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From Richard Lehman's journal blog

"There is a gem of a piece by Lisa Schwartz and Steven Woloshin on the website, with the promise of more Not So Stories to come. Re-enter donepezil, now off-patent at 10 mg, but still patentable at 23 mg for three years' worth of lucrative sales, if only the US Food and Drug Administration could be persuaded. There is actually a head-on study comparing the 10 mg dose with the 23 mg dose and showing no benefit and more adverse effects. So how did Eisai, the drug's manufacturer, persuade the FDA to allow this formulation to be marketed? By the usual box of tricks—direct to public marketing, grossly misleading advertising to doctors, blatantly repeated on the labelling: all of which caused enough demand for the FDA to give way. Quis custodiet ipsos custodes?"

http://www.bmj.com/content/344/bmj.e1086 "

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Cervical disease sufferers could benefit from HPV vaccine

According to this retrospective pooled analysis of trial data (*BMJ* 2012;344:e1401], previous vaccination with quadrivalent HPV vaccine among women who had surgical treatment for HPV related disease significantly reduced the incidence of subsequent HPV related disease, including high grade disease. However, the authors remind us that only long term surveillance of vaccinated populations can determine the population effectiveness of vaccination. Editorialist Jane J Kim says (*BMJ* 2012;344:e1544) that clear communication of the beneficial yet complex properties of HPV vaccines is crucial to ensure that effective and successful decisions can be made on HPV vaccination worldwide.

DR P MARAZZI/SPL

Effectiveness of physical activity promotion based in primary care: systematic review and meta-analysis of randomised controlled trials

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Cite this as: *BMJ* 2012;344:e1389
doi: 10.1136/bmj.e1389

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;344:e1389

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- Editorial: Prescribing exercise in primary care (*BMJ* 2011;343:d4141)
- *BMJ* Learning: Prescribing exercise module

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- Should a patient's physical activity be assessed in every primary care consultation? http://bit.ly/A4nwAB

STUDY QUESTION

Do trials of physical activity promotion based in primary care show sustained effects on physical activity or fitness in sedentary adults, and are exercise referral interventions more effective than other interventions?

SUMMARY ANSWER

Trials of physical activity promotion based in primary care show positive effects on physical activity levels, but not on fitness, over at least 12 months; however, not enough evidence exists to indicate whether exercise referral is more effective than other primary care interventions.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Physical activity promotion in primary care, including exercise referral, is reported to improve physical activity levels in the short term but its longer term effect was unclear. Our review found that promotion of physical activity to sedentary adults identified through primary care significantly improves self reported physical activity levels over at least 12 months; we found few trials of exercise referral interventions with 12 months' follow-up and more trials are needed to determine their relative effectiveness.

Selection criteria for studies

Medline, CINAHL, PsycINFO, Embase, SPORTDiscus, Centre for Reviews and Dissemination, the Cochrane Library, and reference lists were searched for randomised controlled trials of physical activity promotion among sedentary adults recruited in primary care, with minimum follow-up of 12 months, reporting physical activity or fitness (or both) as outcomes, and using intention to treat analyses.

Primary outcome

Physical activity or fitness levels at 12 months after randomisation.

Main results and role of chance

In 13 trials presenting self reported physical activity, we found small to medium positive intervention effects at 12 months (odds ratio 1.42 (95% confidence interval 1.17 to 1.73); standardised mean difference 0.25 (0.11 to 0.38). The number needed to treat with an intervention for one additional sedentary adult to meet internationally recommended levels of activity at 12 months was 12 (7 to 33). In four trials reporting cardiorespiratory fitness, we saw a medium positive effect at 12 months that was non-significant (standardised mean difference 0.51 (−0.18 to 1.20)). Three trials of exercise referral found small non-significant effects on self reported physical activity at 12 months (odds ratio 1.38 (0.98 to 1.95); standardised mean difference 0.20 (−0.21 to 0.61)).

