ΕΦΕΤ

ΕΘΝΙΚΟΣ ΦΟΡΕΑΣ ΕΛΕΓΧΟΥ ΤΡΟΦΙΜΩΝ

# The Journey of the Mediterranean Diet through time and Space: from Tradition and Culture to Scientific Evidence for a Nutritional Model that Promotes Health


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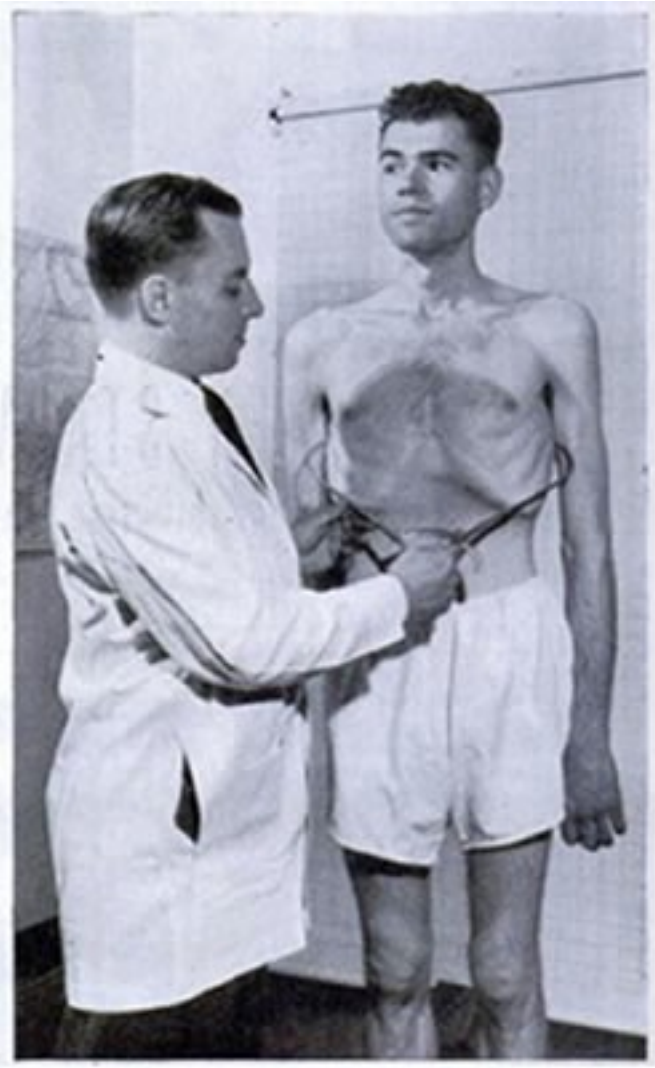


AFTER FIVE MONTHS OF STARVATION DIET CONSCIENTIOUS OBJECTORS SAMUEL LEGG (LEFT) AND EDWARD COWLES HAVE LOST 26 AND 36 POUNDS RESPECTIVELY

# MEN STARVE IN MINNESOTA

CONSCIENTIOUS OBJECTORS VOLUNTEER FOR STRICT HUNGER TESTS TO STUDY EUROPE'S FOOD PROBLEM

**Above:**
**Conscientious objectors during starvation experiment.**
**Life magazine - July 30, 1945. Volume 19, Number 5, p. 43.**
**Credit: Wallace Kirkland/Time Life Pictures/Getty Images.**

**Left:**
**Dr Ancel Keys measures the chest width of James Plaugher.**

# The 'Mediterranean Diet'




## Dr Ancel Keys (1904-2004)

- US Nutritional physiologist, seconded to the UK Ministry of Food during WWII
- Noted a higher mortality in US peers compared to UK when he returned to the US
- Hypothesis that rationing improved health of society – particularly with respect to saturated fat and cardiovascular disease
- Developed the **Seven Countries Collaborative Study** launched 1958
- Monitored 13,000 men aged 40–59 years on diet, health and lifestyle with repeated health assessments after 5 and 10 years

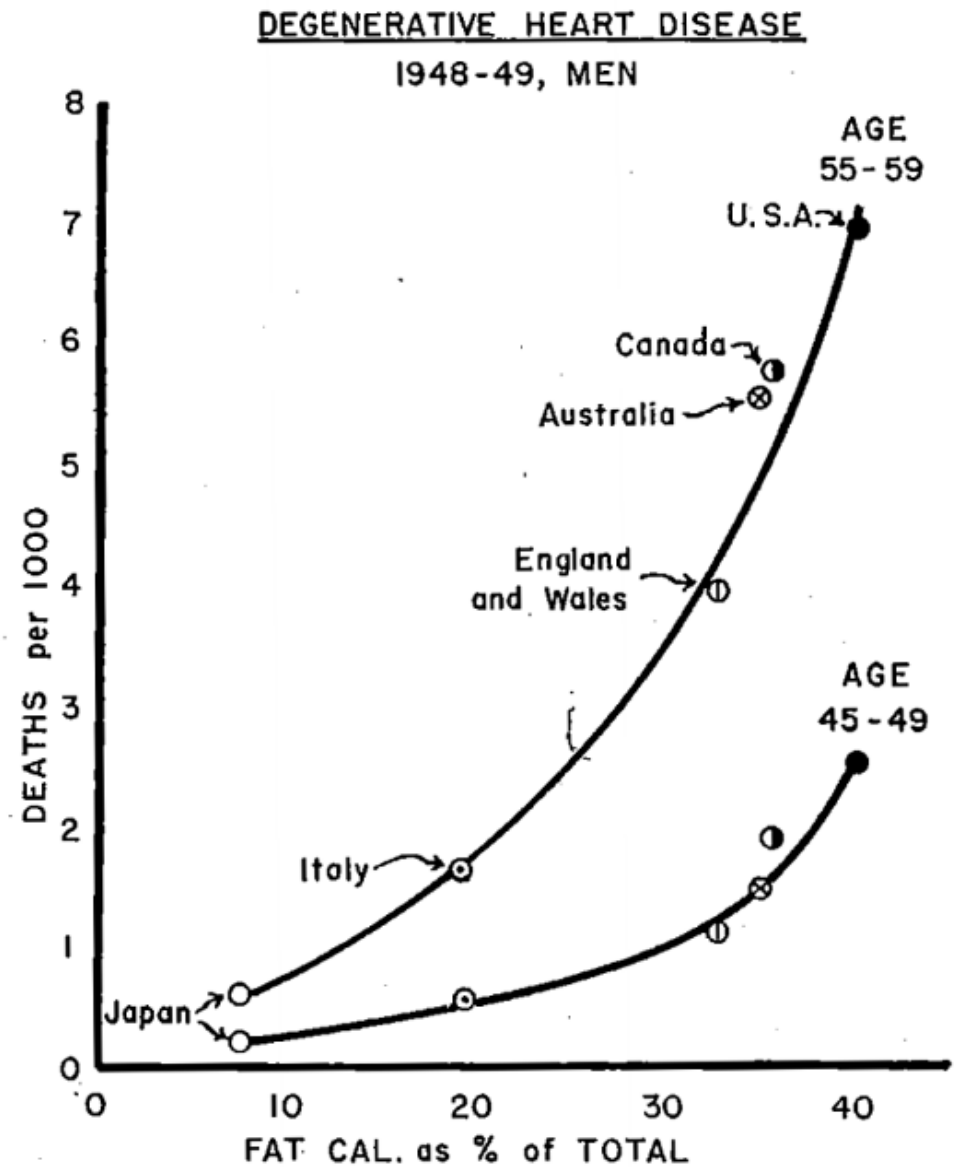
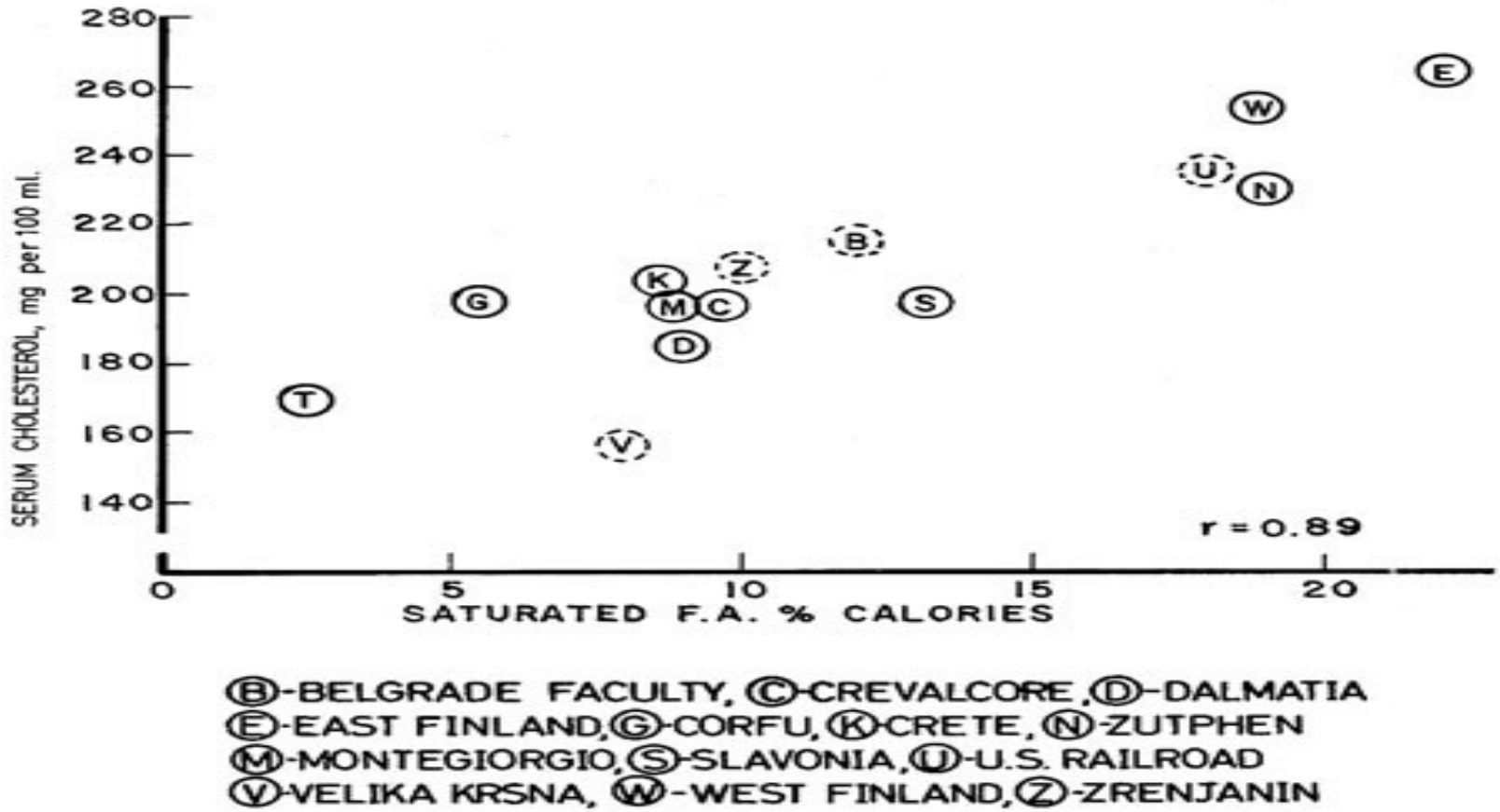



FIG. 2. Mortality from degenerative heart disease (categories 93 and 94 in the Revision of 1938, categories 420 and 422 in the Revision of 1948, International List. National vital statistics from official sources. Fat calories as percentage of total calories calculated from national food balance data for 1949 supplied by the Nutrition Division, Food and Agriculture Organization of the United Nations.

