Pain Characteristics, Cardiovascular Risk Factors, and Cardiovascular Disease.

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ABSTRACT

Background: There is unclear evidence that chronic pain may increase the risk of cardiovascular disease (CVD) incidence and mortality. This work evaluated the association between chronic pain, incidence of CVD and changes in CVD risk factors.

Methods: Cohort of 1091 community-dwelling individuals ≥60years, free from CVD at baseline, followed up for 6 years. Data on psychosocial factors and CVD risk factors was obtained through validated questionnaires and laboratory measurements. A pain scale ranging from 0 (no pain) to 6 (worst pain) was created according to pain frequency, location and intensity.

Results: The cumulative incidence of CVD was 4.2% at 3 years, and 7.7% at 5-years of follow-up. Compared to individuals without pain in the first 3 years (2012-2015), those with maintained scores ≥2 showed a mean reduction of 3.57 (-5.77,-1.37) METs-h/week in recreational physical activity; a 0.38-point (0.04,0.73) increase in psychological distress; and a 1.79 (1.03,3.11) higher odds of poor sleep. These associations held in the second follow-up period, when individuals with maintained pain also worsened their diet quality. A 1-point increase in the pain scale in 2012 was associated with a 1.21 (1.03,1.42) and 1.18 (0.97,1.44) increased CVD incidence in 2015 and 2017, respectively; none of the studied factors mediated this relationship.

Conclusions: Older adults with chronic pain show important reductions in recreational physical activity and deterioration in mental health, sleep and diet quality, which may well aggravate pain. Future studies should evaluate whether these factors mediate the increased risk of CVD observed in older adults with chronic pain.

Keywords: Pain, nutrition, sleep, physical activity

Introduction

Chronic pain, defined as pain on most of the days or every day in the previous six months (3), affects between 35 and 60% of community-dwelling adults aged ≥50 years in Europe, and accounts for the highest number of years lived with disability in the Region (3,4). Not only is it associated with the risk of functional impairments (5-10) or depression (11) in older adults, but studies have shown that chronic pain often co-exists with other prevalent chronic conditions like cardiovascular disease (CVD) (12-14). Although some mechanistic hypotheses exist for the coexistence of these conditions, the exact nature of the relationships is unknown (15-17). Studies in experimental models have illustrated the importance of local inflammation in the development and maintenance of chronic pain. Once the inflammatory reaction is established, the release of pro-inflammatory cytokines and chemokines into the blood can induce endothelial impairment and accelerate the atherosclerotic process underlying CVD (cita). Inflammation also lowers the threshold for nociception, and the resulting persistent pain can disrupt sleep, cause anxiety or depression, all known risk factors of CVD. On the other hand, persistent pain has been associated with increased blood pressure in experimental animals and humans, and this process seems to be mediated by a decrease sensitivity of baroreceptors and by changes in pain inhibitory pathways (citas).

Previous longitudinal studies exploring the association between chronic pain and CVD incidence are limited due to inadequate control of potential confounders like health behaviors (13). For example, there is evidence that pain is frequently associated with fear of movement and decreased physical activity, while both physical inactivity and sedentary time independently increase the risk of CVD . However, there are no well-conducted epidemiological studies evaluating the prospective association between chronic pain, changes in CVD risk factors (e.g. tobacco smoking, alcohol consumption,

obesity, physical activity, sedentary time or diet quality), and incidence of CVD events. Because of the high prevalence of chronic pain in the elderly, understanding these associations is crucial for CVD prevention.

METHODS

Study design and participants

Data were taken from the Seniors-ENRICA study (6), a population-based cohort of Spanish community-dwelling individuals whose age ranged from 60 to 88 years old. Individuals were recruited in 2008-2018, and information was updated in 2012, 2015, and 2017. Information on socio-demographic variables, health behaviours, co-morbidities and health services use was collected by telephone interviews, and in two home visits that included a face-to-face interview, a physical examination, a diet history, and collection of biological samples. Participants also reported their prescribed medications (including glucose lowering, antidepressant, and antihypertensive drugs), which were checked by the study staff against drug packages at home.

Figure 1 shows the flow chart of study participants. Because pain was first assessed in the year 2012, the baseline sample of the present study comprised the 2519 participants. For the analyses on changes in pain and in behavioral risk factors at 3 years, we excluded 273 participants with a history of CVD, 155 without complete information on pain in 2012 or 2015, 370 without a diet history in 2012, 268 with missing values in potential confounders in 2012 or 2015, as well as 84 and 278 participants who either died or were lost to follow-up between 2012 and 2015 (final analytical subsample 1 n=1091). For the analyses on changes in pain at 3 years and changes in behavioral risk factors at 5 years, we further excluded 258 participants who were loss to follow-up between 2015 and 2017, 127 individuals with no diet history in 2017, and 19 with missing values in potential confounders (final analytical subsample 2 n=687). **Supplementary Table 1** presents the

baseline distribution of the main sociodemographic variables and cardiovascular risk factors of study participants according to their inclusion status. Compared to the initial sample of participants free from CVD at baseline (n=2246), participants included in the analyses were younger, showed higher education, were more likely drinkers, showed a slight greater adherence to the Mediterranean diet, watched less TV, and had a lower prevalence of diabetes and hypertension. No differences were observed in terms of sex, tobacco smoke, recreational activity, obesity, sleep characteristics or prevalence of COPD or cancer by inclusion status.

Study participants gave informed written consent, and the study was approved by the Ethics Research Committee.

Study variables

Pain

Information on pain was collected using a 10-item questionnaire from the Survey on Chronic Pain in Europe (3). Participants were classified as having chronic persistent pain (≥2 times/week in the last 6 months), chronic sporadic pain (1 time/week, 1-3 times/month or <1 time/month), or no chronic pain (not having had pain in the last 6 months). The intensity of pain was assessed by a scale measuring the impact of pain on habitual activities of daily living (from 0 'no trouble' to 6 'highly trouble'). The six different localizations of pain reported were a) head and neck; b) back; c) bones and joints; d) legs; e) arms and f) other sites. According to previous literature showing that intensity of pain plateaus in later life and that increasing number of pain sites may be more clinically relevant in older adults (XXX), number of pain sites was selected as the main outcome of study.

