

THIS WEEK'S RESEARCH QUESTIONS

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Bicycle sharing schemes



Last year, the *BMJ* published a systematic review that looked at whether community interventions to promote cycling were successful (*BMJ* 2010;341:c5293). The authors concluded that such schemes had the potential to get people on their bikes—but what are the actual benefits to health?

This week, a modelling study by David Rojas-Rueda and colleagues (p 356) attempts to answer this question in the context of a bike sharing scheme—“Bicing”—in Barcelona, Spain. They estimated that as a result of the physical activity involved in using these bikes, 12.46 deaths would be avoided per year—a large benefit, compared with the risks from inhalation of air pollutants and road traffic incidents—and that the scheme also reduced carbon

dioxide emissions. The reliability of the conclusions is limited by the assumptions made in the model, but in sensitivity analyses the authors found a net benefit for Bicing users in all the scenarios they tested.

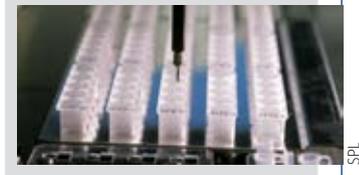
In a rapid response to the article online, Naveen Dutt of the Government Medical College and Hospital, Chandigarh, India, suggests that non-fatal cycle accidents and other ailments related to bicycle use are important to consider, in addition to the three primary outcome measures used in the study (all cause mortality owing to physical activity, air pollution, and road traffic accident mortality), for an unbiased assessment of the benefits of cycling. (<http://bit.ly/oknHD>).

Genetic sensitivity to clopidogrel

CYP2C19 might read like a car number plate, but in fact it denotes a gene related to the cytochrome P450 gene, and both of them code for enzymes that metabolise drugs. Clopidogrel is a good drug, but it doesn't work in 20% of patients. Previous studies have suggested that CYP2C19 might be implicated, leading to intense debate and a warning from the US Food and Drug Administration.

Tim Bauer and colleagues have now scrutinised the association between variants of the CYP2C19 gene and the clinical efficacy of clopidogrel (p 353). Their systematic review and meta-analysis found, however, no robust evidence to recommend individualised clopidogrel treatment driven by CYP2C19 genotype.

For those who want to consider the bigger picture, Michael V Holmes and colleagues' linked editorial discusses the wider challenges of pharmacogenetic research (p 327).



Use of antidepressants in older people

How do you weigh up the risk of antidepressants in older people? Trials are often not designed to address the harms of treatment in older patients with complex conditions. Yet clinicians need guidance to deliver quality care to such patients. So other avenues of evidence must be explored.

Carol Coupland and colleagues say that prescriptions for antidepressants have increased by 35% over five years. A systematic review showed that SSRIs and tricyclic antidepressants have similar benefits in older patients, but more patients discontinue tricyclics. These authors asked: in the over 65s, what is the association between class

of antidepressant prescription for a new episode of depression and a variety of expected adverse events? They conducted a large primary care database study drawing on WHO International Classification of Disease codes and information from death certificates to investigate outcomes.

We hope that their results are useful to working doctors. However, as the authors caution, interpreting their findings is complicated. Observational studies are prone to confounding. Choice of antidepressant is not random. Patient preference, comorbidities, and doctors' judgment mean that there are likely to be

systematic differences between patients who are, and are not, prescribed a particular class of drug.

So what should clinicians do? In his editorial, Professor Ian Hickie gives a few observations and pointers (p 328). Are we prescribing too much medication? Ninety per cent of patients received a prescription. Are non-pharmacological approaches being used appropriately? He was struck by the observation that most adverse events occurred in the first month after starting or stopping an antidepressant, and he calls for weekly monitoring of patients during these periods.

LATEST RESEARCH: For these and other new research articles see www.bmj.com/research

Self correction of refractive error among young people in rural China Mingzhi Zhang and colleagues found that over 96% of young people in rural China with poor vision in at least one eye could improve their vision to $\geq 6/7.5$ in the better seeing eye by self refraction with cheap adjustable spectacles (doi:10.1136/bmj.d4767).

