Best practices of meta-analysis in nutrition research: A case study of food marketing evidence synthesis to inform policy guidelines

Part 4: Interpreting the results of meta-analysis, including statistical heterogeneity

Use of Meta-Analyses in Nutrition Research and Policy:
Best Practices of Conducting Meta-Analysis

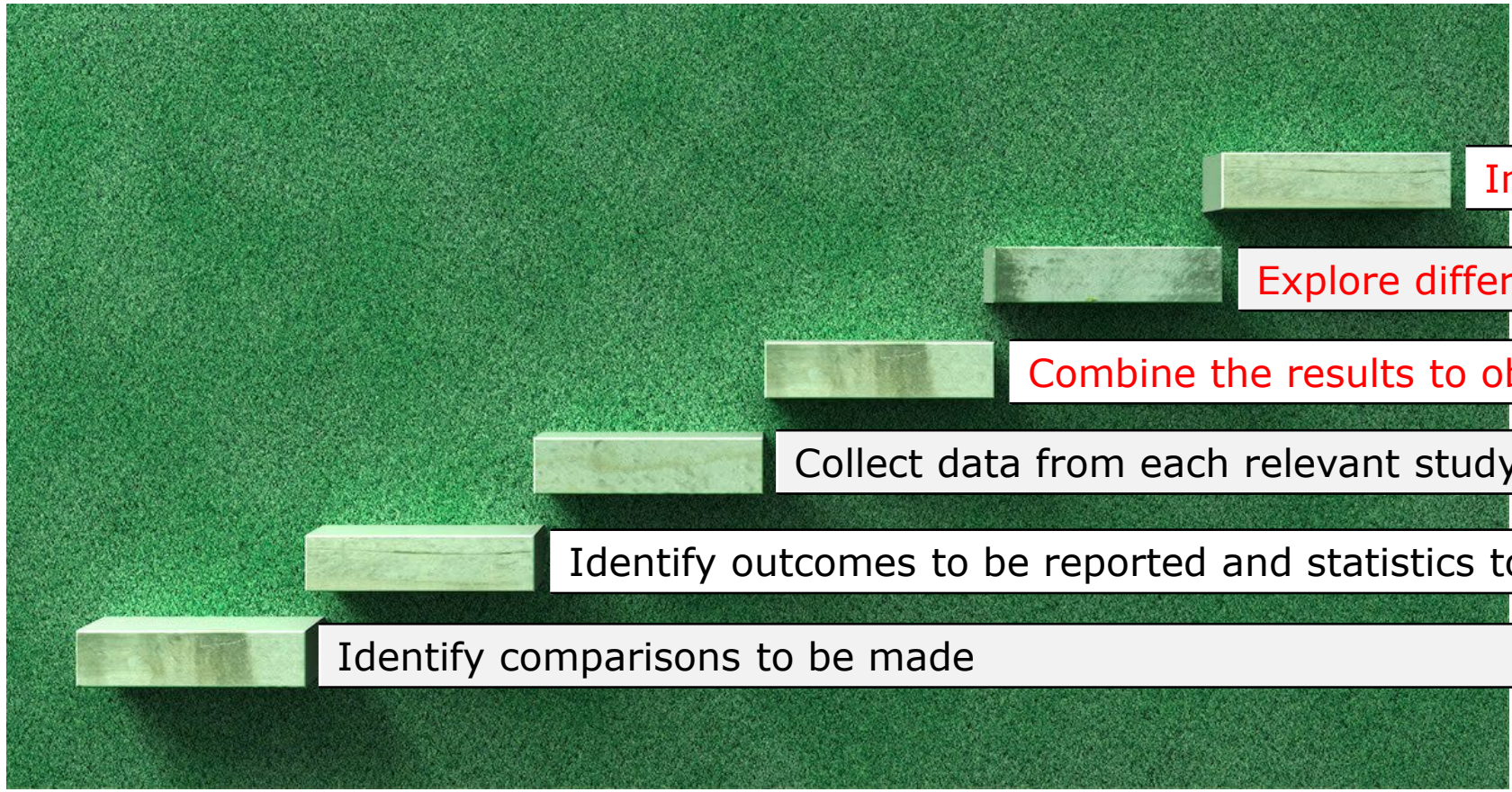
The Second in the Series

September 25, 2022

Interpreting Results of a Meta-Analysis

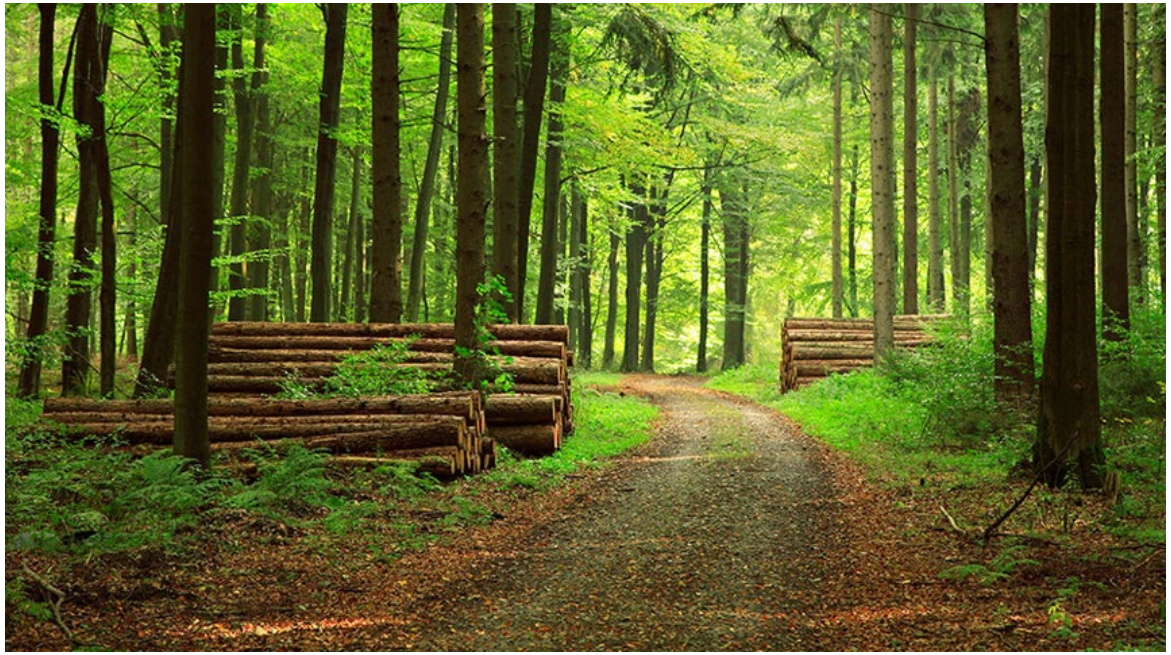
George Wells

Steps in a Meta-Analysis



Presentation of Results – A Forest Plot

A forest plot is a graphical display of estimated results from a number of scientific studies addressing the same question, along with the overall results



Cochrane Library

Cochrane Database of Systematic Reviews

Replacing salt with low-sodium salt substitutes (LSSS) for cardiovascular health in adults, children and pregnant women (Review)

Brand A, Visser ME, Schoonees A, Naude CE

Brand A, Visser ME, Schoonees A, Naude CE.
Replacing salt with low-sodium salt substitutes (LSSS) for cardiovascular health in adults, children and pregnant women.
Cochrane Database of Systematic Reviews 2022, Issue 8. Art. No.: CD015207.
DOI: 10.1002/14651858.CD015207.

www.cochranelibrary.com

WILEY

Objectives

To assess the effects and safety of replacing salt with low-sodium salt substitutes (LSSS) to reduce sodium intake on cardiovascular health in adults, pregnant women and children.

PICO

Types of study designs

- RCTs (participants randomized) [16]
- Cross-over RCTs (data available for 1st phase) [1]
- Cluster RCTs (at least 2 clusters per group) [10]
- Prospective cohort studies [0]

Outcome – Change in Diastolic Blood Pressure

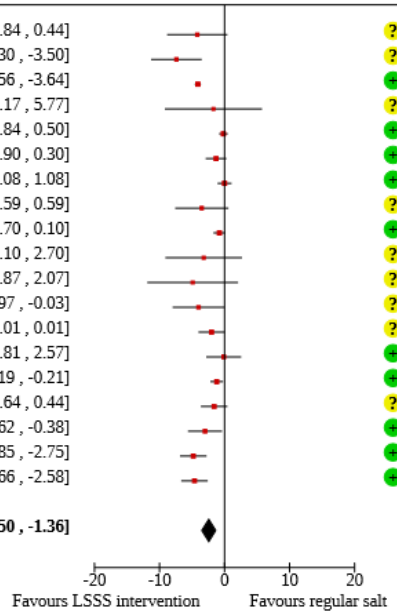
Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

Analysis 1.1. Comparison 1: Low-sodium salt substitutes versus regular salt or no active intervention in adults, Outcome 1: Change in DBP (mmHg)

Study or Subgroup	MD	SE	LSSS intervention Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Allaert 2013 (1)	-4.2	2.36614	21	19	3.2%	-4.20 [-8.84 , 0.44]
Allaert 2017 (2)	-7.4	1.987451	22	19	3.9%	-7.40 [-11.30 , -3.50]
Geleijnse 1994 (3)	-4.1	0.236746	48	49	7.8%	-4.10 [-4.56 , -3.64]
Gilleran 1996 (4)	-1.7	3.8113	11	8	1.6%	-1.70 [-9.17 , 5.77]
Hu 2018 (5)	-0.17	0.341016	243	259	7.7%	-0.17 [-0.84 , 0.50]
Li 2014 (6)	-1.3	0.813878	198	205	6.7%	-1.30 [-2.90 , 0.30]
Li 2016 (7)	0	0.55077	1293	1272	7.3%	0.00 [-1.08 , 1.08]
Mu 2003 (8)	-3.5	2.088178	88	97	3.7%	-3.50 [-7.59 , 0.59]
Neal 2021 (9)	-0.8	0.459154	7436	7081	7.5%	-0.80 [-1.70 , 0.10]
Omvik 1995 (10)	-3.2	3.0103	19	20	2.3%	-3.20 [-9.10 , 2.70]
Pereira 2005 (11)	-4.9	3.557109	12	10	1.8%	-4.90 [-11.87 , 2.07]
Sarkkinen 2011 (1)	-4	2.028073	22	23	3.8%	-4.00 [-7.97 , -0.03]
Suppa 1988 (12)	-2	1.026733	163	159	6.2%	-2.00 [-4.01 , 0.01]
Toft 2020 (13)	-0.116	1.371969	41	49	5.3%	-0.12 [-2.81 , 2.57]
Yu 2021 (14)	-1.2	0.503822	242	234	7.4%	-1.20 [-2.19 , -0.21]
Zhang 2015 (15)	-1.6	1.04338	279	218	6.1%	-1.60 [-3.64 , 0.44]
Zhao 2014 (14)	-3	1.336061	141	141	5.4%	-3.00 [-5.62 , -0.38]
Zhou 2009 (16)	-4.8	1.0459	119	129	6.1%	-4.80 [-6.85 , -2.75]
Zhou 2013 (17)	-4.62	1.043047	213	227	6.1%	-4.62 [-6.66 , -2.58]
Total (95% CI)			**10611**	**10219**	**100.0%**	**-2.43 [-3.50 , -1.36]**

Heterogeneity: Tau² = 3.77; Chi² = 154.08, df = 18 (P < 0.00001); I² = 88%
Test for overall effect: Z = 4.45 (P < 0.00001)
Test for subgroup differences: Not applicable



11 RCTs

8 Cluster RCTs (adjusted for clustering)

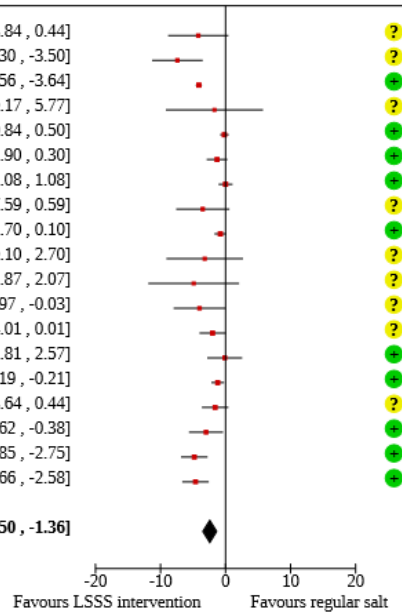
Analysis 1.1. Comparison 1: Low-sodium salt substitutes versus regular salt or no active intervention in adults, Outcome 1: Change in DBP (mmHg)

