Adherencia a la dieta mediterránea y riesgo de infarto cerebral en una población chilena: estudio de casos y controles

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Adherencia a la dieta mediterránea y riesgo de infarto cerebral en una población chilena: estudio de casos y controles

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Availability of data and materials: the datasets generated for this study are the property of the authors and can be requested from the corresponding author.

ABSTRACT

Introduction: Ñuble is the region of Chile with the highest stroke incidence rates in the country. The aim was to estimate the association between adherence to the MED diet and the first ischemic stroke in adult patients living in the Ñuble region.

Methods: a case-control hospital-based study. The cases ($n = 89$) were patients with first ischemic stroke, and controls ($n = 178$) were admitted to the same hospital during the same month the cases were recruited. We selected two controls for one case and paired them for sex and age (± 5 years). We used the food frequency questionnaire and the adherence Mediterranean diet questionnaire. A descriptive analysis of the variables and a conditional logistic regression to determine the association between variables.

Results: 71 % of the sample was ≥ 65 years old and 64 % were male. Cases smoked (11.2 %), consumed at least one drink per month (41.6 %), and had a diagnosis of hypertension (76.4 %) more frequently than controls. In the model adjusted for all variables, it is observed that those who are in quartile 2 of adherence (6-7 points) are 42 % less likely to have a cerebral infarction compared to those who have a lower score ($p < 0.005$).

Conclusions: our findings suggest that moderate adherence to a Mediterranean diet, defined by the PREDIMED score and adjustment for other variables, reduces the probability to first ischemic stroke.

Keywords: Stroke. Mediterranean diet. Case-control. Dietary pattern.

RESUMEN

Objetivo: estimar la asociación entre la adherencia a la dieta Mediterránea y un primer accidente cerebrovascular isquémico en adultos de la región de Ñuble.

Métodos: estudio de casos y controles con base hospitalaria. Los casos (*n* = 89) fueron pacientes con primer accidente cerebrovascula (ACV) isquémico, y los controles (*n* = 178) fueron ingresados en el mismo hospital durante el mismo mes en que se reclutaron los casos. Se seleccionaron dos controles para un caso y se emparejaron por sexo y edad (± 5 años). Se utilizó el cuestionario de frecuencia de consumo de alimentos y el cuestionario de adherencia a dieta mediterránea. Se realizó un análisis descriptivo y una regresión logística condicional para determinar la asociación entre variables.

Resultados: el 71 % de la muestra tenía ≥ 65 años y el 64 % eran hombres. Los casos fumaban (11,2 %), consumían al menos una bebida al mes (41,6 %) y tenían diagnóstico de hipertensión arterial (76,4 %) con mayor frecuencia que los controles. En el modelo ajustado por todas las variables, se observa que aquellos que se encuentran en el cuartil 2 de adherencia (6-7 puntos) tienen un 42 % menos de probabilidades de sufrir un infarto cerebral en comparación con los que tienen una puntuación más baja (*p* < 0,005).

Conclusiones: nuestros hallazgos sugieren que la adherencia moderada a una dieta mediterránea, definida por la puntuación

PREDIMED y el ajuste por otras variables, reduce la probabilidad de un primer ACV isquémico.

Palabras clave: Accidente cerebrovascular. Dieta mediterránea. Casos y controles. Patrón dietético.

INTRODUCTION

Stroke is an important leading cause of death and disability worldwide, the third leading cause of disability-adjusted life-years. The absolute number of strokes continues to increase due to an aging population, with an estimated total of 6.24 million deaths annually (1,2). About 90 % of the risk of stroke is preventable and attributable to modifiable risk factors such as smoking, dyslipidemia, high blood pressure, alcohol consumption, sedentary lifestyle, obesity, and poor eating habits, according to the INTERSTROKE study (3). An unhealthy diet was attributed to stroke at 19 % (11-30 %) (4).

Diet influences the onset of stroke through different mechanisms: effect on blood pressure, blood lipids, coagulation process, oxidative stress, inflammatory processes, endothelial function, glycemic and insulin homeostasis, gut microbiota, and body weight (5). The main mechanism by which diet can influence the etiopathogenesis of stroke is by the atherosclerotic process, mainly produced by fat metabolism.

Different dietary interventions have been implemented to reduce the incidence of stroke while controlling for risk factors such as high blood pressure, obesity, diabetes *mellitus*, and dyslipidemia (6,7). Evidence has shown a protective effect on stroke associated with the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean diet (MED). Both dietary patterns are characterized by a higher intake of fruits and vegetables, whole grains, legumes, and olive oil, and a

moderate intake of dairy products. Lastly, the MED diet added a moderate intake of red wine and nuts (8-10).