As described elsewhere (6), a composite pain scale including frequency, intensity and number of pain sites was also built. Chronic sporadic and frequent pain were assigned

a score of 1 and 2, respectively; light and moderate-high intensity a score of 1 and 2, respectively; and 1–2 and ≥3 sites a score of 1 and 2, respectively. The final scale ranged from 0 (no pain) to 6 (worst pain). According to this scale, changes in pain between waves were defined: 1) No pain at baseline or follow-up (reference category); 2) Chronic mild pain (1 point) at baseline and either mild or no pain at follow-up (labelled as "mild pain" category); 3) Chronic moderate or severe pain (≥2 points) at baseline and either mild or no pain at follow-up ("pain improvement") ; 4) Chronic mild pain (1 point) at baseline and moderate or severe pain (≥2 points) at follow-up ("pain worsening"); 5) Chronic maintained moderate or severe pain (≥2 points) at baseline and follow-up ("pain maintenance").

Cardiovascular risk factors

At baseline and follow-up, data on tobacco smoking (never, former, current), physical activity, television viewing time, night-time sleep duration, sleep quality, psychological distress, and history of previous physician-diagnosed diseases (CVD – myocardial infarction, stroke or heart failure-, diabetes, chronic lung disease, cancer and depression) was collected. Information on recreational physical activity was collected with the validated EPIC-cohort questionnaire and was expressed in metabolic equivalents tasks (METs)-hour/week (18). Time spent watching TV was obtained with the validated Nurses' Health Study Questionnaire and expressed in hours/week (19). Sleep duration was obtained with the question: "Approximately, for how long do you usually sleep per night?"; additionally participants reported whether sleep quality was "very good"/ "good"/"regular"/"poor"/"very poor" and those with "very good"/"good" sleep quality were grouped as good sleepers (20). Psychological distress was estimated using the General Health Questionnaire GHQ-12 (21), with higher scores indicating higher short-term distress. Depression was ascertained with the 10-item version of the Geriatric

Depression Scale (GDS) (22). Participants who presented GDS scores ≥8, self-reported a medical diagnosis of depression, or were on antidepressant medications, were considered as depressed.

During the home visits, weight and height were measured twice using electronic scales and portable extendable stadiometers under standardized procedures, and the mean of the two readings was used to calculate the BMI (weight/height^2 in kg/m^2) (23). Blood pressure was measured with standardized procedures using validated automatic devices (Omron model M6) and 3 cuff sizes according to arm circumference. Two sets of blood pressure readings were made separated by 90 minutes. In each set, blood pressure was measured 3 times at 1-2 minute intervals, after resting 3 to 5 minutes in a seated position. Blood pressure was calculated as the mean of ≥3 of the last 5 readings, and hypertension defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or the current use of antihypertensive drugs (24). Diabetes was defined as a physician diagnosis of diabetes, the current use of glucose lowering drugs, or a fasting serum glucose level ≥126 mg/dl, as determined with the oxidase glucose technique (ADVIA 2400 Chemistry System analyzer, Siemens). Hypercholesterolemia was defined as self-total cholesterol ≥ 200 mg/dL or drug treatment.

Only at baseline and 2017, information was collected on alcohol drinking (never, ex-drinker, moderate drinker, and current drinker), and diet quality. Habitual dietary intake was estimated with a validated diet history developed from the one used in the EPIC cohort study in Spain (25); and energy and nutrients intake were estimated using standard composition tables (26). Adherence to the Mediterranean diet was measured with the Mediterranean Diet Adherence Screener (MEDAS), which consists of 2 questions on food intake habits considered characteristic of the Spanish Mediterranean diet as well as 12 questions on food consumption frequency (i.e. using olive oil as the

main fat for cooking; preferring white meat over red meat; consuming ≥4 tablespoons/day of olive oil; ≥2 servings/day of vegetables; ≥3 pieces/day of fruit; <1 serving/day of red or processed meats; <;1 serving/day of butter, margarine or cream<1 cup/day of sugar-sweetened beverages; ≥7 servings/week of wine; ≥3 servings/week of legumes; ≥3 servings/week of fish or seafood; <2 servings/week of commercial baked goods; ≥3 servings/week of nuts; and ≥2 servings/week of a dish with a traditional sauce of tomatoes, garlic, onion, or leeks sautéed in olive oil (sofrito)). Thus, the MEDAS score ranged from 0 (lowest) to 14 (highest adherence to the Mediterranean diet) (26, 27). A Mediterranean drinking pattern was defined as moderate alcohol consumption (threshold between moderate and heavy intake was 40 g/day for men and 24 g/day for women) with preference for wine and drinking only with meals; due to a lack of information on drinking behaviours this pattern could not be explored in 2017 (27).

Statistical analyses

We first evaluated the baseline cross-sectional association between pain characteristics (frequency, intensity, location, and interference with normal activities) and each of the studied CVD risk. With this purpose we used either linear regression (for continuous outcomes, results presented as mean differences and their confidence intervals); logistic regression (for categorical outcomes with two categories, results presented as odds ratios and their confidence intervals); or multinomial regression (for categorical outcomes with >2 categories, results presented as relative risk ratios and their confidence intervals). The “no pain” category was set as reference in these analyses, which were adjusted for potential confounders, including sex, age, education, baseline comorbidities (diabetes, hypercholesterolemia, chronic obstructive respiratory disease, depression and cancer), systolic blood pressure, psychological distress, and the respective CVD behavioural risk factors (smoking and alcohol consumption, recreational physical

activity, TV viewing time, diet quality, energy intake, BMI, sleep quality, and sleep duration).

To evaluate the association of changes in pain between 2012-2015 and changes in behavioural risk factors at 3-years and 5-years of follow-up, we again used linear, logistic or multinomial regression models, according to the nature of the studied outcome. We adjusted these models for baseline values and for changes in all CVD risk factor during the corresponding 3 or 5-years follow-up period. For these analyses, we used as reference individuals who did not suffer from pain neither in 2012 nor in 2015.

We finally estimated the prospective association between pain characteristics in 2012 and cumulative incidence of CVD in 2015 and 2017 using logistic regression models. To evaluate the potential mediating role of the studied CVD risk factors, models first only adjusted for age, sex and educational level, and then further incorporated information on baseline and prospective values of the respective CVD risk factors.

RESULTS

Table 1 shows the distribution of each CVD risk factor in individuals with and without pain. After adjustment for all other CVD risk factors (**Table 2**), a higher number of locations of pain was associated with a higher prevalence of former smoking, obesity, poor sleep quality, decreased night-time sleep, daytime sleepiness, and depression; as well as with a slightly higher score in MEDAS, more time spent viewing TV, less time on night sleep, and higher psychological distress. Consistent findings were observed for the frequency and intensity of pain, as well as for the overall pain scale (**Supplementary Table 2**).

