How can I support my patient to make meaningful nutrition changes for secondary stroke prevention: Focus on salt and saturated fat

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Salt – Central "*Hypothesis*"

Salt (sodium) intake → Raised blood pressure → Heart attack, Stroke, Death

- assumes that sodium has no other effects on biological systems

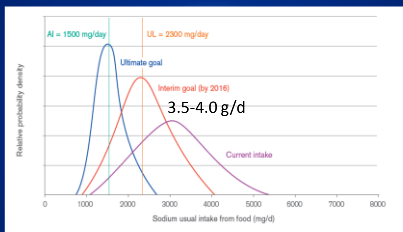
Recommendations (For All)

- **WHO/National Guidelines (e.g. AHA)**
  - Consume less than 2-2.4g/day (5-6g salt/day, or ~1 tsp)
  - FSAI: < 2.4g/day (achievable); < 1.6g/day (target)
- **Guideline Variations**
  - High-risk candidates < 1.5g/day (3.8g salt/day, or ~0.7 tsp)
    - Some guidelines only

Achieving these targets will require substantial change in diet for most people

Population-Wide vs Population-Specific

National Guidelines

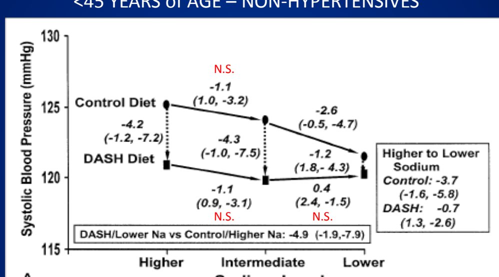


Is this 35%–65% reduction in Na consumption in millions of people necessary, safe, and feasible?

Na vs BP: Observational studies

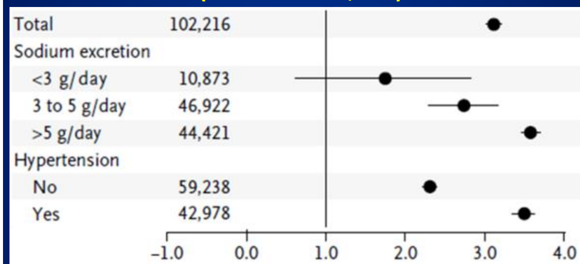
- INTERSALT study (BMJ 1988)
  - cross-sectional study (n=10,079), comparing mean Na intake bs mean BP, from 52 centers
  - weak relationship between Na and BP (0.94/0.03 mm Hg per gram of Na)
- Scottish Heart Study (BMJ 1988)
  - 7354 people aged 40-59
  - age, pulse rate, BMI, alcohol & potassium intake related to BP
  - no relationship between Na and BP
- INTERMAP (Hypertension 2018)
  - 4680 people aged 40-59, 17 centres in 4 countries
  - No relationship between Na and BP (0.22 mmHg per gram)

DASH TRIAL (NEJM 2001)
<45 YEARS of AGE – NON-HYPERTENSIVES



Bray et al, *Am J Cardiol*, 7/2004

SBP change per 1 g increase in Na is non linear (PURE: N=102,216)



Adjusted for covariates

Δ systolic BP, mm Hg

Mente A, et al. NEJM 2014

Effect of Na lowering on systolic BP in RCTs, overall and by Htn status: Meta-analyses

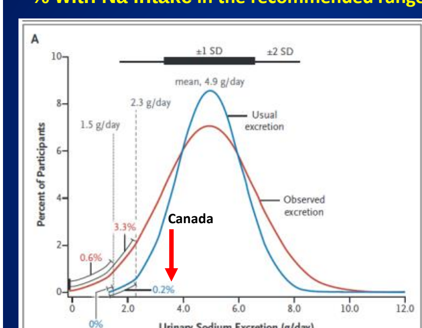
	Studies	N	Change in SBP per 1 g (95% CI)
Overall	34	3230	**2.46 (1.87 to 3.05)**
BP status at BL			
no hypertens.	12	2242	**1.42 (0.76 to 2.09)**
hypertension	22	990	**3.17 (2.62 to 3.89)**

However, most RCTs were < 6 months duration

A 1 mmHg diff in SBP = 2.5% change in CVD

Aburto et al 2013 BMJ & He et al 2013 BMJ

% with Na intake in the recommended range is *rare* (PURE)

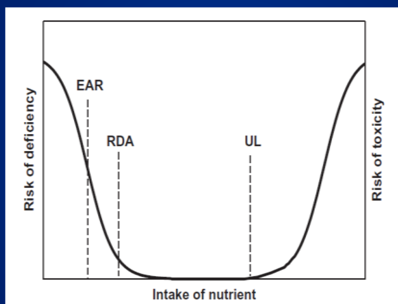


N=102,216

Usual Na intake:
0.2% with Na <2.3 g/d;
0% with Na <1.5 g/d

Mente A, et al. NEJM 2014

Recommendation on Essential Nutrient (IOM)



Heaney R *AJH* 2013

Sodium Intake and CVD in CVD Patients (J-shaped Association)

- N=28,880
- High CV Risk
- ONTARGET/TRANSCEND
- 56 months FU
- Morning fasting Urine to estimate 24-hour intake

Outcomes (N=4729)

- Mortality
- Stroke
- MI
- CHF

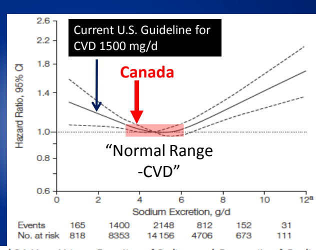
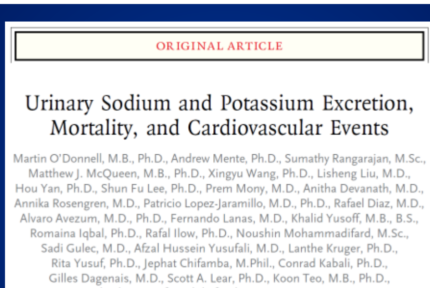


Figure 1. Estimated 24-Hour Urinary Excretion of Sodium and Composite of Cardiovascular Death, Stroke, Myocardial Infarction, and Hospitalization for Congestive Heart Failure

