Selective reporting bias of harm outcomes within studies: findings from a cohort of systematic reviews

Pooja Saini,[1] Yoon K Loke,[2] Carrol Gamble,[3] Douglas G Altman,[4] Paula R Williamson,[3] Jamie J Kirkham[3]

EDITORIAL by Reeves

[1]Department of Public Health and Policy, University of Liverpool, Liverpool, UK
[2]Norwich Medical School, University of East Anglia, Norwich, UK
[3]Department of Biostatistics, University of Liverpool, Liverpool, L69 3GA, UK
[4]Centre for Statistics in Medicine, University of Oxford, Oxford, UK
Correspondence to: J J Kirkham
jjk@liv.ac.uk

Cite this as: *BMJ* 2014;349:g6501
doi: 10.1136/bmj.g6501

This is a summary of a paper that was published on thebmj.com as *BMJ* 2014;349:g6501

STUDY QUESTION

Do authors of primary studies suppress or partially report data on harm outcomes for bias related reasons?

SUMMARY ANSWER

Outcome reporting bias (ORB) may occur when the harm outcome has been measured, but the data are presented or suppressed in a way that would mask the harm profile of particular interventions.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

ORB has previously been identified as a threat to evidence based medicine. Primary data on harm outcomes were missing from at least one eligible study in over 75% of reviews assessed.

Design and size

A 13 point classification system for missing data on harm outcomes in both randomised controlled trials and non-randomised studies was applied to studies included in a large cohort of 92 Cochrane and 230 non-Cochrane systematic reviews of adverse events.

Classification system

Classification	Description	Level of reporting	Risk of bias*
Explicit specific harm outcome			
Measured and compared across treatment groups:			
P1 and P2	States outcome analysed but reported only that P>0.05	Partial	High risk
P3	Insufficient reporting for meta-analysis or full tabulation	Partial	Low risk
Measured but not compared across treatment groups:			
Q	Clear that outcome was measured and clear outcome was not compared	NA	No risk
Measured, not clear whether compared or not across treatment groups†			
R1	Clear that outcome was measured but no results reported	None	High risk
R2	Result reported globally across all groups	None	High risk
R3	Result reported for some groups only	None	High risk
Specific harm outcome not explicitly mentioned			
Clinical judgment says likely measured and likely compared across treatment groups:			
S1	Only pooled adverse events reported (could include specific harm outcome)	None	High risk
S2	No harms mentioned or reported	None	High risk
Clinical judgment says likely measured but no events:			
T1	Specific harm not mentioned but all other specific harms fully reported	None	Low risk
T2	No description of specific harms	None	Low risk
Specific harm outcome not explicitly mentioned, clinical judgment says unlikely measured			
U	No harms mentioned or reported	None	Low risk
Explicit the specific harm outcome was not measured			
V	Report clearly specifies that data on specific harm of interest was not measured	NA	No risk

NA=not applicable (clear that outcome was not going to be compared).
*Bias would occur if specific harm had been measured, but data were presented or suppressed in a way that would mask the harm profile of particular interventions.
†Clinical judgment says likely measured and likely compared across treatment groups.

Source of effectiveness

Using the classification system, methodologists, systematic reviewers, and a senior clinical pharmacologist examined the publications of primary studies to determine the likely reason why a primary review harm outcome was suppressed or partially reported. We considered studies to be at "high risk" of ORB if authors thought the reason for the missing harm data would greatly impact on the treatment effect in meta-analysis.

Data

All new Cochrane reviews published in a six month period and a cohort of reviews synthesising data on harm outcomes identified between 2007 and 2011. Reviews were eligible for further scrutiny if at least one eligible study did not report on the agreed single primary review harm outcome.

Main results

86% (79/92) of reviews in the Cochrane cohort did not include full data from the main harm outcome of interest of each review for all of the eligible studies included within that review; 76% (173/230) for the adverse event cohort. Overall, the single primary harm outcome was inadequately reported in 76% (705/931) of the studies included in the 92 reviews from the Cochrane cohort and not reported in 47% (4159/8837) of the 230 reviews in the adverse event cohort. In a sample of primary studies not reporting on the single primary harm outcome in the review, ORB was suspected in nearly two thirds (63%, 248/393) from scrutiny of the publication.

