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Clinical Research Article

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Myopia and Early-Onset Type 2 Diabetes: A Nationwide Cohort Study

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Abbreviations: BMI, body mass index; HR, hazard ratio; IGF-1, insulin-like growth factor-1; SES, socioeconomic status; T2D, type 2 diabetes.

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Abstract

Context: A correlation between myopia and insulin resistance has been suggested.
Objective: We investigated the association between myopia in adolescence and type 2 diabetes (T2D) incidence in young adulthood.
Methods: This population-based, retrospective, cohort study comprised 1 329 705 adolescents (579 543 women, 43.6%) aged 16 to 19 years, who were medically examined before mandatory military service during 1993 to 2012, and whose data were linked to the Israel National Diabetes Registry. Myopia was defined based on right-eye refractive data. Cox proportional models were applied, separately for women and men, to estimate hazard ratios (HRs) for T2D incidence per person-years of follow-up.
Results: There was an interaction between myopia and sex with T2D ($P < .001$). For women, T2D incidence rates (per 100 000 person-years) were 16.6, 19.2, and 25.1 for those without myopia, and with mild-to-moderate and high myopia, respectively. These

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corresponded to HRs of 1.29 (95% CI, 1.14-1.45) and 1.63 (1.21-2.18) for women with mild-to-moderate and high myopia, respectively, compared to those without myopia, after adjustment for age at study entry, birth year, adolescent body mass index, cognitive performance, socioeconomic status, and immigration status. Results persisted in extensive sensitivity and subgroup analyses. When managed as a continuous variable, every 1-diopter lower spherical equivalent yielded a 6.5% higher adjusted HR for T2D incidence ($P = .003$). There was no significant association among men.

Conclusion: For women, myopia in adolescence was associated with a significantly increased risk for incident T2D in young adulthood, in a severity-dependent manner. This finding may support the role of insulin resistance in myopia pathogenesis.

Key Words: diabetes, myopia, epidemiology, insulin resistance, sex disparities

Myopia, the most common eye disorder, occurs when the eye's optical power is too strong for its axial length; this results in light rays from faraway objects focusing before the retina, causing a blurred image (1, 2). While the exact pathogenesis of myopia is not fully understood, both environmental and genetic factors are known to play a role (1). Myopia prevalence, and especially childhood and adolescent myopia, has been increasing throughout the globe in recent decades. This rise has mostly been attributed to changes in the environment and lifestyle that have been only partially identified (1). Moreover, a recent meta-analysis projected that by 2050 as much as half the world's population will have myopia, and nearly 10% will have high myopia (3). This is worrisome, as even when fully corrected, high myopia is associated with an increased risk of irreversible vision loss from various ocular pathologies (1).

Myopia has been suggested to be caused in part by hyperinsulinemia and insulin resistance (4, 5). Western diet, characterized by high glycemic load foods, induces insulin resistance; this leads to elevated insulin-like growth factor-1 (IGF-1), a potent growth stimulator, and reduced insulin-like growth factor binding protein-3. These changes have been suggested to induce scleral tissue growth and axial elongation, thus promoting myopia, particularly during periods of growth (4, 5). This intriguing notion, linking the "myopia boom" to the global rise in type 2 diabetes (T2D) and obesogenic diets in adolescents and young adults (6, 7) has been supported by more recent studies (8-15). However, to our knowledge no study has examined an association between myopia in childhood or adolescence and incident T2D. We speculate that if myopia is indeed, in part, an early manifestation of insulin resistance, then individuals with myopia would also be at an increased risk for T2D development later in life. Thus, the aim of the present study was to examine associations of myopia in adolescent women and men with incident T2D in a nationwide cohort of 1.3 million adolescents with a follow-up into young adulthood.