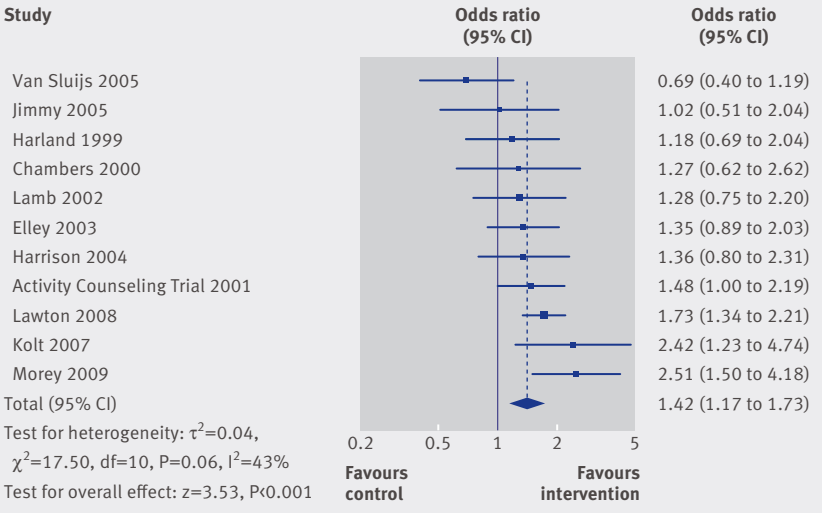
Bias, confounding, and other reasons for caution

Most studies used self reported physical activity as the main outcome and did not blind participants to allocation, which might have led to differential effects of social desirability bias between those receiving an intervention and those receiving a control. In two thirds of studies, trial personnel or outcome assessors were not blinded to allocation, or management of incomplete outcome data was inadequate. These factors would be expected to have biased results by overestimating the intervention effect. Although only one reviewer screened titles and abstracts, and papers could have been missed at this stage, databases were systematically searched on two occasions, supplemented by hand searching of reference lists, and no additional studies were identified by an independent expert.

Study funding/potential competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: support for the submitted work from the National Institute for Health Research and University of Cambridge; no financial relationships with commercial entities that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work other than their involvement in current primary research in the topic area of the systematic review and clinical practice in primary care.

Individual study and pooled effects of physical activity promotion on self reported physical activity at 12 months (dichotomous data)



Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis

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EDITORIAL by Lasserson and Mant

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Cite this as: *BMJ* 2012;344:e1369
doi: 10.1136/bmj.e1369

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;344:e1369

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STUDY QUESTION

What is the comparative effectiveness of DPP-4 inhibitors as first or second line treatment for type 2 diabetes?

SUMMARY ANSWER

DPP-4 inhibitors can be used as second line treatment in patients with type 2 diabetes who do not achieve their glycaemic targets with metformin alone.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Metformin is the first line treatment for people with type 2 diabetes. Indirect meta-analyses assessing the efficacy of various hypoglycaemic drugs suggest that DPP-4 inhibitors achieve similar reductions in glycated haemoglobin (HbA_{1c}) compared with other second line treatments. Our meta-analysis suggests that in patients who do not achieve their glycaemic targets with metformin alone, DPP-4 inhibitors can lower HbA_{1c}, in a similar way to sulfonylureas or pioglitazone, with neutral effect on body weight.

Selection criteria for studies

We searched Medline, Embase, the Cochrane Library, conference proceedings, trial registers, and drug manufacturers' websites for randomised controlled trials of adults with type 2 diabetes mellitus that examined the effect of a DPP-4 compared with metformin as monotherapy or in combination treatment with metformin compared with a sulfonylurea, pioglitazone, a GLP-1 agonist, or basal insulin. The last search was run on 15 March 2011.

Primary outcome

The main outcome was the change in glycated haemoglobin (HbA_{1c}) from baseline to end point.

Main results and role of chance

We identified 27 reports of 19 eligible studies including 7136 patients randomised to a DPP-4 inhibitor and 6745 patients randomised to another hypoglycaemic drug. Compared with metformin as monotherapy, DPP-4 inhibitors were associated with a smaller fall in HbA_{1c} (weighted mean difference 0.20, 95% confidence interval 0.08 to 0.32; I^2=60%). As a second line treatment, DPP-4 inhibitors were marginally less effective than sulfonylureas (0.07, 0.03 to 0.11; I^2 0%), similar to pioglitazone (0.09, −0.07 to 0.24; I^2=40%), and inferior to GLP-1 agonists (0.49, 0.31 to 0.67; I^2=27%). In sensitivity analyses the exclusion of reports at high risk of bias did not alter the effect estimate or heterogeneity. When added to metformin, DPP-4 inhibitors had a favourable effect on body weight compared with sulfonylureas or pioglitazone but not compared with GLP-1 agonists. Only a minimal number of hypoglycaemias were observed in any treatment arm in trials comparing a DPP-4 inhibitor with metformin as monotherapy or with pioglitazone or a GLP-1 agonist as second line treatment. In most trials comparing a DPP-4 inhibitor with sulfonylureas combined with metformin, the risk for hypoglycaemia was higher in the group receiving a sulfonylurea.

