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Predictors of total mortality and their differential association on premature or late mortality in the SUN cohort

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ABSTRACT

Several studies have tried to analyse the association between all-cause mortality and different risk factors, (especially those which are modifiable, such as smoking, diet or exercise), to develop public health preventive strategies. However, a specific analysis of predictors of premature and late mortality is needed to give more precise recommendations. Considering that there are risk factors which exert an influence on some diseases and not on others, we expect that, similarly, they may have a different impact depending on the timing of mortality, separating premature (≤65 years) from late mortality (>65 years). Thus, we prospectively followed-up during a median of 12 years a cohort of 20,272 university graduates comprising an ample range of ages at inception. Time-dependent, covariate-adjusted Cox models were used to estimate adjusted hazard ratios (HR) and their 95 % confidence intervals (CI) for each predictor. The strongest independent predictor of mortality at any age was physical activity which was associated with reduced risk of total, premature and late mortality (range of HRs when comparing the highest vs. the lowest level: 0.24 to 0.48). Specific strong predictors for premature mortality were smoking, HR: 4.22 (95 % CI: 2.42–7.38), and the concurrence of ≥2 metabolic conditions at baseline, HR: 1.97 (1.10–3.51). The habit of sleeping a long nap (≥30 min/d), with HR: 2.53 (1.30–4.91), and poor adherence to the Mediterranean Diet (≤3 points in a 0 to 8 score vs. ≥6 points), with HR: 2.27 (1.08–4.76), were the strongest specific predictors for late mortality. Smoking, diet quality or lifestyles, probably should be differentially assessed as specific predictors for early and late mortality. In the era of precision medicine, this approach will allow tailored recommendations appropriate to each person's age and baseline condition.

1. Introduction

Cancer and cardiovascular disease (CVD) remain the leading causes of death globally (GBD 2019 Diseases and Injuries Collaborators, 2020). Lifestyles are known to have an influence on the development of cancer and cardiovascular disease (Grosso et al., 2017; Katzke et al., n.d.; Pistelli et al., 2021; Doughty et al., 2017; Look AHEAD Research Group et al., 2016) as well as with total mortality (Sotos-Prieto et al., 2018; Nyberg et al., 2020; Ruiz-Estigarribia et al., 2020; Alvarez-Alvarez et al., 2018; Hershey et al., 2021). A huge accrual of epidemiologic and clinical trial evidence supports that high adherence to the traditional Mediterranean diet pattern is related to lower risk of CVD and total mortality (Trevisan et al., 2020; Trichopoulou et al., 2003; Trichopoulou and Vasilopoulou, 2000; van den Brandt, 2011). Likewise, for other healthy lifestyles, such as moderate alcohol consumption in specific populations, not smoking, physical activity and less sedentary time, significant protective associations have also been observed (Sotos-Prieto et al., 2018; Nyberg et al., 2020; Ruiz-Estigarribia et al., 2020). On the other hand, in relation to body mass index (BMI), both a linear effect and a U-shaped association have been described (Wu et al., 2014; Flegal et al., 2013; Veronese et al., 2016).

Some studies have specifically evaluated the effect of some predictors on premature mortality, highlighting that educational levels, (Roy et al., 2020; Pac et al., n.d.) smoking and the absence of prevalent diseases are the most relevant factors (Chan et al., 2014; Magliano et al., 2020; Armas Rojas et al., 2021; Gellert et al., 2012; Iribarren et al.,

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2005). For late mortality a Mediterranean dietary pattern, together with the practice of physical activity, stand out as protective factors (Pac et al., n.d.; McNaughton et al., 2012; Hsu et al., 2018).

However, studies that investigate the different association between predictors and total, premature, or late mortality are still lacking. To the best of our knowledge, the influence of each predictor on premature mortality compared to late mortality has not been analysed in the same cohort. The aim of this study was to investigate the role of each factor on all-cause mortality within different mortality strata, namely, total (occurring at any age), premature (≤65 years) and late (>65 years) to give more precise and specifically targeted public health recommendations.

2. Material and methods

2.1. Study population

The SUN Project is a prospective, multipurpose and dynamic cohort of Spanish university graduates with continually open recruitment. Through Alumni associations of the University of Navarra and other Spanish universities or Spanish professional associations, graduates are contacted and invited to participate in the study. They receive a baseline questionnaire by post, which they can also complete online at the SUN project website. The baseline questionnaire collects information on diet, lifestyle and health conditions. Once the baseline questionnaire is completed, a shorter questionnaire is sent every 2 years and if after up to 5 additional mailings there is no response, a brief questionnaire is sent. Further explanation on design and methods of the SUN cohort have been previously described (Carlos et al., 2018; Seguí-Gómez et al., 2006). Up to December 2019, 22,894 participants had answered the baseline questionnaire (age range at baseline: from 18 to 91 years) For the present analysis, 341 subjects with insufficient follow-up time, 224 subjects with total energy intake out of percentiles 0.5 and 99.5, and 3339 participants with prevalent diseases (cardiovascular disease, depression and cancer) were excluded. Among the remaining 18,990 subjects, 17,747 were successfully followed-up (overall retention: 93.4 %).

This study was approved by the Institutional Review Board of the University of Navarra. Participants of the SUN project received written information on their specific data to be requested by future questionnaires, the protection to safeguard their privacy, and the future feedback from the research team. We also informed all 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.

2.2. Outcome assessment

The primary outcome was all-cause mortality. We analysed total mortality, premature mortality (≤65 years) and late mortality (>65 years). For premature mortality, when participants reported >65 years at baseline or attained 65 years during the follow-up, they were censored. In addition, for late mortality, when participants did not attain 65 years during the follow-up, they were also censored. Continuous contact with participants was maintained and deaths were continually detected. Reports from next of kin, work associates, and the postal system allowed the identification of >85 % of deaths. For the rest of deaths, the National Death Registry was checked once a year to confirm the vital status and the causes of death of all the participants.

