research update

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

Doctor, why am I so fat?

Ah, I'm glad you asked me. I've been puzzling about this for so long that I've become overweight myself. A review article tries to sum up what we know about the mechanisms, pathophysiology, and management of obesity.

Here's a key paragraph: "Genes and environment interact in a complex system that regulates energy balance, linked physiological processes, and weight. Two sets of neurons in the hypothalamic arcuate nucleus that are inhibited or excited by circulating neuropeptide hormones control energy balance by regulating food intake and energy expenditure. Short-term and long-term energy balance is controlled through a coordinated network of central mechanisms and peripheral signals that arise from the microbiome and cells within adipose tissue, stomach, pancreas, and other organs. Brain regions outside the hypothalamus contribute to energy-balance regulation through sensory-signal input, cognitive processes, the hedonic effects of food consumption, memory, and attention."

So it's dead simple, really.

N Engl J Med 2017, doi:10.1056/NEJMra1514009

Sharing decisions about osteoporosis

Osteoporosis is a good example of a long term risk factor that requires informed decision making. I would even take that further and say that it requires informed consent for treatment. Hip fracture in elderly people carries a bad prognosis for continued mobility and independent life. Women with low bone mineral density are especially susceptible. But every one of them must have the chance to decide for herself.

This viewpoint article is sensible in its approach to risk evaluation and lists all the essentials of an adequate dialogue with people who are at risk. The problem is that to do it properly would require two visits of about 30 minutes each for the millions of asymptomatic, but at risk, individuals—just as for statins. For long term preventive treatment, shared decision making is not just desirable, it is a human right. But it requires careful framing and individualisation, and how can we make this feasible in an already overburdened health system?

I don't have the answer, but I'd suggest that it would be a good area for the National Institute for Health and Care Excellence and the chief medical officer to look at.

JAMA 2017, doi:10.1001/jama.2016.19087

Transmission of drug resistant TB

Tuberculosis in Europe used to be known as "the white death," and that is the title of the best book about its history. But in parts of South Africa, extensively drug resistant (XDR) TB might be called the new black death, because there it kills an increasing number of people who are almost invariably poor and black.

It's unusual to see a paper like this one in the *New England Journal of Medicine*, dealing with a disease (I almost wrote "health issue"; bah) among disadvantaged people in a remote country. Three quarters of the 404 patients from KwaZulu-Natal Province had HIV and more than half of them carried the same strain of XDR TB. The rest mostly fell into small clusters of 30 other different TB genotypes, and complex evidence points to person-to-person transmission as the most important factor.

N Engl J Med 2017, doi:10.1056/NEJMoa1604544

When asthma diagnosis goes puff

Speaking of mandatory informed consent for long term treatment, how about asthma? Now I'll go even further and suggest we demand informed consent before putting anyone on the disease register.

Asthma has been a bugbear of mine throughout my clinical life. I saw waves of overdiagnosis and overtreatment crash through British primary care from the late 1980s onwards, each wave encouraged by pharmaceutical capture of the nursing workforce. New drug delivery systems, free peak flow meters, prevention, monitoring, clinics: to what end? Just more and more people on asthma registers. And once there, always there.

Here is a sobering study that undertook full clinical investigation of 701 Canadian adults who had been given a diagnosis of asthma in the previous five years. Twelve had a different and serious diagnosis. And fully a third of them had no evidence of asthma at all when their treatment was withdrawn.

JAMA 2017, doi:10.1001/jama.2016.19627

Promis of fewer and better prostate biopsies

Imagine that you suspect cancer in a breast, but you don't know where it is. Nor is it entirely clear where the breast itself is. You can only feel it through an orifice, and this kind of breast is about the size of a walnut. All you can do is point a biopsy needle up the orifice and try to sample as much of the breast as you can. Moreover, cancer will be detected in most, but only a few cancers will progress. Enough: you get my point.

Men have prostate glands that lie deeply hidden. Unlocking their mysteries has hitherto meant using a biochemical test with terrible predictive characteristics followed by multiple biopsies in unspeakable places. The PROMIS trial used multiparametric magnetic resonance imaging to help locate clinically significant cancers in men with raised prostate specific antigen levels. It was a complex study, but the bottom line (if I may put it that way) is that about 27% fewer men will need to have biopsy needles introduced through their bottoms.

