Healthy Lifestyle Score and Incidence of Glaucoma: the Sun Project

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Abstract

The relationship between healthy lifestyles, diet, and glaucoma remains controversial. In this study, we analyse the effect of Mediterranean Lifestyle (ML) on glaucoma incidence in the “Seguimiento Universidad de Navarra” (SUN) cohort. Participants (n=18 420) initially free of glaucoma were followed for a mean of 10.8 years. The SUN Healthy Lifestyle Score (SHLS) ranging from 0 to 10 points included 10 healthy habits: never having smoked, moderate to high physical activity (>20 MET-hour/week), Mediterranean diet ($\geq 4/8$ adherence points), moderate alcohol consumption (women, 0.1-5.0 g/d; men, 0.1-10.0 g/d), low television exposure (<2 h/day), no binge drinking (≤ 5 alcoholic drinks at any time), a short afternoon nap (<30 min/day), meeting up with friends (> 1 h/day), working at least 40 h/week and low body mass index ($\text{BMI} \leq 22$). Information is collected biennially through self-reported questionnaires. The relationship between new cases of glaucoma and the SHLS was assessed by logistic regression using a hazard ratio. Crude, multi-adjusted and sensitivity analysis were performed. During follow-up, we observed 261 (1.42%) new cases of glaucoma. After adjusting for potential confounders, participants in the healthiest category of SHLS (7-10 points) showed a significantly reduced risk of glaucoma compared to those in the lowest SHLS category (0-3 points) (adjusted HR=0.51, 95% CI=0.28-0.93). For each point added to the SHLS the risk of glaucoma relatively dropped by 5%. In conclusion, higher adherence to a ML, measured by the SHLS, was significantly associated with lower risk of developing glaucoma. The ML is a protective factor for glaucoma incidence.

Background

Glaucoma is one of the most common eye diseases and includes a group of disorders characterized by progressive damage of the optic nerve associated with loss of the visual field ¹. It is considered the second leading cause of blindness worldwide, and a major public health problem ². According to the European Glaucoma Society, the number of people with glaucoma is 76 million in 2020 and is estimated to increase to 112 million in 2040. In addition to early detection of the disease and early reduction of intraocular pressure (IOP), several approaches have been made to search for risk factors in order to reduce the incidence of glaucoma. Some of these risk factors can not be modified, such as age ³, race ⁴, or myopia ⁵, among others. However, the intervention on modifiable risk factors, such as those related to lifestyle or diet, may reduce the incidence and progression of glaucoma. In this way, some of our previous studies obtained that smoking cessation significantly reduces the incidence of glaucoma ⁶. Also, in a previous study we found that high omega 3:6 ratio intake was associated with a significantly higher risk of glaucoma incidence ⁷. Kang et al, in prospective analysis from the Nurses' Health Study and the Health Professionals Follow-up Study found that higher dietary nitrate and green leafy vegetable intake was associated with a lower glaucoma risk ⁸. Despite these results, the relationship between lifestyle and glaucoma incidence remains unclear and previous studies report even contradictory results, therefore this association requires further analysis, especially among larger cohort groups and with longer follow up periods.

Two large studies, in which members of our group collaborated, demonstrated the efficacy of the Mediterranean diet (MD) in preventing cardiovascular diseases and reducing mortality. Thus, the “**Seguimiento Universidad de Navarra**” (University of Navarra Follow-up) (SUN study), in a cohort of 20 127 participants, found that a poor adherence to the Mediterranean diet and low physical activity levels account for almost 30% of all-cause mortality ⁹. In other multicentre study, the “**Prevencion con Dieta Mediterránea**” (PREDIMED study) that included 7447 participant at high cardiovascular risk with a 5 years of follow-up, demonstrated that the incidence of major cardiovascular events was lower among those assigned to a Mediterranean diet supplemented with extra-virgin olive oil or nuts than among those assigned to a reduced-fat diet ¹⁰. These studies suggest the health benefits of adhering to the Mediterranean diet. However, the Mediterranean diet is only a part of the Mediterranean culture and lifestyle (ML) ¹¹. To evaluate adherence to ML we created the SUN Healthy Lifestyle Score (SHLS) that included 10 Mediterranean lifestyle habits. In previous studies we found that a high SHLS score was associated with a lower risk of developing primary cardiovascular disease events ¹², and a lower risk of developing metabolic syndrome ¹³. Our goal in this study is to study the association between ML, using the SHLS, and glaucoma incidence, in order to find new modifiable risk factors and potential lifestyle changes useful to reduce glaucoma incidence. To our knowledge, no previous studies have been published analysing the association between lifestyle scores and glaucoma incidence.

