

Extra Slides for Q and A

Diet Patterns



Randomized Controlled Trials

Two Balanced, Antioxidant–Rich Diet Patterns

5-10 Fruits and Vegetables/day

1. DASH (Dietary Approaches to Stopping Hypertension) Appel, L, NEJM, 1997

- 8 week trial (306 men and women)
- Lowered systolic and diastolic blood pressure, compared to typical American diet
 - “Our results add to the evidence that *dietary interventions can be as effective as – or more effective than – antihypertensive drugs... and should be a routine first-line treatment*” Stephen Juraschek, M.D
- Additional beneficial effects observed in many of the 20 trials
 - Lower: Oxidative stress and inflammatory markers, and other metabolic syndrome risk factors (triglycerides, insulin sensitivity, LDL cholesterol)
 - Benefit is often greater in those with risk factors

Meta-analysis and review: Siervo, M, 2015

DASH Diet Plan

Food Group	Servings for 2000 kcals
Whole grains	6-8/day: 1 slice bread, 1 ounce cereal 1/2 cup cooked rice or cereal
Vegetables	4 to 5/day: 1 cup raw leafy 1/2 cup cut raw or cooked vegetable
Fruits	4 to 5/day: 1/2 cup or medium fruit
Fat-free or low-fat Dairy	2-3/day: cups milk or yogurt or 1 ounce cheese
Lean meats, poultry, fish	6/week: 1 oz meats, poultry, fish, or 1 egg
Nuts, seeds, legumes	4-5/week:
Fats and oils	2-3/day: 1 tsp oils, 1 Tbsp mayo, 2Tb salad dressing
Sweets and added sugars	≤ 5/week (Tbsp sugar or jam), 1/2 cup sorbet

2. Mediterranean Diet

Randomized Controlled Trials

2. Primary Prevention:

PREDIMED (<http://www.predimed.es>)

- **Reduced incidence of CVD and Type 2 diabetes over 4.8 years**
- Associated with reduction of inflammatory markers, blood pressure, BMI, fasting glucose, cholesterol (Meta-analysis: Nordmann, AJ, 2011)

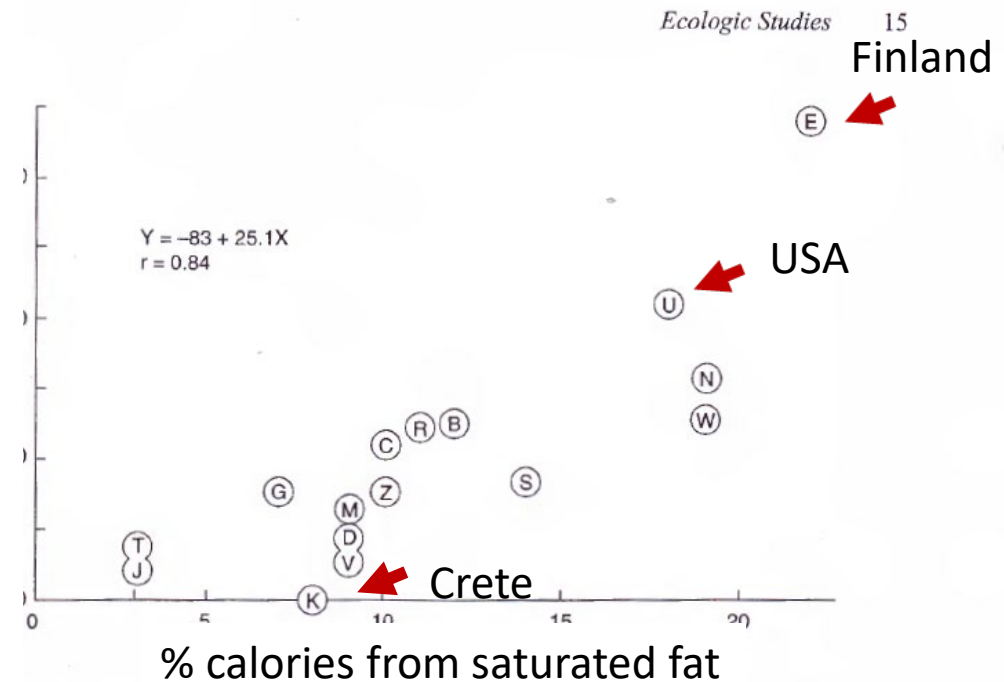
Meta-analysis of prospective studies confirms significant risk lowering for CVD, cancer and total mortality and neurodegenerative diseases (Sofi, F, 2010)

1. Secondary Prevention:

Lyon Heart Study (de Lorgeril, M (1999)
Reduced secondary heart events relative to a low-fat “prudent” diet

