

research update

FROM THE JOURNALS Edited highlights of Richard Lehman's blog on <http://bmj.co/Lehman>



MenB vaccination for students

We've been waiting for decades to get a vaccine against *Neisseria meningitidis* serogroup B. But now that it's arrived, it's hardly the kind of thing that gets people looking for champagne bottles in the fridge. It's an expensive way to prevent a rare disease, and it's actually quite hard to prove that it has saved any lives so far. This report from its use during an outbreak at "University A in New Jersey" illustrates the problem. Although this paper has input from Princeton University, it doesn't actually name this august institution, where an outbreak of meningococcal disease began in December 2013. Nine students were affected and one died. Nearly 6000 were then given meningitis B vaccination and none of the vaccinated students got the disease. In fact, one fifth of the students already had antibodies to menB, and one third of those vaccinated failed to develop any. We are never going to have accurate quantification of its protective effect. As the accompanying editorial says, "4CMenB will not be the last vaccine for which a traditional, pivotal, double-blind, randomized, controlled trial with hard clinical end points is difficult, if not impossible, to generate."

• *N Engl J Med* 2016, doi:10.1056/NEJMoa1514866

Proopiomelanocortin deficiency

No, I'd never heard of it either. However, I decided to take a look at a case report of two patients with this rare syndrome who were treated with setmelanotide, a new melanocortin-4 receptor agonist. "The patients had a sustainable reduction in hunger and substantial weight loss (51.0 kg after 42 weeks in Patient 1 and 20.5 kg after 12 weeks in Patient 2)." Blimey! This is hot. I guess Prader-Willi syndrome may be the next target. And then, if setmelanotide is the safe appetite suppressant the world has been waiting for, who knows?

• *N Engl J Med* 2016, doi:10.1056/NEJMoa1512693

Ovarian stimulation and breast cancer

Sometimes observational research can deliver a nice clean answer: "Among women undergoing fertility treatment in the Netherlands between 1980 and 1995, IVF treatment compared with non-IVF treatment was not associated with increased risk of breast cancer after a median follow-up of 21 years. Breast cancer risk among IVF treated women was also not significantly different from that in the general population."

• *JAMA* 2016, doi:10.1001/jama.2016.9389

Diabetes drugs and outcomes

Other times observational research cannot deliver a nice clean answer. This systematic review and network meta-analysis of glucose lowering drugs concludes that "Among adults with type 2 diabetes, there were no significant differences in the associations between any of nine available classes of glucose-lowering drugs (alone or in combination) and the risk of cardiovascular or all-cause mortality." The authors then suggest that beginning with metformin makes sense and that additional treatment can be "based on patient-specific considerations." In the absence of evidence about long term outcomes, this will have to mean selection according to convenience and adverse effects.

• *JAMA* 2016, doi:10.1001/jama.2016.9400

Tai Chi v physio for knee osteoarthritis

Physiotherapy, or physical therapy, grew up as a therapeutic discipline based on real anatomy and physiology, from small beginnings in the 19th century to huge prevalence in the 20th century. Tai Chi is a martial art, which was systematised in the 16th century and is based on ancient ideas of yin and yang incorporated in 2500 years of Confucian and Taoist teaching. A Canadian trial pits one against the other in the treatment of chronic knee pain due to osteoarthritis. "At 12 weeks, the WOMAC score was substantially reduced in both groups . . . The between-group difference was not significant. Both groups also showed similar clinically significant improvement in most secondary outcomes, and the benefits were maintained up to 52 weeks. Of note, the Tai Chi group had significantly greater improvements in depression and the physical component of quality of life. The benefit of Tai Chi was consistent across instructors. No serious adverse events occurred."

• *Ann Intern Med* 2016, doi:10.7326/M15-2143

Take the aspirin right away

You might already have read about this study, which first appeared on the *Lancet* website two months ago; but if not, better late than never. Common wisdom says that if you think you're having a transient ischaemic attack or a stroke, you should take an aspirin right away. And this study indicates that this is true. Peter Rothwell and colleagues looked at individual data for 15 778 participants from 12 trials of aspirin versus control in secondary prevention. They dug deep and covered a number of questions, but the clear message that emerged was that aspirin is the key intervention and substantially reduces the risk of early recurrent stroke after transient ischaemic attack and minor stroke. It also reduces the severity of early recurrent stroke by 80%-90%.

