

Clinical Evidence Supporting the Role of Healthy Fats to Reduce CVD Risk Factors

Presentation 2 of 2

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Outline

- Clinical trial evidence to support recommendations for unsaturated fatty acids
- New research on minor fatty acids
- Translating recommendations to dietary patterns
- Summary

COMIT: Canola Oil Multi-Centre Intervention Trial

Modification of dietary fatty acid quality toward optimal n-6, n-9 and short and long chain n-3 fatty acid profiles, by the inclusion of novel oil blends, will benefit CVD risk factors



Objectives

1. Examine alterations in plasma lipids, lipoprotein subclasses, and inflammatory cytokines
2. Assess endothelial function in response to treatment oils
3. **Examine changes in body composition using DEXA (dual energy x-ray absorptiometry) scanning**
4. Examine efficiency of FA conversion to EPA/DHA
5. Investigate association between gene mRNA and protein expression with ALA conversion efficiency to EPA/DHA
6. Investigate association between genetic variants with ALA conversion to EPA/DHA



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Eligibility Criteria

Based on International Diabetes Federation Definition of Metabolic Syndrome

- Age: 20-65 y
- BMI: ≥ 22 to ≤ 40 kg/m²
- Waist circumference (WC): Men ≥ 94 cm, Women ≥ 80 cm
- **WC + one of the following metabolic syndrome criteria:**
 - Glucose: ≥ 5.6 mmol/L (100 mg/dL)
 - HDL-C: men < 1.0 mmol/L (40 mg/dL), women < 1.3 mmol/L (50 mg/dL)
 - TG: ≥ 1.7 mmol/L (150 mg/dL)
 - Blood pressure: $>130/85$ mmHg

Fatty Acid Profile of Treatment Oils

Isocaloric base diet

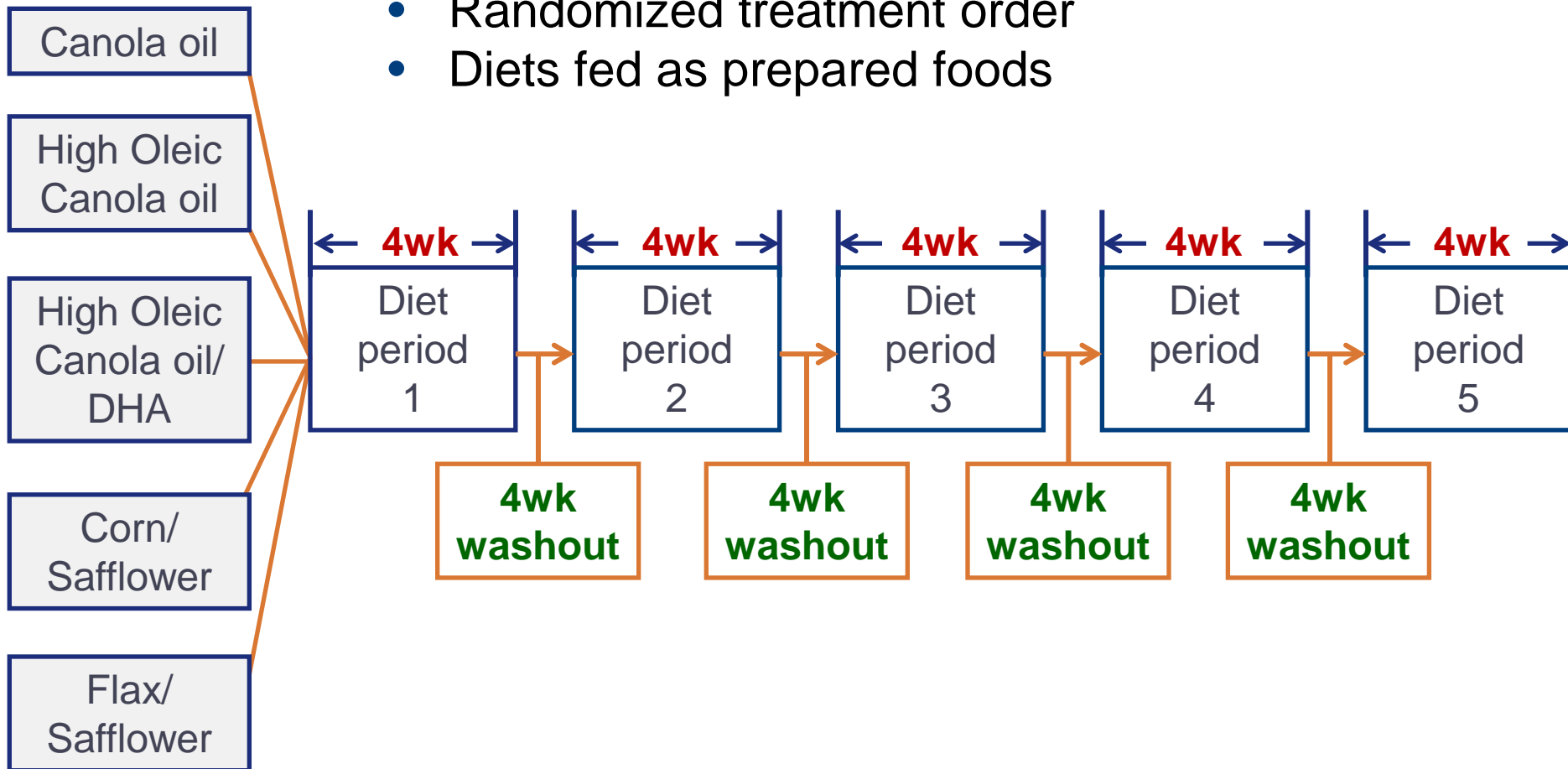
Macronutrient	%
CHO	50
FAT	35
PRO	15

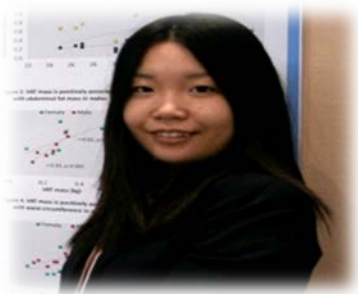
Treatment oils	SFA (%)	MUFA (%)	PUFA (%)	Omega-3 (%)		Omega-6 (%)
				ALA	DHA	LA
Canola	7.2	62.8	29.5	9.8		19.5
High Oleic Canola	6.5	72	17	2.3		14.7
High Oleic Canola + DHA	8.6	63.8	23.3	2.0	5.8	12.7
Corn/Safflower	7.9	17.7	69.6	<1		69.3
Flax/Safflower	8.1	17.9	69.4	32		37.5

60 g of oil/day based on 3000 kcal diet; consumed as a “smoothie”

Study Design

- Double blind cross-over controlled feeding trial
- Randomized treatment order
- Diets fed as prepared foods

