

JACC REVIEW TOPIC OF THE WEEK

A Pesco-Mediterranean Diet With Intermittent Fasting



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ABSTRACT

As opportunistic omnivores, humans are evolutionarily adapted to obtain calories and nutrients from both plant and animal food sources. Today, many people overconsume animal products, often-processed meats high in saturated fats and chemical additives. Alternatively, strict veganism can cause nutritional deficiencies and predispose to osteopenia, sarcopenia, and anemia. A logical compromise is a plant-rich diet with fish/seafood as principal sources of animal food. This paper reviews cumulative evidence regarding diet and health, incorporating data from landmark clinical trials of the Mediterranean diet and recommendations from recent authoritative guidelines, to support the hypothesis that a Pesco-Mediterranean diet is ideal for optimizing cardiovascular health. The foundation of this diet is vegetables, fruits, nuts, seeds, legumes, whole grains, and extra-virgin olive oil with fish/seafood and fermented dairy products. Beverages of choice are water, coffee, and tea. Time-restricted eating is recommended, whereby intermittent fasting is done for 12 to 16 h each day. (J Am Coll Cardiol 2020;76:1484-93) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

As *Homo sapiens*, we are evolutionarily adapted to obtain calories and nutrients from plant and animal sources; accordingly, humans are classified as opportunistic omnivores (1,2). The chemistry and anatomy of our digestive tract testify to our omnivorous lineage. Indigestible fiber—found only in plants—is vital for gastrointestinal tract health; and like herbivores, we have sucrases in our gut enabling us to digest fruit. On the other hand, like carnivores,

we have numerous proteases in our gut specifically designed to help digest animal protein.

Archeological and anthropological data show that pre-agricultural hunter-gatherer societies derived 14% to 50% of calories consumed from animal-based foods such as wild fish, seafood, wild birds, eggs, and game meats, which are typically low in saturated fats and rich in omega-3 fatty acids (ω -3FAs) (1,3). Still, plant-rich diets confer health benefits including



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HIGHLIGHTS

- Although humans as omnivores can subsist on myriad foods, the ideal diet for health remains a dilemma.
- A Pesco-Mediterranean diet of plants, nuts, EVOO, and seafood has strong cardioprotective evidence.
- A daily time-restricted eating window of 8 to 12 h is a central component of this diet.
- This diet is hypothetical and needs prospective and randomized studies to document its efficacy.

reduced risk for cardiovascular disease (CVD). Vegans and vegetarians, compared with nonvegetarians, have lower body mass indexes with favorable levels of blood pressure and low-density lipoprotein cholesterol (LDL-C) (4,5). Lacto-ovo vegetarian diets (no animal-based food except eggs and dairy) generally show no adverse effects; however, veganism (no animal-based food) can result in deficiencies of important nutrients such as vitamin B₁₂, high-quality proteins, iron, zinc, ω-3FA, vitamin D, and calcium (4). Moreover, plant-based diets comprised of sweets, refined grains, fries, chips, and other processed foods correlate with worse CVD outcomes, whereas vegetarian diets emphasizing fresh produce, nuts, legumes, whole grains, tea, and coffee associate with improved outcomes (6).

Dietary sources of vitamins B₁₂ and D are almost solely animal products. Without adequate supplementation, deficiency of these nutrients can cause neurocognitive deficits, anemia, and immunodeficiency (7). Studies suggest that prolonged strict veganism increases the risk for bone fractures and sarcopenia, and depressive symptoms increase with the number of food groups excluded (4,8,9). Attaining optimal health while following a vegan diet requires ongoing attention to detail and a sophisticated understanding of supplementation.

In contrast, many people in modern Western cultures overconsume meat, particularly highly processed meat from animals raised in inhumane conditions, fed unnatural foods, and often treated with hormones and antibiotics (1). This predisposes to a wide range of chronic illnesses prevalent in our society including CVD, diabetes, and cancers of the gastrointestinal tract (4,10). Thus, although many individuals will benefit from a reduction in the

consumption of meat, especially processed meat (11), modest amounts of wholesome animal-based foods such as fish and fermented dairy products continue to play an essential role in the ideal diet (3,4).

In this review, we propose the Pesco-Mediterranean diet as a solution to this “omnivore’s dilemma” about what to eat. Scientific evidence will be presented to support the Pesco-Mediterranean diet, which is modeled on the traditional eating patterns of Mediterranean populations. It is a plant-rich diet with seafood as the predominant source of animal protein. Intermittent fasting is also recommended, because it was an inherent feature of these traditional cultures and it promotes health.

