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Original article

Lifestyles and the risk of depression in the "Seguimiento Universidad de Navarra" cohort

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ABSTRACT

Background: Lifestyles are involved in the pathogenesis of depression and many of these factors can be modified for the potential prevention of depression. Our aim was to assess the association between a healthy-lifestyle score, that includes some less-studied lifestyle indicators, and the risk of depression.
Methods: We followed 14,908 participants initially free of any history of depression in the "Seguimiento Universidad de Navarra" (SUN) cohort. Information was collected biennially from 1999 to December 2016. We calculated a healthy-lifestyle score (0–10 points), previously associated with cardioprotection, by giving one point to each of the following components: never smoking, physical activity (> 20 METs-h/week), Mediterranean diet adherence ($\geq$ 4 points), healthy body mass index ($\leq$ 22 kg/m^2), moderate alcohol consumption (women 0.1–5 g/d; men 0.1–10 g/d of ethanol), avoidance of binge drinking (never more than 5 alcoholic drinks in a row), low television exposure ($\leq$ 2 h/d), short afternoon nap ($\leq$ 30 min/day), time spent with friends (>1 h/d) and working at least 40 h/week.
Results: During a median follow-up of 10.4 years, we observed 774 new cases of major depression among participants initially free of depression. The highest category (8–10 factors) showed a significant inverse association with a 32% relative risk reduction for depression compared to the lowest category (0–3 factors) (multivariable-adjusted hazard ratio: 0.68; 95% CI:0.49-0.95) (p for trend = 0.010).
Conclusions: Adopting a healthy-lifestyle was associated with a lower risk of incident depression in the SUN cohort. This index, including ten simple healthy lifestyle habits, may be useful for a more integrative approach to depression prevention.

1. Introduction

Depression is now considered one of the leading causes of disability worldwide, with 4.4% (332 million) of the world's population affected [1]. Moreover, the number of people with this condition has increased by 18.4% between 2005 and 2015 [2]. The consequences of this increase are enormous owing to the fact that depression affects quality of life, productivity, social roles, as well as, increased medical comorbidities and mortality [3]. Therefore, prevention strategies are urgently needed to alter the current and future burden of this disorder.

There is strong evidence that a range of lifestyle factors, such as diet, physical activity, smoking and alcohol consumption are involved in the pathogenesis of major depressive disorder. Over the past years, several studies have studied modifiable lifestyle behaviors potentially associated with this common condition. Some cross-sectional studies [4–6] and prospective studies [7–9] have reported a beneficial effect of a combination of healthy lifestyle factors on depression risk.

In addition to the traditional lifestyle indicators assessed in these studies, there are various other habits that likely influence depression. For instance, social integration and perceived social support have beneficial effects on depressive symptoms [10]. Napping, specifically a short afternoon nap, leads to improvements in well-being, mood and cognitive performance as well [11]. Moreover, working hours has

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beneficial effects on depression symptomatology through colleague support and a maintained daily routine [12]. On the other hand, duration of TV watching and computer use was associated with moderate or severe depression [13].

To the best of our knowledge, no study has included these non-traditional aspects of lifestyle in a score and then assessed the relationship with depression risk.

The aim of our study was to longitudinally assess the combined impact of 10 simple indicators of a healthy lifestyle on depression risk in a Mediterranean cohort.

2. Methods

2.1. Study population

The Seguimiento Universidad de Navarra (SUN) project is a prospective, dynamic and multipurpose cohort of Spanish university graduates. Information has been gathered biennially since 1999, which has previously been described in detail [14]. A total of 22,564 participants were recruited by December 2016. For the present analysis, we included only those participants recruited before March 2014, in order to allow for a minimal follow-up of two years. Out of 22,279 eligible individuals, we excluded those who reported a lifetime history of clinical diagnosis of depression or reported the use of antidepressants at baseline (n = 2621), those with a depression diagnosis before the first 2 years of follow-up (early cases) (n = 409), those with a total energy intake outside of predefined limits (< 800 kcal/day or > 4000 kcal/day in men, and <500 kcal/day or >3500 kcal/day in women) [15] (n = 1,805), those with prevalent chronic diseases (diabetes, cardiovascular disease and cancer, n = 1,054), and those who were lost to follow-up (did not complete at least one follow-up questionnaire) (n = 1,482, retention rate = 91%). Finally, 14,908 participants were included in the present statistical analyses (Fig. 1).