Study or Subgroup	MD	SE	LSSS intervention Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Allaert 2013 (1)	-4.2	2.36614	21	19	3.2%	-4.20 [-8.84 , 0.44]
Allaert 2017 (2)	-7.4	1.987451	22	19	3.9%	-7.40 [-11.30 , -3.50]
Geleijnse 1994 (3)	-4.1	0.236746	48	49	7.8%	-4.10 [-4.56 , -3.64]
Gilleran 1996 (4)	-1.7	3.8113	11	8	1.6%	-1.70 [-9.17 , 5.77]
Hu 2018 (5)	-0.17	0.341016	243	259	7.7%	-0.17 [-0.84 , 0.50]
Li 2014 (6)	-1.3	0.813878	198	205	6.7%	-1.30 [-2.90 , 0.30]
Li 2016 (7)	0	0.55077	1293	1272	7.3%	0.00 [-1.08 , 1.08]
Mu 2003 (8)	-3.5	2.088178	88	97	3.7%	-3.50 [-7.59 , 0.59]
Neal 2021 (9)	-0.8	0.459154	7436	7081	7.5%	-0.80 [-1.70 , 0.10]
Omvik 1995 (10)	-3.2	3.0103	19	20	2.3%	-3.20 [-9.10 , 2.70]
Pereira 2005 (11)	-4.9	3.557109	12	10	1.8%	-4.90 [-11.87 , 2.07]
Sarkkinen 2011 (1)	-4	2.028073	22	23	3.8%	-4.00 [-7.97 , -0.03]
Suppa 1988 (12)	-2	1.026733	163	159	6.2%	-2.00 [-4.01 , 0.01]
Toft 2020 (13)	-0.116	1.371969	41	49	5.3%	-0.12 [-2.81 , 2.57]
Yu 2021 (14)	-1.2	0.503822	242	234	7.4%	-1.20 [-2.19 , -0.21]
Zhang 2015 (15)	-1.6	1.04338	279	218	6.1%	-1.60 [-3.64 , 0.44]
Zhao 2014 (14)	-3	1.336061	141	141	5.4%	-3.00 [-5.62 , -0.38]
Zhou 2009 (16)	-4.8	1.0459	119	129	6.1%	-4.80 [-6.85 , -2.75]
Zhou 2013 (17)	-4.62	1.043047	213	227	6.1%	-4.62 [-6.66 , -2.58]
Total (95% CI)			**10611**	**10219**	**100.0%**	**-2.43 [-3.50 , -1.36]**

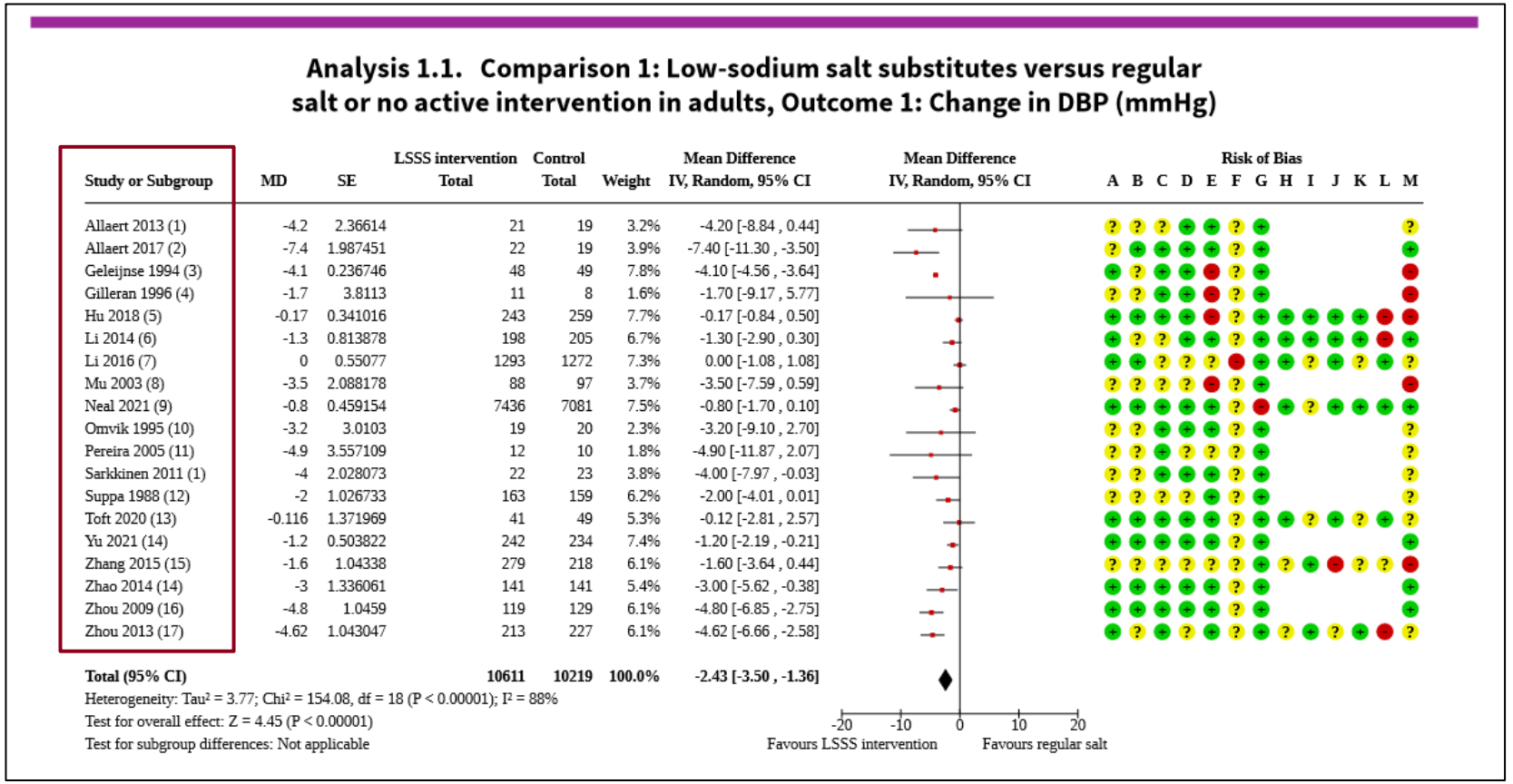
Heterogeneity: Tau² = 3.77; Chi² = 154.08, df = 18 (P < 0.00001); I² = 88%

Test for overall effect: Z = 4.45 (P < 0.00001)

Test for subgroup differences: Not applicable



- Headings at top of the table indicate what the comparison is – LSSS Intervetion and control



- On the left is a list of included studies (often by first author's name, publication year)
- Order of the studies is alphabetical; many prefer by year of study or by treatment effect

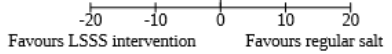
Analysis 1.1. Comparison 1: Low-sodium salt substitutes versus regular salt or no active intervention in adults, Outcome 1: Change in DBP (mmHg)

Study or Subgroup	MD	SE	LSSS intervention Total	Control Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G H I J K L M
Allaert 2013 (1)	-4.2	2.36614	21	19	3.2%	-4.20 [-8.84 , 0.44]		? ? ? + + ? + ?
Allaert 2017 (2)	-7.4	1.987451	22	19	3.9%	-7.40 [-11.30 , -3.50]		? + + + + ? + +
Geleijnse 1994 (3)	-4.1	0.236746	48	49	7.8%	-4.10 [-4.56 , -3.64]		+ ? + + - ? + -
Gilleran 1996 (4)	-1.7	3.8113	11	8	1.6%	-1.70 [-9.17 , 5.77]		? ? + + - ? + -
Hu 2018 (5)	-0.17	0.341016	243	259	7.7%	-0.17 [-0.84 , 0.50]		+ + + + - ? + + + + + - -
Li 2014 (6)	-1.3	0.813878	198	205	6.7%	-1.30 [-2.90 , 0.30]		+ ? ? + + ? + + + + + - +
Li 2016 (7)	0	0.55077	1293	1272	7.3%	0.00 [-1.08 , 1.08]		+ + ? ? ? - + + ? + ? + ?
Mu 2003 (8)	-3.5	2.088178	88	97	3.7%	-3.50 [-7.59 , 0.59]		? ? ? ? - ? + -
Neal 2021 (9)	-0.8	0.459154	7436	7081	7.5%	-0.80 [-1.70 , 0.10]		+ + + + + ? - + ? + + + +
Omvik 1995 (10)	-3.2	3.0103	19	20	2.3%	-3.20 [-9.10 , 2.70]		? ? + + + ? + ?
Pereira 2005 (11)	-4.9	3.557109	12	10	1.8%	-4.90 [-11.87 , 2.07]		? ? + ? ? ? + ?
Sarkkinen 2011 (1)	-4	2.028073	22	23	3.8%	-4.00 [-7.97 , -0.03]		? ? + + + ? + ?
Suppa 1988 (12)	-2	1.026733	163	159	6.2%	-2.00 [-4.01 , 0.01]		? ? ? ? + ? + ?
Toft 2020 (13)	-0.116	1.371969	41	49	5.3%	-0.12 [-2.81 , 2.57]		+ + + + + ? + + ? + + + ?
Yu 2021 (14)	-1.2	0.503822	242	234	7.4%	-1.20 [-2.19 , -0.21]		+ + + + + ? + +
Zhang 2015 (15)	-1.6	1.04338	279	218	6.1%	-1.60 [-3.64 , 0.44]		? ? ? ? ? ? + ? + - ? ? -
Zhao 2014 (14)	-3	1.336061	141	141	5.4%	-3.00 [-5.62 , -0.38]		+ + + + + ? + +
Zhou 2009 (16)	-4.8	1.0459	119	129	6.1%	-4.80 [-6.85 , -2.75]		+ + + + + ? + +
Zhou 2013 (17)	-4.62	1.043047	213	227	6.1%	-4.62 [-6.66 , -2.58]		+ ? + ? + ? + ? + ? ? + - ?
Total (95% CI)			**10611**	**10219**	**100.0%**	**-2.43 [-3.50 , -1.36]**		

Heterogeneity: Tau² = 3.77; Chi² = 154.08, df = 18 (P < 0.00001); I² = 88%

Test for overall effect: Z = 4.45 (P < 0.00001)

Test for subgroup differences: Not applicable



- Individual data are presented for each study – in this case, mean change from baseline and the standard error

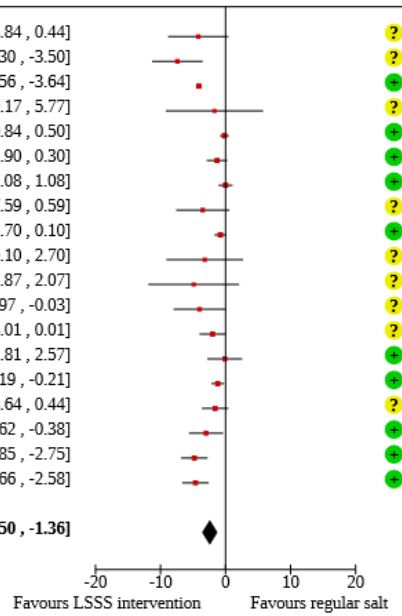
Analysis 1.1. Comparison 1: Low-sodium salt substitutes versus regular salt or no active intervention in adults, Outcome 1: Change in DBP (mmHg)

Study or Subgroup	MD	SE	LSSS intervention Total	Control Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G H I J K L M
Allaert 2013 (1)	-4.2	2.36614	21	19	3.2%	-4.20 [-8.84 , 0.44]	? ? ? + + ? + ?
Allaert 2017 (2)	-7.4	1.987451	22	19	3.9%	-7.40 [-11.30 , -3.50]	? + + + + ? + +
Geleijnse 1994 (3)	-4.1	0.236746	48	49	7.8%	-4.10 [-4.56 , -3.64]	+ ? + + - ? + -
Gilleran 1996 (4)	-1.7	3.8113	11	8	1.6%	-1.70 [-9.17 , 5.77]	? ? + + - ? + -
Hu 2018 (5)	-0.17	0.341016	243	259	7.7%	-0.17 [-0.84 , 0.50]	+ + + + - ? + + + + + - -
Li 2014 (6)	-1.3	0.813878	198	205	6.7%	-1.30 [-2.90 , 0.30]	+ ? ? + + ? + + + + + - +
Li 2016 (7)	0	0.55077	1293	1272	7.3%	0.00 [-1.08 , 1.08]	+ + ? ? ? - + + ? + ? + ?
Mu 2003 (8)	-3.5	2.088178	88	97	3.7%	-3.50 [-7.59 , 0.59]	? ? ? ? - ? + -
Neal 2021 (9)	-0.8	0.459154	7436	7081	7.5%	-0.80 [-1.70 , 0.10]	+ + + + + ? - + ? + + + +
Omvik 1995 (10)	-3.2	3.0103	19	20	2.3%	-3.20 [-9.10 , 2.70]	? ? + + + ? + ?
Pereira 2005 (11)	-4.9	3.557109	12	10	1.8%	-4.90 [-11.87 , 2.07]	? ? + ? ? ? + ?
Sarkkinen 2011 (1)	-4	2.028073	22	23	3.8%	-4.00 [-7.97 , -0.03]	? ? + + + ? + ?
Suppa 1988 (12)	-2	1.026733	163	159	6.2%	-2.00 [-4.01 , 0.01]	? ? ? ? + ? + ?
Toft 2020 (13)	-0.116	1.371969	41	49	5.3%	-0.12 [-2.81 , 2.57]	+ + + + + ? + + ? + ? + ?
Yu 2021 (14)	-1.2	0.503822	242	234	7.4%	-1.20 [-2.19 , -0.21]	+ + + + + ? + +
Zhang 2015 (15)	-1.6	1.04338	279	218	6.1%	-1.60 [-3.64 , 0.44]	? ? ? ? ? ? + ? + - ? ? -
Zhao 2014 (14)	-3	1.336061	141	141	5.4%	-3.00 [-5.62 , -0.38]	+ + + + + ? + +
Zhou 2009 (16)	-4.8	1.0459	119	129	6.1%	-4.80 [-6.85 , -2.75]	+ + + + + ? + +
Zhou 2013 (17)	-4.62	1.043047	213	227	6.1%	-4.62 [-6.66 , -2.58]	+ ? + ? + ? + ? + ? + - ?
Total (95% CI)			**10611**	**10219**	**100.0%**	**-2.43 [-3.50 , -1.36]**	

