Allocation subversion and meta-analysis

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Allocation concealment

- Large amount of evidence (mainly from health care trials) that randomisation is often subverted
- Case studies of individual trials show this to be the case
- Epidemiological studies of RCTs also show statistical evidence of the problem

Comparison of concealment

Allocation Concealment	Effect Size OR	
Adequate	1.0	
Unclear	0.67	P < 0.01
Inadequate	0.59	

Schulz et al. JAMA 1995;273:408.

Case study of surgery

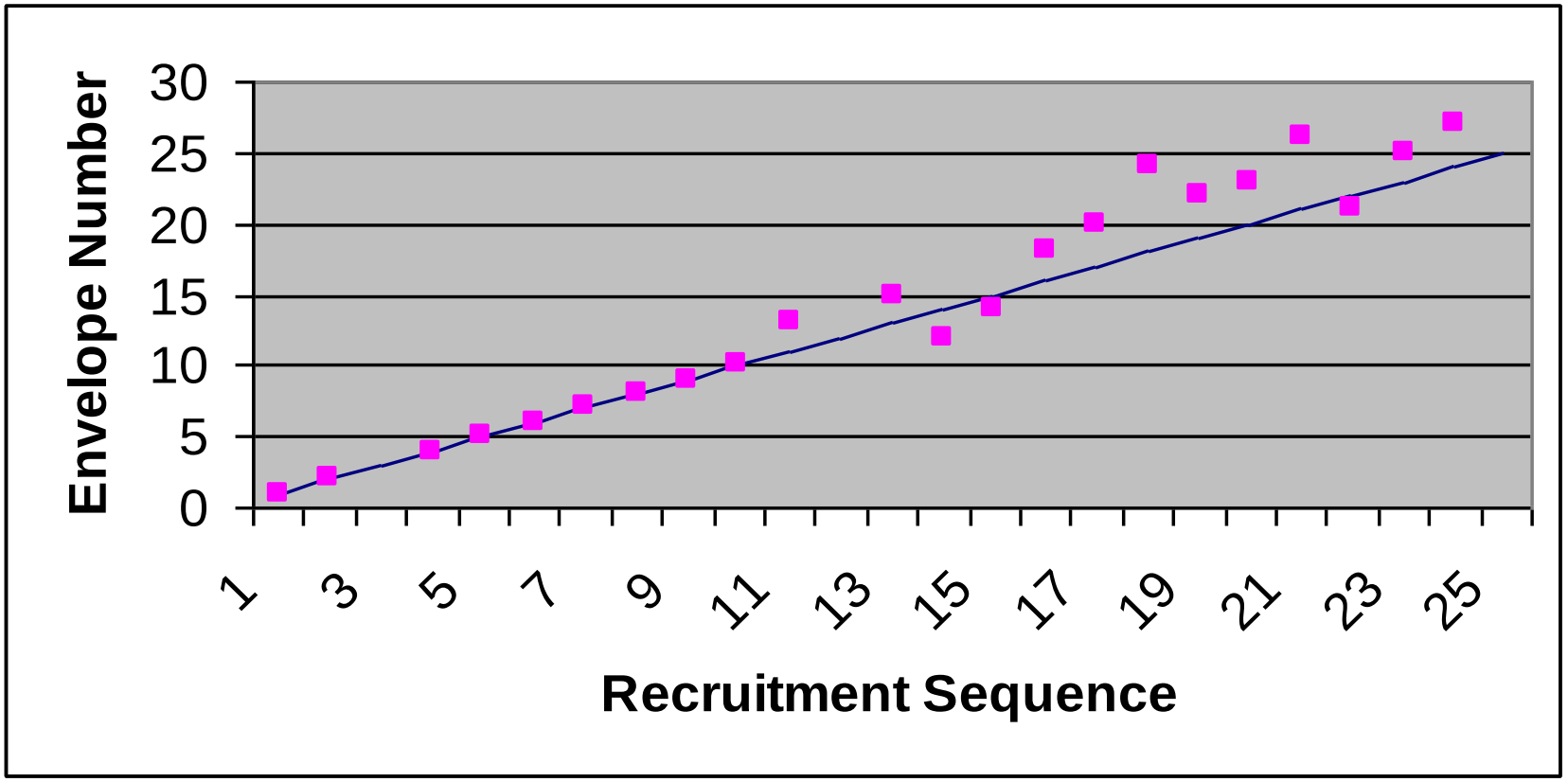
- Randomised trial comparing laparoscopic hernia repair with open repair
- 5 surgical centres holding a sequence of sealed opaque envelopes (Cochrane recommends) showed age imbalance of randomised groups

Kennedy et al, Trials 2017;18:204.

Mean ages of groups

Clinician	Experimental	Control
All $p < 0.01$	59	63
1 $p = .84$	62	61
2 $p = 0.60$	43	52
3 $p < 0.01$	57	72
4 $p < 0.001$	33	69
5 $p = 0.03$	47	72
Others $p = 0.99$	64	59

How did they do it?



The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Efficacy of a Sexual Assault Resistance Program for University Women

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N Engl J Med 2015;372:2326-35.
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ABSTRACT

BACKGROUND

Young women attending university are at substantial risk for being sexually assaulted, primarily by male acquaintances, but effective strategies to reduce this risk remain elusive.

METHODS

We randomly assigned first-year female students at three universities in Canada to the Enhanced Assess, Acknowledge, Act Sexual Assault Resistance program (resistance group) or to a session providing access to brochures on sexual assault, as was common university practice (control group). The resistance program consists of four 3-hour units in which information is provided and skills are taught and practiced, with the goal of being able to assess risk from acquaintances, overcome emotional barriers in acknowledging danger, and engage in effective verbal and physical self-defense. The primary outcome was completed rape, as measured by the Sexual Experiences Survey–Short Form Victimization, during 1 year of follow-up.

RESULTS

A total of 451 women were assigned to the resistance group and 442 women to the control group. Of the women assigned to the resistance group, 91% attended at least three of the four units. The 1-year risk of completed rape was significantly lower in the resistance group than in the control group (5.2% vs. 9.8%; relative risk reduction, 46.3% [95% confidence interval, 6.8 to 69.1]; P=0.02). The 1-year risk of attempted rape was also significantly lower in the resistance group (3.4% vs. 9.3%, P<0.001).

CONCLUSIONS

A rigorously designed and executed sexual assault resistance program was successful in decreasing the occurrence of rape, attempted rape, and other forms of victimization among first-year university women. (Funded by the Canadian Institutes of Health Research and the University of Windsor; SARE ClinicalTrials.gov number, NCT01338428.)