Bias, confounding, and other reasons for caution

We did not conduct separate analyses for each DPP-4 inhibitor because of scarcity of data to explore the relative differences between DPP-4 inhibitors. There was considerable variation in the risk of bias across studies and across the outcomes of the same study. In our analysis comparing DPP-4 inhibitors with metformin we noted a considerable amount of heterogeneity, even after exclusion of studies at high risk of bias. The number of trials directly comparing DPP-4 inhibitors with pioglitazone and GLP-1 agonists combined with metformin was small. The strength of inference is therefore limited. Increased unit cost and uncertainty about their long term safety should also be considered.

Study funding/potential competing interests

This research received no grant from any funding agency. DRM is a member of an advisory board for vildagliptin (Novartis) and has received consulting fees from Novartis, Novo Nordisk, GlaxoSmithKline, Merck, Eli Lilly, Boehringer Ingelheim, AstraZeneca, Johnson and Johnson, and Janssen Global Services. AT is a member of an advisory board for liraglutide (Novo Nordisk), has received lecture fees and a research grant from Novartis and has received support with an educational grant from Novo Nordisk.

Weighted mean difference in change in HbA_{1c} (%) from baseline with DPP-4 inhibitors compared with other hypoglycaemic drugs in people with type 2 diabetes

Type of comparison	No of studies	No of patients analysed	Size of effect (95% CI; I^2)
Monotherapy:			
DPP-4 inhibitor *v* metformin	7	3237	0.20 (0.08 to 0.32; 60%)
Combined with metformin:			
DPP-4 inhibitor *v* sulfonylurea	6	7291	0.07 (0.03 to 0.11; 0%)
DPP-4 inhibitor *v* pioglitazone	3	1021	0.09 (–0.07 to 0.24; 40%)
DPP-4 inhibitor *v* GLP-1 agonists	2	766	0.49 (0.31 to 0.67; 27%)

Cardiovascular disease in kidney donors: matched cohort study

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Cite this as: *BMJ* 2012;344:e1203
doi: 10.1136/bmj.e1203

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;344:e1203

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STUDY QUESTION

Does donating a kidney increase the risk of death and major cardiovascular events?

SUMMARY ANSWER

The risk of major cardiovascular events in donors is no higher in the first decade after kidney donation compared with a similarly healthy segment of the general population. While we will continue to follow people in this study, these interim results add to the evidence base supporting the safety of the practice among carefully selected donors.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

People with reduced kidney function are known to have an increased risk of cardiovascular disease.
We found no increased risk of cardiovascular disease in kidney donors compared with healthy people in the general population.

Participants and setting

All people who were carefully selected to become a living kidney donor in the province of Ontario, Canada, between 1992 and 2009.

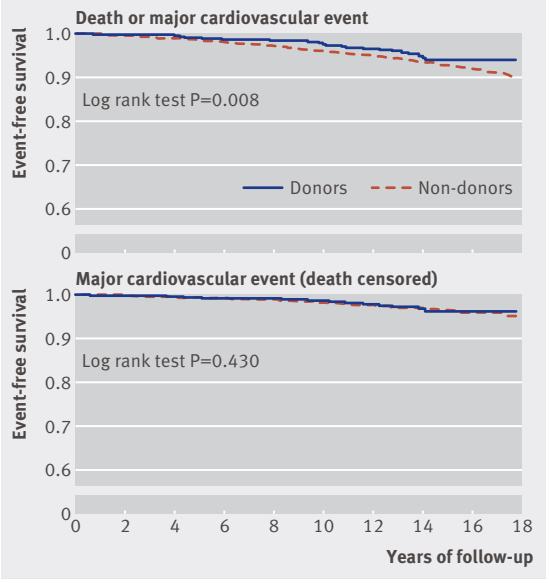
Design, size, and duration

This was a retrospective population based matched cohort study. The information in donor charts was manually reviewed and linked to provincial healthcare databases. Matched non-donors were selected from the healthiest segment of the general population. A total of 2028 donors and 20 280 matched non-donors were followed for a median of 6.5 years (maximum 17.7 years). Median age was 43 at the time of donation (interquartile range 34-50) and 50 at the time of follow-up (42-58).

