# RESEARCH

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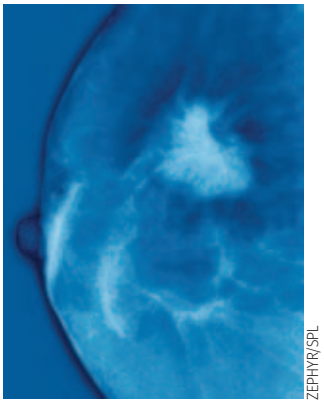
## THIS WEEK'S RESEARCH QUESTIONS



## Surgery rates after breast cancer screening



ZEPHYR/SPL

Among the coauthors of this paper by Pål Suhrke and colleagues (p 575), the names of Jørgensen and Gøtzsche should be familiar to *BMJ* readers from previous articles critical of mammographic breast screening programmes—in particular of the claimed benefits of screening. One of the supposed benefits is that discovering tumours at an earlier stage may reduce mastectomies by increasing the potential for breast conserving treatment.

However, this study of breast surgery rates during the stepwise introduction of screening in Norwegian counties finds an initial increase in mastectomies and an overall increase in surgery in the age group invited to screening (50-69 years). The authors suggest that over-diagnosis is the cause—but as Richard Smith discussed in his *BMJ* blog this week (http://bit.ly/pduPKe), little is known about the rate of natural progression of ductal carcinoma in situ (DCIS), and when this is communicated to women in whom DCIS is discovered, many would rather have the lesion removed than live with uncertainty. A randomised controlled trial of watchful waiting and yearly mammography versus surgery for DCIS is under way, which may improve estimates of risk of natural progression of precancerous breast lesions.

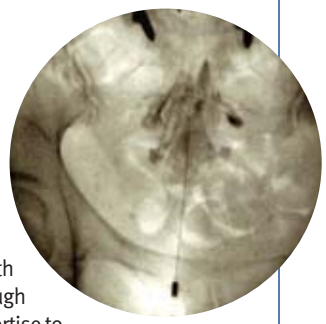
## Multiplicity and meta-analyses

Meta-analyses are considered the highest form of medical evidence, but are general clinicians right to retain some scepticism? Extraction of trial data for meta-analysis can pose a problem, because trials often report the same data in several different ways. Given a choice of numbers to incorporate, reviewers might select particular results according to unconscious (or conscious) preference, so there's a risk of bias. Could this affect the conclusions of meta-analyses?

Britta Tendel and colleagues looked at trials included in a random sample of Cochrane reviews (p 576), and found that presentation of results for multiple subgroups, time points, and scales was common. They also showed that the results of meta-analyses could vary substantially depending on which data were included.

So it does seem that bias in data selection may skew what meta-analyses say—a finding that might seem obvious, but is not well documented. The authors suggest that to reduce potential bias, authors of systematic reviews and trial protocols should provide explicit strategies for handling multiplicity of data.

## Steroid injections for radicular back pain



TOM LARKIN

A third of back pain is predominantly neuropathic, and steroid injections are an increasingly popular management strategy. A group of patients presenting with chronic lumbar radiculopathy entered a trial that compared sham injection with caudal epidural saline or steroid injection, conducted by Trond Iverson and colleagues (p 573). Powered at 80% to detect a 10 point difference on the Oswestry disability index, they found no clinically significant difference in outcomes.

Is this the end for steroid injections? It doesn't seem so. These results add to a heap of other trials and meta-analyses with contradictory findings. Editorialist Steven Cohen has raked through the trial in detail (p 543), and for those who lack the time or expertise to do the same, he raises interesting questions. Did the investigators inject the best place, with the right volume and dose? To what extent did the population drive the results? It seems unlikely that this trial will dramatically alter his practice—what will it do for yours?

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

**Views and experiences of men who have sex with men on the ban on blood donation**
As the government in England, Scotland, and Wales announces that the ban on blood donation by men who have sex with men will be reduced from lifetime to a year (p 589), Pippa Grenfell and colleagues present qualitative evidence supporting the move (doi:10.1136/bmj.d5604).

**Time trends in mortality in patients with type 1 diabetes**
Valma Harjutsalo and colleagues report that survival of people with early onset type 1 diabetes has improved in the Finnish population, owing to a decrease in chronic complications, whereas survival of those with late onset type 1 diabetes has deteriorated since the 1980s, with an increase in deaths caused by acute diabetic complications (doi:10.1136/bmj.d5364).

