University of East Anglia

World Health Organization

Cochrane

Review of evidence and outcomes:

Systematic review of RCTs on the cardiovascular effects of n-3 PUFA in adults

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WHO NUGAG systematic review, December 2017

Aim – broadly for NUGAG

Assess effects of:

- **omega 3 fats**
- omega 6 fats and
- total PUFA

On:

- **All-cause mortality**
- **Cardiovascular diseases (CVD deaths, CVD events, CHD deaths, CHD events, stroke, arrhythmia, lipids)**
- **Adiposity**
- Type 2 diabetes
- Depression
- Cognitive function
- Breast Cancer
- Inflammatory Bowel Disease

Aim – for you

To assess the effect of increasing omega 3 PUFA on all-cause mortality, CVD mortality, CVD events, CHD mortality, CHD events, stroke, arrhythmia, serum lipids and adiposity

Inclusion criteria

- Participants: aged 18+, at any risk for CVD (exclude pregnant and acutely ill)
- Intervention: increased EPA, DHA and/or ALA (dietary or supplemental)
- Compared to: usual or lower intake
- Outcomes: all-cause mortality, CVD mortality, CVD events, CHD mortality, CHD events, stroke, arrhythmia, lipids, adiposity
- Methodology: RCT of ≥12 months duration

Interventions allowed

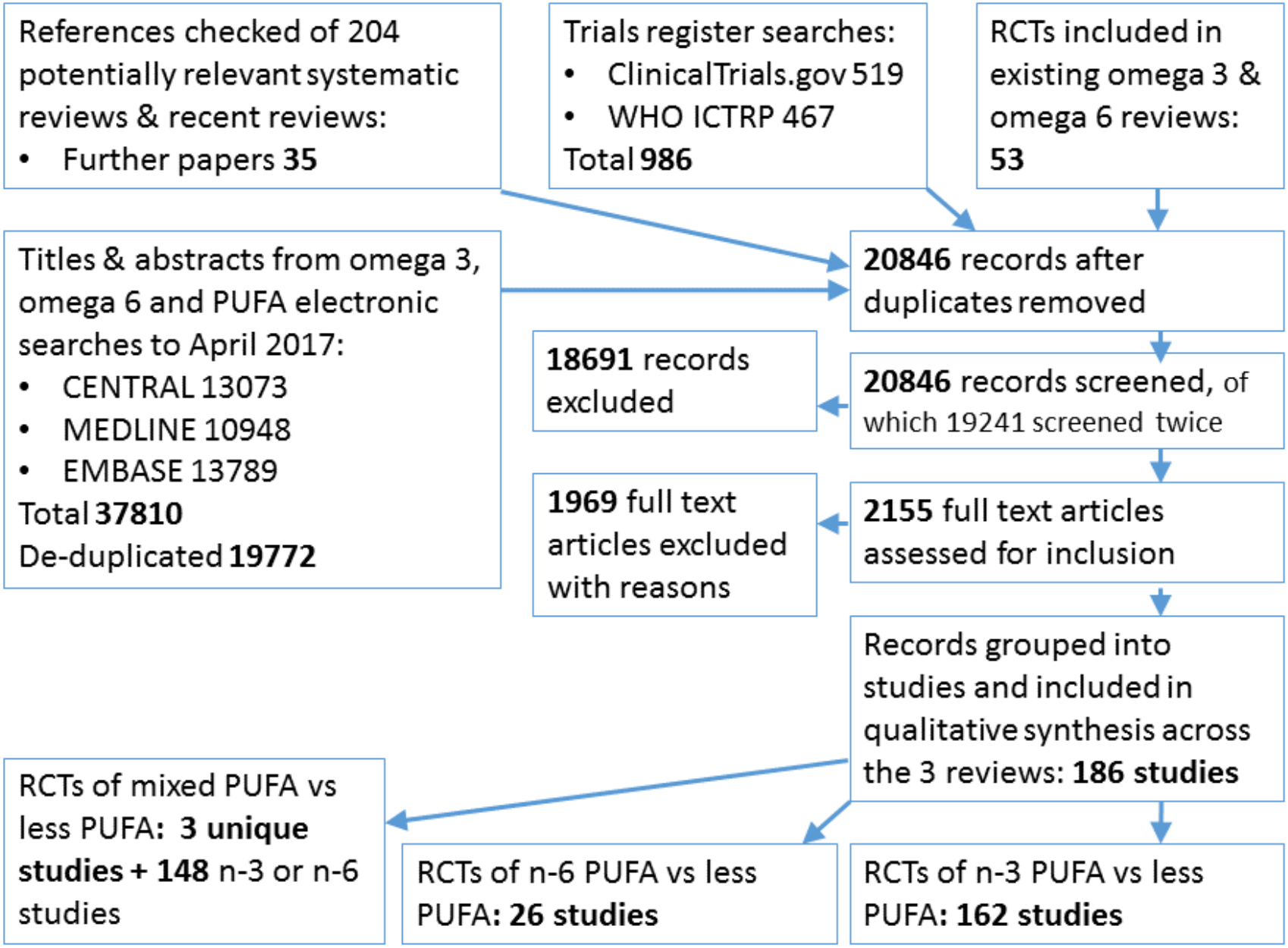
- Dietary supplementation, a provided diet or advice on diet.
- Supplementation may have been in oil or capsule form or as food stuffs provided, to be consumed by mouth (excluding enteral and parenteral feeds and enemas).
- Omega 3 source could be:
  - oily fish (inc mackerel, dogfish, salmon, herring, trout, etc);
  - fish oils (made from the above or a mix of fish, or cod liver oil);
  - Refined EPA, DHA or ALA, or concentrated fish or algal oils
  - linseed (flax), canola (rapeseed), perilla, purslane, mustard seed, candlenut, stillingia or walnut as a food, oil, made into a spreading fat or supplementing another food
  - For ALA sources the product consumed had to have an omega 3 fat content of at least 10% of the total fat content.
- Multifactorial dietary, lifestyle or pill interventions excl.

Outcome definitions

All refer to number of participants experiencing at least 1 event (NOT number of events)

- **all-cause mortality** - wrote to authors to request, where not available CVD mortality used
- **CVD mortality** – death from any cardiovascular cause
- **CVD events** – all available CVD events,
- **CHD mortality** – first of: coronary death, IHD death, fatal MI, cardiac death (latter includes causes of death in addition to CHD, such as cardiomyopathies, congenital & valvular heart diseases, hence SA)
- **CHD events** - first of: CHD or coronary events, total MI, acute coronary syndrome or angina (stable and unstable).
- **Stroke** – included fatal & non-fatal, ischaemic & haemorrhagic
- **Arrhythmia** – included new & recurrent, AF, VF & VT

Search strategy



Search strategy

RCTs of n3 PUFA vs less n3 in the wider database: **162 RCTs**

→ 6 to <12 month duration: **61 RCTs**

RCTs of at least 12 months duration: **101 RCTs**

→ Concern over data veracity: **3 RCTs**
No relevant outcomes available: **19 RCTs**

RCTs reporting at least one of our primary or secondary outcomes:
79 RCTs of which:

- All-cause mortality: 39 RCTs
- CVD mortality: 25 RCTs
- CVD events: 38 RCTs
- CHD deaths: 21 RCTs
- CHD events: 28 RCTs
- Stroke: 28 RCTs
- Arrhythmias: 28 RCTs
- Serum lipids: 33 RCTs
- Adiposity: 25 RCTs

Methods

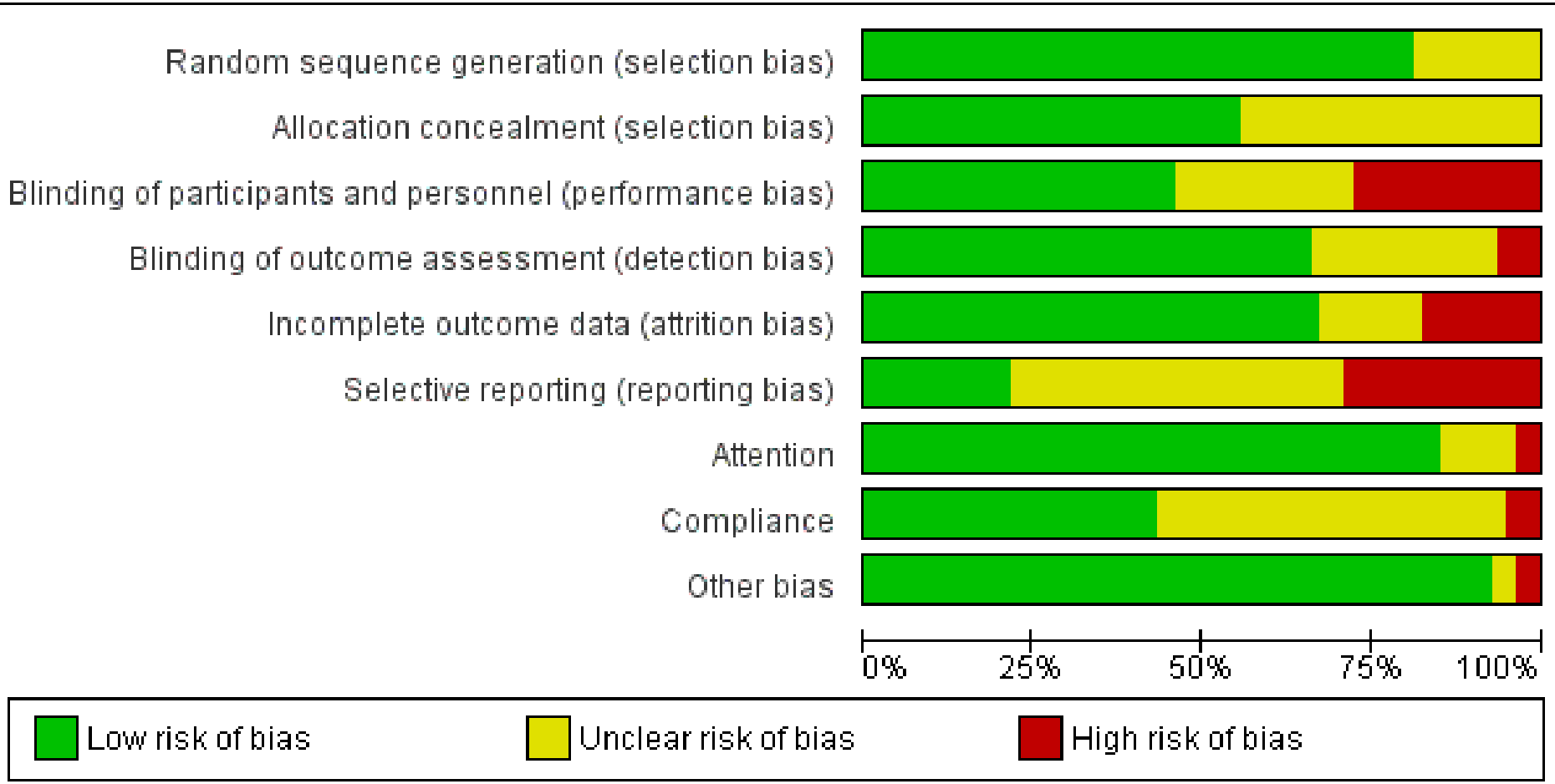
- Duplicated assessment of all titles and abstracts & trials registry entries
- Duplicated assessment of inclusion of all full texts
- Duplicated data extraction
- Duplicated risk of bias assessment
- Wrote to all contact authors who randomised at least 100 participants to clarify data & methods and chase additional outcomes/data

Risk of bias

Low summary risk of bias: Low risk of bias from randomisation, allocation concealment, blinding of participants & staff, blinding of outcome assessors

