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Nutrition Users' Guides: RCTs Part 2 – structured guide for interpreting and applying study results from randomised controlled trials on therapy or prevention questions

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ABSTRACT

This article continues from a prior commentary on evaluating the risk of bias in randomised controlled trials addressing nutritional interventions. Having provided a synopsis of the risk of bias issues, we now address how to understand trial results, including the interpretation of best estimates of effect and the corresponding precision (eg, 95% CIs), as well as the applicability of the evidence to patients based on their unique circumstances (eg, patients' values and preferences when trading off potential desirable and undesirable health outcomes and indicators (eg, cholesterol), and the potential burden and cost of an intervention). Authors can express the estimates of effect for health outcomes and indicators in relative terms (relative risks, relative risk reductions, OR or HRs)—measures that are generally consistent across populations—and absolute terms (risk differences)—measures that are more intuitive to clinicians and patients. CIs, the range in which the true effect plausibly lies, capture the precision of estimates. To apply results to patients, clinicians should consider the extent to which the study participants were similar to their patients, the extent to which the interventions evaluated in the study are applicable to their patients and if all patient-important outcomes of potential benefit and harm were reported. Subsequently, clinicians should consider the values and preferences of their patients with respect to the balance of the benefits, harms and burdens (and possibly the costs) when making decisions about dietary interventions.

CONTEXT: RECALLING THE CLINICAL SCENARIO FROM PART 1

You are a family doctor caring for a 62-year-old Hispanic man with hypertension, dyslipidaemia and a family history of cardiovascular-related mortality. The patient is taking a thiazide diuretic and a statin. Although the patient consumes limited fruits and vegetables, he considers his diet reasonably healthy eating fruits and lots of avocado weekly. He has a friend who has recently switched from eating a Western-style dietary pattern to a Mediterranean-style (hence referred to as Mediterranean diet) diet high in fruits, vegetables, nuts, legumes, grains, olive oil and fish who has suggested he follow the diet to reduce his risk of a serious cardiovascular event. However, the patient is under financial constraints and is concerned about the costs of following a Mediterranean diet, that includes fish, nuts and olive oil, which he estimates would increase his grocery bill by approximately $90 per month. After a few minutes, he acknowledged that he would like to get a second opinion from you.

Listening to the patient's story and his concerns you then ask him to return in 2 weeks. You find the largest relevant randomised controlled trial (RCT), the PREDIMED trial after searching PubMed.[1] The article describes a trial of 7447 participants aged 55–80 years with high cardiovascular risk (ie, either type 2 diabetes mellitus or at least three major cardiovascular risk factors) but no history of a major cardiovascular event at enrolment. Participants were randomly allocated to a Mediterranean diet supplemented with extra-virgin oil, a Mediterranean diet supplemented with mixed nuts or a control diet with advice to reduce dietary fat and followed for a median of 4.8 years. The primary outcome was a composite of major cardiovascular events (myocardial infarctions, strokes and death by cardiovascular causes).

The questions in this article are drawn from the JAMA Users' Guides series,[2] which outline a structured approach for assessing and interpreting an RCT to inform clinical practice, health services and policy. Having concluded in Part 1 of this two-part

Box 1 Questions on risk of bias (and interpreting and applying the results to practice)

Risk of bias **(summary of RCTs Part 1):**

1. Did intervention and control groups start with the same prognosis?
   - 1a. Was randomisation concealed? (*Probably no*—probably high risk of bias).
   - 1b. Were participants in the study similar with respect to known prognostic factors? (*Probably yes*—probably low risk of bias).
2. Was prognostic balance maintained as the study progressed?
   - 2a. To what extent was the study blinded? (*Definitely no*—definitely high risk of bias).
3. Were the study groups prognostically balanced at the study's completion?
   - 3a. Was follow-up complete? (*Probably no*, but sensitivity analysis failed to detect any issues—probably low risk of bias).
   - 3b. Were participants analysed in the groups to which they were randomised? (*Definitely yes*—definitely low risk of bias).
   - 3c. Was the trial stopped early? (*Definitely yes*—definitely high risk of bias).

Study results and application of results:

4. What are the results?
   - 4a. How large was the estimate of the intervention effect?
   - 4b. How precise was the estimate of the intervention effect?
5. How can I apply the results to patient care?
   - 5a. Were the study participants similar to the patient in my practice?
   - 5b. Were the study interventions likely to be reproducible for my patients in my practice?
   - -What was the intervention and comparator?
   - - Were intake differentials achieved?
   - 5c. Were all outcomes of importance to patients considered?
   - 5d. Are the likely benefits of the intervention worth the potential harms and burdens (including costs if applicable) based on my patient's values and preferences?

For assessing the risk of bias (validity) of a clinical trial (part 1), the response items are based on Cochrane Risk of Bias instrument that uses 'definitely high risk of bias', 'probably high risk of bias', 'probably low risk of bias' and 'definitely low risk of bias'. Inevitably, some degree of subjectivity is required in making the risk of bias judgements.

Nutrition Users' Guide article on RCTs[3] that the PREDIMED trial has three (of six) validity domains at low risk of bias and three at high risk of bias (box 1), we recognise that despite some methodological limitations, this is the largest available RCT on the Mediterranean diet evaluating the risk reduction in major cardiovascular events.[4] For this reason, it is worthwhile interpreting the results and assessing the applicability of results to help inform the clinical case in question (box 1).[5]

4. WHAT ARE THE RESULTS?

4a. How large was the estimate of the intervention effect?

Dichotomous (binary) outcomes

Randomised trials can evaluate dichotomous outcomes ('yes' or 'no' classifications such as incidence of stroke, myocardial infarction or cancer) or continuous outcomes (eg, peoples' weight, duration or intensity of symptoms, quality of life). For dichotomous outcomes, studies report the proportion of participants in whom events occur. Consider, for example, an RCT comparing dietary supplementation with placebo in which 20% and 25% of the dietary supplement and placebo groups, respectively, suffered a stroke within 36 months of follow-up (table 1). In this hypothetical example, the frequency of the outcome in each group is the cumulative incidence, also referred to as the risk and is defined as the proportion of study participants in each group who experience a stroke over the duration of the trial (36 months). How can we express these results?

