Dietary Fats and Cardiovascular Disease in PURE: A More Complete Picture

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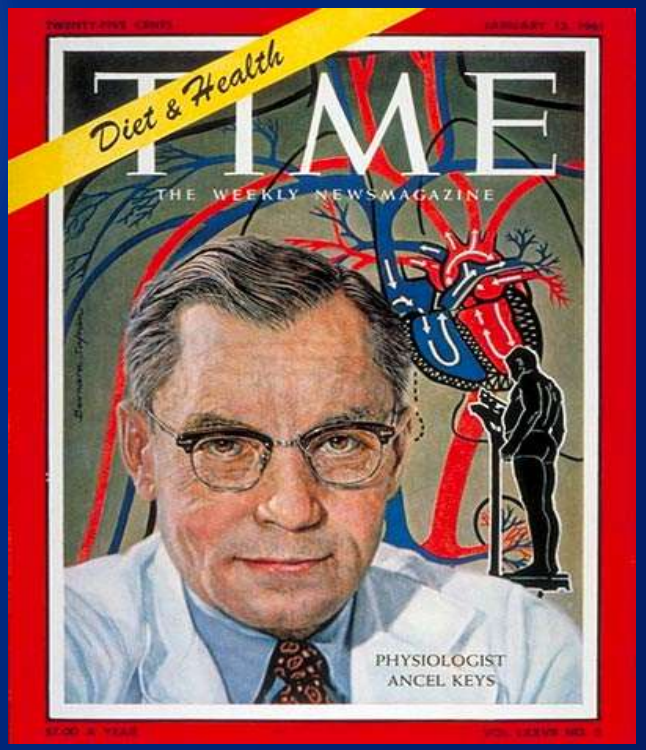
Disclosures

I have no disclosures

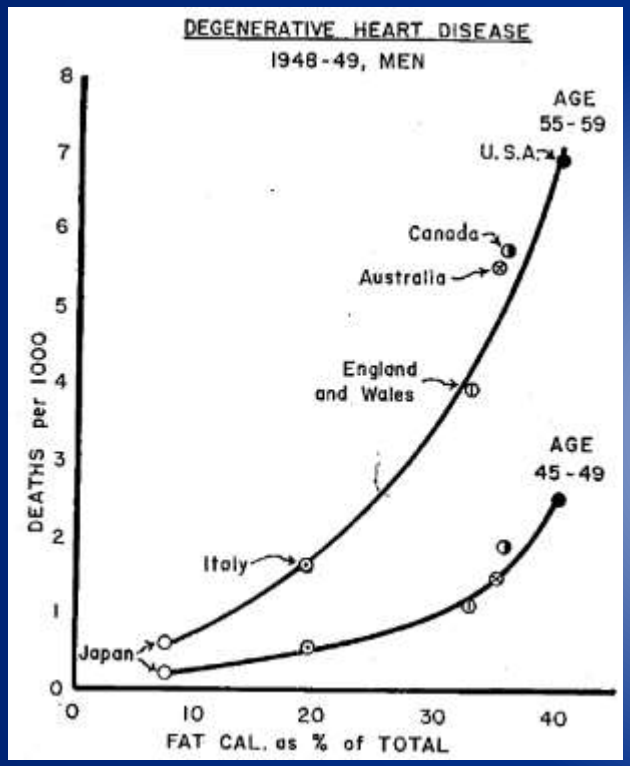
The Diet - Heart Hypothesis: Conventional Wisdom

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



The Original Evidence: Ecological Data from 6 countries

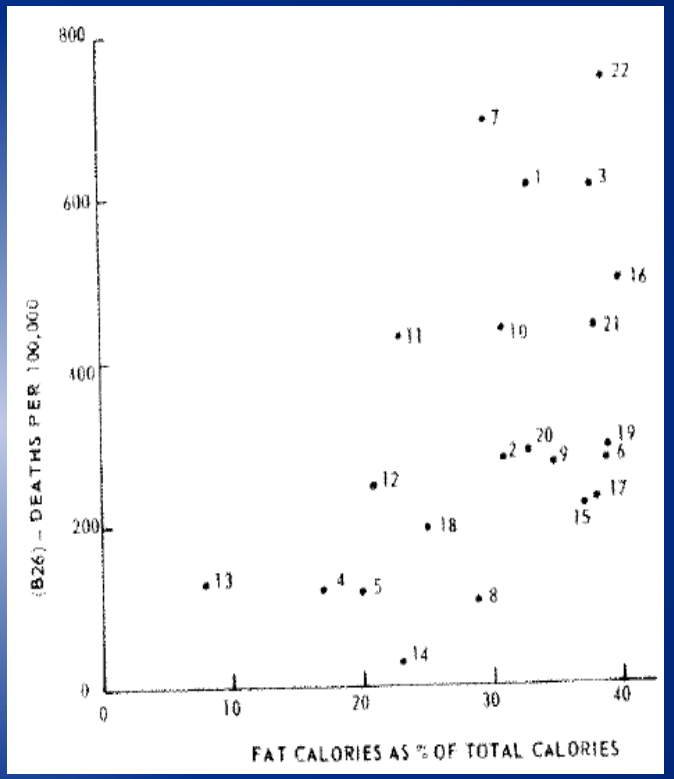
6 Countries [1]



Deaths from heart disease

Fat intake, % of energy

22 Countries [2]



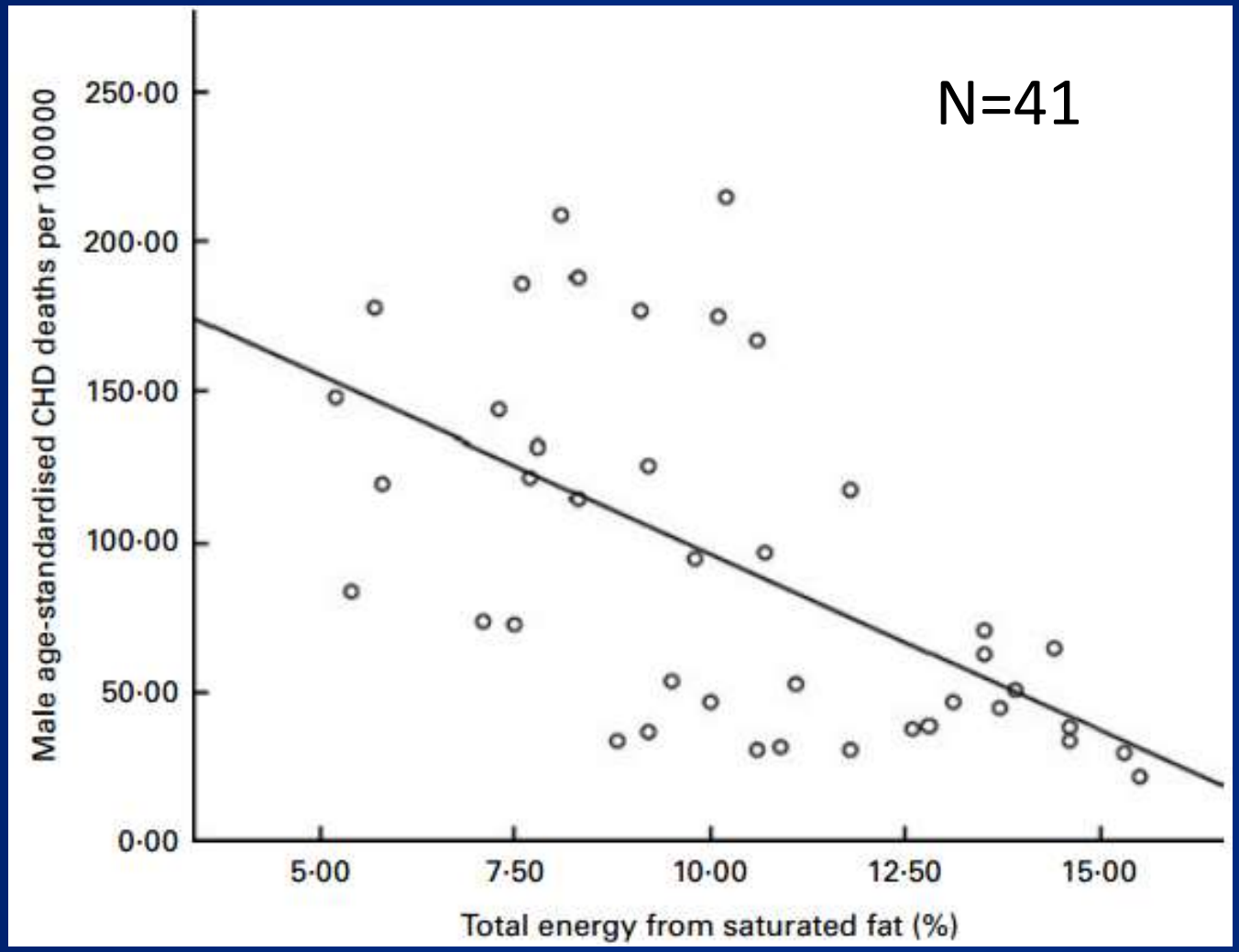
Fat intake, % of energy

[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 (%)

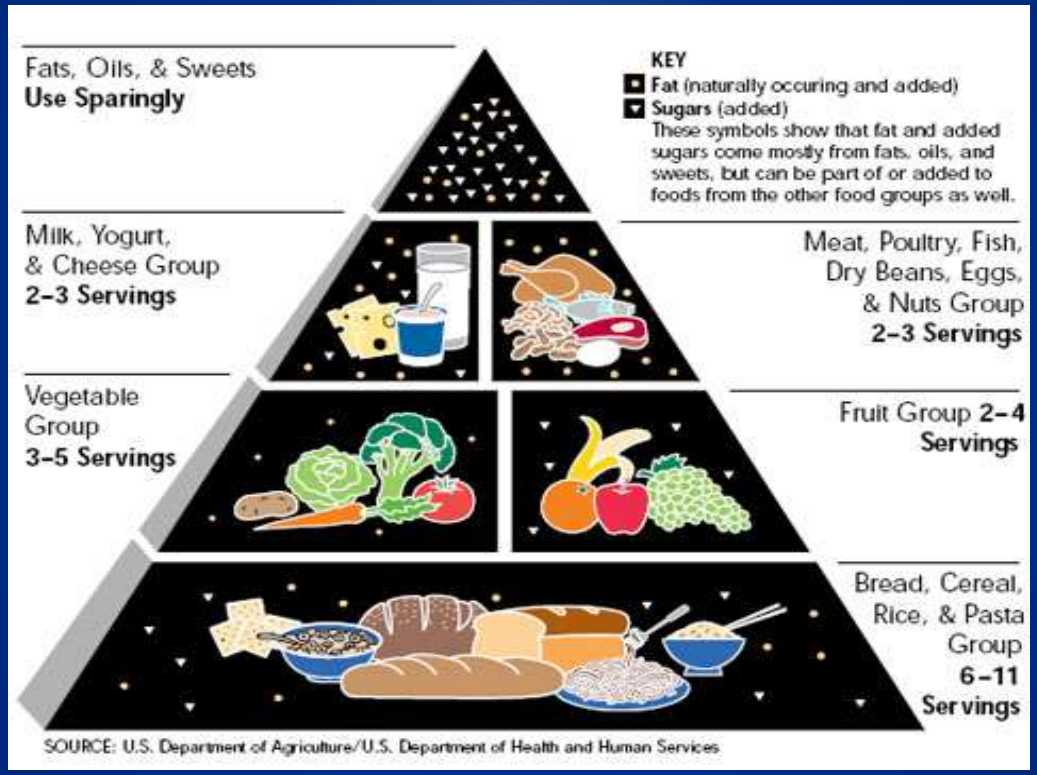
$R^2 = 0.339$, $P<0.01$

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

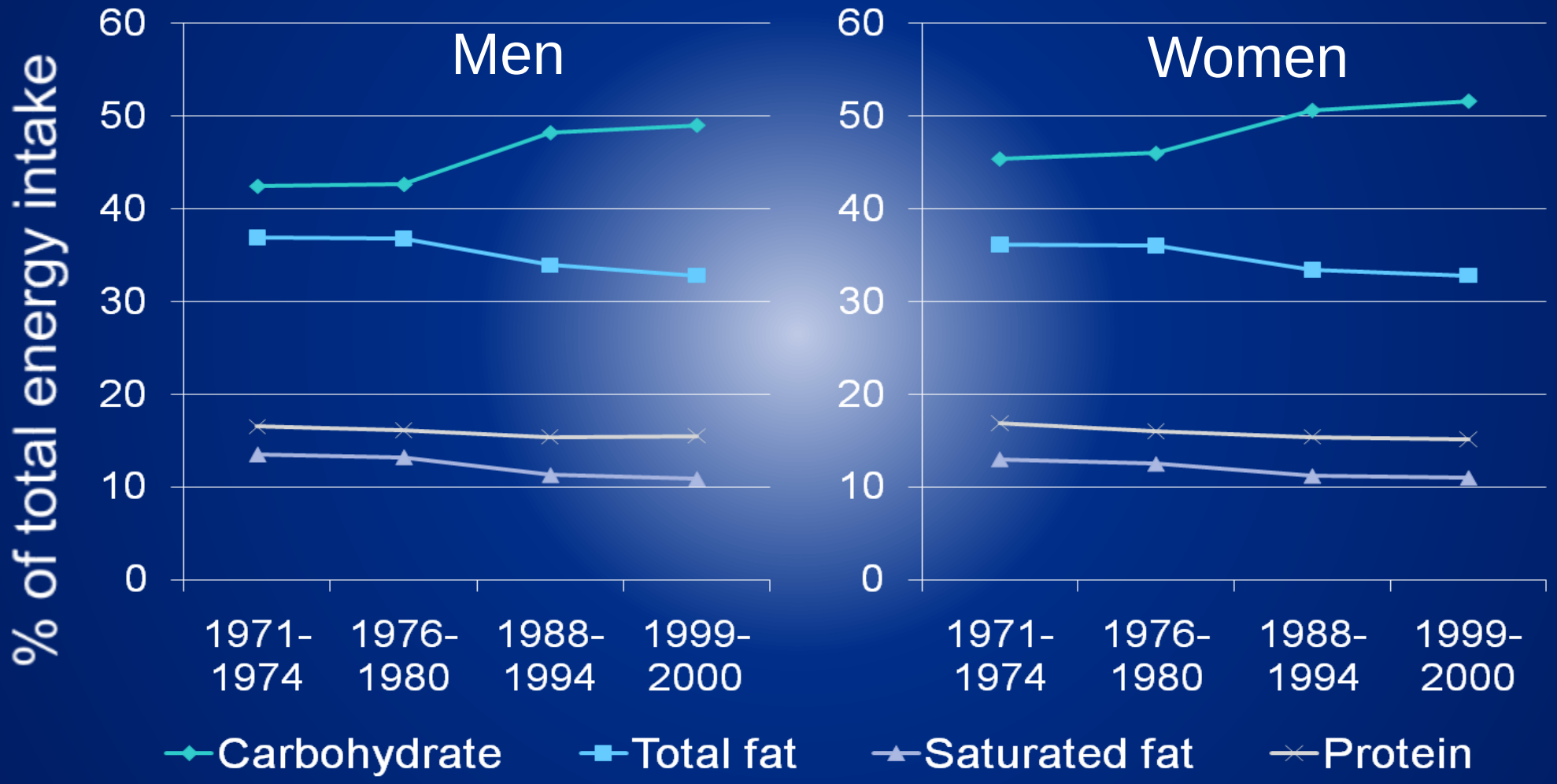
† age-standardized rates

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

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



Trends in macronutrient intake, United States, 1971-2000



http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5304a3.htm

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%**

Macronutrient composition of some popular diets

	Low-carb	Mediterranean	Low-fat
	Eat all you want of meat, dairy and veggies	Veggies, olive oil, nuts, seafood, wine, fruit, some meat/dairy	Whole grains & veggies; no meat
Examples	Atkins	Med. Diet	Ornish
Carbohydrates	10%	50%	70%
Fat	55-65%	35%	10%
Protein	20-30%	15%	20%

