**THIS WEEK’S RESEARCH QUESTIONS**

- **298** In renal disease, which reduces proteinuria more: dietary sodium restriction or angiotensin receptor blockade?
- **299** Does calorie labelling on fast food menus affect the energy content of customers’ purchases?
- **300** Did reductions in deaths from breast cancer appear first in countries with earlier implementation of mammography screening?
- **301** Are there socioeconomic inequalities in the outcome of pregnancies affected by congenital anomalies with a poor prognosis?

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**Cutting proteinuria in patients on high dose ACE inhibitors**

The BMJ doesn’t receive many crossover trials, but here’s one. It addresses what the editors thought to be an interesting and practical question about the comparative effectiveness of a dietary intervention versus polypharmacy. (And the authors adopted a particularly provocative acronym, the HOnEST (HOLLand NEphrology STudy) group, but that’s not why we published the study.)

Patients with chronic kidney disease need to keep hypertension and proteinuria at bay, but simply taking a high dose angiotensin converting enzyme (ACE) inhibitor doesn’t usually tackle the proteinuria adequately. So Maartje Slagman and colleagues enrolled Dutch outpatients with non-diabetic renal disease who were already taking an ACE inhibitor at the maximum dose (p 298). All 52 patients had four treatment periods of six weeks in which they received, in random order, angiotensin receptor blockade or placebo, each combined with, consecutively, a low sodium diet and a regular sodium diet. Dietary sodium restriction to a level recommended in guidelines and reinforced through individual counselling by dietitians was more effective than dual drug blockade for reducing proteinuria and blood pressure.

Just 52 patients may seem an awfully small sample size but—as another paper, co-authored by the BMJ’s senior statistics editor, Doug Altman, explains—“each participant [in a crossover trial] is able to act as his or her own control and permits between and within group comparisons . . . when the new treatment [is] a slight modification to the standard . . . there is likely to be a positive correlation in the responses to the new and old treatments making the crossover design ideal. Crossover studies are most appropriate in studies where the effects of the treatment(s) are short lived and reversible and are best suited to trials related to symptomatic but chronic conditions or diseases” (Trials 2009;10:27, doi:10.1186/1745-6215-10-27).

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**Calorie labelling of fast food**

In response to the obesity epidemic in its citizens, New York City approved a regulation requiring chain restaurants to provide calorie information prominently on all menus and item tags, and this regulation became effective in March 2008. To investigate whether this measure had any effect, surveys of customers’ lunchtime purchases from fast food outlets were conducted in spring 2007 and spring 2009 (one year before and nine months after implementation of the regulation). Tamara Dumanovsky and colleagues now report their findings (p 299).

No overall decline in energy content of purchases was observed, but the 15% of customers who actually bothered to read the calorie information reduced the energy content of their lunch by an average of 106 kcal, enough to make a real difference to body weight if sustained. The study has generated quite a bit of media publicity but with decidedly mixed reactions, with some stories claiming it shows the regulation to have been an abject failure while others have proclaimed it a triumphant success.

In her linked editorial (p 267), Susan Jebbs seems to think the results are about as good as could be expected and concludes: “Calorie labelling will help consumers make an informed choice about what they eat, but sustained improvements in the nation’s diet will require a transformation of the food supply too.”
RESEARCH

Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial

Maartje CJ Slagman,1 Femke Waanders,1 Marc H Hemmelder,2 Arend-Jan Woittiez,3 Wilbert M T Janssen,4 Hiddo J Lambers Heerspink,5 Gerjan Navis,1 Gozewijn D Laverman,1,3 for the HONEST (Holland Nephrology STudy) Group

STUDY QUESTION Does adding dietary sodium restriction reduce proteinuria more than adding maximum dose of angiotensin receptor blockade in patients with renal disease who are already being treated with angiotensin converting enzyme (ACE) inhibition at maximum dose?

SUMMARY ANSWER Yes. Adding sodium restriction induced a similar reduction of proteinuria as dual blockade.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Monotherapy with ACE inhibition or angiotensin receptor blockade is often insufficient to reach proteinuria targets in patients with renal disease; dual blockade is widely used but induces only a modest additional reduction of proteinuria. Moderate dietary sodium restriction is considerably more effective than dual blockade for control of proteinuria and blood pressure.

Design
In this multicentre crossover trial, all patients had four treatment periods of six weeks receiving angiotensin receptor blockade (valsartan 320 mg/day) or placebo, each combined with, consecutively, a low sodium diet (mean 106 (SE 5) mmol Na+/day) and a regular sodium diet (184 (6) mmol Na+/day), in random order. All patients received background ACE inhibition (lisinopril 40 mg/day) throughout the study. The dietary interventions were open label and the pharmacological interventions were double blind, with block randomisation and computer generated allocation.

