Why do we need systematic reviews in nutrition?

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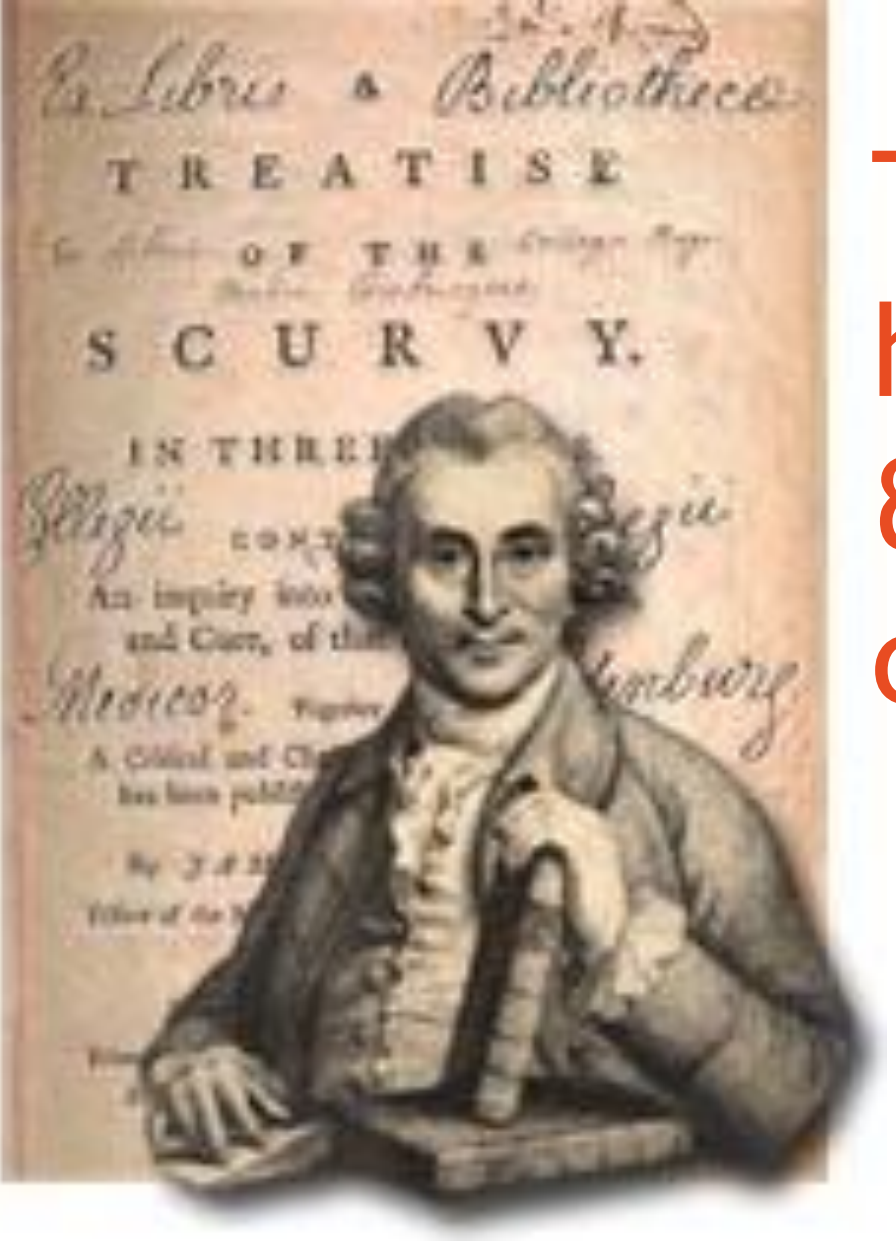
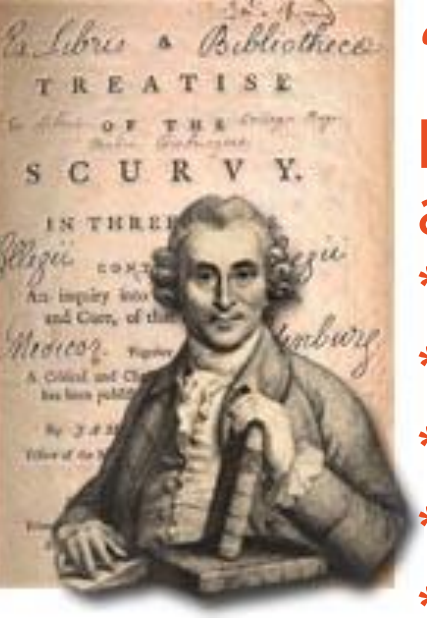


The venerable history of nutrition & evidence-based care

James Lind

Dunn PM. James Lind (1716-94) of Edinburgh and the treatment of scurvy. Archives of Disease in Childhood 1997: 76; F64-65.