Bias, confounding, and other reasons for caution

We chose to look at one primary review harm outcome for assessment from each review. It is possible that the reviewers or pharmacological expert selected the harm outcomes because they were well recognised, important, serious, or common. For pragmatic reasons we only applied the classification system to a sample of reviews with the fewest studies for assessment. We do not suspect that our sampling strategy will have impacted importantly on the results of this study as the reviews were unselected for type of harm, intervention, and population. However, if more studies existed in an area, the expectation that specific harms would have been measured might be greater, so the level of suspicion would be higher in the reviews we did not assess. The consequence of these limitations is such that the harm outcomes we evaluated would have been less prone to ORB. Hence our findings may actually underestimate the greater scale of the problem.

Study funding/potential competing interests

All researchers are independent of the funding body, the Medical Research Council. YL is co-convenor of the Cochrane Adverse Effects Methods Group.

Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population based cohort study

Maarten J G Leening,[1 2 3] Bart S Ferket,[1 4 5] Ewout W Steyerberg,[6] Maryam Kavousi,[1] Jaap W Deckers,[2] Daan Nieboer,[6] Jan Heeringa,[1] Marileen L P Portegies,[1 7] Albert Hofman,[1 3] M Arfan Ikram,[1 4 7] M G Myriam Hunink,[1 4 8] Oscar H Franco,[1] Bruno H Stricker,[1 9 10] Jacqueline C M Witteman,[1] Jolien W Roos-Hesselink[2]

[1]Department of Epidemiology, Erasmus MC-University Medical Center Rotterdam, Rotterdam, Netherlands
[2]Department of Cardiology, Erasmus MC-University Medical Center Rotterdam, Rotterdam, Netherlands
[3]Department of Epidemiology, Harvard School of Public Health, Boston, MA, US
[4]Department of Radiology, Erasmus MC-University Medical Center Rotterdam, Rotterdam, Netherlands
[5]Institute of Healthcare Delivery Science, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY, US
[6]Department of Public Health, Erasmus MC-University Medical Center Rotterdam, Rotterdam, Netherlands
[7]Department of Neurology, Erasmus MC-University Medical Center Rotterdam, Rotterdam, Netherlands
[8]Department of Health Policy and Management, Harvard School of Public Health, Boston, MA, US
[9]Department of Internal Medicine, Erasmus MC-University Medical Center Rotterdam, Rotterdam, Netherlands
[10]Inspectorate for Health Care, The Hague, Netherlands
Correspondence to: B H Stricker, Department of Epidemiology (NA-2818), Erasmus MC-University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, Netherlands
b.stricker@erasmusmc.nl

Cite this as: *BMJ* 2014;349:g5992
doi: 10.1136/bmj.g5992

This is a summary of a paper that was published on thebmj.com as *BMJ* 2014;349:g5992

STUDY QUESTION

What are the differences in lifetime risk of cardiovascular disease and first manifestations of cardiovascular disease between men and women?

SUMMARY ANSWER

At age 55, men and women have similar lifetime risks of cardiovascular disease, though men are more likely to develop coronary heart disease as first event, whereas women are more likely than men to have cerebrovascular disease or heart failure as their first event, although these manifestations appear most often at older age.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Considerable sex differences exist in the lifetime incidence of various forms of cardiovascular disease. The large differences in the first manifestation of cardiovascular disease between men and women found in this study underscore the importance of adequate control of risk factors for stroke and heart failure in primary prevention of cardiovascular disease. Risk factors other than hyperlipidaemia should be considered as lipid lowering therapy has not so far been proved beneficial in reducing risk of heart failure. Lifestyle modification and blood pressure control are the main targets for prevention of heart failure, especially in women, in whom blood pressure has a more prominent role in the development of heart failure.

Participants and setting

People living in the community in Rotterdam, the Netherlands.

