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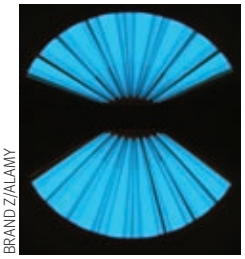
RESEARCH



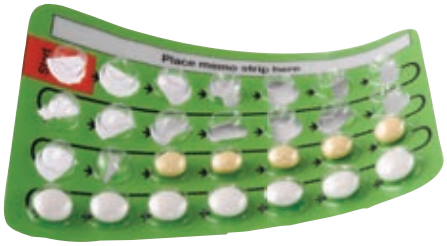
BRAND Z/ALAMY

THIS WEEK'S RESEARCH QUESTIONS

CONSORT 2010

We're delighted to be publishing the updated Consolidated Standards of Reporting Trials Statement this week (p 698), with a full explanation and worked examples online (*BMJ* 2010;340:c332, doi:10.1136/bmj.c332). And Sally Hopewell and colleagues' study shows that the methods of randomised controlled trials have been reported much more fully since the last version of the statement was published nearly a decade ago (p 697). Editorialist Gerd Antes applauds this important initiative, but wishes more authors would prepare their manuscripts using CONSORT: it's up to editors to encourage them or even insist, as we do at the *BMJ* (p 665).

Long term mortality among users and never users of the contraceptive pill



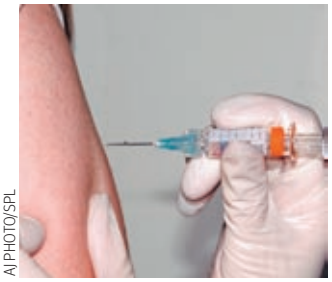
In May 1968, while strikes and student protests gripped France and the Summer of Love warmed up, 1400 British general practitioners got busy recruiting thousands of women on the pill (plus a control group) into the Royal College of General Practitioners' Oral Contraception Study. Early reports from this cohort suggested there was excess mortality from vascular problems among women using oral contraceptives, particularly those who were older or were smokers.

Now, after nearly 40 years' follow-up, Philip C Hannaford and colleagues report that women who used the pill had significantly lower mortality from any cause compared with never users (adjusted relative risk 0.88, 95% confidence interval 0.82 to 0.93; p 695). The authors acknowledge that there may have been unmeasured confounding factors, and they note that the study excluded women with chronic disease and had incomplete follow-up. They are, however, at a loss to explain why these factors would affect calculations of mortality risk for one group and not the other. Despite this cautious interpretation, several rapid responders thought the study's conclusions were too positive (http://www.bmj.com/cgi/eletters/340/mar11_1/c927).

How to get published in the *BMJ*

We've produced a short video to help you find out about getting research published in the *BMJ*. It includes interviews with published authors and clips from short films that accompany some of our important research articles.
We also have a presentation that the *BMJ* editors give at conferences. This slideshow includes, among other things, how to write a research paper, scientific misconduct, and how to please editors.
Find the material at: http://www.bmj.com/video/. We can also supply the video in DVD format if you would like to include it in a presentation but do not have a suitable internet connection—email jhayes@bmj.com for more details.

Vaccination for human papillomavirus (HPV) and pregnancy outcomes



AJ PHOTO/SPL

This study by Sholom Wacholder and colleagues was commissioned by a data and safety monitoring board after a planned interim analysis showed imbalance in the miscarriage rates between the two arms of a large trial of the Cervarix vaccine (p 696). There was, in theory, a chance that the vaccine might alter maternal immune function in early pregnancy and lead to miscarriage, but this robust pooled analysis of data from that trial and another found no such risk overall. The authors couldn't completely rule out the possibility of an increased risk of miscarriage for conceptions within three months of vaccination, but editorialist Karen Canfell says their study provides continuing reassurance on the positive balance of risk for the millions of young females vaccinated against HPV (p 666).

When this study was published on bmj.com a few weeks ago, Jo Waller and Jane Wardle from University College London were concerned that its title, which begins "Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18," might wrongly imply that there is a definite risk (http://www.bmj.com/cgi/eletters/340/mar02_1/c712). *Journal Watch*, which gave the study considerable prominence, avoided this pitfall: their summary of it was simply entitled "Pregnancy outcomes after HPV vaccination" (http://www.jwatch.org/).