Heterogeneity: Tau² = 3.77; Chi² = 154.08, df = 18 (P < 0.00001); I² = 88%

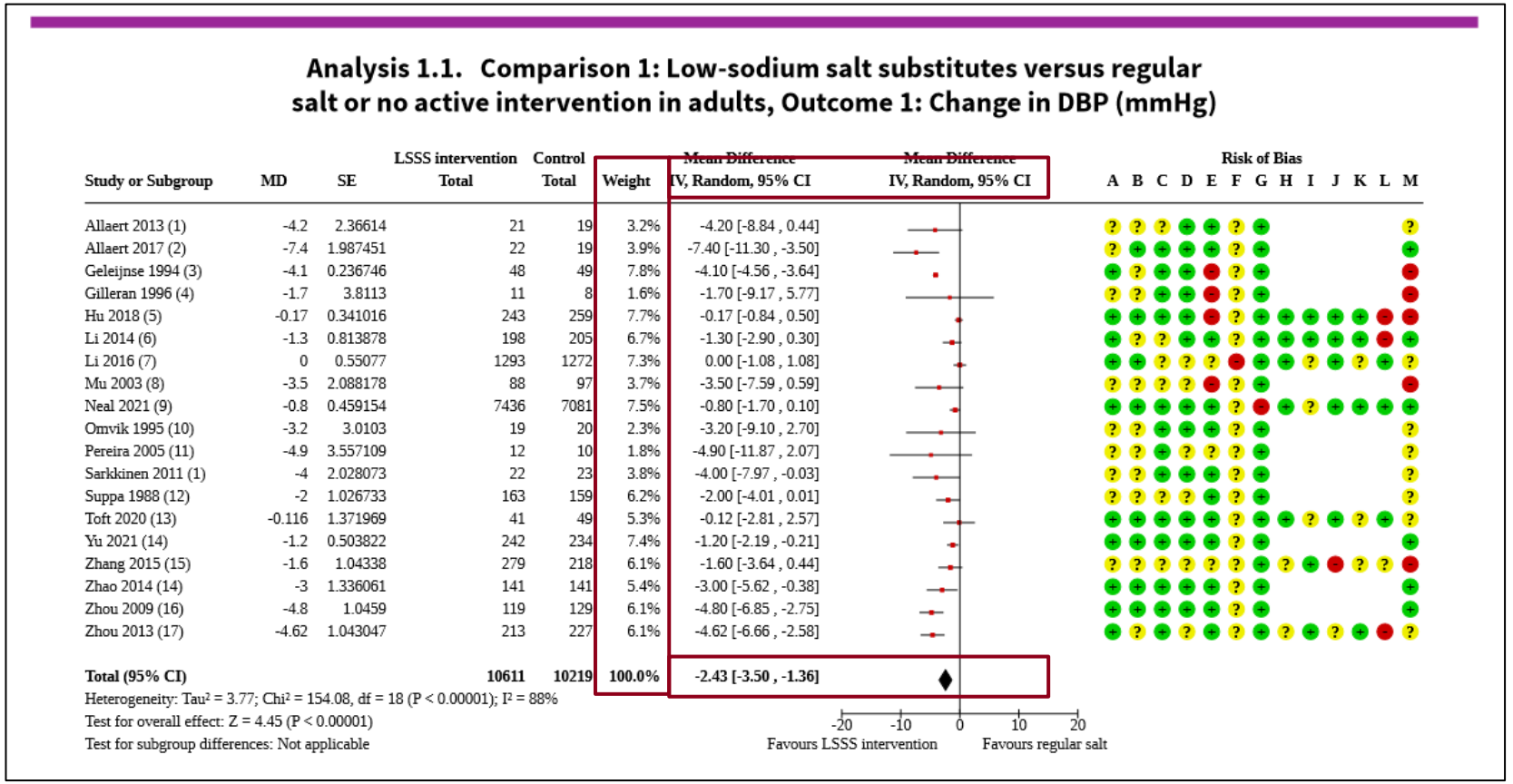
Test for overall effect: Z = 4.45 (P < 0.00001)

Test for subgroup differences: Not applicable



- The simple total of the data for all the included studies is given – the total number of events and participants in the intervention groups and control groups

Analysis 1.1. Comparison 1: Low-sodium salt substitutes versus regular salt or no active intervention in adults, Outcome 1: Change in DBP (mmHg)



- The weight assigned to each study in the meta-analysis is given - sums to 100%
- The weights depend on the chosen model – fixed vs random effects model

Fixed Effects vs Random Effects Model

- RE meta-analyses are:
  - Almost identical to FE when there is no heterogeneity
  - Similar to FE but with wider confidence intervals when there is heterogeneity
  - Different from FE meta-analyses when results are related to study size (RE model gives relatively more weight to smaller studies)

Fixed Effects

$$\text{weight} = \frac{1}{\text{variance of estimate}} = \frac{1}{SE^2}$$

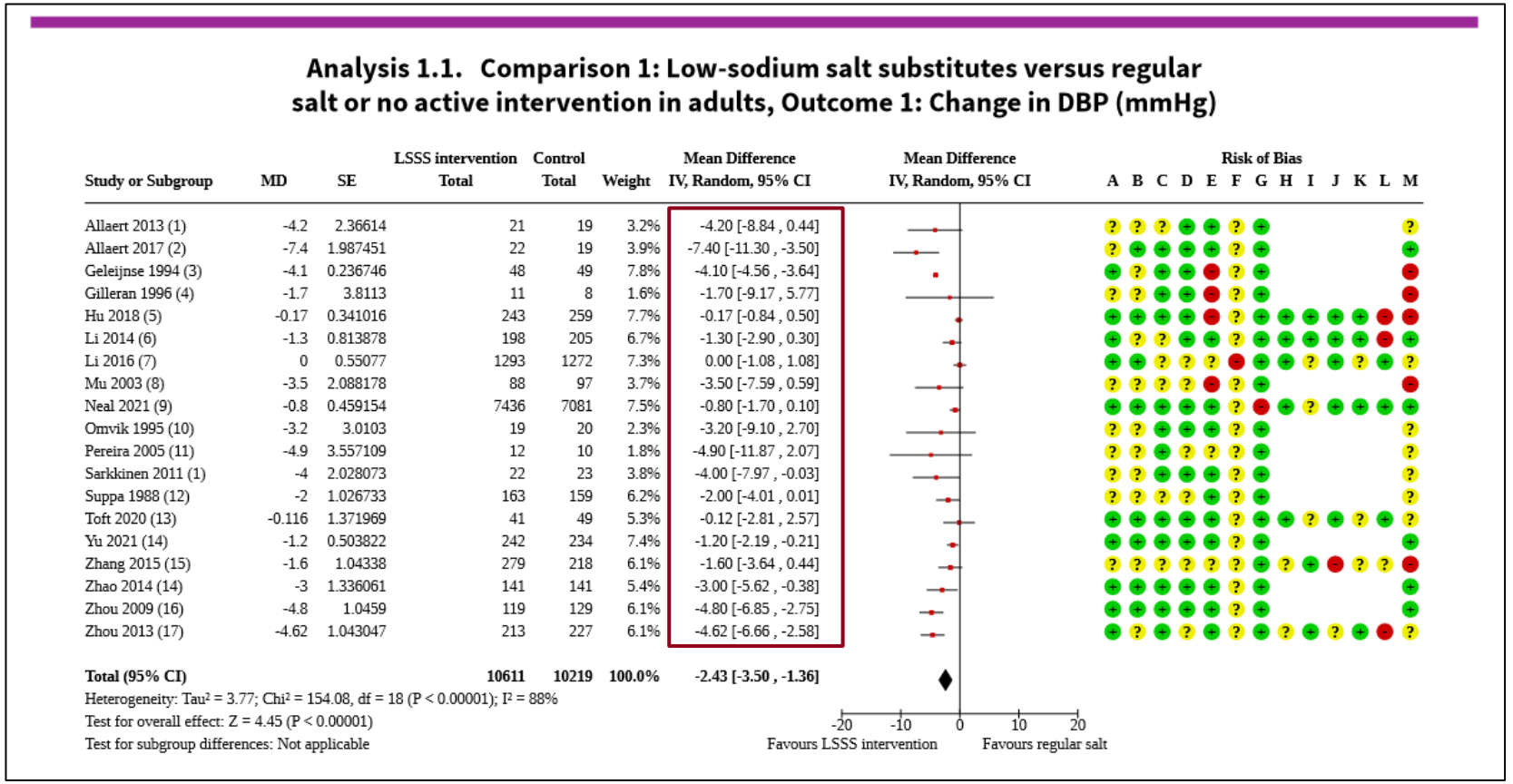
Random Effects

$$\text{weight} = \frac{1}{\text{variance within} + \text{variance between}} = \frac{1}{SE^2 + tau^2}$$

$$\text{pooled estimate} = \frac{\text{sum of (estimate} \times \text{weight)}}{\text{sum of weights}}$$

Choice FE vs RE

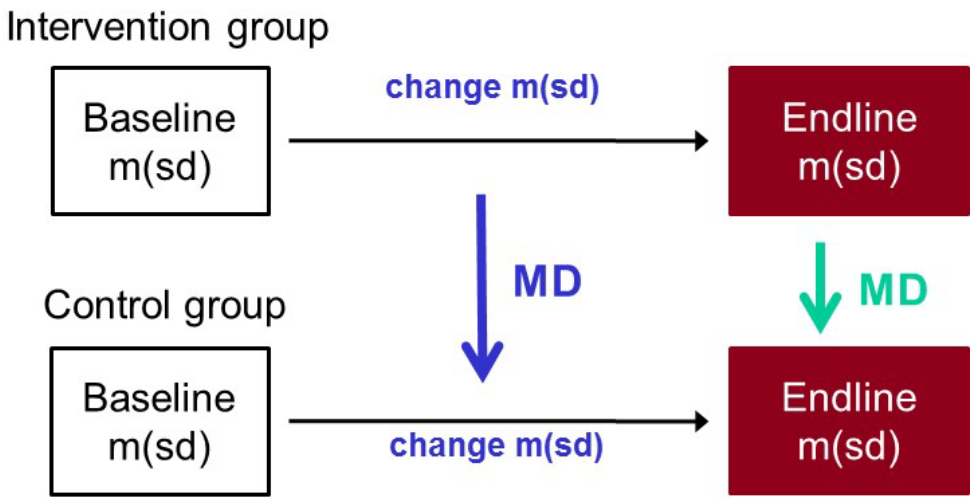
- FE may be unrealistic – ignores heterogeneity
- RE allows for heterogeneity - estimate of distribution of studies may not be accurate if biases present, few studies or few events



- The individual result for each study is given (here, MD with 95% confidence interval)

Effect Measures for Comparing Means: Mean Difference (others Standardized Mean Difference)

Mean Difference (MD)	$MD = (Mean\ in\ Intervention\ Group) - (Mean\ in\ Control\ Group)$	Expresses the difference of the means • Should be presented with a confidence interval • MD=0 indicates the mean of the outcome is the same in the 2 groups

