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Richard T. James Jr. M.D.
Editor/Publisher.
Evidence Is Now Sufficient To Advise Against Routine Supplementation

12-1 ENOUGH IS ENOUGH: STOP WASTING MONEY ON VITAMIN AND MINERAL SUPPLEMENTS

Three articles in this issue of Annals address the role of vitamin and mineral supplements for preventing the occurrence or progression of chronic diseases:

1) Review of trial evidence to update the US Preventive Services Task Force recommendations on the efficacy of vitamin supplements for primary prevention in community dwelling adults with no nutritional deficiencies. Three trials of multivitamin supplements and 24 trials of single or paired vitamins concluded that there was no clear evidence of a beneficial effect on all-cause mortality, cardiovascular disease, or cancer.

2) Evaluated the efficacy of a daily multivitamin to prevent cognitive decline among 5947 men age 65 and older participating in the Physician’s Health Study. After 12 years, there was no difference between the multivitamin and placebo groups in overall cognitive performance or memory. Adherence to the intervention was high. The large sample size resulted in precise estimates showing that multivitamin supplements in a well-nourished elderly population did not prevent cognitive decline. These findings are compatible with a recent review of 12 fair- to good-quality trials that evaluated dietary supplements, including multivitamins, B vitamins, vitamin E and C, and omega-3 fatty acids in persons with mild cognitive impairment or mild or moderate dementia. None of the supplements improved cognitive function.

3) Assessed the benefit of high-dose 28 component multivitamin supplement in 1708 men and women with previous myocardial infarction. After a median follow-up of 4.6 years, there was no significant difference in recurrent cardiovascular events with multivitamins vs placebo.

Other review and guidelines that have appraised vitamin and mineral supplements in primary or secondary prevention of chronic disease have consistently found null results or possible harms. Evidence involving tens of thousands of people randomly assigned in many clinical trials show that beta-carotene, vitamin E, and possibly high doses of vitamin A supplements increased mortality and that other antioxidants, folic acid, and B vitamins and multivitamin supplements had no clear benefit.

Despite this evidence on no benefit and possible harm, use of multivitamin supplements increased among US adults from 30% between 1988-1994 to 39% between 2003-2006, and overall use of dietary supplements increased from 42% to 53%.
Trends show a steady increase in multivitamin supplements and a decline in some individual supplements such as beta-carotene, and vitamin E following reports of adverse outcomes in lung cancer and all-cause mortality respectively.

In contrast, sales of multivitamins and other supplements have continued to grow, reaching $28 billion in 2010. Accumulated evidence is now sufficient to advise against routine supplementation.

The message is simple—most supplements do not prevent chronic disease or death. Their use is not justified. They should be avoided.

This message is especially true for the general population with no clear evidence of deficiency who represent most supplement users in the US.

Vitamin D supplementation, however, is an open area for investigation. Clinical trials have been equivocal. The effect of supplemental D on falls in older people is contradictory. Some trials indicate a less risk of falls; some no benefit; one trial reported an increase. Current widespread use of D is not based on solid evidence that benefits outweigh harms.

Conclusion:

Beta-carotene, vitamin E, and possibly high doses of vitamin A supplements are harmful.

Other antioxidants, folic acid, B vitamins, and multivitamin and mineral supplements are ineffective for preventing mortality due to major chronic diseases.

We believe the case is closed. Supplementing the diet of well nourished adults with (most) minerals and vitamin has no clear benefit and might even be harmful.

These vitamins should not be used for chronic disease prevention.

Annals of Internal Medicine December 17 2013;159:850-51 Editorial. first author Elise Guallar, Johns Hopkins Bloomberg School of Medicine, Baltimore MD


2) Annals Internal Medicine December 17 2013;159:806-14 “Long-Term Multivitamin
Supplementation and Cognitive Function in Men” first author Francine Grodstein, Harvard Medical School, Boston Mass

3) Annals Internal Medicine December 17 2013;159:797-804 “Oral High-Dose Multivitamins and Minerals after Myocardial Infarction” first author Gervaso A Lamas, Mount Sinai Medical Center, Miami Beach FL

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**Maintenance Of D Stores In The Elderly, Combined With Sufficient Dietary Calcium, Remains An Effective Approach For Prevention Of Hip Fractures.**

12-2 VITAMIN D SUPPLEMENTATION : Bones of Contention

Clinical investigators have linked D deficiency or insufficiency with osteoporosis. This seemed logical because osteomalacia (softening of bone in adults due to impaired mineralization) can cause fractures and often co-exists histologically with osteoporosis.