James Lind

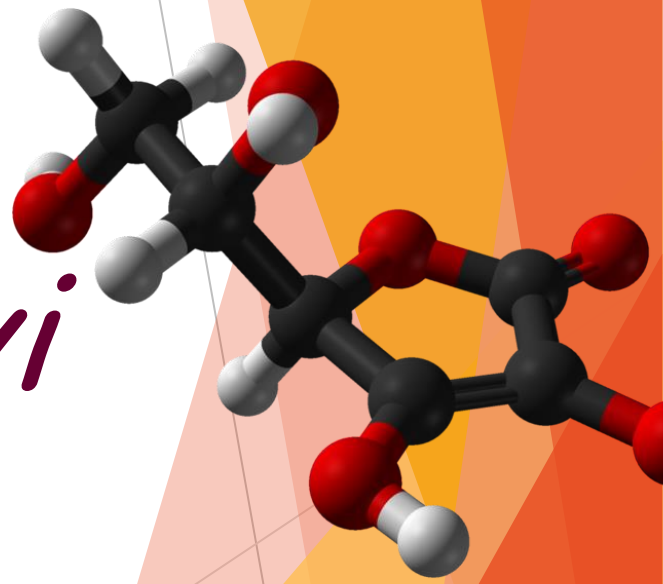
"On the 20th of May 1747, I selected twelve patients in the scurvy, on board the Salisbury at sea…. Two were ordered each…"

* a quart of cyder a day
* twenty-five drops of elixir vitriol three times a day
* two spoonfuls of vinegar three times a day . . .
* a course of sea-water
* two oranges and one lemon …every day
* an electary recommended by a hospital surgeon

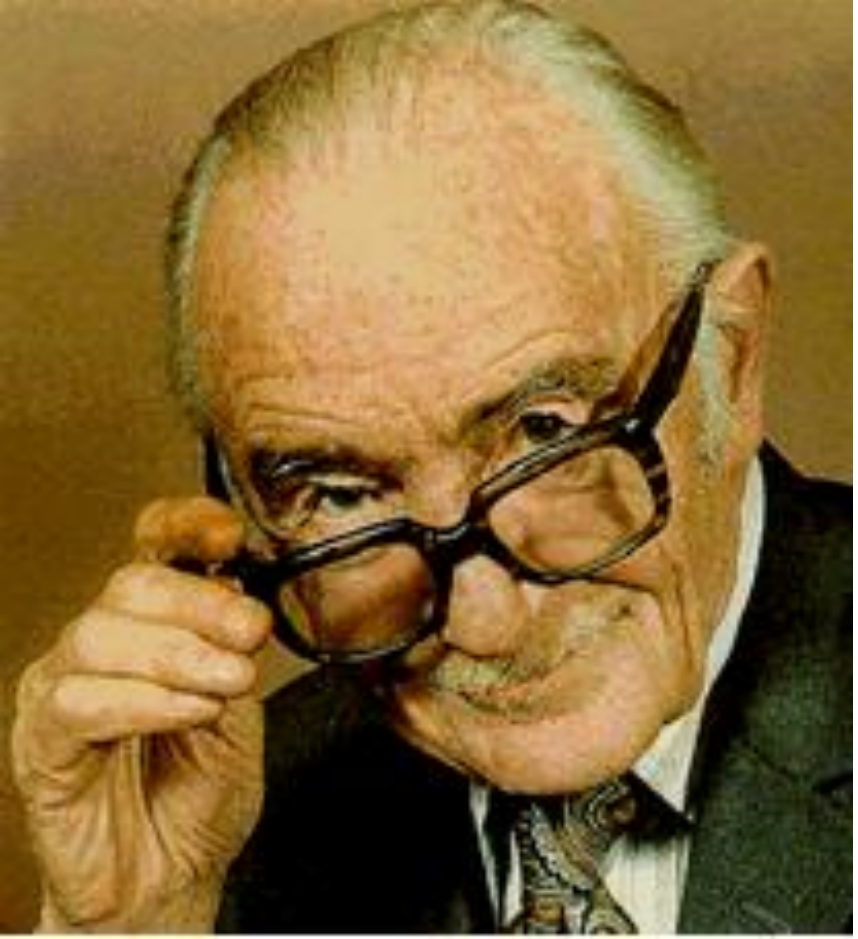
". . the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them, being at the end of six days fit for duty . . . The other was the best recovered of any in his condition; and . . . was appointed to attend the rest of the sick.. . ."

The venerable history of nutrition & evidence-based care

Nagyrápolti Szent-Györgyi Albert



1937: Nobel Prize in Physiology or Medicine "for his discoveries in connection with the biological combustion process with special reference to **vitamin C** and the catalysis of fumaric acid".



