EBSCO Health

Critical Appraisal of a Randomized Trial

Presented by Brian S. Alper, MD, MSPH, FAAFP
Founder of *DynaMed;*
Vice President of Evidence-Based Medicine Research and Development, Quality and Standards

Introduction

- **1993**: Preparation for career in rural family medicine
- **1995**: Founded *DynaMed*
- **Mission**: to provide the most useful information to healthcare professionals at the point of care.
- **2005**: Joined EBSCO
- Currently working as VP of EBM Research and Development, Quality and Standards.

Our Goal in Medicine

Provide the best care…

Provide patients the best information to guide health care decision…

Improve health outcomes…

…based on the "truth" – separating medical knowledge from folklore

How do we know medicine?

- WE = society
- Medicine = clinical knowledge
  - Evidence
    - Scientific investigation
    - Original research published in journals
    - Systematic reviews
  - Guidelines
    - “Collective wisdom”
    - Transforming to be more evidence-based

How do we know medicine?

- WE = individual clinicians
- Medicine = clinical knowledge
  - Consultants
  - Lectures
  - Rounds
  - Guidelines
  - Experts
  - Colleagues
  - Textbooks
  - Precepting
  - CME
  - Experience
- PRACTICAL choices selected for efficiencies.

Evidence-Based Medicine

Definition: Integration of best research evidence with clinical expertise and patient values.

Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. *Evidence-Based Medicine. How to Practice and Teach EBM*. 2nd ed. London: Harcourt Publishers Ltd. 2000. p. 1.

But can best research evidence be easily accessed at the point of care?

Textbooks and Guidelines

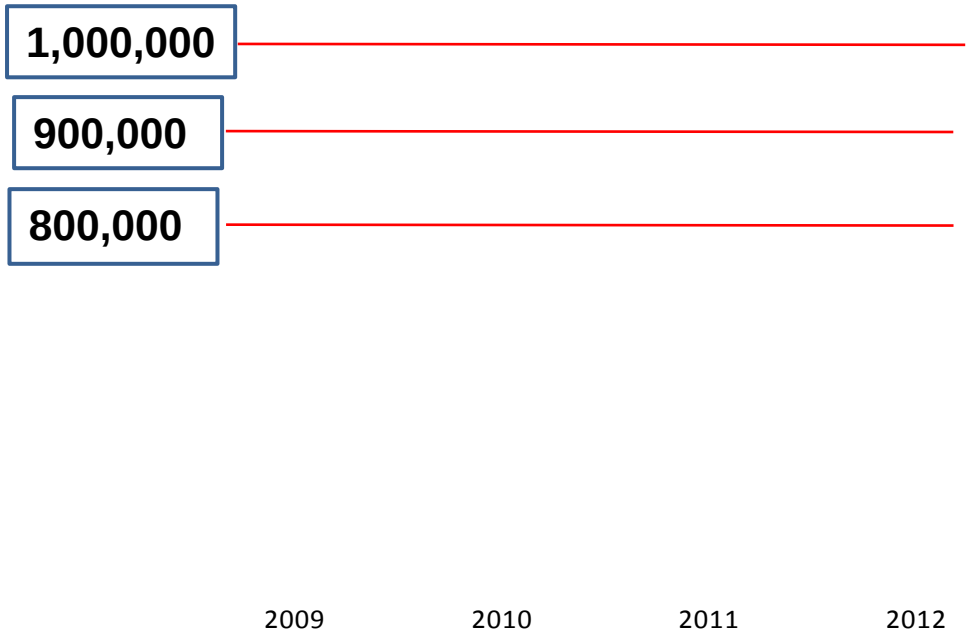
- Not always written for my clinical practice
- May not provide best research evidence
- May be years out-of-date
- Finding specific information within the text can be time-consuming
- May be unavailable for specific question

Evidence: Research Articles and Systematic Reviews

- Specific articles
  - may not relate to specific information needs
  - may not provide complete picture
  - may have bias in research construction
  - may have bias in presentation
- Finding one article can be time-consuming, let alone finding all the relevant articles

Information Overload

Number of articles added to MEDLINE each year:



Evidence: Research Articles and Systematic Reviews

- Specific articles
  - may not relate to specific information need
  - may not provide complete picture
  - may have bias in research construction
  - may have bias in presentation
- Finding one article can be time-consuming, let alone finding all the relevant articles
- Articles are often written to promote research findings, not often written for clinical application
- A current well-done systematic review provides the best evidence and analysis for a focused question

Why is critical appraisal essential?

Published information may be wrong or misleading.

The greatest enemy of knowledge is not ignorance;
it is the illusion of knowledge.

– Stephen Hawking

It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so.

– Mark Twain

Why is critical appraisal essential?

