RESEARCH

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THIS WEEK’S RESEARCH QUESTIONS

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How fast does the Grim Reaper walk? Fiona Stanaway and colleagues estimate how fast older men might have to walk in order to avoid death (doi:10.1136/bmj.d7679).

Relevance of the expression “obs stable” in nursing observations Gregory Scott and colleagues investigate whether use of the term “obs stable” is so liberal as to render it meaningless (doi:10.1136/bmj.d7504).

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Effects of delayed cord clamping in Western settings

Delaying clamping of the umbilical cord after a baby is born allows placental blood to flow to the infant, and this placental transfusion increases the total blood volume of a term infant by about 30%. In developing countries with a high prevalence of iron deficiency anaemia, such delayed cord clamping has been shown to improve iron status in infants within the first months of life, but in Western countries with a low prevalence of iron deficiency anaemia it has been suggested that delayed clamping might lead to over-transfusion and result in polycythaemia, hyperviscosity syndrome, or hyperbilirubinaemia.

To clarify the situation, Ola Andersson and colleagues (p 1244) undertook this randomised clinical trial to compare the effects of delayed and early cord clamping in 400 healthy, term Swedish infants. They found that delayed clamping (≥180 seconds after delivery) improved iron status and decreased the risk for iron deficiency at 4 months of age compared with early clamping (<10 seconds after delivery) and was not associated with neonatal jaundice or other adverse effects. The authors conclude that further study is warranted to establish the long term effects of delayed cord clamping, particularly on neurodevelopment, which can be impaired by iron deficiency.

In his linked editorial (p 1233) Patrick van Rheenen looks at the reasoning and assumptions behind the widespread adoption of early cord clamping in Western medicine and concludes that this study by Andersson and colleagues “is convincing enough to encourage a change of practice.” Indeed, judging from the online responses to the full paper on bmj.com—almost universally positive and mainly from obstetricians asking about practical details of the procedure—the article has sparked considerable interest.

Scores for predicting type 2 diabetes in adults

“Application of prognostic models requires unambiguous definitions of predictors and reproducible measurements using methods available in clinical practice” concluded Karel Moons and colleagues in the last part of their BMJ series on prognostic research (BMJ 2009;338:b6606). Douglas Noble and colleagues have now reinforced and extended that argument with their systematic and realist review of published prognostic scores for type 2 diabetes and related follow-up studies that assessed usability and impact (p 1243).

There’s no shortage of such scores: the authors’ extensive search found 145 examples and they studied 94 in detail. Many scores had been well developed and validated and were technically sound. But few, concluded the authors, are usable in real life. Indeed, just seven of the scores met their criteria for having high potential for use in practice and improving patients’ outcomes.

One of the reviewers for this paper said “perhaps the greatest value of this review is to document an approach for mapping and evaluating the growing number of tools. The authors demur from selecting a single best instrument—as they rightly argue, usefulness depends on context.” She also thought that readers might be reassured to see this validation of their “feelings of perplexity at the growing number of clinical scales and scores that they may be expected to use.”
Statins and prevention of infections: systematic review and meta-analysis of data from large randomised placebo controlled trials

Hester L van den Hoek, Willem Jan W Bos, Athonius de Boer, Ewoudt M W van de Garde

STUDY QUESTION
Do statins lower the risk of infections?

SUMMARY ANSWER
Our systematic review and meta-analysis of data on infectious outcomes in large placebo controlled statin trials did not find evidence to support the hypothesis that statins reduce the risk of infections.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Different observational studies have reported a decreased risk of infections in people taking statins. The presence of biased estimations in these studies cannot be ruled out. In our meta-analysis of large placebo controlled statin trials, no evidence was found for a beneficial effect of statins on risk of infection.

Selection criteria for studies
We carried out a search of Medline, Embase, and the Cochrane Library from inception to 10 March 2011 for randomised placebo controlled trials of statins reported in English that enrolled at least 100 participants and had a follow-up of at least one year.

Primary outcome
The presence of infections reported as adverse event in the publications or provided by principal investigators on request.