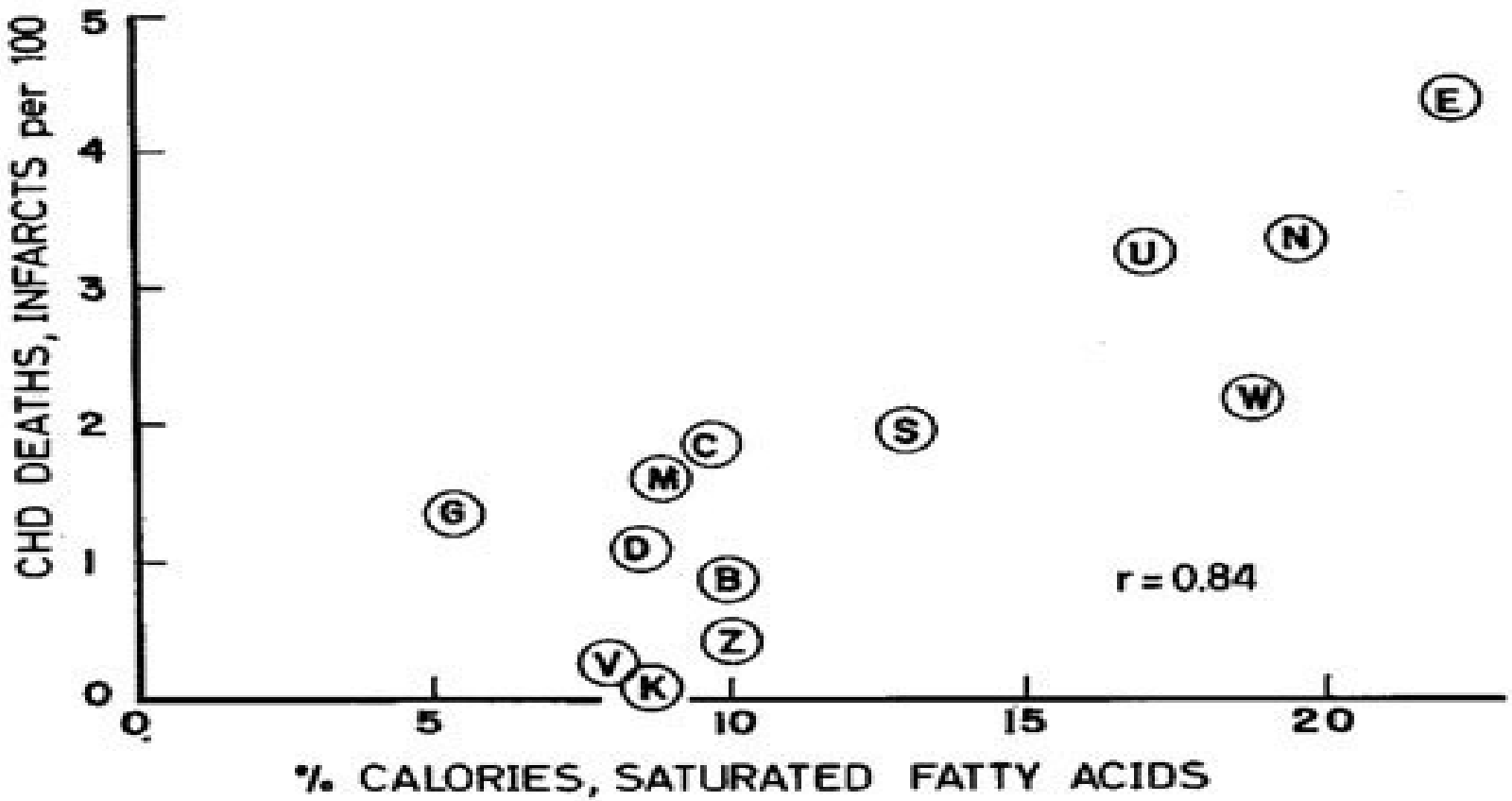
# The Seven Countries Study: The first Cross-Cultural Prospective Study

# Saturated fat and serum cholesterol

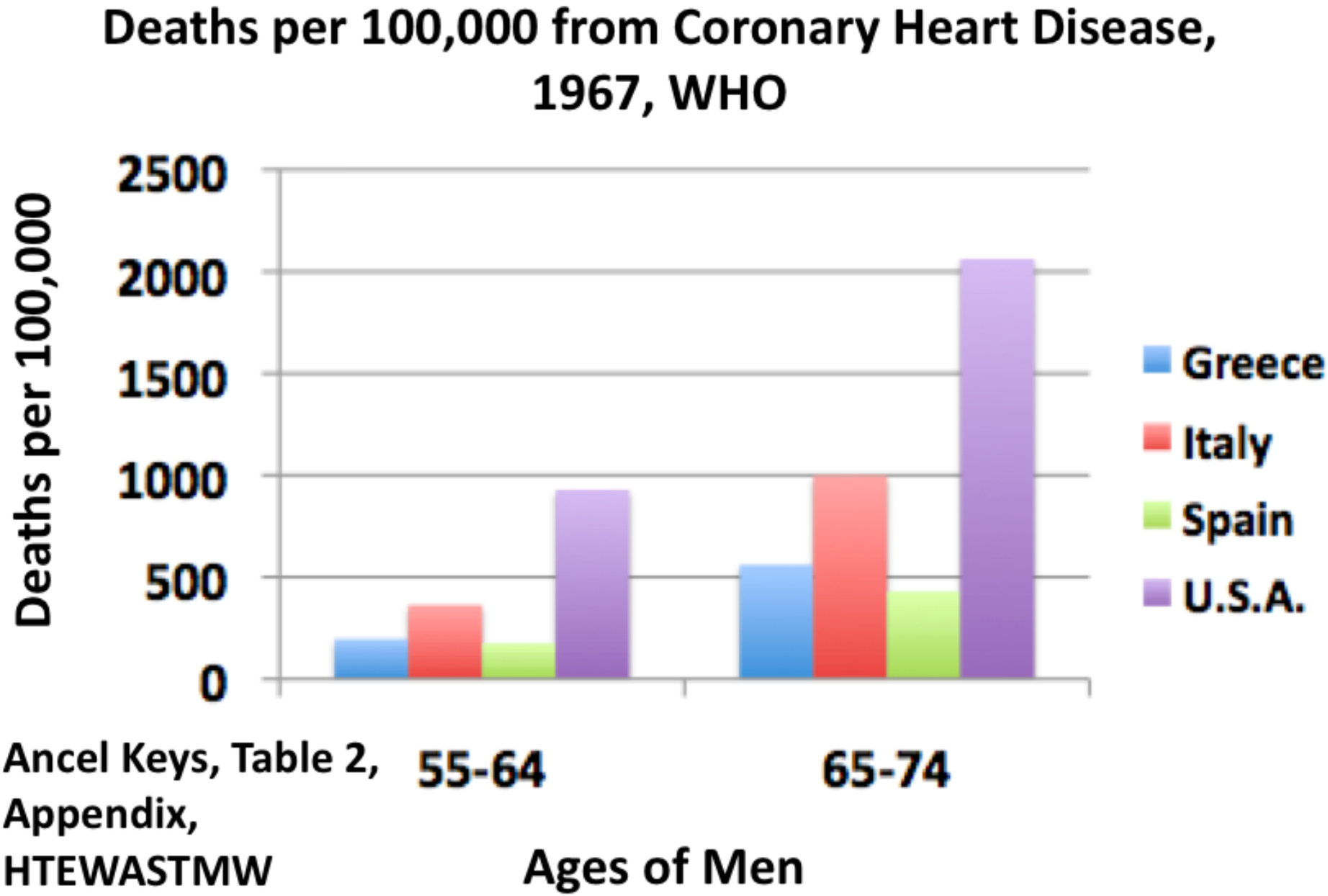



The baseline Seven Countries Study data showed a strong cross-sectional correlation between average saturated fat intake and average serum cholesterol level of 14 cohorts. The average intake of saturated fat varied between 3% of energy in Japan and 22% in Eastern Finland. The average serum cholesterol levels varied between 160 mg/dl (4 mmol/l) in Japan and 270 mg/dl (7 mmol/l) in Eastern Finland.

# Saturated fat and deaths from CHD




(B)-BELGRADE FACULTY, (C)-CREVALCORE, (D)-DALMATIA
(E)-EAST FINLAND, (G)-CORFU, (K)-CRETE, (N)-ZUTPHEN
(M)-MONTEGIORGIO, (S)-SLAVONIA, (U)-U.S. RAILROAD
(V)-VELIKA KRSNA, (W)-WEST FINLAND, (Z)-ZRENJANIN




Ancel Keys, Table 2, Appendix, HTEWASTMW

# Mediterranean Diet Pyramid: a lifestyle for today

Guidelines for Adult population

Serving size based on frugality and local habits

Wine in moderation and respecting social beliefs


*2010 edition*

*s = Serving*



Fundación Dieta Mediterránea

ICAF
International Commission on the Anthropology of Food and Nutrition

FORUM ON MEDITERRANEAN FOOD CULTURES

Prediimed
Prevención con Dieta Mediterránea

Ciiscam

Hebrew University – Hadassah Braun School of Public Health & Community Medicine

H.H.F.
HELLENIC HEALTH FOUNDATION

IUNS

CIHEAM
International Centre for Advanced Mediterranean Agronomic Studies

FANUS

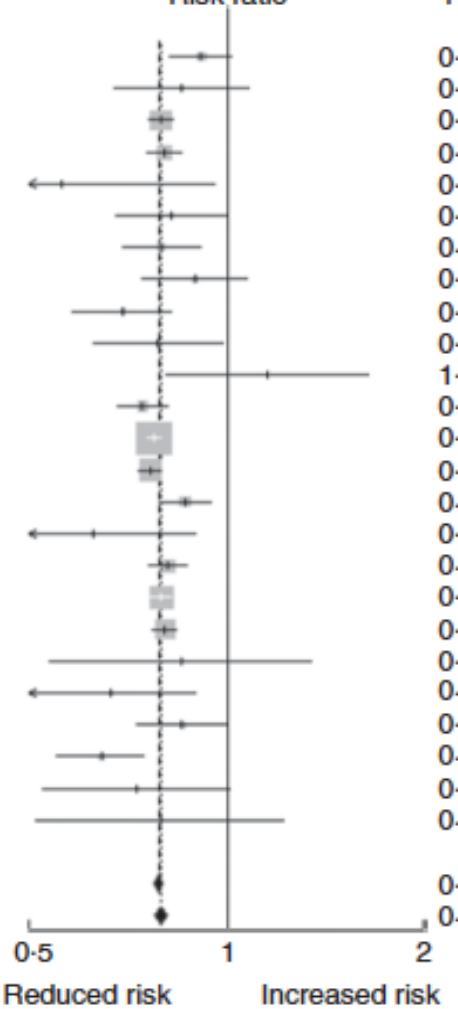
fens
federation of european nutrition societies

# Total Mortality

# Relative risks (RR) and 95% CI of mortality associated with the highest v. the lowest level of Mediterranean diet score from all studies included

| Study | Deaths | *n* | RR | 95 % CI | Weight (%, fixed) | Weight (%, random) |
|---|---|---|---|---|---|---|
| Trichopoulou, 2005 | 4047 | 74 607 | 0·91 | 0·82, 1·01 | 1·7 | 3·8 |
| Lagiou (F), 2006 | 572 | 42 237 | 0·85 | 0·67, 1·08 | 0·4 | 1·0 |
| Mitrou (M), 2007 | 18 126 | 214 284 | 0·79 | 0·76, 0·83 | 10·4 | 10·1 |
| Mitrou (F), 2007 | 9673 | 166 012 | 0·80 | 0·75, 0·85 | 5·2 | 7·6 |
| Sjögren, 2010 | 215 | 924 | 0·56 | 0·33, 0·96 | 0·1 | 0·2 |
| Tognon, 2011 | 630 | 1037 | 0·82 | 0·67, 1·00 | 0·5 | 1·4 |
| Buckland, 2011 | 1855 | 40 622 | 0·79 | 0·69, 0·91 | 1·1 | 2·6 |
| van den Brandt (M), 2011 | 6329 | 58 279 | 0·89 | 0·74, 1·07 | 0·6 | 1·6 |
| van den Brandt (F), 2011 | 3362 | 62 573 | 0·69 | 0·58, 0·82 | 0·7 | 1·8 |
| McNaugton, 2012 | 654 | 972 | 0·78 | 0·62, 0·98 | 0·4 | 1·1 |
| Cuenca-Garcia, 2014 | 358 | 12 449 | 1·15 | 0·81, 1·64 | 0·2 | 0·5 |
| George, 2014 | 5692 | 63 805 | 0·74 | 0·68, 0·81 | 2·6 | 5·2 |
| Reedy (M), 2014 | 54 871 | 242 321 | 0·77 | 0·75, 0·79 | 29·9 | 12·8 |
| Reedy (F), 2014 | 31 548 | 182 341 | 0·76 | 0·73, 0·79 | 12·9 | 10·8 |
| Vormund, 2015 | 3953 | 17 861 | 0·86 | 0·78, 0·94 | 2·3 | 4·8 |
| Prinelli, 2015 | 193 | 974 | 0·62 | 0·43, 0·89 | 0·2 | 0·4 |
| Bellavia, 2016 | 14 697 | 71 333 | 0·81 | 0·76, 0·87 | 4·3 | 6·9 |
| Shvetson (M), 2016 | 27 744 | 87 338 | 0·79 | 0·76, 0·82 | 14·0 | 11·0 |
| Shvetson (F), 2016 | 23 958 | 106 189 | 0·80 | 0·77, 0·84 | 10·4 | 10·1 |
| Bo, 2016 | 220 | 1658 | 0·85 | 0·54, 1·34 | 0·1 | 0·3 |
| Limongi, 2017 | 665 | 2265 | 0·66 | 0·49, 0·89 | 0·2 | 0·6 |
| Stefler, 2017 | 1314 | 19 333 | 0·85 | 0·73, 0·99 | 0·8 | 2·1 |
| Whalen, 2017 | 2513 | 21 423 | 0·64 | 0·55, 0·74 | 0·9 | 2·3 |
| Franzon , 2017 | 479 | 1104 | 0·72 | 0·52, 1·00 | 0·2 | 0·5 |
| Alvarez, 2018 | 305 | 19 467 | 0·79 | 0·51, 1·22 | 0·1 | 0·3 |
| Fixed effect model | | | 0·78 | 0·77, 0·79 | 100·0 | – |
| Random effects model | | | 0·79 | 0·77, 0·81 | – | 100·0 |

Heterogeneity: $I^2 = 42\,\%$, $\tau^2 = 0{\cdot}0011$, $\chi^2_{24} = 41{\cdot}10$ ($P = 0{\cdot}02$)