Average intake of saturated fat, by age and sex (National Diet & Nutrition Survey 2008/2009–2010/2011)

	Men		Women	
	19-64 y	≥65 y	19-64 y	≥65 y
SFA (g/d)	28.8	29.3	22.0	23.2
% total energy	12.0	13.6	12.0	13.7

Mean intake is ~12-13% of total energy in both sexes

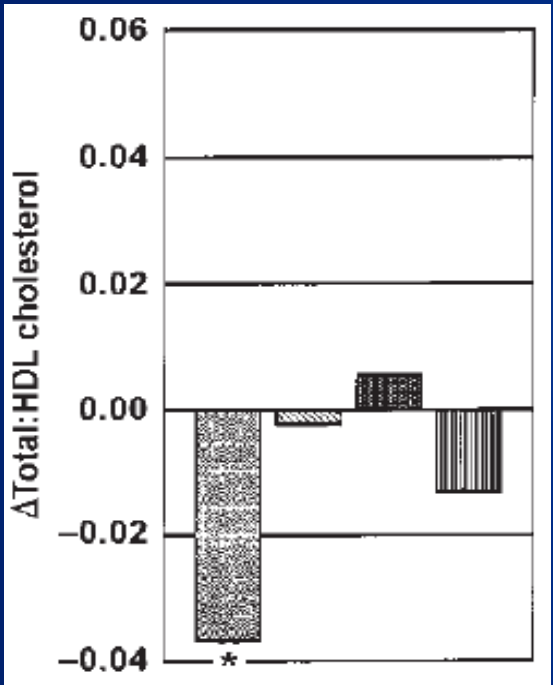
Markey O, et al. 2014. Nutr Bulletin

- 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

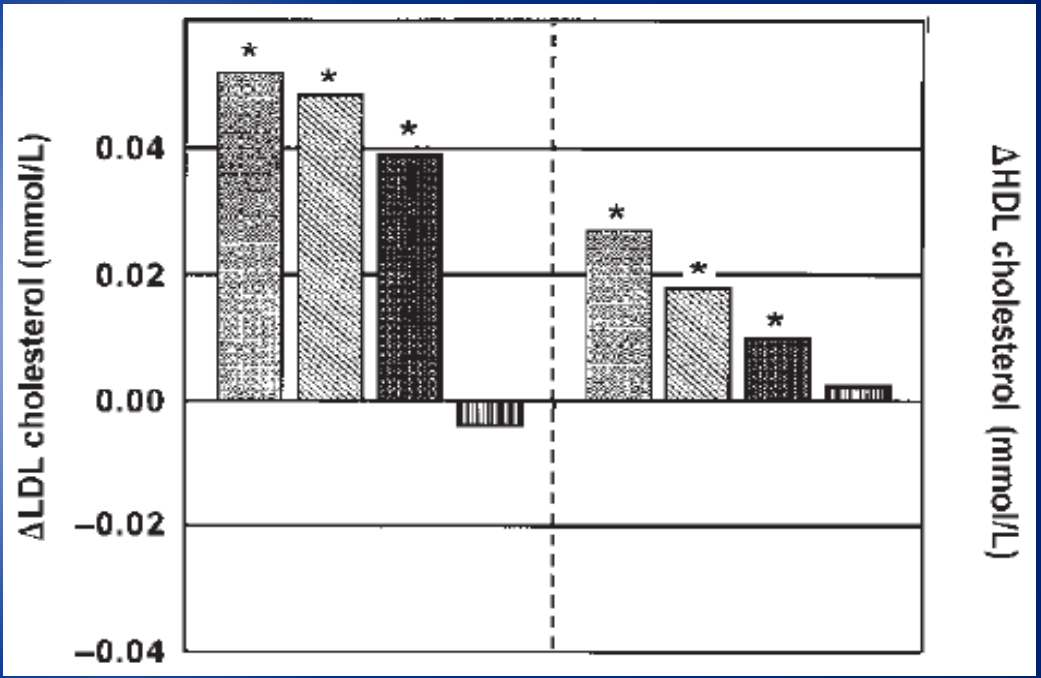
Saturated fat and CV risk markers

Effect of saturated fatty acids on serum cholesterol †

Total Chol: HDL-C



LDL-C HDL-C



Lauric acid | Myristic acid | Palmitic acid | Stearic acid

† when carbohydrates replaced by 1% isoenergetically with SFAs

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

Low-fat vs low-carb on metabolic parameters: Meta-analysis of RCTs with >8wks follow-up

	Bayesian Analysis		
	Between Group Differences [a]		
	Mean (95% CrI	Probability LoCHO Superior	Probability LoFAT Superior
BMI kg/m^2	-0.6 (-1.5, 0.3)	90.1%	
Cholesterol (mg/dl)	9.6 (2.7, 16.4)		99.7%
HDL-C (mg/dl)	5.4 (3.5, 7.2)	> 99.9%	
LDL-C (mg/dl)	9.1 (3.0, 15.2)		99.8%
TG (mg/dl)	-29.8 (-37.0, -22.6)	> 99.9%	
Systolic BP (mmHg)	-2.3 (-4.4, -0.2)	98.2%	

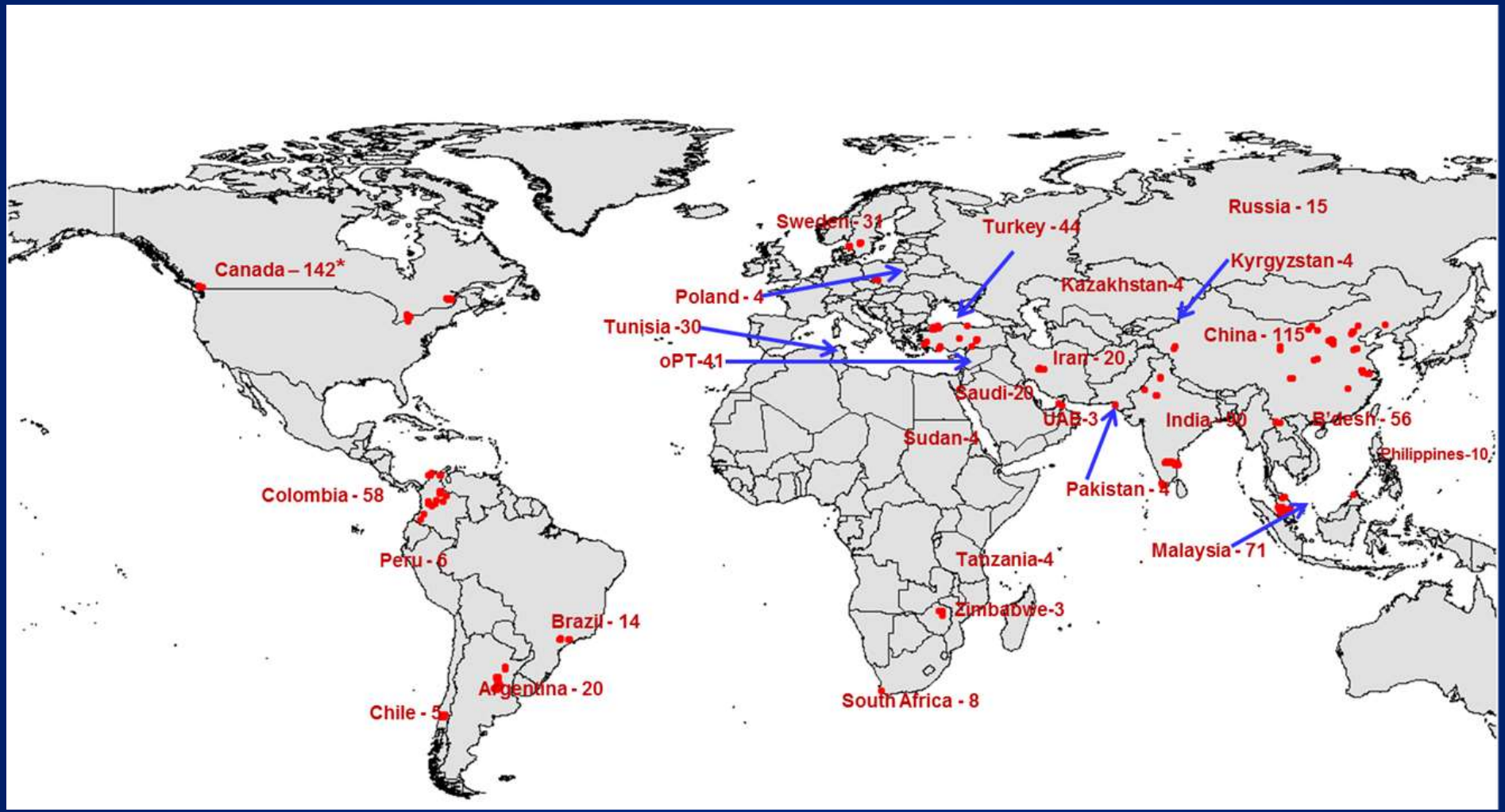
Sackner-Bernstein et al. PLoS One. 2015;10:e0139817

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

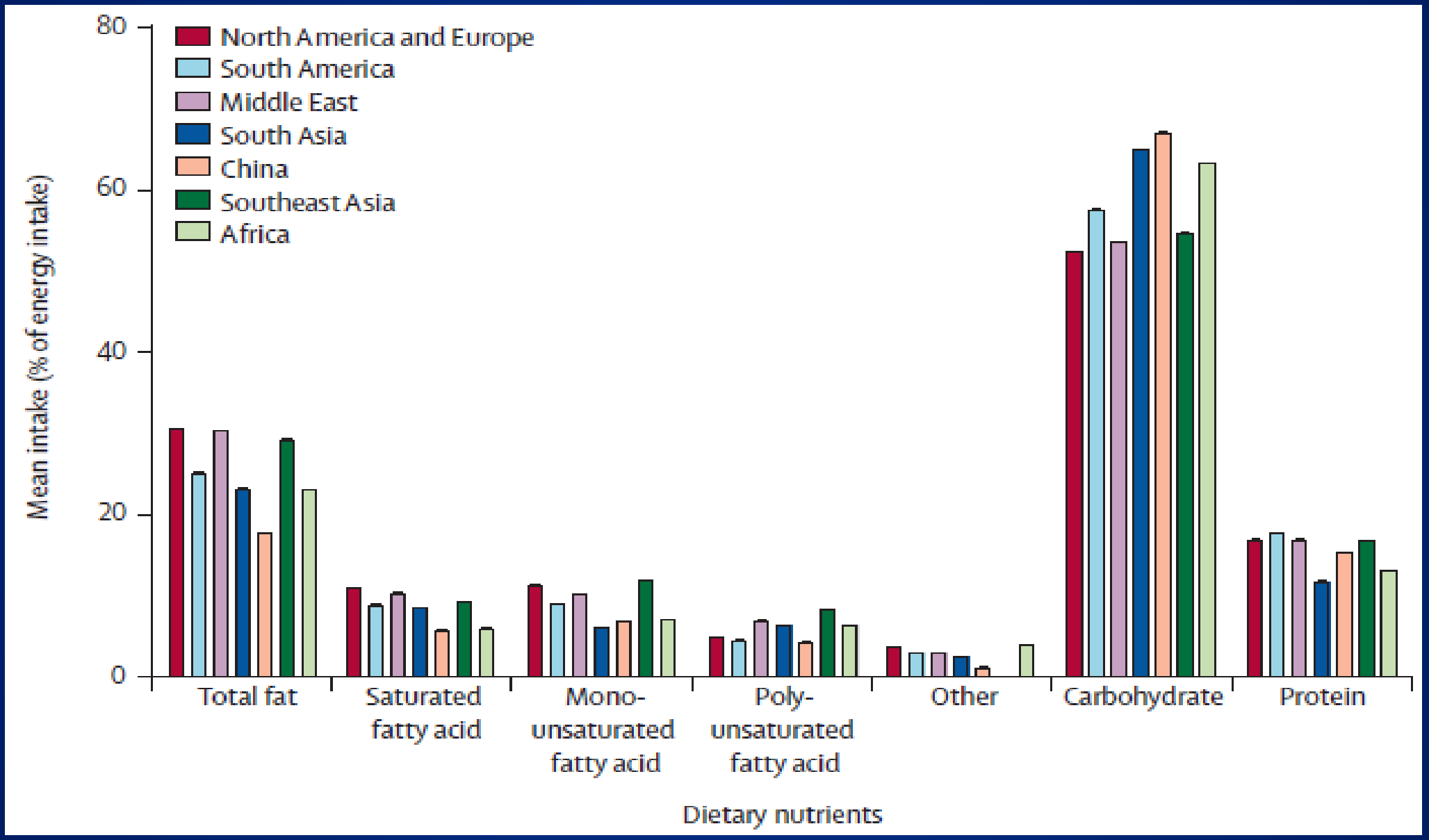
Outcomes: Blood pressure (n=125,287);