How to obtain the confidence interval from a P value Some published articles report P values, but do not give corresponding confidence intervals—or vice versa. A pair of Statistics Notes articles by Doug Altman and Martin Bland explain how to work out either of these missing statistics based on the one available (doi:10.1136/bmj.d2090, doi:10.1136/bmj.d2304).



Impact of CYP2C19 variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis

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EDITORIAL by Holmes

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STUDY QUESTION

Do variants of the cytochrome P450 (CYP) 2C19 genotype influence the clinical efficacy of clopidogrel in patients with coronary artery disease?

SUMMARY ANSWER

The accumulated evidence from genetic association studies does not support a substantial or consistent influence of CYP2C19 gene polymorphisms on the incidence of major adverse cardiovascular events or stent thrombosis in patients taking clopidogrel.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Genetic polymorphisms of CYP2C19 have been proposed as a major influence on the effectiveness of clopidogrel, suggesting the usefulness of genotype guided treatment. The summary risk estimates from published studies, however, indicate no or substantially biased effects of the CYP2C19 genotype on the occurrence of adverse cardiovascular events in patients taking clopidogrel.

Selection criteria for studies

We searched Medline, Embase, the Cochrane Library, and online databases, contents pages, and bibliographies of relevant journals without language restrictions. We retrieved all original full length reports assessing the

number of cardiovascular events over a follow-up period of at least one month in association with the loss of function (at least *2) or gain of function (*17) CYP2C19 allele carrier status in men and women of any ethnicity with a clinical presentation of stable angina pectoris or acute coronary syndrome taking clopidogrel.

Primary outcomes

Primary outcomes were major adverse cardiovascular events or fatal or non-fatal stent thromboses.

Main results and role of chance

Of 4203 screened reports, 15 studies met the inclusion criteria. The random effects summary odds ratio for stent thrombosis in carriers of at least one loss of function allele of CYP2C19 versus non-carriers, from nine studies with a total of 19 328 participants, was 1.77 (95% confidence interval 1.31 to 2.40; $P < 0.001$). This nominally significant odds ratio, however, was subject to considerable bias across the studies (small study effect bias and replication diversity). The corresponding random effects summary odds ratio for major adverse cardiovascular events, from 12 studies with 18 529 participants, was 1.11 (0.89 to 1.39; $P = 0.36$). The random effects summary odds ratio of stent thrombosis in carriers of at least one gain of function CYP2C19*17 allele versus non-carriers, from three studies with 4434 participants, was 0.99 (0.60 to 1.62; $P = 0.96$), and the corresponding odds ratio of major adverse cardiovascular events in five studies with 9128 participants was 0.93 (0.75 to 1.14; $P = 0.48$).

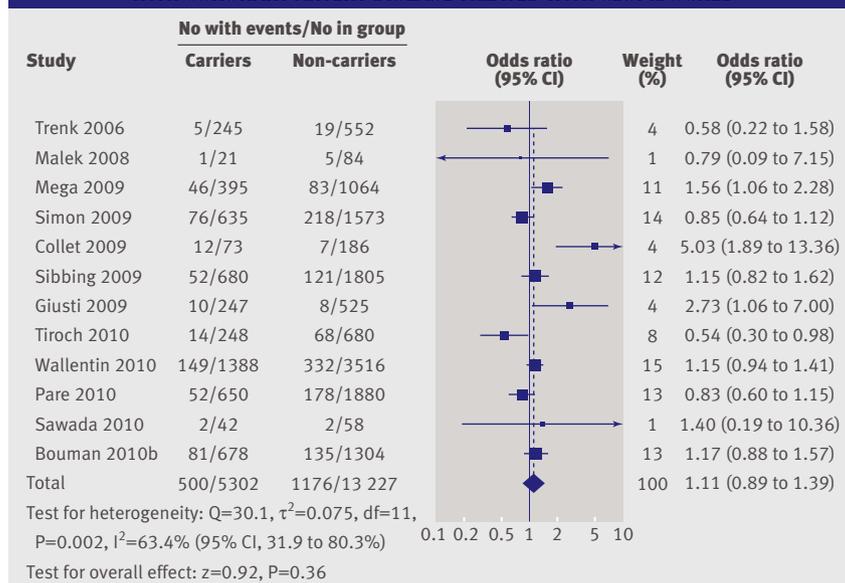
Bias, confounding, and other reasons for caution