TRADITIONAL MEDITERRANEAN DIET: GOLD STANDARD FOR CARDIOVASCULAR HEALTH

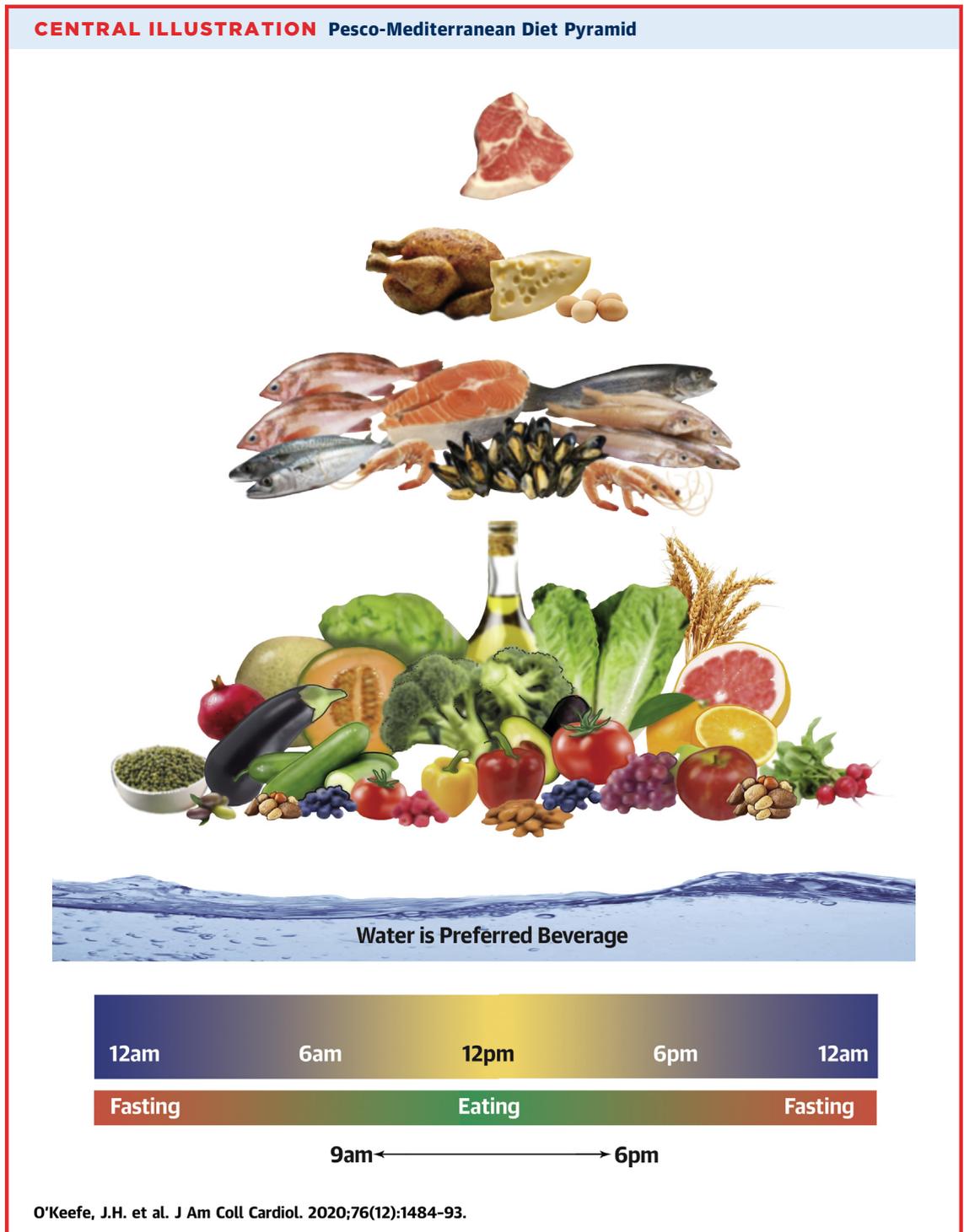
The Mediterranean diet is so named because this was the style of eating adopted by many of the cultures living on or near the shores of the Mediterranean Sea. Elizabeth David wrote that the Mediterranean diet comes “from the blessed lands of sun and sea and the olive trees” (12). Ecological abundance fostered the regular consumption of plant foods (fruits, vegetables, legumes, whole grains, seeds, tree nuts, and olives), fish/seafood, and olive oil as the principal fat source, along with moderate amounts of dairy products (particularly yogurt and cheese) and eggs, as well as modest alcohol consumption (ideally red wine with the evening meal), but few red and processed meats (Central Illustration) (12,13).

Many epidemiological studies and randomized clinical trials indicate that this traditional Mediterranean diet is associated with lower risks for all-cause and CVD mortality, coronary heart disease, metabolic syndrome, diabetes, cognitive decline, neurodegenerative diseases (including Alzheimer’s disease), depression, overall cancer mortality, and breast and colorectal cancers (13,14).

The traditional Mediterranean diet has been endorsed by national guidelines such as the 2015 to 2020 Dietary Guidelines for Americans (15) and the 2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease, which recommends “plant-based and Mediterranean diets along with fruits, nuts, vegetables, legumes and lean vegetable or animal protein—preferably fish” (11). The *U.S. News & World Report* deploys a panel of 25 nationally recognized experts to annually score 35

ABBREVIATIONS AND ACRONYMS

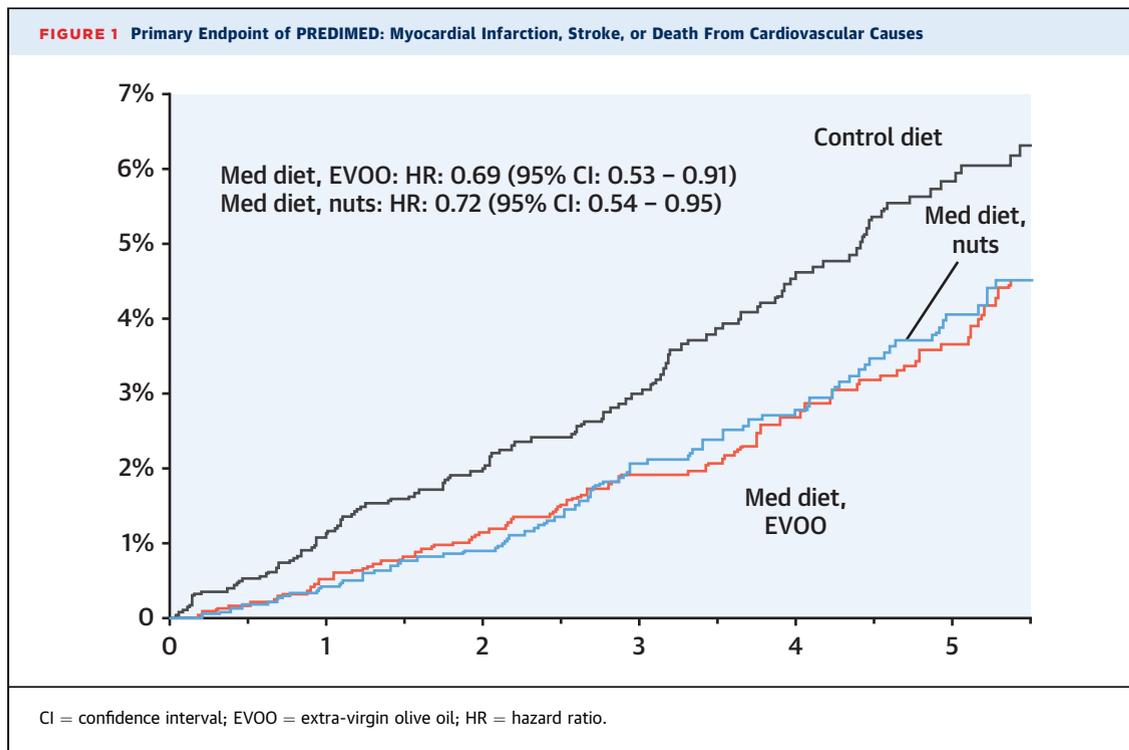
- CAD** = coronary artery disease
- CVD** = cardiovascular disease
- EVOO** = extra-virgin olive oil
- LDL-C** = low-density lipoprotein cholesterol
- MI** = myocardial infarction
- ω-3FA** = omega-3 fatty acid
- RCT** = randomized controlled trials