Material And Methods

Study design

The SUN Project is a dynamic prospective cohort study formed of university graduates. It started in Spain in December 1999 and the recruitment of new participants is permanently open. Participants' information is collected biennially through mailed or electronically mailed self-reported questionnaires. Upon completion of the first questionnaire (Q-0), including a total of 554 items used as baseline information, participants receive follow-up questionnaires biennially. These follow-up questionnaires contain questions to evaluate changes in lifestyle and health-related behaviours, anthropometric measures, incident diseases, and medical conditions. The study methods have been previously published ¹⁴.

Study participants

We preselected a total of 22 475 subjects who had responded the baseline questionnaire Q-0 before September 2 015. We used the information collected after the first two years of follow-up (Q2), and after every two subsequent years (Q4, Q6, Q8, Q10, Q12, Q14). Participants were followed up until the diagnose of glaucoma or until the last follow-up questionnaire available at the time of these analyses, (Q16) that collected information after 16 years of follow-up. Data analysis excluded 1 983 individuals without follow-up questionnaires (90.8% retention rate). Participants who reported extremely low or high total energy intake ¹⁵ (1 925), and participants with a previous diagnosis of glaucoma (59) were also excluded. Finally, 18 420 participants were included in the analysis (Fig. 1). The study was approved by the Human Research Ethics Committee at the University of Navarra (091/2008), and followed the Declaration of

Helsinki Ethical Principles for Medical Research Involving Human Subjects. Voluntary completion of the first questionnaire was considered by this Committee to imply informed consent; this handling of consent was approved by the ethics committee.

Exposure assessment: Healthy Lifestyle Score variables

Dietary exposure was gathered using a semi-quantitative food frequency questionnaire (FFQ) with consume information on 136 items, that has been repeatedly validated in Spain ¹⁶. To Trichopoulou score (score 0–8, excluding alcohol), was used to assess the adherence to the Mediterranean diet ¹⁷. To collect information on alcohol consumption, data were obtained through the FFQ and also through other additional alcohol-intake related items present in the baseline questionnaire.

Mediterranean lifestyle was assessed with the SHLS. For the SHLS calculation, one point was given to each participant for each of these 10 habits: never smoking, moderate-to-high physical activity (> 20 MET-h/wk), Mediterranean diet (≥ 4 adherence points), body mass index (BMI) ≤ 22 , moderate alcohol consumption (women, 0.1-5.0 g/d; men, 0.1–10.0 g/d; abstainers excluded), low television exposure (< 2 h/d), no binge drinking (≤ 5 alcoholic drinks at any time), taking a short afternoon nap (< 30 min/d), regularly meeting up with friends (> 1 h/d), and working at least 40 h/wk. The SHLS scale could range between 0 points (worst lifestyle) and 10 points (best lifestyle).

Outcome assessment

Glaucoma was assessed through a specific question included in the follow-up questionnaires. Participants responded to the question: “*Have you ever been diagnosed of glaucoma by a health professional?*”, along with the date of diagnosis. Validity of self-reported glaucoma diagnosis was assessed in a subgroup of our cohort by an experienced ophthalmologist, blinded to the questionnaires. This validation study showed a Kappa value of 0.85 (95% coefficient interval [CI], 0.834–0.872). The sensitivity found was 0.83 and the specificity 0.99. Prevalent cases of glaucoma at baseline were excluded from this analysis.