Participants and setting
We studied 52 patients with non-diabetic nephropathy in the outpatient clinics of three hospitals in the Netherlands.

Primary outcome(s)
This was proteinuria after six weeks of treatment.

Main results and the role of chance
During ACE inhibition combined with a regular sodium diet, geometric mean residual proteinuria was 1.68 (95% confidence interval 1.31 to 2.14) g/day, exceeding the target of 1.00 g/day or lower. Adding angiotensin receptor blockade reduced proteinuria to 1.44 (1.07 to 1.93) g/day (P=0.003), and adding a low sodium diet reduced it to 0.85 (0.66 to 1.10) g/day (P<0.001). The lowest level of residual proteinuria was achieved by adding both angiotensin receptor blockade and a low sodium diet (0.67 (0.50 to 0.91) g/day; P<0.001). Moreover, the reduction of proteinuria by adding a low sodium diet to ACE inhibition (51% (95% confidence interval 43% to 58%) was significantly larger (P<0.001) than the reduction of proteinuria by adding angiotensin receptor blockade to ACE inhibition (21% (8%) to 32%). However, the reduction of proteinuria by adding both low sodium diet and angiotensin receptor blockade to ACE inhibition (62% (53% to 70%) was not significantly larger (P=0.009, not significant after Bonferroni correction) than that achieved by adding only a low sodium diet to ACE inhibition.

Harms
Seven patients had orthostatic complaints during the regimens with the strongest antihypertensive effect (that is, during dual or single blockade combined with a low sodium diet), necessitating dose tapering in only two patients.

Bias, confounding, and other reasons for caution
The main limitation of this study is that it provides only short term data and no hard end points. Also, the population was relatively small, although this is the largest study of sodium intervention in proteinuric patients so far.

Generalisability to other populations
The dietary intervention was done in an outpatient setting and reflected usual nephrology care. The achieved sodium restriction was in line with guidelines.

Study funding/potential competing interests
The study was supported by an unrestricted grant from Novartis (CVAL489ANL08).

Trial registration number
Netherlands Trial Register NTR675.
Changes in energy content of lunchtime purchases from fast food restaurants after introduction of calorie labelling: cross sectional customer surveys

Tamara Dumanovsky,1 Christina Y Huang,2 Cathy A Nonas,3 Thomas D Matte,4 Mary T Bassett,5 Lynn D Silver3

STUDY QUESTION Did the addition of calorie labelling to menu items in New York’s fast food restaurants affect the energy content of individual customers’ purchases?

SUMMARY ANSWER No overall decline in energy content of purchases was observed, but three of the major restaurant chains showed significant reductions, and the 15% of customers who reported using the calorie information made lower calorie choices.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS In January 2008 New York City fully implemented a regulation requiring chain restaurants to provide calorie information prominently for all items on menus and menu boards. After regulation, one in six lunchtime customers reported seeing and using the calorie information, and these customers made lower energy choices.

Participants and setting

Adult customers of a random sample of 168 fast food restaurants across New York City, with a sample of 7309 customers in spring 2007 and 8489 in spring 2009 (one year before and nine months after full implementation of the regulation requiring chain restaurants’ menus to contain details of the energy content of all menu items).

Design

Customers were approached on entering fast food outlets and asked to provide their register receipts and complete a brief survey when leaving. Data were collected at lunchtime during weekdays. Energy content of individual items on each customer’s receipt were derived from information on the restaurant chain’s website as of 1 March 2007 and 1 March 2009. Data were aggregated by customer to calculate total energy content (kcal) per purchase.

Main results and the role of chance

The overall response rate was 60%. For the full sample, mean calories purchased did not change after introduction of the regulation (828 vs 846 kcal, P=0.22), though a modest decrease was shown in a regression model adjusted for restaurant chain, poverty level for the store location, sex of customers, type of purchase, and inflation adjusted cost (847 vs 827 kcal, P<0.01). Three major chains, which accounted for 42% of customers surveyed, showed significant reductions in mean energy per purchase (McDonald’s 829 vs 785 kcal, P=0.02; Au Bon Pain 555 vs 475 kcal, P=0.001; KFC 927 vs 868 kcal, P=0.01), while mean calorie content increased at one large chain (Subway 749 vs 882 kcal, P=0.001). In the 2009 survey, the 15% (1288/8489) of customers who reported using the calorie information purchased 106 fewer kilocalories than the customers who did not (757 vs 863 kcal, P=0.001) (see table).

Bias, confounding, and other reasons for caution

The analysis did not distinguish between potential mechanisms of effect. For example, after the Subway chain promoted “$5 footlongs” in 2008, sales for these items rose from 25% of purchases in 2007 to 75% in 2009.

