Understanding and Interpreting Meta-Analyses in Nutrition Research

Organized by the American Society for Nutrition's Aging and Chronic Disease Research Interest Section

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Welcome and Introductions

Christy Tangney, PhD

Professor, Clinical Nutrition

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Chair, Aging and

Chronic Disease RIS

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Disclosures for
Terri Pigott, PhD

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Understanding and Interpreting Meta-analyses in Nutrition Research

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Systematic Review

- Systematic reviews are a form of research that use existing studies as the unit of analysis
- Systematic reviews follow the stages of a research process parallel to primary studies
- The goal as in all research is to use systematic and transparent methods to analyze a set of studies

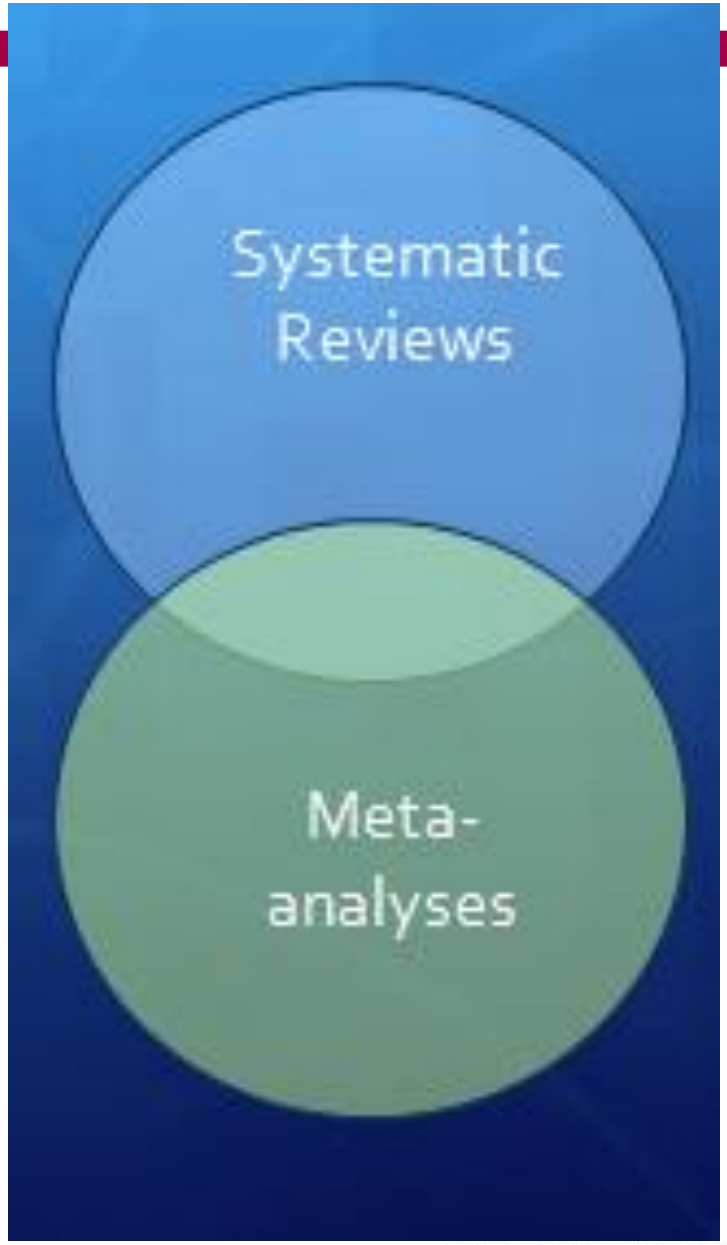
Meta-analysis and Systematic Reviews

- The term systematic review is a broad term, referring to research focused on synthesizing the primary research studies on a given topic
- The term meta-analysis refers to the statistical methods used to synthesize the results from the primary studies
- From each study, we compute an effect size measure and the techniques of meta-analysis help us to analyze those effects

Systematic Reviews and Meta-analysis

- Systematic reviews don't always include meta-analysis
  - Might include narrative synthesis (or no synthesis)
  - Can include multiple meta-analyses

- Meta-analyses are not always based on systematic reviews
  - Many use convenience sample of published studies
  - Vulnerable to publication and dissemination biases



