Non Drug Alternatives to Statins

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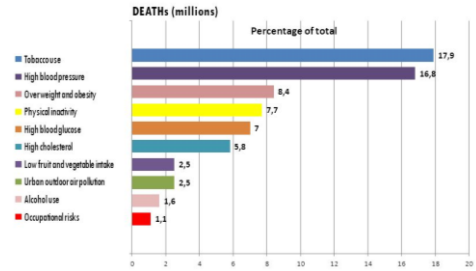
Ranking of selected risk factors: 10 leading risk factor causes of death in high-income countries*, 2004



* Countries grouped by gross national income per capita – low income (US$ 825 or less), high income (US$ 10.066 or more)

Important take home messages

- Major causes of death in high income western society due to lifestyle related factors
- Best approach is to use lifestyle to treat them where possible and appropriate
- The absolute benefits of statins are smaller in primary prevention than in secondary prevention
- Look for the presence of disease and calculate global CV risk
- Dietary change is a powerful therapy in low to intermediate risk patients to lower LDL-C and a great adjunct in high risk patients to achieve target lipid levels
- Overall dietary patterns matters most for chronic disease prevention, rather than focusing on single nutrients (e.g. low fat or low carbohydrate) or single foods

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You cannot supplement or medicate yourself out of poor lifestyle choices

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Non Drug therapy of LDL

WHO IS IT FOR ?

- Patients at low – intermediate risk of cardiovascular events
- To try and lower dose needed of statin medication in those on treatment (secondary prevention) and those experiencing side effects
- 4 areas to focus on:
  - Lowering LDL- C
  - Lowering Triglycerides
  - Raising HDL-C
  - Prevention of events / mortality

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Lifestyle Management

Lifestyle management remains the cornerstone for reducing cardiovascular disease risk including achieving and maintaining optimal lipid levels

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Robert H. Eckel, John M. Jakicic, Jamy D. Ard, Van S. Hubbard, Janet M. de Jesus, I-Min Lee, Alice H. Lichtenstein, Catherine M. Loria, Barbara E. Millen, Nancy Houston Miller, Cathy A. Nonas, Frank M. Sacks, Sidney C. Smith, Jr, Laura P. Svetkey, Thomas W. Wadden and Susan Z. Yanovski

Primary Prevention
Global Risk Assessment

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To estimate 10-year *ASCVD** risk – ACC/AHA 2013

- New Pooled Cohort Risk Equations
  - More accurately identifies higher risk individuals for statin therapy
- Focuses statin therapy on those most likely to benefit
- When Using a risk score calculator, know its limitations and population under consideration Consider MESA score - https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx

10-year ASVD: Risk of first nonfatal myocardial infarction, coronary heart disease death, non-fatal or fatal stroke

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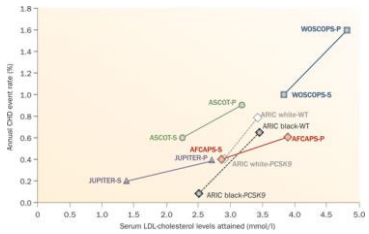
Figure 1 Reductions in CHD annual event rates achieved by decreased serum LDL-cholesterol levels in four major primary prevention trials of statin therapy

nature REVIEWS CARDIOLOGY



Domanski, M. *et al.* (2011) Can we dramatically reduce the incidence of coronary heart disease? *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2011.158

Fall in LDLC by 24 % WOSCOPS – 20 mg pravastain enough to reduce CVS events by 30%

Primary Prevention
Statin Therapy

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- Thresholds for initiating statin therapy derived from 3 exclusively primary prevention RCTs(WOSCOPS , ASCOT, AFCAPS)
- Before initiating statin therapy, clinicians and patients engage in a discussion of the potential for ASCVD risk reduction benefits, potential for adverse effects, drug-drug interactions, and patient preferences
- Calculators don't write Rx, physicians do!

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Coronary Calcium Screening: Early Detection of Heart Disease

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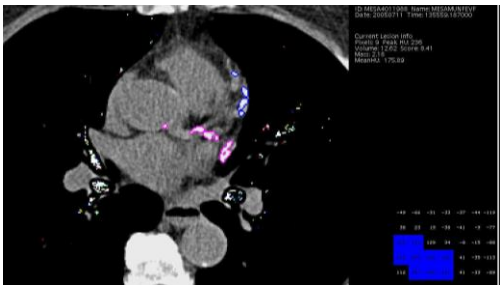

Examples of Coronary Artery Scans

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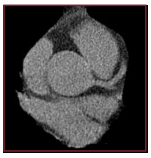
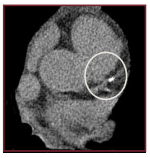


