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The influence of alcohol intake in myopia development or progression: The SUN cohort study

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ABSTRACT

Background: Myopia is a highly prevalent disorder, and one of the first causes of blindness. In turn, alcohol consumption has been shown to be a risk factor for many diseases and a main contributor to the global burden of disease. However, no studies have investigated the relationship between alcohol intake and myopia. Our aim was to prospectively assess the association between alcohol intake and the development or progression of myopia.
Methods: In a Spanish dynamic prospective cohort (the SUN Project) we assessed 15,642 university graduates, recruited between 1999 and 2018 and followed up biennially through mailed questionnaires. Alcohol intake was assessed with a validated 136-item food frequency questionnaire. Development or progression of myopia was collected in subsequent questionnaires during follow-up every two years.
Results: Alcohol intake was linearly and significantly associated with a higher risk of myopia development or progression: the OR for 10-year incidence/progression of myopia was 1.05, 95% CI 1.01–1.09 per each 10-grams increase in alcohol intake.
Conclusions: Alcohol consumption might lead to the development or progression of myopia, although confirmation is needed for the mechanisms through which this association may occur, thus further research is needed to verify these findings.

1. Introduction

Uncorrected refractive error (URE) has been described as the first cause of moderate and severe vision impairment and the second cause of blindness globally (Bourne et al., 2013). In the past years an important increase in the prevalence of myopia all around the world has been observed, with a global estimate of 2.6 billion people as of 2020, and this growth is expected to continue in the years to come (Holden et al., 2016; World Health Organization (WHO), 2019). In 2009 the World Health Organisation (WHO) estimated a global economic burden for URE of $ 268.8 billion after adjustment for country-specific labour force and employment rates (Smith et al., 2009). The epidemiological importance of this disease is, thus evident.

The aetiology of myopia is rather complex, heterogeneous and not fully identified yet, with evidence suggesting the influence of intertwining genetic and environmental factors such as the level of education, the amount of near-work, the time spent outdoors or sleep duration (Enthoven et al., 2019; Jee et al., 2016; Michelle et al., 2018; Rose et al., 2016).

It is known, though, that myopia is associated with many other comorbid health conditions. Regarding eye pathologies, it has been linked to the development of cataracts, glaucoma, or myopic macular degeneration, which are major sources of disability in themselves. High myopia (myopia greater than six diopters) has been shown to be a risk

Abbreviations: BMI, Body Mass Index; BMR, Basal Metabolic Rate; cAMP, cyclic Adenosine Monophosphate; ECM, extracellular matrix; FFQ, Food Frequency Questionnaire; MD, Medical Doctor; MET, Metabolic Equivalent; OR, Odds Ratio; SUN, Seguimiento Universidad de Navarra (University of Navarra Follow-up Study); TGF-β, transforming growth factor-beta; URE, Uncorrected Refractive Error; WHO, World Health Organization.

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factor for the development of psychiatric disorders such as depression and anxiety (Morgan et al., 2012; Yokoi et al., 2014). Moreover, even when corrected, patients who suffer from myopia have a decreased quality of life compared to controls (Chen et al., 2007; Kandel et al., 2017; Rose et al., 2000).

In turn, alcohol consumption has been previously associated with different eye conditions. Its role in eye damage in foetal alcohol syndrome has been widely studied and corroborated (Strömland and Dolores Pinazo-Durán, 2002; Wozniak et al., 2019). These findings suggest that alcohol's influence in the eye may go back to its developmental origins. Regarding its effect on visual function, various studies have reported an association between alcohol consumption and colour vision impairment, however this was primarily explained through a central information processing rather than a problem with the eye itself (Brasil et al., 2015; Castro et al., 2009; Martins et al., 2019). Regarding acute alcohol consumption, several studies from the past century found significant changes in visual acuity with increasing amounts of ethanol, although this information contradicted previous findings on this potential association (Hill and Toffolon, 1990; Watten and Lie, 1996; Wilson and Mitchell, 1983).

To our knowledge, no studies have yet assessed the long-term association between usual alcohol consumption and the subsequent incidence or increase of myopia. Our hypothesis was that alcohol consumption will be associated with a higher incidence and/or progression of myopia.

We believe this study will be useful for health professionals and scientific researchers, as it may help enlighten the scientific community about possible modifiable activities to help reduce the increasing prevalence of myopia and will perhaps open a new line of research in the modifiable risk factors of this highly prevalent eye condition.