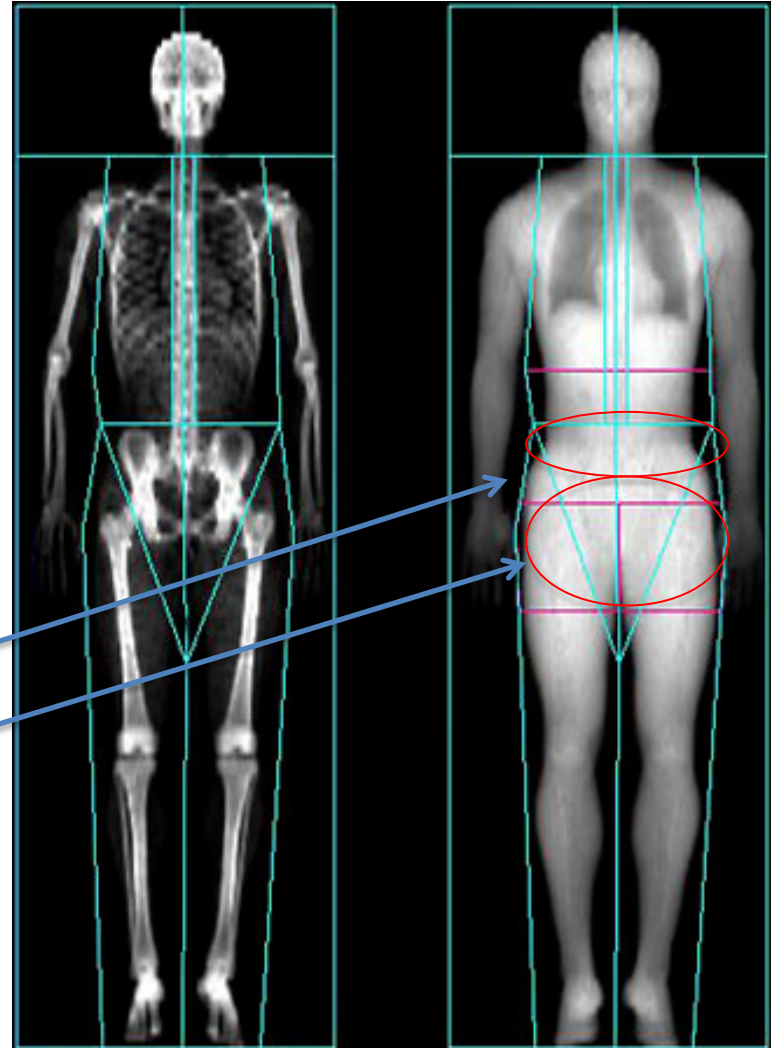




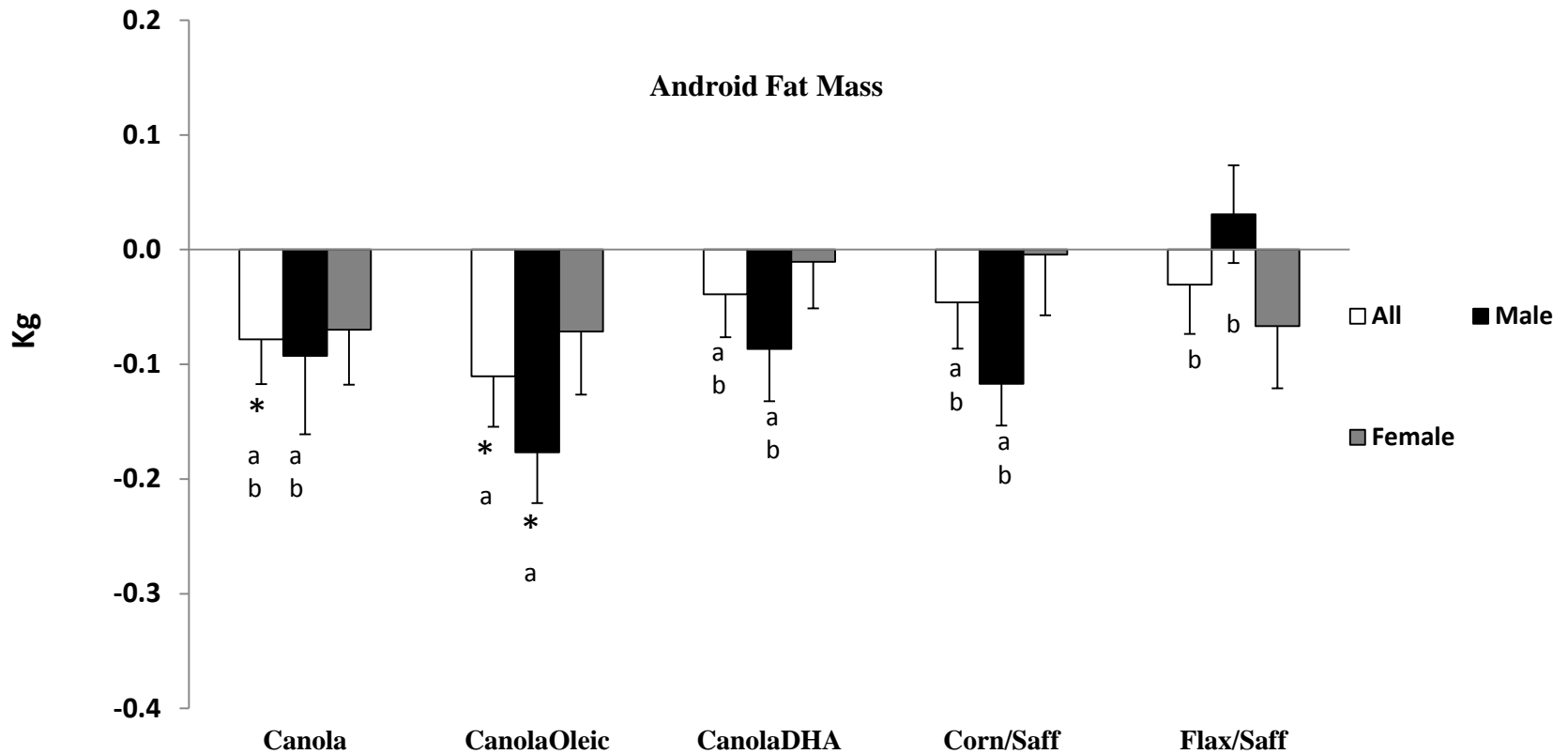
Xiaoran Liu

DEXA Technique

- DEXA measures % body fat and divides the body into three compartments: fat mass, bone mass, and lean mass.
- In addition, the DEXA method determines % fat, fat mass, bone mass and lean mass separately for the arms, trunk (android), and legs. (gynoid)
- **| Android:Gynoid ratio**
decreases risk factors for CVD



Android Fat Mass Changes in Response to Five Experimental Diets (n = 20 males and 34 females)



COMIT Conclusion - Body Composition

- A diet very high in MUFA reduced visceral adipose tissue (i.e., belly fat).
- A decrease in visceral adipose tissue resulted in a decrease in triglycerides and blood pressure.