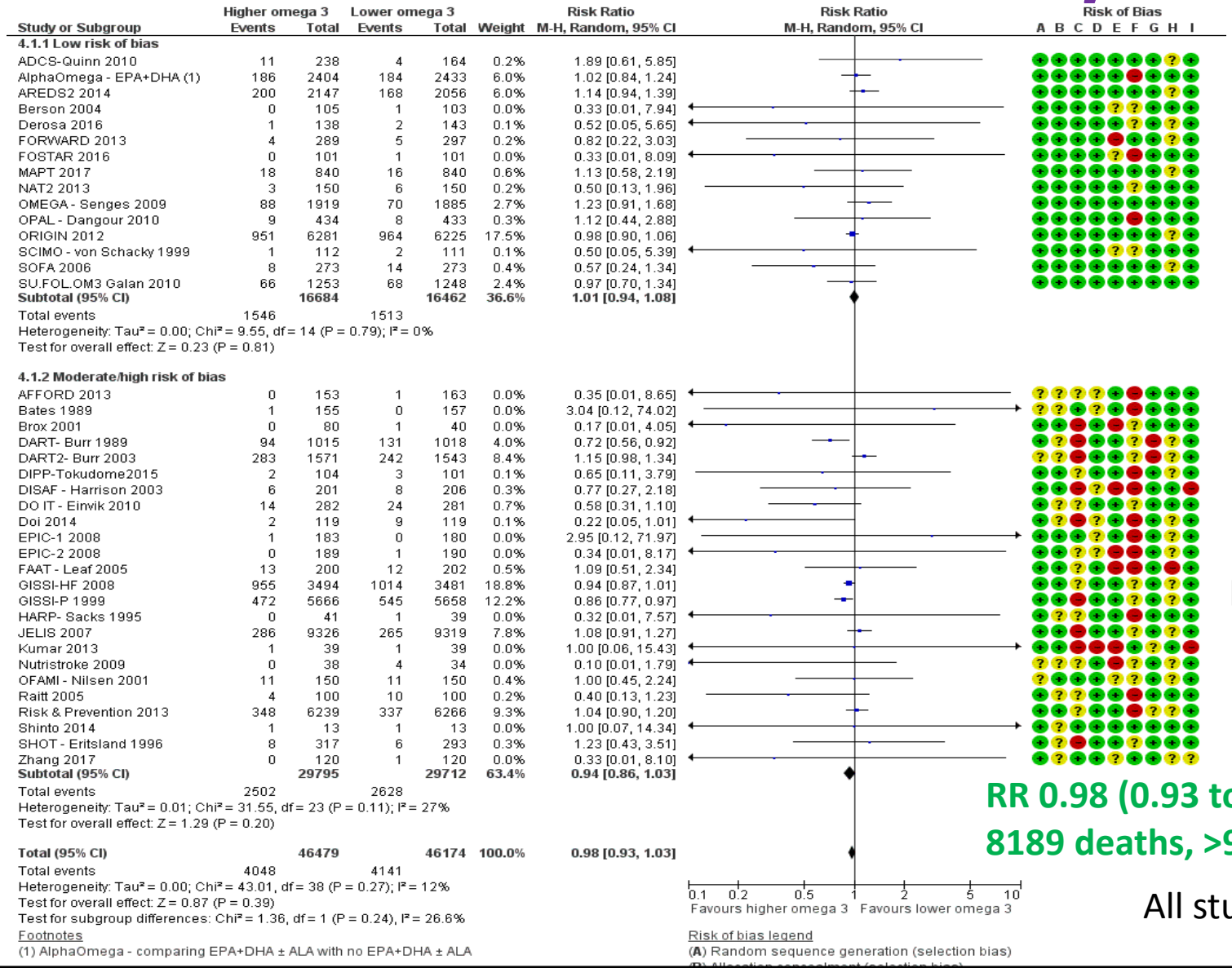
Note slight update from report

79 RCTs of which 25 at low summary risk of bias



Effect of increased LC omega 3 on all-cause mortality

Fig 3.3



Low risk of bias

Moderate to high risk of bias

RR 0.98 (0.93 to 1.03), I^2 12%, 8189 deaths, >92000 participants

All studies combined

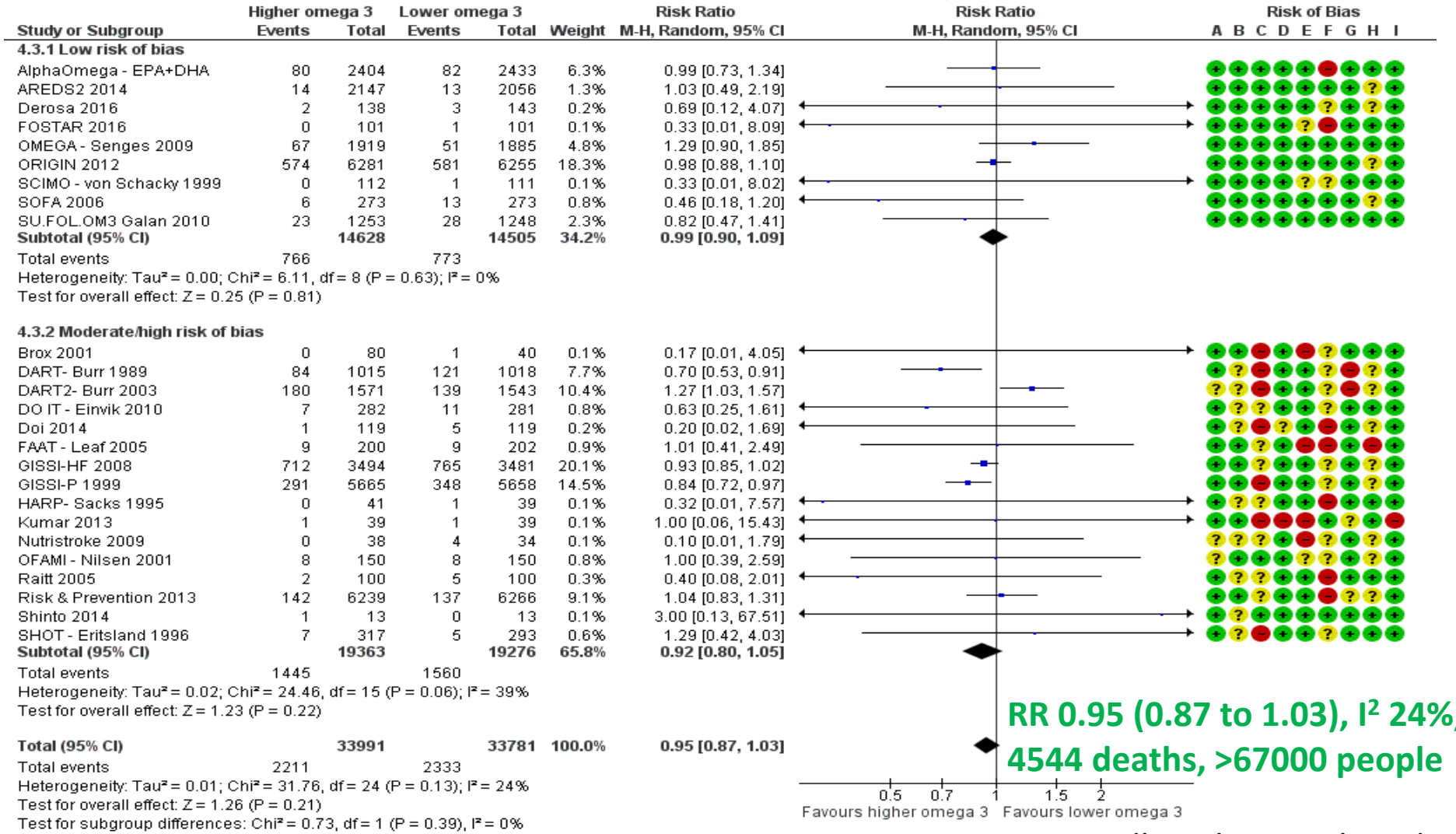
Effect of increased LC omega 3 on all-cause mortality

Figs 3.1 – 3.9

- 39 trials, >92,000 participants, 8189 events, 12 to 72 months (larger trials are longer)
- RR 0.98 (95% CI 0.93 to 1.03), I^2 12%
- RR 1.01 (95% CI 0.94 to 1.08), I^2 0% in low RoB trials
- RR 0.97 (95% CI 0.93 to 1.01), I^2 12% fixed effects
- Funnel plot: if add back missing trials RR would rise
- Subgrouping: no important effects (duration 2 to <4 yr)
- Meta-regression: not run
- GRADE: LCn3 intake makes little or no difference to all-cause mortality (high quality/ certainty evidence)

Effect of increased LC omega 3 on CVD mortality

Fig 4.3



RR 0.95 (0.87 to 1.03), I^2 24%, 4544 deaths, >67000 people

All studies combined

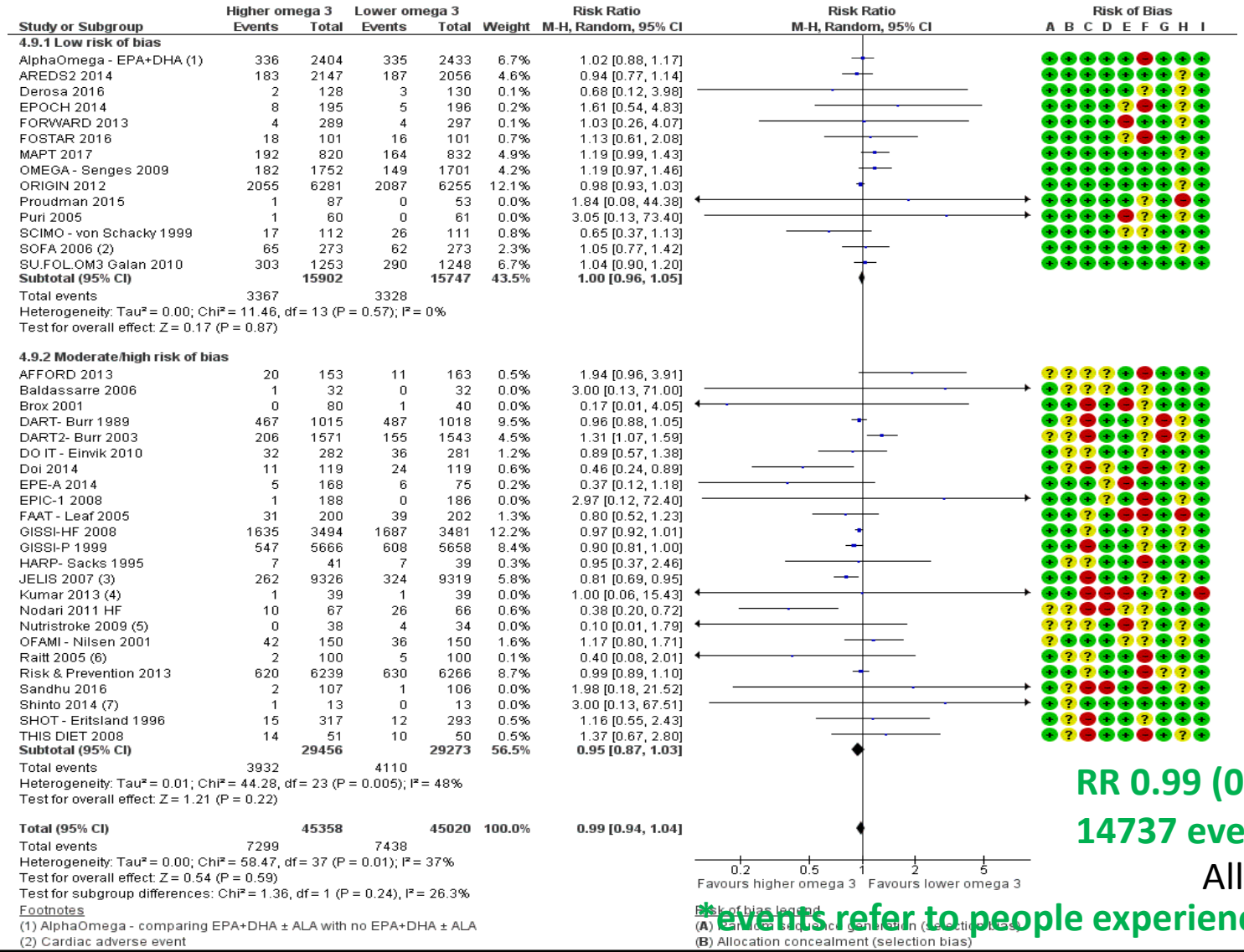
Effect of increased LC omega 3 on CVD mortality

Figs 4.1 – 4.7

- 25 trials, >67000 participants, 4544 CV deaths over 12 months+
- RR 0.95 (95% CI 0.87 to 1.03), I^2 24%
- RR 0.99 (95% CI 0.90 to 1.09), I^2 0% in low RoB trials
- RR 0.94 (95% CI 0.89 to 1.00), I^2 24% fixed effects
- Funnel plot: if add back missing trials RR closer to 1.0
- Subgrouping: no important effects (supplements, medium-long duration, lowest dose group)
- Meta-regression: no LCn3 dose or duration effect
- GRADE: LCn3 intake probably makes little or no difference to CVD deaths (moderate quality/ certainty evidence)