Eleftheriou D et al, Br J Nutr 2018; 120: 1081-97

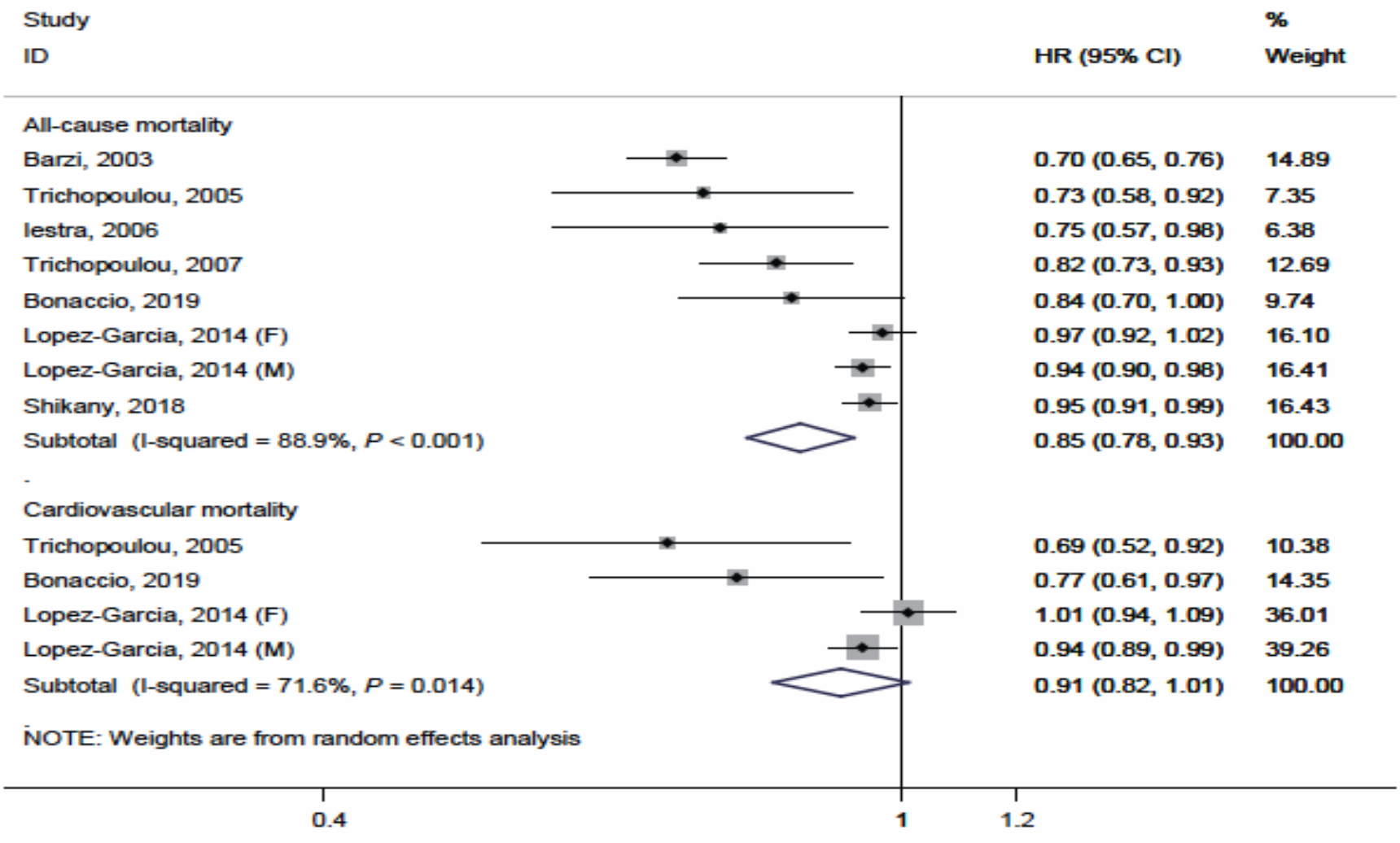
*Systematic Review*

# Mediterranean Diet and Mortality in People with Cardiovascular Disease: A Meta-Analysis of Prospective Cohort Studies

- **Objective** To investigate the association of MD with all-cause and cardiovascular mortality in people with a history of CVD.
- A random-effect model was used to examine the association of a 2-unit increment in MD score with the risk of all-cause and cardiovascular mortality.
- Seven cohort studies (eight datasets) with a total of 37,879 participants who had a history of CVD were eligible for the main analysis.

Tang C et al, Nutrients 2021, 13

# Meta-analysis of associations of each 2-unit increment in a score of adherence to Mediterranean diet with all-cause and cardiovascular mortality in people with a history of cardiovascular disease




Tang C et al, Nutrients 2021, 13

# Cardiovascular Health

# Close adherence to a Mediterranean Diet improves endothelial function in subjects with abdominal obesity

- 90 subjects with AO without cardiovascular disease or type 2 diabetes. Participants were randomly assigned to the intervention or control group.
- Both groups were instructed to follow a Mediterranean-style diet for 2 months.
- Subjects in the intervention group additionally had to follow a specific relevant daily and weekly food plan with close supervision by a dietitian and provision of basic foods.

Rallids L et al Am J Clin Nutr 2009;90:263–8.

# Nutrient intakes of participants at baseline and 2 months after dietary intervention

| | Intervention group ($n$ = 41) | | | Control group ($n$ = 41) | | | $P$ for between-group comparisons[4] |
|---|---|---|---|---|---|---|---|
| | Baseline | 2 mo after | $P$[2] | Baseline[3] | 2 mo after | $P$[2] | |
| Total energy (kcal/d) | 1841 ± 285[5] | 1729 ± 304 | 0.045 | 1794 ± 514 | 1575 ± 491 | <0.001 | 0.228 |
| % Energy from | | | | | | | |
| Carbohydrates | 41.9 ± 6.5 | 38.3 ± 5.3 | 0.009 | 42.4 ± 9.7 | 42.1 ± 7.6 | 0.839 | 0.107 |
| Protein | 16.1 ± 2.3 | 14.3 ± 2.5 | 0.002 | 16.6 ± 3.2 | 18.0 ± 4.8 | 0.079 | <0.001 |
| Total fat | 40.7 ± 6.9 | 47.4 ± 6.4 | <0.001 | 41.6 ± 9.4 | 40.3 ± 9.4 | 0.345 | 0.047 |
| SFAs | 13.9 ± 2.6 | 9.5 ± 1.7 | <0.001 | 14.5 ± 3.3 | 11.8 ± 2.5 | <0.001 | <0.001 |
| MUFAs | 19.6 ± 4.2 | 26.4 ± 3.6 | <0.001 | 20.5 ± 6.6 | 19.8 ± 7.7 | 0.534 | 0.007 |
| PUFAs | 6.6 ± 4.1 | 6.2 ± 2.9 | 0.653 | 5.7 ± 2.2 | 5.7 ± 3.0 | 0.910 | 0.145 |
| Cholesterol (mg/d) | 229.2 ± 71.3 | 142.1 ± 64.2 | <0.001 | 235.9 ± 137 | 193.4 ± 120 | 0.074 | 0.119 |
| Fiber (g/d) | 17.0 ± 6.3 | 21.4 ± 8 | 0.009 | 16.3 ± 6.6 | 16.6 ± 7.5 | 0.833 | 0.023 |
| Vitamin C (mg/d) | 116.7 ± 80.9 | 167.8 ± 83.1 | 0.003 | 113.4 ± 68.8 | 117.1 ± 76.9 | 0.787 | 0.047 |
| α-Tocopherol (mg/d) | 4.5 ± 1.6 | 4.9 ± 4.1 | 0.494 | 5.1 ± 2.9 | 4.4 ± 3.1 | 0.160 | 0.978 |
| β-Carotene (μg/d) | 550.6 ± 532 | 595.9 ± 489 | 0.704 | 456.2 ± 480 | 418.4 ± 384 | 0.587 | 0.091 |
| Alcohol (g/d) | 5.9 ± 8.4 | 12.9 ± 5.3 | <0.001 | 4.2 ± 8.6 | 4 ± 6.4 | 0.872 | <0.001 |

[1] SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.
[2] Derived by using Student's paired $t$ test.
[3] Not significantly different from the corresponding baseline variables of the intervention group (unpaired $t$ test).
[4] Derived by using repeated-measures ANOVA.
[5] Mean ± SD (all such values).

Rallids L et al Am J Clin Nutr 2009;90:263–8.

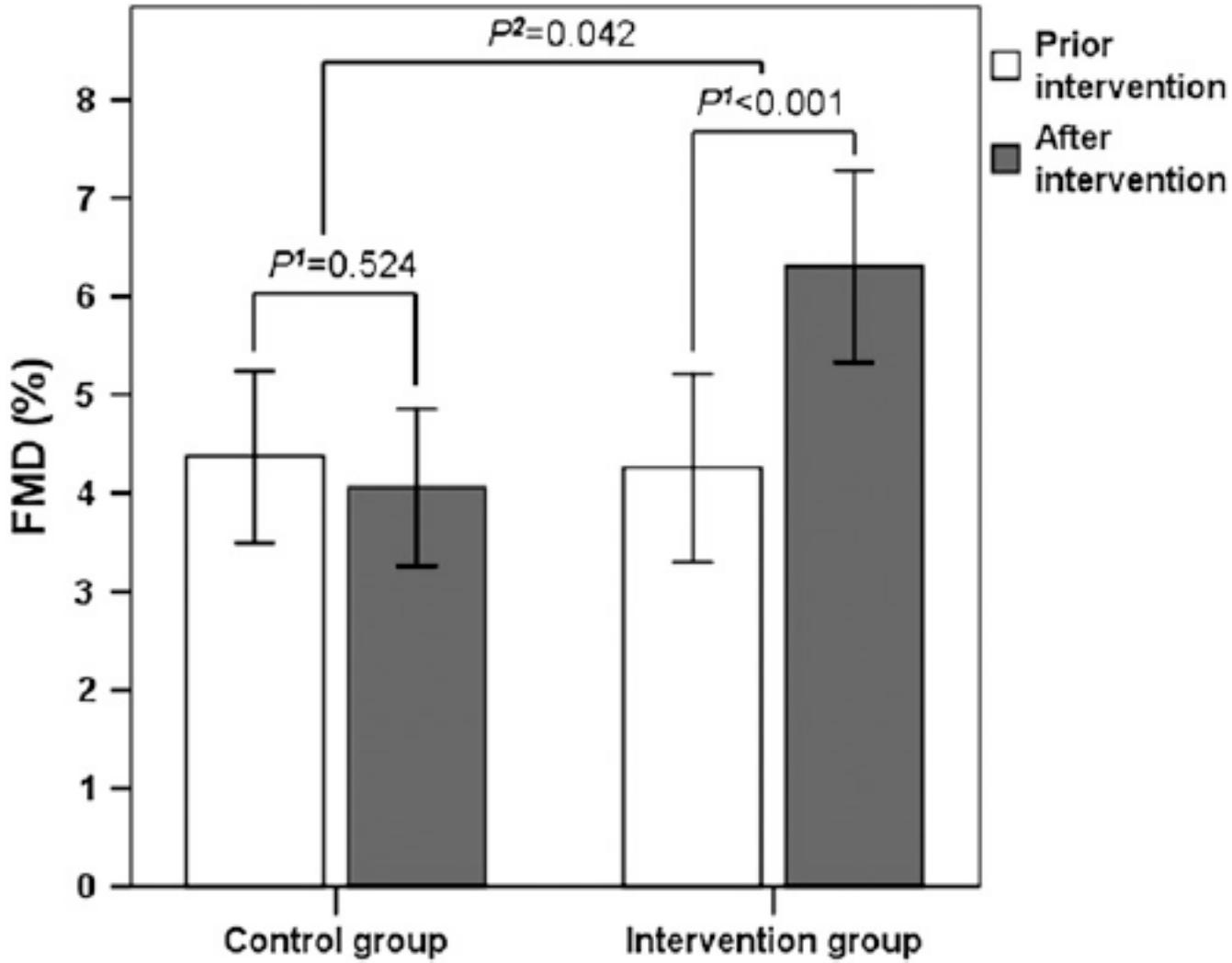
# Characteristics of participants at baseline and 2 months after dietary intervention

| | Intervention group ($n$ = 41) | | | Control group ($n$ = 41) | | | $P$ for between-group comparisons[4] |
|---|---|---|---|---|---|---|---|
| | Baseline | 2 mo after | $P$[2] | Baseline[3] | 2 mo after | $P$[2] | |
| Body weight (kg) | 94.1 ± 13.5[5] | 91.4 ± 13.6 | <0.001 | 94.0 ± 13.3 | 91.9 ± 13.3 | <0.001 | 0.975 |
| BMI (kg/m$^2$) | 31.5 ± 3.8 | 30.6 ± 3.9 | <0.001 | 32.8 ± 4.7 | 32.1 ± 4.6 | <0.001 | 0.149 |
| Waist circumference (cm) | 106.1 ± 9.1 | 103.9 ± 9.3 | <0.001 | 106.7 ± 9.5 | 105.7 ± 10.2 | 0.007 | 0.537 |
| Glucose (mmol/L) | 5.41 ± 0.89 | 5.28 ± 0.77 | 0.190 | 5.36 ± 0.67 | 5.31 ± 0.55 | 0.459 | 0.957 |
| Insulin ($\mu$U/mL) | 14.9 ± 7.8 | 11.8 ± 7.1 | 0.001 | 14.1 ± 5.8 | 15.3 ± 8.6 | 0.310 | 0.354 |
| HOMA-IR score | 3.5 ± 1.8 | 2.6 ± 1.3 | <0.001 | 3.5 ± 1.7 | 3.8 ± 2.3 | 0.301 | 0.072 |
| Total cholesterol (mmol/L) | 5.49 ± 0.80 | 5.33 ± 0.78 | 0.038 | 5.39 ± 0.89 | 5.36 ± 0.83 | 0.705 | 0.581 |
| Triglycerides (mmol/L) | 1.67 ± 0.67 | 1.52 ± 0.42 | 0.071 | 1.46 ± 0.7 | 1.38 ± 0.64 | 0.898 | 0.100 |
| HDL cholesterol (mmol/L) | 1.24 ± 0.33 | 1.21 ± 0.32 | 0.152 | 1.28 ± 0.27 | 1.25 ± 0.25 | 0.105 | 0.693 |
| LDL cholesterol (mmol/L) | 3.71 ± 0.62 | 3.63 ± 0.65 | 0.304 | 3.52 ± 0.83 | 3.63 ± 0.72 | 0.026 | 0.556 |
| C-reactive protein (mg/L) | 2.1 (1.1–4.4)[6] | 2.06 (0.8–3.3) | 0.047 | 2.1 (1–1.7) | 2.05 (1.6–4.2) | 0.100 | 0.970 |
| Systolic BP (mm Hg) | 130.2 ± 14.4 | 122.5 ± 13.9 | <0.001 | 129.6 ± 14.8 | 125.8 ± 13.7 | 0.016 | 0.647 |
| Diastolic BP (mm Hg) | 85.8 ± 7.6 | 79.6 ± 7.4 | <0.001 | 86.3 ± 8 | 85.6 ± 8.8 | 0.465 | 0.041 |

[1] HOMA-IR, homeostasis model assessment–insulin resistance; BP, blood pressure.
[2] Derived by using Student's paired $t$ test or Wilcoxon's test.
[3] Not significantly different from the corresponding baseline variables of the intervention group (unpaired $t$ test or Mann-Whitney $U$ test).
[4] Derived by using repeated-measures ANOVA.
[5] Mean ± SD (all such values).
[6] Median; 25th–75th percentiles in parentheses (all such values).

