RESEARCH

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THIS WEEK'S RESEARCH QUESTIONS

Leap in surgery for obesity

No one needs reminding what a big issue obesity is. The NHS (and the independent sector) is taking the problem seriously, judging by the results of Elaine Burns and colleagues' observational population cohort study on the provision of surgery for obesity (p 546).

The number of bariatric surgery procedures carried out in England increased tenfold in eight years—from 238 in 2000-1 to 2543 in 2007-8—with the proportion performed using minimally invasive laparoscopic techniques increasing from 28% to 74.5%. This increase didn't have any effect on safety though: there was no variation over the study period in postoperative mortality, mortality at one year, or readmissions.

The authors suggest that the number of procedures could well continue to increase. Coauthor Omar Faiz told Associated Press: "We don't know whether we've seen the summit of the peak, but the trend still looks to be going upwards" (http://bit.ly/aVHM3S).

LIFE IN VIEW/SPL

Oral bisphosphonates and risk of oesophageal cancer

DAVID M MARTIN/SPL

Hot on the heels of the recent meta-analysis by Mark Bolland and colleagues on the cardiovascular risks associated with taking calcium supplements (*BMJ* 2010; 341:c3691) comes Jane Green and colleagues' study about the risk of cancer when taking oral bisphosphonates (p 545). This nested case-control analysis of 6 million people in the UK General Practice Research Database—including nearly 3000 people aged 40 or older with oesophageal cancer, around 2000 with gastric cancer, and more than 10 000 with colorectal cancer—found that those prescribed oral bisphosphonates 10 or more times, or for about five years, had a significantly raised relative risk of oesophageal cancer. In Europe or the United States this equates to an increase in cancer incidence from about one case per 1000 population over five years to about two cases per 1000 people with five years' use of oral bisphosphonates at age 60-79.

What should patients wanting to avoid or treat osteoporosis make of such studies? Editorialist Diane Wysowski argues that this latest evidence on oral bisphosphonates is inconclusive and that any risk of cancer must be small, but gives practical advice on minimising oesophageal irritation from these pills (p 516).

Eat your greens

Patrice Carter and colleagues' systematic review of the effects of fruit and vegetables on incidence of type 2 diabetes looked at six eligible prospective cohort studies that assessed the diet of more than 220 000 adults (p 543). Increased consumption of green leafy vegetables was associated with a significantly lower risk of diabetes, but no link was found with eating more fruit or (unspecified) vegetables, or both.

In the linked editorial Jim Mann and Dagfinn Aune highlight the authors' recommendation that an extra portion and a half of spinach or other greens a day can cut the risk of diabetes by 14%, independently of any effect of weight loss (p 514). But they are worried that this message is too narrow and might undermine efforts to get everyone eating five portions of fruit and veg a day.

RESEARCH ONLINE: For this and other new research articles see http://www.bmj.com/channels/research.dtl

Isoniazid resistance and death from tuberculous meningitis

In this retrospective cohort study, Christopher Vinnard and colleagues looked at the relation between isoniazid resistance and subsequent death in patients with tuberculous meningitis, the most devastating form of tuberculosis (doi:10.1136/bmj.c4451). Isoniazid is the only first line antituberculous drug that has bactericidal activity throughout treatment and freely penetrates the blood-brain barrier, properties that are relevant for clinical cure in other types of bacterial meningitis. Clinicians therefore suspected that isoniazid resistance could affect the outcome of tuberculous meningitis to an extent not seen in pulmonary tuberculosis.

This assessment, which included 1896 patients treated for an initial episode of tuberculous meningitis in the United States, did indeed show an association between initial isoniazid resistance and subsequent death in those with cerebrospinal fluid cultures positive for *Mycobacterium tuberculosis*.

In an accompanying editorial, Bjørn Blomberg and Nina Langeland say that the findings emphasise the importance of actions to contain drug resistance, firstly by prudent use of antituberculous drugs (doi:10.1136/bmj.c4677).

A.DOWSETT,HPA/SPL

Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis

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EDITORIAL by Mann and Aune

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STUDY QUESTION

Is increased consumption of fruit and vegetables associated with a reduction in the risk of developing type 2 diabetes?