Our meta-analyses were limited by the published data. We excluded studies that reported clinician driven proxy outcomes (revascularisation, admission to hospital) or existed only as abstracts. All meta-analyses were affected by risks of bias at the individual study level and at the aggregate level and were assigned low grades of overall epidemiological evidence. The associations were not controlled for possible interactions between loss of function and gain of function CYP2C19 polymorphisms, entailing the risk of a systematic overestimation of the single locus effect sizes.

Study funding/potential competing interests

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. JWvW and JMtB received speakers' bureau fees and acted as consultants for companies active in the field of antiplatelet therapy (see full paper on bmj.com for details).

ASSOCIATION BETWEEN LOSS OF FUNCTION POLYMORPHISMS OF CYP2C19 AND MAJOR ADVERSE CARDIOVASCULAR EVENTS IN PATIENTS WITH CORONARY ARTERY DISEASE TREATED WITH CLOPIDOGREL



Antidepressant use and risk of adverse outcomes in older people: population based cohort study

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EDITORIAL by Hickie

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STUDY QUESTION

What are the associations between antidepressant treatment and various adverse outcomes in older people diagnosed as having depression?

SUMMARY ANSWER

Selective serotonin reuptake inhibitors (SSRIs) were associated with the highest risks of falls and hyponatraemia, and the group of other antidepressants (not SSRIs, tricyclic and related antidepressants, or monoamine oxidase inhibitors) was associated with the highest risks of all cause mortality, attempted suicide/self harm, stroke/transient ischaemic attack, fracture, and epilepsy/seizures.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Comparatively little is known about the safety of antidepressant drugs in older people. Use of SSRIs or drugs in the group of other antidepressants may be associated with an increased risk of some adverse outcomes compared with tricyclic antidepressants in older people.

Participants and setting

The study was based in the QResearch primary care database. We included patients diagnosed as having depression between the ages of 65 and 100 years, from 1 January 1996 to 31 December 2007, and followed them up until 31 December 2008.

Design, size, and duration

This was a cohort study of 60 746 patients, followed up for a mean of 5.0 years. We calculated hazard ratios (adjusting for a range of potential confounding variables) for all cause mortality, attempted suicide/self harm, myocardial infarction, stroke/transient ischaemic attack, falls, fractures, upper gastrointestinal bleeding, epilepsy/seizures, road traffic accidents, adverse drug reactions, and hyponatraemia according to antidepressant class.

Main results and the role of chance

A total of 54 038 (89.0%) patients received at least one prescription for an antidepressant during follow-up. The associations with the adverse outcomes differed significantly between the antidepressant classes for seven outcomes. Selective serotonin reuptake inhibitors were associated with the highest adjusted hazard ratios for falls and hyponatraemia compared with when antidepressants were not being used. The group of other antidepressants was associated with the highest adjusted hazard ratios for all cause mortality, attempted suicide/self harm, stroke/transient ischaemic attack, fracture, and epilepsy/seizures. Tricyclic antidepressants did not have the highest hazard ratio for any of the outcomes. Absolute one year risks for all cause mortality were 7.04% for patients while not taking antidepressants, 8.12% for tricyclic antidepressants, 10.61% for SSRIs, and 11.43% for other antidepressants.

Bias, confounding, and other reasons for caution

As this is an observational study, it is susceptible to confounding by indication, channelling bias, and residual confounding. Although we adjusted for many potential confounders, differences in characteristics between patients prescribed different antidepressant drugs may remain that could account for some of the associations between the drugs and the adverse outcomes.

