Interne
Bregenz

Lifestyle Intervention

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Naples, November 17th, 2018

Interne Bregenz

Conflict of Interest:

- Bernhard Föger conducts Phase-III Studies for pharmaceutical companies, as below: Aesca, Astra-Zeneca, MSD, Novartis, Novo-Nordisk, Nycomed, Schering-Plough, Takeda.

- Bernhard Föger attends Speaker boards for pharmaceutical companies, as below: Aesca, Amgen, Astra-Zeneca, Böhringer Ingelheim, Eli Lilly, MSD, Novartis, Novo-Nordisk, Pfizer, Sanofi-Aventis, Takeda.

ESC/EAS 2016

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.6 mmol/L	100 to <155 mg/dL 2.6 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	≥190 mg/dL ≥4.9 mmol/L
<1	No lipid intervention	No lipid intervention	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a] /Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class[a] /Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
≥5 to <10, or high-risk	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class[a] /Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high-risk	Lifestyle intervention, consider drug	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class[a] /Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Evidence for Health Decision Making — Beyond Randomized, Controlled Trials

Thomas R. Frieden, M.D., M.P.H.

1. **RCTs for intermediary endpoints (e.g. BP, LDL-C)**
2. **Prospective cohorts studies for hard-endpoints**
3. **RCTs for hard endpoints (e.g. MACE)**

A CORE
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In large, well-designed trials, randomization evenly distributes known and

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Medical Society.

Roadmap

- not smoking
- exercise
- weight control
- nutrition

European Heart Journal (2016) **37**, 2315–2381
doi:10.1093/eurheartj/ehw106

JOINT ESC GUIDELINES

2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Massimo F. Piepoli* (Chairperson) (Italy), Arno W. Hoes* (Co-Chairperson) (The Netherlands), Stefan Agewall (Norway)[1], Christian Albus (Germany)[9], Carlos Brotons (Spain)[10], Alberico L. Catapano (Italy)[3], Marie-Therese Cooney (Ireland)[1], Ugo Corrà (Italy)[1], Bernard Cosyns (Belgium)[1],

Recommendations for physical activity

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended for healthy adults of all ages to perform at least 150 minutes a week of moderate intensity or 75 minutes a week of vigorous intensity aerobic PA or an equivalent combination thereof.	I	A	258–261
For additional benefits in healthy adults, a gradual increase in aerobic PA to 300 minutes a week of moderate intensity, or 150 minutes a week of vigorous intensity aerobic PA, or an equivalent combination thereof is recommended.	I	A	259, 260

= double that to 300 min moderate or 150 min vigorous exercise

PA is recommended in low-risk individuals without further assessment.	I	C	265, 266
Multiple sessions of PA should be considered, each lasting ≥10 minutes and evenly spread throughout the week, i.e. on 4–5 days a week and preferably every day of the week.	IIa	B	267, 268
Clinical evaluation, including exercise testing, should be considered for sedentary people with CV risk factors who intend to engage in vigorous PAs or sports.	IIa	C	265

PURE: Study Design

- prospective cohort study; very large (n ≈ 130.000); 17 HIC, MIC, LIC; primary outcome: mortality and MACE
- follow-up 6,9 years; patients with manifest CVD excluded
- sociodemographic factors, lifestyle (IPAQ, FFQ), risk factors recorded and multivariably adjusted for
- statistical attempts to control for known weaknesses of cohort studies (confounding, reverse causality)

The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study

Scott A Lear, Weihong Hu, Sumathy Rangarajan, Danijela Gasevic, Darryl Leong, Romaina Iqbal, Amparo Casanova, Sumathi Swaminathan, R M Anjana, Rajesh Kumar, Annika Rosengren, Li Wei, Wang Yang, Wang Chuangshi, Liu Huaxing, Sanjeev Nair, Rafael Diaz, Hany Swidon, Rajeev Gupta, Noushin Mohammadifard, Patricio Lopez-Jaramillo, Aytekin Oguz, Katarzyna Zatonska, Pamela Seron, Alvaro Avezum, Paul Poirier, Koon Teo, Salim Yusuf

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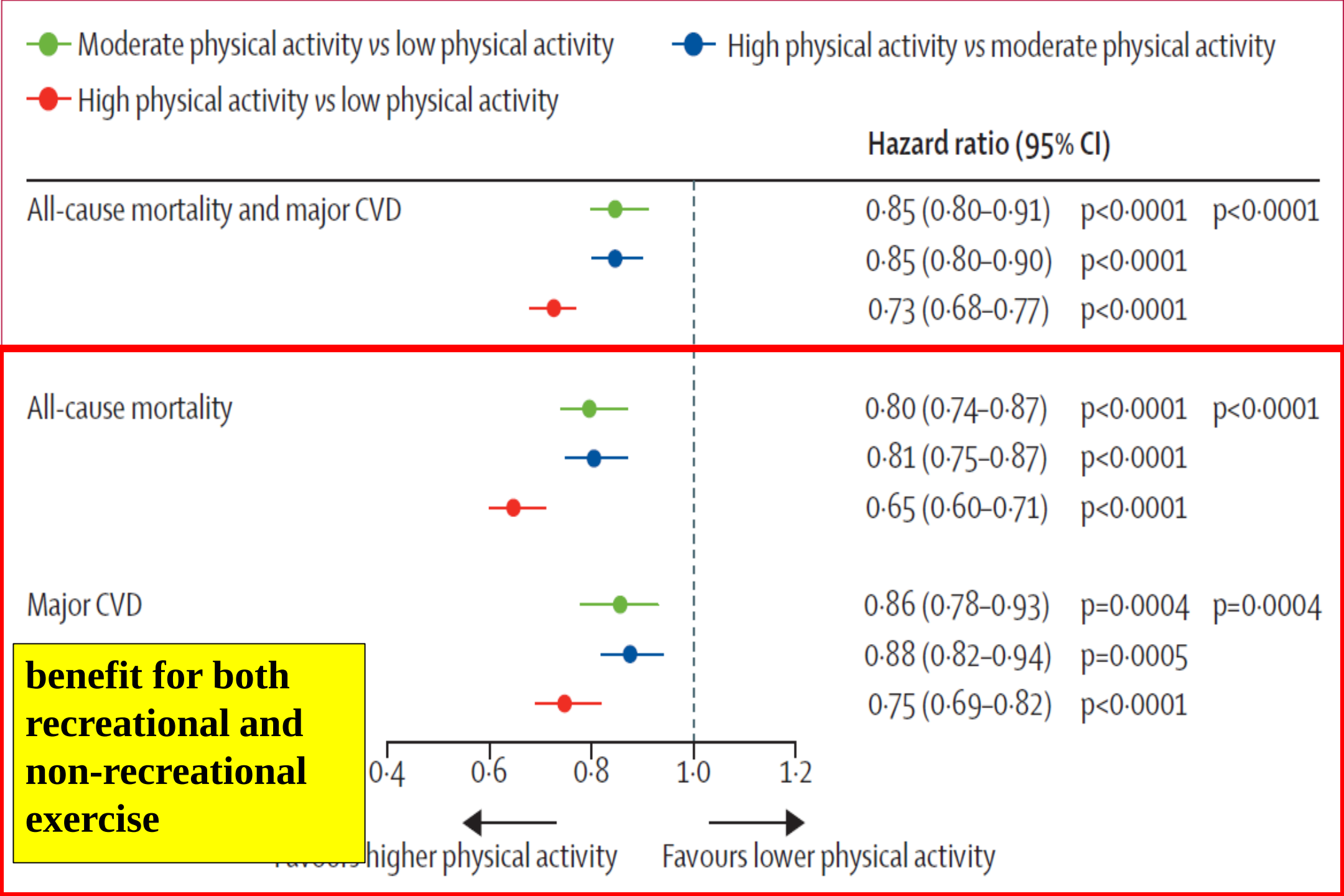
This online publication has been corrected. The corrected version first appeared at thelancet.com on October 5, 2017

Summary

Background Physical activity has a protective effect against cardiovascular disease (CVD) in high-income countries, where physical activity is mainly recreational, but it is not known if this is also observed in lower-income countries, where physical activity is mainly non-recreational. We examined whether different amounts and types of physical activity are associated with lower mortality and CVD in countries at different economic levels.

Methods In this prospective cohort study, we recruited participants from 17 countries (Canada, Sweden, United Arab Emirates, Argentina, Brazil, Chile, Poland, Turkey, Malaysia, South Africa, China, Colombia, Iran, Bangladesh, India, Pakistan, and Zimbabwe). Within each country, urban and rural areas in and around selected cities and towns


Moderate physical activity vs low physical activity
High physical activity vs moderate physical activity
High physical activity vs low physical activity
Hazard ratio (95% CI)
All-cause mortality and major CVD
0·85 (0·80–0·91) p<0·0001 p<0·0001
0·85 (0·80–0·90) p<0·0001
0·73 (0·68–0·77) p<0·0001
All-cause mortality
0·80 (0·74–0·87) p<0·0001 p<0·0001
0·81 (0·75–0·87) p<0·0001
0·65 (0·60–0·71) p<0·0001
Major CVD
0·86 (0·78–0·93) p=0·0004 p=0·0004
0·88 (0·82–0·94) p=0·0005
0·75 (0·69–0·82) p<0·0001
0·4
0·6
0·8
1·0
1·2
higher physical activity
Favours lower physical activity
benefit for both recreational and non-recreational exercise

Roadmap

- not smoking
- exercise
- weight control
- nutrition

Roadmap

- not smoking
- exercise
- weight control
- nutrition

Nutrition

Recommendation on nutrition

Recommendation	Class [a]	Level [b]	Ref [c]
A healthy diet is recommended as a cornerstone of CVD prevention in all individuals.	I	B	311

Gold standard outcome measure: total mortality

Key messages

- Dietary habits influence the risk of CVD and other chronic diseases such as cancer.
- Energy intake should be limited to the amount of energy needed to maintain (or obtain) a healthy weight, that is, a BMI >20.0 but <25.0 kg/m^2.
- In general, when following the rules for a healthy diet, no dietary supplements are needed.

One size fits all ?

Concepts of a healthy diet

- disease #1 → diet A
- disease #2 → diet B
- disease #3 → diet C

or

- one healthy diet suitable for most people ?

Nutrition: 3 levels of analysis

Nutrients: as % Energy

Foods/Food groups: as servings/d

Eating patterns

Saturated fatty acids (SFA)

Table 12 Healthy diet characteristics

• Saturated fatty acids to account for <10% of total energy intake, through replacement by polyunsaturated fatty acids.
• Trans unsaturated fatty acids: as little as possible, preferably no intake from processed food, and <1% of total energy intake from natural origin.

Saturated fatty acids (SFA): It used to be simple…

- SFA are palatable and energy dense (9kcal/g) → weight gain
- SFA lead to LDL-R downregulation → increase LDL-C quite potently (Magnitude +++; LoE A).
- SFA induce insulin resistance
- replace SFA by PUFA (1% En) → reduce CHD by 2-3%

Saturated fatty acids (SFA): however, some questions remained…

- are all SFA created equal ?
- does it matter what you replace SFA with ?
- does it matter what level of consumption we are talking about ?
- does the food group containing SFA matter ?

OPEN ACCESS

Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies

Russell J de Souza,[1,2,3,4] Andrew Mente,[1,2,5] Adriana Maroleanu,[2] Adrian I Cozma,[3,4] Vanessa Ha,[1,3,4] Teruko Kishibe,[6] Elizabeth Uleryk,[7] Patrick Budylowski,[4] Holger Schünemann,[1,8] Joseph Beyene,[1,2] Sonia S Anand[1,2,5,8]

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ABSTRACT

OBJECTIVE

To systematically review associations between intake of saturated fat and trans unsaturated fat and all cause mortality, cardiovascular disease (CVD) and associated mortality, coronary heart disease (CHD) and associated mortality, ischemic stroke, and type 2 diabetes.

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

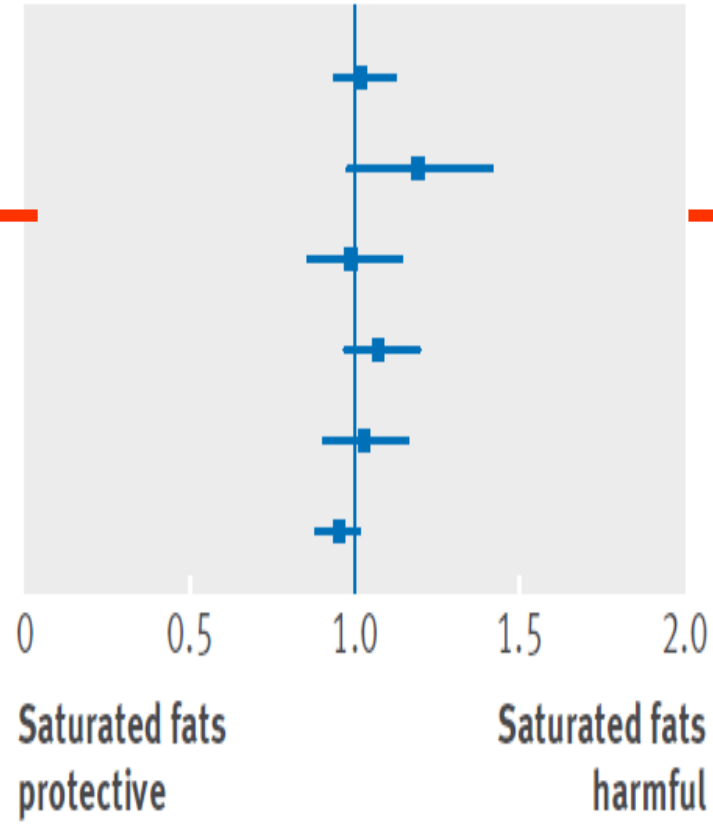
Medline, Embase, Cochrane Central Registry of Controlled Trials, Evidence-Based Medicine Reviews, and CINAHL from inception to 1 May 2015.

