ENSURE - Educating students for developing high quality research skills

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25. October 2019

BIAS

Finn Egil Skjeldestad
Institute of community medicine
UiT The arctic university of Norway
Tromsø
Norway

Recall bias

Ecologic bias

Publication bias

Withdrawal bias

Observer bias

Prevalence-incidence bias

Digit-preference bias

Misclassification bias

Publicity bias

Berkson’s bias

Healthy-worker effect

Diagnostic bias

Information bias

Clever Hans effect

Referral bias

Detection bias

Self selection bias

Loss to follow-up bias

Selection bias

Protopathic bias

Recall bias

Regression-dilution bias

Non-response bias

National committee for medical and health research ethics, Norway, states:

- Bias in research can cause results to not match reality.
  Unintended bias can occur in all stages of the research process.
  Intentional bias is too cheating to count.

- Bias is a challenge in all research.
  Bias can also easily be defined as a "form of systematic error that can affect scientific studies and interfere with the measurement processes"

- Bias can occur in all phases of a research project, such as during hypothesis generation, planning, execution and funding of studies, collection, processing and interpretation of study data, as well as publication of research data.

What can be done to avoid bias?

Bias related to choice of respondents/population?

Bias can occur when choosing a method?

Bias related to presentation and interpretation of results?

Bias linked to the researcher, biased view point, conflict of interest, delusional effect?

Bias, PICO and study design

Bias concepts			PICO	Design	Design
Selection bias	Self selection bias	Referral bias	P	RCT	Cohort/ Case-control/Case series
Recall bias			Exp. Confound.		**Case-control,** retrospective cohorte, retrospective case-series
Diagnostic bias	Misclassification bias		P/Exp./O		All design
Observer bias			O		All prospective studies
Attrition bias	Loss to follow-up bias	Withdrawal bias/ Non-response bias	O		All prospective studies
Publication bias					RCT/Cohort/Case-control/Case series
Publicity bias					

Reference: Hubacher D, Lara-Ricalde R, Taylor DJ, Guerra-Infante F, Guzman-Rodriguez R. Use of copper intrauterine devices and the risk of tubal infertility among nulligravid women. NEJM 2001;345:561-7

Bias, PICO and study design

Bias con	
Selection bias	Self selectio
Recall bias	
Diagnostic bias	Misclassifica bias
Observer bias	
Attrition bias	Loss to follo bias
Publication bias	
Publicity bias	

METHODS We conducted an **unmatched case–control study in three public hospitals in Mexico City, Mexico** (the National Perinatology Institute, Gynecology and Obstetrics Hospital Number 4 of the Mexican Social Security Institute, and the Women's Hospital). All consecutive nulligravid, infertile women 18 years of age or older who were scheduled for diagnostic hysterosalpingography were invited to participate. Infertility was defined by the failure to conceive after one year or more of unprotected intercourse. Criteria for exclusion included previous pregnancy, tubal sterilization, and previous diagnostic laparoscopy. After undergoing hysterosalpingography, the infertile women were classified on the basis of the radiologic evidence as women with tubal occlusion (case subjects) or as infertile controls. From the same hospitals, we recruited a second control group consisting of primigravid women in their first or second trimester. **In face-to-face interviews lasting an average of 20 minutes, all participants were asked about their past use of contraceptives, previous sexual relationships, and history of genital tract infections; the interviews with the infertile women were conducted before they knew whether they had tubal occlusion.** The instruments for recording the results of hysterosalpingography were adapted from the recommendations of the American Fertility Society (now the American Society for Reproductive Medicine).

We recruited 1311 infertile women (358 women with tubal occlusion and 953 controls) and 584 pregnant controls; fewer than 5 percent of the women who met the eligibility criteria declined to participate. We designed the study to have 90 percent power to detect a doubling of the risk of tubal occlusion with IUD use in analyses involving the infertile controls; the study had 87 percent power to detect a doubling of the risk in analyses involving the pregnant controls (two-sided test, 0.05 alpha level).

