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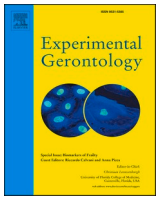

Health-related quality of life and mortality in the 'Seguimiento Universidad de Navarra' prospective cohort study

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ABSTRACT

Objective: To study the association between health-related quality of life (HRQoL) and all-cause mortality in a healthy middle-aged Mediterranean cohort.
Methods: We included 15,390 participants –mean age 42.8 years at first HRQoL ascertainment, all university graduates–. HRQoL was assessed with the self-administered Medical Outcomes Study Short Form-36 (SF-36) twice, with a 4-year gap. We used multivariable-adjusted Cox regression models to address the relation between self-reported health and Physical or Mental Component Summary (PCS-36 or MCS-36) and mortality, and their interaction with prior comorbidities or adherence to the Mediterranean diet (MedDiet).
Results: Over 8.7 years of median follow-up time, 266 deaths were identified. Hazard ratio (HR) for the excellent vs. poor/fair category in self-reported health was 0.30 (95 % confidence interval (CI), 0.16–0.57) in the model with repeated measurements of HRQoL. Both the PCS-36 ($HR_{quartile4(Q4)vs.Q1}$ 0.57 [95%CI, 0.36–0.90], $p_{trend} < 0.001$; $HR_{per+10points}$: 0.64 [95%CI, 0.54–0.75]) and the MCS-36 ($HR_{Q4vs.Q1}$ 0.67 [95%CI, 0.46–0.97], $p_{trend} = 0.025$; $HR_{per+10points}$: 0.86 [95%CI, 0.74–0.99]) were inversely associated with mortality in the model with repeated measurements of HRQoL. Previous comorbidities or adherence to the MedDiet did not modify these associations.
Conclusions: Self-reported HRQoL –assessed as self-reported health, PCS-36 and MCS-36– obtained with the Spanish version of the SF-36 were inversely associated with mortality risk, regardless of the presence of previous comorbidities or adherence to the MedDiet.

1. Introduction

Until the second half of the 20th century, health was defined as an absence of disease (World Health Organization, 2014); such definition failed to incorporate quality of life (QoL) in it (Karimi and Brazier, 2016). Health organizations across the world gradually realized of the significance of wellness throughout all life stages (Phyo et al., 2020; Stocks et al., 2019), leading the World Health Organization (WHO) to redefine health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (World Health Organization, 2014). Such definition, despite showing strong limitations inherent to its subjective nature (Terris, 1975), would influence the framing of surveys such as the Health Status Index (HIS), the Medical Outcomes Study Short Form (SF-36) (Maurish, 2011) or the SF-12 (Gandek et al., 1998). Recent and salient proposals have added insight into this concept with more solid foundations on epidemiologic studies

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(Ryff and Singer, 1996; VanderWeele, 2017).

Self-reported health, composed by one single question, has sometimes been used as a reliable measure of well-being (Ul-haq et al., 2014), although multi-item measures have been suggested to offer multidimensional information on an individual's health self-perception (Ul-haq et al., 2014; Ware, 2000).

Recently, an increasing number of studies have probed whether Health-related Quality of Life (HRQoL) or QoL are predictors of mortality risk (Phyo et al., 2020; Ul-haq et al., 2014; Nilsson et al., 2020; Phyo et al., 2021; Landré et al., 2021). However, few studies have been carried out on general population participants under 50, have long follow-up periods nor used SF-36. A meta-analysis conducted in 2020 summarizing findings from 47 studies found that better QoL or HRQoL was associated with lower mortality risk (Phyo et al., 2020). However just 66 % of those studies had been carried out on the general population, and only 33 % of the latter included participants under 50. Moreover, just one of those studies had >6.5 years of median follow-up time. Some inconsistencies can be found between studies: some found both the physical dimension (PCS, Physical Component Summary) and the mental dimension (MCS, Mental Component Summary) of HRQoL to be significant predictors of mortality (Phyo et al., 2020, 2021), but others found only PCS or MCS to be significantly associated with mortality risk (Phyo et al., 2020; Ul-haq et al., 2014; Haring et al., 2011). Thus, further insight into this matter is needed.

The main objective of our study was to evaluate whether HRQoL assessed by SF-36 was associated with the risk of all-cause mortality in middle-aged adults. As a secondary objective, we assessed whether that association was modified by previous comorbidities or adherence to the Mediterranean diet. Lastly, we evaluated the association between self-perceived HRQoL and risk of mortality according to specific causes of death.

2. Methods

2.1. Study population: the SUN cohort

This study is framed within the SUN (*Seguimiento Universidad de Navarra*) Project. The SUN Project is a Mediterranean dynamic multipurpose prospective follow-up cohort study collecting information from participants every two years through self-administered questionnaires (Martínez-González, 2006). Recruitment started in 1999 and is permanently open just to Spanish university graduates. Participants complete the SF-36 Survey (Ware, 2000) both in the 4-year and the 8-year follow-up questionnaire. Fig. S1 shows the timeline of assessment of exposure and outcome.

The Research Ethics Committee of the University of Navarra approved the study protocol (approval code 010830). The SUN project is conducted according to the principles expressed in the Declaration of Helsinki. The voluntary completion of the baseline questionnaire was considered to imply informed consent (Carlos et al., 2018).