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

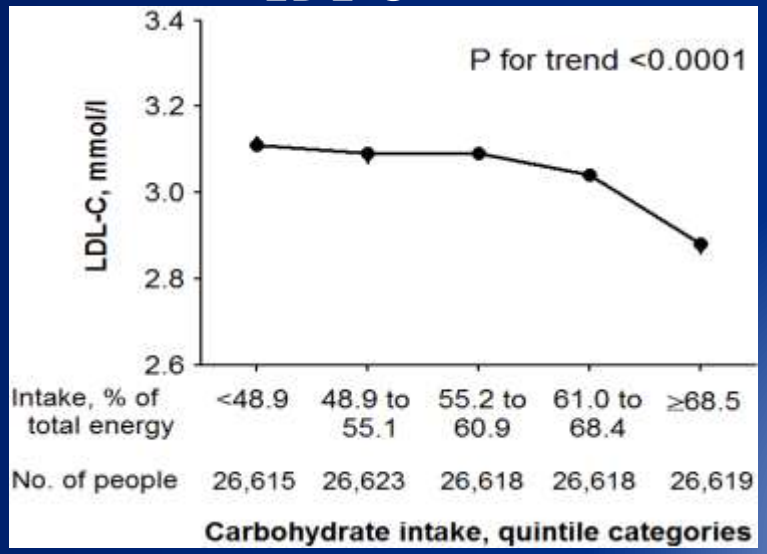
Mean intake of nutrients by geographic region (n=125,287) †



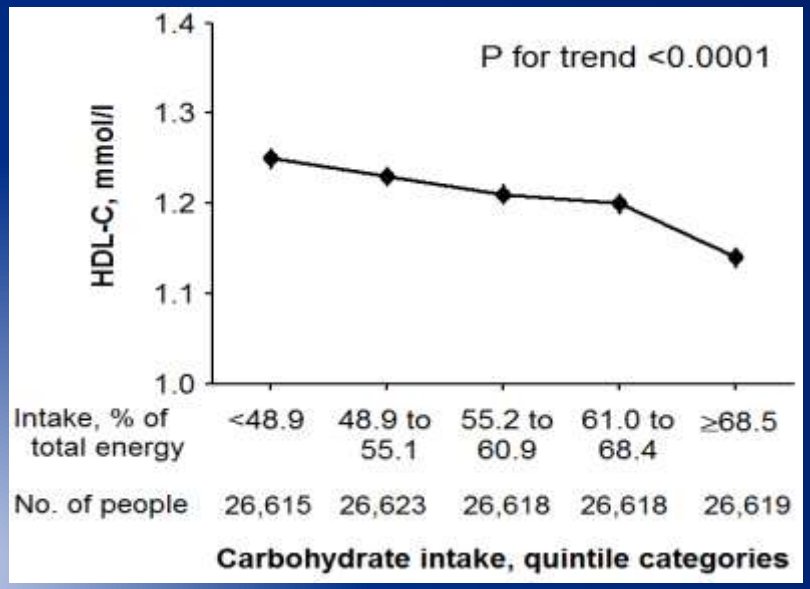
† Means are adjusted for age, sex, and centre.