NO CALCIFICATION "zero score"



MODERATE CALCIFICATION

SIGNIFICANT CALCIFICATION "high score"

Kaplan-Meier survival curves by coronary artery calcium (CAC) scores across increasing risk factor (RF) burden

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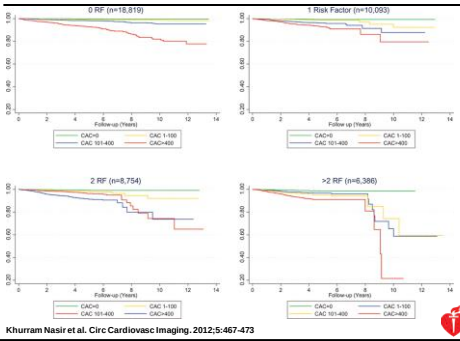


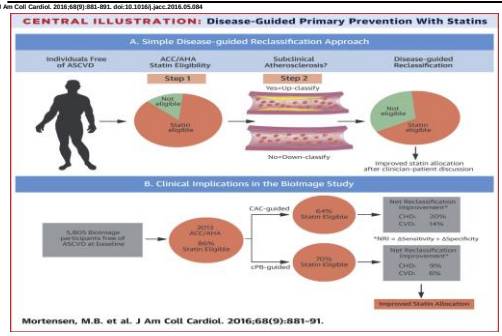
Khurram Nasir et al. Circ Cardiovasc Imaging. 2012;5:467-473

American Heart Association.

JACC Journals

From: A Simple Disease-Guided Approach to Personalize ACC/AHA-Recommended Statin Allocation in Elderly People: The BioImage Study

J Am Coll Cardiol. 2016;68(9):881-891. doi:10.1016/j.jacc.2016.05.084



Mortensen, M.B. et al. J Am Coll Cardiol. 2016;68(9):881-91.

JACC Journals

From: A Simple Disease-Guided Approach to Personalize ACC/AHA-Recommended Statin Allocation in Elderly People: The BioImage Study

J Am Coll Cardiol. 2016;68(9):881-891. doi:10.1016/j.jacc.2016.05.084

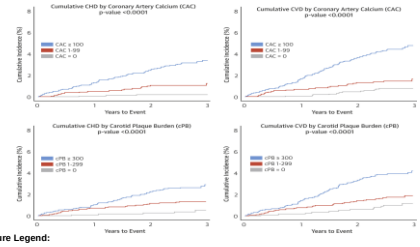


Figure Legend:

Cumulative Incidence of Clinical Events

In the Kaplan-Meier cumulative-event curves for coronary heart disease (CHD) and cardiovascular disease (CVD) events, CAC = 0 and cPB = 0 were associated with low event rates. Abbreviations as in Figure 1.

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Zero Calcium Score = Priceless

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CAC score of 0 predicts an annual mortality rate below 1% out to at least 15 years in those at low or intermediate risk

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LDL targets

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- "normal" : cholesterol values at which level there is no subclinical atherosclerosis
- "abnormal": cholesterol values at which level there is subclinical atherosclerosis, with the severity of "abnormal" depending on the degree of subclinical atherosclerosis.
- Primary prevention : - For patients that need a goal – LDL C < 2.57 mmol/L
- In intravascular ultrasound studies – plaque regression was seen with LDL –C less than 1.8 (SATURN trial)
- " At any level of LDL-C – it depends on your risk "

Intensity statin therapy

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High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** (5) **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Specific statins and doses are noted in bold that were evaluated in RCTs.
Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in italics.

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Supplements with RCT / Level 1 evidence to lower LDL-C (doses)

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- Dietary Fibre (5- 15 g)
- Phytosterols / stanols 1- 2 g (but no effect on clinical endpoints)
- Soy protein / Isoflavones- (50 g)- Likely on basis of reduced saturated fat
- Nuts- (50 g) – almonds, pecans, walnuts
- Red yeast yeast / monocolin K / lovaststin (1 -2 g)

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Fibre

WATER SOLUBLE OR VISCOUS FIBRE

- Carbohydrate derived from unprocessed whole foods
- Reduces absorption of cholesterol, lowers glycemic index
- **Ideally 10g/day for benefit**

- **Good sources** (diet derived)
  - ✓ Oat bran / Barley / B Glucan
  - ✓ Ground flaxseed

- **Supplements**
  - ✓ Psyllium husks
  - ✓ Flax Seed/Meal
  - ✓ a water-soluble, non-digestible fiber made from corn that is called :- *AlphaCyclodextrin* (Nuvexa TM)