O'Donnell, Yusuf, Mente, et al: *JAMA;* 2011



ORIGINAL ARTICLE

Urinary Sodium and Potassium Excretion, Mortality, and Cardiovascular Events

Martin O'Donnell, M.B., Ph.D., Andrew Mente, Ph.D., Sumathy Rangarajan, M.Sc., Matthew J. McQueen, M.B., Ph.D., Xingyu Wang, Ph.D., Lisheng Liu, M.D., Hou Yan, Ph.D., Shun Fu Lee, Ph.D., Prem Mony, M.D., Anitha Devanath, M.D., Annika Rosengren, M.D., Patricio Lopez-Jaramillo, M.D., Ph.D., Rafael Diaz, M.D., Alvaro Avezum, M.D., Ph.D., Fernando Lanas, M.D., Khalid Yusoff, M.B., B.S., Romaina Iqbal, Ph.D., Rafal Ilow, Ph.D., Noushin Mohammadifard, M.Sc., Sadi Gulec, M.D., Afzal Hussein Yusufali, M.D., Lanthe Kruger, Ph.D., Rita Yusuf, Ph.D., Jephat Chifamba, M.Phil., Conrad Kabali, Ph.D., Gilles Dagenais, M.D., Scott A. Lear, Ph.D., Koon Teo, M.B., Ph.D., and Salim Yusuf, D.Phil., for the PURE Investigators*

- N=101,945 from general population (PURE Study)
- Outcomes: CV death, non-CV death, stroke, MI & CHF (3317 events)
- Follow-up: 3.7 years (95% completed follow-up)

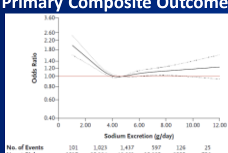
PURE Study (Sodium Intake and CVD)

- **Population**
  - General population (n=101,945)
  - Prior history of CVD: n=8485 (8.3%)
- **Exposure**: Mean sodium excretion 4.93g/day (SD 1.7)
  - Fasting morning urine
  - Validated formula-derived 24 h urinary estimate (Kawasaki formula)
- **Outcomes**: CV death, non-CV death, stroke, MI & CHF (n=3317)
  - Follow-up: 3.7 years (95% completed follow-up)
- **Statistical Analyses**
  - Analytic approaches to address confounding and reverse causality

O'Donnell M, et al. *New Engl J Med* 2014

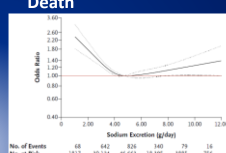
Sodium Intake and Events (PURE)

Primary Composite Outcome



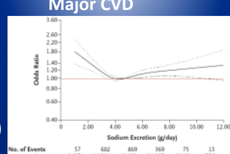
(3,317 events)

Death



(1976 events)

Major CVD



(1991 events)

O'Donnell MJ, et al. 2014, New Engl J Med

PURE Study (Addressing Confounding & Reverse Causality)

	Sodium excretion g/day				
	<3 g/d	3-3.99 g/d	4-5.99 g/d	6-6.99 g/d	≥ 7 g/d
	OR(95%CI)	OR(95%CI)	OR(95%CI)	OR(95%CI)	OR(95%CI)
No. of individuals	10,810	21,131	46,663	12,324	11,017
Composite Death or CV event	462 (4.3%)	662 (3.1%)	1437 (3.1%)	391 (3.2%)	365 (3.3%)
Univariate (GEE)	**1.24 (1.09- 1.41)**	0.96 (0.89- 1.05)	1.00	1.07 (0.96- 1.19)	1.18 (1.05- 1.32)
Multivariable	**1.27 (1.12- 1.44)**	1.01 (0.93- 1.09)	1.00	1.05 (0.94- 1.17)	1.15 (1.02- 1.30)
+ Dietary Factors	**1.19 (1.04- 1.35)**	1.00 (0.92- 1.09)	1.00	1.06 (0.95- 1.18)	1.15 (1.02- 1.30)
Excluding CVD	**1.24 (1.07- 1.42)**	1.00 (0.91- 1.10)	1.00	1.06 (0.95- 1.19)	1.14 (1.01- 1.29)
Excluding Cancer	**1.26 (1.11- 1.43)**	1.02 (0.93- 1.11)	1.00	1.06 (0.95-1.18)	1.15 (1.02- 1.29)
Very low risk cohort	**1.62 (1.29-2.05)**	1.07 (0.90-1.26)	1.00	1.15 (0.98-1.35)	1.14 (0.95-1.36)
Excl. event yr 1 & 2	**1.34 (1.14-1.57)**	1.04 (0.93-1.16)	1.00	1.15 (1.00-1.32)	1.11 (0.96-1.28)

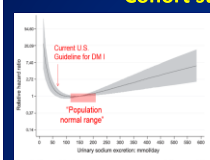
Adjusted for age, cluster, sex, education, prior CVD index, alcohol, diabetes, BMI, smoking

New Engl J Med Commentary on the PURE study results

- "These provocative findings beg for a randomized, controlled outcome trial to compare reduced Na intake with usual diet. In the absence of such a trial, the results argue ***against*** reduction of dietary Na as an isolated public health recommendation".

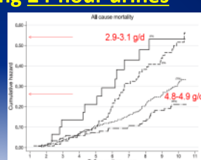
(Oparil S. NEJM 2014;371:677-679)

Cohort studies using <u>24-hour urines</u>



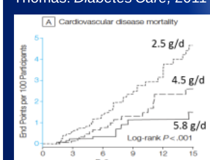
Thomas: *Diabetes Care;* 2011

Population: Type 1 DM
N=2807
Follow-up: 10 yrs
No. events: 217 deaths



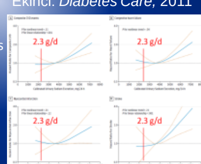
Ekinci: *Diabetes Care;* 2011

Population: Type 2 DM
N=665
Follow-up: 9.9 yrs
No. events: 175 deaths



Stolarz-Skrzypek: *JAMA*; 2011

Population: Healthy adults
N=3681
Follow-up: 7.9 yrs
No. events: 84 CV deaths

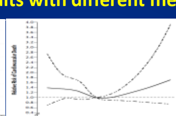


Mills, 2016, *JAMA* (CRIC)

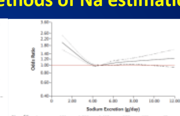
Population: CKD pts.
N=3757
Follow-up: 6.8 yrs
No. events: 804 CVD

Sodium Intake and Mortality + CVD:
Similar pattern of results with different methods of Na estimation

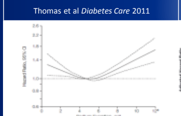
Australian DM Study (n=638; 24-h)
Thomas et al *Diabetes Care* 2011



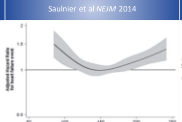
SURDIAGENE (n=1437; DM, EMU)
Saulnier et al *NEJM* 2014



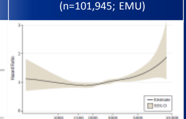
PURE Study NEJM 2014 (n=101,945; EMU)



ONTARGET/TRANSCEND JAMA 2011 (n=28,880; EMU)