2.2. Inclusion and exclusion criteria

The number of participants included in the latest updated SUN project database (December 2019) was 22,894. Participants lacking at least 2-year follow-up beyond the year 4 questionnaire, participants not having fully completed the SF-36 questionnaire, and participants lacking a plausible self-referred total energy intake, were excluded from our analysis. Our final sample consisted of 15,390 participants (retention proportion > 95 %) (Fig. S2).

2.3. Health-related Quality of Life

HRQoL was assessed based on SF-36. The SF-36 is a multipurpose self-reported health survey containing 36 questions. It yields an eight-scale profile of scores (Maurish, 2011) (Fig. S3 and Supplementary material) that are used to obtain two distinct concepts to define an individual's HRQoL (Maurish, 2011): PCS and MCS (Ware, 2000; Lins and Carvalho, 2016). We used a standardized scoring procedure developed for the Spanish version of SF-36 v2 (Vilagut et al., 2008).

The first question of SF-36 corresponds to self-reported health and was considered for PCS, MCS and also as a single variable. It has five possible answers: Poor/Fair/Good/Very Good/Excellent.

As explained above, participants in the SUN Project completed the SF-36 questionnaire twice. Availability of two different measurements of the same parameters with a 4-year gap contributes to obtain more solid evidence on potential relations between HRQoL and mortality.

2.4. Outcome: mortality

Deaths of participants in the SUN project are usually reported by next-of-kin, work colleagues, or the authorities' postal system, and are confirmed by medical records after consent. The remaining cases are confirmed after consultation of the Spanish National Death Index of the National Statistics Institute (Carlos et al., 2018).

Our main outcome was overall mortality. We also assessed separately cardiovascular mortality, cancer mortality and mortality due to other causes.

2.5. Assessment of covariates

Sociodemographic and lifestyle variables were collected in the baseline questionnaire, including age, sex, marital status, and offspring, and health-related behaviors or traits such as smoking status, cumulative smoking habit, alcohol intake, time spent watching TV, time spent working, total energy intake, body mass index (BMI) (Bes-Rastrollo et al., 2005), physical activity (Martinez-Gonzalez et al., 2005), difficulty sleeping, self-perceived tension, self-perceived competitiveness, self-perceived dependence, mid-day sleep, as well as a food frequency questionnaire (Boyle et al., 1993). Adherence to Mediterranean diet was assessed using Trichoupoulou's Mediterranean diet score excluding the alcohol component based on the food frequency questionnaire (Trichopoulou et al., 2003). Medically-diagnosed conditions considered for our analyses were prevalent cardiovascular disease, diabetes, depression, and cancer. Information for all potential confounders was obtained from the baseline questionnaire of the SUN Project and information on medical conditions was updated based on self-reported information from baseline to the 4-year follow-up questionnaire.

2.6. Statistical analysis

Date of completion of the 4-year follow-up SUN study questionnaire was considered the time at entry for our analyses, while exit time was the date of death or the date the last follow-up questionnaire was completed if the participant's decease had not been reported.

Baseline characteristics of our participants were described with means and standard deviation (SD) for quantitative traits and with proportions for qualitative traits according to quartiles of PCS and MCS after adjusting for age and sex using inverse probability weighting.

We described survival during follow-up with Kaplan-Meier curves adjusted for baseline covariates –based on previous literature (Phyo et al., 2020; Stocks et al., 2019; Ul-haq et al., 2014; Phyo et al., 2021; Haring et al., 2011; Jyväkorpi et al., 2020; Liu et al., 2019; Vlassoff, 2007)– using inverse probability weighting, and multivariable Cox regression models were used to study the association between self-reported health or HRQoL scores and mortality and to obtain hazard ratios (HR) and their corresponding 95 % confidence intervals (CI). As for self-reported health, the categories of poor and fair health were grouped together for our analysis, because little number of participants reported these answers, and was considered as the reference category. We also estimated the association per +1 point in this item. As for the aggregated PCS and MCS, participants in the first quartile (Q1) were

considered the reference category. We came up with three models (see supplementary material): Model 1 was age-&-sex-adjusted. Model 2 was additionally adjusted for sociodemographic factors, lifestyle variables, self-perceived variables, and comorbidities: prevalence of cardiovascular disease, diabetes, depression, and cancer. Model 3a was additionally adjusted for cancer, cardiovascular disease, diabetes, and depression in the 4-year period between the baseline questionnaire and the 4-year follow up questionnaire. Model 3b includes Model 3a and updated information up to the 8-year follow-up questionnaire. Linear trends across HRQoL categories were calculated by assigning the median value to each of the categories, considering the subsequent figures as continuous.

We further stratified our analyses by the presence of comorbidities in the first 4 years of follow-up. Multiplicative interactions between SF-36 quartiles and comorbidities were calculated with likelihood ratio tests.

Lastly, we used restricted cubic splines to assess the dose-response

Table 1
Age- and sex-adjusted[a] baseline characteristics of participants according to quartiles of the SF-36 self-administered quality of life questionnaire[b].