Lancet 2017, doi:10.1016/S0140-6736(16)32401-1

ORIGINAL RESEARCH Systematic review of reproducibility studies

Inter-rater agreement in evaluation of disability

Barth J, de Boer WEL, Busse JW, et al

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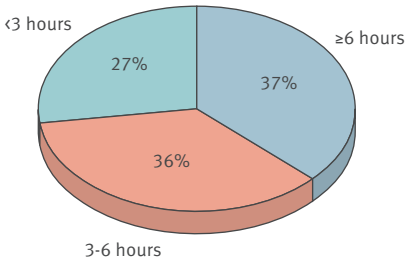
Find this at: http://dx.doi.org/10.1136/bmj.j14

Study question How strong is the agreement between different healthcare providers assessing the same patient claiming disability benefits because of illness or injury, when deciding if they are capable of working?

Methods Review of all published observational studies, in any language, in which healthcare providers assessed disability claimants for their ability to work and reported a measure of agreement between the experts.

Study answer and limitations 23 studies were eligible for review from 12 different countries. Of these, 16 were conducted in an insurance setting (evaluation of disability claimants who were real claimants, actors, claimants' records, case vignettes) and seven in a research setting (evaluation of real patients outside of actual assessments of disability). Study quality was limited, and differences in how agreement was reported precluded statistical pooling across studies. Almost all studies conducted in a research setting (86%, 6/7) reported good to excellent agreement between experts; however, these studies have limited relevance to real world assessment of disability. In contrast, most studies conducted in an insurance setting (63%; 10/16) reported only fair to poor inter-rater agreement, and only two (13%) reported excellent agreement.



Videotaped medical evaluation of clerk aged 49 with recurrent episodes of depression who was claiming disability benefits was independently judged by 22 psychiatric experts for her capacity to work in her last job (three categories: ability to work ≥6 hours; 3-6 hours, <3 hours). Despite identical information, experts' judgments show entirely haphazard distribution. Reproduced from Dickmann and Brooks (*Fortsch Neurol Psychiatr* 2007;75:397-401) with permission from publisher

What this study adds Agreement between different healthcare providers assessing the same disability claimant in an insurance setting is typically low, which reduces confidence in their findings. Assessors that used a standardised approach to the evaluation process achieved higher agreement with other healthcare providers.

Funding, competing interests, data sharing Several of the review authors are consultants for insurance companies or organisations that receive referrals from insurance companies. There are no data to share.

ORIGINAL RESEARCH Randomised controlled trial

Atosiban versus fenoterol as a uterine relaxant for external cephalic version

Velzel J, Vlemmix F, Opmeer BC, et al

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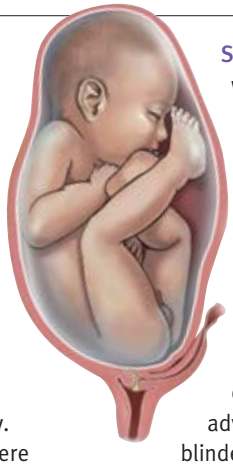
Find this at: http://dx.doi.org/10.1136/bmj.i6773

Study question How effective is the oxytocin receptor antagonist atosiban compared with the beta mimetic fenoterol as a uterine relaxant in women undergoing external cephalic version (ECV) for breech presentation?

Methods This open label randomised controlled trial was carried out in eight hospitals in the Netherlands and included women with a singleton fetus in breech presentation and a gestational age of more than 34 weeks. The women were randomly allocated in a 1:1 ratio to receive either 6.75 mg atosiban intravenously or 40 µg fenoterol intravenously for uterine relaxation. The primary outcome measures were a fetus in cephalic position 30 minutes after the procedure and cephalic presentation at delivery. Secondary outcome measures were mode of delivery, neonatal and maternal complications, and drug related adverse events. All analyses were done on an intention-to-treat basis.



Study answer and limitation 416 women were allocated to atosiban and 414 to fenoterol. Cephalic position 30 minutes after the procedure occurred significantly less in the atosiban group than fenoterol group (34% *v* 40%, relative risk 0.73, 95% confidence interval 0.55 to 0.93). No significant differences were found in neonatal and maternal complications or in drug related adverse events. The study could not be blinded because of the obvious maternal side effects that commonly occur with fenoterol, such as tachycardia, dizziness, and flushing, and the anticipated success rate was lower than expected.

Results for primary and secondary outcomes

Outcomes	No (%)		Relative risk (95% CI)
	Atosiban (n=416)	Fenoterol (n=414)	
Cephalic presentation 30 minutes after external cephalic version*	140 (34)	166 (40)	0.73 (0.55 to 0.93)
Cephalic presentation at delivery†	139 (35)	160 (40)	0.86 (0.72 to 1.03)
Caesarean delivery‡	240 (60)	218 (55)	1.09 (0.96 to 1.22)

*Imputation for primary outcome.
†Missing data: n=402 for atosiban and n=397 for fenoterol.
‡Missing data: n=403 for atosiban and n=398 for fenoterol.