Generalisability to other populations

Similar national legislation has been approved in the United States. In the United Kingdom similar labelling may be implemented in 2011 as part of the Department of Health’s voluntary Responsibility Deal programme. The generalisability of our findings is as yet unknown.

Study funding/potential competing interests

This research was funded by the city of New York and by the Robert Wood Johnson Foundation Healthy Eating Research Program (grant No 65839).
Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database

Philippe Autier,1 Mathieu Boniol,1 Anna Gavin,2 Lars J Vatten3

STUDY QUESTION Did reductions in deaths from breast cancer appear first in countries with earlier implementation of mammography screening?

SUMMARY ANSWER Reductions in breast cancer mortality between country pairs in Europe were similar despite 10 to 15 year differences in implementation of mammography screening.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Breast cancer mortality is decreasing in many countries, and the role of mammography screening compared with treatment in this decline is difficult to appraise. The downward trends in breast cancer mortality were similar in paired countries irrespective of mammography screening.

Participants and setting
We selected pairs of European countries based on the countries being neighbours; the countries having similar population structure, socioeconomic circumstances, quality of healthcare services, and access to treatment; and nationwide mammography screening (70% attendance) in one country having existed since around 1990 (Northern Ireland (United Kingdom), Sweden, the Netherlands), with implementation some years later in the matched country (Republic of Ireland, Norway, Belgium/Flanders).

Design
Retrospective trend analysis.

Primary outcome
Temporal trends in age adjusted breast cancer mortality rates among women of all ages and for age groups <50, 50-69, and 70 and older by country.

Main results and role of chance
Between 1989 and 2006 breast cancer mortality decreased by 16.0% in Sweden (full coverage by 1997) and by 24.1% in the Republic of Ireland (screening began in 2000). In the Netherlands (full coverage by 1997) the overall 25.0% reduction in mortality has been slightly greater than the 19.9% in Belgium (partial coverage by 2005), but Flanders (low screening by 2006) did not differ noticeably compared with the Netherlands (25.0% v 24.6%). From 1989 to 2006, breast cancer mortality decreased by 29.6% in Northern Ireland (full coverage by 1993) and by 26.7% in the Republic of Ireland (screening began in 2000). The decline in mortality started between 1991 and 1996 in Norway, Belgium, Republic of Ireland, Northern Ireland, and the Netherlands. In Sweden, reductions in mortality started in 1972 and remained stable.

Mammography screening cannot explain these changes, as reductions in mortality started too soon after the implementation of screening in the Netherlands and Northern Ireland and because screening was uncommon in the four other countries. It seems more likely that the downward inflexions from 1991 to 1996 stem from adoption of effective cancer treatments. Overall, the greatest reduction in mortality was among women aged <50 years, irrespective of screening. In women aged 70-79, reductions in mortality varied by country, with strong reductions in the Netherlands, Norway, and Republic of Ireland.

Bias, confounding, and other reasons for caution
This was an ecological study. The paired countries, however, were closely matched for obesity, fertility patterns, expenditure, adoption and sale of anticancer drugs, and per capita expenditures on health. The World Health Organization judged the cause of death data to be of high quality in Northern Ireland and the Republic of Ireland and of medium quality in the four other countries. The effect of opportunistic screening for breast cancer in Belgium and the Republic of Ireland was included in screening attendance statistics. In the four other countries, opportunistic screening was uncommon. The observation period of 18 years was enough to make reliable comparisons, as randomised trials showed reductions in mortality eight years after screening started.

Study funding/potential competing interests
The institutions in which the authors work had no influence on the conduct of the research of the writing of the paper. The work of the Northern Ireland Cancer Registry is funded by the Public Health Agency for Northern Ireland.

CHANGES IN BREAST CANCER MORTALITY BETWEEN 1989 AND 2006 IN COUNTRY PAIRS

<table>
<thead>
<tr>
<th>Country pairs</th>
<th>Mean mortality</th>
<th>Overall % change 1989-2006 by age</th>
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<tbody>
<tr>
<td></td>
<td>1987-9</td>
<td>2004-6</td>
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<tr>
<td>All ages 40-49 50-69 70-79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern Ireland (1993)*</td>
<td>37.0</td>
<td>28.1</td>
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<tr>
<td>Republic of Ireland (2000)†</td>
<td>40.3</td>
<td>30.5</td>
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<tr>
<td>Netherlands (1997)*</td>
<td>39.0</td>
<td>30.1</td>
</tr>
<tr>
<td>Belgium (2005)‡</td>
<td>37.5</td>
<td>29.7</td>
</tr>
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<td>Sweden (1997)*</td>
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<td>Norway (2005)*</td>
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<td>21.5</td>
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<tr>
<td>Overall % change 1989-2006 by age</td>
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<tr>
<td>All ages 40-49 50-69 70-79</td>
<td></td>
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</tr>
<tr>
<td>Northern Ireland (1993)*</td>
<td>−29.6</td>
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<td>Republic of Ireland (2000)†</td>
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<td>−45.2</td>
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<td>Netherlands (1997)*</td>
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<tr>
<td>Norway (2005)*</td>
<td>−24.1</td>
<td>−33.5</td>
</tr>
</tbody>
</table>

