**Supplementary Table 1**. Search strategy, database searched until May 19th, 2021.

|  |  |  |
| --- | --- | --- |
| **Database** | **Search strategy** | |
| PubMed | TOPIC: | ((“Mediterranean diet” OR “Mediterranean dietary pattern” OR “Mediterranean diets” OR “Diets, Mediterranean”)) AND ((“Physical Activity” OR “Physical Activities” OR “Activity, Physical”)) AND ((“survival" OR “survive" OR “mortality" OR “fatal" OR “death")) AND  (("follow up" OR "longitudinal studies" OR "cohort studies" OR "prospective studies")) |

**Supplementary Figure 1.** Flow chart of eligible studies for comprehensive review.

Records identified through PubMed search up to May 19th, 2021

74 results

Excluded (n=33)

* Publication date older than 10 years (n=23)
* Non-Human (n=9)
* Not in English (n=1)

Identification

Titles and abstracts assessed for eligibility

47 results

Excluded (n=38)

* Outcome not all-cause mortality (n=31)
* Missing MedDiet or PA (n=4)
* Not a longitudinal observational study (n=3)

Screening

Full text assessed for eligibility

9

Excluded (n=5)

* No relative risk reported for the combined effect of MedDiet and PA

Studies included in comprehensive review

4 results

Inclusion

**n=22,893**

Participants recruited up to

December 2019

n=21,073

Participants

n=22,552

Participants

**341**

Participants; Recruited after March 2017

**1,479**

Participants lost to follow-up after baseline questionnaire.

**420**

Participants in percentiles 1 and 99 for total energy intake according to FFQ

**n=20,653**

Participants

**1,147**

Participants with prevalent CVD, diabetes, or cancer

**n=19,506**

Participants

**60**

Participants with <40 years of age at time of death

**n=19,446**

Participants

(7,416 men & 12,030 women)

(277 deaths)