Carbohydrate intake versus risk markers

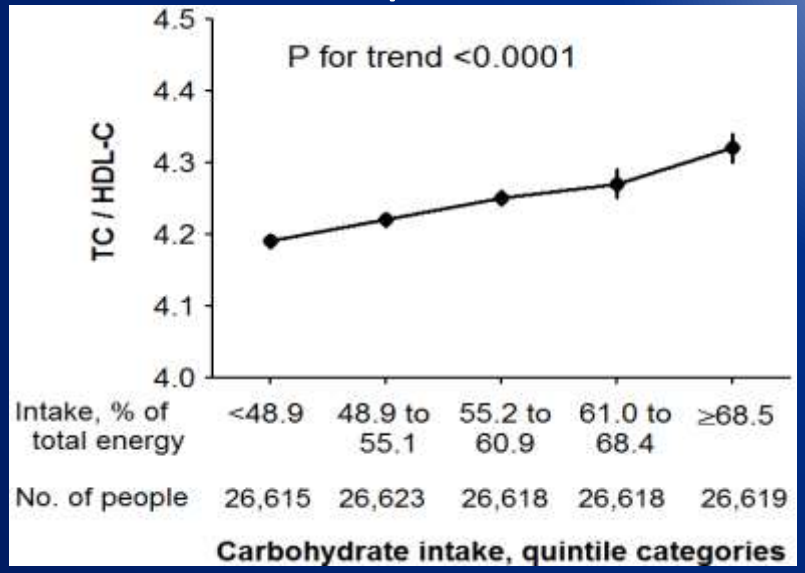
LDL-C



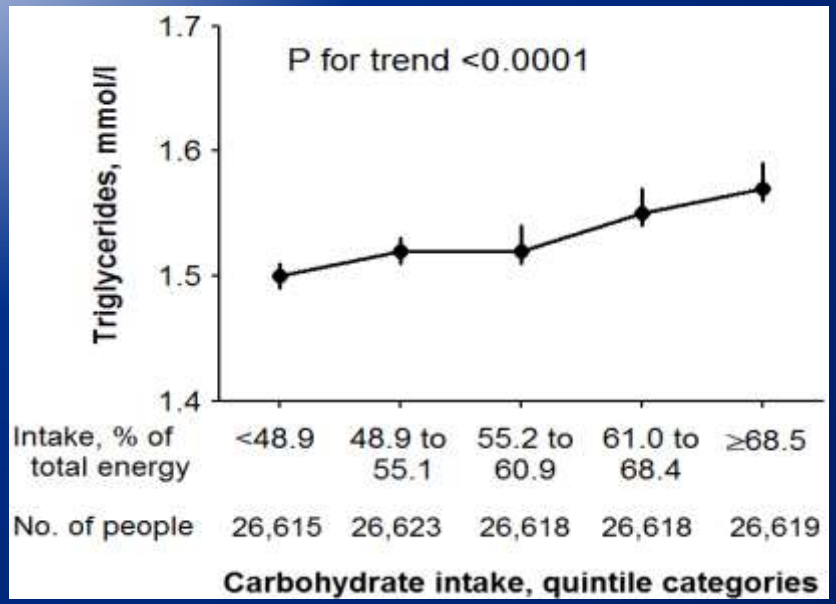
HDL-C



TC / HDL-C

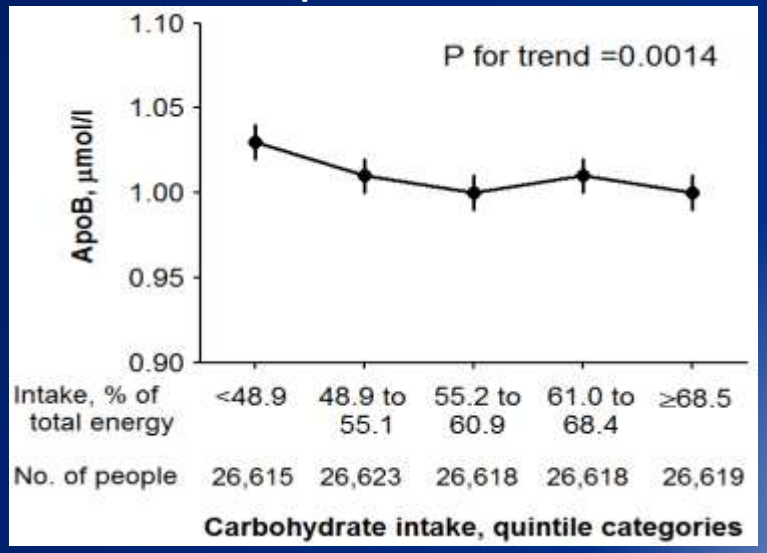


Triglycerides

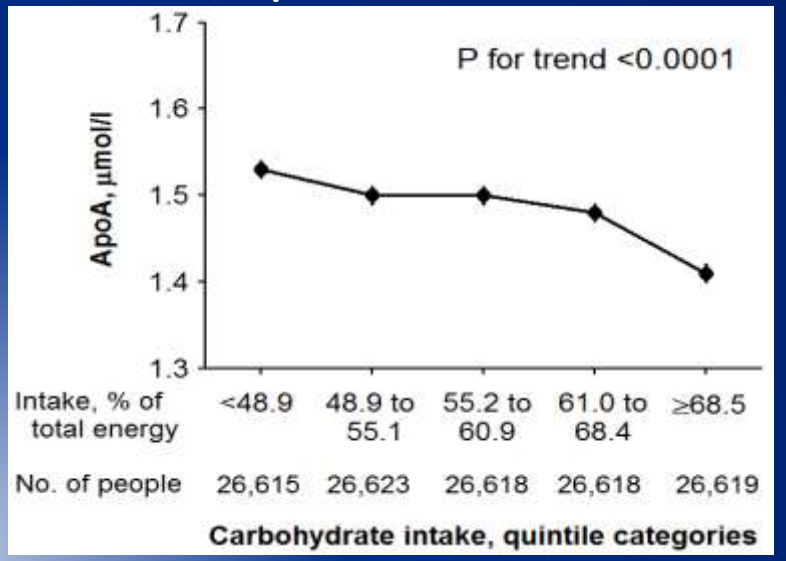


Carbohydrate intake versus risk markers

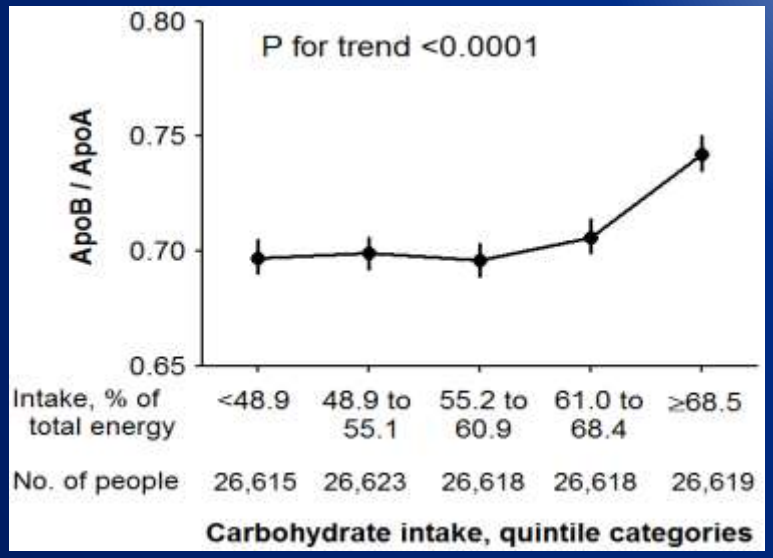
ApoB



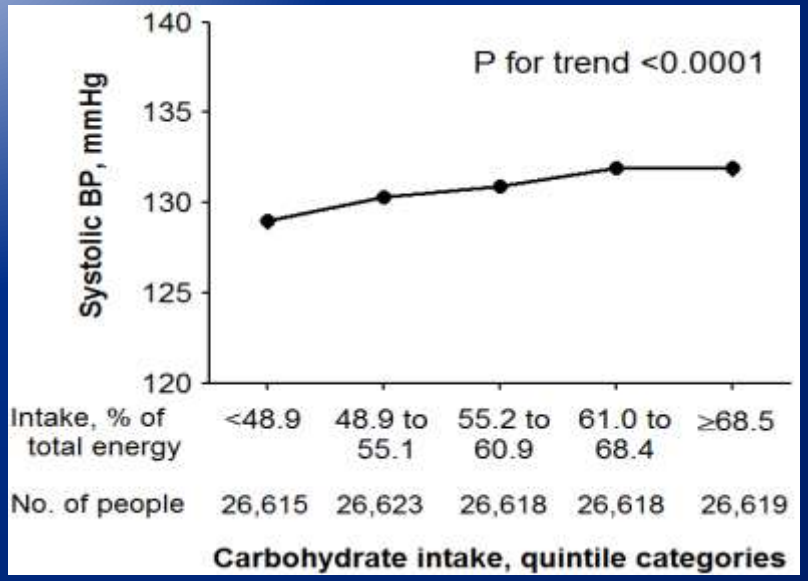
ApoA



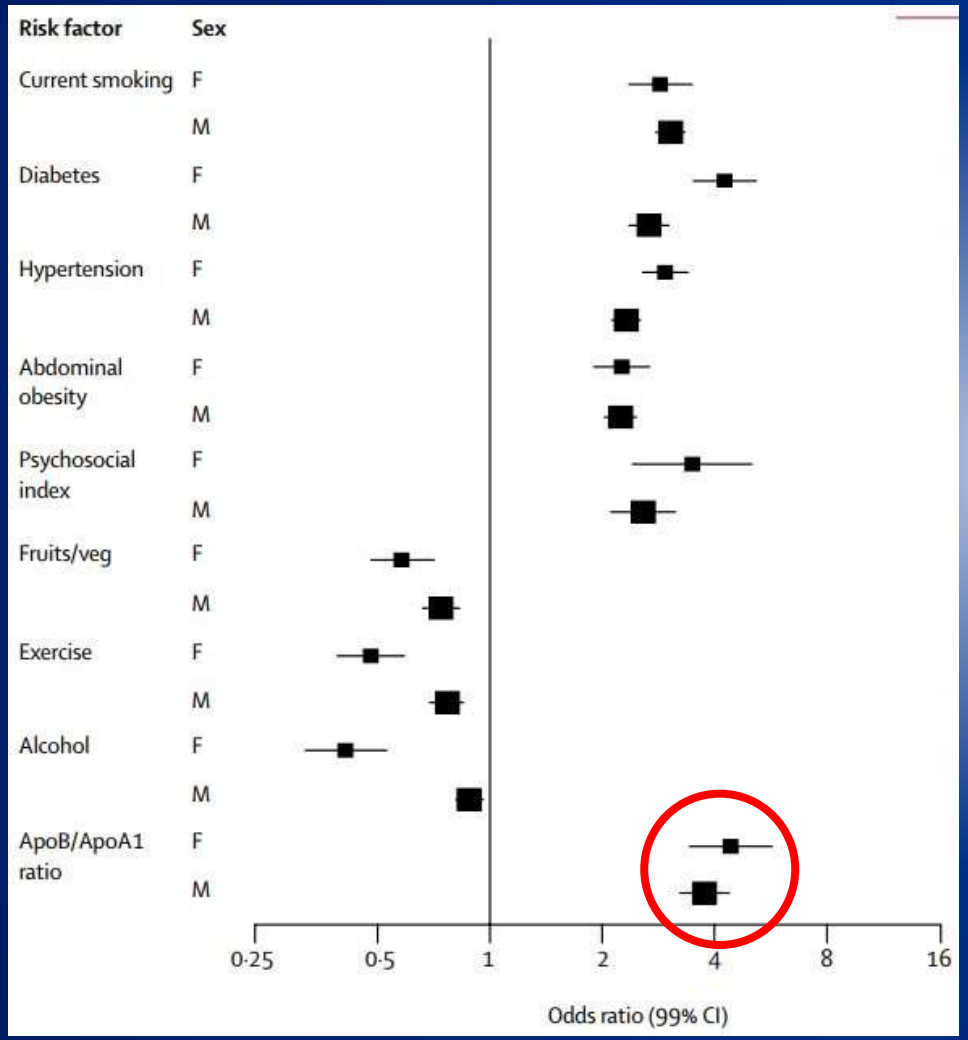
ApoB / ApoA

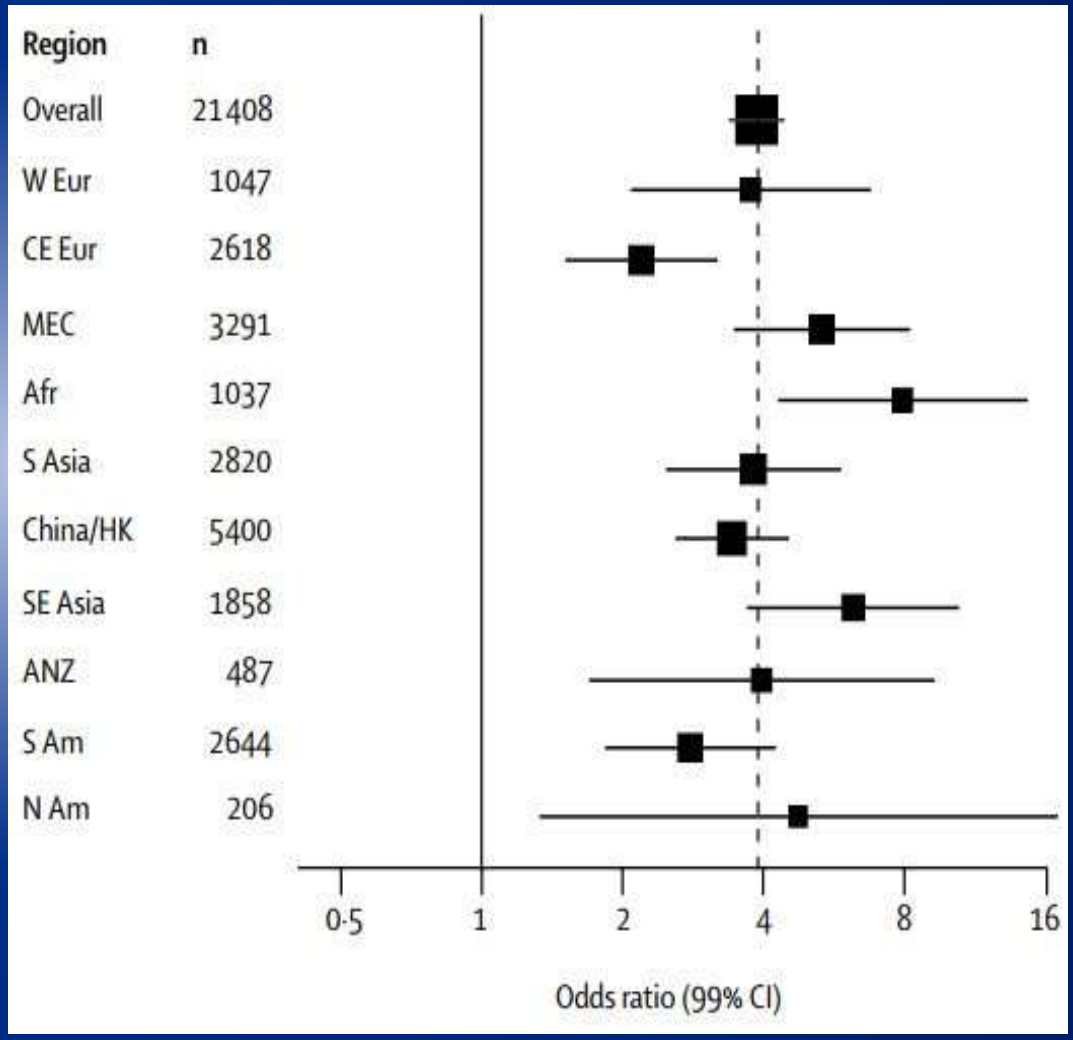


Systolic BP



ApoB/ApoA ratio was the strongest risk marker of MI and stroke in INTERHEART and INTERSTROKE