If we set the power at the standard 80 percent level, we had enough study subjects to detect odds ratios of 1.8 and 1.9 in analyses involving the infertile controls and the pregnant controls, respectively. Before recruitment began, the radiologists met to standardize their approach to classifying tubal pathology. Tubal occlusion was diagnosed if a water-based contrast medium failed to spill from either tube into the peritoneal cavity. Fluoroscopy was used, and the last films were taken 15 minutes after the contrast medium had been injected. The radiologists were unaware of the information collected in the women's interviews. Serologic tests for detecting antibodies to chlamydia are accepted measures of past infection.
28-30
All serum samples were processed as recommended by the manufacturer. Our primary exposure variable was the previous use or nonuse of an IUD containing copper. Other variables that were considered as possibly predictive of tubal infertility included the presence or absence of antibodies to C. trachomatis, the number of lifetime sexual partners, the presence or absence of a history of genital tract infections, the presence or absence of a history of gynecologic symptoms suggestive of infection, the past use or nonuse of other methods of contraception, family income, education, employment status, and the presence or absence of a history of coitus during the teenage years. Regarding their most recent sexual partners

Bias, PICO and study design

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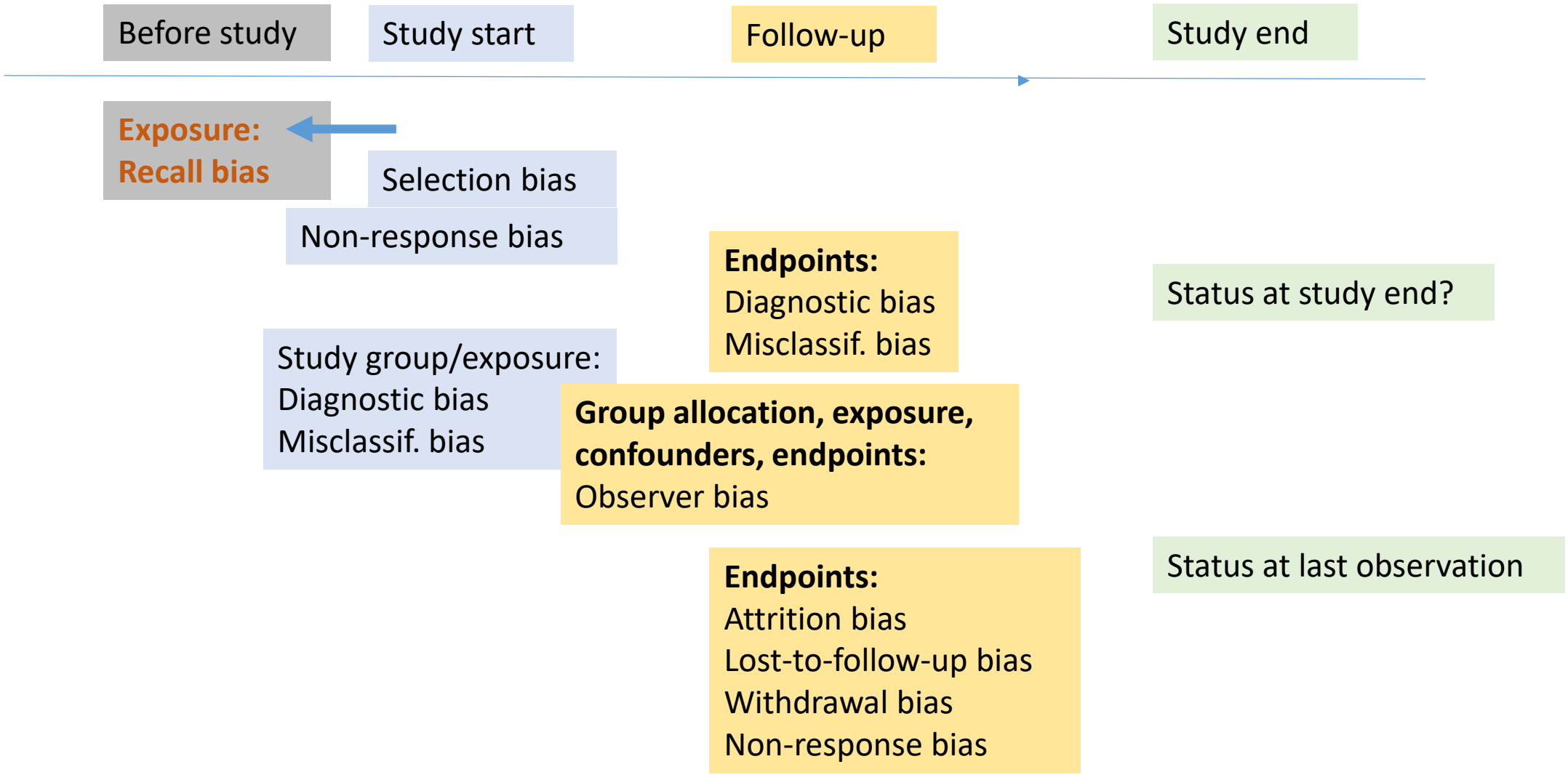
Publicity bias					