Main results and the role of chance

The risk of the primary outcome of death and major cardiovascular events was lower in donors than in non-donors (2.8 *v* 4.1 events per 1000 person years; hazard ratio 0.66, 95% confidence interval 0.48 to 0.90). The risk of major cardiovascular events censored for death was no different in donors than in non-donors (1.7 *v* 2.0 events per 1000 person years; 0.85, 0.57 to 1.27).

Kaplan-Meier estimates of survival probability in living kidney donors



Bias, confounding, and other reasons for caution

Information on kidney function and family history of kidney disease were unavailable in non-donors, and measurements such as blood pressure and body mass index (BMI) before transplantation were unavailable in both donors and non-donors. This information could have allowed for better selection of non-donors. We did not have information on glomerular filtration rate in donors during follow-up, which precluded an assessment of cardiovascular risk according to this feature.

Generalisability to other populations

Given that 75% of Ontario residents are white, these results might generalise less well to non-white donors. These data should not be generalised to the recent practice of accepting donors with health conditions such as obesity or hypertension.

Study funding/potential competing interests

This project was conducted at the Institute for Clinical Evaluative Sciences, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care.

Inverse association between cancer and Alzheimer's disease: results from the Framingham Heart Study

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Cite this as: *BMJ* 2012;344:e1442
doi: 10.1136/bmj.e1442

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;344:e1442

STUDY QUESTION

Is there an inverse relation between cancer and Alzheimer's disease?

SUMMARY ANSWER

In a prospective, community based cohort study, cancer survivors had a 33% decreased risk of ever developing Alzheimer's disease, and people with Alzheimer's disease were 61% less likely to develop cancer.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Patients with Parkinson's disease have a decreased risk of most cancers, and limited evidence suggests a similar pattern in Alzheimer's disease. This study provides additional evidence for an inverse relation between cancer and Alzheimer's disease that is not primarily due to survival bias.

Participants and setting

Participants were a subset of the Framingham Heart Study, a cohort study based in Framingham Massachusetts, United States. Participants underwent biennial examinations and cases of cancer and Alzheimer's disease were verified by study investigators.

Design, size, and duration

The first analysis was a cohort study of 1278 participants with and without a history of cancer who were aged 65 or more and free of dementia at baseline (1986-90). In the second analysis, verified cases of probable Alzheimer's disease (n=327) were matched to controls (n=1128) by age and sex.

Primary outcomes, risks, exposures

In the cohort analysis, history of cancer was the exposure and incident Alzheimer's disease the outcome. In the case-control analysis, Alzheimer's disease was the exposure and incident cancer the outcome.

Main results and the role of chance

Cancer survivors had a lower risk of probable Alzheimer's disease (hazard ratio 0.67, 95% confidence interval 0.47 to 0.97), adjusted for age, sex, and smoking. The association was not changed by limiting the analysis to participants who survived at least to age 80. The risk was lower among survivors of smoking related cancers (0.26, 0.08 to 0.82) than non-smoking related cancers (0.82, 0.57 to 1.19). In the nested case-control analysis, participants with probable Alzheimer's disease had a lower risk of subsequent cancer (0.39, 0.26 to 0.58) than reference participants.

Bias, confounding, and other reasons for caution

As in any longitudinal study, participants with long follow-up represent a select population, and this should be kept in mind when interpreting our results.

Generalisability to other populations

The participants in our study were predominantly white.

Study funding/potential competing interests

The study was funded by a Veterans' Administration career development award (JAD). The Framingham Study is supported by grants from the National Institutes of Health. We have no competing interests.