Materials and Methods

Study Design, Setting, and Population

In Israel, most Jewish citizens and some minorities are obliged to serve in the Israeli Defense Forces. As part of the draft process, they undergo a comprehensive medical evaluation (16) at the age of approximately 17 years, which includes a test for best-corrected visual acuity (17). In addition, data regarding socioeconomic status (SES), education, cognitive performance, and country of birth are also obtained. Fig. 1 shows the construction of the study sample. The study population included all adolescents, aged 16 to 19 years, examined at recruitment centers between January 1, 1993, the first year after which refractive data was consistently available for more than 90% of examinees, and December 31, 2012. Individuals were included in the analysis only if refractive data were available for both eyes, and if body mass index (BMI) data were available, given the critical role attributed to obesity in the development of diabetes among young adults. Individuals were not included in the analysis if they had antimetropia (ie, hypermetropia in one eye and myopia in the other eye), or diabetes or dysglycemia at the time of their examination as reported by their primary care physician. Individuals who attended the highly orthodox educational system, comprising only 2.2% of the targeted age group, were not included in the analysis. These adolescents were not routinely examined, and were subjected to a profoundly different educational system and lifestyle, which was shown to be highly associated with myopia (18). Last, individuals who died before the establishment of the Israel National Diabetes Registry in 2012 were not included because diabetes status before their death could not be determined. The final study sample consisted of 1 329 705 examinees (43.6% women; n = 579 543). Some ethnic minorities (mostly Arab adolescents of both sexes), highly orthodox Jewish individuals of both sexes, orthodox Jewish women, mothers, pregnant women, and married women are exempt from military service and are

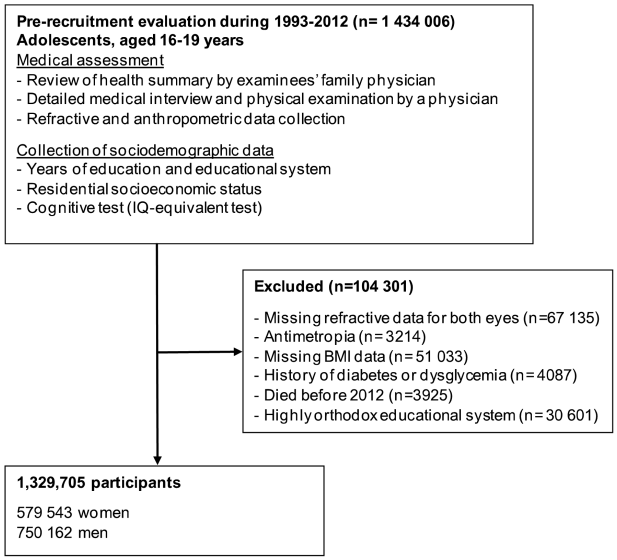

Figure 1. Study design and cohort composition.

thus underrepresented in this cohort. Data were stored in a central database. The institutional review board of the Israel Defense Forces Medical Corps approved the study and waived the requirement for written informed consent, while maintaining strict participant anonymity.

The Israel National Diabetes Registry and Diagnosis of Diabetes

The primary outcome of this study was incident T2D diagnosed by the Israel National Diabetes Registry. As previously described (6), since 2012, all health medical organizations in Israel are requested by law to annually report prevalent cases of diabetes to the Israel National Diabetes Registry. Data in this registry were linked to the Israel Defense Forces database using national identity numbers. This enabled linkage of medical and SES data obtained at adolescence, including refractive data, with diabetes incidence recorded later in life. Follow-up extended from the initial medical assessment until December 31, 2016. Diabetes was defined as meeting one or more of the following criteria in the previous year of the report to the registry: 1) glycated hemoglobin greater than or equal to 6.5% (47.5 mmol/mol), 2) serum glucose concentrations greater than or equal to 200 mg/dL (11.1 mmol/L) in 2 tests performed at an interval of at least 1 month, and 3) 3 or more purchases of glucose-lowering medications. The registry has a sensitivity of 95% and the positive predictive value is 93%.

While the Israel National Diabetes Registry does not contain data regarding the types of diabetes, it includes data on prescribed diabetes medications. Using these data, we differentiated individuals with a diagnosis of type 1 diabetes, which were not considered as valid cases and for whom the follow-up ended once they developed the disease (398 women; 640 men). This was defined as active treatment with short-acting insulin and meeting at least one of the following criteria: 1) the initiation of short-acting insulin treatment within 1 year of diabetes onset, and 2) the prescription of insulin treatment but not oral antidiabetic drugs. If information regarding glucose-lowering medications was missing, the diagnosis was referred to as diabetes of uncertain type. Gestational diabetes is not reported to the Israel National Diabetes Registry.