RESULTS

For saturated fat, three to 12 prospective cohort studies for each association were pooled (five to 17 comparisons with 90 501-339 090 participants). Saturated fat intake was not associated with all cause mortality (relative risk 0.99, 95% confidence interval 0.91 to 1.09), CVD mortality (0.97, 0.84 to 1.12), total CHD (1.06, 0.95 to 1.17), ischemic stroke (1.02, 0.90 to 1.15), or type 2 diabetes (0.95, 0.88 to 1.03). There was no convincing lack of association between saturated fat and CHD mortality (1.15, 0.97 to 1.36; P=0.10). For trans fats, one to six prospective cohort studies for each association were pooled (two to seven comparisons with 12 942-230 135 participants). Total

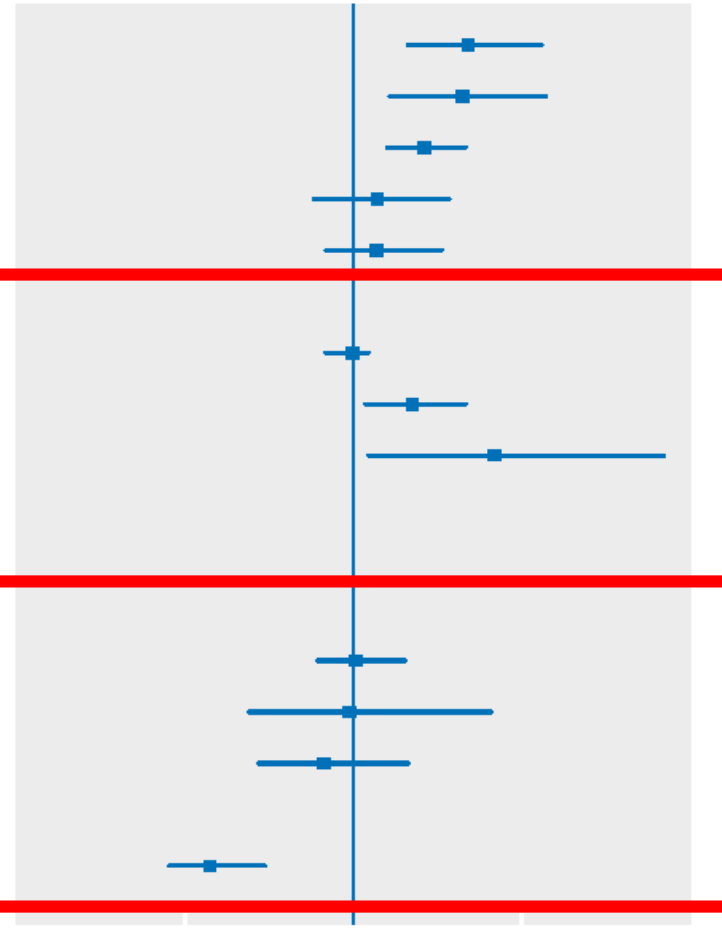
BMJ-Meta-analysis 2015: SFA

Outcome	No of studies /comparisons	No of events /participants	Relative risk (95% CI)	P	P_{het}	I^2 (%)
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



BMJ-Meta-analysis 2015: trans-FA

	/comparisons	/participants	(95% CI)	(95% CI)		(%)
Total trans fats						
All cause mortality	2/2	2141/20 346	1.34 (1.16 to 1.56)	<0.001	0.07	70
CHD mortality	5/6	1234/70 864	1.28 (1.09 to 1.50)	0.003	0.66	0
CHD total	6/7	4579/145 922	1.21 (1.10 to 1.33)	<0.001	0.43	0
Ischemic stroke	3/4	1905/190 284	1.07 (0.88 to 1.28)	0.50	0.03	67
Type 2 diabetes	6/6	8690/230 135	1.10 (0.95 to 1.27)	0.21	0.01	66
Industrial trans fats						
All cause mortality	1/2	11 890/71 464	0.98 (0.92 to 1.04)	0.52	0.52	0
CHD mortality	2/2	3018/93 394	1.18 (1.04 to 1.33)	0.009	0.68	0
CHD total	2/2	454/69 848	1.42 (1.05 to 1.92)	0.02	0.22	34
Ischemic stroke	0	0/0	-	-	-	-
Type 2 diabetes	0	0/0	-	-	-	-
Ruminant trans fats						
All cause mortality	1/2	11 890/71 464	1.04 (0.92 to 1.18)	0.51	0.31	4
CHD mortality	2/3	3018/93 394	1.01 (0.71 to 1.43)	0.95	0.01	79
CHD total	3/4	828/73 546	0.93 (0.73 to 1.18)	0.55	0.13	46
Ischemic stroke	0	0/0	-	-	-	-
Type 2 diabetes	5/5	1153/12 942	0.58 (0.46 to 0.74)	<0.001	0.22	30



Trans fats protective

Trans fats harmful

Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study

Mahshid Dehghan, Andrew Mente, Xiaohe Zhang, Sumathi Swaminathan, Wei Li, Viswanathan Mohan, Romaina Iqbal, Rajesh Kumar, Edelweiss Wentzel-Viljoen, Annika Rosengren, Leela Itty Amma, Alvaro Avezum, Jephat Chifamba, Rafael Diaz, Rasha Khatib, Scott Lear, Patricio Lopez-Jaramillo, Xiaoyun Liu, Rajeev Gupta, Noushin Mohammadifard, Nan Gao, Aytekin Oguz, Anis Safura Ramli, Pamela Seron, Yi Sun, Andrzej Szuba, Lungiswa Tsolekile, Andreas Wielgosz, Rita Yusuf, Afzal Hussein Yusufali, Koon K Teo, Sumathy Rangarajan, Gilles Dagenais, Shrikant I Bangdiwala, Shofiqul Islam, Sonia S Anand, Salim Yusuf, on behalf of the Prospective Urban Rural Epidemiology (PURE) study investigators*

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Summary

Background The relationship between macronutrients and cardiovascular disease and mortality is controversial. Most available data are from European and North American populations where nutrition excess is more likely, so their applicability to other populations is unclear.

	Overall (n=135 335)	China (n=42 152)	South Asia (n=29 560)	Europe and North America (n=14 916)	South America (n=22 626)	Middle East (n=11 485)	Southeast Asia (n=10 038)	Africa (n=4558)
Age (years)	50·29 (9·92)	50·58 (9·82)	48·18 (10·24)	53·01 (9·18)	51·13 (9·69)	48·57 (9·23)	51·47 (9·96)	49·98 (10·35)
Male	56 422 (41·7%)	17 575 (41·7%)	12 887 (43·6%)	6567 (44·0%)	8685 (38·4%)	4930 (42·9%)	4323 (43·1%)	1455 (31·9%)
Urban location	71 300 (52·7%)	20 170 (47·9%)	14 224 (48·1%)	10 488 (70·3%)	12 896 (57·0%)	6526 (56·8%)	4841 (48·2%)	2155 (47·3%)
Systolic blood pressure (mm Hg)	130·9 (22·2)	132·9 (22·2)	125·8 (21·2)	132·0 (20·4)	131·7 (22·7)	127·1 (20·3)	135·2 (23·1)	138·9 (27·5)
Waist-to-hip ratio	0·87 (0·08)	0·86 (0·07)	0·87 (0·09)	0·88 (0·09)	0·890 (0·08)	0·89 (0·09)	0·83 (0·08)	0·84 (0·087)
Current smoker	28 410/134 449 (21·1%)	9588/41 670 (23·0%)	6799/29 468 (23·1%)	2256/14 888 (15·2%)	4709/22 548 (20·9%)	2178/11 485 (19·0%)	1532/9943 (15·4%)	1348/4447 (30·3%)
Education								
Pre-secondary school	57 438/134 981 (42·6%)	14 113/42 036 (33·6%)	15 135/29 432 (51·4%)	1138/14 903 (7·6%)	13 298/22 565 (58·9%)	6935/11 485 (60·4%)	4263/10 032 (42·5%)	2556/4528 (56·5%)
Secondary school	51730/134 981 (38·3%)	21 853/42 036 (52·0%)	10 239/29 432 (34·8%)	4649/14 903 (31·2%)	5471/22 565 (24·3%)	3114/11 485 (27·1%)	4551/10 032 (45·4%)	1853/4528 (40·9%)
Post-secondary school	25 813/134 981 (19·1%)	6070/42 036 (14·4%)	4058/29 432 (13·8%)	9116/14 903 (61·2%)	3796/22 565 (16·8%)	1436/11 485 (12·5%)	1218/10 032 (12·1%)	119/4528 (2·6%)
Physical activity								
Low (<600 MET per min per week)	22 022/125 945 (17·5%)	6424/41 534 (15·5%)	5588/25 999 (21·5%)	826/13 628 (6·1%)	2889/21 567 (13·4%)	2452/11 342 (21·6%)	3315/9428 (35·2%)	528/2447 (21·6%)
Moderate (600–3000 MET per min per week)	47 850/125 945 (38·0%)	17 518/41 534 (42·2%)	8903/25 999 (34·2%)	4757/13 628 (34·9%)	6944/21 567 (32·2%)	5290/11 342 (46·6%)	3336/9428 (35·4%)	1102/2447 (45·0%)
High (>3000 MET per min per week)	56 073/125 945 (44·5%)	17 592/41 534 (42·4%)	11 508/25 999 (44·3%)	8045/13 628 (59·0%)	11734/21 567 (54·4%)	3600/11 342 (31·7%)	2777/9428 (29·5%)	817/2447 (33·4%)
History of diabetes	9634 (7·1%)	1610 (3·8%)	2723 (9·2%)	785 (5·3%)	1530 (6·8%)	1405 (12·2%)	1351 (13·5%)	230 (5·1%)
Energy from carbohydrate (%)	61·2% (11·6)	67·0% (9·8)	65·4% (11·3)	52·4% (8·1)	57·6% (11·4)	53·5% (7·5)	53·9% (8·2)	63·3% (11·5)
Energy from fat (%)	23·5% (9·3)	17·7% (7·8)	22·7% (10·4)	30·5% (6·0)	25·2% (7·7)	30·3% (6·1)	29·2% (5·9)	22·8% (8·3)
Energy from protein (%)	15·2% (3·6)	15·3% (2·3)	11·6% (1·9)	16·7% (2·7)	17·5% (3·8)	16·9% (2·8)	17·1% (3·2)	13·4% (3·0)
Energy from saturated fatty acids (%)	8·0% (4·1)	5·7% (2·7)	8·4% (5·2)	10·9% (3·7)	8·9% (3·4)	10·2% (2·9)	9·2% (2·1)	5·9% (2·8)
Energy from monounsaturated fatty acids (%)	8·1% (3·7)	6·8% (2·9)	5·9% (3·1)	11·2% (2·6)	9·0% (3·2)	10·2% (3·0)	11·8% (3·9)	7·2% (3·2)
Energy from polyunsaturated fatty acids (%)	5·3% (3·0)	4·2% (2·8)	6·2% (4·0)	4·8% (1·3)	4·4% (1·6)	7·0% (1·9)	8·2% (2·0)	6·0% (2·9)

PURE: SFA and Endpoints

	Incidence (per 1000 person-years; 95% CI)					Hazard ratio (95% CI)				p_{trend}
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Quintile 2 vs quintile 1	Quintile 3 vs quintile 1	Quintile 4 vs quintile 1	Quintile 5 vs quintile 1	
Percentage energy from saturated fatty acids										
Median (IQR)	2·8% (2·0–3·4)	4·9% (4·4–5·5)	7·1% (6·5–7·7)	9·5% (8·9–10·2)	13·2% (11·9–15·1)	..	..	..	..	..
Total mortality	7·1 (6·7–7·4)	5·2 (4·9–5·5)	4·3 (4·0–4·6)	3·9 (3·6–4·2)	4·4 (4·1–4·7)	0·96 (0·88–1·05)	0·92 (0·83–1·02)	0·85 (0·75–0·95)	0·86 (0·76–0·99)	0·0088
Major cardiovascular disease	5·2 (4·9–5·5)	4·7 (4·4–5·1)	4·1 (3·8–4·4)	3·9 (3·6–4·2)	4·1 (3·8–4·4)	1·13 (1·02–1·25)	1·06 (0·95–1·18)	1·03 (0·91–1·17)	0·95 (0·83–1·10)	0·49
Myocardial infarction	2·1 (1·9–2·3)	1·8 (1·6–2·0)	1·7 (1·5–1·9)	1·9 (1·7–2·1)	2·5 (2·3–2·7)	1·28 (1·08–1·51)	1·20 (1·00–1·44)	1·16 (0·95–1·41)	1·17 (0·94–1·45)	0·40
Stroke	2·7 (2·5–2·9)	2·6 (2·3–2·8)	1·9 (1·7–2·1)	1·5 (1·4–1·7)	1·3 (1·1–1·4)	1·10 (0·97–1·25)	1·01 (0·87–1·17)	0·93 (0·78–1·11)	0·79 (0·64–0·98)	0·0498
Cardiovascular disease mortality	1·7 (1·6–1·9)	1·5 (1·4–1·7)	1·3 (1·1–1·4)	1·4 (1·2–1·5)	1·4 (1·2–1·6)	1·04 (0·87–1·24)	0·95 (0·78–1·17)	0·99 (0·79–1·23)	0·83 (0·65–1·07)	0·20
Non-cardiovascular disease mortality	4·9 (4·6–5·2)	3·4 (3·1–3·6)	2·8 (2·5–3·0)	2·3 (2·1–2·5)	2·6 (2·4–2·8)	0·94 (0·84–1·04)	0·91 (0·81–1·03)	0·78 (0·68–0·91)	0·86 (0·73–1·01)	0·0108

