate     | 95% CI  | P       | Estimate | 95% CI  | P       | Estimate | 95% CI  | P       |
| Total zinc intake       | −0.58        | −2.2 to 1.03 | .48 | −1.01 | −0.38 to 0.22 | .14 | −1.23 | −2.85 to 0.38 | .13 |
| Age                     | −0.15        | −0.39 to −0.91 | .22 | −0.07 | −0.22 to 0.07 | .35 | −0.60 | −1.38 to 0.16 | .12 |
| Sex                     | −0.32        | −1.00 to 0.35 | .35 | −0.60 | −1.38 to 0.16 | .12 | −0.60 | −1.38 to 0.16 | .12 |
| Total copper intake     | 0.34         | −0.61 to 1.30 | .48 | 0.01 | −0.40 to 0.43 | .95 | −0.06 | −0.02 to 0.07 | .37 |
| Race                    | 0.17         | −0.50 to −0.15 | .29 | −0.17 | −0.50 to −0.15 | .29 | −0.17 | −0.50 to −0.15 | .29 |
| BMI                     | 0.00         | −0.00 to 0.00 | .35 | −0.00 | −0.00 to 0.00 | .35 | −0.00 | −0.00 to 0.00 | .35 |
| Total energy intake     | −0.59        | −1.43 to 0.25 | .17 | −0.59 | −1.43 to 0.25 | .17 | −0.59 | −1.43 to 0.25 | .17 |

Model 1 adjusted for age and sex. Model 2 adjusted for copper intake, age, sex, ethnicity, body mass index, family income, recreational activity, and daily energy intake. BMI = body mass index; CI = confidence interval; SER = spherical equivalent refractive error.
Dietary Zinc Intake and Myopia — Burke et al.

genetic, lifestyle, or dietary differences may have contributed to the variation in results.

According to the World Health Organization, the estimated global prevalence of zinc deficiency is 31%. Prevalence is lower in Europe and North America and higher in areas of the Eastern Mediterranean, South, and Southeast Asia, most likely due to dietary variance. Animal products such as red meat and dairy are major sources of dietary zinc in Western countries; diets based on cereals and legumes, which are lower in animal products, make it difficult to meet zinc requirements. Bioavailability of zinc is also lower in plant foods (cereals, grains, vegetables, and soybeans) because they are high in phytate, a known inhibitor of zinc absorption. Marginal deficiency and suboptimal zinc status are also prevalent but much more difficult to identify, and because of high demand for zinc and limitations in body stores, children are particularly vulnerable to the consequences of reduced zinc levels. The current recommended daily allowance for zinc intake in U.S. children is 8 mg for both boys and girls, and those in adolescents are 11 mg for boys and 9 mg for girls. In this study, the lowest quartile of zinc intake was <6.3 mg/d and included 226 participants, which means that a significant number of subjects had inadequate zinc intake.

A substantial number of proteins and enzymes contain zinc, which explains the importance of zinc in many cell processes. Zinc has several actions in many of these enzymes, such as catalytic, structural, substrate, or regulatory roles in enzyme activity. The extensive number of zinc-reliant enzymes explains zinc’s necessity in DNA, RNA, and protein and lipid metabolism and synthesis. Zinc also plays an important role in maintaining the genome. This requires, among other factors, the antioxidant effects of zinc and its involvement in DNA repair in response to DNA damage and in the compositional makeup of biomolecules (e.g., methionine), which are required for DNA methylation. Zinc also regulates the storage and release of neurotransmitters, so it is clear that there are many potential pathological mechanisms by which zinc deficiency could play a role in myopia. Although no clear relationship between zinc intake and myopia was observed herein, there is sufficient rationale and serum evidence that some of the candidate pathways through which zinc may influence myopia development are worth exploring. These could include disruption of vitamin A metabolism, impairment of antioxidant defenses, disruption of epigenetic regulators, and adverse effects on blood glucose control, among others.

As previously mentioned, retinoic acid, a metabolite of vitamin A, has been shown to be involved in the signaling pathway, which modulates eye growth between the retina and the sclera. The level of zinc in the body affects numerous aspects of vitamin A metabolism, namely, absorption, transport, and usage. Zinc is understood to control vitamin A transport by protein synthesis and oxidative conversion of retinol to retinal, a process that requires the action of zinc-dependent retinal dehydrogenase enzyme. Retinal is subsequently converted to retinoic acid by retinaldehyde dehydrogenases. In animal models, it has been shown that choroidal synthesis of all-trans retinoic acid alters during times of visually induced changes in ocular growth and that this has a distinct effect on scleral extracellular matrix metabolism. More research on these molecular processes and zinc’s possible influence on changes in retinoic acid and scleral remodeling is required.