of the most popular diets for their health benefits. In 2020, for the third consecutive year, the Mediterranean diet was ranked #1 for overall health—described as nutritious, safe, relatively easy to follow, protective against CVD and diabetes, and effective for weight loss (16).

SEAFOOD AS KEY COMPONENT OF THE MEDITERRANEAN DIET

Fish and seafood in general are important components of the Mediterranean diet (17). Epidemiological studies support the cardioprotective properties of fish



and ω -3FA consumed with the usual diet. A meta-analysis of 16 cohort studies with 422,786 observations, focused on dietary fatty acids and CVD risk, reported a significant 13% risk reduction when comparing extremes of omega-3 fatty acid intake (18). Similarly, a consortium of 19 observational studies from 16 countries reported that plasma or adipose tissue levels of ω -3FA (objective biomarkers of intake) were associated with a reduced risk of fatal and nonfatal coronary heart disease comparing extreme quintiles (19). Higher fish consumption (as long as the fish is not fried) has been associated with reduced risk of heart failure (20) and a reduction in the incidence of metabolic syndrome (21).

The 2015 to 2020 Dietary Guidelines for Americans recommend that adults consume fish and/or seafood at least twice per week, totaling at least 8 to 10 oz/week, preferably in place of other protein foods such as red meat, poultry, or eggs (15). In a 2018 Science Advisory, the American Heart Association recommended “1 to 2 seafood meals per week be included to reduce the risk of congestive heart failure, coronary heart disease, ischemic stroke, and sudden cardiac death, especially when seafood replaces the intake of less healthy foods” (22).

HEALTH BENEFITS OF MEDITERRANEAN, VEGETARIAN, AND PESCO-VEGETARIAN DIETS

The PREDIMED (Prevención con Dieta Mediterránea) study was a randomized clinical trial (RCT) of primary CVD prevention conducted in Spain in older individuals at high risk but with no CVD at enrollment, testing 3 diets: a Mediterranean diet supplemented with extra-virgin olive oil (EVOO), a Mediterranean diet supplemented with mixed nuts (walnuts, almonds, and hazelnuts), or a low-fat diet (23). The groups consuming the Mediterranean diet supplemented with EVOO or nuts had statistically significant reductions of 29% for major adverse CVD events—myocardial infarction (MI), stroke, and death from these causes (Figure 1)—and 42% for stroke (23). During the 4.8-year long PREDIMED study, the dietary changes in the groups randomized to the Mediterranean diet that were significantly different from those in the control group were: 1) increased intake of EVOO and nuts; 2) increased intake of fish/seafood and legumes; and 3) increased total fat intake from 39% to 42%, but a decrease in saturated fat consumption from 10% to 9%. Deviations in the randomization protocol affecting 12% of participants occurred in

TABLE 1 Randomized Controlled Trials of the Mediterranean Diet With Outcomes on CVD and Related Endpoints

Parallel Study Design (Ref. #)	Study Subjects	Test Diet	Control Diet	Median Follow-Up	Outcome Test Diet vs. Control Diet (Multivariable-Adjusted Modules)
Lyon Diet Heart Study (24)	605 ♂ and ♀ survivors of MI	MeDiet, rich in vegetables, fruits, and fish + ALA-supplemented margarine	Advice on prudent Western-type diet	46 months	RR fatal CVD, 0.24 (95% CI: 0.07-0.84) RR non-fatal MI plus CVD death, 0.27 (95% CI: 0.12-0.60)
PREDIMED Study (23)	7,447 ♂ and ♀ at high CV risk	2 traditional MeDiets + supplements of EVOO or mixed nuts	Advice on low-fat diet	57.6 months	2 test diets combined HR combined CVD endpoint*, 0.70 (95% CI: 0.55-0.89) HR Stroke, 0.58 (95% CI: 0.42-0.81) HR MI, 0.80 (95% CI: 0.53-1.21) HR fatal CVD, 0.80 (95% CI: 0.51-1.25)
PREDIMED Study (25)	7,447 ♂ and ♀ at high CV risk	2 traditional MeDiets + supplements of EVOO or mixed nuts	Advice on low-fat diet	56.4 months	HR PAD MeDiet with EVOO, 0.36 (95% CI: 0.21-0.65) HR PAD with nuts, 0.54 (95% CI: 0.32-0.92)
PREDIMED Study (26)	6,705 ♂ and ♀ at high CV risk without AF at baseline	2 traditional MeDiets + supplements of EVOO or mixed nuts	Advice on low-fat diet	56.4 months	HR AF MeDiet with EVOO, 0.62 (95% CI: 0.45-0.88) HR AF MeDiet with nuts, 0.90 (95% CI: 0.66-1.23)
PREDIMED Study (27)	3,541 ♂ and ♀ at high CV risk without diabetes at baseline	2 traditional MeDiets + supplements of EVOO or mixed nuts	Advice on low-fat diet	49 months	2 test diets combined HR incident diabetes, 0.70 (95% CI: 0.54-0.92)

*Nonfatal MI, nonfatal stroke and death from CV causes.
AF = atrial fibrillation; ALA = alpha-linolenic acid; CI = confidence interval; CVD = cardiovascular disease; EVOO = extra-virgin olive oil; HR = hazard ratio; MeDiet = Mediterranean diet; MI = myocardial infarction; PAD = peripheral artery disease; PREDIMED = PREvención con Dieta MEDiterránea; RR = risk ratio.