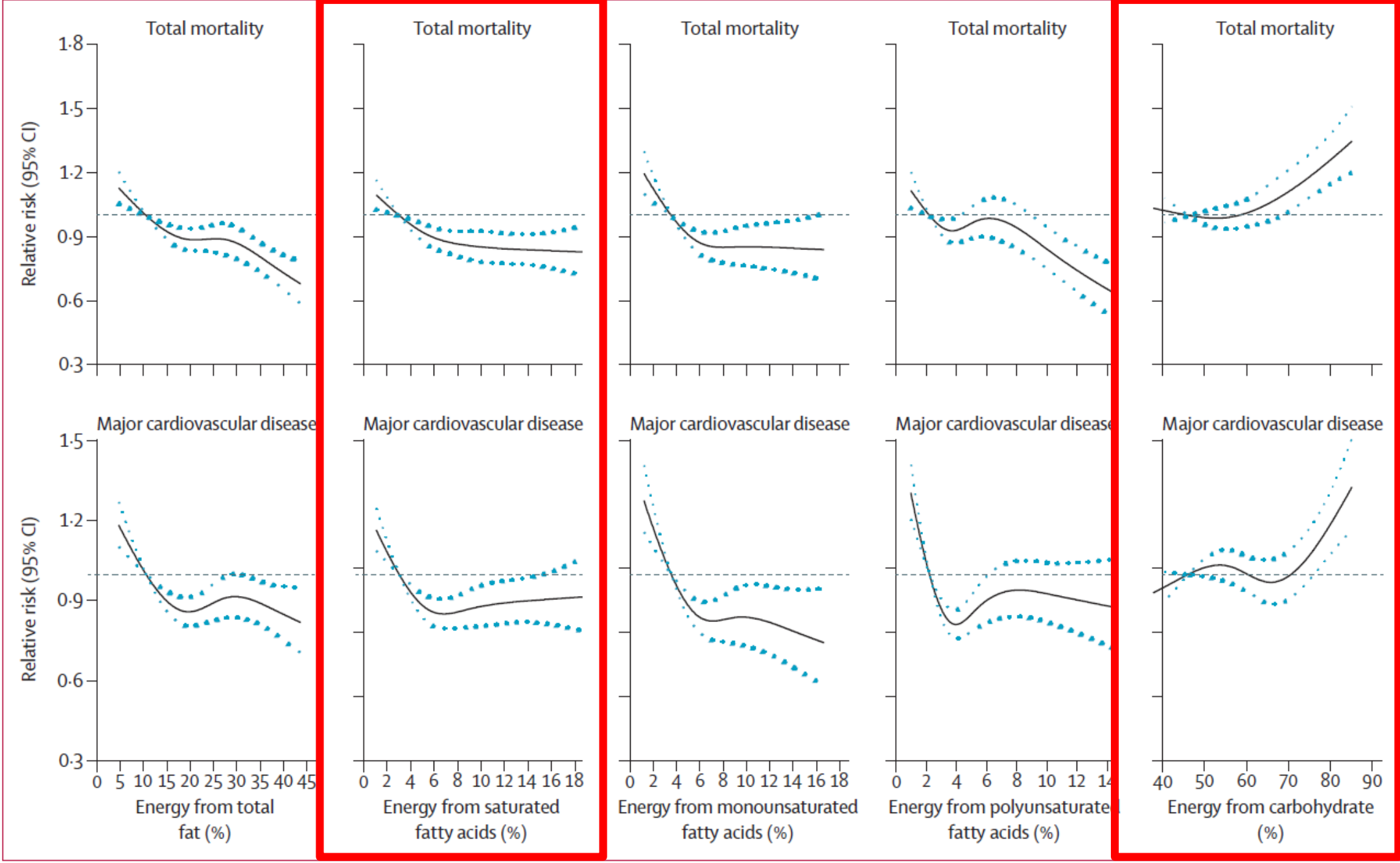
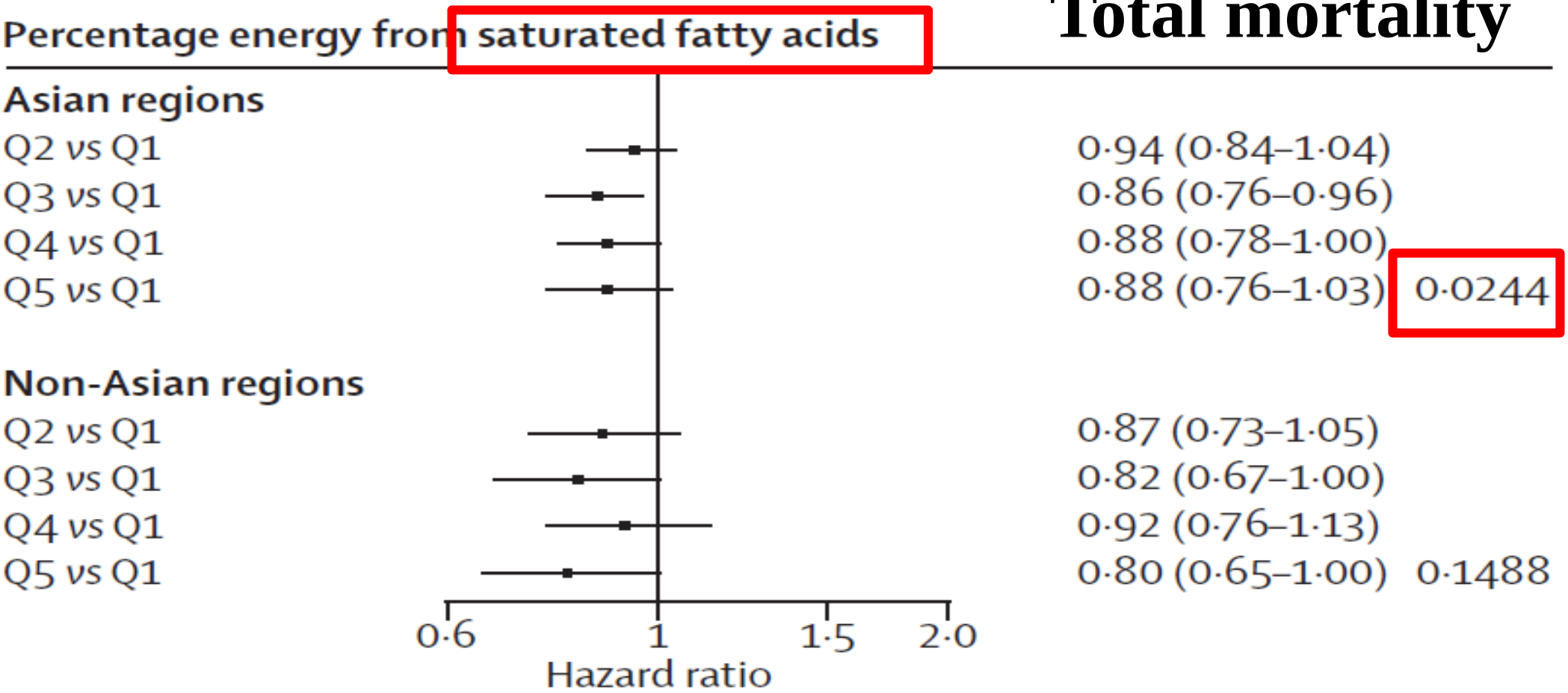


Figure 1: **Association between estimated percentage energy from nutrients and total mortality and major cardiovascular disease (n=135 335)**
Adjusted for age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, centre, geographical regions, and energy intake.

C

Total mortality

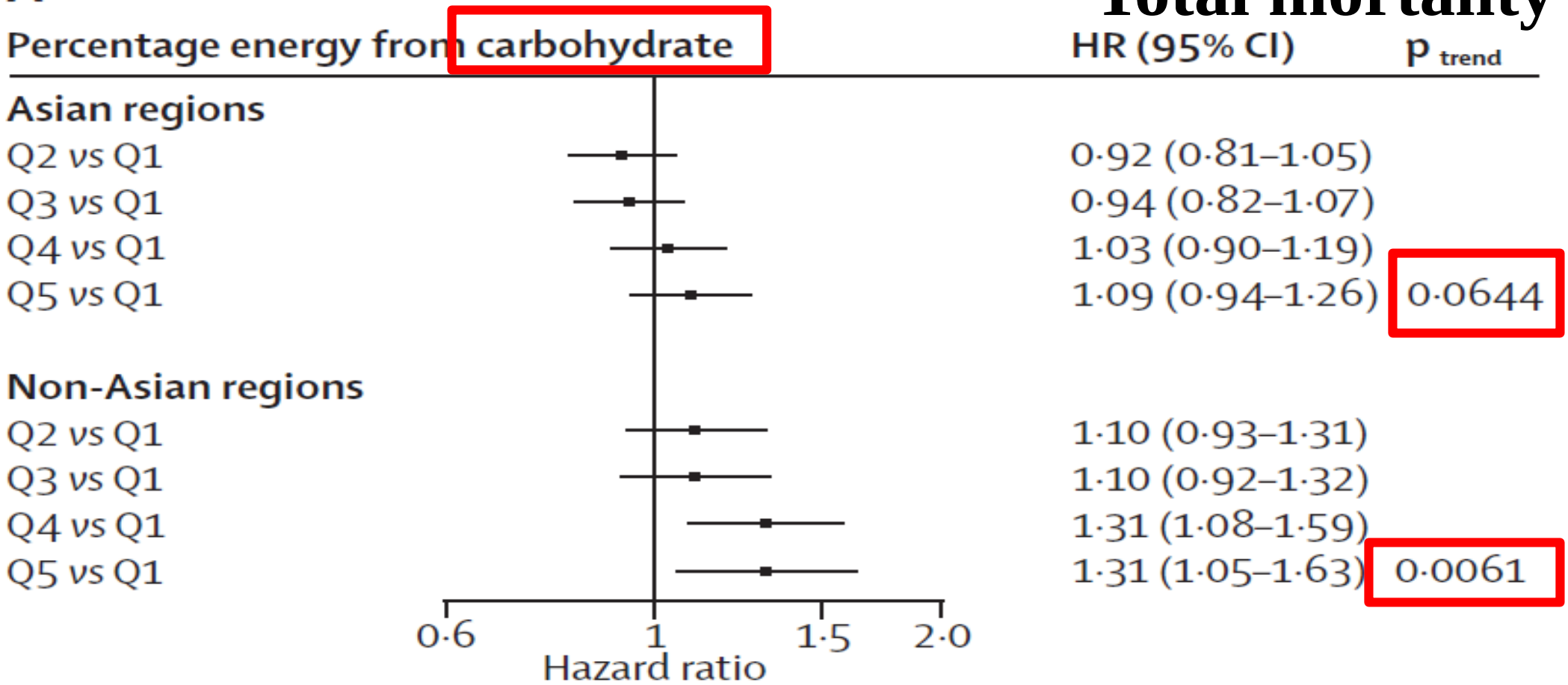


Energy from saturated fatty acids (%; median [IQR])

	Q1	Q2	Q3	Q4	Q5
Asian region	2·3 (1·6–2·8)	3·9 (3·6–4·3)	5·5 (5·0–6·0)	7·7 (7·0–8·4)	12·1 (10·5–14·3)
Non-Asian region	5·1 (4·0–5·8)	7·4 (7·0–7·9)	9·2 (8·8–9·6)	11·0 (10·5–11·6)	14·1 (13·1–15·9)

Total mortality

A



Energy from carbohydrate (%; median [IQR])

	Q1	Q2	Q3	Q4	Q5
Asian region	50·4 (46·5–52·9)	58·8 (57·1–60·3)	64·9 (63·3–66·5)	71·4 (69·7–73·3)	79·4 (77·2–82·2)
Non-Asian region	43·0 (39·5–45·3)	50·2 (48·8–51·5)	55·3 (54·1–56·6)	60·6 (59·2–62·3)	69·5 (66·4–73·6)