In prospective cohort studies, the MED diet has reduced mortality and the risk of cancer, cardiovascular disease, metabolic syndrome, stroke, and neurodegenerative diseases (9,11-17). The beneficial effect of the MED diet is probably due to the additive effect of its nutritional components and not the effect of each food alone (18). On the other hand, the MED diet forms part of the primary prevention of stroke guidelines (19). In a systematic review and meta-analysis, the MED diet had a protective role against stroke, reducing the risk between 10 % (RR = 0.90; 95 % CI, 0.87-0.93) and 36 % (RR = 0.64; 95 % CI, 0.87-0.93) (20). Furthermore, high adherence to the MED diet reduced 27 % (RR = 0.73; 95 % CI, 0.59-0.91) for unspecific stroke and 18 % (RR = 0.82; 95 % CI, 0.73-0.92) for ischemic stroke (9).

The third cause of death in Chile is stroke, accounting for 7.3 % of all deaths in 2019 (21) and a population-estimated incidence of 140 per 100,000/year; that result was moderate incidence. The age-standardized mortality rate of stroke for the year 2015 in Chile (34.4 per 100,000 inhabitants) (22) doubles that of developed countries such as the United States (21.9 per 100,000 inhabitants) and Canada (16.4 per 100,000 inhabitants). In the central-southern regions of Chile, the stroke mortality and case-fatality rates are higher than in the northern and southern regions. The region of Ñuble, located in the central plains of Chile, is a region with low income; 30.6 % lived in rural areas, with 16.1 % living below the poverty line according to income, and 80 % of the population is affiliated with the public health system. Ñuble have incidence rate Stroke of 163.4 (95 % CI, 152.9-174.6) was also higher than the GBD age-adjusted incidence rate of 108 (95 % CI, 100.4-116) for Chile in 2017 (23).

The aim was to estimate the association between adherence to the MED diet and first ischemic stroke in adult living in the Ñuble region.

MATERIALS AND METHODS

A paired case-control hospital-based study (1:2) by sex and age was carried out in adults over 45 years and hospitalized at the Herminda Martín Hospital in Chillan, Ñuble Region of Chile.

Cases

The cases were patients admitted to the Hospital Herminda Martín in Chillán between August 2018 and February 2019 for a first ischemic stroke, which according to the International Statistical Classification of Diseases and Related Problems with Health (ICD-10) corresponds to the code I63 evaluated by the neurologist using the National Institutes of Health Stroke Scale (NIHSS) score. Patients with confirmed hemorrhagic stroke by Computed Tomography (CT) scan and/or Diffusion Weighted Magnetic Resonance Imaging (DWI-MRI) or admitted to the hospital for a cause of non-vascular stroke or with a previous history of any vascular accident or patients with stage IV renal failure or on dialysis, celiac, with any intolerance and /or food allergies, or patients who have modified their diet in the last two weeks were excluded.

The cases were recruited 72 hours after being admitted to the hospital and consecutively until the sample size was completed. For cases that presented a decreased communication capacity, which prevented them from responding to the study questionnaire, the collaboration of a next of kin, defined as the husband or wife or couple, immediate relative, or anybody living in the same house as the case, was utilized.

Controls

For reaching comparability between groups, the controls were patients admitted to the same hospital during the same month the cases were recruited. Controls corresponded to patients hospitalized for any disease unrelated to diet or vascular diseases, and the same exclusion criteria

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were applied in selecting cases. Diagnosis information was obtained through clinical records, and it was checked that the cases did not have stroke events during the hospital stay. All controls were recruited from surgery (56.7 %), general medicine (8.5 %), and the traumatology department (34.4 %) of the hospital. Two controls were consecutively selected for each case (1:2) and matched by sex and age (± 5 years).

Sample size

The sample size was 89 cases and 178 controls, considering an error α = 0.05, a power of 80 %, and a minimum OR associated with the diet of 2.3.

Variables

Socio-demographic, clinical, and anthropometric characteristics

A semi-structured questionnaire was administered to cases and controls, including socio-demographic information, tobacco use, alcohol, and physical activity. The history of arterial hypertension and type 2 diabetes *mellitus* confirmed by medical diagnosis was collected from clinical records.

