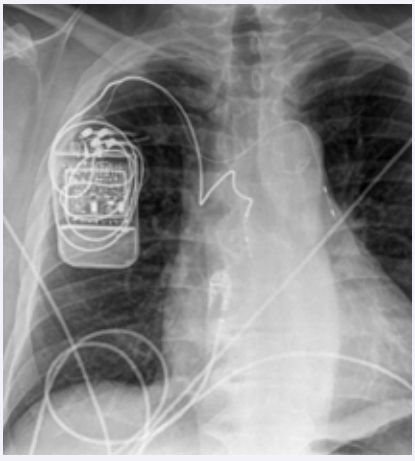
research update

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



Pacing the diaphragm for sleep apnoea

Here's a trial that was done mostly on overweight men with a mean age of 65 and of German or Polish birth who had sleep apnoea. This is a fairly accurate description of me. But in fact over half had coronary heart disease and more than 40% had atrial fibrillation, which isn't yet true of me. And now the penny drops: these people had central sleep apnoea, not common-or-garden obstructive sleep apnoea like mine. Central sleep apnoea is a disorder of the respiratory control centre, common in heart failure and associated with a bad prognosis. In fact 7 of the 151 participants died in the two years covered by this report. Everyone was fitted with a pacing device that transvenously stimulates a nerve causing diaphragmatic contraction similar to normal breathing. In the first six month phase of the trial only half the devices were activated. Retweaking was required to make the device perform comfortably in more than a third of the patients. But it worked very well in reducing the apnoea-hypopnoea index: long term hard endpoints won't be in for a while.

Lancet 2016, doi:10.1016/S0140-6736(16)30961-8

Adding LABAs to steroid inhalers

This week's print *New England Journal of Medicine* contains two trials of adding inhaled long acting adrenergic agents to inhaled corticosteroids. The first recruited 6208 children aged 4 to 11 with asthma and compared the use of fluticasone alone with fluticasone plus salmeterol. We know that salmeterol alone should never be given to children, as the accompanying editorial makes clear: "Monotherapy with a LABA in a child should be considered medical negligence, and we suggest that single LABA inhalers should carry a warning to that effect, as required in the United States by the FDA in 2010." But in this large trial over 26 weeks, serious events did not differ between the two groups, and there were no deaths in either group. Still, as the editorial says, "There is no evidence for the use of a combined inhaler as first-line preventive therapy in children, and this fact needs to be emphasized because such use is increasingly creeping into practice."

N Engl J Med 2016, doi:10.1056/NEJMoa1606356 and doi:10.1056/NEJMe1608508

Drug changes after fragility fracture

What should you start and what should you stop after a patient has had an osteoporotic fracture? I was lucky to work with a GP partner who was interested in such things long before they became fashionable: she made us do regular audits and drug reviews. I'm even prepared to believe that the UK Quality and Outcomes Framework might have subsequently improved practice in this area, because I find it hard to think that UK figures are as bad as the ones in this Medicare sample from the United States. Fewer than 25% of the patients who had fragility fractures received drugs to enhance bone mineral density, even after the event. Drugs such as opioids, benzodiazepines, and other sedatives associated with risk of falls were rarely discontinued. The situation was slightly better for drugs that can sometimes worsen bone fragility, such as proton pump inhibitors, thiazolidinediones, selective serotonin reuptake inhibitor antidepressants, and antipsychotics. Patients taking oral steroids usually remained on them, at the same dose.

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2016.4814

Docs in the wrong ball park

I don't give many lectures, but when I do I often ask medical audiences a few simple questions about the number needed to treat for common drugs. So I'm not entirely surprised by this survey of the understanding of benefits and harms of common medical interventions by American academic internal medicine physicians. For pretty well everything their estimates of both were too high. Then the investigators looked at physicians' use of statistical terms in patient communication, and their awareness of high value healthcare campaigns. But this is embarrassing. I must stop, or else I'd be saying that we currently train doctors to be ignorant about what they do and also how to explain it to their patients. And this surely cannot be.

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2016.5027

Depression treatment upside down

But now for something even spookier. "Most US adults who screen positive for depression did not receive treatment for depression, whereas most who were treated did not screen positive." Questions: "Does this mean that screening for depression is a good thing?" "Does it mean that antidepressants are massively effective?" "Do we know what we are doing?"

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2016.5057

Are recessions harmful to health?

ORIGINAL RESEARCH Systematic literature review

Health outcomes during the 2008 financial crisis in Europe

Parmar D, Stavropoulou C, Ioannidis JPA

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Find this at: http://dx.doi.org/10.1136/bmj.i4588

Study question What does the empirical literature show about the impact of the 2008 financial crisis on health outcomes in Europe?

