



## SHORT COMMUNICATION

## American Heart Association's life simple 7 and the risk of atrial fibrillation in the PREDIMED study cohort

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**Abstract** *Background and aims:* The American Heart Association proposed 7 ideal cardiovascular health metrics (Life's Simple 7 [LS7]) namely, not smoking, body mass index <25 kg/m<sup>2</sup>, healthy diet, moderate physical activity ≥150 min/week, total blood cholesterol <200 mg/dL, blood pressure <120/80 mmHg and fasting blood glucose <100 mg/dL. Our objective was to assess the association between these LS7 metrics and the incidence of atrial fibrillation (AF). *Methods and results:* A total of 6,479 participants of the PREDIMED study were included. We calculated the participants' baseline LS7 index ranging 0–7 points to categorize them according to their adherence to these LS7 health metrics. Multivariable Cox regression models were used to estimate Hazard Ratios (HR) and their 95% Confidence Intervals (95% CI). After a median follow-up of 4.8 years, we identified 250 incident cases of AF. After adjusting for potential confounders, adherence to LS7 index was not associated with the incidence of AF (adjusted HR 0.90 [95% CI: 0.56–1.45] for highest vs. lowest LS7 categories). Body mass index <25 kg/m<sup>2</sup> was the only health metric individually associated with a lower risk of AF (HR 0.36 [95% CI: 0.16–0.78]).

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**Conclusions:** In a high cardiovascular risk Spanish population, adherence to American Heart Association's LS7 metrics was not associated with the risk of incident AF.

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## 1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice [1]. A progressive increase in its prevalence during the following years is expected in relation with population aging and greater diagnosis efforts [2]. The diagnosis of AF is associated with an increased risk of serious health issues, including heart failure, stroke and dementia, higher morbimortality and impaired quality of life [3,4]. Therefore, efficient public health efforts should be directed towards AF prevention to avoid AF related health costs and diminish patients' sufferings.

To promote cardiovascular health, the American Heart Association proposed seven ideal cardiovascular health metrics in 2010 [5]. The classical idea of cardiovascular risk factors took a secondary role in favor of a positive health message. Life's Simple 7 (LS7) index was defined according to 3 healthy behaviors (no smoking, physical activity and following a healthy diet) and 4 health metrics (total cholesterol <200 mg/dL, body mass index <25 kg/m<sup>2</sup>, fasting glucose <100 mg/dL and blood pressure levels ≤120/80 mmHg).

As far as we know, only 3 American population cohorts have shown an inverse association between adherence to LS7 index and the risk of AF [6–8]. However, the magnitude of the effect was small and moreover, the confidence intervals included the null value (pooled HR 0.94 [95% CI: 0.86–1.01]) when the LS7 score was analyzed as a continuous variable in a recent meta-analysis pooling these 3 studies [9].

In a previous analysis within the PREDIMED (Prevenición con Dieta Mediterránea) study, we observed a strong inverse association between the number of LS7 ideal cardiovascular health metrics and the incidence of cardiovascular disease [10]. However, the association between the LS7 and the risk of AF remains elusive in a Mediterranean population. Therefore, the objective of this study was to prospectively analyze the impact of LS7 health metrics on AF risk in a Spanish cohort at high cardiovascular risk.

## 2. Methods

The PREDIMED study is a randomized, controlled, multicenter trial conducted in Spain, that recruited 7,447 participants according to the following criteria: men and women (55–80 years) with no previous cardiovascular

disease but at high cardiovascular risk, defined as prevalent type 2 diabetes mellitus or ≥3 of any of the following cardiovascular risk factors: current smoker, hypertension, hypercholesterolemia, low high-density lipoprotein cholesterol, overweight/obesity, or family history of premature coronary heart disease. We studied all participants at risk of atrial fibrillation at the beginning of the PREDIMED trial. We excluded 75 participants who reported prevalent AF at baseline, 841 participants without available AF follow-up (including 667 participants from 1 center in which AF was not assessed systematically) and 52 participants with energy intake levels out of the predefined limits (<400 kcal or >5000 kcal in women and >6000 kcal in men). We finally included a total sample of 6,479 participants. All participants provided written informed consent and the study protocol was approved by the Research Ethics Committees at each participating center.