Refraction

As previously described (17), best-corrected visual acuity for examinees was determined by a qualified technician, using a standard Snellen chart. Examinees able to read at least all the letters but one on the 6/6 line without optical correction were assumed not to have myopia. Examinees who were able to read at least all the letters but one on the 6/6 line, when using optical correction, were assumed to be properly refracted and the power of the correction was recorded. Examinees unable to read all the letters but one on the 6/6 line underwent noncycloplegic autorefraction (Speedy K; Nikon Corp; KR-8000, KR7000S, and earlier models; Topcon) followed by subjective validation. For some, the refractive error was recorded using paper documentation of the refraction performed by an optometrist.

Myopia Definition

As the Pearson correlation coefficient for right and left eye spherical equivalent was high ($r = 0.93$, $P < .001$, after excluding 3214 individuals with antimetropia), only right eye data were used for homogeneous comparison (17).

As similarly performed (17), mild to moderate myopia was defined as –0.75 diopters (D) myopia or worse in each principal meridian in the right eye and a spherical equivalent of less than or equal to –0.75 D to greater than –6.00 D. High myopia was defined as –0.75 D myopia or worse in each principal meridian and a spherical equivalent of –6.00 D or lower in the right eye. In another subanalysis, very high myopia was defined as –0.75 D myopia or worse in each principal meridian and a spherical equivalent of –9.00 D or lower in the right eye.

Study Variables

Age at assessment and year of birth were treated as continuous variables. Date of birth was obtained from the Israeli Ministry of Internal Affairs database. Weight and height were measured barefoot and with undergarments, or only light clothes. BMI was calculated as weight in kilograms

divided by the squared height in meters. BMI and height were categorized using the US Centers for Disease Control and Prevention percentiles according to sex and age, as this classification was validated for the Israeli population (19). Years of education were categorized at a threshold of 11 years, as this represents the standard number of school years education that could be attained at the time of assessment. Educational system (secular, orthodox, and highly orthodox) was classified according to the school where the adolescent studied, using the Israeli Ministry of Education list, as similarly performed (17, 18). SES was based on place of residence at the time of assessment and classified into low, medium, and high (16). Cognitive performance was determined by a general intelligence score, which was shown to correlate by more than 85% with IQ, and classified into low (< −1 SD), medium (−1 to < 1 SD), and high (≥ 1 SD) (6).

Statistical Analysis

The incidence rate of T2D was calculated per person-years of follow-up. Cox proportional hazard models were applied to estimate hazard ratios (HRs) and 95% CIs for incident diabetes per myopia status; adolescents without myopia served as the reference. Covariates were added gradually. Analyses were performed separately for women and men given an interaction observed between myopia, sex, and incident T2D($P < .001$). Models were prespecified. First, unadjusted models were performed. Next, models were minimally adjusted for age at study entry and birth year. Fully adjusted models were further adjusted for BMI category, years of education, cognitive performance, SES, and immigration status. The fully adjusted model was also applied in subanalyses, in which myopia was treated as a continuous variable and that considered an additional very high myopia group. The assumption of proportionality of the hazards was visually confirmed for all variables. No interaction was observed between myopia and the time of incidence of T2D for women ($P = .68$) or men ($P = .15$).

Subgroup Analyses

First, to minimize confounding by coexisting morbidities, we restricted the Cox analysis to those with unimpaired health status at study entry, defined as the lack of any chronic comorbidity that requires medical therapy, or any history of cancer or a major operation (16). Second, to address the possibility of confounding due to the association that has been described between myopia and the orthodox educational system (17, 18), the main analysis was limited to men and women who had attended the secular educational system (Supplementary Fig. S1) (20). Finally, to address the possibility that the association between myopia and T2D was merely confounded by weight status, the study population was stratified according to BMI category and other model covariates at study entry (Supplementary Fig. S2) (20).