Generalisability to other populations

The study was a large population based study with broad inclusion criteria, so the findings are generalisable to the population of older people diagnosed as having depression in primary care in the United Kingdom.

Study funding/potential competing interests

This project was funded by the NIHR Health Technology Assessment Programme. JH-C is director of QResearch.

HAZARD RATIOS FOR SEVEN ADVERSE OUTCOMES BY ANTIDEPRESSANT CLASS

| Antidepressant class | Adjusted hazard ratio* (95% CI) |
|--|---------------------------------|
| All cause mortality | |
| Tricyclic antidepressants | 1.16 (1.10 to 1.22) |
| Selective serotonin reuptake inhibitors | 1.54 (1.48 to 1.59) |
| Other antidepressants | 1.66 (1.56 to 1.77) |
| Attempted suicide/self harm | |
| Tricyclic antidepressants | 1.70 (1.28 to 2.25) |
| Selective serotonin reuptake inhibitors | 2.16 (1.71 to 2.71) |
| Other antidepressants | 5.16 (3.90 to 6.83) |
| Stroke/transient ischaemic attack | |
| Tricyclic antidepressants | 1.02 (0.93 to 1.11) |
| Selective serotonin reuptake inhibitors | 1.17 (1.10 to 1.26) |
| Other antidepressants | 1.37 (1.22 to 1.55) |
| Falls | |
| Tricyclic antidepressants | 1.30 (1.23 to 1.38) |
| Selective serotonin reuptake inhibitors | 1.66 (1.58 to 1.73) |
| Other antidepressants | 1.39 (1.28 to 1.52) |
| Fracture | |
| Tricyclic antidepressants | 1.26 (1.16 to 1.37) |
| Selective serotonin reuptake inhibitors | 1.58 (1.48 to 1.68) |
| Other antidepressants | 1.64 (1.46 to 1.84) |
| Epilepsy/seizures | |
| Tricyclic antidepressants | 1.02 (0.76 to 1.38) |
| Selective serotonin reuptake inhibitors | 1.83 (1.49 to 2.26) |
| Other antidepressants | 2.24 (1.60 to 3.15) |
| Hyponatraemia | |
| Tricyclic antidepressants | 1.05 (0.87 to 1.27) |
| Selective serotonin reuptake inhibitors | 1.52 (1.33 to 1.75) |
| Other antidepressants | 1.28 (0.98 to 1.67) |

*Compared with when antidepressants were not being used.

Oxytocin bolus versus oxytocin bolus and infusion for control of blood loss at elective caesarean section: double blind, placebo controlled, randomised trial

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doc2doc

Drugs for uterine atony
<http://bit.ly/nweR11>

STUDY QUESTION

Does the addition of an oxytocin infusion to a standard oxytocin bolus reduce the occurrence of major obstetric haemorrhage or the need for an additional uterotonic agent at elective caesarean section?

SUMMARY ANSWER

An additional oxytocin infusion did not affect overall occurrence of major obstetric haemorrhage compared with oxytocin bolus only, but reduced the need for an additional uterotonic agent.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Routine oxytocin reduces postpartum haemorrhage after vaginal birth but the effects at caesarean section have received little attention. Use of an oxytocin bolus and infusion after caesarean delivery reduces the need for additional uterotonic agents but does not reduce major obstetric haemorrhage.

Design

Randomised double blind placebo controlled trial with block randomisation and computer generated allocation. Women were randomly assigned to receive either an intravenous slow bolus of 5 IU oxytocin over 1 minute and 40 IU oxytocin in 500 mL 0.9% saline solution over 4 hours (bolus and infusion) or 5 IU oxytocin bolus over 1 minute and 0.9% saline solution 500 mL over 4 hours (bolus only).