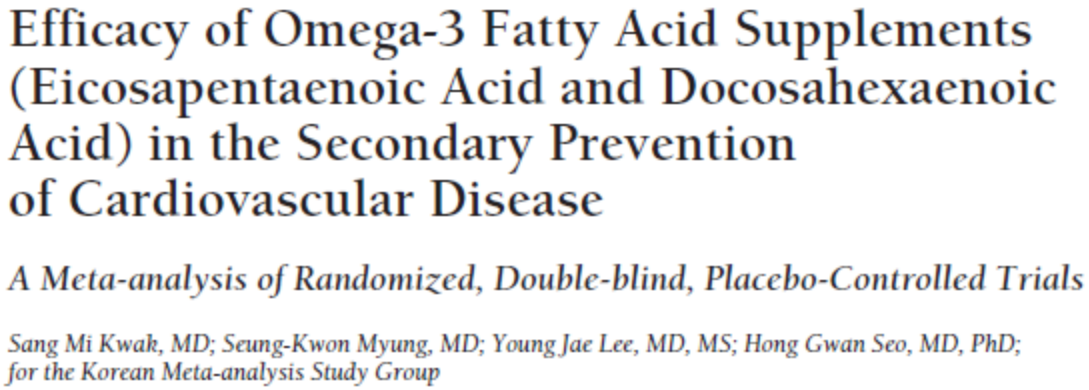
Stages of a research synthesis

- Problem formulation
  - Clarifying your questions
  - Set explicit inclusion/exclusion criteria
- Data collection
  - Literature search
- Data evaluation
  - Criteria for including and excluding studies
  - Assessing study quality

Stages of a research synthesis (cont.)

- Data analysis and interpretation
  - Integrating the effects from collected studies
  - Interpreting analysis results

Example



Efficacy of Omega-3 Fatty Acid Supplements (Eicosapentaenoic Acid and Docosahexaenoic Acid) in the Secondary Prevention of Cardiovascular Disease

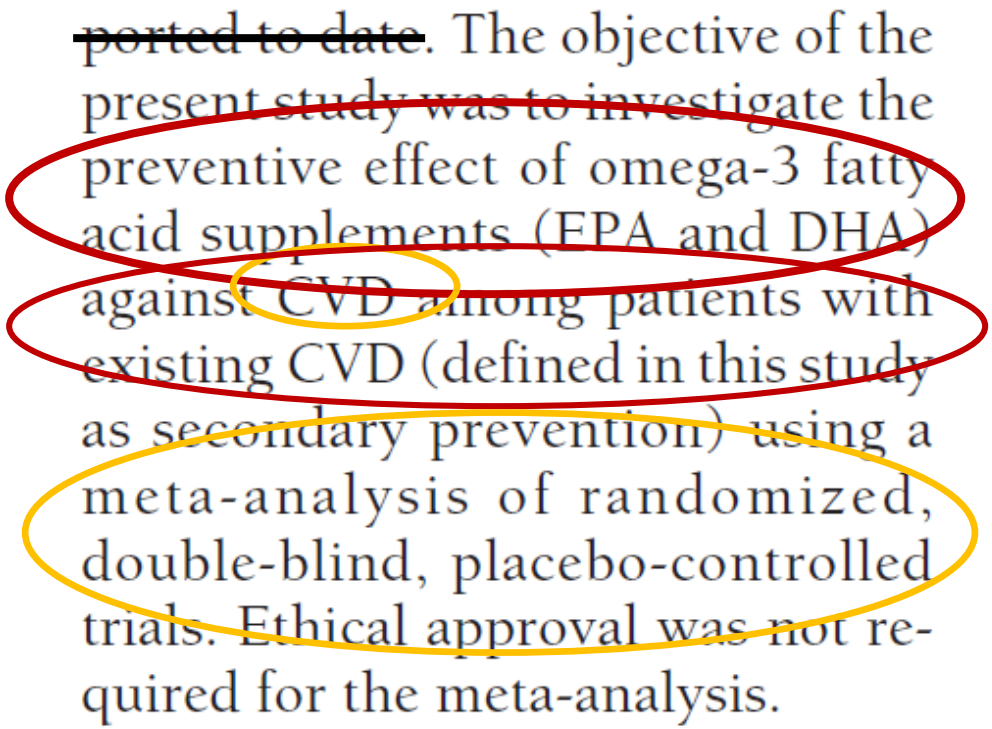
A Meta-analysis of Randomized, Double-blind, Placebo-Controlled Trials

Sang Mi Kwak, MD; Seung-Kwon Myung, MD; Young Jae Lee, MD, MS; Hong Gwan Seo, MD, PhD; for the Korean Meta-analysis Study Group

- We will be using this example as we explore all stages of a systematic review, including the meta-analysis (the analysis and interpretation of the quantitative data)

1. Problem Formulation

- The research question guides every stage of the review
- Definition of the intervention
- Primary outcome
- Population of interest
- Relevant studies



~~ported to date~~. The objective of the present study was to investigate the preventive effect of omega-3 fatty acid supplements (EPA and DHA) against CVD among patients with existing CVD (defined in this study as secondary prevention) using a meta-analysis of randomized, double-blind, placebo-controlled trials. Ethical approval was not required for the meta-analysis.