Published information may be wrong or misleading:

- Due to citation of what is published instead of tracing to original research
- Due to acceptance and citation of conclusions of research instead of evaluating methods and statistics
- Due to re-interpretation of information to match personal biases
- Due to selective summarization and citation from bias or familiarity
- Due to use of abstracts instead of full-text articles
- Due to interpretation of changes in surrogate markers to mean changes in clinical outcomes

Best Research Evidence

- Comprehensive – evidence only known to be best if all the available evidence is known
- Valid – critical appraisal determines potential for bias
- Systematic – selection and evaluation of evidence by protocol reduces author bias, investigator bias, editor bias
- Current – every day brings new evidence that could be best
- Synthesized – one study vs. the whole picture

Evidence-Based Requirements for Clinical Reference

“Evidence-based” requires the following steps:

1. Systematically identifying all applicable evidence
2. Systematically selecting the best available evidence from that identified
3. Systematically evaluating the selected evidence (critical appraisal)
4. Objectively reporting the relevant findings and quality of the evidence
5. Synthesizing multiple evidence reports
6. Deriving overall conclusions and recommendations from the evidence synthesis
7. Changing the conclusions when new evidence alters the best available evidence

DynaMed Levels of Evidence

Level 1 [likely reliable] evidence	***Meeting all quality criteria*** ***Low likelihood of bias*** ***High likelihood of accuracy***
Level 2 [mid-level] evidence	*Comparative evidence but with substantial risk of bias* *Moderate to low likelihood of bias* *Moderate to low likelihood of accuracy*
Level 3 [lacking direct] evidence	*No comparative evidence for clinical outcomes* *Highly subject to bias*

DynaMed Levels of Evidence

***DynaMed* criteria for level 1 (likely reliable) evidence for ….**

- **interventional conclusion (conclusions that an intervention does or does not change an outcome)**
- **a diagnostic conclusion**
- **prognostic conclusion**
- **for conclusions from a systematic review**

Level of Evidence 1 (LOE1)

12 criteria for LOE1 **for interventional conclusion (conclusions that an intervention does or does not change an outcome):**

1. Full-text report available in English (or language well understood by participating editor)
2. Clinical outcome (also called patient-oriented outcomes)
3. Population, intervention, comparison, and outcome in the study is representative of expected clinical practice
4. Random allocation method (i.e. not assigned by date of birth, day of presentation, “every other”)
5. Blinding of all persons (patient, treating clinician, outcome assessor) if possible
6. Follow-up (endpoint assessment) of at least 80% of study entrants AND adequate such that losses to follow-up could not materially change the results
7. Accounting for dropouts (even if not included in analysis)
8. Confidence intervals do not include both presence and absence of clinically meaningful differences

LOE1 cont.

9. In cases of randomized parallel-group trials
   - •Allocation concealment
   - •Intention-to-treat analysis comparing groups according to randomization

10. In cases of randomized crossover trials
   - – 6 specific criteria (see website for details)

11. In cases of early trial termination
   - – 5 specific criteria (see website for details)

12. No other factors contributing to substantial bias, such as

- Differences in management between groups other than the intervention being studied
- Differential loss to follow-up
- Posthoc analysis
- Subgroup analysis
- Baseline differences between groups
- Unclear how missing data are accounted for

Let's walk through "Primary Prevention of Cardiovascular disease with a Mediterranean Diet"

(N Engl J Med 2013; 368:1279-1290)

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*

ABSTRACT

BACKGROUND

Observational cohort studies and a secondary prevention trial have shown an inverse association between adherence to the Mediterranean diet and cardiovascular risk. We conducted a randomized trial of this diet pattern for the primary prevention of cardiovascula

METHODS

In a multicenter trial high cardiovascular risk, ne of three diets: a Medite Medi- terranean diet supple educe dietary fat). Participa ses- sions and, depending e oil, mixed nuts, or small major cardiovascular events cular causes). On the basis pped after a median follow

RESULTS

A total of 7447 persons were enrolled (age range, 55 to 80 years); 57% were women. The two Mediterranean-diet groups had good adherence to the intervention, according to self-reported intake and biomarker analyses. A primary end-point event occurred in 288 participants. The multivariable-adjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.54 to 0.92) and 0.72 (95% CI, 0.54 to 0.96) for the group assigned to a Mediterranean diet with extra-virgin olive oil (96 events) and the group assigned to a Mediterranean diet with nuts (83 events), respectively, versus the control group (109 events). No diet-related adverse effects were reported.

CONCLUSIONS

Among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events. (Funded by the Spanish government's Instituto de Salud Carlos III and others; Controlled-Trials.com number, ISRCTN35739639.)

We'll be looking for:

Do we care?
Does it work?
How much does it work?