Ascertainment of covariates

Baseline questionnaire also gathered information of multiple potential confounding factors such as socio-demographic characteristics (i.e. sex, age, educational level), lifestyle and health-related characteristics (i.e. smoking, physical activity, adherence to the Mediterranean diet, total energy intake, consumption of a special diet, caffeine intake, Omega 3/6 ratio), anthropometric measures (i.e. BMI), and prevalent diseases (i.e. hypertension, cardiovascular disease, cancer, diabetes).

Statistical analyses

According to the baseline score obtained with the SHLS, participants were classified into four groups, to ensure an appropriate sample distribution and a sufficient number of incident cases within each category. These four categories were SHLS 0–2, 3–4, 5–6 and 7–10 points. We estimated hazard ratios (HR) and

95% confidence interval (CI) for glaucoma, for every category of SHLS, using the Cox regression model, defining the first category (0–2) as the reference category, and adjusting for multiple potential confounding factors, such as sex, age, calorie intake, caffeine intake, alcohol intake, omega-3/omega-6 ratio, prevalence of cancer, prevalence of hypertension, prevalence of diabetes mellitus type 2, educational level, and special diets. Linear trends tests were calculated by assigning the median score of each category to all participants in that category and treating this variable as continuous.

To analyse the individual contribution of each specific factor of the SHLS score to the risk of glaucoma, Cox regression models were fitted for each of the ten items of healthy life habits, adjusting for the effect of the rest of the items that constituted the index. The reference category was the absence of the healthy habit (score 0 on the specific item).

Sensitivity analyses were also performed to ensure the robustness of the results in different scenarios. We repeated the analyses stratifying by age (≥ 50), sex and smoking.

All p values presented are two-tailed; $p < 0.05$ was considered statistically significant. Analyses were performed using STATA/SE version 12.0 (STATA Corp LP, College Station, TX, USA).

Results

After a median of 12 years of follow-up (mean 10.8 years), we recorded 261 incident cases of glaucoma. The participants' baseline characteristics according to their classification in the SHLS are shown in Table 1. Compared to the participants at the lowest range of the SHLS (0–3 points), those at the highest category (7–10 points) had a lower BMI, consumed less alcohol, binge drunk less, smoked less and watched less television. On the other hand, they practiced more physical activity, had a higher adherence to the Mediterranean diet, took more weekly naps, met more with friends and worked more hours per week.

The risk of developing glaucoma according to the Sun Healthy Lifestyle Score (Table 2) was significantly lower for those participants with the highest scores than for those with the lowest SHLS, in all the three models: The crude-model (adjusted HR = 0.53, 95%CI = 0.6–0.95), the age-sex adjusted model (adjusted HR = 0.54, 95% CI = 0.3–0.96), and in the multivariable model (multivariable-adjusted HR = 0.51, 95%CI = 0.28–0.93). For each point added in the SHLS the risk of glaucoma relatively dropped by 5% (p for trends: 0.032).

Figure 2 shows the multivariable-adjusted HRs for the risk of glaucoma across the 10 habits included in the SHLS. Only “never smoking” was associated with low glaucoma incidence (adjusted HR = 0.70, 95%CI = 0.53–0.92) when evaluated individually. However, when combined, the effect of the 10 healthy habits is significantly protective against glaucoma incidence. As shown in Table 3, the contribution of each habit to the SHLS, varied from 13,7% (No binge drinking) to 6,6% (BMI).

Discussion

Several Healthy Lifestyle Scores, combining different variables, have been used to study the association between modifiable lifestyles and systemic diseases. Thus, Jiao et al, evaluate 5 habits in 450 416 participants, and found that the combined highest score (5 points) was associated with a 58% reduction in risk of developing pancreatic cancer compared to the lowest combined score (Jiao et al. 2009). Other authors that combined 4 lifestyle factors (Mediterranean diet, moderate alcohol use, physical activity and non smoking), in individuals aged 70 to 90 years, found that poor adherence to that combined score was associated with a population attributable risk of 60% for all deaths¹⁹. Other study monitored 42 847 men using 5 habits updated through self-reported questionnaires, showing that 62% of coronary events in this cohort may have been prevented with better adherence to these 5 healthy lifestyle practices²⁰. Similar results of other scores that included 5 healthy components (diet, physical activity and sedentary behaviours, smoking, social support and network, and sleep) found that this score was associated to the metabolic syndrome²¹. Recently, another study showed how a favourable lifestyle was associated with a lower risk of dementia, even regardless the genetic risk²². All these results reinforce the extraordinary importance of healthy lifestyle in health prevention.