ORIGINAL ARTICLE

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventós, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*



PREDIMED TRIAL: DESIGN

- Men: 55-80 yr
- Women: 60-80 yr
- High CV risk without CVD
 - Type 2 diabetics
 - 3+ risk factors

1. Smoking
2. Hypertension
3. ↑ LDL
4. ↓ HDL
5. Overweight/obese
6. Family history

All free of CVD at baseline

Random

MedDiet + Olive Oil
N=2500



MedDiet + NUTS
N=2500



CONTROL GROUP
n=2500

Difference Between MeDiet + EVOO and MeDiet +Nuts

MeDiet + EVOO



EVOO (1L/week/family = 50 g/day)

MeDiet + Nuts



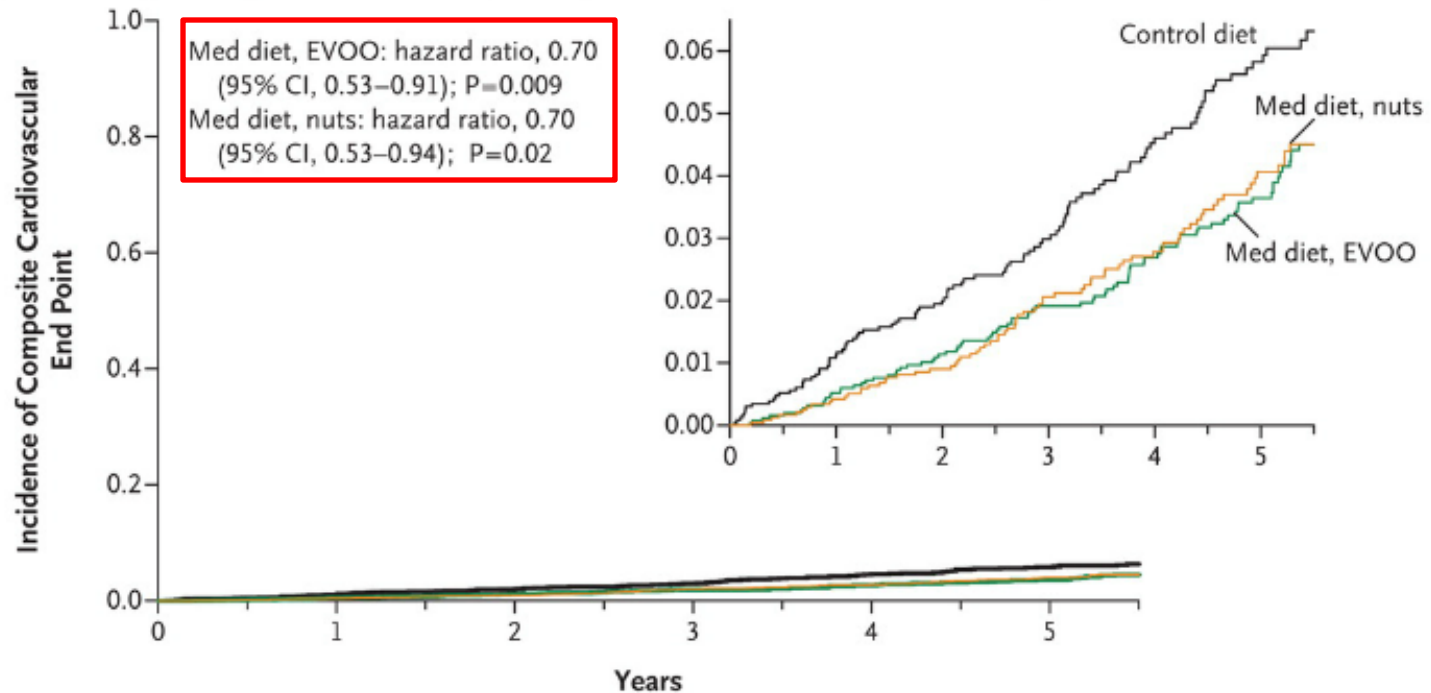
**Walnuts 15 g/d
Almonds 7.5 g/d
Hazelnuts 7.5 g/d**

PREDIMED: Intake of Energy and Nutrients at the End of the Trial by Study Group

Variable	MeDiet + EVOO	MeDiet + Nuts	Control
Energy, kcal	2172	2229	1960
CHO, % E	40	40	44
→ Fat, % E	41	42	37
→ SFA, % E	9	9	9
→ MUFA, % E	22	21	19
PUFA, % E	6	8	6
Linoleic acid, g/d	12	16	10
ALA, g/d	1.3	1.5	1.3
Marine n-3 FA, g/d	0.9	0.8	0.7

PREDIMED Trial: The Incidence of Acute Myocardial Infarction, Stroke, and Death from Cardiovascular Causes by Treatment

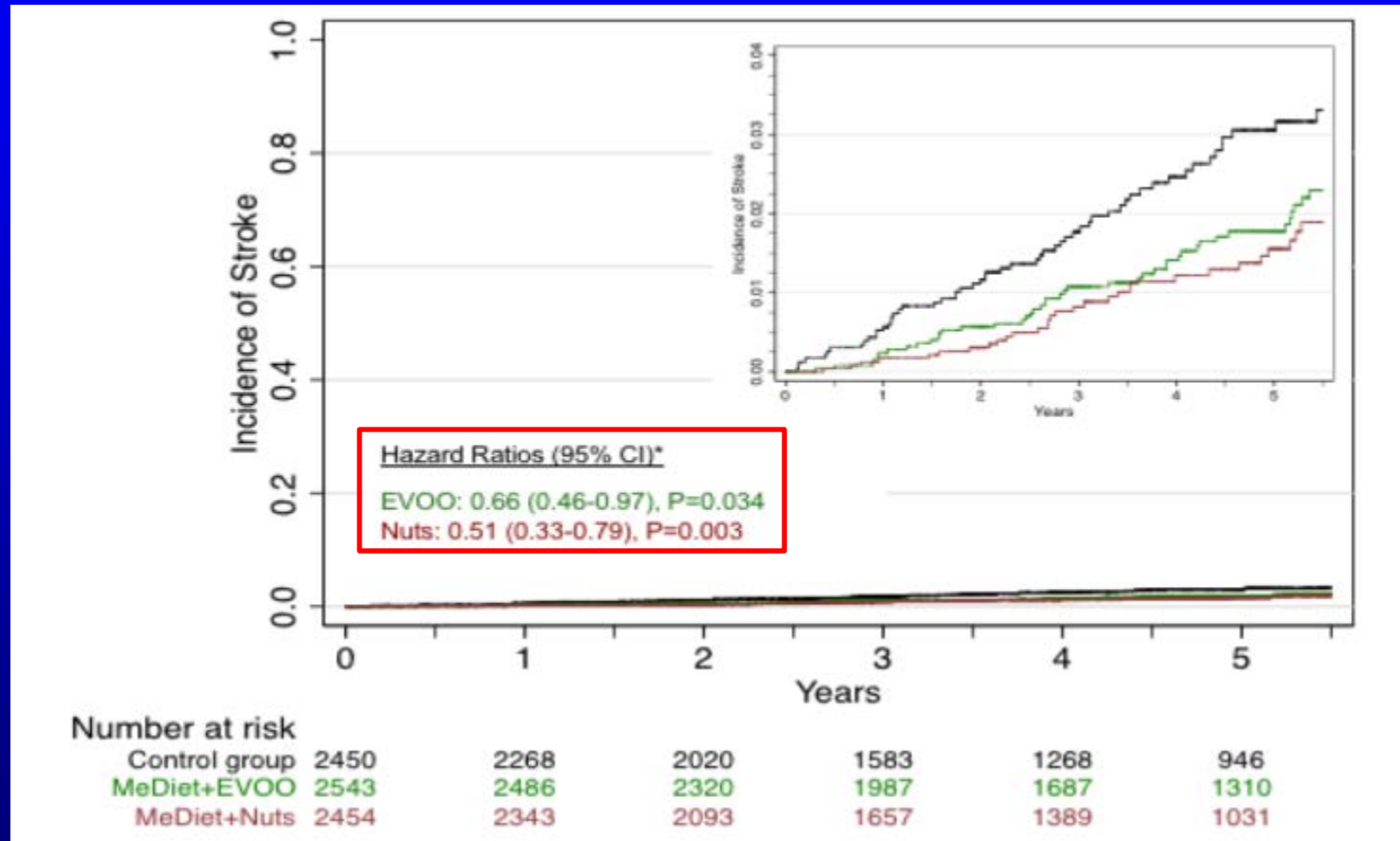
Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)