Methods We conducted a systematic literature review by performing structural searches of key databases, healthcare journals, and organisation based websites. Empirical studies reporting on the impact of the financial crisis on health outcomes in Europe, published from January 2008 to December 2015, were included. All selected studies were assessed for risk of bias. Owing to the heterogeneity of studies in terms of study design and analysis and the use of overlapping datasets across studies, we analysed the studies thematically per outcome and synthesised the evidence on different health outcomes without formal meta-analysis.

Study answer and limitations 41 studies met the inclusion criteria, focusing on suicide, mental health, self rated health, mortality, and other health outcomes. Of those, 30 (73%) were deemed to be at high risk of bias, nine (22%) at moderate risk of bias, and only two (5%) at low risk of bias, limiting the conclusions that can be drawn. Despite differences across countries and groups, there was some indication that suicides increased and mental health deteriorated during the crisis. The crisis did not seem to reverse the trend of decreasing overall mortality. Evidence on self rated health and other indicators was mixed. A major limitation of the review is that it inevitably explored relatively short term effects of the crisis, and it may take some years before the full consequences of the crisis are observed.

What this study adds Most published studies had a substantial risk of bias and therefore, results need to be cautiously interpreted. Overall, the financial crisis in Europe seemed to have had heterogeneous effects on health outcomes, with the evidence being most consistent for suicides and mental health.

Funding, competing interests, data sharing
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JEFF MORGAN/ALAMY

COMMENTARY A government's response can be even more damaging

The 2008 economic crisis led to rising unemployment, homelessness and poverty. Government debt increased, as public money was used to prevent the collapse of the financial system, and many governments then cut public services to reduce this debt. But what has been the effect of all of this on health?

Parmar and colleagues[1] find that most studies investigating the 2008 recession in Europe show it was associated with adverse health outcomes. These findings were strongest for suicides and mental health problems. They find less evidence that the recession had a negative effect on self reported health, mortality, and health behaviours, and conclude that there was a high risk of bias in most the studies reviewed.

Assessing the health effects of recessions is challenging. However, given previous evidence for the damaging health effects of unemployment and poverty, it is very likely that, in the absence of mitigating policies, the increase in these factors during recessions leads to adverse health outcomes.

A government's response to recession also has important consequences for health.

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Austerity measures in England coincided with a further rise in suicides from 2011 that followed the initial increase in suicides in the 2008 recession

Initially, the UK government responded by increasing public spending in 2009 to stimulate growth and protect vulnerable groups, such as unemployed young people.[9 14] In 2010, the Conservative led coalition government reversed this approach, implementing austerity policies to reduce the public deficit by cutting public expenditure,[15] particularly spending on welfare benefits and local government.[16 17] These austerity policies have disproportionately affected more disadvantaged groups.[17-21] and occurred some time after the initial recession (see figure on thebmj.com).

Some of the studies in the review by Parmar and colleagues report the negative health effects of austerity measures that were implemented in response to the recession. Austerity measures in England coincided with a further rise in suicides from 2011 that followed the initial increase in suicides in the 2008 recession (fig). Other observational studies not included in the review also indicate that welfare reforms and austerity measures implemented after the 2008 crisis have adversely affected health.[22-24] Several studies also indicate that adequate welfare policies can mitigate some of the harmful effects of recession.[25-28]

Although this evidence on policy responses might be good enough to inform action, it could be improved. Robust prospective evaluation could take place before policies are implemented. This rarely happens, however, because testing policies could be politically risky.[29] For example, since the 2008 recession, the UK has embarked on one of the largest transformations of its welfare system since its establishment, without any prior evidence of the potential effects on health or any plans to evaluate them.

With the possibility of another recession in post-Brexit Britain, Parmar and colleagues' review shows that recessions can harm health. Government responses can be even more damaging, however. Doctors need to advocate for social and welfare policies that are informed by evidence and evaluated for their health effects, so that they protect people during crises rather than creating further health problems.

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Find this at: http://dx.doi.org/10.1136/bmj.i4631

ORIGINAL RESEARCH Systematic review and meta-analysis

Prospective risk of stillbirth and neonatal complications in twin pregnancies

Cheong-See F, Schuit E, Arroyo-Manzano D, et al; a Global Obstetrics Network (GONet) Collaboration

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Find this at: http://dx.doi.org/10.1136/bmj.i4353

Study question What are the risks of stillbirth and neonatal complications by gestational age in uncomplicated monochorionic and dichorionic twin pregnancies?