The venerable history of nutrition & evidence-based care

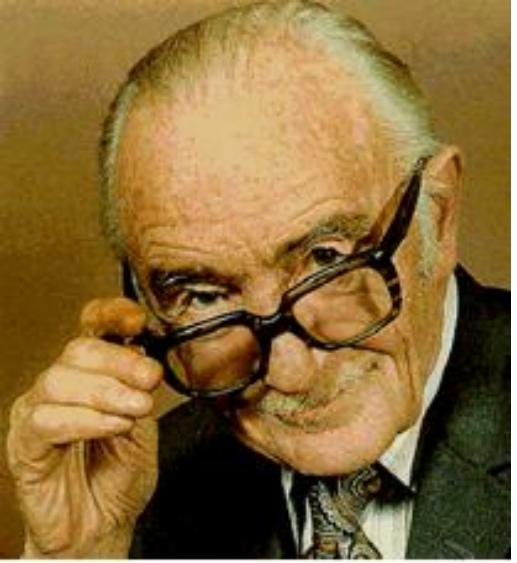
Archie Cochrane

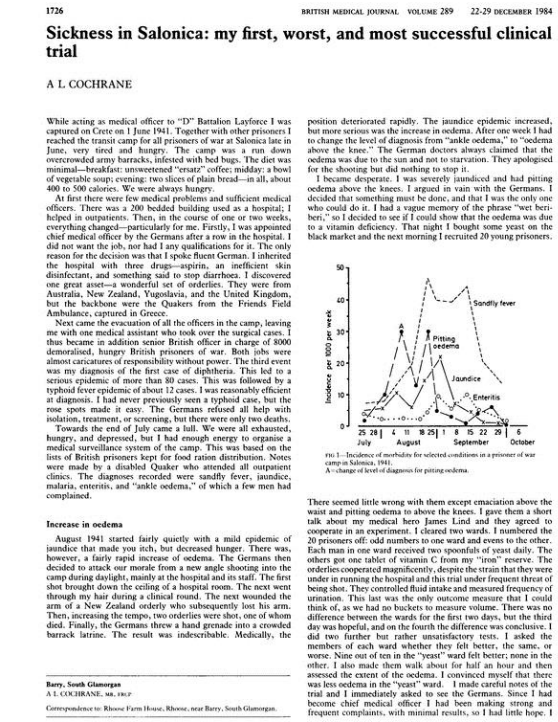
Cochrane AL. Sickness in Salonica: my first, worst, and most successful clinical trial. BMJ 1984:289;1726-7.

The diet was minimal-breakfast: unsweetened "ersatz" coffee; midday: a bowl of vegetable soup; evening: two slices of plain bread- in all, about 400 to 500 calories. We were always hungry.

Cochrane AL. Sickness in Salonica: my first, worst, and most successful clinical trial. BMJ 1984:289;1726-7.

Cochrane AL. Effectiveness and Efficiency 1972, London: Nuffield Provincial Hospitals Trust.





1726 BRITISH MEDICAL JOURNAL VOLUME 289 22-29 DECEMBER 1984

Sickness in Salonica: my first, worst, and most successful clinical trial

A L COCHRANE

While acting as medical officer to "D" Battalion Layforce I was captured on Crete on 1 June 1941. Together with other prisoners I reached the transit camp for all prisoners of war at Salonica late in June, very tired and hungry. The camp was a run down overcrowded army barracks, infested with bed bugs. The diet was minimal—breakfast: unsweetened "ersatz" coffee; midday: a bowl of vegetable soup; evening: two slices of plain bread—in all, about 400 to 500 calories. We were always hungry.

At first there were few medical problems and sufficient medical officers. There was a 200 bedded building used as a hospital; I helped in outpatients. Then, in the course of one or two weeks, everything changed—particularly for me. Firstly, I was appointed chief medical officer by the Germans after a row in the hospital. I did not want the job, nor had I any qualifications for it. The only reason for the decision was that I spoke fluent German. I inherited the hospital with three drugs—aspirin, an inefficient skin disinfectant, and something said to stop diarrhoea. I discovered one great asset—a wonderful set of orderlies. They were from Australia, New Zealand, Yugoslavia, and the United Kingdom, but the backbone were the Quakers from the Friends Field Ambulance, captured in Greece.

Next came the evacuation of all the officers in the camp, leaving me with one medical assistant who took over the surgical cases. I thus became in addition senior British officer in charge of 8000 demoralised, hungry British prisoners of war. Both jobs were almost caricatures of responsibility without power. The third event was my diagnosis of the first case of diphtheria. This led to a serious epidemic of more than 80 cases. This was followed by a typhoid fever epidemic of about 12 cases. I was reasonably efficient at diagnosis. I had never previously seen a typhoid case, but the rose spots made it easy. The Germans refused all help with isolation, treatment, or screening, but there were only two deaths.

Towards the end of July came a lull. We were all exhausted, hungry, and depressed, but I had enough energy to organise a medical surveillance system of the camp. This was based on the lists of British prisoners kept for food ration distribution. Notes were made by a disabled Quaker who attended all outpatient clinics. The diagnoses recorded were sandfly fever, jaundice, malaria, enteritis, and "ankle oedema," of which a few men had complained.

Increase in oedema

August 1941 started fairly quietly with a mild epidemic of jaundice that made you itch, but decreased hunger. There was, however, a fairly rapid increase of oedema. The Germans then decided to attack our morale from a new angle shooting into the camp during daylight, mainly at the hospital and its staff. The first shot brought down the ceiling of a hospital room. The next went through my hair during a clinical round. The next wounded the arm of a New Zealand orderly who subsequently lost his arm. Then, increasing the tempo, two orderlies were shot, one of whom died. Finally, the Germans threw a hand grenade into a crowded barrack latrine. The result was indescribable. Medically, the position deteriorated rapidly. The jaundice epidemic increased, but more serious was the increase in oedema. After one week I had to change the level of diagnosis from "ankle oedema," to "oedema above the knee." The German doctors always claimed that the oedema was due to the sun and not to starvation. They apologised for the shooting but did nothing to stop it.

I became desperate. I was severely jaundiced and had pitting oedema above the knees. I argued in vain with the Germans. I decided that something must be done, and that I was the only one who could do it. I had a vague memory of the phrase "wet beri-beri," so I decided to see if I could show that the oedema was due to a vitamin deficiency. That night I bought some yeast on the black market and the next morning I recruited 20 young prisoners.