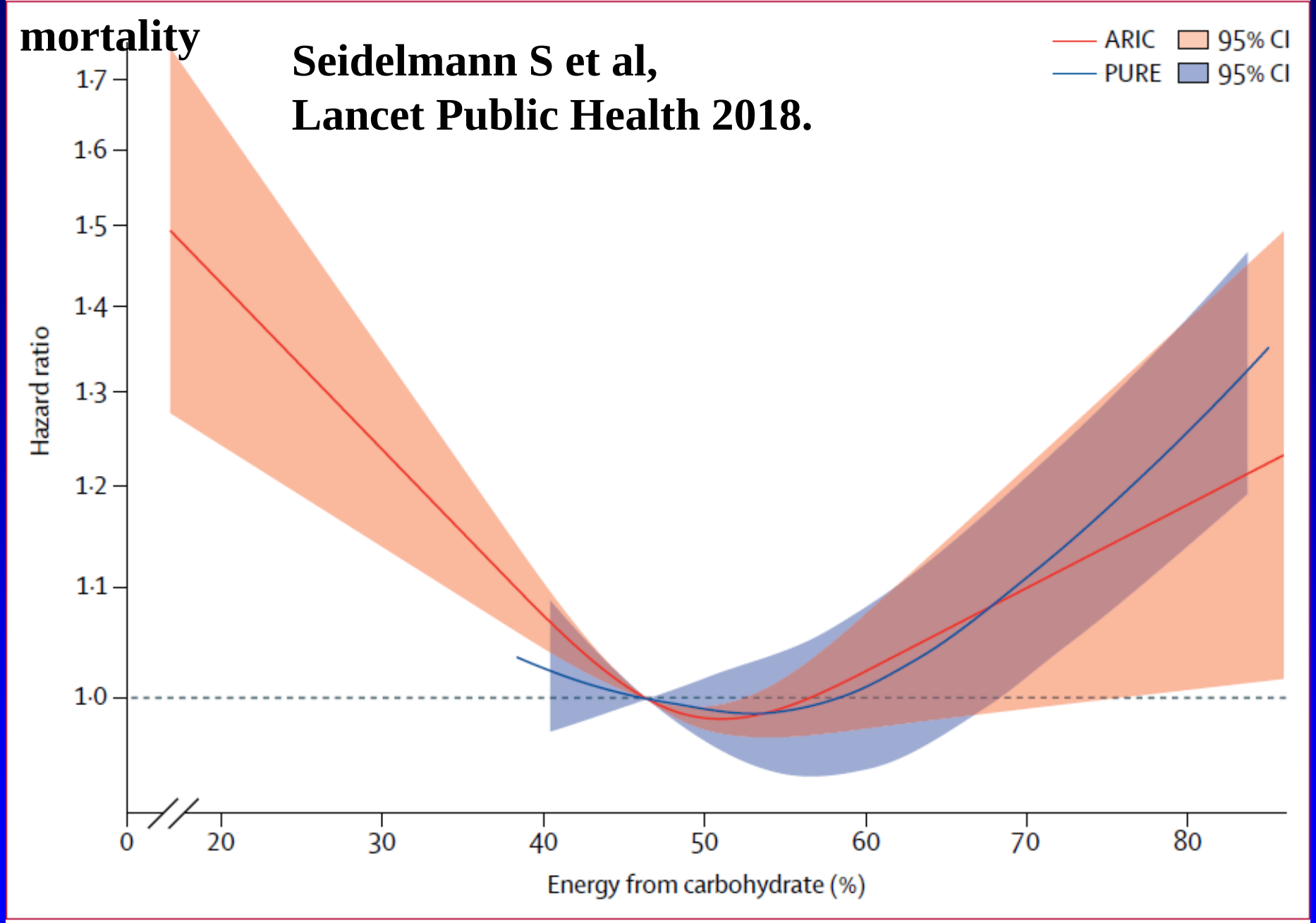


Figure 3: U-shaped association between percentage of energy from carbohydrate and all-cause mortality in the ARIC and PURE cohort studies

= multivariably adjusted

Saturated fatty acids (SFA)

Table 12 Healthy diet characteristics

• Saturated fatty acids to account for <10% of total energy intake, through replacement by polyunsaturated fatty acids.
• Trans unsaturated fatty acids: as little as possible, preferably no intake from processed food, and <1% of total energy intake from natural origin.

Saturated fatty acids (SFA): some answers from PURE ?

- does it matter what level of consumption we are talking about ?

absolutely, >>10% has been proven unsafe if PUFA/MUFA or unrefined CH replaces SFA

- does the food group containing SFA matter ?

absolutely, SFA in dairy appear safe

- does it matter what you replace SFA with ?

absolutely, refined CH may be even worse

European Heart Journal Advance Access published August 27, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw272

ESC/EAS GUIDELINES

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Alberico L. Catapano* (Chairperson) (Italy), Ian Graham* (Chairperson) (Ireland), Guy De Backer (Belgium), Olov Wiklund (Sweden), M. John Chapman (France), Heinz Drexel (Austria), Arno W. Hoes (The Netherlands), Catriona S. Jennings (UK), Ulf Landmesser (Germany), Terje R. Pedersen (Norway), Željko Reiner (Croatia), Gabriele Riccardi (Italy), Marja-Riita Taskinen (Finland), Lale Tokgozoglu (Turkey), W. M. Monique Verschuren (The Netherlands), Charalambos Vlachopoulos (Greece), David A. Wood (UK), Jose Luis Zamorano (Spain)

Anitschkow N, Chalatow S.
Über experimentelle Cholesterin-steatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse.
Zentrbl Allg Pathol Pathol Anat 1913;24:1–9.

Nikolai Anitschkow (1885 - 1964)

Table 9 **Recommendations for lipid analyses as treatment targets in the prevention of cardiovascular disease**

Recommendations	Class [a]	Level [b]	Ref [c]
LDL-C is recommended as the primary target for treatment.	I	A	64, 68
TC should be considered as a treatment target if other analyses are not available.	IIa	A	64, 123
Non-HDL-C should be considered as a secondary treatment target.	IIa	B	103
ApoB should be considered as a secondary treatment target, when available.	IIa	B	103, 124
HDL-C is not recommended as a target for treatment.	III	A	92, 93
The ratios apoB/apoA1 and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	B	103

	Magnitude of the effect	Level of evidence	References
Lifestyle interventions to reduce TC and LDL-C levels			
Reduce dietary trans fat	+++	A	136, 139
Reduce dietary saturated fat	+++	A	136, 137
Increase dietary fibre	++	A	140, 141
Use functional foods enriched with phytosterols	++	A	142, 143
Use red yeast rice supplements	++	A	144–146
Reduce excessive body weight	++	A	147, 148
Reduce dietary cholesterol	+	B	149
Increase habitual physical activity	+	B	150
Use soy protein products	+/-	B	151

Lifestyle interventions to reduce TG-rich lipoprotein levels			
Reduce excessive body weight	+++	A	147, 148
Reduce alcohol intake	+++	A	152, 153
Increase habitual physical activity	++	A	150, 154
Reduce total amount of dietary carbohydrate	++	A	148, 155
Use supplements of n-3 polyunsaturated fat	++	A	156, 157
Reduce intake of mono- and disaccharides	++	B	158, 159
Replace saturated fat with mono- or polyunsaturated fat	+	B	136, 137

Nutrition: 3 levels of analysis

Nutrients: as % Energy

Foods/Food groups:

Eating patterns

PLOS | ONE June 2016

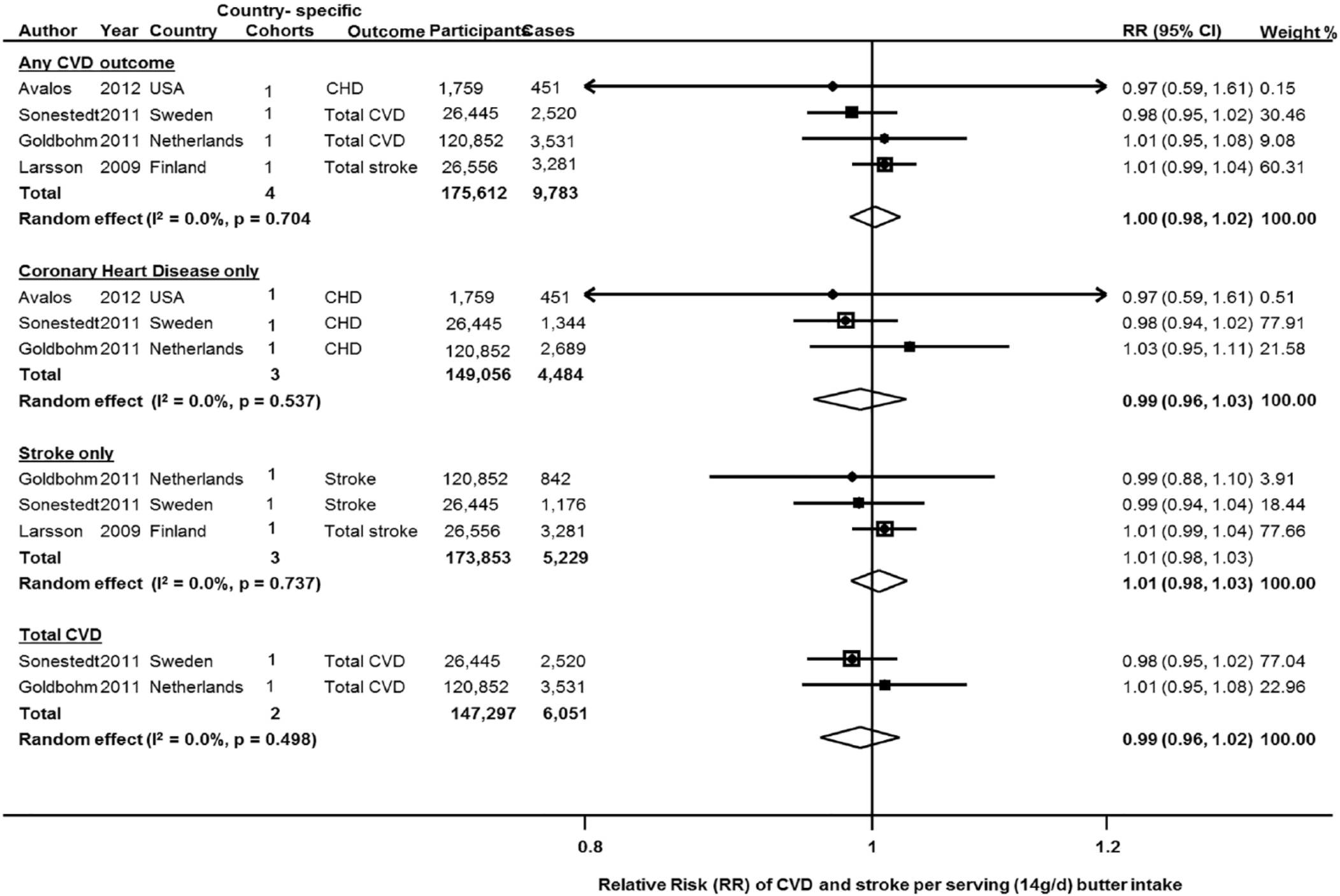
RESEARCH ARTICLE

Is Butter Back? A Systematic Review and Meta-Analysis of Butter Consumption and Risk of Cardiovascular Disease, Diabetes, and Total Mortality