Bias and course of study



Selection bias

Participants in research may differ systematically from the population of interest.
For example, participants included in an influenza vaccine trial may be healthy young adults, whereas those who are most likely to receive the intervention in practice may be elderly and have many comorbidities, and are therefore not representative.
Similarly, in observational studies, conclusions from the research population may not apply to real-world people, **as the observed effect may be exaggerated or it is not possible to assume an effect in those not included in the study**.

The effect of HRT on coronary heart disease (CHD) in women. Several studies showed that HRT reduced coronary heart disease (CHD), but subsequent RCTs showed that HRT might increase the risk of CHD disease. The Women in the observational studies on HRT were more health conscious, more physically active, and had higher socioeconomic status than those not on HRT. This **self-selection** of women **(selection bias) led to confounding and a "healthy-user bias".**

A study of the prevalence of Parkinson's disease (PD) completed a door to door survey of an entire US county
Of the approximately 24,000 residents on prevalence day, 1 January 1978, PD was diagnosed in 31 participants. Thirteen of those 31 had never been seen for medical care. In this survey, if another approach to the **ascertainment** of cases had used only the medical care system, all of those who had not received care (over 40%) would not have been identified. Furthermore, there would have been no definitive way of characterizing the bias introduced if only those identified via health records were used.

Selection bias,
self-seleciton bias,
healthy-user bias,
ascertainment bias,
non-response bias

Preventive steps
To assess the probable degree of selection bias,
authors should include the following information at different stages of the trial or study:

– Numbers of participants screened/invited as well as included in study
- Responders/non-responders
- Screened/not-screened

– Intervention/exposure groups compared at baseline

– To what extent potential participants were re-screened

- Randomisation (RCT)

Reference: Haugan T, Skjeldestad FE, Halvorsen LE, Kahn H. A randomized trial on the clinical performance of Nova T 380 and Gyne T 380 Slimline cc

Design: RCT | **Grade assessment**

Aims

Selection bias?

Conclusion

Country

Year data collection

Easy to read ?