**Dedicated outreach service for hard to reach patients with tuberculosis in London**
Mark Jit and colleagues assessed the cost effectiveness of the "Find and Treat" service, which aims to identify and manage patients with active tuberculosis in populations with social risk factors, such as homeless people and those with drug problems (doi:10.1136/bmj.d5376).

# Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: multicentre, blinded, randomised controlled trial

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**EDITORIAL by Cohen**

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## STUDY QUESTION

Are epidural steroid injections or saline injections effective for patients with chronic lumbar radiculopathy?

## SUMMARY ANSWER

Compared with subcutaneous sham injections, caudal epidural steroid or saline injections do not have significant or clinically important effects in chronic lumbar radiculopathy.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Clinical studies indicate that epidural steroid injections and epidural saline injections reduce pain from acute lumbar radiculopathy in the short term, whereas the middle term and long term effects are unknown. Our findings indicate that neither caudal epidural steroid injections nor caudal epidural saline injections are effective for chronic lumbar radiculopathy and are not recommended as an adjunct to recovery in patients whose symptoms have extended beyond 12 weeks.

### Design

Multicentre, blinded, randomised controlled trial with block randomisation and computer generated allocation including three intervention groups: subcutaneous sham injections of 2 mL 0.9% saline, caudal epidural injections of 30 mL 0.9% saline, and caudal epidural injections of 40 mg triamcinolone acetonide in 29 mL 0.9 % saline. All groups received two injections with a two week interval.

### Participants and setting

Patients were referred from the catchment area of five Norwegian hospitals (population 1 146 076). Of 461 patients assessed, 116 (25%) were randomly allocated to treatment.

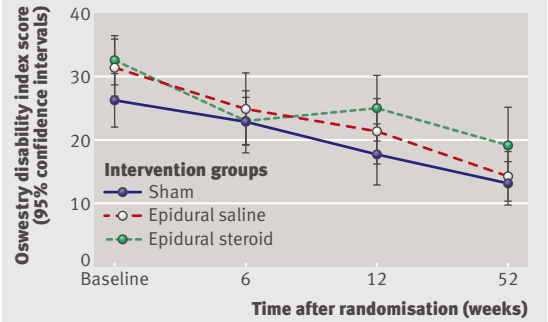
### Primary outcome

Physical function in activities of daily living, measured by the Oswestry disability index, assessed at baseline and at 6, 12, and 52 week follow-up.

### Main results and the role of chance

All intervention groups improved but we found no statistical or clinical differences between the groups (figure). The change in the Oswestry disability index scores for the sham group (n=40) was −4.7 (95% confidence intervals −0.6 to −8.8) at 6 weeks, −11.4 (−6.3 to −14.5) at 12 weeks, and −14.3 (−10.0 to −18.7) at 52 weeks. The differences in outcome for the epidural saline intervention group (n=39) compared with the sham group were −0.5 (−6.3 to 5.4) at 6 weeks, 1.4 (−4.5 to 7.2) at 12 weeks, and −1.9 (−8.0 to 4.3) at 52 weeks. The corresponding differences for the epidural steroid group (n=37) were −2.9 (−8.7 to 3.0) at 6 weeks, 4.0 (−1.9 to 9.9) at 12 weeks, and 1.9 (−4.2 to 8.0) at 52 weeks. Analysis adjusted for duration of leg pain, back pain, and sick leave did not change this trend.

**MEAN OSWESTRY DISABILITY INDEX SCORE AT FOLLOW-UP**




### Harms

No serious complications occurred. Six patients experienced strong local pain during the injection and refused the second injection.

### Bias, confounding, and other reasons for caution

The power calculation required inclusion of 41 patients in each group. The study was seven patients short of reaching this number. Blinding of the anaesthesiologists performing the injections was not possible. Contrast was not used to visualise how the injected medication spread.

### Generalisability to other populations

The study population was homogeneous with low psychosocial strain. We carefully selected patients on the basis of clinical criteria and not on strict magnetic resonance imaging findings, in accordance with clinical practice. Since our patients had longlasting radiculopathy, the results might not be as relevant for patients with shorter duration of symptoms.

### Study funding/potential competing interests

The study was supported by the North Norway Regional Health Authority and Health Region Nord-Trøndelag, Norway.