The best estimate of the effect of the intervention is typically referred to as the point estimate, and this estimate can be expressed as in absolute or relative terms. One possibility is to calculate the absolute difference in the risk (the absolute risk reduction (ARR) or risk difference (RD)) of stroke in the control group and the risk of stroke in the intervention group (table 1), in this case 0.05 (5%), which means that with using the dietary supplement as compared with a placebo 5 fewer per 100 people will suffer a stroke over 36 months. Using the ARR we can calculate the number needed to treat (NNT), the number of people who would need to receive treatment over a specified time period to avoid one stroke, in this case 20 people would need to receive treatment for 36 months to avoid one stroke (NNT=20). Another possibility is to express the impact of intervention as relative risk (RR) or OR (table 1),

Table 1 Expressing randomised controlled trial results of a hypothetical dietary intervention

	Outcome (N° of study participants)			Risk/odds
Group	Stroke	No stroke	Total	
Intervention (dietary supplement)	20	80	100	Risk (R(i)): 20/100=0.2 Odds (O(i)): 20/80=0.25
Control (placebo)	25	75	100	Risk (R(c)): 25/100=0.25 Odds (O(c)): 25/75=0.33

Absolute risk reduction or risk difference: R(c) – R(i) = 0.25 – 0.2 = 0.05 (5%).
Relative risk: R(i)/R(c)=0.2/0.25=0.8 (80%).
OR: O(i)/O(c)=0.25/0.33=0.76 (76%).
Relative risk reduction: 1 – RR = 0.2 (20%).
Relative odds reduction: 1 – OR = 0.24 (24%).
Number needed to treat=1/ARR=20.
ARR, absolute risk reduction; NNT, number needed to treat; O(c), odds of stroke with control; O(i), odds of stroke with intervention; R(c), risk in control group; RD, risk difference; R(i), risk in intervention group; ROR, relative odds reduction; RR, relative risk; RRR, relative risk reduction.

in this example 0.80 (80%) and 0.76 (76%), which are the most commonly presented measures of the interventional effect for dichotomous outcomes. We can also calculate the complement of the RR and OR—relative risk reduction (RRR) or relative odds reduction (ROR). In this example the RRR is 20%, meaning that of the individuals who experience the adverse outcome in the intervention group, 20% fewer (in relative terms) will experience the event if receiving the intervention.

If the investigators take the time-to-an-event into account, what is sometimes called a survival analysis, a method often used to evaluate therapies for patients with cancer, then the calculation of the frequency of the outcome incorporates time and the resulting relative measure is called the HR. Calculating the HR requires using information about the risk collected at different time intervals and it accommodates censoring of patients, common in trials of patients with advanced cancer. The HR suffers somewhat less from the risk of bias associated with missing outcome data, taking into account if the risks differ at different time points. Expressing the relative effect over time as an HR will typically yield estimates similar to an RR or OR, particularly if events are rare (eg, <20%) though they are typically further from 1.0 (null value) than the RR or OR. Occasionally when the risk of events are high, the HR will be substantially different from the RR or OR. The interpretation of HR is similar to the interpretation of RR, however the latter does not take into account the timing of an outcome occurrence.

RRR is a commonly presented measure of effect in clinical studies, and unfortunately, particularly by the media. From clinicians, patients or the general public's point of view, the most useful option by far is the ARR or RD,[6–8] ideally presented alongside the baseline (control group) absolute risk.[9] By contrast, relative effects can be misleading. Consider the following hypothetical example, an RR reduction in a study is 50% and the effect size, at first glance, is considered large. However, a 50% reduced risk may mean a reduction in adverse (eg, stroke) events from 40% to 20% (a 20% ARR), or it can mean a risk reduction from 0.2% (2/1000) to 0.1% (1/1000), a 0.1% ARR (see figure 1). Different ARRs based on the same corresponding RRRs often have very different implications, for example, for a person considering changing their diet or taking an additional nutritional supplement. For full transparency, if the measure of association in an RR or OR, the 'experimental group risk' and the 'control group risk' should always be clearly presented.[9] If the measure of association is an HR based on time-to-event data, there is guidance on calculating the risk in the experimental and control group.[10]