FIG 1—Incidence of morbidity for selected conditions in a prisoner of war camp in Salonica, 1941.
A—change of level of diagnosis for pitting oedema.

There seemed little wrong with them except emaciation above the waist and pitting oedema to above the knees. I gave them a short talk about my medical hero James Lind and they agreed to cooperate in an experiment. I cleared two wards. I numbered the 20 prisoners off: odd numbers to one ward and evens to the other. Each man in one ward received two spoonfuls of yeast daily. The others got one tablet of vitamin C from my "iron" reserve. The orderlies cooperated magnificently, despite the strain that they were under in running the hospital and this trial under frequent threat of being shot. They controlled fluid intake and measured frequency of urination. This last was the only outcome measure that I could think of, as we had no buckets to measure volume. There was no difference between the wards for the first two days, but the third day was hopeful, and on the fourth the difference was conclusive. I did two further but rather unsatisfactory tests. I asked the members of each ward whether they felt better, the same, or worse. Nine out of ten in the "yeast" ward felt better; none in the other. I also made them walk about for half an hour and then assessed the extent of the oedema. I convinced myself that there was less oedema in the "yeast" ward. I made careful notes of the trial and I immediately asked to see the Germans. Since I had become chief medical officer I had been making strong and frequent complaints, with minimal results, so I had little hope. I

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- "On reflection, it was not a good trial. I was testing the wrong hypothesis. The oedema was not wet beri-beri.
- Furthermore, the numbers were too small, the time too short, and the outcome measurements poor.
- Yet the treatment worked. I still do not know why. I imagine that the simplest explanation is that the small amount of protein in the yeast raised the plasma proteins sufficiently to correct fluid balance."

Cochrane AL. Sickness in Salonica: my first, worst, and most successful clinical trial. BMJ 1984:289;1726-7.

Why do we need systematic reviews in nutrition?

- Remarkable ability for humans to get better, regardless of medical treatment
- And to get better despite dreadful nutrition
- So to see effects compared to control we need large numbers of people

So why do we need systematic reviews in nutrition?

- Systematic reviews were not needed to assess effects of citrus fruit on scurvy or of yeast on oedema above the knee.
- We need them because when we study nutrition these days in societies with a background of reasonably good nutrition we are usually looking for small effects
- We can only see these small effects when we study large numbers of people

Special Article

NUTRITION REVIEWS

Lohner S, Kullenberg D, Antes G, Decsi T, Meerpohl JJ. 2014 Nutrition Reviews.

Prebiotics in healthy infants and children for prevention of acute infectious diseases: a systematic review and meta-analysis

Szimonetta Lohner, Daniela Küllenberg, Gerd Antes, Tamás Decsi, and Joerg J Meerpohl

Prebiotics, defined as nondigestible dietary ingredients resistant to gastric acidity and fermented by the intestinal flora, are used to positively influence the composition of intestinal flora, thereby promoting health benefits. The objective of this systematic review was to assess the efficacy of prebiotics in the prevention of acute infectious diseases in children. A systematic literature search was conducted using the Ovid Medline, Scopus, Web of Science, and Cochrane Library's Central databases. Finally, five randomized controlled trials, all of them investigating infants and children 0–24 months of age, were included in the review. Pooled estimates from three studies revealed a statistically significant decrease in the number of infectious episodes requiring antibiotic therapy in the prebiotic group as compared with the placebo group (rate ratio 0.68; 95% confidence interval 0.61–0.77). Studies available indicate that prebiotics may also be effective in decreasing the rate of overall infections in infants and children 0–24 months of age. Further studies in the age group 3–18 years are required to determine whether prebiotics can be considered for the prevention of acute infectious diseases in the older pediatric population.

Study or Subgroup	log[Rate Ratio]	SE	Prebiotic Total	Control Total	Weight	Rate Ratio IV, Random, 95% CI
Arslanoglu, 2007	-0.64	0.26	102	104	5.3%	0.53 [0.32, 0.88]
Bruzzese, 2009	-0.36	0.13	96	105	21.3%	0.70 [0.54, 0.90]
Saavedra, 2002	-0.37	0.07	63	60	73.4%	0.69 [0.60, 0.79]
Stuijvenberg, 2011	0	0	292	300		Not estimable
Total (95% CI)			**553**	**569**	**100.0%**	**0.68 [0.61, 0.77]**

Heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 2 (P = 0.59); I² = 0%

Test for overall effect: Z = 6.37 (P < 0.00001)