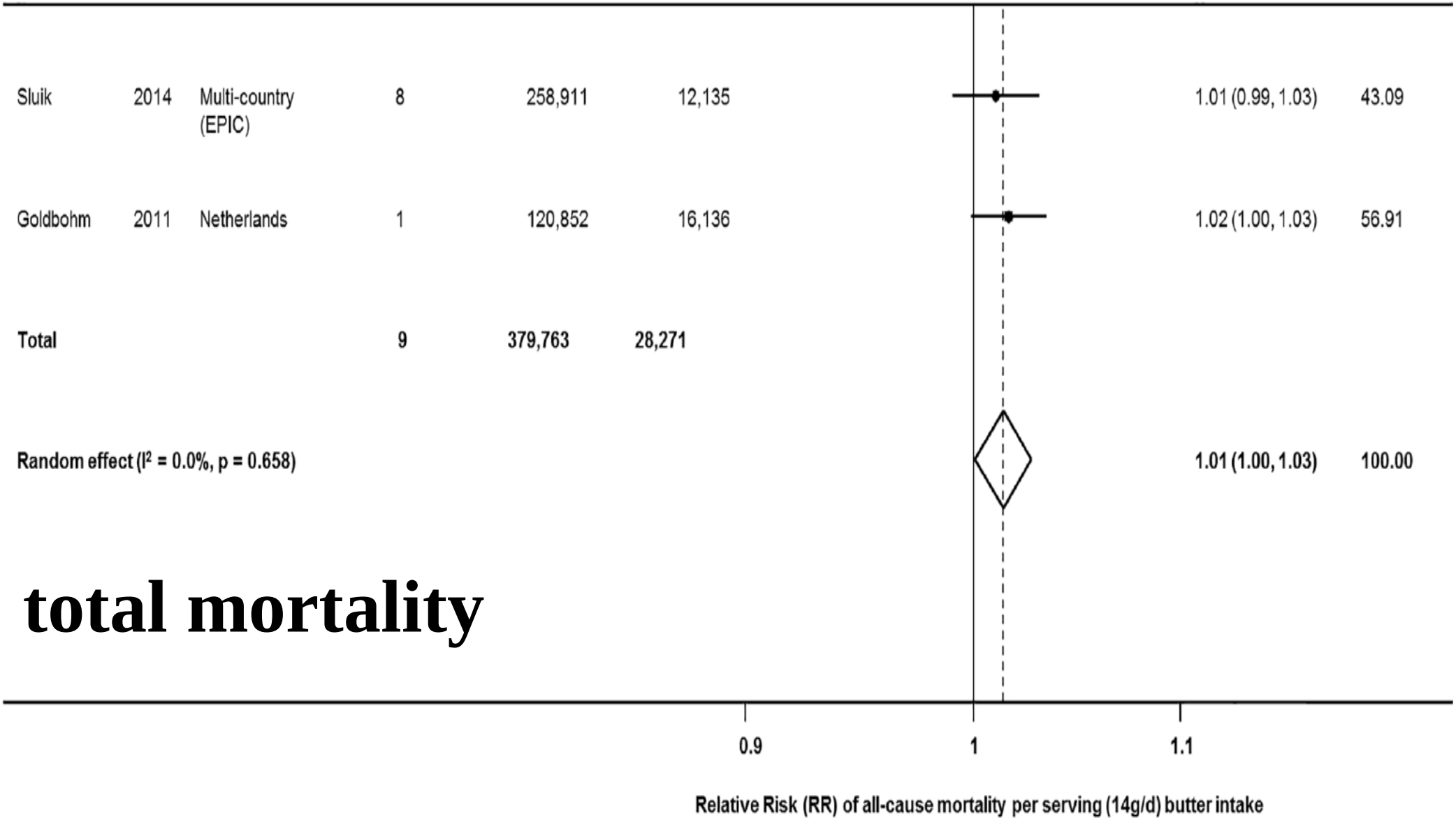
Laura Pimpin[1], Jason H. Y. Wu[2], Hila Haskelberg[2], Liana Del Gobbo[1,3], Dariush Mozaffarian[1]*

1 Friedman School of Nutrition Science & Policy, Tufts University, 150 Harrison Avenue, Boston, MA, United States of America, **2** The George Institute for Global Health, University of Sydney, Sydney, Australia, **3** Cardiovascular Medicine, Stanford School of Medicine, Palo Alto, CA, United States of America

CrossMark


Author Year Country Country- specific Cohorts Outcome Participants Cases RR (95% CI) Weight %
Any CVD outcome
Avalos 2012 USA 1 CHD 1,759 451 0.97 (0.59, 1.61) 0.15
Sonestedt 2011 Sweden 1 Total CVD 26,445 2,520 0.98 (0.95, 1.02) 30.46
Goldbohm 2011 Netherlands 1 Total CVD 120,852 3,531 1.01 (0.95, 1.08) 9.08
Larsson 2009 Finland 1 Total stroke 26,556 3,281 1.01 (0.99, 1.04) 60.31
Total 4 175,612 9,783
Random effect (I² = 0.0%, p = 0.704 1.00 (0.98, 1.02) 100.00
Coronary Heart Disease only
Avalos 2012 USA 1 CHD 1,759 451 0.97 (0.59, 1.61) 0.51
Sonestedt 2011 Sweden 1 CHD 26,445 1,344 0.98 (0.94, 1.02) 77.91
Goldbohm 2011 Netherlands 1 CHD 120,852 2,689 1.03 (0.95, 1.11) 21.58
Total 3 149,056 4,484
Random effect (I² = 0.0%, p = 0.537) 0.99 (0.96, 1.03) 100.00
Stroke only
Goldbohm 2011 Netherlands 1 Stroke 120,852 842 0.99 (0.88, 1.10) 3.91
Sonestedt 2011 Sweden 1 Stroke 26,445 1,176 0.99 (0.94, 1.04) 18.44
Larsson 2009 Finland 1 Total stroke 26,556 3,281 1.01 (0.99, 1.04) 77.66
Total 3 173,853 5,229 1.01 (0.98, 1.03)
Random effect (I² = 0.0%, p = 0.737) 1.01 (0.98, 1.03) 100.00
Total CVD
Sonestedt 2011 Sweden 1 Total CVD 26,445 2,520 0.98 (0.95, 1.02) 77.04
Goldbohm 2011 Netherlands 1 Total CVD 120,852 3,531 1.01 (0.95, 1.08) 22.96
Total 2 147,297 6,051
Random effect (I² = 0.0%, p = 0.498) 0.99 (0.96, 1.02) 100.00
0.8
1
1.2
Relative Risk (RR) of CVD and stroke per serving (14g/d) butter intake

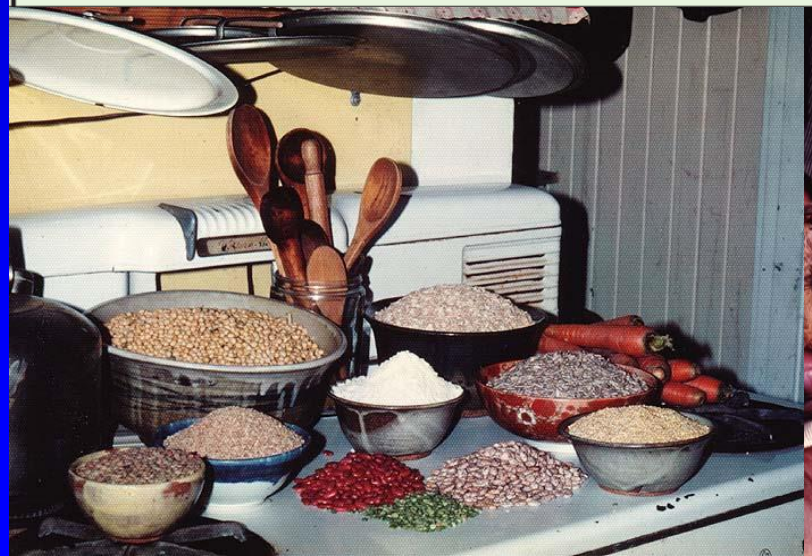
Author	Year	Country	Cohorts (Country-specific)	Participants	Cases	RR (95% CI)	Weight %
Sluik	2014	Multi-country (EPIC)	8	258,911	12,135	1.01 (0.99, 1.03)	43.09
Goldbohm	2011	Netherlands	1	120,852	16,136	1.02 (1.00, 1.03)	56.91
Total			**9**	**379,763**	**28,271**		
Random effect (I^2 = 0.0%, p = 0.658)						**1.01 (1.00, 1.03)**	**100.00**

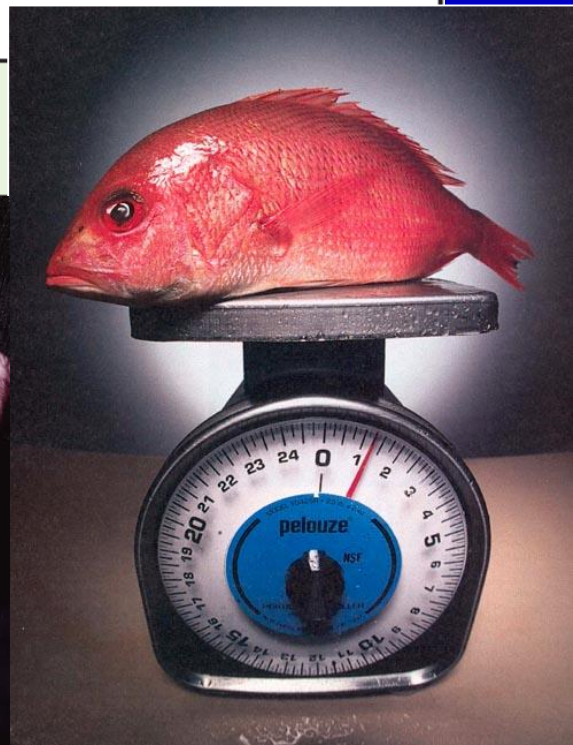


total mortality

Table 12 Healthy diet characteristics

- 30–45 g of fibre per day, preferably from wholegrain products.
- ≥200 g of fruit per day (2–3 servings).
- ≥200 g of vegetables per day (2–3 servings).
- Fish 1–2 times per week, one of which to be oily fish.
- 30 grams unsalted nuts per day.





Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study

*Victoria Miller, Andrew Mente, Mahshid Dehghan, Sumathy Rangarajan, Xiaohe Zhang, Sumathi Swaminathan, Gilles
Viswanathan Mohan, Scott Lear, Shrikant I Bangdiwala, Aletta E Schutte, Edelweiss Wentzel-Viljoen, Alvaro Avezum, Y
Khalid Yusoff, Noorhassim Ismail, Nasheeta Peer, Jephat Chifamba, Rafael Diaz, Omar Rahman, Noushin Mohammadif
Katarzyna Zatonska, Andreas Wielgosz, Afzalhussein Yusufali, Romaina Iqbal, Patricio Lopez-Jaramillo, Rasha Khatib, A
V Raman Kutty, Wei Li, Jiankang Liu, Xiaoyun Liu, Lu Yin, Koon Teo, Sonia Anand, Salim Yusuf, on behalf of the Prospect
Epidemiology (PURE) study investigators**

Lancet 2017; 390: 2037–49

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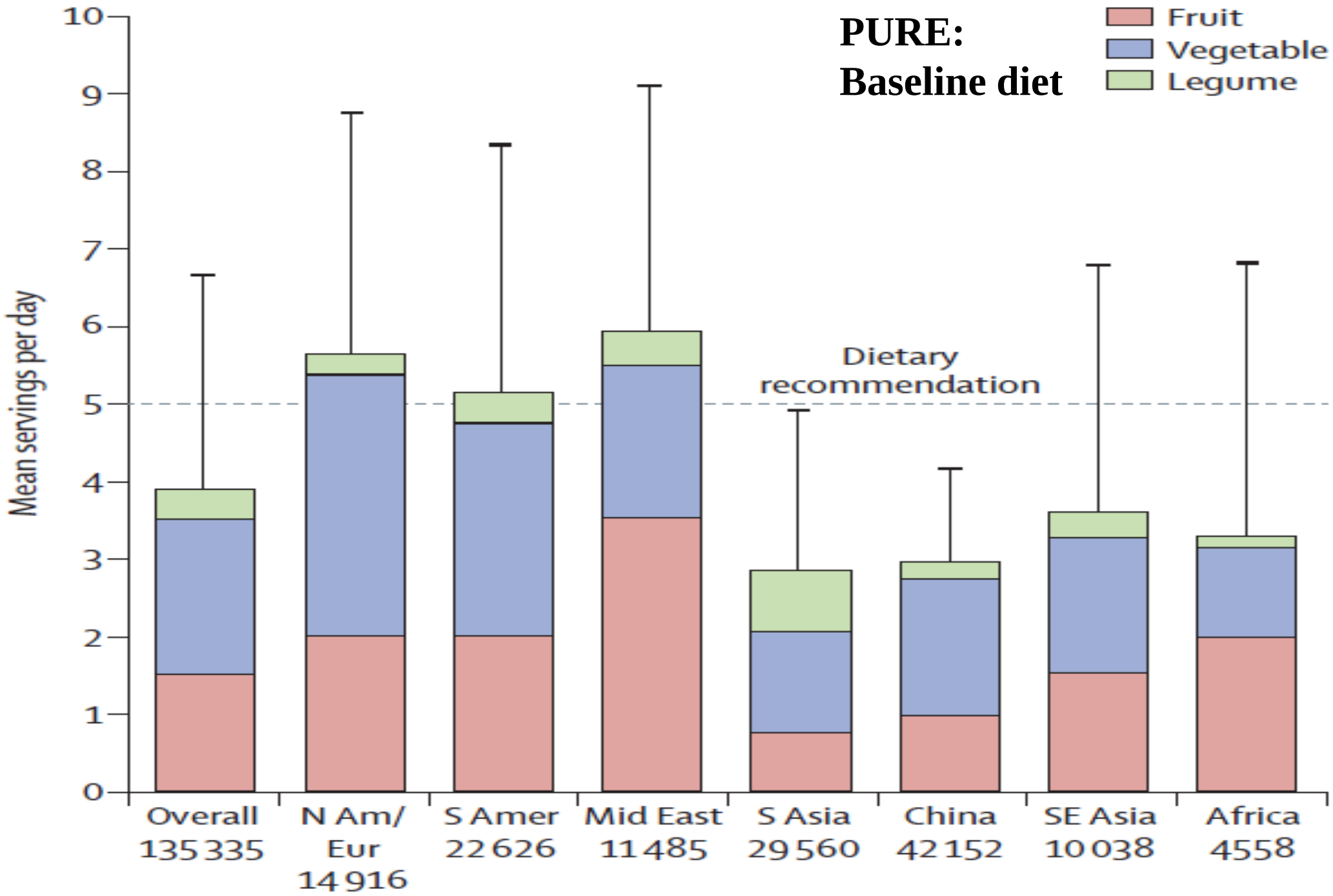
See Comment page 2017

Summary

Background The association between intake of fruits, vegetables, and legumes with cardiovascular disease and deaths has been investigated extensively in Europe, the USA, Japan, and China, but little or no data are available from the Middle East, South America, Africa, or south Asia.