Table 1
Demographic, reproductive and contraceptive characteristics of study subjects

	Type of IUD (%)	
	Nova T®380	Gyne T®380 Slimline
	$n=470$	$n=487$
Year of insertion		
1993	34.9	36.1
1994	60.0	59.8
1995	5.1	4.1
Age at insertion (years)		
18–24	9.8	8.0
25–34	61.1	60.0
35–45		
Marital status		
Married		
Cohabiting		
Single		
Parity		
1		
2		
2+		
Weeks since last pregnancy		
7–12		
≥13		
Contraception used in the l		
None		
Copper IUD		
Barrier	31.9	32.0
Pill	10.4	9.7
Other	5.1	6.0
Ever used IUD?		
No	40.4	38.6
Yes	59.6	61.4
Subjects with prior IUD use	$n=280$	$n=299$
Any complications with prior IUD use?		
No	83.2	83.9
Yes	16.8	17.1

Preventive steps

To assess the probable degree of selection bias, authors should include the following information at different stages of the trial or study:

– **Numbers of participants invited as well as included in study**
- **Invited responders/Invited non-responders**

Checklist, comments

-Is the aim(s) clearly defined?

-Random assignment was conducted at the appropriate level/way?

-The study groups were similar at study start?

-Adequate blinding procedures; health personnel, outcomes?

-The study collected outcome data in the same way, and at the same time, from intervention and control group members?

outcomes, it reports (i) the size of the effect, and whether the size is of policy or practical importance; and (ii) tests showing the effect is statistically significant (i.e., unlikely to be due to chance).

Authors:
Strength
Limitations
Supporting literature
Plausible explanations?
Applicable to "real life"?

Did you learn something ?

Reference:

Design: RCT	Grade assessment	

Aims	M&M	Results	Checklist, comments
	- Recruitment of participants: - Selection of studypopulation: - Inclusion-/exclusion criterias: - Randomization procedures: - Intervention? - Outcome(s): - Validated: - Exposure: - Validated: - Confunders: - Statistical methods:	**Main outcome – related to the aim**	-Is the aim(s) clearly defined? -Random assignment was conducted at the appropriate level/way? -The study groups were similar at study start? -Adequate blinding procedures; health personnel, outcomes? -The study collected outcome data in the same way, and at the same time, from intervention and control group members? -The study obtained outcome data for a high proportion of the sample members originally randomized (low sample "attrition"). -Evaluation of study participants at study end (Lost-to-f-up)? -The study had an adequate sample size, large enough to detect meaningful effects of the intervention? -The study, in estimating the effects of the intervention, kept sample members in the original group to which they were randomly assigned (intention-to-treat/as treated)? -If the study claims that the intervention has an effect on outcomes, it reports (i) the size of the effect, and whether the size is of policy or practical importance; and (ii) tests showing the effect is statistically significant (i.e., unlikely to be due to chance). **Authors:** Strength Limitations Supporting literature Plausible explanations? Applicable to "real life"?
Conclusion			
Country			
Year data collection			
Easy to read ?	**Read several times ?**	**Can something be improved ?**	**Did you learn something ?**

Observer bias

The process of observing and recording information which includes systematic discrepancies from the truth

"Systematic difference between a true value and the value actually observed due to observer variation"

Many healthcare observations are open to systematic variation. For example, in the assessment **of medical images**, one observer might record an abnormality but another might not. Different observers might tend to round up or round down a measurement scale. **Colour change tests** can be interpreted differently by different observers. **Where subjective judgement is part of the observation, there is great potential for variability between observers**, and some of these differences might be systematic and lead to bias.
Observation of objective data, such as death, is at much lower risk of observer bias.

Observer bias - preventive steps

A key method is to ensure that outcome assessors are **blinded to the exposure status of study participants**. This can apply to randomised controlled trials, in which an individual has been allocated a particular intervention, and also to observational studies, which track the progress of study participants with different exposures. Achieving blinding might mean separating access for data on exposures from data on outcomes; in a blinded trial the allocation should remain unknown throughout the study (unless it must be revealed for safety reasons).

Strategies can also include **adequate training for observers in how to record findings, identifying any potential conflicts before recordings commence and clearly defining the methods,** tools and time frames for collecting data.

Another preventive aspect includes training study observers to become aware of their prejudices and habits, in order to improve accuracy.

Whilst observer bias can be reduced, it is likely that observer bias will always remain, and researchers should be aware of this when analysing and evaluating data.