EPIC-Norfolk (n=19857; USE, 12.9 y)
Pfister al *EHJ* 2014



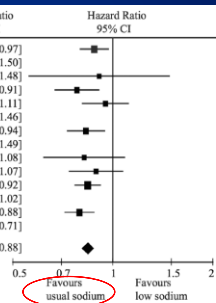
Health ABC (n=2642; FFQ, 10 y)
Kalogeropoulos et al *JAMA-Int Med* 2015

Smyth A, et al. 2015 Curr Hypertens Rep

PROSPECTIVE COHORT STUDIES (*AFTER* PURE)
MODERATE VS LOW SODIUM INTAKE AND ALL CAUSE MORTALITY

Study or Subgroup	N, Usual Sodium	N, Low Sodium	Weight	Hazard Ratio 95% CI
1 NHANES I (Alderman) 1998	8509	2837	20.8%	0.88 [0.80, 0.97]
2 NHANES I (He) 1999	5098	1699	0.0%	1.13 [0.85, 1.50]
3 Tuomilehto 2001	311	634	0.8%	0.91 [0.56, 1.48]
4 NHANES II (Cohen) 2006	3443	3711	8.2%	0.78 [0.67, 0.91]
5 Geleijnse 2007	724	724	7.4%	0.95 [0.81, 1.11]
6 Geleijnse (LRP) 2007	392	392	0.0%	1.12 [0.86, 1.46]
7 NHANES III (Cohen) 2008	4350	2175	11.5%	0.83 [0.73, 0.94]
8 NHANES III (Yang) 2011	6133	3067	0.0%	1.24 [1.03, 1.49]
9 Stolarz-Skrzypek 2011	1220	1250	2.4%	0.82 [0.62, 1.08]
10 Gardener 2012	961	1138	5.5%	0.89 [0.74, 1.07]
11 NORFOLK 2014	11913	3971	24.5%	0.84 [0.77, 0.92]
12 NORFOLK (LRP) 2014	9249	3070	0.0%	0.92 [0.82, 1.02]
13 PURE 2014	67794	10810	18.8%	0.79 [0.72, 0.88]
14 PURE (LRP) 2014	38643	6162	0.0%	0.62 [0.54, 0.71]
Total (95% CI)	99225	27250	100.0%	0.84 [0.81, 0.88]

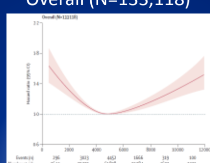
Heterogeneity: Chi² = 5.86, df = 8 (P = 0.66); I² = 0%
Test for overall effect: Z = 7.68 (P < 0.00001)



Graudal N, et al, 2016. Am J Hypertens 29;543-548

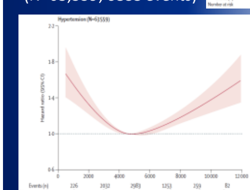
Sodium vs CVD by hypertension status

Overall (N=133,118)

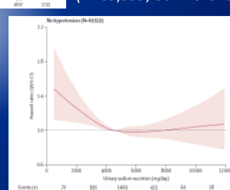


Data from PURE, EPIDREAM & ONTARGET/ TRANSCEND

Hypertension (N=63,559; **6835** events)

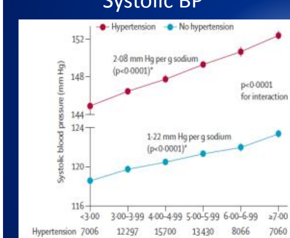


No Hypertension (N=69,559; **3021** events)

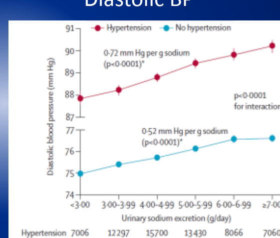


Mean BP by Na excretion and hypertension status (N=133,118) *

Systolic BP



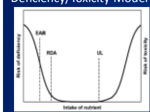
Diastolic BP



* Adjusted for age, sex, education, BMI, alcohol, smoking, and geographic region

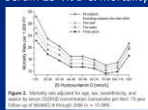
Essential nutrients have an optimal range vs health outcomes (ie, U-shaped relationhip)

Deficiency/Toxicity Model



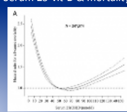
Heaney RP, 2013. AJH

Serum 25-vit D & mortality



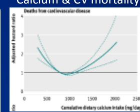
Langsetmo L, 2013 (NHANES-3)

Serum 25-vit D & mortality



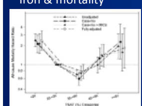
Durup D, 2012. J Clin Endocr Metab

Calcium & CV mortality



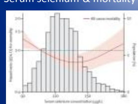
Michaelsson K, 2013. BMJ

Iron & mortality



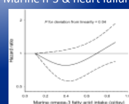
Hatamizadeh P, 2013 Nephrol Dial Trans

Serum selenium & mortality



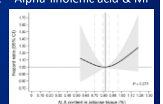
Rayman MP, 2012. Lancet

Marine n-3 & heart failure



Levitan EB, 2009. Eur Heart J

Alpha-linolenic acid & MI



Bork CS, 2016. AJCN

Cochrane review: Low vs high sodium and CV biomarkers

Biomarker	Studies	N	Standard mean difference (95% CI)	P
Renin	29	825	+0.67 (0.53 to 0.82)	<0.0001
Aldosterone	20	585	+0.99 (0.70 to 1.28)	<0.0001
Epinephrine	8	169	+0.21 (-0.00 to 0.43)	0.05
Norepinephrine	12	288	+0.17 (0.00 to 0.33)	0.04
Triglycerides	11	366	+7.78 (2.23 to 13.34)	0.006
LDL	8	273	+2.45 (-3.15 to 8.06)	0.39
HDL	11	342	-0.61 (-2.70 to 1.47)	n.s.
Cholesterol	13	424	+2.48 (-2.18 to 7.14)	0.30

Graudal N, et al. Am J Hypertens 2012;25:1-15

Summary

- Sodium intake > 5 g/d is associated with higher CVD & deaths in analyses at individual & community levels.
- Such high levels of sodium intake is seen mainly in China; less common in other countries
- ***Low*** sodium intake associated with ***higher*** mortality and CVD in *individuals* and persists after adjustment for confounders and control of reverse causality.
-
- Potassium is associated with lower risk of CVD & deaths

Implications

- A ***population strategy*** for sodium reduction appropriate only in populations with high intakes (eg, >5 g/day; China)
- ***A targeted approach*** more appropriate in other countries such as US and Canada (eg those with hypertension and intakes >5 g/d)
- In N America (intake of ~3.5 g/d), policy of reducing Na in all to below 2.3 g/d may ***increase*** mortality
- Large RCTs of low (<3 g/d) vs moderate intake (3 to 5 g/d) are ***essential***

