research update

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

Globulin for graft *v* host disease

The *New England Journal of Medicine* has printed a lot of strangely worded abstract conclusions so far this year. Here is a typical example: "The inclusion of ATG resulted in a significantly lower rate of chronic GVHD after allogeneic transplantation than the rate without ATG. The survival rate was similar in the two groups, but the rate of a composite end point of chronic GVHD-free survival and relapse-free survival was higher with ATG." The plain English version would read: "In this two year, open label trial, our company's antihuman T lymphocyte immune globulin (ATG) halved the rate of chronic graft versus host disease (GVHD) in people who had previously undergone allogeneic haematopoietic stem cell transplantation, but made no difference to mortality." I guess these conclusion sections are the most contested bits of any paper, especially when sales could depend on them. I see this example as evidence of the journal taking pains to ensure that only the prespecified primary outcome measures appear in this section—hence the upside downiness of the language. All very commendable, and from now on Ben Goldacre's COMpare team (http://compare-trials.org/) will be keeping a close eye on the reporting of non-prespecified outcomes.

N Engl J Med 2016, doi:10.1056/NEJMoa1506002

Too late for diet & exercise

When people aged over 65 years are seriously obese—the mean body mass index in this trial was 39.3—they often become breathless on exertion and develop a degree of ankle oedema (especially if they are women), and they may even have audible crackles at their lung bases. This is one of the varieties of HFPEF—so-called heart failure with preserved ejection fraction. There are various confirmatory tests, including levels of B type natriuretic peptide and a restrictive pattern of diastolic filling, but there is still a lot of diagnostic fuzziness. Here's a trial of calorie restriction or exercise in 100 such patients (81 of whom were women). The interventions made no difference to symptom scores but improved the peak amount of oxygen used during exercise (peak Vo2). Sometimes it's too late for half measures: maybe a trial of bariatric surgery would be a better idea. I'm not joking: the mean age of these people was 67 years, and if they really have HEFPF then it is as life shortening as many cancers that you wouldn't hesitate to operate on.

JAMA 2016, doi:10.1001/jama.2015.17346

How much cancer is written in genes?

Now for the traditional approach: twin studies from Scandinavian public registries. They looked at 80 309 monozygotic and 123 382 same sex dizygotic twin individuals: wonderful stuff. "For most cancer types, there were significant familial risks and the cumulative risks were higher in monozygotic than dizygotic twins. Heritability of cancer overall was 33%. Significant heritability was observed for the cancer types of skin melanoma (58%), prostate (57%), nonmelanoma skin (43%), ovary (39%), kidney (38%), breast (31%), and corpus uteri (27%)."

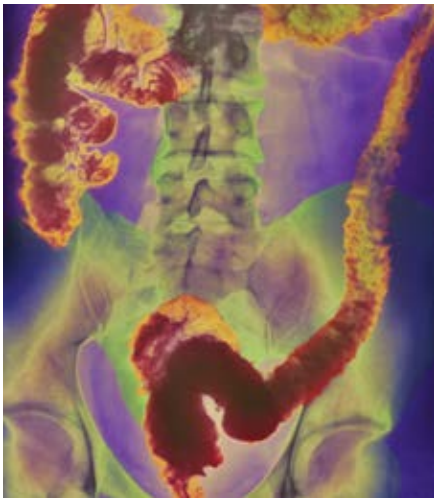
JAMA 2016, doi:10.1001/jama.2015.17703

Three types of IBD

I became a doctor 40 years ago this month. During that time there have been some notable advances in knowledge and treatment, but sadly not many relate to disabling chronic inflammatory diseases, such as multiple sclerosis or chronic inflammatory bowel disease. Here, a magnificent genetic association study questions the way we categorise the latter.

"After quality control, the primary analysis included 29 838 patients (16 902 with Crohn's disease, 12 597 with ulcerative colitis). Three loci (*NOD2*, *MHC*, and *MST1* 3p21) were associated with subphenotypes of inflammatory bowel disease, mainly disease location (essentially fixed over time; median follow-up of 10.5 years). Little or no genetic association with disease behaviour (which changed dramatically over time) remained after conditioning on disease location and age at onset." Mull over that for a minute, and then try to reconcile it with this: "Our data support a continuum of disorders within inflammatory bowel disease, much better explained by three groups (ileal Crohn's disease, colonic Crohn's disease, and ulcerative colitis) than by Crohn's disease and ulcerative colitis as currently defined. Disease location is an intrinsic aspect of a patient's disease, in part genetically determined, and the major driver to changes in disease behaviour over time." What they are saying is that the location of disease is partly genetically determined and that this governs the progression of disease. The wording that continues to fox me is "conditioning on": does that mean "adjusted for"?