The Mediterranean Lifestyle (that includes not only the adherence to the Mediterranean diet, but also other habits such as high sociability, regular physical activity, moderate drinking or adequate rest) has already shown its role in the prevention of chronic diseases in hundreds of peer-reviewed scientific journal articles during the last years²³. The UNESCO recognized the ML as an Intangible Cultural Heritage of Humanity in 2010²⁴. Also, the Mediterranean Diet has been selected as a model for healthy dietary patterns in the Dietary Guidelines for Americans 2015–2020 of the United States Department of Agriculture²⁵ and in several clinical guides both from American and European Scientifics societies^{23,26}. In our SHLC we included 10 ML habits and each of them alone has demonstrated a beneficial effect on health. Some studies demonstrated the relationship between smoking to worse health and chronic diseases²⁷. Moderate alcohol consumption, such as red wine or beer, is considered part of the Mediterranean diet, and many epidemiological studies have demonstrated the protective effect of moderate alcohol consumption in coronary heart disease, even more than abstainers^{28,29}, while binge-drinking (7 drinks 1 day of the week) has been associated with poorer health and stroke³⁰. The short nap in the mid-day (“siesta”) has been considered as a protector factor of cardiovascular diseases in previous studies conducted in Greece³¹ and in Japan³². Conviviality or sociability with friends is another known factor for longevity, cardiovascular and mental health outcomes^{27,33}. Watching television (TV) several hours a day is considered a sign of sedentary life and has been implicated in cardiovascular events³⁴, obesity³⁵ and mortality³⁶. Eating high-calorie foods and sugary drinks in people while watching a lot of TV may also be related to obesity³⁵. A high adherence to the Mediterranean diet has demonstrated a high benefit for the prevention of cardiovascular diseases, diabetes and various types of cancer^{37,38}. The relationship between working hours (> 40 h/week) and health is more controversial²⁷, some studies show higher risk of coronary heart diseases in employees working long hours³⁹, while other study found that longer overtime work was inversely associated with hyperglycaemia or type 2 diabetes in Japanese office workers⁴⁰. In general, we believe that these findings might be affected by the fact that in order to develop

or to remain in a job that requires long working hours a better health status is needed ⁴¹. Many reports describe the protective effect of physical activity on preventing heart disease and stroke, high blood pressure, diabetes mellitus, or metabolic syndrome, among others ⁴². Finally, the BMI > 30 has been associated with all-cause mortality. In a study with 1.46 million white adults, overweight and obesity were associated with increased all-cause mortality, and all-cause mortality is lowest with BMI between 20.0 and 24.9 ⁴³.

The score we have designed, which includes these 10 items, adequately reflects and captures the complexities of the ML, in isolation only one habit has been shown to be related to the incidence of glaucoma (smoking) but when analysed together they show a significant protective effect. The difference in the effect of each isolated healthy habit, as opposed to the combined effect of several healthy factors is that “the whole is more than the sum of its parts” (Aristotle). It is likely that a person who does not smoke and plays sports, has a lower BMI, a better adherence to the Mediterranean diet, or drinks alcohol moderately. It is logical to deduce that adherence to a number of individually beneficial lifestyle habits would lead to a better synergistic effect ¹².