Table 3 shows the prospective association between changes in pain and changes in CVD risk factors during the 3 first years of follow-up (2012-2015). After adjustment for modifications in the respective risk factors, and compared to individuals who did not

suffer from pain neither in 2012 nor in 2015, those who maintained pain scores ≥2 showed a reduction in physical activity (mean difference: -3.57 (95% CI: -5.77, -1.37) METs-h/week), increased psychological distress (mean difference: 0.38 (0.04, 0.73) points in GHQ), higher risk of poor sleep (odds ratio (OR): 1.79 (1.03, 3.11)), and lower probability of reversion of abdominal obesity (relative risk ratio (RRR): 0.42 (0.21, 0.86), data not shown in tables).

Table 4 evaluates the prospective association between changes in pain during the first 3 years of follow-up and changes in CVD risk factors at 5 years of follow-up . After adjustment for modifications in the respective CVD risk factors during the second period, we observed similar findings for those who maintained pain scores ≥2: Compared with individuals with no pain in the first follow-up period, they reduced physical activity (mean difference: 3.94 (95% CI: -6.71, -1.17) METS-h/week); presented increased psychological distress (mean difference: 0.76 (0.34, 1.18) points in the GHQ-12); and showed a higher risk of poor sleep (OR: 2.60 (1.24, 5.45)) and a lower risk of central obesity reversal (RRR: 0.37 (0.15, 0.92), data not shown in tables). Additionally, we found that participants with maintained pain also decreased their MEDAS score (mean difference: -0.40 (-0.83, -0.00)). Participants whose pain got worse at 3 years of follow-up reduced physical activity (mean difference: -2.91 (-5.58, -0.24) METs-h/week) from 2015 to 2017 compared to those with no pain.

The cumulative incidence of CVD was 4.2% in the first follow-up period, and 7.7% in the second. In models that adjusted for non-modifiable confounders (i.e. age, sex and educational level), each 1-point increase in the pain scale in 2012 was associated with an increased odds of CVD of 1.21 (95%CI: 1.03, 1.42) in 2015, and of 1.22 (1.01, 1.46) in 2017 (**Table 5**). These results did not materially change after adjustment for baseline or

follow-up changes in CVD risk factors, which suggests that the association between chronic pain and cardiovascular risk may be not explained by the studied factors.

DISCUSSION

In this cohort of community-dwelling older adults in Spain, baseline chronic pain, including the number of pain locations, was associated with an increased prevalence of smoking, obesity, sleep problems, and depression; while maintained moderate and severe pain over time were associated with short- and middle-term declines in recreational physical activity, sleep quality, mental health, and diet quality. However, our results suggest that these may not be important drivers of the increased risk of CVD observed in individuals with chronic pain.

The cross-sectional association between chronic pain, lifestyle and psychological factors is well characterized in the literature. For example, chronic regional (28) and widespread (29) pain have consistently shown to be associated with distressful psychological conditions, including depression, anxiety and sleep problems; while smoking and obesity are unhealthy risk factors commonly present among individuals with chronic pain (30-32). Also, some of the studied lifestyle behaviours are well-known risk factors of chronic pain (33-35) and chronic pain has been linked to an increase risk of anxiety and depression (36). Less is known, however, about whether maintained pain can promote further changes on health risk behaviours. In this regard, our results suggest that chronic pain can increase some of these factors (e.g. reduced physical activity, maintained obesity or decreased diet quality); given, that these factors are, in turn, pain risk factors, they can help perpetuate a vicious pain cycle that will maintain chronic pain over time (32, 34, 37, 38).

Previous follow-up studies on chronic pain have seldom provided information on CVD mechanisms. In this sense, we have only found one cohort study, with 1484 community dwelling Australian women 70 to 85 years of age, that has systematically addressed the influence of lifestyle risk factors on the incidence of CV outcomes in individuals with pain; in line to what we have observed, authors reported that daily back pain increased the risk of 5-year CVD events independently of baseline smoking, physical activity or BMI (39). Studies of CVD mortality are conflicting, with some showing that the excess mortality in individuals with chronic pain is not mediated by lifestyle factors (40), while others suggesting these are main drivers of the association (41). The role of mental stressors is also unknown (29). Consistent with our findings, a 3-year prospective study with 2606 individuals recruited from family practitioners in the United Kingdom, found that psychological distress did not explain the association between either regional or widespread pain and CV risk (42). Similarly, in a 17-year follow-up study of 2478 women 20 to 50 years in Norway, the association between chronic regional or widespread pain and CVD mortality was not modified after adjustment for sleep problems, feeling anxious or nervous (43). However, other studies on CVD mortality have suggested that psychological factors may be important mediators of the studied relationships (41).

Previous authors have proposed several pathophysiological mechanisms that could explain an independent link between chronic pain and CVD, which would include systemic inflammation (44), microvascular alterations (45, 46), maladaptive chronic activation of the sympathetic nervous system (16), or shared genetic predisposition to both diseases (15). Also, drugs frequently prescribed for pain treatment (i.e. non-steroidal antinflammatory agents (47) may aggravate any existing cardiovascular dysfunction. Moreover, of note is the potential role of the social determinants of health

in the association between chronic pain and CVD. For instance, chronic pain has been associated with loneliness and perceived insufficiency of social support in older adults (insertar citas), which are known risk factors of CVD (insertar citas).

A limitation of the study is that our pain questionnaire does not allow differentiate the type of pain (e.g. neuropathic, nociceptive) or its etiology (e.g. degeneration, rheumatic disease, traumatic injury). However, we employed similar items to other widely used questionnaires, and in previous papers we have shown that the distribution of pain categories across socio-demographics, lifestyle and chronic diseases is consistent with the literature (6, 48). Also, co-morbidity was self-reported, which may underestimate its prevalence, particularly for their milder forms; however, about half of the older women and men in our study visited the primary care practitioner at least once per month which limits under-diagnosis (49). More importantly, some of our findings may be limited due to a low sample size. Among the strengths of the study stands its population-based and prospective design, and the objective assessment of an extensive list of health behaviors and clinical variables that might have contributed to the association between chronic pain and CVD.