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Problem Formulation

- Definition of the intervention: *Preventative effect of omega-3 fatty acid supplements (EPA and DHA)*
- Primary outcome: *Cardiovascular disease*
- Population of interest: *Patients with CVD*
- Relevant studies: *Randomized, double-blind, placebo-controlled trials*

Inclusion Criteria

- The **PICOS** framework:
  - **P**opulation/Participants: Patients with CVD
  - **I**nterventions: Omega-3 fatty acid supplements
  - **C**omparison group: placebo-controlled
  - **O**utcomes: CVD and related outcomes
  - **S**tudy Design: randomized and double-blind

2. Data Collection

- Literature Search
- Databases used: PubMed, EMBASE, Cochrane Library
- Dates of search
- Keywords
- No unpublished documents
- Restricted to English

We searched PubMed (January 1, 1976, through April 30, 2011), EMBASE (January 1, 1985, through April 30, 2011), and the Cochrane Library (January 1, 1987, through April 30, 2011) using common keywords related to omega-3 fatty acids and CVD. The keywords included the following: *omega-3 fatty acid*, *eicosapentaenoic acid* or *EPA*, *docosahexaenoic acid* or *DHA*, *cardiovascular disease*, *angina*, *myocardial infarction*, and *sudden cardiac death*. We reviewed the bibliographies of relevant articles for additional publications. The language of publication was restricted to English.

Questions about Lit Search

- Are all relevant databases searched?
- Do the search terms seem relevant, and fit to the database?
- How are unpublished studies being handled, and is a rationale provided?
- Any language restrictions on the studies?

3. Data Evaluation

Inclusion Criteria

- Adults with CVD
- Use of omega-3 fatty acids supplements
- Randomized, double-blind, placebo-controlled trials
- Outcome measures like angina, unstable angina, CVD, sudden cardiac death, etc.

We included trials that met the following 4 criteria: (1) the trial studied adult patients (male or female aged ≥18 years) with a history of CVD; (2) the patients had used omega-3 fatty acid supplements for at least 1 year; (3) the design was a randomized, double-blind, placebo-controlled trial; and (4) the trial reported outcome measures like angina, unstable angina, CVD or events, sudden cardiac death, cardiovascular death, all-cause mortality, congestive heart failure, transient ischemic attack and stroke, or fatal or nonfatal myocardial infarction.

Process to decide on relevant studies

- Is the process transparent?
- Are there checks on the process of inclusion?
- What happens to multiple reports of the same study?

Two of us (S.M.K. and S.-K.M.) independently evaluated the eligibility of all studies retrieved from the databases according to the selection criteria. Disagreements between evaluators were resolved by discussion or in consultation with another of us (Y.J.L.). If data were duplicated or shared in more than 1 study, the first published or larger study was included in the analysis.

Assessment of study quality

- Use of Jadad scale

Table A1 Jadad scale for reporting randomized controlled trials.

Item	Maximum points	Description	Examples
Randomization	2	1 point if randomization is mentioned	"The patients were randomly assigned into two groups"
		1 additional point if the method of randomization is appropriate	The randomization was accomplished using a computer-generated random number list, coin toss or well-shuffled envelopes
		Deduct 1 point if the method of randomization is inappropriate (minimum 0)	The group assignment was accomplished by alternate assignment, by birthday, hospital number or day of the week
Blinding	2	1 point if blinding is mentioned	"The trial was conducted in a double-blind fashion"
		1 additional point if the method of blinding is appropriate	Use of identical tablets or injectables, identical vials Use of tablets with similar looks but different taste
		Deduct 1 point if the method of blinding is inappropriate (minimum 0)	Incomplete masking
An account of all patients	1	The fate of all patients in the trial is known. If there are no data the reason is stated	"There were 40 patients randomized but the data from 1 patient in the treatment group and 2 in the control were eliminated because of a break in protocol"