2. Materials and methods

2.1. Study design

This piece of research is part of the "Seguimiento Universidad de Navarra" (SUN) study, which is a prospective cohort study, with the recruitment continually open (i.e., a dynamic design). The participants are Spanish university graduates and more than 50% of them are health professionals themselves. The design and methods of the SUN prospective cohort have been described in sufficient detail elsewhere (Martínez-González, 2006; Seguí-Gómez et al., 2006). It uses information from mailed questionnaires regarding lifestyles, health conditions and dietary habits, which are sent to participants every two years from the date of their admission to the study. Informed consent for their participation in the study is implied when an answer to the first questionnaire is received, and participants are informed of their right to refuse to participate or to withdraw their consent to participate at any time. The study protocol was made following the Declaration of Helsinki, and it was accepted by the Institutional Review Board of the University of Navarra.

Information on the number of participants who were included for this study is shown in Fig. 1. A total of 22,894 participants had been recruited in the SUN study as of December 12th 2018 and had therefore agreed to participate. Of those, information from 341 could not be used as they had been in the Study for less than 2 years and 9 months, and follow-up information about refractive change was not available yet (we allowed for 9 extra months to await for their response to the 2-year follow-up questionnaire). Among the rest of participants (22,553), there were 1979 participants who were lost for follow up (global retention: 91.23%), which left 20,574 participants available for analyses. Another group of 1244 had prevalent or incident cataracts, and were excluded as this diagnosis generally implies a change in distance or near vision (DynaMed, n.d.); this exclusion left 19,330 candidates. We also removed 538 participants because they were pregnant or in labour when they answered their questionnaires, situations which have been

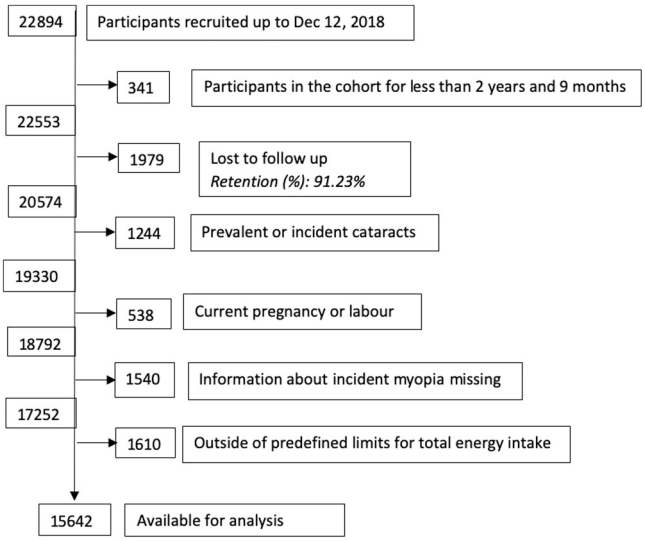

Fig. 1. Flowchart of participants. The SUN Project 1999–2019.

shown to have an influence in diopter changes, and also pregnant women are instructed not to drink alcoholic beverages during their pregnancy (Fernández-Montero et al., 2017; Pizzarello, 2003). From the 18,792 volunteers left, information about incident myopia was missing in 1540; and 1610 had total energy intake in their food frequency questionnaires outside of predefined limits, which means that they were above 3500 or 4000 Kcal/d or below 500/800 Kcal/d (women and men respectively) on their total energy intake and were therefore excluded as we understand these answers probably mean that they did not comprehend well what they were being asked or that another error of the sort might have occurred. All this made information about 15,642 participants available for analysis, which was our total sample size.

2.2. Alcohol consumption assessment

The baseline questionnaire included a total of 136 items in a semi-quantitative food-frequency questionnaire (FFQ). This FFQ has been validated in various occasions. The correlation coefficient was 0.88 when compared to four four-day food records (De La Fuente-Arrillaga et al., 2010; Fernandez-Ballart et al., 2010; Martin-Moreno et al., 1993). Participants were asked how often (never/almost never; 1–3 times a month; 1, 2–4, 5–6 times a week; 1, 2–3, 4–6 or $\geq$ 6 times a day) they consumed a specific serving of red wine, other type of wine, beer or distilled beverages. Alcohol consumption is re-evaluated 10 yeas later with another FFQ. In these calculations, the mid-value of the frequency range was imputed (e.g. for the 1–3 times a month, 2 times a month was used). For the $>$ 6 times a day category, a frequency of 7 was used, adding to the lower bound of the range half of the width of the previous range. This is a common practice in nutritional epidemiology. Taking into account the specific serving sizes and the mean pure alcohol concentration in each type of beverage, the information about each type of alcoholic beverage was then translated into grams of alcohol per day.