PREDIMED, but reanalysis of the data did not change the results (23).

Only 2 large RCTs have examined the effects of the Mediterranean diet on hard CVD events: PREDIMED (23) in primary prevention of CVD, and the Lyon Diet Heart study in MI survivors (24), which also had impressive results (73% reduction in reinfarction rates at 27 months), albeit the intervention arm did not exactly follow a traditional Mediterranean diet (little olive oil consumption and a margarine enriched in alpha-linolenic acid as main dietary fat). Of note, PREDIMED also tested for the first time the effects of the Mediterranean diet on the incidence of other CVD-related outcomes, including peripheral artery disease (25), atrial fibrillation (26), and diabetes (27).

Table 1 summarizes the results of these RCTs.

A meta-analysis of 5 prospective dietary studies evaluated long-term coronary artery disease (CAD) mortality rates among vegetarian and nonvegetarian cohorts from Western countries. Compared with regular meat-eaters, CAD mortality was 34% lower in pescatarian (plant-rich diet with seafood as main source of meat), 34% lower in lacto-ovo-vegetarians, 26% lower in vegans, and 20% lower in occasional meat-eaters (28).

The Adventist Health Study 2 was a 6-year prospective study that enrolled 73,308 subjects in the North American Adventists (5). This study reported a decreased incidence of all-cause mortality when comparing vegetarians with nonvegetarians. However, when the vegetarians were stratified into vegans, lacto-ovo vegetarians, pesco-vegetarians, and semi-vegetarians, the pesco-vegetarians had lowest risks

for all-cause mortality, CVD mortality, and mortality from other causes (Figures 2A to 2C) (5).

In the European Prospective Investigation into Cancer and Nutrition (EPIC) Oxford study, which included 48,188 participants with 18 years of follow-up, the incidence of CAD was significantly lower among vegetarians and pescatarians when compared with meat eaters (29). Unexpectedly, vegetarians, but not pescatarians, had significantly higher rates of hemorrhagic strokes and total strokes when compared with meat eaters (29). However, selection bias and confounding, which may be accounting for some of these findings, are pervasive issues in diet-health studies and may undermine the validity of some findings.

FISH AND SEAFOOD IN THE DIET

The Pesco-Mediterranean eating style is primarily a plant-rich diet, but the aquatic animal food sources provide an array of vitamins, minerals, and other nutrients, some of which are not readily accessible in vegetarian or vegan diets. Fish and other seafood are not just rich in ω-3FA, but are generally good sources of zinc, iodine, selenium, B vitamins, calcium, and magnesium. Furthermore, fish and seafood provide high-quality protein, which is both satiating and helpful for the building and maintenance of muscle and bone mass.

Two recent systematic reviews comprising 106,237 mother-offspring pairs, and 25,960 children reported that fish/seafood consumption was

associated with dose-dependent benefits to neurocognitive development that became significant at 4 oz/week and increased from there (30). Adverse neurocognitive outcomes were not seen even with the highest amounts of fish/seafood consumption (>100 oz/week), despite associated increases in mercury exposures (30). Even so, it is prudent to choose low-mercury fish, such as salmon, sardines, trout, herring, and anchovies, all of which are naturally high in ω -3FA, and scallops, shrimp, lobster, oysters, and clams—which are not as high in ω -3FA, but remain low in mercury (4,28). It is best to use lower temperatures (target internal temperature 145° or until flesh is opaque and separates easily with fork); avoid charring or burning fish/seafood, which can introduce carcinogenic compounds (31).

OTHER KEY COMPONENTS OF THE MEDITERRANEAN DIET: EVOO, NUTS, AND LEGUMES

Unrestricted use of EVOO in the kitchen and at the table is the foundation of the traditional Mediterranean diet, although olive oil quality is crucial (23). Unlike the common variety of olive oil and most edible seed oils—which are refined, EVOO is unrefined. It is obtained by cold pressing olives, and in this sense is equivalent to a pure olive juice. EVOO retains hydrophilic components of olives, among them highly bioactive polyphenols, which are believed to underlie many of EVOO's cardiometabolic benefits, such as reduced LDL-C and increased high-density lipoprotein cholesterol, improved vascular reactivity, enhanced high-density lipoprotein cholesterol functionality, and a lower diabetes risk (23,32). Importantly, the EVOO arm of the PREDIMED trial provided first-level scientific evidence of its cardioprotective effects within the context of the Mediterranean diet (23).

Given the bitter taste of polyphenols, their presence in olive oil is readily perceived as a tingling or burning in the back of the throat that appears a few seconds after swallowing a sample of the EVOO (32). Since vegetables are at the basis of the Pesco-Mediterranean diet, generous use of EVOO (along with vinegar) for dressing salads and vegetable dishes encourages the consumption of higher amounts of these plant foods. EVOO is also recommended for simmering minced tomatoes, garlic, onions, and aromatic herbs as a “sofrito” sauce to use on vegetables, pasta, rice, fish or legumes, as recommended in the PREDIMED Mediterranean diets (Table 2) (23).