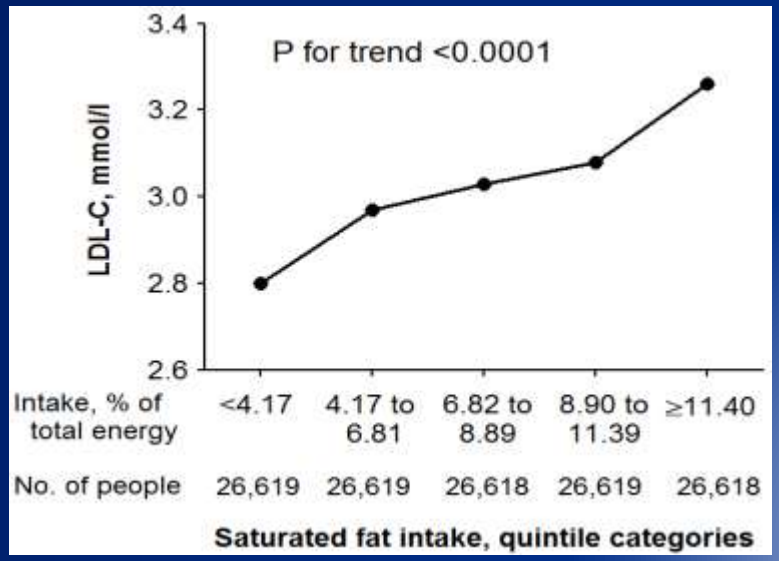




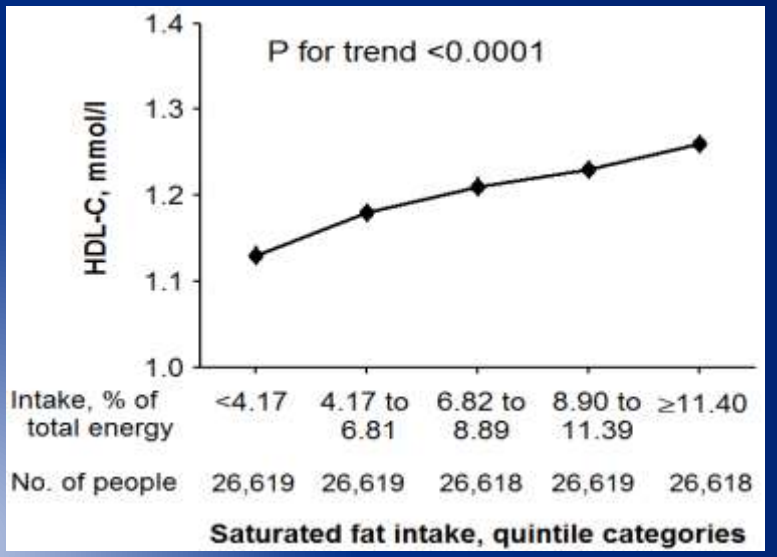
Yusuf S, et al, 2004, Lancet

Saturated fat intake versus risk markers

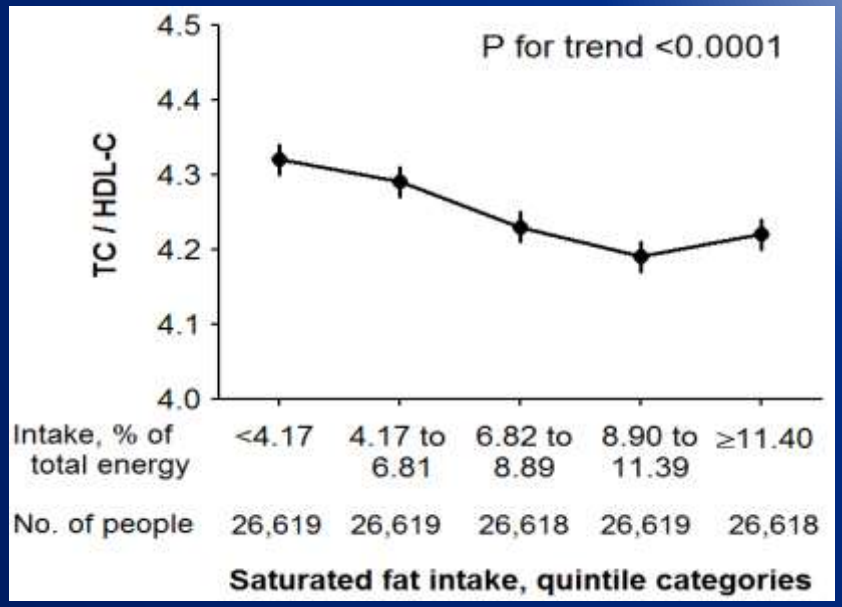
LDL-C



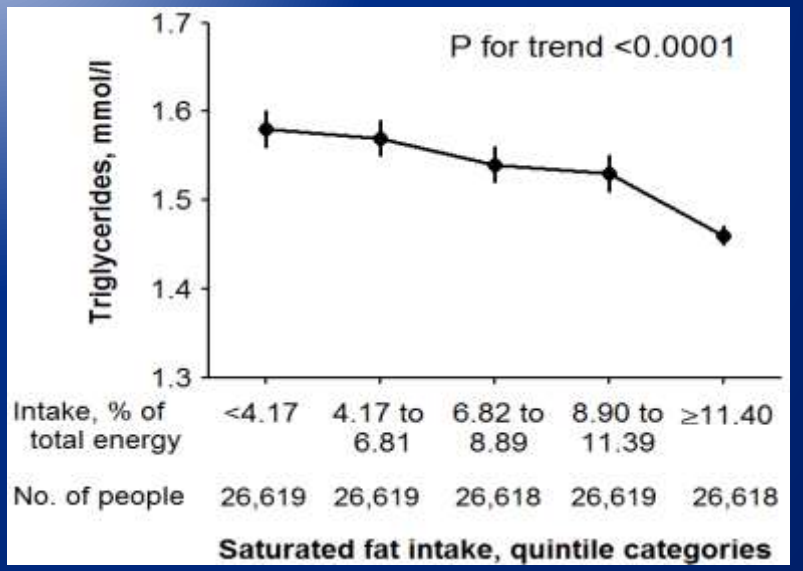
HDL-C



TC / HDL-C

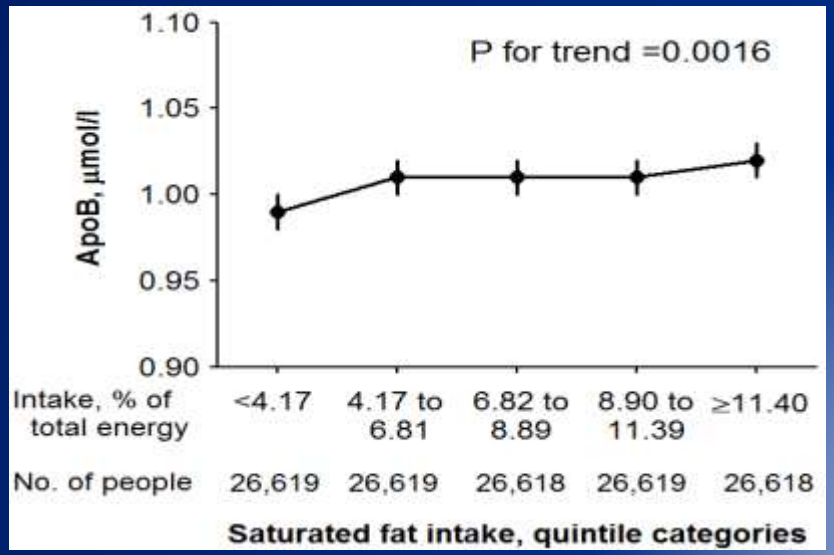


Triglycerides

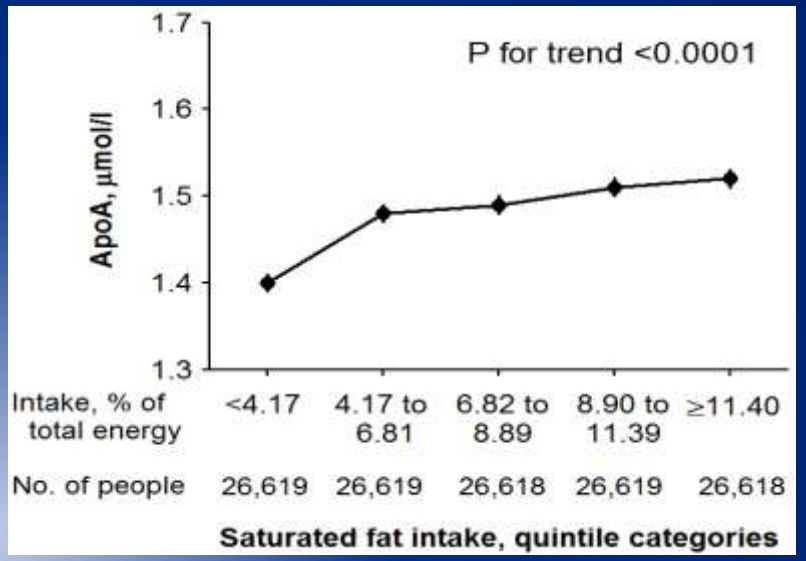


Saturated fat intake versus risk markers

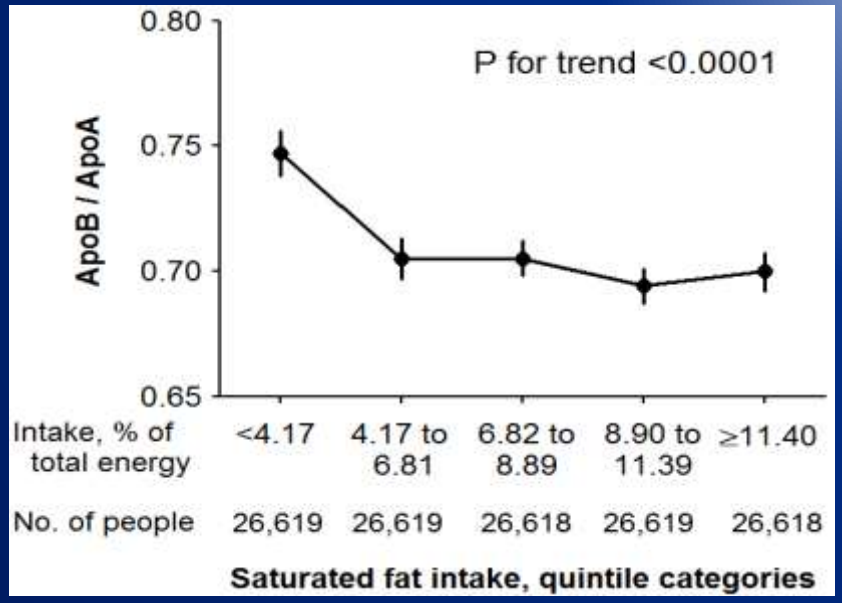
ApoB



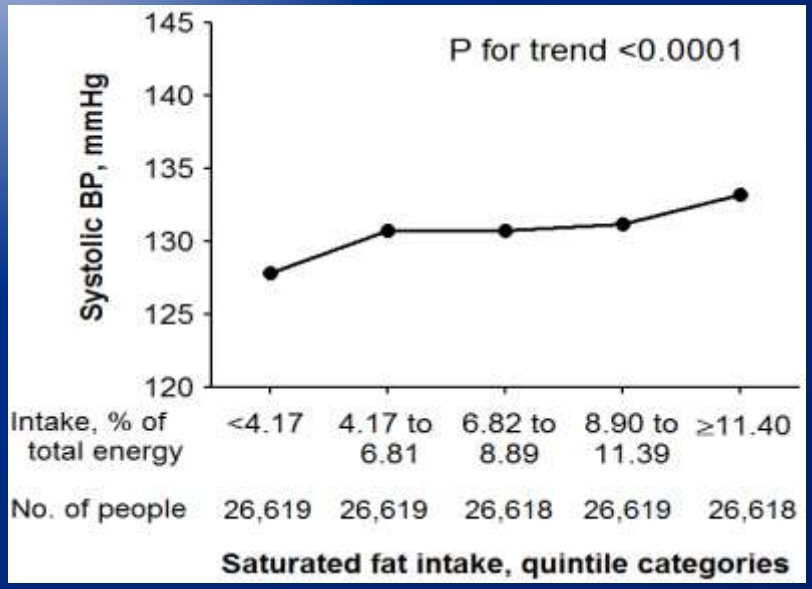
ApoA



ApoB / ApoA

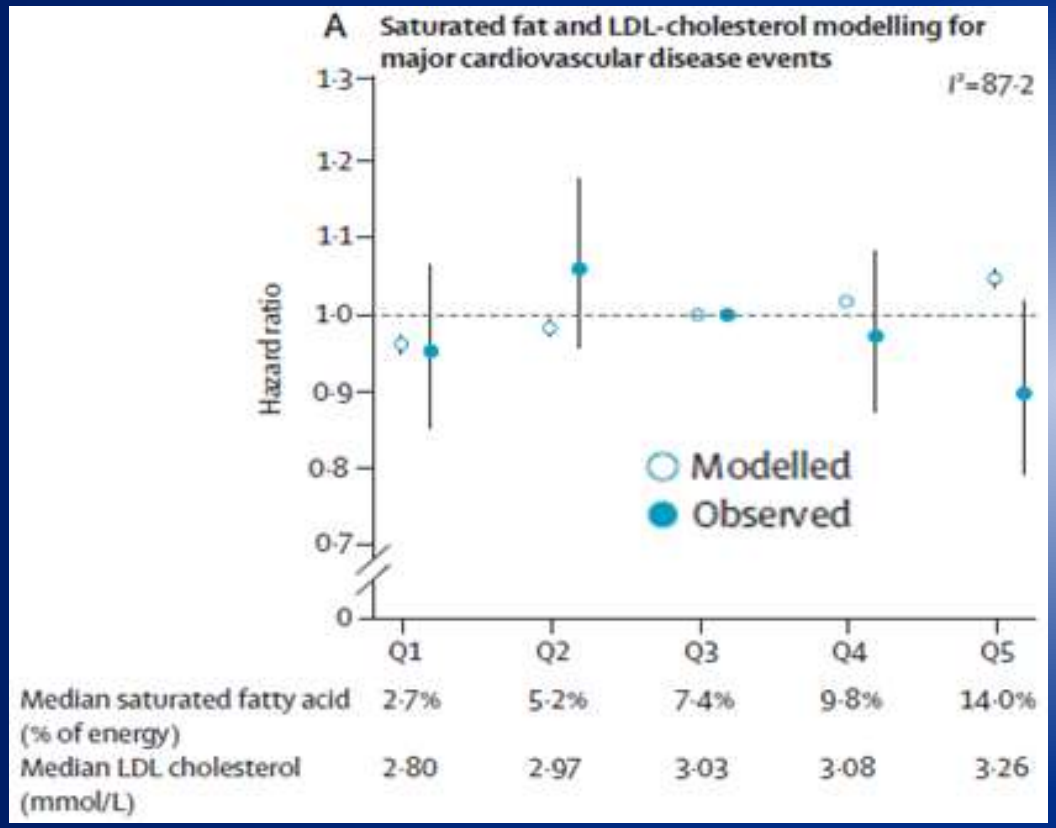


Systolic BP

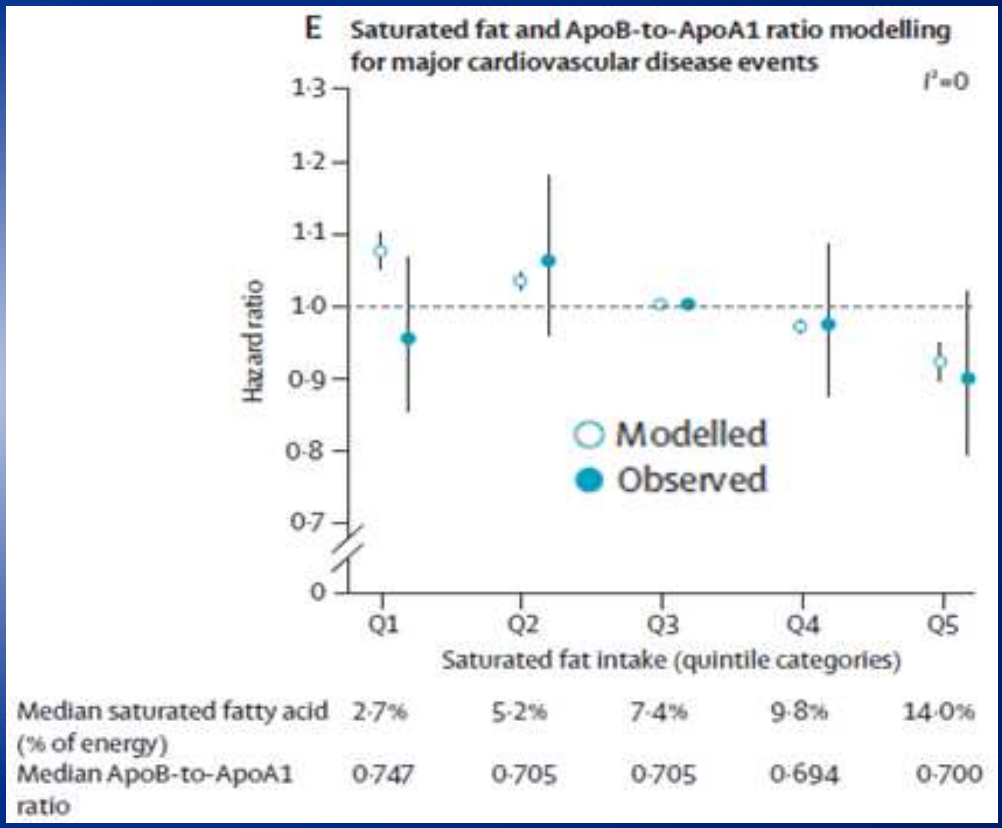


Simulation modelled versus observed hazard ratio of the association between sat. fat & CVD events

LDL-C



ApoB/ApoA



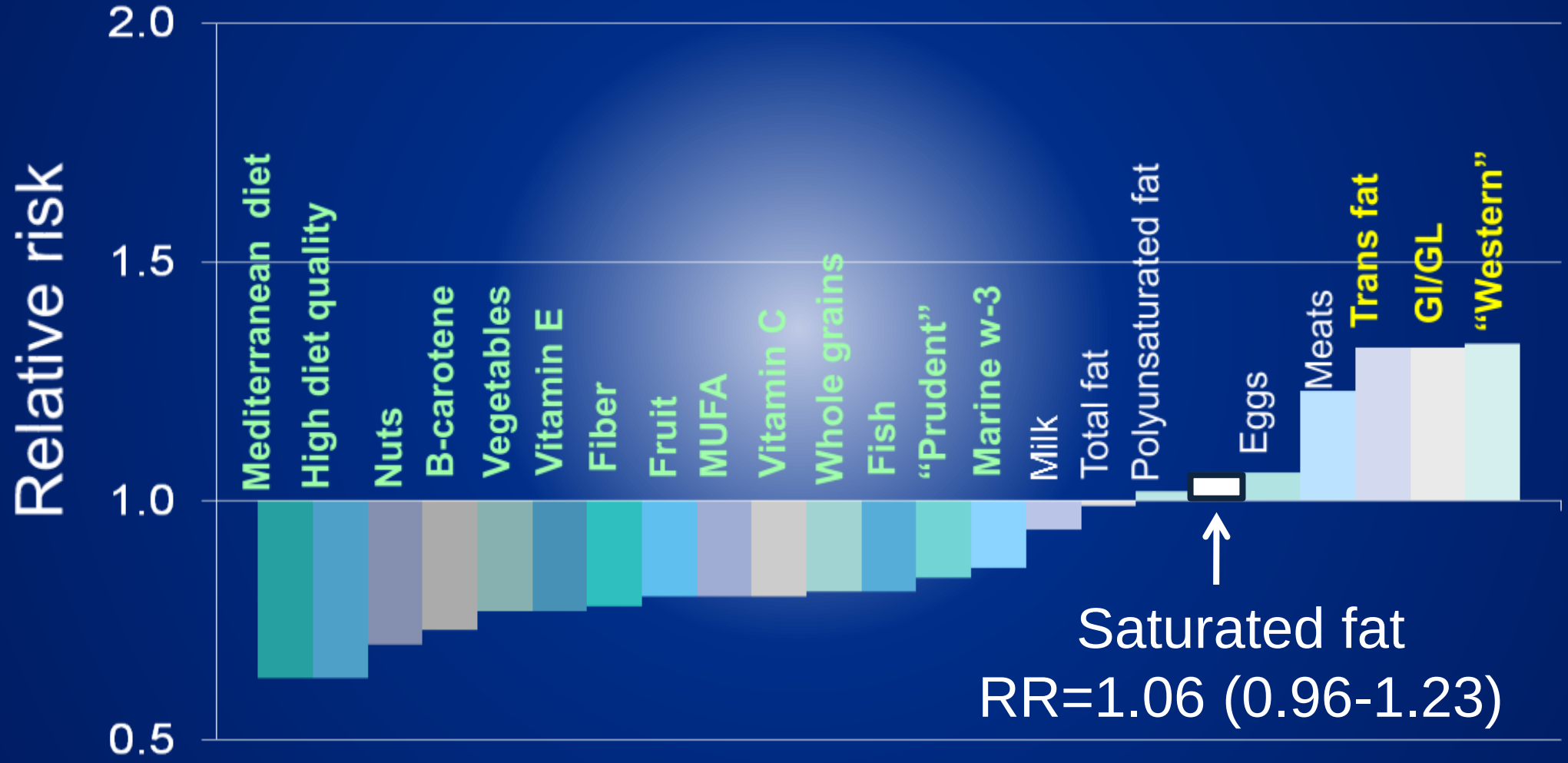
Conclusions

- Reducing sat. fat and replacing it with carbohydrate has an adverse effect on blood lipids
- Focusing on a single lipid marker (ie, LDL) alone does not capture the net clinical effects of nutrients on CVD risk
- Our data are at odds with current recommendations to reduce total fat and saturated fats

Saturated fat and cardiovascular disease

Prospective cohort studies

Relative risk of each dietary exposure in relation to CHD in cohort studies



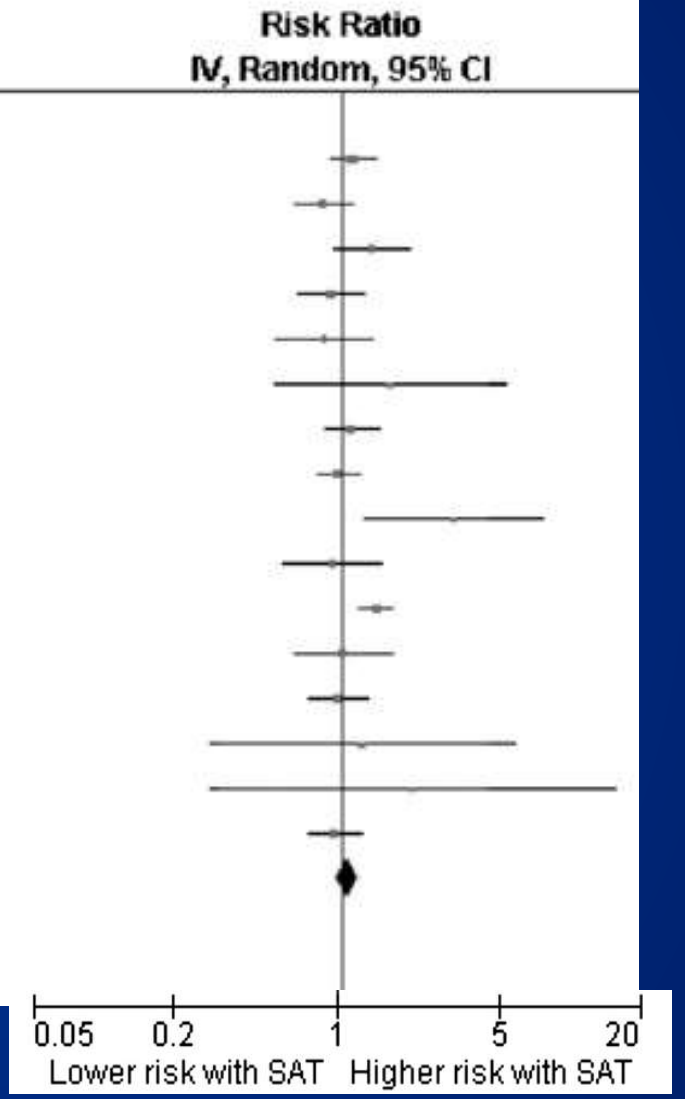
Mente A et al, 2009, *Arch Int Med* 169:659-669