2.3. Myopia assessment

In the follow-up questionnaires sent to the participants separated two years each from the previous one, a question was included that inquired on whether they had been diagnosed by a doctor with myopia for the first time or with an increase in more than ½ myopic diopter since they had answered the previous questionnaire. Participants self-reported the diagnosis and the approximate date of diagnosis and, additionally, they reported the exact eye prescription information at the 8th year questionnaire. Since we had no information on myopia at the

baseline questionnaire, we cannot distinguish between incidence of myopia and its progression, and thus we considered them both as a joint entity throughout these analyses.

2.4. Covariate assessment

We considered as covariates the following: age, body mass index (BMI), years of university, television use (h/week), computer use (h/week), sleep (h/week), leisure time, physical activity (METs-h/week) and tobacco use (never, current, former). Information about them was obtained from the baseline questionnaire.

In order to assess participants' physical activity, Metabolic Equivalents (METs) were used. This was calculated using a frequency questionnaire based on the one used in Harvard School of Public Health and validated for our cohort which evaluates how much time per week is spent doing 17 different types of physical activity, as well as the number of months per year these activities are done (Ainsworth et al., 2011; Martínez-González et al., 2005). A certain number of METs is attributed to each activity, where METs represent the metabolic expenditure compared to the basal metabolic rate (BMR) – meaning that 2 METs is two times the BMR. Adding up the 17 activities and considering the time, total METs-h/week are calculated.

2.5. Statistical analysis

First, we made a description of baseline characteristics of our participants according to their consumption of alcohol classified into five categories (0 g, >0 and ≤10 g, >10 and ≤20 g, >20 and ≤30 g and >30 g). We described the following: age (years), body mass index (BMI, kg/m^2), TV use (h/week), computer use (h/week), physical activity (METs-h/week), sleep (h/week), university studies (years), sex (%) and tobacco use (never smokers, current smokers, former smokers; %). For the quantitative variables, means and standard deviation were calculated, whereas percentages were used for the qualitative ones.

Regarding the analytical process, a multivariable-adjusted logistic regression analysis was performed that prospectively assessed the association between alcohol intake -both as a continuous variable in grams and as categorical variable made up of the five categories explained above- and the incidence or progression of myopic dioptres. The models were adjusted both for sex and age, and for all the covariates stated before: age, BMI, years of university, television use (h/week), computer use (h/week), sleep (h/week), leisure time physical activity (METs-h/week) and tobacco use (never, current, former).

This was done taking the alcohol consumption data from the baseline questionnaire and assessing its influence on the incidence/progression in myopic dioptres in two-, four-, six- and eight-year periods. For this analysis, all participants with any available information were included – for instance, a participant with 4 years of follow-up was included in the 10-year incidence analysis, but only contributed with 4 years of follow-up. The same analysis was repeated using the alcohol intake data from questionnaire number 10 and assessing its association with the incidence/increase of myopia in two-, four- and six-year periods using the questionnaires that followed. The same models were repeated for only male and for only female participants.

In order to assess the linearity of the association, a restricted cubic spline model was fitted (Desquilbet and Mariotti, 2010).

Finally, in order to rule out possible sources of bias, a sensitivity analysis was performed using the variable alcohol intake as continuous in grams per day, and stratifying the participants by sex (men, women), age (<30, 30–50, >50) and body mass index (<22.96 kg/m^2, >22.96 kg/m^2), as well as occupation (health professionals, non-health professionals, Medical Doctors (MD), not MD), diagnosis of myopia at baseline (no myopia at baseline, myopia present at baseline), although information about myopia at baseline was not available, it was possible to obtain a rough estimate by using the exact eye prescription information that was obtained from the 8th year questionnaire and subtracting the self-reported increase or progression of "0.5 dioptres or more" from the previous questionnaires, which would then give us a maximum estimate of the graduation at baseline; this was also done with the objective of increasing sensitivity of the self-reported diagnosis of myopia, excluding participants with other refraction problems (no astigmatism, no hyperopia, no astigmatism or hyperopia) and additionally adjusting for hours of near-sight work. The stratification by occupation was performed in order to assess whether the sensitivity of the self-reported diagnosis of myopia could increase with augmenting knowledge about matters of health. We excluded participants with other refraction problems again in order to increase sensitivity of the diagnosis, as it was possible for participants to have made a mistake in answering the questionnaire and marked, for example, two opposing refractory problems (i.e. myopia and hyperopia), or maybe stated an increase in myopia when the increase could have been in the astigmatism they reported suffering from. Lastly, adjustment for hours of near-sight work was done using information from questionnaire from the 8th year, and assuming it would be similar to that at baseline; it is for this reason this adjustment could not be included in the main multivariable analysis.