D supplementation has become established for prevention of osteoporosis.

A systemic review and meta-analysis\(^1\) (first author Ian R Reid) shows that the story is more complex. The Reid article included 23 randomized, controlled trials of D on bone mineral density (BMD; 4000 participants; mean age 59). Supplementation for 2 years resulted in no change in BMD at 4 major skeletal sites (spine, hip, radius, and total body). There was a significant increase (0.8%) in the femoral neck.

Any benefit of BMD was independent of calcium supplementation, baseline concentrations of 25-OH-D, duration of treatment, or age. The investigators concluded that widespread D prophylaxis in healthy community dwelling adults to prevent osteoporosis is not warranted.

How can these surprising findings be reconciled with clinical practice and public health strategies to prevent osteoporosis?

1) BMD was the primary outcome in the analysis, and is widely used as a surrogate measure for fracture. However, changes in BMD in this age group are a modest predictor of subsequent fractures. Even with bisphosphonates treatment in high-risk elderly patients (> age 70) the BMD increase accounts for less than 50% of the effect on fractures. Thus, the absence of a positive relationship between D supplementation and change in BMD could be dismissed.

2) It is difficult to distinguish between the effect of calcium vs that
of D on skeletal integrity because the main mechanism of action for D is promotion of calcium absorption in the gut, and not direct incorporation of calcium in bone. In the Reid meta-analysis, only half of the trials used both calcium and D. In trials in which calcium was given simultaneously with D, there was a very modest increase in hip bone mineral density, but a significant reduction of 11% in hip fractures. This finding formed the basis of the Institute of Medicine’s recommendation that 1200 mg of calcium and 800 IU of D were optimum intakes for skeletal health in the elderly.

3) Mechanisms of D action on the skeleton have recently been re-examined, leading to a new appreciation of the vitamin’s biological role. During states of adequate calcium intake and normal skeletal homeostasis, D might have little or no role in strengthening bone mass since calcium status is adequate. With severe deficiency, (25-OH-D < 40 nmol/L), or low calcium intake, or both, skeletal micro-architecture (but not necessarily BMD) is disrupted, leading to micro-cracks, skeletal fragility, defects in mineralization, and increased bone resorption. Replacement with D and calcium would restore skeletal homeostasis.

The meta-analysis is consistent with our understanding of D. Supplementation to prevent osteoporosis in healthy adults is not warranted. However, maintenance of D stores in the elderly, combined with sufficient dietary calcium, remains an effective approach for prevention of hip fractures.

Lancet January 11 2014;383:108-10 “Comment” by Clifford J Ross, Maine Medical Research Institute, Scarborough, Maine

1 “Effect of Vitamin D Supplements on Bone Mineral Density: Systematic review and meta-analysis” First author Ian R Reid, University of Auckland, New Zealand.

The interpretation: Continuing widespread use of vitamin D for osteoporosis prevention in community dwelling adults without specific risk factors for vitamin D deficiency seems to be inappropriate.

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*Fortunately, D and calcium are inexpensive.*

*BMD is a surrogate endpoint. We are really interested in fracture rate.*
The articles say nothing about sunlight. Elders, such as I, do not regularly get enough. Serum D levels decline in winter in high latitudes.

Calcium intake in many people, especially adolescents and the elderly may be deficient.

I confess, I take 600 IU of D daily. (The only supplement I take.) I will continue. I am a big milk drinker and do not take supplemental calcium.

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**Turning Grief Due To Loss Into A Mental Disorder**

**12-3 MEDICALISING AND MEDICATING UNHAPPINESS**

Many patients report sadness or distress during consultations with primary care doctors. Such emotions may be related to grief or other life stresses. Sometimes sadness appears out of the blue, without obvious cause.