Methods We did a prospective cohort study (Prospective Urban Rural Epidemiology [PURE] in 135 335 individuals aged


PURE:
Baseline diet
Fruit
Vegetable
Legume
Mean servings per day
0
1
2
3
4
5
6
7
8
9
10
Dietary recommendation
Overall 135 335
N Am/ Eur 14 916
S Amer 22 626
Mid East 11 485
S Asia 29 560
China 42 152
SE Asia 10 038
Africa 4558

Fruits, vegetables and legumes: multivariable adjustment weakens the beneficial effect

A

	n	Events	HR (95% CI)	p_{trend}
Major cardiovascular disease				
<3 per week	37 849	1646	1·00 (1·00–1·00)	
3 per week to <1 per day	31 929	1160	0·94 (0·87–1·02)	
1 to <2 per day	32 850	1034	0·89 (0·81–0·97)	
2 to <3 per day	14 706	419	0·87 (0·77–0·98)	
>3 per day	18 001	525	0·79 (0·70–0·90)	0·0002

unadjusted

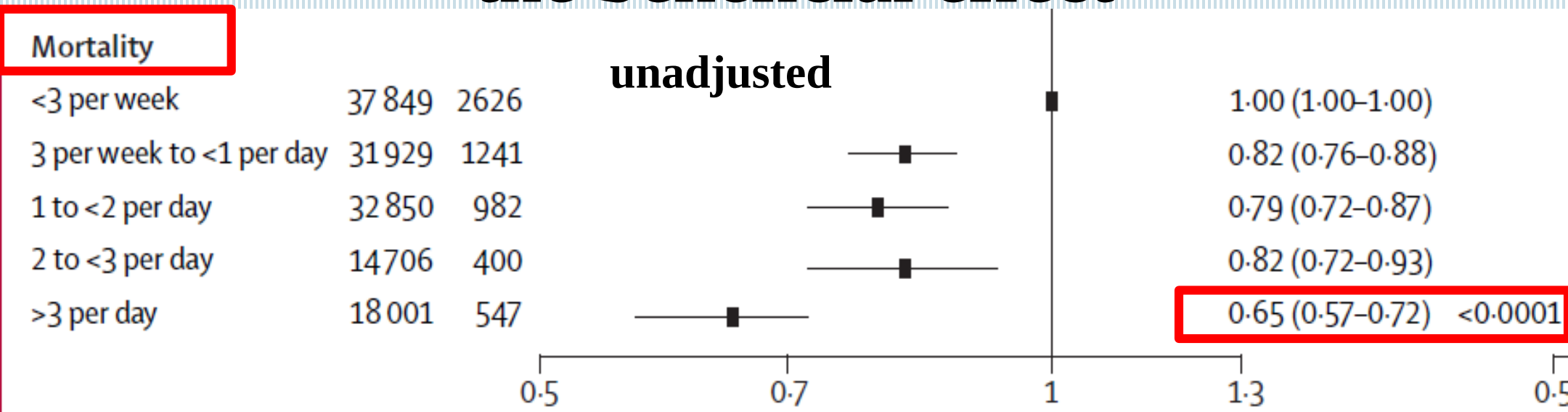
A

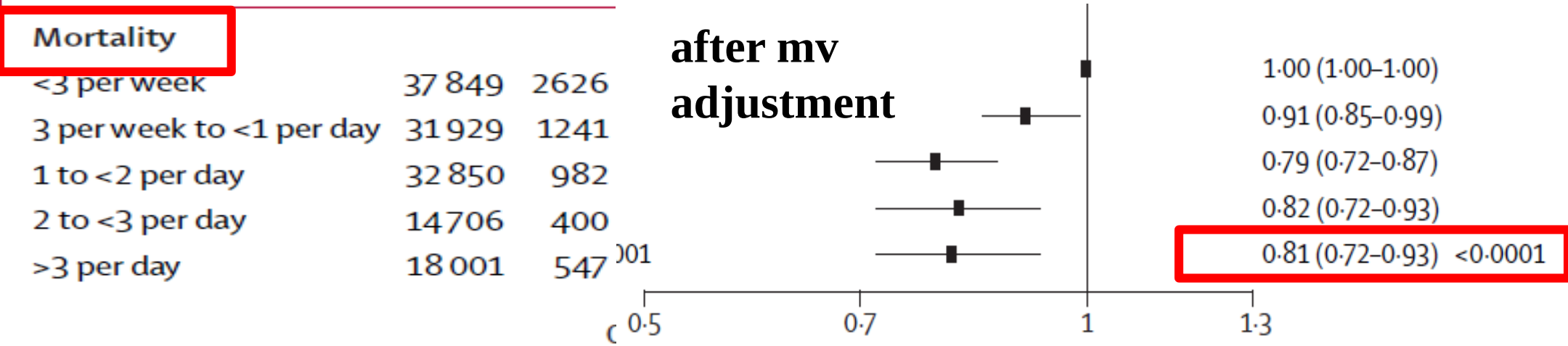
B

	n	Events	HR (95% CI)	p_{trend}
Major cardiovascular disease				
<3 per week	37 849	1646	1·00 (1·00–1·00)	
3 per week to <1 per day	31 929	1160	0·98 (0·90–1·07)	
1 to <2 per day	32 850	1034	0·96 (0·87–1·06)	
2 to <3 per day	14 706	419	0·96 (0·85–1·09)	
>3 per day	18 001	525	0·89 (0·77–1·01)	0·11

after mv adjustment

Fruits, vegetables and legumes: multivariable adjustment weakens the beneficial effect





Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study

*Mahshid Dehghan, Andrew Mente, Sumathy Rangarajan, Patrick Sheridan, Viswanathan Mohan, Romaina Iqbal, Rajeev Gupta, Scott Lear, Edelweiss Wentzel-Viljoen, Alvaro Avezum, Patricio Lopez-Jaramillo, Prem Mony, Ravi Prasad Varma, Rajesh Kumar, Jephat Chifamba, Khalid F Alhabib, Noushin Mohammadifard, Aytekin Oguz, Fernando Lanas, Dorota Rozanska, Kristina Bengtsson Bostrom, Khalid Yusoff, Lungiswa P Tsolkile, Antonio Dans, AfzalHussein Yusufali, Andres Orlandini, Paul Poirier, Rasha Khatib, Bo Hu, Li Wei, Lu Yin, Ai Deeraili, Karen Yeates, Rita Yusuf, Noorhassim Ismail, Dariush Mozaffarian, Koon Teo, Sonia S Anand, Salim Yusuf, on behalf of the Prospective Urban Rural Epidemiology (PURE) study investigators**

Summary

Background Dietary guidelines recommend minimising consumption of whole-fat dairy products, as they are a source of saturated fats and presumed to adversely affect blood lipids and increase cardiovascular disease and mortality. Evidence for this contention is sparse and few data for the effects of dairy consumption on health are available from

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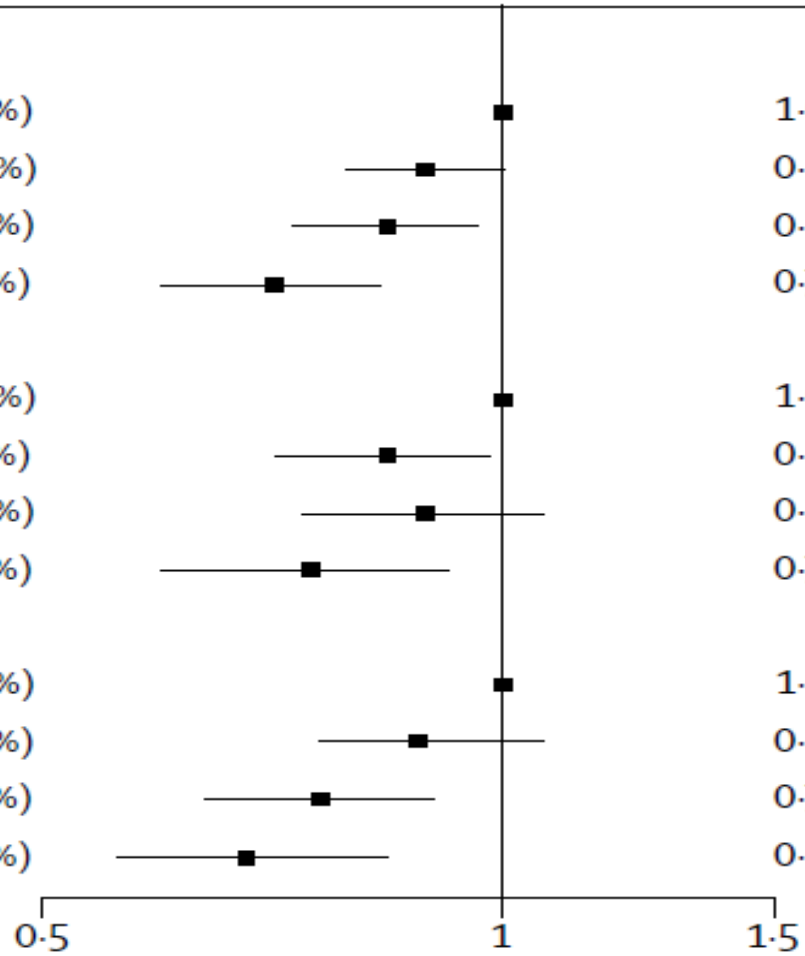
S0140-6736(18)21812-9

A

Whole-fat dairy

	n	Events	HR (95% CI)	p_{trend}
Composite outcome				0·0001
<0·5 servings per day	12 399	968 (7·8%)	1·00 (1·00–1·00)	
0·5–1 servings per day	12 023	789 (6·6%)	0·89 (0·79–1·00)	
1–2 servings per day	8853	519 (5·9%)	0·84 (0·73–0·96)	
>2 servings per day	7552	430 (5·7%)	0·71 (0·60–0·83)	
Total mortality				0·01
<0·5 servings per day	12 399	547 (4·4%)	1·00 (1·00–1·00)	
0·5–1 servings per day	12 023	374 (3·1%)	0·84 (0·71–0·98)	
1–2 servings per day	8853	317 (3·6%)	0·89 (0·74–1·06)	
>2 servings per day	7552	248 (3·3%)	0·75 (0·60–0·92)	
Major cardiovascular disease				0·0001
<0·5 servings per day	12 399	624 (5·0%)	1·00 (1·00–1·00)	
0·5–1 servings per day	12 023	538 (4·5%)	0·88 (0·76–1·06)	
1–2 servings per day	8853	308 (3·5%)	0·76 (0·64–0·90)	
>2 servings per day	7552	278 (3·7%)	0·68 (0·56–0·84)	



Median intake per day (IQR)

	<0·5 serving	0·5–1 servings	1–2 servings	>2 servings
Only whole-fat dairy	0·2 g (0·10–0·34)	0·9 g (0·81–0·98)	1·4 g (1·14–1·78)	2·9 g (2·45–3·96)

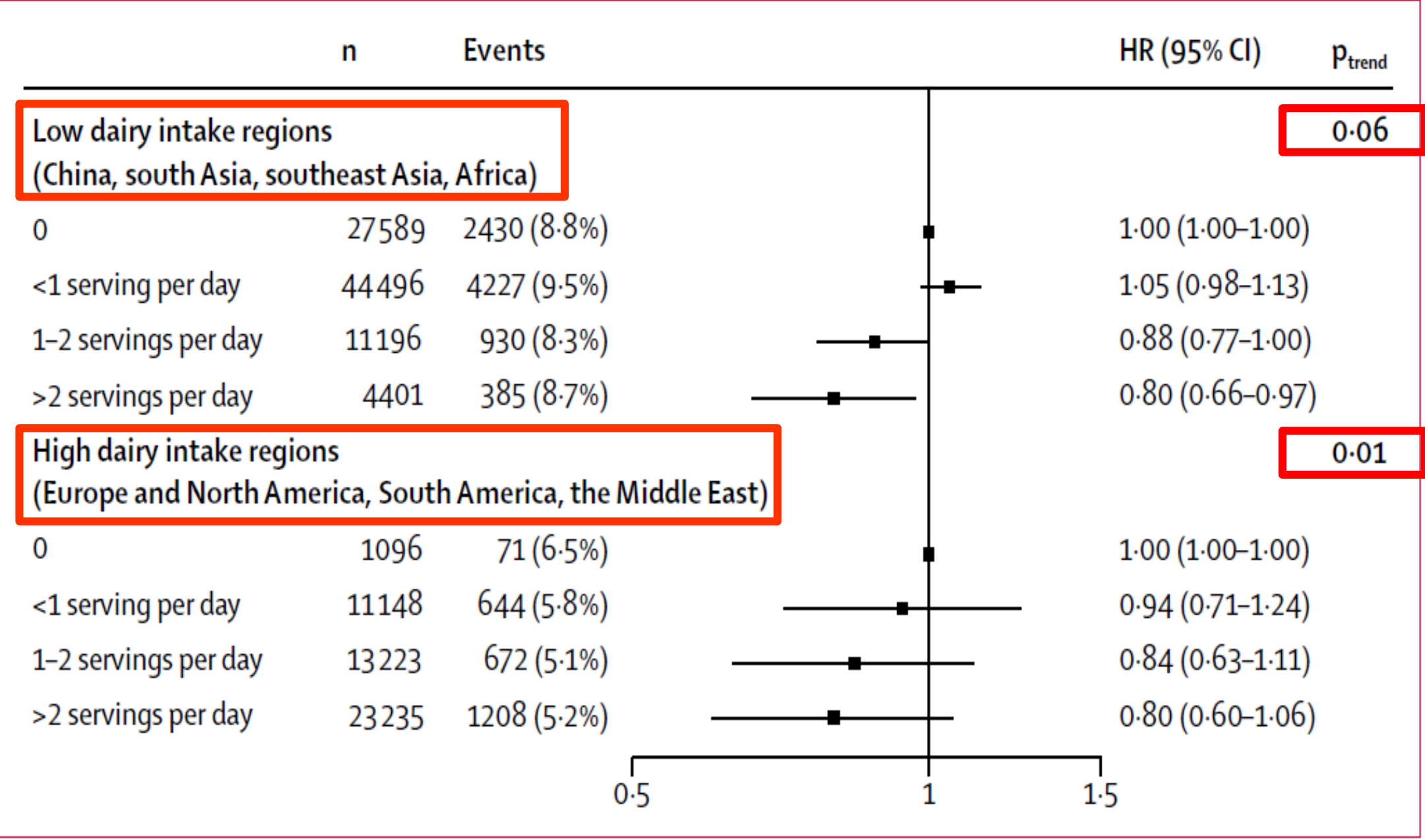


Figure 3: Association between total dairy intake with risk of the composite outcome and cardiovascular disease in low and high dairy intake regions