Rallids L et al Am J Clin Nutr 2009;90:263–8.

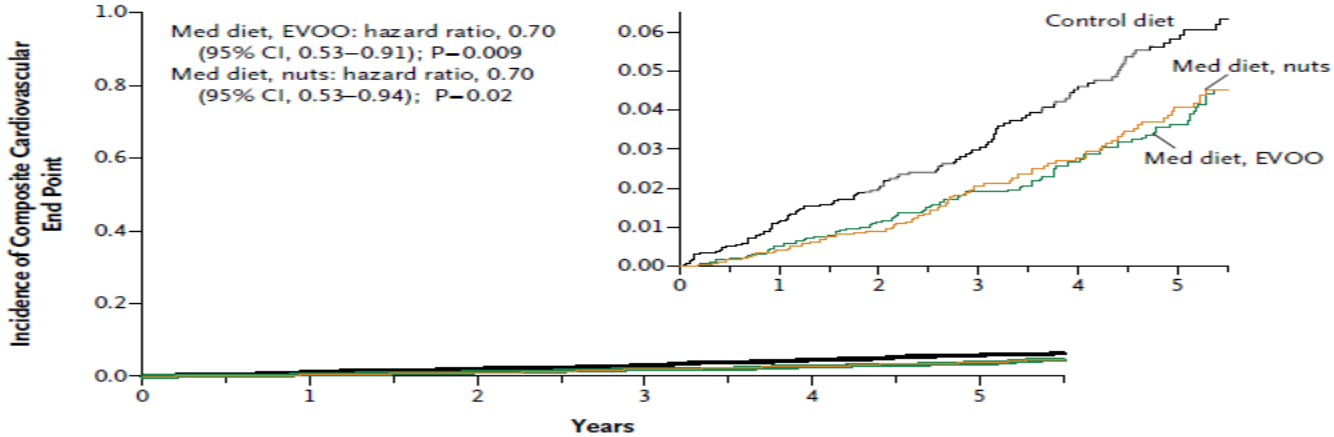
# Mean (95% CI) flow-mediated dilatation (FMD) at the beginning and 2 months after dietary intervention in individuals with abdominal obesity




Rallids L et al Am J Clin Nutr 2009;90:263–8.

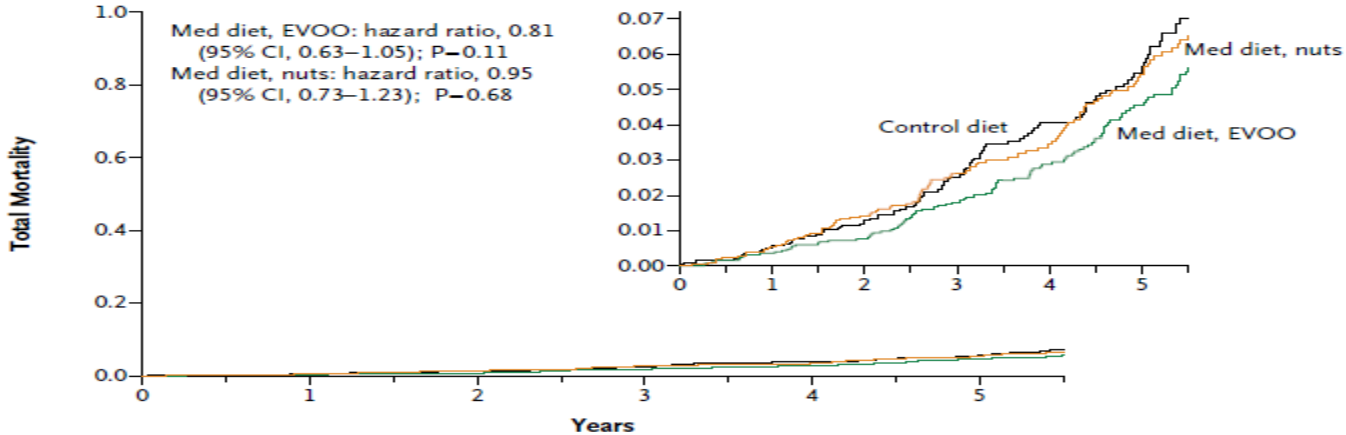
# Primary Prevention of CVD with a Mediterranean Diet: The Predi Med Study

**A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)**




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Control diet | 2450 | 2268 | 2020 | 1583 | 1268 | 946 |
| Med diet, EVOO | 2543 | 2486 | 2320 | 1987 | 1687 | 1310 |
| Med diet, nuts | 2454 | 2343 | 2093 | 1657 | 1389 | 1031 |

**B Total Mortality**




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Control diet | 2450 | 2268 | 2026 | 1585 | 1272 | 948 |
| Med diet, EVOO | 2543 | 2485 | 2322 | 1988 | 1690 | 1308 |
| Med diet, nuts | 2454 | 2345 | 2097 | 1662 | 1395 | 1037 |

Estruch R et al, N Engl J Med 2013;368:1279-90

# Effect of interventions for secondary prevention on risk of CV events and all-cause mortality in meta-analyses and reviews, randomized controlled trials, and prospective cohort studies

| Study or analysis | Author, year | CV events(s)[§] RR or OR (95% CI) | All-cause mortality RR or OR (95% CI) |
|---|---|---|---|
| Lifestyle Interventions | | | |
| Exercise-based cardiac rehabilitation [Systematic Review] | Andersen, 2016[3] | 0.74 (0.64-0.86)[a] | 0.96 (0.88-1.04) |
| Smoking cessation in CHD [Systematic Review] | Critchley, 2004[4] | 0.68 (0.57—0.82)[b] | 0.64 (0.58-0.71) |
| Mediterranean Diet Post-MI [Lyon Heart Study] | DeLorgeril, 1999[5] | 0.53 (0.38-0.74)[c] | 0.44 (0.21-0.94) |
| Alternative Healthy Eating Index 2010 [Prospective Cohort Study] | Li, 2013[6] | 0.73 (0.51-1.04)[d] | 0.76 (0.60-0.96) |
| Pharmacotherapies | | | |
| Aspirin in CHD [Meta-analysis] | Antithrombotic Trialists, 2009[7] | 0.80 (CI 0.73-0.88)[e] | NR |
| Statins [Meta-analysis] | Cholesterol Treatment Trialists, 2015[8] | 0.79 (0.77-0.82)[f] | 0.91 (0.88-0.93) |
| Beta-blockers Post-MI [Meta-analysis] | Freemantle, 1999[9] | NR[g] | 0.77 (0.69-0.85) |
| Percutaneous Coronary Intervention | | | |
| PCI vs. OMT in stable CHD with ischemia [Meta-analysis] | Stergiopaulos, 2014[10] | 1.24 (0.99-1.56)[h] | 0.90 (0.71-1.16) |

Aggarwal M et al, Am J Cardiol 2021;145:1–11

# Summary of dietary intervention studies assessing stroke incidence or stroke risk factors in people at risk of stroke

| | | | | | |
|---|---|---|---|---|---|
| Low-fat diet[29] | RCT | 48 835 | Post-menopausal women; 1656 (3%) had previous CVD; 19 984 (41%) had hypertension but no previous CVD; mean age 63 years (SD=7) | Usual diet | No effect (cumulative and post-intervention)—all women: HR 1·00 (95% CI 0·91 to 1·10); women with previous CVD: HR 1·05 (95% CI 0·76 to 1·15); women with hypertension but no previous CVD: HR 0·92 (95% CI 0·81 to 1·04) |
| Low-fat diet[30] | Meta-analysis of seven RCTs | 50 952 | Adults; largest included RCT[35] included 48 835 post-menopausal women; mean age across included RCTs not reported; sex across included RCTs not reported | Usual diet | No effect—all: RR 0·92 (95% CI 0·68 to 1·25), $I^2$=9%; adults with existing CVD disease: RR 1·01 (95% CI 0·86 to 1·18), $I^2$=0% |
| Mediterranean-style diet (plus tree nuts or olive oil)[31] | RCT | 7447 | Older adults at risk of CVD; 6162 (83%) had hypertension; 5383 (72%) had dyslipidaemia; 3614 (49%) had diabetes; mean age 67 years (SD=6); 3154 (43%) of participants were male | Low-fat diet | Decreased risk—Mediterranean-style diet (plus tree nuts or olive oil): HR 0·58 (95% CI 0·42 to 0·82); Mediterranean-style diet plus olive oil: HR 0·65 (95% CI 0·44 to 0·50); Mediterranean-style diet plus tree nuts: HR 0·54 (95% CI 0·35 to 0·82); these results are at a median follow-up of 4·8 years |
| Mediterranean-style diet[32] | Meta-analysis of five cohort studies | 79 287 (2663 cases of stroke) | Adults with diabetes; mean age 64 years (SD=9); 19 401 (24%) of participants were male | Highest versus lowest adherence | Decreased risk:‡ RR 0·80 (95% CI 0·71 to 0·90), $I^2$=0%; every two-point increment in the Mediterranean-diet score indicating greater adherence: RR 0.90 (95% CI 0·85 to 0·96), $I^2$=35% |
| Mediterranean-style diet[33] | Cohort study | 5200 (143 cases of stroke) | Adults aged ≥65 years; mean age 72 years (SD=5); 2652 (51%) of participants were male | Highest versus lowest adherence | Decreased risk:‡ HR 0·58 (95% CI 0·36 to 0·95) |
| DASH diet[34] | Network meta-analysis of 67 RCTs | 17 230§ | Adults with hypertension or pre-hypertension; mean age ranged from 24 to 71 years; sex across included RCTs not reported | Low-fat diet | Decreased blood pressure: systolic: –5·05 mm Hg (95% CI –7·08 to –3·03), and diastolic: –3·10 mm Hg (95% CI –4·52 to 1·68) |

English C et al Lancet Neurol 2020, doi.org/10.1016/S1474-4422(20)30433-6

# Dietary patterns and the risk of major adverse cardiovascular events in a global study of high-risk patients with stable coronary heart disease

**Ralph A. H. Stewart[1]*, Lars Wallentin[2], Jocelyne Benatar[1], Nicolas Danchin[3], Emil Hagström[2], Claes Held[2], Steen Husted[4], Eva Lonn[5], Amanda Stebbins[6], Karen Chiswell[6], Ola Vedin[2], David Watson[7], and Harvey D. White[1], on Behalf of the STABILITY Investigators**

**Objective** To determine whether dietary pattern assessed by a simple self-administered food frequency questionnaire is associated with major adverse cardiovascular events (MACE) in high-risk patients with stable coronary artery disease

**Methods** At baseline, 15 482 (97.8%) patients (mean age 67+9 years) with stable coronary heart disease from 39 countries who participated in the Stabilisation of atherosclerotic plaque by initiation of darapladib therapy (STABILITY) trial completed a life style questionnaire which included questions on common foods. A Mediterranean diet score (MDS) was calculated for increasing consumption of whole grains, fruits, vegetables, legumes, fish, and alcohol, and for less meat, and a 'Western diet score' (WDS) for increasing consumption of refined grains, sweets and deserts, sugared drinks, and deep fried foods