Saturated fat intake and CHD

Study or Subgroup	Risk Ratio IV, Random, 95% CI	Year
Coronary Heart Disease		
Shekelle et al(17)	1.11 [0.91, 1.36]	1981
McGee et al(9)[1]	0.86 [0.67, 1.12]	1984
Kushi et al(13)	1.33 [0.95, 1.87]	1985
Posner et al(16)	0.92 [0.68, 1.24]	1991
Goldbourt et al(35)[1]	0.86 [0.56, 1.35]	1993
Fehily et al(28)	1.57 [0.56, 4.42]	1994
Ascherio et al(4)[1]	1.11 [0.87, 1.42]	1996
Esrey et al(6)	0.97 [0.80, 1.18]	1996
Mann et al(32)	2.77 [1.25, 6.13]	1997
Pietinen et al(15)	0.93 [0.60, 1.44]	1997
Boniface et al(5)[1]	1.37 [1.17, 1.60]	2002
Jakobsen et al(8)[1]	1.03 [0.66, 1.60]	2004
Oh et al(33)	0.97 [0.74, 1.27]	2005
Tucker et al(18)[1]	1.22 [0.31, 4.77]	2005
Xu et al(10)	1.91 [0.31, 11.84]	2006
Leosdottir et al(14)	0.95 [0.74, 1.21]	2007
Subtotal (95% CI)	**1.07 [0.96, 1.19]**	

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 25.54$, df = 15 (P = 0.04); $I^2 = 41\%$

Test for overall effect: Z = 1.22 (P = 0.22)



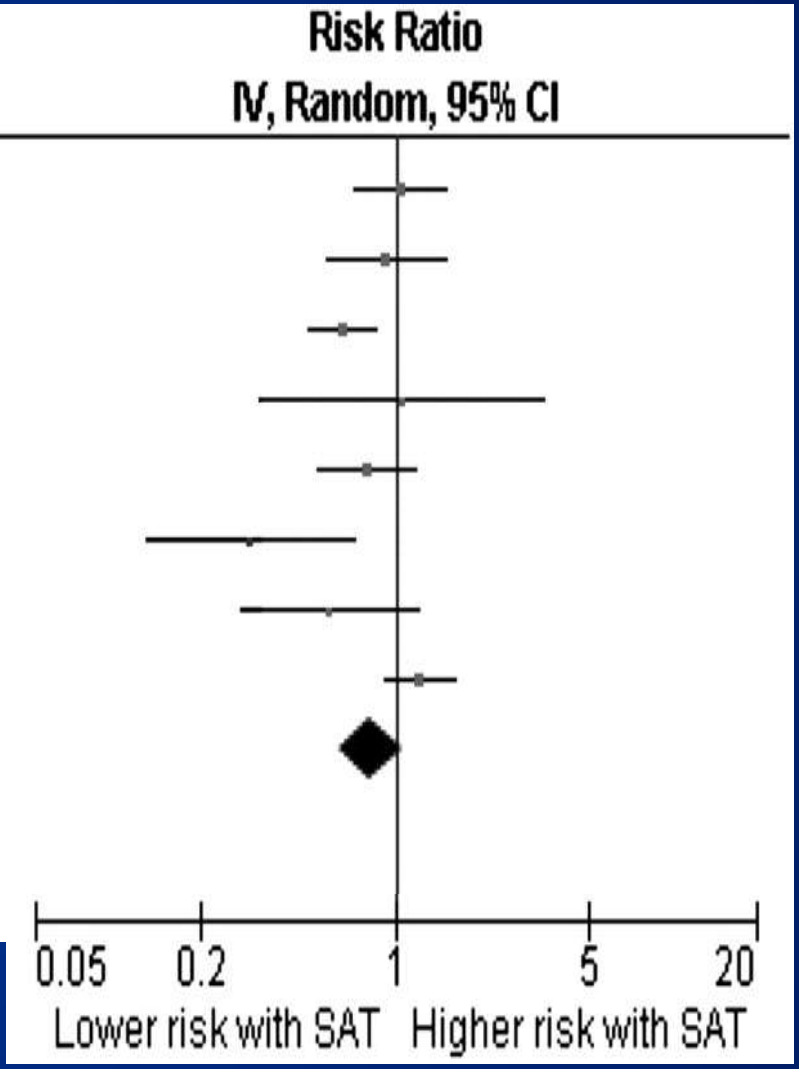
Siri-Tarino et al, Am J Clin Nutr 2010

Saturated fat intake and stroke

Study or Subgroup	Risk Ratio IV, Random, 95% CI	Year
McGee et al(9)[1]	1.04 [0.72, 1.50]	1984
Goldbourt et al(35)[1]	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)[1]	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: $Tau^2 = 0.08$; $Chi^2 = 18.03$, $df = 7$ ($P = 0.01$); $I^2 = 61\%$

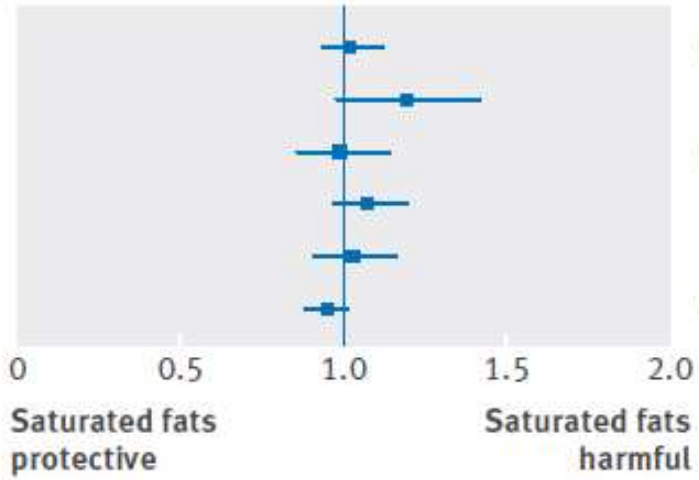
Test for overall effect: $Z = 1.58$ ($P = 0.11$)



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	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



De Souza RJ, Mente A, et al. 2015. BMJ 351:h3978

Randomized controlled trials

Saturated fat and CVD events

Meta-analyses of RCTs in past 4 years: SFA & CHD

Meta-analysis	N Studies	Relative Risk (95% CI)
Ramsden, 2013	7	0.98 (0.82, 1.19)
Schwingshackl, 2014	12	0.93 (0.72, 1.19)
Harcombe, 2015	7	0.99 (0.78, 1.25)
Hooper, 2015	11	0.90 (0.80, 1.01)
Ramsden, 2016	8	1.07 (0.80, 1.41)
Hamley, 2017	5	1.06 (0.86, 1.31)

Summary of cohort studies and RCTs of saturated fat & clinical events

- Saturated fats are not associated with all cause mortality, CVD, CHD, stroke, or type 2 diabetes
- Replacing saturated fat with mostly n-6 PUFA is unlikely to reduce CHD events, CHD mortality or total mortality

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**

Dehghan M, et al, 2017, The Lancet

Study Methods

Design: Prospective cohort 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

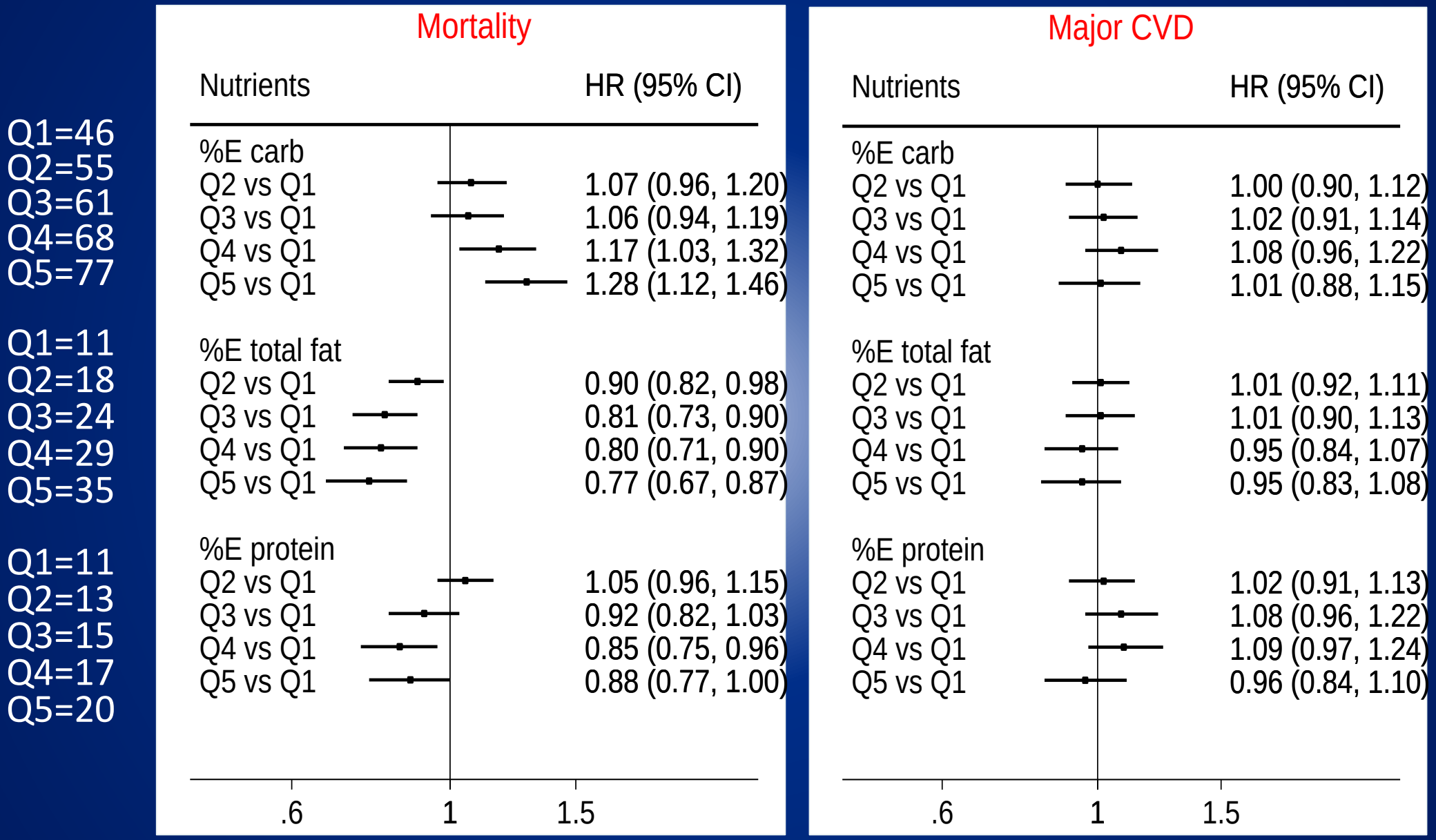
Covariates: Demographics, other lifestyle, health history, center

Outcomes: Major CVD (CV death and nonfatal MI, stroke, and heart failure) (n=4784), using standardized definitions; total mortality (n=5796)

Follow-up: Median 7.4 years

Statistical analyses: Multivariable Cox frailty analysis with study centre as random intercept

Risk of mortality and major CVD by macronutrient intake



Q1=46
Q2=55
Q3=61
Q4=68
Q5=77

Q1=11
Q2=18
Q3=24
Q4=29
Q5=35

Q1=11
Q2=13
Q3=15
Q4=17
Q5=20

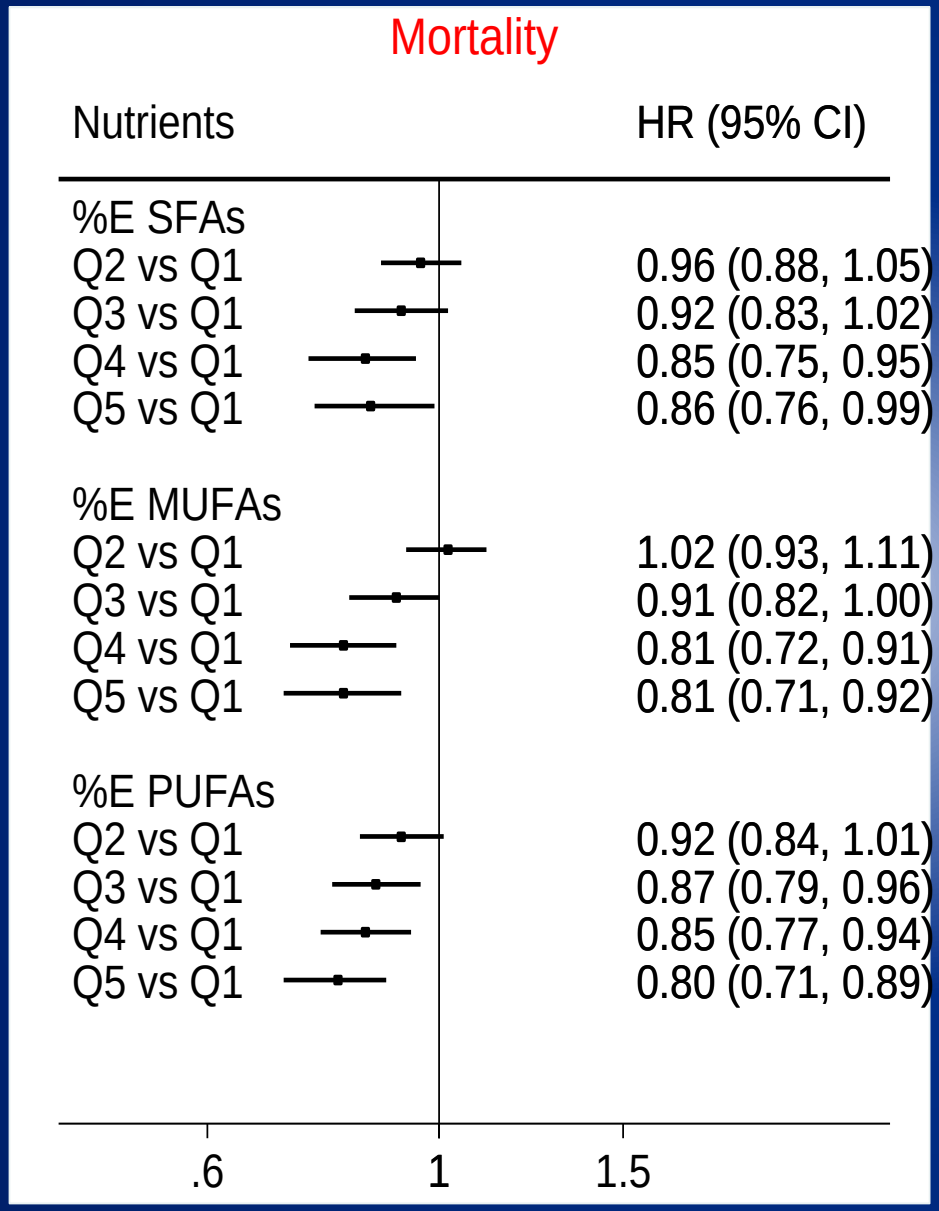
Adjusted for age, sex, activity, location, smoking, educ, WHR, energy, and centre (random effect)