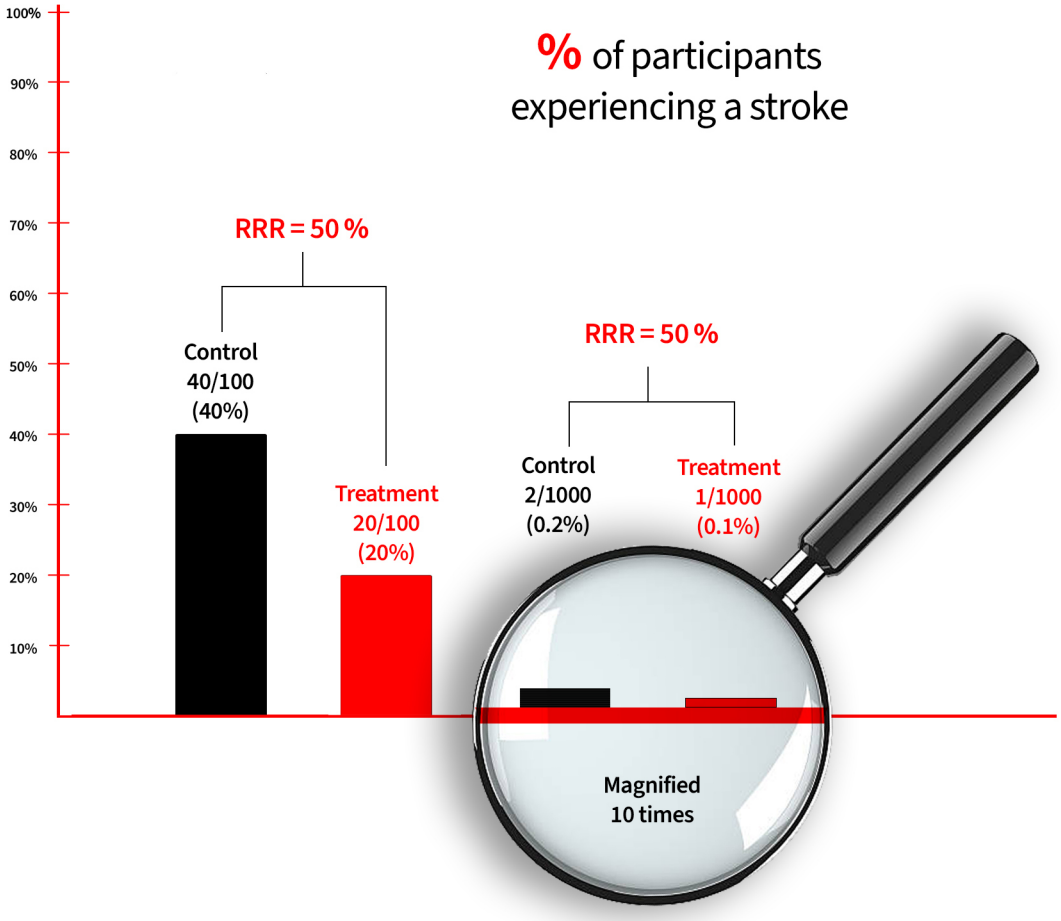

Figure 1 Relative and absolute effects in context to baseline risk. RRR, relative risk reduction.

Table 2 Expressing results for continuous data of a randomised controlled trial of probiotics for infection*

	Outcome: HRQoL (symptom duration in days and symptom severity on a scale 0–133 per day)		
Group	**Duration (days)**	**Severity (points)**	**Total population (n)**
Intervention (probiotic)	5.58	100.43	101
Control (placebo)	7.11	157.3	97

Mean difference (MD) for duration of symptoms=mean (i) – mean (c) = 5.58 – 7.11 = –1.53.
MD for severity of symptoms=mean (i) – mean (c) = 100.43 – 157.3 = –56.87.
MD; the study reported HRQoL as duration and severity of symptoms using the Wisconsin Upper Respiratory Symptom Survey-2.
*Smith *et al*.[13]
HRQoL, health-related quality of life .

Continuous outcomes

In the case of continuous outcomes, such as blood pressure, weight or patient/proxy reported health-related quality of life (HRQoL), studies can report mean scores in the intervention and control group. With continuous data, the 'difference' between the means of the two groups (ie, mean difference) conveniently indicates the absolute estimate of effect (table 2).

Measures of HRQoL are often the outcomes of greatest importance to patients. To better express the size or magnitude of effect estimates for HRQoL measures, the estimate and 95% CI should be interpreted based on a clinically (or patient) important threshold of change referred to as the minimal important difference (MID), if such an estimate exists. The MID provides a measure of the smallest change in an HRQoL instrument that patients perceive as important. As with measures of effect or association, an MID is also an 'estimate'. As opposed to distribution-based approaches, the anchor-based MID approach is the most appropriate method for determining the size of an effect.[11 12]

In table 2, a study of probiotics for the treatment of upper respiratory infections (URI), investigators randomised 198 college students to probiotics or placebo and compared the duration of respiratory symptoms and their severity between groups. The use of probiotics reduced the mean duration of URI symptoms by 1.53 days (95% CI 0.2 to 2.86).[13] In this study, the best estimate of the reduction in duration of URI symptoms is 1.53 days, but the true reduction may be as small as 0.2 (4.8 hours) days or as much as 2.86 days (68 hours). The use of probiotics reduced symptom severity by 56.87 (95% CI 11.19 to 102.55) on a scale from 0 to 133. For this scale, the (anchor-based) MID was reported to be 10.3,[14] suggesting a large and important reduction (ie, the reduction was 5× that of the MID) in the severity of symptoms.

4b. How precise was the estimate of the intervention effect?

Measures of treatment effect observed in a study, presented in table 2 and box 2, are called point estimates (eg, MD, RR, RD) and represent the best estimate of the size of the true effect of the intervention.

To describe the precision of the estimate, we refer to the range of plausible estimates around the point estimate which is called the CI—the range of values in which the true effect of the intervention likely lies.[2] More specifically, if a point estimate were true and one was to repeat an identical study a multitude of times, 95% of the time the estimate would fall within the interval. Our definition of a 95% CI and the 'true' estimate applies if, and only if, 'all the assumptions used to compute the intervals are correct'.[15] Box 2 presents an example that illustrates the use of the CI in a trial reporting on a binary outcome, and box 3 returns to the opening clinical scenario to resolve the how large (or small) the results are based on PREDIMED.

Box 2 Precision of estimates based on sample size

The trial shown in table 1 randomised 200 participants to a dietary supplement or a control group (placebo), 25 participants out of 100 had a stroke in the placebo group and 20 participants out of 100 had a stroke in the dietary supplement group. The point estimate of the relative risk (RR) for stroke is 0.80. However, the true relative risk might be smaller or larger. As depicted in figure 1 (below), in Study 1 you might even suspect that the intervention does not provide any benefit (an RR of 1.0) or is harmful (an RR>1.0). The effect estimate from this trial, according to the CI, suggests the possibility of benefit and harm. That is, the upper bound of the 95% CI, an RR of 1.34 indicates that those receiving the dietary intervention are, in relative terms, 34% more likely to have a stroke than those in the control group, while the lower bound of the 95% CI, an RR of 0.48 indicates that those receiving the dietary intervention are 52% less likely to have a stroke than those in the control group. Study 1 does not provide results that can definitively help us decide whether we should offer the dietary supplement. With a larger number of participants included in a study and the same rate of events (for simplification purposes, although it is rather unlikely to have the same point estimate in a different study) CI will likely become more narrow and our confidence that the true RR is close to 0.80 is much greater (figure 2). For instance, with a 10-fold increase in participants and events (Study 2), the 95% CI for the RR for such a large trial falls on the beneficial side of the null value (an RR of 1.0) ranging from 0.68 to 0.94, providing a more precise (narrow) 95% CI that may warrant spending more time with a patient discussing dietary supplement use—if, as we have just learnt, the (baseline) risk of a stroke is great enough. If the risk of a stroke for a particular group of individuals is only 5 in 1000, lowering the risk to 4 (as would occur with a 20% RRR), then taking a supplement may not appear an attractive option given the associated burden or expense.