2.3. Predictors assessment

2.3.1. Dietary habits and alcohol consumption

The baseline questionnaire collected previously validated information on anthropometric (Bes-Rastrollo et al., 2005) sociodemographic, medical and lifestyle variables (Martínez-González et al., 2005). For dietary assessment, the previously validated 136-item semiquantitative Food Frequency Questionnaire (FFQ) (de la Fuente-Arrillaga et al., 2010) was used to estimate the adherence to Mediterranean Diet using the 0 to 9 Mediterranean Diet Score (MDS) proposed by Trichopoulou (Trichopoulou et al., 2003) but excluding one of the 9 items, moderate alcohol consumption, which was evaluated separately as a continuous variable estimating the HR for each additional 10 g/d of alcohol. We categorized MDS into tertiles of the distribution of values (low: <3 points, medium: 3–5, high: ≥6).

2.3.2. Physical activity

Physical activity information was assessed with different sport and lifestyle variables related to exercise and sedentary lifestyles included in baseline questionnaire (Martínez-González et al., 2005). In this study, we used a Physical Activity Score (PAS, 0 to 8 points) previously described in the SUN cohort (Alvarez-Alvarez et al., 2018). Briefly, the included items were: 1) doing exercise; 2) expending at least 16.1 METs-h/wk (the cohort median); 3) practicing sports with vigorous intensity; 4) adopting usually a brisk/very brisk walking pace; 5) walking for ≥30 min/d; 6) climbing upstairs ≥3 floors/d; 7) watching television for <1.5 h/d; and 8) spending <5 h/d sitting down. Hence, the PAS included 6 items related to PA (each weighted as +1) and 2 items about sedentary activities (each weighted as −1). Finally, according to previous categorizations of this score (Ruiz-Estigarribia et al., 2020; Alvarez-Alvarez et al., 2018) the sum of the 8 items was divided in 3 groups (low: ≤2 points, medium: 3–5, high: ≥6) of physical activity.

2.3.3. Metabolic conditions

Participants reported the evolution of their medical condition in each questionnaire as well as the existence of prevalent diseases. For this score, diseases such as diabetes, hypertension, obesity, hypercholesterolemia, or hypertriglyceridemia declared by the participants at baseline have been classified as metabolic conditions. This variable was categorized into 3 groups: no metabolic conditions, 1 condition, ≥2 conditions. In addition, those participants who did not report any disease but did habitually consume specific medications for these prevalent diseases were assumed to have a metabolic condition.

2.3.4. Smoking habit

The baseline questionnaire included information on smoking behaviour with variables such as number of cigarettes/d, brand, time since start, time since quitting and smoking of pipes or cigars. For this study, exposure to tobacco (never, former, current) was considered as well as the cumulative exposure to tobacco, measured as pack-years. To this end, the smoking habit variable was classified into 4 groups: never smokers, former smokers, smokers but <10 pack-years and smokers of ten or more packs-year.

2.3.5. Other predictors

Other predictors that were considered relevant to the study objectives were also analysed.

Sociodemographic variables were collected at baseline: sex (male, female), years of university education (doctoral degree, only graduated) and marital status (five categories: single, married, divorced, widow, missing/other). Furthermore, for the anthropometric variables, height and weight data were used to calculate the body mass index (BMI) for each participant (kg/m^2, continuous). Lastly, for lifestyle information, we studied variables like hours of television watching (<2 h per day, >2 h per day) or nap time-siesta, and its duration in min/day (no siesta, >0 and <30 min, ≥30 min).

2.4. Statistical analyses

Baseline characteristics of participants were analysed for different age strata: total, age under 65 or over 65 years old at baseline. Means and standard deviations were used to describe continuous variables, and percentages were used for categorical variables. The association between the different predictors and mortality strata was assessed using time-dependent Cox proportional hazard models. When assessing premature mortality enter time was considered as the date of returning the baseline questionnaire (including only those who were younger than 65 years at inception). Exit time was the date of death (for participants who died before attaining 65 years old), date of returning the last follow-up questionnaire or their 65th birthday if they attained 65 years dying follow-up. Therefore, in the analysis of premature mortality, we censored survivors when they reached 65 years during follow-up. For late mortality, only participants who had attained 65 years at baseline or during follow-up were included. Follow-up started from the baseline questionnaire (or at their 65th birthday) until their late death (>65 years), last contact, or end of follow-up. Participants who were older than 65 years at baseline were not included in analyses for premature mortality. Age was the underlying time variable (birthday date as origin). Multivariate models were stratified by age groups (10-year periods) and year of recruitment (1999/2003; 2004/2009; >2009). Models were also adjusted for all the following predictors: sex (dichotomous), BMI (kg/m2, continuous) alcohol intake (per 10 g/day, continuous), smoking habit (four groups and pack-years, four categories), punctuation in the Mediterranean Diet Score at baseline (three categories), time spent watching TV (<2 h/day, dichotomous), number of metabolic conditions at baseline (hypercholesterolemia, hypertriglyceridemia, diabetes, obesity, hypertension; three categories) educational level (doctoral degree, dichotomous), marital status (five categories), nap time-siesta (minutes/day, three categories), punctuation in the Physical Activity Score at baseline (physical activity intensity, energy expenditure, walking speed, walking time, climbing upstairs, television time, sitting time; three categories).

In addition, the relative risk ratios (RRR) between late and premature mortality for the most significant predictors were graphically represented.

All *p* values were 2 tailed. The level of confidence was 95 for confidence intervals (95 % CI). The analyses were performed using STATA/SE version 16.0 (Stata Corp, College Station, TX, USA).