What is the problem here?

- There were 3 sites
- “Randomization was performed in permuted blocks of two with the use of the online tool Randomize.net, with stratification according to site”
- 452 assigned to control group and 464 to resistance group

Email correspondence

"Now it is me being v stupid confused or both. If you used a block of two stratified by site then the allocation will be perfectly balanced at each site every 2 women. If recruitment finished mid way through a block at each site then with 3 sites the biggest imbalance across the trial should be 3, shouldn't it?"
David

Dear David:

You are correct that, when the randomization process works perfectly, the maximum imbalance when stratified across 3 sites would be 3 subjects.

However, in practice, the computerized randomization process does not always work perfectly because of the human element. In our trial on several occasions, the research assistants mistakenly re-randomized subjects believing their online randomization had not been recorded or re-randomized subjects in an attempt to correct spelling mistakes, or mistakenly sent subjects to the wrong session.

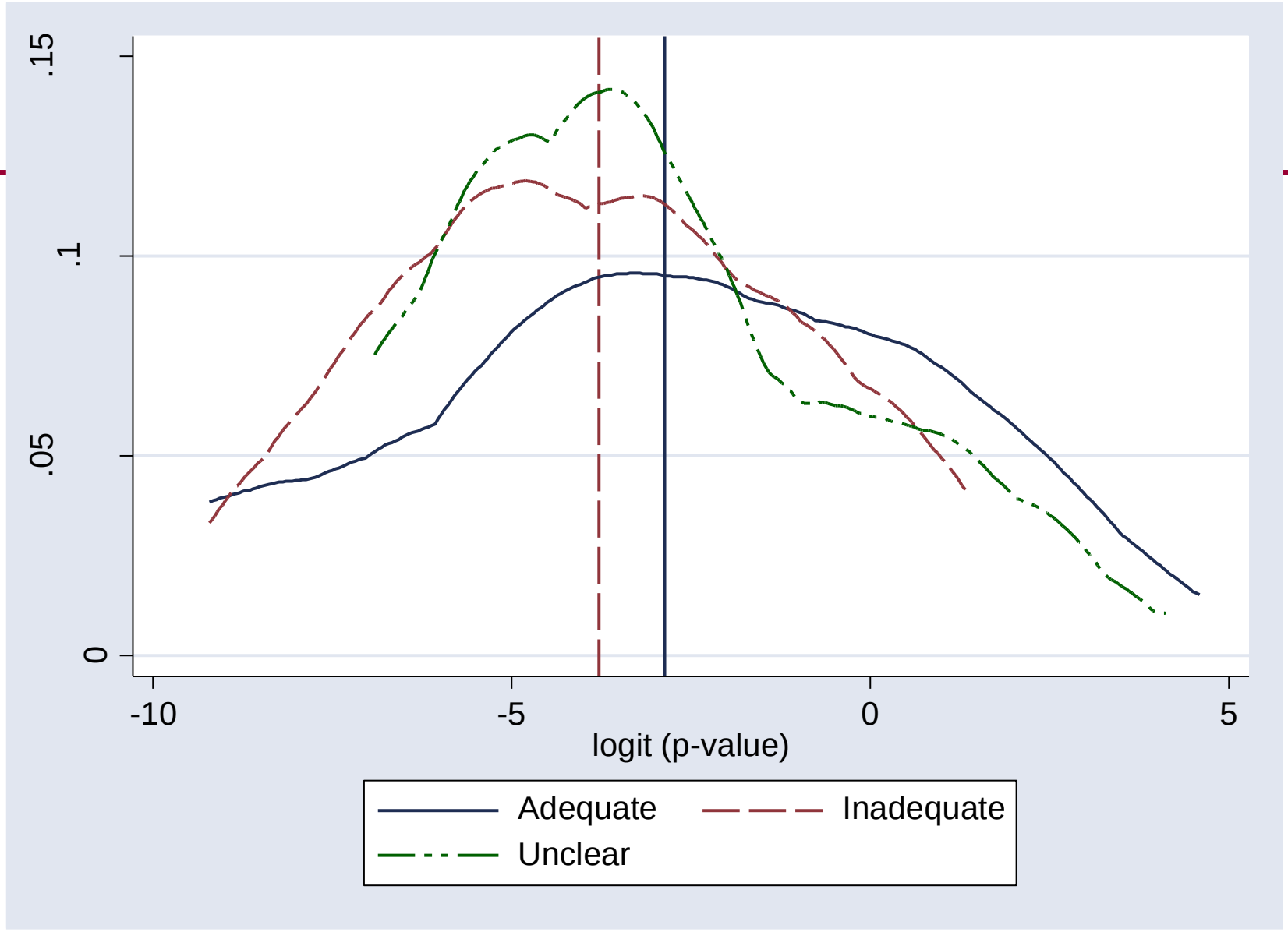
Despite the mistakes made at the time of randomization, none of the women were aware of their group assignment at the time of signing informed consent or completing the baseline survey.

Note all 10 of misallocations fell into the intervention group

Statistical Evidence

- Hewitt and colleagues examined the association between p values and adequate concealment in 4 major medical journals.
- Inadequate concealment largely used opaque envelopes.
- The average p value for inadequately concealed trials was 0.022 compared with 0.052 for adequate trials (test for difference p = 0.045).