• *Lancet* 2016, doi:10.1016/S0140-6736(16)30468-8

Pregnancy outcomes after treatment for CIN

ORIGINAL RESEARCH Systematic review and meta-analysis

Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth

Kyrgiou M, Athanasiou A, Paraskevaidi M, et al

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Study question What impact does treatment for cervical intraepithelial neoplasia (CIN) have on obstetric outcomes and how is risk modified by the extent of the treatment and the comparison group used?

Methods Systematic review and meta-analysis of studies assessing obstetric outcomes in women with or without a previous cervical

treatment (1948 to April 2016). Studies were classified according to method and obstetric endpoint. Pooled risk ratios were calculated with a random effects model with inverse variance method, and heterogeneity between studies was assessed with I^2 statistics. The main outcome was the difference in the incidence of preterm birth between women treated for CIN and the given reference group.

Study answer and limitations Women with CIN have a higher baseline risk for prematurity. Both excisional and ablative treatments further increase that risk, and the frequency and severity of adverse sequelae increase with increasing cone depth. All the included studies were cohort studies, nearly all retrospective in setting, with known risk of recall bias and inadequate adjustment for confounders.

What this study adds Increased risk of adverse obstetric outcomes correlates directly to the treatment technique and cone depth. The increase in risk with small excisions when compared with just having CIN remains uncertain and is likely to be small, if any; more data are required. Choice of comparison group could overinflate or underestimate the effect from treatment because of the background increased risk of preterm birth in women with CIN.

Funding, competing interests, data sharing This work was supported by the BSCCP Award, Imperial College Healthcare Charity, Genesis Research Trust, Sigrid Jusélius Foundation, the Imperial Healthcare NIHR BRC, COHEAHR Network, Institut National du Cancer (Paris), EFC, Joint Action CANCON. The authors have no competing interests, and there are no additional data.

COMMENTARY New analyses will help women balance effectiveness and safety

Young women of reproductive age presenting to the colposcopy clinics with preinvasive cervical lesions pose a challenge for clinicians. Surgical excision or ablation are effective treatments, but they can potentially weaken the cervix, leading to preterm birth and all consequent adverse sequelae. The treatment, usually a cone biopsy, needs to be deep enough to prevent recurrence but shallow enough to protect subsequent pregnancies. For years a debate on the best size and depth of the cone to satisfy both has left clinicians uncertain how radical they should be.

Deeper cones, greater risk

Kyrgiou and colleagues report a comprehensive meta-analysis comparing relative risks for treated versus untreated women using various comparison groups—both internal and external—and exploring both cone depth/volume and repeated treatments.

They found that the risk of preterm birth is almost 1.8 times higher for treated women relative to untreated women when all treatment methods are considered (ablative and excisional). Repeat treatments of any kind were associated with a higher risk of preterm birth than single treatments. Furthermore, the depth of the cone was



A cone biopsy needs to be deep enough to prevent recurrence but shallow enough to protect subsequent pregnancies

positively and progressively linked with the relative risk for preterm birth. Cones deeper than 20 mm increased the risk almost fivefold relative to untreated women, while this risk was only slightly raised after smaller cones.

The question of whether an excisional biopsy of the cervix is an independent factor that can cause preterm birth, or whether women can be predisposed to both preinvasive lesions and preterm birth from an underlying common factor (i.e. HPV infection) is not new. Kyrgiou and colleagues confirmed that untreated women with preinvasive lesions also have an increased risk of preterm birth relative to the general population. Cone biopsies less

than 10 mm in depth did not increase the risk significantly, compared with these untreated women. For deeper cones the additional adverse effect of the surgical intervention became much clearer.

Kyrgiou and colleagues' findings should be interpreted cautiously as their meta-analysis included mainly retrospective cohort studies with well known inherent flaws and biases. Some of the subgroup analyses were based on a small number of studies without enough power for firm conclusions. Finally, confounding probably inflated relative risks in the external population based comparisons. In analyses that used internal comparators to help control confounding, the relative risks were attenuated but remained significantly increased in most subgroup analyses.

Despite limitations, this new meta-analysis adds to growing evidence that cervical treatment for preinvasive disease can lead to preterm birth and adverse neonatal outcomes. Women and their clinicians must navigate the difficult trade-off between oncological safety now and the safety of future pregnancies. Both can be reassured that a small excisional biopsy aiming to remove the lesion completely and prevent a second treatment most likely confers the best balance of outcomes.