Our findings provide additional evidence that chronic pain increases the risk of CVD risk factors while suggest the need to promote healthy lifestyle behaviours in older adults with maintained pain. Future mediation studies should evaluate whether these factors mediate the increased risk of CVD observed in older adults with chronic pain.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Not applicable.

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Table 1: Sociodemographic factors, lifestyle related factors, chronic morbidities and pain (n=1091).

	No pain	Pain	P value
Characteristics			
Age; mean (SD)	67.4 (5.5)	67.2 (5.4)	0.55
Male; n (%)	346 (55.4)	168 (36.1)	<0.01
≥High school; n (%)	176 (28.2)	92 (19.7)	<0.01
Tobacco consumption; n (%)			
Never smokers	365 (58.4)	289 (62.0)	
Current smokers	54 (8.6)	42 (9.0)	0.37
Alcohol drinking; n (%)			
Ex-drinkers	89 (14.2)	86 (18.5)	
Moderate-drinkers	406 (65.0)	263 (56.4)	
Heavy drinkers	39 (6.2)	25 (5.4)	0.01
MEDAS index; mean (SD)	7.6 (1.7)	7.6 (1.6)	0.60
Obesity; n (%)	178 (28.5)	168 (36.1)	<0.01
Recreational PA (MET-h/wk); mean (SD)	22.8 (13.4)	21.4 (14.0)	0.11
TV[d] viewing time (hours/wk); mean (SD)	17.7 (9.6)	19.8 (10.3)	<0.01
Night-time sleep duration (h); mean (SD)	7.1 (1.3)	6.6 (1.4)	<0.01
Poor sleep quality; n (%)	127 (20.3)	181 (38.8)	<0.01
Daytime sleepiness; n (%)	33 (5.3)	46 (10.9)	<0.01
GHQ-12 scores; mean (SD)	1.0 (2.0)	2.0 (2.7)	<0.01
Depression; n (%)	53 (8.5)	85 (18.2)	<0.01
Diabetes; n (%)	119 (19.0)	87 (18.7)	0.88
Hypertension; n (%)	466 (74.5)	349 (74.9)	0.90
Hypercholesterolemia; n (%)	301 (48.2)	265 (57.4)	<0.01
Chronic obstructive respiratory disease; n (%)	49 (7.8)	75 (16.1)	<0.01
Cancer; n (%)	22 (3.5)	18 (3.9)	0.77

SD: Standard Deviation; MEDAS: Mediterranean Adherence Diet Score; PA: Physical Activity; TV: Television viewing; GHQ: General Health Questionnaire

*p-values for differences in means were obtained from ANOVA or Kruskall Wallis, as appropriate; while p-values for differences in proportions were obtained from chi squared tests.

Table 2: Cross-sectional association between number of pain locations and lifestyle-related cardiovascular risk factors among older adults with no history of cardiovascular disease at baseline (n=1091).

	No pain	N of pain locations		
		1-2	>2	P-value[a]
	n=654	n=248	n=218	
Lifestyle-related factors				
Smoking; RRR (95%CI)				
Former (vs never)	1.00	1.30 (0.889,1.92)	1.84 (1.17,2.92)	<0.01
Current (vs never)	1.00	1.55 (0.88,2.71)	1.69 (0.84,3.39)	0.08
Alcohol; RRR (95%CI)				
Ex-drinkers (vs never)	1.00	0.83 (0.48,1.43)	0.91 (0.51,1.651)	0.69
Moderate drinkers (vs never)	1.00	0.78 (0.50,1.23)	0.89 (0.55,1.44)	0.53
Heavy drinkers (vs never)	1.00	0.66 (0.31,1.43)	0.74 (0.30,1.78)	0.40
Mediterranean drinking pattern; RRR (95%CI)				
No MDP (vs never)	1.00	0.79 (0.43,1.47)	1.13 (0.58,2.21)	0.74
MDP (vs never)	1.00	0.63 (0.37,1.07)	0.72 (0.40,1.29)	0.80
Diet quality; MD (95%CI)	1.00	0.15 (-0.09,0.40)	0.38 (0.10,0.66)	<0.01
Recreational PA (Mets-h/week); MD (95%CI)		1.97 (0.02,3.93)	-0.45 (-2.68,1.79)	0.86
TV viewing time (h/week); MD (95%CI)		1.00 (-0.40,2.39)	1.52 (-0.06,3.11)	0.04
Anthropometric factors				
Overweight (vs normoweight); RRR (95%CI)	1.00	1.51 (0.98,2.31)	1.24 (0.76,2.01)	0.18
Obesity (vs normoweight); RRR (95%CI)	1.00	1.58 (0.98,2.53)	1.69 (1.00,2.85)	0.02
Sleep quality and duration				
Night-time sleep duration (h); MD (95%CI)		-0.21 (-0.40, -0.02)	-0.56 (-0.77, -0.34)	<0.01
Poor sleep quality; OR (95%CI)	1.00	1.35 (0.94,1.93)	2.68 (1.85,3.86)	<0.01
Mental health				
Psychol. distress; MD (95%CI)		-0.05 (-0.34,0.25)	0.36 (0.02,0.70)	0.08
Depression; OR (95%CI)	1.00	1.70 (1.03,2.81)	1.52 (0.90,2.57)	0.08

[a]P values for trend were obtained considering categorical variables as continuous

OR: odds ratio; RRR: Relative risk ratio; MD: Mean difference. MEDAS: Mediterranean Adherence Diet Score; TV: Television viewing; GHQ: General Health Questionnaire. Logistic regression models used participants with no chronic pain as reference category.

All models were adjusted for sex, age, educational level (primary or less, secondary, or university), tobacco consumption (never, former, current), alcohol drinking (never, former, moderate, or heavy), adherence to a Mediterranean dietary pattern (MEDAS score), energy intake (kcal/day), body mass index (normoweight, overweight, obese), recreational physical activity (METs-h/week), television viewing time (h/week), night-time sleeping duration, poor sleep quality, psychological distress (GHQ-12 scores), systolic blood pressure, diabetes, cancer, chronic obstructive respiratory and depression

Table 3: Association between changes in pain and changes in lifestyle-related cardiovascular risk factors between 2012 and 2015 among older adults with no history of cardiovascular disease (n=1091).

