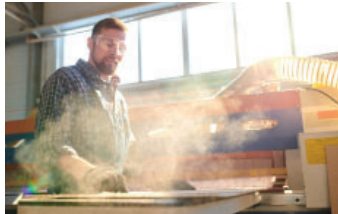


research



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ORIGINAL RESEARCH: SPECIAL PAPER Mini-review of literature

Exploratory analyses in aetiologic research and considerations for assessment credibility

Luijken K, Dekkers OM, Rosendaal FR, Groenwold RHH

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Study question Which aspects of reporting and interpretation might improve the assessment of the credibility of exploratory analyses in aetiologic research?

Methods This study focused on causal research, namely aetiologic studies, which investigates the causal effect of one or multiple risk factors on a health outcome

or disease. A mini-review of the literature was done to report the number of exposure-outcome associations published in four epidemiology journals. Based on existing reporting guidance, an account of exploratory research principles was given.

Study answer and limitations The journal articles reported a mean 33 (range 1-120) exposure-outcome associations for the primary analysis, 30 (0-336) for sensitivity analyses, and 163 (0-1467) for additional analyses. Six considerations for assessing the credibility of exploratory analyses were the research problem, protocol,

cautious assessment of statistical criteria, interpretation of findings, completeness of reporting, and implications of exploratory findings for future aetiologic research. This mini-review is only intended to illustrate the large number of results that might be presented in aetiologic studies.

What this study adds This study provides six considerations for reporting of exploratory analyses in aetiologic research.

Funding, competing risks, and data sharing RHHG was supported by the Netherlands Organisation for Scientific Research and Leiden University Medical Centre. No competing interests declared. No additional data available.

| Considerations for reporting of exploratory aetiologic research | |
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| Considerations | Comments |
| Explicitly state the objective of all analyses, including exploratory analyses | State the objective of an exploratory analysis to clarify how the results are to be interpreted. Outline the objective of the definite analysis of interest and clarify why an exploratory analysis should be conducted first |
| Establish a study protocol before data analysis and make the protocol available to readers | Specify the objective, design, and analysis plan in a protocol, even when existing data are analysed or when an analysis is considered exploratory |
| Do not base judgments on significance values only | Avoid selective reporting of results based on significance values, particularly because exploratory analyses are commonly conducted with less rigorously collected data and suboptimal ability to adjust for confounding. Also, statistical properties of exploratory tests are less well known than those of confirmatory tests |
| Interpret findings in line with the nature of the analysis | Be transparent about the exploratory aim of the analysis and avoid overstating the credibility of findings. Minimise suggestions on generalisability and clinical relevance for exploratory findings |
| Report (summarised) results of all exploratory analyses that were performed | Report results of all exploratory analyses that were conducted (possibly in a supplementary file) to provide a transparent and honest account of the analysis that facilitates interpretation of findings |
| Accompany exploratory analyses by a proposed research agenda | Formulate a research agenda prioritising future research and how this research should be set up. This process ensures researchers take responsibility for the presented exploratory findings and follow-up research that should be performed |

Corticosteroid and local anaesthetic injection for hip OA

ORIGINAL RESEARCH Single blind, parallel group, three arm, randomised controlled trial

Clinical effectiveness of one ultrasound guided intra-articular corticosteroid and local anaesthetic injection in addition to advice and education for hip osteoarthritis (HIT trial)

Paskins Z, Bromley K, Lewis M, et al

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Study question What is the clinical effectiveness of adding a single ultrasound guided intra-articular corticosteroid and local anaesthetic injection to advice and education in adults with hip osteoarthritis?

Methods Between 18 January 2016 and 21 May 2018, adults aged ≥ 40 years with hip osteoarthritis and at least moderate pain were recruited from community musculoskeletal services and randomly assigned to receive advice and education (best current treatment (BCT)) and either



no injection, ultrasound guided intra-articular corticosteroid (40 mg triamcinolone acetonide) and local anaesthetic injection (4 mL 1% lidocaine hydrochloride), or ultrasound guided intra-articular local anaesthetic injection (5 mL 1% lidocaine). Outcomes were self-reported at two weeks and at two, four, and six months. The primary outcome was current hip pain intensity (0-10 numerical rating scale) over six months.

