RESEARCH

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SATURN STILLS/SPL

THIS WEEK'S RESEARCH QUESTIONS

237 Does intensive dietary advice improve glycaemic control in patients with poorly controlled type 2 diabetes?

238 Is access to renal transplantation consistent across the UK for patients with end stage kidney disease?

239 What is the efficacy of quadrivalent human papillomavirus vaccine in preventing low grade cervical and anogenital lesions over four years?

240 Does the risk of neonatal death at term vary in relation to time and day of birth?

241 Could the tendency of small trials to report larger treatment effects distort the results of meta-analyses in studies of osteoarthritis?

Time of birth, time of death...

A labour ward is a 24 hour environment, but the results of a study in this week's journal suggest that it may not be consistently safe around the clock. In a retrospective cohort study, Dharmintra Pasupathy and colleagues looked at whether the risk of neonatal death varied according to time and day of birth among just over a million term babies born in Scotland between 1985 and 2004. After adjusting for several possible confounders, they found that babies born outside of the hours 09.00-17.00 Monday to Friday were more likely to die around the time of birth than those born during "office hours." Out of hours deliveries were responsible for an additional one to two extra deaths per 10 000 live births, with anoxia being the main cause of mortality (p 240).

SAMUEL ASHFIELD/SPL

Although the study was unable to determine the cause of the small but significant difference, it raised concerns that staff issues were at the heart of the problem—reflected by responses to the paper on bmj.com (http://bit.ly/a57gT4). Malcolm John Dickson, a consultant obstetrician/gynaecologist from Rochdale Infirmary, blamed the falling number of "flying hours" required to be senior resident on call for a labour ward. Monica Tolofari, a consultant midwife at Heart of Birmingham teaching PCT, asked how NHS maternity services can respond positively while considering the financial implications of changing shift patterns. For Pauline M Hull, editor of electivecesarean.com, the findings suggested a benefit of knowing who will deliver your baby and when—providing a retort to those who criticise as irresponsible the "convenience" factor of maternal request caesarean delivery.

Twenty-four hour safety in the labour ward is a hot topic outside the UK too. The Netherlands lags behind in the steady decrease in perinatal mortality in Western countries, and in 2008 health minister Ab Klink installed a steering committee on pregnancy and birth to come up with a solution. One of the key recommendations of their report in December 2009 (http://bit.ly/dzfxQe) was that gynaecologists and paramedics should be available for obstetric and perinatal care 24 hours, 7 days a week. When called, they must be able to reach the hospital within 15 minutes. Klink has pledged that extra funds will be provided where necessary to reach the target of decreasing perinatal mortality by 50%.

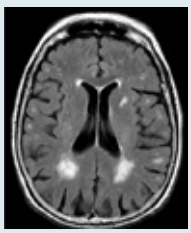
David Field and Lucy Smith conclude in their editorial that women should be informed about the risks and benefits of giving birth in different settings, even though the reasons for these variations remain unclear (p 210).

Access to kidney transplant

LIFE IN VIEW/SPL

As a report from the King's Fund this week calls on the NHS to reduce variation in clinical practice (p 213), here's yet more evidence that health care in the UK varies importantly from place to place. Rommel Ravanan and colleagues assessed equity in access to kidney transplantation at 65 renal centres in the UK (p 238). They found significant variability between centres, both for the time taken to activate patients on the waiting list and the time to receive a transplant, which couldn't be explained simply by case mix. Inter-centre differences were more pronounced for access to kidneys obtained from live donors and after cardiac death, sources that are particularly likely to be affected by local practices and policies. The authors call for further research on whether the differences are due to variations in resources or whether certain centres are simply more organised.

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



Do white matter hyperintensities matter?

As magnetic resonance imaging has become widely available and practised, clinicians often have to deal with incidental discovery of white matter lesions that appear as hyperintensities on images. Several studies have assessed the relation between these findings and cerebrovascular problems, with partly conflicting results. Stéphanie Debette and H S Markus systematically reviewed and meta-analysed longitudinal studies that examined the association between white matter hyperintensities and risk of stroke, dementia, and death, in the general population and in hospitals. They found that white matter hyperintensities indicate an increased risk of stroke, dementia, and death when identified as part of diagnostic investigations and their appearance should prompt detailed screening for risk factors (doi:10.1136/bmj.c3666).