Methods Medline, Embase, and Cochrane databases searched (up to December 2015) without language restrictions for studies of women with uncomplicated twin pregnancies, which reported rates of stillbirth and neonatal outcomes at various gestational ages. Pregnancies with unclear chorionicity, monoamnionicity, and twin-to-twin transfusion syndrome were excluded. Meta-analyses of observational studies and cohorts nested within randomised studies were undertaken. Prospective risk of stillbirth for each study was computed at a given week of gestation and compared with the risk of neonatal death among deliveries in the same week. Gestational age specific risk differences for stillbirths and neonatal deaths were calculated in monochorionic and dichorionic twin pregnancies after 34 weeks' gestation.

Study answer and limitations 32 studies (29 685 dichorionic, 5486 monochorionic pregnancies) were included. In dichorionic twin pregnancies beyond 34 weeks (15 studies, 17 830 pregnancies), the prospective weekly risk of stillbirths from expectant management and the risk of neonatal death from delivery were balanced at 37 weeks' gestation (risk difference 1.2/1000; 95% confidence interval −1.3 to 3.6, I^2=0%). Delay in delivery by a week (until 38 weeks) led to an additional 8.8 perinatal deaths per 1000 pregnancies (3.6 to 14.0/1000, I^2=0%) compared with delivery in the previous week. In monochorionic pregnancies beyond 34 weeks (13 studies, 2149 pregnancies), there was a trend towards increase in stillbirths compared with neonatal deaths after 36 weeks, with an additional 2.5 per 1000 perinatal deaths, which was not significant (−12.4 to 17.4/1000, I^2=0%). The rates of neonatal morbidity showed a consistent reduction with increasing gestational age in monochorionic and dichorionic pregnancies, and admission to the neonatal intensive care unit was the most common neonatal complication. The actual risk of stillbirth near term might be higher than reported estimates because of the policy of planned delivery in twin pregnancies.

Conclusions To minimise perinatal deaths, delivery should be considered at 37 weeks' gestation in uncomplicated dichorionic twin pregnancies and at 36 weeks in monochorionic pregnancies.

Funding, competing interests, data sharing The study received no funding; the authors declared no competing interests; and there are no additional data to share.

ORIGINAL RESEARCH Systematic review and meta-analysis

Atrial fibrillation and risks of cardiovascular disease, renal disease, and death

Odutayo A, Wong C X, Hsiao A J, et al

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Find this at: http://dx.doi.org/10.1136/bmj.i4482

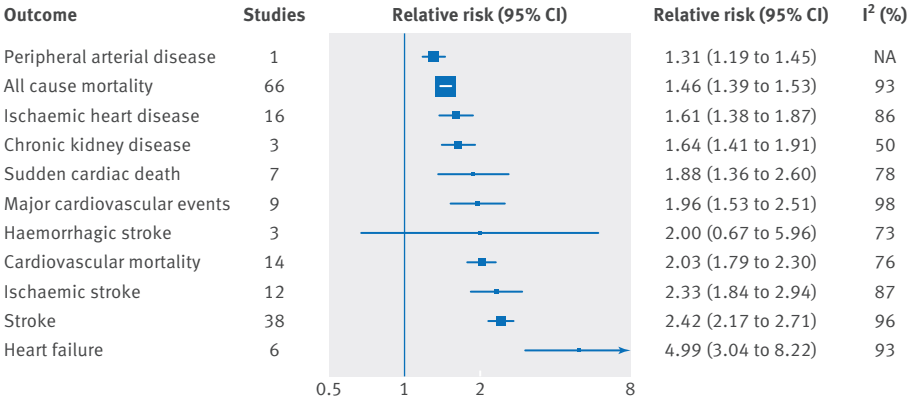
Study question What are the associations between atrial fibrillation and cardiovascular disease, renal disease, and death?

Methods Systematic review and meta-analysis of cohort studies. Included studies compared adults with and without atrial fibrillation and assessed the association between atrial fibrillation and cardiovascular disease, renal disease, and death. Relative risks of associated outcomes were extracted for all cause mortality, cardiovascular mortality, major cardiovascular events, any stroke, ischaemic stroke, haemorrhagic stroke, ischaemic heart disease, sudden cardiac death, congestive heart failure, chronic kidney disease, and peripheral arterial disease.

Study answer and limitations Data were pooled from 104 studies. Atrial fibrillation was associated with an increased risk of all cause mortality (relative risk 1.46, 95% confidence interval 1.39 to 1.54), cardiovascular mortality (2.03, 1.79 to 2.30), major cardiovascular events (1.96, 1.53 to 2.51), stroke (2.42, 2.17 to 2.71), ischaemic stroke (2.33, 1.84 to 2.94), ischaemic heart disease (1.61, 1.38 to 1.87), sudden cardiac death (1.88, 1.36 to 2.60), heart failure (4.99, 3.04 to 8.22), chronic kidney disease (1.64, 1.41 to 1.91), and peripheral arterial disease (1.31, 1.19 to 1.45), but not haemorrhagic stroke (2.00, 0.67 to 5.96). Among the outcomes examined, the highest absolute risk increase was for heart failure (11.1 events/1000 participant years, 5.7 to 20). Associations between atrial fibrillation and included outcomes were broadly consistent across subgroups and in sensitivity analyses. Because of the observational design of the studies in this meta-analysis, there is invariably residual confounding that affects the relative risk estimates.