We'll be looking for:

Full-text
Clinical outcome
PICO representative
Random allocation
Allocation concealment
Blinding of all
Adequate follow up
Accounting for dropouts
ITT analysis
Confidence intervals
No other factors

Do we care?: Assessment of Clinical Outcome

Full-text
Clinical outcome
PICO representative
Random allocation
Allocation concealment
Blinding of all
Adequate follow up
Accounting for dropouts
ITT analysis
Confidence intervals
No other factors

END POINTS

The primary end point was a composite of myocardial infarction, stroke, and death from cardiovascular causes. Secondary end points were stroke, myocardial infarction, death from cardiovascular causes, and death from any cause. We used four sources of information to identify end points: repeated contacts with participants, contacts with family physicians, a yearly review of medical records, and consultation of the National Death Index. All medical records related to end points were examined by the end-point adjudication committee, whose members were unaware of the study-group assignments. Only end points that were confirmed by the adjudication committee and that occurred between October 1, 2003, and December 1, 2010, were included in the analyses. The criteria for adjudicating primary and secondary end points are detailed in the Supplementary Appendix.

Assessment of randomization: Random allocation method

- Full-text
- Clinical outcome
- PICO representative
- **Random allocation**
- Allocation concealment
- Blinding of all
- Adequate follow-up
- Accounting for dropouts
- ITT analysis
- Confidence intervals
- No other factors

THE TRADITIONAL MEDITERRANEAN DIET is characterized by a high intake of olive oil, fruit, nuts, vegetables, and cereals; a moderate intake of fish and poultry; a low intake of dairy products, red meat, processed meats, and sweets; and wine in moderation, consumed with meals.[1] In observational cohort studies[2,3] and a secondary prevention trial (the Lyon Diet Heart Study),[4] increasing adherence to the Mediterranean diet has been consistently beneficial with respect to cardiovascular risk.[2-4] A systematic review ranked the Mediterranean diet as the most likely dietary model to provide protection against coronary heart disease.[5] Small clinical trials have uncovered plausible biologic mechanisms to explain the salutary effects of this food pattern.[6-9] We designed a randomized trial to test the efficacy of two Mediterranean diets (one supplemented with extra-virgin olive oil and another with nuts), as compared with a control diet (advice on a low-fat diet), on primary cardiovascular prevention.

METHODS

STUDY DESIGN

The PREDIMED trial (Prevención con Dieta Mediterránea) was a parallel-group, multicenter, randomized trial. Details of the trial design are provided elsewhere.[10-12] The trial was designed and conducted by the authors, and the protocol was approved by the institutional review boards at all study locations. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

PARTICIPANTS

Eligible participants were men 55 to 80 years of age and women 60 to 80 years of age who were free of cardiovascular disease but were at high cardiovascular risk because they had type 2 diabetes mellitus or at least three of the following major risk factors: current smoking, hypertension, dyslipidemia, overweight or obesity, or a family history of premature coronary heart disease. Detailed enrollment criteria are provided in the Supplementary Appendix, available at NEJM.org. All participants provided written informed consent.

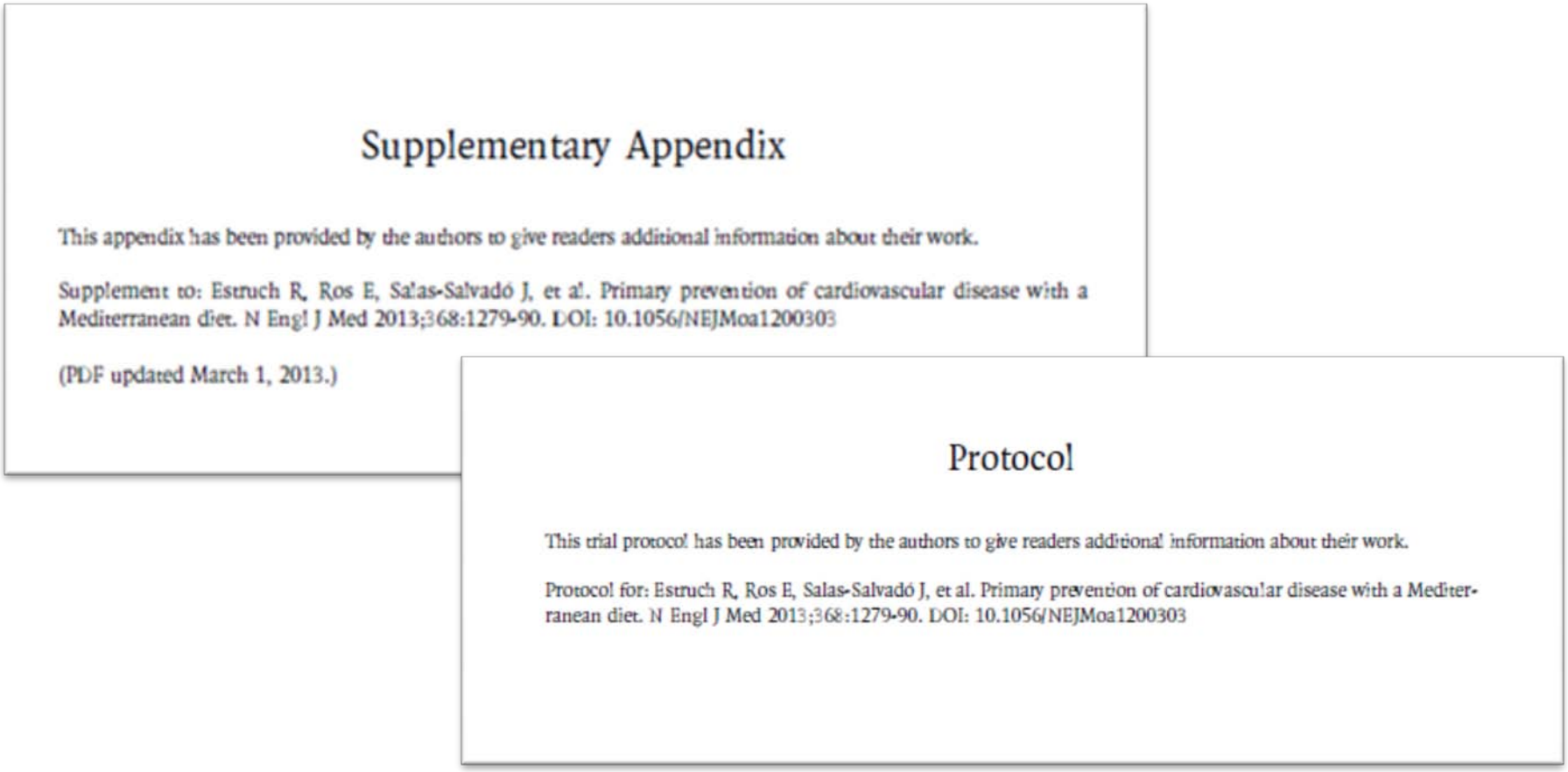
Beginning on October 1, 2003, participants were randomly assigned, in a 1:1:1 ratio, to one of three dietary intervention groups: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with nuts, or a control diet. Randomization was performed centrally by means of a computer-generated random-number sequence.