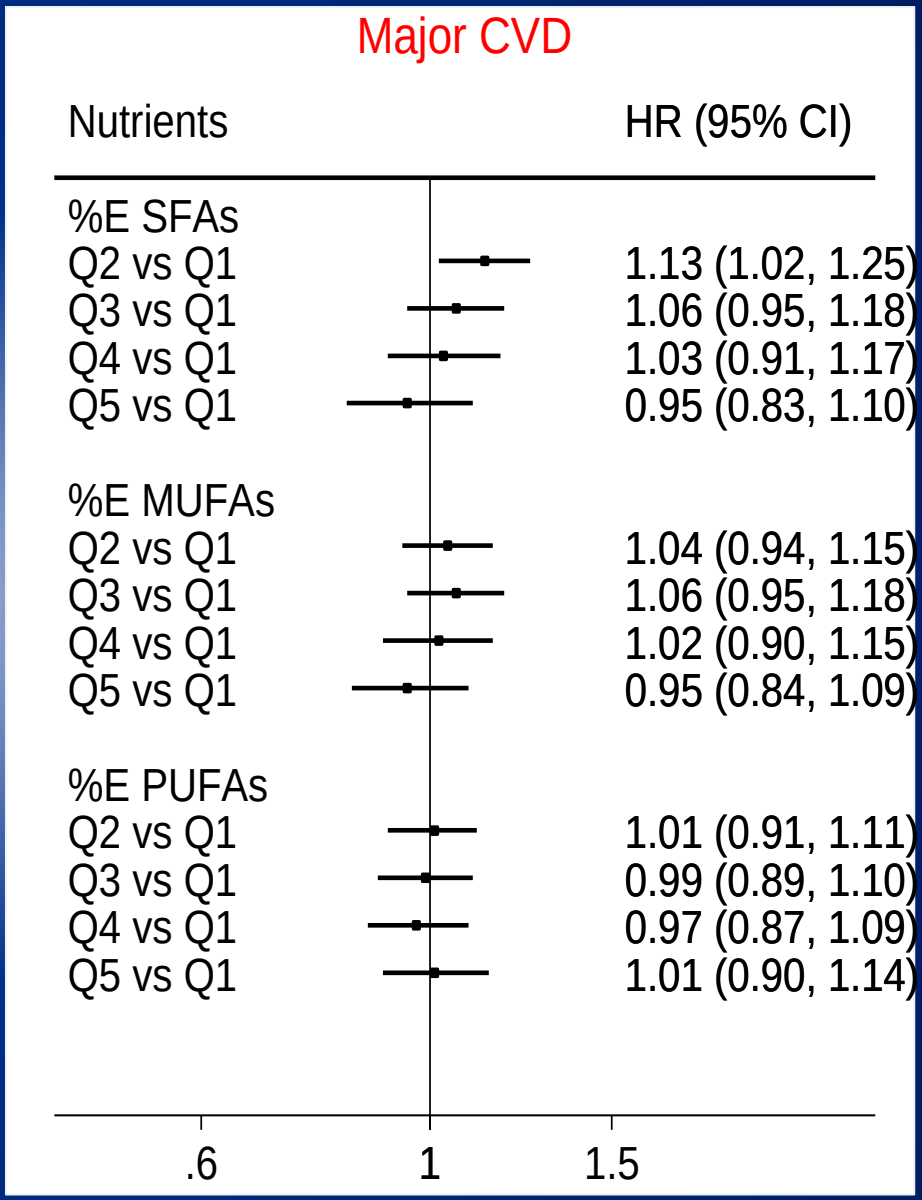
Risk of mortality and major CVD by type of fat

Q1=3
Q2=6
Q3=8
Q4=10
Q5=13

Q1=4
Q2=6
Q3=8
Q4=10
Q5=13

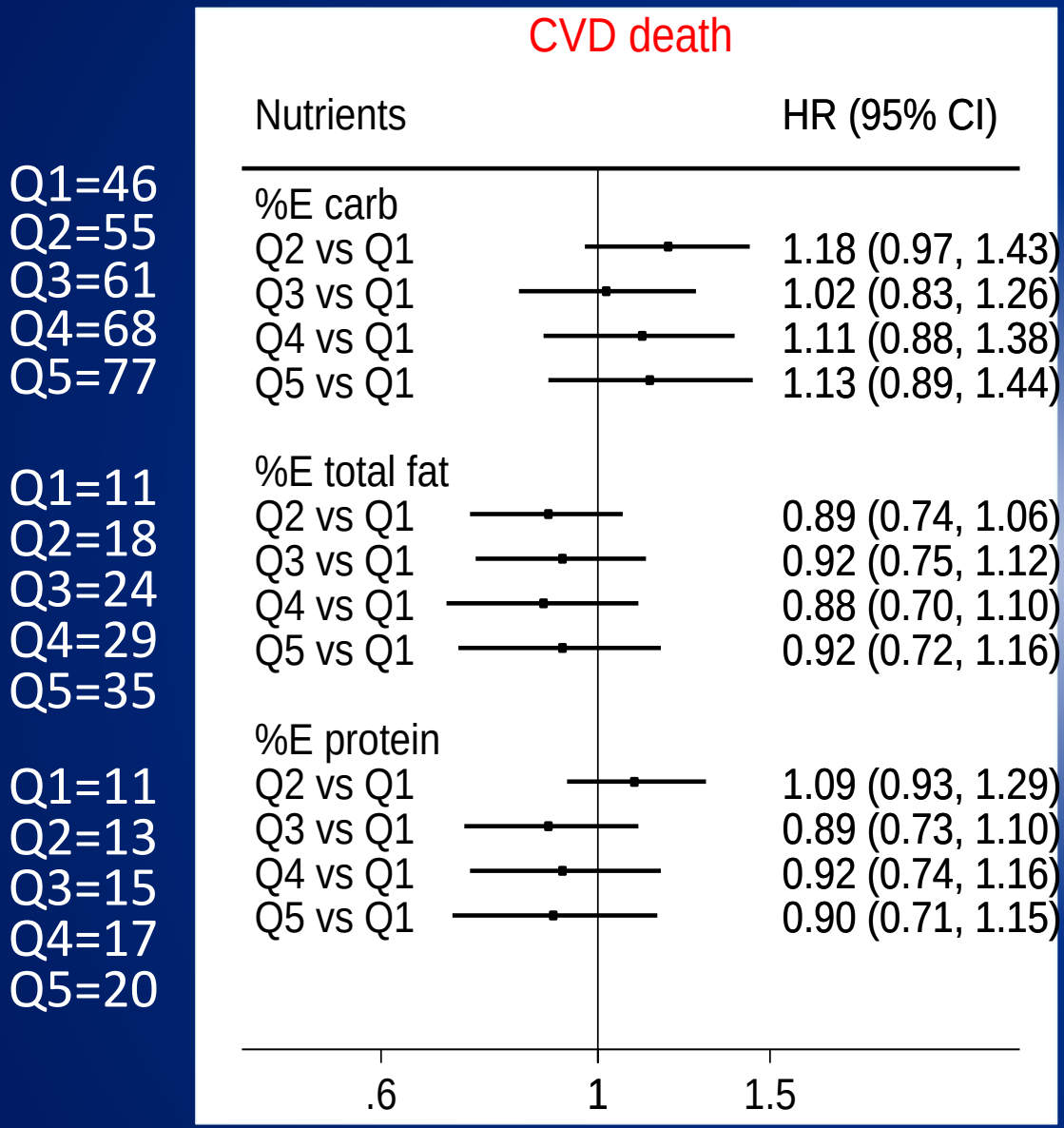
Q1=2
Q2=4
Q3=5
Q4=6
Q5=9

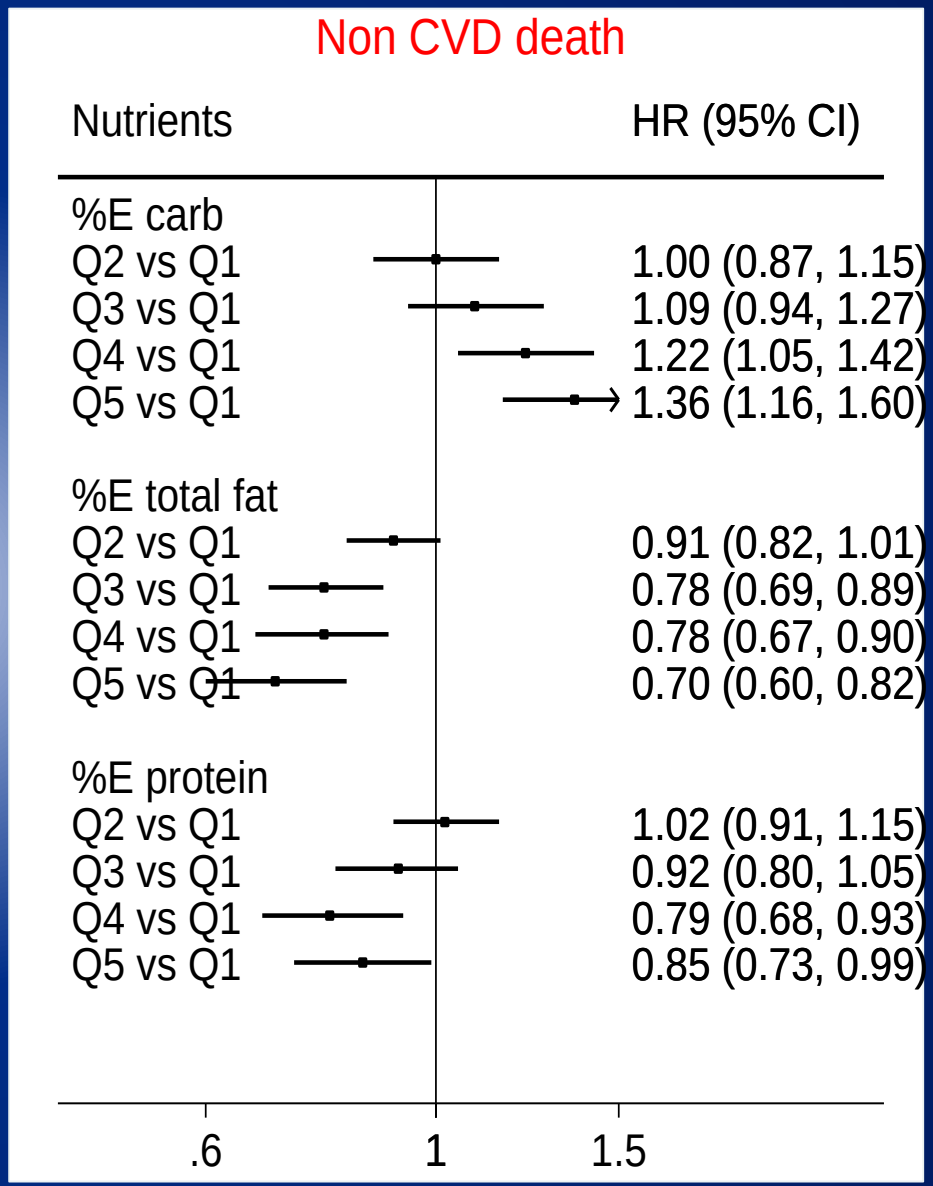




Adjusted for age, sex, activity, location, smoking, educ, WHR, energy, and centre (random effect)

