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LETTERS



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FINANCIAL TIES THAT MIGHT BIND

Delve deeper to find the links

The finding by Yank et al of no connection between results in meta-analyses and financial ties is surprising,¹ given the greater deficiencies for reporting of harm outcomes among trials that were solely funded by industry (median 56% per trial) than among trials that were not (27%).² Evidently the Oxman-Guyatt measure of scientific quality of research reviews used by Yank et al cannot capture discrepancies in original research protocols and their published form and the selective reporting of outcomes, both of which are prevalent in randomised trials.²

Firstly, bias in reporting outcomes acts in addition to and in the same direction as publication bias of entire studies to produce inflated estimates of the effects of treatment.²

Secondly, the antidote is to require registration of all trials and protocols in the public domain before completing the study and to assure that they be made available along with any manuscript undergoing peer review for journal publication.

Thirdly, belief that the collected raw data are somehow unaffected by the artefacts of research design, sampling, and measurement is mistaken. Epstein's dismissal of the importance of the findings of Yank et al and his strained argument to justify problematic practices of the drug and medical device industry are based on such misunderstanding.³ Epstein's assertion that nothing in the work of Yank et al suggests that the raw data from the drug sponsored studies were defective³ overlooks the use of the Oxman-Guyatt measure of research quality as a statistical control variable.

Epstein's choice of more studies whose quality may be more biased over fewer studies of presumably better quality makes no sense except from the self interested perspective of the industry. His argument that government

intervention in the form of legal restrictions would be economically dysfunctional asserts the interests of industry,⁴ whereas in welfare economics regulatory intervention is sometimes the solution for market failure. Widespread premeditated bias in published and unpublished reports of clinical trials linked to industry sponsorship is "smoking gun" evidence of market failure.⁵

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- 4 Epstein RA. Pharma furore: why two high-profile attacks on big drug companies flunk the test of basic economics. *Legal Affairs* 2005 (Jan/Feb).
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Consider palliative coronary intervention

The recommendation by Yank et al, that pharma sponsored drug trials should be interpreted with caution, is well made.¹ Most percutaneous coronary intervention (PCI) procedures entail the implantation of a coronary stent. Most stent studies are funded by equipment manufacturers and are designed and conducted by researchers who believe in coronary intervention despite the lack of hard evidence of cost effectiveness or clinical superiority over optimal medical therapy.^{2,3}

Therapists' irrational faith in intuitive based practice adds an extra dimension to the "positive spin" effect described in the paper. Given the paucity of independently funded coronary stent studies and the total lack of a placebo controlled study of this palliative therapy, healthcare commissioners have a hard time unravelling spin, especially when professional bodies weigh in with their spin on the evidence.

The RITA-2 study showed that, although palliative PCI was associated with a small and transient improvement in symptoms, it increased the incidence of myocardial

infarction or death by nearly 80% and was £2684 more costly than medical therapy.^{4,5} Despite these worrying results the British Cardiovascular Intervention Society (BCIS) strongly lobbied for an expansion of PCI. What grounds did BCIS have for supporting the rapid expansion of palliative PCI despite its poor showing in RITA-2?

The study reported by Yank et al implies that it would be prudent to take account of the relation between BCIS and industry when assessing BCIS's recommendations. A search through UK professional bodies' websites shows that BCIS seems to be the only UK professional body to admit to having two industry representatives on its council.

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Competing interests: MRC provides advice to PCT/PBC Commissioners on patient centred angina service redesign.

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RCGP'S ORAL CONTRACEPTION STUDY

Study shows greater cancer risk

Hannaford et al reported a significant 12% reduction in the risk of any cancer (adjusted relative risk 0.88, 95% confidence interval 0.83 to 0.94), which was widely cited in the popular media as reassuring evidence of the safety of oral contraceptives.¹ But although it was prudent to exclude participants under age 38 at time of loss to follow-up, since use of oral contraceptives after that time would be unknown, the authors selectively excluded only non-users at the time of loss to follow-up.

In their discussion, Hannaford et al report

that an analysis of the data with all participants under 38 at time of loss to follow-up excluded gave a null result (0.95, 0.88 to 1.02). Hence they disproved their own overall result, clearly showing that their significant overall protective effect of oral contraception was an artefact resulting from the biased exclusion criterion.