In the baseline interview, physical examination included weight, height, and blood pressure measurements. Laboratory analyses were performed to determine the lipid profile and fasting glucose concentration, among other parameters.

The LS7 metrics used were obtained from baseline data as described in our previous analysis [10]. Participants with blood pressure <120/80 mmHg but treated hypertension and participants with total cholesterol <200 mg/dL but treated hypercholesterolemia were scored with a 0 for the LS7 metric. A healthy diet was defined according to the Mediterranean diet adherence screener (MEDAS) dietary pattern, (9 or more points out of the total 14-point scale) [11]. The minimum adequate physical activity was the equivalent of 500 METs-h/week, assessed with the validated Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire [12,13].

Information about incident AF cases was obtained by annual review of medical records or yearly ECGs performed during the follow-up visits in the study. New AF cases were confirmed by a blinded Adjudication Committee. We included all incident AF cases from baseline until the end of the trial in December of 2010. Additional information about the diagnosis of AF has already been discussed elsewhere [14].

Cox multivariable regression models were fitted to calculate the risk of AF during follow-up according to the number of LS7 metrics (4 categories). The upper and lower ends of the range were collapsed, as there were few participants with 0 or with more than 5 metrics. Hazard

Ratios (HR) and their 95% confidence intervals (95% CI) were calculated using the group with 0–1 metrics as the reference category. We calculated person-years of follow-up from the date of the baseline visit to the date of AF diagnosis, death, or the end of follow-up, whichever occurred first. A predefined multiplicative interaction was analyzed between sex and the PREDIMED dietary intervention and LS7 score via a likelihood ratio test. To control for potential confounding factors, a multivariable model was stratified by sex, center, and intervention group, and it was adjusted for age, height, sleep apnea, heart failure and non-atherosclerotic coronary disease. All p values were 2-sided and were considered statistically significant at  $p < 0.05$ .

### 3. Results

Participants were followed-up for a median time of 4.8 years. There were 250 incident cases of AF. The participants' baseline characteristics according to LS7 metrics are shown in Table 1. Participants with a higher adherence to LS7 cardiovascular health metrics were more likely to be women (70%) and had a higher scoring in the Mediterranean dietary pattern. No participants reached 7 metrics and only 0.02% and 1.48% of participants achieved 6 and 5 metrics, respectively.

The incidence of AF did not differ significantly between participants who achieved more LS7 health metrics (4–7 points) in comparison to participants in the lower category of LS7 health metrics (0–1 points), even after adjustment for potential confounding variables in multivariate Cox

regression analysis (HR 0.90 [95% CI: 0.56–1.45];  $p$  for trend = 0.92) (Table 2). For each additional point in the LS7 score, the multivariate HR for the risk of AF was 1.01 (95% CI: 0.90–1.14) (Table 2).

Body mass index  $<25 \text{ kg/m}^2$  was the only LS7 health metric individually associated, independently of the other LS7 metrics, with a lower risk of AF during follow-up (HR 0.36 [95% CI: 0.16–0.78]).

We did not find any significant interaction between sex and LS7 score ( $p$  for interaction = 0.33) or between the PREDIMED dietary interventions and LS7 score ( $p$  for interaction = 0.56).

### 4. Discussion

In this prospective analysis nested within the PREDIMED study, we did not find any significant association between the ideal cardiovascular health metrics proposed by the American Heart Association in the LS7 index and the risk of AF. In individual analyses of each LS7 component, we found a significant 64% relative reduction of incident AF only among those participants that met the ideal health criteria for low body mass index ( $<25 \text{ kg/m}^2$ ).

In a recent meta-analysis, Liu et al. [9] found no significant association between LS7 as a continuous variable and AF in a pooled analysis of 3 cohort studies with a total of 3,700 incident cases of AF (HR 0.94 [95% CI: 0.86–1.01];  $I^2 = 97.7\%$ ), although the individual studies reported a small but significant decrease in the risk of AF. There was substantial heterogeneity between these studies and differences may be related to diverse reasons. In the

**Table 1** Baseline characteristics of participants according to the number of Life's Simple 7 health metrics in the Prevención con Dieta Mediterránea (PREDIMED) study.