INTERVENTIONS AND MEASUREMENTS

The dietary intervention[8,10-13] is detailed in the Supplementary Appendix. The specific recommended diets are summarized in Table 1. Participants in the two Mediterranean-diet groups received either extra-virgin olive oil (approximately 1 liter per week) or 30 g of mixed nuts per day (15 g of walnuts, 7.5 g of hazelnuts, and 7.5 g of almonds) at no cost, and those in the control group received small nonfood gifts. No total calorie restriction was advised, nor was physical activity promoted.

For participants in the two Mediterranean-diet groups, dietitians ran individual and group dietary-training sessions at the baseline visit and quarterly thereafter. In each session, a 14-item dietary screener was used to assess adherence to

Other sources



Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279-90. DOI: 10.1056/NEJMoa1200303

(PDF updated March 1, 2013.)

Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279-90. DOI: 10.1056/NEJMoa1200303

Assessment of randomization: Allocation concealment

- **Randomization**: The study nurse randomly assigns ea
corresponding intervention group following tables of random allo
recruitment order in blocks of 50 participants, balanced by sex an
and ≥ 70 years). These tables have been centrally elaborated by th
provide a stratified random sequence of allocation for each FC
The four strata for stratified randomization are built according to
point: 70 years). The Primary Care physicians do not partici
randomization. The study nurses are independent of the nurse staf
they are not involved in the usual clinical care of participants, thei
being to collect the data for the PREDIMED trial.

-Protocol, page 14

Full-text
Clinical outcome
PICO representative
Random allocation
Allocation concealment
Blinding of all
Adequate follow-up
Accounting for dropouts
ITT analysis
Confidence intervals
No other factors

Blinding and Management of patients: Attention Control

Full-text
Clinical outcome
PICO representative
Random allocation
Allocation concealment
Blinding: Inadequate attention control
Adequate follow-up
Accounting for dropouts
ITT analysis
Confidence intervals
Other factors: Differing management

Heart Study),[4] increasing adherence to the Mediterranean diet has been consistently beneficial with respect to cardiovascular risk.[2-4] A systematic review ranked the Mediterranean diet as the most likely dietary model to provide protection against coronary heart disease.[5] Small clinical trials have uncovered plausible biologic mechanisms to explain the salutary effects of this food pattern.[6-9] We designed a randomized trial to test the efficacy of two Mediterranean diets (one supplemented with extra-virgin olive oil and another with nuts), as compared with a control diet (advice on a low-fat diet), on primary cardiovascular prevention.

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Supplemental foods were donated, including extra-virgin olive oil (by Hojiblanca and Patrimonio Comunal Olivarero, both in Spain), walnuts (by the California Walnut Commission), almonds (by Borges, in Spain), and hazelnuts (by La Morella Nuts, in Spain). None of the sponsors had any role in the trial design, data analysis, or reporting of the results.

PARTICIPANT SELECTION AND RANDOMIZATION

Eligible participants were men (55 to 80 years of age) and women (60 to 80 years of age) with no cardiovascular disease at enrollment, who had either type 2 diabetes mellitus or at least three of the following major risk factors: smoking, hypertension, elevated low-density lipoprotein

were randomly assigned, in a 1:1:1 ratio, to one of three dietary intervention groups: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with nuts, or a control diet. Randomization was performed centrally by means of a computer-generated random-number sequence.