Study answer and limitations Of the 199 participants recruited, 67 were randomly assigned to BCT, 66 to BCT plus ultrasound-triamcinolone-lidocaine, and 66 to BCT plus ultrasound-lidocaine. Average weighted follow-up rate across time points was 93%. An ultrasound guided injection of corticosteroid and local anaesthetic combined with advice and education led to improvements in pain; mean difference

COMMENTARY The tear, flare, and repair model of osteoarthritis

Rheumatology practice has rapidly progressed in the past three decades, including many new evidence-based treatment options and strategies for patients with inflammatory arthritis. Treatment options for osteoarthritis remain scarce, however, and might decrease further once osteoarthritis guidance from the UK's National Institute for Health and Care Excellence is updated later this year.¹

A recommendation not to use paracetamol is highly probable because of its lack of efficacy, its established toxicities that worsen when combined with other non-steroidal anti-inflammatory agents,² and a proposal already made during consultation for the previous guideline (known as CG177).³

In this issue, Paskins and colleagues conducted a large, randomised controlled trial including 199 adults with hip osteoarthritis and at least moderate pain.⁴ Over six months, the trial compared

The benefits reported were bigger than those associated with other available treatments, except perhaps joint replacement

guided local anaesthetic injection with or without triamcinolone acetonide to best current treatment. The primary outcome of current hip pain intensity improved significantly among participants given the combined local anaesthetic (lidocaine) and corticosteroid injections (triamcinolone) in comparison with the control group that was given best current treatment alone. Participants in the combined intervention group had their pain scores halved at two weeks, with a mean 25% improvement over six months and corresponding sustained benefits across multiple secondary outcomes.

For the combined injection, numbers needed to treat at two months were just 2 for no sleep disturbance; 3 for feeling better; and 3 for reporting no limits to usual activities. At six months, numbers needed to treat were 3 for would have the same treatment again, although pain relief was

not sustained at six months. The authors' summary messages imply that this evidence is for patients with mild to moderate hip osteoarthritis contrasted with previous trials in severe disease, but it would be more accurate to describe these participants as having clinically moderate disease because they all had a mean pain score of at least 4 in the two weeks before their trial intervention, and radiographic score data were not reported to confirm they were radiographically mild.

Paskins and colleagues' trial is bigger and longer than previous studies, including our own,⁵ and shows expected, but nevertheless impressive, differences between treatment groups. The benefits reported after combined injection of local anaesthetic and triamcinolone acetonide were bigger than those associated with other currently available treatments, except perhaps joint replacement. The new trial⁴ also supports the premise that steroid works better for patients with baseline synovitis or effusion, justifying both the so-called "tear, flare, and repair" model of osteoarthritis⁶ and the anti-inflammatory injection strategy.

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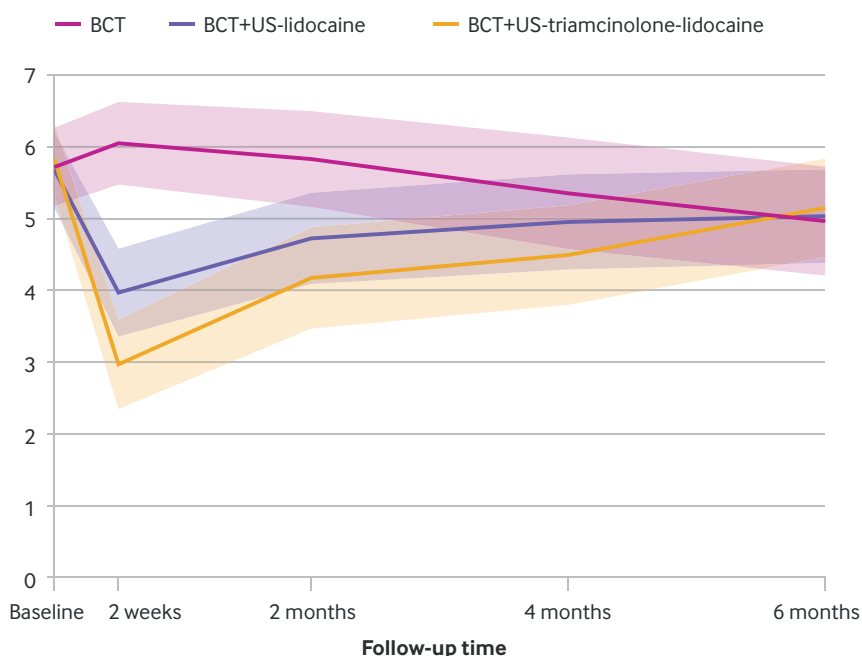
See bmj.com for author details