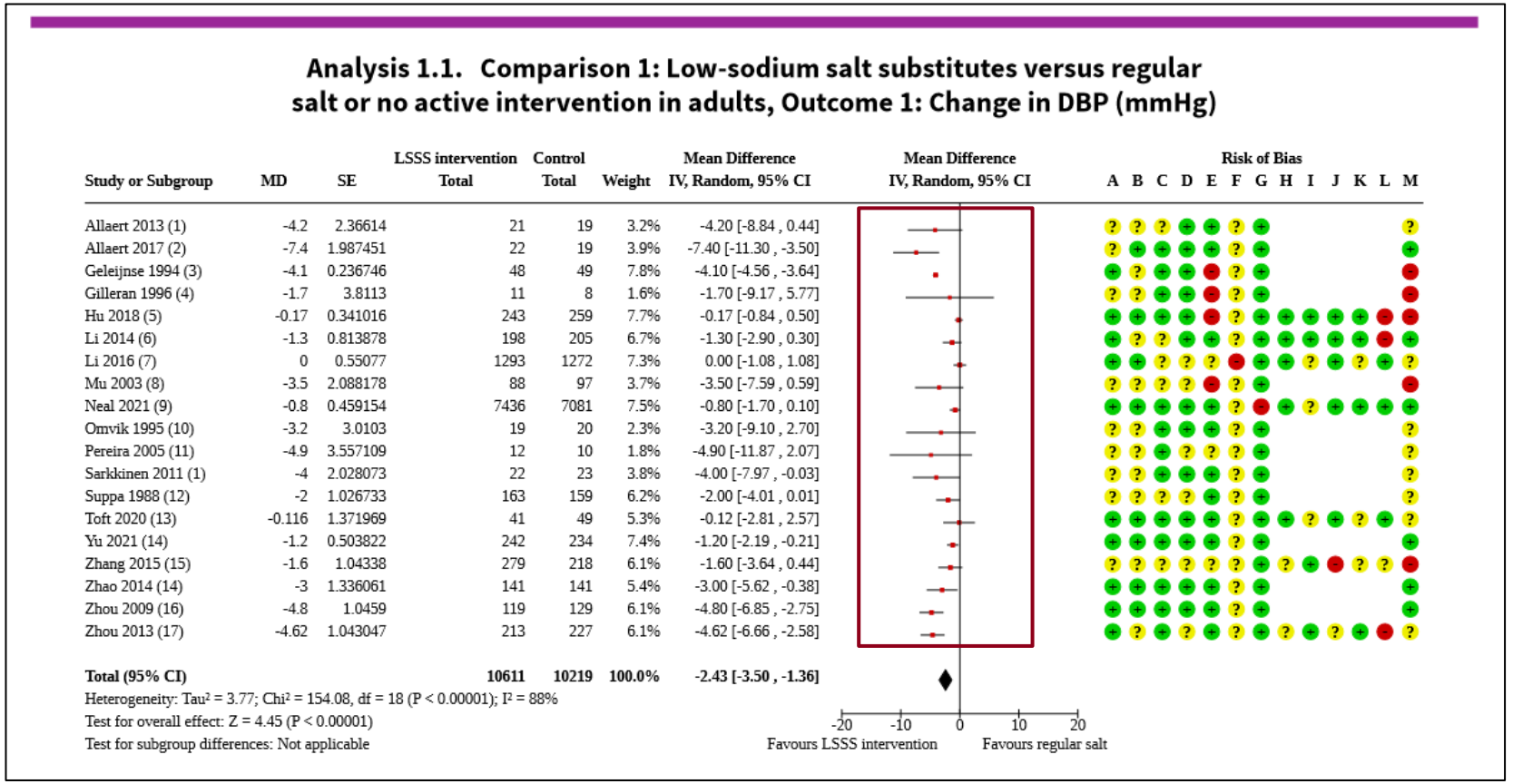


Point and Confidence Interval Estimators of Effect Measures

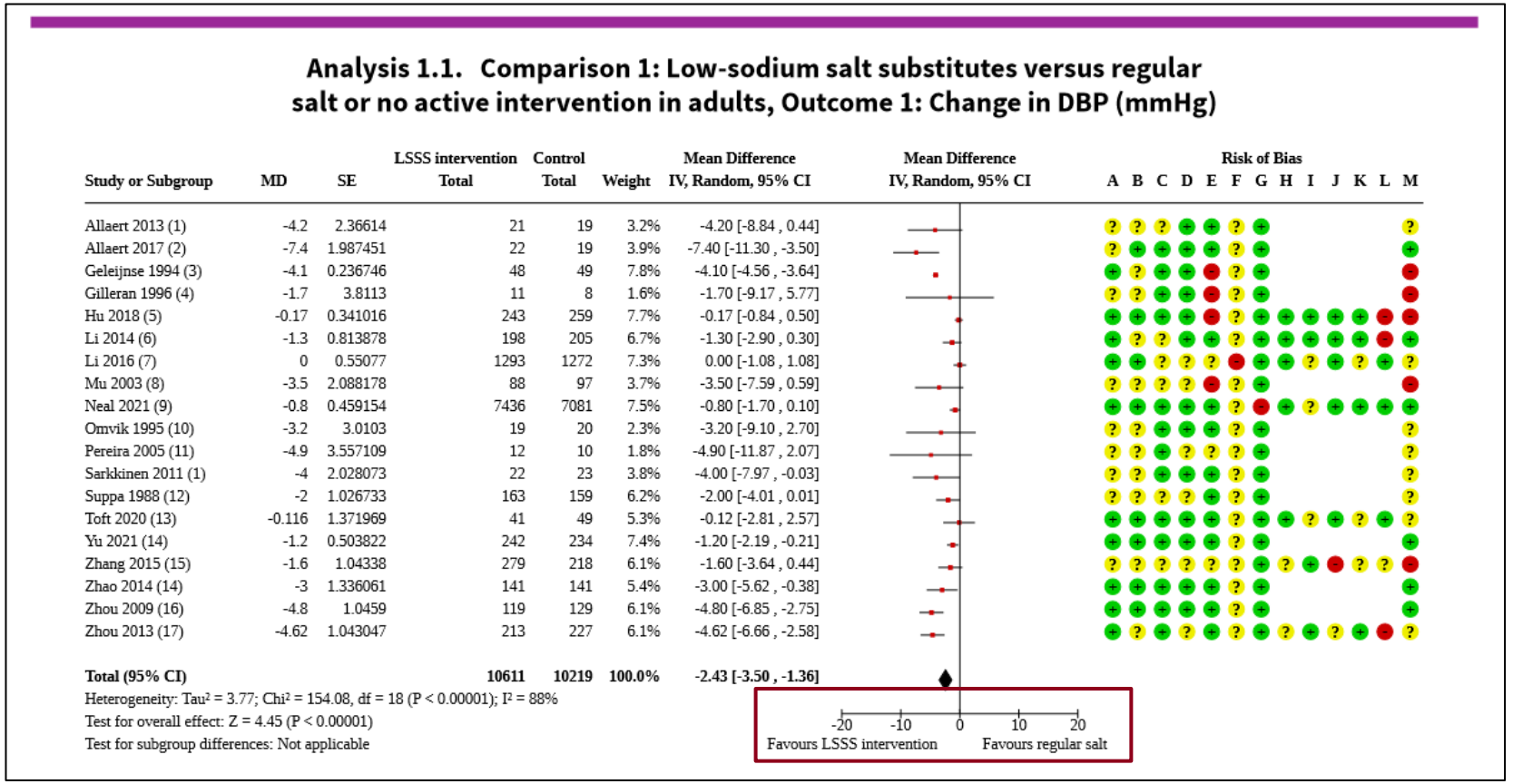
- 95% Confidence Interval (CI): 19 times out of 20 the 'true' value of the effect measure will be the specified range

Point estimator of effect measure	±	Percentile of distribution of point estimator	X	Standard error of point estimator

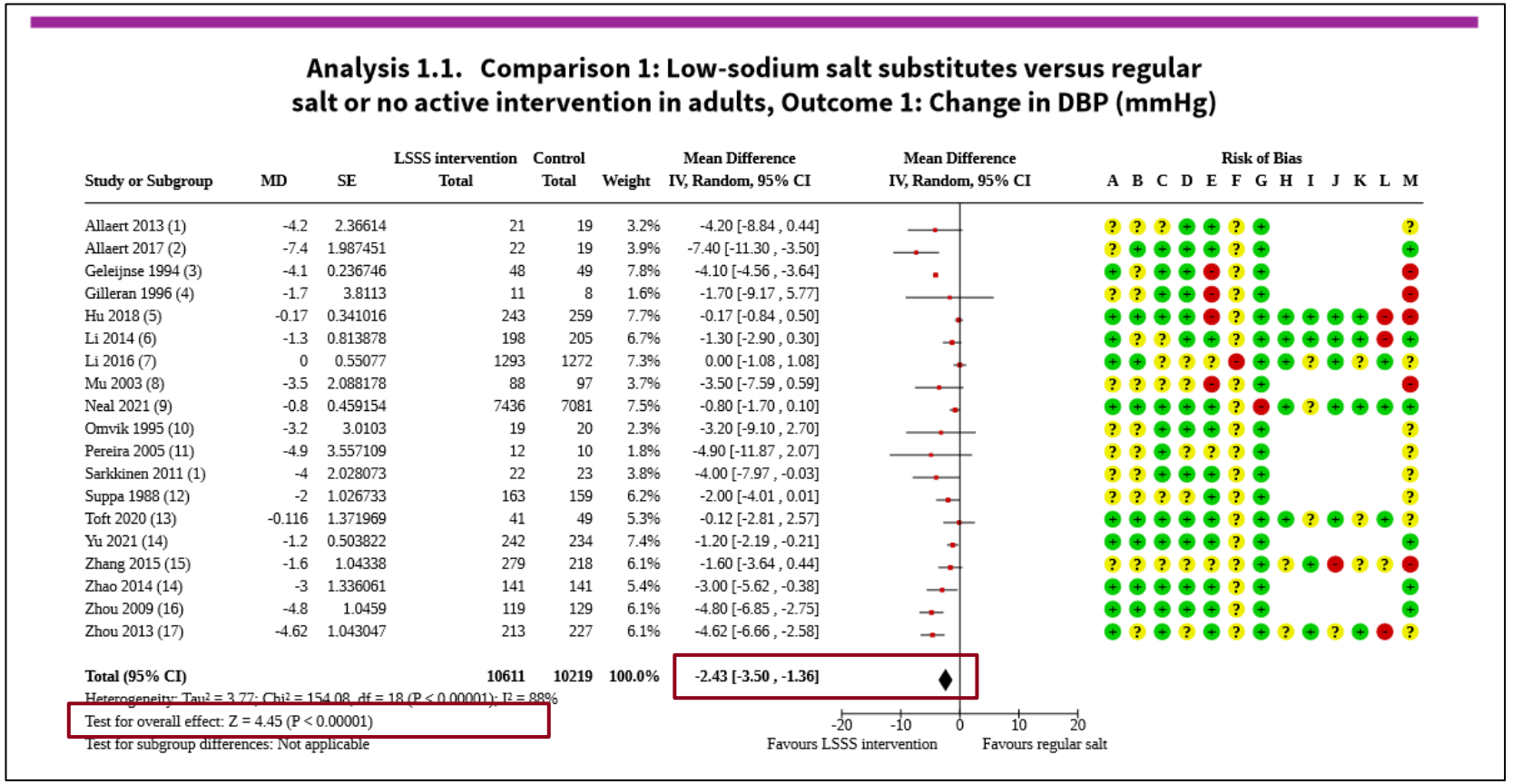
- Important to present estimates with a CI
  - Point estimate is the best guess of the effect measure
  - CI expresses uncertainty – range of values that can reasonably include the true effect
  - A narrow confidence interval means we have a precise estimate of the effect



- Individual study results are presented graphically
  - Coloured square represents the effect estimate with the size of the square proportional to the weight given to the study
  - Horizontal line represenst the confidence interval (in this case 95% CI)
- Vertical line indicates the line of no effect (in this case for a MD=0)
- If 95% CI crosses vertical line it means result for that study is not statistically significant