Lancet 2016, doi:http://dx.doi.org/10.1016/S0140-6736(15)00465-1



CNRI/SPL

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The online version is published along with peer and patient reviews for the paper, and a statement about how the authors will share data from their study.

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ORIGINAL RESEARCH Prospective cohort study

ALAMY

Pre-pregnancy potato consumption and risk of gestational diabetes mellitus

Bao W, Tobias D K, Hu F B, Chavarro J, Zhang C

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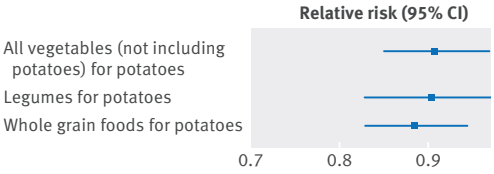
Find this at: http://dx.doi.org/10.1136/bmj.h6898



Risk of gestational diabetes mellitus associated with substitution of all vegetables (not including potatoes), legumes, or whole grain foods for potatoes at same serving amount (two servings/week). Adjusted for age (months), parity (0, 1, 2, ≥3), race/ethnicity (white, African-American, Hispanic, Asian, others), family history of diabetes (yes, no), cigarette smoking (never, past, current), physical activity (fourths), total energy intake (fourths), alternate healthy eating index 2010 (fourths), and pre-pregnancy body mass index (nine categories: <21, 21-22.9, 23.0-24.9, 25.0-26.9, 27.0-28.9, 29.0-30.9, 31.0-32.9, 33.0-34.9 and ≥35.0)

Study question What is the association between potato consumption before pregnancy and the risk of gestational diabetes mellitus?

Methods This prospective cohort study included 15 632 women from the Nurses' Health Study II (1991-2001). They had no previous gestational diabetes mellitus or chronic diseases before pregnancy. Consumption of potatoes and other foods was assessed every four years. Incident first time gestational diabetes mellitus was ascertained from self reports of a physician diagnosis of gestational diabetes mellitus, which was previously validated by medical records.

Study answer and limitations Over the 10 year follow-up there were 854 incident cases of gestational diabetes mellitus among 21 693 singleton pregnancies. After adjustment for age, parity, and dietary and non-dietary factors, women who consumed more potatoes before pregnancy had higher rates of developing gestational diabetes mellitus. Substitution of two servings a week of total potatoes with other vegetables, legumes, and whole grain foods was significantly associated with a 9-12% lower risk of gestational diabetes mellitus. Consumption and diabetes were self reported, and severity of diabetes was unknown. More than 90% of women were white. A causal association cannot be assumed.

What this paper adds Higher levels of potato consumption before pregnancy are associated with greater risk of gestational diabetes mellitus, and substitution of potatoes with other vegetables, legumes, or whole grain foods might lower the risk.

Funding, competing interests, data sharing Funding was received from the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institutes of Health, and the American Diabetes Association (No 7-12-MN-34). The authors have no competing interests or additional data to share.

Fully adjusted relative risks (95% confidence intervals) for gestational diabetes mellitus according to potato consumption before pregnancy

	Consumption (servings/week)				
	<1	1	2-4	≥5	P for trend
French fries	1.00	1.02 (0.84 to 1.24)	1.16 (0.94 to 1.45)	1.18 (0.91 to 1.53)	0.14
Baked, boiled, mashed	1.00	1.13 (0.95 to 1.35)	1.25 (1.04 to 1.51)	1.52 (1.11 to 2.07)	0.004
Total potatoes	1.00	1.20 (0.97 to 1.48)	1.27 (1.04 to 1.55)	1.50 (1.15 to 1.96)	0.006

Cardiovascular risks associated with clarithromycin

ORIGINAL RESEARCH Population based study

Cardiovascular outcomes associated with use of clarithromycin

Wong AYS, Root A, Douglas IJ, et al

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Find this at: http://dx.doi.org/10.1136/bmj.h6926

Study question What is the association between clarithromycin use and cardiovascular outcomes?