3. Results

Table 1 presents baseline characteristics of the participants (n = 17,747) stratified into those aged equal or under 65 years (n = 17,382) or over 65 years at baseline (n = 365). The mean age of the cohort at baseline was 37.2 years (SD = 11.9) with 39.45 % male participants. Participants younger than 65 had similar characteristics to the total cohort. However, participants older than 65 years at baseline had a higher BMI, more alcohol consumption and were heavier smokers. They also had more prevalent diseases and spent more time in sedentary activities such as TV watching or naps for >30 min. On the other hand, they had higher scores in the MDS and PAS. Finally, they were more highly educated, had more frequently obtained doctoral studies, and most of them were married. However, many of these differences may be due to age and sex.

During a median follow-up of 11.60 years (interquartile range: 8.36–14.99), 310 participants (75.16 % men) died. Among subjects who died, their mean age at death was 65.1 (SD 16.5) years. The leading cause of death in under-65 s was cancer (60.8 %) followed by other causes (22.2 %) and CVD (17.0 %). Also, their mean age at death was 51.3 (SD: 10.50). Likewise, those with late mortality, their main cause of death were cancer (44.0 %), followed by other causes (34.4 %) and CVD (21.7 %). Their main age at death was 78.5 (SD: 8.01).

The association of the different predictors assessed with total, premature and late mortality was significant in different ways for each age group and are presented below (Tables 2, 3 and 4).

Table 1
Baseline characteristics of participants according to baseline age of participants.

	Global *N* = 17,747	≤65 years N = 17,382	>65 years *N* = 365
Men	39.45 %	38.62 %	79.18 %
Age	37.2 (11.9)	36.5 (11.0)	70.8 (5.3)
Mean age at death among deceased participants	65.9 (16.1)	51.7 (10.1)	78.5 (7.8)
Doctoral degree	9.88 %	9.71 %	17.81 %
Marital status			
Single	45.79 %	46.49 %	12.33 %
Married	49.46 %	48.94 %	74.52 %
Divorced/separated	2.01 %	2.00 %	2.74 %
Widow/widower	2.03 %	1.89 %	8.49 %
Missing/other	0.71 %	0.68 %	1.92 %
Body mass index (kg/m^2)	23.4 (3.5)	23.4 (3.5)	26.2 (3.4)
Alcohol per + 10 g/d	0.75 (1.1)	0.74 (1.07)	1.27 (1.71)
Smoking habit-(pack year)			
Non smokers	49.85 %	50.23 %	31.51 %
Former smokers	27.82 %	27.30 %	52.60 %
Current smokers & <10 pack-years	13.50 %	13.71 %	3.29 %
Current smokers & ≥10 pack-years	8.84 %	8.76 %	12.60 %
Mediterranean diet score (Trichopoulou, 0 to 8)			
<3 points	21.15 %	21.38 %	10.41 %
3–5 points	59.04 %	59.12 %	55.34 %
≥6 points	19.81 %	19.50 %	34.25 %
Number of metabolic conditions[a]			
No metabolic conditions	74.51 %	75.44 %	30.41 %
1 metabolic condition	16.93 %	16.53 %	35.62 %
2 or more metabolic conditions	8.56 %	8.03 %	33.97 %
Nap (siesta)			
No siesta	36.74 %	37.15 %	17.53 %
≤30 min/day	49.51 %	49.52 %	49.32 %
>30 min/day	13.74 %	13.34 %	33.15 %
Physical activity score (0 to 8 score)[b]			
<3 points	18.60 %	18.69 %	12.79 %
3–5 points	53.34 %	53.31 %	55.81 %
>5 points	28.05 %	28.00 %	31.40 %
Less than 2 h/day of television watching	69.06 %	69.24 %	60.27 %

[a] Metabolic conditions at baseline: hypercholesterolemia, hypertriglyceridemia, diabetes, obesity, hypertension.

[b] Physical activity score: 1) doing exercise; 2) expending at least 16.1 METs-h per week (the cohort median); 3) practicing sports with vigorous intensity; 4) adopting usually a brisk/very brisk walking pace; 5) walking for ≥30 min/d; 6) climbing upstairs ≥3 floors/d; 7) watching television for <1.5 h/d; and 8) spending <5 h/d sitting down.

3.1. Alcohol consumption

An independent significant association with total mortality (for the total analysis, regardless of the age at death) was observed when alcohol consumption was studied as a continuous variable (HR = 1.08, 95 % CI 1.01–1.16). An 8 % higher relative all-cause mortality risk was found, with a significant direct linear dose-response relationship between every 10 g of alcohol consumption per day and the risk of death. However, in the age-stratified mortality analysis, multivariable-adjusted models lost their significance for late mortality and only approached the limit of significance for premature mortality (HR = 1.10, 95 % CI 1.00–1.22, p = 0.043).

3.2. Smoking habit

As shown in Tables 2 and 3, being a heavy smoker (current smokers and more or equal to 10 packs of tobacco per year) represented a variable strongly associated with total mortality (HR = 2.98, 95 % CI 1.89–4.72, for all ages) and premature mortality (HR = 4.22, 95 % CI 2.42–7.38). However, for late mortality, its significance was lost (HR = 1.05, 95 % CI 0.38–2.87).

Table 2
Predictors of total mortality.