Results for included studies

Table 2. Methodological Quality of 14 Trials According to Scores on the Scale by Jadad et al[38]

	Score on the Scale by Jadad et al[38]					
Source	Randomization	Description of Randomization Methods	Double-blind Design	Use of Identical Placebo	Follow-up Reporting	Total
Sacks et al,[20] 1995	1	0	1	1	1	4
Singh et al,[21] 1997	1	0	1	1	1	4
Leng et al,[22] 1998	1	0	1	1	1	4
von Schacky et al,[23] 1999	1	1	1	1	1	5
Nilsen et al,[24] 2001	1	0	1	1	0	3
Raitt et al,[25] 2005	1	1	1	1	1	5
Leaf et al,[26] 2005	1	1	1	1	1	5
Brouwer et al,[27] 2006	1	0	1	1	1	4
Svensson et al,[28] 2006	1	1	1	1	1	5
Tavazzi et al,[29] 2008	1	1	1	1	1	5
Garbagnati et al,[30] 2009	1	0	1	1	1	4
Galan et al,[31] 2010	1	1	1	1	1	5
Kromhout et al,[32] 2010	1	0	1	1	1	4
Rauch et al,[33] 2010	1	0	1	1	1	4

Wide range of description of randomization methods

Other Coding

Coding for:

- History of CVD
- Inland vs. Coastal
- Duration of treatment
- Fish oil supplements only
- Oils vs non-oil placebo
- Jadad scale
- Country
- Concomitant meds

We performed the following subgroup analyses: history of CVD, geographic area (inland vs coastal), duration of treatment (<2 vs ≥2 years), dosage of EPA or DHA (<1.7 vs ≥1.7 g/d), use of fish oil supplementation only as treatment, type of placebo material in the trial (oil vs nonoil), methodological quality of the trial (≤4 vs 5 points), country (United States, Asia, Western Europe, or Northern Europe), and concomitant medication use (lipid-lowering agents, no lipid-lowering agents, or use of antiplatelet agents only).

Questions about coding

- Does the study code for:
  - Relevant study and design characteristics, such as placebo type and randomization strategy?
  - Relevant participant/population characteristics such as gender or severity of condition?
  - Relevant outcome type?
  - Relevant setting type?
  - Other issues that might help explain differences in findings across studies?

So far we have covered:

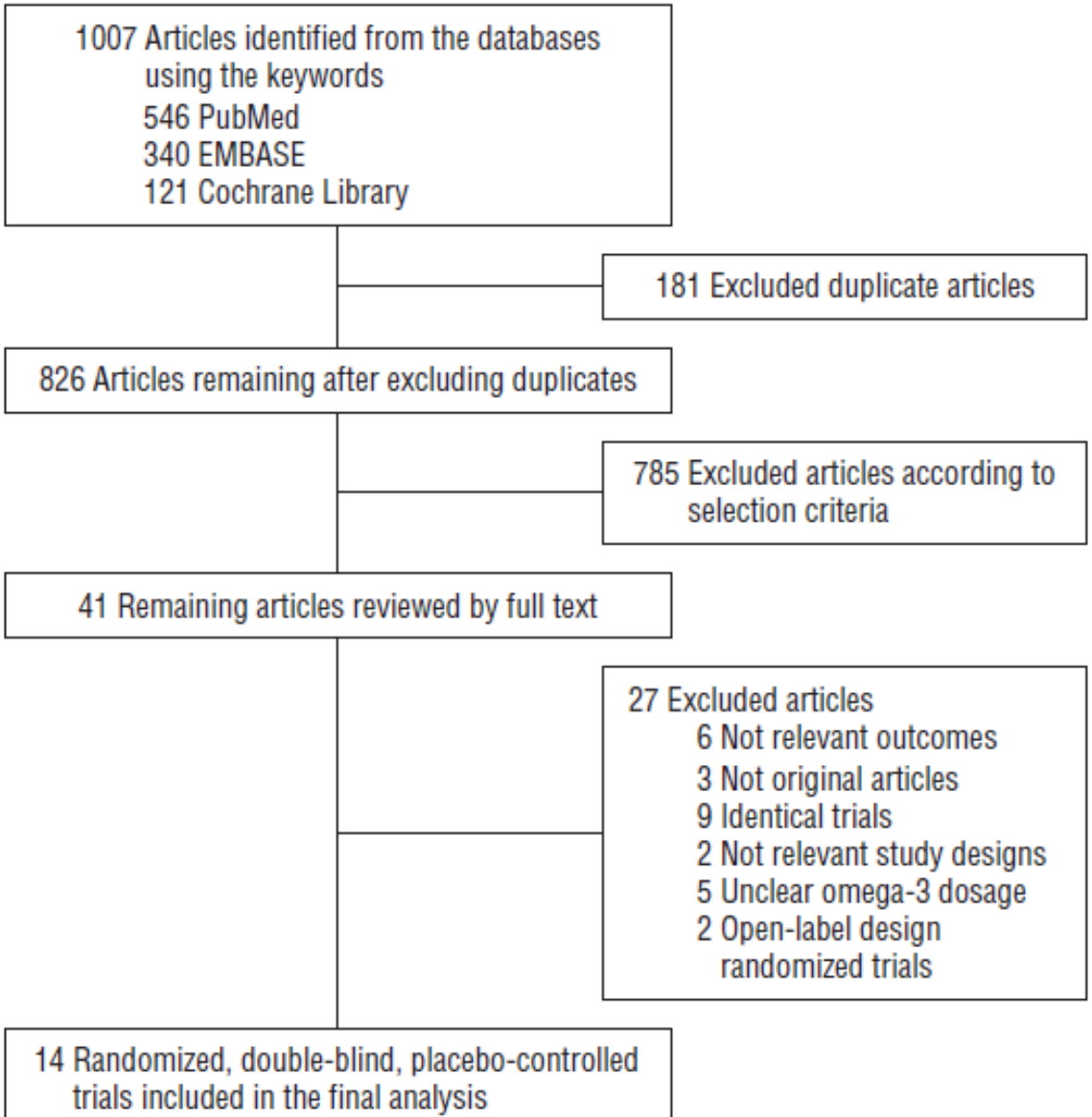
√ 1. Problem formulation

√ 2. Data collection

√ 3. Data evaluation

Now we need to cover Data analysis and Interpretation

Data analysis: Results of Search



Characteristics of included studies

- Across the 14 included trials, we have 20,000+ patients, about half in an intervention, and the other randomized to placebo control
- Average age 63.4, 78.5% were male
- Question: Is this set of studies relevant to your practice?

Among 14 randomized, double-blind, placebo-controlled trials, we identified 20 485 patients with a history of CVD, 10 226 randomized to an intervention group and 10 259 randomized to a placebo group. Among the trials in which patient age and sex were reported, the mean age of participants was 63.4 years (age range, 40-80 years), and 78.5% of participants were male. **Table 1**

Effect Size

- Risk Ratio:

(Events in the treatment group / treatment group n) ÷

(Events in the control group / control group n)

- Interpreted as "The ratio of risk in the treatment group relative to the risk in the control group"
- Sacks et al. study: 7/31 in treatment, 7/28 in control
- RR: (7/31) ÷ (7/28) = (7/31) x (28/7) = (28/31) = .9
- Risk of treatment group is .9 (close to 1) of risk relevant to control group = essentially the same risk

Meta-analysis

- We start by computing the effect size and its standard error within each study
- As in any statistical analysis, we will be interested in computing the overall mean effect across all studies, and the standard error of the overall mean
- We will also look at how much variation there is across studies in their estimate of the risk ratio – heterogeneity of estimates

Table 1 - Summary

Table 1. Characteristics of 14 Randomized, Double-blind, Placebo-Controlled Trials Included in the Meta-analysis

Source (Country Location)	Participants (Follow-up Period)	Intervention vs Control	Primary Outcome Measures in the Trial	Main Outcome Measures Used in the Present Meta-analysis	RR (95% CI)	No./Total No. (%)			
						Intervention Group		Placebo Group	
						Event Rate	Lost to Follow-up	Event Rate	Lost to Follow-up
Sacks et al,[20] 1995 (United States)	59 Patients with angiographically documented CHD (2.3 y)	Omega-3 FA (6 g/d), DHA (2.88 g/d), and EPA (1.92 g/d) (n = 31) vs placebo olive oil capsules	Change in minimal diameter of atherosclerotic coronary arteries	Cardiovascular events (nonfatal MI, PCI, UA, CHF, coronary death, stroke)	0.90 (0.36-2.25)	7/31 (22.6)	10/31 (32.3)	7/28 (25.0)	11/28 (39.3)