The biological pathway behind this association remains unclear. Some studies suggests that chronic and low-grade inflammation is a key factor in the pathogenesis of glaucoma ^{44,45}. Interleukin-6 (IL-6) has a major role in the pathology of glaucoma, among others systemic inflammatory diseases ⁴⁶ and high plasma C-reactive protein (CRP) levels have been associated with normal tension glaucoma ⁴⁷. Some ML components are associated with better endothelial function, and lower inflammation levels and oxidative stress. Systematic review and meta-analysis showed that a ML significantly improved chronic inflammation markers such as CRP, pro-inflammatory cytokines such as IL-6, and adiponectin (AD) as well as endothelial function parameters such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and E-Selectin ⁴⁸. The PREDIMED study found that high consumption of Mediterranean diet products such as cereals, fruit, nuts, and virgin olive oil was associated with lower serum concentrations of IL-6, CRP, VCAM-1, and ICAM-1 ⁴⁹. These inflammatory markers can be associated with glaucoma incidence explaining the results found. Another plausible explanation for the association between ML and glaucoma is through the nitric oxide (NO) pathway. Some studies suggest that NO is a direct regulator of the IOP and the dysfunction of the NO- Guanylate Cyclase (NO-GC) pathway has been associated with glaucoma incidence ⁵⁰. Blood flow regulation is likely mediated by NO and NO-GC-cyclic guanosine monophosphate ⁵⁰, and NO also has well known anti-inflammatory and anti-apoptotic properties ⁵¹. MD is rich in polyphenols, and these components increase the endothelial NO synthase expression, secondarily increasing plasma NO levels ^{52 53}. The intimate mechanism of the protective effect of ML on glaucoma is still not well defined, and it is probably a combined mechanism. However, ML decreases chronic inflammation markers and endothelial dysfunction parameters while increasing NO plasma levels, and these changes in biological markers might be the cause of the protective effect of ML on glaucoma incidence. More specialized studies are needed to better understand the intrinsic and complex mechanism of the association between ML and glaucoma.

The current study has some strengths. It is a prospective study, performed in a large cohort followed-up for over 10 years. A wide variety of potential confounders have been taken into account avoiding the possibility of inverse causation bias, which is a frequent phenomenon in cross-sectional or case-control studies. Also the self-reported diagnosis of glaucoma was previously validated in a subsample.

This study also has some limitations, that need to be addressed. It is possible that some participants might have overestimated or exaggerated their healthy habits. However, if there was some degree of misclassification, it could be expected to be non-differential, which would make the bias more likely to the null, not affecting the association found. Lifestyle information was collected on the baseline questionnaire, and although dietary habits and other lifestyle habits may change over time, they are usually stable and reflect both the characteristics of an individual person and those of a type of culture^{19,54}. Despite these limitations, this study is robust in terms of the number of patients and follow-up time, and is the first to find that a healthy lifestyle score can decrease the incidence of glaucoma, providing a new modifiable risk factor to prevent the glaucoma disease.

Our study shows that a SHLS > 6 is a protective factor for glaucoma incidence, and that for each point added to this healthy habits score the risk of glaucoma decreases by 5%. Thus, the ML is a potentially modifiable factor in the incidence of glaucoma. Further studies are required to validate our results in other cohorts and to better understand the cellular mechanisms behind the association of Mediterranean lifestyle and the incidence of glaucoma.

Declarations

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Conflict of Interest:

No conflicting relationship exists for any author.

Availability of data and material:

The principal investigators, Javier Moreno-Montañés and Alejandro Fernández-Montero have full access to all of the study data and are responsible for the integrity of the data and the accuracy of the data

analysis.

Authors' contributions:

Each author participated sufficiently, intellectually and practically, in the work to take public responsibility for the content of the article. MR-C and MAM-G designed the study; MAM-G was in charge of collecting the data; AF-M, EG and IG-R analyzed the data; JM-M, AF-M and LM-G wrote the manuscript; JM-M and MR-C provided of significant advice. All authors read and approved the final manuscript.

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Tables

Table 1

Baseline characteristics of participants according to number of healthy lifestyle factors. (The SUN Project).