Main results and role of chance
After screening of the corresponding abstracts and full text papers of 632 identified trials, 11 remained eligible. These 11 trials totalled 30 947 patients, of whom 14 103 (45.6%) received statins and 16 844 (54.4%) received placebo. Overall, the quality of the included trials was satisfactory and the trials were judged to be at low risk of bias. A total of 4655 participants experienced an infection during treatment as an adverse event or cause of death, of whom 2368 were assigned to statins and 2287 to placebo. Meta-analysis of the data showed no effect of statins on the risk of infections (relative risk 1.00, 95% confidence interval 0.96 to 1.05) or on infection related death (0.97, 0.83 to 1.13). In sensitivity analysis the exclusion of data from one trial that lacked double blinding did not significantly alter the results of infection related mortality (0.98, 0.84 to 1.14).

Bias, confounding, and other reasons for caution
Only a few large placebo controlled trials of statins reported on the incidence of infections. Subgroup analyses were therefore not possible. Also, we had no information on the validity of the infectious outcomes, as these were not predefined study outcomes.

Study funding/potential competing of interests
This study received no specific funding. We have no competing interests.

<table>
<thead>
<tr>
<th>Study Description</th>
<th>No of events/No of participants</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study of Heart and Renal Protection 2010</td>
<td>1/1054 6/4191</td>
<td>0.66 (0.08 to 5.50)</td>
<td>72.7 (0.96 to 1.06)</td>
<td>0.88 (0.34 to 2.27)</td>
</tr>
<tr>
<td>Fellstrom 2009</td>
<td>976/1399 956/1778</td>
<td>4.3 (0.98 to 1.46)</td>
<td>9.4 (0.81 to 1.06)</td>
<td>1.6 (0.71 to 3.38)</td>
</tr>
<tr>
<td>Newman 2008</td>
<td>8/1428 9/1410</td>
<td>98.9 (0.84 to 1.07)</td>
<td>100.0 (0.96 to 1.05)</td>
<td>0.94 (0.84 to 1.07)</td>
</tr>
<tr>
<td>GISSI-heart failure 2008</td>
<td>191/2285 160/2289</td>
<td>118.8 (0.71 to 1.38)</td>
<td>0.94 (0.84 to 1.07)</td>
<td>100.0 (0.96 to 1.05)</td>
</tr>
<tr>
<td>Kjekshus 2007</td>
<td>344/2514 370/2497</td>
<td>0.01 0.1 1 10</td>
<td>Favours treatment Favours control</td>
<td>0.94 (0.84 to 1.07)</td>
</tr>
<tr>
<td>Bone 2007</td>
<td>129/485 32/119</td>
<td>0.94 (0.84 to 1.07)</td>
<td>100.0 (0.96 to 1.05)</td>
<td>0.94 (0.84 to 1.07)</td>
</tr>
<tr>
<td>Amarenco 2006</td>
<td>414/2365 439/2366</td>
<td>118.8 (0.71 to 1.38)</td>
<td>0.94 (0.84 to 1.07)</td>
<td>100.0 (0.96 to 1.05)</td>
</tr>
<tr>
<td>Random effects total (P=0.927)</td>
<td>2063/11520 1972/14250</td>
<td>0.01 0.1 1 10</td>
<td>Favours treatment Favours control</td>
<td>0.94 (0.84 to 1.07)</td>
</tr>
</tbody>
</table>
Risk models and scores for type 2 diabetes: systematic review

Douglas Noble,¹ Rohini Mathur,¹ Tom Dent,² Catherine Meads,¹ Trisha Greenhalgh¹

STUDY QUESTION
What are the properties of published risk models and scores for predicting type 2 diabetes in adults and how do they perform in practice?

SUMMARY ANSWER
145 risk models and scores were identified; many had robust statistical properties but only a handful were in routine use.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
The many known risk factors for type 2 diabetes can be combined in statistical models to produce risk scores. There is no universal ideal risk score, since the utility of any score depends not merely on its statistical properties but also on its context of use, including which types of data are available to be included.

Selection criteria for studies
We searched Medline, PreMedline, Embase, and Cochrane databases. We removed duplicates, scanned titles and abstracts, and rejected non-cohort studies. Papers in any language describing the development or external validation, or both, of models and scores to predict risk of an adult developing type 2 diabetes were included. Included studies were citation tracked in Google Scholar to identify follow-on studies of usability or impact. We extracted data on the statistical properties of the models, details of internal or external validation, or both, and use of risk scores beyond the studies that developed them. We also used realist review methods to identify mechanisms by which use of the risk model or score might improve patient outcomes using realist methodology.