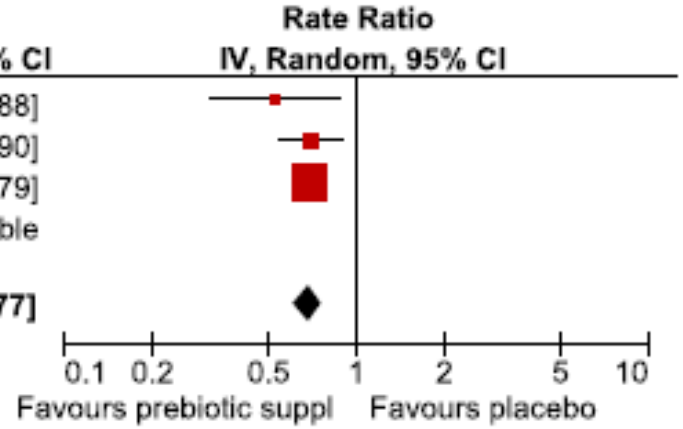
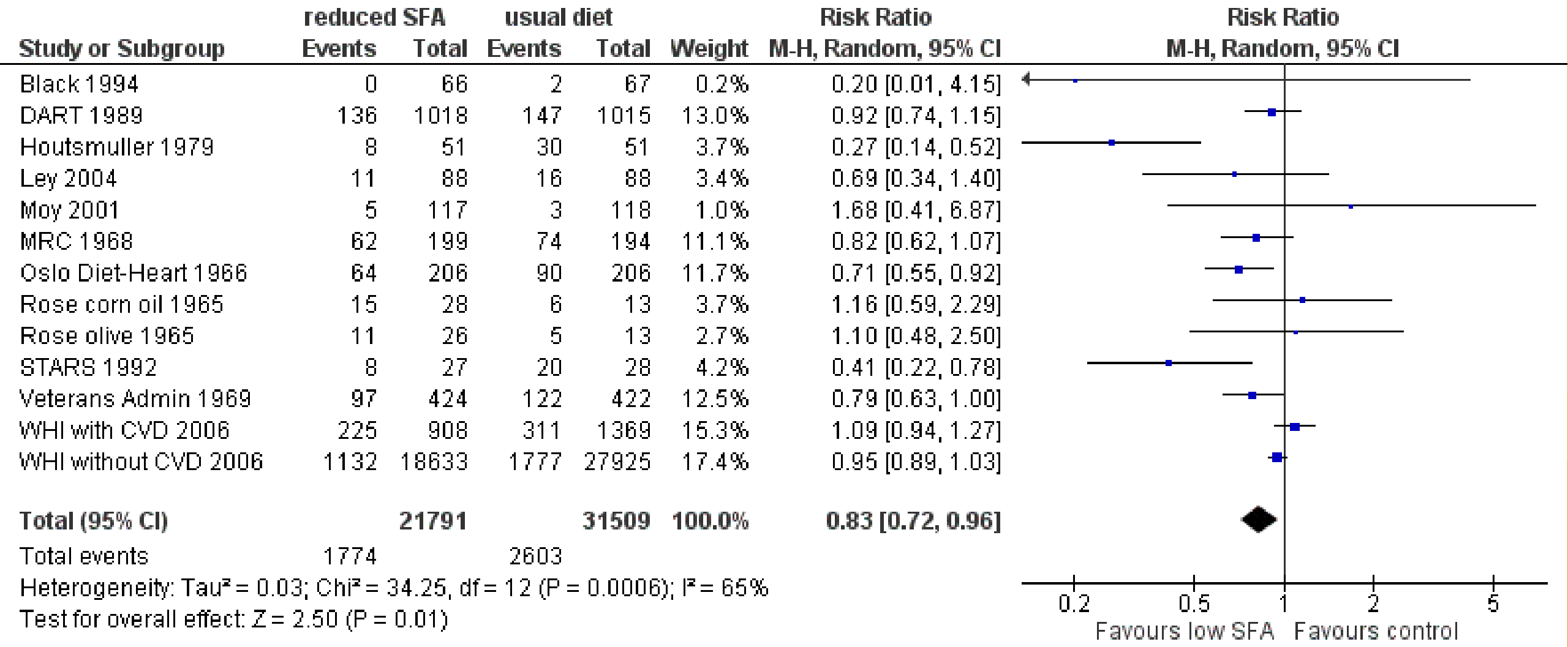


Figure 3 **The rate of infections requiring antibiotic treatment (events per person/year) in infants and children supplemented with prebiotics versus placebo.**



Forest plot assessing effect of a diet low in saturated fats compared to a usual diet on cardiovascular events, in RCTs of at least 2 years duration

Study or Subgroup	log[Rate Ratio]	SE	Prebiotic Total	Control Total	Weight	Rate Ratio IV, Random, 95% CI
Saavedra, 2002	-0.45	0.07	63	60	49.7%	0.64 [0.56, 0.73]
Stuijvenberg, 2011	0.01	0.06	292	300	50.3%	1.01 [0.90, 1.14]
Total (95% CI)			**355**	**360**	**100.0%**	**0.80 [0.51, 1.26]**

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 24.89$, df = 1 ($P < 0.00001$); $I^2 = 96\%$

Test for overall effect: Z = 0.95 (P = 0.34)