What this study adds Atrial fibrillation is associated with a wide range of cardiovascular events. The increase in the relative and absolute risk associated with some of these events is greater than the increased risk of stroke.

Funding, competing interests, data sharing This study was unfunded. The authors declare no conflicts of interest. Data and code are available from the lead author on request.



Association between atrial fibrillation and various outcomes

Adding tests to risk based guidelines: evaluating improvements in prediction for an intermediate risk group

Paynter NP, Cook NR

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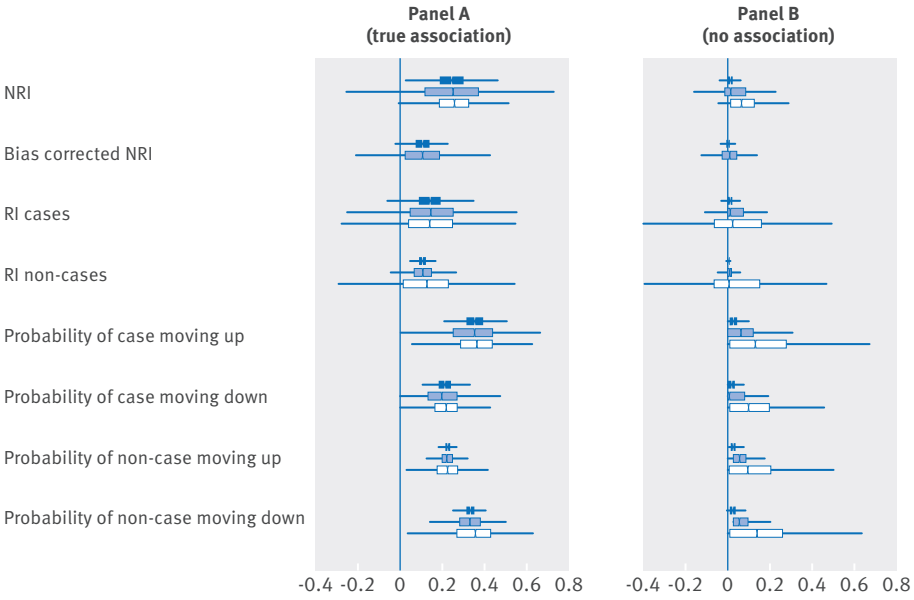
Decisions about treatment attempt to best balance risks and benefits, with guidelines in multiple settings using risk cut points to inform treatment decisions. These cut points often result in three implicit or explicit strata: risk high enough to confidently treat, risk low enough to confidently not treat, and those in between, or the "intermediate risk" group. In contrast with evaluating a new marker or test for inclusion in the overall risk model, the process for evaluating prediction improvement in the intermediate risk group is not well developed.

Measures of prediction improvement in the intermediate risk group can be biased (non-zero) even when there is no true relation between the new marker and the outcome. This can be seen in the figure, which shows the results of a simulation for prediction measures for a risk model including a new marker with a true association and with no association. Using only the intermediate risk group of the established score to estimate the risk model (white bars), the net reclassification improvement was significant 27% of the time instead of the expected 5% when there was no association. Using the full population (dark blue bars), or a random sample of the full population equivalent in size to the intermediate risk group (light blue bars), reduces the type 1 error and also allows for calculation of the expected value and bias correction for hypothesis testing.



Distribution of measures using cardiovascular disease cut points (5% and 7.5%) in a group at intermediate risk when new marker has a true association (odds ratio of 2 for a 2 standard deviation difference) with the outcome (panel A) and no association (panel B). The boxes show the results when different populations are used to calculate the risk model with the new marker: dark blue boxes use the full population, light blue boxes use the scaled population (a random sample of the full population with the same number of participants as the intermediate risk population), and white boxes use the intermediate risk population as determined by the original model only. NRI=net reclassification improvement; RI=reclassification improvement

Therefore, recommendations for additional testing, even when the intermediate risk group is of primary interest, should be based on research conducted across the full spectrum of risk. The first step should be to assess the relation between the new marker and the outcome, independent of established risk factors. If the new marker is an independent predictor with a significant model coefficient using the full population, then other measures of prediction can be examined. The observed prediction measure for the intermediate risk group, such as the net reclassification improvement, can then be bias corrected using the expected value under no association to interpret the overall impact.