European Heart Journal (2017) **0**, 1–9
doi:10.1093/eurheartj/ehw549

REVIEW

Controversies in Cardiovascular Medicine

The technical report on sodium intake and cardiovascular disease in low- and middle-income countries by the joint working group of the World Heart Federation, the European Society of Hypertension and the European Public Health Association

Giuseppe Mancia[1*], Suzanne Oparil[2], Paul K. Whelton[3], Martin McKee[4], Anna Dominiczak[5], Friedrich C. Luft[6], Khalid AlHabib[7], Fernando Lanas[8], Albertino Damasceno[9], Dorairaj Prabhakaran[10], Giuseppe La Torre[11], Michael Weber[12], Martin O'Donnell[13], Sidney C. Smith[14], and Jagat Narula[15]

"***We support the conduct of definitive RCTs, comparing low sodium intake (< 2.4 g/day) to moderate intake (2.4–5 g/day) on cardiovascular events and mortality***……. insufficient information to reliably answer this question… competing evidence from BP trials (which report reductions in BP) and epidemiologic studies (reporting higher risk with low sodium intake)". **European Heart J 2017**

Comment

Salt—too much or too little?

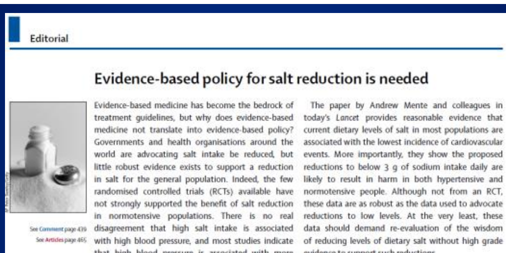
When apparent dogma is challenged, we should speak not of controversy but rather accede to the all-encompassing expression of so-called scientific uncertainty, so as to avoid unbecoming rhetoric. The issue of population strategies for salt consumption is a good case in point. There is no argument other than "excessive salt in the diet raises blood pressure", and that strategies to reduce salt in individuals with hypertension prevent the cardiovascular consequences of the disease. However, the corollary that reducing sodium intake across populations will be beneficial to all, has been challenged with the assertion that doing so might

annually, it behoves the scientific community to evaluate any population-based strategy, such as salt reduction, that might halt this epidemic. The editorial argued that the issue could only be decided by doing a randomised, controlled outcome trial, and that "in the absence of such a trial, the results argue against reduction of dietary sodium as an isolated public health recommendation".[6]

Support for this viewpoint has been added to by a large meta-analysis[7] and a cohort study,[8] but the most persuasive evidence is reported in this issue of *The Lancet* by Andrew Mente and colleagues.[9] Sodium excretion in 133 118 individuals from more than 40 countries of

Published Online
May 20, 2016

"The corollary that reducing sodium intake across populations will be beneficial to all, has been challenged with the assertion that doing so might indeed be harmful."
--O'Brien E, 2016. *The Lancet*, 2016; 388:439



Editorial

Evidence-based policy for salt reduction is needed

Evidence-based medicine has become the bedrock of treatment guidelines, but why does evidence-based medicine not translate into evidence-based policy? Governments and health organisations around the world are advocating salt intake be reduced, but little robust evidence exists to support a reduction in salt for the general population. Indeed, the few randomised controlled trials (RCTs) available have not strongly supported the benefit of salt reduction in normotensive populations. There is no real disagreement that high salt intake is associated with high blood pressure, and most studies indicate

See Comment page 439
See Articles page 465

The paper by Andrew Mente and colleagues in today's *Lancet* provides reasonable evidence that current dietary levels of salt in most populations are associated with the lowest incidence of cardiovascular events. More importantly, they show the proposed reductions to below 3 g of sodium intake daily are likely to result in harm in both hypertensive and normotensive people. Although not from an RCT, these data are as robust as the data used to advocate reductions to low levels. At the very least, these data should demand re-evaluation of the wisdom of reducing levels of dietary salt without high grade

"Before non-legislated salt reduction programmes are imposed, the public should demand that the harms, as well as the benefits, are based solely on robust scientific evidence. Enacting potentially harmful changes without strong supportive evidence should be avoided."
--*Editorial in The Lancet*, 2016; 388:438

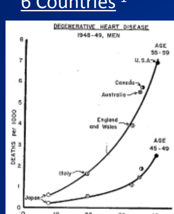
The Diet - Heart Hypothesis: Conventional Wisdom

Total fat, Saturated fat → Serum total & LDL cholesterol → Coronary heart disease

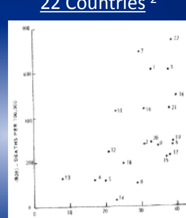
- assumes that fats have no other effects on biological systems

The Original Evidence: Ecological Data from 6 countries

6 Countries [1]



22 Countries [2]



Deaths from heart disease

Fat intake, % of energy

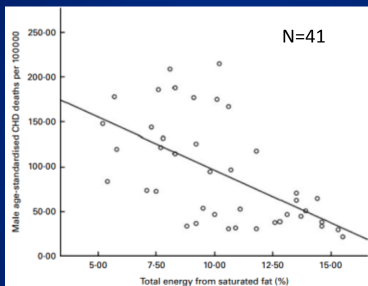
Fat intake, % of energy

[1] Keys A, 1953. *J Mt Sinai Hosp*

[2] Yerushalmy and Hillebow, 1957. *NY State J Med*

Saturated fat intake and CHD mortality among men in Europe, 1998

CHD deaths per 100,000 †



Total energy from saturated fat (%)

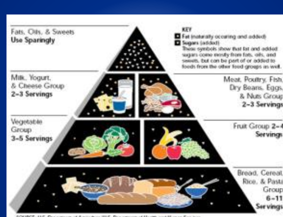
R^2 = 0.339, P<0.01

Results were similar for women and for CHD & stroke outcomes (all P<0.01)

† age-standardized rates

Hoenselaar R. *Br J Nutr* 2012;108:939–942

1961: American Heart Association adopts low-fat diet to fight heart disease



Dietary guidelines by various health organizations

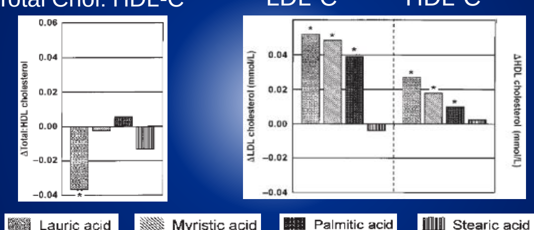
Nutrients	IOM/USDA	AHA	NCEP	WHO
Carbohydrate	45-65%			55-75%
Total fat	20-35%	<30%	<30%	15-30%
Saturated fatty acids	**As low as possible (<10%)**	**<7%**	**<7%**	**<10%**