Effect of increased LC omega 3 on CVD events

Fig 4.10



Study or Subgroup	Higher omega 3 Events	Higher omega 3 Total	Lower omega 3 Events	Lower omega 3 Total	Weight	Risk Ratio M-H, Random, 95% CI
4.9.1 Low risk of bias						
AlphaOmega - EPA+DHA (1)	336	2404	335	2433	6.7%	1.02 [0.88, 1.17]
AREDS2 2014	183	2147	187	2056	4.6%	0.94 [0.77, 1.14]
Derosa 2016	2	128	3	130	0.1%	0.68 [0.12, 3.98]
EPOCH 2014	8	195	5	196	0.2%	1.61 [0.54, 4.83]
FORWARD 2013	4	289	4	297	0.1%	1.03 [0.26, 4.07]
FOSTAR 2016	18	101	16	101	0.7%	1.13 [0.61, 2.08]
MAPT 2017	192	820	164	832	4.9%	1.19 [0.99, 1.43]
OMEGA - Senges 2009	182	1752	149	1701	4.2%	1.19 [0.97, 1.46]
ORIGIN 2012	2055	6281	2087	6255	12.1%	0.98 [0.93, 1.03]
Proudman 2015	1	87	0	53	0.0%	1.84 [0.08, 44.38]
Puri 2005	1	60	0	61	0.0%	3.05 [0.13, 73.40]
SCIMO - von Schacky 1999	17	112	26	111	0.8%	0.65 [0.37, 1.13]
SOFA 2006 (2)	65	273	62	273	2.3%	1.05 [0.77, 1.42]
SU.FOL.OM3 Galan 2010	303	1253	290	1248	6.7%	1.04 [0.90, 1.20]
Subtotal (95% CI)		**15902**		**15747**	**43.5%**	**1.00 [0.96, 1.05]**
Total events	3367		3328			
Heterogeneity: Tau² = 0.00; Chi² = 11.46, df = 13 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.87)						
4.9.2 Moderate/high risk of bias						
AFFORD 2013	20	153	11	163	0.5%	1.94 [0.96, 3.91]
Baldassarre 2006	1	32	0	32	0.0%	3.00 [0.13, 71.00]
Brox 2001	0	80	1	40	0.0%	0.17 [0.01, 4.05]
DART- Burr 1989	467	1015	487	1018	9.5%	0.96 [0.88, 1.05]
DART2- Burr 2003	206	1571	155	1543	4.5%	1.31 [1.07, 1.59]
DO IT - Einvik 2010	32	282	36	281	1.2%	0.89 [0.57, 1.38]
Doi 2014	11	119	24	119	0.6%	0.46 [0.24, 0.89]
EPE-A 2014	5	168	6	75	0.2%	0.37 [0.12, 1.18]
EPIC-1 2008	1	188	0	186	0.0%	2.97 [0.12, 72.40]
FAAT - Leaf 2005	31	200	39	202	1.3%	0.80 [0.52, 1.23]
GISSI-HF 2008	1635	3494	1687	3481	12.2%	0.97 [0.92, 1.01]
GISSI-P 1999	547	5666	608	5658	8.4%	0.90 [0.81, 1.00]
HARP- Sacks 1995	7	41	7	39	0.3%	0.95 [0.37, 2.46]
JELIS 2007 (3)	262	9326	324	9319	5.8%	0.81 [0.69, 0.95]
Kumar 2013 (4)	1	39	1	39	0.0%	1.00 [0.06, 15.43]
Nodari 2011 HF	10	67	26	66	0.6%	0.38 [0.20, 0.72]
Nutristroke 2009 (5)	0	38	4	34	0.0%	0.10 [0.01, 1.79]
OFAMI - Nilsen 2001	42	150	36	150	1.6%	1.17 [0.80, 1.71]
Raitt 2005 (6)	2	100	5	100	0.1%	0.40 [0.08, 2.01]
Risk & Prevention 2013	620	6239	630	6266	8.7%	0.99 [0.89, 1.10]
Sandhu 2016	2	107	1	106	0.0%	1.98 [0.18, 21.52]
Shinto 2014 (7)	1	13	0	13	0.0%	3.00 [0.13, 67.51]
SHOT - Eritsland 1996	15	317	12	293	0.5%	1.16 [0.55, 2.43]
THIS DIET 2008	14	51	10	50	0.5%	1.37 [0.67, 2.80]
Subtotal (95% CI)		**29456**		**29273**	**56.5%**	**0.95 [0.87, 1.03]**
Total events	3932		4110			
Heterogeneity: Tau² = 0.01; Chi² = 44.28, df = 23 (P = 0.005); I² = 48%						
Test for overall effect: Z = 1.21 (P = 0.22)						
Total (95% CI)		**45358**		**45020**	**100.0%**	**0.99 [0.94, 1.04]**
Total events	7299		7438			
Heterogeneity: Tau² = 0.00; Chi² = 58.47, df = 37 (P = 0.01); I² = 37%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Chi² = 1.36, df = 1 (P = 0.24), I² = 26.3%						

Risk Ratio M-H, Random, 95% CI

0.2 0.5 1 2 5

Favours higher omega 3 Favours lower omega 3

Risk of bias

A B C D E F G H I

Footnotes

(1) AlphaOmega - comparing EPA+DHA ± ALA with no EPA+DHA ± ALA

(2) Cardiac adverse event

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

Low risk of bias

Moderate to high risk of bias

RR 0.99 (0.94 to 1.04), I^2 37%, 14737 events*, >90000 people

All studies combined

***events refer to people experiencing ≥1 CVD events**

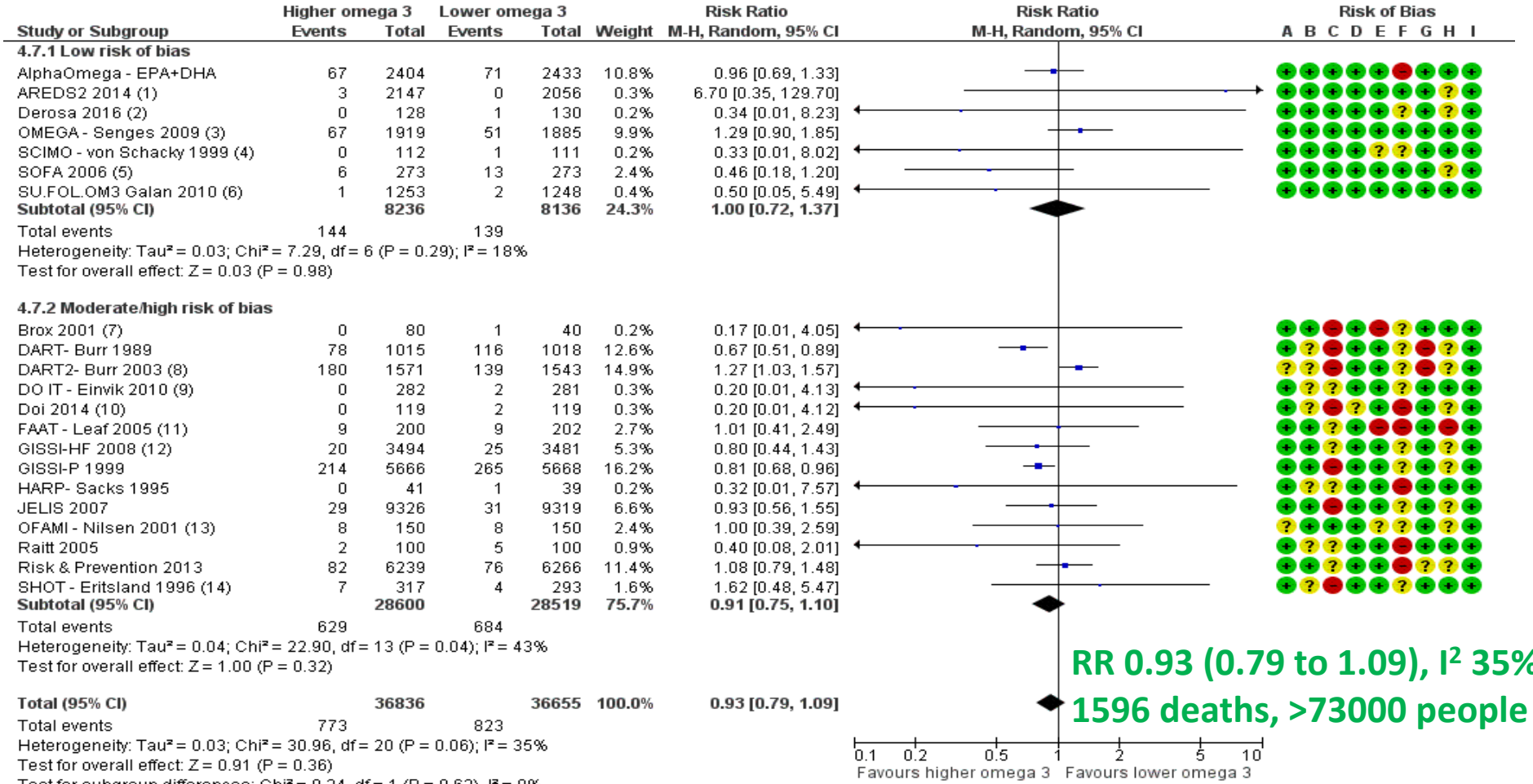
Effect of increased LC omega 3 on CVD events

Figs 4.8 – 4.13

- 38 trials, >90,000 participants, 14737 people experiencing CV events over 12 months+
- RR 0.99 (95% CI 0.94 to 1.04), I^2 37%
- RR 1.00 (95% CI 0.96 to 1.05), I^2 0% in low RoB trials
- RR 0.98 (95% CI 0.95 to 1.00), I^2 37% fixed effects
- Funnel plot: if add back missing trials RR rises
- Subgrouping: no important effects
- Meta-regression: no LCn3 dose or duration effects
- GRADE: LCn3 intake makes little or no difference to risk of CVD events (high quality/ certainty evidence)

Effect of increased LC omega 3 on CHD mortality

Fig 4.17



Study or Subgroup	Higher omega 3 Events	Higher omega 3 Total	Lower omega 3 Events	Lower omega 3 Total	Weight	Risk Ratio M-H, Random, 95% CI
4.7.1 Low risk of bias						
AlphaOmega - EPA+DHA	67	2404	71	2433	10.8%	0.96 [0.69, 1.33]
AREDS2 2014 (1)	3	2147	0	2056	0.3%	6.70 [0.35, 129.70]
Derosa 2016 (2)	0	128	1	130	0.2%	0.34 [0.01, 8.23]
OMEGA - Senges 2009 (3)	67	1919	51	1885	9.9%	1.29 [0.90, 1.85]
SCIMO - von Schacky 1999 (4)	0	112	1	111	0.2%	0.33 [0.01, 8.02]
SOFA 2006 (5)	6	273	13	273	2.4%	0.46 [0.18, 1.20]
SU.FOL.OM3 Galan 2010 (6)	1	1253	2	1248	0.4%	0.50 [0.05, 5.49]
Subtotal (95% CI)		**8236**		**8136**	**24.3%**	**1.00 [0.72, 1.37]**
Total events	144		139			
Heterogeneity: Tau² = 0.03; Chi² = 7.29, df = 6 (P = 0.29); I² = 18%						
Test for overall effect: Z = 0.03 (P = 0.98)						
4.7.2 Moderate/high risk of bias						
Brox 2001 (7)	0	80	1	40	0.2%	0.17 [0.01, 4.05]
DART- Burr 1989	78	1015	116	1018	12.6%	0.67 [0.51, 0.89]
DART2- Burr 2003 (8)	180	1571	139	1543	14.9%	1.27 [1.03, 1.57]
DO IT - Einvik 2010 (9)	0	282	2	281	0.3%	0.20 [0.01, 4.13]
Doi 2014 (10)	0	119	2	119	0.3%	0.20 [0.01, 4.12]
FAAT - Leaf 2005 (11)	9	200	9	202	2.7%	1.01 [0.41, 2.49]
GISSI-HF 2008 (12)	20	3494	25	3481	5.3%	0.80 [0.44, 1.43]
GISSI-P 1999	214	5666	265	5668	16.2%	0.81 [0.68, 0.96]
HARP- Sacks 1995	0	41	1	39	0.2%	0.32 [0.01, 7.57]
JELIS 2007	29	9326	31	9319	6.6%	0.93 [0.56, 1.55]
OFAMI - Nilsen 2001 (13)	8	150	8	150	2.4%	1.00 [0.39, 2.59]
Raitt 2005	2	100	5	100	0.9%	0.40 [0.08, 2.01]
Risk & Prevention 2013	82	6239	76	6266	11.4%	1.08 [0.79, 1.48]
SHOT - Eritsland 1996 (14)	7	317	4	293	1.6%	1.62 [0.48, 5.47]
Subtotal (95% CI)		**28600**		**28519**	**75.7%**	**0.91 [0.75, 1.10]**
Total events	629		684			
Heterogeneity: Tau² = 0.04; Chi² = 22.90, df = 13 (P = 0.04); I² = 43%						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)		**36836**		**36655**	**100.0%**	**0.93 [0.79, 1.09]**
Total events	773		823			
Heterogeneity: Tau² = 0.03; Chi² = 30.96, df = 20 (P = 0.06); I² = 35%						
Test for overall effect: Z = 0.91 (P = 0.36)						
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.62), I² = 0%						