3. Results

Table 1 shows the baseline characteristics of the 15,642 participants categorised according to their alcohol intake. Higher alcohol consumption (>30 g) was associated with being older (mean 46.8 years of age), having a higher BMI (mean 25.9 kg/m^2), sleeping less hours per week (mean 49.7), being male (85.5%) and being current or former smokers (31.3% and 50.6%, respectively).

The logistic regression model showed a direct association between alcohol intake and myopia incidence/progression, both when consumption of alcohol was categorised and when it was kept as a continuous variable, with statistical significance for the continuous analysis and for some of the categories throughout all the time periods assessed, as it is shown in Table 2. In the study of alcohol intake as a continuous variable, the following results were obtained for each additional 10-grams increase in alcohol intake: odds ratio (OR) for 2-year incidence/

Table 1
Distribution of baseline characteristics of participants according to alcohol consumption.

Alcohol (g/day)	0	> 0 & ≤ 10	> 10 & ≤ 20	> 20 & ≤ 30	> 30
N	3229	9224	2070	623	496
Age (years)	36.3 (11.3)	36.4 (11.2)	38.7 (11)	44.3 (11.5)	46.8 (9.9)
BMI (kg/m^2)	22.9 (3.5)	23.3 (3.4)	24.3 (3.3)	25.1 (3.4)	25.9 (3.4)
TV use (h/week)	11.2 (8.7)	11.1 (8)	11.3 (7.6)	11.3 (7.2)	11.4 (7.2)
Computer use (h/week)	14.1 (13.7)	15.5 (13.5)	16.9 (13.4)	15.7 (12.6)	15.7 (12.8)
Physical activity (METs-h/week)	20.2 (24.1)	21.6 (22)	24.6 (24)	25.7 (22.9)	22.7 (22.3)
Sleep (h/week)	51.3 (5.4)	51.4 (5)	50.8 (4.9)	50.2 (5)	49.7 (5.3)
University studies (years)	4.87 (1.46)	5.04 (1.5)	5.28 (1.57)	5.24 (1.58)	5.19 (1.48)
Sex					
Male (%)	21.6	36.2	61.9	74.8	85.5
Female (%)	78.4	63.8	38.1	25.2	14.5
Tobacco use					
Never smokers (%)	65.4	50.2	35.8	26.6	18.1
Current smokers (%)	14.8	21.8	30.2	29.8	31.3
Former smoking (%)	19.8	28	34	43.5	50.6

[1] Unless stated otherwise, mean (SD).

Table 2
Association between alcohol intake and the incidence or progression of myopia. OR (95% CI) for incidence or progression in myopic diopters according to alcohol intake.