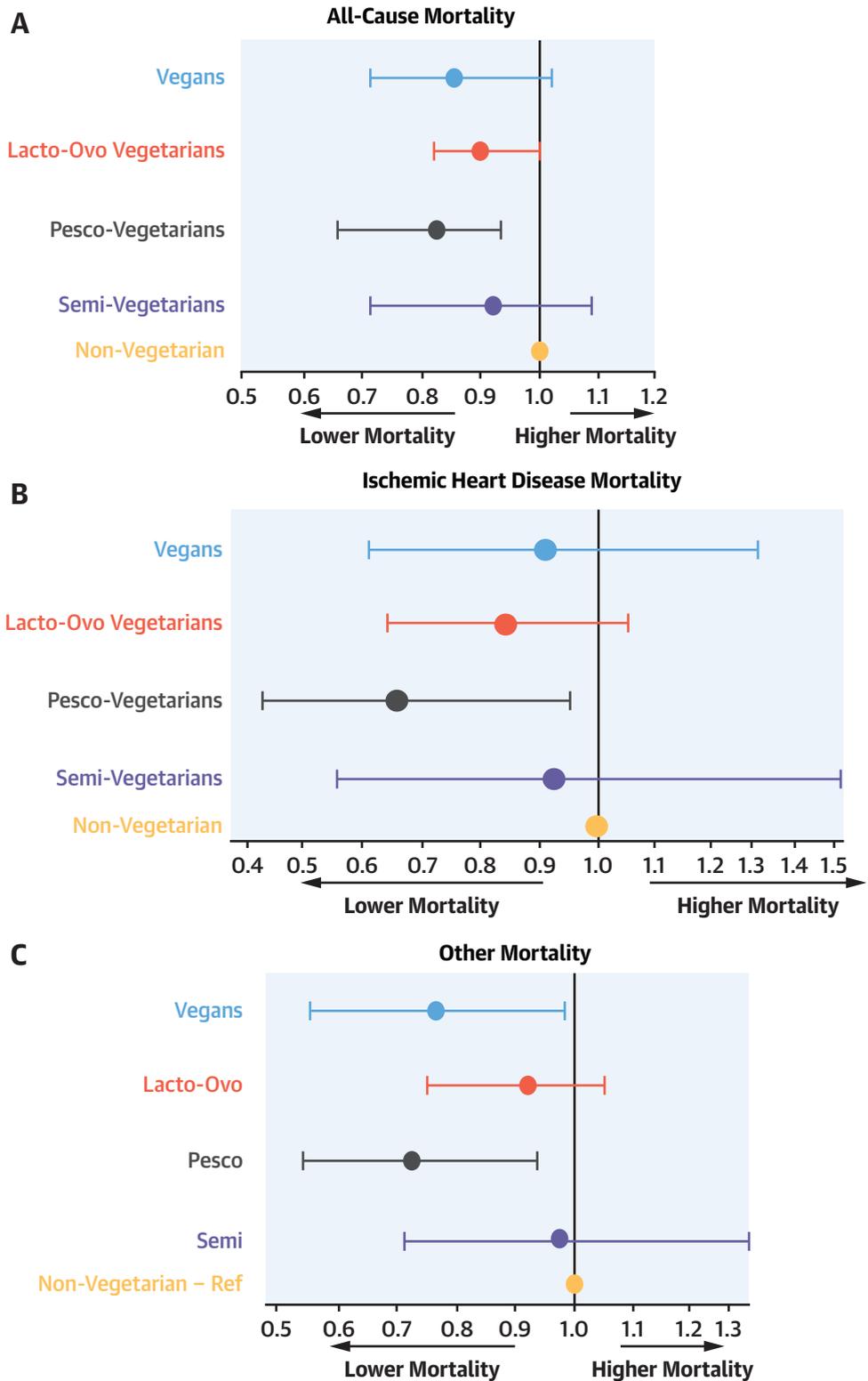
Tree nuts are an integral component of the traditional Mediterranean diet (33). Nuts are nutrient-dense foods rich in unsaturated fats, fiber, protein, polyphenols, phytosterols, tocopherols, and non-sodium minerals. This unique nutritional profile makes nuts one of the most effective foods for improving long-term health outcomes (34). RCTs have shown that diets enriched with nuts produce cardiometabolic benefits including improvements in insulin sensitivity, LDL-C, inflammation, and vascular reactivity (33,34). Observational studies have suggested that nut consumption is associated with decreased incidence and mortality rates from both CVD and CAD, as well as decreased risks of atrial fibrillation and diabetes (35). In 1 arm of the PREDIMED trial, 1 daily serving of mixed nuts resulted in a 28% reduction in CVD risk, again providing first-level scientific evidence for the cardioprotective effect of nuts within the context of the Mediterranean diet (23). Generous intake of nuts does not promote weight gain because of increased satiety and reduced metabolizable energy (part of nuts' fat is lost in the feces because of incomplete digestion) (33,36).

Legumes also play a central role in the traditional Mediterranean diet, and they are an excellent source of vegetable protein, folate, and magnesium and fiber, and like other seeds, are rich in polyphenols (37). Consumption of legumes has been linked to a reduced risk of incident and fatal CVD and CAD, as well as improvements in blood glucose, cholesterol, blood pressure, and body weight (37). Legumes, like fish, are a satiating and healthy substitute for red meat and processed meats.

Two important sources of protein in the usual diet, dairy products and eggs, need to be mentioned. Dairy products contribute important nutrients to the diet, including protein, nonsodium minerals, probiotics, and vitamin D. Although there is no clear consensus among nutrition experts on the role of dairy products in CVD risk, they are allowed in this Pesco-Mediterranean diet. Fermented low-fat versions, such as yogurt, kefir, and soft cheeses, are preferred; butter and hard cheese are discouraged, because they are high in saturated fats and salt (38).