What this study adds Uterine relaxation with atosiban for ECV resulted in a lower rate of fetuses in cephalic position after the procedure compared with fenoterol.

Funding, competing interests, data sharing This study was supported by the Dutch Obstetric Consortium. The authors declare no competing interests. The full dataset is available from the corresponding author on reasonable request.
Study registration Dutch Trial Register, NTR 1877.

Psychological distress in relation to site specific cancer mortality

Batty GD, Russ TC, Stamatakis E, et al

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Find this at: http://dx.doi.org/10.1136/bmj.j108

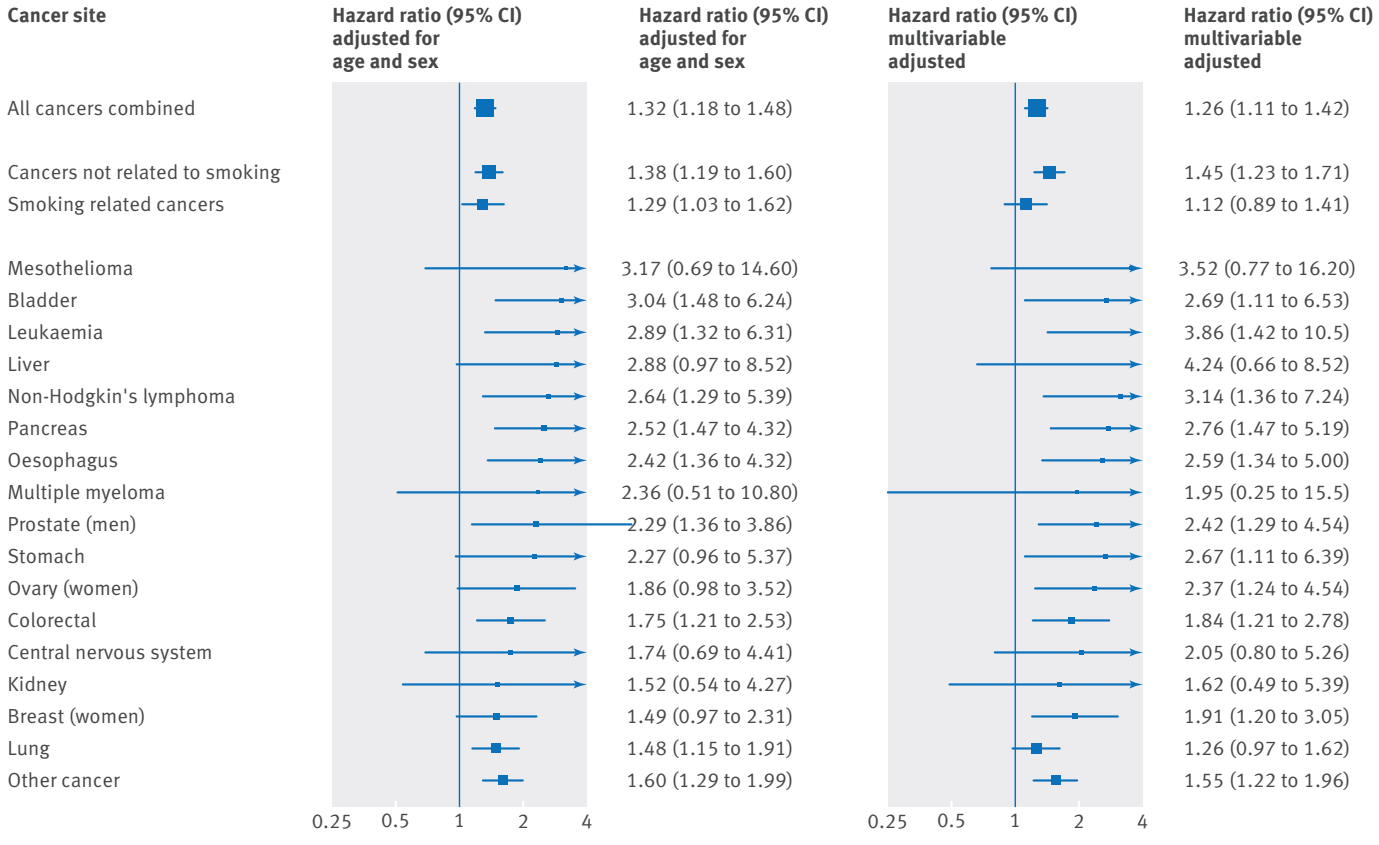
Study question Is psychological distress (anxiety and depression) a potential predictor of site specific cancer mortality?