Risk Ratio M-H, Random, 95% CI

Risk of Bias A B C D E F G H I

0.1 0.2 0.5 1 2 5 10

Favours higher omega 3 Favours lower omega 3

RR 0.93 (0.79 to 1.09), I^2 35%

1596 deaths, >73000 people

Footnotes

(1) Fatal MI

(2) Fatal MI

(3) Cardiac death

Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

Effect of increased LCn3 on CHD mortality

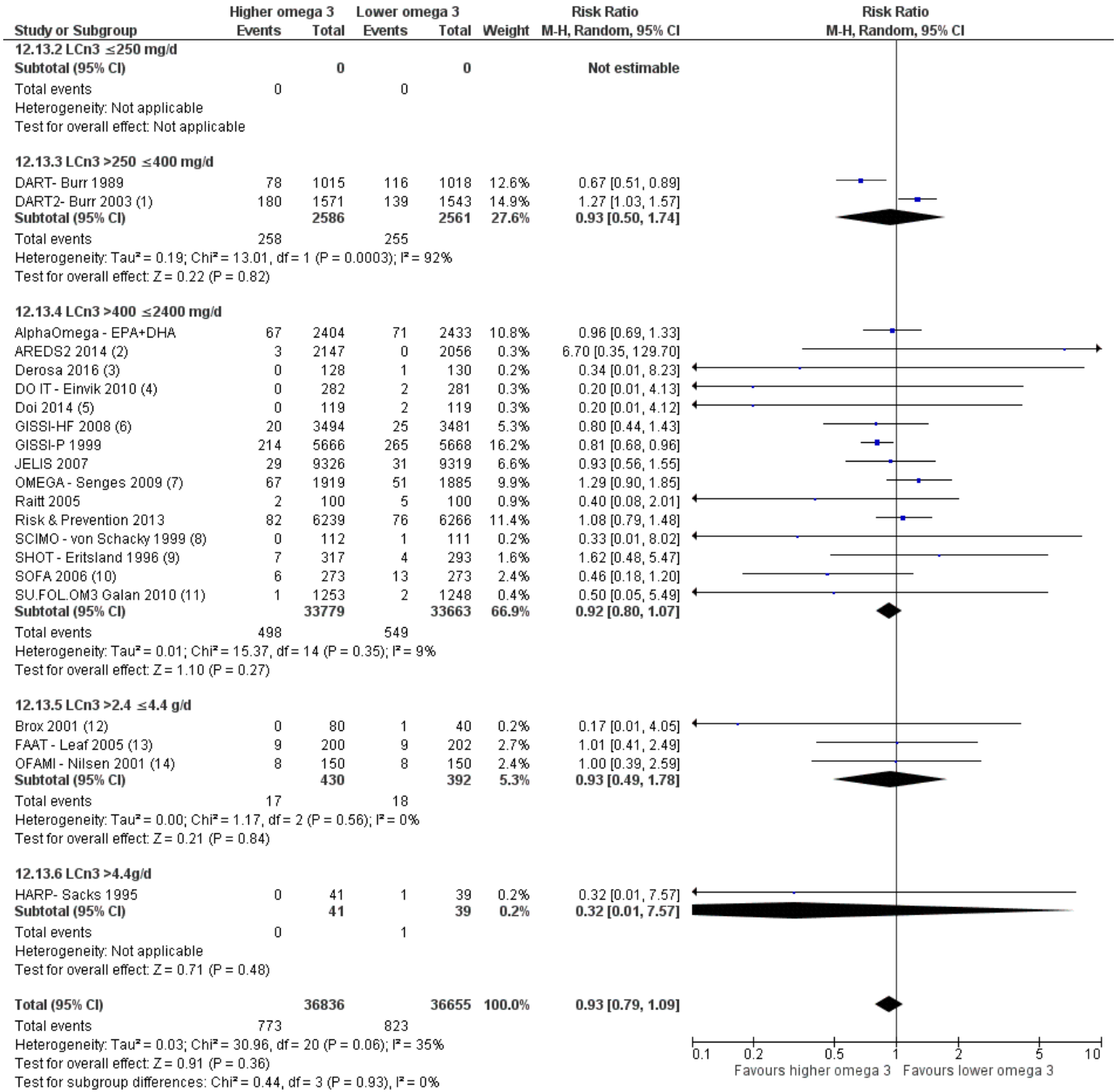


Fig not shown

No suggestion of a LCn3 dose response relationship in subgrouping (shown) or meta-regression

Effect of increased LC omega 3 on CHD mortality

Fig 4.19

- CHD - atherosclerosis in the coronary arteries, leading to myocardial infarction or angina (ischaemia)
- To make best use of our data we pre-specified what outcomes we counted and which order: coronary death, IHD death, fatal MI, cardiac death
- SCD is arrhythmic not ischaemic (included in CVD deaths, not CHD deaths) so not included
- You can't sum coronary death, IHD death & fatal MI etc within a single study as they overlap
- Sensitivity analysis run omitting cardiac death as potentially includes causes of death additional to CHD, such as cardiomyopathies, congenital and valvular heart diseases (numbers are likely to be small).

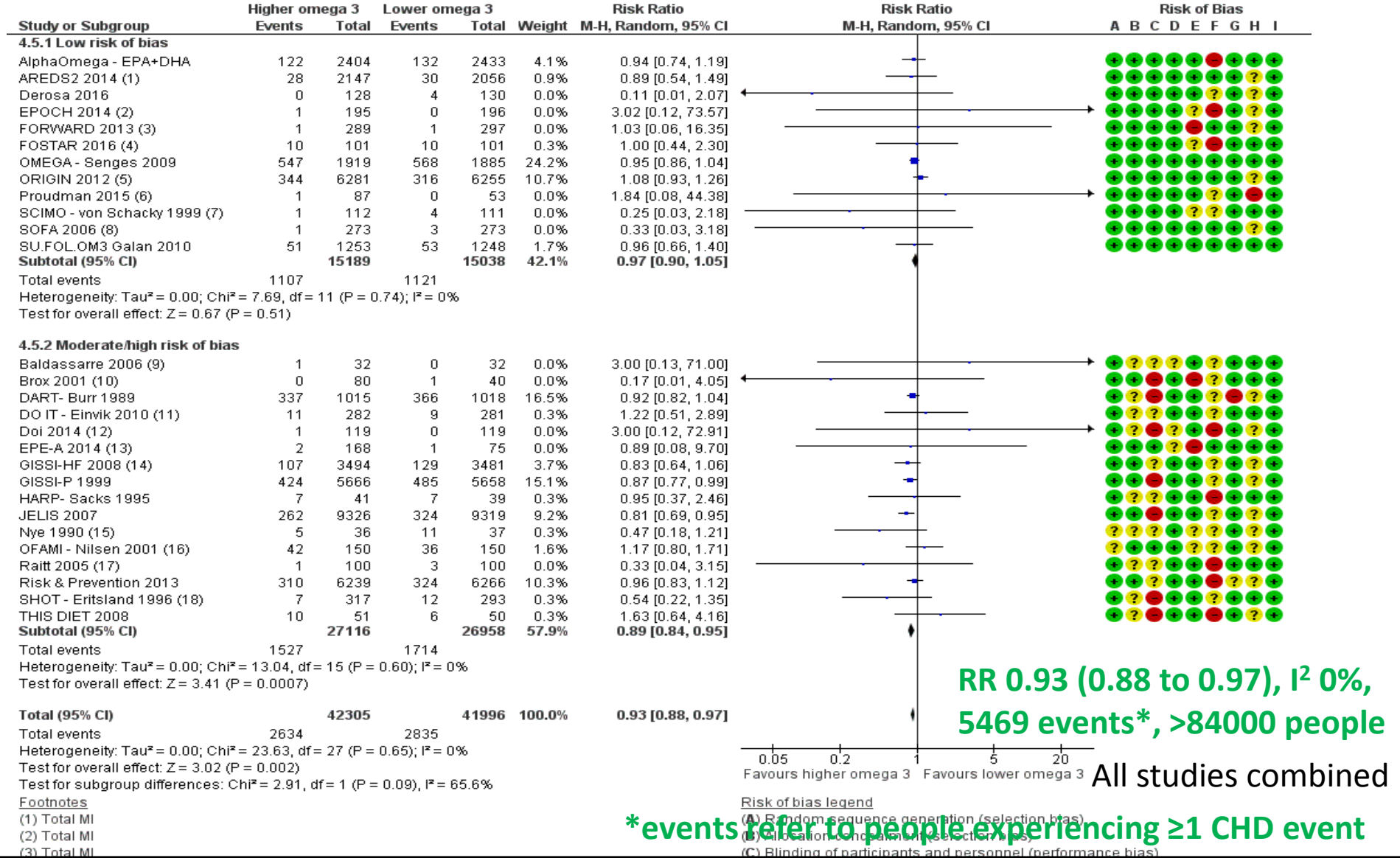
Effect of increased LC omega 3 on CHD mortality

Figs 4.14 – 4.20

- 21 trials, >73,000 participants, 1596 CHD deaths
- RR 0.93 (95% CI 0.79 to 1.09), I^2 35%
- RR 0.83 (95% CI 0.74 to 0.94), I^2 0%, omitting cardiac death
- RR 1.00 (95% CI 0.72 to 1.37), I^2 18% in low RoB trials
- RR 0.95 (95% CI 0.69 to 1.30), I^2 0%, omitting cardiac death in low RoB trials
- RR 0.94 (95% CI 0.85 to 1.03), I^2 35% fixed effects
- Funnel plot: if add back missing trials RR would rise
- Subgrouping: no important effects (duration)
- Meta-regression: no LCn3 dose (p=0.94) or duration (p=0.41) effects
- GRADE: LCn3 intake probably makes little or no difference to CHD deaths (moderate quality/ certainty evidence)

Effect of increased LC omega 3 on CHD events

Fig 4.23



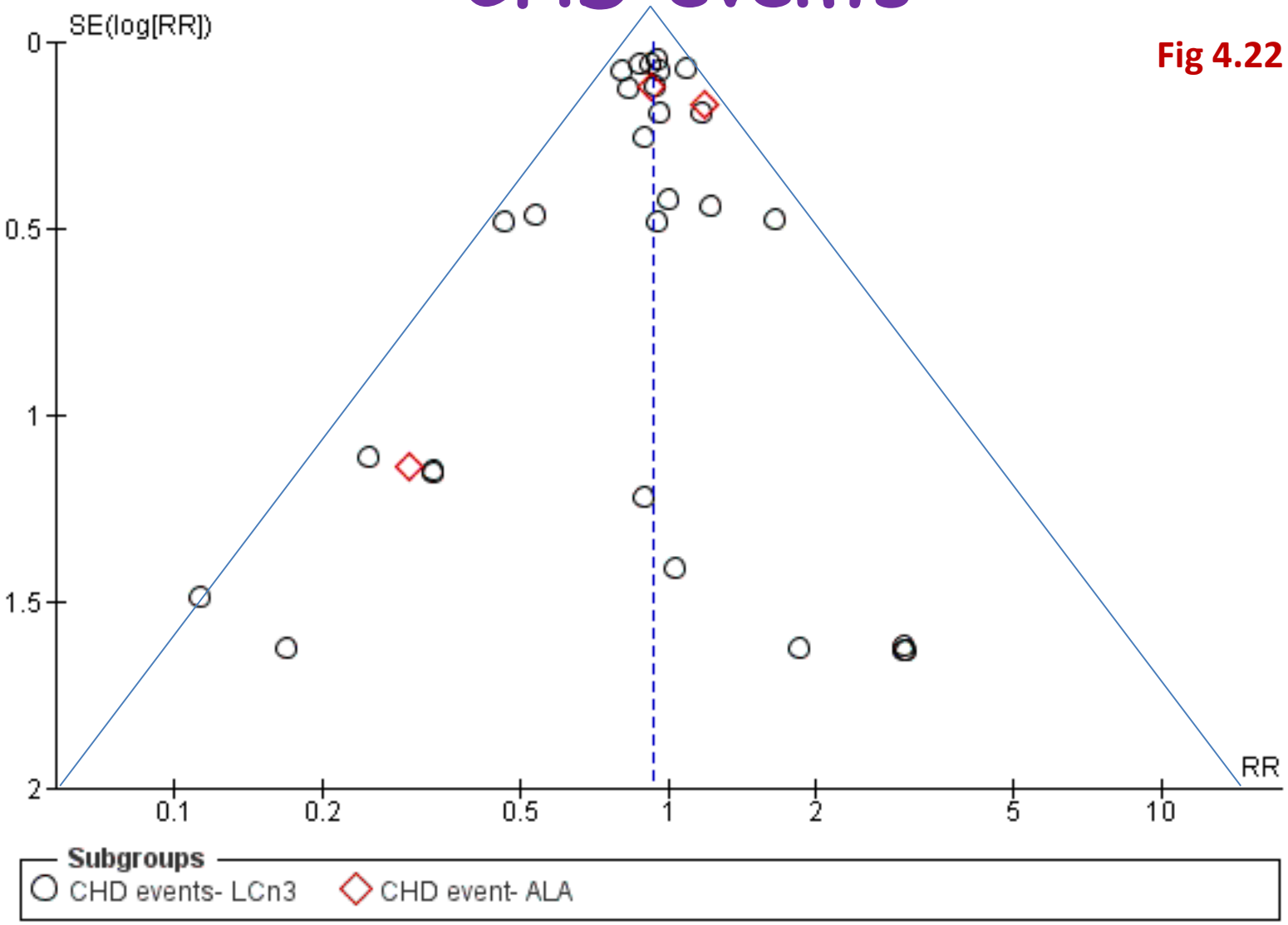
RR 0.93 (0.88 to 0.97), I^2 0%, 5469 events*, >84000 people

All studies combined

*events refer to people experiencing ≥1 CHD event

Effect of increased LC omega 3 on CHD events

Fig 4.22



*events refer to people experiencing ≥1 CHD event

Effect of increased LC omega 3 on CHD events

Figs 4.21 – 4.27

- 28 trials, >84,000 participants, 5469 people experiencing CHD events over 12 months+
- RR 0.93 (95% CI 0.88 to 0.97), I^2 0%
- RR 0.97 (95% CI 0.90 to 1.05), I^2 0% in low RoB trials
- RR 0.92 (95% CI 0.88 to 0.97), I^2 0% fixed effects
- Funnel plot: if add back missing trials RR rises
- Subgrouping: no important effects (1 signif subgroup each)
- Meta-regression: no LCn3 dose or duration effects
- GRADE: LCn3 intake probably makes little or no difference to CHD events (moderate quality/ certainty evidence).