Eggs are composed of beneficial nutrients including all essential amino acids, in addition to minerals (selenium, phosphorus, iodine, zinc), vitamins (A, D, B₂, B₁₂, niacin), and carotenoids (lutein, zeaxanthin). Although each yolk contains about 184 mg of dietary cholesterol, large prospective cohorts suggest that egg consumption is unrelated to serum cholesterol, and does not increase CVD risk (39,40). Eggs are allowed in the Pesco-Mediterranean diet, preferably no more than 5 yolks/week (egg

FIGURE 2 Association of Dietary Patterns With All-Cause, Ischemic Heart Disease, and Other Mortality From Adventist Health Study 2



(A) Association of dietary patterns with all-cause mortality from Adventist Health Study 2. **(B)** Association of dietary patterns with ischemic heart disease mortality from Adventist Health Study 2. **(C)** Association of dietary patterns with other mortality from Adventist Health Study 2.

TABLE 2 Pesco-Mediterranean Diet

Recommended	Goal	Caution	Goal	Avoid
Fish/seafood	≥3 times/week	Lean fresh red meat	≤1 time/week	Processed meats (e.g., bacon, sausage, hot dogs, ham, deli meats, cold cuts)
Vegetables	≥3 servings/day	White meat	≤2 times/week	Sweets
Fresh fruits	≥2 servings/day	Eggs	≤5 yolks/week	Butter and margarine
Legumes	≥3 servings/week	Dry red wine	≤6 oz/day ♀	Most refined carbohydrates such as products made with added sugars and/or white flour (e.g., commercial bakery goods, cookies, cakes, pies, candy, mashed potatoes, rolls, tortillas, and chips)
Whole grains	≤3 servings/day		≤12 oz/day ♂	
Tree nuts	≥1 serving/day			
EVOO	≥4 tablespoons/day	Soft cheeses		Soda drinks and sweetened fruit juices
Sofrito*	≥2 servings/week	Dark chocolate	>50% cocoa	Artificially sweetened beverages and foods

*A sauce made with tomato and onion, typically including garlic and aromatic herbs slowly simmered in olive oil.
 EVOO = extra-virgin olive oil.

whites can be consumed without limit). Eggs are another satiating and healthy substitute for red meat and processed meats.

Whole grains, such as barley, whole oats, rye, corn, buckwheat, brown rice, and quinoa, are an integral part of the traditional Mediterranean diet. Anecdotally, Americans often consider pasta, pizza, and white bread to be central components of the Mediterranean diet. Commercial, precooked pasta or pizza should be consumed only in small amounts in the Pesco-Mediterranean diet, but homemade pizza and mixed pasta dishes, or mixed rice dishes like paella, a staple in many regions of Spain, are legitimate and healthy Mediterranean foods (41). Pasta is an example of a starchy food that has a low glycemic index despite being a refined carbohydrate. In the context of a low glycemic index dietary pattern such as the Mediterranean diet, pasta does not adversely affect adiposity and may even help reduce body weight according to a recent meta-analysis of RCTs (42). The results of 2 recent large Italian cross-sectional studies concur with the RCTs' findings (43,44). Likewise, there is no evidence that consumption of pasta promotes cardiometabolic risk factors (41,44,45).

Concerning white (refined) rice, its consumption was not associated with CVD or CAD in an analysis of 3 large U.S. cohorts (46). According to the meta-analysis by Hu et al. (47), white rice consumption was associated with an increased risk of type-2 diabetes in 3 Asian cohorts but not in 4 Western cohorts. This geographically contrasting diabetes risk is likely due to the way rice is prepared in Asia (plain cooked) and in Western cultures (cooked in mixed dishes with vegetables and vegetable oil). In Mediterranean cultures, white rice, like pasta, is usually prepared with a sofrito sauce including EVOO, tomatoes, other vegetables, and aromatic herbs, thereby adding beneficial

nutrients and bioactives to these starchy but nutritive foods that are likely to further lower their glycemic index. So, if homecooked and prepared the Mediterranean way, mixed pasta and white rice dishes are both tasty and healthy ingredients to the Pesco-Mediterranean diet.

The staple beverage of this diet is water—either still or carbonated, which can be flavored but not sweetened. Unsweetened tea and coffee are noncaloric beverages rich in antioxidants, particularly polyphenols, and are associated with improved CVD outcomes (48,49). If alcohol is consumed at all, dry red wine is recommended, with the ideal amount being a single glass (≤6 oz) for women and 1 or 2 glasses/day for men (6 to 12 oz) consumed with meals (50).

INTERMITTENT FASTING/ TIME-RESTRICTED EATING

Unlike modern humans, our ancient ancestors did not have access to an unlimited supply of food throughout the year. Nor did they routinely eat 3 large meals plus snacks on a daily basis. Instead, they were typically engaged in a daily struggle to hunt and gather food, often in harsh milieus with sparse resources and seasonal scarcity (10). These environmental challenges were the grist for the evolutionary mill, whereby *Homo sapiens* became genetically adapted to respond to intermittent fasting by becoming more resistant to stress (51).

Time-restricted eating, 1 type of intermittent fasting, is the practice of limiting the daily intake of calories to a window of time usually between 6 to 12 h each day. Intermittent fasting when done on a regular basis has been shown to decrease intra-abdominal adipose tissue and reduce free-radical production (51,52). This ancient evolutionarily conserved adaptation also

elicits powerful cellular responses that improve glucose metabolism and reduce systemic inflammation, and may also reduce risks of diabetes, CVD, cancer, and neurodegenerative diseases (52).