Food habits

Food habits were measured through a validated Food Frequency Questionnaire (FFQ) of 149 foods. The questionnaire included regular consumption foods in Chile; this instrument was applied to patient or next of kin with trained nurses during the hospital stay by face-to-face interview. The frequency of consumption of each food included in the questionnaire was asked and recorded based on monthly, weekly, and daily intake.

Adherence to Mediterranean diet

The Spanish version of the Questionnaire of Adherence to the Mediterranean diet-MEDAS measured adherence to a Mediterranean diet to the local Chilean terms (24). The MEDAS is a 14-point questionnaire validated and used in the PREDIMED study to assess adherence to a Mediterranean diet pattern; 12 items are related to the dimension frequency of food consumption, and two items are related to food intake habits considered characteristic of the Spanish Mediterranean diet. Each question ranged from 0 to 1, obtaining a final score between 0-14 points (25,26). Higher scores were associated with higher adherence. That questionnaire was applied to the Chilean population, and the cultural translation was carried out: the word "ration" was changed to "portion"; the phrase "piece of fruit" for "units of fruit" and "carbonated drinks" for "soda drinks."

The adherence to the Mediterranean diet was classified into three categories (26): Low (0-3 points), Medium (4-7 points), and High (8-14 points). In addition, we measured by quartile score (p25, p50 and p75).

Statistical analyses

A descriptive analysis of the variables was performed using absolute frequencies and proportions, the normality of the variables was evaluated with the Shapiro Wilk test. A conditional logistic regression was performed to determine the association between the individual components of the Mediterranean diet and the risk of a first stroke while adjusting for age, sex, diabetes *mellitus*, tobacco use (current smoker), alcohol consumption (at least one drink/month), and educational level.

We investigated the association between adherence to the Mediterranean diet and the risk of stroke using conditional logistic regression while adjusting for age, sex, diabetes *mellitus*, tobacco use (current smoker), alcohol consumption (at least one drink/month), and educational level. We used a linear regression model to evaluate the relationship between adherence to the Mediterranean Diet when the

measurement was a continuous variable and the risk of stroke. All statistical analyses were performed with Stata 12.0. An alpha error < 0.05 was considered significant.

Ethics approval and consent to participate

This research was carried out following the guidelines of the Declaration of Helsinki. Each participant signed their informed consent and was approved by the Scientific Ethics Committee of the Herminda Martín of Chillan's Hospital.

RESULTS

Table I shows the distribution of cases and controls according to socio-demographic, clinical, and behavioral variables. The average age of the sample was 71.8 ± 13.97 SD and 64 % were male. Cases smoked (11.2 %) more frequently than controls, and consumed at least one drink per month (41.6 %) and had a diagnosis of hypertension (76.4 %) or diabetes *mellitus* (41.6 %) more frequently than controls. No significant statistical differences were observed between cases and controls.

Table II shows the association between the individual components of the Mediterranean diet and the risk of stroke. It is observed that the cases consumed in lower proportion olive oil (12.4 %), vegetables (84.3 %), legumes (58.4 %), and white meats (40.4 %) compared to the controls. It was consuming commercial pastry less than three times a week that reduced by 70 % the probability of having a first stroke (OR = 0.30; 95 % CI, 0.079-0.98) after adjusting for age, sex, educational level, alcohol consumption, tobacco consumption, and diagnosis of diabetes *mellitus*. An inverse relationship was observed between stroke and higher consumption of olive oil (OR = 0.76; 95 % CI, 0.36-1.59), vegetables (OR = 0.75; 95 % CI, 0.34-1.68), legumes (OR = 0.83; 95 % CI, 0.48-1.43), nuts (OR = 0.60; 95 % CI, 0.20-1.75), and white meats (OR = 0.67; 95 % CI, 0.38-1.19) as well as stroke and lower consumption

of red meat (OR = 0.91; 95 % CI, 0.31-2.60), animal fat (OR = 0.74; 95 % CI, 0.37-1.51), and sugar-sweetened beverages (OR = 0.90; 95 % CI, 0.32-2.61), such as sodas and store-bought juices that include added sugars. However, none of these associations were statistically significant.

Table III shows a more significant protective effect when the adherence to the Mediterranean diet was greater, without reaching statistical significance. In the model adjusted for all variables, it is observed that those who are in quartile 2 of adherence (6-7 points) are 42 % less likely to have a cerebral infarction compared to those who have a lower score ($p < 0.005$). In the linear regression model, for each point that increases adherence according to the MEDAS questionnaire, the probability of having a cerebral infarction decreased by 8 % (OR = 0.92; 95 % CI, 0.76-1.11). The mean MEDAS score is 6.1 (SD = 1.5).