Total mortality	Crude	Sex & age-adjusted	Multivariable
Female vs male	0.54 (0.41–0.71)	0.54 (0.41–0.71)	0.84 (0.56–1.26)
Doctoral degree	0.84 (0.61–1.16)	0.77 (0.56–1.06)	0.85 (0.54–1.34)
Marital status			
Married	1 (ref.)	1 (ref.)	1 (ref.)
Single	0.95 (0.68–1.33)	1.05 (0.74–1.47)	1.09 (0.69–1.73)
Divorced/separated	1.72 (0.95–3.09)	1.96 (1.09–3.54)	1.03 (0.41–2.57)
Widow	0.91 (0.53–1.56)	1.11 (0.64–1.92)	1.23 (0.62–2.46)
Missing/other	1.31 (0.49–3.56)	1.38 (0.51–3.75)	0.74 (0.10–5.52)
Body mass index (kg/m^2)	1.07 (1.03–1.10)	1.05 (1.02–1.09)	1.02 (0.97–1.07)
Alcohol per + 10 g/d	1.14 (1.09–1.20)	1.12 (1.06–1.18)	1.08 (1.01–1.16)
Smoking habit + pack-years			
Never smokers	1 (ref.)	1 (ref.)	1 (ref.)
Former smokers	1.63 (1.23–2.16)	1.51 (1.14–2.01)	1.42 (0.96–2.09)
Current smokers & <10 pack-years	0.79 (0.43–1.46)	0.83 (0.45–1.53)	0.87 (0.41–1.81)
Current smokers & ≥10 pack-years	2.72 (1.94–3.81)	2.49 (1.77–3.50)	2.98 (1.89–4.72)
Mediterranean diet score (Trichopoulou, 0 to 8)			
Low adherence (<3 points)	1 (ref.)	1 (ref.)	1 (ref.)
Moderate adherence (3–5 points)	0.69 (0.51–0.92)	0.71 (0.53–0.96)	0.77 (0.52–1.13)
High adherence (≥6 points)	0.50 (0.35–0.72)	0.53 (0.37–0.76)	0.58 (0.35–0.94)
Number of metabolic conditions[a]			
No metabolic conditions at baseline	1 (ref.)	1 (ref.)	1 (ref.)
1 metabolic condition	1.44 (1–07-1.93)	1.39 (1.03–1.86)	1.35 (0.91–2.00)
2 or more metabolic conditions	2.55 (1.90–3.43)	2.37 (1.77–3.18)	1.77 (1.15–2.71)
Nap (siesta)			
No siesta	1 (ref.)	1 (ref.)	1 (ref.)
≤30 min siesta	1.33 (0.99–1.79)	1.29 (0.96–1.74)	1.33 (0.91–1.93)
>30 min siesta	1.82 (1.30–2.55)	1.76 (1.26–2.46)	1.95 (1.29–2.94)
Physical activity score (0 to 8 score)[b]			
<3 points	1 (ref.)	1 (ref.)	1 (ref.)
3–5 points	0.43 (0.31–0.60)	0.42 (0.30–0.59)	0.46 (0.32–0.65)
>5 points	0.33 (0.22–0.51)	0.32 (0.21–0.49)	0.38 (0.24–0.61)
Less than 2 h/day of television watching vs. >2 h/day	0.79 (0.63–1.00)	0.78 (0.62–0.99)	1.17 (0.84–1.62)

Multivariable model: adjusted for sex (dichotomous), BMI (kg/m^2, continuous) alcohol intake (per 10 g/day, continuous), smoking habit (four groups and pack-years, four categories), punctuation in the Mediterranean Diet Score at baseline (three categories), time spent watching tv (<2 h/day, dichotomous), number of metabolic conditions at baseline (hypercholesterolemia, hypertriglyceridemia, diabetes, obesity, hypertension; three categories) educational level (doctoral degree, dichotomous), marital status (five categories), nap time-*siesta* (minutes/day, three categories), punctuation in the Physical Activity Score at baseline (physical activity intensity, energy expenditure, walking speed, walking time, climbing upstairs, television time, sitting time; three categories).

[a] Metabolic conditions at baseline: hypercholesterolemia, hypertriglyceridemia, diabetes, obesity, hypertension.

[b] Physical activity score: 1) doing exercise; 2) expending at least 16.1 METs-h per week (the cohort median); 3) practicing sports with vigorous intensity; 4) adopting usually a brisk/very brisk walking pace; 5) walking for ≥30 min/d; 6) climbing upstairs ≥3 floors/d; 7) watching television for <1.5 h/d; and 8) spending <5 h/d sitting down.

3.3. Mediterranean diet score

The Mediterranean diet was a protective factor for overall mortality. High adherence to the Mediterranean diet (≥6 points on the Trichopoulou's score) was significantly protective against total mortality at any age (HR = 0.58, 95 % CI 0.35–0.94) and late mortality (HR = 0.44, 95 % CI 0.21–0.93) hence, when reversing the reference category, having <3 points in the MDS was associated with more than a twofold higher relative mortality, HR: 2.27 (1.08–4.76), as compared to ≥6 points in the MDS. On the other hand, an inverse association of the Mediterranean diet with premature mortality was suggested but it lost its significance in multivariate adjustment (HR = 0.62, 95 % CI 0.31–1.22, when comparing the highest versus the lowest category).

3.4. Metabolic conditions

The presence of 2 or more metabolic conditions at baseline (diabetes, obesity, hypertension, hypertriglyceridemia, or hypercholesterolemia) exhibited a direct association with total (HR = 1.77, 95 % CI 1.15–2.71) and premature mortality (HR = 1.97, 95 % CI 1.10–3.51). However, for late mortality, it lost its significance when multivariate adjustment was applied (HR = 1.51, 95 % CI 0.80–2.87).

3.5. Nap-siesta

The daily habit of long-lasting napping, for >30 min, significantly increased the risk of total (HR = 1.95, 95 % CI 1.29–2.94) and late mortality (HR = 2.53, 95 % CI 1.30–4.91) as compared to those who did not nap. However, in younger people this increased risk was not statistically significant (HR = 1.60, 95 % CI 0.92–2.78).

3.6. Physical activity score

This score, which considers sedentary and physical activity habits, was the only predictor in the analysis that was significant, at medium and high scores, for total (HR = 0.38, 95 % CI 0.24–0.61), premature (HR = 0.48, 95 % CI 0.27–0.84) and late mortality (HR = 0.24, 95 % CI 0.10–0.84). In addition, having >5 points in the score implied a 76 % relative risk reduction of mortality in people over 65 years of age.

3.7. Other predictors

All other predictors studied lacked statistical significance or lost significance after multivariable adjustment. Female sex, doctoral studies and watching <2 h of television per day were inversely related to mortality. On the other hand, single, divorced or widowed marital status, as well as an increase in the BMI were positively related to overall mortality.