After a 12-h overnight fast, insulin levels are typically low, and glycogen stores have been depleted. In this fasted state, the body starts mobilizing fatty acids from adipose cells to burn as metabolic fuel instead of glucose. This improves insulin sensitivity. Time restricted eating is not more effective for weight loss than standard calorie-restriction diets, but it does appear to enhance cardiovascular health even in nonobese people (53,54). Fasting may also lower blood pressure and resting heart rate, and improve autonomic balance with augmented heart-rate variability (53-55). However, the evidence regarding time restricted eating remains preliminary, mostly based on animal models and observational human studies. The most popular form of time-restricted eating involves eating 2 rather than 3 meals and compressing the calorie-consumption window. No head-to-head studies have been performed to assess the optimal time window, but a 16:8 fasting to eating ratio is the most popular (56).

CONCLUSIONS

For millennia, the traditional Mediterranean diet has been based predominantly on fresh whole foods, such as vegetables, fruits, nuts, and olive oil, with fish from the sea. This style of eating bestows a range of health benefits, especially with respect to long-term cardiovascular health and longevity. The Pesco-Mediterranean diet with daily time-restricted eating (window of 8- to 12-h) and emphasis on consuming fish and seafood as the principle sources of animal protein, is proposed as an ideal cardioprotective diet.

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REFERENCES

- Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr* 2005; 81:341-54.
- Root-Bernstein M, Ladle R. Ecology of a widespread large omnivore, *Homo sapiens*, and its impacts on ecosystem processes. *Ecol Evol* 2019; 9:10874-94.
- Kaplan H, Thompson RC, Trumble BC, et al. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet* 2017;389:1730-9.
- O'Keefe JH, DiNicolantonio JJ, Sigurdsson AF, Ros E. Evidence, not evangelism, for dietary recommendations. *Mayo Clin Proc* 2018;93:138-44.
- Orlich MJ, Singh PN, Sabate J, et al. Vegetarian dietary patterns and mortality in Adventist Health Study 2. *JAMA Intern Med* 2013;173:1230-8.
- Satija A, Bhupathiraju SN, Spiegelman D, et al. Healthful and unhealthful plant-based diets and the risk of coronary heart disease in U.S. Adults. *J Am Coll Cardiol* 2017;70:411-22.
- Green R. Vitamin B12 deficiency from the perspective of a practicing hematologist. *Blood* 2017;129:2603-11.
- Iguacel I, Miguel-Berges ML, Gomez-Bruton A, Moreno LA, Julian C. Veganism, vegetarianism, bone mineral density, and fracture risk: a systematic review and meta-analysis. *Nutr Rev* 2019;77:1-18.
- Matta J, Czernichow S, Kesse-Guyot E, et al. Depressive symptoms and vegetarian diets: results from the Constances Cohort. *Nutrients* 2018;10:1695.
- O'Keefe JH Jr., Cordain L. Cardiovascular disease resulting from a diet and lifestyle at odds with our Paleolithic genome: how to become a 21st-century hunter-gatherer. *Mayo Clin Proc* 2004;79:101-8.
- Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;74:1376-414.
- David E. *A Book of Mediterranean Food*. United Kingdom: Penguin UK; 1950.
- Martinez-Gonzalez MA, Gea A, Ruiz-Canela M. The Mediterranean diet and cardiovascular health. *Circ Res* 2019;124:779-98.
- Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. *Eur J Clin Nutr* 2018;72:30-43.
- Millen B, Lichtenstein AH, Abrams S, et al. *Dietary Guidelines for Americans 2015-2020*. Eighth Edition. U.S. Department of Health and Human Services. Washington, DC: U.S. Department of Health and Human Services, U.S. Department of Agriculture, 2015.
- U.S. News & World Report. *Best diets overall*. 2020. Available at: <https://health.usnews.com/best-diet/best-diets-overall>. Accessed July 30, 2020.
- Molina-Vega M, Gómez-Pérez AM, Tinahones FJ. Fish in the Mediterranean Diet (Chapter 25). In: *The Mediterranean Diet. An Evidence-Based Approach*, 2nd Ed. Preedy VR, Watson RR, eds. London: Academic Press, 2020;275-84.
- Chowdhury R, Warnakula S, Kunutsor S, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. *Ann Intern Med* 2014;160:398-406.
- Del Gobbo LC, Imamura F, Aslibekyan S, et al. omega-3 polyunsaturated fatty acid biomarkers and coronary heart disease: pooling project of 19 cohort studies. *JAMA Intern Med* 2016;176:1155-66.
- Belin RJ, Greenland P, Martin L, et al. Fish intake and the risk of incident heart failure: the Women's Health Initiative. *Circ Heart Fail* 2011;4:404-13.
- Kim YS, Xun P, Iribarren C, et al. Intake of fish and long-chain omega-3 polyunsaturated fatty acids and incidence of metabolic syndrome among American young adults: a 25-year follow-up study. *Eur J Nutr* 2016;55:1707-16.
- Rimm EB, Appel LJ, Chiuve SE, et al. Seafood long-chain n-3 polyunsaturated fatty acids and cardiovascular disease: a science advisory from the American Heart Association. *Circulation* 2018;138:e35-47.
- Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a

Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018;378:e34.

24. de Lorgeril M, Salen P, Caillat-Vallet E, Hanauer MT, Barthelemy JC, Mamelle N. Control of bias in dietary trial to prevent coronary recurrences: The Lyon Diet Heart Study. *Eur J Clin Nutr* 1997;51:116-22.

25. Ruiz-Canela M, Estruch R, Corella D, Salas-Salvado J, Martinez-Gonzalez MA. Association of Mediterranean diet with peripheral artery disease: the PREDIMED randomized trial. *JAMA* 2014;311:415-7.

26. Martinez-Gonzalez MA, Toledo E, Aros F, et al. Extravirgin olive oil consumption reduces risk of atrial fibrillation: the PREDIMED (Prevencion con Dieta Mediterranea) trial. *Circulation* 2014;130:18-26.

27. Salas-Salvado J, Bullo M, Estruch R, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. *Ann Intern Med* 2014;160:1-10.