CME

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Nutritional intervention in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment—Lifestyle Over and Above Drugs in Diabetes (LOADD) study: randomised controlled trial

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EDITORIAL by Clifton

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Previous CME articles
- Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts (*BMJ* 2010;341:c3493)
- Faecal calprotectin for screening of patients with suspected inflammatory bowel disease (*BMJ* 2010;341:c3369)
- Method of attempted suicide as predictor of subsequent successful suicide (*BMJ* 2010;341:c3222)
- Novel approach to antibiotic prophylaxis in percutaneous endoscopic gastrostomy (*BMJ* 2010;341:c3115)
- Primary total hip arthroplasty versus hemiarthroplasty for displaced intracapsular hip fractures in older patients (*BMJ* 2010;340:c2332)

STUDY QUESTION

To what extent can intensive evidence based dietary advice influence glycaemic control and cardiovascular risk factors in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment?

SUMMARY ANSWER

Intensive evidence based dietary advice significantly improved glycaemic control and anthropometric measures in these patients.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The benefit of lifestyle modification in type 2 diabetes has not been established in those who remain hyperglycaemic despite maximum tolerated drug treatment. Nutritional treatment can benefit such patients, for whom treatment options are limited.

Design

This was a six month randomised controlled trial. Participants were randomised to intensive dietary advice in addition to usual medical surveillance or usual surveillance only. Dietary advice, based on the evidence based nutritional recommendations of the European Association for the Study of Diabetes, was individualised with consideration of participants' dietary preferences and socioeconomic circumstances.

Participants and setting

We recruited 93 people aged less than 70 with type 2 diabetes from the community. Their haemoglobin A_{1c} (HbA_{1c}) was more than 7% despite optimised drug treatments, and they had at least two of overweight or obesity, hypertension, and dyslipidaemia.

Primary outcome(s)

HbA_{1c} was the primary outcome. Secondary outcomes included measures of adiposity, blood pressure, and lipid profile.

Main results and the role of chance

The adjusted difference in HbA_{1c} between the intervention and control groups at six months was highly statistically significant, as were the decreases in body mass index and waist circumference. A decrease in saturated fat (−1.9% total energy, −3.3% to −0.6%, P=0.006) and an increase in protein (1.6% total energy, 0.04% to 3.1%; P=0.045) in the intervention group were the main differences in nutrient intake between the two groups.

Harms

No adverse events were reported.

Bias, confounding, and other reasons for caution

Participants in the intervention group may have increased their level of physical activity more than the control group did, despite both having standard advice about exercise.

Generalisability to other populations

The flexibility of current evidence based nutritional recommendations permit adaption to a range of dietary patterns and preferences, so the findings of our study are likely to be generalisable to other populations.

Study funding/potential competing interests

This study was funded by the Health Research Council of New Zealand and the Southern Trust, New Zealand.

Trial registration number

Clinical trials NCT00124553.

PRIMARY AND SECONDARY END POINTS (MEAN (SD)) AT BASELINE AND SIX MONTHS AND ADJUSTED DIFFERENCES BETWEEN GROUPS

	Dietary intervention (n=45)		Control (n=48)			
Measures	Baseline	6 months	Baseline	6 months	Difference* (95% CI)	P value*
HbA_{1c} (%)	8.9 (1.4)	8.4 (1.0)	8.6 (1.3)	8.6 (1.2)	−0.4 (−0.7 to −0.1)	0.007
Glucose (mmol/l)	9.0 (2.6)	8.1 (2.2)	8.3 (2.4)	8.3 (2.9)	−0.6 (−1.5 to 0.3)	0.181
Body mass index†	35.1 (6.1)	34.3 (5.8)	34.2 (6.0)	34.0 (5.9)	−0.5 (−0.9 to −0.1)	0.026
Waist circumference (cm)	111.4 (13.7)	108.9 (13.6)	108.0 (12.8)	107.4 (12.7)	−1.6 (−2.7 to −0.5)	0.005
Systolic blood pressure (mm Hg)	131.9 (15.8)	127.8 (15.6)	131.7 (16.1)	129.2 (16.4)	−1.4 (−6.1 to 3.2)	0.536
Total cholesterol (mmol/l)	4.35 (0.93)	4.11 (0.97)	3.93 (0.84)	3.87 (0.94)	−0.14 (−0.38 to 0.10)	0.248
Triglycerides (mmol/l)	1.71 (0.83)	1.67 (1.04)	1.61 (0.65)	1.59 (0.68)	0.01 (−0.26 to 0.28)	0.933

*Adjusted for age, sex, and baseline measurements.
†Calculated as weight in kilograms divided by square of height in metres.