**Supplementary Figure 2.** Flowchart for selection of participants in the SUN cohort

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mediterranean Diet** | | | | | **Physical Activity** | |
|  | **Q1 MDS**  **(0-3 pts.)** | **Q2 MDS**  **(4 pts.)** | **Q3 MDS**  **(5-6 pts.)** | **Q4 MDS**  **(7-9 pts.)** | **Low PA**  **(0-3 pts.)** | | **High PA**  **(4-8 pts.)** |
| N (%) | 6,772 (34.8) | 3,968 (20.4) | 6,527 (33.6) | 2,179 (11.2) | 6,840 (35.2) | | 12,606 (64.8) |
| PA score (points) | 4.0 (1.8) | 4.2 (1.8) | 4.4 (1.8) | 4.7 (1.8) | 2.2 (0.9) | | 5.3 (1.1) |
| MDS (points) | 2.3 (0.8) | 4.0 (0.0) | 5.4 (0.5) | 7.3 (0.5) | 4.0 (1.8) | | 4.4 (1.8) |
| Women (%) | 62.6 | 62.6 | 61.5 | 59.4 | 67.0 | | 59.1 |
| Age (years) | 34.6 (10.6) | 37.0 (11.6) | 39 (12.1) | 42.6 (12.7) | 37.7 (11.7) | | 37.3 (11.9) |
| BMI (kg/m2) | 23.1 (3.5) | 23.3 (3.4) | 23.6 (3.5) | 23.8 (3.5) | 23.8 (3.9) | | 23.2 (3.2) |
| Masters or doctorate (%) | 17.7 | 17.4 | 17.8 | 18.7 | 16.6 | | 18.5 |
| Smoking status (%) |  |  |  |  |  | |  |
| Never | 65.5 | 67.3 | 70.4 | 41.4 | 45.0 | | 50.9 |
| Current | 23.0 | 24.0 | 21.1 | 20.7 | 26.9 | | 19.8 |
| Former | 23.2 | 26.7 | 31.0 | 37.2 | 27.4 | | 28.5 |
| Family history of CVD (%) | 11.6 | 12.9 | 14.3 | 17.3 | 14.1 | | 13.0 |
| Hypertension at baseline (%) | 4.6 | 5.1 | 7.7 | 9.9 | 7.1 | | 5.9 |
| Hypercholesterolemia (%) | 11.9 | 15.0 | 18.0 | 24.9 | 16.5 | | 15.8 |
| Depression (%) | 10.5 | 11.6 | 11.3 | 12.7 | 12.6 | | 10.5 |
| Energy intake (kcal/d) | 2,357 (741) | 2,499 (783) | 2,614 (802) | 2,704 (724) | 2,473 (784) | | 2,531 (775) |
| Carbohydrate intake (%E) | 41.3 (7.1) | 43.2 (7.3) | 44.6 (7.2) | 46.8 (7.0) | 42.7 (7.5) | | 43.8 (7.3) |
| Protein intake (%E) | 18.1 (3.3) | 18.0 (3.3) | 18.0 (3.2) | 17.7 (3) | 18.0 (3.3) | | 18.0 (3.2) |
| Fat intake (%E)  Saturated fat (g/d)  Polyunsaturated fat (g/d)  Monounsaturated fat (g/d) | 39.0 (6.0) | 36.8 (6.3) | 35.3 (6.3) | 32.9 (6.4) | 37.4 (6.6) | | 36.2 (6.5) |
| 38.0 (15.7) | 35.7 (15.4) | 33.4 (14.4) | 29.1 (11.5) | 35.3 (14.9) | | 34.9 (15.1) |
| 14.2 (6.9) | 14.6 (7.3) | 15.1 (7.2) | 15.4 (6.9) | 14.9 (7.3) | | 14.6 (6.9) |