SUMMARY ANSWER

Increased consumption of green leafy vegetables is associated with a significant reduction in risk of type 2 diabetes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The prevalence of type 2 diabetes is increasing dramatically across the world. High intakes of fruit and vegetables have a role in the prevention of cancer and cardiovascular disease, and modelling studies have suggested that lifestyle changes can help in the prevention of type 2 diabetes. Though summary estimates showed no significant benefits of increased consumption of fruit, vegetables, or fruit and vegetables combined, there was a specific benefit with a higher intake of green leafy vegetables in the diet.

Selection criteria for studies

Medline, Embase, CINAHL, British Nursing Index (BNI), and the Cochrane Library were searched for medical subject headings and keywords on diabetes, prediabetes, fruit, and vegetables. We sought expert opinion, checked references, and contacted authors of relevant articles. Included studies were prospective cohort studies with an individual measure of intake of either fruit, vegetables, or fruit and vegetables, that assessed development of type 2 diabetes, and provided associated relative risks or hazard ratios.

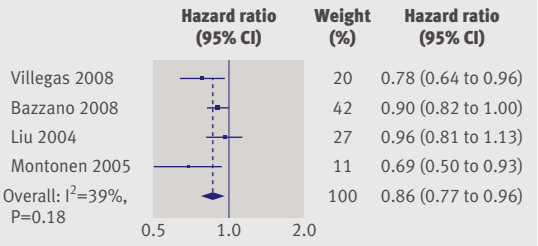
Primary outcome

Combined summary estimates of risk.

Main results and role of chance

Six studies met all inclusion criteria. The combined population included 223 512 participants aged 30-74. The median study length was 13.4 years (range 4.6-23). Only two studies included men. Four of the studies also included separate data on the intake of green leafy vegetables. Combined summary estimates showed no significant benefit for increasing consumption of fruit (hazard ratio 0.93, 95% confidence interval 0.83 to 1.01, P=0.27), vegetables (0.91, 0.76 to 1.09, P=0.32), or fruit and vegetables combined (1.00, 0.92 to 1.09, P=0.97). Combined summary estimates showed a significant benefit for the increased consumption of green leafy vegetables (0.86, 0.77 to 0.96, P=0.01).

HAZARD RATIO FOR TYPE 2 DIABETES IN THOSE WITH HIGHEST VERSUS LOWEST INTAKE OF GREEN LEAFY VEGETABLES



Bias, confounding, and other reasons for caution

As there was significant heterogeneity between the studies, we carried out a sensitivity analysis. We examined quality of study, sex, length of follow-up, location, and different fractions of intake as potential sources of bias. There were no significant interactions between the variables, thus the heterogeneity between studies remained unexplained. We included the most fully adjusted hazard ratio presented in each article, though not all authors of the primary articles made the same adjustments, and the possibility remains that other variables were not accounted for that could have affected the overall results. The results should therefore be interpreted with caution.

Study funding/potential competing interests

PC is being funded for a PhD by the Cardiovascular Research Department, University of Leicester. All members of the research team are either employees of the University of Leicester or the University Hospitals of Leicester NHS Trust. We acknowledge the ongoing support from NIHR-CLAHRC. KK and MJD have received grants from the National Institute of Health Research (NIHR) for studies on the prevention of type 2 diabetes.

BMJ pico: advice to authors

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CME

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EDITORIAL by Carcillo

Choice of fluids for resuscitation in children with severe infection and shock: systematic review

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STUDY QUESTIONS

Should crystalloids or colloids be used for fluid resuscitation in children with severe infections and shock, and are the current guidelines supported by evidence from clinical trials?

SUMMARY ANSWER

The current evidence for choice of fluids for resuscitation in children with severe infections and shock is weak and not robust enough to make any definitive recommendations.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Fluid resuscitation with colloids or crystalloids results in overall similar survival in adults. Use of crystalloids, however, results in better survival in patients with gastroenteritis and adults with traumatic conditions but equipoise remains in those with sepsis. There is some weak, low quality evidence that volume expansion with colloids could result in better survival than crystalloids in children with certain severe infections.