Participants and setting

This was a large pragmatic clinical trial within five centres in the Republic of Ireland. The study population included healthy women at term (>36 weeks) with singleton pregnancies booked for elective caesarean section (n=1037 bolus and infusion and n=1032 bolus only). We excluded women with placenta praevia, thrombocytopenia, coagulopathies, previous major obstetric haemorrhage (>1000 mL), known fibroids, or receiving anticoagulant therapy, and those who did not understand English or were younger than 18 years. Clinicians could exclude other patients at their discretion if they expected major haemorrhage, in keeping with recommendations of the research ethics committee.

Primary outcomes

Occurrence of major obstetric haemorrhage and use of an additional uterotonic agent (oxytocin infusion, oxytocin bolus, misoprostol, ergometrine, syntometrine, or 15-methyl-prostaglandin F_{2α}). We defined major obstetric haemorrhage as calculated blood loss of more than 1000 mL. Blood loss calculation: estimated blood volume × (preoperative PCV – postoperative PCV)/preoperative PCV (where PCV=packed cell volume, estimated blood volume=booking weight (kg) × 85).

Main results and the role of chance

We found no difference in occurrence of major obstetric haemorrhage between the groups (bolus and infusion 15.7% (n=158/1007) v bolus only 16.0% (n=159/994); odds ratio 0.98, 95% CI 0.77 to 1.25, P=0.86). The need for an additional uterotonic agent in the bolus and infusion group was lower than in the bolus only group (12.2% (n=126/1033) v 18.4% (n=189/1025); 0.61, 0.48 to 0.78, P<0.001).

Harms

An additional oxytocin infusion did not increase the occurrence of side effects.

Bias, confounding, and other reasons for caution

We did not include a placebo bolus group because this would have been unacceptable under participating hospitals' guidelines. We chose two primary outcomes, both reflecting uterine atony. Major obstetric haemorrhage is the most relevant clinical outcome because it is a leading cause of maternal death worldwide. However, clinicians intervene in the event of uterine atony to prevent major obstetric haemorrhage by using an additional uterotonic agent, which in itself is an important outcome.

Generalisability to other populations

We carefully defined the population, with a range of indications for caesarean section and varying grades of operator. The results are generalisable to similar populations.

Study funding/potential competing interests

This trial was funded by the Health Research Board of Ireland (RP/2007/171), with additional financial support from the Coombe Women and Infants University Hospital, Dublin. The funding sources had no involvement in any aspects of trial design, writing of the report, or the decision to submit the paper for publication. The authors declare no competing interests.

Trial registration number

ISRCTN17813715.

OCCURRENCE OF PRIMARY OUTCOMES

| | Bolus and infusion No (%) | Bolus only No (%) | Adjusted odds ratio (95% CI)* | P value | Number needed to treat (95% CI) |
|---|---------------------------|-------------------|-------------------------------|---------|---------------------------------|
| Major obstetric haemorrhage (blood loss >1000 mL) | 158/1007 (15.7) | 159/994 (16.0) | 0.98 (0.77 to 1.25) | 0.86 | – |
| Additional uterotonic agent | 126/1033 (12.2) | 189/1025 (18.4) | 0.61 (0.48 to 0.78) | <0.001 | 16 (11 to 32) |

*Odds ratios calculated from models adjusted for centre and previous caesarean section.

The health risks and benefits of cycling in urban environments compared with car use: health impact assessment study

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STUDY QUESTION

What are the risks and benefits to health of travel by bicycle, using a bicycle sharing scheme, compared with travel by car in an urban environment?

SUMMARY ANSWER

Travelling by bicycle in an urban environment using a bicycle sharing scheme such as Bicing in Barcelona has greater benefits than risks to health compared with travel by car, when factors such as physical activity, air pollution, and road traffic incidents are considered.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Bicycle sharing schemes provide a sustainable mode of transport for short urban trips. Public bicycle sharing schemes can help improve public health.

Participants and setting

181 982 subscribers to the public bicycle sharing initiative, Bicing, in Barcelona, Spain, in 2009.