Hewitt et al. BMJ;2005: March 10th.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.1
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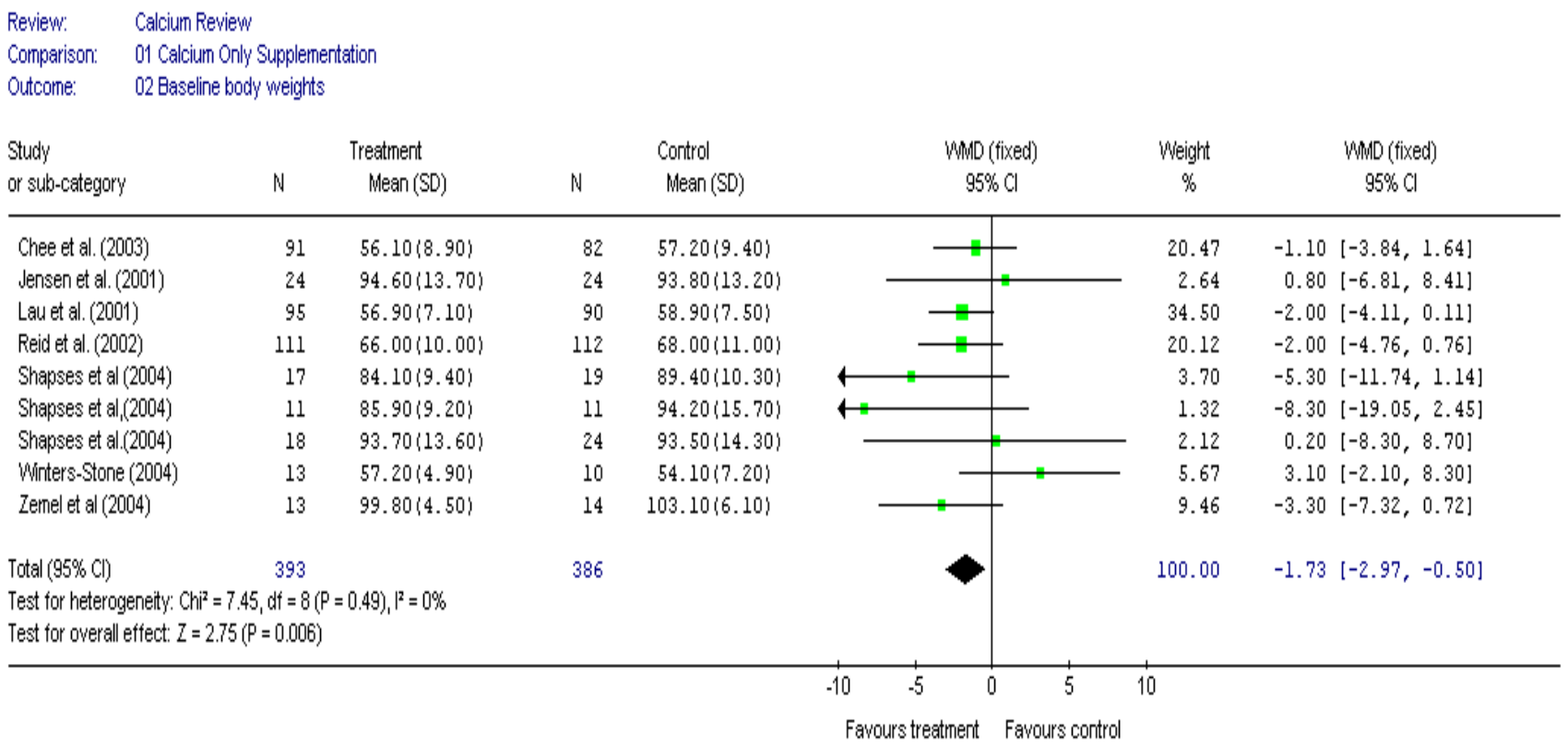
0
-10
-5
0
5
logit (p-value)
Adequate
Inadequate
Unclear

Systematic review of calcium for weight loss

- MSc student undertook a systematic review of calcium supplements for weight loss – comparing body weights at final follow-up showed a statistically signficant difference between the groups (-1.79 kg favouring calcium group; p = 0.005).
- But there was also a difference of baseline body weights.

Trowman et al. Br J of Nutrition 2006;95:1033-38

Forest plot – baseline weight



Symptoms of bias

- Baseline variables should be balanced across trials. An individual trial might be in imbalance by chance but meta-analysis of several trials should generate an estimate close to zero with no heterogeneity
- If there is heterogeneity and or imbalance then some component trials could be biased and the whole review is tainted

Review of Systematic Reviews

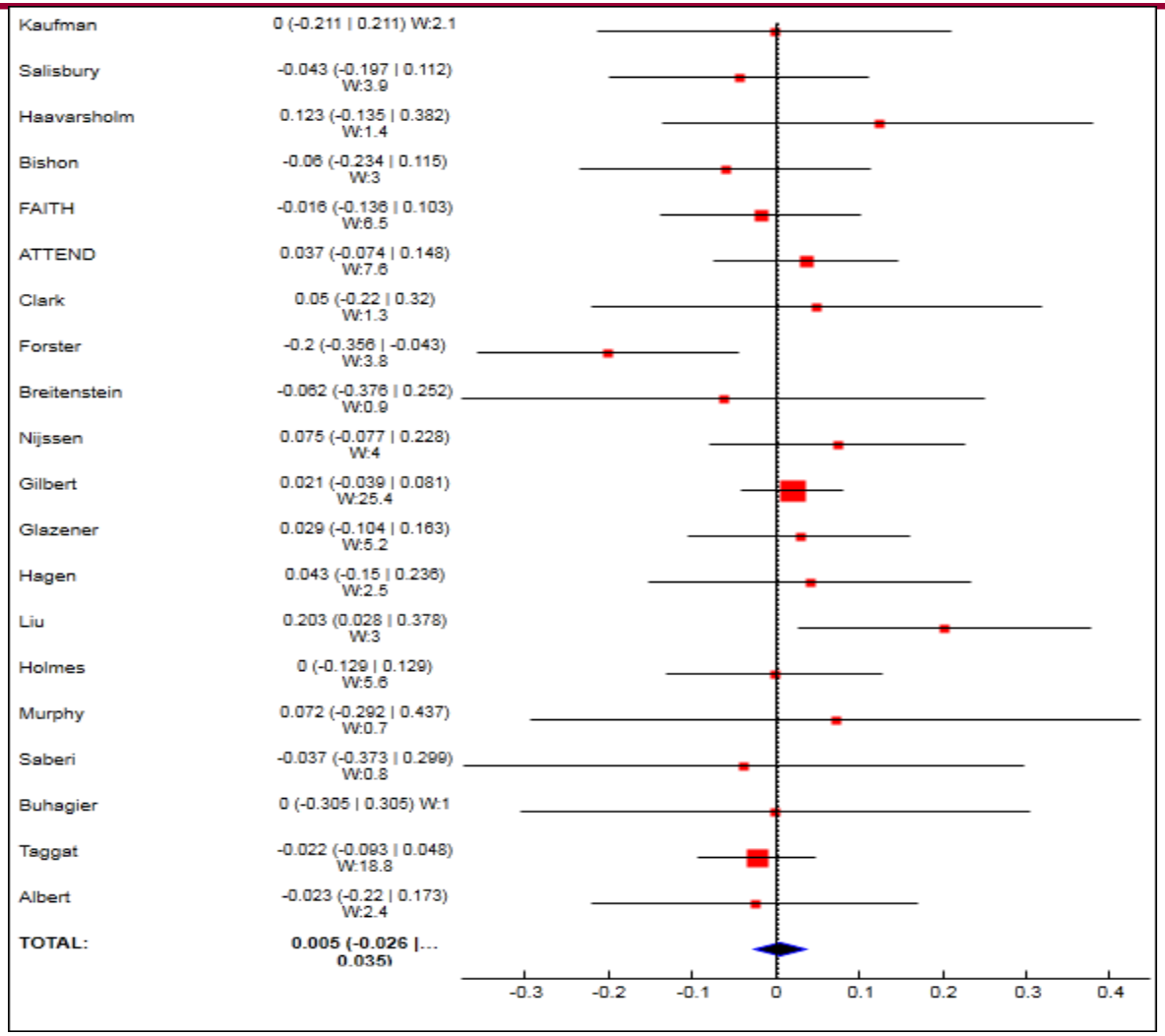
- 12 systematic reviews and meta-analyses were identified from the four most cited medical journals in 2012
- Meta-analysis of age was undertaken for each systematic review