Association between history of cancer at examination 20 (baseline) and incident dementia in Framingham Heart Study, after adjustment

	No of cancers		Hazard ratio (95% CI)*		
				Alzheimer's disease	
Model 1 (n=1274)†	At baseline	Incident cases	Any dementia (n=322)	Possible (n=256)	Probable (n=220)
All‡	175	247	0.83 (0.63 to 1.10)	0.81 (0.59 to 1.11)	0.67 (0.47 to 0.97)
Smoking related	54	96	0.79 (0.45 to 1.39)	0.62 (0.31 to 1.26)	0.26 (0.08 to 0.82)
Non-smoking related	127	177	0.84 (0.62 to 1.13)	0.87 (0.62 to 1.21)	0.82 (0.57 to 1.19)

*Calculated using Cox proportional hazards modelling.
†Adjusted for age, sex, smoking, and incident cancer.
‡Does not include non-melanoma skin cancers.

Patient safety in developing countries: retrospective estimation of scale and nature of harm to patients in hospital

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Cite this as: *BMJ* 2012;344:e832
doi: 10.1136/bmj.e832

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;344:e832

STUDY QUESTION

In developing and transitional economies, what is the frequency and nature of harm to patients admitted to hospital that can be attributed to their healthcare rather than their disease?

SUMMARY ANSWER

About 8% of admissions to hospital in eight countries were associated with at least one adverse event linked to the patient, of which 83% were judged preventable and 30% were associated with death.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Harm from healthcare in patients in hospital, as measured by adverse events, has been reported for developed countries. The same methods have not been applied to reporting from developing and transitional countries. Although in this study the adverse event rates were similar to those in developed countries, their preventability and associated mortality were considerably higher.

Participants and setting

A convenience sample of 28 hospitals from Egypt, Jordan, Kenya, Morocco, Tunisia, South Africa, Sudan, and Yemen was obtained with assistance from the Eastern Mediterranean and African Regional Offices of the World Health Organization and the Ministries of Health in each country. The study was performed under the auspices of WHO Patient Safety as a response to World Health Assembly resolution WHAA55.

Design, size, and duration

15 548 patient records were randomly selected from 26 hospitals in eight countries from the Middle East and Africa and subject to a two stage retrospective review for the presence of adverse events, by previously published methods. Records that were screened positive for an adverse event were then further reviewed to determine the preventability and nature of the patient injury.

Primary outcome

The primary outcomes were the detection of an adverse event by review of the medical record and the recorded outcome of the patient.

Main results and the role of chance

Of the 15 548 records reviewed, 8.2% showed at least one adverse event, with a range of 2.5% to 18.4% per country. In 83% the event was judged to be preventable, while about 30% were associated with the death of the patient. About 34% of the events were from therapeutic errors in relatively non-complex clinical situations. Most adverse events were contributed to by inadequate training and supervision of clinical staff or the failure to follow policies or protocols.

Bias, confounding, and other reasons for caution

We chose retrospective review of medical records because it was consistent with previously published large studies in developed countries. It depends on the adequacy of the medical record, the training of reviewers, and the inherent effects of retrospective review. In addition, the logistical issues in this study allowed only a convenience sample of hospitals in each of the countries. These factors suggest that our estimates would be an under-reporting of the adverse event rate but are probably accurate about the nature of detected adverse events.

Generalisability to other populations

The study shows that adverse events in patients in hospital are a major source of morbidity and mortality in developing and transitional countries and hence a serious public health problem, as they are in developed healthcare systems. Results varied widely between countries, however, and limitations acknowledged above suggest that the reported adverse event rate might be an underestimate and that further studies will be needed to more precisely quantify the scale of harm in each country and to inform future solutions.

Study funding/potential competing interests

This study was funded by WHO Patient Safety, the Eastern Mediterranean and African regional offices of WHO, and health ministries in Egypt, Jordan, Kenya, Morocco, Tunisia, South Africa, Sudan, and Yemen.

Adverse event rate and preventability in patients admitted to hospital in developing countries

Country	No of hospitals	No of records reviewed	Adverse event rate/100 admissions (95% CI)	% preventability (95% CI)
A	3	1358	6.0 (4.7 to 7.3)	72.5 (62.8 to 82.2)
B	5	3769	2.5 (2.0 to 2.9)	83.3 (75.7 to 90.9)
C	2	1938	14.5 (12.9 to 16.1)	76.6 (71.6 to 81.6)
D	2	984	14.8 (12.6 to 17.0)	85.6 (79.9 to 91.3)
E	2	931	8.2 (6.4 to 10.0)	55.1 (43.9 to 66.3)
F	6	3977	5.5 (4.8 to 6.2)	84.0 (79.1 to 88.9)
G	2	930	8.3 (6.5 to 10.1)	85.7 (77.9 to 93.5)
H	4	1661	18.4 (16.5 to 20.3)	92.8 (89.9 to 95.7)
Total	26	15 548	8.2	83.0