The Seven Country Study: Ten-year Coronary Heart Disease Death Rates

Deaths
Per 10,000
People



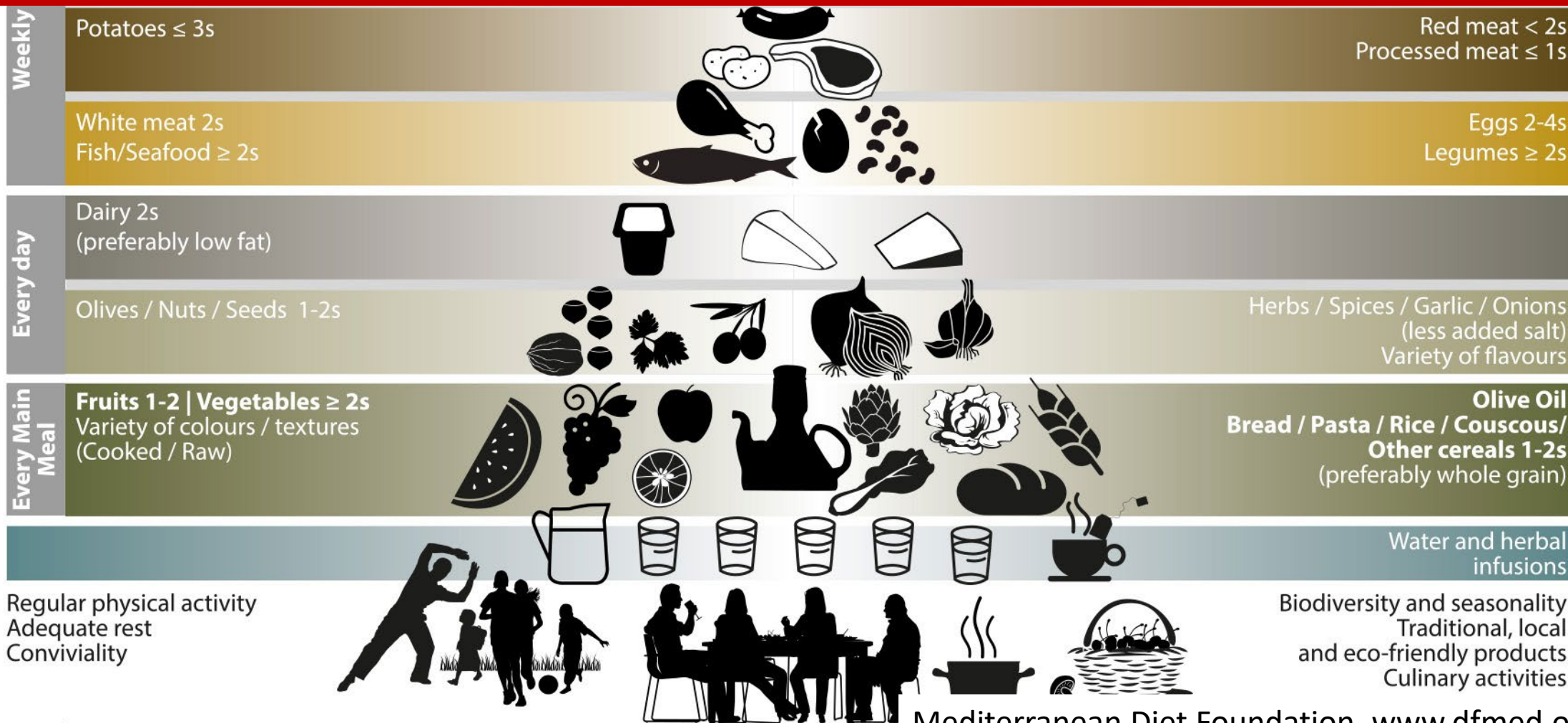
Keys, A: Seven Countries: A multivariate analysis of death and coronary disease. Harvard University Press, 1980

Mediterranean Diet

Conclusive for cardiovascular disease and diabetes

Suggestive for cognitive neurodegeneration

Benefit likely but untested: AMD, glaucoma



PREDIMED and Other Mediterranean Diet Patterns Not Identical

- Emphasize:
 - Fruits and vegetables $\geq 5/\text{day}$, nuts $>3/\text{week}$, seeds, legumes $\geq 3/\text{week}$
 - Olive Oil (or encourage high monounsaturated fat/saturated fat ratio)
 - Legumes
 - Fish
 - White instead of red meat
 - Wine with meals
- Dairy: Allowed, but not promoted (Some variations suggest 2-3 serving/day) by most, but Alternative plans encourage 2-3/day
- PREDIMED intervention groups provided olive oil (1L/week) and nuts (30g/day)



Observational Studies of Mediterranean–*Like* Diet Patterns and Retinal Neurodegeneration