DISCUSSION

In this case-control hospital-based study, 15 % of participants strongly adherence to the Mediterranean diet. This result is concordant with the previous Chilean cross-sectional study (27). Furthermore, regular adherence to the Mediterranean diet is associated with a lower probability of the first ischemic stroke in the Ñuble population after adjustment by confounding variables. These results are consistent with previous retrospective and prospective studies, which reported a lower risk of stroke with high adherence to a Mediterranean diet pattern (28-30). All authors in two systematic reviews chose the Mediterranean diet to reduce stroke or CVD risk and mortality rates. Moreover, six meta-analyses were conducted, choosing that high adherence to the MEDAS diet was associated with decreased stroke risk, overall mortality, and cardiovascular disease incidence or mortality. This study will likely not achieve a significant statistic between high adherence and the risk of ischemic stroke by sample size (31,32).

We have not observed significant associations between individual components of the MEDAS diet and stroke, indicating a synergic effect between individual components. Therefore, it is necessary to analyze the MEDAS pattern overall (33).

Reductions in blood pressure and slight reductions in blood lipids mediate the protective effect of the MEDAS diet. Other probable mechanisms are related to the anti-inflammatory effect of all the foods that make up the Mediterranean diet pattern (34-36). For this reason, the nutrients of interest for public health, due to the protective and beneficial effect on people's cardiovascular health, are fiber, potassium, calcium, and vitamin D. Its main mechanisms are lipid-lowering capacity and blood pressure regulation. However, the low consumption of fruits, vegetables, low-fat dairy products, and whole grains in Chile has led to their consumption not exceeding half of the recommendations (37).

In this case-control study, the mean MEDAS score was 6 (SD = 1.5), which is similar to the found in 368 stroke patients in cross-sectional study (mean 6 SD = 2.3) (27) and similar to the mean 5.7 (SD = 1.6) found in a validation study that used a self-applicable questionnaire for a Chilean Mediterranean dietary index (38) and higher than found in intervention study in 96 Chilean workers (39) whom had a basal score of 4.8 (SD = 1.4) and post dietary intervention the score increase to 7.4 (SD = 1.5).

Chile has a Mediterranean climate and is a producer of the foods that make up the Mediterranean diet, however, there are structural and economic barriers that hinder access and availability of these foods for the population. Evidence supports that the Mediterranean diet is an effective primary prevention strategy for ischemic stroke (28-30), therefore, it would be important to implement public policies that facilitate access to foods from the Mediterranean diet such as fish, olive oil, nuts to the population.

The strengths of this study are that using the PREDIMED questionnaire to assess adherence to the Mediterranean diet allowed us to compare with other studies on the same topic carried out in other countries for its international validation. However, 28 other scores evaluate the same pattern (40). Furthermore, in Chile, the research related to exploring the relationship between diet and diseases is incipient; for that reason, this study is a contribution. This study is carried out in Ñuble, one of the six regions in Chile in which 20 % or more of the population is classified as poor according to the multidimensional poverty index; in this line, Ñuble is similar to many underserved populations in Latin America and other regions in the world.

Limitations of this observational study do not allow for establishing causal relationships, and, likely, some results do not reach the significance statistics probably due to sample size. On the other hand, the fact that participants are from the same hospital limits external validity. There may exist recall bias, but when we contrast the MEDAS diet answer with the FFQ, the results are concordant. Finally, this study did not use biochemical parameters (For example, inflammatory markers) as adjustment variables, which could have been interesting to include.

Our findings suggest that moderate adherence to a Mediterranean diet, defined by the PREDIMED score and adjustment for other variables, reduces the probability to first ischemic stroke but more local research with higher sample size is needed to complement our results. Evidence shows that changing dietary habits and improving adherence to the Mediterranean diet decrease cardiometabolic risk factors and stroke in high-risk populations, but it is unclear whether it could be used as a population-level primary prevention strategy (41,42).