Variation between centres in access to renal transplantation in UK: longitudinal cohort study

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STUDY QUESTION

Does equity exist in access to renal transplantation in the UK after adjustment for case mix in incident patients with end stage renal disease?

SUMMARY ANSWER

Significant variation exists in access to renal transplantation between centres within the UK that cannot be explained by differences in case mix.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Patient specific factors and patient independent factors such as insurance status have been shown to affect access to renal transplantation in other healthcare systems. Variations in access to renal transplantation exist in the UK, even after adjustment for case mix.

Participants and setting

We considered for inclusion all patients under 65 years old starting renal replacement treatment between 1 January 2003 and 31 December 2005 in centres returning data to the UK Renal Registry. Information on date of starting renal replacement treatment and relevant patient specific data including age (grouped as 18-29, 30-39, 40-49, 50-59, and ≥60 years), sex, ethnicity (white, non-white, and missing), and primary renal diagnosis (diabetes, non-diabetes, and missing) came from the UK Renal Registry; the date of activation on the waiting list, date of transplantation, or both came from the UK Transplant Registry at NHS Blood and Transplant.

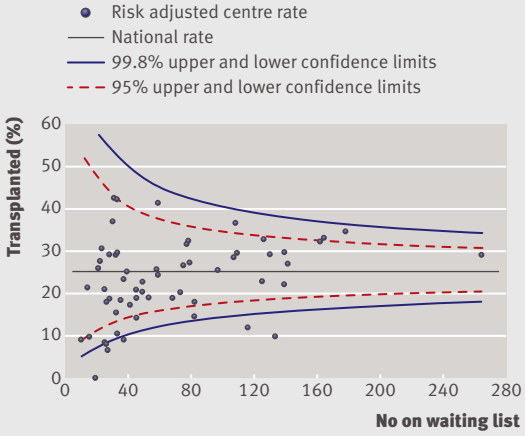
Design, size, and duration

We followed up a final cohort of patients (n=7863) who satisfied the inclusion criteria in a longitudinal fashion. We followed all patients to 31 December 2007 or until placed on the waiting list for a kidney transplant or kidney plus pancreas transplant. To estimate the proportion of patients on the waiting list who received a transplant within two years of listing, we followed patients placed on the waiting list before 31 December 2006 (n=4061) until 31 December 2008.

Main results and the role of chance

We found that recipients' age, ethnicity, and primary renal diagnosis were associated with the likelihood of accessing the waiting list or receiving a transplant. After adjustment for case mix, we found significant inter-centre variability in access to the waiting list (change in −2LogL=89.9, df=1, P<0.001), time to inclusion on the waiting list (change in −2LogL=247.4, df=64, P<0.001), receipt of a transplant from a donor after brain stem death (change in −2LogL=15.1, df=1, P=0.001), and receipt of a transplant from a donor after cardiac death or a living kidney donor (change in −2LogL=46.1, df=1, P<0.001).

PERCENTAGE OF PATIENTS RECEIVING TRANSPLANT FROM DONOR AFTER CARDIAC DEATH OR LIVING KIDNEY DONOR WITHIN TWO YEARS OF BEING REGISTERED FOR TRANSPLANTATION



Risk adjusted for effect of recipient's age, sex, ethnicity, and primary renal diagnosis.

Bias, confounding, and other reasons for caution

In the absence of comprehensive patient specific data permitting complete adjustment for case mix, our results should be interpreted with caution, as patient related factors other than those analysed as part of the study may be important in influencing access to renal transplantation. Even though our analysis adjusts for ethnicity over the entire study period, we could not adjust for the effect of all of the changes resulting from the change in the organ allocation scheme on centre specific transplant rates from donors after brain stem death before and after April 2006.