Synonymous concepts: Observer bias – detection bias – ascertainment bias

Reference:

Design: RCT	Grade assessment	

Checklist, comments

Aims	M&M	Results

Conclusion

Country

Year data collectio

Easy to read ?

Table 2
Reasons for removal before Month 61

Reasons for removal	Type of IUD [*n* (%)]	
	Nova T®380 (*n*=470)	Gyne T®380 Slimline (*n*=487)
Insertion failure	4 (0.9)	7 (1.4)
Contraceptive failure	14 (3.0)	6 (1.2)
Total expulsion	9 (1.9)	6 (1.2)
Partial expulsion	4 (0.9)	14 (2.9)
Bleeding	94 (20)	95 (19.5)
Pain	19 (4.7)	20 (4.1)
Dysmenorrhea	8 (1.7)	4 (0.8)
PID	1 (0.2)	1 (0.2)
Other medical reasons	16 (3.4)	6 (1.2)
Personal reasons	98 (22.8)	122 (25.0)
Planning pregnancy	54 (11.5)	83 (17.0)
No longer in need of contraception	17 (3.6)	16 (3.3)
Wish to change method	25 (5.3)	19 (3.9)
Other	2 (0.4)	4 (0.8)
Lost to follow-up	27 (5.7)	24 (4.9)
Planned termination at 60 months (continued use)	173 (36.8)	182 (37.4)

Observer bias

Endpoints:

The process of observing and recording information which includes systematic discrepancies from the truth

-The study obtained outcome data for a high proportion of the sample members originally randomized (low sample "attrition").

-Evaluation of study participants at study end (Lost-to-f-up)?

-The study had an adequate sample size, large enough to detect meaningful effects of the intervention?

-The study, in estimating the effects of the intervention, kept sample members in the original group to which they were randomly assigned (intention-to-treat/as treated)?

-If the study claims that the intervention has an effect on outcomes, it reports (i) the size of the effect, and whether the size is of policy or practical importance; and (ii) tests showing the effect is statistically significant (i.e., unlikely to be due to chance).

Authors:

Strength

Limitations

Supporting literature

Plausible explanations?

Applicable to "real life"?

Did you learn something ?

Attrition bias

Unequal loss of participants from study groups in a trial.

Attrition occurs when participants leave during a study. It almost always happens to some extent.

Different rates of loss to follow-up in the exposure groups, or losses of different types of participants, whether at similar or different frequencies, may change the characteristics of the groups, irrespective of the exposure or intervention. Losses may be influenced by such factors as **unsatisfactory treatment efficacy or intolerable adverse events. (underreporting of endpoints – "false estimate/effect"**

When participants leave, it may not be known whether they continue or discontinue an intervention**; there may be no data on outcomes for these participants after that time.**

In some cases, those who leave a study are likely to be different from those who continue.
For instance, in an intervention study of diet in people with depression, those with more severe depression might find it harder to adhere to the diet regimen and therefore more likely to leave the study.

Reference:

Design: RCT | **Grade assessment**

Aims

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A rule of thumb states that <5% attrition leads to little bias, while >20% poses serious threats to validity.

Checklist, comments

-Is the aim(s) clearly defined?

-Random assignment was conducted at the appropriate level/way?

-The study groups were similar at study start?

-Adequate blinding procedures; health personnel, outcomes?

-The study collected outcome data in the same way, and at the same time, from intervention and control group members?

-The study obtained outcome data for a high proportion of the sample members originally randomized (low sample "attrition").

-Evaluation of participants at study end (LFU)?

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Authors:
Strength
Limitations
Supporting literature
Plausible explanations?
Applicable to "real life"?

Did you learn something ?

Attrition bias - preventive steps

Techniques for preventing losses follow-up include ensuring good communication between study staff and participants, accessibility to clinics, effective communication channels, incentives to continue, and ensuring that the study is of relevance to the participants.