Characteristics	Physical component summary				Mental component summary			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
n (frequency)	3848	3847	3848	3847	3848	3847	3851	3844
HRQoL score								
Range	7.72–50.74	50.74–54.18	54.18–56.73	56.73–71.26	3.65–46.49	46.49–51.74	51.74–55.04	55.04–67.36
Median	46.54	52.77	55.45	58.35	37.47	49.73	53.41	56.91
Age (years)	41.7	39.4	37.3	35.3	36.6	36.8	38.5	41.9
Sex (%)								
Male	38.5	41.5	42.5	36.5	32.3	38.1	42.3	46.4
Female	61.5	58.5	57.5	63.5	67.7	61.9	57.7	53.6
Marital status (%)								
Single	45.5	42.6	41.4	43.6	45.3	41.8	41.5	45.2
Married	49.4	53.3	54.1	51.5	49.4	53.8	53.9	50.4
Others	5.1	4.1	4.5	4.9	5.3	4.4	4.6	4.4
Offspring (% yes)	44.2	47.9	48.7	47.1	44.6	48.1	48.8	45.6
Time spent working (%)								
Does not work outside home	11.0	10.0	9.1	9.8	11.4	8.7	10.1	11.1
Up to 40 h/week	40.3	38.0	38.5	36.8	38.3	39.0	38.4	37.1
More than 40 h/week	48.7	52.0	52.4	53.4	50.2	52.3	51.5	51.8
Total energy intake (kcal/day)	2514 (778)	2531 (771)	2478 (751)	2501 (769)	2571 (807)	2507 (748)	2487 (745)	2465 (761)
BMI (%)								
Normal weight	67.2	70.2	72.1	74.3	69.3	73.0	71.6	68.9
Overweight	26.0	25.3	24.5	22.9	25.7	23.7	23.8	26.2
Obesity	6.8	4.6	3.4	2.8	5.0	3.3	4.6	4.9
Physical activity (METs-h/week)	19.7 (21.5)	20.9 (20.9)	22.7 (23.8)	23.4 (23.7)	19.7 (21.3)	21.2 (21.3)	22.8 (23.7)	22.7 (23.8)
Cumulative smoking habit (packs-years)	6.3 (10.3)	6.0 (9.6)	5.8 (9.6)	6.0 (9.8)	6.8 (10.7)	5.9 (9.9)	6.0 (9.7)	5.7 (9.6)
Smoking (%)								
Never smoker	47.4	48.8	49.9	49.9	46.4	50.1	49.1	50.7
Current smoker	21.9	21.6	21.0	21.4	24.8	19.1	21.6	19.8
Former smoker	30.7	29.6	29.1	28.7	28.8	30.8	29.3	29.5
Alcohol intake (g/day)	6.5 (10.0)	6.9 (11.0)	6.9 (11.1)	7.3 (10.7)	7.2 (11.0)	7.0 (11.1)	6.9 (11.1)	6.4 (9.7)
Time spent watching TV (hours/day)	1.7 (1.2)	1.6 (1.2)	1.6 (1.1)	1.6 (1.2)	1.7 (1.2)	1.6 (1.2)	1.6 (1.1)	1.6 (1.1)
Difficulty sleeping (% yes)	12.4	8.4	7.4	9.7	15.7	9.9	7.5	6.3
Competitiveness (%)								
Low	8.5	7.6	8.1	7.3	9.2	8.2	6.8	7.3
Medium	48.2	49.9	48.6	44.8	46.2	49.2	50.1	47.0
High	43.3	42.5	43.3	47.9	44.6	42.6	43.1	45.7
Self-perceived tension (%)								
Low	20.3	24.3	24.4	20.3	13.7	19.7	24.7	31.3
Medium	47.8	48.2	49.9	48.1	45.3	50.7	50.1	48.3
High	31.9	27.5	25.7	31.6	41.0	29.6	25.2	20.4
Self-perceived Dependency (%)								
Low	64.0	66.6	68.4	65.8	59.8	66.3	68.3	70.0
Medium	18.5	16.7	15.9	17.2	22.7	17.3	15.3	13.3
High	17.5	16.7	15.7	17.0	17.5	16.4	16.4	16.7
Mid-day sleep (%)								
Never	49.4	49.6	49.7	50.5	47.5	50.4	49.2	52.2
Siesta $\leq$ 30 min	38.0	39.0	39.5	39.3	39.7	39.3	38.9	37.7
Siesta $>$ 30 min	12.6	11.4	10.8	10.2	12.8	10.3	11.9	10.1
Adherence to Mediterranean diet[c] (%)								
Low	40.6	40.3	39.2	36.8	40.1	39.6	38.3	38.4
Medium	40.5	39.2	39.2	41.0	40.3	39.8	41.2	39.6
High	18.9	20.5	21.6	22.2	19.6	20.6	20.5	22.0
Medically diagnosed conditions at baseline								
Prevalent cardiovascular disease[d] (%)	6.7	4.3	2.9	3.1	5.9	4.0	3.9	4.3
Prevalent diabetes (%)	2.2	1.7	1.3	0.9	1.8	1.3	1.7	1.7
Prevalent depression (%)	14.9	9.6	8.1	12.8	21.0	10.3	8.1	6.9
Prevalent cancer (%)	3.2	2.4	2.5	1.5	2.5	2.4	2.5	3.0

Abbreviations: BMI, Body Mass Index; METs, metabolic equivalents; TV, television; HRQoL, Health-related quality of life.

[a] Adjusted through inverse probability weighting.

[b] Values are means and (SDs) or numbers of participants (percentages).

[c] Adherence to the Mediterranean Diet was assessed using the score proposed by Trichopoulou et al. (2003) without the alcohol component.

[d] Prevalent cardiovascular disease was considered as having at least one of the following events before entering the cohort: myocardial infarction, stroke, angina pectoris, revascularization, tachycardia, atrial fibrillation, aneurysm, cardiac insufficiency, pulmonary embolism, deep vein thrombosis, or intermittent claudication.

relation between HRQoL and its corresponding HR (95 % CI).

