research update

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

"Subclinical hypothyroidism" in pregnancy

Observational studies have shown an association between high levels of thyroid stimulating hormone (TSH, or thyrotropin) or low levels of free thyroxine (T4), or both in mothers and lowered measures of intelligence in their children. As so often happens, guidelines ran ahead of the evidence and recommended screening long before there was evidence that treatment with levothyroxine would make any difference. Now comes the trial evidence, and it's negative. In this context "subclinical hypothyroidism" is the name given to a high TSH level accompanied by a normal circulating T4 level, whereas a low circulating T4 level is called hypothyroxinaemia. Bear in mind that both are defined by arbitrary cut-off points in continuously distributed biochemical variables, occurring in people without symptoms. For this reason, and more than I have space to mention, I'm not surprised that "Treatment for a subclinical hypothyroidism or hypothyroxinemia beginning between 8 and 20 weeks of gestation did not result in significantly better cognitive outcomes in children through 5 years of age than no treatment for those conditions."

N Engl J Med 2017, doi:10.1056/NEJMoa1606205

Later cancers in survivors of childhood cancer

It will be hard for some of you to believe this, but when I first started writing these reviews 18 years ago I was quite a fan of oncology trials. The treatment of childhood cancer seemed to me a great illustration of how incremental advances that seemed small in themselves could eventually achieve major improvements in survival. And so they have, although at a cost. In this study of 23 603 survivors of childhood cancer, there were 1026 new malignancies over a mean follow-up of 20.5 years. The strongest association was with radiation dosage, which tended to fall between the 1970s and the 1990s. Just one more reminder that ionising radiation is bad for children, and treatment regimens that reduce the need for it are likely to be a good thing.

JAMA 2017, doi:10.1001/jama.2017.0693

Early life deprivation

Remember those awful pictures of Romanian orphans from 25 years ago? A longitudinal study compares those who were adopted by English parents with UK controls who had not experienced early life deprivation. Cognitive impairment in the group who spent more than six months in an institution remitted from noticeably higher rates at ages 6 years and 11 years compared with UK controls, to normal rates at young adulthood. But for psychosocial adjustment it was a different story: "extended early deprivation was associated with long-term deleterious effects on wellbeing that seem insusceptible to years of nurturance and support in adoptive families." Please could the *Lancet* use a retired English schoolteacher to take a red pencil to this stuff? "Nurturance"? Deleterious, insusceptible. Pah. The most striking fact here is that the kids who had spent more than six months in Romanian orphanages coped reasonably while they were with their foster parents, but from the age of 15 onwards showed increasing levels of emotional distress and educational and social failure.

Lancet 2017, doi:10.1016/S0140-6736(17)30045-4

Early onset type 2 diabetes is bad news

Here's an observational study comparing 1746 patients who developed type 1 diabetes before the age of 20 with 272 who had type 2 diabetes, also with onset before 20. The prevalence of diabetic kidney disease, retinopathy, and peripheral neuropathy was statistically significantly greater in patients with type 2 diabetes, even after adjustment for differences in glycated haemoglobin (HbA_{1c}), body mass index, waist to height ratio, and mean arterial blood pressure. This is very worrying. One could quibble about the adjustments and the detail, but this survey provides more proof that with type 2 diabetes, age of onset is a crucial factor. Once it is established, this syndrome does major damage that we are still largely unable to control.

JAMA 2017, doi:10.1001/jama.2017.0686

Antithrombotics and subdural haemorrhage

The Danish population registry shows that the incidence of subdural haemorrhage almost doubled between 2000 and 2015. By comparing 10 010 cases with 400 380 matched controls, the investigators in this study were able to calculate how much of this might be due to drugs that impair clotting. The odds ratio for people taking aspirin was 1.25, whereas for direct oral anticoagulants it was 1.73. Surprisingly, clopidogrel came in at 1.87. But by far the greatest increase in risk was associated with vitamin K antagonists, at 3.69. Beware the elderly patient taking warfarin who "goes off," with or without a headache.

JAMA 2017, doi:10.1001/jama.2017.0639

REMIND me—what was I supposed to take?

Poor adherence to prescribed medicines is not just a problem of elderly people taking numerous different pills. The REMIND trial recruited 53 480 people aged between 18 and 64 years who were taking no more than three types of drugs a day but nevertheless showed "non-adherence," meaning less than 80% of indicated use. The participants were block randomised to receive a pill bottle strip with toggles, a digital timer cap, a standard pill bottle, or nothing. Never mind trying to work out the strip-and-toggle bit: none of these interventions made any difference.

