research update

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

Kallikrein rises from the footnotes

The curious word "kallikrein" first appeared in 1934, when Eugen Werle discovered an inflammatory chemical in plasma which he thought came from the pancreas. Kallikrein is supposed to be derived from the Greek word for pancreas. Anyway, the disease in humans most closely associated with too much plasma kallikrein is hereditary angioedema with C1 inhibitor deficiency. We had a patient in our practice with the condition, which is why I know a tiny bit about it. It has a prevalence of between 1 in every 10 000 and 1 in every 50 000 population, so you wouldn't have thought it was worth people's time and money to develop a monoclonal antibody to kallikrein. But they have, and it's called lanadelumab, and the *New England Journal of Medicine* has thought fit to devote some of its hallowed pages to a phase Ib trial of it in 24 patients with hereditary angioedema with C1 inhibitor deficiency, who were compared with 12 patients given placebo. From day 8 to day 50 the 300 mg and 400 mg groups had 100% and 88% fewer attacks, respectively, than the placebo group. The idea is to use this as long term preventive treatment, which may make C1 inhibitor deficiency into an expensive condition to live with.

N Engl J Med 2017, doi:10.1056/NEJMoa1605767

MRI and metallic cardiac devices

As everybody knows, magnetic resonance imaging machines can send metal objects flying around and shouldn't be used on people with certain kinds of metal inside them, because the scanners operate with a magnetic field of 1.5 teslas. I don't quite understand what a tesla is, but this a lot of them. If you have an MRI scan and have an implanted cardiac device, the worry is not that it will fly out of your chest but that you will get magnetic field induced cardiac lead heating, which could result in myocardial thermal injury and detrimental changes in pacing properties. But here is a reassuring study from America: non-thoracic MRI was performed in 1000 cases in which patients had a pacemaker and in 500 cases in which patients had an implantable cardioverter defibrillator. No deaths, lead failures, losses of capture, or ventricular arrhythmias occurred. And these devices were of the "ordinary" kind, with no special protective features.

N Engl J Med 2017, doi:10.1056/NEJMoa1603265

Life expectancy breaks the 90 barrier

I have to say that as I get older, I value longevity less. This is probably simply an excuse to avoid activity. As you will have read in the papers, life expectancy is still trending ever upwards in most developed countries (the USA excepted) and especially in South Korea. Women in particular will face the dreadful prospect of living past the age of 90. South Korean women should form cooperatives to plant vineyards, so that those extra years are worth living in that wine deprived country.

Lancet 2017, doi:10.1016/S0140-6736(16)32381-9

Testosterone fuelled plaque?

This is testosterone week in the two leading *JAMA* journals. Seven trials called TTrials (you can guess why) tested the effect of testosterone gel on various aspects of male health over one year. Reading the findings, I admit that my ignorance is considerably deepened. The first concerns the effect of a year's testosterone gel on non-calcified coronary plaque formation. The volume of plaque was measured at the start and end of the trial, and there was more plaque in the chaps who used the gel. This sounds unfortunate, but its importance is entirely unclear. A study in *JAMA Internal Medicine* suggests that men receiving any kind of testosterone "therapy" actually have a lower rate of observed cardiovascular events. Maybe measuring plaque volume over a year is just a way of giving men large doses of ionising radiation. This just wasn't worth doing.

JAMA 2017, doi:10.1001/jama.2016.21043, *JAMA Intern Med* 2017, doi:10.1001/jamainternmed.2016.9539

Testosterone continued . . .

More on the men who had testosterone gel for a year. What happened to their bone density? It increased, more in trabecular than in peripheral bone, and more in the spine than hip. Well, we kinda knew that already. What we still don't know is whether it safely prevents actual fractures in the long term.

The TTrials explored the relation of testosterone gel, prescribed for low testosterone levels in men, with a surrogate measure of coronary risk: the Agatston score of atheroma on computed tomography. That was a randomised trial. The study here is based on observational data collected for younger men taking testosterone gel for the same reason, and the data show that they had fewer cardiovascular events over 3.4 years than men with the same testosterone "deficiency" who didn't receive treatment. So here is the problem: do you believe a properly randomised study with a lousy surrogate outcome, or an observational study with a clinically meaningful outcome? The answer is that you don't "believe" either. You ask for a randomised trial with clinically important outcomes over a sufficient period in a large number of men with a typical age distribution.