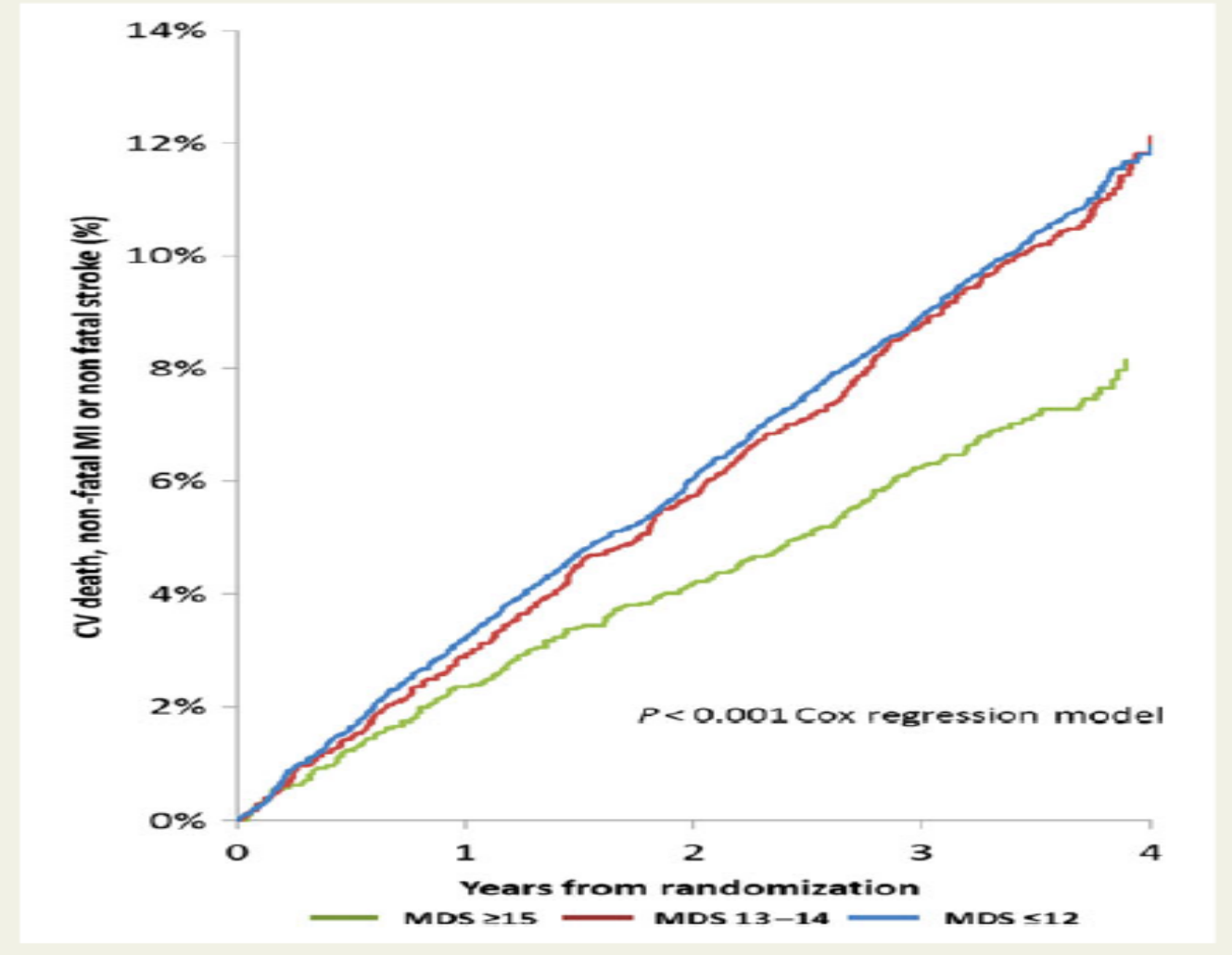
Stewart RAH et al, Eur Heart J 2016; 37: 1993–2001

# Associations between Mediterranean and western dietary scores and outcomes before and after adjusting for co-variates

| Diet score and outcome | HR (95% CI) for adverse event for a one point increase in diet score[a] | *P*-value | HR (95% CI) for adverse event for a one point increase in diet score in the fully adjusted models[b] | *P*-value |
|---|---|---|---|---|
| MDS >12 | | | | |
| MACE | 0.93 (0.90, 0.96) | <0.0001 | 0.95 (0.92, 0.99) | 0.007 |
| Myocardial infarction | 0.95 (0.90, 0.99) | 0.02 | 0.96 (0.91, 1.01) | 0.12 |
| Stroke | 0.89 (0.82, 0.97) | 0.006 | 0.91 (0.83, 0.99) | 0.02 |
| Cardiovascular death | 0.94 (0.89, 0.99) | 0.01 | 0.97 (0.92, 1.03) | 0.29 |
| All-cause death | 0.93 (0.89, 0.97) | <0.0001 | 0.96 (0.92, 1.00) | 0.06 |
| Other dietary patterns | | | | |
| WDS and MACE | 1.00 (0.98, 1.02) | 0.36 | 0.99 (0.97, 1.01) | 0.27 |
| MDS ≤12 and MACE | 0.99 (0.96, 1.02) | 0.62 | 1.00 (0.98, 1.04) | 0.61 |

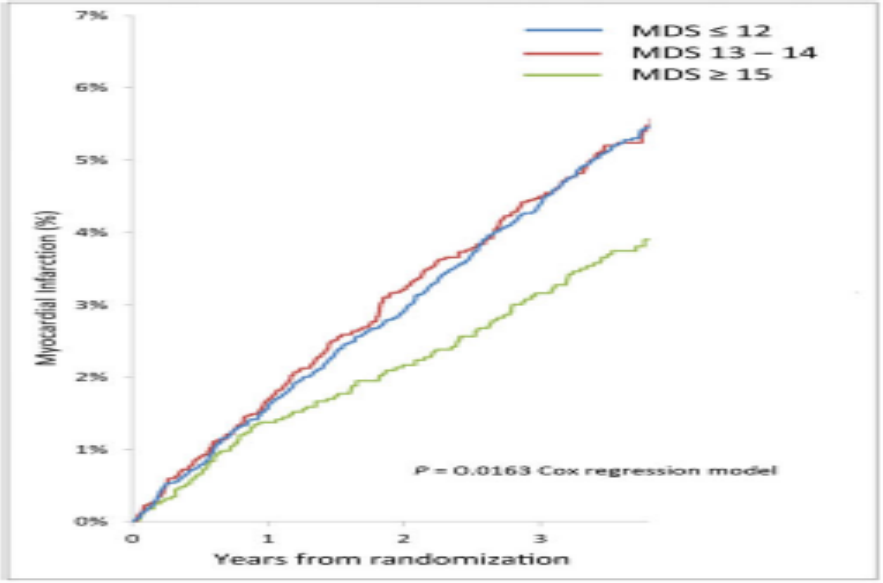
Stewart RAH et al, Eur Heart J 2016; 37: 1993–2001

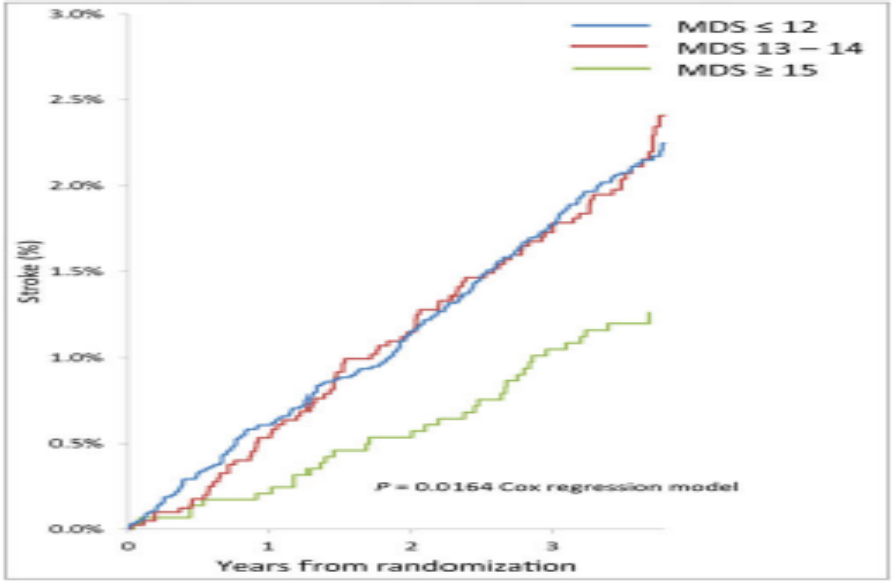
# Kaplan–Meier plots of major adverse cardiovascular events by Mediterranean diet score group

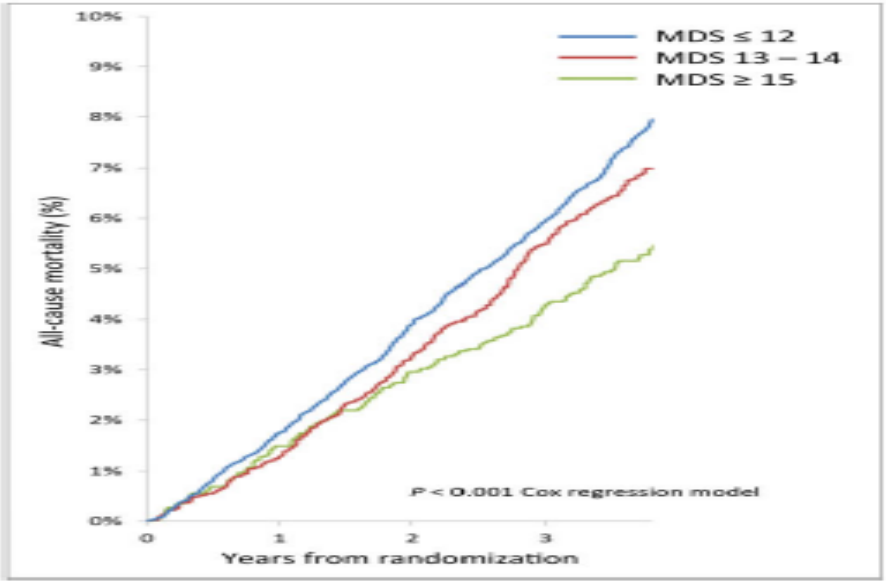


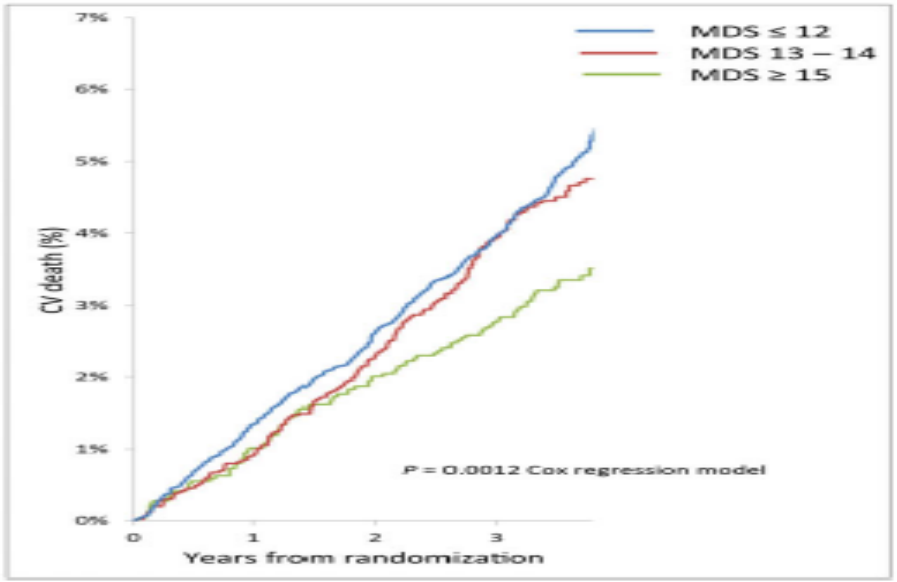

Stewart RAH et al, Eur Heart J 2016; 37: 1993–2001

# Kaplan-Meier plots of secondary outcomes by MD score group

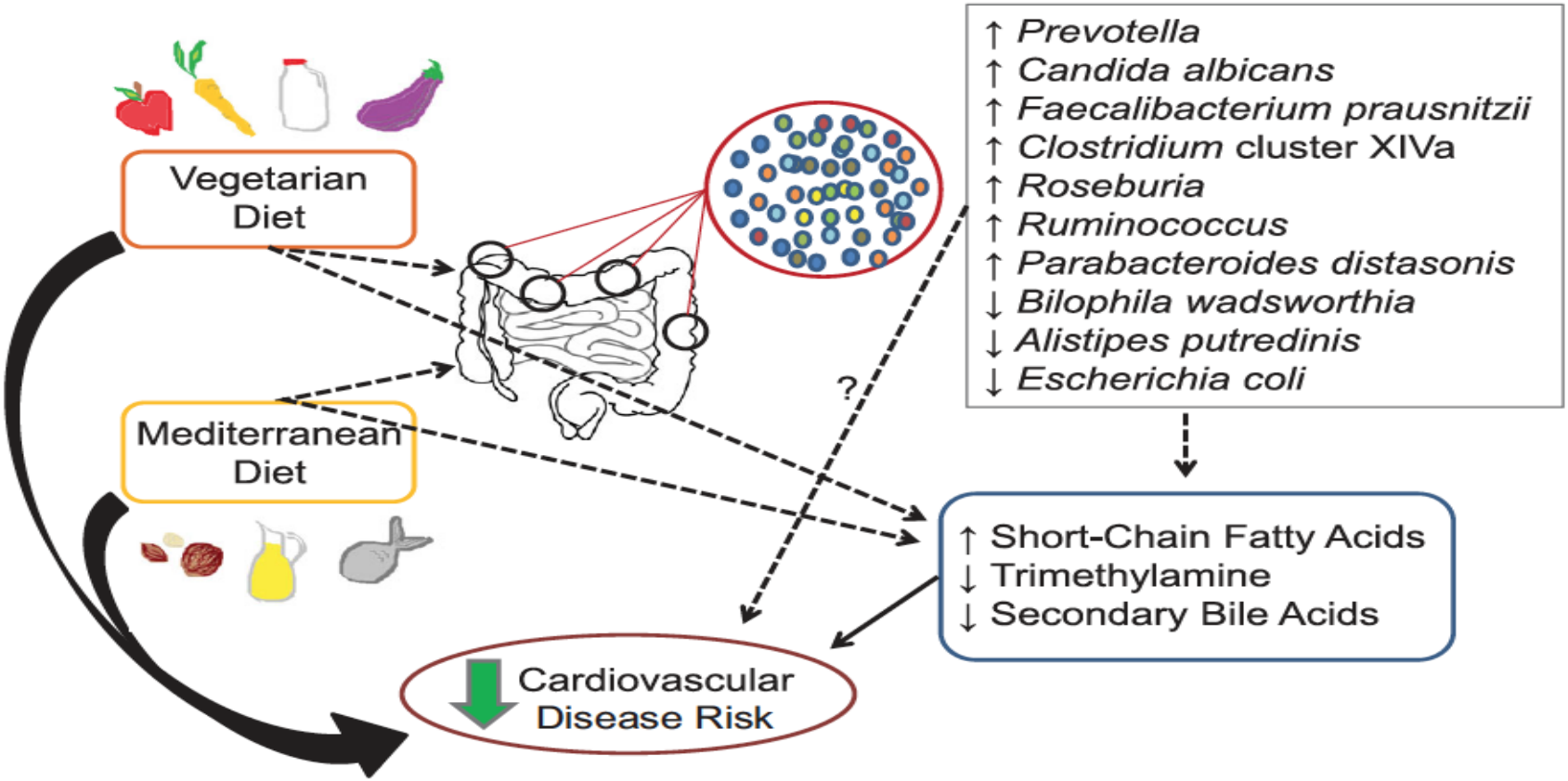



Stewart RAH et al, Eur Heart J 2016; 37: 1993–2001




known and proposed interactions between diet and cardiometabolic risk illustrates the known risk-reducing properties of Vegetarian and Mediterranean diets on cardiometabolic diseases and the proposed interactions between the Vegetarian and Mediterranean diets with the gut microbiome and gut-derived metabolites that can reduce cardiovascular disease risk. The thick, solid-black arrows represent a large pool of evidence to support a pathway; narrow, solid-black arrows represent an intermediate amount of evidence to support a pathway; narrow, dotted black lines represent emerging evidence to support a pathway; and narrow, dotted black lines with a question mark represent other possible mechanistic pathways. Vegetarian and Mediterranean diets can alter the presence or absence of various bacteria and, in turn, also alter the gut metabolome. The direct effect of the gut microbial environment on cardiovascular disease risk is unknown. Vegetarian and Mediterranean diets can also affect the production of gut metabolites by serving as substrate for the resident bacteria