Sensitivity Analyses

To account for individuals with missing dates of T2D diagnosis (but the diagnosis was known to have occurred after myopia onset), logistic regression models were applied and the baseline characteristics of those who developed T2D with and without a date of diagnosis were compared (Supplementary Fig. S3 and Table S1) (20). Second, to minimize misclassification of T2Ddiagnosis, several sensitivity analyses were conducted (Supplementary Fig. S4) (20). Finally, we accounted for other possible confounding factors by several additional models, which included adjustment to height, educational system, and recently described T2D risk factors of this cohort (Supplementary Fig. S5) (20).

All the tests were 2-tailed, and statistical significance was defined as P less than .05. Statistical analyses were performed with SPSS version 25.0 (IBM Corp).

Results

Baseline characteristics of the 579 543 women and 750 162 men who were included in the study are presented in Table 1 according to myopia status. At study entry, mean age and BMI were similar across the study groups. Myopia was more prevalent among women than men (28.1% vs 23.4%). Most examinees attained at least 11 years education (97.5% of women; 93.1% of men) and were born in Israel (82.2% of women; 81.1% of men). The proportions who were Israeli born, with high cognitive score, and with high SES were higher among those with than without myopia, for both sexes (see Table 1).

An interaction was observed between myopia and sex, with incident T2D ($P < .001$). Among women, 1414 incidences of type 2 diabetes were recorded during 8 087 922 person-years. Among men, 2856 incidences were recorded during 10 490 979 person-years. Mean follow up periods for both sexes were 14.0 ± 5.7 years.

For women, T2D incidence (per 100 000 person-years) increased with the presence and severity of myopia: 16.6 (95% CI, 15.6-17.7), 19.2 (95% CI, 17.4-21.2), and 25.1 (95% CI, 18.7-33.1) for those without myopia, with mild-to-moderate, and with high myopia, respectively (Table 2). An unadjusted Cox model analysis yielded HRs of 1.22 and 1.53 in the 2 latter groups, respectively; and was nearly unchanged in the fully adjusted model; 1.29 (95% CI, 1.14-1.45; $P < .001$) and 1.63 (95% CI, 1.21-2.18; $P = .001$), respectively (see

Table 1. Characteristics of the study cohort at baseline, according to myopia categories

		Total	No myopia	Myopia level	
				Mild-moderate	High
Women					
	Examinees, No.	579 543	416 598	149 780	13 165
	Mean age ± SD, y	17.2 ± 0.4	17.2 ± 0.4	17.2 ± 0.4	17.3 ± 0.4
	Mean BMI ± SD	21.8 ± 3.7	21.8 ± 3.7	21.9 ± 3.7	21.9 ± 3.8
	With obesity, %	4.0	3.9	4.1	4.0
	Mean height ± SD, cm	162.2 ± 6.2	162.1 ± 6.2	162.2 ± 6.3	162.6 ± 6.4
	≥ 11 y education, %	97.5	97.1	98.4	98.7
	High cognitive score, %	9.9	8.7	12.7	16.1
	High socioeconomic status, by residence, %	22.9	22.5	23.6	25.2
	Israeli born, %	82.2	81.6	83.6	85.0
Men					
	Examinees, No.	750 162	574 302	160 715	15 145
	Mean age ± SD, y	17.3 ± 0.5	17.3 ± 0.5	17.3 ± 0.5	17.4 ± 0.5
	Mean BMI ± SD	22.0 ± 3.8	22.0 ± 3.7	22.0 ± 3.8	21.9 ± 3.9
	With obesity, %	6.5	6.4	6.8	6.7
	Mean height ± SD, cm	174.2 ± 6.8	174.2 ± 6.8	174.2 ± 6.9	174.2 ± 7.0
	≥ 11 y education, %	93.1	92.3	96.0	95.4
	High cognitive score, %	14.3	12.5	19.8	23.1
	High socioeconomic status, by residence, %	20.1	19.8	21.1	20.2
	Israeli born, %	81.1	80.2	83.8	87.2

Abbreviation: BMI, body mass index.