*Full coverage.
†Organised screening programme first implemented, full coverage in 2008.
‡Partial coverage.
Socioeconomic inequalities in outcome of pregnancy and neonatal mortality associated with congenital anomalies: population based study

Lucy K Smith, Judith L S Budd, David J Field, Elizabeth S Draper

STUDY QUESTION Are there socioeconomic inequalities in the outcome of pregnancies affected by congenital anomalies with a poor prognosis?

SUMMARY ANSWER While antenatal screening for congenital anomalies has reduced absolute neonatal mortality through termination of pregnancy, socioeconomic variation in termination of pregnancy after antenatal detection has resulted in wide socioeconomic inequalities in liveborn infants with a congenital anomaly and subsequent neonatal mortality.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Screening for congenital anomaly and access to termination services have reduced neonatal mortality rates in many countries. We found that antenatal detection rates of anomalies with a poor prognostic outcome are similar for all deprivation groups, yet rates of termination of pregnancy for congenital anomaly are lower in more deprived areas, leading to socioeconomic inequality in the rate of live birth associated with congenital anomaly and consequent neonatal mortality.

Participants and setting
All registered cases of nine selected congenital anomalies with poor prognostic outcome were audited as part of the United Kingdom’s Fetal Anomaly Screening Programme in East Midlands and South Yorkshire regions of England (representing about 10% of births in England and Wales).

Design, size, and duration
Retrospective population based registry study of 1579 fetuses affected by chromosomal (trisomy 13 and trisomy 18) and non-chromosomal (anencephaly, spina bifida, hypoplastic left heart, bilateral renal agenesis, lethal skeletal dysplasia, exomphalos, daphragmatic hernia) anomalies. All pregnancies had an end date between 1 January 1998 and 31 December 2007.

Main results and the role of chance
There was no evidence of variation in the overall risk of these anomalies with deprivation (rate ratio 1.05, 95% confidence interval 0.90 to 1.23). The rate ratio varied with type of anomaly and maternal age (1.43 (1.17 to 1.74) for non-chromosomal anomalies; 0.85 (0.63 to 1.15) for chromosomal anomalies). Of the nine anomalies, 86% were detected in the antenatal period, and there was no evidence that this varied with deprivation. The rate of termination after antenatal diagnosis of a congenital anomaly, however, was lower in the most deprived areas (63%) compared with the least deprived areas (79%). Consequently, there were significant socioeconomic inequalities in the rate of live birth and neonatal mortality associated with the presence of any of the nine anomalies. The most deprived areas had a 61% higher rate of live births and a 98% higher neonatal mortality rate associated with a congenital anomaly compared with the least deprived areas. These patterns were similar after adjustment for type of anomaly and maternal age.

Bias, confounding, and other reasons for caution
Alternative definitions of anomalies with a poor prognostic outcome could affect the results, but our sensitivity analyses of all registered cases of congenital anomaly showed similar findings. We lacked detailed data on individual deprivation measures. Despite this, the results are treated cautiously, our methods are relatively straightforward and provide a way for data from a congenital anomaly registry to be used to monitor up to date trends.

Generalisability to other populations
While this work concentrates on a specific region of the UK, our results are probably generalisable to the whole of the UK and might also be relevant in countries with a similar policy on termination of pregnancy.

Study funding/potential competing interests
The study is funded by the UK Department of Health’s National Institute of Health Research (RM62G0225). EMSYCAR is funded by the Primary Care Trust in the areas covered by the register.

<table>
<thead>
<tr>
<th>RATE RATIOS (95% CI) FOR EFFECT OF DEPRIVATION (MOST DEPRIVED 10TH v LEAST DEPRIVED 10TH) ON OUTCOME IN PREGNANCY AFFECTED BY FETAL ANOMALY</th>
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<tbody>
<tr>
<td>All selected anomalies (n=1579)*</td>
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<tr>
<td>Registered cases/10 000 births</td>
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<tr>
<td>% of all cases detected antenatally</td>
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<td>% terminations in cases detected antenatally</td>
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<tr>
<td>Stillbirth or fetal loss/10 000 births</td>
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<tr>
<td>Live birth/10 000 live births</td>
</tr>
<tr>
<td>Neonatal deaths/10 000 live births</td>
</tr>
</tbody>
</table>

*Unadjusted.
†Adjusted for maternal age.