Clark et al. *Journal of Clinical Epidemiology* 2014: 67;1016-1024.

Why age?

- Two main reasons:
  - » Easy characteristic for someone to use to subvert trial (e.g., older in control group)
  - » Most trial reports will produce, by group, mean and SD of ages by allocated group

Age meta-analysis – arbitrary sample of 23 RCTs in health care



Difference = 0.005 (95% CI -0.026 to 0.035) I^2 = 0%

Review results ranked by I^2

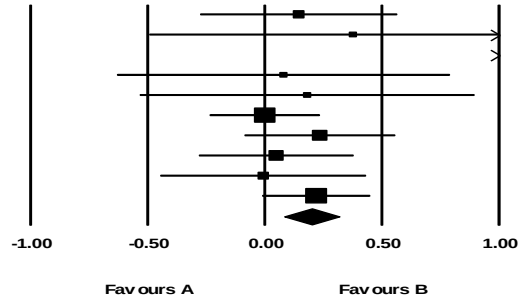
Systematic Review	Number of studies available for MA	Area		Intervention age mean (SD)	Control age. Mean (SD)	I squared value	P-value of difference in age
Anothaisintawee et al 2012	10	Drug		44.85 (5.56)	42.84 (5.67)	84.42	0.001
Rutjes et al 2012	38	Drug		62.17 (4.34)	62.44 (3.82)	67.92	0.835
Hemmingsen et al 2012	14	Drug		58.07 (4.13)	58.54 (3.98)	53.03	0.156
Thangaratinam et al 2012	20	Pregnancy and childbirth		28.15 (2.27)	27.95 (2.05)	50.11	0.113
Umpierre et al 2011	26	Lifestyle		58.29 (4.27)	58.79 (4.44)	42.72	0.173
Neumann et al 2012	9	Drug		64.18 (2.45)	63.94 (2.94)	33.46	0.029
Heneghan et al 2011	8	Other		63.15 (7.61)	62.71 (9.11)	31.62	0.024
Palmer et al 2012	11	Drug		51.99 (8.35)	52.86 (8.95)	29.03	0.173
Orrow et al 2012	10	Lifestyle		62.57 (10.29)	62.82 (9.72)	16.18	0.736
Coombes et al 2010	18	Drug		48.08 (6.9)	48.08 (7.25)	0.00	0.362
Leucht et al 2012	21	Drug		40.31 (9.24)	39.92 (9.78)	0.00	0.008
Hempel et al 2012	26	Drug		41.84 (24.43)	42.19 (25.24)	0.00	0.818

Heterogeneity: age difference

Meta Analysis

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Cheah 2003	0.145	0.216	0.047	-0.278	0.568	0.671	0.502
Bates 2007	0.377	0.445	0.198	-0.495	1.248	0.847	0.397
Nickel, downey et al 2004	2.731	0.348	0.121	2.050	3.412	7.857	0.000
Ieskinen 1999	0.080	0.364	0.132	-0.633	0.793	0.219	0.827
Shoskes 1999	0.181	0.366	0.134	-0.536	0.898	0.495	0.621
Nickel, Krieger et al 2008	0.000	0.121	0.015	-0.238	0.238	0.000	1.000
Alexander 2004	0.235	0.165	0.027	-0.089	0.559	1.421	0.155
Wagenlehner 2009	0.049	0.170	0.029	-0.284	0.381	0.288	0.774
Nicke, Downey, Clark et al 2003	-0.007	0.225	0.051	-0.449	0.435	-0.030	0.976
Pontari 2010	0.220	0.119	0.014	-0.013	0.452	1.850	0.064
	0.198	0.060	0.004	0.081	0.315	3.307	0.001

Statistics for each study



Meta Analysis

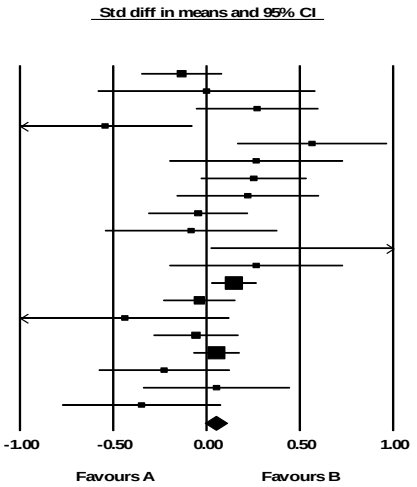
Difference in age p value = 0.001; I2 = 84.42

Heterogeneity: no age difference

Meta Analysis

Studyname	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Jackson 2011	-0.133	0.112	0.012	-0.352	0.086	-1.192	0.233
Hui 2004	0.000	0.299	0.089	-0.586	0.586	0.000	1.000
Barakat 2009	0.271	0.169	0.028	-0.059	0.602	1.608	0.108
Santos 2005	-0.544	0.240	0.058	-1.014	-0.073	-2.265	0.024
Hopkins 2010	0.566	0.206	0.042	0.162	0.969	2.746	0.006
Cavalcante 2009	0.266	0.239	0.057	-0.202	0.734	1.115	0.265
Hui 2011	0.253	0.146	0.021	-0.033	0.539	1.732	0.083
Haakstad 2011	0.221	0.196	0.038	-0.163	0.605	1.130	0.259
Garshasbi 2005	-0.045	0.137	0.019	-0.314	0.224	-0.328	0.743
Erkkola and Makela 1976	-0.083	0.237	0.056	-0.546	0.381	-0.349	0.727
Marquez-Sterling 1998	1.129	0.566	0.320	0.020	2.238	1.995	0.046
Baciuk 2008	0.266	0.239	0.057	-0.202	0.734	1.115	0.265
Crowther 2005	0.147	0.063	0.004	0.023	0.271	2.317	0.021
Phelan 2011	-0.038	0.100	0.010	-0.234	0.157	-0.385	0.700
Wolff 2008	-0.438	0.287	0.082	-1.000	0.125	-1.525	0.127
Khoury 2005	-0.056	0.118	0.014	-0.287	0.174	-0.480	0.632
Landon 2009	0.053	0.065	0.004	-0.074	0.180	0.821	0.411
Quinlivan 2011	-0.227	0.180	0.032	-0.581	0.126	-1.262	0.207
Asbee 2009	0.054	0.202	0.041	-0.342	0.450	0.265	0.791
Guelinckx 2010	-0.348	0.219	0.048	-0.776	0.081	-1.591	0.112
	0.048	0.030	0.001	-0.011	0.107	1.583	0.113