Table 2, Fig. 2). In a fully adjusted analysis in which myopia was treated as a continuous variable, the HR for T2D incidence was 6.5% higher for each diopter deduction in spherical equivalent (HR 1.065; 95% CI, 1.021-1.110; $P = .003$). In a sensitivity analysis that further defined very high myopia, T2D incidence was 32.6 (95% CI, 17.1-56.6) per 100 000 person-years and the adjusted HR was 1.95 (95% CI, 1.08-3.54; $P = .03$). The association between myopia and incident T2D persisted for women in the various subgroup and sensitivity analyses (Supplementary Figs. S1-S5) (20).

In men, T2D incidence per 100 000 person-years was highest among those with high myopia (31.6; 95% CI, 24.7-39.9); however, those with mild-to-moderate myopia had a lower incidence per 100 000 person-years (24.9; 95% CI, 22.8-27.0) than those without myopia (27.7; 95% CI, 26.6-28.9). The HRs for the unadjusted and fully adjusted models in men were not statistically significant for those with myopia compared to those without (see Table 2, Fig. 2). Subgroup and sensitivity analyses for men also did not show a consistent or significant association between myopia and incident T2D (see Supplementary Figs. S1-S5) (20).

Discussion

In this nationwide, population-based cohort study, we found that women, but not men, with myopia at adolescence were at an increased risk for T2D development later in life. This risk rose gradually with increasing myopia status, from 29% to 63% and more than 95% adjusted HR for women with mild-to-moderate, high, and very high myopia, respectively. The adjusted HR for incident T2D was 6.5% higher for every 1-diopter lower spherical equivalent.

The prevalence of diabetes worldwide has quadrupled, from 108 million people in 1980 to 463 million in 2019 (7, 21). The prevalence in myopia has paralleled this increase, with an estimated global rise from 22.9% in 2000 to 34.0% in 2020 (3). Myopia and T2D share a number of common risk factors. As societies around the world are becoming more modernized, some risk factors of myopia, such as screen time, educational stress, and time indoors, are increasing. However, these factors, coupled with the energy-rich Western diet, also correlate with a more sedentary lifestyle, physical inactivity, and being overweight or obese (22, 23), which are all linked to cardiometabolic morbidity, including T2D (6, 21). Furthermore, myopia may preferably drive indoor activity and thereby increase diabetes risk. Nonetheless, accumulating evidence suggests that myopia and T2D potentially share a pathophysiological pathway, which is mediated by insulin resistance (24). Studies on chick eyes demonstrated that receptors for insulin and IGF-1 are expressed in the sclera, choroid, and retina (14, 15); and that intravitreal injections of insulin and IGF-1 induced

Table 2. Risk estimates of the association between adolescent myopia and incident type 2 diabetes in young adulthood

		Total	No myopia	Myopia level	
				Mild-moderate	High
Women					
	Examinees, No.[a]	578 331	415 757	149 445	13 129
	Incident type 2 diabetes, No.	1414	974	393	47
	Mean follow-up ± SD, y	14.0 ± 5.7	14.1 ± 5.8	13.7 ± 5.6	14.3 ± 5.5
	Person-y of follow-up	8087922	5859221	2041584	187117
	Incidence[a] (per 10^{-5} person-y)	17.5	16.6	19.2	25.1
	95% CI	16.6-18.4	15.6-17.7	17.4-21.2	18.7-33.1
	Unadjusted HR		1	1.22	1.53
	95% CI			1.08-1.37	1.14-2.05
	P			.001	.004
	Adjusted[b] HR		1	1.29	1.63
	95% CI			1.14-1.45	1.21-2.18
	P			< .001	.001
Men					
	Examinees, No.[a]	749 334	573 658	160 547	15 129
	Incident type 2 diabetes, No.	2856	2247	542	67
	Mean follow-up ± SD, y	14.0 ± 5.7	14.1 ± 5.7	13.6 ± 5.6	14.0 ± 5.7
	Person-y of follow-up	10 490 979	8 099 684	2 179 588	211 707
	Incidence[a] (per 10^{-5}person-y)	27.2	27.7	24.9	31.6
	95% CI	26.2-28.2	26.6-28.9	22.8-27.0	24.7-39.9
	Unadjusted HR		1	0.96	1.15
	95% CI			0.87-1.05	0.90-1.47
	P			.35	.25
	Adjusted[b] HR		1	1.09	1.23
	95% CI			0.99-1.20	0.96-1.57
	P			.09	.10

Abbreviation: HR, hazard ratio.