Logistic and multinomial logistic regression models were used to impute qualitative covariates and missing values of continuous covariates were imputed with linear regression models.

All analyses were performed on Stata 16 (STATA Corp., TX, USA) with the latest updated available SUN database (December 2019). A 2-sided *p*-value <0.05 was considered as statistically significant.

3. Results

3.1. Sample characteristics and overall HRQoL scores

The final sample consisted of 15,390 participants, 60.3 % of whom were female. Mean age of participants at the time of the first HRQoL ascertainment (4-year) was 42.8 years (SD = 12.1 years), and the median follow-up time was 8.7 years. Overall, 133,078 persons-years of follow-up and 266 deaths were documented.

Table 1 shows the age- and sex-adjusted baseline characteristics of participants according to quartiles of SF-36 scoring (crude baseline characteristics displayed in Table S1). Overall, the higher the quartile the healthier the participants' health habits.

3.2. Kaplan-Meier survival estimates

Fig. 1 shows the Kaplan-Meier curve for survival estimates of participants across HRQoL quartiles, both for PCS and MCS. Regarding PCS, survival proportion was higher for participants in Q2, Q3 and Q4 of HRQoL. As to MCS, a different pattern was found, showing a similar survival proportion for participants across quartiles throughout time, although it was still slightly higher for participants in quartiles 3–4.

3.3. Cox regression mortality models for self-reported health

Table 2 shows HR and 95 % CI for the association between self-reported health and all-cause mortality. Based on the fully multivariate-adjusted model (model 3a), participants in the highest self-reported health category self-reported health had 63 % relatively lower risk of all-cause mortality compared to participants in the lowest self-reported health category. A 30 % mortality relative risk (RR) reduction was found in the fully adjusted model per +1 point in self-reported health. When repeated measurements (using SF-36 from both 4-year and 8-year questionnaires) were used to update participant's self-reported health, a similar result was found. Based on the fully multivariate-adjusted model (model 3b), participants in the highest category of updated self-reported health had even higher inverse relative mortality risk reduction.

3.4. Cox regression mortality models for the PCS of SF-36

The PCS of HRQoL was inversely associated with all-cause mortality (Table 2). Based on the fully multivariate-adjusted model (model 3a), participants in Q4 of HRQoL had 44 % relatively lower risk of all-cause mortality compared to participants in Q1 of HRQoL (significant inverse dose-response relation, $p_{trend} < 0.001$). A RR of 0.70 for all-cause mortality was observed in the fully adjusted model per +10 points in SF-36. Repeated measurements were performed using both 4-year and 8-year follow-up data to update participant's self-perceived QoL. An even stronger inverse relation between PCS of HRQoL and all-cause mortality was found. Based on the fully multivariate-adjusted model (model 3b), participants in Q4 of HRQoL had a 43 % relatively lower risk of all-cause mortality compared to participants in Q1 [HR 0.57 (95%CI 0.36–0.90)] with a significant inverse dose-response relation ($p_{trend} < 0.001$). The RR for mortality per +10 points in SF-36 was 0.64 (95%CI 0.54–0.75).

3.5. Cox regression mortality models in the MCS of SF-36

A non-significant association between quartiles of MSC and mortality was found on the multivariate-adjusted model (HR 0.74, 95%CI 0.51–1.07) ($p_{trend} = 0.107$) based on one single assessment of the MSC (Table 2). When repeated measurements were performed, significant associations between quartiles of MSC and mortality were found on the multivariate-adjusted model (model 3b). Based on that model, participants in Q4 of HRQoL had 33 % relatively lower risk of all-cause mortality compared to participants in Q1 (HR 0.67 [95%CI 0.46–0.97]) with a significant inverse dose-response relationship ($p_{trend} < 0.025$). The relative mortality risk reduction per +10 points in SF-36 was 14 % (95% CI 1 %–26 %).