Design, size, and duration

We used a health impact assessment framework to estimate the potential effects on health of cycling compared with travel by car. We used exposure-response functions derived from existing studies and calibrated for current exposure and health conditions in Barcelona. We chose to model the effects of all cause mortality due to physical activity, road traffic incidents, and exposure to air pollution (particulate matter <2.5 µm) and focused on

residents of Barcelona who started cycling regularly using Bicing after its implementation. We also estimated savings in carbon dioxide emissions.

Main results and the role of chance

The estimated annual change in mortality of car users compared with Bicing users in Barcelona was 0.03 deaths from road traffic incidents (attributable fraction 0.0007) and 0.13 deaths from air pollution (0.002). As a result of physical activity, 12.46 deaths were avoided (0.23). We found a benefit:risk ratio of 77. As a result, 52.15 deaths would have been expected each year, but because cycling was used as a typical means of transport, the number was reduced by 12.28 to 39.87. Annual carbon dioxide emissions were reduced by an estimated 9 062 344 kg. A tornado plot showed that the results were most sensitive to variations imposed on the relative risk associated with physical activity and mortality, average duration of bicycle trip, number of days travelled by bicycle per year per person in Barcelona, and proportion of cyclists who started cycling when Bicing was implemented.

Bias, confounding, and other reasons for caution

As in all risk assessments, our study was limited by the availability of data and the necessity to make assumptions to model likely scenarios. We carried out sensitivity analyses to assess the stability of our results and tested effects of deviations from our main assumptions and data choices. Included in the sensitivity analysis were the relative risk functions from the literature, choice and toxicity of pollutants, age distribution, shift in mode of travel, and environmental and travel conditions in Barcelona. Importantly, we found that in all the scenarios we tested a net benefit was always evident for Bicing users.

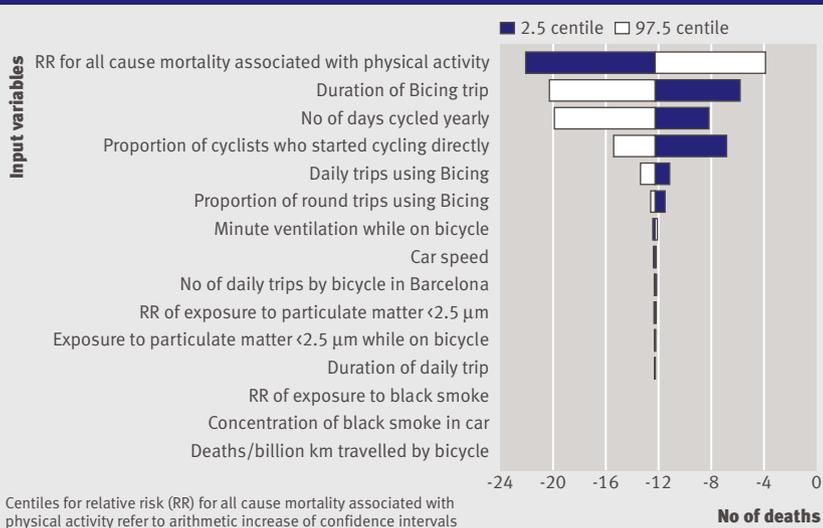
Generalisability to other populations

Public bicycle sharing systems are implemented in urban areas with similar characteristics of transport demand and are designed for short urban trips. The results of this study could be expected to be generalisable to other cities with large bicycle sharing initiatives.

Study funding/potential competing interests

This work is part of the European wide project Transportation Air pollution and Physical Activities: an integrated health risk assessment programme of climate change and urban policies (TAPAS), which has partners in Barcelona, Basel, Copenhagen, Paris, Prague, and Warsaw. TAPAS is a four year project funded by the Coca-Cola Foundation, AGAUR, and CREAL.

SENSITIVITY ANALYSIS TORNADO PLOT OF EFFECT OF VARYING EACH INPUT VARIABLE INDIVIDUALLY



Effectiveness and cost effectiveness of cardiovascular disease prevention in whole populations: modelling study

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STUDY QUESTION

Are public health programmes that prevent cardiovascular disease in entire populations cost effective?