Mean intake is ~12% of total energy in both sexes

- Natural foods containing saturated fat also contain
  - Vitamins B1, B2, B6, B11, B12
  - Protein
  - Zinc
  - Magnesium
  - Retinol
  - Selenium
  - Calcium
  - Vitamin D
- May result in inadequate intake of key nutrients in certain populations

Effect of saturated fatty acids on serum cholesterol †

Total Chol: HDL-C LDL-C HDL-C



† when carbohydrates replaced by 1% isoenergetically with SFAs

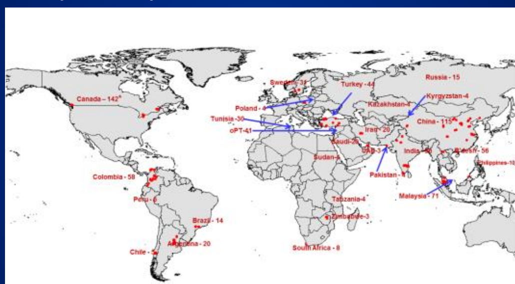
Mensink RP, 2003, *AJCN* 77:1146-55

Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study

*Andrew Mente, Mahshid Dehghan, Sumathy Rangarajan, Matthew McQueen, Gilles Dagenais, Andreas Wielgosz, Scott Lear, Wei Li, Hui Chen, Sun Yi, Yang Wang, Rafael Diaz, Alvaro Avezum, Patricio Lopez-Jaramillo, Pamela Seron, Rajesh Kumar, Rajeev Gupta, Viswanathan Mohan, Sumathi Swaminathan, Raman Kutty, Katarzyna Zatonska, Romaina Iqbal, Rita Yusuf, Noushin Mohammadifard, Rasha Khatib, Nafiza Mat Nasir, Noorhassim Ismail, Aytekin Oguz, Annika Rosengren, AfzalhusseinYusufali, Edelweiss Wentzel-Viljoen, Thandi Puoane, Jephat Chifamba, Koon Teo, Sonia S Anand, Salim Yusuf, on behalf of the Prospective Urban Rural Epidemiology (PURE) study investigators**

Mente A, et al, 2017, Lancet Diab Endocrinol

PURE: 135,335 from 667 communities in 18 (Phase 1) countries from 5 continents



Target: 200,000 people

Countries

Geog. region	Countries	N
South Asia	Bangladesh, India, Pakistan	29,560
China	China	42,152
Southeast Asia	Malaysia	10,038
Africa	South Africa, Zimbabwe	4,558
North America	Canada, Poland, Sweden,	14,916
Middle East	Iran, Occupied Palestinian Territory, Turkey, UAE	11,485
South America	Argentina, Brazil, Chile, Colombia	22,626
Overall		**135,335**

Study Methods

Design: Cross-sectional study

Population: Unbiased selection from general population in 667 urban/rural communities in 18 countries
N=135,335; aged 35-70 years, without CVD at baseline

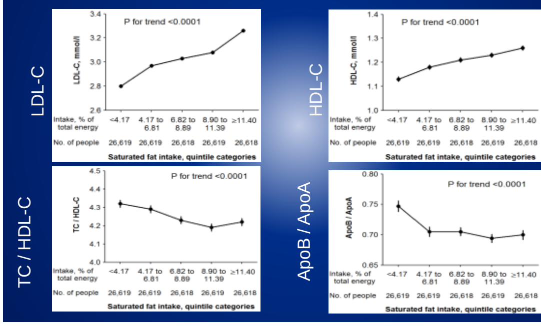
Diet: Country-specific, validated food frequency questionnaires

Covariates: Demographics, other lifestyle, health history, center

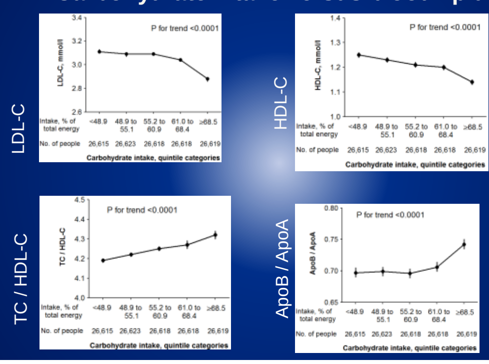
Outcomes: Blood pressure (n=125,287);
Blood lipids – LDL, HDL, TC/HDL ratio, Trig. (n=104,486);
ApoB, ApoA & ApoB/ApoA ratio (n=18,330)

Statistical Analyses: Multivariable linear regression, with random effect models to account for community level clustering

Saturated fat intake versus blood lipids



Carbohydrate intake versus blood lipids



Saturated fat intake versus blood lipids

A reduction in LDL-C of 1.0 mmol/L would be expected to reduce risk of CVD by about 25%

A reduction in LDL-C of 0.20 mmol/L (seen in the RCTs of SFA lowering) would be expected to reduce CVD by 5%

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Meta-analyses of RCTs: Saturated fat intake and events

Comparison 1. SFA reduction vs usual diet - Primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	12	55858	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.05]
2 Cardiovascular mortality	12	53421	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.12]
3 Combined cardiovascular events	13	53300	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.72, 0.96]

Comparison 2. SFA reduction vs usual diet - secondary health events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Myocardial infarctions	11	53167	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
2 Non-fatal MI	9	52834	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.13]
3 Stroke	8	50952	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.89, 1.12]
4 CHD mortality	10	53159	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.84, 1.15]
5 CHD events	12	53199	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.74, 1.03]
6 Diabetes diagnoses	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Hooper M et al. The Cochrane Collaboration 2015

43

Other meta-analyses of RCTs in past 5 years: Saturated fat intake and CHD events

Meta-analyses	N Studies	N	Relative Risk (95% CI)
Ramsden, 2016	8	9,423	1.07 (0.80, 1.41)
Harcombe, 2015	7	2,467	0.99 (0.78, 1.25)
Schwingshackl, 2014	12	7,150	0.93 (0.72, 1.19)