Tindall AM et allJ Nutr 2018;148:1402–

*Article*

# Adherence to the Mediterranean Diet and Chronic Disease in Australia: National Nutrition and Physical Activity Survey Analysis

- Secondary analysis of data from the National Nutrition and Physical Activity Survey (NNPAS), which is the largest health study in Australia and the first nutrition-specific national-based study.
- The primary aim of this analysis was to determine the proportion of Australian adults adhering to the MD and to examine the association between adherence to the MD and markers of noncommunicable diseases, such as cardiovascular disease, diabetes mellitus and chronic kidney disease.
- Out of the 9435 participants included in the study mean age = 48.6  17.6 years), 65% were in the middle tertile of the MD score

Aridi, YS et al, Nutrients 2020;12; 1251

# Association between Mediterranean diet score, diabetes mellitus prevalence and chronic kidney disease prevalence

| | | | Mediterranean Diet Score | | | |
|---|---|---|---|---|---|---|
| | Prevalence of Diabetes Mellitus | All | Tertile 1 (0–3) (*n* (%)) | Tertile 2 (4–6) (*n* (%)) | Tertile 3 (6–9) (*n* (%)) | *p*-value |
| Fasting plasma glucose (mmol/L) | ≥7.0 mmol/L | 211 (6.6) | 36 (6.1) | 146 (7.0) | 29 (5.7) | 0.49 |
| HbA1c (%) | ≥6.5% | 253 (6.7) | 44 (6.3) | 176 (7.1) | 33 (5.6) | 0.39 |
| | Prevalence of CKD | | | | | |
| CKD | | 451 (12.8) | 89 (14.1) | 300 (12.8) | 62 (11.2) | 0.34 |

Aridi, YS et al, Nutrients 2020, 12, 1251

# Association between the Mediterranean diet score and plasma lipid profiles (cholesterol, HDL, triglycerides and LDL)

| | | | Mediterranean Diet Score | | | |
|---|---|---|---|---|---|---|
| | | All | Tertile 1 (0–3) (*n* (%)) | Tertile 2 (4–6) (*n* (%)) | Tertile 3 (6–9) (*n* (%)) | *p*-value |
| Total cholesterol (mmol/L) | Normal (<5.5 mmol/L) | 2377 (63.1) | 411 (59.3) | 1577 (63.5) | 389 (65.7) | **0.04** |
| HDL cholesterol (mmol/L) | Normal (≥1.0 mmol/L) | 3353 (89.0) | 615 (88.7) | 2206 (88.8) | 532 (89.9) | 0.75 |
| Fasting triglycerides (mmol/L) | Normal (<2.0 mmol/L) | 2681 (84.4) | 488 (83.1) | 1757 (84.3) | 436 (85.8) | 0.47 |
| Fasting LDL cholesterol (mmol/L) | Normal (<3.5 mmol/L) | 2006 (63.9) | 350 (60.3) | 1346 (65.5) | 310 (61.4) | **0.03** |
| Dyslipidaemia | Does not have dyslipidaemia | 965 (30.8) | 152 (26.3) | 648 (31.6) | 165 (32.8) | **0.03** |

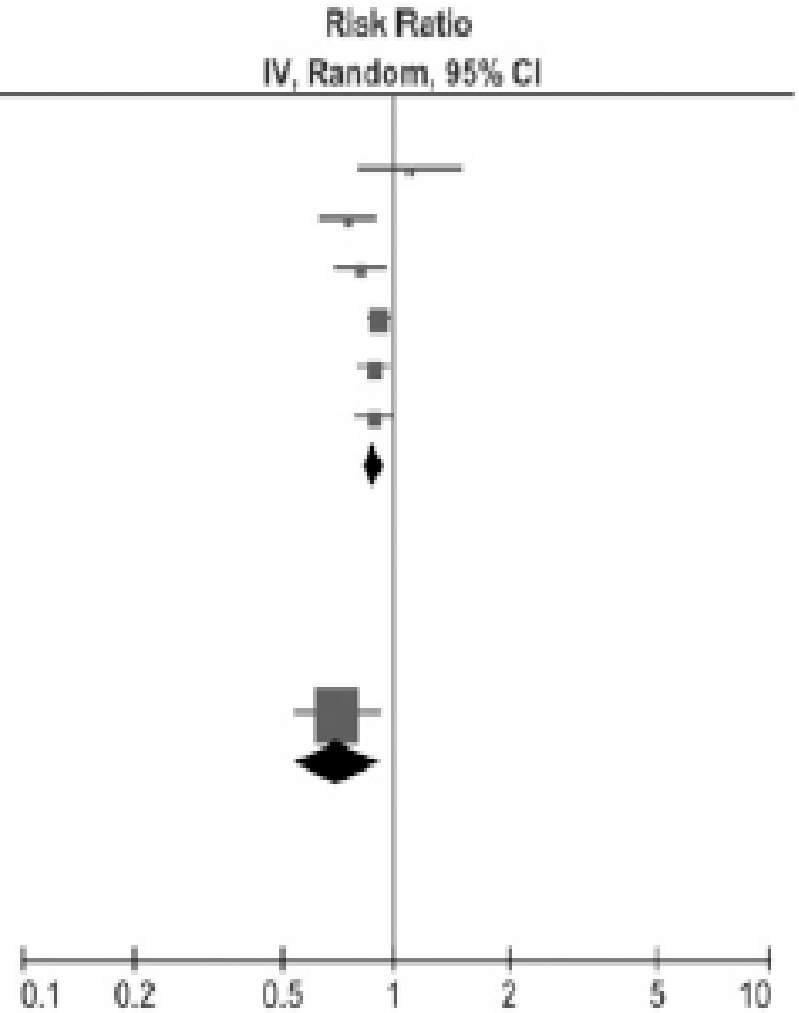
Aridi, YS et al, Nutrients 2020, 12, 1251

# Diabetes Mellitus

# Meta-analysis of prospective studies presenting the RRs and 95% CIs for type 2 diabetes incidence for the highest compared with the lowest intake of the Mediterranean diet

**A**

| Study or Subgroup | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|
| 1.1.1 Observational studies | | |
| Abiemo et al. MESA (18) | 3.5% | 1.09 [0.80, 1.49] |
| De Koning et al. HPFS (23) | 9.6% | 0.75 [0.63, 0.90] |
| Dominguez et al. SUN (26) | 11.7% | 0.81 [0.69, 0.95] |
| Jacobs et al. MEC (36) | 34.1% | 0.91 [0.85, 0.98] |
| Romaguera InterAct (52) | 22.7% | 0.88 [0.79, 0.98] |
| Rossi et al. EPIC-Greece (53) | 18.4% | 0.88 [0.78, 0.99] |
| **Subtotal (95% CI)** | **100.0%** | **0.87 [0.82, 0.93]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.71$, df = 5 (P = 0.24); $I^2 = 26\%$ | | |
| Test for overall effect: Z = 4.36 (P < 0.0001) | | |
| 1.1.2 Intervention study | | |
| Salas-Salvado et al. PREDIMED (54) | 100.0% | 0.70 [0.54, 0.91] |
| **Subtotal (95% CI)** | **100.0%** | **0.70 [0.54, 0.91]** |
| Heterogeneity: Not applicable | | |
| Test for overall effect: Z = 2.62 (P = 0.009) | | |




**B**

Jannasch F et al J Nutr 2017;147:1174–82

*Review*

# Preventive Role of Diet Interventions and Dietary Factors in Type 2 Diabetes Mellitus: An Umbrella Review

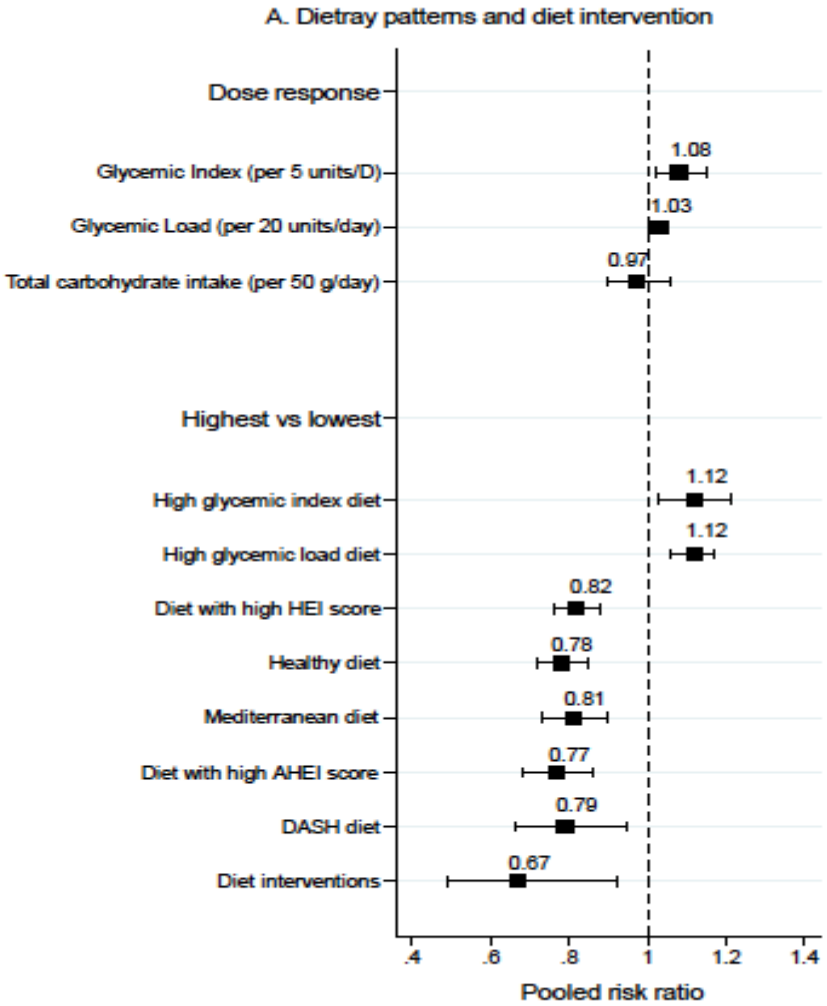
Phung Lam Toi [1,2,†], Thunyarat Anothaisintawee [1,3,*,†], Usa Chaikledkaew [1,4], Jamaica Roanne Briones [1], Sirimon Reutrakul [5] and Ammarin Thakkinstian [1,6]

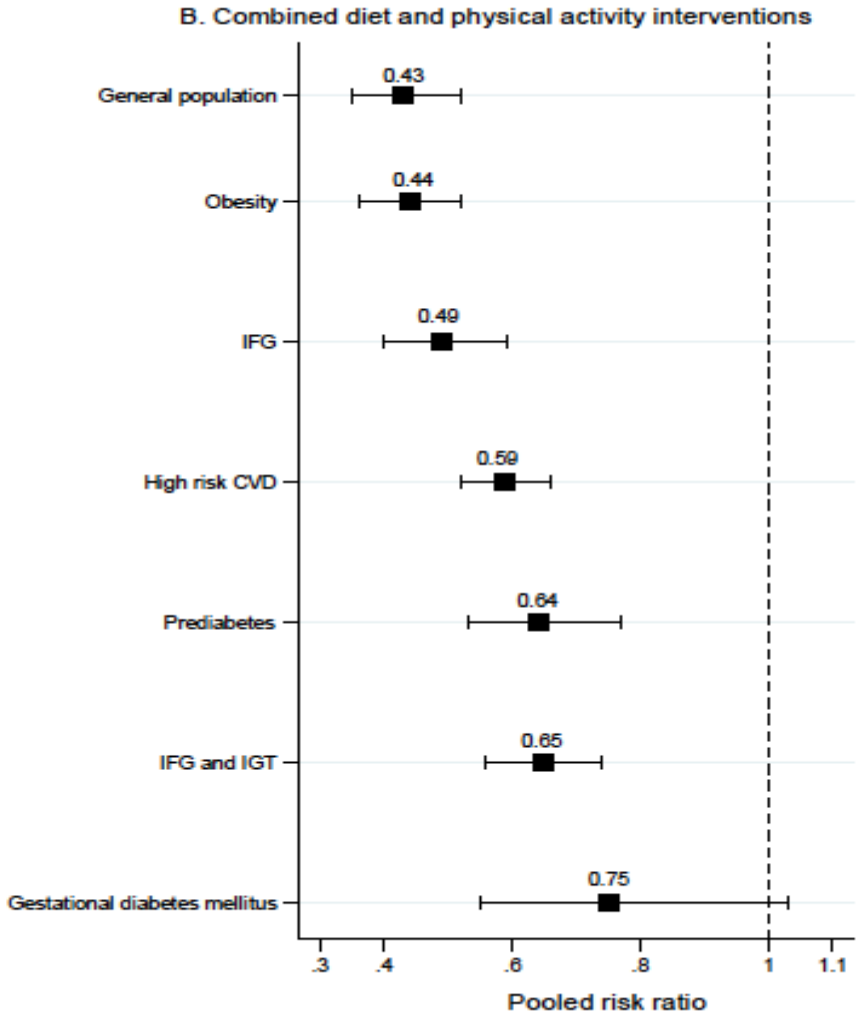
**Results:** Sixty systematic reviews and meta-analyses were eligible. Results of the review suggest that healthy dietary patterns such as MD and DASH diets, and high consumption of whole grains, low-fat dairy products, yogurt, olive oil, chocolate, fiber, magnesium, and flavonoid significantly reduced the risk of T2DM.