Finally, Fig. 1, shows the association between each factor and premature or late mortality. It is observed that alcohol, smoking habit and having one or more metabolic conditions at baseline increases the risk of premature mortality compared to late mortality. On the other hand, taking a nap for >30 min increased the risk of late mortality. Likewise, protective factors such as the Mediterranean diet or physical activity shower a greater effect in preventing late mortality than premature mortality.

4. Discussion

In the present analysis, we found that there are predictors of mortality which influence differently according to age group and type of mortality (at any age, premature or late). In this SUN cohort, being a heavy smoker or having a baseline metabolic disease was found to be

Table 3
Predictors of premature mortality.

≤65 mortality	Crude	Sex & age adjusted	Multivariable
Female vs male	0.55 (0.39–0.78)		0.79 (0.49–1.30)
Doctoral degree	0.75 (0.44–1.29)	0.68 (0.39–1.16)	0.76 (0.38–1.55)
Marital status			
Married	1 (ref.)	1 (ref.)	1 (ref.)
Single	1.09 (0.70–1.70)	1.15 (0.73–1.82)	1.08 (0.61–1.93)
Divorced	2.06 (0.99–4.27)	2.35 (1.13–4.88)	1.64 (0.64–4.18)
Widow	0.66 (0.16–2.70)	0.73 (0.18–2.95)	0.87 (0.21–3.62)
Missing/other	1.91 (0.47–7.79)	2.06 (0.50–8.41)	1.30 (0.17–9.96)
Body mass index (kg/m^2)	1.09 (1.04–1.14)	1.07 (1.02–1.12)	1.02 (0.96–1.09)
Alcohol per + 10 g/d	1.24 (1.15–1.34)	1.20 (1.11–1.31)	1.10 (1.00–1.22)
Smoking habit + pack-years			
Never smokers	1 (ref.)	1 (ref.)	1 (ref.)
Former smokers	1.40 (0.91–2.15)	1.36 (0.89–2.10)	1.47 (0.85–2.54)
Current smokers & <10 pack-years	0.74 (0.34–1.58)	0.78 (0.36–1.67)	0.92 (0.39–2.15)
Current smokers & ≥10 pack-years	4.12 (2.66–6.38)	3.89 (2.51–6.02)	4.22 (2.42–7.38)
Mediterranean diet score (Trichopoulou, 0 to 8)			
Low adherence (<3 points)	1 (ref.)	1 (ref.)	1 (ref.)
Moderate adherence (3–5 points)	0.75 (0.51–1.12)	0.78 (0.52–1.15)	0.92 (0.57–1.49)
High adherence (≥6 points)	0.49 (0.29–0.85)	0.51 (0.30–0.88)	0.62 (0.31–1.22)
Number of metabolic conditions[a]			
No metabolic conditions at baseline	1 (ref.)	1 (ref.)	1 (ref.)
1 metabolic condition	1.58 (1.05–2.39)	1.47 (0.97–2.23)	1.30 (0.77–2.19)
2 or more metabolic conditions	2.66 (1.72–4.12)	2.32 (1.49–3.63)	1.97 (1.10–3.51)
Nap (siesta)			
No siesta	1 (ref.)	1 (ref.)	1 (ref.)
≤30 min siesta	1.38 (0.94–2.03)	1.34 (0.91–1.97)	1.21 (0.76–1.92)
>30 min siesta	1.85 (1.14–2.99)	1.78 (1.10–2.89)	1.60 (0.92–2.78)
Physical activity score (0 to 8 score)[b]			
<3 points	1 (ref.)	1 (ref.)	1 (ref.)
3–5 points	0.38 (0.25–0.60)	0.36 (0.23–0.57)	0.43 (0.27–0.68)
>5 points	0.39 (0.23–0.66)	0.37 (0.22–0.63)	0.48 (0.27–0.84)
Less than 2 h/day of television watching vs. >2 h/day	0.93 (0.66–1.32)	0.92 (0.65–1.30)	1.34 (0.87–2.05)

Multivariable model: adjusted for sex (dichotomous), BMI (kg/m^2, continuous) alcohol intake (per 10 g/day, continuous), smoking habit (four groups and pack-years, four categories), punctuation in the Mediterranean Diet Score at baseline (three categories), time spent watching tv (<2 h/day, dichotomous), number of metabolic conditions at baseline (hypercholesterolemia, hypertriglyceridemia, diabetes, obesity, hypertension; three categories) educational level (doctoral degree, dichotomous), marital status (five categories), nap time-*siesta* (minutes/day, three categories), punctuation in the Physical Activity Score at baseline (physical activity intensity, energy expenditure, walking speed, walking time, climbing upstairs, television time, sitting time; three categories).

[a] Metabolic conditions at baseline: hypercholesterolemia, hypertriglyceridemia, diabetes, obesity, hypertension.

[b] Physical activity score: 1) doing exercise; 2) expending at least 16.1 METs-h per week (the cohort median); 3) practicing sports with vigorous intensity; 4) adopting usually a brisk/very brisk walking pace; 5) walking for ≥30 min/d; 6) climbing upstairs ≥3 floors/d; 7) watching television for <1.5 h/d; and 8) spending <5 h/d sitting down.

significantly associated with premature mortality, while have >3 points on the physical activity score was found to be protective against premature death. On the other hand, other factors have been found to be associated with late mortality, such as take naps of >30 min a day. Additionally, scores higher than 6 (over 8) in the Mediterranean Diet Score and higher than 3 out of 8 points in physical activity behaved as protective factors against late mortality.