AMD

- Lower risk of one or more (early or late AMD) phenotypes in five cohorts:
 - Prospective
 - AREDS Cohort over 13-years (Merle, B, 2015; Agron, E, 2018-Poster# 0047; Chui, CJ, 2014)
 - European Eye Study (Hogg, RE, 2016)
 - Eye-Risk Consortium, Merle,B,2018,abstract#3010)
 - Longitudinal Prevalence Studies
 - Melbourne Collaborative Cohort Study (Islam, FMA, 2014)
 - CAREDS (Mares, 2011)

Glaucoma

- No studies

Specific Diet Components Which May Account for Lower Age-Related Retinal Neurodegeneration in Mediterranean Diet- like: Lifestyles Patterns

- Conclusive Evidence
 - Antioxidants (Vitamins C, E, Carotenoids) (Fruits and Vegetables)
 - Zinc
- Suggestive Evidence
 - Other Non-nutrient Antioxidants: **Lutein**, Flavonoids
 - Nitrates
 - **Omega- 3 fatty acids, Vitamin D, B vitamins**

2015-2020 Dietary Guidelines for Americans

<https://www.choosemyplate.gov/dietary-guidelines>



Supplements

If you have macular degeneration....

Some US doctors recommend a supplement which lowered risk of progressing from intermediate to advanced AMD 25% over 6 years.

- **AREDS Supplement:**
 - Beta-carotene: 15 mg
 - Vitamin C: 500 mg
 - Vitamin E: 400 IU
 - Zinc: 80 mg (with 2 mg copper)
- **Some supplements**
 - Add:
 - Lutein and zeaxanthin
 - Fish oils
 - Selenium
 - Reduce:
 - Vitamin E
 - Zinc

While further conclusive evidence for benefits to slow or prevent retinal neurodegeneration is obtained we can prevent deficiencies by monitoring status for :

- Serum (OH) vitamin D

- Recommending Vitamin D supplements for bone health (safe up to 4,000 IU)
- Physical activity outside (30 minutes) for everyone

- Vitamin B₁₂

Check: Homocysteine and methyl malonate levels for vitamin B₁₂ inadequacy

If present: vitamin B₁₂ supplements (considered safe; high doses (1mg) tested in HOPE trial)



- Vitamin B₁₂

- Part of a supplement which lowered risk for macular degeneration
- Getting the daily requirement is especially important:
 - If not eating food sources (milk, eggs, fish, poultry or dairy)
 - In people who have low absorption from foods (10-30% of people over 50 years)
 - Possibly in people who get high levels (More than 100 micrograms/day) of synthetic folic acid from fortified breads and cereal, or supplements (rather than natural folate from foods).
 - The synthetic form elevates blood folate more than the natural form.
 - Research of other disorders of the central and peripheral nervous systems indicate that clinical manifestations of B12 insufficiency are exacerbated by high folate status

If you have a *family history* of macular degeneration but not the condition yet...

Supplement Use:

- Benefit is unknown
- A vitamin D containing supplement might help
- May be risks in using high-dose supplements long-term

Research supports potential benefits of:

- Healthy Foods
- Exercise
- Breastfeeding

Supplements Which *Might* Help

-Whether you have AMD or a Family History-



- Vitamin D

- Adequate vitamin D could lower odds of having AMD, *especially if you have certain high risk genes* *

* Millen. AE, et al. Arch Ophthalmol. 2011;129(4):481-89
Millen AE, et al. JAMA Ophthalmology. 2015 Oct 1;133(10):1171-9

What about herbals?



- Bilberry, Wolfberry (Goji berry), Astaxanthin
- Folk traditions suggest benefit- research is not sufficient to prove or disprove
- The amount in pills is not regulated
 - Safety is untested
- The substances they provide can be found in foods

Omega-3 fatty acids



- **Supplements:**

- Randomized clinical trials of DHA and/or EPA are inconclusive for development of advanced AMD

AREDS2: No benefit after 5 years

- 2080 men and women at high risk of progressing to advanced AMD randomized:
- DHA (350 mg) and EPA (650 mg) vs control

Nutritional AMD Treatment 2 (NAT2) After 3 years no benefit (except in those without ARMS2 risk alleles)

- 263 men and women randomized to:
- DHA (840 mg) and EPA (270 mg)
- Pooled risk 0.96 (0.84, 1.10) (Evans JR, 2014)

Cohort studies of supplements are limited

Omega-3 fatty acids



- **Status is dependent on intake and genes**

- FADS1 AMD risk alleles (encodes protein to synthesize DHA/EPA from alpha-linolenic acid)

Biological Plausibility:

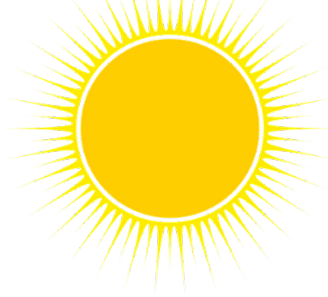
- Membranes, especially photoreceptor outer segments
 - Fluidity and function
 - Synthesis of anti-inflammatory cytokines