In recent years, some evidence has suggested oxidative stress as an important factor in altered pathways in myopia and the development of associated eye diseases. It is known that lack of zinc increases oxidative stress, resulting in oxidative damage to DNA, proteins, and lipids. Physiologically, zinc levels in the retina, choroid, sclera, and ciliary muscle are higher than those in other intraocular tissues. Zinc is capable of reducing oxidative stress by several mechanisms: activation of antioxidant proteins, molecules, and enzymes (metallothioneins, glutathione, superoxide dismutase); reduction of highly reactive hydroxyl radical; and the inhibition of activities of oxidant-promoting enzymes, such as inducible nitric oxide synthase and NADPH oxidase. In an animal model of myopia, Huibi et al. detected reduced superoxide dismutase, nitric oxide synthase activity, and nitric oxide content in the retinal pigment epithelium-choroid homogenate of chick eyes. Interestingly, after administration of the trace element zinc, these three parameters were increased, and axial elongation and myopia progression were inhibited.

It is thought that genes expressed in the retina, retinal pigment epithelial, choroid, and sclera, which are involved in the normal emmetropization process, could be involved in myopia development. Specifically, the irregular expression of these genes so that the emmetropization mechanism is disturbed may cause an increase in axial length and consequential development of myopia. Zinc has the ability to influence the expression of many genes, and it is part of the structure of more than 2500 transcription factors. Myopia development is thought to be influenced by environmental factors, and environmental factors can also influence gene expression through epigenetic changes. Several key enzymes and zinc finger proteins play an important role in epigenetics (DNA methylation and histone modification). A study by Zhou et al. investigated whether myopia development was associated with changes in scleral DNA methylation of collagen gene COL1A1 in chicks. This group found that increased DNA methylation resulted in suppression of transcription of scleral COL1A1 (inhibiting scleral collagen synthesis) and suggested that low to moderate myopia might not be associated with DNA sequences alone but instead may relate to epigenetic changes in such regulatory genes.

In the human body, zinc is also highly concentrated in the pancreas, where it engages in several functions related to blood glucose control. Adequate dietary zinc intake has been associated with reduced fasting glucose levels. It has been hypothesized that overconsumption of foods with a high glycemic load, as part of the modern diet, results in an increase in circulating insulin levels, which aid unregulated scleral tissue growth through an increase in insulinlike growth factor 1 and depletion of the retinoic acid signal giving rise to myopia. If this hypothesis is correct, zinc deficiency or lower levels of zinc may contribute to the pathogenesis of myopia in this way or through a complex interplay of many but as-yet uncertain mechanisms such as those highlighted here.

Although the strengths of this study include its large nationally representative sample, minimal selection bias, and independently collected data, this study does have several limitations. All National Health and Nutrition Examination Study dietary data are collected by 24-hour recall interview. All self-reported measures of dietary intake are subject to error; although the automated multiple-pass method of data collection mitigates this risk, recall may still be inaccurate or biased. Also, as discussed previously, phytate content of foods may affect zinc absorption, so dietary intake often does not reflect zinc status. In this context, a biological biomarker such as serum or hair zinc may be a better, more accurate parameter to assess any potential role of zinc on myopia or other ocular health outcomes. In this study, refractive status was not checked under cycloplegic conditions; thus, myopia status may have been overestimated because of involuntary accommodation. In addition, other variables such as recreational activity and family income...
were self-reported, leaving measurements open to bias.\textsuperscript{52,53} Also, this study might be confounded by lack of data on other relevant variables such as information on total time spent outdoors and parental myopic status.

Dietary zinc intake is not associated with myopia in a teenage U.S. population; however, further investigation is warranted using a biomarker of zinc status rather than relying exclusively on dietary intake as a proxy for zinc status.

**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. Jung SK, Lee JH, Kakizaki H, et al. Prevalence of Myopia and Its Association with Body Stature and Educational Level in 19-year-old Male Conscripts in Seoul, South Korea. Invest Ophthalmol Vis Sci 2012;53:5579–83.

3. Smith TS, Fricke 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.

4. Wang TY, Ferreira A, Hughes R, et al. Epidemiology of Apolipoprotein A-I as a Retinoic Acid Binding Protein in the Eye. J Biol Chem 2016;291:18991–5.