LATEST RESEARCH: For these and other new research articles see http://www.bmj.com/channels/research.dtl

Advance care planning for end of life care
In this randomised controlled trial, medical inpatients aged 80 or more were allocated (or not) to receive expert help in making plans about treatment and death. Then they were followed for six months or until death to see whether their wishes were known and respected by their doctors.

Sunbed use in children aged 11-17 in England: face to face quota sampling surveys in the National Prevalence Study and Six Cities Study

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EDITORIAL by Elwood and Gallagher

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STUDY QUESTION What is the pattern of sunbed use among young people across England?

STUDY ANSWER Use of sunbeds is widespread in young people in England, is often inadequately supervised, and constitutes a health risk.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS The incidence of malignant melanoma is increasing and exposure to ultraviolet radiation, including that from tanning beds and lamps, is the single most important avoidable cause. Across England 6% of teenagers have used a sunbed but this figure rises to around 50% in girls aged 15-17 in Liverpool and Sunderland.

Participants and setting
Over 9000 children aged 11-17 were interviewed; 3101 in the National Prevalence Study throughout England and 6209 in the Six Cities Study in Liverpool, Stoke/Stafford, Sunderland, Bath/Gloucester, Oxford/Cambridge, and Southampton.

Design
Two random location sampling surveys.

Primary outcomes
Prevalence of sunbed use, geographical variation in use, and levels of supervision.

Main results and the role of chance
In the National Prevalence Study, 6.0% (95% confidence interval 5.1% to 6.8%) of those aged 11-17 had used a sunbed. Use was higher in girls than in boys (8.6% (7.2% to 10.0%) *v* 3.5% (2.6% to 4.4%), respectively), in those aged 15-17 compared with those aged 11-14 (11.2% (9.5% to 12.9%) *v* 1.8% (1.2% to 2.4%)), and in those from lower rather than higher social grades (7.6% (5.7% to 9.5%) *v* 5.4% (4.5% to 6.3%)). Sunbed use was higher in the north (11.0%, 8.9% to 13.0%) than in the midlands (4.2%, 2.5% to 5.8%) and the south (4.2%, 3.3% to 5.2%). Worryingly, 14.9% (13.7% to 16.2%) who had not used a sunbed said they might do so in the future.

In the Six Cities Study, sunbed use was highest in Liverpool and Sunderland (20.0% (17.5% to 22.4%) *v* 18.0% (15.6% to 20.3%)), with rates especially high in girls, those aged 15-17, or those from lower social grades. Mean age of first sunbed use was 14, but 7.0% (5.0% to 8.9%) of children said they first used a sunbed while at primary school. Nearly two in five children used a sunbed at least weekly (38.4%, 34.7% to 42.1%). Nearly a quarter (23.0%, 19.8% to 26.1%) of children had used a sunbed at home, and 24.7% (21.0% to 28.4%) had used sunbeds unsupervised in a tanning/beauty salon or gym/leisure centre. Of 213 children asked "When your sunbed use was supervised, did someone show you how to use a sunbed, and give you information about harm that sunbeds can cause?" 42 (19.9%, 14.5% to 25.2%) replied "no."

Bias, confounding, and other reasons for caution
The strength of both studies lies in their size and robust design, with reliable estimates obtained of the English (within 1%), regional (within 5%), and city (within 3%) prevalence of sunbed use by children. Data were collected in face to face interviews, with revalidation of at least 10% of participants to ensure the correct classification and answers to key questions. Bias in selection of the study populations is a potential weakness, but the random location sampling technique largely overcomes the usual flaws of quota sampling.

Generalisability to other populations
Previous studies of sunbed use in UK children have been small or less geographically diverse, but high sunbed use has previously been reported in teenagers in Merseyside. International studies report similar effects of sex and age on sunbed use by children.

Study funding/potential competing interests
Cancer Research UK was commissioned by the National Cancer Action Team, supported by the Department of Health to undertake this research. The Department of Health funded the pilot studies; the National Cancer Action Team funded the full studies.

SUPERVISION OF SUNBED USE IN TANNING/BEAUTY SALON OR GYM/LEISURE CENTRE IN SIX CITIES STUDY

	No	% (95% CI)
Shown how to use and given information	78	36.6 (30.1 to 43.1)
Shown how to use but not given information	84	39.3 (32.7 to 45.8)
Not shown how to use but given information	9	4.2 (1.5 to 7.0)
Not shown or given any information	42	19.9 (14.5 to 25.2)

By children who said they had used sunbed in a supervised setting.