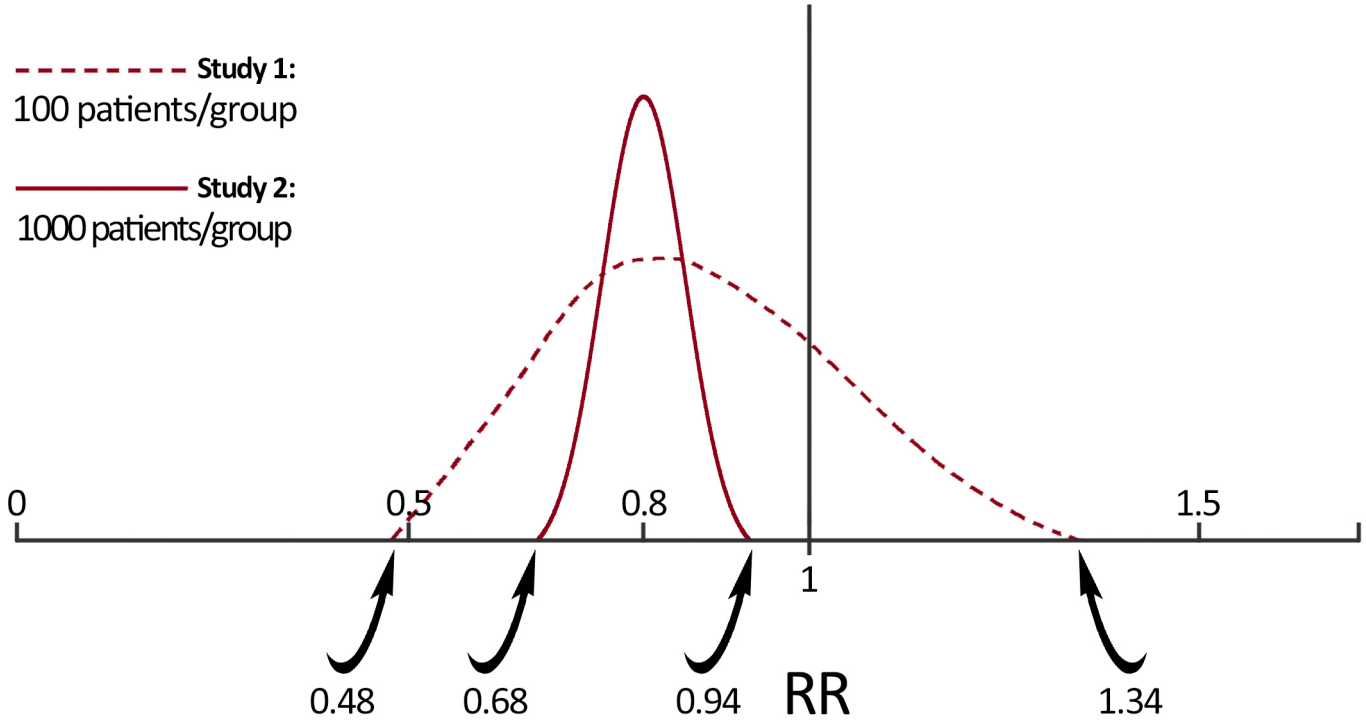

Figure 2 CIs in studies of different size. RR, relative risk; x-axis, different possible RR; y-axis, probability of the true relative risk reduction having indicated value; see description box 2; 95% CI calculated using the standard formula for 95% CI, which takes into account the data presented in table 1 and the width of the CI.

5. HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Once clinicians understand the magnitude and precision of the intervention effect, they then need to consider the applicability of the study results to their patients.

5a. Were the study patients similar to the patient in my practice?

It is reasonable to consider that the results of a trial are sufficiently applicable to your patient if he or she meets the eligibility criteria for enrolment in the RCT. Often, however, your patient will differ from the participants in the trial (eg, your patient is older, has a more severe disease, consumes a different pre-intervention dietary pattern, is better or more poorly nourished or has additional comorbidities).

It is possible that the results of the study can be applied even if there are differences between your patient and those enrolled in the trial. The question clinicians should ask themselves is whether those differences would lead to a substantially different effect on the outcome of interest; the answer will often be no, leaving the clinicians confident in applying the results. In cases in which the answer is 'maybe', clinicians will be less confident in applying the results, but if benefits in the eligible population clearly outweigh the harms and burdens, then recommending nutritional intervention may still be appropriate.