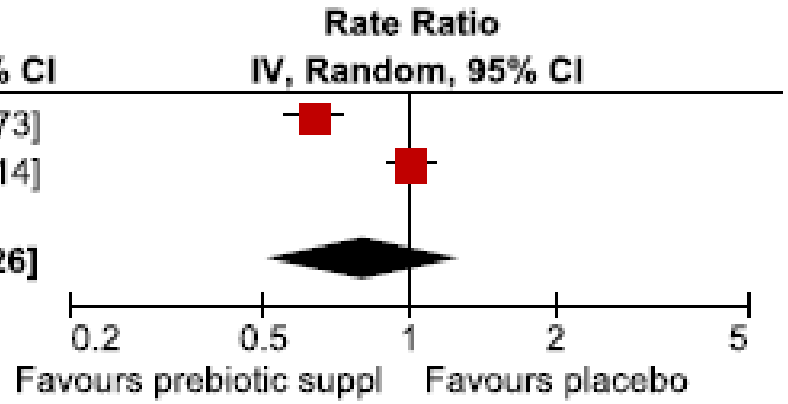
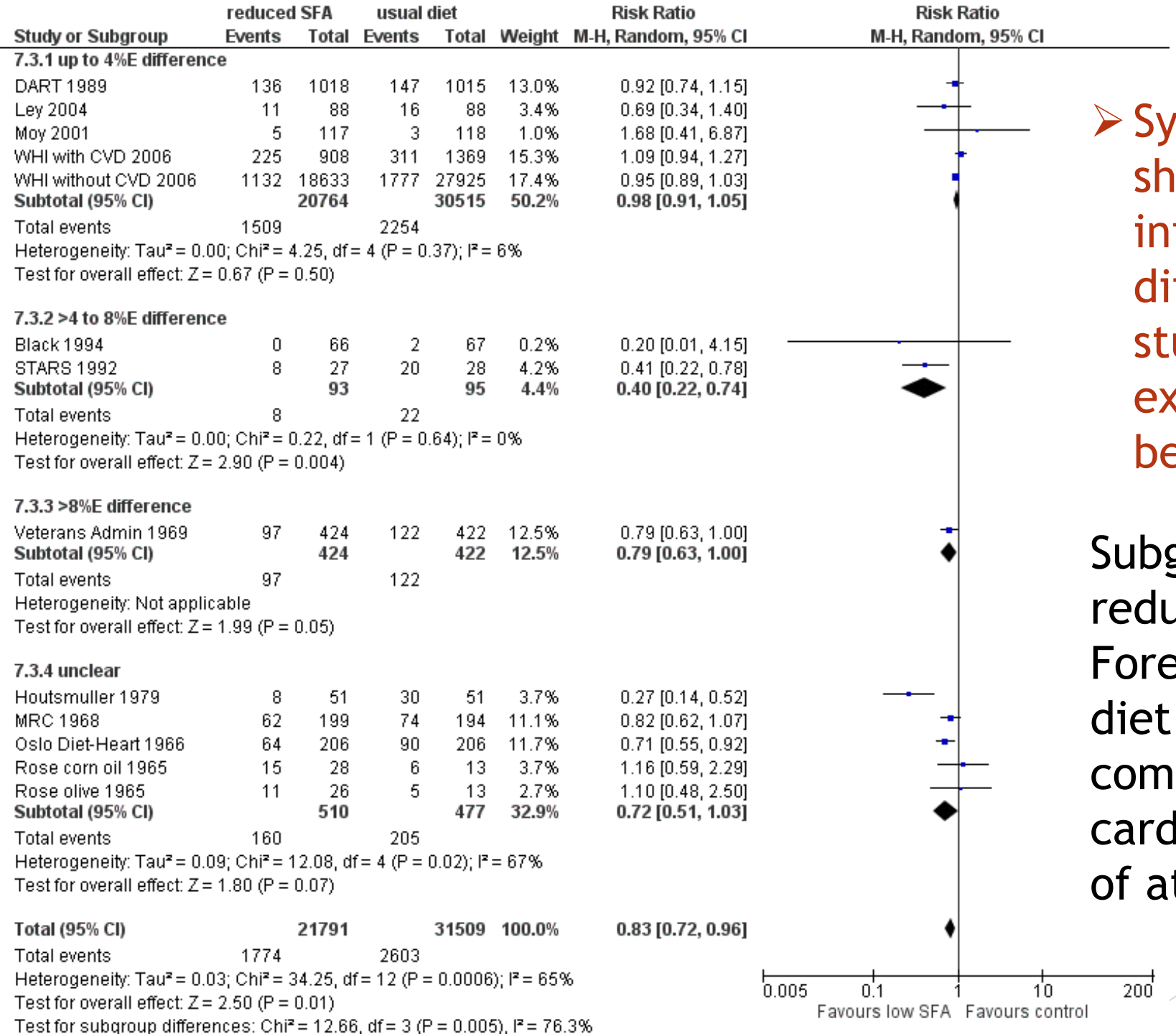


Figure 2 **The rate of febrile episodes (events per person/year) in infants and children supplemented with prebiotics versus placebo.**