Risk ratio with 95% CI : Note that equal risk = 1 is covered by CI

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Overall mean effect size

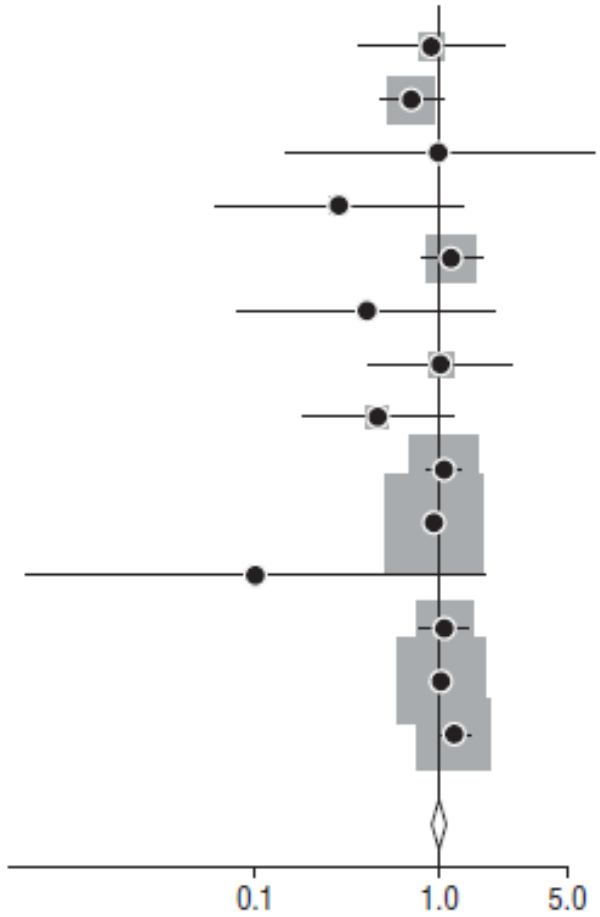
- To get the overall mean effect size across studies, we want to take into account the fact that studies have different sample sizes, and thus different levels of precision.
- For example, the Sacks study has 59 subjects while the Tavazzi study has almost 7000
- We weight studies by the variance of the effect size which is related to sample size, so that larger studies have larger weight

Graph of effect size: Forest plot

- Forest plots show:
  - The risk ratio for each study
  - The 95% confidence interval for each study
  - The "weight" for each study which is the inverse of the variance of the risk ratio (proportional to the sample size)
  - If the confidence interval of the study includes a ratio of 1.0, then the treatment and control groups have an equal chance of a cardiac event

Forest Plot

Source	RR (95% CI)	Weight, %
Sacks et al,[20] 1995	0.90 (0.36-2.25)	1.18
Singh et al,[21] 1997	0.71 (0.48-1.05)	5.48
Leng et al,[22] 1998	1.00 (0.15-6.87)	0.27
von Schacky et al,[23] 1999	0.28 (0.06-1.33)	0.42
Nilsen et al,[24] 2001	1.17 (0.80-1.71)	5.82
Raitt et al,[25] 2005	0.40 (0.08-2.01)	0.39
Leaf et al,[26] 2005	1.01 (0.41-2.49)	1.21
Brouwer et al,[27] 2006	0.46 (0.18-1.20)	1.09
Svensson et al,[28] 2006	1.05 (0.84-1.32)	12.58
Tavazzi et al,[29] 2008	0.93 (0.85-1.02)	27.62
Garbagnati et al,[30] 2009	0.10 (0.01-1.79)	0.12
Galan et al,[31] 2010	1.06 (0.78-1.44)	8.48
Kromhout et al,[32] 2010	1.02 (0.88-1.17)	21.07
Rauch et al,[33] 2010	1.20 (0.98-1.48)	14.27
Overall (I^2=27.1%, P=.16)	0.99 (0.89-1.09)	100.00



