research update

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

CPAP and cardiovascular events

Here is a trial that randomly assigned 2717 eligible adults aged between 45 and 75 with moderate to severe obstructive sleep apnoea and coronary or cerebrovascular disease to receive continuous positive airways pressure treatment plus usual care or usual care alone. Over 3.7 years, "No significant effect on any individual or other composite cardiovascular end point was observed. CPAP significantly reduced snoring and daytime sleepiness and improved health-related quality of life and mood." It's remarkable that it even did that, because the mean duration of adherence to CPAP treatment was just 3.3 hours per night. In the NHS you wouldn't be allowed a machine if you used it so little. Additionally, I wonder if the selection process distinguished accurately between obstructive sleep apnoea and central sleep apnoea. I don't think this trial tells us a great deal.

N Engl J Med 2016, doi:10.1056/NEJMoa1606599

Cord blood for minimal residual disease

The disease referred to here—and the same way in the paper's title—is acute leukaemia or the myelodysplastic syndrome. The 582 consecutive patients underwent myeloablation and then had a haematopoietic cell transplant from an unrelated cord-blood donor (140 patients), an unrelated donor matched for human leucocyte antigen (HLR) (n=344), or an HLA mismatched unrelated donor (n=98). The problem in this specialty is that it can be hard to find an HLA matched donor in a hurry, as we know from newspaper stories. So the relative success of cord-blood transfusion in this series is a hopeful signal, although short of definitive: "Our data suggest that among patients with pretransplantation minimal residual disease, the probability of overall survival after receipt of a transplant from a cord-blood donor was at least as favorable as that after receipt of a transplant from an HLA-matched unrelated donor and was significantly higher than the probability after receipt of a transplant from an HLA-mismatched unrelated donor. Furthermore, the probability of relapse was lower in the cord-blood group than in either of the other groups."

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Gluten-free fashions

A few weeks ago, the *New Yorker* ran a cartoon of two girls meeting for lunch and one of them saying "I've only been gluten-free for a week, and already I'm really annoying." I'm afraid that I may be distantly implicated in this: around 1997 I heard about a new blood test (antiendomysial antibody) for gluten enteropathy and alerted my work partner Harold Hin to its potential for detecting coeliac disease in the community. His was the first primary care study in the UK (www.bmj.com/content/318/7177/164) to show that the prevalence of histologically confirmed coeliac disease was 10-100 times greater than previously thought, and that its symptoms could be almost anything, or nothing. So now people with almost any, or no, symptoms have taken to gluten-free diets, even though they test negative for coeliac disease. This is confirmed in the US National Health and Nutrition Examination Surveys (NHANESs) 2009-14.

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2016.5254

Stents, bare and eluting

There are stent wars, and statin wars, and *Star Wars*. And now, at last, comes a large long term randomised trial comparing bare metal stents with drug eluting stents: the very thing we needed all along. "In patients undergoing percutaneous coronary intervention, there were no significant differences between those receiving drug-eluting stents and those receiving bare-metal stents in the composite outcome of death from any cause and nonfatal spontaneous myocardial infarction. Rates of repeat revascularization were lower in the group receiving drug-eluting stents." Imagine if health systems around the world had waited for the actual evidence: tens of billions of pounds/dollars might have been saved in needlessly expensive stents and antiplatelet agents.

N Engl J Med 2016, doi:10.1056/NEJMoa1607991

MRI in early pregnancy

Magnetic resonance imaging is safe in the first trimester of pregnancy. In a case-control study of the whole population of Ontario, investigators found no difference in the risk of stillbirth or neonatal death within 28 days of birth and any congenital anomaly, neoplasm, and hearing or vision loss evaluated from birth to age 4 years. Add in gadolinium contrast agent, however, and the picture gets nasty: "Gadolinium MRI at any time during pregnancy was associated with an increased risk of a broad set of rheumatological, inflammatory, or infiltrative skin conditions and for stillbirth or neonatal death." I don't know to what extent this was already known, but it sounds as if it would now be medical negligence to give gadolinium to any woman of childbearing age without first excluding pregnancy.