	No pain	**Mild pain**	**Pain improvement**	**Pain worsening**	**Pain maintenance**
	2012: No pain 2015: No pain n=440	2012: Pain score 1 2015: Pain score 0-1 n=47	2012: Pain score ≥2 2015: Pain score 0-1 n=196	2012: Pain score 0-1 2015: Pain score ≥2 n=185	2012: Pain, score ≥2 2015: Pain score ≥2 n=223
Changes in lifestyle related factors (2012-2015)					
Smoking; RRR (95%CI)					
RRR for quitting (n=20) vs continuing smoking (n=76)	1.00	1.03 (0.15,6.69)	1.31 (0.30,5.73)	2.44 (0.56,10.6)	0.18 (0.01,1.97)
RRR for restarting (n=15) vs maintaining ex-smoker status (n=326)	1.00	-	0.69 (0.11,4.24)	1.37 (0.31,6.08)	1.46 (0.29,7.26)
Recreational physical activity; MD (95%CI)		-3.70 (-7.44,0.05)	0.53 (-1.59,2.64)	-0.48 (-2.62,1.65)	-3.57 (-5.77,-1.37)
TV viewing time*;* MD (95%CI)		-0.73 (-3.48,2.01)	0.83 (-0.73,2.39)	-0.19 (-1.76,1.38)	0.64 (-0.98,2.26)
Changes in anthropometric factors (2012-2015)					
General obesity; RRR (95%CI)					
RRR for incident obesity (n=22) vs never obese (n=723)	1.00	1.02 (0.11,9.63)	1.26 (0.36,4.35)	1.44 (0.42,4.91)	0.85 (0.21,3.48)
RRR for reverting (n=74) vs maintaining obesity (n=272)	1.00	1.58 (0.37,6.71)	0.92 (0.43,1.98)	0.94 (0.43,2.05)	0.69 (0.32,1.50)
Changes in sleep quality and duration (2012-2015)					
Night-time sleep duration (h); MD (95%CI)		0.32 (-0.01,0.66)	0.00 (-0.19,0.19)	0.04 (-0.15,0.23)	-0.13 (-0.32,0.06)
Poor sleep quality; RRR (95%CI)					
RRR for incident poor sleep quality (n=124) vs never having poor sleep quality (n=659)	1.00	0.69 (0.20,2.40)	1.00 (0.56,1.75)	0.96 (0.54,1.74)	1.79 (1.03,3.11)
RRR for ceasing (n=123) vs maintaining poor sleep quality (n=184)	1.00	0.84 (0.25,2.84)	0.85 (0.42,1.73)	0.58 (0.27,1.21)	0.46 (0.24,0.89)
Changes in mental health (2012-2015)					
Psychological distress (changes in GHQ-12 scores); MD (95%CI)		-0.22 (-0.81,0.37)	0.06 (-0.28,0.39)	0.13 (-0.20,0.47)	0.38 (0.04,0.73)
Depression					
OR for incident depression (n=47) vs never depressed (n=906)	1.00	1.10 (0.23,5.30)	0.62 (0.22,1.69)	1.22 (0.50,2.93)	0.99 (0.41,2.37)

OR: odds ratio; RRR: Relative risk ratio; MD: Mean difference; CI: Confidence interval; TV: Television; GHQ: General Health Questionnaire.

All models were adjusted for baseline (2012) age, sex, educational level (primary or less, secondary, or university), alcohol drinking (never, former, moderate, or heavy), adherence to a Mediterranean diet pattern (MEDAS score), and energy intake (kcal/day); as well as for changes (2012-2015) in tobacco consumption, body mass index (units), recreational physical activity (METs-h/week), television viewing time (h/week), night-time sleeping duration, sleep quality, psychological distress (GHQ-12 scores), systolic blood pressure, diabetes, chronic obstructive respiratory and depression

Table 4: Association between changes in pain between 2012-2015 and changes in lifestyle-related cardiovascular risk factors between 2012-2017 among older adults with no history of cardiovascular disease (n=687).

	No pain	**Mild pain**	**Pain improvement**	**Pain worsening**	**Pain maintenance**
	2012: No pain 2015: No pain n=272	2012: Pain score 1 2015: Pain score 0-1 n=37	2012: Pain score ≥2 2015: Pain score 0-1 n=127	2012: Pain score 0-1 2015: Pain score ≥2 n=117	2012: Pain score ≥2 2015: Pain score ≥2 n=134
Changes in lifestyle related factors (2012-2017)					
Smoking; OR (95%CI)					
RRR for quitting (n=21) vs continuing smoking (n=35)	1.00	0.81 (0.10,6.63)	1.29 (0.22,7.64)	3.78 (0.65,22.1)	1.60 (0.24,10.7)
RRR for restarting (n=7) vs maintaining ex-smoker status (n=11)	1.00	-	-	0.40 (0.02,7.39)	1.38 (0.08,22.9)
Alcohol consumption					
RRR for quitting (n=57) vs maintaining moderate drinking (n=336)	1.00	0.47 (0.06,3.92)	2.45 (1.06,5.66)	2.56 (1.10, 5.96)	2.65 (1.10,6.41)
RRR for increasing from moderate to heavy drinking (n=23) vs maintaining moderate drinking (n=336)	1.00	0.63 (0.06,6.64)	0.98 (0.18, 5.32)	2.13 (0.61,7.40)	2.80 (0.70,11.28)
RRR for decreasing from heavy drinking to moderate drinking (n=23) vs maintaining heavy drinking (n=12)	1.00	-	1.00 (0.11, 8.96)	-	2.62 (0.28,24.4)
OR for restarting drinking (n=34) vs maintaining ex-drinking status (n=72)	1.00	3.94 (0.42,36.91)	2.70 (0.78, 9.35)	3.37 (0.88,12.91)	2.06 (0.55,7.67)
MEDAS score; MD (95%CI)		0.01 (-0.63, 0.66)	-0.13 (-0.53, 0.27)	-0.18 (-0.59,0.23)	-0.40 (-0.83, -0.00)
Recreational physical activity; MD (95%CI)		-2.20 (-6.41, 2.02)	-0.83 (-3.44, 1.78)	-2.91 (-5.58, -0.24)	-3.95 (-6.71, -1.17)
TV viewing time*;* MD (95%CI)		-3.26 (-6.40, -0.12)	2.58 (0.62, 4.54)	0.42 (-1.57, 2.42)	0.60 (-1.47, 2.68)
Changes in anthropometric factors (2012-2017)					
General obesity; RRR (95%CI)					
RRR for incident obesity (n=24) vs never obese (n=449)	1.00	0.95 (0.11, 8.32)	0.42 (0.09, 2.03)	0.83 (0.22, 3.16)	2.04 (0.65, 6.39)
RRR for reverting (n=53) vs maintaining obesity (n=161)	1.00	0.30 (0.03, 2.63)	0.27 (0.08, 0.88)	0.54 (0.21, 1.32)	1.08 (0.45, 2.58)
Changes in sleep quality and duration (2012-2017)					
Night-time sleep (h); Mean change(95%CI)		0.11 (-0.29, 0.51)	0.12 (-0.1121, 0.37)	0.02 (-0.23, 0.27)	0.00 (-0.25, 0.26)
Poor sleep quality; RRR (95%CI)					
RRR for incident poor sleep quality (n=76) vs never having poor sleep quality (n=414)	1.00	0.58 (0.12, 2.71)	0.90 (0.42, 1.96)	1.30 (0.3, 2.68)	2.60 (1.24, 5.45)
RRR for ceasing (n=72) vs maintaining poor sleep quality (n=125)	1.00	3.32 (0.76, 14.5)	1.49 (0.59, 3.74)	2.30 (0.89, 5.91)	0.50 (0.20, 1.23)
Changes in mental health (2012-2017)					
Psychological distress; MD (95%CI)		0.15 (-0.48, 0.78)	-0.06 (-0.45, 0.33)	0.10 (-0.30, 0.49)	0.76 (0.34, 1.18)
Depression, OR depression (n=36) vs never depressed (n=572)	1.00	-	0.20 (0.04, 0.98)	1.43 (0.54, 4.79)	1.05 (0.38, 2.94)