### Trial registration number:

Current Controlled Trials ISRCTN No 12574253.

# Trimethoprim-sulfamethoxazole induced hyperkalaemia in elderly patients receiving spironolactone: nested case-control study

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**EDITORIAL by Wei and colleagues**

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## STUDY QUESTION

What is the risk of admission to hospital for hyperkalaemia in elderly patients treated with trimethoprim-sulfamethoxazole in combination with spironolactone?

## SUMMARY ANSWER

Compared with amoxicillin, prescription of trimethoprim-sulfamethoxazole is associated with a more than 12-fold increase in the risk of hospital admission for hyperkalaemia among older patients receiving spironolactone.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Trimethoprim (which is generally combined with sulfamethoxazole in North America) and spironolactone can both cause hyperkalaemia, yet the risks associated with this drug combination are unknown. Prescription of trimethoprim-sulfamethoxazole to elderly patients receiving spironolactone was associated with a major increase in the risk of hyperkalaemia.

### Participants and setting

We did a population based, nested case-control study of Ontario residents aged 66 years or older treated with spironolactone between 1 April 1992 and 1 March 2010.

### Design, size, and duration

Within the cohort of continuous users of spironolactone, we defined cases as those admitted to hospital with a diagnosis of hyperkalaemia (ICD-9 code 276.7, ICD-10 code E87.5) within 14 days of receiving a prescription for one of four study antibiotics: trimethoprim-sulfamethoxazole, norfloxacin, nitrofurantoin, or amoxicillin. We selected up to four controls for each case from the same cohort. Controls were required to have received one of the study antibiotics within 14 days before the index date. We matched controls and cases on age at the index date (within a year), sex, diabetes, and chronic kidney disease.

### Primary outcome(s), risks, exposures

We determined the odds ratio for the association between admission to hospital with hyperkalaemia and receipt of a study antibiotic in the preceding 14 days. We used multivariable conditional logistic regression analysis to adjust for conditions and drugs that may influence the risk of hyperkalaemia.

### Main results and the role of chance

We identified 165 754 patients treated with spironolactone during the 18 year study period, of whom 17 850 (10.8%) received at least one prescription for trimethoprim-sulfamethoxazole during the study period. After multivariable adjustment, patients admitted to hospital with hyperkalaemia were more than 12 times more likely to have received a recent prescription for trimethoprim-sulfamethoxazole than for amoxicillin (adjusted odds ratio 12.4, 95% confidence interval 7.1 to 21.6). The population attributable fraction was 59.7%, suggesting that approximately 60% of all cases of hyperkalaemia in older patients taking spironolactone and treated with an antibiotic for a urinary tract infection could be avoided if trimethoprim-sulfamethoxazole was not prescribed. Treatment with nitrofurantoin was also associated with an increase in the risk of hyperkalaemia (adjusted odds ratio 2.4, 1.3 to 4.6), but we observed no such risk with norfloxacin (1.6, 0.8 to 3.4).

**ASSOCIATION BETWEEN HOSPITAL ADMISSION INVOLVING HYPERKALAEMIA AND RECENT ANTIBIOTIC USE**

| Use of antibiotic in preceding 14 days | Odds ratio (95% CI) | Adjusted odds ratio* (95% CI) |
|---|---|---|
| TMP-SMX | 11.0 (6.8 to 17.8) | 12.4 (7.1 to 21.6) |
| Nitrofurantoin | 2.5 (1.4 to 4.4) | 2.4 (1.3 to 4.6) |
| Norfloxacin | 1.5 (0.8 to 2.9) | 1.6 (0.8 to 3.4) |
| Amoxicillin | 1.0 (reference) | 1.0 (reference) |

TMP/SMX=trimethoprim-sulfamethoxazole.
*Adjusted for age category, congestive heart failure, chronic liver disease, chronic kidney disease, Charlson co-morbidity index, fifth of income, living in long term care facility, number of prescription drugs in previous year, number of years of spironolactone treatment, and drugs (β adrenergic receptor blockers, potassium sparing diuretics, non-potassium sparing diuretics, non-steroidal anti-inflammatory drugs, potassium supplements, renin-angiotensin-aldosterone inhibitors).