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For participants in the two Mediterranean-diet groups, dietitians ran individual and group dietary training sessions at the baseline visit and quarterly thereafter. In each session, a 14-item dietary screener was used to assess adherence to the Mediterranean diet[8,14] (Table S1 in the Supplementary Appendix) so that personalized advice could be provided to the study participants in these groups.

Participants in the control group also received dietary training at the baseline visit and completed the 14-item dietary screener used to assess baseline adherence to the Mediterranean diet. Thereafter, during the first 3 years of the trial, they received a leaflet explaining the low-fat diet (Table S2 in the Supplementary Appendix) on a yearly basis. However, the realization that the more infrequent visit schedule and less intense support for the control group might be limitations of the trial prompted us to amend the protocol in October 2006. Thereafter, participants assigned to the control diet received personalized advice and were invited to group sessions with the same frequency and intensity as those in the Mediterranean-diet groups, with

Accounting for everyone: Follow Up

7447 were randomly assigned to one of the three study groups (Fig. S2 in the Supplementary Appendix). Their baseline characteristics according to study group are shown in Table 2. Drug-treatment regimens were similar for participants in the three groups, and they continued to be balanced during the follow-up period (Table S4 in the Supplementary Appendix).

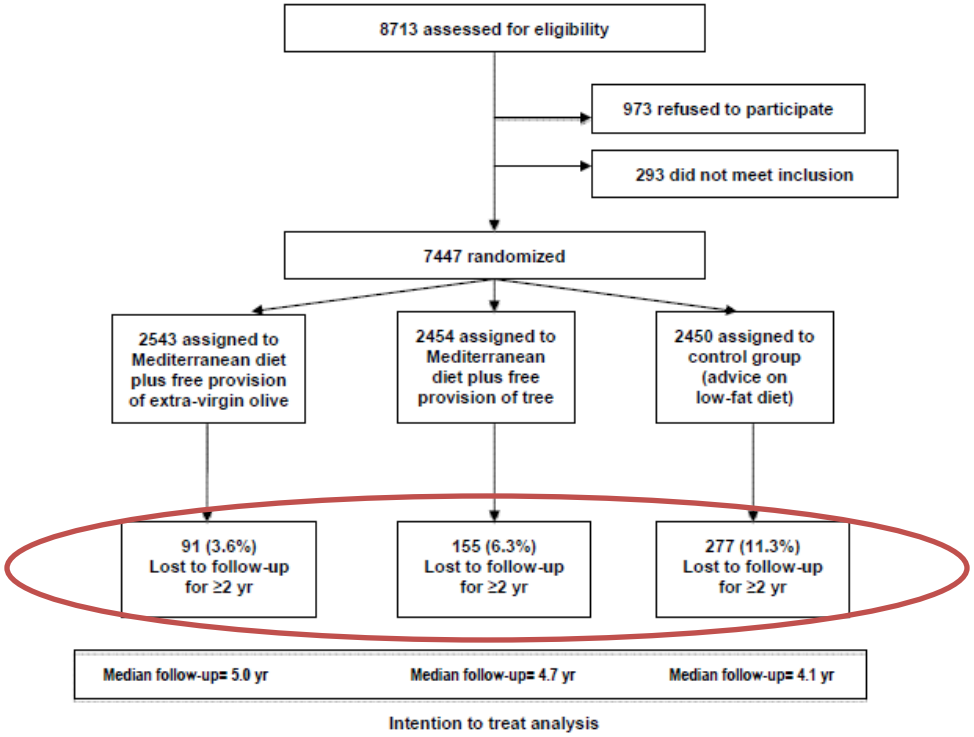
Participants were followed for a median of 4.8 years (interquartile range, 2.8 to 5.8). After the initial assessment, 209 participants (2.8%) chose not to attend subsequent visits, and their follow-up was based on reviews of medical records. By December 2010, a total of 523 participants (7.0%) had been lost to follow-up for 2 or more years. Dropout rates were higher in the control group (11.3%) than in the Mediterranean-diet groups (4.9%) (Fig. S2 in the Supplementary Appendix). As compared with participants who remained in the trial, those who dropped out were younger (by 1.4 years), had a higher BMI (the weight in kilograms divided by the square of the height in meters; by 0.4), a higher waist-to-height ratio (by 0.01), and a lower score for adherence to the Mediterranean diet (by 1.0 points on the 14-item dietary screener) ($P<0.05$ for all comparisons).

COMPLIANCE WITH THE DIETARY INTERVENTION

Participants in the three groups reported similar adherence to the Mediterranean diet at baseline (Table 2, and Fig. S3 in the Supplementary Appendix) and similar food and nutrient intakes. During follow-up, scores on the 14-item Mediterranean-diet screener increased for the participants in the two Mediterranean-diet groups (Fig. S3 in the Supplementary Appendix). There were significant differences between these groups and the control group in 12 of the 14 items at 3 years (Table S5 in the Supplementary Appen-

ITT Analysis

Figure S2. Trial Profile.