In contrast, high glycemic index and glycemic load diets, high consumption of red and processed meat, and sugar or artificial sugar-sweetened beverages significantly increased risk of T2DM

Toi PL et al, Nutrients 2020;12:2722

# Pooled risk ratios of dietary patterns, diet and combined diet and physical activity interventions and risk of T2DM. (A) Dietary patterns and diet intervention. (B) Combined diet and physical activity interventions




Toi PL et al, Nutrients 2020;12:2722

# Cancer

*Review*

# Adherence to Mediterranean Diet and Risk of Cancer: An Updated Systematic Review and Meta-Analysis

- RCTs, cohort (for specific tumors only incidence cases were used) studies, and case-control studies
- Observational studies (cohort and case-control studies), and intervention trials were meta-analyzed separately
- Total number of studies evaluated: 83 studies
- An overall population of 2,130,753 subjects was included

Schwingshackl L et al  Nutrients 2017, 9, 1063; doi:10.3390/nu9101063

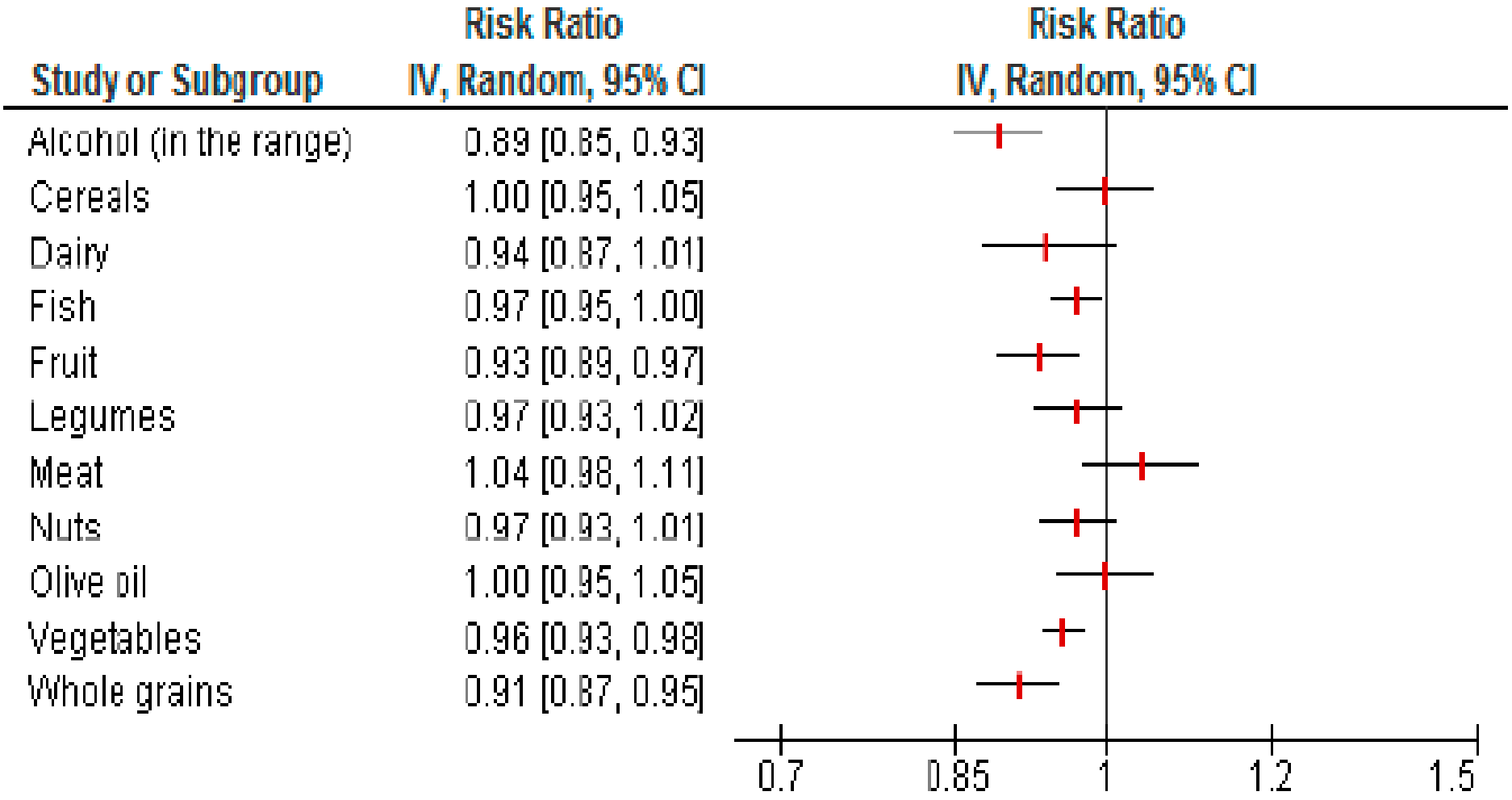
*Review*

# Adherence to Mediterranean Diet and Risk of Cancer: An Updated Systematic Review and Meta-Analysis

- The highest adherence score to a MedD was inversely associated with a lower risk of **cancer mortality** (RRcohort : **0.86**, 95% CI 0.81 to 0.91, I2 = 82%; n = 14 studies)
- **Colorectal cancer** (RRobservational : **0.82**, 95% CI 0.75 to 0.88, I2 = 73%; n = 11 studies)
- **Breast cancer** (RRRCT : **0.43**, 95% CI 0.21 to 0.88, n = 1study) (RRobservational : 0.92, 95% CI 0.87 to 0.96, I2 = 22%, n = 16 studies)
- **Gastric cancer** (RRobservational : **0.72**, 95% CI 0.60 to 0.86, I2 = 55%; n = 4 studies)
- **Liver cancer** (RRobservational : **0.58,** 95% CI 0.46 to 0.73, I2 = 0%; n = 2 studies)
- **Head and neck cancer** (RRobservational **: 0.49**, 95% CI 0.37 to 0.66, I2 = 87%; n = 7 studies)
- **Prostate cancer** (RRobservational : **0.96**, 95% CI 0.92 to 1.00, I2 = 0%; n = 6 studies)

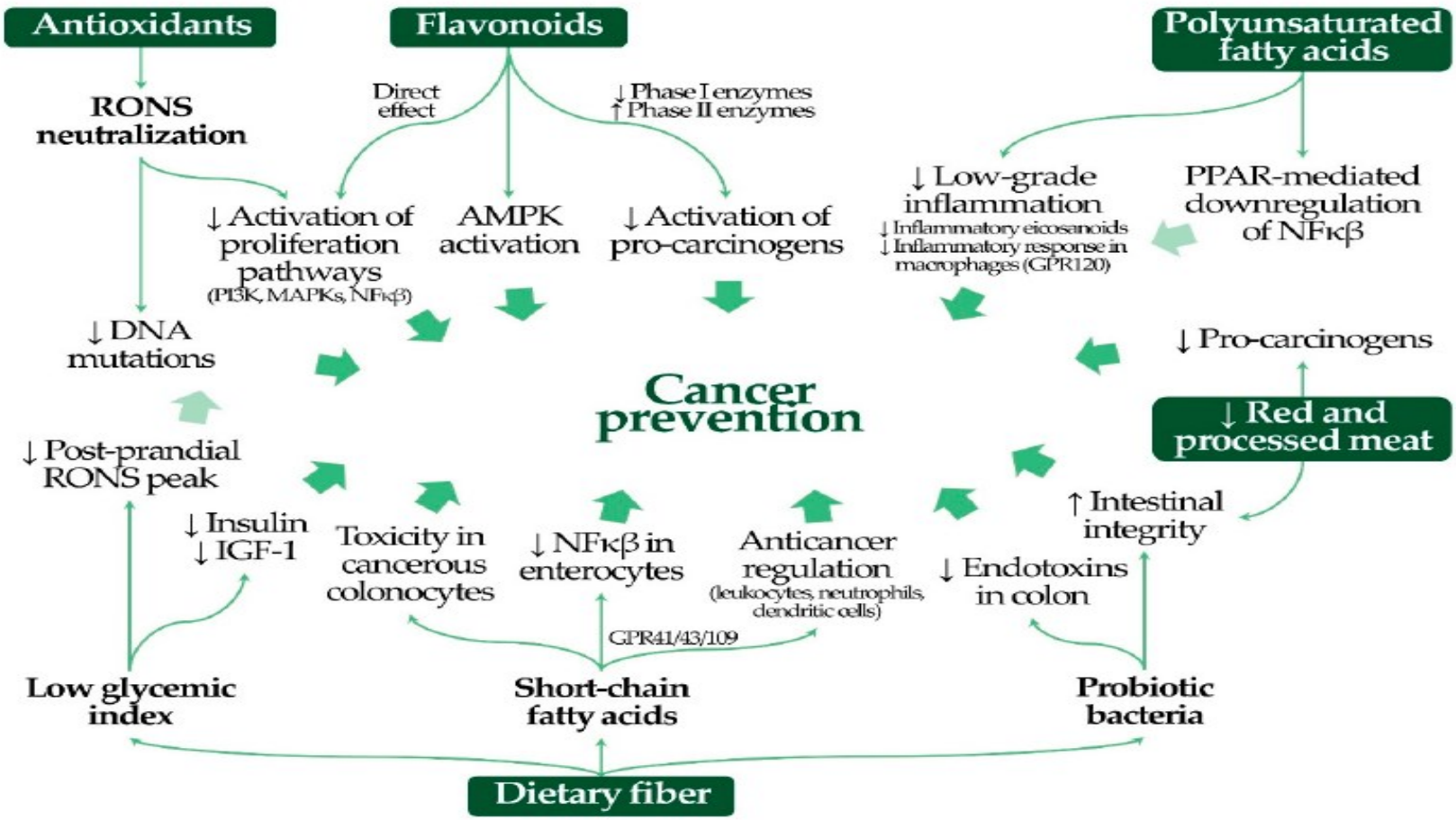
Schwingshackl L et al Nutrients 2017, 9, 1063; doi:10.3390/nu9101063

# Pooled risk ratios of individual Mediterranean diet components and overall cancer risk




Schwingshackl L et al Nutrients 2017, 9, 1063; doi:10.3390/nu9101063

# Molecular mechanisms of Mediterranean diet bioactive dietary components on cancer prevention

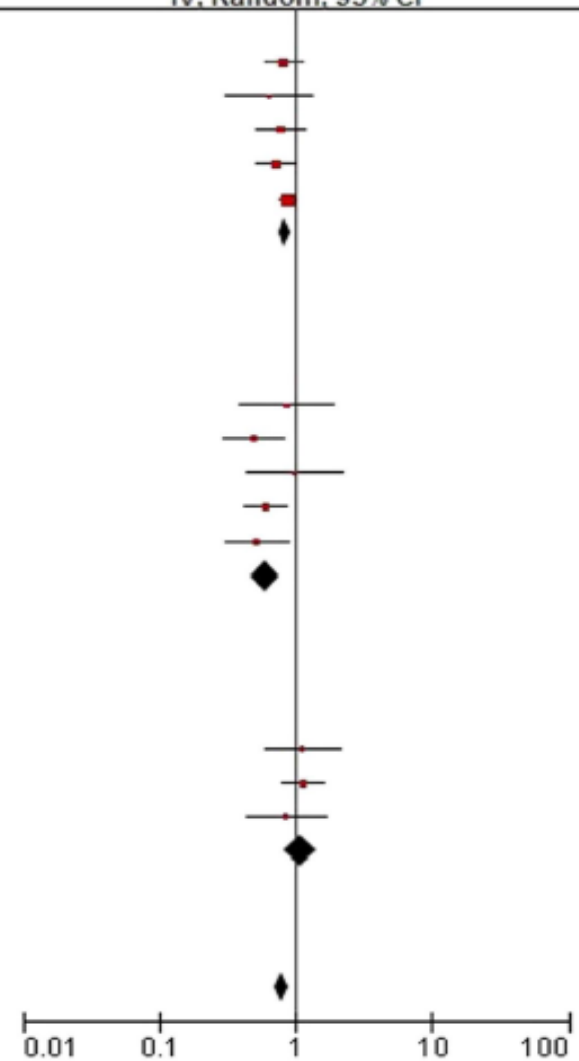



AMPK: AMP-mediated protein kinase; IGF-1: insulin-like growth factor-1; MAPKs: mitogen-activated protein kinases; NFκβ: nuclear factor kappa beta; PI3K: phosphoinositol-3-kinase; PPAR: peroxisome proliferator-activated receptor; RONS: reactive species of oxygen and nitrogen.