Number of Life's Simple 7 Health Metrics	Number of Life's Simple 7 Health Metrics			
	0–1	2	3	4–7
N	1,536	2,351	1,850	742
Sex, n (% women)	653 (42.5)	1,339 (57)	1,227 (66.3)	519 (70.0)
Age (years), mean $\pm$ SD	66.1 $\pm$ 6.2	67.2 $\pm$ 6.2	67.5 $\pm$ 6.2	67.3 $\pm$ 5.8
BMI ( $\text{kg/m}^2$ ), mean $\pm$ SD	31.0 $\pm$ 3.9	30.3 $\pm$ 3.6	29.6 $\pm$ 3.8	28.2 $\pm$ 3.9
Mediterranean dietary pattern (points), mean $\pm$ SD	7.8 $\pm$ 1.6	8.5 $\pm$ 1.9	9.2 $\pm$ 1.9	10.2 $\pm$ 1.5
Height (cm), mean $\pm$ SD	162.2 $\pm$ 9.2	159.8 $\pm$ 8.8	158.9 $\pm$ 8.6	158.8 $\pm$ 8.2
Sleep apnea, n (%)	37 (2.4)	46 (2.0)	27 (1.5)	10 (1.4)
Cardiopathy <sup>a</sup> , n (%)	55 (3.6)	67 (2.9)	53 (2.9)	29 (3.9)
Total cholesterol (mg/dL), mean $\pm$ SD	211.1 $\pm$ 33.2	211.9 $\pm$ 33.4	210.3 $\pm$ 36.0	207.1 $\pm$ 38.6
LDL-cholesterol (mg/dL), mean $\pm$ SD	132.7 $\pm$ 37.6	132.3 $\pm$ 36.4	136.3 $\pm$ 34.8	133.1 $\pm$ 34.5
HDL-cholesterol (mg/dL), mean $\pm$ SD	50.0 $\pm$ 12.0	53.0 $\pm$ 13.0	54.0 $\pm$ 14.0	56.0 $\pm$ 15.1
Systolic blood pressure (mmHg), mean $\pm$ SD	150.2 $\pm$ 18.2	149.4 $\pm$ 19.1	147.7 $\pm$ 19.0	144.4 $\pm$ 20.1
Diastolic blood pressure (mmHg), mean $\pm$ SD	83.6 $\pm$ 9.9	83.0 $\pm$ 10.1	82.2 $\pm$ 10.2	81.0 $\pm$ 10.5
Blood glucose (mg/dL), mean $\pm$ SD	134.5 $\pm$ 37.0	124.5 $\pm$ 34.8	113.9 $\pm$ 35.8	102.8 $\pm$ 32.0
Diabetes, n (%)	897 (58.4)	1,216 (51.7)	743 (40.2)	263 (35.4)
Life's Simple 7 metrics (yes/no), n (%)				
Nonsmoker	486 (31.6)	1,431 (60.9)	1,423 (76.9)	662 (89.2)
BMI $<25 \text{ kg/m}^2$	21 (1.4)	86 (3.7)	188 (10.2)	185 (24.9)
Blood pressure $\leq 120/80 \text{ mmHg}$	3 (0.20)	26 (1.1)	54 (2.9)	83 (11.2)
Total cholesterol $<200 \text{ mg/dL}$	55 (3.6)	298 (12.7)	396 (21.4)	281 (37.9)
Blood glucose $<100 \text{ mg/dL}$	72 (4.7)	469 (20.0)	881 (47.6)	536 (72.2)
Mediterranean dietary pattern $>9$ points	102 (6.6)	631 (26.8)	970 (52.4)	604 (81.3)
Exercise $>500 \text{ METs-h/week}$	590 (38.4)	1,761 (74.9)	1,638 (88.5)	715 (96.4)

BMI: body mass index; LDL: low density lipoprotein; HDL: high density lipoprotein; METs-h: metabolic equivalent of task per hour.

<sup>a</sup> Heart failure and non-atherosclerotic coronary disease.