[a]Participants included in the survival analysis.

[b]Adjusted for age at study entry, birth year, body mass index category, years of education, cognitive performance score, immigration status, and socioeconomic status. Input from 5056 (0.9%) women and 9076 (1.2%) men were excluded from the adjusted analysis because of missing data.

a considerable increase in ocular elongation rate and myopia (9, 11). A combination of IGF-1 and fibroblast growth factor-2 induced extreme myopia, in excess of 15 diopters in chick eyes (15). Furthermore, insulin and IGF-1 were shown to surpass the inhibitory effect of plus lenses on eye elongation in chick models (9). In humans, *IGF-1* gene polymorphism was associated with myopia in several populations (25-27), with some genotypes associated with increased IGF-1 levels (25). However, these results were contradicted elsewhere (28, 29). Notably, among individuals with primary growth hormone receptor insensitivity (Laron syndrome), the mean ocular axial length was significantly longer in those treated than not treated with supplemental IGF-1 (22.53 ± 0.81 vs 21.94 ± 1.74 mm) (13). We are unaware of any other cohort studies that examined a temporal correlation between juvenile or adolescent myopia and later-onset T2D. Evidence of an association between myopia and diabetes is limited to cross-sectional studies, and cohort studies that predominantly included older patients or those with poorly controlled diabetes in whom a myopic shift was attributed to lens-induced changes brought on by hyperglycemia (30-33). Such studies may also be confounded by a myopic shift associated with cataract, which, like the prevalence of T2D, also increases with age (2, 21).

We found that women, but not men, with myopia at adolescence were at an increased risk for developing T2D in young adulthood, even though T2D incidence was higher in men. We speculate that this sex dimorphism may be attributed to differences in insulin resistance during childhood and early adolescence, which are critical periods for myopia development (17, 34, 35). Puberty, which starts at an earlier age in girls than boys, is known to increase insulin resistance and IGF-1 levels (36, 37). Furthermore, data from the Early Bird Study showed higher insulin resistance and IGF-1 levels in girls than boys from as early as age 5 years (36)—a difference that was sustained until late adolescence (38). Thus, juvenile-onset myopia may be in part a manifestation of high circulating insulin or IGF-1 levels, and girls are