Largest weight = Largest study

Source	RR (95% CI)	Weight, %
Sacks et al,[20] 1995	0.90 (0.36-2.25)	1.18
Singh et al,[21] 1997	0.71 (0.48-1.05)	5.48
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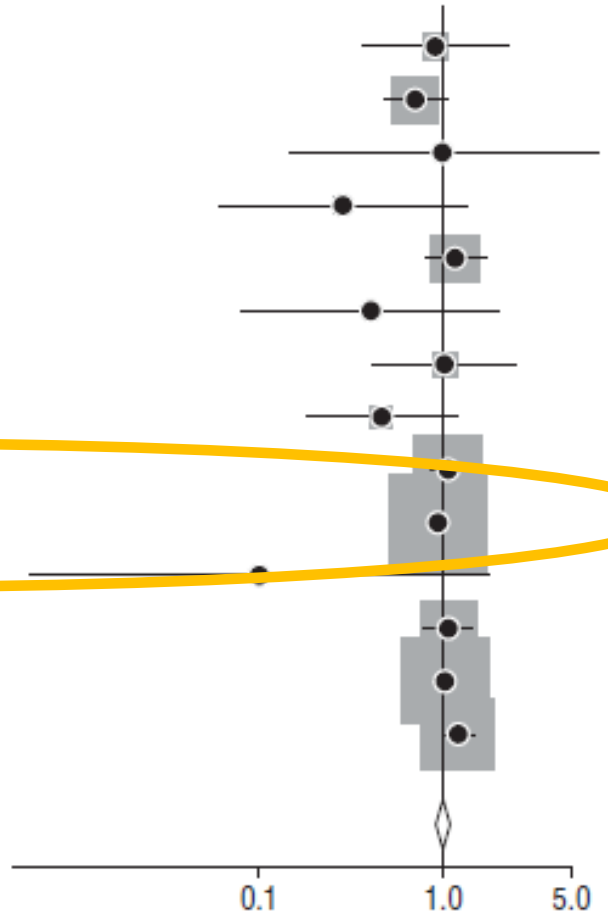

Overall weighted mean = no effect

Source	RR (95% CI)	Weight, %
Sacks et al,[20] 1995	0.90 (0.36-2.25)	1.18
Singh et al,[21] 1997	0.71 (0.48-1.05)	5.48
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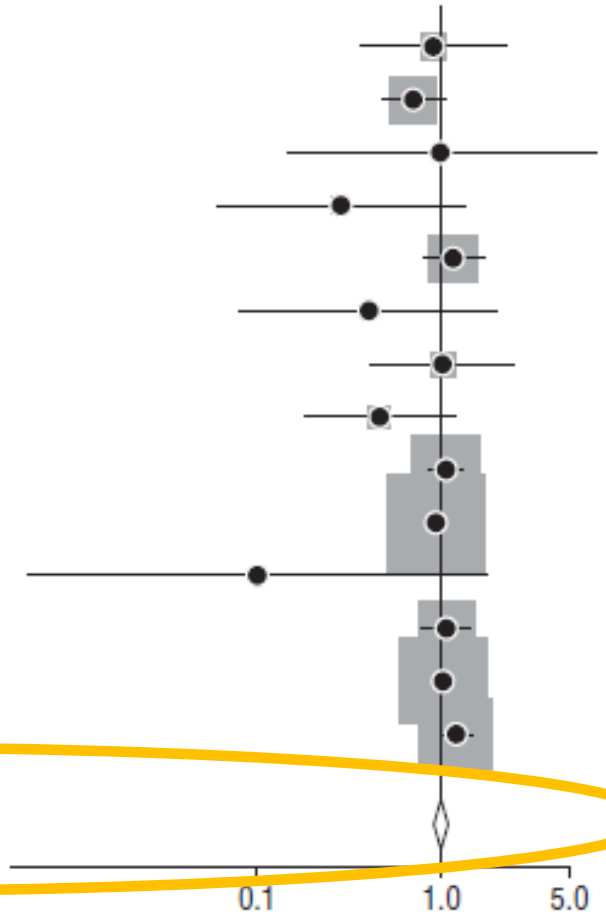

How much variation across studies?

- Examine heterogeneity
- One measure is I^2
- Interpretation of I^2 from Cochrane Collaboration:
  - 0% to 40%: might not be important;
  - 30% to 60%: may represent moderate heterogeneity;
  - 50% to 90%: may represent substantial heterogeneity;
  - 75% to 100%: considerable heterogeneity.
- In this case, low heterogeneity (27.1%)

Sub-group analyses

- We sometimes want to know if variation across studies is related to study differences such as patient characteristics, type of placebo, geographic location
- Table 3 looks at whether the efficacy of omega-3 supplements differs for type of outcome
- Table 4 looks at whether the risk ratios differ by characteristics of the study

Table 3

Table 3. Efficacy of Omega-3 Fatty Acid Supplements Against the Risk of Overall Cardiovascular Events