Recently, there has been an increasing tendency, especially in primary care, to diagnose depression (commonly as major depressive disorder MDD) in patients presenting with sadness or distress. Anti-depressant drugs are frequently prescribed.

This analysis offers a critical review of diagnosis of MDD and shows how and why this broad diagnostic label results in overdiagnosis and overtreatment.

Evolving view of what constitutes depression:

No formal definition existed until the 3rd version of the American Psychiatric Association’s classification of mental disorder (DS-III) appeared in 1980 and entered the term major depressive disorder. (MDD)

Since then, MDD has received more research attention than any other diagnosis in psychiatry. It has created many problems. It captures too heterogeneous a population for research studies, and is so structured that, in every day clinical practice, ordinary sadness can be easily confused with clinical depression.

Unhelpful classifications of mental disorders:

Under DSM-III, the term MDD was combined with what had formerly been described as “melancholia”, a severe, disabling, and sometimes life-threatening depression.
Reactive depression contrasts in almost every way with melancholia. Its onset is closely linked to a defined life event and with milder symptoms—sadness, loss of interest, feelings of guilt and unworthiness. Patients tend to get better over time and respond well to placebo and psychotherapy.

Those with melancholia are more likely to have disturbed sleep. They respond to drug therapy and electroconvulsive therapy.

DSM-5 broadens the definition of MDD. It allows diagnosis in just 2 weeks after a bereavement. The change in the diagnostic status of grief due to bereavement (not a mental illness) to a depressive episode (a mental illness) introduced by DSM-5 was designed to provide more patients with access to effective treatment. This is particularly relevant in insurance based health systems, which require a specific diagnosis before funds will be paid.

It has, however, provoked both controversy and concern that has focused on the medicalization of the normal human experience of loss.

Homogenisation of depression has been a mistake:

People with uncomplicated episodes of MDD (lasting no more than 2 months, and not including suicidal ideation, psychotic ideation, psychomotor retardation, or feelings of worthlessness) are hardly more likely to have further episodes within 12 months than people with no history of MDD.

These episodes, along with mild and non-melancholic episodes, may be better understood as normal intense sadness.

Including people (as the DSM-5 classification does) who are experiencing grief only 2 weeks after the loss of a loved one is a mistake. Uncomplicated bereavement is not associated with an increase in suicidality.

Increase in diagnosis of depression and antidepressant drug prescriptions:

The prevalence of depressive disorders in the population is stable.

Meanwhile, rates of diagnosis have increased considerably, doubling in Medicare beneficiaries between 1995 and 2005. Over diagnosis was more common than underdiagnosis, and most patients were taking anti-depressant drugs. This trend may increase as DSM-5 criteria for diagnosis loosens. Rates of prescriptions for antidepressants for patients who have no evidence of MDD, or fewer symptoms than DSM-5 would advise, are increasing in primary care.
About 11% of the US population age 12 and over now take an antidepressant, including 23% of women in their 40s and 50s. This is explained mainly by increases in long-term prescriptions.

Drivers of overdiagnosis:

Is in part due to heavy marketing by drug companies. The rate of diagnosis of depression has increased substantially since marketing of selective serotonin reuptake inhibitors.

Primary care clinicians (PCC) and the public are complicit in this. For PCC a diagnosis of depression may be an attractive instrument for managing uncertainty, especially since the most common treatment comes from a once daily pill, and is encouraged by guidelines. Patients often request treatment for symptoms of sadness and doctors and patients often feel obliged to offer and accept a diagnosis of MDD.

There is a trend in Western societies to expect the right to happiness and to restrict the range of negative emotions.

What the evidence shows:

The weight of evidence from meta-analyses and placebo controlled trials shows that antidepressant drugs have little or no effect on mild depression. Although there is some evidence that the benefits of treatment compared with placebo are not related to baseline severity, there are continued concerns about publication bias in data provided by drug companies.

The placebo effect of antidepressant drugs is substantial, partly because less severely depressed people now take part in drug trials.

The role of regression to the mean in assessing the effects of antidepressants is important because many people with reactive depression get better with time, regardless of treatment.