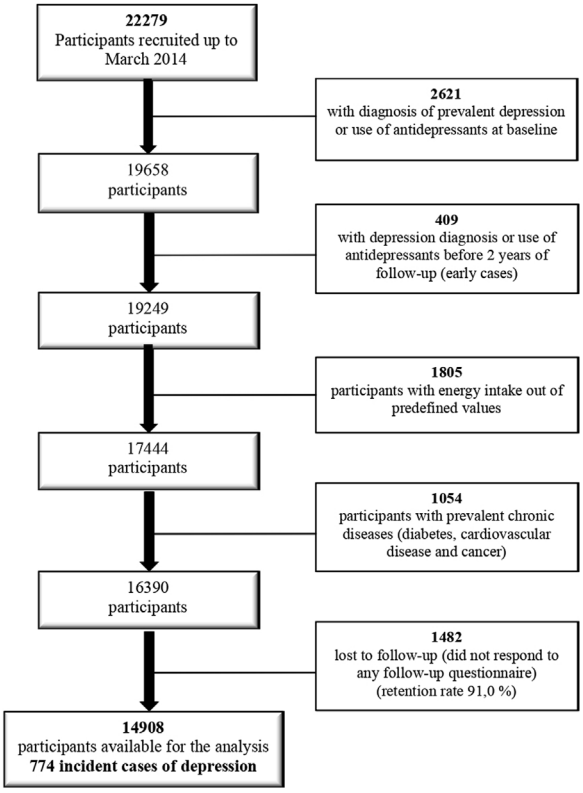

Fig. 1. Flow chart of participants. The SUN Project.1999–2014.

Ethical approval was given by the Institutional Review Board of the University of Navarra. Participants were informed in writing of the study, and voluntary completion of the first self-administered questionnaire was considered to imply informed consent.

2.2. Main exposure variables

The baseline questionnaire collected information on socio-demographic, lifestyle aspects, anthropometric variables, and medical history. The reproducibility and validity of the reported anthropometrics [16] and physical activity [17] data were evaluated in cohort subgroups. A previously validated [18–20] 136-item semi-quantitative food-frequency questionnaire was used to measure food habits at baseline. Alcohol consumption was recorded via this questionnaire and other items related to alcohol consumption were also collected in the baseline questionnaire. Adherence to the Mediterranean Diet Score (MDS) was estimated with the score (0–8 points) developed by Trichopoulou et al. [21], although alcohol was excluded.

We assessed the adherence to a healthy lifestyle score (HLS) (0–10 points) previously reported to be inversely associated with hard cardiovascular events in this cohort [22] (Table 1). Each participant received one point for each of the following: never smoking, moderate-to-high physical activity (>20 MET-h/week), medium-to-high MDS adherence ($\geq$ 4/8 points), low body mass index (BMI) $\leq$ 22 kg/m^2, 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), avoidance of binge drinking (never > 5 drinks in a row), taking a short afternoon nap ($\leq$ 30 min/d), meeting up with friends > 1 h/d, and working at least 40 h/week. Participants were categorized into 4 groups to ensure an adequate distribution of the sample with a sufficient number of participants in each score category. Therefore, the HLS categories were 0–3 points (worst lifestyle), 4–5 points, 6–7 points, and 8–10 points (best lifestyle).

2.3. Outcome assessment

Incident cases of depression were defined as participants who were free of any previous history of depression at baseline, were not using any antidepressant treatment at baseline, and positively responded in any of the follow-up questionnaires to the question, “Have you ever been diagnosed with depression by a medical doctor?”; or reported habitual new use of antidepressant treatment in any of the follow-up questionnaires. Either of both criteria (medical diagnosis or onset of habitual antidepressants) was sufficient to be classified as a new case of depression. The prescription of antidepressants for conditions other than depression is highly unusual in Spain. Therefore, we considered it a valid criterion to define incident depression. The self-reported diagnosis of depression has been previously validated in a subsample of our cohort using the Structured Clinical Interview for DSM-IV (conducted by a senior psychiatrist or clinical psychologist) as gold standard, yielding a specificity of 96% (the percentages of confirmed depression and confirmed non-depression were 74.2% (95% CI 63.3–85.1) and 81.1% (95% 69.1–92.9), respectively) [23].

2.4. Assessment of covariates

Information regarding energy intake, sociodemographic variables (marital status, living status), years of university education, analgesic consumption [24] were assessed with the baseline questionnaire. Personality traits (self-perceived level of competitiveness, psychological tension and dependency) were associated with depression risk in our cohort [25]. Information regarding these items was also obtained with the baseline questionnaire including the following questions: a) Do you consider yourself a

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Table 1
Healthy lifestyle score.