Variable	No. of Trials	RR (95% CI)	I^2 Value, %
Cardiovascular events			
Overall	14 Trials[20-33]	0.99 (0.89-1.09)	27.1
Excluding Tavazzi et al,[29] 2008	13 Trials[20-28,30-33]	1.09 (0.89-1.14)	21.8
All-cause mortality	13 Trials[20,22-33]	0.96 (0.90-1.02)	0.0
Sudden cardiac death	5 Trials[21,25,26,29,33]	0.93 (0.66-1.30)	23.7
Cardiovascular death			
Overall	11 Trials[20-27,29,30,32]	0.91 (0.84-0.99)	0.0
Excluding Singh et al,[21] 1997	10 Trials[20,22-27,29,30,32]	0.92 (0.35-1.01)	0.0
Myocardial infarction	11 Trials[20-25,27-29,31,32]	0.81 (0.65-1.01)	24.9
Fatal	5 Trials[20,23,29,31,32]	0.87 (0.67-1.13)	0.0
Nonfatal	7 Trials[20-24,29,31]	0.86 (0.65-1.14)	24.3
Angina and unstable angina	7 Trials[20-22,24,25,27,28]	0.77 (0.50-1.18)	45.2

- All of the RR CIs cover 1.0 (equal risk)
- Angina has moderate heterogeneity across studies

Table 4

Table 4. Subgroup Analyses of the Efficacy of Omega-3 Fatty Acid Supplements Against the Risk of Overall Cardiovascular Events

Variable	No. of Trials	RR (95% CI)	I^2 Value, %
Duration of treatment, y			
Short, <2	7 Trials[21,22,24,26,27,30,34]	0.95 (0.70-1.26)	46.0
Long, ≥2	7 Trials[20,23,25,28,29,31,32]	0.96 (0.90-1.03)	0.0
Dosage of EPA or DHA, g/d			
Low, <1.7	7 Trials[25,27,29-33]	1.00 (0.87-1.14)	48.2
High, ≥1.7	7 Trials[20-24,26,28]	0.97 (0.81-1.16)	5.9
Methodological quality of the trial, No. of points on the scale by Jadad et al[38]			
5	7 Trials[23,25-29,31]	0.95 (0.83-1.08)	16.8
≤4	7 Trials[20-22,24,30,32,33]	1.03 (0.87-1.21)	29.7
Use of fish oil supplementation only as treatment	11 Trials[20-29,33]	0.97 (0.85-1.12)	31.9
Country location			
United States	3 Trials[20,25,26]	0.85 (0.47-1.54)	0.0
Asia	1 Trial[21]	0.71 (0.48-1.05)	. . .
Western Europe	8 Trials[22,23,27,29-33]	0.99 (0.87-1.14)	45.6
Northern Europe	2 Trials[24,28]	1.08 (0.89-1.32)	0.0
Geographic area			
Inland	3 Trials[21,23,33]	0.83 (0.48-1.45)	75.5
Coastal	9 Trials[20,22,24-26,28-30,32]	0.97 (0.90-1.04)	0.0

- All CI's include RR = 1.0
- 3 Inland studies have large heterogeneity

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Overall conclusions

- In this set of studies, average risk ratio is not different from zero, and is homogeneous
- Significant variation (large heterogeneity) across some studies (e.g., for angina as an outcome, or for studies that use non-oil placebos) but average risk ratio still not different from 1

What do we conclude?

- Are the methods transparent, i.e., do we have a rationale for the decisions made about the conduct of the systematic review, and do we agree with those decisions?
- Can we generalize the studies in this review to the population we care about? For example, are we comfortable generalizing these results to our female patients?

My contact information

- If you have any questions after the webinar, please contact me at

tpigott@luc.edu

Thank you!

Questions & Answers

Please type your questions
using the “chat box” at the bottom right side of your screen.

Questions

- Remember these questions are about the methodology
- Or about interpretation of the methodological approach

Questions

- What software do you recommend to perform meta-analyses?
- Tell us more about publication bias: Begg Funnel plot and Egger test… What is diagnostic here?
- How do we know whether they scored correctly using the Jadad scale?
  - "Use of identical placebo": olive, sunflower, mixed, AlOH, unspecified----yet all get a "1"!!!

Questions (ctd)

- Is there an minimum number of studies one should include? What parameters can tell us we have a reasonable number (Sample size)?
- How typical ("kosher"?) is it for researchers to add in 2 RCTs (such as they did with the open label trials, GISSI & JELIS)?

A Few Reminders

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Q & A

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Thank you!

- A reminder: a short survey will be sent to all registrants to get your feedback about this program.