| 42.3 (16.3) | 43.9 (17.5) | 45.0 (18.0) | 45.1 (17.2) | 44.1 (17.6) | | 43.7 (17.0) |
| Monounsaturated:saturated fat (%E) | 1.14 (0.2) | 1.3 (0.3) | 1.4 (0.3) | 1.6 (0.4) | 1.3 (0.3) | | 1.31 (0.4) |
| Fiber intake (g/d) | 21.5 (9.0) | 28.0 (11.3) | 34.6 (14.2) | 42.2 (15.8) | 27.6 (13.3) | | 30.6 (14.4) |
| Vegetables (g/d) | 377 (240) | 520 (318) | 659 (398) | 800 (431) | 513 (351) | | 567 (377) |
| Fruits (g/d) | 230 (218) | 342 (326) | 453 (359) | 575 (408) | 327 (319) | | 387 (346) |
| Legumes (g/d) | 19.3 (18.0) | 23.3 (19.4) | 26.1 (21.1) | 30.4 (18.9) | 23.1 (20.4) | | 23.9 (19.5) |
| Cereals (g/d) | 87 (69) | 108 (82) | 122 (84) | 144 (81) | 106 (80.0) | | 111 (81.0) |
| Meat (g/d) | 197 (90) | 188 (89) | 178 (89) | 152 (75) | 188 (93.0) | | 181 (87.0) |
| Fish (g/d) | 74 (59) | 98 (71) | 118 (68) | 142 (76) | 98 (66.0) | | 103 (73.0) |
| Dairy products (g/d) | 284 (236) | 220 (212) | 168 (192) | 92 (107) | 203 (204) | | 214 (221) |
| Nuts (g/d) | 5.3 (8.3) | 6.9 (12.5) | 9.6 (15.6) | 14.7 (22.8) | 7.0 (13.8) | | 8.7 (14.6) |
| Olive oil (g/d) | 14.7 (13.1) | 19.0 (15.4) | 22.4 (16.5) | 25.9 (16.6) | 19.7 (16.3) | | 19.3 (15.4) |
| Alcohol consumption (g/d) | 5.0 (9.8) | 6.4 (10.4) | 7.5 (10.3) | 9.9 (10.3) | 6.3 (11.0) | | 6.8 (9.8) |
| Do exercise (%) | 65.5 | 67.3 | 70.4 | 74.1 | 36.2 | | 86.0 |
| Intensity (METs/h) | 4.9 (1.1) | 4.9 (1.1) | 4.9 (1.1) | 4.9 (1.1) | 4.3 (1.0) | | 5.2 (1.1) |
| Energy expenditure (METs-h/wk) | 19.0 (20.9) | 21.0 (21.6) | 23.5 (24.7) | 27.7 (26.8) | 7.3 (9.3) | | 29.8 (24.6) |
| Walking pace: brisk or very fast (%) | 55.7 | 55.4 | 56.6 | 59.3 | 34.6 | | 68.1 |
| Walking (min/d) | 35.7 (31.0) | 37.3 (31.2) | 39.4 (32.0) | 42.2 (32.3) | 25.1 (22.5) | | 44.9 (33.6) |
| Climbing stairs (floors/d) | 3.6 (3.9) | 3.6 (3.8) | 3.6 (3.8) | 3.8 (3.9) | 2.3 (2.8) | | 4.3 (4.1) |
| Watching television (h/d) | 1.6 (1.2) | 1.6 (1.2) | 1.6 (1.1) | 1.6 (1.1) | 1.9 (1.3) | | 1.5 (1.1) |
| Sitting down (h/d) | 5.4 (2.1) | 5.3 (2.1) | 5.2 (2.1) | 5.0 (2.0) | 5.8 (2.0) | | 5.0 (2.0) |

**Supplementary Table 2**: Baseline characteristics according to adherence to Trichopoulou’s Mediterranean diet score and an 8-item physical activity score in the SUN cohort.