–1.43 (95% confidence interval –2.15 to –0.72), $P < 0.001$; standardised mean difference –0.55 (–0.82 to –0.27). When comparing the injection groups, no difference in hip pain intensity was reported (–0.52, –1.21 to 0.18) over six months. One participant in the BCT plus ultrasound-triamcinolone-lidocaine group with a bioprosthetic aortic valve died from subacute bacterial endocarditis four months after the intervention, deemed possibly related to the trial treatment. Important limitations were assessing outcomes by self-report and not including radiographical outcomes.

What this study adds Adding an ultrasound guided corticosteroid and local anaesthetic injection to advice and education offers rapid and sustained improvements in pain and function for adults with hip osteoarthritis.

Funding, competing interests, and data sharing Funded by the National Institute for Health Research. See full paper on bmj.com for competing interests. Data sharing is possible on request.

Study registration EudraCT 2014-003412-37; ISRCTN 50550256.



Summary of pain numerical rating scale (primary outcome measure) by treatment group. BCT=best current treatment; US=ultrasound. Shaded areas represent 95% confidence intervals

The end of “wear and tear”

This conclusion should mark the end of discussions about “wear and tear” with patients or any other stakeholder. The “wear and tear” model was negatively framed, is inconsistent with evidence and advice on physical activity, and is woefully inaccurate, reinforcing expectations of inevitable decline and reduced quality of life.

Patients and clinicians will warmly welcome this treatment option; however, the following considerations should inform shared decision making. Firstly, although the trial is described as a study of two sites, participants were recruited from a functionally single site with unusual integration of musculoskeletal services, which might limit external validity.

Secondly, was 40 mg of triamcinolone acetonide an optimal dose? Arguably not: previous trials have tested higher doses,⁵ including one that reported a prolonged effect without toxicity with 80 mg triamcinolone acetonide.⁸ A higher dose could have had longer effects and perhaps even extended analgesic benefits to six

months, based on the trajectory observed over 12 weeks.

Thirdly, what about risk of infection? One participant with a bioprosthetic aortic valve died from bacterial endocarditis four months after ultrasound guided injection of triamcinolone plus lidocaine. As such, patient selection is likely to be important going forward. People with prosthetic valves, prosthetic joints, or other relative contraindications, should be counselled about the risks of treatment.

A final consideration is a risk of infection in or around the prosthesis in patients undergoing subsequent hip replacement. A recent systematic review and meta-analysis concluded that a small risk of infection persists for three months after a corticosteroid injection.⁹ Anecdotally, orthopaedic surgeons often impose a delay of six months or even up to 12 months between a steroid injection and a total hip replacement (personal communication, Mike Reed, 2022). This advice is not based on evidence and might result in refusal of an effective treatment owing to fear of missing out on surgery. Patients most suited to hip

injection currently might be those unable to have surgery, or those motivated enough to delay surgery.

Corticosteroid injections are cheap and widely available, as are effective site-specific training strategies,¹⁰ so this treatment could be a realistic option for patients in many countries.

The new trial by Paskins and colleagues⁴ involved a patient advisory group, but no patient coauthor. Comprehensive patient partnership is a good way to keep education, research, and clinical care focused on the quintuple aim: better patient outcomes, efficiency, learning, and an experience that is enjoyable for patients, and staff and students.¹¹ Initiatives such as the national, patient focused educational partnership in the UK¹² are also embedding this approach in undergraduate medical education. We welcome Paskin and colleagues’ study and the empowering choices the trial’s findings support for eligible patients.