### Bias, confounding, and other reasons for caution

We used administrative data and had no access to data on serum potassium concentrations, indices of renal function (including estimated glomerular filtration rate), adherence to drug treatment, or use of non-prescription drugs that may have influenced the risk of hyperkalaemia. Because some clinicians may recognise the risk of hyperkalaemia with trimethoprim-sulfamethoxazole, differential outcome ascertainment is a possible source of bias. This is unlikely to have affected our findings, however, as electrolyte concentrations are routinely measured in older patients presenting to hospital.

### Generalisability to other populations

These findings may not apply to younger patients with fewer risk factors for hyperkalaemia.

### Study funding/potential competing interests

This project was supported by research funds from the Ontario Drug Policy Research Network and by the Institute for Clinical Evaluative Sciences, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care. During the past three years, TA has received unrestricted research grants from GlaxoSmithKline, Merck, and Pfizer for different studies.

# Effect of mammography screening on surgical treatment for breast cancer in Norway: comparative analysis of cancer registry data

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**STUDY QUESTION** How does mammography screening affect surgical treatment for breast cancer?

**SUMMARY ANSWER** Mammography screening in Norway was associated with a noticeable increase in rates for breast cancer surgery in women aged 50-69 (the age group invited to screening) and also an increase in mastectomy rates.

**WHAT IS KNOWN AND WHAT THIS PAPER ADDS**

Mammography screening increases overall rates of breast surgery. Mammography screening is associated with an increase in mastectomy rates, especially when screening is in its introduction phase.

## Participants and setting

35 408 Norwegian women aged 40-79 with invasive breast cancer or ductal carcinoma in situ treated surgically from 1993 to 2008. Mammography screening of women aged 50-69 was introduced sequentially in Norway from 1996 to 2004.

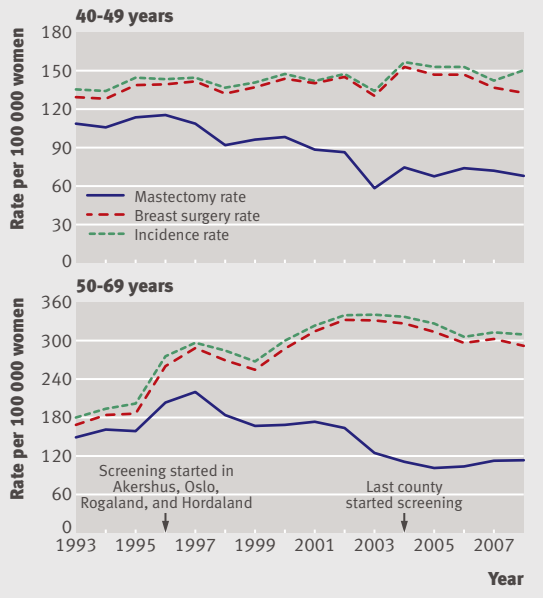
## Design

Comparative analysis of data from Norwegian cancer registry.

## Primary outcomes

Rates of breast surgery (mastectomy plus breast conserving treatment) and rates of mastectomy for three age groups of women: 40-49, 50-69, and 70-79. Changes in rates from pre-screening period (1993-5) to introduction of screening phase (1996-2004) and then to screening period (2005-8) are presented as hazard ratios in invited and non-invited women.

**AGE SPECIFIC MASTECTOMY, BREAST SURGERY, AND INCIDENCE RATES IN NORWEGIAN WOMEN WITH INVASIVE BREAST CANCER OR DUCTAL CARCINOMA IN SITU**




## Main results and the role of chance

The annual rate for breast surgery from the pre-screening period (1993-5) to the screening period (2005-8) in Norway increased by 70% (hazard ratio 1.70, 95% confidence interval 1.62 to 1.78), from 180 to 305 per 100 000 women in the invited age group (50-69 years). In the younger, non-invited age group (40-49 years), however, the increase was only 8% (1.08, 1.00 to 1.16), from 133 to 144 per 100 000 women per year. The rates for mastectomy decreased similarly from the pre-screening period to the screening period in invited and non-invited women. From the pre-screening period to the introduction phase of screening (1996-2004), however, the annual mastectomy rate in women aged 50-69 invited to screening increased by 9% (1.09, 1.03 to 1.14), from 156 to 167 per 100 000 women, and in the younger non-invited women declined by 17% (0.83, 0.78 to 0.90), from 109 to 91 per 100 000 women. In consequence, the mastectomy rate was 31% (1.31, 1.20 to 1.43) higher in the invited than the non-invited younger age group. Over-diagnosis is likely to have caused the initial increase in mastectomy rates and the overall increase in surgery rates in the age group screened. The more recent decline in mastectomy rates has affected all age groups and is likely to have resulted from changes in surgical policy.