JAMA 2016, doi:10.1001/jama.2016.12126

Population surveillance for microcephaly in Europe

ORIGINAL RESEARCH Population based study

Prevalence of microcephaly in Europe

Morris J K, Rankin J, Garne E, et al

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Study question What is the current prevalence of microcephaly in Europe, is diagnosis consistent across the region, and would any changes in prevalence due to the Zika virus be detected with the existing European surveillance performed by EUROCAT (European Surveillance of Congenital Anomalies)?

Methods 24 EUROCAT registries covering 570 000 births annually in 15 countries recorded 2443 diagnoses of microcephaly not associated with a genetic condition among live births, fetal deaths from 20 weeks' gestation, and terminations of pregnancy for fetal anomaly at any gestation. Sixteen registries responded to a questionnaire, of which 44% (7/16) used the EUROCAT definition of microcephaly (a reduction in the size of the brain with a skull circumference more than 3 SD below the mean for sex, age, and ethnic origin), 19% (3/16) used a 2 SD cut off, 31% (5/16) were reliant on the criteria used by individual clinicians, and one registry changed criteria between 2003 and 2012. The prevalence of microcephaly was analysed with random effects Poisson regression models to account for heterogeneity across registries.

Study answer and limitations The prevalence of microcephaly in Europe was 1.53 (95% confidence interval 1.16 to 1.96) per 10 000 births, with registries varying from 0.4 (0.2 to 0.7) to 4.3 (3.6 to 5.0) per 10 000. Registries with a 3 SD cut off reported a prevalence of 1.74 per 10 000 (0.86 to 2.93) compared with those with the less stringent 2 SD cut off of 1.21 per 10 000 (0.21 to 2.93). EUROCAT could detect increases in the prevalence of microcephaly due to the Zika virus of a similar magnitude to those observed in Brazil. Due to the rarity of microcephaly and discrepant diagnostic criteria among EUROCAT registries, however, the smaller increases expected (because *Aedes* mosquitoes are not indigenous in most of Europe) would be probably not be detected.

What this study adds The reported prevalence of microcephaly varies considerably across Europe because of the different diagnostic criteria applied and varying levels of ascertainment. Annual fluctuations in the total European prevalence are likely to occur because of the rarity of microcephaly.

Funding, competing interests, data sharing Funding was from the European Union FP7. There were no competing interests. Aggregate data, updated biannually, are available from the EUROCAT website (www.eurocat-network.eu/accessprevalencedata/prevalencetables).

COMMENTARY Surveillance is an essential part of the response to Zika and must be improved

The Zika virus is highly teratogenic.[1] The nature and severity of birth defects associated with exposure in utero challenge even the most well resourced perinatal surveillance programmes. Considerable activity has focused on the baseline prevalence of central nervous system anomalies, particularly microcephaly. A linked paper by Morris and colleagues shows just how difficult it can be to ascertain accurate data on the baseline prevalence of these congenital defects within existing surveillance systems.[2] The authors conclude that shortcomings in surveillance coupled with the rarity of microcephaly mean that changes in prevalence potentially due to the Zika virus could be missed.

Morris and colleagues examined the prevalence of microcephaly in 24 regions of Europe during 2003-12.[2] The point estimates for microcephaly vary by an order of magnitude from 0.4 to 4.3 per 10 000 births, with an overall estimate of 1.53 per 10 000 births.

This relatively low figure[2] could be partly due to the conservative case definition used, and the exclusion of cases with known genetic disorders. But why so much variability across the 24 participating registries? Random variability is one likely contributor, given the small populations involved. Other possibilities include heterogeneity in diagnostic criteria or their application by clinicians, variation in availability of prenatal diagnosis, rates of elective termination, methods of ascertainment in the birth defects registry, and the registry's ability to capture cases of infants who received a diagnosis after the initial stay in hospital or outside hospital care settings.