Why is risk of bias (RoB) important?

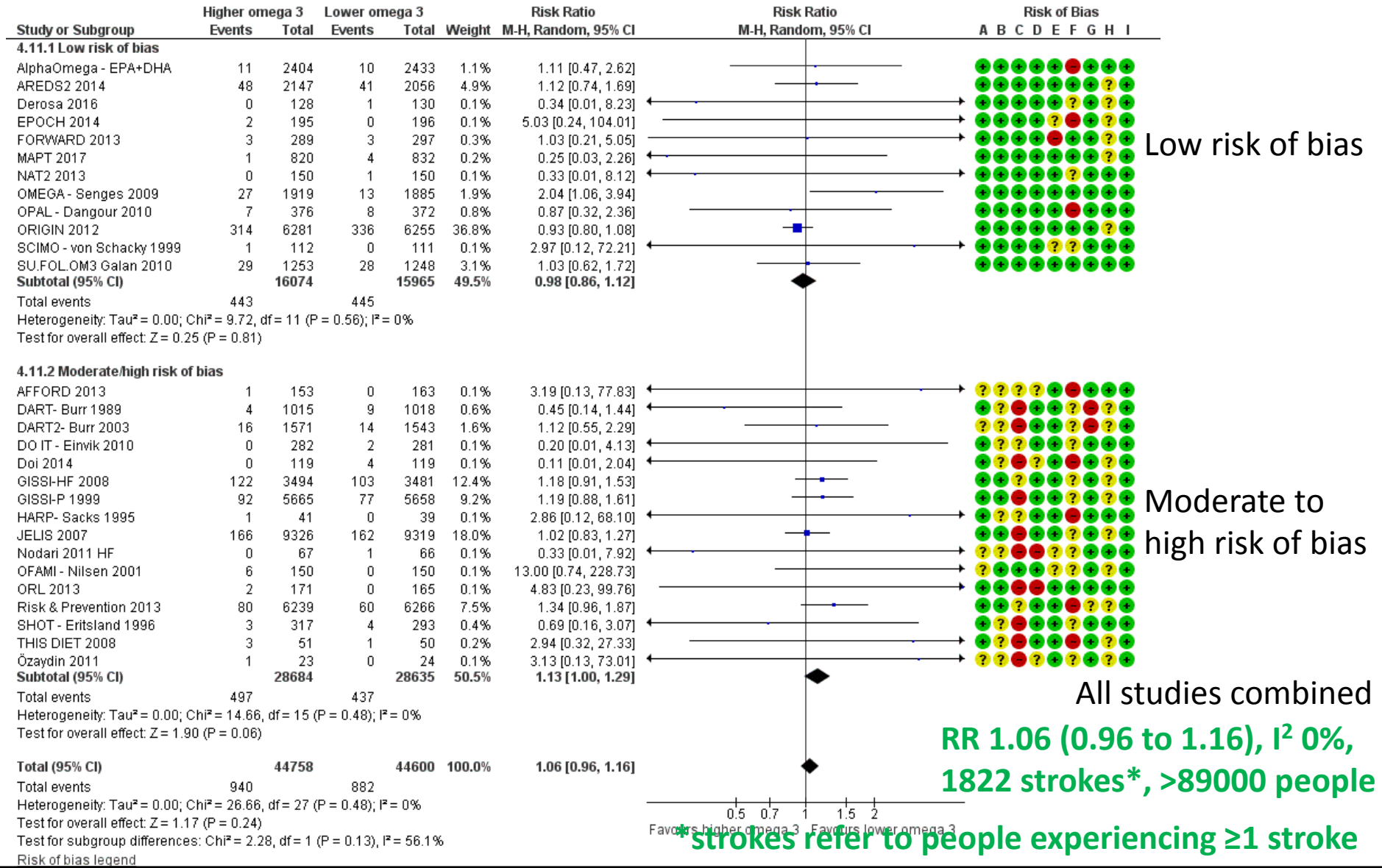
- Consistently see that studies at lower risk of bias show outcomes closer to null (RR 1.0)

Fig 4.23

- For example, for CHD events
- Overall effect RR 0.93 (95% CI 0.88 to 0.97, I^2 0%)
- Low RoB RR 0.97 (95% CI 0.90 to 1.05, I^2 0%)
- Moderate to high RoB RR 0.89 (0.84 to 0.95, I^2 0%)
- Suggested difference between subgroups (p=0.09)
- Studies in moderate to high RoB group include GISSI-P and JELIS, which carry 24% of the weight of the whole meta-analysis but were not placebo controlled, could not be masked (blinded) so open to clear bias

Effect of increased LC omega 3 on stroke

Fig 4.30



Low risk of bias

Moderate to high risk of bias

All studies combined

RR 1.06 (0.96 to 1.16), I^2 0%, 1822 strokes*, >89000 people

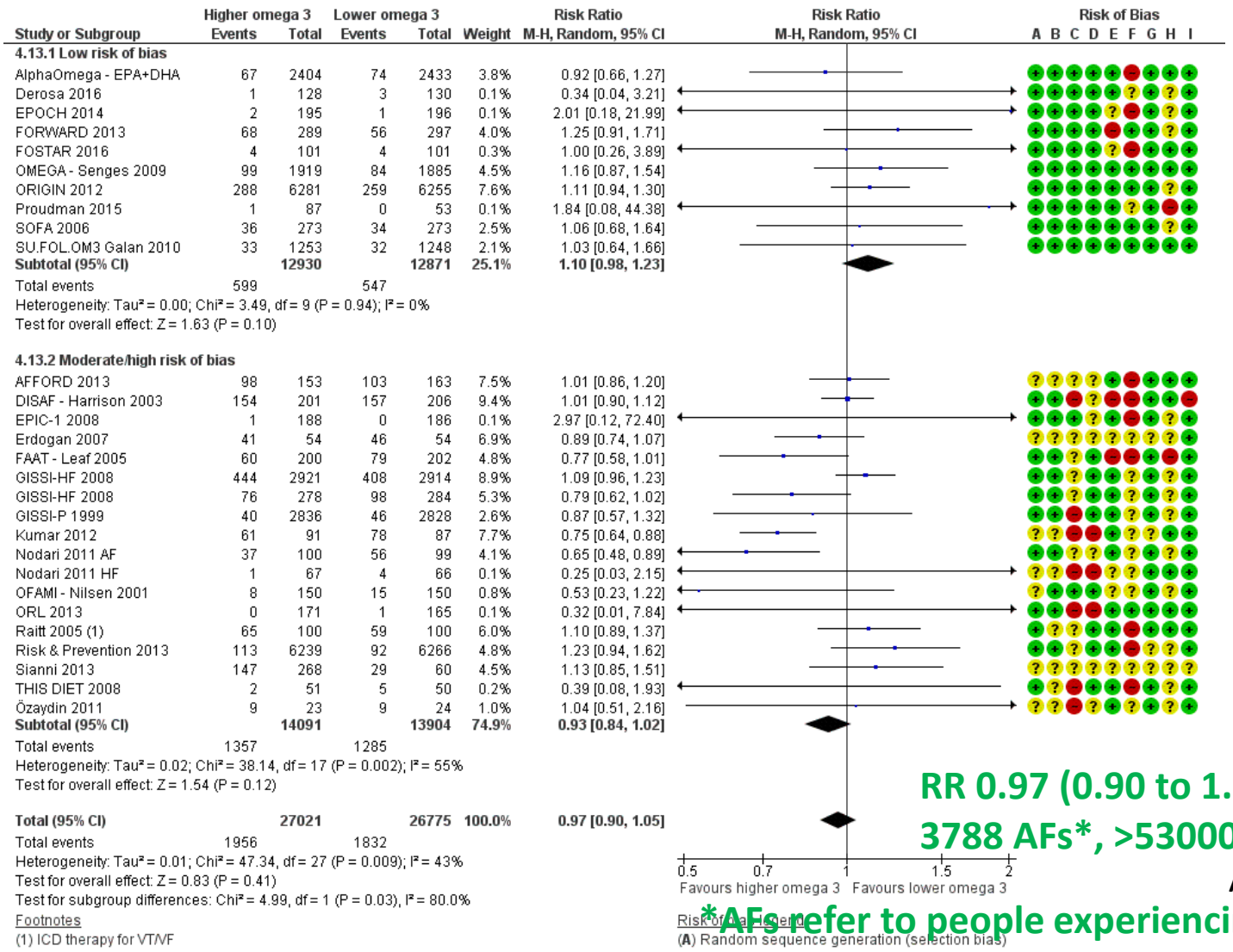
*strokes refer to people experiencing ≥1 stroke

Effect of increased LC omega 3 on stroke

Figs 4.28 – 4.35

- 28 trials, >89,000 participants, 1822 people experiencing ≥1 stroke over 12 months+
- RR 1.06 (95% CI 0.96 to 1.16), I^2 0%
- RR 0.99 (95% CI 0.86 to 1.12), I^2 0% in low RoB trials
- RR 1.06 (95% CI 0.97 to 1.16), I^2 0% fixed effects
- Funnel plot: if add back missing trials RR closer to 1.0
- Subgrouping: no important effects (low statin use, 2° prevention)
- No statistically significant effects for haemorrhagic or ischaemic stroke (separately)
- Meta-regression: no LCn3 dose effect, shorter trials increased stroke more (p=0.012), more strokes with LCn3 in 2° prevention
- GRADE: LCn3 intake probably makes little or no difference to risk of stroke (moderate quality/ certainty evidence)

Effect of increased LC omega 3 on atrial fibrillation (or VF or VT)