MDS: Trichopoulou’s Mediterranean diet score, PA: physical activity, N: population size, BMI: body mass index, CVD: cardiovascular disease, kcal: kilocalories, d:day, E: total energy intake, g: grams, METs: metabolic equivalent of task, h: hours, wk: week, min: minutes

Values for continuous variables are presented as means ± (SD) and categorical variables are specified as a percentage (%).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MDS items** | |  | | | | n (%) with point | | | | | | |  | | |
| 1-point criteria | | All | | | | | Low PA | | | High PA | | | *p-value* | | |
| Vegetables | | |  | | | |  | | |  | | |  | | |
| ≥ median (473.8 g/d) | | | 9,694 (49.9) | | | | 3,019 (44.1) | | | 6,675 (53.0) | | | *<0.001* | | |
| Legumes | | |  | | | |  | | |  | | |  | | |
| ≥ median (20.6 g/d) | | | 9,201 (47.3) | | | | 3,113 (45.5) | | | 6,088 (48.3) | | | *<0.001* | | |
| Fruits | | |  | | | |  | | |  | | |  | | |
| ≥ median (286.9 g/d) | | | 9,722 (50.0) | | | | 2,953 (43.2) | | | 6,769 (53.7) | | | *<0.001* | | |
| Dairy products | | |  | | | |  | | |  | | |  | | |
| < median (139.8 g/d) | | | 9,725 (50.0) | | | | 3,464 (50.6) | | | 6,261 (49.7) | | | *0.193* | | |
| Cereals | | |  | | | |  | | |  | | |  | | |
| ≥ median (85.7g/d) | | | 9,709 (49.9) | | | | 3,264 (47.7) | | | 6,445 (51.1) | | | *<0.001* | | |
| Meat | | |  | | | |  | | |  | | |  | | |
| < median (174.3 g/d) | | | 9,738 (59.5) | | | | 3,312 (48.4) | | | 6,426 (51.0) | | | *0.001* | | |
| Fish | | |  | | | |  | | |  | | |  | | |
| ≥ median (88.3 g/d) | | | 13,300 (68.4) | | | | 4,504 (46.8) | | | 8,796 (51.6) | | | *<0.001* | | |
| Monounsaturated:saturated fat | | |  | | | |  | | |  | | |  | | |
| ≥ median (1.23) | | | 9,723 (50.0) | | | | 3,355 (49.1) | | | 6,368 (50.5) | | | *0.051* | | |
| Alcohol | | |  | | | |  | | |  | | |  | | |
| 10-50 g/d men &  5-25 g/d women | | | 5,612 (28.9) | | | | 1,802 (26.4) | | | 3,810 (30.2) | | | *<0.001* | | |
| Total MDS (mean ±SD) | | | 4.26 (1.8) | | | | | 4.02 (1.8) | | 4.39 (1.8) | | | | *<0.001* | | |  | |
| **PA score items** | | n (%) with point | | | | | | | | | | | | |  | | | |
| 1-point criteria | All | | | | Q1 MDS | | | | Q2 MDS | | Q3 MDS | Q4 MDS | | | | | | *p-value* |
| Do you exercise? |  | | |  | | | | |  | |  |  | | | | | |  |
| yes | 13,320 (68.5) | | | 4,438 (65.5) | | | | | 2,671 (67.3) | | 4,597 (70.4) | 1,614 (74.1) | | | | | | *<0.001* |
| Exercise intensitya |  | | |  | | | | |  | |  |  | | | | | |  |
| Vigorous (≥ 6) | 12,184 (62.7) | | | 4,118 (60.8) | | | | | 2,430 (61.2) | | 4,145 (63.5) | 1,491 (68.4) | | | | | | *<0.001* |
| Energy expenditure |  | | |  | | | | |  | |  |  | | | | | |  |
| ≥ 16.1 METs-h/wk | 9,571 (49.2) | | | 2,887 (42.6) | | | | | 1,934 (48.7) | | 3,425 (52.5) | 1,325 (60.8) | | | | | | *<0.001* |
| Walking paceb |  | | |  | | | | |  | |  |  | | | | | |  |
| Brisk or very fast | 10,954 (56.3) | | | 3,773 (55.7) | | | | | 2,197 (55.4) | | 3,693 (56.6) | 1,291 (59.3) | | | | | | *0.017* |
| Walking time |  | | |  | | | | |  | |  |  | | | | | |  |
| ≥ 0.5 h/d | 8,071 (41.5) | | | 2,556 (37.7) | | | | | 1,610 (40.6) | | 2,857 (43.8) | 1,048 (48.1) | | | | | | *<0.001* |
| Climbing upstairs |  | | |  | | | | |  | |  |  | | | | | |  |
| ≥ 3 floors/d | 9,449 (48.6) | | | 3,222 (47.6) | | | | | 1,922 (48.4) | | 3,152 (48.3) | 1,153 (52.9) | | | | | | *<0.001* | |
| Television viewing time |  | | |  | | | | |  | |  |  | | | | | |  | |
| < 1.5 h/d | 10,266 (52.8) | | | 3,537 (52.2) | | | | | 2,031 (51.2) | | 3,505 (53.7) | 1,193 (54.8) | | | | | | *0.015* | |
| Sitting timec |  | | |  | | | | |  | |  |  | | | | | |  | |
| < 5 h/d | 8,498 (43.7) | | | 2,709 (40.0) | | | | | 1,686 (42.5) | | 3,007 (46.1) | 1,096 (50.3) | | | | | | *<0.001* |
| Total PA score (mean ±SD) | 4.23 (1.8) | | | 4.02 (1.8) | | | | | 4.15 (1.8) | | 4.35 (1.8) | 4.69 (1.8) | | | | | | *<0.001* | |