This is a summary of a paper published on bmj.com as *BMJ* 2010;340:c877

Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study

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bmj.com "There is a magnificent amount of data in this study that renders it worthy of publication, however, despite addressing the weakness of the study the authors have neglected two major weaknesses; first is the self selection that lies in the reason for not taking the pill in the first place . . . Second, there is no mention of body weight or any other anthropometric measures in the data collected"
Hany Lashen, senior clinical lecturer and honorary consultant in reproductive medicine, University of Sheffield in a rapid response. To submit a response go to any article on bmj.com and click "respond to this article"

This article is a summary of a paper that was published on bmj.com as: *BMJ* 2010;340:c927

STUDY QUESTION Does the mortality risk among women who have ever used oral contraceptives differ from that of those who have never used them?

SUMMARY ANSWER Oral contraceptive users have a lower long term overall risk of death than do never users.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Ever users of oral contraception have a reduced overall risk of incident cancer, but whether this translates into an important mortality benefit is not known. Compared with never users, ever users of oral contraceptives had a lower long term risk of death from any cause, producing an estimated absolute reduction of 52 per 100 000 woman years.

Participants and setting

We observed 46 112 women recruited by 1400 general practices throughout the United Kingdom during the late 1960s.

Design, size, and duration

This was a prospective, observational cohort study using mortality data supplied by participating general practitioners, the National Health Service central registries, or both. We combined periods of observation relating to current and past users of oral contraception into an ever user group; women recruited as never users who subsequently started oral contraception were included in the ever user group from the date of starting. Women were followed for up to 39 years, resulting in 378 006 woman years of observation among never users of oral contraception and 819 175 woman years among ever users. The main outcome measures were directly standardised adjusted relative risks between never users and ever users of oral contraception for all cause mortality and cause specific mortality.

Main results and the role of chance

During follow-up, 1747 deaths occurred in never users of oral contraception and 2864 in ever users. Compared with never users, ever users of oral contraception had a significantly lower rate of death from any cause (adjusted relative risk 0.88, 95% confidence interval 0.82 to 0.93). The overall reduction resulted from lower rates of different specific causes of death, including cancer and circulatory disease. These reductions offset a higher rate of violent death among oral contraceptive users. We found no association between overall mortality and duration of oral contraceptive use, although some disease specific relations were apparent. The estimated absolute reduction in all cause mortality among ever users of oral contraception was 52 per 100 000 woman years.

Bias, confounding, and other reasons for caution

We adjusted for age, smoking, parity, social class, and (for some subset analyses) use of hormone replacement therapy, but residual confounding may account for our findings. Potential sources of bias include large losses to follow-up, healthy survivorship bias, and the possibility of misclassification of exposure status in a small number of women.

Generalisability to other populations

Our findings may not reflect the experience of women using oral contraceptives today if the risks and benefits of currently available preparations differ from those of earlier products or if differences in patterns of usage affect the mortality risk. The balance of risks and benefits will also vary in populations with different patterns of background risk of disease.

Study funding/potential competing interest

The Centre of Academic Primary Care has received payments from Schering Plough and Wyeth Pharmaceutical for lectures and advisory board work provided by PCH. The study received funding from the Royal College of General Practitioners, Medical Research Council, Imperial Cancer Research Fund, British Heart Foundation, Cruden Foundation, Schering AG, Schering Health Care, Wyeth Ayerst International, Ortho Cilag, and Searle.

RISK OF DEATH AMONG NEVER AND EVER USERS OF ORAL CONTRACEPTIVES IN FULL DATASET

	Never users		Ever users		Adjusted relative risk† (95% CI)
Cause of death	Observed rate (No)	Standardised rate*	Observed rate (No)	Standardised rate*	
All causes	462.16 (1747)	417.45	349.62 (2864)	365.51	0.88 (0.82 to 0.93)
All cancers	205.29 (776)	194.55	160.16 (1312)	165.45	0.85 (0.78 to 0.93)
All circulatory diseases	132.54 (501)	115.18	93.14 (763)	99.15	0.86 (0.77 to 0.96)
All digestive diseases	18.25 (69)	16.53	15.38 (126)	15.67	0.95 (0.71 to 1.27)
Violence	13.49 (51)	12.86	19.04 (156)	19.20	1.49 (1.09 to 2.05)
All other diseases	92.06 (348)	77.80	61.4 (503)	65.59	0.84 (0.74 to 0.97)

*Standardised rate per 100 000 woman years, adjusted for age, parity, smoking, and social class.
†Baseline=never users.

Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomised controlled trials

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EDITORIAL by Canfell

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STUDY QUESTION Does vaccination against human papillomavirus (HPV) increase the risk of miscarriage for any subset of pregnancies defined by time between vaccination and conception?

SUMMARY ANSWER There is no evidence overall for an association between HPV vaccination and risk of miscarriage.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Evidence about the effect of the antigen and adjuvant used in Cervarix on the risk of miscarriage is limited. The small increase seen in risk of miscarriage in the subgroup of pregnancies conceived within three months of vaccination is compatible with chance, but does raise a potential concern for a vaccine that is likely to be administered to millions of women of reproductive age.

Selection criteria for studies

Data were from two independent large double blinded randomised clinical trials evaluating the efficacy of Cervarix for prevention of cervical lesions and persistent infection with HPV 16 and 18. Participants were randomised to receive HPV vaccine or hepatitis A vaccine (HVA) as control.

Primary outcome

The primary outcome was the difference in rates of miscarriage between the vaccinated and unvaccinated women, for pregnancies conceived within various intervals after vaccination. Our test statistic was the lowest P value among several tests of the same hypothesis in overlapping subsets of pregnancies defined by time between vaccination and conception. Our test procedure controls the chance of falsely reporting a positive conclusion when the vaccine has no effect, and has reasonable power for pregnancy subsets that might be at increased risk of miscarriage, albeit with less power than the standard test if the precise subset at increased risk were specified correctly.

Main results and role of chance

The estimated rate of miscarriage was 11.5% in women in the HPV arm and 10.2% in the control arm. The one sided P value for the primary analysis was 0.16; thus, overall, there was no significant increase in miscarriage among women assigned to the HPV vaccine arm. Miscarriage rates were 14.7% in the HPV vaccine arm and 9.1% in the control arm in pregnancies that began within three months after nearest vaccination. We found no sign of a detrimental effect of HPV vaccination on miscarriage rates for pregnancies conceived beyond three months after vaccination, even though power to detect an effect with a relative risk of about 2 during this time period was substantial. We found no evidence of a decrease either in total new pregnancies or in new pregnancies ending in live birth in the HPV arm and, thus, no evidence that the HPV vaccine affected loss of undetected pregnancies.

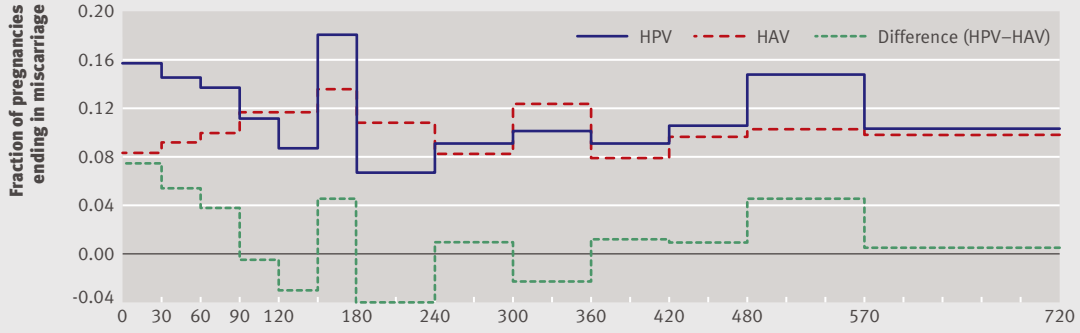
Bias, confounding, and other reasons for caution

There might be an increased risk among pregnancies conceived within three months of vaccination.

Study funding/potential competing interests

This analysis was funded by the Intramural Research Program of National Cancer Institute, US.