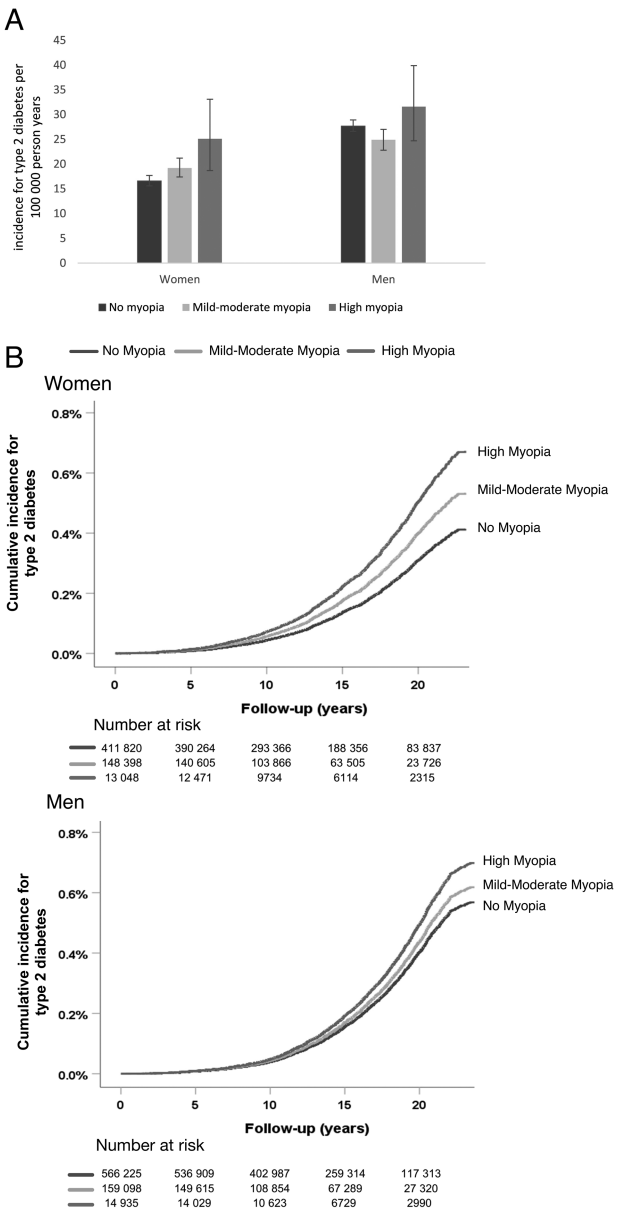

Figure 2. The association between adolescent myopia and incident type 2 diabetes in young adulthood. A, The histogram shows incidence values per 100 000 person-years. B, Adjusted Cox one-minus survival curves. The number of individuals at risk is indicated below each panel for the given myopia status.

more insulin resistant than boys during myopiagenic-sensitive ages. Supporting this notion is a reported inverse association of later age at menarche with myopia severity (39). Moreover, the latter findings coincide with several studies that found a higher prevalence of myopia in adolescent women than men (17, 40-42). Furthermore, a similar sex asymmetry was demonstrated by the recent report of increased probability of myopia among girls with high refined carbohydrate consumption, and decreased risk among boys (12).

Understanding myopia pathogenesis may help slow its rising prevalence and associated global economic burden, which was estimated at US $244 billion (for uncorrected myopia) for the year 2015 (43). If insulin resistance is indeed involved in the development of myopia, preventive efforts should focus also on dietary and physical activity habits. However, regardless of underlying mechanisms and mediators, myopia may at least serve as a risk marker in women for early-onset T2D. The latter poses a considerable public health burden that has increased disproportionately in the last decade, afflicting an estimated 4.9 million individuals in the United States alone, in 2018 (7, 44).

This study has several limitations. First, we assessed noncycloplegic refraction, which may lead to myopia overestimation (1). However, to reduce over classification of myopia we used a threshold of less than or equal to –0.75 D, compared to less than or equal to –0.50 D (17). We also lacked data on cumulative exposure to myopia. Second, we lacked lifestyle data at childhood, baseline, and throughout the study period including screen-time exposure, outdoor time, diet, and physical activity habits. Of note, the results were nearly unchanged after adjustment and stratification of BMI category, which may be a good surrogate for lifestyle-related variables (45). Finally, we lacked active screening of blood glucose levels and other indexes for insulin resistance at baseline and throughout the cohort. The strengths of the study include the systematic collection of measured refraction, weight, and height; and the comprehensive assessment of overall health status and sociodemographic data. The linkage of 2 national databases provided high case density and mitigated selection bias.

To conclude, women with myopia at adolescence are at an increased risk for T2D in early adulthood, in a severity-dependent manner. This may support the role of insulin resistance in myopia pathogenesis. Risk reduction of concomitant diabetes risk factors is warranted in this population. Further studies are needed to examine this association for other populations.

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Author Contributions: A.P. and G.T. conceived and designed the study, analyzed and interpreted the data, and drafted and revised the manuscript. I.Z., M.L., and D.T. conducted database management quality assurance, interpreted the data, contributed to the discussion, and critically revised the manuscript. J.M., O.P.H., A.E.L., Y.M., E.P., T.C.Y., O.M., A.T., H.C.G., and A.A. interpreted the data, contributed to the discussion, and critically revised the manuscript. E.D. conducted the statistical analysis and interpreted the data. G.T. is the guarantor of this work and as such had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Additional Information

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Disclosures: The authors have nothing to disclose.

Data Availability: The current data set is subject to military restrictions, and therefore its availability is limited. Data request or queries may be addressed to the corresponding author.

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