Risk of CVD and non-CVD death by macronutrient intake





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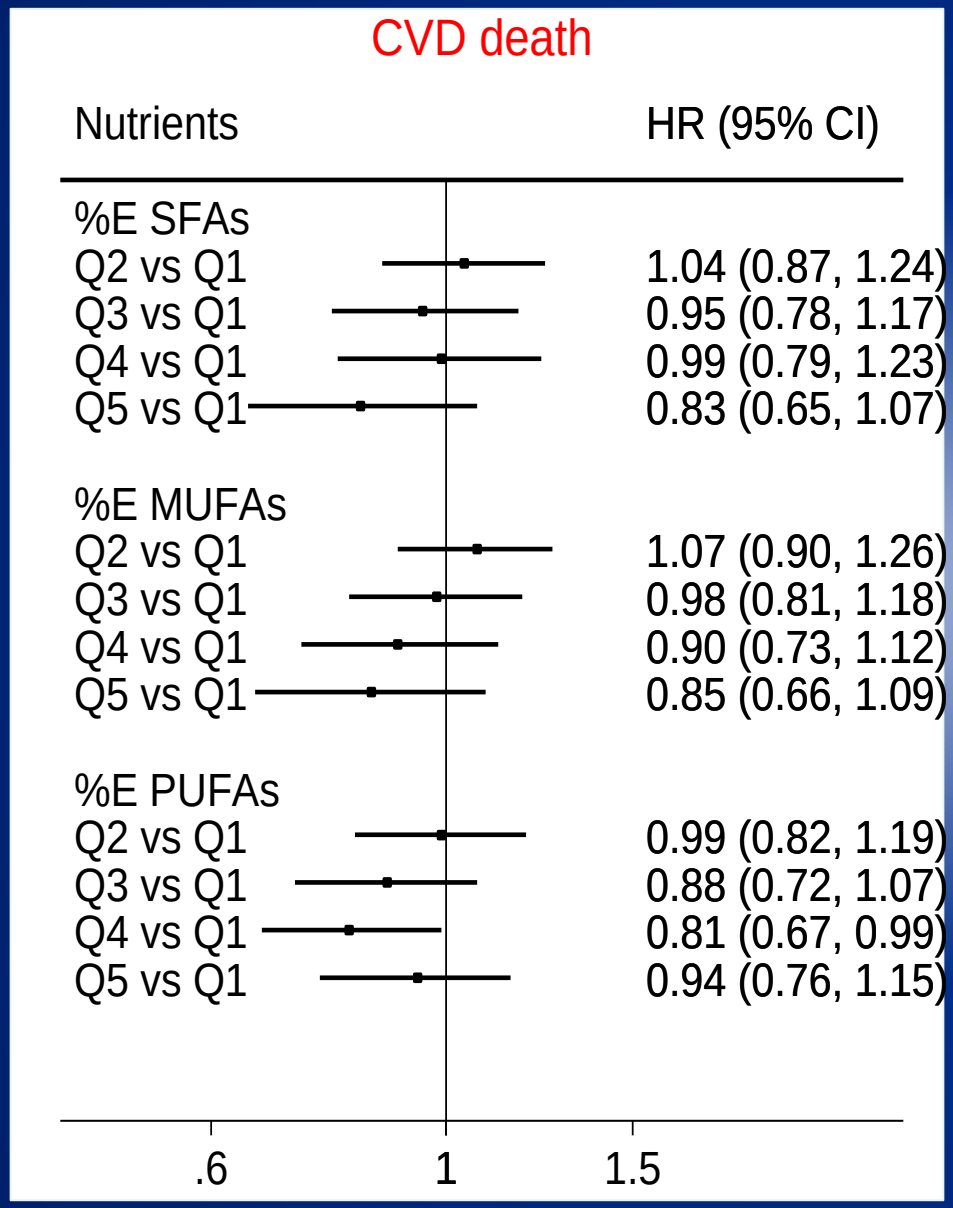
Adjusted for age, sex, activity, location, smoking, educ, WHR, energy, and centre (random effect)

Risk of CVD and non-CVD death by type of fat



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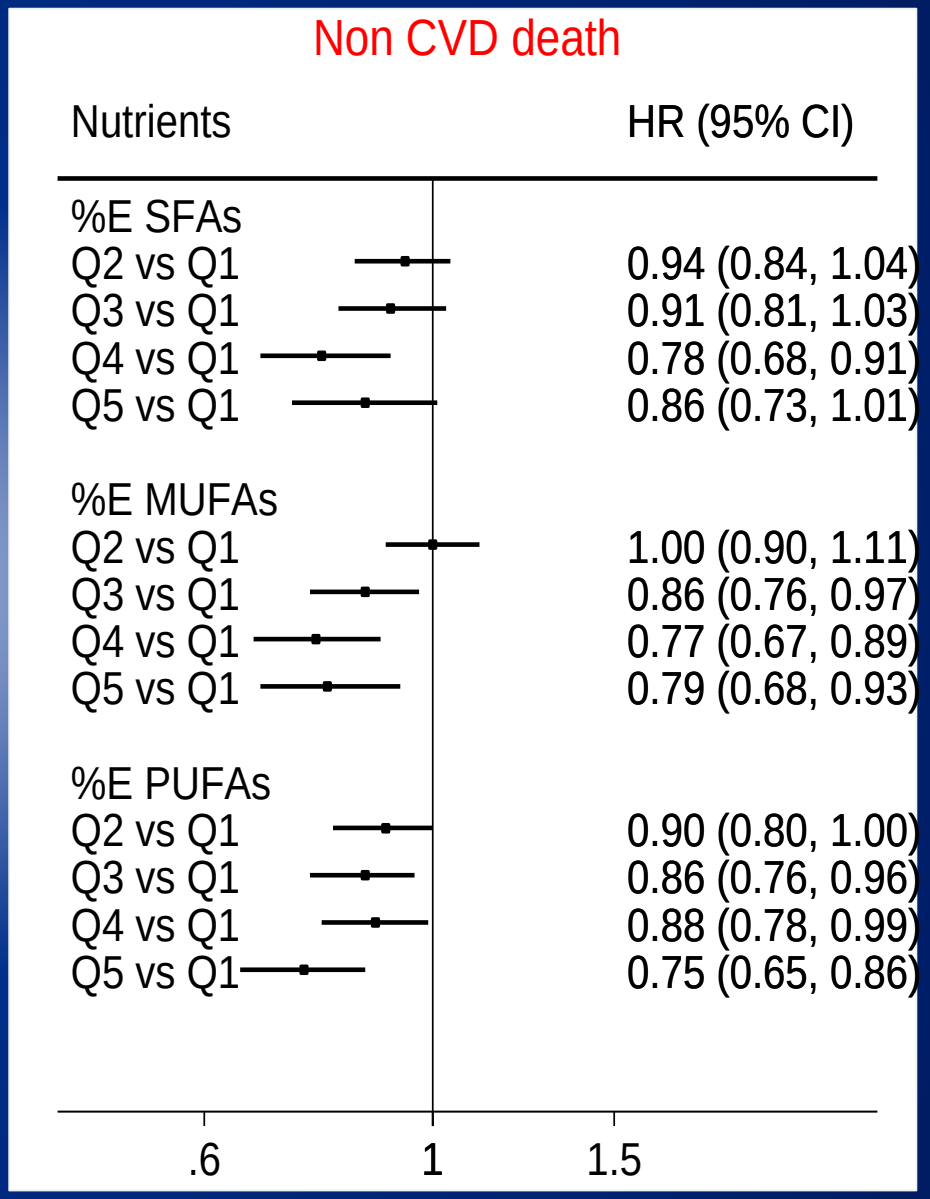


Adjusted for age, sex, activity, location, smoking, educ, WHR, energy, and centre (random effect)

Strengths

- Prospective design, large, and covers 5 continents representing diverse diets globally
- Standardized and validated methods to measure diet using country specific food frequency questionnaire
- Extensively adjusted for dietary and non-dietary covariates

Limitations

- Random measurement error in assessment of diet; may dilute real associations
- High-carbohydrate and low-fat diets may be a proxy for poverty
- Unable to measure trans fat; data on vegetable oil use not included (separate paper)
- Fewer events within countries or regions
  - Ongoing follow-up with larger sample size in PURE will provide clear answers by region

Conclusions and implications

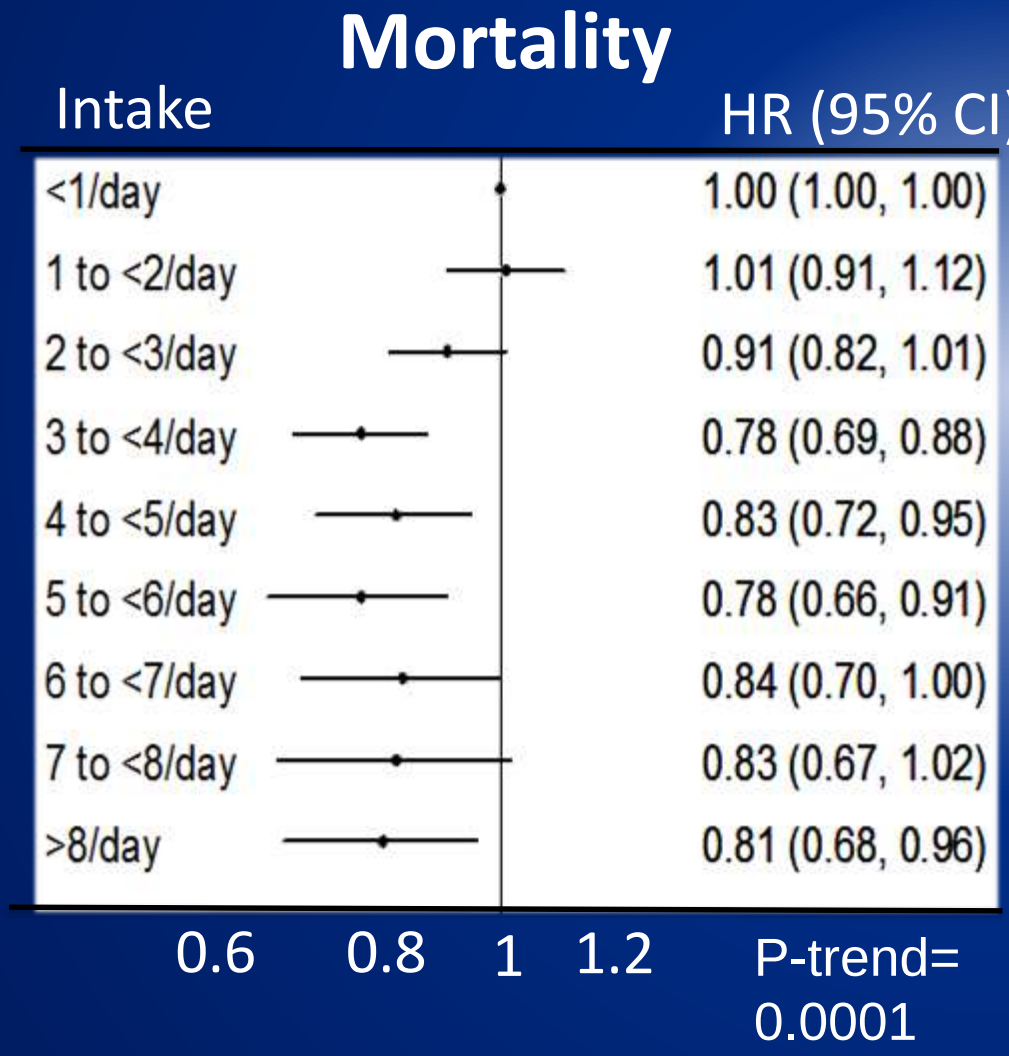
- A high carbohydrate diet (>50-55%E) is associated with higher risk of mortality
- Fats, including saturated and unsaturated fats, are associated with lower risk of mortality
- No association between total fat, types of fat and CVD events

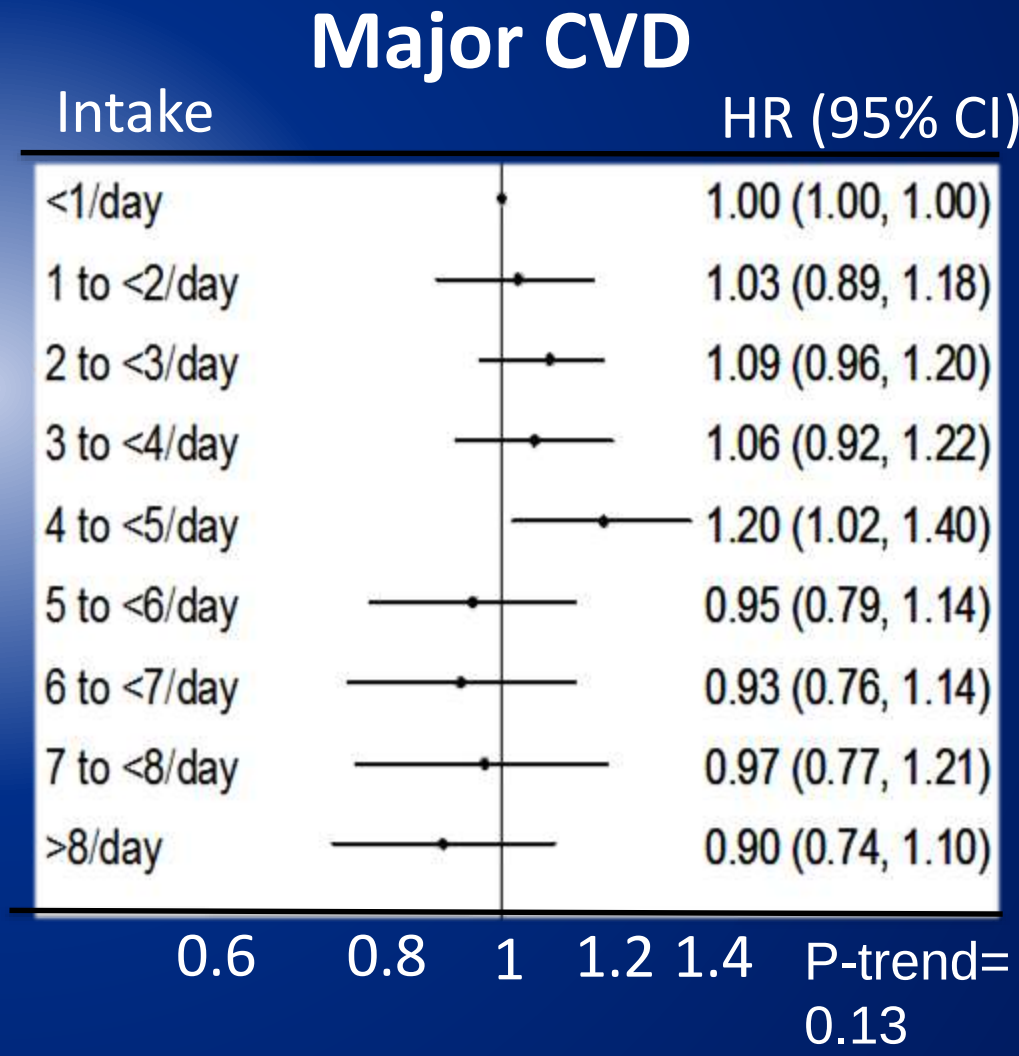
Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study

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

Miller V, et al, 2017, The Lancet

Risk of mortality and major CVD by total fruit, vegetable and legume intake (servings/day)





Conclusions and implications

- Current advice to limit total fat to <30%E and saturated fat to <10%E are not supported by this global study

Conclusion

- Foods containing SFA such as dairy and meat may be part of a healthy dietary pattern shown to reduce CVD (eg, 'Mediterranean diet')

- Focus on eating natural foods, reduce intake of refined or starchy carbohydrate foods, and be less concerned about targets for individual nutrients

PURE Investigators Meeting, New Delhi, India
November 2017

Acknowledgement