No. at Risk

Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

Figure S6. Kaplan-Meier Estimates of Incidence of the Significant Separate Component (Stroke) of the Primary Endpoint



α -Linolenic Acid (ALA) and Risk of Cardiovascular Disease: A Systematic Review and Meta-Analysis

An Pan, Mu Chen, Rajiv Chowdhury, Jason HY Wu, Qi Sun, Hannia Campos, Dariush Mozaffarian, and Frank B Hu

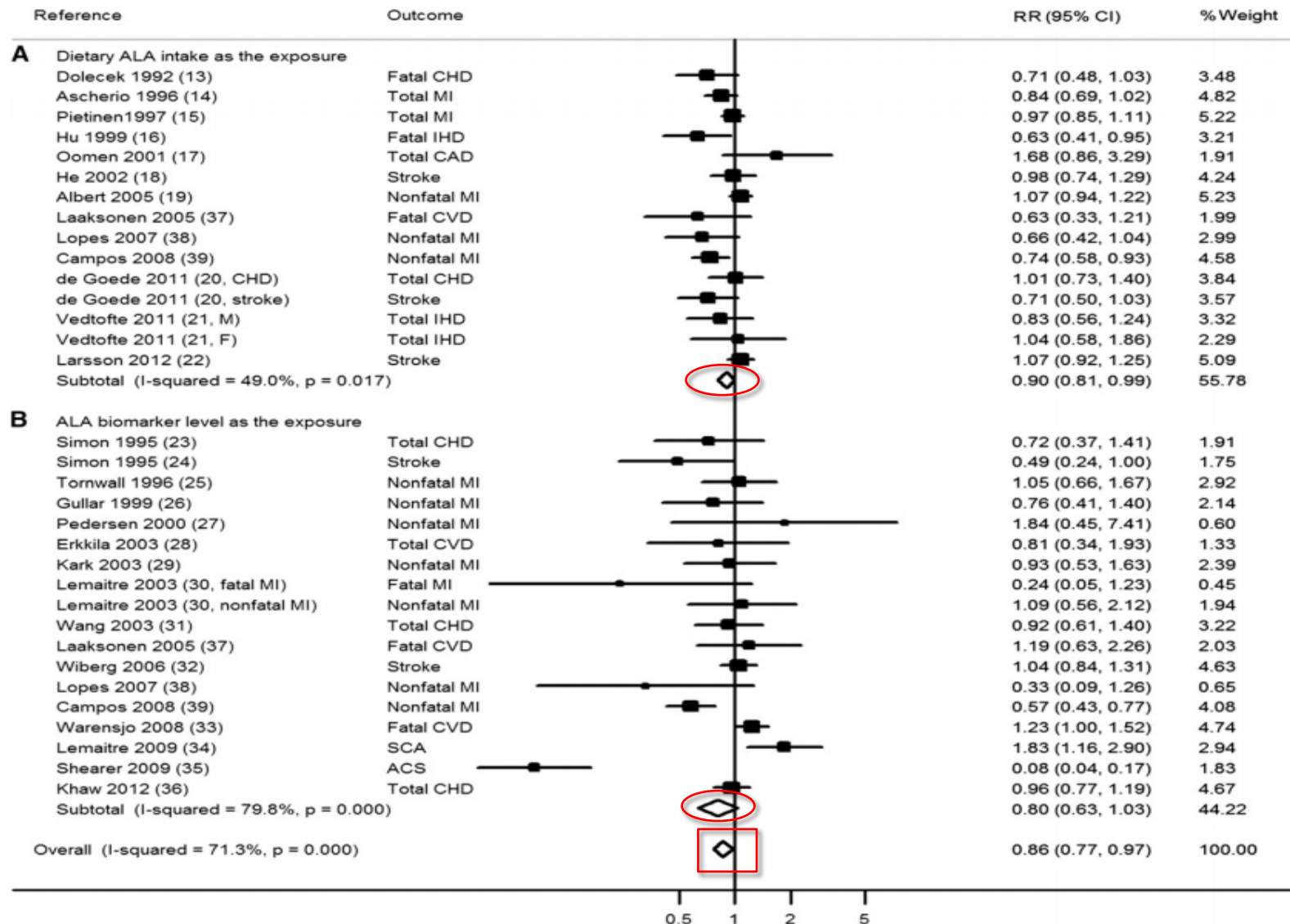
Conclusions: In observational studies, higher ALA (18:3n3) exposure is associated with a moderately lower risk of CVD. The results were generally consistent for dietary and biomarker studies but were not statistically significant for biomarker studies. However, the high unexplained heterogeneity highlights the need for additional well-designed observational studies and large randomized clinical trials to evaluate the effects of ALA on CVD.