Watchful waiting can have a stronger effect than antidepressant drugs.

There is no substantive evidence that people with uncomplicated bereavement benefit from antidepressants.

Many conditions now diagnosed as MDD, especially those related to loss, are better understood with a model of grief that does not assume drug treatment.
Harms from overdiagnosis:

Turning grief due to loss into a mental disorder is a medical intrusion into private emotions. It substitutes a medical ritual for deep and time honored cultural ones and stigmatizes the experience. It leads people to act under the description of a psychiatric diagnosis, believing themselves to be someone with a mental illness.

Bringing grief within the category of MDD adds unnecessary medication with its inevitable adverse effects and costs.

How to do better:

Diagnostic criteria should be tightened. Milder symptoms must persist throughout the day, be present at least a month or two, and cause significant distress or impairment before a diagnosis of MDD is made.

For diagnosis of moderate and severe MDD, existing diagnostic criteria should be accurately applied, so the diagnosis is made only in the presence of substantive symptoms and clear associated impairment.

Patients with milder or loss related symptoms should not be dismissed, but more attention should be given to benefits of support, time, advice, social networks, and psychological interventions.

Primary care clinicians should focus on identifying patients with severe depression and provide them with better access to adequate evidence based care. This includes those with symptoms of melancholia, and those with severe persistent symptoms associated with socioeconomic disadvantage and disability.

Patients can be helped by listening carefully to their story, promoting the value of time as a healer, and encouraging them to build resistance through exercise, support, and (where possible) making changes in their circumstances in dealing with everyday life problems. A diagnosis of depression may not be necessary.

Patients should be encouraged to exchange experiences and learn from others. Watchful waiting over multiple visits can enable doctors to see if the problems will resolve without intervention, an approach that plays to the strengths of primary care doctors.

When I started to abstract this article, I had no intention of so lengthy an abstract. However, I found it most interesting. It presents an important consideration for primary care—over treatment.

There are many examples of over treatment. Dietary supplements and vitamins are prime examples.

As the article states, we are now treating normal human emotions and normal degenerative changes of aging (eg, testosterone decline) as diseases.

12-4 STATIN THERAPY FOR PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE: 2013 Cochrane Collaboration Meta-analysis

Statin use increased from 16 million Americans in 2000 to 30 million in 2005—an increase from $7.7 billion to $19.7 billion.

This article summarizes the benefits and harms of statin use for primary prevention, particularly among young people with low risk for CVD.

Evidence profile
18 randomized clinical trials1994-2008
56 934 participants
Men 60%; women 40%; 86% white
Mean age 57
Multi-country
Primary outcome: All-cause mortality; fatal and non-fatal CHD, CVD; and stroke

Summary of findings in primary prevention:

Pravastatin was most commonly used in trials that ran from 2 to 5 years. All were funded by pharmaceutical companies, but the overall quality was high. Three trials were stopped prematurely due to a significant reduction in the primary outcome.
**Summary:**

<table>
<thead>
<tr>
<th></th>
<th>No. of trials</th>
<th>Relative risk statin vs placebo</th>
<th>NNTs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>13</td>
<td>0.80</td>
<td>138</td>
</tr>
<tr>
<td>Total CVD events</td>
<td>8</td>
<td>0.75</td>
<td>49</td>
</tr>
<tr>
<td>Totals CHD</td>
<td>14</td>
<td>0.73</td>
<td>88</td>
</tr>
<tr>
<td>Total stroke</td>
<td>10</td>
<td>0.78</td>
<td>155</td>
</tr>
<tr>
<td>Revascularization</td>
<td>7</td>
<td>0.62</td>
<td>96</td>
</tr>
<tr>
<td>Any adverse drug event</td>
<td>12</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>2</td>
<td>1.18</td>
<td>99**</td>
</tr>
</tbody>
</table>

(* Number needed to treat for 5 years to prevent on event. **To cause diabetes.)

Rates of adverse events (17%) and stopping treatment (12%) were similar in statin and placebo groups. One trial found an increased risk for diabetes. One trial found no increased risk.