An often relevant issue is a patient's baseline nutritional status. Nutritional status can vary in its definition and includes the overall state of nourishment as well as markers of tissue nutrient concentrations. Unlike many drugs, nutrients are absorbed, metabolised and retained to some degree to meet homeostatic functions; however, individuals can vary considerably in markers of baseline status, and lower status indicators generally increase the risk of nutrient deficiency. Vitamin D is a well-studied example whereby plasma 25(OH)D3 is regarded as a marker of vitamin D status. Consider, for example, a trial in critically ill patients with vitamin D deficiency of vitamin D supplementation.[16] The Correction of Vitamin D Deficiency in Critically Ill Patients (VITdAL-ICU) trial randomised and analysed 475 patients in Austria to a high dose of vitamin D3 (a bolus of 540 000 IUs followed by 5 monthly doses of 90 000 IU) or placebo. After 6 months follow-up, investigators found similar length of hospital stay, hospital mortality and 6-month mortality. However, it is reasonable to query whether effects in this trial differed by baseline vitamin D status, a known effect modifier of the response to vitamin D supplementation.[17]

RCTs may present results from subgroup analyses in which the effects of the intervention are tested in subsets of participants according to one or more baseline participant characteristics (potential effect modifiers such as nutrient status). Before applying the results of a subgroup analysis, users of the literature should assess its validity using published criteria that include 11 questions (eg, statistically significant test of interaction (a statistical test for the difference in the treatment effect between subgroups), consistent findings across-related outcomes).[18] Based on the VITdAL-ICU trial, the criteria for the assessment of the validity of subgroup analysis are presented in table 3. While valid subgroup findings

Box 3 Calculating more precise absolute estimates of effect for a specific patient/individual

Returning to our opening clinical scenario, using the PREDIMED trial that evaluated a Mediterranean diet with supplemental extra virgin olive oil vs a control 'low-fat' diet (on evaluation the control group consumed on average 37% fat and the diet reflected more of a Mediterranean dietary pattern when considering control group 'Mediterranean Diet Adherence Screener' scores), the HR for a major cardiovascular event was 0.69 (95% CI 0.53 to 0.91),[1] a 31% relative risk reduction (RRR) if we assume the HR is approximately equivalent to a relative risk. The least optimistic value of the 95% CI still suggests a benefit—a 9% RRR—which, for patients with a high risk of major cardiovascular events, may be important. For the Mediterranean diet with nuts (primarily walnuts), the HR for a major cardiovascular event was 0.72 (95% CI 0.54 to 0.95), a 28% overall RRR with the least optimistic reduction being a 5% RRR. Fortunately, the PREDIMED trial also reported the 5-year absolute risk reduction (ARR) for the diet with olive oil (2.1%, 95% CI 1.8% to 2.4%) and with nuts (1.7%, 95% CI 1.5% to 1.9%). To calculate an absolute estimate of the effect more specific to your patient, you elect to use the freely available atherosclerotic cardiovascular disease calculator from the American College of Cardiology and the American Heart Association, which provides the risk of a major cardiovascular event over a 10-year horizon. For your 62-year-old male patient the risk of a cardiovascular event (myocardial infarction, stroke or death due to cardiovascular disease) within the next 10 years is 12.2%. Based on available guidance on calculating absolute effects from HRs,[10] using the 31% RRR from the diet plus olive oil arm of the PREDIMED trial, we multiply 0.31 by 12.2% to get an ARR of 3.78%. To summarise, the Mediterranean diet (with added extra virgin olive oil) may reduce the risk of major events by 31%, thus from 12.2% to 8.4% over 10 years, an ARR of 3.8%. The same calculations can be made for the Mediterranean diet plus nuts intervention as well as the 95% CIs to understand the range of possible absolute effects.

that can be confidently applied to practice are rare, the more criteria that are met the more likely the subgroup effect is real or valid. In the VITdAL-ICU trial authors reported baseline vitamin D status, and the effect of vitamin D3 on hospital mortality differed significantly (p value for interaction=0.04) between patients with severe deficiency (HR 0.56; 95% CI 0.35 to 0.90) versus in patients with less severe deficiency (HR 1.12; 95% CI 0.72 to 1.77).

Having answered 'yes' to 9 of 11 questions, the subgroup on severity of vitamin D deficiency is highly valid. Such examples of highly valid subgroups are hard to find, and readers should bear this in mind when interpreting subgroups reported in RCTs. To verify one's findings for the validity of RCT subgroups, readers should continuously look to see if the subgroup findings have been replicated in emerging RCTs (ie, question 9) and particularly in systematic reviews of such RCTs using similar validity criteria.[19]

Unfortunately, many RCTs, despite being directly spawned by observational epidemiology comparing high versus low nutrient status indicators, fail to incorporate baseline nutrient status in their screening and enrolment criteria. Indeed, significant bodies of observational epidemiology comparing high versus low 25(OH)D and erythrocyte omega 3 status (eicosapentaenoic acid [EPA]+docosahexaenoic acid [DHA] as % total fatty acids) indicate potential risk reductions in a variety of chronic disease endpoints,[20 21] though questions about the causal nature of such relationships remain. Trials that have measured baseline omega 3 status have noted that baseline levels are higher than typical in Western diets and close to protective ranges seen in the epidemiological literature,[22] whereas others that have reported a lower baseline status and achieved a modest protective status on supplementation, observed protective effects only in a subgroup with low fish intake.[23] Many nutrients, unfortunately, do not have a readily measurable nutrient status indicator[24] and it remains challenging to assess effect modification by baseline status; self-reported dietary intakes or supplement use may aid in discriminating individuals based on habitual intake and/or status, though this too is not often readily accessible or valid.

5b. Were the study interventions likely to be reproducible for my patients in my practice?

What was the intervention and comparator?

It is tempting to assume that the PREDIMED trial demonstrated that simply recommending a Mediterranean diet with liberal use of olive oil and nuts to a patient will provide similar benefits to those observed in PREDIMED. However, as an unblinded RCT aimed at achieving an intake differential in two specific dietary patterns (Mediterranean diet vs low-fat) via food-based dietary counselling, it is necessary to closely investigate the intervention and comparator groups. While it may be obvious to state that the effect of the intervention will occur relative to the control group, in most nutrition studies, the control group is exposed to the intervention variable(s) and thus, the intake differential achieved between the control and the intervention will depend on both the baseline nutrient status and the background dietary intakes (ie, throughout follow-up).

Were intake differentials achieved?