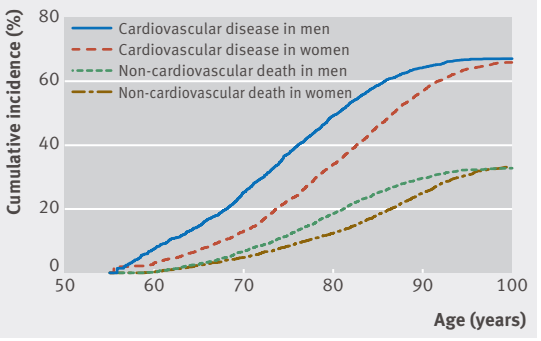
Design, size, and duration

A prospective population based cohort study among 8419 people (60.9% women), aged ≥55 and free from cardiovascular disease at baseline (1990-93 or 2000-01). We calculated lifetime risks of cardiovascular disease and its first incident manifestations, adjusted for competing non-cardiovascular death based on up to 20 years of follow-up. We defined first manifestations as coronary heart disease (myocardial infarction, coronary revascularisation, and coronary death), cerebrovascular disease (stroke, transient ischaemic attack, and carotid revascularisation), heart failure, or other cardiovascular death.

Main results and the role of chance

A total of 2888 participants developed cardiovascular disease (826 manifested with coronary heart disease, 1198 with cerebrovascular disease, 762 with heart failure, and 102 with other cardiovascular death). At age 55, lifetime risks of cardiovascular disease were 67.1% (95% confidence interval 64.7% to 69.5%) for men and 66.4% (64.2% to 68.7%) for women. The cumulative incidence of cardiovascular disease in men increased steadily with age, whereas in women up to the age of 70 the cumulative incidence remained low and increased more steeply thereafter. Lifetime risks of first incident manifestations of cardiovascular disease in men were 27.2% (24.1% to 30.3%) for coronary heart disease, 22.8% (20.4% to 25.1%) for cerebrovascular disease, 14.9% (13.3% to 16.6%) for heart failure, and 2.3% (1.6% to 2.9%) for other deaths from cardiovascular disease. For women the figures were 16.9% (13.5% to 20.4%), 29.8% (27.7% to 31.9%), 17.5% (15.9% to 19.2%), and 2.1% (1.6% to 2.7%), respectively. Differences in number of events that developed over the lifespan in women compared with men (per 1000 women) were −7 for any cardiovascular disease, −102 for coronary heart disease, 70 for cerebrovascular disease, 26 for heart failure, and −1 for other cardiovascular death; all outcomes manifested at a higher age in women.

Cumulative incidence of cardiovascular disease and competing non-cardiovascular death for 55 year old men and women



Bias, confounding, and other reasons for caution

Non-invasively managed angina was not adjudicated. Also, lifetime risks of cardiovascular disease are somewhat underestimated because of the lack of data on non-fatal peripheral vascular disease and non-fatal abdominal aortic aneurysms.

Generalisability to other populations

Lifetime risk of cardiovascular disease and its manifestations are known to vary by race and our results might therefore not be generalisable to non-white populations.

Study funding and competing interests

This work was supported by the Erasmus MC Thorax Foundation; the Physico Foundation; De Drie Lichten Foundation; the Netherlands Organisation for Health Research and Development; and the Netherlands Organisation for Scientific Research. The authors report no competing interests related to this work.

Oral contraceptive use and mortality after 36 years of follow-up in the Nurses' Health Study: prospective cohort study

Brittany M Charlton,[1-3] Janet W Rich-Edwards,[1 4 5] Graham A Colditz,[6] Stacey A Missmer,[1 5 7] Bernard A Rosner,[5] Susan E Hankinson,[1 5 8] Frank E Speizer,[5 9] Karin B Michels[1 5 10]

[1]Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, MA, USA
[2]Division of Adolescent and Young Adult Medicine, Boston Children's Hospital, Boston, MA, USA
[3]Department of Pediatrics, Harvard Medical School, Boston, MA, USA
[4]Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital, Harvard Medical School, Boston, USA
[5]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[6]Department of Surgery, Washington University School of Medicine, St Louis, MO, USA
[7]Division of Reproductive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[8]Division of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA, USA
[9]Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA
[10]Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
Correspondence to: K B Michels **kmichels@research.bwh.harvard.edu**

Cite this as: *BMJ* 2014;349:g6356
doi: 10.1136/bmj.g6356

This is a summary of a paper that was published on thebmj.com as *BMJ* 2014;349:g6356

thebmj.com
Read responses to this article at http://www.bmj.com/content/349/bmj.g6356/rapid-responses

STUDY QUESTION

Is oral contraceptive use associated with total and cause specific mortality?