However, for many studies, complete follow up is unlikely.

Intention to treat analysis: Because anything that happens after randomisation can affect the chance that a study participant has the outcome of interest, it is important that all patients (even those who fail to take their medicine or accidentally or intentionally receive the wrong treatment) are analysed in the groups to which they were allocated.

Methods for dealing with missing data include last observation (or baseline value) carried forward, mixed models, imputation and sensitivity analysis using 'worst case' scenarios (assuming that those with no information all got worse) and 'best case' scenarios (assuming that all got better).

A rule of thumb states that <5% attrition leads to little bias, while >20% poses serious threats to validity.

While this is useful, it is important to note that even small proportions of patients lost to follow-up can cause significant bias. One way to determine whether losses to follow-up can seriously affect results is to assume a **worst-case scenario for the outcomes** in those with missing data and look to see if the results would change. If this method doesn't change the study's conclusions, the loss to follow-up is likely not a threat to the study's validity.

Publication bias

When the likelihood of a study being published is affected by the findings.

Publication bias as the failure to publish the results of a study “on the basis of the direction or strength of the study findings.”

This **non-publication** introduces a **bias** which impacts the ability to accurately synthesize and describe the evidence in a given area. **Publication bias is a type of reporting bias** and closely related to **dissemination bias**, although dissemination bias generally applies to all forms of results dissemination, not simply journal publications.

A variety of distinct biases are often grouped into the overall definition of publication bias

Preventive steps - publication bias

Certain journals have made the solicitation and publication of null results a part of their core mission. However many of the documented barriers to publication cannot be addressed by the presence of journals receptive to null results.

The preceding decade has seen various initiatives in the US and EU requiring certain trials to report results directly onto **clinical trial registries in structured data format within 12 months of completion, providing an additional data source without the barriers to publication in academic journals.** Sadly there is growing evidence that these laws and guidelines are undermined by loopholes and poor compliance.

Authors of systematic reviews and meta-analyses can also take steps to reduce the impact of non-publication on their work. The search for evidence should not be limited to only journal articles indexed in repositories such as PubMed or Ovid. Authors can and should search for results through other routes including trial registries, regulatory documents, and contacting trialists of known or suspected unpublished work.

They can also use **statistical methods** to estimate if their sample of studies is likely impacted by publication bias.

Drug-industry-funded research – publication bias

- A Cochrane review concluded that drug-industry-funded studies overestimated efficacy and underestimated potential side effects (Lundh A et al., 2012)

- These are examples of reporting bias and publication bias

OPEN ACCESS

Financial ties of principal investigators and randomized controlled trial outcomes: cross sectional study

Rosa Ahn,[1] Alexandra Woodbridge,[2] Ann Abraham,[2] Susan Saba,[3] Deborah Korenstein,[4] Erin Madden,[2] W John Boscardin,[2,5] Salomeh Keyhani[2,5]

[1]Oregon Health and Science University, Portland, OR 97239, USA
[2]San Francisco VA Medical Center, San Francisco, CA 94121, USA
[3]Stanford Univer... Medicine, Palo A... USA
[4]Memorial Sloan... Cancer Center, N... 10065, USA
[5]University of California, San Francisco, San Francisco, CA 94121, USA
Correspondence to: S Keyhani
salomeh.keyhani@ucsf.edu
Additional material is published online only. To view please visit the journal online.

ABSTRACT

OBJECTIVE
To examine the association between the presence of individual principal investigators' financial ties to the manufacturers of the study drug and the trial's outcomes.

SETTING
Studies published in "core clinical" journals, as identified by Medline, between 1 January 2013 and 31 December 2013.

PARTICIPANTS
Random sample of RCTs focused on drug efficacy.

MAIN OUTCOME MEASURE

3.23, 95% confidence interval 1.7 to 6.1). In the primary multivariate analysis, a financial tie was significantly associated with positive RCT outcome after adjustment for the study funding source (odds ratio 3.57 (1.7 to 7.7). The secondary analysis controlled for additional appreciably affect the relation between financial ties and study outcomes (odds ratio 3.37, 1.4 to 7.9).