Statistics for each study



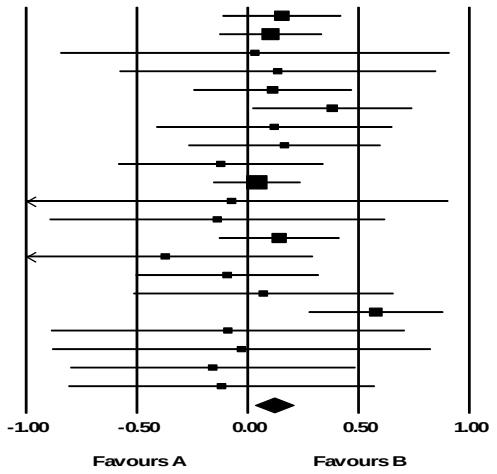
Meta Analysis

Difference in age p = 0.113; I2 = 50

Age imbalance no heterogeneity

Meta Analysis

Studyname	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
			Statistics for each study				
Arato 2002	0.154	0.138	0.019	-0.116	0.424	1.120	0.263
Beasley 2003	0.103	0.120	0.014	-0.131	0.337	0.864	0.388
Boonstra 2011	0.033	0.449	0.202	-0.848	0.914	0.073	0.942
Clark 1975	0.136	0.365	0.134	-0.581	0.852	0.371	0.711
Cooper 2000	0.112	0.184	0.034	-0.247	0.472	0.613	0.540
Crow 1986	0.381	0.185	0.034	0.018	0.744	2.060	0.039
Gross 1974	0.120	0.273	0.075	-0.415	0.655	0.440	0.660
Hirsch 1973	0.166	0.223	0.050	-0.270	0.602	0.745	0.456
Hirsch 1996	-0.122	0.238	0.056	-0.587	0.344	-0.512	0.609
Kane 2011	0.041	0.102	0.010	-0.158	0.241	0.407	0.684
Kane 1979	-0.073	0.500	0.250	-1.054	0.907	-0.146	0.884
Kane 1982	-0.137	0.387	0.150	-0.896	0.622	-0.354	0.724
Kramer 2007	0.142	0.140	0.020	-0.132	0.416	1.016	0.310
Kurland 1975	-0.372	0.341	0.116	-1.041	0.297	-1.090	0.276
Nishikawa 1984	-0.093	0.212	0.045	-0.509	0.323	-0.437	0.662
Levine 1980	0.071	0.301	0.090	-0.519	0.660	0.235	0.814
Peuskens 2007	0.578	0.156	0.024	0.272	0.884	3.705	0.000
Sampath 1992	-0.090	0.408	0.167	-0.890	0.711	-0.219	0.826
Vandecasteele 1974	-0.028	0.437	0.191	-0.884	0.828	-0.064	0.949
Wistedt 1981	-0.158	0.329	0.108	-0.803	0.487	-0.479	0.632
Zissis 1982	-0.118	0.354	0.125	-0.812	0.576	-0.334	0.739
	0.117	0.044	0.002	0.030	0.203	2.645	0.008

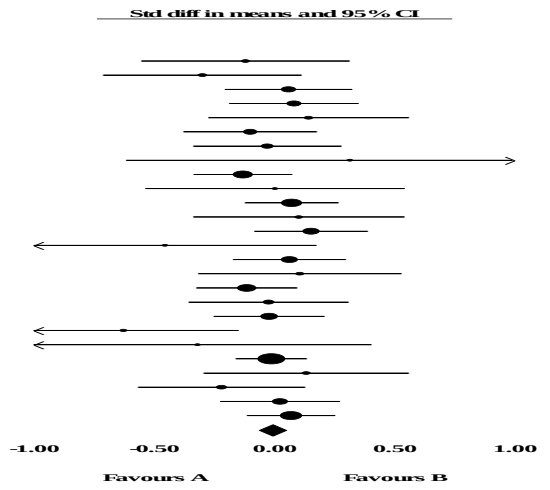


Meta Analysis

Difference in age (p = 0.008;) hetererogeneity = 0.00

How it should be!

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Borgia 1982	-0.115	0.224	0.050	-0.553	0.324	-0.512	0.609
Beausoleil 2007	-0.294	0.213	0.045	-0.712	0.124	-1.378	0.168
Song 2010	0.064	0.137	0.019	-0.204	0.333	0.471	0.638
de Bortoli 2007	0.087	0.139	0.019	-0.186	0.361	0.627	0.531
Wenus 2008	0.148	0.215	0.046	-0.274	0.570	0.688	0.491
McFarland 1995	-0.095	0.144	0.021	-0.377	0.187	-0.659	0.510
Correa 2005	-0.023	0.160	0.025	-0.336	0.290	-0.147	0.884
Jirapinyo 2002	0.320	0.477	0.228	-0.616	1.256	0.670	0.503
Park 2007	-0.125	0.107	0.011	-0.334	0.084	-1.174	0.240
Felley 2001	0.008	0.278	0.077	-0.536	0.552	0.030	0.976
Duman 2005	0.078	0.102	0.010	-0.122	0.277	0.763	0.445
Szymanski 2008	0.107	0.227	0.051	-0.337	0.552	0.474	0.635
Thomas 2001	0.158	0.123	0.015	-0.082	0.398	1.290	0.197
Safdar 2008	-0.449	0.324	0.105	-1.084	0.185	-1.387	0.165
Kotowska 2005	0.069	0.122	0.015	-0.171	0.308	0.562	0.574
Schrezenmeir 2004	0.112	0.218	0.047	-0.315	0.539	0.513	0.608
Yoon 2011	-0.109	0.110	0.012	-0.324	0.106	-0.997	0.319
Hickson 2007	-0.018	0.172	0.030	-0.356	0.319	-0.107	0.914
Conway 2007	-0.016	0.120	0.014	-0.251	0.218	-0.137	0.891
Lewis 1998	-0.622	0.247	0.061	-1.106	-0.139	-2.522	0.012
Koning 2008	-0.314	0.371	0.137	-1.040	0.413	-0.846	0.397
Song 2010	-0.007	0.078	0.006	-0.159	0.146	-0.089	0.929
Szajewska 2009	0.138	0.220	0.048	-0.293	0.570	0.628	0.530
Merenstein 2009	-0.214	0.179	0.032	-0.566	0.138	-1.193	0.233
Ruszczynski 2008	0.030	0.129	0.017	-0.224	0.283	0.229	0.819
Sanpalis 2010	0.075	0.096	0.009	-0.112	0.263	0.786	0.432
	-0.007	0.028	0.001	-0.062	0.049	-0.231	0.818