Selection criteria for studies

We searched Medline (1950-2008), the Cochrane Library, Embase (1980-2008), and reference lists of relevant papers. We included published studies in children aged >1 month to ≤12 years that compared fluid resuscitation with any colloid versus crystalloid in any infectious disease. In all studies fluid was given as a bolus. Trials in gastroenteritis, burns, and trauma were excluded. Controlled trials, quasi-randomised trials, cohort studies, and randomised controlled trials were included. All outcomes reported were included.

Primary outcomes

Outcomes of interest were efficacy in the treatment of shock, mortality, and incidence of adverse events.

Main results and role of chance

Nine trials fulfilled criteria and were included. Eight studies compared crystalloids with colloids, and one compared colloid with colloid. All trials were conducted in resource poor settings and predominantly included patients with malaria or dengue haemorrhagic shock. None of the trials had mortality as a definitive outcome. Three out of the six studies that reported at least one death showed better survival in children resuscitated with colloids compared with crystalloids, though we did not calculate a combined summary estimate because the trials were clinically heterogeneous. No significant differences were found in recovery from shock in patients resuscitated with colloids or crystalloids in various severe infections except in dengue shock, where colloids were found to be superior to crystalloids. Pulmonary oedema, unrelated to the intervention, was reported in two of 200 (1%) children who received saline. No other incidences of pulmonary oedema were reported. Febrile or allergic reactions were reported in 16/263 (6%) children who received dextran, 1/191(0.5%) who received hydroxyethyl starch, and 6/100 (6%) who received gelatins, but none in those who received human albumin solution.

Bias, confounding, and other reasons for caution

Studies contributing most data on mortality had some methodological limitations (small sample size, no calculation of sample size) so caution is recommended when interpreting the results on mortality as the trend seen could be caused by chance alone. The review was limited by inclusion of only published studies.

Study funding/potential competing interests

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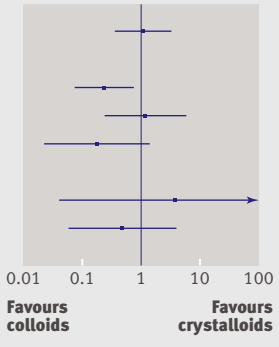
MORTALITY IN CHILDREN RESUSCITATED WITH COLLOIDS OR CRYSTALLOIDS

Study or subgroup	Events/total: Colloids	Events/total: Crystalloids	Adequate sequence generation	Peto fixed odds ratio (95% CI)
Sepsis				
Upadhyaya 2005[45]	9/29	9/31	Yes	1.1 (0.4 to 3.3)
Malaria				
Maitland 2005[38]	2/56	11/61	Yes	0.23 (0.07 to 0.74)
Maitland 2005[39]	4/23	3/20	Yes	1.2 (0.24 to 5.9)
Maitland 2003[37]	0/20	4/32	No	0.18 (0.02 to 1.4)
Dengue				
Wills 2005[43]	1/384	0/128	Yes	3.8 (0.04 to 350)
Cifra 2003[44]	1/11	3/16	No	0.48 (0.06 to 4.0)



CME

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EDITORIAL by Wysowski

Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within UK primary care cohort

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STUDY QUESTION Test of a prior hypothesis: does use of oral bisphosphonates increase the risk of oesophageal cancer?

SUMMARY ANSWER In a large UK primary care cohort, having 10 or more prescriptions for oral bisphosphonates, or prescriptions over about five years, was associated with a doubling of risk for oesophageal cancer, but no increased risk of cancers of the stomach and colorectum.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Oral bisphosphonates are known to cause oesophageal irritation and have been linked in case reports to a possible increased risk in oesophageal cancer. People prescribed oral bisphosphonates 10 or more times, or for about five years, had a significantly elevated relative risk of oesophageal cancer.

Participants and setting

We included 2954 men and women aged 40 years or over with oesophageal cancer, 2018 with gastric cancer, and 10 641 with colorectal cancer identified in the UK General Practice Research Database (GPRD), plus five controls per case matched for age, sex, general practice, and observation period.

Design, size, and duration

This was a nested case-control analysis within a UK primary care cohort of 6 million people, with prospectively recorded data on bisphosphonate prescriptions and a mean study observation period of 7.5 years.