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When hospitals switch to electronic records

ORIGINAL RESEARCH Observational study

Adverse inpatient outcomes during the transition to a new electronic health record system

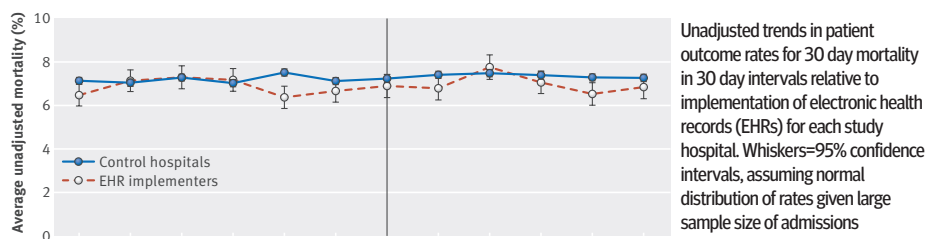
Barnett ML, Mehrotra A, Jena AB

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Study question What is the short term association between implementation of inpatient electronic health records and patient outcomes of mortality, readmissions, and adverse safety events?

Methods This was an observational study with difference-in-differences analysis using data from the US Medicare programme in 2011-12. The study included patients admitted to 17 US hospitals with a verifiable “go live” date for implementation of inpatient electronic health records during 2011-12, and 399 control hospitals in the same hospital referral region. The main outcome measures were all cause readmission within 30 days of discharge, all cause mortality within 30 days of admission, and adverse safety events, as defined by the patient safety for selected indicators (PSI)-90 composite measure. These outcomes were



measured among Medicare beneficiaries admitted 90 days before and 90 days after implementation of electronic health records (n=24 071 and 22 790 admissions), compared with the control group of all contemporaneous admissions to hospitals in the same hospital referral region (n=237 305 and 231 534 admissions). Analyses were adjusted for beneficiaries’ sociodemographic and clinical characteristics.

Study answer and limitations After adjustment, no significant change was associated with implementation of electronic health records in any outcome assessed between pre-implementation and post-implementation periods (all P≥0.13). This study was limited by lack of information on

the approaches to implementation used by the hospitals and the focus on an inpatient Medicare population.

What this study adds Despite concerns that implementation of electronic health records may adversely impact patient care during the acute transition period, this study found no overall negative association of implementation with short term mortality, readmissions, or adverse safety events in patients admitted to hospital.

Funding, competing interests, data sharing This study was supported by grants from the Office of the Director, National Institutes of Health (AB), NIH early independence award, grant 1DP5OD017897-01 and Health Resources and Services Administration (MLB, T32-HP10251). No additional data available.

COMMENTARY If nothing goes wrong, is everything all right?

Barnett and colleagues studied the consequences of one of the most disruptive events a hospital can experience—implementing a new electronic health record (EHR) system.¹ The investigators estimated changes in a set of outcome measures before and after implementation of a new EHR in 17 US hospitals; they then compared those changes with changes in the same measures in 399 control hospitals over the same regions and dates. The authors report no substantive differences between the groups in mortality, readmissions, or patient safety.

While this is laudable, should it really be reassuring? One of the most vexing aspects of safety is that only its absence, not its presence, is detectable.⁵ A single incident is sufficient to prove lack of safety, but even long experience cannot logically establish its presence.⁶ Asiana Airlines had operated for 20 years without a passenger fatality, but that experience was uninformative

Mortality and readmissions would likely not change much if some new intervention forced caregivers to do all their work standing on one leg

about the hazards leading to the 2013 crash of Asiana 214 at San Francisco International.⁷

Secondly, mortality and readmissions are quite distal to EHR implementation and so are insensitive reflections of risk. The patient safety measure (PSI-90) has been similarly criticised.⁹ However, the biggest challenge to the usefulness of these results lies in the study’s design, which contains a hidden assumption—that hospitals are mechanical, linear systems in which, when one component changes, all other components continue to operate as before. This is never the case for complex sociotechnical systems such as hospitals.

Hospital staff typically anticipate and attempt to compensate for disruptions from the deployment of a new EHR, as they do for hurricanes, winter storms, sporting events,

and other predictable stressors. They are also sensitive and responsive to disruptions in their patients’ care trajectories and for the most part can compensate for them, producing the usual unremarkable success of everyday clinical work.¹¹

Mortality and readmissions would likely not change much if some new intervention forced caregivers to do all their work standing on one leg. The lack of obvious failure in such a circumstance would not support a conclusion that the one leg policy was unproblematic; and it would not be surprising that frontline workers hated it, despite the lack of “evidence” of problems. The fact that people can continue to perform reasonably well using a new technology is not in itself an endorsement of that technology. A study showing how, and at what cost in terms of effort, hospitals accomplished their successful implementations is a sorely needed next step.