	Score	N
Smoking		
Never smokers	1	7289
Smokers (active and former smokers)	0	7619
Physical activity (METs-h/week)		
Physically active (> 20 METs-h/week)	1	7604
Not physically active (≤ 20 METs-h/week)	0	7304
Mediterranean dietary pattern (Modified Trichopoulou score)[a]		
High adherence (≥ 4)	1	9098
Low adherence (< 4)	0	5810
Body Mass Index (kg/m^2)		
≤ 22	1	5679
< 22	0	9229
Alcohol intake (g per day)[b]		
Moderate alcohol intake (women 0.1-5 g/d; men 0.1-10 g/d)	1	7428
Abstainer or high alcohol intake (women > 5 g/d; men > 10 g/d)	0	7480
TV watching (hours per day)		
< 2 h/d	1	10564
≥ 2 h/day	0	4344
Binge drinking[c] **(alcoholic drinks on any occasion)**		
Never binge drinking (≤ 5 alcoholic drinks on any occasion)	1	10155
Binge drinking (> 5 alcoholic drinks on any occasion)	0	4753
Sleeping mid-day nap (hours per day)		
Sleeping short mid-day nap (0.1-0.5 h/d)	1	8522
No sleeping or sleeping longer mid-day nap (> 0.5 h/d)	0	6386
Time spent with friends (hours per day)		
Spend time with friends (> 1 h/day)	1	6440
Not spending time with friends (≤ 1 h/d)	0	8468
Time working (hours per week)		
Working (≥ 40 h/week)	1	8011
Working (< 40 h/week)	0	6897

[a] Trichopoulou score (from 0 to 8, higher scores indicate greater adherence, alcohol consumption was excluded).
[b] grams of ethanol per day.
[c] Drinking more than 5 alcoholic drinks at any time.

competitive, nonconformist, fighter person, who demands everything of yourself at work and sometimes even more of what you can afford?, b) Do you consider yourself a tense, aggressive, usually feeling overloaded, highly strung person or you think of yourself as a relaxed and calm person, and c) Do you think you have enough resources, preparation and autonomy to solve any problems at work, or do you exclusively depend on others to do it?. For each question, 11 possible answers could be chosen by the participant ranging from 0 (more conformist, relaxed or autonomous) to 10 (more competitive, tense or dependent).

2.5. Statistical analysis

Baseline characteristics of participants adjusted for age and sex, using the inverse probability weighting method, [26] were described according to categories of the HLS using relative frequencies, means and standard deviations.

Cox regression models were fitted (with age as the underlying time scale) to assess the risk of incident depression during follow-up according to 4 categories of the HLS. We calculated Hazard Ratios (HR) and their 95% confidence intervals (CI) defining the reference category as those participants with the lowest lifestyle scores (0–3 points). Person-years of follow-up were calculated for each participant, from the date of completion of the baseline questionnaire until the date of completion of the last follow-up questionnaire, the date of diagnosis of depression or the date of death, whichever occurred first. We performed linear trend tests considering the HLS as a continuous variable.

In order to control for possible confounding factors, a multivariable model was used with age as the scale of time. In addition, we stratified the model by deciles of age and by 5 categories of calendar years according to the date of entry into the cohort. The multivariable model was adjusted for the following possible additional confounding factors: sex, total energy intake (kcal/day, quartiles), marital status (single, married, widow, divorced, others), living status (living alone or with others), years of university studies (continuous), regular use of aspirin and non-aspirin analgesic (≥ 2 times/week), and personality traits: self-perceived level of competitiveness, tension and dependency (continuous).

A predefined multiplicative interaction between the HLS and age was analyzed via a likelihood ratio test.

The individual contribution of each specific healthy-lifestyle factor to depression risk was evaluated. Cox models were fitted for each of the 10 healthy-lifestyle habits as independent variables adjusting the models for the effect of the other healthy-lifestyle factors. The reference category for each independent analysis was the absence of the healthy-lifestyle habit (0 points in the specific factor).

To test the robustness of our results, we conducted several sensitivity analyses. The models were rerun after changing the range of moderate alcohol consumption in the score for 10–50 g/day for men and 5–25 g/day for women as suggested by Trichopoulou [21], after changing the criteria of exclusion for energy limits (percentile 5–95), after excluding those participants with a weight gain of 5 kg or more in the last 5 years before answering the baseline questionnaire, or after excluding pregnant women.

Very importantly, we reran our analyses after changing the definition of incident depression for a more specific definition, considering only those participants who reported a new medically-diagnosed depression and also a new habitual use of antidepressant medication simultaneously, i.e., both criteria were needed to be classified as an incident case.