CONCLUSIONS
Financial ties of principal investigators were independently associated with positive clinical trial results. These findings may be suggestive of bias in the evidence base.

Conclusions:
Financial ties of principal investigators were independently associated with positive clinical trial results.

BMJ 2017; 356: i6770

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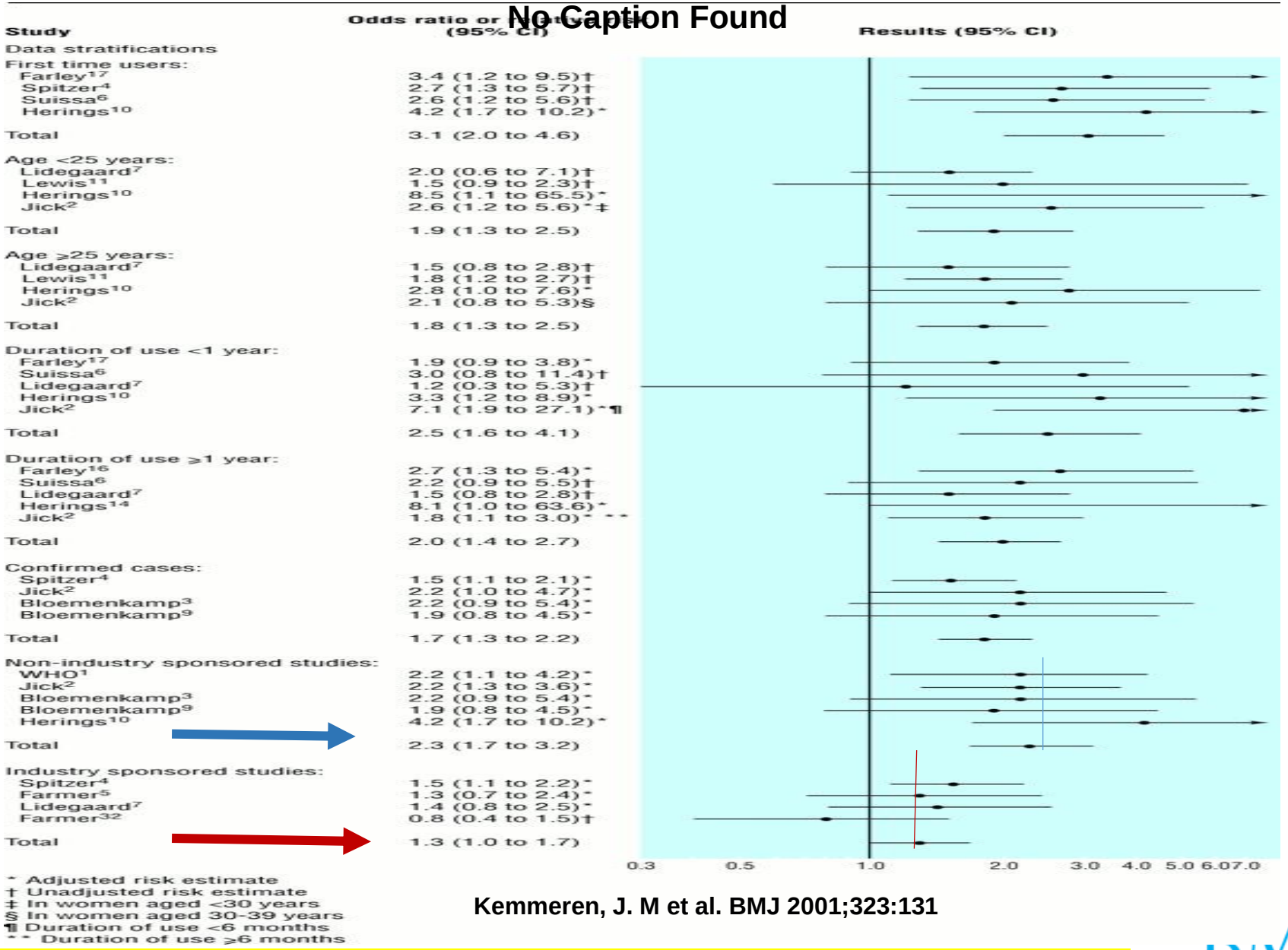