**Supplementary Table 3**. Frequency of each item and comparison across Mediterranean diet and physical activity scores in the SUN cohort.

MDS: Trichopoulou’s Mediterranean diet score, PA: physical activity, n: number of participants, g: grams, d:day, h: hour, METs: metabolic equivalent of task, wk: week

aExercise intensity was measured on a scale from 0 (minimum intensity) to 10 (maximum intensity)

bResponses included slow, normal/average, brisk, or very fast

cIncludes working and leisure time

**Supplementary Table 4.**Methods for interaction analyses on multiplicative and additive scales.

|  |
| --- |
| Multiplicative Interaction: |
| **Likelihood ratio test –** Comparison of cox regression models using the likelihood ratio test.  **STATA code:**  generate I\_A=g\*e  stcox e g c1 c2 c3  est store A  stcox I\_A e g c1 c2 c3  lrtest A .  g = 1; low Mediterranean diet score (Q1: 0-3 points) e = 1; low physical activity (0-3 points)  g = 0; reference (Q4: 7-9 points) e = 0; reference (4-8 points)  c = covariables |
| Additive Interaction: |
| **Relative excess risk due to interaction (RERI) –** Proportion of the *effect* of both exposures on the additive scale that is due to their interaction.  RERIHR = HR11 – HR10 – HR01 + 1  HR11 is the adjusted hazard rate ratio comparing the doubly exposed higher risk combination to the reference combination with the lowest risk HR00.1 RERI = 0 means no interaction or exactly additivity; RERI > 0 means positive interaction or more than additivity; RERI < 0 means negative interaction or less than additivity; RERI can go from – infinity to + infinity. 2  **STATA code:**  stcox I\_A e g c1 c2 c3  nlcom (exp(\_b[I\_A] + \_b[g] + \_b[e]) - exp(\_b[g]) - exp(\_b[e]) + 1) |
| **Attributable proportions due to the joint effect –** proportion of the joint effect (total hazard) that is due to each component among those who present both exposures.  Portion of the effect attributable to the MedDiet alone: (HR10 – 1) / (HR11 – 1)  Portion of the effect attributable to PA alone: (HR01 – 1) / (HR11 – 1)  Portion of the effect attributable to their interaction: (RERIHR – 1) / (HR11 – 1)  **STATA CODE:**  nlcom (exp(\_b[g])-1)/(exp(\_b[I\_A]+\_b[g]+\_b[e])-1)  nlcom (exp(\_b[e])-1)/(exp(\_b[I\_A]+\_b[g]+\_b[e])-1)  nlcom (exp(\_b[I\_A]+\_b[g]+\_b[e])- exp(\_b[g]) - exp(\_b[e]) + 1)/(exp(\_b[I\_A]+\_b[g]+\_b[e])-1) |
| **References:**  1. Li R, Chambless L. Test for Additive Interaction in Proportional Hazards Models. *Ann Epidemiol*. 2007;17(3):227-236. doi:10.1016/j.annepidem.2006.10.009  2. Rothman KJ. *Modern Epidemiology*. 1st ed. Boston: Little, Brown; 1986.  3. VanderWeele TJ. Causal interactions in the proportional hazards model. *Epidemiology*. 2011;22(5):713-717. doi:10.1097/EDE.0b013e31821db503 |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | N | Deaths *(%)* | | Time at risk (person-years) | | | | Multivariable adjusted HR\* | 95% CI | |
| Lower limit | Upper limit |
| **Continuous exposures** | | | | | | | | | | |
| 9 item MDS 19,446 277 *(1.42)* | | | | | | | 225,057 0.90 0.84 0.97 | | | |
| 8 item PA score 19,446 277 *(1.42)* | | | | | | | 225,057 0.88 0.82 0.94 | | | |
| **Individual effects** | | | | | | | | | | |
| Q1 MDS *(0-3 pts.)* | 6,772 | | 71 *(1.05)* | | 80,629 | | | 1 Ref. |  |  |
| Q2 MDS *(4 pts.)* | 3,968 | | 58 *(1.46)* | | 46,437 | | | 0.94 | 0.65 | 1.35 |
| Q3 MDS *(5-6 pts.)* | 6,527 | | 110 *(1.69)* | | 74,063 | | | 0.98 | 0.71 | 1.35 |
| Q4 MDS *(7-9 pts.)* | 2,179 | | 38 *(1.74)* | | 23,929 | | | 0.59 | 0.38 | 0.91 |
| Low PA *(0-3 pts.)* | 6,840 | | 121 *(1.77)* | | 79,189 | | | 1 Ref. |  |  |
| High PA *(4-8 pts.)* | 12,606 | | 156 *(1.24)* | | 14,5869 | | | 0.76 | 0.59 | 0.98 |
| **4x2 Joint effects** | | | | | | | | | | |
| Q1 MDS-low PA | 2,705 | | 35 (1.29) | | 32,007 | | | 1 Ref. |  |  |
| Q2 MDS-low PA | 1,442 | | 29 (2.01) | | | 16,929 | | 1.07 | 0.64 | 1.79 |
| Q3 MDS-low PA | 2,121 | | 45 (2.12) | | | 23,941 | | 0.94 | 0.59 | 1.48 |
| Q4 MDS-low PA | 572 | | 12 (2.10) | | 6,312 | | | 0.57 | 0.28 | 1.14 |
| Q1 MDS-high PA | 4,067 | | 36 (0.89) | | 48,622 | | | 0.79 | 0.48 | 1.28 |
| Q2 MDS-high PA | 2,526 | | 29 (1.15) | | 29,508 | | | 0.65 | 0.39 | 1.09 |
| Q3 MDS-high PA | 4,406 | | 65 (1.48) | | 50,122 | | | 0.77 | 0.50 | 1.18 |
| Q4 MDS-high PA | 1,607 | | 26 (1.62) | | 17,617 | | | 0.43 | 0.25 | 0.75 |

**Supplementary Table 5.** Individual and joint effects (HR) between protective factors for adherence to the Mediterranean diet and physical activity on all-cause mortality.

HR: hazard ratio: CI: confidence intervals, MDS: Mediterranean diet score, N: sample population size, PA: physical activity, pts: points

\*Adjusted for sex, BMI, education level, smoking status, cigarettes smoked, alcohol, total energy intake, family history of CVD, prevalent hypertension, hypercholesterolemia, depression, and stratified by year entering the cohort and age in decades. Individual exposures were additionally adjusted for the remaining lifestyle factor.

**Supplementary Figure 3**. Hazard ratios (95%CI) for the combinations of adherence to the MedDiet and PA levels on all-cause mortality.

Chart, box and whisker chart

Description automatically generated

HR: hazard ratio: CI: confidence intervals, MedDiet: Mediterranean dietary pattern, PA: physical activity

\*Multivariable Cox proportional hazard models adjusted for sex, BMI, education level, smoking status, cigarettes smoked, alcohol, total energy intake, family history of CVD, prevalent hypertension, hypercholesterolemia, depression, and stratified by year entering the cohort and age in decades.