**Discussion:**

Benefits of statins are consistent with the Cholesterol Treatment Trialist’s Collaboration. Their findings demonstrated benefits of statins in people with levels of risk lower than currently eligible criteria used by previous guidelines (2001;2007).

**Comparison of findings with current guidelines:**

The recently released ACC/AHA guidelines recommends moderate- to high-dose statins for primary prevention of atherosclerotic cardiovascular disease in adults:

1) Persons with LDL-cholesterol 190 and higher
2) Persons age 40-75 with type 1 or type 2 diabetes
3) Persons age 40-75 with LDL- levels between 70 and 180 and 7.5% or higher estimated 10-year risk of atherosclerotic cardiovascular disease.

It is also reasonable to offer moderate-dose statins to individual with an estimated 10-year risk of 5% to 7.4%/ (Grade B recommendation)

**Areas in need of study:**

Cost-effective estimates for statins in low-risk people.

Further evidence of unintended adverse effects from large observational studies is required to clarify potential hazards of type 2 diabetes, adverse quality of life, and hemorrhagic stroke.
Conclusion:

When used for primary prevention, statins are associated with lower rates of all-cause mortality, major vascular events, and revascularizations compared with placebo.

Statin therapy is not associated with increased rates of life-threatening adverse events such as cancer.

JAMA December 11, 2013; 310:2451-52 “JAMA Clinical Symposium” first author Fiona C Taylor, London School of Hygiene and Tropical Medicine
An updated version of the 2011 Cochrane meta-analysis.

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*Statins get my vote for the most important drug application since penicillin.*

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**12-5 ACCUMULATING EVIDENCE FOR STATINS IN PRIMARY PREVENTION**

Many voices in the public and the medical community argue strongly against the widespread use of statins for primary prevention. They give several reasons: concern about adverse events; lack of total mortality benefit; cost; and a philosophical aversion to drug therapy.

Meta-analyses now provide extensive evidence that statins reduce cardiovascular events more than has previously been appreciated.

And do so with an excellent margin of safety.

Participants were no more likely to discontinue statins than placebo.

The 2013 Cochrane meta-analysis\(^1\) was a part of the evidence base for the 2013 AHA/ACC guidelines\(^2\) for treatment of cholesterol to prevent atherosclerotic cardiovascular disease in adults. The guidelines were the result of rigorous reviews of high quality randomized trials and systematic reviews and meta-analyses of drug therapy to reduce atherosclerotic cardiovascular disease.

The recommendation by the AHA/ACC to use statins for individuals with 7.5% of higher 10-year risk was based on strong evidence that the reduction in ASCVD events outweigh the potential adverse effects.

This cut point is lower than recommended by the Adult Treatment Panel III (2004) and is consistent with the Cochrane meta-analysis (2913).
Notably, the 2013 guideline cut point was derived from placebo rates for MI, stroke, and cardiovascular disease deaths observed in 3 exclusive primary prevention trials.

The recent statin meta-analyses provide evidence that largely refutes the major criticisms against statin use for primary prevention. Costs are no longer relevant. Five of the currently available statins are generics. Recent analyses have found statins to be highly cost-effective and even cost-saving in lower risk individuals, and can provide a large social benefit.

The accumulated evidence should convince those with philosophical aversion to statin therapy for primary prevention to reconsider. Many more adults could benefit from use of statins.

Despite decades of exhortation for improvement, the high prevalence of poor lifestyle behaviors leading to elevated cardiovascular disease factors persists. MI and stroke remain the leading causes of death in the US.

JAMA December 11, 2013; 310:2405-06 Editorial by Jennifer G Robinson, University of Iowa, Iowa City
1 See preceding abstract
2 See Practical Pointers November 2013

I believe lifestyle interventions will reduce risks more than statins.

Long-Term Intervention With A High-Quality Dietary Pattern Akin To The Traditional MD, Reduced The Incidence Of Diabetes

12-6 PREVENTION OF DIABETES WITH MEDITERRANEAN DIETS: Subgroup analysis of a randomized trial

Compelling evidence shows that diabetes can be prevented by lifestyle changes. Intensive lifestyle modifications promoting weight loss through energy-restricted diets and increased physical activity can decrease incidence of diabetes as much as 50%. Indeed, lifestyle modification has performed better that pharmacological approaches (eg, metformin) in prevention.