Methods In this population based study the authors compared cardiovascular outcomes in adults aged 18 or more receiving oral clarithromycin or amoxicillin during 2005-09 in Hong Kong. Based on age within five years, sex, and calendar year at use, each clarithromycin user was matched to one or two amoxicillin users. The cohort analysis included patients who received clarithromycin (n=108 988) or amoxicillin (n=217 793). The self controlled case series and case crossover analysis included those who received *Helicobacter pylori* eradication treatment containing clarithromycin. The primary outcome was myocardial infarction. Secondary outcomes were all cause, cardiac, or non-cardiac mortality, arrhythmia, and stroke.

Study answer and limitations The propensity score adjusted rate ratio of myocardial infarction 14 days after the start of antibiotic treatment was 3.66 (95% confidence interval 2.82 to 4.76) comparing clarithromycin use (132 events, rate 44.4 per 1000 person years) with amoxicillin use (149 events, 19.2 per 1000 person years), but no long term increased risk was observed. Similarly, rate ratios of secondary outcomes increased significantly only with current use of clarithromycin versus amoxicillin, except for stroke. In the self controlled case analysis, there was an association between current use of *H pylori* eradication treatment containing clarithromycin and cardiovascular events. The risk returned to baseline after treatment had ended. The case crossover analysis also showed an increased risk of cardiovascular events during current use of *H pylori* eradication treatment containing clarithromycin. The adjusted absolute risk difference for current use of clarithromycin versus amoxicillin was 1.90 excess myocardial infarction events (95% confidence interval 1.30 to 2.68) per 1000 patients.

What this study adds Current use of clarithromycin was associated with an increased risk of myocardial infarction, arrhythmia, and cardiac mortality short term but no association with long term cardiovascular risks among the Hong Kong population.

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COMMENTARY A growing literature suggests these risks are not negligible

Concerns about the cardiovascular risks of macrolide antibiotics surfaced in the 1980s, with case reports and clinical studies describing arrhythmias and QT prolongation with erythromycin.[1 2] These concerns subsequently extended to azithromycin[3] and clarithromycin.[4] For example, both observational[4] and randomised evidence[5] suggests an increase in cardiovascular mortality associated with clarithromycin.

The study by Wong and colleagues[6] further characterises the association between clarithromycin and cardiovascular events in Hong Kong's national healthcare database. Unlike most previous studies, Wong and colleagues chose incident myocardial infarction as their primary outcome, and arrhythmia, stroke, all cause mortality, and cardiovascular mortality as secondary outcomes. They used three separate study designs and each analysis identified an increased short term risk of all cardiovascular events, except stroke, associated with the current use of clarithromycin; no long term risk was identified. The adjusted risk difference for current use of clarithromycin compared with amoxicillin was 1.9 extra myocardial infarctions (95% confidence intervals 1.3 to 2.68), 0.95 extra cardiac deaths (0.51 to 1.51), and 0.2 extra arrhythmias (0.04 to 0.49) for every 1000 patients treated.

> Clinicians and patients should consider these potentially serious adverse events when prescribing macrolides

The strength and consistency of the associations across different designs is persuasive, and consistent with previous work. How should these findings inform practice? Absolute risks and measures such as number needed to harm (NNH) are useful when considering the clinical relevance of statistically significant associations. Although the NNH was not calculated in the current study, Schembri and colleagues analysed two cohorts of older adults admitted to hospital and estimated that for acute coronary syndrome, arrhythmia, or new or worsening heart failure, the NNH for clarithromycin ranged from 8 (among those with acute exacerbations of chronic obstructive pulmonary disease) to 11 (among those with community acquired pneumonia).[8] While these values reflect the use of clarithromycin among a relatively high risk subpopulation, they nevertheless suggest that the potential risks are not negligible.

As patients and clinicians try to incorporate this evidence into decision making, a few fundamental concepts are worth noting. All drugs have risks, most drugs have serious risks, and given that as many as a quarter to half of all antibiotics[9 10] prescribed are not clinically indicated, the opportunities to use these products more judiciously without compromising quality of care are manifold. Clinicians and patients should consider these potentially serious adverse events when prescribing macrolides, especially to those at highest baseline risk.

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Influenza vaccine for children with egg allergy

ORIGINAL RESEARCH Multicentre prospective cohort study

Safety of live attenuated influenza vaccine in young people with egg allergy

Turner PJ, Southern J, Andrews NJ, Miller E, Erlewyn-Lajeunesse M, on behalf of the SNIFFLE-2 Study Investigators

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DR P MARAZZI/SPL

Study question How safe is live attenuated influenza vaccine (LAIV), which contains egg protein, in young people with egg allergy?