Nutrition: 3 levels of analysis

Nutrients: as % Energy

Foods/Food groups:

Eating patterns

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts

R. Estruch, E. Ros, J. Salas-Salvadó, M.-I. Covas, D. Corella, F. Arós, E. Gómez-Gracia, V. Ruiz-Gutiérrez, M. Fiol, J. Lapetra, R.M. Lamuela-Raventos, L. Serra-Majem, X. Pintó, J. Basora, M.A. Muñoz, J.V. Sorlí, J.A. Martínez, M. Fitó, A. Gea, M.A. Hernán, and M.A. Martínez-González, for the PREDIMED Study Investigators*

NEJM 2018 (republished)

ABSTRACT

BACKGROUND

Observational cohort studies and a secondary prevention trial have shown inverse associations between adherence to the Mediterranean diet and cardiovascular risk.

PREDIMED: Study Design

- multicenter RCT in Spain, open. 3 diets: MD with EVOO, MD with mixed nuts, vs. control diet („low fat“).
- n=7.447 (57% Women), 55-80 years, no manifest CVD, but high cv risk.
- median follow-up of 4,8 years
- primary endpoint: triple MACE

Table 2. Baseline Characteristics of the Participants, According to Intervention Group.*

Characteristic	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)
Female sex — no. (%)†	1493 (58.7)	1326 (54.0)	1463 (59.7)
Age — yr†	67.0±6.2	66.7±6.1	67.3±6.3
Race or ethnic group — no. (%)‡			
White, from Europe	2470 (97.1)	2390 (97.4)	2375 (96.9)
Hispanic, from Central or So	35 (1.4)	29 (1.2)	38 (1.6)
Other	38 (1.5)	35 (1.4)	37 (1.5)
Smoking status — no. (%)			
Never smoked	1572 (61.8)	1465 (59.7)	1527 (62.3)
Former smoker	618 (24.3)	634 (25.8)	584 (23.8)
Current smoker	353 (13.9)	355 (14.5)	339 (13.8)
Body-mass index†§	29.9±3.7	29.7±3.8	30.2±4.0
Waist circumference — cm	100±10	100±10	101±11
Waist-to-height ratio†¶	0.63±0.06	0.63±0.06	0.63±0.07
Hypertension — no. (%)‖	2088 (82.1)	2024 (82.5)	2050 (83.7)
Type 2 diabetes — no. (%)†**	1282 (50.4)	1143 (46.6)	1189 (48.5)
Dyslipidemia — no. (%)††	1821 (71.6)	1799 (73.3)	1763 (72.0)

Medication:
ACE-I 49%,
Statins 41%,
ASS 19%

Table 1. Summary of Dietary Recommendations to Participants in the Mediterranean-Diet Groups and the Control-Diet Group.

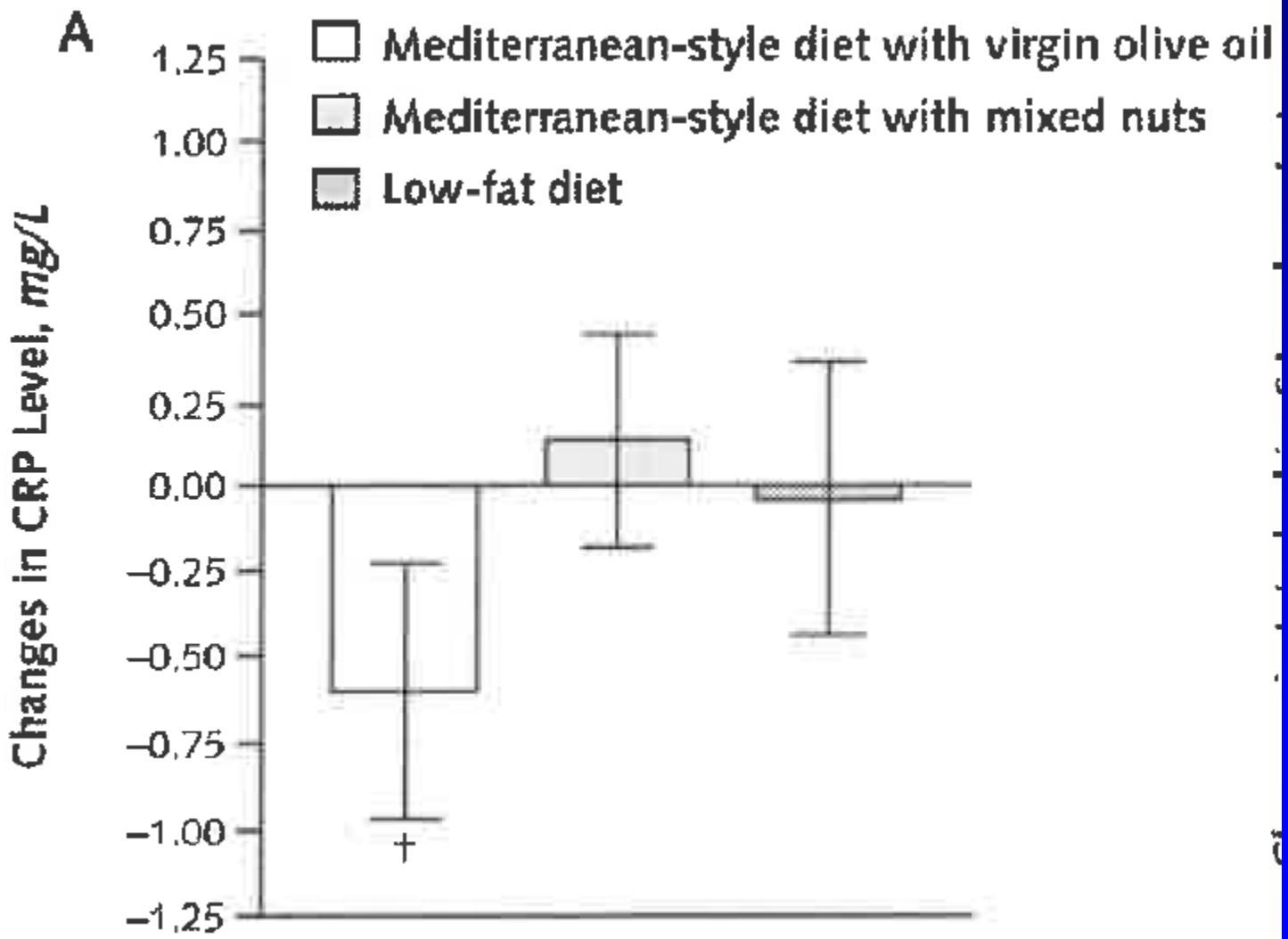
Food	Goal
Mediterranean diet	
Recommended	
Olive oil*	≥4 tbsp/day
Tree nuts and peanuts†	≥3 servings/wk
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Fish (especially fatty fish), seafood	≥3 servings/wk
Legumes	≥3 servings/wk
Sofrito‡	≥2 servings/wk
White meat	Instead of red meat
Wine with meals (optionally, only for habitual drinkers)	≥7 glasses/wk
Discouraged	
Soda drinks	<1 drink/day
Commercial bakery goods, sweets, and pastries§	<2 servings/wk
Spread fats	<1 serving/day
Red and processed meats	<1 serving/day

Table 4. Changes in Adiposity, Blood Pressure, and Cardiovascular Risk Factors*

Ann Int Med 2006; 145:1-11

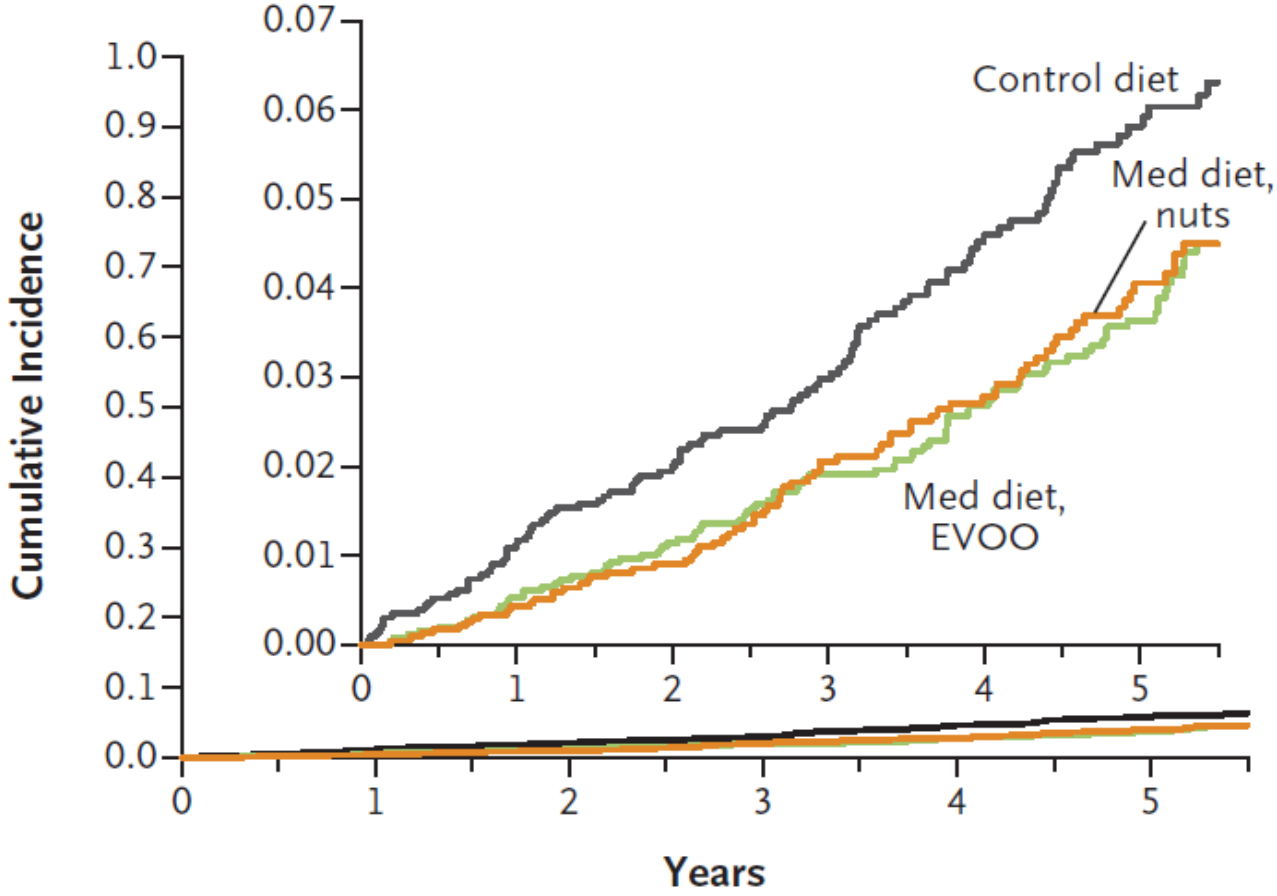
Variable	Mean Changes from Baseline at 3 mo (95% CI)			Mediterranean Diet with Olive Oil vs. Low-Fat Diet		Mediterranean Diet with Nuts vs. Low-Fat Diet	
	Mediterranean Diet with Virgin Olive Oil (n = 257)	Mediterranean Diet with Mixed Nuts (n = 257)	Low-Fat Diet (n = 256)	Mean (95% CI) Between-Group Difference†	P Value	Mean (95% CI) Between-Group Difference†	P Value
Weight, *kg*	−0.19 (−0.46 to 0.07)	−0.26 (−0.59 to 0.08)	−0.24 (−0.48 to 0.01)	0.01 (−0.39 to 0.42)	0.96	0.01 (−0.40 to 0.43)	0.95
BMI, *kg/m²*	−0.12 (−0.24 to 0.06)	−0.09 (−0.24 to 0.05)	−0.21 (−0.38 to −0.05)	0.09 (−0.12 to 0.29)	0.40	0.15 (−0.06 to 0.35)	0.165
Waist, *cm*	−0.82 (−1.80 to 0.14)	−0.29 (−0.96 to 0.37)	−0.37 (−1.20 to 0.44)	−0.57 (−1.60 to 0.61)	0.37	0.12 (−1.00 to 1.30)	0.84
Systolic BP, *mm Hg*	−4.8 (−6.7 to −2.7)	−6.5 (−8.7 to −4.3)	0.64 (−1.30 to 2.30)	−5.9 (−8.7 to −3.1)	<0.001	−7.1 (−10.0 to −4.1)	<0.001
Diastolic BP, *mm Hg*	−2.5 (−3.5 to −1.5)	−3.6 (−4.7 to −2.5)	−0.85 (−1.79 to 0.09)	−1.60 (−3.00 to −0.01)	0.048	−2.6 (−4.2 to 1.0)	0.001
Fasting glucose level					0.017		0.039
mmol/L	−0.21 (−0.41 to −0.01)	−0.14 (−0.31 to 0.03)	0.19 (−0.06 to 0.04)	−0.39 (−0.72 to −0.07)		−0.30 (−0.58 to −0.01)	
mg/dL	−3.8 (−7.4 to −0.2)	−2.5 (−5.5 to 0.5)	3.5 (−1.0 to 8.0)	−7.0 (−13.0 to −1.3)		−5.4 (−10.5 to −0.2)	
Fasting insulin level, *pmol/L*‡	−9.7 (−15.3 to −3.8)	−9.7 (−15.9 to −3.5)	6.5 (−3.8 to 16.7)	−16.7 (−27.1 to −0.4)	0.001	−20.4 (−31.9 to −9.7)	<0.001
HOMA index‡	−0.53 (−0.83 to −0.23)	−0.54 (−0.82 to −0.26)	0.32 (−0.15 to 0.79)	−0.91 (−1.40 to −0.46)	<0.001	−1.1 (−1.6 to −0.55)	<0.001
Total cholesterol level					0.26		0.040
mmol/L	−0.10 (−0.21 to 0.01)	−0.13 (−0.22 to −0.04)	0.02 (−0.10 to 0.14)	−0.09 (−0.25 to 0.07)		−0.16 (−0.31 to −0.01)	
mg/dL	−3.90 (−8.10 to 0.35)	−5.0 (−8.6 to −1.4)	0.74 (−3.80 to 5.30)	−3.5 (−9.5 to 2.6)		−6.20 (−12.00 to −0.28)	
LDL cholesterol level					0.177		0.119
mmol/L	−0.15 (−0.25 to −0.05)	−0.10 (−0.19 to −0.01)	−0.15 (−0.12 to 0.09)	−0.10 (−0.25 to 0.04)		−0.09 (−0.23 to 0.05)	
mg/dL	−5.8 (−9.8 to −1.8)	−3.90 (−7.30 to −0.39)	0.56 (−4.60 to 3.50)	−3.9 (−9.5 to 1.7)		−3.4 (−8.9 to 2.1)	
HDL cholesterol level					<0.001		0.006
mmol/L	0.62 (0.08 to 0.04)	0.020 (0.002 to 0.050)	−0.01 (−0.03 to 0.01)	0.08 (0.04 to 0.10)		0.04 (0.01 to 0.07)	
mg/dL	2.4 (3.1 to 1.6)	0.94 (0.10 to 1.80)	−0.37 (−1.20 to 0.40)	2.9 (1.7 to 4.0)		1.60 (0.45 to 2.70)	