27 papers included:

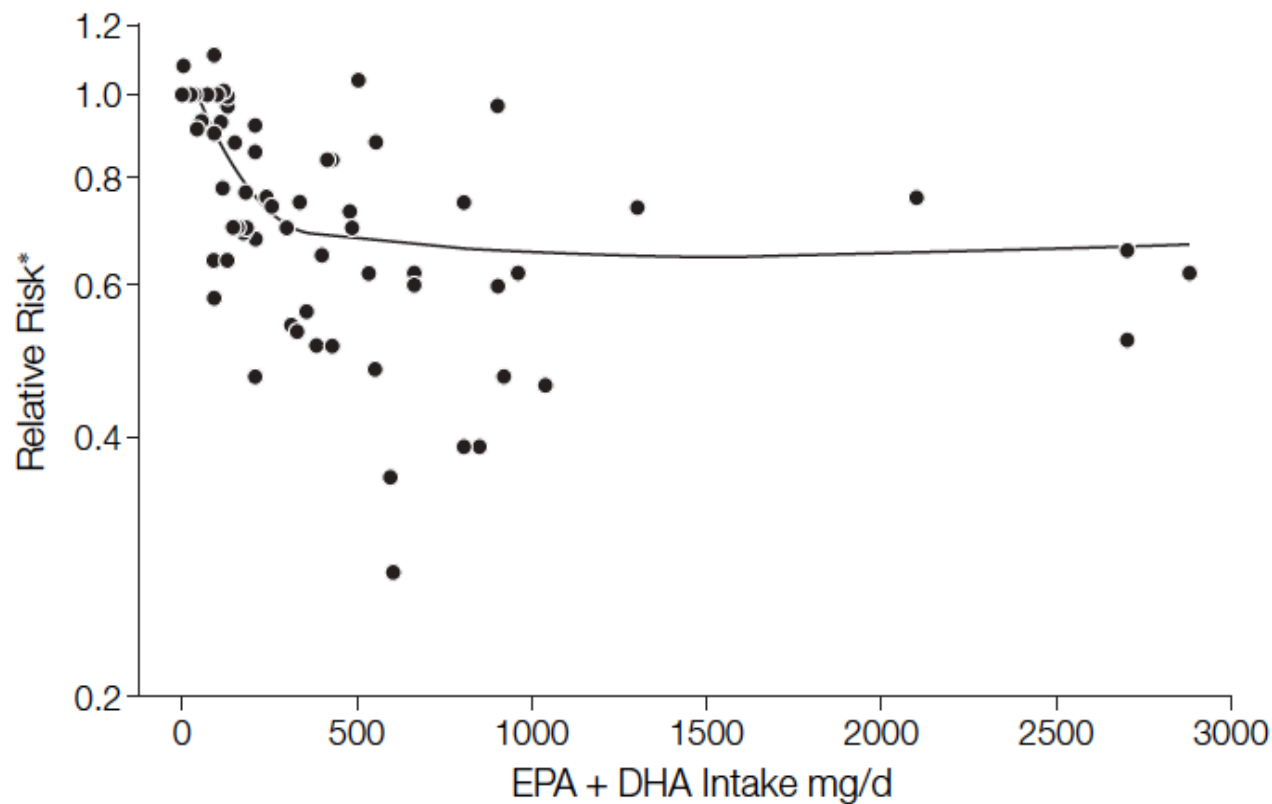
16 Diet & CVD

14 Biomarker & CVD

RR of ALA Intake and Risk of Total CVD Stratified by Dietary Intake and Biomarker Concentration

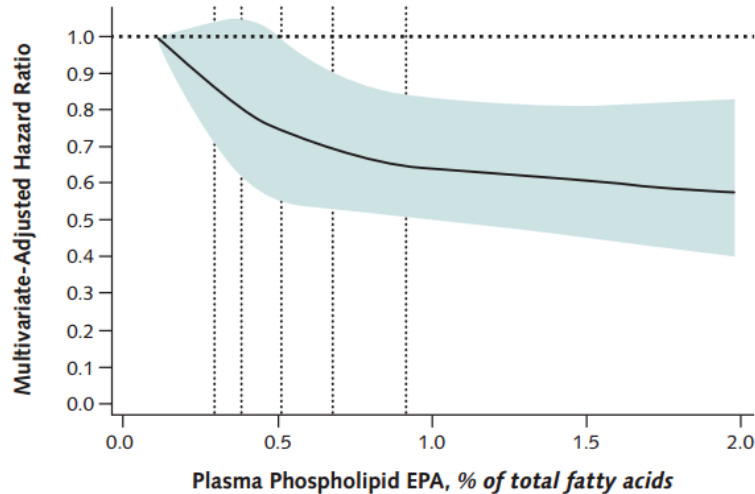


Relationship between Intake of Fish or Fish Oil and Relative Risks of CHD Death in Prospective Cohort and RCTs



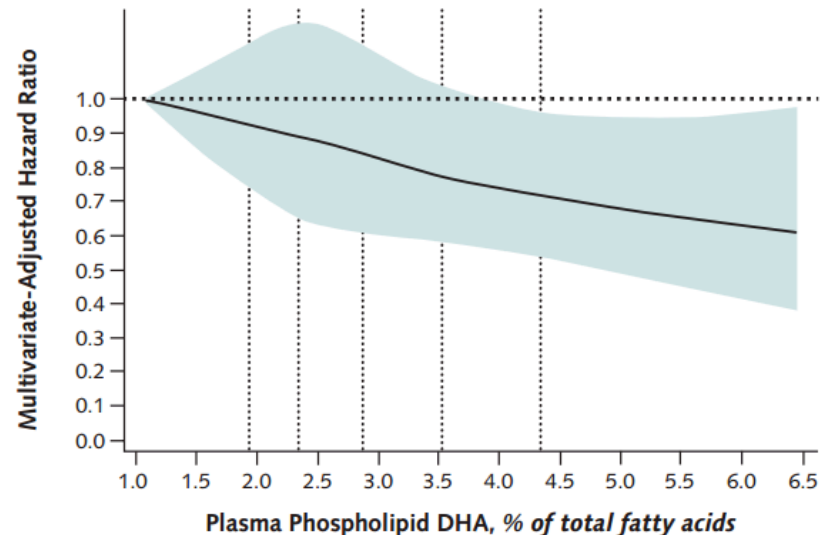
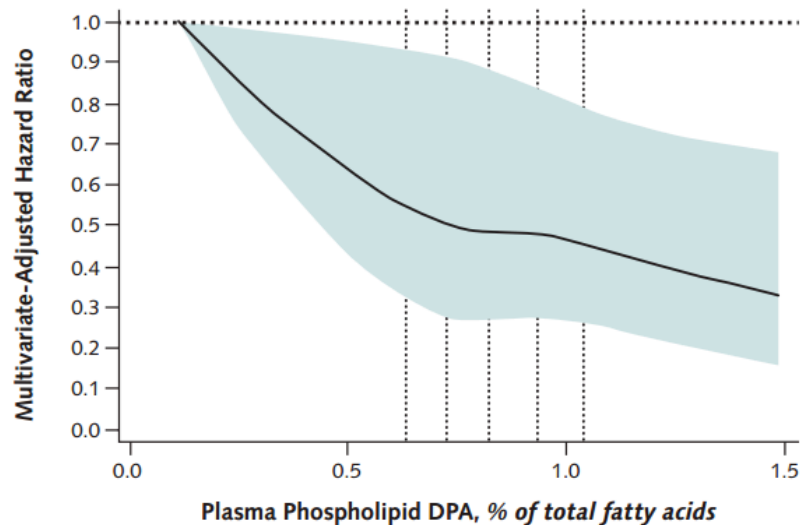
Between 0 and 250 mg/day, mortality risk was decreased by 14.6%;
between 250 and 500 mg/day, risk was decreased by 25%.