MISCARRIAGES AND PREGNANCIES ACCORDING TO TIME BETWEEN NEAREST VACCINATION AND DATE OF ESTIMATED CONCEPTION



Count of miscarriages													
HPV	24	18	16	12	9	14	11	11	13	13	11	20	12
HAV	11	10	13	14	12	13	19	11	20	11	12	11	9
Pregnancies at risk													
HPV	153	124	117	108	104.5	77.5	165.5	121.5	129	144	104.5	136	117
HAV	133	109.5	131	120.5	103	96	176.5	134.5	161.5	139.5	124.5	107.5	92

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c712

The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed

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EDITORIAL by Antes
RESEARCH METHODS & REPORTING, p 698

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STUDY QUESTION Has the documentation of methodological details in reports of randomised trials improved after publication of the Consolidated Standards of Reporting Trials (CONSORT) Statement in 2001?

SUMMARY ANSWER Reporting of several important aspects of trial methods improved between 2000 and 2006, particularly in those journals that endorse the statement; however, the quality of reporting remains well below an acceptable level.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS The CONSORT Statement provides recommendations for authors about how to prepare articles reporting the findings of randomised trials. Previous studies show that before revision of the CONSORT Statement in 2001, important methodological details were inadequately described in more than half of trial reports. Many trial reports still omit important information about trial conduct; thus it is remains difficult to gauge the validity of the trial findings in published reports.

Selection criteria for studies

We included all primary reports of randomised trials indexed in PubMed in December 2000 (n=519) and December 2006 (n=616), including parallel group, crossover, cluster, factorial, and split body study designs.

Design

This study is a "before and after" comparison of two cross sectional investigations.

Primary outcome(s)

The primary outcome was defined as the proportion of methodological items reported in randomised trials published in 2000 and 2006, stratified by year and study design. For the 2006 sample we also compared the quality of reporting for randomised trials published in journals that endorse the CONSORT Statement compared to those that do not.

Main results and the role of chance

In both 2000 and 2006, the majority of trials involved two study arms (379/519 (73%) in 2000 *v* 468/616 (76%) in 2006), had parallel group design (383/519 (74%) *v* 477/616 (78%)), with a median of 80 participants per trial, and were published in specialty journals (482/519 (93%) *v* 555/616 (90%)). The proportion of articles that reported drug trials decreased between 2000 and 2006 (from 393/519 (76%) to 356/616 (58%)), whereas the proportion of surgical trials increased (from 51/519 (10%) to 128/616 (21%)). We identified an increase between 2000 and 2006 in the proportion of trial reports that included details of the primary outcome (risk ratio (RR) 1.18, 95% CI 1.04 to 1.33), sample size calculation (RR 1.66, 95% CI 1.40 to 1.95), and the methods of random sequence generation (RR 1.62, 95% CI 1.32 to 1.97) and allocation concealment (RR 1.40, 95% CI 1.11 to 1.76). There was no difference in the proportion of trials that provided specific details on who was blinded (RR 0.91, 95% CI 0.75 to 1.10). We also identified a significantly higher rate of reporting of key methodological items in CONSORT endorsing journals in 2006.

Bias, confounding, and other reasons for caution

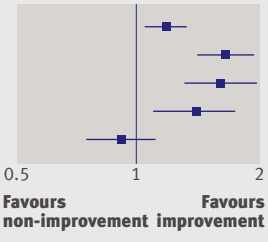
Single data extraction was carried out and it is possible that errors may have accrued, although we did our best to minimise any inconsistency in reviewers' interpretation of the data extraction form. In addition, data extraction in 2000 and in 2006 was carried out by different teams of reviewers; however, all reviewers conferred to try to ensure consistency in the interpretation of data extraction items.

Study funding/potential competing interests

This study was carried out as part of a larger study funded by a grant from the UK National Institute for Health Research to support the work of the CONSORT Group. The funder had no role in the design, analysis, or interpretation of the study, or in writing the manuscript. DGA is a member of the CONSORT executive group and SH works as a CONSORT senior research fellow.

DIFFERENCES IN REPORTING OF METHODOLOGICAL ITEMS BETWEEN 2000 AND 2006

Subgroup	Events/Total PubMed 2006	Events/Total PubMed 2000	Risk ratio (95% CI)
Primary outcome	324/616	232/519	1.18 (1.04 to 1.33)
Sample size calculation	279/616	142/519	1.66 (1.40 to 1.95)
Sequence generation	209/616	109/519	1.62 (1.32 to 1.97)
Allocation concealment	156/616	94/519	1.40 (1.11 to 1.76)
Blinding	160/616	148/519	0.91 (0.75 to 1.10)



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