28. Key TJ, Fraser GE, Thorogood M, et al. Mortality in vegetarians and nonvegetarians: detailed findings from a collaborative analysis of 5 prospective studies. *Am J Clin Nutr* 1999;70:516S-24S.

29. Tong TYN, Appleby PN, Bradbury KE, et al. Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: results from the prospective EPIC-Oxford study. *BMJ* 2019;366:l4897.

30. Hibbeln JR, Spiller P, Brenna JT, et al. Relationships between seafood consumption during pregnancy and childhood and neurocognitive development: Two systematic reviews. *Prostaglandins Leukot Essent Fatty Acids* 2019;151:14-36.

31. Bonaccio M, Ruggiero E, Di Castelnuovo A, et al. Fish intake is associated with lower cardiovascular risk in a Mediterranean population: prospective results from the Moli-sani study. *Nutr Metab Cardiovasc Dis* 2017;27:865-73.

32. Romani A, Ieri F, Urciuoli S, et al. Health effects of phenolic compounds found in extra-virgin olive oil, by-products, and leaf of *Olea europaea* L. *Nutrients* 2019;11:1776.

33. Ros E. Contribution of Nuts to the Mediterranean Diet (Chapter 15). In: *The Mediterranean Diet: An Evidence-Based Approach*, 2nd ed. Preedy VR, Watson RR, eds. London: Academic Press, 2020;141-50.

34. Ros E. Eat Nuts, Live Longer. *J Am Coll Cardiol* 2017;70:2533-5.

35. Becerra-Tomas N, Paz-Graniel I, WC Kendall C, et al. Nut consumption and incidence of cardiovascular diseases and cardiovascular disease mortality: a meta-analysis of prospective cohort studies. *Nutr Rev* 2019;77:691-709.

36. Jackson CL, Hu FB. Long-term associations of nut consumption with body weight and obesity. *Am J Clin Nutr* 2014;100 Suppl 1:408S-11S.

37. Freeman AM, Morris PB, Aspary K, et al. A clinician's guide for trending cardiovascular nutrition controversies: part II. *J Am Coll Cardiol* 2018;72:553-68.

38. Willett WC, Ludwig DS. Milk and health. *N Engl J Med* 2020;382:644-54.

39. Key TJ, Appleby PN, Bradbury KE, et al. Consumption of meat, fish, dairy products, and eggs and risk of ischemic heart disease. *Circulation* 2019;139:2835-45.

40. Dehghan M, Mente A, Rangarajan S, et al. Association of egg intake with blood lipids, cardiovascular disease, and mortality in 177,000 people in 50 countries. *Am J Clin Nutr* 2020;111:795-803.

41. Huang M, Li J, Ha MA, Riccardi G, Liu S. A systematic review on the relations between pasta consumption and cardio-metabolic risk factors. *Nutr Metab Cardiovasc Dis* 2017;27:939-48.

42. Chiavaroli L, Kendall CWC, Braunstein CR, et al. Effect of pasta in the context of low-glycaemic index dietary patterns on body weight and markers of adiposity: a systematic review and meta-analysis of randomised controlled trials in adults. *BMJ Open* 2018;8:e019438.

43. Pounis G, Castelnuovo AD, Costanzo S, et al. Association of pasta consumption with body mass index and waist-to-hip ratio: results from Moli-sani and INHES studies. *Nutr Diabetes* 2016;6:e218.

44. Vitale M, Masulli M, Rivellese AA, et al. Pasta consumption and connected dietary habits: associations with glucose control, adiposity measures, and cardiovascular risk factors in people with type 2 diabetes-TOSCA.IT Study. *Nutrients* 2019;12:101.

45. Rosi A, Tesan M, Cremonini A, et al. Body weight of individuals with obesity decreases after a 6-month high pasta or low pasta Mediterranean

diet weight-loss intervention. *Nutr Metab Cardiovasc Dis* 2020;30:984-95.

46. Muraki I, Wu H, Imamura F, et al. Rice consumption and risk of cardiovascular disease: results from a pooled analysis of 3 U.S. cohorts. *Am J Clin Nutr* 2015;101:164-72.

47. Hu EA, Pan A, Malik V, Sun Q. White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review. *BMJ* 2012;344:e1454.

48. O'Keefe JH, DiNicolantonio JJ, Lavie CJ. Coffee for cardioprotection and longevity. *Prog Cardiovasc Dis* 2018;61:38-42.

49. Lavie CJ, DiNicolantonio JJ, O'Keefe JH. Editorial commentary: Coffee, tea, and cardiovascular morbidity and mortality. *Trends Cardiovasc Med* 2019;29:351-2.

50. O'Keefe EL, DiNicolantonio JJ, O'Keefe JH, Lavie CJ. Alcohol and CV health: Jekyll and Hyde J-curves. *Prog Cardiovasc Dis* 2018;61:68-75.

51. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. *N Engl J Med* 2019;381:2541-51.

52. Di Francesco A, Di Germanio C, Bernier M, de Cabo R. A time to fast. *Science* 2018;362:770-5.

53. Most J, Gilmore LA, Smith SR, Han H, Ravussin E, Redman LM. Significant improvement in cardiometabolic health in healthy non-obese individuals during caloric restriction-induced weight loss and weight loss maintenance. *Am J Physiol Endocrinol Metab* 2018;314:E396-405.

54. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. *Cell Metab* 2018;27:1212-21.e3.

55. Stein PK, Soare A, Meyer TE, Cangemi R, Holloszy JO, Fontana L. Caloric restriction may reverse age-related autonomic decline in humans. *Aging Cell* 2012;11:644-50.

56. Naiman T, Scher B. Time-restricted eating - a detailed intermittent fasting guide. *DietDoctor* 2020. Available at: <https://www.dietdoctor.com/intermittent-fasting/time-restricted-eating>. Accessed July 30, 2020.

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