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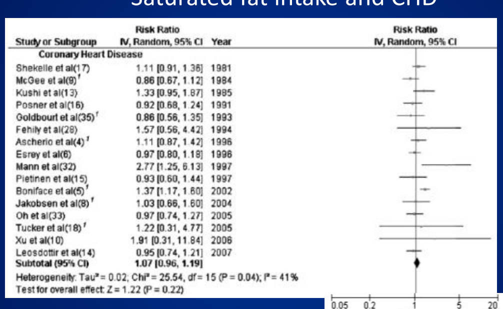
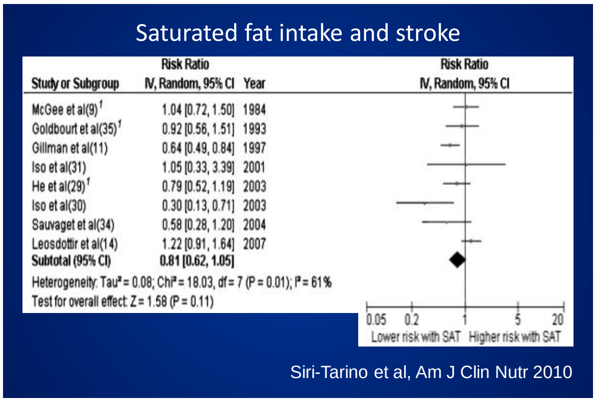
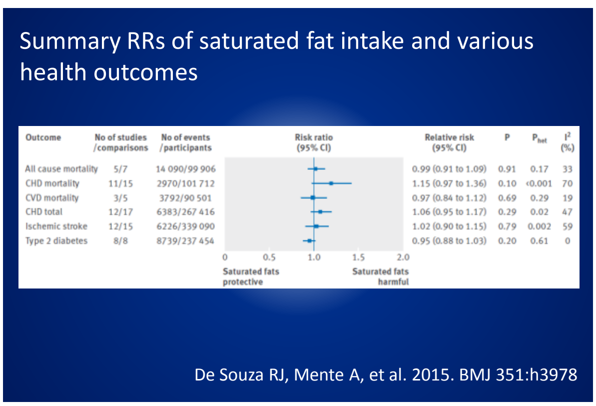
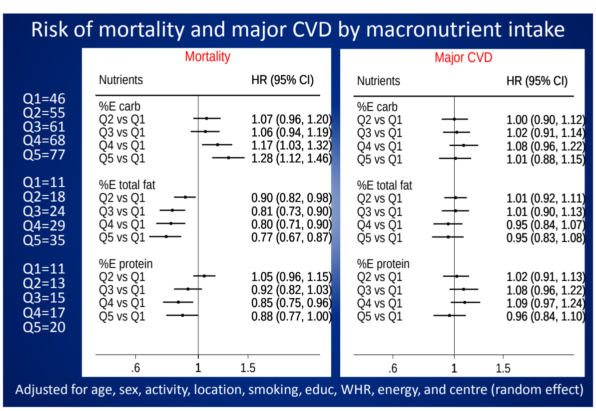
Saturated fat intake and CHD

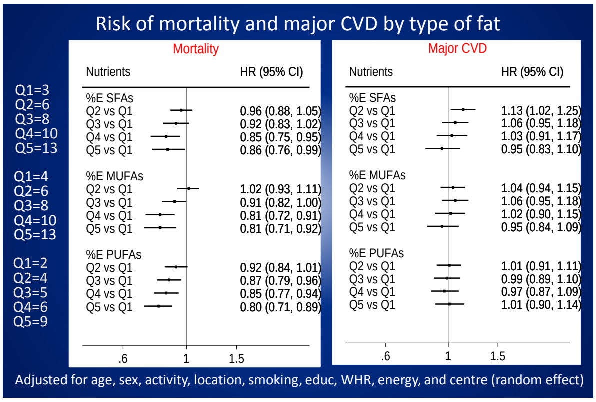


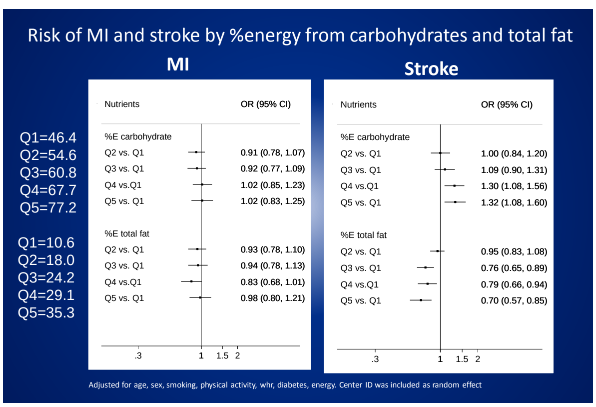
Siri-Tarino et al, Am J Clin Nutr 2010

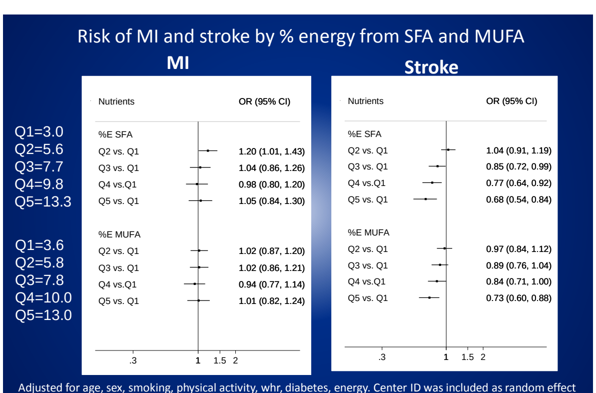

Saturated fat intake and stroke
Study or Subgroup
Risk Ratio
IV, Random, 95% CI
Year
Risk Ratio
IV, Random, 95% CI
McGee et al(9)† 1.04 [0.72, 1.50] 1984
Goldbourt et al(35)† 0.92 [0.56, 1.51] 1993
Gillman et al(11) 0.64 [0.49, 0.84] 1997
Iso et al(31) 1.05 [0.33, 3.39] 2001
He et al(29)† 0.79 [0.52, 1.19] 2003
Iso et al(30) 0.30 [0.13, 0.71] 2003
Sauvaget et al(34) 0.58 [0.28, 1.20] 2004
Leosdottir et al(14) 1.22 [0.91, 1.64] 2007
Subtotal (95% CI) 0.81 [0.62, 1.05]
Heterogeneity: Tau² = 0.08; Chi² = 18.03, df = 7 (P = 0.01); I² = 61%
Test for overall effect: Z = 1.58 (P = 0.11)
0.05 0.2 1 5 20
Lower risk with SAT Higher risk with SAT
Siri-Tarino et al, Am J Clin Nutr 2010


Summary RRs of saturated fat intake and various health outcomes
Outcome | No of studies /comparisons | No of events /participants | Risk ratio (95% CI) | Relative risk (95% CI) | P | Phet | I² (%)
All cause mortality 5/7 14 090/99 906 0.99 (0.91 to 1.09) 0.91 0.17 33
CHD mortality 11/15 2970/101 712 1.15 (0.97 to 1.36) 0.10 <0.001 70
CVD mortality 3/5 3792/90 501 0.97 (0.84 to 1.12) 0.69 0.29 19
CHD total 12/17 6383/267 416 1.06 (0.95 to 1.17) 0.29 0.02 47
Ischemic stroke 12/15 6226/339 090 1.02 (0.90 to 1.15) 0.79 0.002 59
Type 2 diabetes 8/8 8739/237 454 0.95 (0.88 to 1.03) 0.20 0.61 0
0 0.5 1.0 1.5 2.0
Saturated fats protective
Saturated fats harmful
De Souza RJ, Mente A, et al. 2015. BMJ 351:h3978