Generalisability to other populations

Centres' practice patterns determine the effectiveness and efficiency of the patients' pathway beginning with a diagnosis of end stage renal disease and progressing to renal transplantation. Differences in centres' practice result in variation in access to renal transplantation despite the "free at the point of delivery" healthcare model in the United Kingdom. Such variations are therefore possible in other populations of patients within the UK, as well as in other countries with different healthcare systems

Study funding/potential competing interests

We received no funding for the study.

CME

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Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial

The FUTURE I/II Study Group

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Members of the FUTURE I/II Study Group are listed in the full paper on bmj.com

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;341:c3493

STUDY QUESTION What is the prophylactic efficacy of the quadrivalent human papillomavirus (HPV) vaccine in preventing low grade cervical, vulvar, and vaginal intraepithelial neoplasias and condylomas (anogenital warts)?

SUMMARY ANSWER Quadrivalent vaccination (against HPV types 6, 11, 16, and 18) provided sustained protection against low grade lesions attributable to vaccine HPV types and substantially reduced the burden of diseases through 42 months of follow-up.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS The total disease burden of low grade anogenital lesions that is preventable by quadrivalent HPV vaccination has not been well elucidated. This study shows the vaccine provides strong and sustained protection for up to four years, by ≥96% against lesions attributable to HPV types 6, 11, 16, and 18 and by 30%-83% against lesions due to any HPV type.

EFFICACY OF QUADRIVALENT HPV VACCINE AGAINST LOW GRADE LESIONS RELATED TO HPV INFECTION

Lesion and related HPV type*	No of cases/No of subjects: Vaccine group	No of cases/No of subjects: Placebo group	Vaccine efficacy (% (95% CI))
Cervical intraepithelial neoplasia grade I			
Related to vaccine HPV types†:	7/7629	168/7632	96 (91 to 98)
HPV 6 or 11	0/6688	45/6619	100 (92 to 100)
HPV 16	6/6448	97/6257	94 (87 to 98)
HPV 18	1/7158	47/7092	98 (88 to 100)
Related to any HPV type‡	241/4616	346/4680	30 (17 to 41)
Vulvar intraepithelial neoplasia grade I			
Related to vaccine HPV types†:	0/7665	16/7669	100 (74 to 100)
HPV 6 or 11	0/6718	16/6647	100 (74 to 100)
HPV 16	0/6455	0/6269	N/A
HPV 18	0/7190	0/7119	N/A
Related to any HPV type‡	4/4689	16/4735	75 (22 to 94)
Vaginal intraepithelial neoplasia grade I			
Related to vaccine HPV types†:	0/7665	12/7669	100 (64 to 100)
HPV 6 or 11	0/6718	6/6647	100 (16 to 100)
HPV 16	0/6455	7/6269	100 (33 to 100)
HPV 18	0/7190	2/7119	100 (<0 to 100)
Related to any HPV type‡	**21/4689**	**41/4735**	**48 (10 to 71)**
Condyloma			
Related to vaccine HPV types†:	2/7665	190/7669	99 (96 to 100)
HPV 6 or 11	2/6718	186/6647	99 (96 to 100)
HPV 16	0/6455	23/6269	100 (83 to 100)
HPV 18	0/7190	11/7119	100 (61 to 100)
Related to any HPV type‡	29/4689	169/4735	83 (74 to 89)

*A diagnosed lesion with HPV DNA detected in tissue from same lesion
†Based on per protocol susceptible population (who received all 3 vaccinations; tested negative for vaccine HPV types (6, 11, 16, and 18) at day 1 and through month 7; and generally did not deviate from protocol. Case counting began after month 7
‡Based on generally HPV naive population (who received ≥1 vaccination; tested negative at day 1 for vaccine HPV types and for non-vaccine, high risk HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, and 59); and had any follow-up visit. Case counting began after day 1

Participants and setting

Women entered the FUTURE I and FUTURE II trials from primary care centres and university or hospital associated health centres in 24 countries and territories.

Design, size, and duration

Between December 2001 and May 2003, 17 622 women aged 16-26 years were enrolled. Subjects were randomised to three doses of quadrivalent HPV vaccine (for serotypes 6, 11, 16, 18) or placebo at day 1, month 2, and month 6. Major exclusion criteria were lifetime number of sexual partners (>4), history of abnormal cervical smear test results, and pregnancy. Detailed cervicovaginal examinations were performed at day 1, month 7, and at 6 month or 12 month follow-up intervals until month 48.