Review of the self-reported dietary intake assessments at baseline in the PREDIMED trial reveals that all three groups scored ~8.5 on a 14-point Mediterranean diet score scale, derived from a Mediterranean Diet Adherence Screener (MEDAS) used to assess dietary intake,[25] a relatively high value compared with typical Western-style diets (two to four). At the study end, the Mediterranean diet groups achieved a modestly higher MEDAS score (1.4–1.8 points) than the control, driven by changes in legumes and seafood, as well as extra virgin olive oil (EVOO) and nuts (~0.5 points), though the control group slightly increased its MEDAS score from baseline to follow-up. Similarly, all groups reported mixed intakes of both EVOO and refined olive oil at baseline (37–39 g/day), as well as nuts (~12.5 g/day). By the study end, the Mediterranean diet+EVOO had increased reported EVOO

Table 3 Example of assessing the validity of subgroup analysis on severity of vitamin D deficiency and hospital mortality using the VITdAL-ICU trial[16]

Criteria	
Design	**Assessment**
1. Is the subgroup variable a characteristic measured at baseline rather than after randomisation?	Yes, measured at baseline.
2. Is the effect suggested by comparisons within rather than between studies?	Yes, within study comparison.
3. Was the hypothesis specified a priori?	Yes, predefined before unblinding and data analysis.
4. Was the direction of the subgroup effect specified a priori	Yes, authors stated that they expected a 'greater effect with more severe deficiency'.
5. Was the subgroup effect one of a small number of hypothesised effects tested?	Yes, only one tested.
Analysis	
6. Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	Yes, p value for interaction test=0.04.
7. Is the significant subgroup effect independent?	Yes, only one interaction tested.
Context	
8. Is the size of the subgroup effect large?	Yes, in patients with severe deficiency (HR 0.56; 95% CI 0.35 to 0.90) vs those with less severe deficiency (HR 1.12; 95% CI 0.72 to 1.77).
9. Is the interaction consistent across studies?	No, not confirmed in at least one other larger RCT (n=1078) in an ICU population with higher risk conditions; there are ongoing studies.[38]
10. Is the interaction consistent across closely-related outcomes within the study?	No, while close (p=0.10, 0.06, 0.12), no statistically significant interactions for all other mortality outcomes (ICU, 28-day and 6-month mortality, respectively).
11. Is there indirect evidence that supports the hypothesised interaction (biological rationale)?	Yes, based on mechanistic data[39] and meta-analysis of observational studies, vitamin D deficiency is associated with increased hospital mortality in critically ill patients.[40]

ICU, intensive care unit; RCT, randomised controlled trial.

intake by 27 g/day and decreased reported refined olive oil intake by 13 g/day, relative to the control, amounting to approximately 20% of kilocalories derived from EVOO in the intervention versus 10% in the control group. The Mediterranean diet+nuts achieved around 8.2% of kilocalories from nuts, compared with 2.6% and 1.6% in the Mediterranean+EVOO and control groups, respectively. Despite counselling to achieve a lower fat intake, the control diet only reduced their kilocalories coming from fat from 39% at baseline to 37% at the end of the trial.

Interpretation of PREDIMED's reported dietary intake data supports a more nuanced view of the intervention, indicating that the intervention manifested primarily as a significant substitution (10% kcal) of refined olive oil intake with reported EVOO or increased nut intake (predominantly walnuts at the expense of refined olive oil and carbohydrate food intake) alongside reported modest changes in other Mediterranean diet components (such as seafood and legumes). By comparison, the control group reported a modestly lower Mediterranean diet score, and a largely unsuccessful reduction in fat consumption. The trial shows a reduction in major cardiovascular disease (CVD) events when EVOO or nuts (primarily walnuts) are added to a Mediterranean-style diet rather than a Western-style diet. It also remains reasonable to hypothesise that some individual dietary components, which involved reported increased polyphenol intake in each of the Mediterranean diets, may have played a meaningful role. See online supplemental appendix 1 for more.

Another issue when considering applicability as related to both the patient and intervention is the likelihood that the patient will adhere to the suggested intervention. Adherence remains a significant challenge in nutrition and other lifestyle interventions and can be influenced by individual factors, such as food preferences, the intensity of intervention (swapping single vs multiple vs entire food patterns), financial resources and self-efficacy with food preparation, or external factors, such as family and work schedules and other cultural barriers. For instance, many dietary programmes involving a shift in entire food patterns are useful for weight loss and cardiovascular risk reduction over the short term, but given the obesogenic environments we typically inhabit, most participants

have difficulty maintaining adherence to most dietary programmes beyond 1 year.[26 27]

5c. Were all outcomes of important to patients considered?

Clinicians use interventions if they provide benefits important for patients. Demonstrating that a single intervention such as a reduced salt diet modestly decreases blood pressure, or that a dietary supplement slightly improves lipid profiles in an otherwise healthy patient does not alone provide adequate justification for administering an intervention. On the other hand, dietary pattern studies that involve multiple dietary changes (eg, increased monounsaturated fat and increased fruits and vegetables high in potassium, fibre) such as a Mediterranean-style diet may have additive effects and may be more likely to impact outcomes important to patients (eg, stroke risk).[1]

Researchers often use surrogate (intermediate) outcomes rather than those that patients consider important. In such instances, clinicians should avoid assuming meaningful improvements in patient-important outcomes-based solely on changes in surrogate outcomes. Referring back to the vitamin D example, even if it reduces bone mineral density loss, this does not mean patients will experience a favourable outcome that is important—that is, a reduction in bone fractures. What is optimal to support the decision to implement a dietary intervention is evidence that the intervention improves outcomes that are important to patients, such as quality of life or an appreciable reduction in the risk of bone fractures, myocardial infarction, stroke or mortality.