JAMA Intern Med 2017, doi:10.1001/jamainternmed.2016.9627

Renal function after renin-angiotensin system blockade

ORIGINAL RESEARCH Cohort study

Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks

Schmidt M, Mansfield KE, Bhaskaran K, et al

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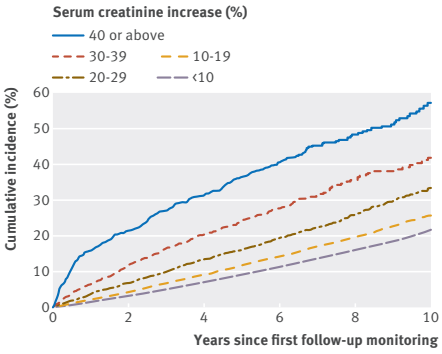
Study question Are increased concentrations of creatinine after starting treatment with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) associated with long term adverse cardiac and renal outcomes?

Methods This was a population based cohort study using electronic health records from the Clinical Practice Research Datalink and Hospital Episode Statistics (1997-2014). Rates of outcomes (end stage renal disease, myocardial infarction, heart failure, and death) were compared among ACEI/ARB users with post-initiation creatinine increases of 30% or more versus those without, as well as for each 10% increase in creatinine. Analyses were adjusted for age, sex, calendar period, socioeconomic status, lifestyle factors, chronic kidney disease, diabetes, cardiovascular comorbidities, and use of other antihypertensive drugs and non-steroidal anti-inflammatory drugs.

Study answer and limitations Among 122 363 patients in routine clinical care, the 2078 (1.7%) who had an increase in creatinine of 30% or more after starting ACEI/ARB treatment were at increased risk of end stage renal disease, adverse cardiac outcomes, and death. In addition, a graduated increased risk of all outcomes for each 10% increment in creatinine was seen in the 19 918 (16.3%) patients with a greater than 10% increase in creatinine. Cardiorenal risks were highest in the first year after ACEI/ARB initiation, but they remained elevated for most outcomes up to 10 years later. Only patients with both baseline and follow-up creatinine measurements could be included.



Cumulative mortality according to levels of creatinine increase after renin-angiotensin system blockade

What this study adds Existing guidelines recommend consideration of cessation of ACEI/ARB treatment for patients with post-initiation creatinine increases of 30% or more. These results suggest that increases below 30% are also associated with increased risk of adverse outcomes and should prompt further monitoring and consideration of the risks and benefits of ongoing treatment.

Funding, competing interests, data sharing
See full paper online for authors' sources of funding.

COMMENTARY Small increases in creatinine could signal a higher risk of poor outcomes

Schmidt and colleagues' study suggests that a 10-30% rise in serum creatinine after the start of treatment with renin-angiotensin system blockers can predict increased risk of adverse renal and cardiac outcomes or death, even after correction for baseline renal function. What does this study tell us that can help to optimise use of these important drugs? As the authors point out, the basis of current guidelines to stop treatment above a creatinine increase cut-off of 30% may be questionable.

This study shares the strengths and limitations of any population based cohort study; confirming a causal relation between drug associated changes in creatinine concentration and later outcomes is not possible, and we are reliant on the quality and completeness of the data available. Their cohort was necessarily limited to patients with follow-up creatinine values, which potentially selected a group thought to be at higher risk. Surrogate markers were used to identify end stage renal disease, there was no untreated comparator group, and the observed number of events was low, amounting to less than 10 per 100 patient years.

Clinicians need to get their house in order and appropriately monitor patients exposed to renin-angiotensin system blockers

Some notable baseline differences existed between patients with increases in creatinine concentration above and below 30%. However, the authors corrected for confounding factors as far as possible, and the "dose response" they identified is striking.

Given the increased risk of worse outcomes associated with even small increases in creatinine concentration, should we consider changing practice? The same group of authors recently reported that monitoring of creatinine and potassium concentrations on starting treatment with ACEI or ARB was done to guideline standards in just 10% of patients. They further reported that treatment continued in 80% of patients whose creatinine concentrations increased by more than 30%.[8] So rather than changing guidelines, we should be encouraging much better adherence to existing guidelines.