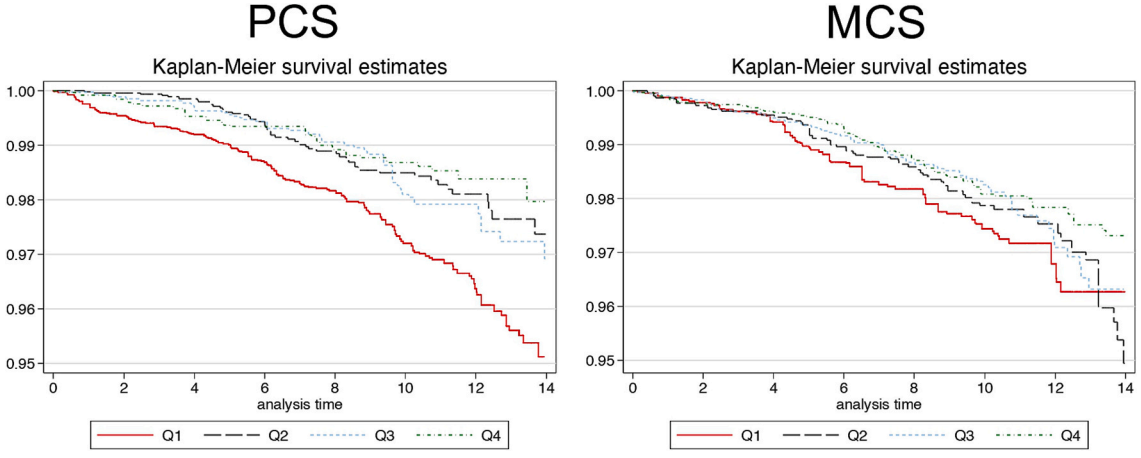

Fig. 1. Kaplan Meier survival estimates across HRQoL quartiles for both physical component summary and mental component summary.
Abbreviations: PCS, Physical Component Summary; MCS, Mental Component Summary
Adjusted for: marital status (three categories), offspring (dichotomous), time spent working (three categories), total energy intake (kcal/day, continuous), BMI (three categories), physical activity (METs-h/week, continuous), cumulative smoking habit (packs-years, continuous), smoking (three categories), alcohol intake (g/day, continuous), time spent watching TV (hours/day, continuous), difficulty sleeping (dichotomous), self-perceived tension (three categories), competitiveness (three categories), self-perceived dependence (three categories), Siesta-sleeping (three categories), adherence to the Mediterranean diet (Trichopoulou et al., 2003) (without the alcohol component, three categories), prevalent cardiovascular disease (dichotomous), prevalent diabetes (dichotomous), prevalent depression (dichotomous), and prevalent cancer (dichotomous), incident cancer (dichotomous), cardiovascular disease (dichotomous), diabetes (dichotomous) and depression (dichotomous) between the baseline questionnaire and the 4-year follow up questionnaire.

Table 2
Hazard ratios (HR) (95 % confidence intervals) for the association between self-reported health, the Physical Component Summary and the Mental Component Summary of the self-reported SF-36 questionnaire and all-cause mortality in the SUN Project (n = 15,390).

Self-reported health					
	Poor/fair	Good	Very good	Excellent	HR per +1 point
n	828	6897	6230	1435	
Deaths	65	121	69	11	
Persons-years	6679	59,653	54,218	12,528	
Mortality rate/1000 p-y	9.73	2.03	1.27	0.88	
Model 1	1.00 (Ref.)	0.33 (0.24–0.46)	0.35 (0.24–0.50)	0.29 (0.15–0.57)	0.65 (0.55–0.75)
Model 2	1.00 (Ref.)	0.37 (0.26–0.52)	0.40 (0.27–0.59)	0.35 (0.18–0.70)	0.69 (0.58–0.81)
Model 3a	1.00 (Ref.)	0.38 (0.27–0.54)	0.42 (0.28–0.62)	0.37 (0.18–0.73)	0.70 (0.59–0.83)
Repeated measures after 8-year follow-up questionnaire					
Model 1	1.00 (Ref.)	0.27 (0.19–0.37)	0.26 (0.18–0.38)	0.24 (0.13–0.45)	0.60 (0.51–0.70)
Model 2	1.00 (Ref.)	0.29 (0.20–0.41)	0.29 (0.19–0.44)	0.29 (0.15–0.55)	0.64 (0.54–0.76)
Model 3b	1.00 (Ref.)	0.30 (0.21–0.42)	0.30 (0.20–0.45)	0.30 (0.16–0.57)	0.64 (0.54–0.77)

Physical component summary						
	Q1	Q2	Q3	Q4	p for trend	HR per +10 points in SF-36
n	3848	3847	3848	3847		
Deaths	141	51	45	29		
Persons-years	32,598	33,346	33,575	33,559		
Mortality rate/1000 p-y	4.32	1.53	1.34	0.86		
Model 1	1.00 (Ref.)	0.50 (0.36–0.69)	0.57 (0.40–0.81)	0.48 (0.31–0.73)	<0.001	0.63 (0.54–0.73)
Model 2	1.00 (Ref.)	0.53 (0.38–0.75)	0.63 (0.44–0.91)	0.56 (0.36–0.85)	<0.001	0.69 (0.59–0.81)
Model 3a	1.00 (Ref.)	0.54 (0.39–0.76)	0.65 (0.45–0.93)	0.56 (0.37–0.86)	<0.001	0.70 (0.60–0.82)
Repeated measures after 8-year follow-up questionnaire						
Model 1	1.00 (Ref.)	0.46 (0.33–0.64)	0.54 (0.38–0.77)	0.49 (0.31–0.76)	<0.001	0.57 (0.50–0.67)
Model 2	1.00 (Ref.)	0.51 (0.36–0.71)	0.63 (0.44–0.90)	0.57 (0.36–0.89)	<0.001	0.63 (0.54–0.74)
Model 3b	1.00 (Ref.)	0.51 (0.36–0.72)	0.63 (0.44–0.90)	0.57 (0.36–0.90)	<0.001	0.64 (0.54–0.75)