Hernaez A & Estruch R Nutrients 2019, 11, 2155

# Cognitive Disorders

| Study or Subgroup | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|
| **MCI** | | |
| Haring, 2016 | 10.8% | 0.82 [0.59, 1.14] |
| Olsson, 2015 | 2.9% | 0.64 [0.31, 1.32] |
| Roberts, 2010 | 7.3% | 0.78 [0.51, 1.19] |
| Scarmeas, 2009-MCI | 11.0% | 0.72 [0.52, 1.00] |
| Tsivgoulis, 2013 | 27.1% | 0.87 [0.76, 1.00] |
| **Subtotal (95% CI)** | **59.1%** | **0.83 [0.75, 0.93]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.78, df = 4 (P = 0.78); I² = 0% | | |
| Test for overall effect: Z = 3.22 (P = 0.001) | | |
| **AD** | | |
| Feart, 2009 | 2.4% | 0.86 [0.39, 1.90] |
| Morris, 2015 | 5.1% | 0.49 [0.29, 0.83] |
| Olsson, 2015 | 2.3% | 0.99 [0.44, 2.23] |
| Scarmeas, 2006 | 9.6% | 0.60 [0.42, 0.86] |
| Scarmeas, 2009-AD | 4.7% | 0.52 [0.30, 0.90] |
| **Subtotal (95% CI)** | **24.2%** | **0.60 [0.48, 0.77]** |
| Heterogeneity: Tau² = 0.00; Chi² = 3.09, df = 4 (P = 0.54); I² = 0% | | |
| Test for overall effect: Z = 4.18 (P < 0.0001) | | |
| **Dementia** | | |
| Feart, 2009 | 3.8% | 1.12 [0.60, 2.09] |
| Haring, 2016 | 9.6% | 1.13 [0.79, 1.62] |
| Olsson, 2015 | 3.4% | 0.85 [0.44, 1.64] |
| **Subtotal (95% CI)** | **16.7%** | **1.07 [0.81, 1.42]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 2 (P = 0.75); I² = 0% | | |
| Test for overall effect: Z = 0.48 (P = 0.63) | | |
| **Total (95% CI)** | **100.0%** | **0.79 [0.70, 0.90]** |
| Heterogeneity: Tau² = 0.01; Chi² = 15.38, df = 12 (P = 0.22); I² = 22% | | |
| Test for overall effect: Z = 3.63 (P = 0.0003) | | |
| Test for subgroup differences: Chi² = 9.94, df = 2 (P = 0.007), I² = 79.9% | | |




Association between Mediterranean diet score (High vs. Low) and the incident risk of cognitive disorders by outcome type. MCI, mild cognitive impairment; AD, Alzheimer's disease.

Wu L & Sun D Sci. Rep. 7, 41317; doi:10.1038/srep41317 (2017)

# The Impact of the Mediterranean Diet on the Cognitive Functioning of Healthy Older Adults: A Systematic Review and Meta-Analysis

- Systematic review and meta-analysis examines the impact of the MeDi on the cognitive functioning of healthy older adults
- Fifteen cohort studies with 41,492 participants and 2 RCTs with 309 and 162 participants in intervention and control groups, respectively, were included
- The primary outcome of interest was cognitive function, divided into domains of memory and executive function

Loughrey DG et al. Adv Nutr 2017;8:571–86

# The Impact of the Mediterranean Diet on the Cognitive Functioning of Healthy Older Adults: A Systematic Review and Meta-Analysis

- Meta-analysis of cohort studies revealed a significant association between **MeDi and older adults' episodic memory** (n = 25,369, r = 0.01, P = 0.03) **and global cognition** (n = 41,492, r = 0.05, P = 0.001), but not working memory (n = 1487, r = 0.007, P = 0.93) or semantic memory (n = 1487, r = 0.08, P = 0.28)
- Meta-analysis of RCTs revealed that compared with controls, the **MeDi improved delayed recall** (n = 429, P = 0.01), **working memory** (n = 566, P = 0.03), **and global cognition** (n = 429, P = 0.047), but not episodic memory (n = 566, P = 0.15), immediate recall (n = 566, P = 0.17), paired associates (n = 429, P = 0.20), attention (n = 566, P = 0.69), processing speed (n = 566, P = 0.35), or verbal fluency (n = 566, P = 0.12)

Loughrey DG et al. Adv Nutr 2017;8:571–86

# Non-genetic risk and protective factors and biomarkers for neurological disorders: a meta-umbrella systematic review of umbrella reviews

**Background:** The etiologies of chronic neurological diseases, which heavily contribute to global disease burden, remain far from elucidated. Despite available umbrella reviews on single contributing factors or diseases, no study has systematically captured non-purely genetic risk and/or protective factors for chronic neurological diseases

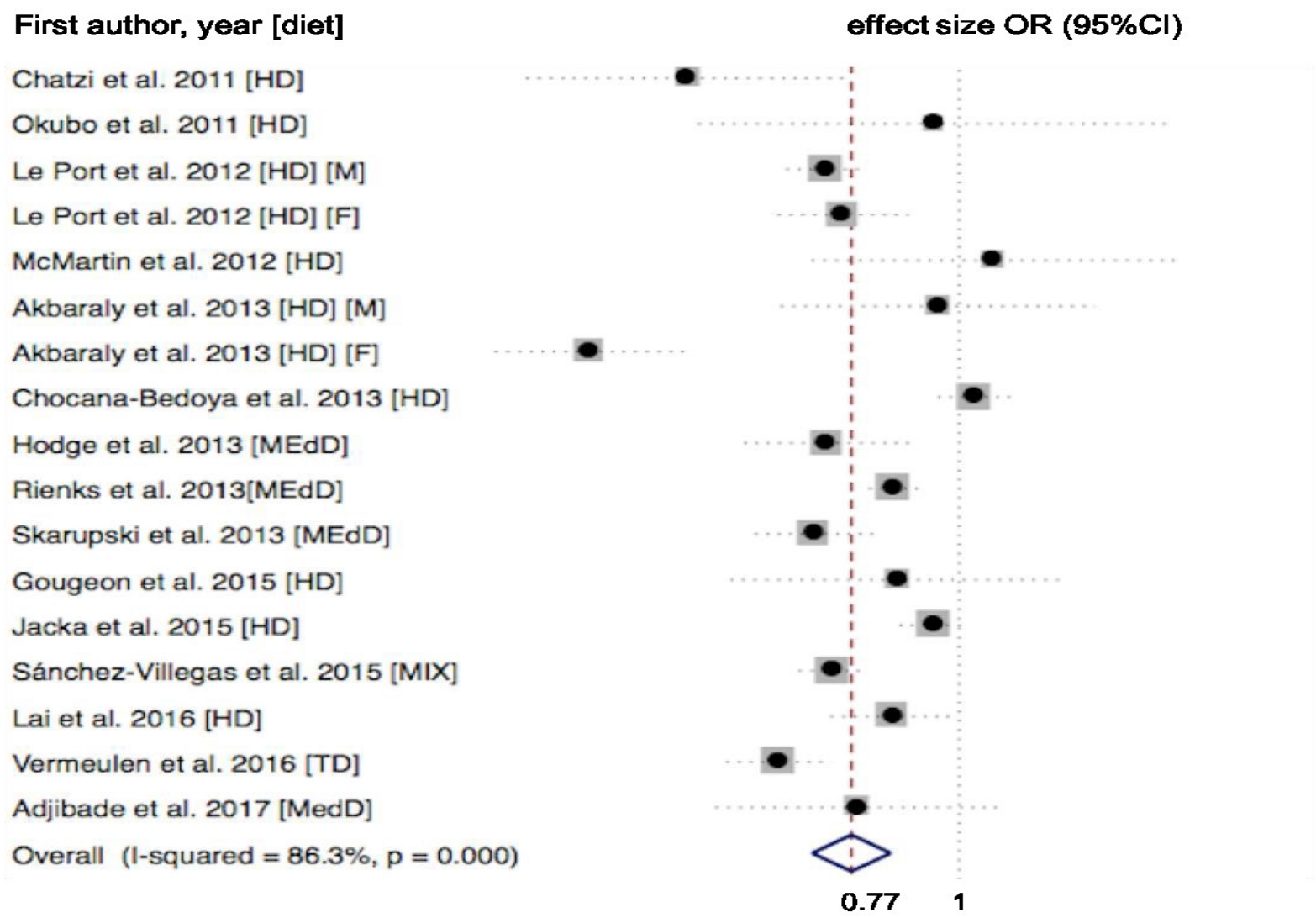
**Methods:** Systematic analysis of umbrella reviews (meta-umbrella)

Results: **Mediterranean diet was associated with lower risk of dementia, Alzheimer disease (AD), cognitive impairment, stroke, and neurodegenerative diseases in general**

In Parkinson disease (PD) and AD/dementia, coffee consumption, and physical activity were protective factors

Mentis AF et al. BMC Medicine 2021; 19:6

# Forest-plot showing that adherence to a high-quality diet is associated with decreased odds on incident depression




HD = Healthy Diet, MedD = Mediterranean Diet, MIX = mixture of healthy diets

Molendijk M et al, J Affect Dis 2017

# Fatty Liver

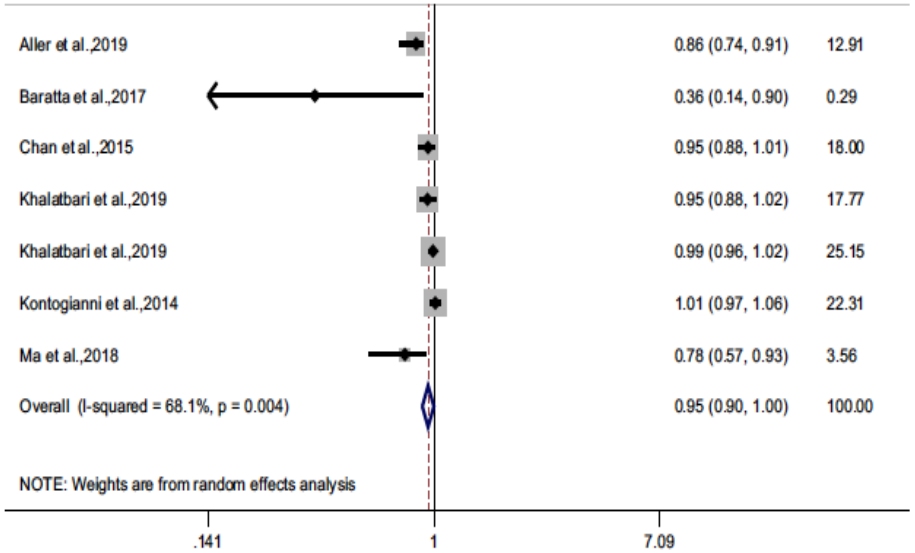
# Mediterranean diet for patients with non-alcoholic fatty liver disease, a systematic review and meta-analysis of observational and clinical investigations

Masoumeh Akhlaghi[1] · Maryam Ghasemi-Nasab[2] · Maryamsadat Riasatian[2]

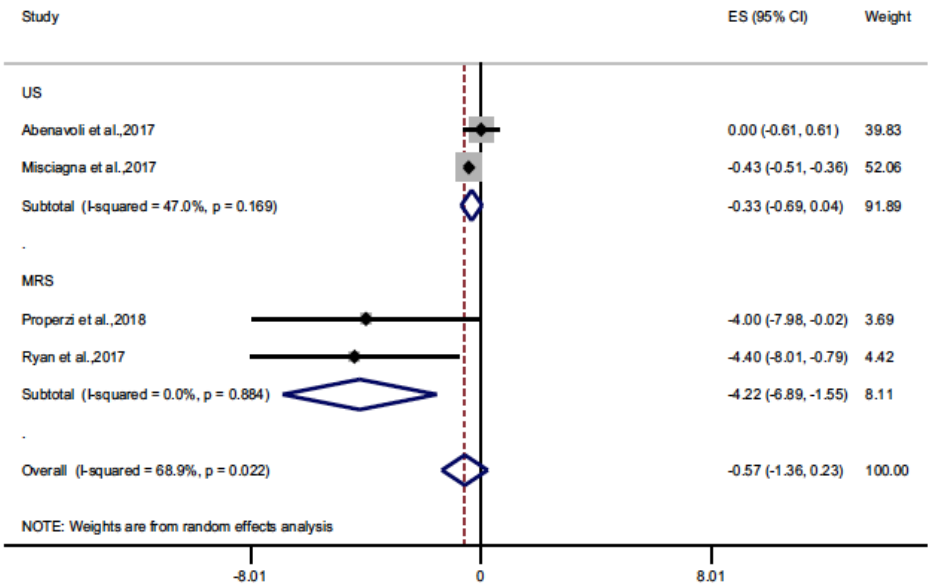
**Aim** Assessed the association between MD and liver steatosis and cardiometabolic risk factors in patients with NAFLD.
**Methods** PubMed, Scopus, and Embase were searched to find observational and clinical studies on the issue. No restriction on date and language was made. Outcomes included body mass index (BMI), waist circumference, blood pressure, triglycerides (TG), cholesterol fractions, glucose, insulin, insulin resistance, and liver transaminases.
**Results** Seven observational reports and 6 trials met our inclusion criteria and entered in the meta-analysis.

Akhlaghi M et al J Diabetes Metab Disord 2020;19:575–84

Forest plot of observational studies evaluating the association of MDand NAFLD




Forest plot of trials examining the effect of Mediterranean diet on liver steatosis in NAFLD patients with subgroup analysis based on the method of hepatosteatosis evaluation




Akhlaghi M et al J Diabetes Metab Disord 2020;19:575–84

**Thank you very much for your attention!**