Primary outcome(s), risks, exposures

The primary outcome was incident invasive cancer of the oesophagus, stomach, or colorectum. We used conditional logistic regression to estimate relative risks and 95% confidence intervals for gastrointestinal cancers in relation to prospectively collected information on previous prescription of bisphosphonates, with adjustment for smoking, alcohol, and body mass index.

Main results and the role of chance

Incidence of oesophageal cancer was significantly increased in people with 10 or more prescriptions for oral bisphosphonates (see table). The relative risk for oesophageal cancer in those with about five years' use versus no prescription was 2.24 (95% confidence interval 1.47 to 3.43). We found no significant difference in risk of oesophageal cancer by bisphosphonate type, and bisphosphonate associated risk of oesophageal cancer did not vary significantly by age, sex, smoking, alcohol, or body mass index; by diagnosis of osteoporosis, fracture, or upper gastrointestinal disease; or by prescription of acid suppressants, non-steroidal anti-inflammatory drugs, or corticosteroids. Cancers of the stomach and colorectum, included for comparison, were not associated with bisphosphonate prescription. In Europe and North America, the incidence of oesophageal cancer at age 60-79 is typically 1 per 1000 population over five years and is estimated to increase to about 2 per 1000 with five years' use of oral bisphosphonates.

Bias, confounding, and other reasons for caution

Information on exposure and potential confounders was collected prospectively, avoiding reporting bias. We adjusted for known risk factors for oesophageal cancer (smoking, alcohol intake, and body mass index) to minimise potential confounding by these factors. The possibility that the associations observed reflect other, unknown, factors that are linked both to prolonged use of bisphosphonates and to increased risk of oesophageal cancer cannot be excluded. The results were similar when restricted to fatal cases, meaning that investigation bias is unlikely to explain the association of oesophageal cancer with prolonged prescribing of bisphosphonates. The specificity of the association for oesophageal cancer argues against methodological problems in the selection of cases and controls or in the analysis.

Generalisability to other populations

The GPRD includes 7% of the UK population, and the results should be broadly generalisable.

Study funding/potential competing interests

The Medical Research Council funded access to the GPRD dataset for this study, and Cancer Research UK provided further study funding.

RELATIVE RISKS FOR INCIDENT GASTROINTESTINAL CANCER AT SPECIFIED SITES, IN RELATION TO PRESCRIPTION OF ORAL BISPHOSPHONATES

	Oesophagus		Stomach		Colorectum	
Oral bisphosphonates	No of cases/ controls	Relative risk* (95% CI)	No of cases/ controls	Relative risk* (95% CI)	No of cases/ controls	Relative risk* (95% CI)
Not prescribed	2864/14 376	1.00	1969/9737	1.00	10 365/51 467	1.00
Prescribed	90/345	1.30 (1.02 to 1.66)	49/270	0.87 (0.64 to 1.19)	276/1555	0.87 (0.77 to 1.00)
1-9 prescriptions	40/214	0.93 (0.66 to 1.31)	28/160	0.84 (0.56 to 1.27)	164/880	0.92 (0.77 to 1.09)
≥10 prescriptions	50/131	1.93 (1.37 to 2.70)	21/110	0.91 (0.57 to 1.47)	112/675	0.82 (0.67 to 1.00)

*Adjusted for smoking status, alcohol intake, and body mass index.

Response on bmj.com

"I did a rapid search of my practice computer, which has been used for consultations for more than 20 years. I searched the patients past, present, and dead and found that 11% of women over the age of 50 had had at least one prescription for oral bisphosponates in that time."

George R Cook, general practitioner, Grassendale Medical Practice, Liverpool

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Introduction of laparoscopic bariatric surgery in England: observational population cohort study

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STUDY QUESTION

What are the national trends in the provision of bariatric surgery and the factors influencing outcome after such surgery in England?

SUMMARY ANSWER

Bariatric surgery has been introduced safely, and its provision has increased exponentially in England over the past 8 years.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Obesity is an increasing problem, and bariatric surgery is recommended for morbidly obese patients and overweight patients with coexisting disease who could benefit from weight loss. Laparoscopic bariatric surgery seems to have been introduced into the English NHS in a safe manner.