JAMA Intern Med 2017, doi:10.1001/jamainternmed.2016.9546

Fresh evidence links adiposity with multiple cancers

ORIGINAL RESEARCH An umbrella review of the literature

Adiposity and cancer at major anatomical sites

Kyrgiou M, Kalliala I, Markozannes G, et al

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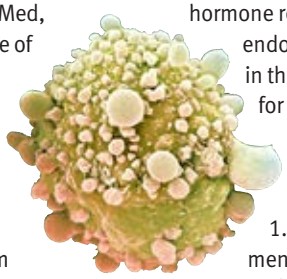
Find this at: http://dx.doi.org/10.1136/bmj.j477

Study question What are the strength and validity of evidence for the association between adiposity and risk of developing or dying from cancer?

Methods The authors searched PubMed, Embase, and the Cochrane Database of Systematic Reviews for systematic reviews and meta-analyses of observational studies. The evidence was graded as strong, highly suggestive, suggestive, or weak using criteria including the statistical significance of the random effects summary estimate and of the largest study in each meta-analysis, the number of cancer cases, heterogeneity between studies, 95% prediction intervals, small study effects, excess significance bias, and sensitivity analysis with credibility ceilings.



Study answer and limitations Of the 95 meta-analyses that included cohort studies with continuous measurement of adiposity, only 12 (13%) associations for development of nine cancers were supported by strong evidence. Adiposity was associated with a higher risk of developing oesophageal adenocarcinoma; multiple myeloma; biliary tract system, pancreatic, and kidney cancer; colon and rectal cancer in men; postmenopausal breast cancer in women who have never used hormone replacement therapy; and endometrial cancer. The increase in the risk of developing cancer for every 5 kg/m^2 increase in body mass index ranged from 9% (relative risk 1.09, 95% confidence interval 1.06 to 1.13) for rectal cancer among men (23 167 cases/4 293 489 in cohort) to 56% (1.56, 1.34 to 1.81) for biliary tract system cancer (6981/6 008 270). The risk of postmenopausal breast cancer among women who have never used HRT (10 283/342 249) increased by 11% for each 5 kg of weight gain in adulthood (1.11, 1.09 to 1.13), and the risk of endometrial cancer (2447/394 340) increased by 21% for each 0.1 increase in waist to hip ratio (1.21, 1.13 to 1.29). Five additional associations were supported by strong evidence when categorical measures of adiposity were used: weight gain with colorectal cancer risk, body mass index with risk of gallbladder, gastric cardia, and ovarian cancer, and mortality from multiple myeloma. This review relied on previously published meta-analyses; assessing the quality of primary studies was beyond its scope.

What this study adds 36 primary cancers and subtypes were included in our main analysis, but the association with obesity was supported by strong evidence for only 11 cancers (oesophageal adenocarcinoma, multiple myeloma, and cancers of the gastric cardia, colon, rectum, biliary tract system, pancreas, breast, endometrium, ovary, and kidney). Other associations could be genuine, but uncertainty remains.

Funding, competing interests, data sharing Full details in the version on bmj.com.

COMMENTARY The association is now clear; it's time to get serious about prevention

The study by Kyrgiou and colleagues[2] took up the challenge of evaluating the robustness of multiple, sometimes overlapping, meta-analyses that reported an association between body adiposity measures (such as body mass index, weight gain, and waist circumference) and cancer. The authors identified a total of 204 individual meta-analyses. They further examined the 95 meta-analyses that reported the association between body fatness measured on a continuous scale (mostly body mass index in 5 kg/m^2 increase) and cancer in cohort studies. After a rigorous evaluation for strength and validity of reported associations, 13% (12 of 95) of meta-analyses were judged to provide strong evidence on the basis of their statistical criteria. Twenty four per cent of meta-analyses found no association between body fatness and cancer.