OR: odds ratio; RRR: Relative risk ratio; MD: Mean difference; CI: Confidence interval; TV: Television; GHQ: General Health Questionnaire.

All models were adjusted for age, sex, and educational level (primary or less, secondary, or university); as well as for changes (2012-2017) in tobacco consumption, alcohol drinking, adherence to a Mediterranean diet pattern (MEDAS score), energy intake (kcal/day), body mass index (units), recreational physical activity (METs-h/wk), television viewing time (h/wk), night-time sleeping duration, sleep quality, psychological distress (GHQ-12 scores), systolic blood pressure, diabetes, chronic obstructive respiratory and depression

Table 5: Association between pain characteristics in 2012 and incidence of self-reported physician diagnosis of cardiovascular disease (2015 or 2017)

	No pain	Pain persistency			Pain intensity			Pain experience			Nº locations of pain			Pain scale*
		< 2 times/week	≥2 times/week	P-val†	Mild/moderate	Severe	P-val†	Not bad	Bad	P-val†	1-2	>2	P-val†	
CVD 2015	**n=625**	**n=123**	**n=343**		**n=261**	**n=205**		**n=180**	**n=286**		**n=248**	**n=218**		
‡Model 1	1.00	1.65 (0.64,4.22)	2.08 (1.08,4.00)	0.03	1.69 (0.82,3.49)	2.33 (1.12,4.88)	0.02	1.55 (0.66,3.64)	2.22 (1.13,4.37)	0.02	1.92 (0.94,3.90)	2.01 (0.94,4.28)	0.05	1.21 (1.03,1.42)
§Model 2	1.00	1.48 (0.56,3.95)	2.17 (1.07,4.38)	0.03	1.65 (0.77,3.50)	2.47 (1.10,5.51)	0.03	1.51 (0.63,3.64)	2.30 (1.10,4.80)	0.03	1.94 (0.93,4.06)	1.95 (0.86,4.44)	0.07	1.23 (1.03,1.47)
CVD 2017	**n=394**	**n=76**	**n=217**		**n=172**	**n=121**		**n=119**	**n=174**		**n=161**	**n=132**		
‡Model 1	1.00	2.65 (1.03,6.80)	2.04 (0.95,4.38)	0.06	1.83 (0.81, 4.12)	2.89 (1.23,6.78)	0.01	1.95 (0.79,4.81)	2.40 (1.09,5.27)	0.03	2.36 (1.09,5.13)	1.99 (0.81,4.89)	0.07	1.22 (1.01,1.46)
‖Model 2	1.00	2.75 (1.04,7.30)	1.77 (0.78,4.01)	0.13	1.72 (0.74, 3.99)	2.68 (1.07,6.70)	0.03	1.93 (0.76,4.89)	2.14 (0.93,4.92)	0.06	2.26 (1.01,5.04)	1.74 (0.66,4.55)	0.14	1.18 (0.97,1.44)

CVD: Cardiovascular Disease.