Relationship of Plasma Phospholipid EPA, DPA, and DHA Levels with Total Mortality - The Cardiovascular Health Study

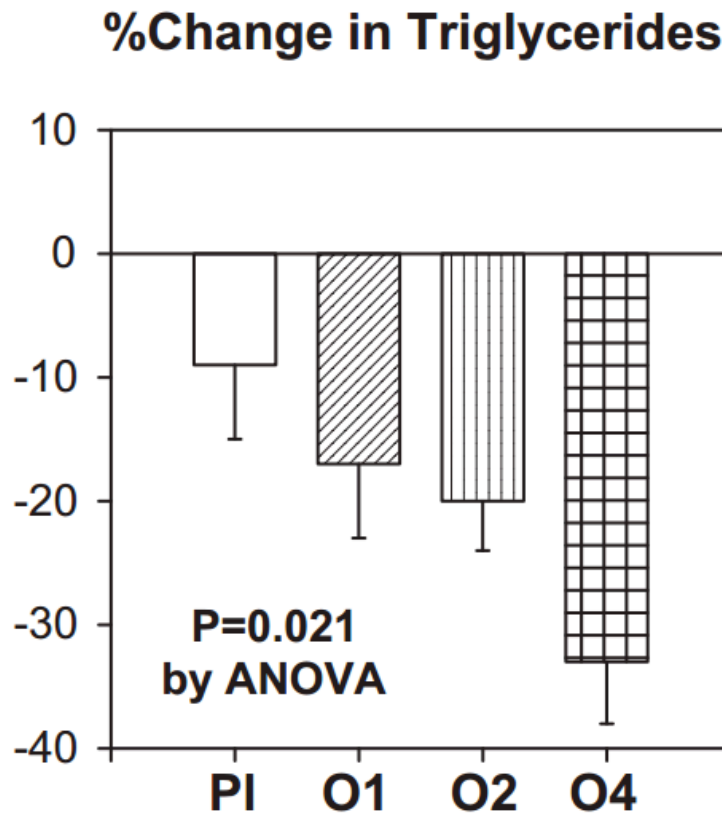


Higher circulating individual and total n3-PUFA levels are associated with lower total mortality, especially CHD death, in older adults (> 65 yr) not taking supplements:

- 0.83 for EPA (95% CI, 0.71 to 0.98; P for trend = 0.005),
- 0.77 for DPA (CI, 0.66 to 0.90; P for trend = 0.008),
- 0.80 for DHA (CI, 0.67 to 0.94; P for trend = 0.006), and
- 0.73 for total n3-PUFAs (CI, 0.61 to 0.86; P for trend < 0.001).



Omega-3 fatty acid treatment (O1, O2, or O4), dose-dependently and significantly reduced triglyceride levels



42 patients on placebo (PI)
44 patients on omega-3 FA 1 g (O1),
43 patients on omega-3 FA 2 g (O2)
44 patients on omega-3 FA 4 g (O4)

Emerging Science on Fatty Acids and Health

- Stearidonic acid (SDA; C18:4n-3) - precursor of EPA
- Palmitoleic acid (C16:1n-7) - mixed results on cardiometabolic risk
- MCTs - benefits on body weight & weight loss
- Pentadecanoic acid (C15:0), heptadecanoic acid (C17:0), and *trans* palmitoleate (*trans* C16:1n-7) in dairy fat - emerging evidence that certain dairy products might reduce CVD risk
- Coconut oil - increases TC, LDL-C and HDL-C

SDA-enhanced soybean oil can significantly improve an emerging marker of cardiovascular health, the omega-3 index (RBC EPA+DHA)

	RBC EPA			RBC DPA			RBC DHA			Omega-3 Index		
	%											
	Ref (17)	Ref (15)	Ref (16)	Ref (17)	Ref (15)	Ref (16)	Ref (17)	Ref (15)	Ref (16)	Ref (17)	Ref (15)	Ref (16)
Base-line	0.96	0.42	0.47	3.16	n/r	2.6	4.23	3.59	3.87	5.19	4.02	4.34
End	1.44	1.21	1.05	3.46	n/r	3.49	3.96	3.59	3.64	5.4	4.8	4.69
Δ	0.48	0.79	0.58	0.3		0.89	−0.27	0	−0.23	0.21	0.78	0.35
% Δ	50	188	123	9		34	−6	0	−6	4	19	8

SDA doses, durations of treatment, and sample sizes (for the SDA treatment groups) were:

(17)= 1 g/d (mean) for 6 weeks, n= 15 (*James et al. Am J Clin Nutr. 2003;77:1140–1145*)

(15)= 3.7 g/d for 16 weeks, n=11 (*Harris et al. Lipids. 2008;43:805–811*)

(16)= 4.2 g/d for 12 weeks, n= 54 (*Lemke et al. Am J Clin Nutr. 2010;92:766–775*)

Multivariate-Adjusted Relationships of Trans-Palmitoleic Acid With Metabolic Risk Factors

Factor	Quintiles of <i>Trans</i> -Palmitoleic Acid Level					P Value for Trend
	1	2	3	4	5	
Median total fatty acid level, %	0.13	0.16	0.18	0.21	0.25	
Adiposity						
Body mass index, <i>kg/m</i> ²	26.7	27.0	26.8	26.9	26.2	0.058
Waist circumference, <i>cm</i>	97.7	98.4	97.2	97.4	96.0†	0.009
Blood lipids						
LDL cholesterol level						0.63
<i>mmol/L</i>	3.26	3.32	3.29	3.26	3.34	
<i>mg/dl</i>	126	128	127	126	129	
HDL cholesterol level						0.043
<i>mmol/L</i>	1.37	1.35	1.35	1.39	1.40	
<i>mg/dL</i>	53.0	52.0	52.1	53.7	54.0	
Triglyceride level						<0.001
<i>mmol/L</i>	1.66	1.51	1.45	1.36	1.34	
<i>mg/dL</i>	147	134‡	128§	120§	119§	
Total cholesterol–HDL cholesterol ratio	4.3	4.3	4.2	4.1‡	4.1‡	<0.001
Inflammation						
C-reactive protein level, <i>nmol/L</i>	27.6	26.7	24.8	25.7	23.8	0.050
Fibrinogen level, <i>μmol/L</i>	9.3	9.6‡	9.7‡	9.8†	9.6‡	0.006
Glucose–insulin homeostasis						
Fasting glucose level						0.103
<i>mmol/L</i>	5.7	5.8	5.7	5.7	5.7	
<i>mg/dL</i>	104	105	103	103	103	
Fasting insulin level, <i>pmol/L</i>	78.5	76.4	74.3	70.8‡	68.1§	<0.001
Insulin resistance, <i>units</i>	3.0	2.9	2.8†	2.7‡	2.5§	<0.001

Circulating palmitoleic acid and risk of metabolic abnormalities and new-onset diabetes¹⁻⁴

Dariusz Mozaffarian, Haiming Cao, Irena B King, Rozenn N Lemaitre, Xiaoling Song, David S Siscovick, and Gökhan S Hotamisligil