Study or Subgroup	Higher omega 3 Events	Higher omega 3 Total	Lower omega 3 Events	Lower omega 3 Total	Weight	Risk Ratio M-H, Random, 95% CI
4.13.1 Low risk of bias						
AlphaOmega - EPA+DHA	67	2404	74	2433	3.8%	0.92 [0.66, 1.27]
Derosa 2016	1	128	3	130	0.1%	0.34 [0.04, 3.21]
EPOCH 2014	2	195	1	196	0.1%	2.01 [0.18, 21.99]
FORWARD 2013	68	289	56	297	4.0%	1.25 [0.91, 1.71]
FOSTAR 2016	4	101	4	101	0.3%	1.00 [0.26, 3.89]
OMEGA - Senges 2009	99	1919	84	1885	4.5%	1.16 [0.87, 1.54]
ORIGIN 2012	288	6281	259	6255	7.6%	1.11 [0.94, 1.30]
Proudman 2015	1	87	0	53	0.1%	1.84 [0.08, 44.38]
SOFA 2006	36	273	34	273	2.5%	1.06 [0.68, 1.64]
SU.FOL.OM3 Galan 2010	33	1253	32	1248	2.1%	1.03 [0.64, 1.66]
Subtotal (95% CI)		**12930**		**12871**	**25.1%**	**1.10 [0.98, 1.23]**
Total events	599		547			
Heterogeneity: Tau² = 0.00; Chi² = 3.49, df = 9 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
4.13.2 Moderate/high risk of bias						
AFFORD 2013	98	153	103	163	7.5%	1.01 [0.86, 1.20]
DISAF - Harrison 2003	154	201	157	206	9.4%	1.01 [0.90, 1.12]
EPIC-1 2008	1	188	0	186	0.1%	2.97 [0.12, 72.40]
Erdogan 2007	41	54	46	54	6.9%	0.89 [0.74, 1.07]
FAAT - Leaf 2005	60	200	79	202	4.8%	0.77 [0.58, 1.01]
GISSI-HF 2008	444	2921	408	2914	8.9%	1.09 [0.96, 1.23]
GISSI-HF 2008	76	278	98	284	5.3%	0.79 [0.62, 1.02]
GISSI-P 1999	40	2836	46	2828	2.6%	0.87 [0.57, 1.32]
Kumar 2012	61	91	78	87	7.7%	0.75 [0.64, 0.88]
Nodari 2011 AF	37	100	56	99	4.1%	0.65 [0.48, 0.89]
Nodari 2011 HF	1	67	4	66	0.1%	0.25 [0.03, 2.15]
OFAMI - Nilsen 2001	8	150	15	150	0.8%	0.53 [0.23, 1.22]
ORL 2013	0	171	1	165	0.1%	0.32 [0.01, 7.84]
Raitt 2005 (1)	65	100	59	100	6.0%	1.10 [0.89, 1.37]
Risk & Prevention 2013	113	6239	92	6266	4.8%	1.23 [0.94, 1.62]
Sianni 2013	147	268	29	60	4.5%	1.13 [0.85, 1.51]
THIS DIET 2008	2	51	5	50	0.2%	0.39 [0.08, 1.93]
Özaydin 2011	9	23	9	24	1.0%	1.04 [0.51, 2.16]
Subtotal (95% CI)		**14091**		**13904**	**74.9%**	**0.93 [0.84, 1.02]**
Total events	1357		1285			
Heterogeneity: Tau² = 0.02; Chi² = 38.14, df = 17 (P = 0.002); I² = 55%						
Test for overall effect: Z = 1.54 (P = 0.12)						
Total (95% CI)		**27021**		**26775**	**100.0%**	**0.97 [0.90, 1.05]**
Total events	1956		1832			
Heterogeneity: Tau² = 0.01; Chi² = 47.34, df = 27 (P = 0.009); I² = 43%						
Test for overall effect: Z = 0.83 (P = 0.41)						
Test for subgroup differences: Chi² = 4.99, df = 1 (P = 0.03), I² = 80.0%						

Risk Ratio M-H, Random, 95% CI

0.5 0.7 1 1.5 2

Favours higher omega 3 Favours lower omega 3

Risk of Bias: Higher

(A) Random sequence generation (selection bias)

Footnotes

(1) ICD therapy for VT/VF

Figs 6.1 – 6.7 Shown for new & recurrent

Low risk of bias

Moderate to high risk of bias

RR 0.97 (0.90 to 1.05), I^2 43%, 3788 AFs*, >53000 people

All studies combined

***AFs refer to people experiencing ≥1 AF or VF or VT**

Effect of increased LC omega 3 on new or recurrent arrhythmia (AF, VF or VT)

- 28 trials, >53,000 participants, 3788 people experiencing new or recurrent arrhythmia ~12 mo+
- RR 0.97 (95% CI 0.90 to 1.05), I^2 43%
- RR 1.10 (95% CI 0.98 to 1.23), I^2 0% in low RoB trials
- RR 1.01 (95% CI 0.96 to 1.07), I^2 43% fixed effects
- Funnel plot: not interpretable
- Subgrouping: no important effects (2.4- 4.4g/d)
- Meta-regression: no LCn3 dose or duration effects
- GRADE: LCn3 intake probably makes little or no difference to risk of arrhythmia (moderate quality/ certainty evidence)

Summary of LCn3 evidence

- Searched hard to find data for all primary outcomes from all possible trials
  - ✓ Extensive search
  - ✓ Wrote to authors to request data on further outcomes
- Specific about how we have grouped outcomes
- Consistently see that studies at lower risk of bias show outcomes closer to null (RR 1.0)
- Consistently see publication bias - adding missing data would move outcomes towards null (RR 1.0)
- Meta-regression and subgrouping do not show dose or duration effects
- **Summary – no effect of LCn3 fats on key outcomes**

Effect of increased LCn3 on individual CVD events (2° outcomes)

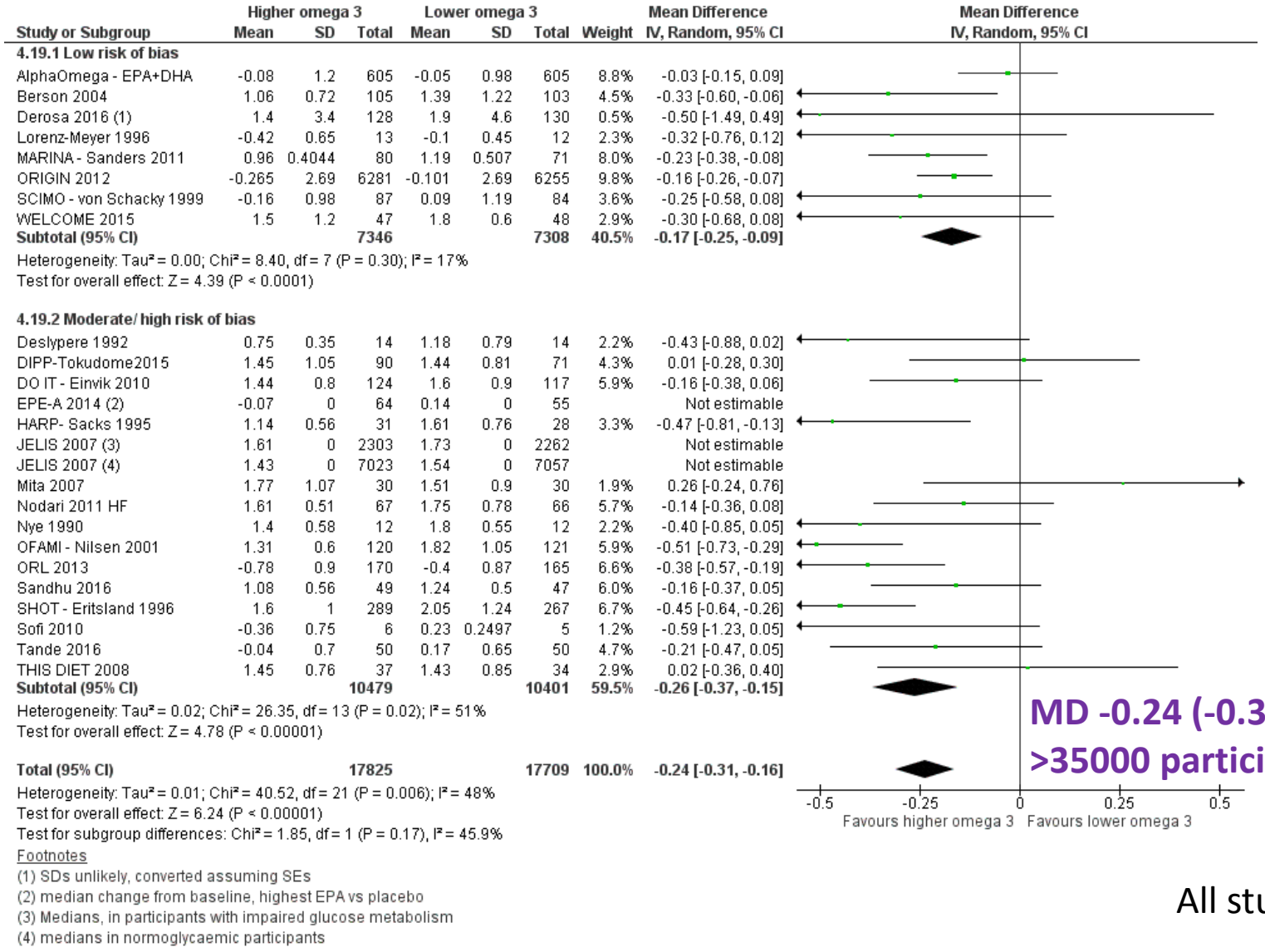
- Total MI RR 0.95 (95% CI 0.88 to 1.03), I^2 0%
- Fatal MI RR 0.87 (95% CI 0.67 to 1.13), I^2 21%
- Non-fatal MI RR 0.97 (95% CI 0.86 to 1.08), I^2 0%
- Sudden cardiac death RR 0.97 (0.80 to 1.18), I^2 38%
- Angina RR 0.99 (95% CI 0.91 to 1.06), I^2 0%
- Heart failure RR 0.93 (95% CI 0.85 to 1.03), I^2 31%
- Revascularisation RR 0.98 (0.94 to 1.03), I^2 0%
- PV events RR 0.93 (95% CI 0.74 to 1.18), I^2 0%
- Acute coronary synd. RR 1.19 (0.71 to 2.00), I^2 0%

Effect of increased LCn3 on risk factors (2°outcomes)

- Weight, kg MD -0.01 (95% CI -0.84 to 0.82), I^2 49%
- BMI, kg/m^2 MD 0.04 (95% CI -0.16 to 0.24), I^2 40%
- Waist circumf, cm MD 0.66 (-0.09 to 1.42), I^2 0%
- Total chol, mmol/L MD -0.01 (-0.05 to 0.04), I^2 19%
- Serum TG, mmol/L MD -0.24 (-0.32 to -0.17), I^2 49%
- HDL, mmol/L MD 0.02 (95% CI 0.00 to 0.04), I^2 48%
- LDL, mmol/L MD 0.01 (95% CI -0.01 to 0.03), I^2 0%
- sBP, mmHg MD 0.02 (95% CI -0.32 to 0.35), I^2 0%
- dBP, mmHg MD -0.02 (95% CI -0.22 to 0.17), I^2 0%

Effect of increased LCn3 on serum triglycerides, mmol/L (2° outcomes)

Fig 3.3



Low risk of bias

Moderate to high risk of bias

MD -0.24 (-0.31 to -0.16), I^2 48%, >35000 participants

All studies combined

Footnotes

(1) SDs unlikely, converted assuming SEs

(2) median change from baseline, highest EPA vs placebo

(3) Medians, in participants with impaired glucose metabolism

(4) medians in normoglycaemic participants

Effect of increased ALA on CVD (1° outcomes)

- All-cause death RR 1.00 (95% CI 0.84 to 1.20), I^2 0%
- CVD deaths RR 0.96 (95% CI 0.74 to 1.25), I^2 0%
- CVD events RR 0.97 (95% CI 0.80 to 1.17), I^2 21%
- CHD deaths RR 0.95 (95% CI 0.72 to 1.26), I^2 0%
- CHD events RR 1.00 (0.78 to 1.29), I^2 24%
- Stroke RR 1.16 (95% CI 0.65 to 2.05), I^2 0%
- Arrhythmia RR 0.79 (95% CI 0.57 to 1.10), I^2 -

Other SRs – comments by Global Organization for EPA & DHA (GOED)

Discuss

- our results – omitted SCD from CHD death
- two SRs commissioned by GOED (Alexander 2017, Maki 2017), then
- A set of other systematic reviews that they suggest provide evidence of effects of LCn3 fats on coronary death
- Comparison with WHO Na & K guidance

GOED – Alexander 2017

- forest plot for CHD death not shown, reported in tables
- Coronary death (all RCTs), excludes SCD:
- 5 trials, SRRE 0.81 (95% CI 0.65 to 1.00)
- Only include data from GISSI-P, DART, CART, JELIS & Risk & Prevention (most data probably from GISSI-P & JELIS which were not placebo controlled)

GOED – Maki 2017

Expression of concern

Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one year follow up

In the *BMJ* of 18 April 1992, we published a paper by Ram B Singh, Shanti S Rastogi, Rakesh Verma, B Laxmi, Reema Singh, S Ghosh, and Mohammad A Niaz (1992;304:1015-9). We now wish to express concern about the validity of this paper. This expression of concern is based on investigations the *BMJ* has carried out into the work of the paper's lead author and what has emerged about it and its reliability in the course of these investigations. An account of these investigations is published on page 281.[1] As a result of these investigations, we have reasonable grounds to doubt the validity of the 1992 paper.