5. Prasad AS. Zinc is an Antioxidant and Anti-inflammatory Agent: Its Role in Human Health. Front Nutr 2014;1:1–14.

6. Wessells KR, Brown KH. Estimating the Global Prevalence of Zinc Deficiency: Results Based on Zinc Availability in National Food Supplies and the Prevalence of Stunting. PLoS One 2012;7:e50568.

7. Lönnerdal B. Dietary Factors Influencing Zinc Absorption. J Nutr 2000;130:1447S–50.

8. Powell SR. The Antioxidant Properties of Zinc. J Nutr 2000;130:1447S–54.

9. Mertz JR, Wallman J. Choroidal Retinoic Acid Modulation of Apolipoprotein A-I. Invest Ophthalmol Vis Sci 1998;39:684–91.

10. Fedor M, Socha K, Urban B, et al. Serum Concentration of Zinc, Copper, Selenium, and the Visions of Middle School Students. Chin J Sch Health 2006;4:318–9.

11. Fedor M, Liu H, Cao J. The Relationship between Serum Zinc, Copper, and Myopia. Biol Trace Elem Res 2017;176:1–9.

12. Xie X, He H, Wang J, et al. Clinical Significance of Zinc Concentration in Children and the Role of Zinc in Myopic Primary School Students in Dongguan District. Cent Clin Chin Med 2009;1:20–2.

13. Hsu M, Liu H, Cao J. The Relationship between Serum zinc, Copper, and Myopia. J Huaihai Med 2003;4:279–80.

14. Karcioğlu ZA. Zinc in the Eye. Surv Ophthalmol 1982;27:114–22.

15. Summers JA, Harper AR, Feasley CL, et al. Identifying Apolipoprotein A-I as a Retinoic Acid-Binding Protein in the Eye. J Biol Chem 2016;291:18991–9005.

16. Zhu Y, Li W. Effect of Zinc on the Expression of Retinaldehyde Dehydrogenase Activity during Recovery from Form Deprivation Myopia. Invest Ophthalmol Vis Sci 2016;57:4886–97.

17. Christian P, West KP, Jr. Interactions between Zinc and Vitamin A: An Update. Am J Clin Nutr 1998;68(Suppl. 2):435S–41.

18. Mertz JR, Wallman J. Choroidal Retinoic Acid Synthesis: A Possible Mediator between Retinoid and Compensatory Eye Growth. Exp Eye Res 2000;70:519–27.

19. Seko Y, Shimizu M, Tokoro T. Retinoic Acid Increases Hydrogenase Activity during Recovery from Form Deprivation Myopia. Invest Ophthalmol Vis Sci 2016;57:4886–97.

20. Zieg G, Chiappa M, Porter KS, et al. National Health and Nutrition Examination Survey: Plan and Operations, 1999–2010. Vital Health Stat 2013;1:111–21.

21. Bataninire BK, Cunningham MG. Zinc: The Brain's Dark Horse. Synapse 2009;63:1029–49.

22. Harper AR, Wang X, Moiseyev G, et al. Postnatal Chick Choroids Exhibit Increased Retinaldehyde Dehydrogenase Activity during Recovery from Form Deprivation Myopia. Invest Ophthalmol Vis Sci 2016;57:4886–97.

23. Christian P, West KP, Jr. Interactions between Zinc and Vitamin A: An Update. Am J Clin Nutr 1998;68(Suppl. 2):435S–41.

24. Mertz JR, Wallman J. Choroidal Retinoic Acid Synthesis: A Possible Mediator between Retinoid and Compensatory Eye Growth. Exp Eye Res 2000;70:519–27.

25. Seko Y, Shimizu M, Tokoro T. Retinoic Acid Increases Hydrogenase Activity during Recovery from Form Deprivation Myopia. Invest Ophthalmol Vis Sci 2016;57:4886–97.

26. Zieg G, Chiappa M, Porter KS, et al. National Health and Nutrition Examination Survey: Plan and Operations, 1999–2010. Vital Health Stat 2013;1:111–21.

27. Bataninire BK, Cunningham MG. Zinc: The Brain's Dark Horse. Synapse 2009;63:1029–49.

28. Harper AR, Wang X, Moiseyev G, et al. Postnatal Chick Choroids Exhibit Increased Retinaldehyde Dehydrogenase Activity during Recovery from Form Deprivation Myopia. Invest Ophthalmol Vis Sci 2016;57:4886–97.

29. Zieg G, Chiappa M, Porter KS, et al. National Health and Nutrition Examination Survey: Plan and Operations, 1999–2010. Vital Health Stat 2013;1:111–21.