Alcohol consumption (g/day)	0	> 0 & ≤ 10	> 10 & ≤ 20	> 20 & ≤ 30	> 30	per every 10 g
Baseline alcohol intake and 2-year incidence/progression of myopia						
Cases/N	326/3229	976/9224	194/2070	62/623	45/496	1603/15,642
Age and sex-adjusted model	1 (ref)	1.11 (0.97–1.27)	1.13 (0.93–1.37)	1.35 (1.01–1.82)	1.30 (0.92–1.82)	1.07 (1.02–1.13)
Multi-variable adjusted model[a]	1 (ref)	1.12 (0.97–1.28)	1.14 (0.93–1.39)	1.37 (1.02–1.85)	1.31 (0.93–1.85)	1.07 (1.02–1.14)
Baseline alcohol intake and 4-year incidence/progression of myopia						
Cases/N	497/3229	1400/9224	289/2070	103/623	76/496	2365/15,642
Age and sex-adjusted model	1 (ref)	1.03 (0.92–1.15)	1.05 (0.90–1.24)	1.40 (1.10–1.78)	1.31 (1.00–1.73)	1.07 (1.03–1.12)
Multi-variable adjusted model[a]	1 (ref)	1.03 (0.92–1.16)	1.07 (0.90–1.26)	1.43 (1.12–1.82)	1.35 (1.02–1.78)	1.08 (1.03–1.13)
Baseline alcohol intake and 6-year incidence/progression of myopia						
Cases/N	583/3229	1623/9224	343/2070	121/623	83/496	2753/15,642
Age and sex-adjusted model	1 (ref)	1.01 (0.91–1.12)	1.04 (0.89–1.21)	1.32 (1.05–1.66)	1.11 (0.86–1.45)	1.05 (1.00–1.09)
Multi-variable adjusted model[a]	1 (ref)	1.02 (0.91–1.13)	1.05 (0.90–1.23)	1.35 (1.07–1.70)	1.14 (0.87–1.49)	1.05 (1.01–1.10)
Baseline alcohol intake and 8-year incidence/progression of myopia						
Cases/N	633/3229	1753/9224	376/2070	126/623	92/496	2980/15,642
Age and sex-adjusted model	1 (ref)	1.00 (0.90–1.11)	1.04 (0.90–1.20)	1.23 (0.99–1.54)	1.12 (0.87–1.44)	1.04 (1.00–1.09)
Multi-variable adjusted model[a]	1 (ref)	1.01 (0.92–1.12)	1.05 (0.91–1.12)	1.26 (1.01–1.58)	1.14 (0.89–1.48)	1.05 (1.01–1.09)
Baseline alcohol intake and 10-year incidence/progression of myopia						
Cases/N	695/3229	1911/9224	419/2070	140/623	104/496	3269/15,642
Age and sex-adjusted model	1 (ref)	0.99 (0.89–1.09)	1.04 (0.90/1.20)	1.22 (0.99–1.51)	1.12 (0.88–1.43)	1.04 (1.00–1.09)
Multi-variable adjusted model[a]	1 (ref)	1.00 (0.90–1.10)	1.06 (0.91–1.22)	1.25 (1.01–1.55)	1.15 (0.90–1.47)	1.05 (1.01–1.09)
10-year questionnaire alcohol intake and 12-year incidence/progression of myopia						
Cases/N	27/803	136/2524	34/651	8/174	10/160	215/4312
Age and sex-adjusted model	1 (ref)	1.52 (0.99–2.32)	1.38 (0.81–2.34)	1.16 (0.51–2.64)	1.48 (0.68–3.20)	1.01 (0.89–1.15)
Multi-variable adjusted model[a]	1 (ref)	1.49 (0.97–2.28)	1.32 (0.77–2.26)	1.08 (0.47–2.48)	1.32 (0.60–2.90)	0.99 (0.72–1.42)
10-year questionnaire alcohol intake and 14-year incidence/progression of myopia						
Cases/N	44/803	203/2524	58/651	16/174	14/160	335/4312
Age and sex-adjusted model	1 (ref)	1.43 (1.02–2.01)	1.52 (1.00–2.31)	1.50 (0.81–2.76)	1.50 (0.81–2.76)	1.04 (0.94–1.15)
Multi-variable adjusted model[a]	1 (ref)	1.41 (1.00–1.98)	1.46 (0.95–2.23)	1.42 (0.76–2.63)	1.31 (0.68–2.52)	1.04 (0.79–1.38)
10-year questionnaire alcohol intake and 16-year incidence/progression of myopia						
Cases/N	59/803	228/2524	67/651	16/174	17/160	387/4312
Age and sex-adjusted model	1 (ref)	1.21 (0.89–1.63)	1.34 (0.92–1.96)	1.16 (0.64–2.09)	1.33 (0.73–2.09)	1.05 (0.96–1.16)
Multi-variable adjusted model[a]	1 (ref)	1.19 (0.87–1.61)	1.28 (0.87–1.88)	1.09 (0.60–1.97)	1.26 (0.69–2.29)	1.04 (0.94–1.14)
10-year questionnaire alcohol intake and 18-year incidence/progression of myopia						
Cases/N	62/803	238/2542	72/651	17/174	19/160	408/4312
Age and sex-adjusted model	1 (ref)	1.21 (0.90–1.62)	1.40 (0.97–2.03)	1.20 (0.67–2.14)	1.46 (0.83–2.58)	1.07 (0.97–1.17)
Multi-variable adjusted model[a]	1 (ref)	1.19 (0.88–1.60)	1.35 (0.93–1.96)	1.12 (0.63–2.01)	1.39 (0.78–2.47)	1.05 (0.96–1.15)