4.1. Alcohol consumption

We observed that alcohol consumption was a linear predictor of higher total mortality and early mortality, but not of late mortality. In agreement with our results, previous evidence supports that any dose of alcohol is harmful (Holmes et al., 2014; Stockwell et al., 2016; Naimi et al., 2019; GBD 2016 Alcohol Collaborators, 2018), but there is a need to take age and other factors relate to underlying causes of death into account (Barbería-Latasa et al., 2022; GBD 2020 Alcohol Collaborators, 2022). Furthermore, alcohol has been reportedly associated with an increased risk of premature mortality and there is evidence to support that alcohol should be avoided in young people (Naimi et al., 2019; Martínez-González et al., 2021; Stringhini et al., 2017; Sohi et al., 2021). On the other hand, there are studies supporting that moderate alcohol consumption is protective against total and cardiovascular disease mortality, but the drinking patterns and the underlying age and conditions can very likely act as effect modifiers (Trichopoulou et al., 2003; Martínez-González et al., 2019; Arriola et al., 2010; Costanzo et al., 2011; Ricci et al., 2018). In any case, it should be noted that in the present study we assessed the absolute amount of alcohol, not the Mediterranean drinking pattern previously studied in this cohort showing protective effects (Morales et al., 2021; Gea et al., 2014; Sánchez-Villegas et al., 2009).

4.2. Smoking habit

Smoking habit has been associated with increased total and premature mortality (Iribarren et al., 2005; Stringhini et al., 2017; Samet, 2013). Our study confirms previous findings that smoking increases the risk of premature death from any cause. We also observed a dose-response effect with a higher risk in current smokers who smoked >10 pack-years. This suggested that it is not just the fact of smoking, but the magnitude of exposure that is significant (Zhu et al., 2021; Inoue-Choi et al., 2020). However, in the late-life mortality study, an increased risk was observed in the preliminary adjustments, but it lost its statistical significance in the multivariable model. Although smoking has been mostly associated with premature mortality in the literature, there are some studies that also associate it with late mortality (Gellert et al., 2012) and the scarce number of older participants in our cohort may be related to suboptimal statistical power to identify this association.

4.3. Mediterranean diet score

High adherence to the Mediterranean diet pattern, as measured by the MDS, was significantly protective against total and late mortality. Moderate adherence also suggested a protective, but non-significant, association. This score has been widely used in several cohorts with similar results (Trevisan et al., 2020; Trichopoulou et al., 2003; Eleftheriou et al., 2018; Walker et al., 2020; Bonaccio et al., 2021) even in non-Mediterranean cohorts (McNaughton et al., 2012). These findings suggest a greater protective effect of the Mediterranean pattern in the long term (Trichopoulou and Vasilopoulou, 2000; Dominguez et al., 2021; Trichopoulou, 2004) This highlights the importance of adopting a healthy eating pattern over time, starting from a young age (Hershey et al., 2021; van den Brandt, 2011; Martínez-González et al., 2012) even

Table 4
Predictors of late mortality.

>65 mortality	Crude	Sex & age adjusted	Multivariable
Female vs male	0.52 (0.33–0.84)		1.08 (0.51–2.31)
Doctoral degree	0.90 (0.61–1.33)	0.82 (0.55–1.22)	1.00 (0.53–1.86)
Marital status			
Married	1 (ref.)	1 (ref.)	1 (ref.)
Widow	1.03 (0.57–1.86)	1.34 (0.73–2.49)	1.30 (0.55–3.07)
Other/missing	0.85 (0.54–1.34)	0.98 (0.62–1.55)	0.72 (0.34–1.52)
Body mass index (kg/m^2)	1.04 (1.00–1.09)	1.04 (0.99–1.09)	0.99 (0.92–1.06)
Alcohol per + 10 g/d	1.09 (1.01–1.17)	1.07 (0.99–1.15)	1.04 (0.94–1.16)
Smoking habit + pack-years			
Never smokers	1 (ref.)	1 (ref.)	1 (ref.)
Former smokers	1.41 (0.79–2.50)	1.25 (0.69–2.24)	1.40 (0.77–2.57)
Current smokers & <10 pack-years	0.98 (0.34–2.76)	1.01 (0.36–2.86)	0.90 (0.19–4.18)
Current smokers & ≥10 pack-years	1.77 (1.22–2.58)	1.57 (1.06–2.32)	1.05 (0.38–2.87)
Mediterranean diet score (Trichopoulou, 0 to 8)			
Low adherence (<3 points)	1 (ref.)	1 (ref.)	1 (ref.)
Moderate adherence (3–5 points)	0.62 (0.40–0.95)	0.65 (0.42–1.00)	0.55 (0.29–1.05)
High adherence (≥6 points)	0.49 (0.30–0.81)	0.52 (0.32–0.86)	0.44 (0.21–0.93)
Number of metabolic conditions[a]			
No metabolic conditions at baseline	1 (ref.)	1 (ref.)	1 (ref.)
1 metabolic condition	1.31 (0.86–1.98)	1.33 (0.88–2.02)	1.25 (0.67–2.35)
2 or more metabolic conditions	2.40 (1.60–3.59)	2.40 (1.60–3.59)	1.51 (0.80–2.87)
Nap (siesta)			
No siesta	1 (ref.)	1 (ref.)	1 (ref.)
≤30 min siesta	1.26 (0.79–1.99)	1.23 (0.78–1.94)	1.55 (0.80–3.00)
>30 min siesta	1.76 (1.09–2.85)	1.71 (1.05–2.76)	2.53 (1.30–4.91)
Physical activity score (0 to 8 score)[b]			
<3 points	1 (ref.)	1 (ref.)	1 (ref.)
3–5 points	0.50 (0.29–0.86)	0.50 (0.29–0.86)	0.49 (0.27–0.88)
>5 points	0.26 (0.12–0.54)	0.26 (0.12–0.53)	0.24 (0.10–0.55)
Less than 2 h/day of television watching vs. >2 h/day	0.69 (0.50–0.94)	0.68 (0.50–0.94)	1.12 (0.66–1.92)

Multivariable model: adjusted for sex (dichotomous), BMI (kg/m^2, continuous) alcohol intake (per 10 g/day, continuous), smoking habit (four groups and pack-years, four categories), punctuation in the Mediterranean Diet Score at baseline (three categories), time spent watching tv (<2 h/day, dichotomous), number of metabolic conditions at baseline (hypercholesterolemia, hypertriglyceridemia, diabetes, obesity, hypertension; three categories) educational level (doctoral degree, dichotomous), marital status (three categories), nap time-*siesta* (minutes/day, three categories), punctuation in the Physical Activity Score at baseline (physical activity intensity, energy expenditure, walking speed, walking time, climbing upstairs, television time, sitting time; three categories).