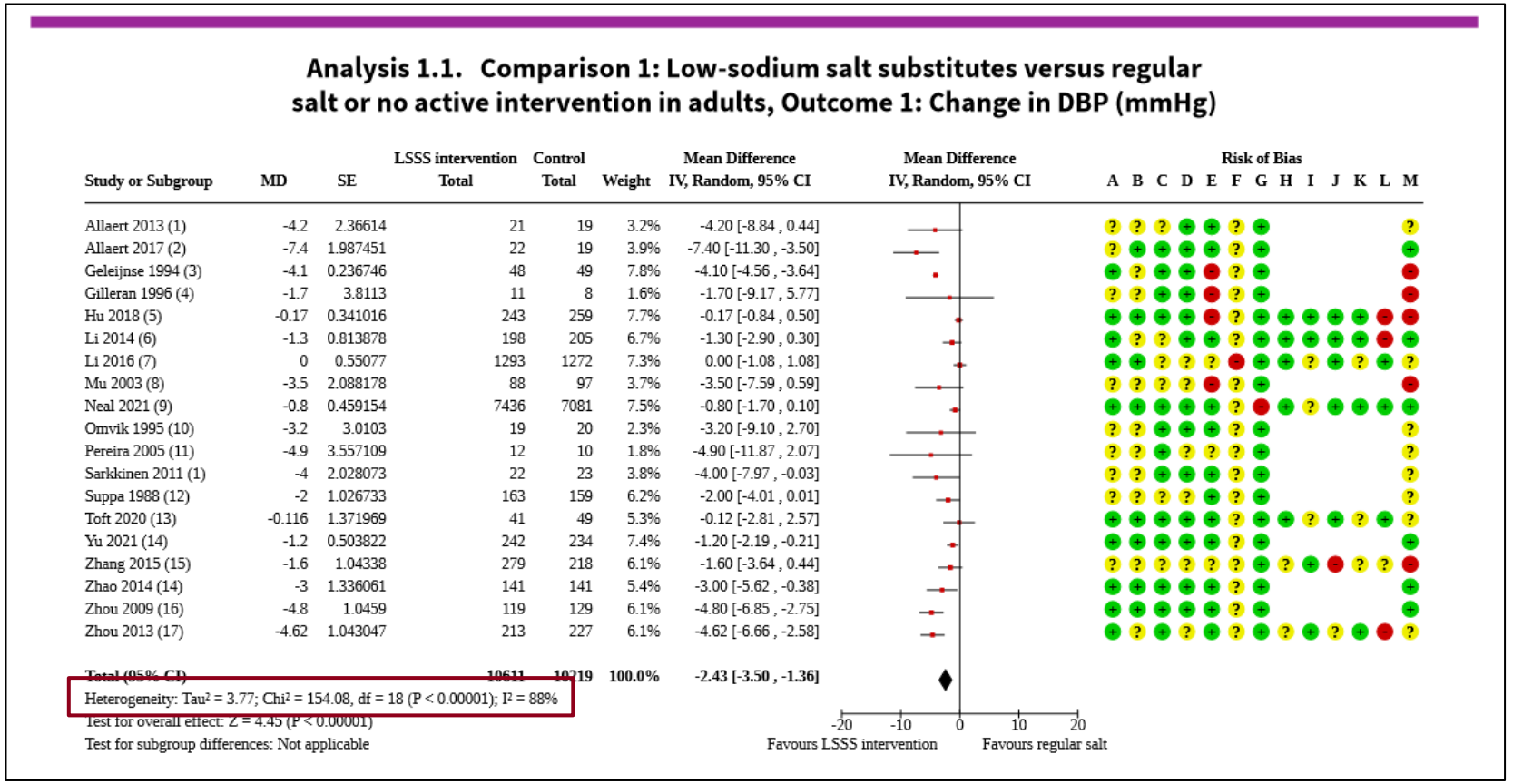


- The scale - for absolute effects (such as MD), scale is symmetrical, showing positive and negative values around 0 as the point of no effect.
- The scale labels – indicates the side of the plot that favours the intervention. This will depend on the outcome; the right side of the scale always indicates a higher score for the intervention



- The pooled effect estimate for all the studies combined is presented, both in graphically and nunerically
  - Graphically result is presented as a black diamond - the top and bottom points of the diamond correspond to the overall effect estimate, and the width of the diamond represents the CI
  - Numerically the pooled esimate and 95% CI is provided; if the 95% CI crosses vertical line it means result for that study is not statistically significant (at least with a p-value <0.05)
- Test for the overall effect is provided with the exact p-value

Analysis 1.1. Comparison 1: Low-sodium salt substitutes versus regular salt or no active intervention in adults, Outcome 1: Change in DBP (mmHg)



Study or Subgroup	MD	SE	LSSS intervention Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Allaert 2013 (1)	-4.2	2.36614	21	19	3.2%	-4.20 [-8.84 , 0.44]
Allaert 2017 (2)	-7.4	1.987451	22	19	3.9%	-7.40 [-11.30 , -3.50]
Geleijnse 1994 (3)	-4.1	0.236746	48	49	7.8%	-4.10 [-4.56 , -3.64]
Gilleran 1996 (4)	-1.7	3.8113	11	8	1.6%	-1.70 [-9.17 , 5.77]
Hu 2018 (5)	-0.17	0.341016	243	259	7.7%	-0.17 [-0.84 , 0.50]
Li 2014 (6)	-1.3	0.813878	198	205	6.7%	-1.30 [-2.90 , 0.30]
Li 2016 (7)	0	0.55077	1293	1272	7.3%	0.00 [-1.08 , 1.08]
Mu 2003 (8)	-3.5	2.088178	88	97	3.7%	-3.50 [-7.59 , 0.59]
Neal 2021 (9)	-0.8	0.459154	7436	7081	7.5%	-0.80 [-1.70 , 0.10]
Omvik 1995 (10)	-3.2	3.0103	19	20	2.3%	-3.20 [-9.10 , 2.70]
Pereira 2005 (11)	-4.9	3.557109	12	10	1.8%	-4.90 [-11.87 , 2.07]
Sarkkinen 2011 (1)	-4	2.028073	22	23	3.8%	-4.00 [-7.97 , -0.03]
Suppa 1988 (12)	-2	1.026733	163	159	6.2%	-2.00 [-4.01 , 0.01]
Toft 2020 (13)	-0.116	1.371969	41	49	5.3%	-0.12 [-2.81 , 2.57]
Yu 2021 (14)	-1.2	0.503822	242	234	7.4%	-1.20 [-2.19 , -0.21]
Zhang 2015 (15)	-1.6	1.04338	279	218	6.1%	-1.60 [-3.64 , 0.44]
Zhao 2014 (14)	-3	1.336061	141	141	5.4%	-3.00 [-5.62 , -0.38]
Zhou 2009 (16)	-4.8	1.0459	119	129	6.1%	-4.80 [-6.85 , -2.75]
Zhou 2013 (17)	-4.62	1.043047	213	227	6.1%	-4.62 [-6.66 , -2.58]
Total (95% CI)			**10611**	**10219**	**100.0%**	**-2.43 [-3.50 , -1.36]**

Heterogeneity: $Tau^2 = 3.77$; $Chi^2 = 154.08$, df = 18 ($P < 0.00001$); $I^2 = 88\%$

Test for overall effect: $Z = 4.45$ ($P < 0.00001$)

Test for subgroup differences: Not applicable

Mean Difference IV, Random, 95% CI

-20 -10 0 10 20

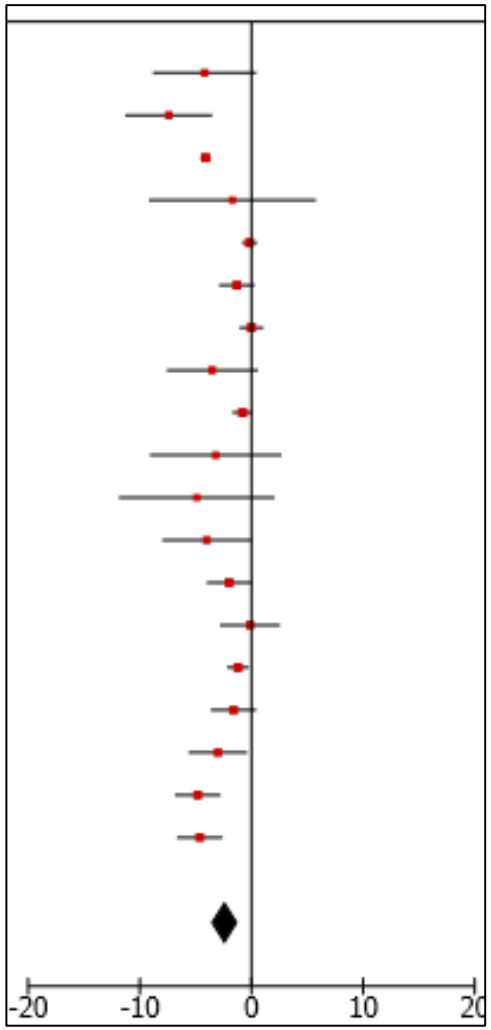
Favours LSSS intervention Favours regular salt

Risk of Bias

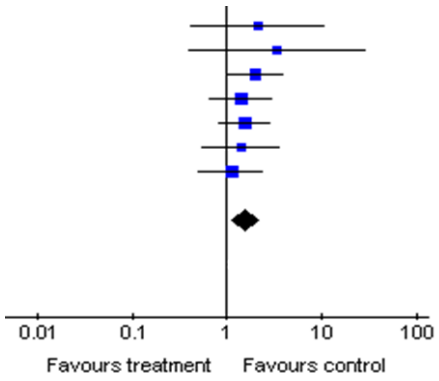
A B C D E F G H I J K L M

- Heterogeneity – variations across the studies
  - Identifying heterogeneity (visual inspection of forest plots, chi-square test (Q test), I^2 statistic)
  - Types of heterogeneity
  - Exploring heterogeneity

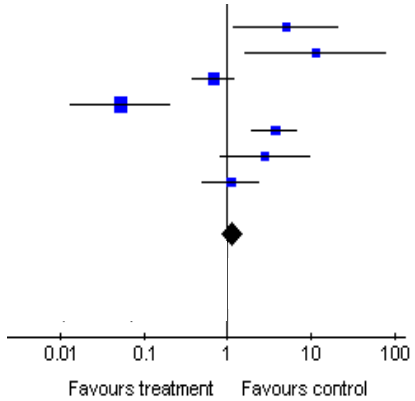
1. Visual Inspection of the Forest Plot



Consistent



Inconsistent



- Look for overlap in the CI not just differences in effect estimate
- Can have consistent studies whose results are slightly on either side of the line
- Can have inconsistent studies even though results on same side of the line

2. Chi-square test (Q test)

Heterogeneity: $Tau^2 = 3.77$; $Chi^2 = 154.08$, $df = 18$ ($P < 0.00001$); $I^2 = 88\%$
Test for overall effect: $Z = 4.45$ ($P < 0.00001$)
Test for subgroup differences: Not applicable

- Test of the null hypothesis of homogeneity
- A small p-value means homogeneity rejected (studies are too different to combine)
- Test not reliable
  - When few studies, then test is not sensitive enough and can wrongly conclude that there is no heterogeneity (low power)
  - When many studies, then test may be too sensitive and can detect that there is heterogeneity but it might detect heterogeneity that is not very important (may detect clinically unimportant differences)
- Only yes/no test for heterogeneity

3. I^2 statistic to quantify heterogeneity

Heterogeneity: $Tau^2 = 3.77$; $Chi^2 = 154.08$, df = 18 ($P < 0.00001$); $I^2 = 88\%$
Test for overall effect: $Z = 4.45$ ($P < 0.00001$)
Test for subgroup differences: Not applicable

- I^2 statistic describes percentage of observed variability in effect estimates due to heterogeneity rather than random chance (0% to 100%)
  - Low values indicate no or little heterogeneity
  - High values indicate a lot of heterogeneity
- I^2 statistic is more informative than a simple yes/no test for heterogeneity
- No universal cut-off points for interpretation, roughly speaking
  - Below 30-40% might represent low or unimportant heterogeneity
  - 30-60% might represent moderate heterogeneity
  - 50-90% might represent substantial heterogeneity
  - 75-100% might represent quite high heterogeneity

Types of Heterogeneity

Type	Description
Clinical	Across studies • Participants may vary by type or severity of condition, demographics, location • Interventions may vary in implementation (e.g., dose or intensity), components included, experience of practitioners, nature of control (placebo, none, standard care) • Outcomes may vary by measurement methods, event definition, cut-points, follow-up duration
Methodological	• Studies may vary in how they are designed and conducted • Design (e.g., randomized vs non-randomied, crossover vs parallel, individual vs cluster) • Conduct (e.g., risk of bias), approach to analysis (e.g., statistics used, imputation of missing data)
Statistical	• True differences in the underlying effect that studies are trying to measure that can be caused by clinical and methodological variation • Results observed are more different across studies than expected to occur by chance (there will always be random variation of results across studies)

Exploring Heterogeneity – Subgroups and Meta-Regression

- Two methods available to assess effect modification - what factors appear to modify the effect
  - Subgroup analysis - group studies by pre-specified factors, look for differences in results and heterogeneity
  - Meta-regression - examine interaction with variables

Exploring Heterogeneity - Sensitivity Analysis

- Robustness of results
  - Sensitivity analysis is done by repeating the meta-analysis using alternative options to assess consistency/robustness of the results
  - Can evaluate alternative options during the review (e.g., inclusion of studies)