1 White C. Suspected research fraud: difficulties of getting at the truth. *BMJ* 2005;331:281-8.

Included trials of ≥6 months of supplements only (no foods) without ICDs

Could not obtain cardiac death data for GISSI or Leng so used CVD deaths

Included SCD in their CHD death data

Relies heavily for statistical significance on JELIS and GISSI which were NOT placebo controlled

Includes the Singh study – caution (BMJ & Lancet expressed concern)

RR 0.92 (95% CI 0.86 to 0.98)

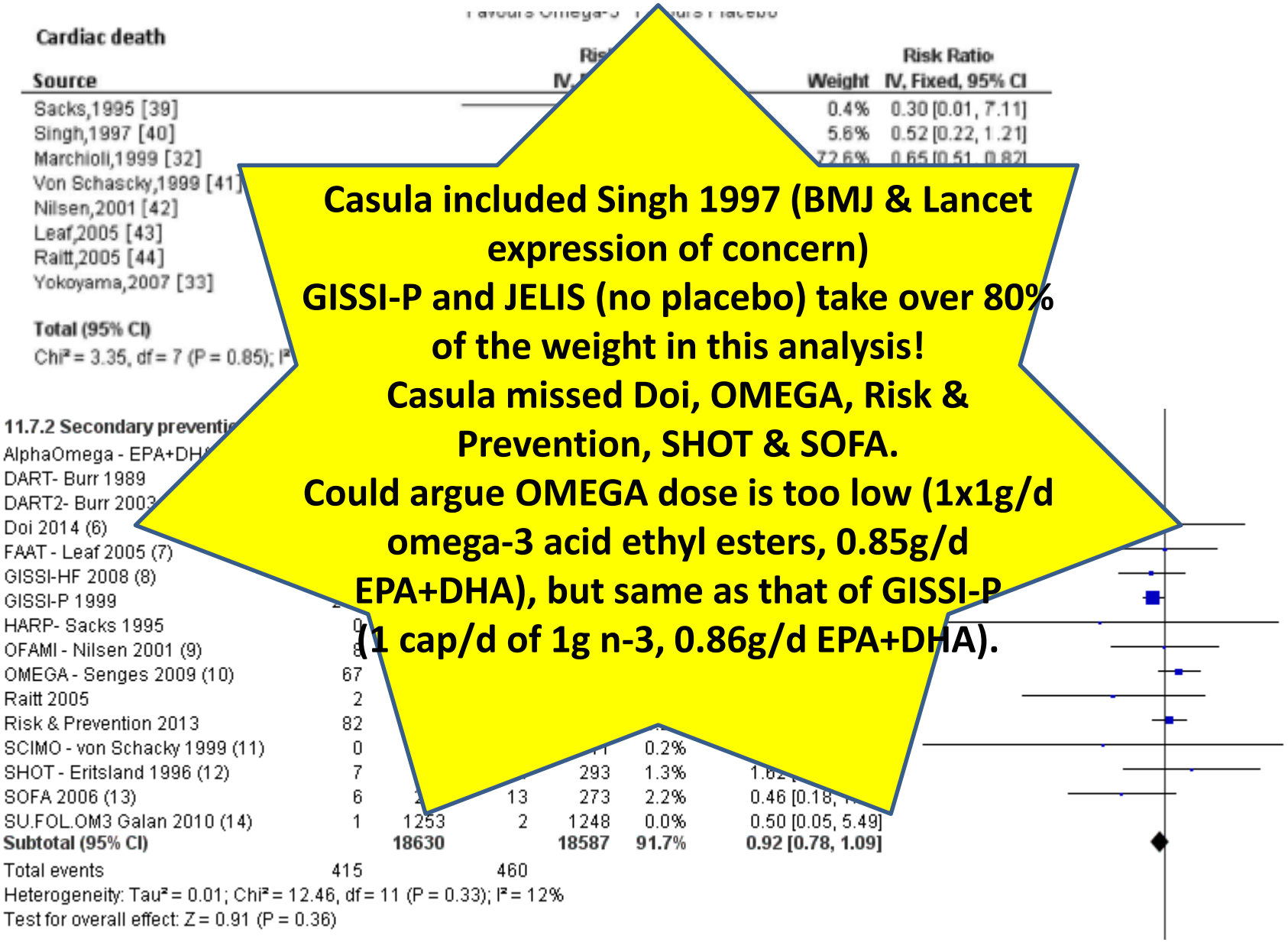
GOED – Alexander & Maki

Systematic reviews commissioned by GOED

- One included only 5 trials, the other 14 trials
- Both had methodological problems, relying heavily for significance on JELIS & GISSI-P
- One found marginal statistical significance, the other suggests statistical significance, but included a Singh study, included SCD in their CHD data, and added in CVD deaths

- Difficult to be authoritative when they make such very different (and worrying) decisions

GOED other SRs – Casula 2013



Casula included Singh 1997 (BMJ & Lancet expression of concern)
GISSI-P and JELIS (no placebo) take over 80% of the weight in this analysis!
Casula missed Doi, OMEGA, Risk & Prevention, SHOT & SOFA.
Could argue OMEGA dose is too low (1x1g/d omega-3 acid ethyl esters, 0.85g/d EPA+DHA), but same as that of GISSI-P (1 cap/d of 1g n-3, 0.86g/d EPA+DHA).

GOED other SRs – Chen 2011

Inclusion criteria:

- **Only included trials that reported sudden cardiac death (their primary outcome)**
- **so trials that reported cardiac death but did not report sudden cardiac death were excluded.**

Not a systematic review of effects on CHD deaths

GOED other SRs – Delgado-Lista

Inclusion criteria:

- **Only included trials that reported mortality and cardiovascular events were included (their primary outcomes)**
- **Trials that reported cardiac death but did not report mortality and cardiovascular events were excluded.**

Not a systematic review of effects on CHD deaths

GOED other SRs – Kotwal 2012

Did not report on cardiac death – the numbers quoted are for vascular death (which included MI, stroke & sudden death)

Not a systematic review of effects on CHD deaths

GOED other SRs – Kwak 2012

Review aimed to assess effects of secondary prevention on cardiovascular events

- **Did not report on cardiac death**
- **Numbers quoted are probably for cardiovascular death (though the number of trials is incorrect)**

Not a systematic review of effects on CHD deaths

GOED other SRs – León 2009

- **Inclusion criteria: unclear inclusion criteria, but appear to have included studies for cardiac death, and included studies of <6 months**
- **However, meta-analysis did not include most relevant trials. Missed AREDS2, Brox, DART, DART2, Derosa, DO IT etc.**

Notes presence of publication bias for this outcome.

Not a complete systematic review of effects on CHD deaths

GOED other SRs – Marik 2009

Inclusion criteria:

- **Only included trials that reported cardiovascular death were included (their primary outcomes) –**
- **Trials that reported cardiac death but did not report cardiovascular death were excluded.**

Not a systematic review of effects on CHD deaths

GOED other SRs – Rizos 2012

Published in JAMA
Review conclusion (abstract):

"Overall omega-3 PUFA supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke based on relative and absolute measures of association"

…. and so on

Level of evidence for guidance

GOED suggest that as WHO guidance for sodium & potassium were set on intermediate outcomes (BP) so should guidance for LCn3

BUT NO effect of LCn3 on:

- Total cholesterol or LDL
- Blood pressure (no evidence of any effect, though not systematically reviewed)
- Adiposity
- LCn3 do reduce TGs but not a strong enough intermediate outcome for guidance
- The saturated fat guidance was based on effects on CVD events backed up by lipid data

Summary of SR of RCT data

Evidence for establishing Nutrient Reference Values for Non-Communicable Disease for EPA & DHA

- Despite large numbers of participants taking part in RCTs over a long duration there is little evidence that LCn3 fats, including EPA & DHA, have any important effect on all-cause mortality, cardiovascular outcomes (including CHD deaths) or CVD risk factors
- There are no data suggesting dose effects with which to establish thresholds
- LCn3 fats reduce serum triglycerides & raise HDL - but these are not strong enough CVD risk factors on which to establish guidance or thresholds

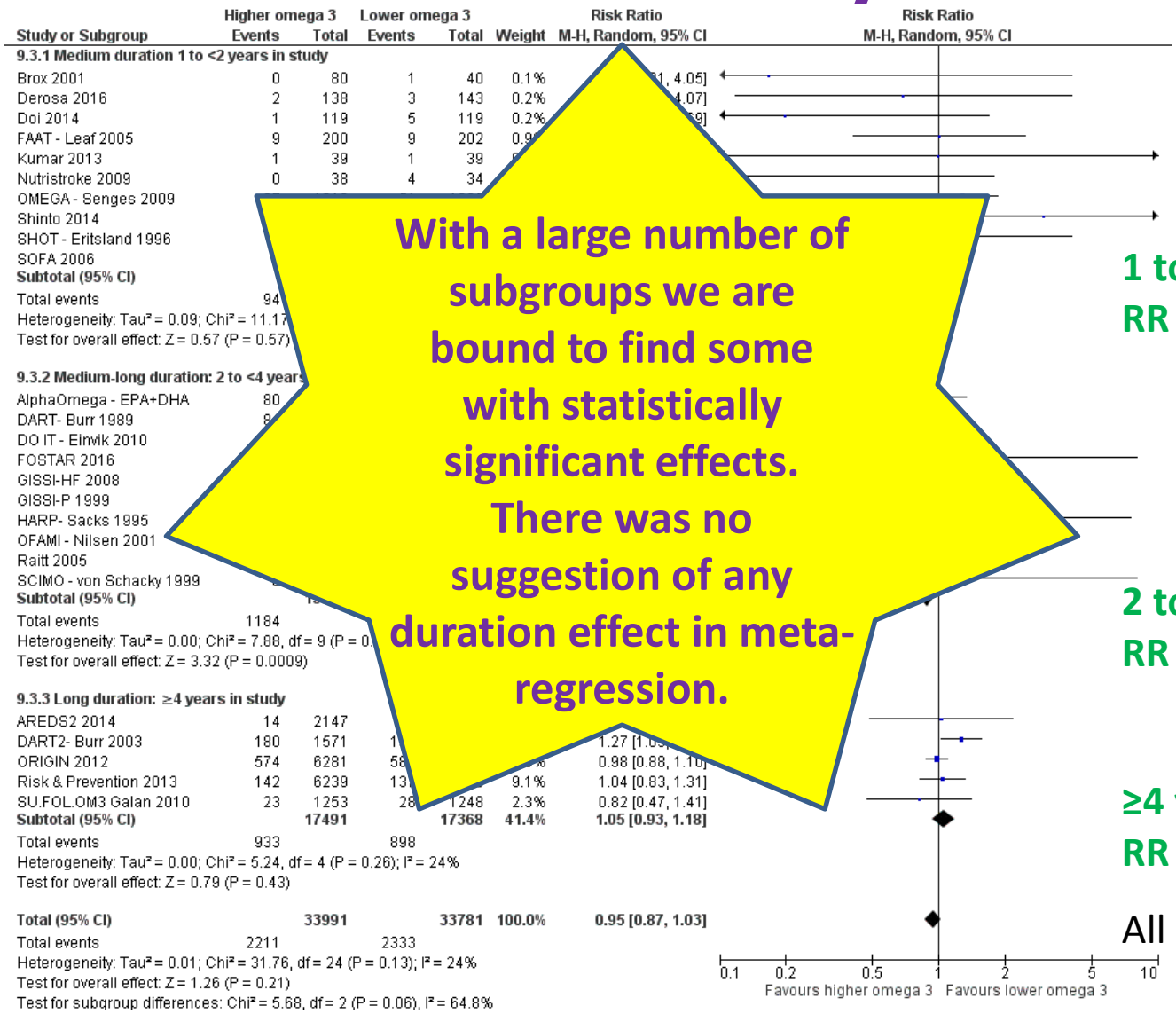
omega 3 fat SR

Thank you for your attention!

Thank you too to the team who have worked VERY hard on this:

- Asmaa Abdelhamid
- Julii Brainard
- Tracey Brown
- Sarah Hansen
- Sarah Ajabnoor
- Xia Wang
- Priti Biswas
- Gabby Thorpe
- Fujian Song
- Katherine Deane
- Nicole Martin
- Charlene Bridges
- Alex O'Brien
- Faye Alabdulgafoor
- Lauren Winstanley
- Daisy Donaldson
- Zoya Ahmed

Effect of increased LC omega 3 on CVD mortality – duration



With a large number of subgroups we are bound to find some with statistically significant effects. There was no suggestion of any duration effect in meta-regression.