30. Bataninire BK, Cunningham MG. Zinc: The Brain's Dark Horse. Synapse 2009;63:1029–49.

31. Harper AR, Wang X, Moiseyev G, et al. Postnatal Chick Choroids Exhibit Increased Retinaldehyde Dehydrogenase Activity during Recovery from Form Deprivation Myopia. Invest Ophthalmol Vis Sci 2016;57:4886–97.

32. Zieg G, Chiappa M, Porter KS, et al. National Health and Nutrition Examination Survey: Plan and Operations, 1999–2010. Vital Health Stat 2013;1:111–21.

33. Bataninire BK, Cunningham MG. Zinc: The Brain's Dark Horse. Synapse 2009;63:1029–49.

34. Harper AR, Wang X, Moiseyev G, et al. Postnatal Chick Choroids Exhibit Increased Retinaldehyde Dehydrogenase Activity during Recovery from Form Deprivation Myopia. Invest Ophthalmol Vis Sci 2016;57:4886–97.

35. Zieg G, Chiappa M, Porter KS, et al. National Health and Nutrition Examination Survey: Plan and Operations, 1999–2010. Vital Health Stat 2013;1:111–21.

36. Bataninire BK, Cunningham MG. Zinc: The Brain's Dark Horse. Synapse 2009;63:1029–49.

37. Harper AR, Wang X, Moiseyev G, et al. Postnatal Chick Choroids Exhibit Increased Retinaldehyde Dehydrogenase Activity during Recovery from Form Deprivation Myopia. Invest Ophthalmol Vis Sci 2016;57:4886–97.

38. Zieg G, Chiappa M, Porter KS, et al. National Health and Nutrition Examination Survey: Plan and Operations, 1999–2010. Vital Health Stat 2013;1:111–21.

39. Bataninire BK, Cunningham MG. Zinc: The Brain's Dark Horse. Synapse 2009;63:1029–49.

40. Harper AR, Wang X, Moiseyev G, et al. Postnatal Chick Choroids Exhibit Increased Retinaldehyde Dehydrogenase Activity during Recovery from Form Deprivation Myopia. Invest Ophthalmol Vis Sci 2016;57:4886–97.

41. Zieg G, Chiappa M, Porter KS, et al. National Health and Nutrition Examination Survey: Plan and Operations, 1999–2010. Vital Health Stat 2013;1:111–21.

42. Bataninire BK, Cunningham MG. Zinc: The Brain's Dark Horse. Synapse 2009;63:1029–49.
Selenium, and Vitamins A, E and C in the Spanish Pop-
ulation: Findings from the ANIBES Study. Nutrients
2017;9:E697.

45. Moore LD, Le T, Fan G. DNA Methylation and Its
Basic Function. Neuropsychopharmacology 2012;38:
23–38.

46. Zhou X, Ji F, An J, et al. Experimental Murine Myo-
pia Induces Collagen Type Iα1 (COL1A1) DNA Methyla-
tion and Altered COL1A1 Messenger RNA Expression in
Sclera. Mol Vis 2012;18:1312–24.

47. Kelleher SL, McCormick NH, Velasquez V, et al.
Zinc in Specialized Secretory Tissues: Roles in the
Pancreas, Prostate, and Mammary Gland. Adv Nutr
2011;2:101–11.

48. Wang Y, Jia XF, Zhang B, et al. Dietary Zinc Intake
and Its Association with Metabolic Syndrome Indicators
among Chinese Adults: An Analysis of the China Nutritional
Transition Cohort Survey 2015. Nutrients 2018;10.

49. Cordain L, Eaton SB, Brand Miller J, et al. An Evolu-
tionary Analysis of the Aetiology and Pathogenesis of
Juvenile-onset Myopia. Acta Ophthalmol Scand 2002;
80:125–35.

50. Ahluwalia N, Dwyer J, Terry A, et al. Update on
NHANES Dietary Data: Focus on Collection, Release,
Analytical Considerations, and Uses to Inform Public
Policy. Adv Nutr 2016;7:121–34.

51. Wieringa FT, Dijkhuizen MA, Fiorentino M, et al. De-
termination of Zinc Status in Humans: Which Indicator
Should We Use? Nutrients 2015;7:3252–63.

52. Sternefeld B, Goldman-Rosas L. A Systematic Ap-
proach to Selecting an Appropriate Measure of Self-
reported Physical Activity or Sedentary Behaviour.
J Phys Act Health 2012;9(Suppl. 1):S19–28.

53. Moore JC, Stinson LL, Welnick EJ. Income Measure-
ment Error in Surveys: A Review. J Off Stat 2000;16:
331–61.