Confirming ITT Analysis

All primary analyses were performed on an intention-to-treat basis by two independent analysts. Time-to-event data were analyzed with the use of Cox models with two dumm
(one for the Mediterranean diet with
olive oil and another for the Medite

Table 3. Outcomes According to Study Group.*

End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)	P Value† Mediterranean Diet with EVOO vs. Control Diet	P Value† Mediterranean Diet with Nuts vs. Control Diet
Person-yr of follow-up	11,85				
Primary end point‡					
No. of events	96				
Crude rate/1000 person-yr (95% CI)	8.1 (6.6-				
Secondary end points					
Stroke					
	49				
	4.1 (3.1-				
	37				
	3.1 (2.2-				
	26				
	2.2 (1.4-				
	118				
	10.0 (8.2-				
Primary end point					
	(0.53				
	(0.53				
	(0.54				
	(0.46				
	(0.51				
	(0.41				
Death from any cause	0.82 (0.64				

We'll be looking for:

Do we care?
Does it work?
How much does it work?

Confidence intervals do not include both presence and absence of clinically meaningful differences

Full-text
Clinical outcome
PICO representative
Random allocation
Allocation concealment
Blinding: Inadequate attention control
Adequate follow-up
Accounting for dropouts
ITT analysis
Confidence intervals
Different management
Differential loss to follow-up

Reporting Outcomes: Composite Outcome

Table 3. Outcomes According to Study Group.*

End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)	P Value†	
				Mediterranean Diet with EVOO vs. Control Diet	Mediterranean Diet with Nuts vs. Control Diet
Person-yr of follow-up	11,852	10,365	9763		
Primary end point‡					
No. of events	96	83	109		
Crude rate/1000 person-yr (95% CI)	8.1 (6.6–9.9)	8.0 (6.4–9.9)	11.2 (9.2–13.5)	0.009	0.02
Secondary end points					
Stroke					
No. of events	49	32	58		
Crude rate/1000 person-yr (95% CI)	4.1 (3.1–5.5)	3.1 (2.1–4.4)	5.9 (4.5–7.7)	0.03	0.003
Myocardial infarction					
No. of events	37	31	38		
Crude rate/1000 person-yr (95% CI)	3.1 (2.2–4.3)	3.0 (2.0–4.2)	3.9 (2.8–5.3)	0.31	0.25
Death from cardiovascular causes					
No. of events	26	31	30		
Crude rate/1000 person-yr (95% CI)	2.2 (1.4–3.2)	3.0 (2.0–4.2)	3.1 (2.1–4.4)	0.15	0.85
Death from any cause					
No. of events	118	116	114		
Crude rate/1000 person-yr (95% CI)	10.0 (8.2–11.9)	11.2 (9.3–13.4)	11.7 (9.6–14.0)	0.11	0.68
Hazard ratio for each Mediterranean diet vs. control (95% CI)					
Primary end point					
Unadjusted	0.70 (0.53–0.91)	0.70 (0.53–0.94)	1.00 (ref)	0.009	0.02
Multivariable-adjusted 1§	0.69 (0.53–0.91)	0.72 (0.54–0.97)	1.00 (ref)	0.008	0.03
Multivariable-adjusted 2¶	0.70 (0.54–0.92)	0.72 (0.54–0.96)	1.00 (ref)	0.01	0.03
Secondary end points‖					
Stroke	0.67 (0.46–0.98)	0.54 (0.35–0.84)	1.00 (ref)	0.04	0.006
Myocardial infarction	0.80 (0.51–1.26)	0.74 (0.46–1.19)	1.00 (ref)	0.34	0.22
Death from cardiovascular causes	0.69 (0.41–1.16)	1.01 (0.61–1.66)	1.00 (ref)	0.17	0.98
Death from any cause	0.82 (0.64–1.07)	0.97 (0.74–1.26)	1.00 (ref)	0.15	0.82

Reporting Outcomes: Risk

END POINTS

The median follow-up period was 4.8 years. A total of 288 primary-outcome events occurred: 96 in the group assigned to a Mediterranean diet with extra-virgin olive oil (3.8%), 83 in the group assigned to a Mediterranean diet with nuts (3.4%), and 109 in the control group (4.4%). Taking into account the small differences in the accrual of person-years among the three groups, the respective rates of the primary end point were 8.1, 8.0, and 11.2 per 1000 person-years (Table 3). The unadjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.53 to 0.91) for a Mediterranean diet with extra-virgin olive oil and 0.70 (95% CI, 0.53 to 0.94) for a Mediterranean diet with nuts (Fig. 1) as compared with the control diet (P=0.015, by the likelihood ratio test, for the overall effect of the intervention).