Difference in age p = 0.81; I2 = 0.00

Comment

- Out of 12 meta-analyses published in 4 leading medical journals:
  - » Only 3 showed the expected zero heterogeneity and zero imbalance

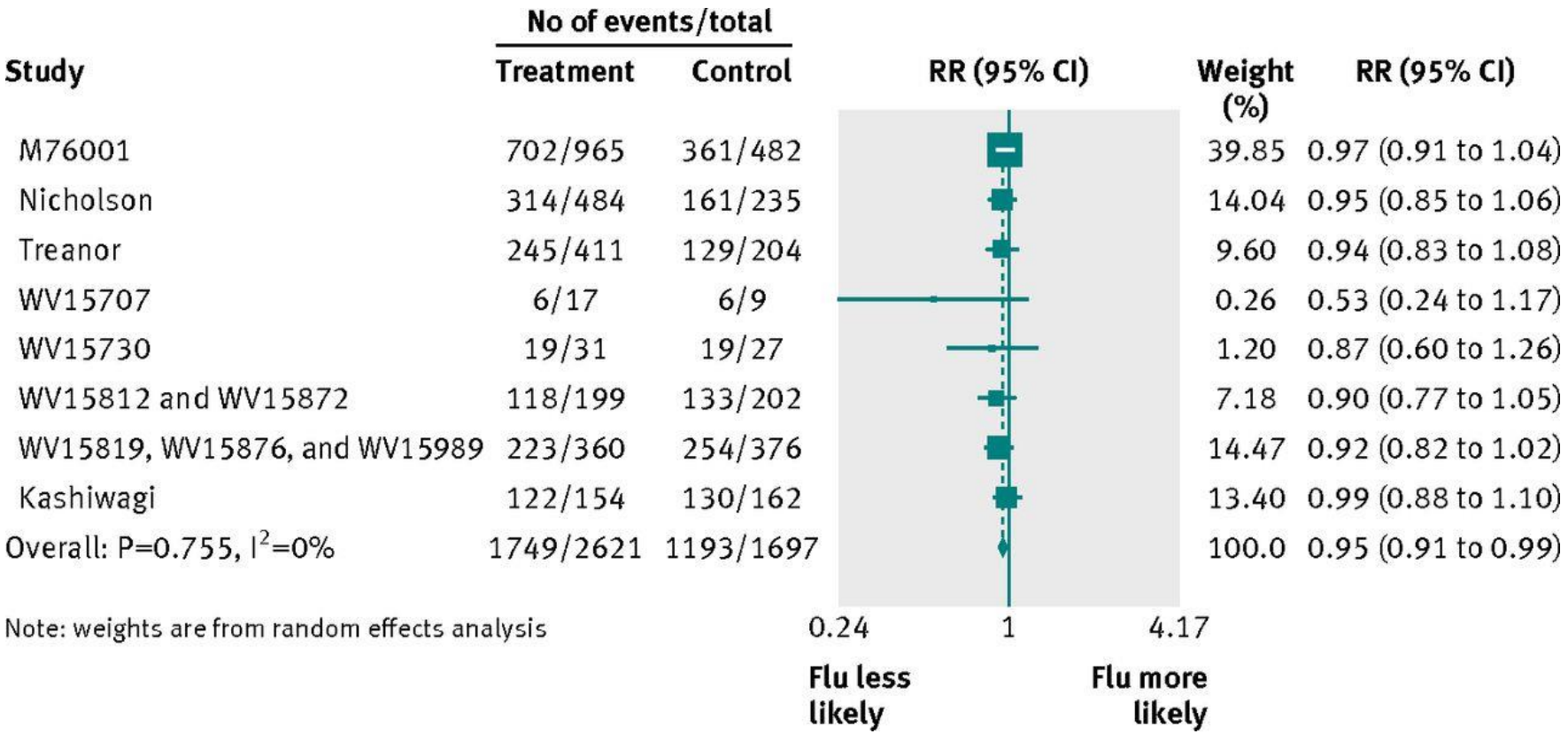
A review conclusion

- In the review with >50% I2 it was concluded that:
  - » *Dietary and lifestyle interventions can reduce maternal gestational weight gain and improve outcomes for both mother and baby*
- Is such a result believable – given the likelihood of biased trials?

Comments from reviewers/researchers

- Perhaps some characteristics of setting intervention affects heterogeneity
  - » Bonkers
- But the baseline difference is non-existence/clinically irrelevant
  - » But this is a marker for subversion some other unreported co-variate might be worse!
- Could it be due to publication bias?
  - » Don’t think so

Anti-body exposure to ‘flu



Study	No of events/total: Treatment	No of events/total: Control	RR (95% CI)	Weight (%)	RR (95% CI)
M76001	702/965	361/482		39.85	0.97 (0.91 to 1.04)
Nicholson	314/484	161/235		14.04	0.95 (0.85 to 1.06)
Treanor	245/411	129/204		9.60	0.94 (0.83 to 1.08)
WV15707	6/17	6/9		0.26	0.53 (0.24 to 1.17)
WV15730	19/31	19/27		1.20	0.87 (0.60 to 1.26)
WV15812 and WV15872	118/199	133/202		7.18	0.90 (0.77 to 1.05)
WV15819, WV15876, and WV15989	223/360	254/376		14.47	0.92 (0.82 to 1.02)
Kashiwagi	122/154	130/162		13.40	0.99 (0.88 to 1.10)
Overall: P=0.755, I^2=0%	1749/2621	1193/1697		100.0	0.95 (0.91 to 0.99)