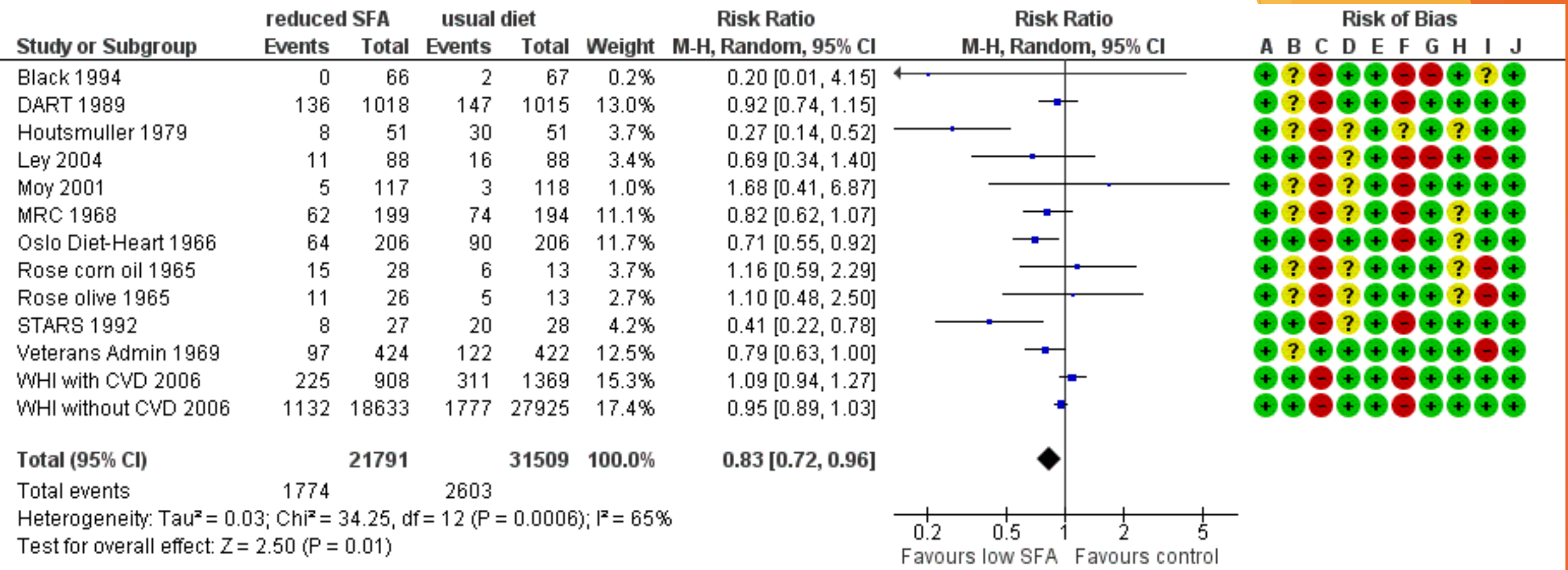
- Systematic reviews can show us when interventions work differently in different studies – so that we can explore why this may be

Lohner S, Kullenberg D, Antes G, Decsi T, Meerpohl JJ. 2014 Nutrition Reviews.



- Systematic reviews can show us when interventions work differently in different studies – so that we can explore why this may be

Subgrouping by degree of reduction in saturated fats - Forest plot assessing effect of a diet low in saturated fats compared to a usual diet on cardiovascular events, in RCTs of at least 2 years duration



Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding (performance bias and detection bias)
(**D**) Incomplete outcome data (attrition bias)
(**E**) Selective reporting (reporting bias)
(**F**) Free of systematic difference in care?
(**G**) Stated aim to reduce SFA
(**H**) Achieved SFA reduction
(**I**) Achieved TC reduction
(**J**) Other bias

- Systematic reviews can show us when interventions work differently in different studies – so that we can explore why this may be
- Sometimes this can relate to study validity

Why do we need systematic reviews in nutrition?

- Systematic reviews allow us to understand when interventions work, and when they do not (using heterogeneity of included studies)
- May be due to differences in dose, type or mode of intervention, duration, participants or setting

Fekete et al. Nutrition Journal 2012, 11:75
http://www.nutritionj.com/content/11/1/75

NUTRITION JOURNAL

REVIEW Open Access

Effect of folate intake on health outcomes in pregnancy: a systematic review and meta-analysis on birth weight, placental weight and length of gestation

Katalin Fekete[1*], Cristiana Berti[2], Monica Trovato[2], Szimonetta Lohner[3], Carla Dullemeijer[4], Olga W Souverein[4], Irene Cetin[2] and Tamás Decsi[3]

We can use systematic reviews to explore a variety of questions:

- Efficacy of interventions

Annals of Nutrition & Metabolism

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Gender Differences in the Long-Chain Polyunsaturated Fatty Acid Status: Systematic Review of 51 Publications

Szimonetta Lohner[a] Katalin Fekete[b] Tamás Marosvölgyi[a] Tamás Decsi[a]

Departments of [a]Pediatrics and [b]Biochemistry and Medical Chemistry, University of Pécs, Pécs, Hungary

We can use systematic reviews to explore a variety of questions:

- Efficacy of interventions
- Nutritional status in different populations

Hindawi Publishing Corporation
Journal of Nutrition and Metabolism
Volume 2012, Article ID 470656, 13 pages
doi:10.1155/2012/470656

Review Article

Folate Intake and Markers of Folate Status in Women of Reproductive Age, Pregnant and Lactating Women: A Meta-Analysis

Cristiana Berti,[1] Katalin Fekete,[2] Carla Dullemeijer,[3] Monica Trovato,[1] Olga W. Souverein,[3] Adriënne Cavelaars,[3] Rosalie Dhonukshe-Rutten,[3] Maddalena Massari,[1] Tamás Decsi,[2] Pieter van't Veer,[3] and Irene Cetin[1]

We can use systematic reviews to explore a variety of questions:

- Efficacy of interventions
- Nutritional status in different populations
- Relationships between intake and status

Methods of assessment of zinc status in humans: a systematic review[1–5]

Nicola M Lowe, Katalin Fekete, and Tamás Decsi

ABSTRACT

Background: Zinc is an essential micronutrient for human health and has numerous structural and biochemical roles. The search for a reliable, sensitive, and specific index of zinc status has been the subject of considerable research, which has resulted in the identification of a number of potentially useful biomarkers.