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Table I. Description of sample

Variables	Cases (*n* = 89) n/%	Controls (*n* = 178) n/%	*p*-value
Age			
≤ 55 y	17 (19.1)	26 (14.6)	
56-64 y	10 (11.2)	25 (14)	0.570
≥ 65 y	62 (69.7)	127 (71.4)	
Sex			
Men	57 (64)	114 (64)	1.000
Women	32 (36)	64 (36)	
Educational level			
≤ 8 y	61 (68.5)	128 (71.9)	
9-12 y	24 (27)	40 (22.5)	0.691
≥ 13 y	4 (4.5)	10 (5.6)	
Tobacco			
Never	68 (77.5)	149 (83.7)	
Currently	10 (11.2)	9 (5.1)	0.162
Have quit smoking	11 (12.3)	20 (11.2)	
Alcohol			
Never	52 (58.4)	127 (71.3)	0.064
At least once a month	37 (41.6)	51 (28.7)	

Physical activity			
Yes	3 (3.4)	5 (2.8)	0.254
No	86 (96.6)	173 (97.2)	
Arterial hypertension	68 (76.4)	129 (72.5)	0.491
Yes	21 (23.6)	49 (27.5)	
No			
Diabetes mellitus			
Yes	37 (41.6)	63 (35.4)	0.325
No	52 (58.4)	115 (64.6)	

Table II. Odds ratios and confidence interval 95% for stroke by individuals´ components of Mediterranean diet

Components	Cases *n* (%)	Controls *n* (%)	OR* (95 % CI)	OR† (95 % CI)
Use olive oil as the principal source of fat	11 (12.4)	28 (15.9)	0.76 (0.36-1.59)	0.60 (0.28-1.31)
Consume > 2 spoons of olive oil per day	9 (10.1)	27 (15.3)	0.64 (0.29-1.40)	0.55 (0.25-1.26)
Consume ≥ 2 portions of vegetables per day	75 (84.3)	153 (86.9)	0.75 (0.34-1.68)	0.77 (0.33-1.77)
Consume < 3 portions of fruits per day	83 (93.2)	167 (94.8)	1.33 (0.47-3.74)	1.50 (0.50-4.54)
Consume < 1 portions of red meat per day	81 (91)	161 (91.4)	0.91 (0.31-2.60)	0.73 (0.24-2.24)
Consume < 1 portion of butter per day	75 (84.3)	141 (80.1)	0.74 (0.37-1.51)	0.75 (0.36-1.57)
Consume < 1 portion of sugar-sweetened beverage per day	84 (94.4)	165 (93.7)	0.90 (0.32-2.61)	0.77 (0.25-2.39)
Consume ≥ 3 glasses of wine per week	8 (8.9)	14 (7.9)	0.87 (0.37-2.08)	0.95 (0.34-2.08)
Consume ≥ 3 portions of legumes per week	52 (58.4)	111 (62.4)	0.83 (0.48-1.43)	0.79 (0.44-1.41)
Consume < 3 portions of fish or seafood per week	88 (98.8)	171 (96.1)	3.99 (0.45-35.0)	4.42 (0.49-39.9)
Consume < 3 portions of	86 (96.6)	176 (98.8)	0.34	0.30

			(0.09-1.28)	(0.079-0.98)
commercial sweetx or pastries per week				
Consume > 1 portions of nuts per week	7 (7.8)	9 (5.1)	0.60 (0.20-1.75)	0.64 (0.21-1.95)
Consume chicken or turkey	36 (40.4)	86 (48.3)	0.67 (0.38-1.19)	0.70 (0.39-1.26)
Consume cooked vegetables, pasta, rice or other dishes prepared with olive oil	7 (7.9)	17 (9.6)	0.81 (0.33-2.00)	0.79 (0.32-1.99)

*Adjustment by year and sex. †Adjustment by year, sex, educational level, alcohol, tobacco, and diabetes *mellitus* type 2.

Table III. Odds ratios and confidence interval 95% for stroke by Mediterranean diet adherence score

Mediterranean diet adherence	Cases n (%)	Controls n (%)	OR (95 % CI)*	OR (95 % CI)†
Quartils				
Q1 (0-5 score)	39	58	Ref	Ref
Q2 (6-7 score)	39	89	0.64 (0.36-1.13)	0.58 (0.32-0.98)
Q3 (8-11 score)	11	29	0.55 (0.23-1.28)	0.50 (0.20-1.19)
PREDIMED score				
Low (0-4 score)	7	17	Ref	Ref
Moderate (5-7 score)	71	130	1.30 (0.48-3.50)	1.40 (0.49-3.98)
High (8-14 score)	11	29	0.90 (0.26-3.14)	0.94 (0.26-3.44)
Score (continuous)			0.94 (0.78-1.13)	0.92 (0.76-1.11)

*Adjustment by sex and year. †Adjustment by sex, year, educational level, tobacco, alcohol consumption, and diabetes *mellitus* type 2.