The challenges for surveillance of birth defects should be addressed now

Ironically, the National Birth Defects Prevention Network (NBDPN) in the US made the decision to discontinue annual reporting of microcephaly by state beginning with 2007-11 because of extreme variability in state level prevalence reports, and microcephaly was not included among the conditions in the most recent report of US national prevalence estimates.[4 5] A forthcoming report evaluating the prevalence of microcephaly in the US found a pooled prevalence of 8.8 per 10 000 live births, with variation by whether case finding used passive or active ascertainment as well as demographic characteristics and perinatal outcomes,[6] demonstrating that shortcomings in surveillance are not confined to Europe.

While Zika virus is an unlikely threat in much of Europe, the challenges for surveillance of birth defects should be addressed now to strengthen the quality and effectiveness of this essential public health function. Although microcephaly is a marker for a pregnancy potentially exposed to Zika virus, affected women might have no symptoms, and affected infants might not present with microcephaly. Some exposed infants receive a diagnosis of microcephaly in early childhood, and would be missed by registries that do not follow cohorts beyond the first year after birth. Registers of pregnancies affected by Zika virus with longitudinal follow-up of both mother and child must be established urgently to fully understand the natural course of the Zika syndrome and its impact on child growth and development.

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Electronic cigarettes and smoking cessation in England

ORIGINAL RESEARCH Time series analysis of population trends

Association between e-cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England

Beard E, West R, Michie S, Brown J

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Study question Have changes in prevalence of e-cigarette use in England been associated with changes in quit success, quit attempts, and use of licensed stop smoking treatments and behavioural cessation support?

Methods Time series data between November 2006 and March 2015 from the Smoking Toolkit Study, a series of population surveys of individuals aged 16 years and older, and monitoring data from the national behavioural support programme were used. Prevalence of e-cigarette use was used to predict quit success, rate of quit attempts, use of prescription pharmacotherapy, use of nicotine replacement therapy obtained on prescription or over the counter, and engagement with behavioural support provided through stop smoking services.

Study answer and limitations The success rate of quit attempts increased by 0.098% (95% confidence interval 0.064 to 0.132; P<0.001) and 0.058% (0.038 to 0.078; P<0.001) for every 1% increase in the prevalence of e-cigarette use by smokers and during a recent quit attempt, respectively. No clear association was found with rate of quit attempts or use of other quitting aids or support, except for nicotine replacement therapy on prescription, where the association was negative. The study relied on self reported data, and findings may not generalise to other countries because England has a strong climate of tobacco control and relatively liberal regulation of e-cigarettes.

What this study adds Using a time series approach, this empirical study estimates the possible population impact of e-cigarettes on key smoking cessation activities and outcomes. The findings do not support the hypothesis that e-cigarette use undermines quitting, and use of these devices may be positively associated with quit success.

Funding, competing interests, data sharing The Smoking Toolkit Study is primarily funded by Cancer Research UK. Full details on funding, competing interests, and data sharing can be found on thebmj.com.
Study registration The analysis plan was preregistered (https://osf.io/fbgj2/).

COMMENTARY E-cigarettes and the falling prevalence of smoking

Electronic cigarettes, now used by over two million UK smokers,[1] are possibly the most disruptive new technology in the nicotine market since the cigarette. Although still controversial, there is a growing consensus that e-cigarettes could prevent a substantial proportion of premature mortality and morbidity among the nine million smokers in the UK.[2] However, there remain many uncertainties including concerns that e-cigarettes could reduce smokers' motivation to quit and undermine uptake of smoking cessation services.

A study in *The BMJ*[3] explores these concerns. The authors' analysis of longitudinal data from England identifies a significant direct association between e-cigarette use and successful quitting, a significant inverse association with use of prescription nicotine replacement therapy (NRT), and no significant associations with other outcomes. Simple visual inspection of the time trends also suggests a rapid increase in e-cigarette use among all smokers between 2011 and 2013, and overall downward trends in the proportion of smokers making a quit attempt each year and the proportion purchasing over-the-counter NRT, although with a brief surge in quit attempts during 2013. Use of all prescription medicines and the numbers of smokers setting quit dates with stop smoking services increased until late 2011, and have since fallen.