Objective: The objective was to assess the usefulness of biomarkers of zinc status in humans.

fish, shellfish, nuts, seeds, legumes, and whole-grain cereals (1, 2). However, plant sources are considered to be less bioavailable because of the presence of phytic acid that binds to zinc-forming insoluble complexes, which thus inhibits zinc's absorption (1). The current recommendations for dietary zinc intake in adults range from 7 mg/d (UK Reference Nutrient Intake) to 11 mg/d (US Recommended Dietary Allowance) (2). This broad range reflects in part the variation in requirements

We can use systematic reviews to explore a variety of questions:

- Efficacy of interventions
- Nutritional status in different populations
- Relationships between intake and status
- Testing methods of assessment of nutrient status

Why do we need systematic reviews in nutrition?

- Systematic reviews allow us to address a variety of types of question important to nutrition
- not only questions of efficacy

So why do we need systematic reviews in nutrition?

- They allow us to re-examine our understanding of nutrition
- Some tennets of nutrition we take as established – but when we re-examine the evidence in the context of a systematic review it may not be so clear-cut
- They allow us to check what we do know, and see where there are gaps to fill

Why do we need systematic reviews in nutrition?

- Systematic reviews (done well):
  - Are high quality publications
  - Are relatively inexpensive
  - Often challenge perceived wisdom

Why do we need systematic reviews in nutrition?

- Systematic reviews (done well):
  - Feed into guidance
  - Locally, nationally, internationally
  - This is a way that our research can have real impact on health and well-being

Why are systematic reviews in nutrition difficult?

Where nutritional factors are thought to have small effects over many years (for example, dietary fats or fruit and vegetables on cardiovascular disease)

- Randomised controlled trials to show effectiveness need to be very large and over long periods of time
- Or we need to trust to surrogate outcomes
- Or we need to review cohort studies (but in observational studies confounding is a serious risk)
- Or use eg Mendelian randomisation

The thorny case of Folic acid, systematic reviews and cardiovascular disease…

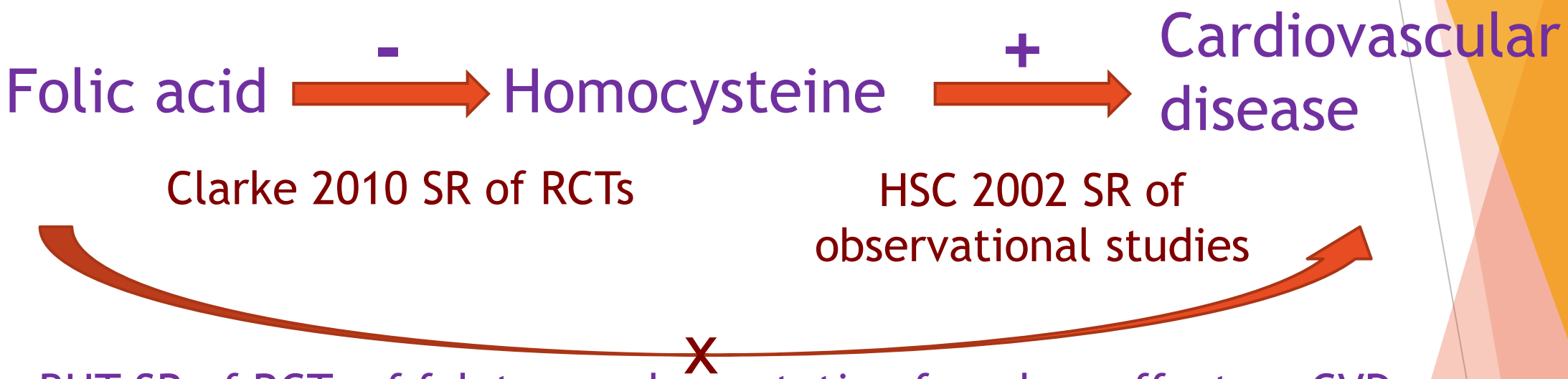
Clarke 2010 SR of RCTs

HSC 2002 SR of observational studies

Additionally, systematic review of Mendelian randomisation studies - those with constitutional raised homocysteine are at higher risk of cardiovascular disease – the homocysteine – cardiovascular disease relationship is causal (Wald 2011)

So supplementation with folic acid should reduce homocysteine and reduce the risk of cardiovascular disease

The thorny case of Folic acid, systematic reviews and cardiovascular disease…



BUT SR of RCTs of folate supplementation found no effect on CVD or any other outcome, and no dose or duration effects (Clarke 2010)

- So are we being misled about homocysteine being in the causative pathway?
- Should you or I be taking folic acid to lower our CVD risk?

Summary….Why do we need systematic reviews in nutrition?

- Systematic reviews (done well):
  - Are cost effective
  - Can answer important questions and challenge assumptions
  - Have an impact on health and well-being

Hungarian
Cochrane Branch

The Cochrane Collaboration