Anti-inflammatory effects in PREDIMED



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

Med diet, EVOO: hazard ratio, 0.69 (95% CI, 0.53–0.91)
Med diet, nuts: hazard ratio, 0.72 (95% CI, 0.54–0.95)

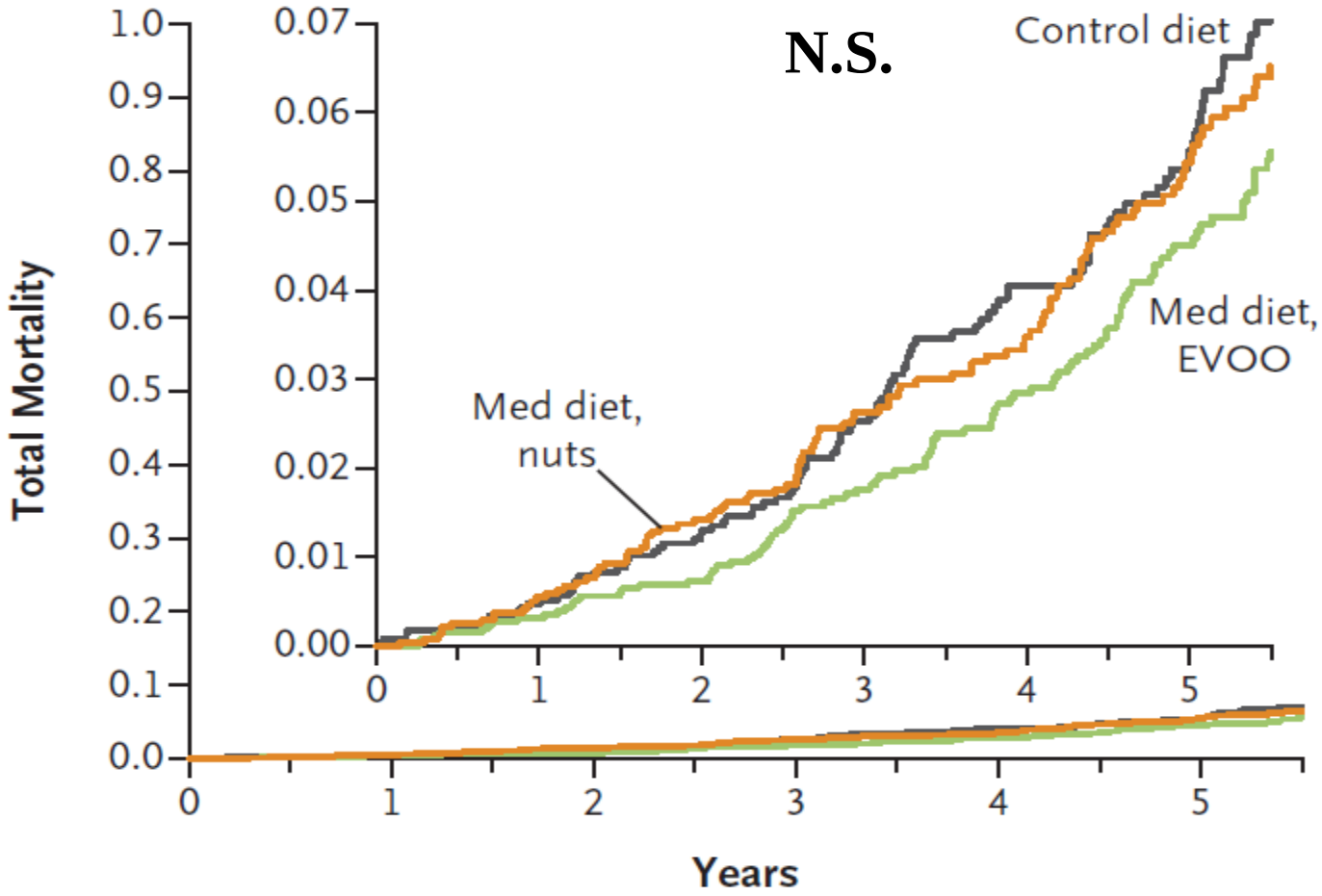


No. at Risk

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

Med diet, EVOO: hazard ratio, 0.90 (95% CI, 0.69–1.18)
Med diet, nuts: hazard ratio, 1.12 (95% CI, 0.86–1.47)



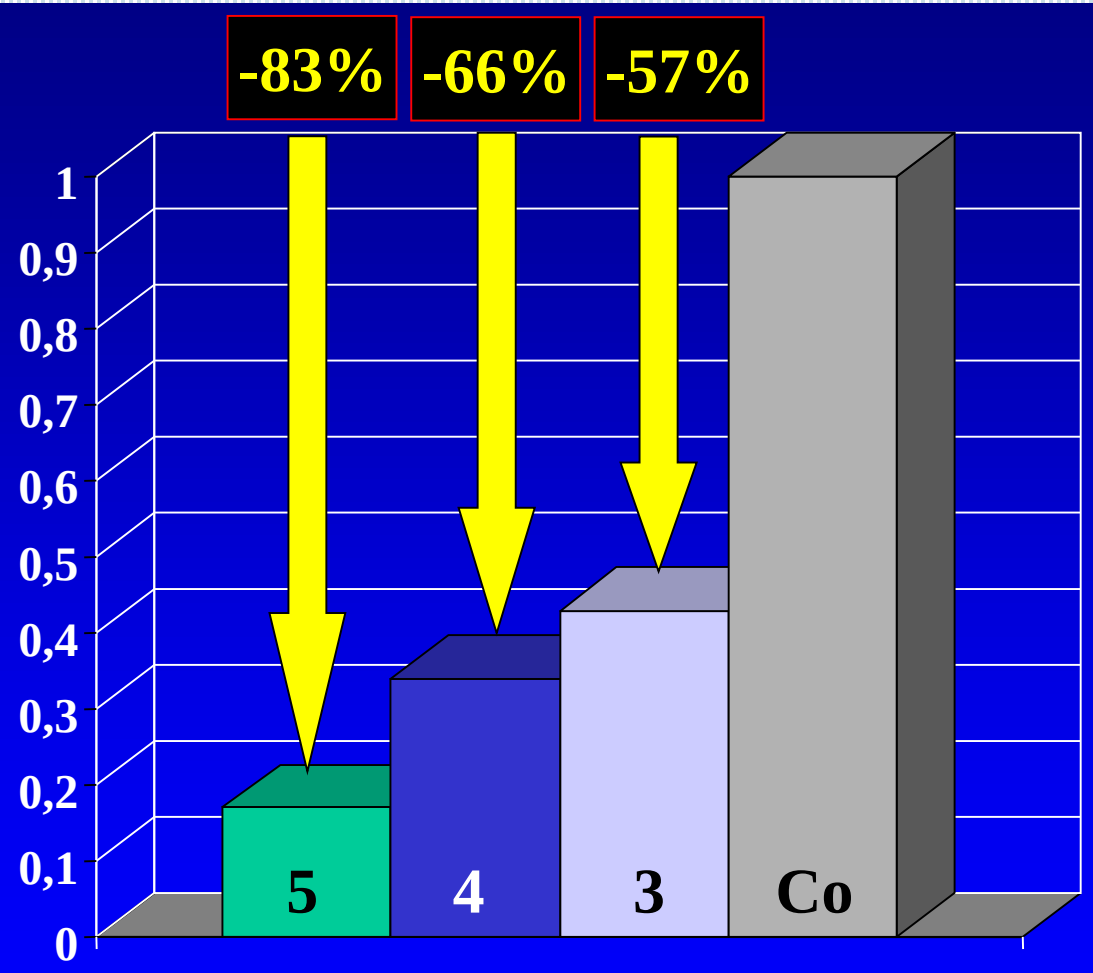
No. at Risk

Control diet	2450	2270	2027	1586	1272	949
Med diet, EVOO	2543	2486	2324	1991	1691	1310
Med diet, nuts	2454	2345	2097	1662	1395	1037

PREDIMED: Conclusions

- first positive RCT of mediterranean diet vs. control diet
- less stroke may be due to BP ↓
- unclear which component responsible (food-synergy ?)
- additional positive effects on ↓ of AF and ↓ of invasive BC (HR-positive)
- currently the best established eating pattern

Primary prevention of CHD by lifestyle 1



5 Anti-RF
4 Anti-RF
3 Anti-RF
Controls

n=84,129

5 Anti-RF:

- ♥ not smoking
- ♥ BMI<25
- ♥ >3 drinks/w
- ♥ >30 min „exercise“/d
- ♥ healthy diet

Stampfer et al., NEJM 2000; 343:16

Primary prevention of CHD by lifestyle 2

6 factors of a healthy diet:

- ♥ soluble fibre (whole grain)(>4,2g)
- ♥ n-3 Fettsäuren (>0,1% Energy)
- ♥ Folic acid (>525 µg/d)
- ♥ high P/S-ratio (>0,43)
- ♥ low *trans*-Fettsäuren (<1,56% Energy)
- ♥ low glycemic index (GL<723 U/d)

Stampfer et al., NEJM 2000; 343:16

Interne
Bregenz

and AKS

Thank you !

FASS DIR EIN HERZ

SCREENING UND REGISTER FÜR
FAMILIÄRE HYPERCHOLESTERINÄMIE