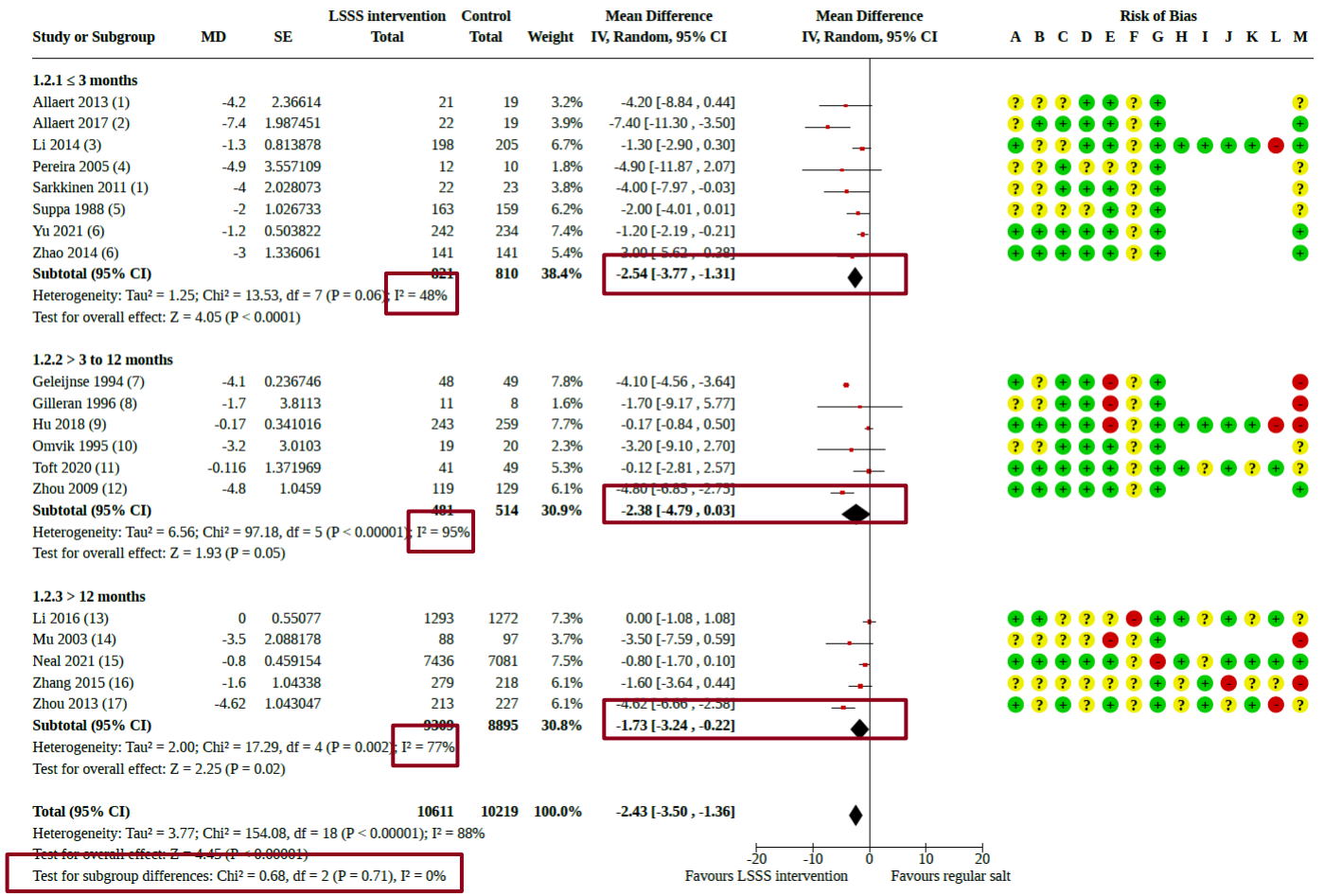
Subgroup Analysis - Interpreting

- Consider heterogeneity within subgroups
  - Is heterogeneity within each subgroup different from overall heterogeneity indicating studies more consistent within than between subgroups
- Are the subgroups really different
  - Must directly compare subgroups to see whether findings are consistent with the possibility that the true underlying effects in each subgroup are the same
  - Statistical tests for subgroup difference
- Can be more confident if
  - Effect clinically plausible and supported by evidence from outside the review

Sensitivity Analysis - Interpreting

- Consider heterogeneity
  - Consistency of the results in the sensitivity analysis

Analysis 1.2. Comparison 1: Low-sodium salt substitutes versus regular salt or no active intervention in adults, Outcome 2: Change in DBP (mmHg); subgroup study duration



Test for difference in subgroups

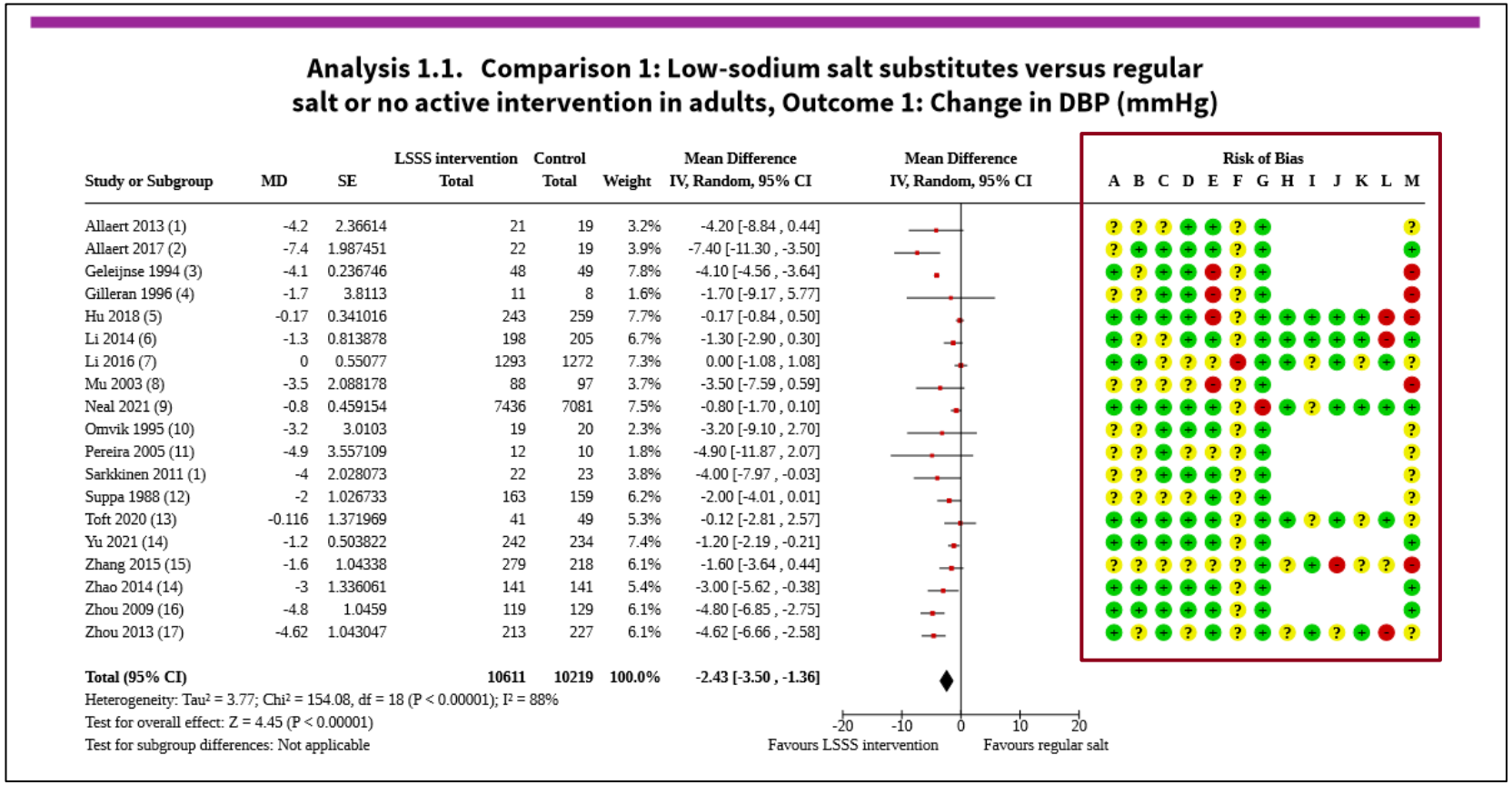
Subgroup and Sensitivity Analysis

Subgroup (factor)	Subgroups MD [95% CI] (I^2)				P-value
Overall	**-2.43 [-3.50 , -1.36] (88%)**				
Study duration	≤3 months -2.54 [-3.77 , -1.31] (48%)	> to 12 months -2.38 [-4.79 , 0.03] (95%)	>1.12 months -1.73 [-3.24 , -0.22] (77%)		P = 0.71
Age	≥ 65 years -3.16 [-5.67 , -0.64] (95%)	< 65 years -2.36 [-3.44 , -1.28] (67%)	Unknown -0.55 [-2.05 , 0.94] (46%)		P = 0.09
Gender	Mixed -2.69 [-3.85 , -1.54] (88%)	Unknown -0.55 [-2.05 , 0.94] (46%)			P=0.03
Ethnicity	Asian -1.72 [-2.64 , -0.80] (77%)	Conducted in Europe (ethnicity unspecified) -3.28 [-4.76 , -1.79] (54%)	Mixed -4.90 [-11.87 , 2.07] (NA)		P = 0.16
BMI	Normal (18.5 to 24.9 kg/m2 for adult Europids, 18.5 to 22.9 kg/m2 for adult Asians) -3.50 [-7.59 , 0.59] (NA)	Overweight (25 to 29.9 kg/m2 for adult Europids, 23 to 24.9 kg/m2 for adult Asians) -2.58 [-4.07 , -1.09] (88%)	Obese (≥ 30 kg/m2 for adult Europids, ≥ 25 kg/m2 for adult Asians) -2.75 [-6.60 , 1.10] (89%)	Unknown -1.88 [-3.41 , -0.35] (68%)	P = 0.85

Subgroup and Sensitivity Analysis

Subgroup (factor)	Subgroups MD [95% CI] (I^2)				P-value
Blood pressure status	Participants with hypertension -2.80 [-4.22 , -1.37] (84%)	Participants with normal blood pressure -2.87 [-5.93 , 0.20] (88%)	Unknown -0.55 [-2.05 , 0.94] (46%)	Mixed -2.07 [-4.09 , -0.05] (82%)	P = 0.17
LSSS implementation	Discretionary only -2.11 [-3.00 , -1.23] (72%)	Non-discretionary only -0.12 [-2.81 , 2.57] (NA)	Discretionary and non-discretionary -4.10 [-4.56 , -3.64] (0%)		P < 0.0001
Type of LSSS	≥ 30% KCl -2.35 [-3.86 , -0.84] (90%)	< 30% KCl -1.72 [-3.01 , -0.43] (73%)	Non-potassium containing LSSS -6.06 [-9.15 , -2.96] (7%)		P = 0.0001
Baseline sodium excretion (mmol/24-h)	High baseline 24-h sodium excretion (≥ 172 mmol Na/24-h, 3.95 g Na/24-h or 9.88 g NaCl/24-h) -2.41 [-4.76 , -0.05] (84%)	Low baseline 24-h sodium excretion (< 172 mmol Na/24-h, 3.95 g Na/24-h or 9.88 g NaCl/24-h) -3.07 [-4.83 , -1.32] (81%)	Unknown/Not 24-h -1.73 [-2.93 , -0.52] (73%)		P = 0.45
Baseline potassium excretion (mmol/24-h)	High baseline 24-h potassium excretion (≥ 59 mmol K/24-h or 2.3 g K/24-h) -3.28 [-4.76 , -1.79] (54%)	Low baseline 24-h potassium excretion (< 59 mmol K/24-h or 2.3 g K/24-h) -1.99 [-3.72 , -0.27] (84%)	Unknown/Not 24-h -1.73 [-2.93 , -0.52] (73%)		P = 0.27
Sensitivity analysis: study quality	k=14 -2.36 [-3.37 , -1.34] (71%)				
Sensitivity analysis: study design	k=12 studies -3.45 [-4.64 , -2.25] (69%)				

Analysis 1.1. Comparison 1: Low-sodium salt substitutes versus regular salt or no active intervention in adults, Outcome 1: Change in DBP (mmHg)



+ Low Risk **? Uncertain Risk** **- High Risk**

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias
(H) Recruitment bias (cluster-RCTs)
(I) Comparability with individually randomised trials (cluster-RCTs)
(J) Loss of clusters (cluster-RCTs)
(K) Baseline imbalance (cluster-RCTs)
(L) Incorrect analysis (cluster-RCTs)
(M) Overall risk of bias

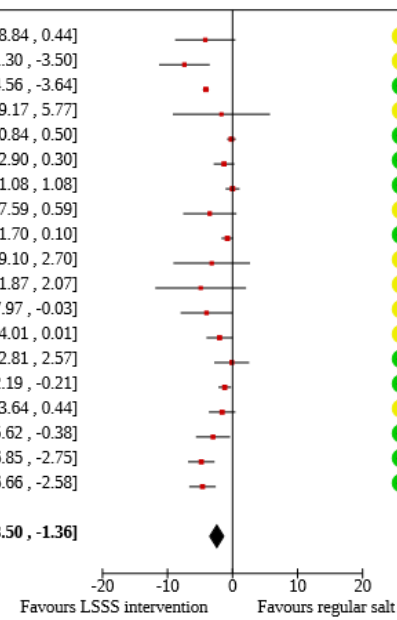
Analysis 1.1. Comparison 1: Low-sodium salt substitutes versus regular salt or no active intervention in adults, Outcome 1: Change in DBP (mmHg)