## Bias, confounding, and other reasons for caution

Since we used aggregated data, our options to adjust for factors other than the introduction of screening were limited, even though in addition to the stage and size of tumours, surgical treatment is influenced by several other patient, surgeon, and hospital factors. By using the age group 40-49 as a control group, we limited potential bias from geographical differences. Some cancers that presently are detected by screening in women aged 50-69 would, in the absence of screening, have been diagnosed after age 69 years. This is expected to result in reduced incidence and surgery rates for women aged 70-79. However the decline in incidence and breast surgery rates in women aged 70-79 was small and can only compensate for a fraction of the increase in incidence and breast surgery rates in women invited to screening.

## Generalisability to other populations

Since surgical treatment can be influenced by several factors, practice might differ in other countries.

## Study funding/potential competing interests

The institutions in which the authors work had no influence on the conduct of the research or the writing of the paper. PS is supported by funding from the South-Eastern Norway Regional Health Authority.

# Multiplicity of data in trial reports and the reliability of meta-analyses: empirical study

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## STUDY QUESTION

Does the inclusion of multiple data for the same outcome in trial reports affect the results of meta-analyses?

## SUMMARY ANSWER

Multiplicity of data in trial reports is substantial and has an important effect on meta-analytical results.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Considerable observer variation exists in data extraction owing to different choices and errors. We found that multiplicity of data in trial reports can compromise the reliability of meta-analysis results. To reduce the risk of bias in data extraction, reviews and meta-analyses should be conducted according to prespecified protocols.

### Data sources

We selected all Cochrane systematic reviews from issue 3 in 2006 to issue 2 in 2007 that presented a result as a standardised mean difference (SMD). We retrieved trial reports contributing to the first SMD result in each review and downloaded review protocols. We used these SMDs to identify a specific outcome for each meta-analysis from its protocol.

### Data extraction and analyses

Based on protocols and the index outcome, two observers independently extracted the data necessary to calculate SMDs from the original trial reports for any intervention group, time point, or outcome measure compatible with the protocol. Based on the extracted data, all possible SMDs for the meta-analyses were calculated in Monte Carlo simulations, meaning that the meta-analysis was repeated 10 000 times for each index SMD, with a random selection of one SMD per trial in every repetition.

### Main results and the role of chance

We identified 19 eligible meta-analyses (including 83 trials). Published protocols of the reviews often lacked information about which data to choose. Twenty-four (29%) trials reported data for multiple intervention groups, 30 (36%) reported data for multiple time points, and 29 (35%) reported the index outcome measured on multiple scales. In 18 meta-analyses, we found multiplicity of data in at least one trial report; the median difference between the smallest and largest SMDs within a meta-analysis was 0.40 standard deviation units (range 0.04 to 0.91) (table).

**VARIABILITY IN META-ANALYSES RESULTS**

| Source of multiplicity | No (%) of meta-analyses with multiplicity of data (n=19) | SMD range within the same meta-analysis (median, range) |
|---|---|---|
| Intervention groups | 11 (58) | 0.09 (0.01 to 0.43) |
| Time points | 13 (68) | 0.19 (0.03 to 0.82) |
| Measurement scales | 12 (63) | 0.23 (0.01 to 0.45) |
| Any source | 18 (95) | 0.40 (0.04 to 0.91) |

### Bias, confounding, and other reasons for caution

We only included published trial reports to ensure data transparency. Therefore, we probably underestimated the true level of multiplicity, since selective reporting of trial outcomes is common. We only included reviews with protocols, because the absence of a protocol increases the risk of a biased result due to data-driven decisions. We did not take into account other sources of multiplicity, such as different types of analyses of the same outcome. This study aimed to show the potential for bias, and our random selection of which data to combine in meta-analyses might not reflect what review authors do in practice, if implicit hierarchies and decision rules are not included in the protocol.

### Study funding/potential competing interests

This study was part of a PhD (BT) funded by IMK Charitable Fund. The fund had no involvement in the conduct of the study or preparation of the manuscript. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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