Mental component summary						
	Q1	Q2	Q3	Q4	p for trend	HR per +10 points in SF-36
n	3848	3847	3851	3844		
Deaths	63	55	64	84		
Persons-years	32,733	33,571	33,666	33,109		
Mortality rate/1000 p-y	1.92	1.63	1.90	2.53		
Model 1	1.00 (Ref.)	0.94 (0.65–1.36)	0.79 (0.55–1.13)	0.70 (0.50–0.99)	0.040	0.88 (0.77–1.00)
Model 2	1.00 (Ref.)	0.95 (0.65–1.40)	0.80 (0.55–1.16)	0.72 (0.50–1.03)	0.073	0.88 (0.77–1.01)
Model 3a	1.00 (Ref.)	0.98 (0.66–1.43)	0.82 (0.56–1.19)	0.74 (0.51–1.07)	0.107	0.89 (0.78–1.02)
Repeated measures after 8-year follow-up questionnaire						
Model 1	1.00 (Ref.)	0.81 (0.56–1.16)	0.69 (0.48–0.98)	0.67 (0.48–0.94)	0.012	0.85 (0.74–0.97)
Model 2	1.00 (Ref.)	0.81 (0.56–1.17)	0.69 (0.48–1.01)	0.64 (0.45–0.92)	0.013	0.84 (0.72–0.97)
Model 3b	1.00 (Ref.)	0.83 (0.57–1.21)	0.72 (0.49–1.06)	0.67 (0.46–0.97)	0.025	0.86 (0.74–0.99)

Abbreviations: Ref., reference value; p-y: per year.
Model 1: adjusted for age (underlying variable) and sex (dichotomous).
Model 2: additionally adjusted for marital status (three categories), offspring (dichotomous), time spent working (Three categories), total energy intake (kcal/day, continuous), BMI (three categories), physical activity (METs-h/week, continuous), cumulative smoking habit (packs-years, continuous), smoking (three categories), alcohol intake (g/day, continuous), time spent watching TV (hours/day, continuous), difficulty sleeping (dichotomous), self-perceived tension (three categories), competitiveness (three categories), self-perceived dependence (three categories), Siesta-sleeping (three categories), adherence to the Mediterranean diet (Trichopoulou et al., 2003) (without the alcohol component, three categories), prevalent cardiovascular disease (dichotomous), prevalent diabetes (dichotomous), prevalent depression (dichotomous), and prevalent cancer (dichotomous).
Model 3a: additionally adjusted for incident cancer, cardiovascular disease, diabetes and depression between the baseline questionnaire and the 4-year follow up questionnaire.
Model 3b: as 3a but also updated up to the 8-year follow-up questionnaire.

3.6. Interaction with prior comorbidities

To estimate to what extent participants' prior comorbidities (cancer, cardiovascular diseases, diabetes or depression) could modify the association between their HRQoL and their mortality risk, we stratified our analyses by presence of comorbidities at the time of the first HRQoL ascertainment (Table 3). For PCS, a stronger inverse association between HRQoL and all-cause mortality was found in all models for participants suffering from prior comorbidities. The RR reduction per +10 points of HRQoL was significant in both cases. The interaction between the PCS and presence of comorbidities was not statistically significant ($p_{interaction}$ = 0.51, degrees of freedom = 3).

As to MCS, a stronger inverse association between HRQoL and all-cause mortality was also found in all models for participants suffering from prior comorbidities than those lacking prior comorbidities. The multiplicative interaction between the MCS and presence of

Table 3
Hazard ratios (HR) and 95 % confidence intervals for the association between SF-36 self-reported quality of life questionnaire scoring and all-cause mortality in the SUN Project stratified by presence of comorbidities[a].

Physical component summary	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p for trend	HR per +10 points in SF-36
Without prior comorbidities						
n	3014	3014	3015	3012		
Deaths/persons-years	62/26,001	24/26,336	27/26,483	19/26,469		
Mortality rate/1000 person years	2.38	0.91	1.01	0.72		
Model 1	1.00 (Ref.)	0.47 (0.29–0.76)	0.62 (0.39–0.98)	0.57 (0.33–0.98)	0.006	0.67 (0.53–0.84)
Model 2a	1.00 (Ref.)	0.47 (0.28–0.76)	0.62 (0.39–1.00)	0.63 (0.36–1.09)	0.015	0.72 (0.56–0.91)
With prior comorbidities						
n	834	834	834	833		
Deaths/persons-years	66/6788	31/6955	27/6978	10/7068		
Mortality rate/1000 person years	9.72	4.46	3.87	1.41		
Model 1	1.00 (Ref.)	0.47 (0.30–0.75)	0.66 (0.41–1.05)	0.34 (0.17–0.68)	<0.001	0.65 (0.53–0.78)
Model 2b	1.00 (Ref.)	0.47 (0.29–0.76)	0.66 (0.40–1.09)	0.36 (0.18–0.75)	0.001	0.67 (0.54–0.82)
Model 3a	1.00 (Ref.)	0.47 (0.29–0.77)	0.67 (0.41–1.10)	0.37 (0.18–0.77)	0.002	0.67 (0.55–0.83)

Mental component summary	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p for trend	Per 10 more points in SF-36
Without prior comorbidities						
n	3014	3015	3013	3013		
Deaths/persons-years	25/26,051	33/26,543	32/26,554	42/26,142		
Mortality rate/1000 person years	0.96	1.24	1.21	1.61		
Model 1	1.00 (Ref.)	1.18 (0.69–2.02)	0.82 (0.48–1.41)	0.75 (0.45–1.27)	0.221	0.92 (0.73–1.15)
Model 2a	1.00 (Ref.)	1.24 (0.72–2.13)	0.90 (0.51–1.58)	0.82 (0.47–1.41)	0.425	0.95 (0.75–1.21)
With prior comorbidities						
n	834	834	834	833		
Deaths/persons-years	26/6696	30/7081	34/6964	44/7048		
Mortality rate/1000 person years	3.88	4.24	4.88	6.24		
Model 1	1.00 (Ref.)	0.96 (0.56–1.66)	0.93 (0.54–1.59)	0.79 (0.48–1.32)	0.411	0.94 (0.81–1.10)
Model 2b	1.00 (Ref.)	0.74 (0.41–1.33)	0.75 (0.42–1.33)	0.57 (0.32–1.02)	0.076	0.87 (0.73–1.03)
Model 3a	1.00 (Ref.)	0.75 (0.41–1.35)	0.75 (0.42–1.35)	0.58 (0.32–1.04)	0.088	0.87 (0.73–1.04)