The results of multivariate analyses showed a similar protective effect of the two Mediterranean diets versus the control diet with respect to the primary end point (Table 3). Regarding components of the primary end point, only the comparisons of stroke risk reached statistical significance (Table 3, and Fig. S6 in the Supplementary Appendix). The Kaplan–Meier curves for the primary end point diverged soon after the trial started, but no effect on all-cause mortality was apparent (Fig. 1). The results of several sensitivity analyses were also consistent with the findings of the primary analysis (Table S9 in the Supplementary Appendix).

SUBGROUP ANALYSES

Reductions in disease risk in the two Mediterranean-diet groups as compared with the control group were similar across the prespecified subgroups (Fig. 2, and Table S10 in the Supplementary Appendix). In addition, to account for the protocol change in October 2006 whereby the intensity of dietary intervention in the control group was increased, we compared hazard ratios

We'll be looking for:

Do we care?
Does it work?
How much does it work?

Reporting Outcomes: Relative Risk

Table 3. Outcomes According to Study Group.*

End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)	P Value†	
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Hazard ratio for each Mediterranean diet vs. control (95% CI)					
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Multivariable-adjusted 2¶	0.70 (0.54–0.92)	0.72 (0.54–0.96)	1.00 (ref)	0.01	0.03
Secondary end points‖					
Stroke	0.67 (0.46–0.98)	0.54 (0.35–0.84)	1.00 (ref)	0.04	0.006
Myocardial infarction	0.80 (0.51–1.26)	0.74 (0.46–1.19)	1.00 (ref)	0.34	0.22
Death from cardiovascular causes	0.69 (0.41–1.16)	1.01 (0.61–1.66)	1.00 (ref)	0.17	0.98
Death from any cause	0.82 (0.64–1.07)	0.97 (0.74–1.26)	1.00 (ref)	0.15	0.82

Hazard ratio for each Mediterranean diet vs. control (95% CI)
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Myocardial infarction 0.80 (0.51–1.26) 0.74 (0.46–1.19) 1.00 (ref) 0.34 0.22
Death from cardiovascular causes 0.69 (0.41–1.16) 1.01 (0.61–1.66) 1.00 (ref) 0.17 0.98
Death from any cause 0.82 (0.64–1.07) 0.97 (0.74–1.26) 1.00 (ref) 0.15 0.82

Reporting Outcomes: Absolute Risk

Table 3. Outcomes According to Study Group.*

End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)	P Value†	
				Mediterranean Diet with EVOO vs. Control Diet	Mediterranean Diet with Nuts vs. Control Diet
Person-yr of follow-up	11,852	10,365	9763		
Primary end point‡					
No. of events	96	83	109		
Crude rate/1000 person-yr (95% CI)	8.1 (6.6–9.9)	8.0 (6.4–9.9)	11.2 (9.2–13.5)	0.009	0.02
Secondary end points					
Stroke					
No. of events	49	32	58		
Crude rate/1000 person-yr (95% CI)	4.1 (3.1–5.5)	3.1 (2.1–4.4)	5.9 (4.5–7.7)	0.03	0.003
Myocardial infarction					
No. of events	37	31	38		
Crude rate/1000 person-yr (95% CI)	3.1 (2.2–4.3)	3.0 (2.0–4.2)	3.9 (2.8–5.3)	0.31	0.25
Death from cardiovascular causes					
No. of events	26	31	30		
Crude rate/1000 person-yr (95% CI)	2.2 (1.4–3.2)	3.0 (2.0–4.2)	3.1 (2.1–4.4)	0.15	0.85
Death from any cause					
No. of events	118	116	114		
Crude rate/1000 person-yr (95% CI)	10.0 (8.2–11.9)	11.2 (9.3–13.4)	11.7 (9.6–14.0)	0.11	0.68
Hazard ratio for each Mediterranean diet vs. control (95% CI)					
Primary end point					
Unadjusted	0.70 (0.53–0.91)	0.70 (0.53–0.94)	1.00 (ref)	0.009	0.02
Multivariable-adjusted 1§	0.69 (0.53–0.91)	0.72 (0.54–0.97)	1.00 (ref)	0.008	0.03
Multivariable-adjusted 2¶	0.70 (0.54–0.92)	0.72 (0.54–0.96)	1.00 (ref)	0.01	0.03
Secondary end points‖					
Stroke	0.67 (0.46–0.98)	0.54 (0.35–0.84)	1.00 (ref)	0.04	0.006
Myocardial infarction	0.80 (0.51–1.26)	0.74 (0.46–1.19)	1.00 (ref)	0.34	0.22
Death from cardiovascular causes	0.69 (0.41–1.16)	1.01 (0.61–1.66)	1.00 (ref)	0.17	0.98
Death from any cause	0.82 (0.64–1.07)	0.97 (0.74–1.26)	1.00 (ref)	0.15	0.82

Reporting Outcomes: Absolute Risk

- Control event rate 5.9 per 1,000 person-years
- Intervention event rate 3.1 per 1,000 person-years
- Absolute difference = 5.9-3.1
  = 2.8 per 1,000 person-years

Secondary end points					
Stroke					
No. of events	49	32	58		
Crude rate/1000 person-yr (95% CI)	4.1 (3.1–5.5)	3.1 (2.1–4.4)	5.9 (4.5–7.7)	0.03	0.003

Reporting Outcomes: NNT

- **NNT**
  - Can be calculated as 1,000 person-years/absolute risk difference
  - 1,000/2.8 becomes NNT 358 person-years
  - 358/5 becomes 5-year NNT 72.