- Cardiovascular Health Study - 3630 U.S. men and women
- Higher palmitoleic acid concentrations were associated with:
 - Lower LDL-C
 - Higher HDL-C
 - Lower total cholesterol:HDL-C
 - Lower fibrinogen
 - Higher TG
- Higher adiposity was associated with higher palmitoleic acid concentrations
- Conclusion: Circulating palmitoleic acid is robustly associated with multiple metabolic risk factors but in mixed directions for health

Purified palmitoleic acid for the reduction of high-sensitivity C-reactive protein and serum lipids: A double-blinded, randomized, placebo controlled study

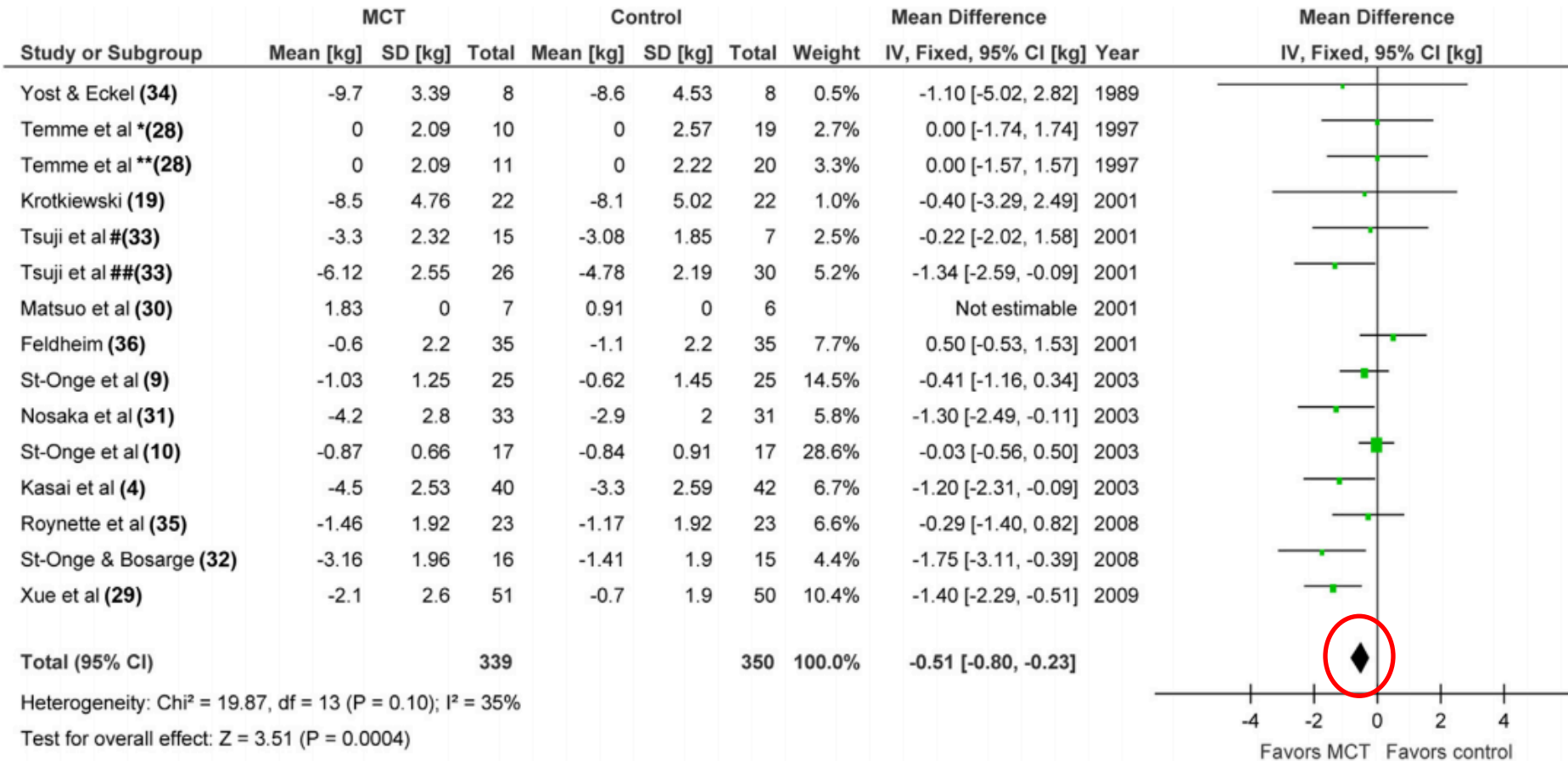
Journal of
Clinical
Lipidology

Adam M. Bernstein, MD, ScD*, Michael F. Roizen, MD, Luis Martinez, MD, MPH

- This was the first randomized controlled trial of purified palmitoleic acid supplementation in humans. It was 30-day parallel, double-blinded, randomized, placebo-controlled study with 60 healthy participants.

CONCLUSIONS: Purified palmitoleic acid may be useful in the treatment of hypertriglyceridemia with the beneficial added effects of decreasing LDL and hs-CRP and raising HDL.