**Table 2** Hazard Ratio and 95% Confidence Interval of incident Atrial Fibrillation according to the number of Life's Simple 7 health metrics in the Prevención con Dieta Mediterránea (PREDIMED) study.

	Participants, n	Cases/person-years, n/N	Crude	Multivariate adjusted <sup>a</sup>
<b>Number of Life's Simple 7 health metrics</b>				
0–1	1,536	58/6,558	1 (Ref.)	1 (Ref.)
2	2,351	94/10,243	1.04 (0.75–1.43)	0.99 (0.69–1.42)
3	1,850	72/8,316	1.01 (0.71–1.43)	1.13 (0.79–1.61)
4–7	742	26/3,451	0.87 (0.55–1.36)	0.90 (0.56–1.45)
<b>Life's Simple 7 score as a continuous variable (for each additional point)</b>				
<b>Individual Life's Simple 7 factors</b>				
Not smoking	4,002	136/17,821	0.71 (0.55–0.91)	0.92 (0.66–1.27)
BMI <25 kg/m <sup>2</sup>	480	10/2,157	0.50 (0.27–0.91)	0.36 (0.16–0.78)
Mediterranean dietary pattern <sup>b</sup>	2,307	94/10,490	1.12 (0.87–1.45)	1.06 (0.80–1.39)
Moderate physical activity <sup>c</sup>	4,704	192/20,861	1.14 (0.85–1.52)	1.17 (0.84–1.63)
Total cholesterol <200 mg/dL	1,030	55/4,557	1.48 (1.09–2.00)	1.24 (0.89–1.73)
Blood pressure <120/80 mmHg	166	5/722	0.87 (0.36–2.12)	0.96 (0.40–2.34)
Fasting blood glucose <100 mg/dL	1,958	71/8,765	0.95 (0.72–1.26)	1.00 (0.74–1.35)

<sup>a</sup> Adjusted for center, intervention group, sex, age, height, heart failure and sleep apnea.

<sup>b</sup> Mediterranean diet adherence screener (MEDAS)  $\geq 9$  points (from 0 to 14 points; higher scores indicate better adherence).

<sup>c</sup> 500 METs-h/week (Minnesota Leisure Time Physical Activity Questionnaire).

REGARDS study [7] the analyses were limited to self-reported AF cases and information regarding the time to event was not collected. In the MESA [8] study the method of AF case ascertainment was stricter, as investigators decided to include only the most severe cases requiring hospitalization. Finally, in the ARIC study [6] AF cases requiring hospitalization and also those detected on routine ECG were taken into account, so paroxysmal AF cases were more unlikely to be included.

Unlike previous research [6–8], we considered incident AF cases when AF was detected on the ECG performed at the annual follow-up visit or when an explicit diagnosis was made by a physician, without the need for hospitalization. This is a strength of our study, since we had a higher likelihood of including cases with less severe AF and a lower burden of AF.

We stratified our analyses by the intervention group of the PREDIMED trial (Mediterranean diet enriched either with extra-virgin olive oil or nuts versus a control low-fat diet) in order to account for potential changes in dietary habits during the study time. Thus, minimizing misclassification of diet in relation to the trial allocation.

In accordance with PREDIMED's inclusion criteria, participants were at high risk of cardiovascular disease at the beginning of the study. Participants in the PREDIMED study had a lower proportion of LS7 metrics and a higher cardiovascular risk profile. This is a relevant difference compared to participants included in previous studies and it may have precluded the prevention of AF substrate

development through the lifestyle factors included in the LS7 index. In addition, we found no significant association between adherence to the Mediterranean diet at baseline, used as one metric for the LS7, and AF risk. This negative result contrasts with the protective effect on AF development of the Mediterranean diet group enriched with extra-virgin olive oil compared to the control group, observed in the PREDIMED trial [14]. This difference suggests the need of an intensive intervention where the consumption of extra-virgin olive oil is promoted in the context of a Mediterranean dietary pattern.

In summary, adherence to LS7 metrics may be useful for improving cardiovascular health, however a tailored approach towards AF prevention to counteract the emerging epidemic of AF is urgently needed.

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### Declaration of competing interest

The authors declared no potential conflicts of interest.

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