Primary outcomes
Performance as assessed by discrimination, calibration, external validation, or both, and use of risk scores beyond the studies that developed them. We also used realist review methods to identify mechanisms by which use of the risk model or score might improve patient outcomes using realist methodology.

Main results and role of chance
In all, 8864 titles were scanned, 115 full text papers considered, and 43 papers included in the final sample. These described prospective development or validation, or both, of 145 risk prediction models and scores, 94 of which we studied in detail. They had been tested on 6.88 million participants followed for up to 28 years. Primary studies were highly heterogeneous, which precluded meta-analysis. The number of components in a single risk score varied from 3 to 14 (n=84, mean 7.8, SD 2.6). Some but not all risk models or scores had robust statistical properties (for example, good discrimination and calibration) and had been externally validated on a different population. We classified seven risk scores as having high potential for use in practice. Most authors described their score as “simple” or “easily implemented,” although few were specific about who was intended to use it, on whom, and in what circumstances. Ten mechanisms were identified by which measuring the risk of diabetes might improve outcomes. Follow-on studies that applied a risk score as part of an intervention aimed at reducing actual risk in individuals were sparse. There is a largely unexplored research agenda on usability and impact.

Bias, confounding, and other reasons for caution
Most diabetes models and risk scores have been derived by analysing a cohort or database previously assembled for a different purpose and therefore have an inherent selection bias.

Study funding/potential competing interests
This study was funded by grants from Tower Hamlets, Newham, and City and Hackney primary care trusts. TG received a senior investigator award from the National Institute of Health Research.

Components of seven diabetes risk models or scores with potential for adaptation for use in routine clinical practice

<table>
<thead>
<tr>
<th>Risk score</th>
<th>Risk factors included in score</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUSDRISK, Australia; Chen 2010</td>
<td>Age, sex, ethnicity, parental history of diabetes, history of high blood glucose levels, use of antihypertensive drugs, smoking, physical inactivity, waist circumference</td>
</tr>
<tr>
<td>Cambridge Risk Score; Rahman 2008</td>
<td>Age, sex, current use of corticosteroids, use of antihypertensive drugs, family history of diabetes, body mass index, smoking</td>
</tr>
<tr>
<td>FINDRISC, Lindstrom 2003</td>
<td>Age, body mass index, waist circumference, use of antihypertensive drugs, history of high blood glucose levels, physical inactivity, daily consumption of vegetables, fruit, or berries</td>
</tr>
<tr>
<td>QDScore, Hippisley-Cox 2009</td>
<td>Age, sex, ethnicity, body mass index, smoking, family history of diabetes, Townsend deprivation score, treated hypertension, cardiovascular disease, current use of corticosteroids</td>
</tr>
<tr>
<td>Score derived from Framingham Offspring Study, Wilson 2007</td>
<td>Fasting plasma glucose level, body mass index, high density lipoprotein level, parental history of diabetes, triglyceride level, blood pressure</td>
</tr>
<tr>
<td>San Antonio Risk Score, Stern 2002</td>
<td>Age, sex, ethnicity, fasting plasma glucose level, systolic blood pressure, high density lipoprotein cholesterol level, body mass index, family history of diabetes in first degree relative</td>
</tr>
</tbody>
</table>
Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial

Ola Andersson,1,2 Lena Hellström-Westas,2 Dan Andersson,1 Magnus Domellöf3

STUDY QUESTION
Does a delay in clamping the umbilical cord affect infant haemoglobin and iron status in a European setting?

SUMMARY ANSWER
Delayed cord clamping improved all measures of iron status and reduced the prevalence of iron deficiency but had no effect on haemoglobin at 4 months of age.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Delayed umbilical cord clamping results in a substantial transfusion of blood from the placenta into the newborn child, improving iron status in infants in low and middle income countries. Delayed cord clamping also improves iron status and decreases the risk for iron deficiency among infants born at term in a high income country with a low prevalence of iron deficiency anaemia, without showing any neonatal adverse effects.