[a] Adjusted for sex, age, BMI, years of university, television use (h/week), computer use (h/week), sleep (hours/week), leisure time physical activity (METs-h/week), tobacco use (never, current, former).

progression 1.07, 95% CI 1.02–1.14; OR for 4-year incidence/progression 1.08, 95% CI 1.03–1.13; OR for 10-year incidence/progression 1.05, 95% CI 1.01–1.09. In the categorised analysis, the results showed an ascending trend of myopia increase/progression with increasing amounts of alcohol consumption, the group of alcohol consumption > 20 and ≤ 30 g being the one that showed the greatest association in every time period assessed, with statistically significant results (OR for 2-year incidence/progression 1.37, 95% CI 1.02–1.85; OR for 4-year incidence/progression 1.43, 95% CI 1.12–1.82; OR for 10-year incidence 1.25, 95% CI 1.01–1.55) as compared to the abstainers group. A positive association was also found when we performed the analysis using data from the 10-year follow-up questionnaire onwards, although statistical significance was generally lost probably due to a lack of power because of a reduced sample size (N = 4312). Additional adjustment for prevalent diabetes, height and antidepressants use did not change the results. Excluding from the model one covariate at a time neither substantially changed the main results. When the analysis was repeated stratifying by sex, similar results were obtained, as can be seen in tables S1 and S2; and when we restricted the analysis to only those participants who were followed-up for the whole period, the results did not substantially change.

The restricted cubic spline model shown in Fig. 2 interestingly captures the linearity of the association between the two variables, with confidence intervals that overall do not include the null value. This linear association is, however, constricted to the observed range of alcohol intake and may depart from linearity for higher levels of intake.

Finally, in the multiple sensitivity analyses performed (Table 3), the association between alcohol intake and myopia increase/incidence was similar to that found in the main analysis, with values for OR ranging between 1.04 and 1.13 for each 10 g/d increase in alcohol intake. No significant differences were found in any of the stratifications.

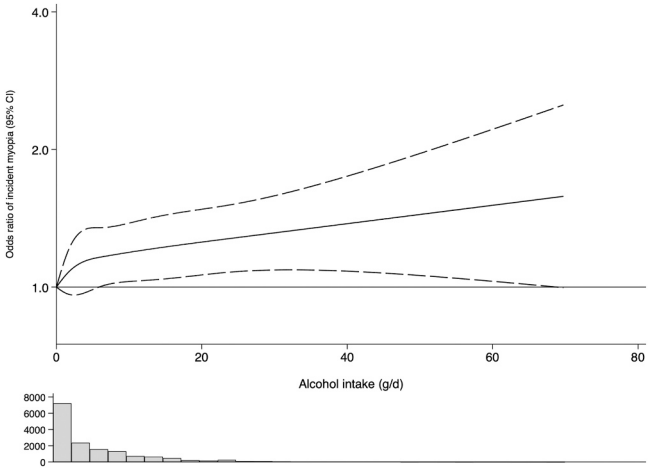

Fig. 2. Association between alcohol intake and incidence or progression of myopia (restricted cubic spline).

4. Discussion

To our knowledge, this is the first prospective study to ever assess the

Table 3
Sensitivity analyses for incidence or progression in myopic dioptres according to alcohol consumption (per every 10 g per day).