Methods Pooling of raw data from 16 nationally representative prospective cohort studies from England and Scotland (initiated 1994-2008) resulting in the inclusion of 163 363 men and women aged ≥16 at study baseline. Study members were free from a cancer diagnosis when they self reported their psychological distress scores (measured with the general health questionnaire (GHQ-12)). Cancer deaths were ascertained by linking consenting study members to routinely gathered health records.

Study answer and limitations After an average of 9.5 years of mortality surveillance, there were 16 267 deaths (4353 from cancer). After multivariable adjustment, and with reverse causality (by left censoring) and missing data (by imputation) taken into account, relative to people in the least distressed group, death rates in the most distressed were consistently higher for cancer of all sites combined and cancers not related to smoking, as well as carcinoma of the colorectum, prostate, pancreas, and oesophagus and leukaemia. As the data were observational, cause and effect cannot be established, and residual confounding could have occurred.

What this study adds The identification of these new associations between distress and cancer adds to the growing evidence that psychological distress may have some predictive capacity for certain somatic diseases.

Funding, competing interests, data sharing Data collection for the health surveys for England was funded by the Department of Health (1994-2004) and the NHS Information Centre (from 2005), and for the Scottish health surveys by the Scottish Executive Health Department. Baseline data for the surveys are available for non-commercial purposes from the economic and social data service. The authors have no competing interests.



Psychological distress and selected cancer death outcomes

Thyroid hormone treatment among pregnant women with subclinical hypothyroidism

Maraka S, Mwangi R, McCoy RG, et al

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Find this at: http://dx.doi.org/10.1136/bmj.i6865

Study question How effective and safe is thyroid hormone treatment in pregnant women with subclinical hypothyroidism?

Methods This cohort study included pregnant women with subclinical hypothyroidism, defined as untreated thyroid stimulating hormone (TSH) concentration 2.5-10 mIU/L, from a large US administrative database. Women treated with thyroid hormone were compared with untreated women for risk of pregnancy loss and other pregnancy related adverse outcomes.

Study answer and limitations Compared with untreated women (n=4562), treated women (n=843) had lower adjusted odds of pregnancy loss (odds ratio 0.62, 95% confidence interval 0.48 to 0.82) but higher odds of preterm delivery (1.60, 1.14 to 2.24), gestational diabetes (1.37, 1.05 to 1.79), and pre-eclampsia (1.61, 1.10 to 2.37). The adjusted odds of pregnancy loss were lower among treated women than untreated women if their pre-treatment TSH concentration was 4.1-10 mIU/L (odds ratio 0.45, 0.30 to 0.65; P<0.01). The study is limited by its observational design and use of administrative data that do not allow for causal inferences.

What this study adds Thyroid hormone treatment was associated with decreased risk of pregnancy loss but also with increased risk of other important complications. The benefit of thyroid hormone use on pregnancy loss was observed only among women with pre-treatment TSH concentrations of 4.1-10.0 mIU/L, not 2.5-4.0 mIU/L.

Funding, competing interests, data sharing This study was funded by the Mayo Clinic Robert D and Patricia E Kern Center for the Science of Health Care Delivery.

Clinical outcomes associated with thyroid hormone treatment

Adverse outcomes*	No (%) events: Thyroid hormone treatment (n=843)	No (%) events: No thyroid hormone treatment (n=4562)	Adjusted odds ratio (95% CI)	P value
Pregnancy loss†	89 (10.6)	614 (13.5)	0.62 (0.48 to 0.82)	<0.01
Preterm delivery	60 (7.1)	236 (5.2)	1.60 (1.14 to 2.24)	0.01
Preterm labour	111 (13.2)	569 (12.5)	1.14 (0.89 to 1.46)	0.29
Premature rupture of membranes	42 (5.0)	220 (4.8)	0.97 (0.66 to 1.42)	0.87
Placental abruption	7 (0.8)	36 (0.8)	1.60 (0.65 to 3.93)	0.30
Gestational diabetes	101 (12.0)	401 (8.8)	1.37 (1.05 to 1.79)	0.02
Gestational hypertension‡	49 (5.8)	221 (4.8)	1.27 (0.88 to 1.82)	0.21
Pre-eclampsia‡	46 (5.5)	177 (3.9)	1.61 (1.10 to 2.37)	0.01
Poor fetal growth	78 (9.3)	397 (8.7)	1.12 (0.84 to 1.50)	0.45
Tachycardia	18 (2.1)	90 (2.0)	1.77 (1.00 to 3.11)	0.05

*Adjusted for age and thyroid stimulating hormone (TSH) concentration as continuous variables and for ethnicity, income, Charlson index, hypertension, obesity, and history of thyroid disease.
†Additionally adjusted for history of pregnancy loss.
‡Adjusted for age and TSH concentration as continuous variables and for ethnicity, income, Charlson index, obesity, and history of thyroid disease.