Note: weights are from random effects analysis

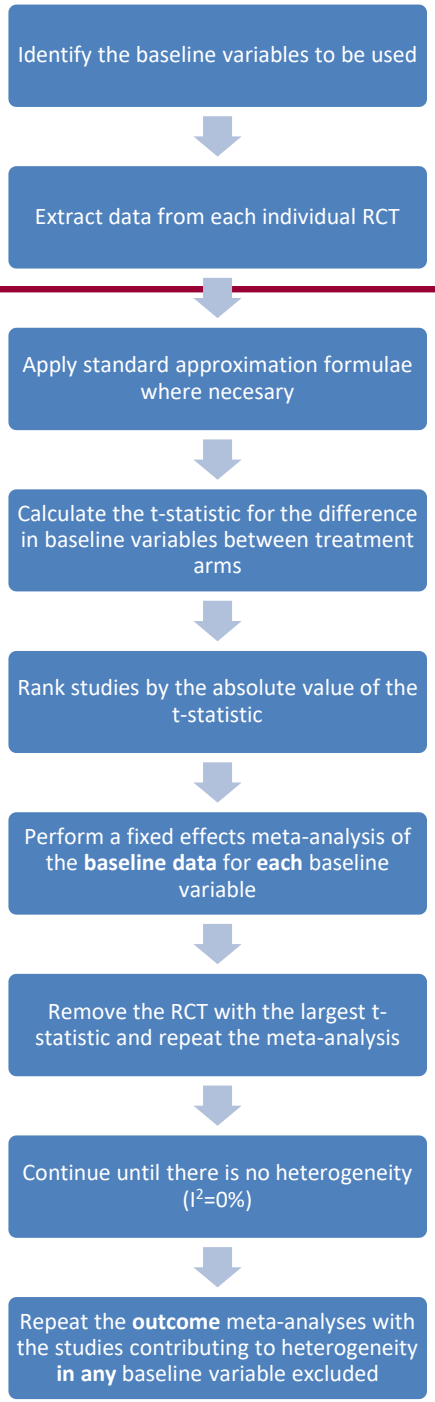
Ebell 2013; Methodological concerns about studies on oseltamivir for flu (BMJ 2013;347:f7148)

Comment

- We have a BIG problem – the evidence suggests significant numbers of subverted trials are entering the ‘food chain’
- Unless we scrap all the evidence of the last 50 years and start again what can we do?

Some suggestions/Discussion

- First routinely do baseline meta-analyses of age and another strong predictor of outcome SRs that pass this are likely to be OK
- Other suggestions:
  - » Sort by baseline imbalance exclude those with a pre-specified baseline imbalance
  - » Start a cumulative, by imbalance, meta-analysis stop when heterogeneity appears
  - » Remove most severe studies in imbalance



Hicks et al. *J Clinical Epidemiology* 2018;95:55-62.

Studies in meta-analysis ranked by t value of age difference

Study	Mean Difference (kg)	t-statistic	absolute value of t-statistic	Heterogeneity[a] I^2 (%) (35.4% total)
Hopkins	2	2.618964	2.618964	29.3
Crowther	0.8	2.319949	2.319949	25.5
Santos	-2.6	-2.306597	2.306597	12.8
Marquez-Sterling	3.5	2.142188	2.142188	1.07
Hui	1.4	1.738516	1.738516	0.0
Clapp	1	1.732051	1.732051	0.0
Barakat	0.9	1.615753	1.615753	0.0
Guelinckx	-1.4	-1.603391	1.603391	0.0
Wolff	-2	-1.542686	1.542686	0.0
Barakat	1	1.294297	1.294297	0.0
Quinlivan	-1.2	-1.265797	1.265797	0.0
Jackson	-0.8	-1.193001	1.193001	0.0
Haakstad	0.9	1.133327	1.133327	0.0
Baciuk	1.4	1.120274	1.120274	0.0
Erkkola	0.4	1.025268	1.025268	0.0
Landon	0.3	0.821535	0.821535	0.0
Bung	-1	-0.625135	0.625135	0.0
Khoury	-0.2	-0.479653	0.479653	0.0
Phelan	-0.2	-0.385095	0.385095	0.0
Erkkola + Makela	0.2	0.368133	0.368133	0.0
Garshasbi	-0.21	-0.328250	0.328250	0.0
Asbee	0.3	0.265534	0.265534	0.0
Huang	0.22	0.262568	0.262568	0.0
Khaledan	0.15	0.093955	0.093955	0.0
Sedaghati	0.02	0.026337	0.026337	0.0
Hui[b]	0	0	0	0.0
Vinter[b]	0	0	0	0.0