Additionally, we changed the BMI cut-off point in our score to be 20–25 kg/m^2 and in another sensitivity analysis we also eliminated all participants with a BMI < 18.5, taking into account that a lower BMI could be related to a possible eating behaviour disorder, an altered appetite or weight dysregulation.

All analyses were conducted with Stata version 15.0 (StataCorp, College Station, TX). All p values presented are two-sided and were considered statistically significant at < 0.05.

3. Results

We followed 14,908 participants, 8,876 (59.5%) women and 6,032 (40.5%) men. Participants mean age at recruitment was 36.7 years (SD:11.7). Table 2 shows the baseline characteristics of participants according to the HLS. Participants in the highest categories of the score were more likely to be single, never-smokers, tended to have a lower BMI, higher physical activity, lower alcohol intake, lower percentage of binge drinking and a greater adherence to the Mediterranean dietary pattern. Moreover, they tended to work more hours, use less analgesics, and spend less time watching television. Regarding personality traits, they tended to have a higher competitiveness level, but lower psychological tension and dependency.

3.1. Depression cases

Among participants who were initially free of medically-diagnosed depression or use of antidepressant medications, 774 cases of depression were reported after a median follow-up of 10.4 years (interquartile range: 6.7–14.1 years). A greater number of healthy-lifestyle factors was associated with a lower risk of depression in both adjusted and unadjusted models. Participants with the best healthy-lifestyle score (8–10 points) showed a 32%

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Table 2
Baseline characteristics of the participants according to the Healthy Lifestyle Scores (HLS).[a]

Categories of the HLS	0-3	4-5	6-7	8-10
Subjects (n)	1715	5941	5878	1374
Smoking (%)				
Never smoker	292 (17.1)	2228 (37.5)	3600 (61.2)	1202 (87.3)
Former smoker	573 (33.5)	1662 (28.0)	1154 (19.6)	92 (6.7)
Current smoker	787 (45.9)	1860 (31.3)	999 (17.0)	76 (5.5)
Physical activity (MET-h/week)	17.4 ± 18.1	23.3 ± 21.5	30.8 ± 25.1	40.0 ± 27.8
Mediterranean dietary pattern[b]	3.1 ± 1.5	3.8 ± 1.7	4.4 ± 1.7	5.0 ± 1.4
Body Mass Index (kg/m^2)	24.7 ± 3.5	23.8 ± 3.4	23.1 ± 3.3	22.1 ± 2.9
Alcohol intake (g/day)	10.3 ± 14.7	7.3 ± 10.1	5.1 ± 7.0	3.9 ± 4.4
Binge drinking[c] (%)	1057 (61.7)	2318 (39.0)	1260 (21.4)	119 (8.7)
TV watching (h/day)	2.3 ± 1.4	1.8 ± 1.3	1.4 ± 1.0	1.1 ± 0.7
Sleeping mid-day nap (h/day)	0.33 ± 0.4	0.27 ± 0.3	0.24 ± 0.2	0.23 ± 0.2
Time spent with friends (h/day)	1.1 ± 1.0	1.3 ± 1.1	1.4 ± 1.0	1.6 ± 1.0
Working ≥ 40/h per week (%)	447 (26.1)	2707 (45.6)	3707 (63.1)	1140 (82.8)
Total energy intake (kcal/day)	2289 ± 623	2328 ± 614	2386 ± 613	2428 ± 598
Years of university education	4.9 ± 1.4	5.0 ± 1.5	5.1 ± 1.6	5.3 ± 1.7
Marital status (%)				
Single	653 (38.4)	2598 (44.0)	2763 (47.4)	701 (51.2)
Married	980 (57.8)	3074 (52.1)	2836 (48.6)	602 (43.9)
Widower-divorced-other	66 (3.9)	231 (3.9)	235 (4.0)	67 (4.9)
Living alone (%)	99 (5.8)	351 (5.9)	377 (6.4)	130 (9.5)
Personality traits[d] (%)				
Competitiveness level	1009 (58.9)	3887 (65.4)	4166 (70.9)	1039 (75.5)
Psychological tension	761 (44.4)	2607 (43.9)	2614 (44.5)	575 (41.8)
Dependence level	406 (23.7)	1304 (22.0)	1326 (22.6)	276 (20.1)
Analgesic intake (%)	204 (11.9)	653 (11.0)	548 (9.3)	108 (7.9)

[a] Adjusted for age and sex with the inverse probability weighting method [50]. Data represent n (%) or means ± standard deviation (SD).
[b] Trichopoulou's score (from 0 to 8, higher scores indicate greater adherence, alcohol consumption was excluded).
[c] Drinking more than 5 alcoholic drinks at any time.
[d] Personality traits (scale 0–10): Competitiveness level (≥ 7 points), tension (≥ 7 points) and dependency level (≥ 7 points).