[a] Metabolic conditions at baseline: hypercholesterolemia, hypertriglyceridemia, diabetes, obesity, hypertension.

[b] Physical activity score: 1) doing exercise; 2) expending at least 16.1 METs-h per week (the cohort median); 3) practicing sports with vigorous intensity; 4) adopting usually a brisk/very brisk walking pace; 5) walking for ≥30 min/d; 6) climbing upstairs ≥3 floors/d; 7) watching television for <1.5 h/d; and 8) spending <5 h/d sitting down.

though it has a greater impact on late mortality.

4.4. Metabolic conditions

Metabolic diseases at baseline are considered a risk factor for mortality (Chen et al., 2019; Krakauer and Krakauer, 2018; Sotos-Prieto et al., 2021). In agreement with previously published literature, a direct association with mortality was observed for those participants who reported metabolic diseases. However, only the category 2 or more metabolic conditions maintained statistical significance for total and premature mortality. This suggests, as seen in other studies (Chan et al., 2014; Magliano et al., 2020; Armas Rojas et al., 2021; He et al., 2009; Hirko et al., 2015) that in younger ages the presence of these diseases increases the risk of premature death. These results may be influenced by a possible survival bias however, they highlight the importance of public health interventions to improve the metabolic health of the young population.

4.5. Nap-siesta

Daily naps have been associated in different studies with a lower risk of mortality and cardiovascular disease (Ruiz-Estigarribia et al., 2020; Díaz-Gutiérrez et al., 2018; Wang et al., 2019; Pan et al., 2020). However, as we have observed in our analysis, naps longer than 30 min are significantly associated with total and late mortality. Furthermore, previous evidence linked long naps with an increased risk of other diseases such as type 2 diabetes (Liu et al., 2018), obesity (Wang et al., 2020b), and metabolic syndrome (Gribble et al., 2021), especially in older adults (Koc Okudur and Soysal, 2021; Soysal et al., 2021). In view of these results, it is important to limit the length of naps. Although the exact length of time for naps to be beneficial has not yet been determined, there are articles that advocate naps of <30 min (Ruiz-Estigarribia et al., 2020; Díaz-Gutiérrez et al., 2018) or even 15 min (Gribble et al., 2021). In addition, they suggested that naps were beneficial only if there was <6 h of night-time sleep (Wang et al., 2019).

4.6. Physical activity score

The physical activity score used is a comprehensive tool that includes the time and type of physical activity, as well as the intensity of exercise or walking speed. In addition, it considers the time spent in sedentary activities such as watching TV or sitting down (Hsu et al., 2018). Of all the predictors analysed, this score was the only one whose protective effect was statistically significant for all the types of mortality studied. We have also observed, in agreement with previous studies (Hsu et al., 2018; Arem et al., 2015; Chipperfield, 2008), strong relative risk reductions for medium and high levels of physical activity (52 %–57 % for premature mortality and 51–76 % for late mortality). These results suggest that it is important to be active at all ages. In addition, a dose-response effect has been observed as suggested by other studies (Löllgen et al., 2009). Overall, it should be noted that with a minimum of physical activity there is already a beneficial effect (Wen et al., 2011; Long et al., 2015) especially for late mortality (Hsu et al., 2018; Chipperfield, 2008).

4.7. Other predictors

The remaining predictors studied showed no significant association with any of the mortality categories used as outcomes in the multivariable models. This could be due to residual confounding or inadequate sample size in some strata. Body mass index was assessed as a risk factor for mortality per unit increase. There is literature that defends the u-shaped distribution of BMI. They argue that both low-normal weight and high obesity are associated with increased mortality, while overweight-light obesity decreases the risk of mortality especially in elderly (Wu et al., 2014; Flegal et al., 2013; Janssen and Mark, 2007; Corrada et al.,