Main results and the role of chance

In the per protocol susceptible population, vaccine efficacy against lesions attributable to vaccine HPV types (6, 11, 16, and 18) was 96% for cervical intraepithelial neoplasia grade I (95% confidence interval 91% to 98%), 100% for both vulvar and vaginal intraepithelial neoplasia grade I (95% CIs 74% to 100%, 64% to 100% respectively), and 99% for condyloma (96% to 100%) (see table). Vaccine efficacy against any lesion (regardless of HPV type) in the generally HPV naive population was 30% (17% to 41%), 75% (22% to 94%), and 48% (10% to 71%) for cervical, vulvar, and vaginal intraepithelial neoplasia grade I, respectively, and 83% (74% to 89%) for condyloma.

Bias, confounding, and other reasons for caution

Limitations of the study include the fact that the generally HPV naive population was tested only for the presence of the four vaccine HPV types and 10 other prevalent HPV types related to cervical cancer. However, other HPV types may contribute to condylomas, and there are several uncommon HPV types that we did not test for (such as HPV 68 and 73) that are classified as oncogenic.

Generalisability to other populations

Although enrolment was limited to women with no more than four sexual partners in their lifetime, the study's generalisability probably remains high as the population studied was enrolled globally.

Study funding/potential competing interests

These studies were funded by Merck & Company. Many of the authors had financial links with or were employees of Merck & Company, and several had other financial links (see full paper on bmj.com for details).

Time of birth and risk of neonatal death at term: retrospective cohort study

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EDITORIAL by Field and Smith

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STUDY QUESTION Does the risk of neonatal death at term vary in relation to time and day of birth?

SUMMARY ANSWER Delivering outside the normal working week was associated with an increased risk of neonatal death from intrapartum anoxia.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Perinatal death from intrapartum anoxia at term is regarded as a sensitive measure of care during labour and delivery. About one in four deaths from intrapartum anoxia at term could have been prevented if all births had the same risk of this event as observed during the normal working week.

Participants and setting

Liveborn term singletons with cephalic presentation in Scotland. Perinatal deaths from congenital anomalies excluded. Final sample comprised 1 039 560 live births.

Design, size, and duration

This was a population based retrospective cohort study with data from the linked Scottish morbidity records, Stillbirth and Infant Death Survey, and birth certificate database of live births in Scotland, 1985-2004. Information on both the day and time of birth was used to classify the timing of birth into births between 0900 and 1700 Monday to Friday (working week), births between 1701 Monday to Friday and 0859 the following day, and births from 0900 at a weekend to 0859 the following day. Out of hours births were defined as all births at any time other than 0900-1700, Monday to Friday.

Main results and the role of chance

There were 539 neonatal deaths (5.2 per 10 000 live births, 95% confidence interval 4.8 to 5.6) in the study cohort. About half of these deaths were ascribed to intrapartum anoxia (n=273, 51%). The risk of neonatal death was 4.2 per 10 000 live births (3.5 to 5.0) during the working week and higher at all other times. This was explained by a significant excess risk of death from anoxia (unadjusted odds ratio 1.7, 95% confidence interval 1.3 to 2.3) and was similar in multivariable analysis (adjusted odds ratio 1.7, 95% confidence interval 1.2 to 2.3). The magnitude (adjusted odds ratio, 95% confidence interval) of the increased risk of anoxic death was similar for 1701-0859 Monday to Friday (1.6, 1.2 to 2.2) and the weekends (1.7, 1.2 to 2.5). Exclusion of elective caesarean deliveries attenuated the association between delivery out of hours and the risk of neonatal death from anoxia (1.5, 1.1 to 2.0). The attributable fraction of neonatal deaths associated with delivery out of hours was 26% (95% confidence interval 5% to 42%) for deaths from intrapartum anoxia.

Bias, confounding, and other reasons for caution

We adjusted for year of delivery; maternal age, parity, and height; socioeconomic deprivation; gestational age; birthweight centile; fetal sex; onset of labour; and hospital throughput. We accounted for changes in obstetric practice over time, hospital throughput, and the effect of operative delivery and induction of labour. Our findings could be a result of factors such as staffing, immediate availability of senior clinicians, and access to clinical facilities. We lacked data to evaluate the effect of any of these factors on the association observed, and our findings might reflect multiple characteristics of delivery out of hours.