Table 3
HR and 95% CI of incident depression according to the number healthy lifestyle factors.

Number of healthy-lifestyle factors	0-3	4-5	6-7	8-10	*p* trend value
Subjects (n)	1715	5941	5878	1374	
Cases/person-years	108/17699	329/61770	282/59146	55/13151	
Sex and age adjusted	1 (Ref.)	0.84 (0.67-1.04)	0.76 (0.61-0.95)	0.67 (0.48-0.94)	0.006
Multivariable adjusted[a]	1 (Ref.)	0.82 (0.66-1.01)	0.76 (0.61-0.95)	0.68 (0.49-0.95)	0.010

[a] Adjusted for sex, age, year of completion of the questionnaire, total energy intake, marital status, living status, years of university studies (continuous), regular use of aspirin and non-aspirin analgesics (≥ 2 times/week), and personality traits (competitiveness, psychological tension and dependency).

relative risk reduction of depression, when compared with the lowest category (0–3 points). (HR: 0.68; 95% CI:0.49-0.95)) (Table 3).

The HLS as a continuous variable was significantly inversely associated with the risk of depression (HR: 0.92; 95% CI:0.89-0.97, per unit increase in the score). We did not find any significant effect modification by age (p for interaction = 0.240).

When factors of the score were analyzed individually, we only found a significant inverse association for medium-to-high MDS adherence (HR:0.84; 95% CI:0.73-0.98). However, we found trends of inverse associations for never smoking, being physically active, healthy BMI, never binge drinking, reduced TV watching, sleeping mid-day nap, spending time with friends and working-hours, yet they were not statistically significant (Table 4) (Fig. 2). Moderate alcohol consumption was the only factor that showed a direct (though non-significant) association. However, with a different cut-off point (5–15 g/d) [27] of moderate alcohol intake, the HR was 0.79 (0.60–1.05) for men and 0.73 (0.58-0.93) for women.

The greatest benefit in terms of reducing the risk of depression was obtained by combining all the factors in the HLS (Fig. 2).

Sensitivity analyses also showed that the association between the HLS and the risk of depression did not change under different scenarios (Table 5).

Importantly, when we considered as incident depression cases only those participants initially free of depression who simultaneously reported a new medically-diagnosed depression during follow-up and a new habitual use of antidepressant medication, the results not only remained in the same direction as the estimates obtained in the main analyses, but the point estimates were even farther from the null, representing a stronger inverse association.

4. Discussion

In this analysis of the SUN Project, a combined HLS was associated with a 32% relative risk reduction for depression. As expected, the positive impact of adopting a healthy-lifestyle is in accordance with existing evidence. Some studies with a cross-sectional design [4–6] and a few other longitudinal studies [7–9] have reported a significant protective effect of combined healthy-lifestyle indicators on depression risk.

Almeida et al. [7] analyzed the combined longitudinal association between low physical activity, smoking, risky alcohol use (≥4 drinks/day), abnormal body mass index (< 18.5 or > 25 kg/m^2) and diet (excessive consumption of red meat, low consumption of fish, additional use of salt and full-cream milk) and depression risk in a

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Table 4
HR and 95% CI of incident depression according to healthy lifestyle habits.