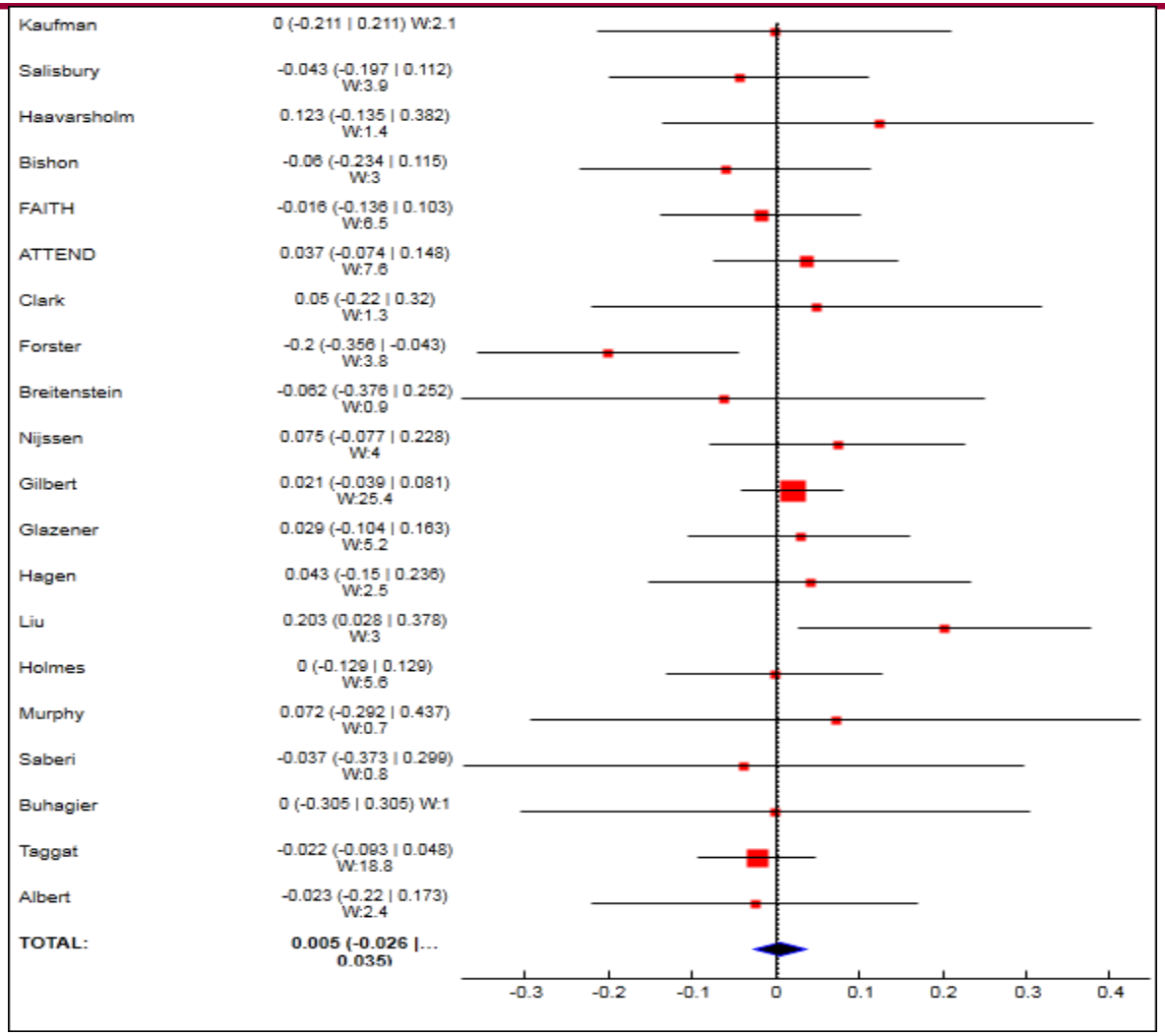
[a]heterogeneity observed in meta-analysis of baseline age when this study (and those with higher t-statistic) removed

[b]studies with same t-statistic ranked according to sample size (largest first)

Cluster trials

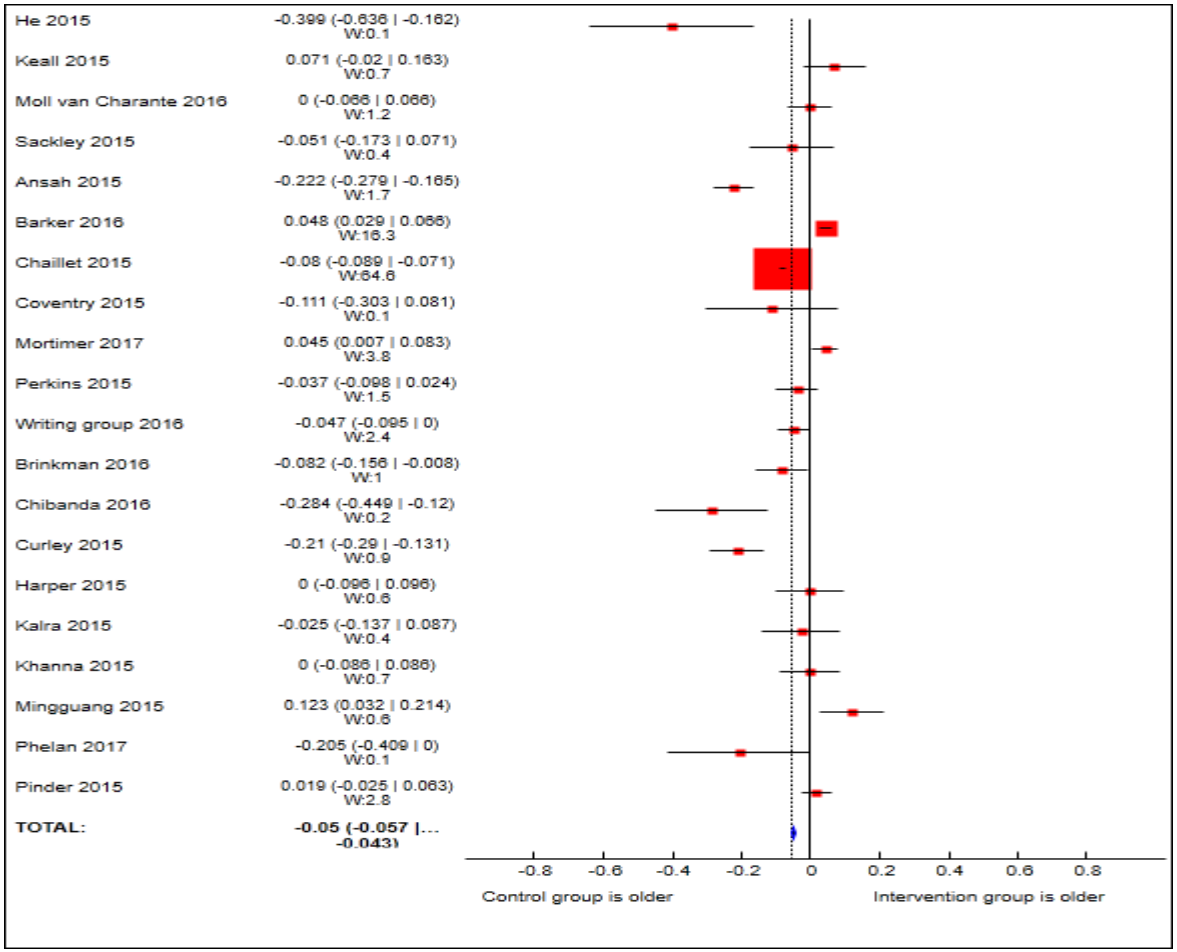
- Many cluster trials (where a group is the unit of randomisation e.g., schools) recruit individual participants after randomisation has occurred
- This is essentially ‘open’ allocation and biased recruitment can take place as within individual randomised trials

Age meta-analysis – arbitrary sample of 23 RCTs in health care



Difference = 0.005 (95% CI -0.026 to 0.035) I^2 = 0%

Cluster trials any better?



Difference in age: -0.05 (95% CI -0.057 to -0.0426) I^2 = 93.2%

Bolzern et al, *J Clinical Epidemiology* 2018;99:106-112.

Conclusion

- Significant proportion of randomised trials, in health care, are ‘subverted’ and are not really randomised
- This subversion feeds into meta-analyses results
- The same problem will apply to non-health care trials – therefore the same identification technique might be useful