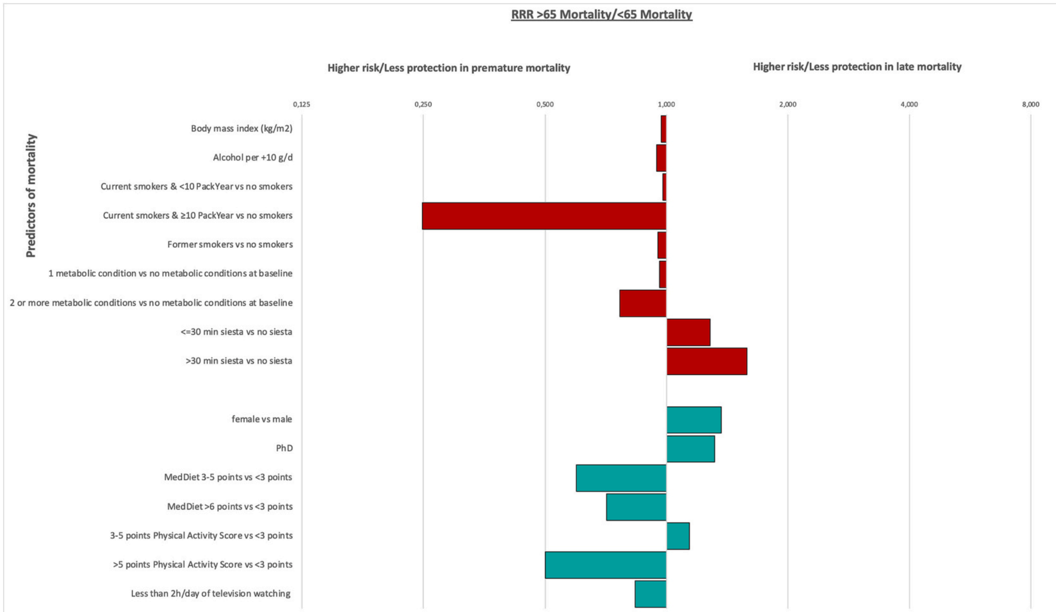

Fig. 1. Relative Risk Ratios (RRR (HR >65 Mortality/HR ≤65 Mortality)) for predictors of mortality.
In this figure, the Relative Risk Ratios (RRR = Relative risk of late mortality/Relative risk of premature mortality) for 2 types of factors are shown: those with an inverse association with mortality are presented in yellow background, and those with a direct association with mortality are presented in blue background. The association between each factor and premature or late mortality is presented in Tables 3-4. Using those estimated HR, Relative Risk Ratios (RRR) were calculated. There are 3 scenarios: RRR = 1; the factor is equally associated with both premature and late mortality. RRR < 1; the association between the factor and mortality is stronger for premature mortality than for late mortality. RRR > 1; the association between the factor and mortality is stronger for late mortality than for premature mortality. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2006). However, other studies explain that the U-shaped pattern found was due to methodological errors because of an overrepresentation of chronic diseases in the low BMI categories (Veronese et al., 2016). Thus, they argue for a linear distribution with a lower mortality for BMI of 18.5–22.4 accompanied by a healthy lifestyle (Veronese et al., 2016). Sex is a non-modifiable predictor that has been widely studied because of its numerous interactions. The influence of sex as a predictor of mortality is differential, women live longer despite having greater morbidity late in life (Austad and Fischer, 2016). Although the mechanisms explaining this association are currently unknown, hormonal, immune or neuroendocrine mechanisms are thought to be involved (Austad and Fischer, 2016; Austad, 2006, 2019). Educational status is known to be a protective factor, especially for premature mortality (Roy et al., 2020; Alicandro et al., 2018) but also for late mortality (Pac et al., n.d.). Our results reflected a possible protective association of doctoral studies. However, our cohort is a university cohort, so the level of education is already high. Likewise, watching <2 h of television per day was associated with a lower risk of mortality but it lost statistical significance when we adjusted for other predictors, probably because long hours of television watching was already included as one of the eight items in the PA score (negatively weighted). In relation to the existing evidence, longer hours of TV watching have been associated with a higher risk of mortality, type 2 diabetes or cardiovascular disease (Basterra-Gortari et al., 2014; Grøntved and Hu, 2011; Grace et al., 2017). Finally, we found that being divorced was strongly associated with higher total and premature mortality in age- and sex-adjusted models. But similar to other predictors, it lost statistical significance in multivariable analysis. These results were consistent with previous studies which found a lower risk of total and late mortality for those participants who were married as compared to divorced, separated, widowed or single subjects (Wu et al., 2014; Zueras et al., 2020; Manzoli et al., 2007; Wang et al., 2020a).

4.8. Limitations

This study had some limitations that should be addressed. First, most of the study variables were self-reported so it is possible to have some degree of misclassification. However, as it is a highly educated and motivated cohort, a self-reported data quality is assumed. Furthermore, many of the self-reported variables, such as physical activity (Martínez-González et al., 2005), BMI (Bes-Rastrollo et al., 2005) and the dietary habits questionnaire (Martin-Moreno et al., 1993) have been previously validated in specific substudies. Second, the SUN cohort is not representative of the general population, which limits the external validity of the results. However, generalisability of the results should be based on biological plausibility. Third, our cohort is characterised as a young cohort with some health knowledge, so conditions such as cardiovascular disease, typical of older age or worse lifestyles, are less well represented. Therefore, the late mortality group has a smaller number of subjects than the under-65 s group. Fourth, some of the variables studied as predictors, for example physical activity, could express reverse causality because participants who were sick at baseline and therefore did less physical exercise or had a more sedentary lifestyle may have adopted these lifestyles as a consequence of an underreported disability or disease associated with higher risk of mortality. Fifth, Tables 2-4 showed a lack of statistical significance for some predictors in the multivariate adjustment. This may be due to over-fitting as some of the variables may be in the middle of the causal chain of mortality or may overlap with some of the variables including scores. Therefore, the results of age- and sex-adjusted estimates, for example for marital status or television viewing, may be relevant. Lastly, unmeasured and residual confounding bias cannot be excluded.

The strengths of this study reside in the large sample size, the long follow-up time, a high retention rate, the use of repeated measurements as well as the adjustment for major potential sources of confounding. Also, being an exclusively university cohort, the data reported by the participants are assumed to be of higher quality, and possible confounding by educational or socio-economic level is reduced due to the homogeneity of the cohort.

In conclusion, in the era of precision medicine, this study has shown the necessity to make different recommendations according to age groups and underlying conditions related to the projected timing of expected deaths. The risk factors which behave as predictors of mortality are likely to be different according to differences in the underlying causes of premature and late deaths. Thus, further studies should focus on age-specific effect of each exposure to provide more accurate and targeted public health interventions.

CRediT authorship contribution statement

Conceptualization, A.G. and M.A.M.G.; methodology, M.B.L A.G. and M.A.M.G.; formal analysis, M.B.L, M.A.M.G. and A.G.; resources, M.A.M.G, M.B.R. and S.C.; data curation, M.B.L, S.C. and C.D.L.F; writing M.B.L; review and editing, all authors; supervision, A.G., M.A.M.G. and M.B.R; funding acquisition, M.A.M.G., M.B.R and A.G. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

Authors declare no conflict of interest.

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Ethics approval

The present study was approved by the Institutional Review Board of the University of Navarra.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2022.112048.

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