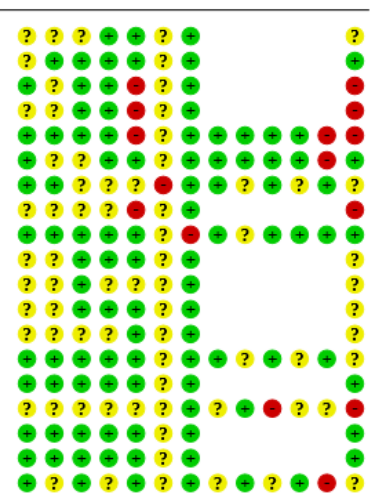
Study or Subgroup	MD	SE	LSSS intervention Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Allaert 2013 (1)	-4.2	2.36614	21	19	3.2%	-4.20 [-8.84 , 0.44]
Allaert 2017 (2)	-7.4	1.987451	22	19	3.9%	-7.40 [-11.30 , -3.50]
Geleijnse 1994 (3)	-4.1	0.236746	48	49	7.8%	-4.10 [-4.56 , -3.64]
Gilleran 1996 (4)	-1.7	3.8113	11	8	1.6%	-1.70 [-9.17 , 5.77]
Hu 2018 (5)	-0.17	0.341016	243	259	7.7%	-0.17 [-0.84 , 0.50]
Li 2014 (6)	-1.3	0.813878	198	205	6.7%	-1.30 [-2.90 , 0.30]
Li 2016 (7)	0	0.55077	1293	1272	7.3%	0.00 [-1.08 , 1.08]
Mu 2003 (8)	-3.5	2.088178	88	97	3.7%	-3.50 [-7.59 , 0.59]
Neal 2021 (9)	-0.8	0.459154	7436	7081	7.5%	-0.80 [-1.70 , 0.10]
Omvik 1995 (10)	-3.2	3.0103	19	20	2.3%	-3.20 [-9.10 , 2.70]
Pereira 2005 (11)	-4.9	3.557109	12	10	1.8%	-4.90 [-11.87 , 2.07]
Sarkkinen 2011 (1)	-4	2.028073	22	23	3.8%	-4.00 [-7.97 , -0.03]
Suppa 1988 (12)	-2	1.026733	163	159	6.2%	-2.00 [-4.01 , 0.01]
Toft 2020 (13)	-0.116	1.371969	41	49	5.3%	-0.12 [-2.81 , 2.57]
Yu 2021 (14)	-1.2	0.503822	242	234	7.4%	-1.20 [-2.19 , -0.21]
Zhang 2015 (15)	-1.6	1.04338	279	218	6.1%	-1.60 [-3.64 , 0.44]
Zhao 2014 (14)	-3	1.336061	141	141	5.4%	-3.00 [-5.62 , -0.38]
Zhou 2009 (16)	-4.8	1.0459	119	129	6.1%	-4.80 [-6.85 , -2.75]
Zhou 2013 (17)	-4.62	1.043047	213	227	6.1%	-4.62 [-6.66 , -2.58]
Total (95% CI)			**10611**	**10219**	**100.0%**	**-2.43 [-3.50 , -1.36]**

Heterogeneity: Tau² = 3.77; Chi² = 154.08, df = 18 (P < 0.00001); I² = 88%

Test for overall effect: Z = 4.45 (P < 0.00001)

Test for subgroup differences: Not applicable





Outcome – Cardiovascular Events

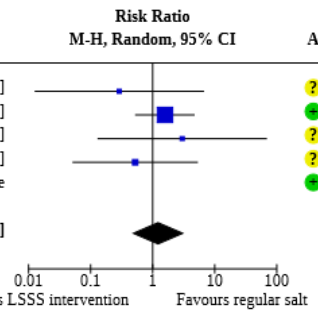
Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

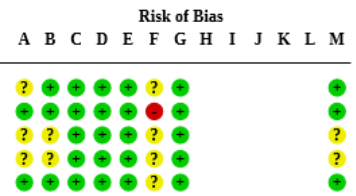
Cochrane Database of Systematic Reviews

Analysis 1.32. Comparison 1: Low-sodium salt substitutes versus regular salt or no active intervention in adults, Outcome 32: Cardiovascular events: various events

Study or Subgroup	LSSS intervention Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Allaert 2017 (1)	0	22	1	19	8.4%	0.29 [0.01 , 6.72]
CSSS Collaborative Group 2007 (2)	8	306	5	302	67.9%	1.58 [0.52 , 4.77]
Omvik 1995 (3)	1	20	0	20	8.4%	3.00 [0.13 , 69.52]
Sarkkinen 2011 (4)	1	22	2	23	15.3%	0.52 [0.05 , 5.36]
Zhou 2009 (5)	0	119	0	129		Not estimable
Total (95% CI)		**489**		**493**	**100.0%**	**1.22 [0.49 , 3.04]**
Total events:	10		8			

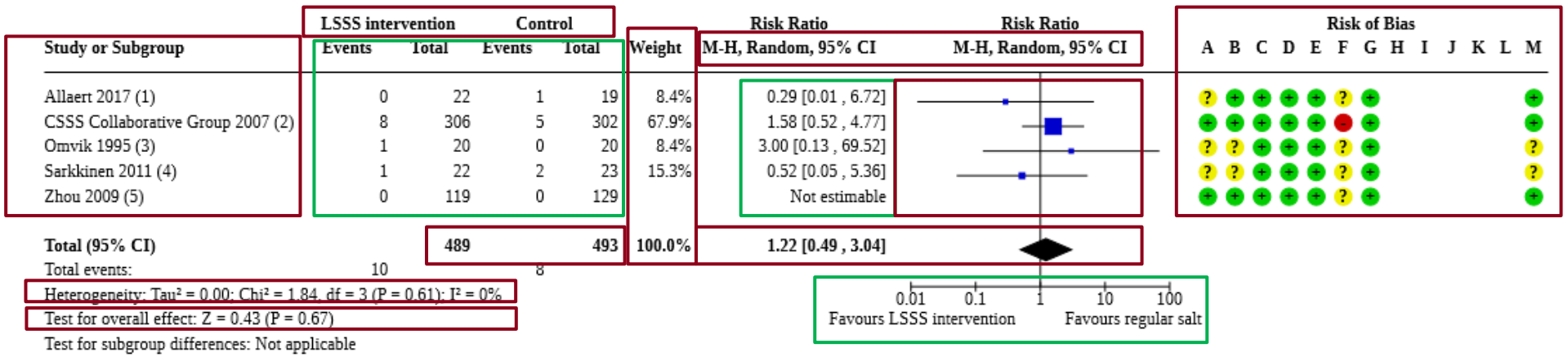
Heterogeneity: Tau² = 0.00; Chi² = 1.84, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable





5 RCTs

Analysis 1.32. Comparison 1: Low-sodium salt substitutes versus regular salt or no active intervention in adults, Outcome 32: Cardiovascular events: various events



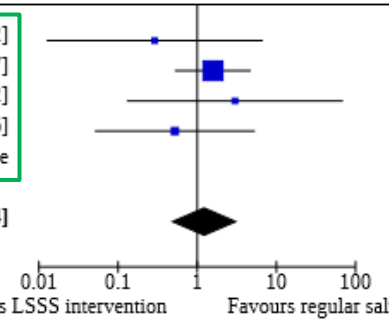
Analysis 1.32. Comparison 1: Low-sodium salt substitutes versus regular salt or no active intervention in adults, Outcome 32: Cardiovascular events: various events

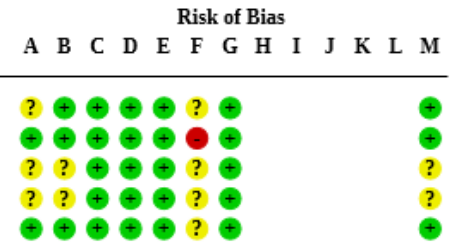
Study or Subgroup	LSSS intervention Events	LSSS intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Allaert 2017 (1)	0	22	1	19	8.4%	0.29 [0.01 , 6.72]
CSSS Collaborative Group 2007 (2)	8	306	5	302	67.9%	1.58 [0.52 , 4.77]
Omvik 1995 (3)	1	20	0	20	8.4%	3.00 [0.13 , 69.52]
Sarkkinen 2011 (4)	1	22	2	23	15.3%	0.52 [0.05 , 5.36]
Zhou 2009 (5)	0	119	0	129		Not estimable
Total (95% CI)		**489**		**493**	**100.0%**	**1.22 [0.49 , 3.04]**
Total events:	10		8			

Heterogeneity: Tau² = 0.00; Chi² = 1.84, df = 3 (P = 0.61); I² = 0%

Test for overall effect: Z = 0.43 (P = 0.67)

Test for subgroup differences: Not applicable





Effect Measure for Events: Risk Ratio (others Odds Ratio, Risk Difference)

Risk	$Risk = \frac{Number\ of\ participants\ \ with\ event}{Total\ number\ of\ participants}$	Expresses the chances that an event will occur

	Event	No event	Total
Intervention	8	298	306
Control	5	297	302

Risk=8/306=0.0261=2.61%

Risk=5/302=0.0165=1.65%

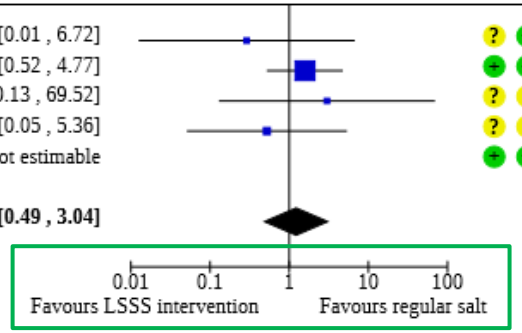
RR=(8/306)/(5/302)= 1.58

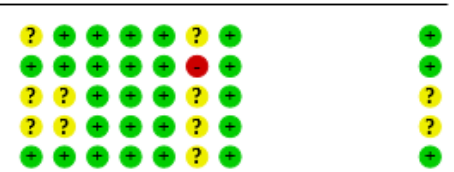
Risk Ratio RR (Relative Risk)	$RR = \frac{Risk\ of\ event\ in\ Intervention\ group}{Risk\ of\ event\ in\ Control\ group}$	Expresses the relative chance that an event will occur when 2 groups are compared (i.e., ratio of 2 risks (risk ratio)) • Range (0, ∞) • RR=1 indicates the risk of event is equally likely in the 2 groups

Analysis 1.32. Comparison 1: Low-sodium salt substitutes versus regular salt or no active intervention in adults, Outcome 32: Cardiovascular events: various events

Study or Subgroup	LSSS intervention Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Allaert 2017 (1)	0	22	1	19	8.4%	0.29 [0.01 , 6.72]
CSSS Collaborative Group 2007 (2)	8	306	5	302	67.9%	1.58 [0.52 , 4.77]
Omvik 1995 (3)	1	20	0	20	8.4%	3.00 [0.13 , 69.52]
Sarkkinen 2011 (4)	1	22	2	23	15.3%	0.52 [0.05 , 5.36]
Zhou 2009 (5)	0	119	0	129		Not estimable
Total (95% CI)		**489**		**493**	**100.0%**	**1.22 [0.49 , 3.04]**
Total events:	10		8			

Heterogeneity: Tau² = 0.00; Chi² = 1.84, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable





- The scale - for relative effects (such as RR), scale is a log scale. The lowest value a ratio can take is 0, 1 represents no effect, and highest value it can take is ∞. Data are presented on a log scale to make the scale and the confidence intervals appear symmetrical.
- The scale labels – indicates the side of the plot that favours the intervention. This will depend on the outcome; the right side of the scale always indicates a higher event rate for the intervention

P I C O

Intervention

- LSSS interventions/exposures of any type or duration provided aimed to replace the dietary intake of any amount of sodium with another mineral or compound
- Included studies investigating either discretionary (i.e. salt on table or added during cooking) or non-discretionary use of LSSS (i.e. included during food manufacturing)

Control

- Includes use of regular salt or no active intervention to reduce salt intake
- Included studies where control group received only basic information on sodium reduction at baseline

Multicomponent Interventions

- Included if effects of LSSS could be isolated from the multifactorial design
- Excluded if additional intervention components were not aimed primarily at promoting LSSS but focussed more broadly on reducing sodium intake or aimed at improving health in general such that LSSS effects could not be isolated.