Design
We conducted a randomised, controlled, parallel group trial. Randomisation (1:1) was done in advance by computer in blocks of 20. When delivery was imminent the midwife opened an envelope containing the treatment allocation. The intervention consisted of delayed clamping of the umbilical cord (≥180 s after delivery) or early clamping of the umbilical cord (≤10 s). Investigators and study staff involved in data collection after delivery were blinded to treatment allocation.

Participants and setting
400 full term infants born after a low risk pregnancy at a Swedish county hospital.

Primary outcome(s)
The primary outcome was haemoglobin and iron status (serum ferritin, transferrin saturation, transferrin receptors, reticulocyte haemoglobin, mean cell volume, and mean cell haemoglobin concentration) at 4 months of age with the power estimate based on serum ferritin levels.

Main results and the role of chance
At 4 months of age, infants allocated to delayed cord clamping had 45% (95% CI 23 to 71) higher mean ferritin levels than those allocated to early cord clamping (117 µg/L v 81 µg/L, P<0.001). The relative risk reduction of iron deficiency was 90%. The number needed to treat to prevent one case of iron deficiency, with or without anaemia, was 20 (95% CI 17 to 67). There was no difference in haemoglobin at 4 months. At 2 days of age the delayed cord clamping group had lower prevalence of neonatal anaemia (2 (1.2%) v 10 (6.3%), P=0.02); the relative risk reduction was 80%, and the number needed to treat to prevent one case of neonatal anaemia was 20 (15 to 111).

Harms
There were no demonstrable differences between groups regarding postnatal respiratory symptoms, polycythaemia, hyperbilirubinaemia, or need for phototherapy.

Bias, confounding, and other reasons for caution
The two groups were similar in maternal and infant baseline data. We did not specifically power the study to measure adverse effects or harms.

Generalisability to other populations
The study included only full term, low risk deliveries by healthy mothers from a well nourished population. The findings may not be applicable to pregnancies and infants with various perinatal risk factors such as maternal diabetes or intrauterine growth restriction.

Study funding/potential competing interests
All authors are independent from the study funders (the Regional Scientific Council of Halland; the HASNA foundation, Halmstad; HRH Crown Princess Lovisa’s Foundation for child care, Stockholm; and the Framework of Positive Scientific Culture, Hospital of Halland, Halmstad).

Trial registration number
Clinical Trials NCT01245296.

Proportion of infants randomised to early or delayed cord clamping with iron status indicators outside reference limits at 4 months old

<table>
<thead>
<tr>
<th>Iron status indicator</th>
<th>Early (175/400)</th>
<th>Delayed (125/400)</th>
<th>P value</th>
<th>Relative risk reduction (95% CI)</th>
<th>Number needed to treat (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin &lt;20 µg/L</td>
<td>13 (7.5%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
<td>1.0 (0.71 to 1.00)</td>
<td>14 (14 to 25)</td>
</tr>
<tr>
<td>Mean cell volume &lt;7.3fl</td>
<td>9 (5.2%)</td>
<td>4 (3.2%)</td>
<td>0.26</td>
<td>0.54 (0.39 to 0.85)</td>
<td>NA</td>
</tr>
<tr>
<td>Transferrin saturation &lt;10%</td>
<td>3 (1.6%)</td>
<td>0 (0%)</td>
<td>0.02</td>
<td>0.57 (0.15 to 0.79)</td>
<td>13 (8 to 6.2)</td>
</tr>
<tr>
<td>Transferrin receptors &gt;7 mg/L</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Iron deficiency*</td>
<td>10 (6%)</td>
<td>1 (1%)</td>
<td>0.01</td>
<td>0.90 (0.38 to 0.98)</td>
<td>20 (17 to 67)</td>
</tr>
<tr>
<td>Anaemia (Hb&lt;105 g/L)</td>
<td>21 (13%)</td>
<td>21 (17%)</td>
<td>1.0</td>
<td>−0.04 (−0.83 to 0.41)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA=not applicable.
*Defined as ≥2 iron status indicators outside reference range.
Non-alcoholic fatty liver disease and mortality among US adults: prospective cohort study

Mariana Lazo,1 Ruben Hernaez,1 Susanne Bonekamp,2 Ihab Kamel,2 Frederick L Brancati,1,3 Eliseo Guallar,1,3,4 Jeanne M Clark1,3

STUDY QUESTION
Is non-alcoholic fatty liver disease associated with all cause and cause specific mortality in a representative sample of the US general population?