DynaMed Summary

Clinical outcomes:

- **Mediterranean diet may reduce stroke in high-risk patients without cardiovascular disease (level 2 [mid-level] evidence)**
  - based on randomized trial with inadequate attention control
  - 7,447 patients aged 55-80 years at risk of cardiovascular disease were randomized to 1 of 3 diets in Spain
    - Mediterranean diet supplemented with extra-virgin olive oil (about 1 L per week)
    - Mediterranean diet supplemented with mixed nuts (walnuts, hazelnuts, and almonds) 30 g per day
    - control diet with advice to reduce dietary fat
  - there were no calorie restrictions and physical activity was not promoted
  - patients in Mediterranean diet groups had individual and group training at baseline and follow-up sessions 4 times yearly
  - control group had training at baseline and annual leaflet explaining low-fat diet for first 2 years of trial; but protocol was amended in third year for equal attention control
  - all patients had type 2 diabetes or at least ≥ 3 other cardiovascular risk factors including
    - smoking
    - hypertension
    - elevated low-density lipoprotein cholesterol or low high-density lipoprotein cholesterol levels
    - overweight or obesity
    - family history of premature coronary heart disease
  - primary outcome was cardiovascular events including myocardial infarction, stroke, and cardiovascular death
  - early trial termination due to predetermined stopping criteria at median follow-up 4.8 years
  - loss to follow-up in
    - 3.6% with Mediterranean diet plus extra-virgin olive oil
    - 6.3% with Mediterranean diet plus nuts
    - 11.3% with control diet
  - all patients were included in intention-to-treat analyses
  - rates of stroke per 1,000 person-years
    - 5.9 with control diet
    - 4.1 with Mediterranean diet plus extra-virgin olive oil ($p = 0.03$ vs. control, NNT 556 person-years [5-year NNT 112])
    - 3.1 with Mediterranean diet plus nuts ($p = 0.003$ vs. control, NNT 358 person-years [5-year NNT 72])
  - total cardiovascular event rates were significantly reduced in each Mediterranean diet group compared to control, but difference primarily due to differences in stroke rates
  - no significant differences in rates of myocardial infarction, cardiovascular death, or all-cause death among groups
  - no diet-related adverse events occurred in any group
  - Reference - PREDIMED trial (N Engl J Med 2013 Apr 4;368(14):1279 full-text), editorial can be found in N Engl J Med 2013 Apr 4;368(14):1279

Comparing conclusions post-critical analysis

RESULTS

A total of 7447 persons were enrolled (age range, 55 to 80 years); 57% were women. The two Mediterranean-diet groups had good adherence to the intervention, according to self-reported intake and biomarker analyses. A primary end-point event occurred in 288 participants. The multivariable-adjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.54 to 0.92) and 0.72 (95% CI, 0.54 to 0.96) for the group assigned to a Mediterranean diet with extra-virgin olive oil (96 events) and the group assigned to a Mediterranean diet with nuts (83 events), respectively, versus the control group (109 events). No diet-related adverse effects were reported.

CONCLUSIONS

Among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events. (Funded by the Spanish government's Instituto de Salud Carlos III and others; Controlled-Trials.com number, ISRCTN35739639.)

PREDIMED study conclusion

DynaMed Conclusion

Clinical outcomes:

- **Mediterranean diet may reduce stroke in high-risk patients without cardiovascular disease (level 2 [mid-level] evidence)**
  - based on randomized trial with inadequate attention control
  - 7,447 patients aged 55-80 years at risk of cardiovascular disease were randomized to 1 of 3 diets in Spain
    - Mediterranean diet supplemented with extra-virgin olive oil (about 1 L per week)
    - Mediterranean diet supplemented with mixed nuts (walnuts, hazelnuts, and almonds) 30 g per day
    - control diet with advice to reduce dietary fat
  - there were no calorie restrictions and physical activity was not promoted
  - patients in Mediterranean diet groups had individual and group training at baseline and follow-up sessions 4 times yearly
  - control group had training at baseline and annual leaflet explaining low-fat diet for first 2 years of trial; but protocol was amended attention control
  - all patients had type 2 diabetes or at least ≥ 3 other cardiovascular risk factors including

Final notes

- LOE1 criteria are specific to the type of conclusion.
- Critical appraisal is needed to understand the evidence accurately (impact and reliability)
- A systematic process is needed to ensure the best research evidence is available at the point-of-care.