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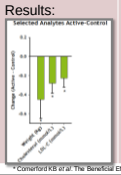
Effect on lipid levels in healthy overweight

Study:	Comerford KB et al.
Study Design:	Double-blind, controlled crossover study
Treatment:	2 FBCx tablets with each fat containing meal (total of 6 tablets per day)
Participant Profile:	N = 28, overweight not obese (BMI :25-29.9 kg/m²), 18-65 years, both males and females
Duration:	t = baseline, 30 days & 60 days
Results:	 • **Reduction in total cholesterol (-5.3%) and in LDL cholesterol (-6.7%) - both p<0.05** • Body weight lower in the active group(0.41± 0.2)kg when compared to placebo (p<0.05) in the absence of dietary change • A trend in reduction of blood insulin, ApoB, and total cholesterol/HDL-cholesterol ratio levels was observed

* Comerford KB et al. The Beneficial Effects α–Cyclodextrin on Blood Lipids and Weight Loss in Healthy Humans. Obesity 19 (2011) 1200–1204

Red Rice Yeast

- Supplement is made by fermenting white rice with the yeast, *Monascus purpureus*.
- Fermentation process turns the yeast red and produces mevinic acids.
- Monacolin K or mevinolin is also found in the statin drug, **lovastatin**.
- These acids inhibit HMG CoA reductase and reduce cholesterol production from the liver.
- Red rice yeast also contains sterols, including beta-sitosterol (also in vegetables), isoflavones (also in soy), and monounsaturated fatty acids (also in olive oil).
- Practice Point:- poor standardization amongst formulations

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Red Rice Yeast cont'd

- Shares the same side effect profile as other statin medications and liver enzymes /CK should be monitored
- 600mg tablets = 2.5 mg Lovastatin
- 4 X 600mg tablets – for 10 mg Lovastatin equivalent = reduce LDL-C 10-20%

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Randomised controlled trial

Effect of a Dietary Portfolio of Cholesterol-Lowering Foods Given at 2 Levels of Intensity of Dietary Advice on Serum Lipids in Hyperlipidemia

JAMA. 2011;306(8):831-839. Jenkins et al

Summary: The Portfolio Diet

- The portfolio diet is a Mediterranean style eating plan
- It has been found to reduce LDL cholesterol by about 30% (similar to 20 mg lovastatin), when the foods were provided and more intense follow up and by 13% when only the dietary recommendations were provided.

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The portfolio diet

- **Daily amounts for 2000 cal(8368 KJ) / day diet)**
- 30 grams of almonds – about 23 almonds (30g). Walnuts, cashews, Brazil nuts and macadamia nuts are also beneficial.
- 20 grams of viscous fiber from foods such as oats, barley, psyllium, and certain fruits and vegetables.
- 50 grams of soy protein from foods such as tofu, soy meat alternatives and soy milk. 10 grams of soy can be obtained from 1 to 2 cups of soy milk, 100g of tofu, or 1/2 cup of textured soy protein
- 2 grams of plant sterols from foods such as Pro- Activ spread (one Tbsp. = 1gm). Other food sources include: avocado, soybeans, olive oil and green leafy vegetables
- Increased consumption of peas, beans, lentils, and peanuts (legumes).

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Portfolio diet sample diet plan

- **Breakfast**: Hot oat bran cereal, soy beverage, strawberries, raw sugar, psyllium, oat bran bread, plant-sterol-enriched margarine, jam
- **Snack**: Almonds, fresh fruit
- **Lunch**: Black bean soup, sandwich made from soy deli slices, oat bran bread, plant-sterol-enriched margarine, lettuce, tomato, and cucumber
- **Snack**: Almonds, psyllium, fresh fruit
- **Dinner**: Tofu (baked with eggplant, onions, and capsicum) pearled barley, vegetables (broccoli, cauliflower, etc.)
- **Snack:** Fresh fruit, psyllium, soy beverage

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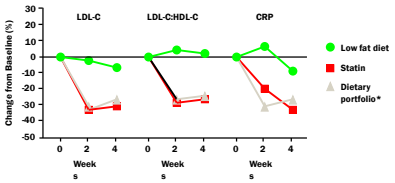
Diet Evidence: Effect on Lipid Parameters and CRP

46 dyslipidemia patients randomized to a low fat diet, a low fat diet and lovastatin (20 mg), or a dietary portfolio* for 4 weeks



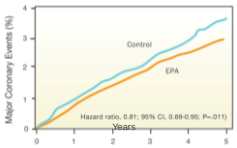
*Enriched in plant sterols, soy protein, viscous fiber, and almonds