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Bariatric surgery and fractures

ORIGINAL RESEARCH Nested case-control study

Change in fracture risk and fracture pattern after bariatric surgery

Rousseau C, Jean S, Gamache P, et al

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Study question Does bariatric surgery increase risk of fracture?

Methods This retrospective nested case-control study used healthcare administrative databases in the province of Québec (Canada) to compare incidence and sites of fracture in 12 676 patients who had undergone bariatric surgery between 2001 and 2014 with those of 38 028 obese and 126 760 non-obese controls matched for age and sex. Fracture risk by type of bariatric procedure was investigated for the period spanning from 2006 to 2014. Results were adjusted for fracture history, number of

comorbidities, material and social deprivation, and area of residence.

Study answer/limitations Both before and after (mean 4.4 years) surgery, patients undergoing bariatric surgery were more likely to have fractures than were obese or non-obese controls. Postoperative adjusted fracture risk was higher in the bariatric group than in the obese (relative risk 1.38, 95% confidence interval 1.23 to 1.55) and non-obese (1.44, 1.29 to 1.59) groups. Fracture risk was site specific, changing from a pattern associated with obesity (increased risk of distal lower limb and decreased risk of upper limb fractures) to a pattern typical of osteoporosis after surgery (predisposition for upper limb, clinical spine, pelvic, hip and femur fractures). Only biliopancreatic diversion was clearly associated with fracture risk; however, results for Roux-en-Y gastric bypass and sleeve gastrectomy remain inconclusive. The major limitation



of this study is the lack of information in the administrative databases on body mass index and on several factors affecting fracture risk.

What this study adds Severely obese patients undergoing bariatric surgery are at increased risk of fracture before surgery compared with obese and non-obese controls, and this risk remains higher after surgery. Fracture risk assessment and management should be part of bariatric care.

Funding, competing interests, data sharing This research received no funding. Additional data are available from the corresponding author at claudia.gagnon@crchudequebec.ulaval.ca.

COMMENTARY Surgeons should consider assessing fracture risk in post-surgical patients

Although bariatric surgery has emerged as an effective treatment for obesity,¹ many commentators still question the surgical approach. Scepticism has been fuelled by some evidence of negative long term effects including increased risks for nephrolithiasis and chronic kidney disease,² relapse of type 2 diabetes mellitus,^{3,4} alcohol consumption,⁵ and suicide.⁶ Bariatric surgery may also have detrimental effects on bone health, indicated by a reduced bone mineral density postoperatively.⁷⁻¹⁰ However, whether this translates into a higher fracture risk is unclear.

Key findings

Rousseau and colleagues aims to fill this gap in knowledge and evidence.¹¹ Their retrospective, nested case-control study included patients after bariatric surgery (n=12 676), as well as obese (n=32 028) and non-obese (n=126 760) controls matched for sex and age. They used data from claim databases to compare the risk and site of fractures in bariatric patients and controls, making comparisons both before and after surgery. The first key finding is that bariatric

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I will certainly consider including assessment of fracture risk in the post-bariatric care of my patients

surgery patients were more likely to sustain fractures than were obese and non-obese controls. Secondly, fracture sites changed after bariatric surgery to a distribution typically associated with osteoporosis. Thirdly, fracture risk was significantly associated only with biliopancreatic diversion, which represents less than 5% of bariatric procedures performed worldwide.¹

However, epidemiological registry data have limitations that must be taken into account when interpreting their findings.

Firstly, the authors do not report any potential differences among the groups in overall use of drugs (for example, steroids), vitamin D supplementation, menopausal status, or the cause of fractures. Secondly, the bariatric surgery group and the obese control group are hard to compare confidently without information on body weight or body mass index.

Thirdly, different observation periods are compared before and after the surgery. The authors do not rule out the possibility

that postoperative differences between groups may be simply due to the fact that the bariatric group already had a higher incidence of fractures preoperatively.

Unanswered questions

The study by Rousseau and colleagues represents an important contribution to the evidence supporting the long term management of patients after bariatric surgery. However, it cannot answer the question “does bariatric surgery increase the risk of fractures?” Causal relations between a treatment and an event should ideally be investigated in prospective randomised controlled trials.

As long as our understanding of bone physiology after bariatric surgery remains limited, and the clinical consequences of physiological alterations remain untested in prospective studies, we have to continue to follow guidelines on nutritional supplementation that include the best available evidence.¹⁵ Following this study, I will certainly consider including assessment of fracture risk in the post-bariatric care of my patients.

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