Abbreviations: Ref., reference value; BMI, Body Mass Index; METs, metabolic equivalents.
Model 1: adjusted for age (underlying variable) and sex (dichotomous).
Model 2a: additionally adjusted for marital status (three categories), offspring (dichotomous), time spent working (Three categories), total energy intake (kcal/day, continuous), BMI (three categories), physical activity (METs-h/week, continuous), cumulative smoking habit (packs-years, continuous), smoking (three categories), alcohol intake (g/day, continuous), time spent watching TV (hours/day, continuous), difficulty sleeping (dichotomous), self-perceived tension (three categories), competitiveness (three categories), self-perceived dependence (three categories), Siesta-sleeping (three categories), Trichopoulou's Med Diet score (Trichopoulou et al., 2003) (without the alcohol component, three categories).
Model 2b: additionally adjusted for marital status (three categories), offspring (dichotomous), time spent working (Three categories), total energy intake (kcal/day, continuous), BMI (three categories), physical activity (METs-h/week, continuous), cumulative smoking habit (packs-years, continuous), smoking (three categories), alcohol intake (g/day, continuous), time spent watching TV (hours/day, continuous), difficulty sleeping (dichotomous), self-perceived tension (three categories), competitiveness (three categories), self-perceived dependence (three categories), Siesta-sleeping (three categories), Trichopoulou's Med Diet score (Trichopoulou et al., 2003) (without the alcohol component, three categories), prevalent cardiovascular disease (dichotomous), prevalent diabetes (dichotomous), prevalent depression (dichotomous), and prevalent cancer (dichotomous).
Model 3a: additionally adjusted by incident cancer, cardiovascular disease, diabetes and depression in the 4-year period between the baseline questionnaire and the 4-year follow up questionnaire.
[a] Includes cancer, cardiovascular disease, diabetes and depression.

comorbidities was not statistically significant ($p_{interaction} = 0.96$, degrees of freedom = 3).

3.7. Interaction with Mediterranean diet

Neither the interaction between the PCS (4 categories) and baseline adherence to the Mediterranean diet (continuous) ($p_{interaction} = 0.72$, degrees of freedom = 3) nor the interaction between the MCS (4 categories) and baseline adherence to the Mediterranean diet (continuous) ($p_{interaction} = 0.24$, degrees of freedom = 3) were statistically significant.

3.8. Restricted cubic splines in the 4-year follow-up ascertainment

A restricted cubic spline model (Fig. S4) was fitted to show the relationship between HRQoL and all-cause mortality. Participants with a PCS score < 50 showed a higher all-cause mortality. The *p* value did not suggest a deviation from linearity (p for non-linearity = 0.62).

Regarding MCS, the graph had a similar shape to that of PCS, but no significant associations were observed (p for non-linearity = 0.78).

3.9. Association between HRQoL and cause-specific mortality

Fig. S5 shows the HR for all-cause mortality, cardiovascular disease mortality, cancer mortality and mortality due to other causes, both for PCS and MCS. Regarding PCS, point estimates for cardiovascular mortality, cancer mortality, and mortality due to other causes were similar than for overall mortality but the lower number of cases for these outcomes yielded wider CIs for all categories. MCS was inversely associated with cardiovascular mortality.

4. Discussion

In our study, self-reported HRQoL was found to be inversely related with mortality risk. Importantly, we found an inverse linear relationship

between self-reported health and mortality risk. The strong observed association of this simple, self-reported item and the strictly objective outcome of all-cause mortality is a major finding, and it indirectly contributes to support the validity of other self-reported information collected in this highly educated and motivated cohort. We also found an inverse linear association between the PCS of the SF-36 questionnaire and mortality risk. As to the MCS, we found an inverse significant association between +10 points in the MCS and mortality risk when we used repeated measurements. No significant interaction was observed by prior comorbidities. No substantial differences were observed for deaths attributable to different causes.

Our findings are novel for middle-aged adults using the Spanish version of SF-36, but they are consistent with previous studies conducted abroad. The strong inverse relation between self-reported health and mortality we found may suggest that the value of brief assessment conducted with the Spanish version of self-reported health may be valid as an initial approach to estimating a person's mortality risk, pending the administration of a more comprehensive questionnaire such as SF-36. A strong inverse relation between the PCS and HRQoL has also been observed in previous studies (Terris, 1975; Sajjad et al., 2017). In contrast with other studies, our participants were healthier [average BMI = 23.5 kg/m^2, (SD = 3.5); average conformity to the Mediterranean Diet Score = 4.0 (SD = 1.7), as proposed by Trichopoulou et al. (2003), without the alcohol component; average leisure time physical activity = 2.5 METs-h/wk (SD = 1.1), and younger than participants in previous studies. Our participants also showed a very low prevalence of baseline comorbidities. The association between PCS and mortality remained present even after restricting our analyses to participants who did not suffer from any prior chronic disease. This suggests that the Spanish version of SF-36 may be a reliable predictor for total mortality both for older populations with comorbidities and younger and healthier adult populations.