Summary of Findings (SoF) table and the GRADE approach for assessing the certainty of evidence …

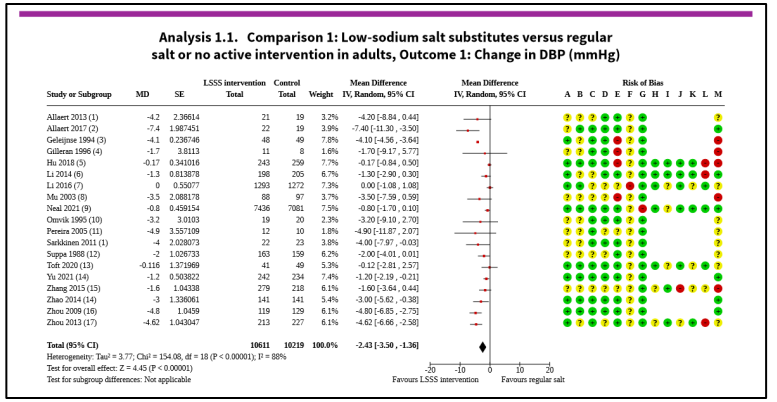
https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_4313866816113987744

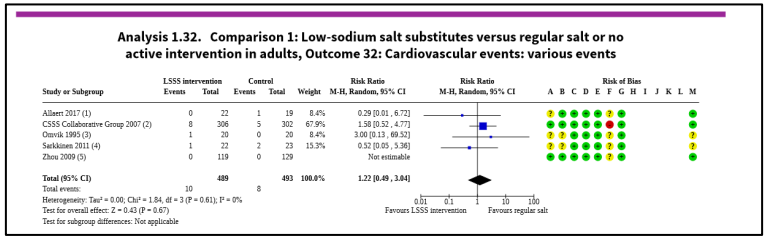
Summary of findings 1. Summary of findings table - LSSS intervention compared to regular salt in adults (≥ 18 years) in the general population

LSSS intervention compared to regular salt in adults (≥ 18 years) in the general population

Patient or population: adults (≥ 18 years) in the general population
Setting: any setting in any country
Intervention: LSSS intervention
Comparison: regular salt

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with regular salt	Risk with LSSS intervention				
Change in DBP (mmHg) follow-up: range 56 days to 3 years	The mean change in DBP (mmHg) was **-0.74** mmHg	MD **2.43 mmHg lower** (3.5 lower to 1.36 lower)	-	20830 (19 RCTs)	⨁⨁⨁◯ Moderate[a]	LSSS interventions probably reduce DBP (mmHg) slightly.
Change in SBP (mmHg) follow-up: range 56 days to 3 years	The mean change in SBP (mmHg) was **-1.32** mmHg	MD **4.76 mmHg lower** (6.01 lower to 3.5 lower)	-	21414 (20 RCTs)	⨁⨁⨁◯ Moderate[b]	LSSS interventions probably reduce SBP (mmHg) slightly.
Hypertension follow-up: 18 months	580 per 1000	**563 per 1000** (522 to 598)	**RR 0.97** (0.90 to 1.03)	2566 (1 RCT)	⨁⨁◯◯ Low[c,d]	LSSS interventions may result in little to no difference in hypertension.
Blood pressure control follow-up: range 8 weeks to 3 months	128 per 1000	**271 per 1000** (169 to 436)	**RR 2.12** (1.32 to 3.41)	253 (2 RCTs)	⨁◯◯◯ Very low[e,f,g]	The evidence is very uncertain about the effect of LSSS interventions on blood pressure control.
Cardiovascular events: various follow-up: range ≤ 3 to > 3-12 months	1623 per 100,000	**1980 per 100,000** (795 to 4933)	**RR 1.22** (0.49 to 3.04)	982 (5 RCTs)	⨁◯◯◯ Very low[h,i]	The evidence is very uncertain about the effect of LSSS interventions on various other cardiovascular events.





a Serious inconsistency: Substantial heterogeneity (I^2 = 88%), not explained by subgroup analyses (study duration, ethnicity, BP status, type of LSSS, baseline Na excretion) or meta-regression (type of LSSS, baseline Na excretion, overall risk of bias)
h Serious indirectness: Pooled effect is driven by a large study in high-risk individuals (participants selected based on high risk of future vascular disease) that is less likely to be directly applicable to the general population
i Very serious imprecision: Using the OIS approach, the ratio of the upper to the lower boundary of the 95% CI is more than 3 (RR); 18 events in total

GRADE – many reasons for uncertainty of the evidence of an effect

HIGH	⨁⨁⨁⨁
MODERATE	⨁⨁⨁◯
LOW	⨁⨁◯◯
VERY LOW	⨁◯◯◯

- Are the studies poorly conducted? Risk of bias
- Are the results inconsistent across studies? Inconsistency
- Do the results not really apply to my question? Indirectness
- Are there too few people, wide confidence intervals? Imprecision
- Are we missing studies, or have selective studies? Publication bias
- Plus large effect, dose response, opposing confounding

Levels of Evidence

Levels of Evidence	Statement
High certainty	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Cochrane Library

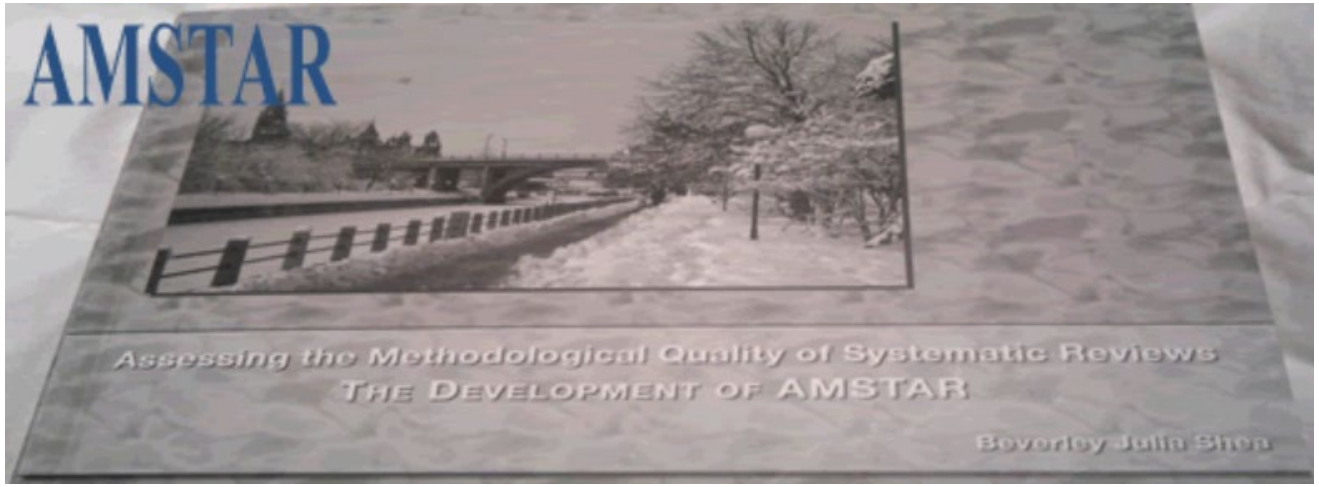
Cochrane Database of Systematic Reviews

Replacing salt with low-sodium salt substitutes (LSSS) for cardiovascular health in adults, children and pregnant women (Review)

Authors' conclusions

When compared to regular salt, LSSS probably reduce blood pressure, non-fatal cardiovascular events and cardiovascular mortality slightly in adults. However, LSSS also probably increase blood potassium slightly in adults. These small effects may be important when LSSS interventions are implemented at the population level. Evidence is limited for adults without elevated blood pressure, and there is a lack of evidence in pregnant women and people in whom an increased potassium intake is known to be potentially harmful, limiting conclusions on the safety of LSSS in the general population. We also cannot draw firm conclusions about effects of non-discretionary LSSS implementations. The evidence is very uncertain about the effects of LSSS on blood pressure in children.

Critical appraisal tool for systematic reviews



RESEARCH METHODS AND REPORTING

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

Beverley J Shea,[1,2,3] Barnaby C Reeves,[4] George Wells,[3,5] Micere Thuku1,[2] Candyce Hamel,[1] Julian Moran,[6] David Moher,[1,3] Peter Tugwell1,[2,3,7] Vivian Welch,[2,3] Elizabeth Kristjansson,[8] David A Henry[9,10,11]

BMJ 2017;358:j4008 http://dx.doi.org/10.1136/bmj.j4008

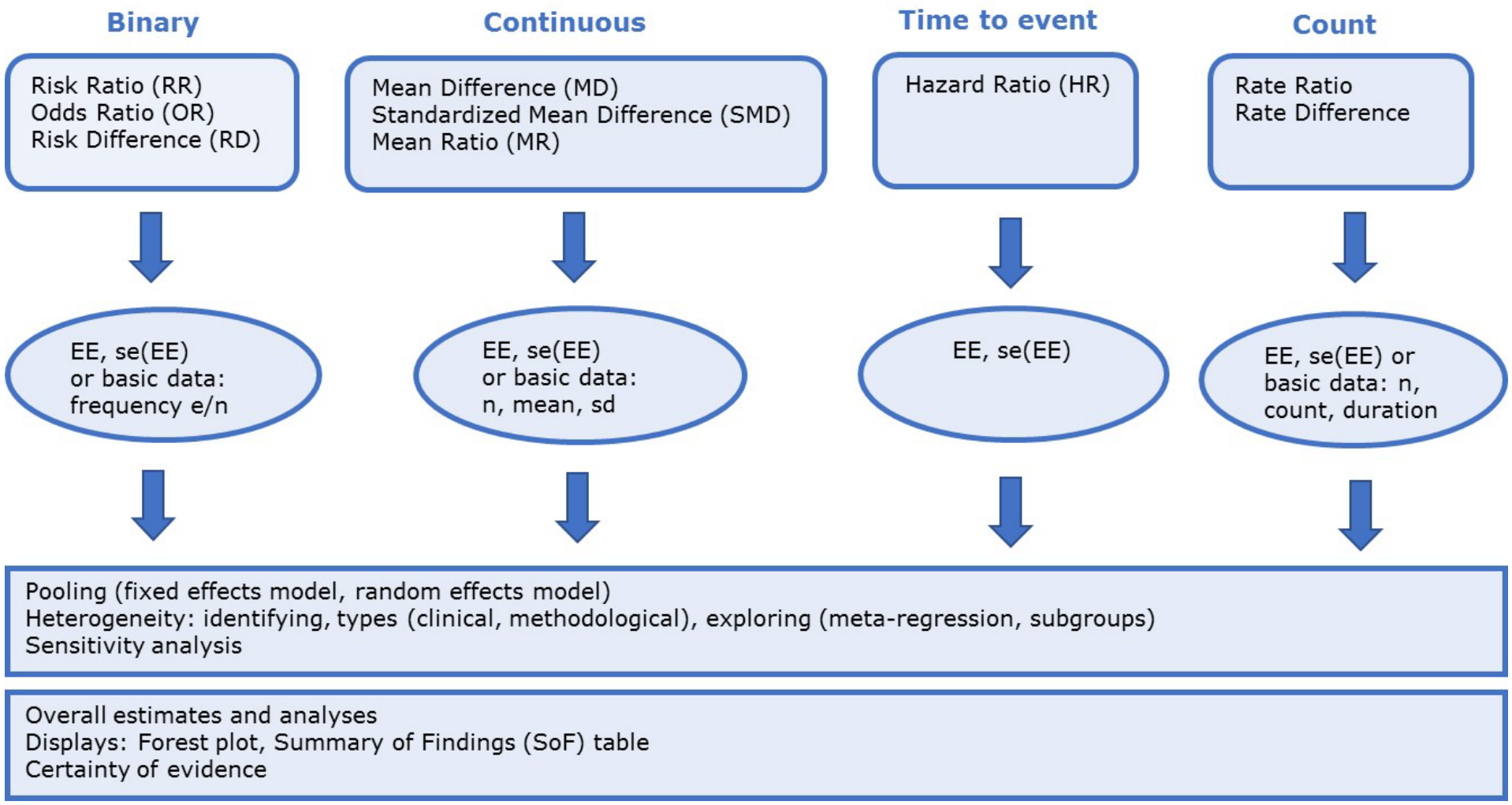
AMSTAR Website
https://amstar.ca/

Shea 2017 - AMSTAR2

AMSTAR2 Instrument

AMSTAR2 Guidance Document

Overview


Binary
Risk Ratio (RR)
Odds Ratio (OR)
Risk Difference (RD)
EE, se(EE)
or basic data:
frequency e/n
Continuous
Mean Difference (MD)
Standardized Mean Difference (SMD)
Mean Ratio (MR)
EE, se(EE)
or basic data:
n, mean, sd
Time to event
Hazard Ratio (HR)
EE, se(EE)
Count
Rate Ratio
Rate Difference
EE, se(EE) or
basic data: n,
count, duration
Pooling (fixed effects model, random effects model)
Heterogeneity: identifying, types (clinical, methodological), exploring (meta-regression, subgroups)
Sensitivity analysis
Overall estimates and analyses
Displays: Forest plot, Summary of Findings (SoF) table
Certainty of evidence

Questions or Thoughts