Patients with increases in creatinine concentration after starting treatment with renin-angiotensin system blockers should be treated as a high risk group. Perhaps a raised creatinine should be used as a marker to identify patients who need closer monitoring, further cardiovascular risk assessment and lifestyle advice, and potentially more aggressive treatment of underlying disorders.

First and foremost, however, the message from this study is that clinicians need to get their house in order and appropriately monitor patients exposed to renin-angiotensin system blockers, especially in the first three months of treatment.

Marie Valente
Sunil Bhandari Sunil.bhandari@hey.nhs.uk
See bmj.com for author details

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ORIGINAL RESEARCH Population based study

Maternal and infant genetic variants, maternal periconceptional use of selective serotonin reuptake inhibitors, and risk of congenital heart defects in offspring

Nembhard W N, Tang X, Hu Z, et al

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Study question Is there an association between maternal periconceptual use of selective serotonin reuptake inhibitors (SSRIs) and increased risk of congenital heart defects in offspring and is any association modified by maternal or infant genetic variants in folate, homocysteine, or transsulfuration pathways?

Methods Data were extracted from the US National Birth Defects Prevention Study on 1180 liveborn infants with congenital heart defects (cases) and 1644 controls (no major defects), born 1997-2008. DNA from mothers, fathers, and infants were genotyped with an Illumina GoldenGate custom single nucleotide polymorphism panel. A log linear model based hybrid design was used to calculate relative risks to identify single nucleotide polymorphisms associated with congenital heart defects through interaction with SSRI use.

Study answer and limitations Common maternal or infant genetic variants in folate, homocysteine, or transsulfuration pathways are associated with increased risk of certain congenital heart defects among children of women taking SSRIs during early pregnancy. For women who reported taking SSRIs periconceptionally, maternal SHMT1 (rs9909104) GG and AG genotypes were associated with a 5.9 and 2.4 increased risk of select congenital heart defects in offspring, respectively, versus the AA genotype (bayesian false discovery probability (BFDP)=0.69). Compared with the AA genotype, BHMT (rs492842 and rs542852) GG and AG genotypes were associated with twice the risk of congenital heart defects (BFDP=0.74 and 0.79, respectively). MGST1 (rs2075237) CC and AC genotypes were associated with an increased risk compared with the GG genotype (8.0 and 2.8, respectively; BFDP=0.79). Single nucleotide polymorphisms in infant genes in the folate (MTHFS rs12438477), homocysteine (TRDMT1 rs6602178 and GNMT rs11752813), and transsulfuration (GSTP1 rs7941395 and MGST1 rs7294985) pathways were also associated with an increased risk of congenital heart defects. Information concerning periconceptional SSRI use could be subject to measurement error and recall bias as women were asked 12-24 months after delivery to report on their SSRI use. The authors did not assess dietary intake of folate and its role in the association between SSRI use and risk of congenital heart defects in this population.

What this study adds Common allelic variants in maternal and infant genes involved in the folate, homocysteine, and glutathione/transsulfuration metabolic pathways could modify the association between maternal periconceptional use of SSRIs and risk of congenital heart defects.

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

ORIGINAL RESEARCH Results of the Stepping Up pragmatic cluster randomised controlled clinical trial

Supporting insulin initiation in type 2 diabetes in primary care

Furler J, O'Neal D, Speight J, et al

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Study question How effective is a novel model of care ("Stepping Up") in normalising insulin initiation as part of routine primary care for type 2 diabetes to improve glycaemic outcomes?

Methods In this two arm, cluster randomised controlled trial over 12 months in primary care in Victoria, Australia, eligible patients had glycated haemoglobin (HbA_{1c}) ≥7.5% and were receiving maximal oral treatment. 266 patients and 74 practices with a mean cluster size of 4 (range 1-8) participated. The Stepping Up model of care intervention involved theory based practice system change and reorientation of health professional roles. The core component was an enhanced role for the practice nurse in leading insulin initiation, with mentoring by a registered nurse with diabetes educator credentials. The primary endpoint was change in HbA_{1c}. Secondary endpoints included the proportion of participants who transitioned to insulin and change in depressive symptoms and generic health status.