Furthermore, they report an increase in breast cancer risk, peaking (relative risk 2.45) between 15 and 20 years after cessation of use instead of disappearing 10 years after cessation of use, as others have reported.² They also report a significant risk increase (1.22) for any cancer and for breast cancer with more than eight years of using oral contraceptives. Although they note that fewer than a quarter of users in their study had used oral contraceptives for that long, current patterns of use are usually for much longer periods and also more often start before first full term pregnancy, a use pattern producing threefold increases in the risk of breast cancer.³ A further finding is the strong association for cancers of the central nervous system or pituitary, with the relative risk for these cancers steadily rising to 5.51 with more than eight years' use.

Their conclusion that the cancer benefits associated with oral contraception outweigh the risks is therefore irresponsible, as their results imply the opposite.

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- 1 Hannaford PC, Selvaraj S, Elliott AM, Angus V, Iversen L, Lee AJ. Cancer risk among users of oral contraceptives; cohort data from the Royal College of General Practitioners' oral contraception study. *BMJ* 2007;335:651. (29 September.)
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Authors' reply

We presented all relevant results so that readers could decide for themselves whether their interpretation of our findings fits with ours. Brind thinks that the analysis in which both ever and never users lost to follow-up before the age of 38 were excluded (adjusted relative risk 0.95, 95% confidence interval 0.88 to 1.02) shows serious bias and invalidates the main dataset results in which only never users younger than 38 were excluded (0.88, 0.83 to 0.94). Since the total population in each analysis is different, their results should not be compared directly (in the same way that the results from the main and the

general practitioner observation dataset should not be compared directly, as indicated in the footnote to table 2).

Furthermore, the different standard populations inevitably result in some variation in the point estimates from each analysis. The point estimate of 0.95 from the "fully excluded" analysis is not materially different from that of 0.88 from the "partially excluded" analysis, although the latter is based on more data. In addition, the upper 95% confidence interval of the fully excluded point estimate was just above unity, suggesting no increased risk of overall cancer.

The subgroup analyses of duration and time since last use of oral contraception included a large number of comparisons, some of which may have reached significance by chance. Although the relative risk of breast cancer was raised among ever users who had stopped 15-20 years previously, it was decreased in those who had stopped more than 20 years previously (0.54, 0.35 to 0.82) and the trend over time was not significant. We cannot explain the increased risk of central nervous system/pituitary cancer among ever users, although the number of women affected was small (49 of the 3877 cancers in the main dataset). We highlighted and discussed the increased risk of any cancer among women using oral contraception for more than eight years in the paper, press releases, and media interviews. Our interpretation remains that oral contraception was not associated with an overall increased risk of cancer—indeed it may even produce a net public health gain.

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Competing interests: PCH's academic department has recently received payment from Wyeth Pharmaceuticals for a lecture on the role of hormone replacement therapy in clinical practice. Wyeth also manufactures oral contraceptives.

CIRCUMCISION: RIGHT OR WRONG?

Summary of responses

The head to head debate on whether infant male circumcision is an abuse of the rights of the child provoked almost 100 responses,¹⁻⁴ all forceful and emotive opinions on a custom whose foundations seem to be primarily sociocultural and religious. Respondents—most of them men—included a doctor who had never received any complaints from his circumcised patients in many years of practice and respondents



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reporting their own beneficial or adverse effects of the procedure; advocates of circumcision and adversaries who see it as an act of trauma, betrayal, or aggression, tantamount to amputation or mutilation.

Reasons for infant circumcision include medical indications and protective effects in the transmission of sexually transmitted infections (especially HIV/AIDS).

Reasons against include the lack of a medical indication, without which it is "cosmetic" surgery at best and abuse and mutilation at worst. The side effects can be serious, and deaths have been reported.

The foreskin has a role in male sexual health, and circumcision is more than merely another disagreeable experience like vaccination that infants are being subjected to. Were circumcision a new procedure, ethics approval, scientific support, cooperation from colleagues, trial participants, and government or charity funding would not be forthcoming. The costs to the NHS of an "unnecessary" procedure also need to be taken into consideration. In the United States reconstructive surgery is a lucrative industry.

Many respondents suggest postponing circumcision to adolescence or even adulthood to avoid conflict between the rights of the child and those of the parents. Others think that it is the parents' right to decide to have their baby boy circumcised, in the same way that they decide what's best for him in other respects.

Some call for studies of a cohort of circumcised men to establish how much they may have been harmed physically and psychologically from being circumcised as babies. Some think that stopping male circumcision world wide would end female genital mutilation too.

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- 2 Rapid responses. Is infant male circumcision an abuse of the rights of the child? No. *bmj.com* 2007 www.bmj.com/cgi/content/full/335/7631/1181
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