The challenges of conducting adequately powered randomised trials of dietary interventions such as foods or food patterns that measure critically important health outcomes (eg, mortality) have led the nutrition field to rely heavily on surrogate (intermediate) outcomes. While surrogate outcomes are useful, including their ability to link individual dietary components across a dose-response range to a potential disease risk in controlled feeding trials, the reliance on them presents substantial challenges. Diseases are highly complex processes involving multiple factors across pathways for which many potential surrogates, sometimes of unknown causal significance, exist. Complicating this further, diets contain numerous components that can impact surrogate outcomes in opposing directions. This can be seen most clearly in the case of macronutrients (eg, fats, protein and carbohydrates) and atherosclerotic cardiovascular disease, where there has been a long focus on the reduction of saturated fatty acids (SFA) with any macronutrient and its ability to lower low density lipoprotein [LDL-C], a surrogate biomarker with an arguably known causal relationship with atherosclerotic disease. Systematic reviews with meta-analyses of over 80 controlled feeding trials in humans[28] demonstrate that replacing SFA with any macronutrient source lowers LDL-C. However, in the case of carbohydrate replacing SFA in the diet, there is a concomitant delirious increase in triglyceride and a reduction in high density lipoprotein-cholesterol [HDL-C]. This simple example only considering one domain of cardiovascular risk factors (ie, blood lipids) readily demonstrates the challenges of predicting major disease outcomes (eg, cardiovascular mortality) from surrogate outcomes. The promiscuous pleiotropy of nutrients within biological systems readily lends themselves to influencing multiple circulating biomarkers (surrogates) of potential relevance to diseases and requires careful considerations when being used to link dietary intake, particularly in the context of dietary patterns, to disease risk.

Even when a trial reports favourable results of an intervention on one outcome of importance to patients, clinicians must also consider the effects of the intervention on other patient-important outcomes. For example, potential environmental issues aside, reducing red meat consumption may result in very small reductions in the lifetime risk of cancer,[29] but may also decrease patient satisfaction with diet and/or quality of life sufficiently that even if benefits were real, informed patients would choose to continue their preferred diet.[30 31] RCTs often neglect to document satisfaction with diet or the impact of dietary interventions on quality of life.[26 32]

As with PREDIMED, clinical trials frequently report on composite outcomes to reduce the required sample sizes and the duration of follow-up. Composite outcomes can, however, be misleading if components vary in importance (eg, death vs angina event), particularly if a favourable result is driven by the least important component.[33] For instance, the St Thomas' Atherosclerosis Regression Study (STARS) randomised men with angina referred for angiography to dietetic advice (total fat no more than 27%, saturated fat 8–10% and omega-3 and omega-6 polyunsaturated fatty acid [PUFA] at 8% daily energy intake) plus usual care versus usual care alone.[34] The dietetic advice group achieved the targeted fat intakes and a large ARR compared with usual care, demonstrating 41 fewer combined cardiovascular events per 100 people followed (95% CI 18 to 66, p=0.0006). However, combined cardiovascular events, a composite, included cardiovascular deaths, fatal and non-fatal myocardial infarction, stroke, as well as coronary heart disease events (angina, angioplasty, coronary artery bypass surgery). Based on one event in the dietetic group and three events in the usual care group, the ARR was 7 fewer cardiovascular deaths per 100 people followed (95% CI 6 to 20, p=0.3084), while the ARR was 24 fewer coronary heart disease events per 100 people followed (95% CI 3 to 46, p=0.0239) based on 3 events in the dietetic group and 10 events in the usual care group, indicating that coronary events, outcomes of far less importance to patients, drove the combined cardiovascular events estimate.[34] As compared with STARS, PREDIMED's composite outcomes were fewer (three vs seven) and consisted of outcomes that were of similar patient importance, though cardiovascular death would be of more importance than stroke or infarction. Among the three outcomes, only stroke proved statistically significant (5-year absolute risk 1.7%, 1.5% and 3.0% for

Mediterranean+EVOO, Mediterranean+nuts and low-fat arms, respectively; with small but likely important absolute RDs ranging from 1.3% to 1.5%).

5d. Are the likely benefits of the intervention worth the potential harms and burdens (including cost if applicable) based on my patient's values and preferences?

Based on the above issues for consideration, if you have decided that the results of a study are applicable to your patient, the last issue to consider is the balance between the probable benefits and harms of an intervention and the associated burden (eg, dietary satisfaction, access to food) and costs. The impact of an intervention is related not only to the RR reduction for a target outcome(s) important to patients, but the ARR (ie, RD) based on the baseline (or control group) risk of the outcome(s).[8] Returning to the PREDIMED trial, the Mediterranean diet supplemented with EVOO reduced the RR for major cardiovascular events by 31% (95% CI 9% to 46%), that is, in about one-third.[1] This may sound impressive, but the likelihood of the intervention impacting your patient may be very small. Again, this is best understood by considering the between-group RD (ie, ARR) of an outcome (ie, major cardiovascular event), in this case 2.1% over 5 years. Expressed in different absolute terms, out of 1000 patients followed, 21 fewer will have a major cardiovascular event with EVOO as compared with control. Below we discuss two patients who might consider a Mediterranean diet supplemented with four tablespoons of EVOO per day.

In the first case, a 45-year-old woman of European origin presents with the following risk factors for CVD: treated hypertension with a current blood pressure [BP] of 130/80 mm Hg, HDL cholesterol of 35 mg/dL, a total cholesterol of 200 mg/dL and who has given up smoking a month ago. She has no signs of current heart disease and the patient tells you she is following a new smoking cessation programme. As in box 3, you use the atherosclerotic cardiovascular disease calculator to find that her risk of a major cardiovascular event (myocardial infarction, stroke or death due to CVD) within the next 10 years is 2.3%. The Mediterranean diet (with added EVOO as compared with the control 'low-fat' diet (on evaluation the control group consumed on average 37% fat and the diet reflected more of a Mediterranean dietary pattern when considering the control group 'Mediterranean Diet Adherence Screener' (MEDAS) scores) may reduce the risk of major events by 31%, thus to 1.6%, an ARR of 0.7%. It is possible that the ARR may be more pronounced when applied to an American setting wherein the patients diet reflects more of a Western/Standard American Diet higher in fat, salt and sugar. Given the relatively small decrease in the risk of cardiovascular events, the potential impact of a dietary change on the patient's quality of life, particularly while she is trying to quit smoking and the additional cost and inconvenience of following a Mediterranean diet supplemented with a half a litre of EVOO per week, the patient might prefer smoking cessation alone.