Risk of mortality and major CVD by macronutrient intake
Mortality
Nutrients HR (95% CI)
Q1=46 Q2=55 Q3=61 Q4=68 Q5=77
%E carb
Q2 vs Q1 1.07 (0.96, 1.20)
Q3 vs Q1 1.06 (0.94, 1.19)
Q4 vs Q1 1.17 (1.03, 1.32)
Q5 vs Q1 1.28 (1.12, 1.46)
Q1=11 Q2=18 Q3=24 Q4=29 Q5=35
%E total fat
Q2 vs Q1 0.90 (0.82, 0.98)
Q3 vs Q1 0.81 (0.73, 0.90)
Q4 vs Q1 0.80 (0.71, 0.90)
Q5 vs Q1 0.77 (0.67, 0.87)
Q1=11 Q2=13 Q3=15 Q4=17 Q5=20
%E protein
Q2 vs Q1 1.05 (0.96, 1.15)
Q3 vs Q1 0.92 (0.82, 1.03)
Q4 vs Q1 0.85 (0.75, 0.96)
Q5 vs Q1 0.88 (0.77, 1.00)
.6 1 1.5
Major CVD
Nutrients HR (95% CI)
%E carb
Q2 vs Q1 1.00 (0.90, 1.12)
Q3 vs Q1 1.02 (0.91, 1.14)
Q4 vs Q1 1.08 (0.96, 1.22)
Q5 vs Q1 1.01 (0.88, 1.15)
%E total fat
Q2 vs Q1 1.01 (0.92, 1.11)
Q3 vs Q1 1.01 (0.90, 1.13)
Q4 vs Q1 0.95 (0.84, 1.07)
Q5 vs Q1 0.95 (0.83, 1.08)
%E protein
Q2 vs Q1 1.02 (0.91, 1.13)
Q3 vs Q1 1.08 (0.96, 1.22)
Q4 vs Q1 1.09 (0.97, 1.24)
Q5 vs Q1 0.96 (0.84, 1.10)
.6 1 1.5
Adjusted for age, sex, activity, location, smoking, educ, WHR, energy, and centre (random effect)


Risk of mortality and major CVD by type of fat
Mortality
Major CVD
Nutrients
HR (95% CI)
Q1=3
Q2=6
Q3=8
Q4=10
Q5=13
%E SFAs
Q2 vs Q1 0.96 (0.88, 1.05) 1.13 (1.02, 1.25)
Q3 vs Q1 0.92 (0.83, 1.02) 1.06 (0.95, 1.18)
Q4 vs Q1 0.85 (0.75, 0.95) 1.03 (0.91, 1.17)
Q5 vs Q1 0.86 (0.76, 0.99) 0.95 (0.83, 1.10)
Q1=4
Q2=6
Q3=8
Q4=10
Q5=13
%E MUFAs
Q2 vs Q1 1.02 (0.93, 1.11) 1.04 (0.94, 1.15)
Q3 vs Q1 0.91 (0.82, 1.00) 1.06 (0.95, 1.18)
Q4 vs Q1 0.81 (0.72, 0.91) 1.02 (0.90, 1.15)
Q5 vs Q1 0.81 (0.71, 0.92) 0.95 (0.84, 1.09)
Q1=2
Q2=4
Q3=5
Q4=6
Q5=9
%E PUFAs
Q2 vs Q1 0.92 (0.84, 1.01) 1.01 (0.91, 1.11)
Q3 vs Q1 0.87 (0.79, 0.96) 0.99 (0.89, 1.10)
Q4 vs Q1 0.85 (0.77, 0.94) 0.97 (0.87, 1.09)
Q5 vs Q1 0.80 (0.71, 0.89) 1.01 (0.90, 1.14)
.6 1 1.5
Adjusted for age, sex, activity, location, smoking, educ, WHR, energy, and centre (random effect)

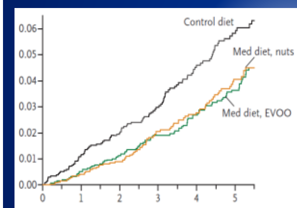

Risk of MI and stroke by %energy from carbohydrates and total fat
MI
Stroke
Nutrients
OR (95% CI)
Q1=46.4
Q2=54.6
Q3=60.8
Q4=67.7
Q5=77.2
%E carbohydrate
Q2 vs. Q1 0.91 (0.78, 1.07) 1.00 (0.84, 1.20)
Q3 vs. Q1 0.92 (0.77, 1.09) 1.09 (0.90, 1.31)
Q4 vs.Q1 1.02 (0.85, 1.23) 1.30 (1.08, 1.56)
Q5 vs. Q1 1.02 (0.83, 1.25) 1.32 (1.08, 1.60)
Q1=10.6
Q2=18.0
Q3=24.2
Q4=29.1
Q5=35.3
%E total fat
Q2 vs. Q1 0.93 (0.78, 1.10) 0.95 (0.83, 1.08)
Q3 vs. Q1 0.94 (0.78, 1.13) 0.76 (0.65, 0.89)
Q4 vs.Q1 0.83 (0.68, 1.01) 0.79 (0.66, 0.94)
Q5 vs. Q1 0.98 (0.80, 1.21) 0.70 (0.57, 0.85)
.3 1 1.5 2
Adjusted for age, sex, smoking, physical activity, whr, diabetes, energy. Center ID was included as random effect


Risk of MI and stroke by % energy from SFA and MUFA
MI
Stroke
Nutrients
OR (95% CI)
Q1=3.0
Q2=5.6
Q3=7.7
Q4=9.8
Q5=13.3
%E SFA
Q2 vs. Q1 1.20 (1.01, 1.43) 1.04 (0.91, 1.19)
Q3 vs. Q1 1.04 (0.86, 1.26) 0.85 (0.72, 0.99)
Q4 vs.Q1 0.98 (0.80, 1.20) 0.77 (0.64, 0.92)
Q5 vs. Q1 1.05 (0.84, 1.30) 0.68 (0.54, 0.84)
Q1=3.6
Q2=5.8
Q3=7.8
Q4=10.0
Q5=13.0
%E MUFA
Q2 vs. Q1 1.02 (0.87, 1.20) 0.97 (0.84, 1.12)
Q3 vs. Q1 1.02 (0.86, 1.21) 0.89 (0.76, 1.04)
Q4 vs.Q1 0.94 (0.77, 1.14) 0.84 (0.71, 1.00)
Q5 vs. Q1 1.01 (0.82, 1.24) 0.73 (0.60, 0.88)
.3 1 1.5 2
Adjusted for age, sex, smoking, physical activity, whr, diabetes, energy. Center ID was included as random effect