Healthy-lifestyle factors	n	Cases/person-years	Sex and age adjusted	Multivariable adjusted[a]
Never smoking				
No (current and former smoker)	7619	440/78632	1 (Ref.)	1 (Ref.)
Yes (never smoker)	7289	334/73134	0.86 (0.74-0.99)	0.88 (0.76-1.02)
Physical activity (>20 METs-h/week)				
No	7304	419/74524	1 (Ref.)	1 (Ref.)
Yes	7604	355/77241	0.87 (0.75-1.00)	0.89 (0.77-1.03)
Mediterranean dietary pattern[b](score≥4)				
No	5810	342/61055	1 (Ref.)	1 (Ref.)
Yes	9098	432/90710	0.82 (0.71-0.95)	0.84 (0.73-0.98)
BMI (≤22 kg/m^2)				
No	9229	478/93669	1 (Ref.)	1 (Ref.)
Yes	5679	296/58097	0.91 (0.77-1.08)	0.90 (0.76-1.07)
Moderate alcohol intake (women 0.1-5 g/d; men 0.1-10 g/d)				
No	7480	393/76232	1 (Ref.)	1 (Ref.)
Yes	7428	381/75533	1.06 (0.92-1.22)	1.08 (0.93-1.24)
Avoidance of binge drinking[c]				
Any binge drinking	4753	222/48552	1 (Ref.)	1 (Ref.)
Never binge drinking	10155	552/103213	0.96 (0.82-1.14)	0.95 (0.81-1.12)
Reduced TV watching				
≥ 2 h/d	4344	245/44734	1 (Ref.)	1 (Ref.)
< 2 h/d	10564	529/107031	0.90 (0.78-1.05)	0.90(0.77-1.04)
Sleeping short mid-day nap (≤30 min/day)				
No mid-day nap or longer mid-day nap	6386	339/66216	1 (Ref.)	1 (Ref.)
Yes	8522	435/85549	0.96 (0.83-1.11)	0.97 (0.84-1.11)
Time spent with friends (> 1 h/d)				
No	8468	460/87277	1 (Ref.)	1 (Ref.)
Yes	6440	314/64488	0.98 (0.84-1.14)	0.98 (0.85-1.16)
Time working (h/week)				
< 40 h/week	6897	377/69524	1 (Ref.)	1 (Ref.)
≥ 40 h/week	8011	397/82241	0.91 (0.78-1.06)	0.89 (0.76-1.03)

[a] Adjusted for sex, age, year of completion of the questionnaire, regular use of aspirin and non-aspirin analgesics (>2times/week), marital status, total energy intake, personality traits (competitiveness, psychological tension and dependence) and all variables shown in the table.
[b] Trichopoulou's score (range of scores, 0 to 8, with higher scores indicating greater adherence, excluding alcohol intake).
[c] Drinking more than 5 alcoholic drinks at any time.

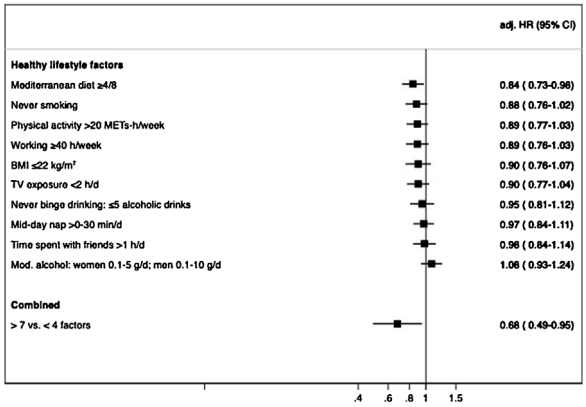

Fig. 2. Hazard ratio of depression associated with each of the ten healthy lifestyle factors and their combination.

sample of older men, and they found that the combination of these four modifiable lifestyle factors predicted the highest probability of incident depression. Sánchez-Villegas et al. [8], longitudinally assessed the association between an overall Mediterranean lifestyle (MDS adherence, physical activity and socializing activities) and the risk of depression in our cohort. They found that participants with the highest adherence to the Mediterranean lifestyle showed a 50% relative risk reduction in depression risk as compared to those participants with the lowest adherence. Furthermore, Adjibade et al. [9], calculated a lifestyle index composed of never smoking, low alcohol consumption, healthy weight, moderate-to-high physical activity and healthy diet in a French cohort, and found that a 1-point increase in the lifestyle index, was associated with a 10% reduction in the risk of depressive symptoms.

In addition to the lifestyle-factors analyzed in previous studies, we included other non-conventional healthy-lifestyle indicators such as low television exposure, taking a short afternoon nap, meeting up with friends and conventional working hours.

Prolonged television viewing has been associated with higher risk of all-cause mortality among adults [28], and it is considered a significant risk factor for depression [13]. In fact, there is a new concept of "Binge TV-watching" as a result of dependence on digital media and its association with depression [29]. In our study, when we analyzed the HLS factors individually, reduced TV watching showed an inverse association, although it was not statistically significant. This could be due to an underestimation of the screen-exposure time (we did not take into account smartphones and computer use outside of work) as well as the characteristics of our population.

Moreover, there is evidence that a short-day-nap is beneficial for well-being and cognitive functions [11] and might also be able to reverse some of the stress and immune damage caused by sleep-deprivation, which is a common risk factor of depression [30]. Taking a short-afternoon-nap showed a beneficial although non-significant association when we analyzed this factor alone.