Primary and secondary endpoints of Stepping Up model of care trial. Values are mean (SD) or median (interquartile range) unless stated otherwise

Endpoints	Intervention arm	Control arm	Adjusted data for clustering	
			Treatment effect (95% CI)	P value
HbA_{1c} (%):				
Baseline	8.7 (8.1-9.7)	8.5 (8-9.6)		0.37
Follow-up	7.4 (6.9-8.2)	8 (7.1-9)		
Change	−1.3 (1.4)	−0.6 (1.5)	−0.6 (−0.9 to −0.3)	<0.001
No (%) of participants using insulin at follow-up	105 (69.5)	25 (21.7)	8.3* (4.5 to 15.4)	<0.001
Change in depressive symptoms (PHQ-9)	−1.1 (3.5)	−0.1(2.9)	−0.8 (−1.6 to −0.01)	0.047
Change in weight (kg)	1.7 (5.2)	−1.1(5.1)	2.8 (1.6 to 4.0)	<0.001

PHQ-9=nine item patient health questionnaire.
*Odds ratio.

Study answer and limitations HbA_{1c} improved in both study arms, with a clinically significant between arm difference (mean difference −0.6%, 95% confidence interval −0.9% to −0.3%) favouring the intervention. At 12 months, statistically significantly more patients in intervention practices had started insulin (70% in the intervention arm, compared with 22% in the control arm). Depressive symptoms did did not worsen and no severe hypoglycaemia was reported. This study had limitations: patients were recruited after randomisation of the practices, the sample might not be representative, the drugs data might have accuracy limitations as they were extracted from routine medical records, and data on hypoglycaemia are possibly under-reported.

What this study adds The novel Stepping Up model of care was associated with increased insulin initiation rates in primary care and improvements in glycated haemoglobin without worsening emotional wellbeing. It is possible to overcome delays in starting insulin treatment, enabling timely intensification of treatment.

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

Standards for Reporting Implementation Studies (StaRI) Statement

Pinnock H, Barwick M, Carpenter CR, et al, for the StaRI Group

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Implementation research bridges the gap between evidence based findings and their incorporation into routine clinical practice. Implementation studies are often poorly reported, reducing their potential to improve healthcare services. The Standards for Reporting Implementation Studies (StaRI) Checklist addresses this problem by promoting comprehensive reporting of implementation studies.

Underpinning StaRI is the distinction between, on the one hand, the evidence based strategies used to promote implementation and, on the other, the intervention being implemented. Thus StaRI defines dual strands, prompting authors to report the context, strategies, and implementation outcomes as well as to describe the intervention and its effects (table). This distinction is not only helpful for academics, authors, reviewers, and editors of implementation science papers. It is equally pertinent for healthcare professionals, managers and policymakers, who will find it helpful to distinguish between the planned service improvement (eg, core components, resources, expected health outcomes) and the evidence based implementation strategies used to embed the intervention into health systems (eg, adaptation to local context and routines, engaging stakeholders, training, incentives). Explicating the mechanism(s) through which an initiative is expected to be implemented and improve health outcomes will help leaders plan service improvements.

There are challenges to using StaRI. In particular, the requirement for detailed descriptions of context, implementation strategies, and interventions as well as reporting a broad range of implementation, process, economic, and health outcomes could be restricted by journal word counts. The Explanation and Elaboration document (*BMJ Open* 2017; doi:10.1136/bmjopen-2016-013318) suggests some practical ways to summarise information in tables or figures. Application of StaRI to online grey literature descriptions of health service initiatives could enhance the value of these reports to colleagues planning similar projects.

Improving the reporting of implementation studies will help translate effective interventions into routine practice, ultimately to benefit the health of individuals and populations.

Overview of the dual strands of the StaRI Checklist using an illustration of a study implementing supported self management for asthma

Section	Implementation strategy	Intervention
Title and abstract	Identification as an implementation study	
Introduction	Implementation is poor: only about a third of people with asthma have an action plan	Asthma self management improves asthma control and reduces use of healthcare resources
Methods	A programme of professional training, templates for reviews, access to resources, facilitation, audit, and feedback	Provision of asthma self management in routine asthma reviews, including completion of action plans
Outcomes/results	Adoption of the intervention by professionals, and proportion of people with asthma who have an action plan Cost of the implementation initiative	Proportion of people with asthma requiring unscheduled care for asthma and/or patient reported asthma control Cost of delivering the intervention
Discussion	Practical learnings related to implementation (eg, adaptation to context, barriers/facilitators, scalability)	Practical learnings related to the intervention (eg, fidelity, barriers and solutions, sustainability)