Jenkins DJ et al. *JAMA* 2003;290:502-10

ω-3 Fatty Acids Evidence: Primary and Secondary Prevention

Japan Eicosapentaenoic acid Lipid Intervention Study (JELIS)

18,645 patients with hypercholesterolemia randomized to EPA (1800 mg) with a statin or a statin alone for 5 years



ω-3 fatty acids provide CV benefit, particularly in secondary prevention

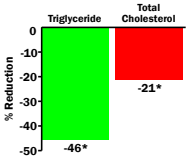
18 % reduction in cardiovascular events

*Composite of cardiac death, myocardial infarction, angina, PCI, or CABG

Yokoyama M et al. Lancet. 2007;369:1090-8

ω-3 Fatty Acids Evidence: Effect on Lipid Parameters

27 patients with hypertriglyceridemia and low HDL-C treated with ω-3 fatty acid (4 grams/day) for 7 months



HDL-C=High-density lipoprotein cholesterol
*P≤.05
Source: Abe Y et al. *Arterioscler Thromb Vasc Biol* 1998;18:723-731

Fish Oil

PRACTICE POINTS

- The recommended dose of EPA + DHA is **1000 mg daily for prevention** and up to **4000 mg daily for lowering triglycerides**. (4 – 6 high strength capsules a day)
- **Dosing fish oil:** Fish oil capsules will often come in a total oil dose of 500-1000 mg.
- When dosing for therapeutic benefit, to look at the amount of EPA + DHA in each capsule.
- If 1 gm of fish oil capsule has 300 mg of EPA and 200 mg of DHA (total of 500 mg EPA + DHA), - need to prescribe 2 capsules to = 1 gm of therapeutic omega-3 essential fatty acids.
- *Freezing the capsules and taking them at night can also reduce side effect of burping and fishy taste .*

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Summary Benefits From LDLC /TG lowering therapies

Therapy	Result
Soluble fiber in diet (5–15 g/d) (oat bran, fruit, and vegetables)	↓ LDL-C 1% to 10%
Soy protein (50g/d)	↓ LDL-C 5% to 7%
Plant Sterol esters (2 g/d) (inhibit cholesterol absorption)	↓ LDL-C 10% to 15%
Fish oils (3–9 g/d) (n-3 fatty acids)	↓ Triglycerides 25% to 35%

Jones P.J. *Curr Atheroscler Rep.* 1999;1:230-235.
Lichtenstein AH. *Curr Atheroscler Rep.* 1999;1:210-214.
Rambjor GS et al. *Lipids.* 1996;31:S45-S49.
Ripsin CM et al. *JAMA.* 1992;267:3317-3325.

Lifestyle Modifications to Raise HDL-C Levels

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- Smoking Cessation
  - HDL-C levels are lower in smokers (by 7%-20%), and return towards normal after smoking cessation
- Whole Food ,Plant Based , Mostly green
- Weight Reduction
  - For every 3 kg of weight loss, HDL-C levels increase by 2-4%, but only after stabilization at new lower weight
- Exercise
  - Aerobic exercise (40 min, 3-4 x weekly) may increase HDL-C by 5-10%
  - Physical exercise also reduced TG and reduced statin initiation.

Rösener S et al. *Atherosclerosis.* 1987;64:125-130.
Wood PD et al. *N Engl J Med.* 1988;319:1173-1179.
Ornish D et al. *JAMA.* 1998;280:2001-2007.
Cullen P et al. *Eur Heart J.* 1998;19:1632-1641.
Kokkinos PF et al. *Arch Intern Med.* 1995;155:415-420.
Kodama S et al. *Arch Intern Med.* 2007;167:999-1008

What doesn't work / little evidence/ Could be promising

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- *Krill oil* – no outcomes data – higher doses needed
- *Policosanol*- wax derived from sugar cane - may be promising
- *Coconut oil* - ?? Raise HDL – limited studies
- *Garlic* – limited effect on LDL- C in large study , Budoff has shown aged garlic may retard atherosclerosis progression.
- *Polyphenols* – anti-oxidant effects – resveratrol
- *Tea* – may reduce LDL by 0.5 mmol - more data needed.
- *Probiotics* - Lactobacillus plantarum- may promote breakdown bile salts , absorb cholesterol from GUT. – limited in Vivo studies. Small studies, industry sponsored

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FROM NEW ENGLAND JOURNAL MEDICINE 2013

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-Raventos, 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*