Nine obesity related cancers were supported by strong evidence: oesophageal adenocarcinoma, colon and rectal cancer (in men), biliary tract system, pancreatic, and kidney cancer, endometrial cancer (premenopausal women), breast cancer (postmenopausal), and multiple myeloma. A positive association between body mass index and liver, ovarian, or thyroid cancer was highly suggestive or suggestive; a negative association with oesophageal squamous cell carcinoma or lung cancer was highly suggestive. In additional analyses using obesity categories (obesity versus normal weight), strong evidence also supported increased risks of gastric cardia and ovarian cancer in obese individuals.

The unavoidable conclusion from these data is that preventing excess adult weight gain can reduce the risk of cancer

A recent report by the International Agency for Research on Cancer (IARC) working group[1] and Kyrgiou and colleagues' umbrella review consistently and strongly concluded that excess body fat increases the risk of most digestive system cancers as well as endometrial and postmenopausal breast cancer. However, for gastric cardia, and cancers of the liver, ovary, or thyroid the strength of evidence differed between the two approaches, which can be explained by differences in the method used to summarise the evidence.

Though some specifics remain to be worked out, the unavoidable conclusion from these data is that preventing excess adult weight gain can reduce the risk of cancer. Furthermore, emerging evidence suggests that excess body fat in early life also has an adverse effect on risk of cancer in adulthood.[6-10] Given the critical role of healthcare providers in obesity screening and prevention,[11 12] clinicians, particularly those in primary care, can be a powerful force to lower the burden of obesity related cancers, as well as the many other chronic diseases linked to obesity such as diabetes, heart disease, and stroke. The data are clear. The time for action is now.

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Neuraminidase inhibitors during pregnancy and risk of adverse neonatal outcomes and congenital malformations

Graner S, Svensson T, Beau AB, et al

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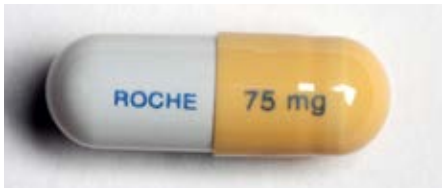
Study question Do associations exist between in utero exposure to neuraminidase inhibitors (oseltamivir or zanamivir) and poor fetal growth, low Apgar score, neonatal morbidity, mortality, and congenital malformations?

Methods This population based multinational cohort study included 5824 exposed and 692 232 unexposed women and their infants. The infants were born from 2008 to 2010 in Denmark, Norway, Sweden, or the Haute-Garonne district in France. Only infants born after gestational week 22 were included, and exposure was defined as having filled a prescription for either oseltamivir or zanamivir during pregnancy.

Study answer and limitations In the adjusted analysis, no increased risks in association with exposure to oseltamivir or zanamivir were found for low Apgar score (odds ratio 0.87, 0.67 to 1.14), preterm birth (hazards ratio 0.97, 0.86 to 1.10), small for gestational age birth (odds ratio 0.72, 0.59 to 0.87), stillbirth (odds ratio 0.81, 0.51 to 1.29), neonatal mortality (odds ratio 1.13, 0.56 to 2.28), or neonatal morbidity (odds ratio 0.92, 0.86 to 1.00). No overall increased risk of congenital malformations was seen in women exposed during the first trimester (adjusted odds ratio 1.06, 0.77 to 1.48). The study did not assess risks of adverse outcomes before gestational week 22, and some women could have filled a prescription without taking the drug, which may bias the risk estimates towards the null.

What this study adds The inclusion of almost 6000 exposed infants and 700 000 unexposed infants allowed calculation of reasonably precise risk estimates. The findings suggest that the use of neuraminidase inhibitors is not associated with increased risks of adverse fetal or neonatal outcomes.