Participants and setting

We included all elective patients admitted for bariatric surgery to NHS hospitals in England between April 2000 and April 2008, with data extracted from the Hospital Episode Statistics database.

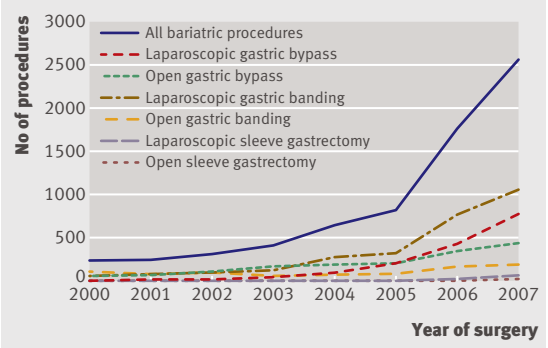
Design, size, and duration

This observational study included 6953 patients who had bariatric surgery over an eight year period. The main outcome measures examined were postoperative mortality, unplanned readmission, and length of stay in hospital.

Main results

Of the 6953 bariatric procedures carried out, 3649 were gastric banding, 3191 were gastric bypass, and 113 were sleeve gastrectomy procedures. Overall, 0.3% (19/6953) of patients died within 30 days of surgery. The median duration of in-hospital stay was 3 (interquartile range 2-6) days. An unplanned readmission to hospital within 28 days of surgery occurred in 8% (556/6953) of procedures. We found a marked increase in the number of procedures carried out over the study period and a significant rise in the number of patients selected for laparoscopy (27.7% (66/238) laparoscopic procedures in 2000 compared with 74.5% (1894/2543) in 2007). We found no variation in postoperative mortality (P=0.618), mortality at one year (P=0.614), or readmissions (P=0.817) over the study period, despite the exponential increase in use of minimal access surgery. Hospital stay in patients who had a gastric bypass procedure was greater than in those who had gastric banding (median length of stay, 5 (3-7) days (n=3191) for gastric bypass *v* 2 (1-3) days (n=3649) for gastric banding; P<0.001), and readmission rates postoperatively were higher (28 day readmission 9.7% (308/3191) for gastric bypass *v* 6.4% (232/3649) for gastric banding; P<0.001). The risk of postoperative (30 day in-hospital) mortality was lower for patients who had laparoscopic banding than for those who had laparoscopic bypass (odds ratio 0.10, 95% confidence interval 0.01 to 0.79; P=0.029). Gastric bypass and increasing comorbid status were predictors of higher postoperative mortality. Male sex, gastric bypass and sleeve gastrectomy procedure, open approach, increasing age, increasing comorbid status, lower socioeconomic status, and lower trust and consultant volume were predictors of prolonged length of stay.

CHANGES IN TYPE OF OPERATION OVER TIME AND TRENDS IN UPTAKE OF LAPAROSCOPIC SURGERY



Bias, confounding, and other reasons for caution

This was a retrospective study that used an administrative dataset. Confounding factors such as body mass index are not available from this dataset. Outcome measures evaluated were limited to postoperative mortality, readmission, and duration of in-hospital stay. Postoperative weight loss was not examined.

Generalisability to other populations

Widespread adoption of bariatric surgery is under way across most developed countries. Safe dissemination of this surgery has been shown in England, including the use of the minimal access approach, but whether international experiences are similar is unclear.

Study funding/potential competing interests

The Dr Foster Unit at Imperial is affiliated with the Centre for Patient Safety and Service Quality at Imperial College Healthcare NHS Trust, which is funded by the National Institute of Health Research. We are grateful for support from the NIHR Biomedical Research Centre funding scheme. The unit is largely funded by a research grant from Dr Foster Intelligence (an independent health service research organisation).

Response on bmj.com

"Despite increased spending on medical and surgical NHS interventions, rates of obesity continue to increase inexorably. Around 25% of adults in England are now considered to be obese, with a BMI of 30 or greater. The failure of medical treatments for obesity is further illustrated by the withdrawal of rimonabant and sibutramine because of concerns about their safety." Azeem Majeed, professor of primary care, Imperial College London

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