Kemmeren, J. M et al. BMJ 2001;323:131

Third generation oral contraceptives and risk of venous thrombosis: meta-analysis

Publicity bias – small studies of poor quality are repeated

- **Breakthrough in «research field»**
- **Large professional attention**
- **Large media attention**

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Renal denervation

Renal denervation (RDN) is a minimally invasive procedure to treat resistant hypertension.

The procedure uses radiofrequency ablation to burn the nerves in the **renal** arteries.

This process causes a reduction in the nerve activity, which decreases blood pressure?

Renal denervation (1)

Indication: Treatment-resistant hypertension

- Esler MD, Krum H, Sobotka PA, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial.
- **Results**: Intervention: BP reduced by **32/12 mmHg**
  Treatment as ususal: **1/0 mmHg**

- Conclusion: Catheter-based renal denervation **can safely be used to substantially reduce blood pressure** in treatment-resistant hypertensive patients

Lancet. 2010;376(9756):1903

Renal denervation (2)

- Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months.
- **Results**: Office bloodpressure reduced **25/11 mmHg** at 6 months
  32/14 mmHg after 24 months
- Good efficacy!!

Hypertension. 2011;57(5):911

Renal denervation (3)

- Mahfoud F, Ukena C, Schmieder RE, et al. Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension.

- **Results**: Office BP reduced by **23/9 mmHg**.
  24 hours BP reduced by **10/5 mmHg**

- **Good efficacy!**

Circulation. 2013;128(2

Renal denervation (4)

- Davis MI, Filion KB, Zhang D. Effectiveness of renal denervation therapy for resistant hypertension: a systematic review and **meta-analysis**.

- Conclusion: “RDN resulted in a **substantial reduction** in mean BP at 6 months in patients with resistant hypertension. The decrease in BP was similar irrespective of study design and type of catheter employed.
- **Large randomized controlled trials with long-term follow-up are needed** to confirm the sustained efficacy and safety of RDN”

J Am Coll Cardiol. 2013;62(3):231.

Renal denervation

- Implemented as treatment in 80 countries by 2014

Renal denervation (5)

- Bhatt DL, Kandzari DE, O'Neill WW, et al: SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension.
- Results: Systolic BP reduced by **14 mmHg** 6 mo after denervation
  12 mmHg after sham surgery
  24 hours BP reduced by **6,7 mmHg**
  4,8 mmHg

- Conclusion: “This blinded trial **did not show a significant reduction** of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control”

- No effect

N Engl J Med. 2014 Apr;370(15):1393-401. Epub 2014 Mar 29

Renal denervation (1)

- Esler MD, Krum H, Sobotka PA, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial.

- **Results**: Intervention: BP reduced by **32/12 mmHg**
  Treatment as ususal: **1/0 mmHg**

- Conclusion: Catheter-based renal denervation **can safely be used to substantially reduce blood pressure** in treatment-resistant hypertensive patients

Lancet. 2010;376(9756):1903

- Sample size: n=106
- Open, not blinded, RCT
- Office BP

Renal denervasjon (2)

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- Patientseries

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Circulation. 2013;128(2):132

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  patients with resistant hypertension 6 r
  sham control”
- No effect

- Sample size > 500 pasients
- Randomised
- Dobbleblinded
- Placebo-controlled (sham surgery)

N Engl J Med. 2014 Apr;370(15):1393-401. Epub 2014 Mar 29

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