Neuraminidase inhibitors during pregnancy and risks of neonatal outcomes

Outcome	No (%) exposed (n=5824)	No (%) unexposed (n=692 232)	Adjusted odds ratio* (95% CI)
Birth weight <2500 g	169 (2.9)	23 995 (3.5)	0.77 (0.65 to 0.91)
Apgar score ≤6 at 5 min	61 (1.0)	8442 (1.2)	0.87 (0.67 to 1.14)†
Preterm birth <37 gestational weeks	288 (4.9)	38 578 (5.6)	0.97 (0.86 to 1.10)‡
Small for gestational age§	115 (2.0)	17 425 (2.8)	0.72 (0.59 to 0.87)
Stillbirth	20 (0.3)	2855 (0.4)	0.81 (0.51 to 1.30)
Neonatal mortality	8 (0.1)	1005 (0.1)	1.13 (0.56 to 2.28)†
Neonatal morbidity	912 (16.6)†	96 773 (14.4)†	0.92 (0.86 to 1.00)†
Congenital malformations¶	44 (3.9)	19 509 (2.9)	1.06 (0.77 to 1.48)

*Adjusted for country (Scandinavian countries), year of birth, maternal age, maternal comorbidity, and smoking.
†Scandinavian data only.
‡Hazard ratio.
§Corresponding to birth weight ≤2 standard deviations of national reference curve.
¶Infants exposed in first trimester included (Scandinavian data only) .

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Impact of searching clinical trial registries in systematic reviews of pharmaceutical treatments

Baudard M, Yavchitz A, Ravaud P, Perrodeau E, Boutron I

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Find this at: http://dx.doi.org/10.1136/bmj.j448

Study question Does searching clinical registries for additional randomised trials (ie, unincluded eligible trials registered as completed or terminated) affect the results of systematic reviews?

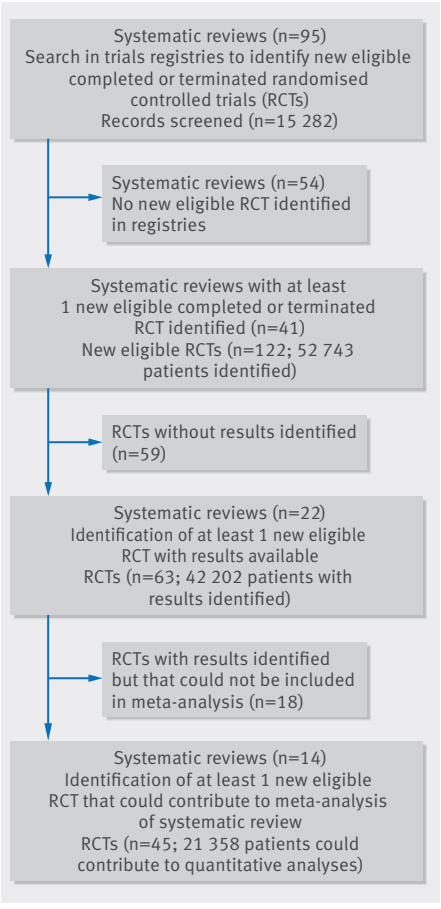
Methods The authors searched Medline to identify systematic reviews of randomised controlled trials assessing pharmaceutical treatments published between June 2014 and January 2015. For all systematic reviews that did not report a trial registry search but reported the information to perform it, the authors searched the World Health Organization International Trials Registry Platform search portal for completed or terminated randomised controlled trials not originally included in the systematic reviews. They then searched the results of these randomised controlled trials. When additional data were retrieved, the authors reanalysed the meta-analyses and calculated the weight of the additional randomised controlled trial and the change in summary statistics compared with the original meta-analysis.

Study answer and limitations 116 of 223 (52%) systematic reviews included did not report a search of clinical trial registries. After further searches for 95 systematic reviews, for 54 (57%) the authors found no additional randomised controlled trials and for 41 (43%) they identified 122 additional trials, 63 of which had results available. The weight of the additional trials in the recalculated meta-analyses ranged from 0% to 58% and the change in summary statistics from 0% to 29%. Once the new trials were added, however, none of the changes to summary effect estimates led to a qualitative change in the interpretation of the results.

What this study adds Trial registries are an important source for identifying additional randomised controlled trials. The additional number of trials and patients included if a search was performed varied across systematic reviews.

Funding, competing interests, data sharing This study was not funded and none of the authors have any competing interests to declare. Data will be shared on request.

PAUL BOSTON



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