PREDIMED Trial

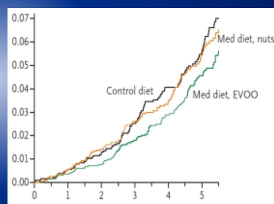
Incidence of outcome events by diet group

Primary outcome: CVD



Years

All-cause mortality



Years

Estruch et al. *NEJM* 2013

Mediterranean diet (olive oil) vs. Control diet

	HR (95% CI)	P-value
Primary outcome (CVD)		
Unadjusted	0.70 (0.53–0.91)	0.009
MV adjusted 1	0.69 (0.53–0.91)	0.008
MV adjusted 2	0.70 (0.54–0.92)	0.01
Secondary outcomes		
Stroke	**0.67 (0.46–0.98)**	**0.04**
Myocardial infarction	0.80 (0.51–1.26)	0.34
Death from CV causes	0.69 (0.41–1.16)	0.17
Death from any cause	0.82 (0.64–1.07)	0.15

Estruch et al. *NEJM* 2013

Mediterranean diet (nuts) vs. Control diet

	HR (95% CI)	P-value
Primary outcome (CVD)		
Unadjusted	0.70 (0.53–0.94)	0.02
MV adjusted 1	0.72 (0.54–0.97)	0.03
MV adjusted 2	0.72 (0.54–0.96)	0.03
Secondary outcomes		
Stroke	**0.54 (0.35–0.84)**	**0.006**
Myocardial infarction	0.74 (0.46–1.19)	0.22
Death from CV causes	1.01 (0.61–1.66)	0.98
Death from any cause	0.97 (0.74–1.26)	0.82

Estruch et al. *NEJM* 2013

Table S8 in Appendix

'Mediterranean diet' groups had similar, if not higher, SFA intake than low-fat control diet

	Between-group changes (differences vs. control)					
	MeDiet + Extra-Virgin Olive Oil vs. Control Diet			MeDiet + Nuts vs. Control Diet		
	Mean	*(95% CI)*	P value*	*Mean*	*(95% CI)*	P value*
Energy (kcal)	141	(97, 185)	<0.001	180	(134, 225)	<0.001
Total protein (% E)	-0.98	(-1.19, -0.73)	<0.001	-0.62	(-0.96, -0.40)	<0.001
Total carbohydrate (% E)	-2.79	(-3.37, -2.23)	<0.001	-3.15	(-3.74, -2.58)	<0.001
Fiber (g/d)	0.64	(-0.08, 1.36)	0.10	2.29	(1.56, 3.03)	<0.001
Total fat (% E)	3.99	(3.41, 4.57)	<0.001	4.03	(3.44, 4.62)	<0.001
Saturated fatty acids (% E)	0.24	(0.06, 0.41)	0.004	0.12	(-0.06, 0.30)	0.30
Monounsaturated fatty acids (% E)	3.05	(2.65, 3.46)	<0.001	1.89	(1.45, 2.26)	<0.001
Polyunsaturated fatty acids (% E)	0.62	(0.45, 0.79)	<0.001	1.96	(1.77, 2.14)	<0.001
Linoleic acid, (g/d)	1.94	(1.45, 2.43)	<0.001	5.05	(4.51, 5.58)	<0.001
α- linolenic acid, (g/d)	0.20	(0.14, 0.26)	<0.001	0.69	(0.63, 0.76)	<0.001
Marine n-3 fatty acids (g/d)	0.11	(0.07, 0.16)	<0.001	0.12	(0.08, 0.16)	<0.001
Olive oil (% E)	4.97	(4.31, 5.62)	<0.001	1.08	(0.43, 1.72)	<0.001
Nuts (% E)	0.82	(0.53, 1.10)	<0.001	5.65	(5.30, 6.01)	<0.001
Cholesterol (mg/d)	7.48	(-2.34, 17.30)	0.19	3.97	(-5.69, 13.62)	0.70

Table S8 in Appendix

'Mediterranean diet' groups had similar, if not higher, SFA intake than low-fat control diet

	Between-group changes (differences vs. control)					
	MeDiet + Extra-Virgin Olive Oil vs. Control Diet			MeDiet + Nuts vs. Control Diet		
	Mean	*(95% CI)*	P value*	*Mean*	*(95% CI)*	P value*
Energy (kcal)	141	(97, 185)	<0.001	180	(134, 225)	<0.001
Total protein (% E)	-0.98	(-1.19, -0.73)	<0.001	-0.62	(-0.96, -0.40)	<0.001
Total carbohydrate (% E)	-2.79	(-3.37, -2.23)	<0.001	-3.15	(-3.74, -2.58)	<0.001
Fiber (g/d)	0.64	(-0.08, 1.36)	0.10	2.29	(1.56, 3.03)	<0.001
Total fat (% E)	3.99	(3.41, 4.57)	<0.001	4.03	(3.44, 4.62)	<0.001
Saturated fatty acids (% E)	0.24	(0.06, 0.41)	0.004	0.12	(-0.06, 0.30)	0.30
Monounsaturated fatty acids (% E)	3.05	(2.65, 3.46)	<0.001	1.89	(1.45, 2.26)	<0.001
Polyunsaturated fatty acids (% E)	0.62	(0.45, 0.79)	<0.001	1.96	(1.77, 2.14)	<0.001
Linoleic acid, (g/d)	1.94	(1.45, 2.43)	<0.001	5.05	(4.51, 5.58)	<0.001
α- linolenic acid, (g/d)	0.20	(0.14, 0.26)	<0.001	0.69	(0.63, 0.76)	<0.001
Marine n-3 fatty acids (g/d)	0.11	(0.07, 0.16)	<0.001	0.12	(0.08, 0.16)	<0.001
Olive oil (% E)	4.97	(4.31, 5.62)	<0.001	1.08	(0.43, 1.72)	<0.001
Nuts (% E)	0.82	(0.53, 1.10)	<0.001	5.65	(5.30, 6.01)	<0.001
Cholesterol (mg/d)	7.48	(-2.34, 17.30)	0.19	3.97	(-5.69, 13.62)	0.70

Summary

- A high carbohydrate diet (>50-55%E) is associated with higher risk of mortality
- Fats, including saturated and unsaturated fats, are associated with lower risk of mortality
- No association between total fat, types of fat and CVD events
- Current advice to limit total fat to <30%E and saturated fat to <10%E are not supported by this global study

Conclusions: Foods and Health

Eat more:
- Fruit
- Vegetables
- Nuts
- Legumes
- Dairy
- Meats

Eat less:
- Refined grains and sugar
- Processed meats
- Sweetened drinks

AVOID
- Industrial trans-fat

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