Generalisability to other populations

The findings would apply to other countries with similar rates of neonatal death and access to obstetric health care.

Study funding/potential competing interests

DP was supported by the Medical Research Council and the Royal College of Obstetricians and Gynaecologists (Florence and William-Blair Bell Memorial Fellowship Fund) clinical research fellowship. His current affiliation is clinical lecturer in Maternal and Fetal Medicine in the Academic Department of Women's Health, King's College London.

CAUSE SPECIFIC NEONATAL DEATH BY DAY AND TIME OF BIRTH, SCOTLAND 1985-2004

		Incidence of neonatal death per 10 000 (95% CI)		
Day of week and time of birth	No (%) of live births	All cause	Anoxia	Not anoxia
Weekday, 0900-1700	287 545 (27.7)	4.2 (3.5 to 5.0)	1.7 (1.3 to 2.3)	2.5 (1.9 to 3.1)
Weekday, 1701-0859	491 025 (47.2)	5.5 (4.8 to 6.2)	2.9 (2.5 to 3.4)	2.6 (2.1 to 3.1)
Weekend, 0900-0859	260 990 (25.1)	5.7 (4.8 to 6.7)	3.1 (2.4 to 3.8)	2.6 (2.1 to 3.3)
All out of hours	752 015 (72.3)	5.6 (5.0 to 6.1)	3.0 (2.6 to 3.4)	2.6 (2.2 to 3.0)

Response on bmj.com

"Surely now is the time not to think about 24/7 resident consultant cover for labour wards, but to provide 24/7 consultant cover without argument and irrespective of cost. After all, babies are born 24/7. Anything less could well be regarded as a breach of care."
Malcolm John Dickson, consultant obstetrician and gynaecologist, Rochdale Infirmary, Lancashire.
To submit a rapid response, go to any article on bmj.com and select "Respond to this article"

Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study

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Study funding/potential competing interests
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STUDY QUESTION To what extent do small study effects affect results in clinical osteoarthritis research?

SUMMARY ANSWER I

n six out of 13 meta-analyses included, results were more beneficial in an analysis including all trials compared with an analysis restricted to large trials, or a prediction of treatment effects for large trials using meta-regression models.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Small study effects refer to a tendency of small trials to report larger treatment benefits than larger trials. Small study effects often affect results of meta-analyses in osteoarthritis research.

Selection criteria for studies

We studied 13 meta-analyses including 153 randomised controlled trials that compared therapeutic interventions with placebo or non-intervention control in terms of pain intensity reported by patients with osteoarthritis of the hip or knee. We compared estimated treatment benefits between large trials (with at least 100 patients per arm) and small trials; explored funnel plots supplemented with lines of predicted effects and contours of statistical significance; and used three approaches to estimate treatment effects: meta-analyses including all trials irrespective of sample size, meta-analyses restricted to large trials, and treatment effects predicted for large trials.

Primary outcome

Difference in treatment effect estimates between small and large trials.

Main results and role of chance

On average, treatment effects were more beneficial in small compared with large trials (difference in effect sizes, −0.21, 95% confidence interval −0.34 to −0.08, P=0.001). Depending on criteria used, six to eight funnel plots indicated the presence of small study effects. The figure shows examples of four funnel plots suggesting the presence of small study effects and two funnel plots without apparent asymmetry. In six of 13 meta-analyses, the overall pooled estimate including all trials suggested a clinically relevant, significant treatment benefit, whereas analyses restricted to large trials and predicted effects in large trials yielded smaller, non-significant estimates.

Bias, confounding, and other reasons for caution

Large trials tend to be of higher quality than small trials and the observed association between sample size and treatment effect could be confounded by methodological quality. Adjustment for intention to treat analyses suggested that problems with exclusions from the analysis after randomisation might contribute to the observed small study effects. We cannot exclude true clinical heterogeneity as an alternative explanation of small study effects.

EXAMPLES OF FUNNEL PLOTS TO DETERMINE SMALL STUDY EFFECTS