

APPENDIX

Supplement 1: Overview of heterogeneous dietary interventions and comparators

While nutrition RCTs may appear straightforward, many often require careful interpretation including consideration of several unique elements. These include the complexity of foods as intervention vehicles, the lack of a placebo for food-based interventions, background exposure to the intervention variable of interest via the diet or supplements including the background nutrient status (e.g., Vitamin D, omega-3 status), and inherent substitution effects (e.g., if fat intake is reduced, what is it replaced with) in many study designs.

Dietary interventions can vary considerably in their design, including entirely controlled feeding studies replacing a single food with an isocaloric comparator to free-living dietary studies advising participants to consume different diets. The design of studies is typically classified as either ad libitum, additive, subtractive, or substitutive depending on the nature of the intervention. Such designs may or may not indicate a specific comparator group, ranging from a passive control instructed to consume their habitual intakes to highly specific advice to replace one dietary component with another. Dietary interventions occur in the context of overall energy balance (positive, negative, neutral) and can complicate the interpretation of the study results based on the hypotheses about the weight-independent effects of interventions. Regardless of design, critical readers of nutrition literature must ground their interpretation in the inherent relativistic effects of dietary interventions. Appreciation of such concepts should leave readers immediately skeptical of the framing of manuscripts or media headlines around specific foods as independently influencing measured outcomes, as this either ignores a food substitution that occurred to maintain isocaloric intervention arms or ignores confounding from calorie intake differences and likely weight change that occurred from the addition or removal of kilocalories. In the absence of a placebo, generally only found in nutrient supplementation trials, readers should always ask: "...compared to what?".

The PREDIMED intervention makes evident the need to consider background dietary exposures as well as substitutions that occur in response to dietary interventions and demonstrates the hurdles to interpreting food- and dietary pattern-based interventions for which there is no placebo or single, explicitly defined isocaloric comparator. For example, it is reasonable to question the degree to which changes in the overall Mediterranean Diet score vs changes in individual food components may have driven intervention effects. Fully adjusted observational analyses using

reported baseline dietary MEDAS scores from the PREDIMED trial have demonstrated that an increase of 2 points, similar to those achieved during the intervention period of the trial, were associated with reductions in major CVD events (21 to 25% relative risk reduction), though individual score items did not show such an inverse relationship(1), suggesting additive effects of individual changes across Mediterranean Diet score domains. It also remains, however, reasonable to hypothesize that some individual dietary components, such as the polyphenol component of the diet, may have played a meaningful role, as replacement of refined olive oil (low polyphenol) with EVOO (high polyphenol) was a significant component of Mediterranean diet score changes. The reduction in stroke has also led some investigators to question the impact of the intervention on other individual nutrients, such as sodium and potassium intake, though this is challenging to objectively and rigorously quantify(2). As PREDIMED was a complex, unblinded food-based intervention without a clear dietary element driving its effects, our ability to glean concrete, actionable dietary modifications remains limited outside of the context of the original trial's findings, which are themselves, derived from self-reported intakes subject to various sources of error. The trial shows a reduction in CVD risk when EVOO or nuts (primarily walnuts) are added to a Mediterranean-style diet rather than a Western-style diet.

1. Schröder H, Salas-Salvadó J, Martínez-González MA, et al. Baseline adherence to the Mediterranean diet and major cardiovascular events: Prevención con Dieta Mediterránea trial. *JAMA Intern Med.* 2014 Oct 1;174(10):1690-2. <https://doi.org/10.1001/jamainternmed.2014.3463>

2. Appel LJ, Van Horn L. Did the PREDIMED trial test a Mediterranean diet?. *N Engl J Med.* 2013 Apr 4;368(14):1353-4. <https://doi.org/10.1056/NEJMe1301582>