	Cases/N	OR (95% CI)	p value	p for interaction
Overall	1603/ 15,642	1.07 (1.02–1.14)	0.011	
Sex				
Men	502/ 6211	1.04 (0.97–1.12)	0.231	0.415
Women	1101/ 9431	1.13 (1.02–1.26)	0.023	
Age (years)				
< 30	809/ 5214	1.12 (0.98–1.28)	0.091	0.309
30–50	591/ 8036	1.02 (0.93–1.11)	0.697	
> 50	203/ 2392	1.12 (1.02–1.23)	0.014	
BMI				
< 22.96 kg/m^2	921/ 7847	1.12 (1.01–1.25)	0.035	0.495
> 22.96 kg/m^2	682/ 7795	1.06 (0.99–1.13)	0.095	
Occupation				
Health professionals	843/ 8600	1.06 (0.97–1.15)	0.178	0.910
Not health professionals	760/ 7042	1.09 (1.01 −1.18)	0.026	
MD	277/ 2774	1.02 (0.88–1.18)	0.832	0.045
Not MD	1326/ 12,868	1.09 (1.02–1.15)	0.007	
Myopia at baseline				
No myopia at baseline	1032/ 11,267	1.06 (0.99–1.13)	0.083	0.131
Myopia present at baseline	571/ 4375	1.11(1.00–1.23)	0.052	
Additional exclusions				
Other refraction				
No astigmatism in C8	745/ 8173	1.12 (1.04–1.21)	0.004	
No hyperopia in C8	1345/ 12,223	1.08 (1.01–1.15)	0.024	
No astigmatism or hyperopia in C8	1135/ 10,850	1.07 (1.00–1.15)	0.060	
Allowed energy limits				
Percentiles 1st and 99th	1784/ 16,908	1.08 (1.03–1.14)	0.003	
Additional adjustments				
Adjusted for hours of near-sight work		1.12 (1.05–1.20)	0.001	

[1]Adjusted for sex, age, BMI, years of university, television use (h/week), computer use (h/week), sleep (hours/week), leisure time physical activity (METs-h/week), tobacco use (never, current, former).

association between the intake of alcohol and the subsequent development or progression of myopia in the mid-long term. The results of this prospective cohort study show a positive, linear association between alcohol intake and myopia incidence or progression. In other words, we found that, should causality be proven, a consumption of alcoholic drinks may lead to the development or progression of myopia, with a relationship that shows a dose-response trend. The magnitude of the association that we found is not very large, but due to the commonness of the consumption of alcohol, the importance of myopia as a health condition and the newness of this assessment, we believe these findings to be of relevance to the scientific community.

Due to the novelty of this investigation, there is very little evidence with which to compare these results. However, they do seem to be consistent with those found in two clinical trials that measured the acute short-term effects of alcohol on vision: Wilson and Mitchel carried out a controlled clinical trial in 1983 in which they gave their participants orange juice with 0.375 g/kg of 10% ethanol and measured their visual acuity at 6 m at baseline, 20, 40 and 60 min, finding a statistically significant ($p < 0.05$) decrease for all measured intervals (Wilson and Mitchell, 1983); similarly, Watten and Lie found in a placebo-controlled clinical trial carried out in 1996 that augmenting amounts of alcohol in blood had an increasing acute myopic effect on visual acuity ($p < 0.05$) (Watten and Lie, 1996). There are, however, other studies that contradict these findings, such as that by Hill and Toffolon in 1990 which showed no significant effect on visual function with increasing amounts of blood alcohol (Hill and Toffolon, 1990). On another note, alcohol consumed by the mother during foetal development has been shown to have an influence on the development of some eye cells like corneal endothelial cells (central corneal thickness and endothelial cell density) or retinal cells (decreased nerve fibre layer and ganglion cell layer), and interestingly enough, children who had a prenatal exposure to alcohol have been demonstrated to have a decreased visual acuity and increased incidence of myopia in their teen years (Castillo et al., 2018; Sati et al., 2018). This, together with the known fact that alcohol from the blood can enter the vitreous chamber -reality used for forensic purposes-, means that a biological way for the alcohol in the blood to reach the eye does exist (Yip, 1995).

About the pathophysiology of myopia, the sclera has been shown to undergo different biomechanical and metabolic variations like abnormal thinness, reduction of glycosaminoglycan and collagen, decreased integrin expression, disorganisation of its fibril assembly and a relative loss in its extracellular matrix (ECM) (Harper and Summers, 2015; McBrien et al., 2009; Metlapally and Wildsoet, 2015). Particularly, evidence suggests that scleral ECM changes affect what are called its "creep properties", which refer to the increase in the eye's axial length when a constant intraocular pressure in applied, thus its myopisation (Harper and Summers, 2015). Interestingly, the effect of alcohol consumption has been widely associated with other tissues' ECM alterations before, such as the brain, the breast or the liver (Lasek, 2016; Seth et al., 2010; Wang et al., 2017). Specifically, alterations in two of the ECM components that most solidly vary in myopia –transforming growth factor-beta (TGF-β), which is reduced, and cyclic AMP (cAMP), which is increased– have been found to be affected by alcohol consumption in other body tissues (Harper and Summers, 2015; McBrien et al., 2009; Seth et al., 2010; Volicer and Gold, 1975). Through this mechanism, alcohol consumption may lead to changes in the ECM of the sclera that develop into an elongation of the axial length of the eye, therefore making it more myopic. Other potential mechanism by which the influence of alcohol in myopia may take place is through oxidative stress, a process which has been extensively associated with alcohol consumption and which has been found to be one of the main pathophysiological events in the genesis of myopia (Bosch-Morrel et al., 2015; Volicer and Gold, 1975).