For the MCS we found an inverse significant association between +10 points in the MCS and mortality risk when we used repeated measurements, as well as for the comparison across extreme quartiles. MCS is more rarely found to be significantly associated with mortality risk (Ul-haq et al., 2014; Haring et al., 2011; Brown et al., 2015; Lahelma et al., 2016). It has been suggested that SF-36 questionnaire might not finely capture particular aspects of mental functioning, hypothetically leading to absent associations (Phyo et al., 2021). Other authors suggested that the association between mental health and mortality might partly be explained by poor perceived physical health, and therefore contribute little to mortality risk by itself (Sajjad et al., 2017). In line with that, some authors suggest that less emphasis should be put on the mental-related QoL measure when monitoring for the population's health (Brown et al., 2015). However, mental symptoms have been associated with unnatural mortality (Lahelma et al., 2016) and mental illnesses are known to be associated with mortality in patients suffering from cancer (Silinger and Zafar, 2018; Vythilingam et al., 2003). Despite all of the above-mentioned individual studies did not find an association between MCS and mortality risk, a meta-analysis conducted by *Phyo AZZ.* et al. in 2020 (Phyo et al., 2020) did show a statistically significant relation between MCS and mortality risk. Further investigation in larger samples is needed in this area.

Participants having a higher than 50 SF-36 scoring would have a statistically significant lower risk of all-cause mortality compared to the general population, and vice versa, as suggested by the restricted cubic spline model. This is consistent with what the *User's Manual for the SF-36v2 Health Survey Third Edition* (Maurish, 2011) describes.

The reason behind the analysis stratified by prior existence of chronic disease was to ensure that our data were not influenced by previous illnesses suffered by participants, for whom HRQoL may have different implications and reflect a higher risk of death than among counterparts without any baseline comorbidity.

This study has some limitations. First, all our analyses were based on data from the SUN Project, which collects information of participants through self-administered questionnaires. Although participants are recruited among university graduates to ensure all participants are suitable candidates to correctly understand and fill in the questionnaires, self-reported information can still be misclassified. We included repeated ascertainments of HRQoL to reduce the possibility of misclassification. In addition, participants showed a high percentage of valid responses in the SF-36 questionnaire. Second, even after using multivariable-adjusted Cox regression models, the likelihood of residual confounding is still possible.

On the other hand, our study has many strengths. Our data comes from a large, long-term follow-up prospective cohort (SUN Project), with a retention proportion > 95 %. It is mainly integrated by previously healthy participants who in general show healthy lifestyles, so the risk of previously diagnosed diseases or particularly harmful behaviors interacting with our main exposure (HRQoL) is somewhat low. Moreover, the questionnaire (SF-36 survey) that was used to collect the HRQoL is a previously validated and long-used form. The Spanish version of SF-36 has a consistent and similar performance than its original version (Vilagut et al., 2005; Alonso et al., 1998). To ensure the validity of our outcome variable (participant's death), SUN project researchers consult the Spanish National Death Index and the National Statistics Institute (Carlos et al., 2018) in case of participants being lost to follow-up.

5. Conclusions

Self-reported HRQoL was inversely associated with mortality risk in a middle-aged cohort, regardless of participants suffering from previous illnesses or their baseline adherence to the Mediterranean diet. On the one hand, the self-reported health was inversely associated with mortality risk in the SUN Project and may stand as a valid total mortality risk predictor, pending the administration of a more comprehensive questionnaire such as SF-36. On the other hand, both the PCS and the MCS were inversely associated with mortality risk in the SUN Project.

CRediT authorship contribution statement

Javier López-Herreros: Software, Formal Analysis, Investigation, Original Draft-Writing, Review and Editing, Visualization; **Miguel Ángel Martínez-González**: Conceptualization, Methodology, Investigation, Resources, Data Curation, Review and Editing, Visualization, Supervision, Project Administration, Funding Acquisition; **Alfredo Gea**: Methodology, Software, Investigation, Data Curation, Review and Editing, Visualization, Supervision, Funding Acquisition; **Almudena Sánchez-Villegas**: Review and Editing, Visualization; **Trinidad Dierssen-Sotos**: Review and Editing, Visualization; **José Juan Jiménez-Moleón**: Review and Editing, Visualization; **Miguel Ruiz-Canela**: Methodology, Review and Editing, Visualization; **Estefanía Toledo**: Conceptualization, Methodology, Software, Formal Analysis, Investigation, Resources, Data Curation, Review and Editing, Visualization, Supervision, Project Administration, Funding Acquisition.

Declaration of competing interest

All authors declare having no conflict of interest to disclose.

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Statements of ethical approval

The Research Ethics Committee of the University of Navarra approved the study protocol before any data was collected (approval code 010830). The SUN project is conducted according to the principles expressed in the Declaration of Helsinki. Informed consent to participate in the study was obtained according to the protocol approved by the Research Ethics Committee.

Participants received written information about the specific data required in que questionnaires, the protection to safeguard their privacy, and the future feedback from the research team. We also informed the potential candidates of their right to refuse to participate in the SUN study or to withdraw their consent to participate at any time without reprisal, according to the principles of the Declaration of Helsinki. The voluntary completion of the baseline questionnaire was considered to imply informed consent. The Research Ethics Committee of the University of Navarra approved this method to request the informed consent of participants.

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Appendix A. Supplementary data

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