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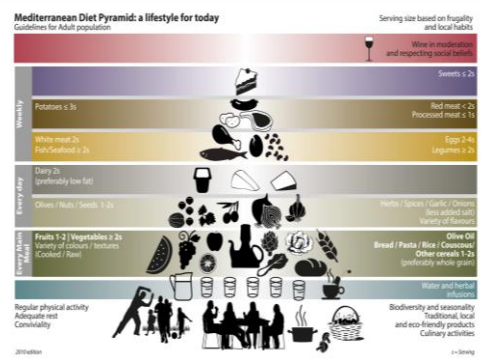

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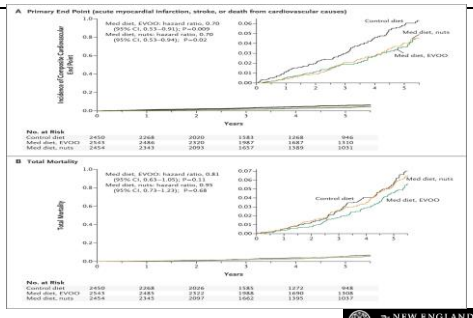
Kaplan–Meier Estimates of the Incidence of Outcome Events in the Total Study Population.



The NEW ENGLAND JOURNAL of MEDICINE

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- Among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events.
- Most striking things is supplemental foods – not dietary advice- nuts(30g/day) ,EVOO (1 Litre / week)
- Reduction in cardiovascular events most evident in stroke.

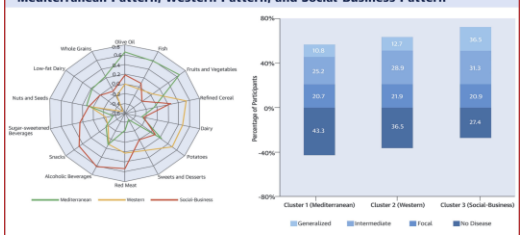
The NEW ENGLAND JOURNAL of MEDICINE

JACC Journals

From: Association Between a Social-Business Eating Pattern and Early Asymptomatic Atherosclerosis

J Am Coll Cardiol. 2016;68(8):805-814. doi:10.1016/j.jacc.2016.05.080

CENTRAL ILLUSTRATION: Social Eating and Atherosclerosis: Comparison of Mediterranean Pattern, Western Pattern, and Social-Business Pattern



Peñalvo, J.L. et al. J Am Coll Cardiol. 2016;68(8):805-14.

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Important take home messages

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- Major causes of death in high income western society due to lifestyle related factors
- Best approach is to use lifestyle to treat them where possible and appropriate
- The absolute benefits of statins are smaller in primary prevention than in secondary prevention
- Look for the presence of disease and calculate global CV risk
- Dietary change is a powerful therapy in low to intermediate risk patients to lower LDL-C and a great adjunct in high risk patients to achieve target lipid levels
- Overall dietary patterns matters most for chronic disease prevention, rather than focusing on single nutrients (e.g. low fat or low carbohydrate) or single foods

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Impact of Lifetime Activities on Longevity

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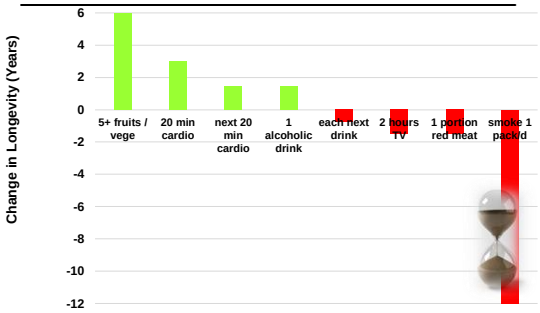

Adapted from Spielgelhalter D, BMJ 2012;345:e8223

Preventative Cardiology Research at MUHSC

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- Arterial Stiffness and Pulse Wave analysis (Dr Mark Butlin, Prof Hosen Kiat)
- Ambulatory BP project for optimisation of BP control (A/Prof Edward Barin, Prof Alberto Alvolio)
- CT Coronary Angiography and Calcium Scoring (Dr Chris Nauom, Dr Jason Kaplan)

Macquarie University Health Sciences Centre

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Leveraging and integrating the world-class Macquarie University Hospital; the University's newly created fifth Faculty, the Faculty of Medicine and Health Sciences; and our new entity, Macquarie University Clinical Associates, Macquarie is on a journey of transformational leadership in the Australian healthcare sector.

Heal. Learn. Discover

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Macquarie University Health Sciences Centre Cardiology

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Thank you

JASON.KAPLAN@MUHSC.ORG.AU

August 2016

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