Our study has some limitations that need to be addressed. First, all of the information about the participants' diet was self-reported with the FFQ, therefore a certain degree of misclassification is possible. However, the questionnaire was validated specifically for the SUN cohort, and the correlation coefficient for alcohol consumption (r 0.88) was the highest among all nutrients (Martin-Moreno et al., 1993) Information about incidence/progression of myopia was also self-reported. Although we inquired about a medical diagnosis, self-reported myopia was not confirmed using medical records. However, as more than half of the participants are health professionals, a minor potential degree of misclassification could be expected. Furthermore, should there be a misclassification of the exposure or the outcome, this measurement error would more likely tend towards the null value as it would be non-differential. Second, alcohol consumption as a whole involves more areas than only the precise amount of alcohol ingested. There is a tendency in other sectors of nutritional epidemiology lately to use instead dietary patterns to assess the association between the consumption of a particular food or nutrient with chronic conditions, as it is believed that nutrition is a rich and complex variable for which a simplistic analysis may not comprise the full extent of it (Pan et al., 2012). We decided to

take the first approach as a primary insight into the relationship between alcohol consumption and myopia, and we believe these results may open a new line of research that should include the analysis of different patterns of alcohol consumption. Third, alcohol consumption was only taken at baseline and after 10 years of follow-up. This means, that although some participants were followed for ten years, the exposure to alcohol that was used was the available information at baseline for all of them, when really there could have been changes in alcohol consumption along those ten years. In an attempt to counteract this potential measurement error, we performed the same analysis taking information about alcohol consumption from a time point other than baseline (questionnaire number 10 from the SUN study) and assessing its association with the development or progression of myopia in two-, four- and six-year periods counting from the new baseline point. In the second analysis, the participants were some of those already included in the first analysis –those who had stayed in the SUN cohort for up to sixteen years. The results from the first and second analysis were fairly similar. A fourth issue may be the fact that, because participants from the SUN cohort are all university graduates, we assessed the influence of alcohol on myopia in age periods in which the eye is not so prone to change anymore, as myopia is a condition with a natural course that starts in the early school years and that moves towards stabilisation generally around the late teens (Hardy et al., 2013). This statement is, of course, not absolute, and thus we were able to see significant differences in our cohort, even when the whole situation would make our results tend towards the null. It does, however, leave an open question as to what the effect of alcohol consumption in adolescents may be with regards to the development of myopia –an open call for further research.

In spite of these limitations, our study also has some important strengths worth mentioning, such as its prospective nature -which avoids recall bias and limits reverse causality–, its large sample size, its substantial retention rate and the sensible adjustment for possible confounders. Additionally, the SUN cohort is made up of a population quite homogeneous in terms of educational and socio-economic status as the participants are all university graduates, which helps minimise confounding factors and allows for more reliable information to be collected. Another positive point is the use of validated FFQs, with particularly high correlation for alcohol intake.

In conclusion, this pioneer study shows that, if the association is proven to be causal, consumption of alcohol might lead to development or progression of myopia. However, further research is needed to confirm our findings. If so, ophthalmologists may also join the battle against the harmful effects of alcohol intake.

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CRediT authorship contribution statement

Covadonga Menéndez-Acebal: Conceptualization, Formal analysis, Data curation, Writing – original draft, **Miguel A. Martínez-González**: Conceptualization, Resources, Funding acquisition, Data curation, Writing – review & editing, Supervision, **Maira Bes-Rastrollo**: Conceptualization, Resources, Funding acquisition, Writing – review & editing, Supervision, **Javier Moreno-Montañés**: Conceptualization, Writing – review & editing, Supervision, **Alfredo García-Layana**: Conceptualization, Writing – review & editing, Supervision, **Alfredo Gea**: Conceptualization, Formal analysis, Resources, Funding acquisition, Data curation, Writing – original draft. All authors have read and approved the final manuscript.

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Declarations of interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2021.109149.

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