SUMMARY ANSWER

Any intervention achieving even a modest population-wide reduction in any major cardiovascular risk factor would produce a net cost saving to the National Health Service, as well as improving health.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Population-wide prevention programmes (such as salt reduction, *trans* fat eradication, or smoke-free legislation) seem to be very effective, reducing cardiovascular events and deaths and saving costs in the United States and Australia. Compared with no additional intervention, a UK national programme reducing population cardiovascular risk by 1% would prevent approximately 25 000 cases of cardiovascular disease and generate public sector savings of approximately £30m a year.

Main results

A programme across the entire population of England and Wales (50 million people) that reduced cardiovascular events by just 1% would result in health service savings worth at least £30m (£34m; \$48m) a year compared with no additional intervention. Reducing mean population cholesterol or blood pressure levels by 5% (as already achieved by similar interventions in some other countries) would result in annual savings worth at least £80m or £100m. Legislation or other measures to reduce dietary salt intake by 3 g/day (current mean intake approximately 8.5 g/day) would prevent approximately 30 000 cardiovascular events, with savings worth at least £40m a year. Legislation to reduce industrial *trans* fat intake by approximately 0.5% of total energy content might gain 570 000 life years and generate NHS savings worth at least £230m a year.

Design

We developed a spreadsheet economic model that quantified the reduction in cardiovascular disease in the population of England and Wales over a decade.

Sources of effectiveness

National programmes elsewhere using legislation, regulation, or taxation consistently show effectiveness.

Data sources

Life expectancy data came from the government actuary's department. We used Framingham risk equations to generate the expected pattern of first cardiovascular events according to the person's age, sex, and cardiovascular risk. All new costs and inflation indices came from *Unit Costs of Health and Social Care* (Curtis 2008). All other NHS unit costs and quality of life data came from the ScHARR prevention model.

Results of sensitivity analysis

We did an extensive series of sensitivity analyses. Substantial absolute savings occurred even when the background risk was increased or reduced by 50%.

Limitations

The deaths avoided, life years gained, and cost savings are likely to be underestimates, making the analysis somewhat conservative. This is because we did not consider recurrent events and subsequent deaths, we excluded people aged over 80 years, and lifetime gains would be greater than the 10 year timeframe used here. Our results depend on several assumptions. We assumed that the population risk of cardiovascular disease would remain constant, whereas it may decline further; that effects of interventions were relatively uniform across age and risk groups, whereas some groups may gain more than others; and that the proposed population-wide dietary changes were feasible, having been achieved in comparable populations elsewhere.

Study funding/potential competing interests

KMcP, AB, and SC were members of the NICE Programme Development Group on cardiovascular disease prevention in populations. PB and LA were funded by the National Institute for Health and Clinical Excellence (NICE). West Midlands Health Technology Assessment Collaboration (WMHTAC) and Peninsula Technology Appraisal Group (PenTAG) were funded to provide support to the NICE Centre for Public Health Excellence.

DISCOUNTED OUTCOMES FOR POPULATION-WIDE INTERVENTIONS SUSTAINED OVER 10 YEARS

| Intervention | Cases prevented | Deaths prevented | Life years gained | QALYs gained | Total savings in 10 years (£m) | Annual equivalent savings (£m) |
|---|-----------------|------------------|-------------------|--------------|--------------------------------|--------------------------------|
| Cholesterol reduction of 5% | 64 000 | 8 800 | 190 000 | 260 000 | 690 | 80 |
| Systolic blood pressure reduction of 5% | 81 000 | 11 000 | 240 000 | 330 000 | 880 | 100 |
| Salt intake reduction of 3 g/day | 32 000 | 4 400 | 95 000 | 130 000 | 340 | 40 |
| Eradication of <i>trans</i> fat | 190 000 | 27 000 | 570 000 | 750 000 | 2 000 | 240 |

All estimates rounded to two significant figures.
QALY=quality adjusted life year.