In the second case, an overweight 59-year-old African American man presents with type II diabetes who is treated for hypertension with a current BP of 130/80 mm Hg, HDL cholesterol of 35 mg/dL and total cholesterol of 200 mg/dL. He is very motivated to take preventive measures. Using the same calculator his risk of cardiovascular event within the next 10 years is 26.1%. An RR reduction of 31% for a major cardiovascular event in such a high-risk patient generates a reduction in absolute terms of 8.1%. Even when the RCT has risk of bias issues (eg, randomisation unconcealed at some centres, stopped early) many patients might still consider following a Mediterranean dietary pattern supplemented with EVOO.

When applicable, equity issues with respect to the absolute difference in risk of an outcome between the groups is a critically important issue to consider before deciding to follow an intervention. As illustrated by the example above, assuming the same RRR for a certain intervention, the benefit for the patient is more likely if the risk of a negative outcome without intervention is higher. That is, a 26.1% baseline risk in a 59-year-old African American man shows an 8.1% ARR, while the 2.3% baseline risk in 45-year-old Hispanic woman shows a 0.7% ARR with a Mediterranean diet+EVOO intervention. Further, the 10-year cardiovascular risks will often differ in men versus women and sometimes between races; sometimes trivially, but sometimes the difference in baseline risks are substantial. For instance, for an African American woman, the baseline risk of having a major cardiovascular event is 6.0% lower (20.1%) than an African American man (26.1%) and the corresponding ARR, assuming the same RRR for the intervention, is 6.2% rather than 8.1% with a Mediterranean diet+EVOO intervention. Please note, the equity scenarios above use 'heart disease risk calculators' with multiple assumptions, and so the estimates are accompanied by some uncertainty.

In weighing the benefits and harms of intervention, we also need information on the adverse effects of intervention (while noting that RCTs evaluating the effects of interventions often include too few patients to detect rare but serious adverse events). Despite RCT results of the Women's Health Initiative Calcium/Vitamin D Supplementation trial, the safety of calcium with vitamin D has been questioned for the management of osteoporosis. In a re-analysis of 16 718 women who were not using personal calcium supplementation at randomisation, the HR for an increased risk in major cardiovascular events in those randomised to calcium and vitamin D was 1.16 (95% CI 1.01 to 1.34) (non-fatal myocardial infarction or revascularisation, p=0.04), whereas in the women already using calcium supplements at randomisation, the cardiovascular risk did not change after allocation to calcium and vitamin D.[35] However, it must be noted, when interpreting the validity of this apparent subgroup effect using the 11 questions in table 3 (above), the answer to about half of the questions is 'no' suggesting the subgroup effect is not necessarily valid. Regardless, in some instances, patients may be incurring out-of-pocket

costs for nutritional interventions that have the possibility of harm, or no desirable benefit.

Finally, we need to consider and explain the trade-offs between potential benefits, harms, burden and costs (if relevant) of different options in an equitable way to our patients and help them choose the option that is most compatible with their personal values and preferences.

Clinical scenario resolution

The PREDIMED study that we identified in the opening scenario found a decreased risk of a composite outcome of cardiovascular death, stroke and myocardial infarction among participants at high risk of cardiovascular events assigned to a Mediterranean-style diet supplemented with EVOO or nuts, compared with a modestly less intense Mediterranean-style (rather than low fat) diet.[1] The authors reported no relevant diet-related adverse events, though there were approximately 1% more withdrawals in the intensified Mediterranean diet groups. The trial shows a 1.7–2.1% 5-year ARR in major CVD events when olive oil or nuts (primarily walnuts) as well as when modest increases in legumes and seafood are added to a Mediterranean-style diet rather than a low-fat or Western-style diet. Before applying the results of this study, it is also important to consider the current diet of your patient and the degree of dietary change they are likely to implement. If your patient follows a Western-style diet, and they can adopt a Mediterranean-style diet, we may assume that the effects will be similar or even more pronounced, particularly for stroke, the only composite event with a statistically significant reduction. In addition, we already concluded in Part 1 that the PREDIMED trial had methodological limitations with three of six validity questions at high risk of bias, therefore one needs to be cautious in applying the results of this study to your patient.

After explaining the potential benefits relative to the burden, your patient explains their hesitations to you. The patient is very motivated and finds the Mediterranean diet to be acceptable but is concerned about the financial costs of daily olive oil or nuts. You explain that the components of a Mediterranean diet allow some flexibility in defining the pattern to follow and that the costs could be reduced by focusing on a number of foods that are relatively cheap (EVOO, walnuts, whole grain oats, inexpensive legumes and fish (catfish, mackerel, sardines), as well as fruits and vegetables such as apples, oranges and carrots). The patient can purchase most of these foods in bulk, including canned or frozen fruits, vegetables and fish (if more convenient), for as little as $75 per month. Ultimately, the patient accepts that the addition of these foods to his diet would be beneficial. The patient chooses to change his diet towards a Mediterranean pattern by regularly consuming the above foods for 3 months, at which time he will return for a follow-up visit.

Overall, in addition to assessing the potential for risk of bias in the trial,[3] clinicians must consider the results, from trivial to potentially large effects on all desirable (benefits) and undesirable (harms) outcomes reported.[36] Subsequently, they must assess the applicability of the study based on the unique circumstances of their patient, including their patients values and preferences.[5 31 36 37] While PREDIMED has risk of bias issues, the results are reasonably compelling and may appeal to some patients.

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