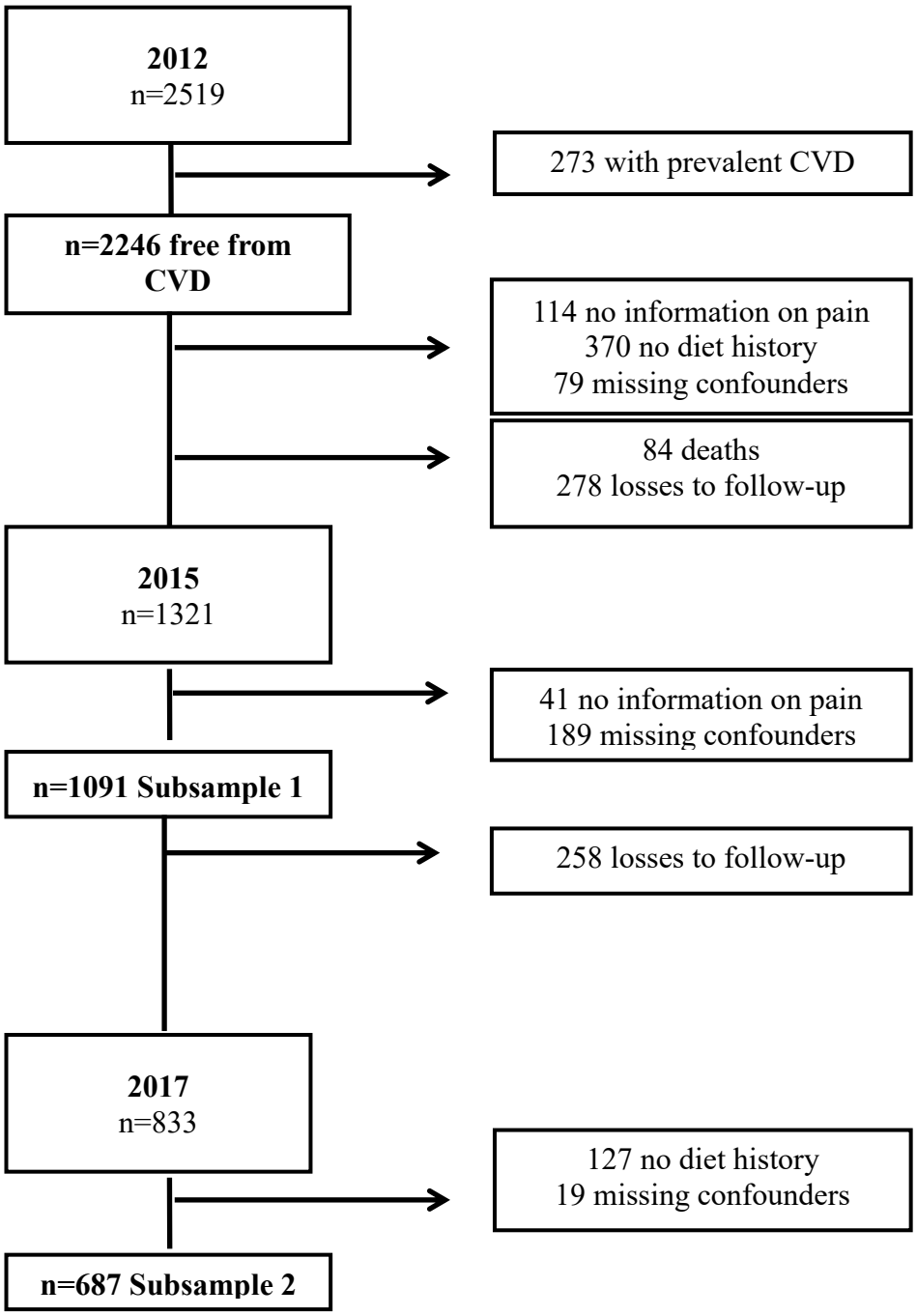
* The mean (SD) scores of the pain scale in 2015 and 2017 were 1.40 (1.81) and 1.36 (1.78), respectively.

† P values for trend were obtained considering categorical variables as continuous

‡Model 1 for CVD in 2015 and 2017 were adjusted for baseline age, sex and educational level (primary or less, secondary, or university)

§Model 2 for CVD in 2015 was adjusted for baseline age, sex, educational level (primary or less, secondary, or university), alcohol drinking (never, former, moderate, or heavy), adherence to a Mediterranean diet pattern (MEDAS score), and energy intake at baseline(kcal/day); as well as for changes between 2012 and 2015 in tobacco consumption, body mass index (units), recreational physical activity (METs-h/wk), television viewing time (h/wk), night-time sleeping duration, sleep quality, psychological distress (GHQ-12 scores), systolic blood pressure, diabetes and other chronic morbidities (chronic obstructive respiratory disease, cancer and depression. ‖Model 2 for CVD in 2017 was adjusted for baseline age, sex, and educational level (primary or less, secondary, or university); as well as for changes between 2012 and 2017 in tobacco consumption, alcohol drinking (never, former, moderate, or heavy), adherence to a Mediterranean diet pattern (MEDAS score), and energy intake (kcal/day), body mass index (units), recreational physical activity (METs-h/wk), television viewing time (h/wk), night-time sleeping duration, sleep quality, psychological distress (GHQ-12 scores), systolic blood pressure, diabetes, chronic obstructive respiratory and depression

Figure 1: Flow chart of study participants.



Supplementary Table S1. Baseline distribution of the main sociodemographic variables and cardiovascular disease risk factors in older adults from the Seniors-ENRICA-1 cohort, according to inclusion status

	Participants free from CVD at baseline (n=2246)	**Subsample 1** (n=1091)	**P-value**†	**Subsample 2** (n=687)	**P-value**†
N					
Age, y, mean (SD)	68.3 (6.2)	67.3 (5.4)	<0.00	66.8	<0.00
Male, %	53.8	52.9	0.38	52.2	0.31
≥High School education, %	45.9	51.2	<0.00	52.8	<0.00
Tobacco consumption, %					
Never smokers	59.0	59.9		60.3	
Current smokers	8.9	8.9	0.72	8.1	0.59
Alcohol consumption , %					
Ex-drinker	17.9	16.0		14.9	
Moderate drinker	58.9	61.3		61.5	
Heavy drinker	5.6	5.9	0.03	6.8	0.02
MEDAS, mean (SD)	7.5 (1.6)	7.6 (1.7)	<0.00	7.6 (1.7)	0.01
BMI ≥30, %	31.8	31.7	0.61	31.3	0.94
Recreational PA, mean (SD)	21.3 (13.4)	21.1 (13.6)	0.11	22.1 (13.8)	0.09
TV viewing time, mean (SD)	19.4 (107)	18.6 (10.0)	<0.00	17.9 (9.5)	<0.00
Nighttime sleep, mean (SD)	6.9 (1.4)	6.9 (1.4)	0.97	6.8 (1.3)	0.65
Poor sleep quality, %	28.1	28.3	0.91	29.1	0.52
Daytime sleepiness, %	7.9	7.3	0.32	7.9	0.98
GHQ-12 scores, mean (SD)	1.6 (2.6)	1.4 (2.4)	<0.00	1.4 (2.2)	<0.00
Diabetes mellitus, %	21.2	18.9	<0.00	17.0	<0.00
Hypertension, %	78.4	74.7	<0.00	75.7	0.04
Hypercholesterolemia, %	50.1	52.1	0.06	53.9	0.02
COPD, %	11.5	11.4	0.54	10.3	0.15
Cancer, %	4.5	3.7	0.06	3.7	0.20

CVD: Cardiovascular disease

† P-values for the null hypothesis that there are no differences in participants characteristics compared to those in the sample free of CVD at baseline were obtained from chi-square (categorical variables) or ANOVA tests (continuous variables).

*Participants with CVD were excluded from all the analyses.

Supplementary Table 2: Cross-sectional association between pain characteristics other than the number of pain locations, pain scale and lifestyle-related cardiovascular risk factors among older adults with no history of cardiovascular disease at baseline (n=1091).