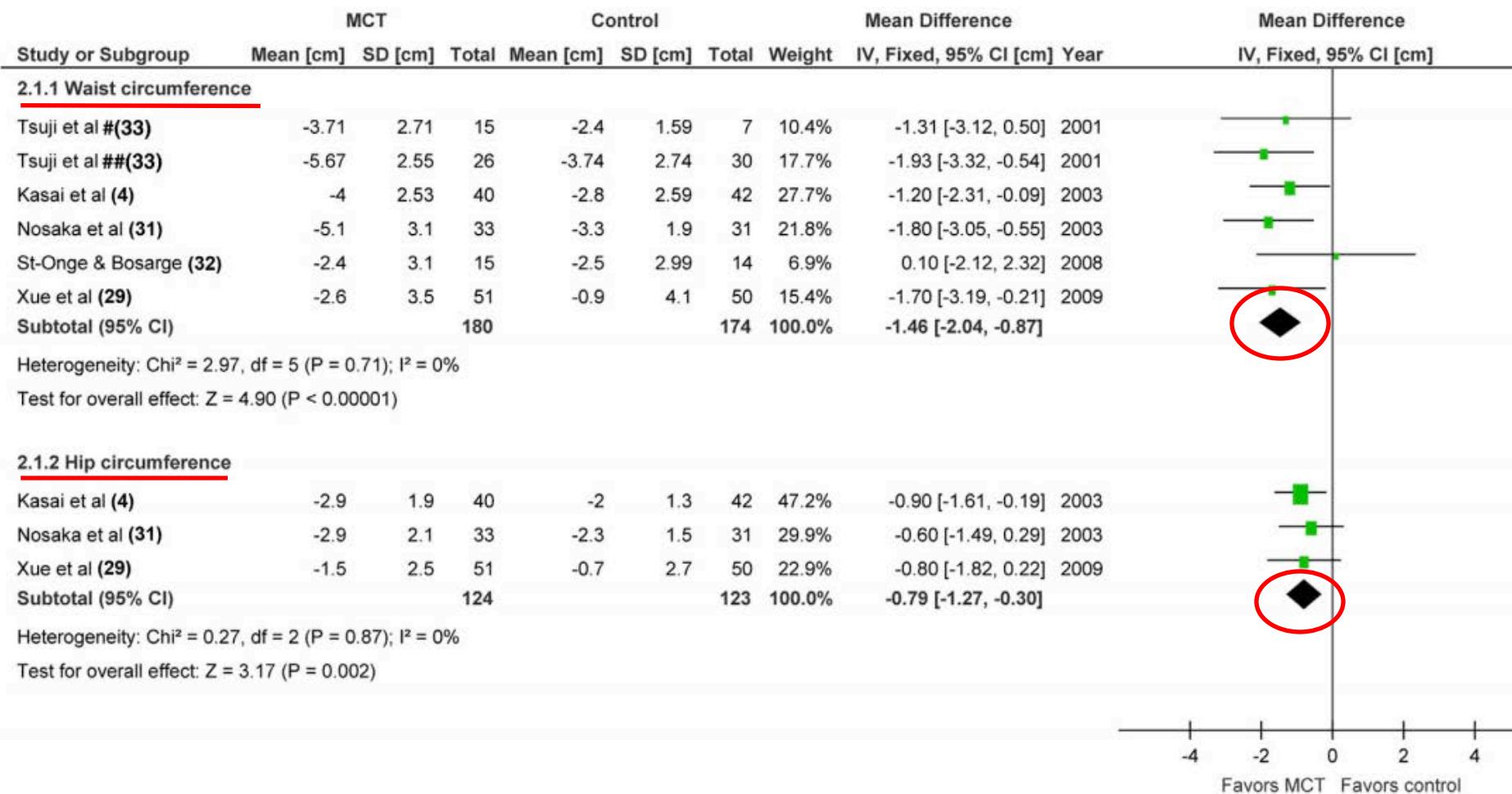
Meta-analysis of RCTs comparing dietary MCTs with a longer-chain triglyceride (control) shows a favorable effect of MCT intervention on body weight (kg).



*Oleic acid as control.

**Myristic acid as control.

Meta-analysis of RCTs comparing dietary MCTs with a longer-chain triglycerides (control) shows a favorable effect of MCT intervention on waist and hip circumference (cm).



Association between Dairy Food Consumption and CVD

- Dairy fat or some other component may protect persons at increased risk of having a first MI (Biong et al., *Eur J Clin Nutr.* 2006;60:236-244).
- In the Swedish Mammography Cohort trial, total cheese intake was inversely associated with MI [HR: 0.74(95% CI: 0.60, 0.91)]. Butter was positively associated with MI risk (HR: 1.34(95% CI: 1.02, 1.75) (Patterson et al., *J Nutr.* 2013;143:74-79).
- In the EPIC-Norfolk Cohort, C15:0 and C17:0 were inversely associated with CVD incidence (OR 0.73, CI 0.59-0.91) (Khaw et al. *PLoS Med.* 2012;9(7). E1001255).

Coconut Oil and Health



- **Coconut Oil Claims**

- Protection against heart disease
- Lose body fat, especially from your abdomen or trunk
- May prevent and even treat cancer, diabetes, and HIV/AIDS
- Boost brain function in people with Alzheimer's disease
- Stimulate thyroid function
- Fight off bacterial, viral, and yeast infections

There is little evidence to support any of these claims.

What Does Coconut Oil Research Reveal?

BODY FAT LOSS?



- There are very few human studies on coconut oil and body fat loss.
- A small pilot study showed that obese men (n = 20) consuming virgin coconut oil (30 ml/d) had a significant reduction in waist circumference over six weeks. However, there was no control group. (*Liau et al. ISRN Pharmacol. 2011;2011:949686.*)
- A randomized, double-blind clinical study that compared supplementation with coconut versus soybean oil (30 ml/d) among obese women (n = 20 for each group) consuming low-calorie diets and walking 50 minutes/d found no differences in body weight between groups, but the coconut oil group had a significant decrease in waist circumference. (*Assunção et al. Lipids. 2009;44;593-601.*)

What Does Coconut Oil Research Show?

Effects on Lipids and Lipoproteins



- “There are few published studies in humans that have examined the effect of coconut oil or virgin coconut oil on lipids/lipoproteins, and all were conducted outside the U.S.”
- The research shows that the SFAs in coconut oil increase TC, LDL-C and HDL-C. The increase in HDL-C is of uncertain clinical relevance, but the increase in LDL-C would be expected to have an adverse effect on ASCVD risk.
- The NLA Expert Panel consensus view is that, if coconut oil is used it is recommended that it be used within the context of a healthy dietary pattern. One tablespoon of coconut oil contains 11.7 g of SFA. This would contribute a significant portion of the recommended SFA daily.

Recommended Dietary Patterns: How Do Fats and Oils Fit?

DGAC 2015 Composition of the Healthy Vegetarian and Healthy Med-style Patterns, and Healthy US Patterns, at 2000 kcals

Food Group/subgroup (units)	Healthy US Patterns	Healthy Vegetarian Patterns	Healthy Med-style Patterns
Fruits (cup eq)	2	2	2.5
Vegetables (cup eq)	2.5	2.5	2.5
Dark Green	1.5/wk	1.5/wk	1.5/wk
Red/Orange	5.5/wk	5.5/wk	5.5/wk
Starchy	5/wk	5/wk	5/wk
Legumes	1.5/wk	3/wk*	1.5/wk
Other	4/wk	4/wk	4/wk
Grains (oz eq)	6	6.5	6
Whole	3	3.5	3
Refined	3	3	3
Dairy (cup eq)	3	3	2
Protein Foods (oz eq)	5.5	3.5	6.5
Meats (red and processed)	12.5/wk	--	12.5/wk
Poultry	10.5/wk	--	10.5/wk
Seafood	8/wk	--	15/wk
Eggs	3/wk	3/wk	3/wk
Nuts/seeds	4/wk	7/wk	4/wk
Processed Soy (incl. tofu)	0.5/wk	8/wk	0.5/wk
Oils (grams)	27	27	27
Solid fats limit (grams)	18	21	17
Added sugars limit (grams)	30	36	29

Summary

- Dietary Guidelines advise decreasing SFA and TFA. DGAC 2015 recommends replacing them with unsaturated fat, particularly PUFA.
- MUFA beneficially affects cardiometabolic risk and decreases visceral adiposity; evidence base is growing.
- Exciting new research frontiers for “minor” dietary fatty acids and health - There is a lot to learn.

Call to Action

- Keep SFA low
- Replace SFA calories with unsaturated fatty acids
- Assure that both MUFA and PUFA (both n-6 and n-3, including ALA, EPA and DHA) are consumed
- Major food sources of unsaturated fatty acids are liquid vegetable oils, nuts and seeds, and seafood
 - Other less predominant food sources are soy, avocado, algae

Thank you