The quality of social relationships predicts future depression, and the magnitude of the effect of social relationship quality on the risk of depression is comparable with the effect of well-established biological risk factors for cardiovascular disease [31]. Furthermore, social network size and contact frequency were positively and independently related to well-being [10]. Spending time with friends showed an inverse (though non-significant) association with the risk of depression in our study.

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Table 5
Sensitivity analyses and 95% CI of incident depression according to the number of healthy lifestyle factors..

Number of healthy-lifestyle factors	0-1	2	3	4	*p* for trend
Overall	1 (Ref.)	0.82 (0.66-1.01)	0.76 (0.61-0.95)	0.68 (0.49-0.96)	0.010
After changing the definition of incident depression[a]	1 (Ref.)	0.66 (0.45-0.97)	0.61 (0.41-0.92)	0.46 (0.24-0.90)	0.011
After changing the range of moderate alcohol consumption in the score[b]	1 (Ref.)	0.81 (0.67-0.99)	0.67 (0.54-0.84)	0.61 (0.42-0.90)	0.004
After changing the criteria of exclusion in energy limits[c]	1 (Ref.)	0.88 (0.71-1.10)	0.79 (0.63-1.00)	0.63 (0.45-0.89)	0.003
After excluding those with a weight gain ($\geq$ 5 kg)[d]	1 (Ref.)	0.93 (0.72-1.20)	0.84 (0.64-1.11)	0.78 (0.54-1.10)	0.010
After excluding pregnant women	1 (Ref.)	0.78 (0.62-0.99)	0.82 (0.64-1.04)	0.69 (0.46-1.01)	0.075
After changing the cut-off point of BMI in the score[e]	1 (Ref.)	0.88 (0.70-1.11)	0.78 (0.61-0.99)	0.70 (0.50-0.97)	0.009
After eliminating those with extremely low BMI[f]	1 (Ref.)	0.81 (0.65-1.01)	0.78 (0.62-0.98)	0.70 (0.50-0.99)	0.010

[a] A more specific definition, considering incident cases only those participants who both reported a new medically-diagnosed depression and started the habitual use of antidepressant medication, ie., both criteria need to be simultaneously met to be classified as incident case of depression.
[b] Moderate alcohol consumption in the score for 10–50 g/day for men and 5–25 g/day for women.
[c] Criteria of exclusion in energy limits (percentile 5–95).
[d] Weight gain of 5 kg or more in the last 5 years before answering the baseline questionnaire.
[e] BMI between 20–25 kg/m^2 = 1 point.
[f] After eliminating those participants with a BMI < 18.5 kg/m^2. Therefore, BMI 18.5–22 kg/m^2 = 1point.

The association of working hours and depression risk is controversial due to the available evidence on the negative effects of long-working hours on health [32,33] and the potential for a "healthy-worker" effect [34]. However, working conventional hours could be beneficial due to a structured environment, social realization, economic security and social support [35]. In fact, a study showed that people diagnosed with depression who continued attending work, had a better management of depressive symptoms, as well as economic and health benefits [12]. In our study working $\geq$ 40 h per week was associated with a lower risk of depression, although differences were not statistically significant. This may be due to the different working conditions analyzed in other studies, such as shift-workers [33] or extended working hours (> 55 h/week) [32], which could be related to consequences of disruption of the circadian rhythm, job strain and increased unhealthy habits. Nevertheless, our results should be interpreted with caution due to the risk of bias from healthy workers. The homogeneity of the study population and the control for multiple confounding factors reduces this possible bias, yet does not eliminate it.

Moderate alcohol was the only lifestyle habit that did not show an inverse association with depression risk in our score, although it was not statistically significant. This may be partly due to the potential role of personality differences between alcohol drinking patterns. Non-drinkers and hazardous drinkers are more likely to have higher levels of depression, anxiety, social inadequacy and more work-related stress compared to moderate drinkers [36]. Nevertheless, we do not imply that abstainers should start to drink since there is evidence that an increasing involvement with alcohol increases risk of depression [37].

Concerning the most studied modifiable lifestyle-related factors involved in the pathogenesis of depression; such as smoking [38], physical activity [39] and BMI [40], adherence to the MDS was the only factor in our score that individually showed an inverse and significant association with depression risk.

The effect of the Mediterranean diet on depression has been evaluated through several studies [41–43]. The beneficial effects of this pattern have been attributed to some food items such as olive oil, nuts, legumes, fish through their anti-inflammatory and antioxidant properties. However, other non-nutritional aspects such as social, cultural and environmental features of this Mediterranean lifestyle model, have been suggested to enhance the beneficial effects of the Mediterranean diet alone [8] and could partly explain our results.