- **Dietary Fish or Long-chain Omega-3 Fatty Acids:**

- Associated with advanced AMD in 20 studies, across 14 samples in different populations (Recent Review: Souied, E, 2015)



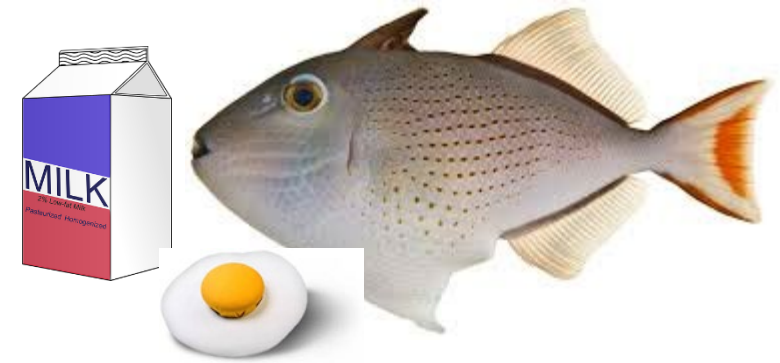
Vitamin D



- **Inadequacy Common:** 15% of the world's population
- **Biologic Plausibility**
 - Vitamin D receptors in retina
 - 4 Clinical studies: Status correlated with retinal thickness (Macula, GCL, RNFL)
 - Experiments in Cells, Rodents:
 - Neuroprotective
 - Anti-angiogenic and anti-inflammatory
- **Large Observational Studies**
 - **AMD-** Suggestive (but inconsistent)
 - **Open-angle Glaucoma, or Risk Factors-** Suggestive but more limited
- **Randomized Clinical Trials**
 - None

B vitamins

B₁₂, B₆, folate



- **Randomized Clinical Trials**

- One Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS), combined folic acid, B₆, and B₁₂: 34% reduction in late AMD over 7 years (only 55 cases)

- **Mechanisms**

- Preventing elevation in homocysteine
- Moderately elevated levels is a strong risk factor for vascular dementia and Alzheimer's disease (Reviewed: Smith, AD,2016)

- **Large Observational Studies- suggestive, but limited**

- **AMD (any)**

- Homocysteine related to increased risk: 2 studies (NS trends in 4)
- Dietary B₁₂: Protective trend : 2 studies
- Serum B₁₂, and supplement use related to any AMD: 1 study

- **Glaucoma: limited**

- **Vitamin B₁₂ inadequacy is common in people not consuming supplements or fortified foods (cereals):**

- 10 to 30% of persons over 50 years have low absorption from foods

Avoid Excess

- If you smoke: take a supplement without beta-carotene
- Multivitamins: OK??
 - Might have most benefit in people who are deficient
- Sources of vitamins and minerals add up:
 - Cereals, nutrition bars, multiple vitamin pills
- Too much may not be good :
 - Vitamin E, zinc, beta-carotene, vitamin A, folate, selenium, vitamin C

Antioxidants and Glaucoma

- **Mechanisms- Suggestive**

- Oxidative stress contributes to glaucomatous changes:
 - Trabecular meshwork (cultured cells)
 - Ganglion Cells
 - Dysregulation of ocular blood flow
- Allelic variant in a vitamin C transporter gene (SLC23A2) was associated with POAG and low serum vitamin C (Zanon-Moreno, V, 2011)



Antioxidants and Glaucoma

- **Prospective Cohort Studies- Inconsistent and Limited**
- **Recent exceptions:**
 - Recent meta-analysis including 940 cases of open-angle glaucoma (n=123,697)
Ramdas, WD, 2018
 - **Protective associations:**
 - Carotenoid precursors to vitamin A (especially dark green vegetables)
 - Vitamin C
 - Recent 25-year follow-up of NHS and MHPS, including 1483 cases of POAG
Kang, JH, 2016
 - Protective associations: Dietary nitrate (an exogenous supply of nitrous oxide) and leafy greens lowered POAG (20-30%), especially POAG with early paracentral VF loss (40-50%)
- **Randomized Clinical Trials- Limited**
 - No effects of combined antioxidants with or without omega-3 fatty acid supplementation for two years in 117 patients (Garcia-Medina, J, 2014)



Supplements in Slowing or Preventing Glaucoma

- Not well studied
- In one clinical trial:
 - Selenium Increased Risk
 - Nutrition Prevention of Cancer Trial:
 - 200 mcg Selenium *increased* glaucoma risk two fold
 - Continued use after trial ended increase risk ten-fold

MISC



“A Walk in Nature Never Fails to
Deliver More Than I Expect”

Aldo Leopold