Fig 4.5

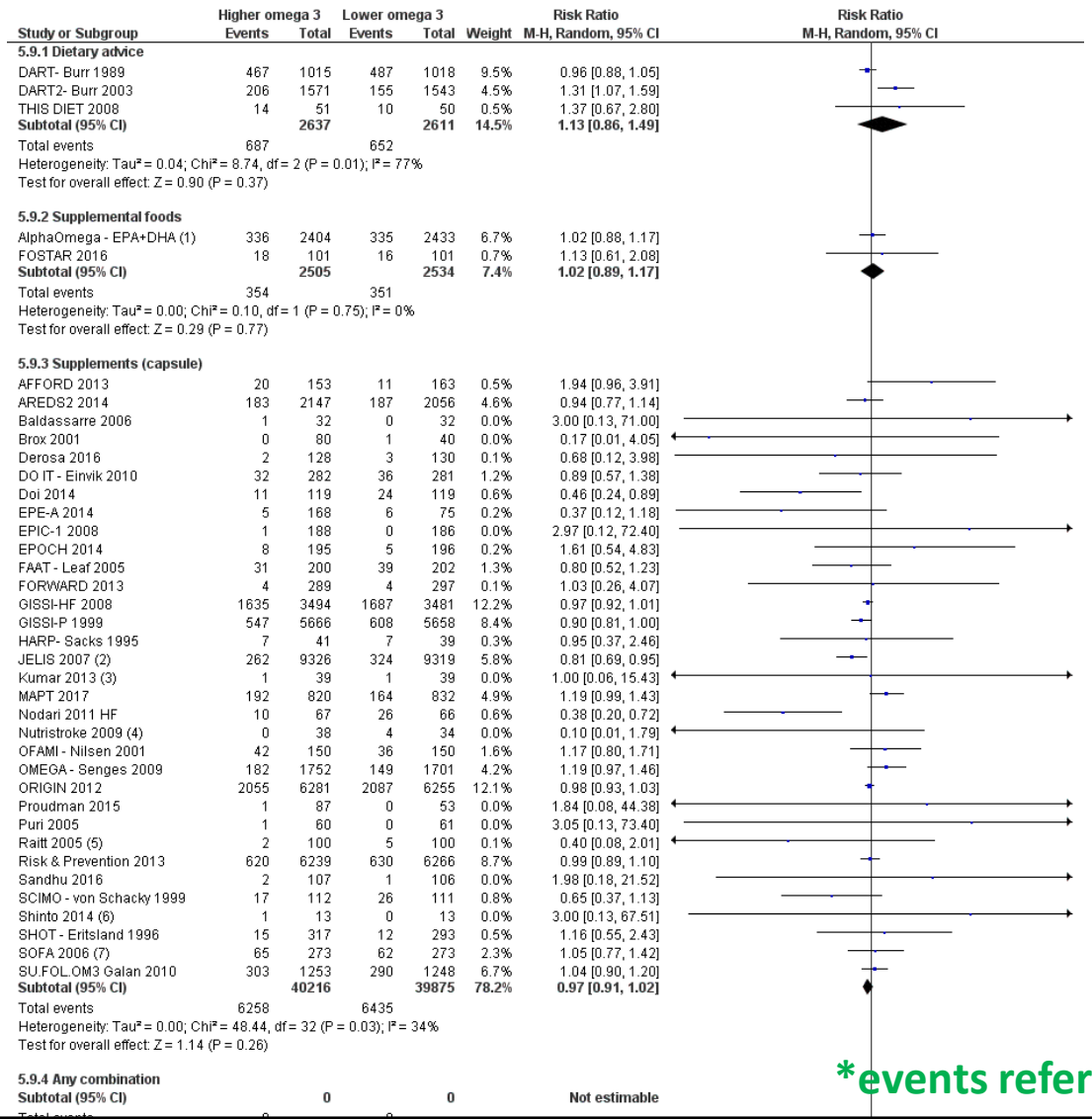
1 to <2 years, 186 deaths, RR 0.88 (0.57 to 1.36), I^2 19%

2 to <4 years, 2527 deaths, RR 0.89 (0.82 to 0.95), I^2 0%,

≥4 years, 1831 deaths, RR 1.05 (0.93 to 1.18), I^2 24%,

All studies combined

Effect of increased LC omega 3 on CVD events – intervention type



Study or Subgroup	Higher omega 3 Events	Higher omega 3 Total	Lower omega 3 Events	Lower omega 3 Total	Weight	Risk Ratio M-H, Random, 95% CI
5.9.1 Dietary advice						
DART- Burr 1989	467	1015	487	1018	9.5%	0.96 [0.88, 1.05]
DART2- Burr 2003	206	1571	155	1543	4.5%	1.31 [1.07, 1.59]
THIS DIET 2008	14	51	10	50	0.5%	1.37 [0.67, 2.80]
Subtotal (95% CI)		**2637**		**2611**	**14.5%**	**1.13 [0.86, 1.49]**
Total events	687		652			
Heterogeneity: Tau² = 0.04; Chi² = 8.74, df = 2 (P = 0.01); I² = 77%						
Test for overall effect: Z = 0.90 (P = 0.37)						
5.9.2 Supplemental foods						
AlphaOmega - EPA+DHA (1)	336	2404	335	2433	6.7%	1.02 [0.88, 1.17]
FOSTAR 2016	18	101	16	101	0.7%	1.13 [0.61, 2.08]
Subtotal (95% CI)		**2505**		**2534**	**7.4%**	**1.02 [0.89, 1.17]**
Total events	354		351			
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
5.9.3 Supplements (capsule)						
AFFORD 2013	20	153	11	163	0.5%	1.94 [0.96, 3.91]
AREDS2 2014	183	2147	187	2056	4.6%	0.94 [0.77, 1.14]
Baldassarre 2006	1	32	0	32	0.0%	3.00 [0.13, 71.00]
Brox 2001	0	80	1	40	0.0%	0.17 [0.01, 4.05]
Derosa 2016	2	128	3	130	0.1%	0.68 [0.12, 3.98]
DO IT - Einvik 2010	32	282	36	281	1.2%	0.89 [0.57, 1.38]
Doi 2014	11	119	24	119	0.6%	0.46 [0.24, 0.89]
EPE-A 2014	5	168	6	75	0.2%	0.37 [0.12, 1.18]
EPIC-1 2008	1	188	0	186	0.0%	2.97 [0.12, 72.40]
EPOCH 2014	8	195	5	196	0.2%	1.61 [0.54, 4.83]
FAAT - Leaf 2005	31	200	39	202	1.3%	0.80 [0.52, 1.23]
FORWARD 2013	4	289	4	297	0.1%	1.03 [0.26, 4.07]
GISSI-HF 2008	1635	3494	1687	3481	12.2%	0.97 [0.92, 1.01]
GISSI-P 1999	547	5666	608	5658	8.4%	0.90 [0.81, 1.00]
HARP- Sacks 1995	7	41	7	39	0.3%	0.95 [0.37, 2.46]
JELIS 2007 (2)	262	9326	324	9319	5.8%	0.81 [0.69, 0.95]
Kumar 2013 (3)	1	39	1	39	0.0%	1.00 [0.06, 15.43]
MAPT 2017	192	820	164	832	4.9%	1.19 [0.99, 1.43]
Nodari 2011 HF	10	67	26	66	0.6%	0.38 [0.20, 0.72]
Nutristroke 2009 (4)	0	38	4	34	0.0%	0.10 [0.01, 1.79]
OFAMI - Nilsen 2001	42	150	36	150	1.6%	1.17 [0.80, 1.71]
OMEGA - Senges 2009	182	1752	149	1701	4.2%	1.19 [0.97, 1.46]
ORIGIN 2012	2055	6281	2087	6255	12.1%	0.98 [0.93, 1.03]
Proudman 2015	1	87	0	53	0.0%	1.84 [0.08, 44.38]
Puri 2005	1	60	0	61	0.0%	3.05 [0.13, 73.40]
Raitt 2005 (5)	2	100	5	100	0.1%	0.40 [0.08, 2.01]
Risk & Prevention 2013	620	6239	630	6266	8.7%	0.99 [0.89, 1.10]
Sandhu 2016	2	107	1	106	0.0%	1.98 [0.18, 21.52]
SCIMO - von Schacky 1999	17	112	26	111	0.8%	0.65 [0.37, 1.13]
Shinto 2014 (6)	1	13	0	13	0.0%	3.00 [0.13, 67.51]
SHOT - Eritsland 1996	15	317	12	293	0.5%	1.16 [0.55, 2.43]
SOFA 2006 (7)	65	273	62	273	2.3%	1.05 [0.77, 1.42]
SU.FOL.OM3 Galan 2010	303	1253	290	1248	6.7%	1.04 [0.90, 1.20]
Subtotal (95% CI)		**40216**		**39875**	**78.2%**	**0.97 [0.91, 1.02]**
Total events	6258		6435			
Heterogeneity: Tau² = 0.00; Chi² = 48.44, df = 32 (P = 0.03); I² = 34%						
Test for overall effect: Z = 1.14 (P = 0.26)						
5.9.4 Any combination						
Subtotal (95% CI)		**0**		**0**		**Not estimable**

Risk Ratio M-H, Random, 95% CI

Dietary advice, 1339 events*, RR 1.13 (0.86 to 1.49), I^2 77%

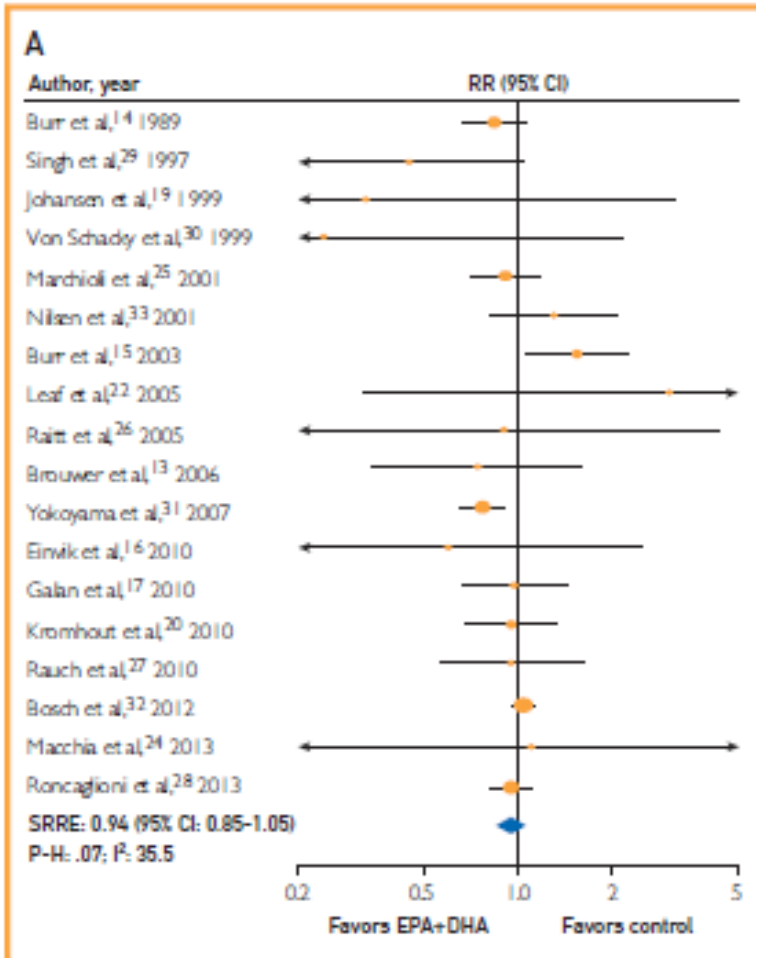
Supplementary foods, 705 events*, RR 1.02 (0.89 to 1.17), I^2 0%

Fig 4.12

Supplements, 12693 events*, RR 0.97 (0.91 to 1.02), I^2 34%

***events refer to people experiencing ≥1 CVD events**

GOED – Alexander 2017



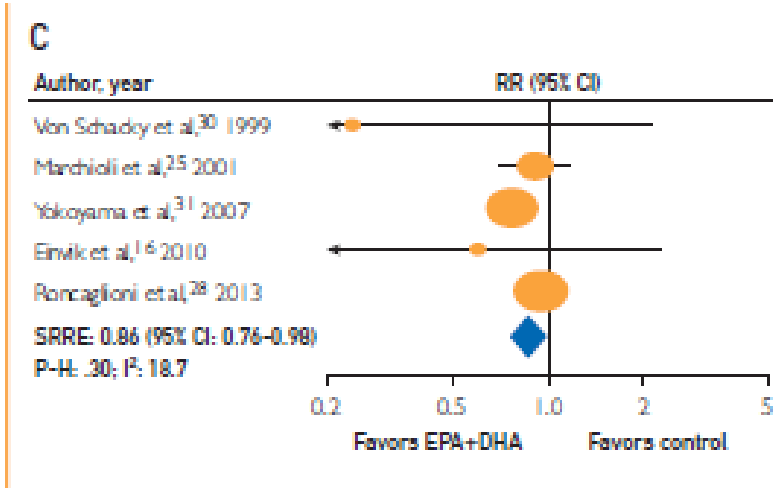


Fig 2c Effect of LCn3 on any CHD event in those with raised LDL – statistically significant effect

This subgroup effect relies heavily on JELIS (Yokoyama 2007) and GISSI-P (Marchioli 2001) which were NOT placebo controlled

Fig 2a Effect of LCn3 on any CHD event, main analysis. No statistically significant effect