	No pain	Pain persistency			Pain intensity			Pain experience			Pain scale†
		< 2 times/week	≥2 times/week	P-val*	Mild/ Moderate	Severe	P-val *	Not bad	Bad	P-val *	
	n=654	n=123	n=343		n=261	n=205		n=180	n=286		
Lifestyle-related factors											
Smoking; RRR (95%CI)											
Former (vs never)	1.00	1.43 (0.86,2.37)	1.51 (1.04,2.20)	0.03	1.57 (1.07,2.30)	1.33 (0.84,2.12)	0.08	1.16 (0.75,1.78)	1.84 (1.22,2.78)	<0.01	1.14 (1.03,1.26)
Current (vs never)	1.00	2.14 (1.08,4.25)	1.37 (0.77,2.43)	0.19	1.74 (1.00,3.06)	1.41 (0.70,2.84)	0.16	1.49 (0.81,2.75)	1.71 (0.91,3.20)	0.07	1.11 (0.96,1.29)
Alcohol; RRR (95%CI)											
Ex-drinkers (vs never)	1.00	1.23 (0.62,2.46)	0.75 (0.45,1.25)	0.30	0.79 (0.45,1.37)	0.97 (0.55,1.71)	0.81	0.68 (0.35,1.34)	0.97 (0.58,1.63)	0.84	0.97 (0.86,1.10)
Moderate-drinkers (vs never)	1.00	0.85 (0.46,1.56)	0.83 (0.55,1.26)	0.36	0.87 (0.55,1.37)	0.77 (0.47,1.26)	0.30	1.07 (0.63,1.80)	0.69 (0.44,1.08)	0.14	0.94 (0.85,1.05)
Heavy drinkers (vs never)	1.00	0.85 (0.32,2.25)	0.64 (0.30,1.35)	0.24	0.75 (0.35,1.58)	0.62 (0.35,1.58)	0.27	0.91 (0.39,2.10)	0.57 (0.25,1.29)	0.18	0.89 (0.73,1.08)
Mediterranean drinking pattern											
No MDP (vs never)	1.00	0.79 (0.45,1.37)	1.06 (0.60,1.87)	0.97	0.97 (0.53,1.77)	0.86 (0.43,1.70)	0.70	1.28 (0.66,2.51)	0.75 (0.41,1.38)	0.39	0.98 (0.85,1.14)
MDP (vs never)	1.00	0.97 (0.55,1.71)	0.65 (039,1.07)	0.07	0.77 (0.46,1.29)	0.50 (0.27,0.93)	0.03	0.71 (0.38,1.33)	0.63 (0.37,1.08)	0.07	0.89 (0.76,1.00)
Diet quality; MD (95%CI)	1.00	0.17 (-0.15,0.49)	0.28 (0.04,0.51)	0.02	0.27 (0.02,0.51)	0.21 (-0.07,0.50)	0.06	0.15 (-0.13,0.42)	0.32 (0.07,0.57)	0.01	0.08 (0.02,0.14)
rPA (Mets-h/week); MD (95%CI)		1.06 (-1.48,3.61)	0.97 (-0.91,2.84)	0.29	1.80 (-0.14,3.74)	-0.26 (-2.52,1.99)	0.76	1.98 (-0.23,4.18)	0.23 (-1.79,2.25)	0.60	0.00 (-0.48,0.49)
TV viewing (h/week); MD (95%CI)		0.85 (-0.97,2.66)	1.36 (0.03,2.70)	0.04	1.56 (0.17,2.93)	0.68 (-0.92,2.28)	0.18	1.22 (-0.35,2.79)	1.20 (-0.24,2.64)	0.07	0.31 (-0.04,0.65)
Anthropometric factors; RRR (95%CI)											
Overweight (vs normoweight)	1.00	1.10 (0.65,1.85)	1.57 (1.04,2.38)	0.04	1.42 (0.93,2.17)	1.36 (0.83,2.21)	0.11	1.31 (0.83,2.08)	1.48 (0.94,2.33)	0.07	1.10 (0.99,1.22)
Obesity (vs normoweight)	1.00	1.01 (0.56,1.84)	1.99 (1.27,3.12)	<0.01	1.73 (1.09,2.75)	1.47 (0.86,2.51)	0.06	1.35 (0.80,2.26)	1.88 (1.16,3.07)	<0.00	1.17 (1.04,1.31)
Sleep quality and duration											
Night-time sleep (hours); MD (95%CI)		-0.24 (-0.44,-0.05)	-0.51 (-0.73,-0.29)	<0.01	-0.22 (-0.44,-0.00)	-0.45 (-0.65,-0.25)	<0.01	-0.21 (-0.40,-0.01)	-0.56 (-0.77,-0.34)	<0.01	-0.12 (-0.17, -0.08)
Poor sleep quality; OR (95%CI)	1.00	1.54 (0.98,2.43)	1.99 (1.44, 2.74)	<0.01	1.64 (1.16,2.32)	2.18 (1.50,3.17)	<0.01	1.66 (1.12,2.45)	2.01 (1.42,2.83)	<0.01	1.22 (1.13,1.33)
Mental health											
Psychol. distress; MD (95%CI)		-0.17(-0.56,0.21)	0.25 (-0.04,0.53)	0.12	-0.09 (-0.38,0.21)	0.43 (0.09,0.77)	0.04	-0.22 (-0.55,0.11)	0.38 (0.08,0.69)	0.04	0.10 (0.03,0.17)
Depression; OR (95%CI)	1.00	1.11 (0.55,2.24)	1.81(1.15,2.87)	<0.01	1.30 (0.77,2.20)	1.98 (1.20,3.27)	<0.01	1.28 (0.70,2.34)	1.82 (1.13,2.93)	0.01	1.16 (1.04,1.29)

* P values for trend were obtained considering categorical variables as continuous

† The mean (SD) score in the pain scale was 1.4 (1.81)

OR: odds ratio; RRR: Relative risk ratio; MD: Mean difference. MEDAS: Mediterranean Adherence Diet Score; rPA: Recreational Physical Activity; TV: Television viewing; GHQ: General Health Questionnaire. Logistic regression models used participants with no chronic pain as reference category.

All models were adjusted for sex, age, educational level (primary or less, secondary, or university), tobacco consumption (never, former, current), alcohol drinking (never, former, moderate, or heavy), adherence to a Mediterranean dietary pattern (MEDAS score), energy intake (kcal/day), body mass index (normoweight, overweight, obese), recreational physical activity (METs-h/week), television viewing time (h/week), night-time sleeping duration, poor sleep quality, psychological distress (GHQ-12 scores), systolic blood pressure, diabetes, cancer, chronic obstructive respiratory and depression