There is little information whether changes in the overall dietary pattern (without energy restriction, increased physical activity, or weight loss) may be effective in preventing diabetes.
Prospective epidemiologic studies strongly suggest that dietary patterns characterized by high concentrations of fruit, vegetables, whole grains, and fish, and reduced consumption of red and processed meat, sugar-sweetened beverages and starchy foods delay onset of diabetes. This study assessed the efficacy of the MD for primary prevention of type-2 diabetes.

STUDY
1. Participants (men and women) were age 55-80 living in communities in Spain. None had diabetes at baseline.
2. Participants were randomly assigned to 1 of 3 diets:
   1) MD supplemented with extra-virgin olive oil (EVOO 50 mL / day) for cooking and dressing.
   2) MD supplemented with mixed nuts. (30 g/day of walnuts, almonds, and hazelnuts)
   3) Control diet with advice to reduce all types of fat.
3. A behavioral intervention promoting the MD was implemented in those assigned to the MD. There was no intervention to increase physical activity or to lose weight.
4. The MD included higher intake of vegetables, fruits, legumes, fish, white meat, and dressing of dishes with “sofrito” sauce (tomato, garlic, onion, and spices simmered with olive oil); and avoidance of red and processed meats, butter, fast foods, sweets, pastries, and sugar-sweetened drinks. Reduction of all alcoholic beverages, except wine, was advised for all. Wine in moderation, with meals, was advised for those who were habitual drinkers.
5. At baseline and quarterly, dietary sessions assessed adherence to the MD. Fasting blood was checked for glucose.
6. From 2003-2009, 3541 suitable candidates were enrolled in the study. All were at high CVD risk. None had diabetes.
7. The main objective was to determine the effect of the 3 diets on primary prevention of diabetes.

RESULTS
1. During follow-up, 3541 (none with diabetes at baseline) were assessed for onset of diabetes.
2. At baseline: mean age 66; mean BMI 30; mean waist circumference 99 cm. Clinical characteristics at baseline were similar between groups.
3. During median 4.1 years of follow-up:

   Adherence to the MD and intake of nuts and EVOO was good.

   Changes in body weight, waist circumference and physical activity were minor.

   A total of 273 developed diabetes.

4. 

<table>
<thead>
<tr>
<th>Developed diabetes</th>
<th>MD +EVOO</th>
<th>MD + nuts</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence / 1000 person-years</td>
<td>80 (6.9%)</td>
<td>92 (7.4%)</td>
<td>101 (8.9%)</td>
</tr>
<tr>
<td>Hazard ratio **</td>
<td>0.60</td>
<td>0.82*</td>
<td>1.00</td>
</tr>
<tr>
<td>(*) Not statistically significant ** multivariate adjusted</td>
<td></td>
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</table>

DISCUSSION

1. Long-term intervention with a high-quality dietary pattern akin to the traditional MD, reduced the incidence of diabetes in older persons.

2. The benefit was mainly due to the overall consumption of the dietary pattern, and not due to calorie restriction, increased physical activity, or weight loss.

3. After 4 years of follow-up, there was a statistically significant 40% reduction in diabetes onset in the EVOO group. and a non-statistically significant reduction of 18% in the nut group as compared with the control group.

4. These diets are palatable and have high potential for long-term sustainability, with public health implications for primary prevention of diabetes.

CONCLUSION

This trial provides strong evidence that long-term adherence to a supplemented MD (high in mono-unsaturated fat, and without energy restrictions) results in a substantial reduction in risk of type-2 diabetes among older persons with high cardiovascular risk.

Annals Internal Medicine January 7, 2014;160:1-10 First author Jordi Salas-Salvado, Universitat Rovira i Virgili, Reus, Spain

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See Practical Pointers February 2013 for the original study reporting a benefit of the supplemented MD in reducing incident cardiovascular disease in this high-risk group.
This is the first study I have encountered providing evidence that the quality of the diet (not the quantity) lessens risk of incident diabetes.

There would be no reason why EVOO and nuts could not be combined.