SUMMARY ANSWER
Non-alcoholic fatty liver disease was not associated with an increased risk of death from all causes, cardiovascular disease, cancer, or liver disease.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Non-alcoholic fatty liver disease is highly prevalent and frequently encountered in clinical practice and there is a strong association between it and cardiovascular risk factors such as diabetes and obesity. Non-alcoholic fatty liver disease was not associated with an increased risk of deaths from all causes, cardiovascular disease, cancer, or liver disease in a general population sample over an average of 14.5 years of follow-up.

Participants and setting

Design, size, and duration
Prospective cohort study. Median follow-up was 14.5 (maximum 18.0) years. In the absence of a standard definition, we defined non-alcoholic fatty liver disease as the presence of moderate to severe hepatic steatosis with normal levels of liver enzymes. Non-alcoholic steatohepatitis was defined as the presence of moderate to severe hepatic steatosis with increased levels of liver enzymes in the absence of antibodies to hepatitis B and hepatitis C and without evidence of iron overload.

Main results and the role of chance
The overall prevalence of non-alcoholic fatty liver disease (excluding steatohepatitis) and steatohepatitis was 16.4% and 3.1%, respectively. Compared with participants without hepatic steatosis, those with non-alcoholic fatty liver disease were more likely to be older, men, Mexican-American, less educated, sedentary, obese, to have a high waist circumference, diabetes, hypercholesterolaemia, hypertension, and a history of cardiovascular disease, less likely to be current smokers or to have low to moderate alcohol consumption. In addition, they had higher levels of glycated haemoglobin, triglyceride:high density lipoprotein cholesterol ratio, insulin resistance, and liver enzymes (alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase). People with non-alcoholic steatohepatitis were similar to those with non-alcoholic fatty liver disease, although slightly younger and with a slightly worse metabolic risk profile. At the end of follow-up the cumulative mortality from all causes was 22.0% (1836 deaths). For cause specific deaths the cumulative mortalities were 10.9% for cardiovascular disease (716 deaths), 6.0% for cancer (480 deaths), and 0.5% for liver disease (44 deaths). The risk of death from all causes in participants with non-alcoholic fatty liver disease or non-alcoholic steatohepatitis at baseline was not increased compared with participants without hepatic steatosis.

Bias, confounding, and other reasons for caution
For non-alcoholic steatohepatitis, in the absence of liver biopsy, we used increases in the liver enzyme levels alanine aminotransferase or aspartate aminotransferase in the presence of steatosis to define non-alcoholic steatohepatitis and thus errors in measurements are possible. The analyses for cause specific mortality are limited by small numbers and relatively short follow-up.

Generalisability to other populations
Our results are generalisable to the general population.

Study funding/potential competing interests
This research was supported by grant R01 DK083393-01 from the National Institute of Health/National Institute of Diabetes and Digestive and Kidney Diseases.

<table>
<thead>
<tr>
<th>Mortality type</th>
<th>No hepatic steatosis (n=8856)</th>
<th>Non-alcoholic fatty liver disease (n=2089)</th>
<th>Non-alcoholic steatohepatitis (n=426)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause (unweighted events)</td>
<td>1310</td>
<td>569</td>
<td>57</td>
</tr>
<tr>
<td>Adjusted model*</td>
<td>1 (reference)</td>
<td>0.92 (0.78 to 1.09)</td>
<td>0.80 (0.52 to 1.22)</td>
</tr>
<tr>
<td>Cardiovascular disease (unweighted events)</td>
<td>508</td>
<td>192</td>
<td>16</td>
</tr>
<tr>
<td>Adjusted model*</td>
<td>1 (reference)</td>
<td>0.86 (0.67 to 1.12)</td>
<td>0.59 (0.29 to 1.20)</td>
</tr>
<tr>
<td>Cancer (unweighted events)</td>
<td>350</td>
<td>115</td>
<td>14</td>
</tr>
<tr>
<td>Adjusted model*</td>
<td>1 (reference)</td>
<td>0.92 (0.67 to 1.27)</td>
<td>0.53 (0.26 to 1.10)</td>
</tr>
</tbody>
</table>

*Adjusted for sex, race, education, smoking, alcohol consumption, physical activity, body mass index, hypertension, hypercholesterolaemia, and diabetes.