Methods In this open label, phase IV intervention study, 779 young people (2-18 years) with egg allergy were recruited from 30 UK allergy centres and immunised with LAIV. The cohort included 270 (34.7%) young people with previous anaphylaxis to egg, of whom 157 (20.1%) had experienced respiratory and/or cardiovascular symptoms; 445 (57.1%) had doctor diagnosed asthma or recurrent wheeze. Participants were observed for at least 30 minutes after vaccination and followed-up by telephone 72 hours later. Participants with a history of recurrent wheeze or asthma underwent further follow-up four weeks later. The main outcome measure was incidence of an adverse event within two hours of vaccination in young people with egg allergy.

Study answer and limitations No systemic allergic reactions occurred (upper 95% confidence interval for population 0.47% and in participants with anaphylaxis to egg 1.36%). Nine participants (1.2%, 95% CI 0.5% to 2.2%) experienced mild symptoms, potentially consistent with a local, IgE mediated allergic reaction. Delayed events potentially related to the vaccine were reported in 221 participants. 62 participants (8.1%, 95% CI for population 6.3% to 10.3%) experienced lower respiratory tract symptoms within 72 hours, including 29 with parent reported wheeze. No participants were admitted to hospital. No increase in lower respiratory tract symptoms occurred in the four weeks after vaccination (assessed with asthma control test). The study cohort may represent young people with more severe allergy requiring specialist input, since they were recruited from secondary and tertiary allergy centres.

What this study adds LAIV is associated with a low risk of systemic allergic reactions in young people with egg allergy. The vaccine seems to be well tolerated in those with well controlled asthma or recurrent wheeze.

Funding, competing interests, data sharing Full details on funding and competing interests are listed at the end of the online article on thebmj.com. No additional data are available.

Study registration ClinicalTrials.gov (NCT02111512) and the EU Clinical Trials Register EudraCT (2014-001537-92).

COMMENTARY Policies should change after compelling new evidence of safety

Influenza vaccine is egg derived and has been contraindicated in people with egg allergy. No study has shown that these vaccines are riskier for egg allergic recipients than for the general population.[2] But governmental agencies and vaccine manufacturers have continued to issue this contraindication annually.[2 3]

The infectious risk attributable to this contraindication is substantial. Influenza infection caused 49 000 deaths between 1976 and 2006, and each year in the United States it contributes to 294 128 admissions to hospital.[4 5] Egg allergy affects approximately 2-6% of children. One third of these children have asthma, making egg allergic children a vulnerable subgroup at high risk of influenza related complications.[6 7]

In 2012, after multiple studies showed that injectable influenza vaccine was safe in egg allergic recipients, the US Centers for Disease Control and Prevention revised its contraindication. The CDC now recommends that those with mild egg allergy can receive injectable influenza vaccine, whereas those with severe egg allergy should seek advice from an allergist before vaccination.[8] Live attenuated influenza vaccine, given intranasally, remains contraindicated. No evidence exists that the live attenuated vaccine increases the risk of allergic reaction in egg allergic recipients, but studies are limited and safety data inadequate.

Turner and colleagues fill this important gap.[10] Despite a relatively small sample, the authors conclude with 95% confidence that the true risk of systemic allergic reactions among egg allergic children is less than 0.5%. No systemic reactions developed among vaccinated children, and only 1.2% (n=9) developed mild, localised nasopharyngeal reactions. These are very important findings that could substantially improve the healthcare of children in these high risk groups.

In published literature to date, 955 egg allergic children have safely received live attenuated influenza vaccine. This should serve as sufficient evidence that the intranasal vaccine is safe and should no longer be contraindicated in children with egg allergy.[13 14] Turner and colleagues' study may not be as big as some would like, but this volume of data was more than enough to inform CDC policies on both injectable influenza vaccine in 2012 and the combined MMR (measles, mumps, rubella) vaccine in the 1990s.[15 16] No data suggest there has been a spike in allergic reactions in egg allergic recipients since.

The desire for larger study samples to improve confidence intervals is understandable, but it is not feasible to recruit the 10 000 or so egg allergic children required to demonstrate safety with 99% confidence. There is, however, a substantial opportunity cost in perpetuating the myth that ovalbumin in influenza vaccines endangers children with egg allergy and in continuing to withhold an effective vaccine from a vulnerable group.

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