SUMMARY ANSWER

Total all cause mortality did not differ significantly between women who had ever used and those who had never used oral contraceptives. Oral contraceptive use was associated with certain specific causes of death, including increased violent or accidental as well as breast cancer deaths and decreased mortality due to ovarian cancer.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Oral contraceptive use may reduce some health risks, such as ovarian cancer while increasing others, such as venous thromboembolism and myocardial infarction, but the long term risks, including mortality, remain unclear. Our study draws from one of the largest cohorts with the longest follow-up to examine lifetime of oral contraceptive use and mortality. We observed no association between ever use of oral contraceptives and all cause mortality but an increase in breast cancer mortality.

Participants and setting

Nurses' Health Study, data collected between 1976 and 2012.

Design, size, and duration

Prospective cohort study. A total of 121 701 participants were prospectively followed for 36 years. Lifetime oral contraceptive use was recorded biennially from 1976-82.

Main results and the role of chance

In our population of 121 577 women with information on oral contraceptive use, 63 626 were never users (52%) and 57 951 were ever users (48%). After 3.6 million person years, we recorded 31 286 deaths. No association was observed between ever use of oral contraceptives and all cause mortality. However, violent or accidental deaths were more common among ever users (hazard ratio 1.20, 95% confidence interval 1.04 to 1.37) but this was not associated with longer duration of use. Longer duration of use was more strongly associated with certain causes of death, including increased rates of breast cancer (test for trend P<0.0001) and decreased rates of ovarian cancer (P=0.002). Longer time since last use was also associated with certain outcomes, including a positive association with violent or accidental deaths (P=0.005).

Bias, confounding, and other reasons for caution

We adjusted for numerous potential confounders, including use of other exogenous hormones, such as postmenopausal hormone therapy throughout follow-up. The increase in violent and accidental deaths might not be causally related to oral contraceptive use, as we found no association with duration of use. One might speculate that it may be due to increased intimate partner violence among ever users, since these women may be in relationships where violence may take place, but this could not be adequately evaluated in our study. Nonetheless, compared with more common causes of death, the absolute risk of a violent or accidental death was low.

Generalisability to other populations

The generalisability of our findings may be limited by the fact that our population was homogenous for race and formulations of oral contraceptives. The results of the present study pertain to earlier oral contraceptive formulations with higher hormone doses rather than the now more commonly used third and fourth generation formulations with lower oestrogen doses.

Study funding/potential competing interests

The Nurses' Health Study was supported by research grants P01CA87969, R01HL034594, and R01HL088521 from the National Institutes of Health. BMC was supported by T32HD060454 and T32CA09001 from the National Institutes of Health. We have no competing interests.

Total and cause specific mortality in ever and never users of oral contraceptives among 121 577 participants of the Nurses' Health Study, 1976-2012

Cause of death	Never users	Ever users	Adjusted hazard ratio (95% CI)
All causes	20 646	10 640	1.02 (0.99 to 1.04)
All cancers	7420	4361	1.01 (0.97 to 1.05)
Breast cancer	1387	908	1.08 (0.98 to 1.18)
Ovarian cancer	538	314	0.86 (0.74 to 1.00)
All cardiovascular diseases	4257	1775	1.00 (0.94 to 1.06)
All digestive diseases	549	306	1.10 (0.95 to 1.28)
Violence/accidents	640	444	1.20 (1.04 to 1.37)
Suicide	111	130	1.41 (1.05 to 1.87)
Other diseases	6182	3030	1.05 (1.00 to 1.10)
Unconfirmed	2916	1465	0.98 (0.91 to 1.04)