It is worth mentioning that we considered the BMI cut-off point of $\leq$ 22 kg/m^2 in our score due to previous findings that showed a higher risk of metabolic risk factors above this threshold [44,45]. Importantly, the recent Global Burden of Disease Study attributed deaths to a high BMI, already from 22 kg/m^2 [46]. Therefore, even though most of risk scores are based on a cut-off point of 25, there is evidence that a lower cut-off point should be considered.

The majority of components of the score individually did not show any statistically significant association with depression risk. However, the sum of the factors accounted for a significant association when considered together. This may be due to the cumulative effect and the interaction (potential synergistic or antagonistic effects) among multiple lifestyle components. Unlike assessing individual factors, an overall score better reflects the complexity of lifestyle influence on depression.

We have included some novel lifestyle indicators in our score, that may broaden the scope of other studies. Nevertheless, there are many other lifestyle-related factors that may influence depression. For instance, living with pets provide benefits to those with mental health conditions through the connectivity with their owners and emotional support [47]. Meditation and mindfulness exercises may also have beneficial effects on anxiety and depression [48]. On the other hand, excessive daily time using smartphones has been linked to higher depression risk [49]. Therefore, it is necessary to increase investigation efforts on more integrative interventions to better understand the influence of modern lifestyles on depression.

Primordial prevention, that is, to change behaviors that might increase the development of traditional risk factors for major depressive disorder, should be a priority. This multidimensional HLS with a positive approach instead of a risk-focused perspective, could be a useful tool to promote primordial prevention to be used by health professionals. Moreover, this message could be easier to deliver to the general population and could empower individuals to improve their habits and consequently, their health.

4.1. Limitations

Limitations of our study should be recognized. First, the SUN project is not representative of the general Spanish population. However, generalization of results in epidemiology should be based on biological mechanisms rather than on statistical representativeness [50].

Second, incident cases were not exclusively defined as a self-reported medical diagnosis of depression. Therefore, we could have increased higher sensitivity at the expense of losing specificity.

Third, some of the variables used for the computation of the HLS score were self-reported and their reproducibility was not validated. Fourth, the lifestyle information was collected at baseline, assuming that the habits remained stable throughout the study. Unfortunately, we did not have enough information in the follow-up questionnaires regarding some factors of our score to assess changes over time. However, the potential changes would

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probably lead to underestimation of the protective effects of a healthy lifestyle. Fifth, it is also possible that other factors such as personality and socioeconomic status may be driving the association between the HLS depression risk. Nevertheless, we adjusted our analysis for some personality traits previously related with depression risk in our cohort [25], and for educational level (information on income and occupation were not assessed). Sixth, even though we excluded participants with prevalent chronic diseases (diabetes, cardiovascular disease and cancer), we did not exclude those with family history of depression for the analyses. Participants with this background, could probably have a higher overall risk for onset of this disorder [51]. Finally, despite the results were adjusted for several major potential confounders, we cannot eliminate the presence of residual confounding.

Strengths of this study deserve to be recognized. The reliability of this study is strengthened by the prospective longitudinal design, with an extended follow up period, a relatively large sample size, a high retention rate and a good ability to control major sources of confounding. Furthermore, the restriction of our study population to university graduates reduces the possible confounding effects related to educational level and also improves the quality of the self-reported information provided. Additionally, some lifestyle-related factors, such as binge TV watching, might be a consequence of depression rather than vice versa. Therefore, the exclusion of participants with a depression diagnosis during the first two years of follow-up reduces the possibility of reverse causation bias due to subclinical cases of depression present at baseline. The robustness of our results along multiple sensitivity analyses is another strong point of our study.

5. Conclusions

A combined HLS previously shown to be inversely associated with cardiovascular disease was also monotonically associated with a lower risk of incident depression in a Spanish cohort of university graduates. Our results reinforce the importance of promoting a multi-dimensional healthy lifestyle for the prevention of depression. Our score could be a useful tool for a more integrative approach to depression prevention in clinical settings or for general health promotion. Future longitudinal and intervention studies would be needed to analyze the impact of the lifestyle habits in different populations.

Authors contributions

MÁM-G, MB-R contributed to the conception or design of the work. LR-E, MB-R, JD-G, and MÁM-G contributed to the acquisition, analysis, or interpretation of data for the work. LR-E drafted the manuscript. AS-V and FL-R contributed to the interpretation of results and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work.

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