The challenge for public health is to embrace the potential of this new technology, and put it to full use

A simple causal interpretation of these trends is that e-cigarettes help smokers to quit; that their emergence also generated a brief upsurge in numbers trying to quit; and that uptake of prescription medicines and stop smoking service support has fallen. This suggests that e-cigarettes are an alternative rather than a complement to conventional cessation services.

But there are other potential explanations for the falling uptake of prescribed pharmacotherapy and stop smoking services since 2011. Spending on anti-smoking mass media campaigns, a major driver of motivation to quit,[4 5] fell precipitously after the election of a new UK government in 2010. Future funding and job security for NHS stop smoking services were destabilised from 2010 by the announcement of a proposal to move these services from the NHS to local authority control,[6] which was implemented in 2012.[7] Funding for these services has since fallen dramatically.[8] Uncertainties over the safety and role of e-cigarettes also generated reluctance in many stop smoking services, at least until recently,[9] to integrate e-cigarettes into treatment protocols; potentially discouraging e-cigarette users from accessing the services. These are all potentially strong confounders of the reported associations, but the authors were able to control only for spending on mass media campaigns.

It therefore remains unclear whether, or by how much, the availability of e-cigarettes has influenced quitting behaviour in the UK. However, the key arbiter of this and other controversies over the role of e-cigarettes lies less in these data than in trends in smoking prevalence, which in 2015 fell by nearly one percentage point relative to 2014.[10] This significant year-on-year fall indicates that something in UK tobacco control policy is working, and successful quitting through substitution with e-cigarettes is one likely major contributor.[11] The challenge for public health is to embrace the potential of this new technology, and put it to full use.[12]

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Hyperglycaemia and risk of adverse perinatal outcomes

Farrar D, Simmonds M, Bryant M, et al

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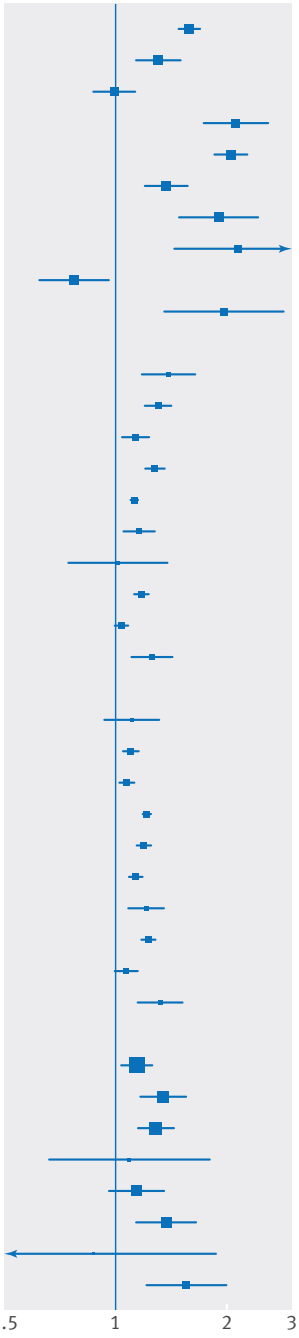
Study question What is the association between blood glucose concentrations in pregnant women without gestational or existing diabetes and birth outcomes?

Methods Databases including Medline and Embase were searched up to October 2014 and combined with individual participant data from two additional birth cohorts. Results were extracted from oral glucose tolerance (OGTT) or challenge (OGCT) tests at fasting and one and two hour post-load timings. Included studies had to report on at least one adverse perinatal outcome.

Study answer and limitations 25 reports from 23 studies and two cohorts with information including up to 207 172 women and their infants were included. Most of the studies were well conducted. In some studies, the doctors and midwives were not blinded to the women's blood glucose concentrations, which could have affected treatment and, as a result, the outcomes. When results from all studies were combined there was a linear association between glucose concentrations and caesarean section, induction of labour, large for gestational age, and shoulder dystocia. For each 1 mmol/L increase in concentration, the risk of these adverse outcomes increased by a similar amount. There was no clear evidence of a threshold effect. In general, associations were stronger for fasting concentration than for post-load concentration. The associations were similar in studies in different geographical areas across the world and in those studies with and without adequate blinding. There is currently no evidence from sub-Saharan Africa regarding these associations and little evidence from other low and middle income countries.