Number of healthy lifestyle factors	0–2	3–4	5–6	7–10
Participants, n	702	4,972	8,305	4,180
Sex, women (%)	49.3	55.0	59.4	69.9
Age, years	41.4 (13)	39.9 (12.7)	37.8 (12.1)	34.3 (10.8)
Body mass index, kg/m ²	25.5 (3.6)	24.6 (3.5)	23.5 (3.5)	22.1 (3.0)
Alcohol consumption, g/d	12.6 (19)	8.5 (12.5)	6.2 (8.8)	4.2 (5.7)
Smoking, pack year	13.5 (14)	9.2 (11.5)	5.5 (9.3)	2.1 (5.9)
Physical activity, MET-h/week	12.1 (12.3)	16.9 (17.4)	23 (21.9)	32 (25.3)
Mediterranean diet pattern	3.4 (1.4)	3.9 (1.7)	4.2 (1.8)	4.7 (1.7)
Watching television, h/d	2.6 (1.4)	2 (1.4)	1.5 (1.2)	1.1 (0.9)
No binge drinking (%)	35.3	55.9	72.3	85.9
Afternoon nap, min/d	0.2 (0.4)	0.4 (0.5)	0.6 (0.5)	0.8 (0.4)
Meeting up with friends, h/d	0.9 (0.9)	1.2 (1.0)	1.3 (1.0)	1.6 (1.0)
Working ≥ 40 h/wk (%)	17.5	38.3	54.5	70.8
Diabetes (%)	2.6	2.0	2.0	1.3
Hypertension (%)	17.2	14.3	10	6.1
Prevalent cancer (%)	2.9	4.3	3.7	3.3
Educational level				
No college (%)	8.9	8.4	9.5	10.4
College (%)	24.2	24.8	23.4	23.2
Post-graduate (%)	52.9	50.1	48.4	46.7
Master (%)	6.7	6.8	8.2	9.4
Doctorate (%)	7.4	9.9	10.4	10.2
Caffeine, mg/d	49.6 (43.2)	44.1 (41.3)	42.7 (39.6)	38.6 (36.9)
Diet (%)	9.0	8.8	8.0	8.4

Number of healthy lifestyle factors	0–2	3–4	5–6	7–10
Caloric consumption	2271.5 (629.5)	2295.1 (625.1)	2344 (614.1)	2411.7 (604.1)

Values are expressed as mean (standard deviation) unless otherwise noted

Table 2

Glaucoma risk at 10 -year follow-up, according to number of healthy lifestyle factors. (The SUN Project).

	Number of healthy lifestyle factors				P for trend
	0–2	3–4	5–6	7–10	
Participants, n	702	4 972	8 305	4 180	
Incident cases	18	76	135	32	
Crude	1 (ref.)	0.63 (0.38– 1.06)	0.81 (0.50– 1.33)	0.53 (0.30– 0.96)	0.032
Adjusted for age and sex	1 (ref.)	0.66 (0.39– 1.11)	0.84 (0.51– 1.37)	0.54 (0.30– 0.97)	0.022
Multivariable adjustment*	1 (ref.)	0.65 (0.39– 1.10)	0.82 (0.50– 1.35)	0.52 (0.29– 0.94)	0.150

* Adjusted for age, sex, calorie intake, caffeine intake, alcohol intake, omega-3/omega-6 ratio, prevalence of cancer, prevalence of hypertension, prevalence of diabetes mellitus type 2, educational level, sex and following a special diet.

Table 3

Contribution of each point to the total variability in the Healthylife Score. (SUN project)

Healthylife Score	% Contribution of point
No binge drinking	13.7%
Watching television (< 2 h/d)	13.4%
Spending time with friends (> 1 h/d)	11.7%
Afternoon nap (0–30 min/d)	10.7%
Working (> = 40 h/wk)	10.0%
Moderate alcohol consumption (women, 0.1-5.0 g/d; men 0.1–10.0 g/d)	9.3%
Never smoking	8.6%
Mediterranean diet (> = 4/8)	8.2%
Physical activity (> 20 METs-h/wk)	7.8%
BMI (< = 22)	6.6%

Figures

Figure 1

Flow-chart of the subjects in the Seguimiento Universidad de Navarra (SUN) Project, 12 years of follow-up. * Values out of predefined limits according to Willet (55).

Figure 2

Risk of incident glaucoma for each factor of the Healthy Lifestyle Score. (The SUN Project). Adjusted for age, sex, calorie intake, caffeine intake, alcohol intake, omega-3/omega-6 ratio, prevalence of cancer, prevalence of hypertension, prevalence of diabetes mellitus type 2, educational level, sex and following a special diet.