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Variation in revascularisation use and outcomes of patients in hospital with acute myocardial infarction

Cram P, Hatfield LA, Bakx P et al

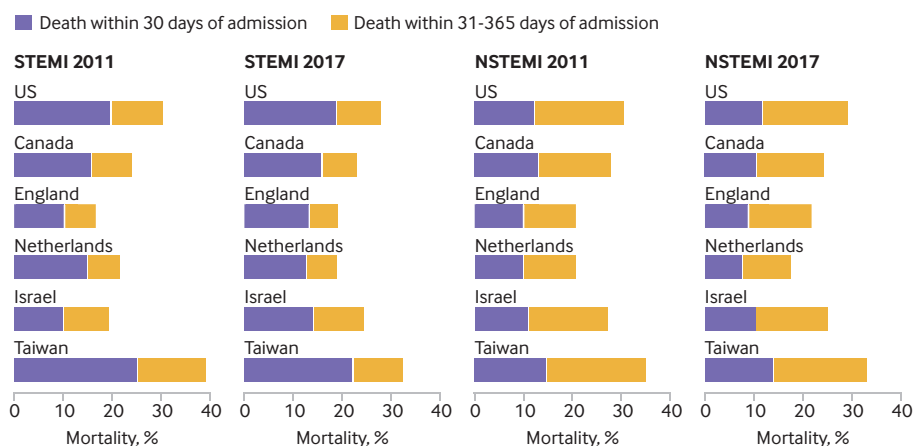
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Study question How do treatment and outcomes compare for patients admitted to hospital with a primary diagnosis of ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI) in six high income countries?

Methods This retrospective, cross sectional cohort study used primary administrative data files from the United States, Canada (Ontario and Manitoba), England, The Netherlands, Israel, and Taiwan. The cohort consisted of adults aged 66 years and older admitted to hospital with a primary diagnosis of STEMI or NSTEMI between 1 January 2011 and 31 December 2017. The three categories of outcomes were coronary revascularisation (percutaneous coronary intervention or coronary artery bypass graft surgery) in hospital and within 90 days of admission; mortality within 30 days and one year of admission; and efficiency (hospital length of stay and 30 day readmission). Rates were standardised to the age and sex distribution of the US population with acute myocardial infarction in 2017.

Study answer and limitations The total number of hospital admissions ranged from 19 043 in Israel to 1 064 099 in the US. Large differences were found between countries for all outcomes. For example, the proportion of patients admitted to hospital with STEMI who



Mortality within 30 days and one year of index hospital admission for acute myocardial infarction. Colour coding indicates proportion of deaths occurring within 30 days and 31-365 days of admission. Rates standardised to age and sex distribution of US population with acute myocardial infarction in 2017. 2013 data shown for The Netherlands; 2011-12 data unavailable. NSTEMI=non-ST elevation myocardial infarction; STEMI=ST elevation myocardial infarction



received percutaneous coronary intervention in hospital during 2017 ranged from 36.9% (England) to 78.6% (Canada; 71.8% in the US); and use of percutaneous coronary intervention for STEMI increased in all countries between 2011 and 2017, with particularly large rises in Israel (48.4-65.9%) and Taiwan (49.4-70.2%). The proportion of patients with NSTEMI who underwent coronary artery bypass graft surgery within 90 days of admission during 2017 was lowest in The Netherlands (3.5%) and

highest in the US (11.7%). Death within one year of admission for STEMI in 2017 ranged from 18.9% (The Netherlands) to 27.8% (US) and 32.3% (Taiwan). Mean hospital length of stay in 2017 for STEMI was lowest in The Netherlands and the US (5.0 and 5.1 days, respectively) and highest in Taiwan (8.5 days); 30 day readmission after STEMI was lowest in Taiwan (11.7%) and the US (12.2%) and highest in England (23.1%). Coding potentially differed between countries, and detailed clinical variables were lacking.

What this study adds Important differences were found between countries in revascularisation rates, mortality, and efficiency.

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The online version is published along with signed peer and patient reviews for the paper, and a statement about how the authors will share data from their study. It also includes a description of whether and how patients were included in the design or reporting of the research.

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