What this study adds There is a graded linear association between fasting and post-load glucose concentration across the whole glucose distribution and most adverse perinatal outcomes in women without pre-existing or gestational diabetes. The lack of a clear threshold at which risk increases means that decisions regarding thresholds for diagnosing gestational diabetes are somewhat arbitrary.

Outcome	No of studies	No of women	Odds ratio (95% CI)	I^2 (%)	Odds ratio (95% CI)
Combined 75 g and 100 g - Fasting					
C section	6	47 746		0	1.59 (1.49 to 1.70)
Induction	2	12 484		0	1.31 (1.14 to 1.50)
Instrumental birth	3	17 257		0	0.99 (0.87 to 1.13)
LGA	7	46 680		1	2.11 (1.73 to 2.58)
Macrosomia	6	28 303		0	2.06 (1.86 to 2.28)
Neonatal hypoglycemia	2	19 998		0	1.37 (1.2 to 1.57)
PIH/pre-eclampsia	3	5551		0	1.91 (1.49 to 2.43)
Pre-eclampsia	4	39 345		5	2.15 (1.45 to 3.19)
Preterm birth	3	17 257		0	0.77 (0.62 to 0.96)
Shoulder dystocia	4	18 615		0	1.97 (1.36 to 2.85)
50 g OGCT					
C section	7	36 616		6	1.39 (1.18 to 1.64)
Induction	1	13 902		0	1.30 (1.20 to 1.41)
Instrumental birth	2	3791		0	1.14 (1.04 to 1.23)
LGA	4	30 626		0	1.28 (1.21 to 1.36)
Macrosomia	7	64 851		0	1.13 (1.10 to 1.15)
Neonatal hypoglycemia	3	15 619		0	1.16 (1.05 to 1.28)
PIH/pre-eclampsia	1	1157		0	1.02 (0.75 to 1.38)
Pre-eclampsia	6	58 270		0	1.18 (1.13 to 1.23)
Preterm birth	2	27 126		0	1.04 (1.00 to 1.08)
Shoulder dystocia	2	27 688		0	1.25 (1.10 to 1.43)
Two hour post-load 75 g OGTT					
C section	7	41 130		22	1.11 (0.93 to 1.31)
Induction	2	12 485		0	1.10 (1.04 to 1.16)
Instrumental birth	4	18 661		0	1.07 (1.03 to 1.12)
LGA	9	48 321		0	1.21 (1.18 to 1.24)
Macrosomia	5	19 524		0	1.19 (1.14 to 1.25)
Neonatal hypoglycemia	2	19 998		0	1.13 (1.09 to 1.18)
PIH/pre-eclampsia	2	4174		0	1.21 (1.08 to 1.35)
Pre-eclampsia	3	35 720		0	1.23 (1.18 to 1.28)
Preterm birth	5	18 816		0	1.07 (0.99 to 1.15)
Shoulder dystocia	3	17 260		0	1.32 (1.14 to 1.52)
Two hour post-load 100 g OGTT					
C section	2	3915			1.14 (1.04 to 1.25)
LGA	2	1645			1.35 (1.17 to 1.55)
Macrosomia	2	3877			1.29 (1.15 to 1.44)
Neonatal hypoglycemia	1	287			1.09 (0.66 to 1.80)
PIH/pre-eclampsia	1	1358			1.14 (0.96 to 1.35)
Pre-eclampsia	1	3628			1.37 (1.14 to 1.65)
Preterm birth	1	249			0.87 (0.41 to 1.87)
Shoulder dystocia	2	1645			1.56 (1.21 to 1.99)



Odds ratios for outcomes associated with glucose concentration. LGA=large for gestational age; PIH=pregnancy induced hypertension

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