Trends in socioeconomic inequalities in risk of sudden infant death syndrome, other causes of infant mortality, and stillbirth in Scotland: population based study

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Cite this as: *BMJ* 2012;344:e1552
doi: 10.1136/bmj.e1552

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;344:e1552

STUDY QUESTION

How did the relation between socioeconomic deprivation and the risk of sudden infant death syndrome change from 1985 to 2008 and were comparable changes observed for other types of postneonatal infant death, neonatal death, or stillbirth?

SUMMARY ANSWER

There was a sharp decline in the rate of sudden infant death syndrome among women living in areas of low socioeconomic deprivation between 1990 and 1993. Among women living in areas of high socioeconomic deprivation, there was a much slower decline between 1992 and 2004. This led to a transient but marked increase in relative disparity for sudden infant death syndrome, which was not observed for other causes of postneonatal infant death, neonatal death, or stillbirth.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Sudden infant death syndrome is strongly related to prone sleeping position and rates fell dramatically in the 1990s associated with the "Back to Sleep" campaign. The decline was of later onset and was slower among women living in areas of high deprivation, leading to increased relative health disparity.

Participants and setting

We studied nationally collected data from Scotland, 1985-2008. We included singleton births of infants weighing >500 g and born at 28-43 weeks' gestation.

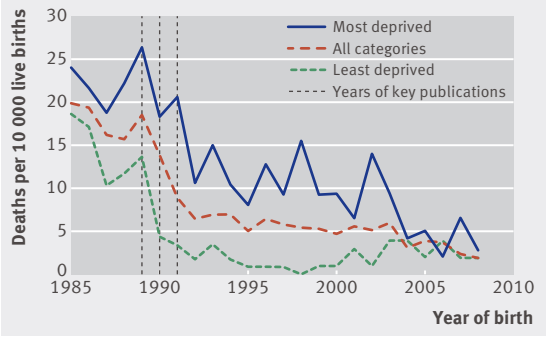
Design, size, and duration

We conducted a retrospective cohort study using records from 1 386 967 eligible births. The primary exposure was the socioeconomic deprivation category of the woman's area of residence. The primary outcome was sudden infant death syndrome. Secondary outcomes were other causes of postneonatal infant death, neonatal death, and stillbirth. We compared associations across four epochs of six years: 1985-90, 1991-6, 1997-2002, and 2003-8. We adjusted analyses for maternal age, height, parity, marital status, and hospital throughput and maternal smoking status when available (from 1992 onwards).

Main results and the role of chance

Among women living in areas of low deprivation, the decline in rates of sudden infant death syndrome started among infants born in 1990 and continued to fall sharply until 1993. Among women living in areas of high deprivation, the decline started among infants born in 1992 and continued to fall over the next 10-15 years. The unadjusted odds ratios for sudden infant death syndrome across the range of deprivation scale rose from about 2.0 in 1985-90, to 7.5 in 1991-6, and 9.5 in 1997-2002. Furthermore, multivariate analysis showed no independent association between deprivation and the risk of sudden infant death syndrome in 1985-90, but about a fourfold risk after adjustment for maternal characteristics in the next 12 years. The decline in the rate of sudden infant death syndrome among women living in areas of low deprivation preceded the "Back to Sleep" campaign, probably reflecting dissemination of research findings in the press. These changes were specific to sudden infant death syndrome. Although rates of other causes of postneonatal infant death, neonatal death, and stillbirth were related to deprivation, all these associations remained relatively constant over the same period.

Rates of postneonatal infant death from sudden infant death syndrome in relation to year of birth



Bias, confounding, and other reasons for caution

We adjusted for several maternal characteristics, but maternal smoking is an important potential confounder and this was available only from 1992 onwards. The interaction between epoch and deprivation, however, remained significant when we adjusted for smoking using data from 1992 onwards.

Generalisability to other populations

Our results are probably widely generalisable: a dramatic fall in the rate of SIDS was observed in many high income countries in the 1990s.

Study funding/potential competing interests

The study was supported by the NIHR Cambridge Comprehensive Biomedical Research Centre. DP was funded by an MRC clinical training fellowship.