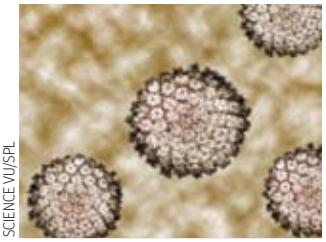
RESEARCH

The *BMJ* is an Open Access journal. We set no word limits on *BMJ* research articles, but they are abridged for print. The full text of each *BMJ* research article is freely available on bmj.com



SCIENCE VU/SPL

THIS WEEK'S RESEARCH QUESTIONS

1191 Can the specificity of a human papillomavirus test used in cervical screening be improved, without reducing its sensitivity?

1192 Are lateral wedge insoles better than flat control insoles for people with medial knee osteoarthritis?

1193 Does supplementation with L-arginine and antioxidant vitamins prevent pre-eclampsia in pregnant women at high risk?

1194 What is the association between dietary intake of calcium and risk of fracture and osteoporosis?

Nutritional supplements and pre-eclampsia

As a general medical journal the *BMJ* has published what might seem a surprisingly high number of rather specialised papers on the risks, natural history, and possible causes of pre-eclampsia. But given the condition's high burden of disease, we're pleased to keep receiving such submissions. Now Felipe Vadillo-Ortega and colleagues' three arm randomised controlled trial asks whether nutritional supplements with potential to improve placental haemodynamics might prevent pre-eclampsia in women at high risk (p 1193). They randomised pregnant women in Mexico to receive food bars containing either the amino acid L-arginine plus antioxidant vitamins, those vitamins alone, or placebo. The incidence of pre-eclampsia was significantly lower (P<0.001) in women randomised to L-arginine plus antioxidant vitamins compared with placebo (absolute risk reduction 0.17, 95% confidence interval 0.12 to 0.21).

Editorialists Liam Smeeth and David Williams point out that pre-eclampsia accounts for more than a quarter of maternal deaths in Latin America and agree on the need for a low cost intervention (p 1161). They discuss the pros and cons of this new trial, and conclude that its findings are important. But it's crucial, they say, that no more trials should be done until we have a rigorous systematic review of the numerous inconsistent strands of evidence relating to L-arginine and its possible effects on pre-eclampsia.

JACOB SILBERBERG/PANOS

Performance of HPV test used in screening for cervical cancer

The NHS screening programme has just started to use testing for human papillomavirus (HPV) DNA to triage women with borderline or low grade cervical abnormalities and reduce the need for unnecessary interventions and anxiety. As of April 2011, this approach is being rolled out in England (http://bit.ly/jQC0i9). But what is the best way to test for HPV DNA? To date, use of these tests has proved to be more sensitive than cervical cytology but not very specific, yielding a lot of false positives.

So Matejka Rebolj and colleagues did a systematic review, examining four randomised controlled trials of primary cervical screening using the widely used hybrid capture 2 test for HPV, to determine the test cutoffs that will optimise sensitivity, specificity, and positive predictive value (p 1191). Again, this is a rather specialised paper, but the *BMJ* published much of the earlier work on HPV triage in cervical screening, and we thought this paper was an important new brick in that wall. Its detailed findings will mostly interest those who design cervical screening programmes and run testing. But the overall message, that cervical screening is getting more reliable and effective and less invasive and unpleasant for women, should interest many *BMJ* readers.

Dietary calcium and risk of fracture

PASIEKA/SPL

Might increasing dietary intake of calcium help to protect older bones against osteoporosis and fractures? Previous evidence has led to uncertain conclusions, as reflected by the wide variety of daily calcium recommendations for individuals older than 50 (700 mg in the UK, 800 mg in Scandinavia, 1200 mg in the United States, and 1300 mg in Australia and New Zealand).

Eva Warensjö and colleagues attempted to clarify the association in a prospective longitudinal study of women in the Swedish Mammography Cohort (p 1194). They divided the results by quintiles of dietary calcium intake, with the middle quintile as the reference; women with the lowest levels of intake had an increased risk of fracture and osteoporosis, but the risk varied little between the other quintiles. The rate of hip fracture was even increased in those who consumed the most calcium.

Does this help to clarify what intake of calcium should be recommended? Although the investigators controlled for some important confounders—such as nulliparity, smoking, socioeconomic status, physical activity, nutrients other than calcium, educational level, and comorbidity—residual confounding is still possible, as in all observational studies, so some uncertainty remains. However, the findings are useful in suggesting that increasing calcium intake may be beneficial only up to a point.

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

Effect of length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment
In an analysis of individual patients' data from seven trials, Florent Boutitie and colleagues found that three months of anticoagulant treatment achieved a similar risk of recurrent venous thromboembolism after stopping anticoagulation to a longer course of treatment. Unprovoked proximal deep vein thrombosis and pulmonary embolism had a high risk of recurrence whenever treatment was stopped (doi:10.1136/bmj.d3036).

Human papillomavirus testing in primary cervical screening and the cut-off level for hybrid capture 2 tests: systematic review

Matejka Rebolj,[1] Jesper Bonde,[2 3] Sisse Helle Njor,[1] Elsebeth Lynge[1]

EDITORIAL
by Sasieini and Castanon

[1]Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, DK-1014 København K, Denmark
[2]Clinical Research Center, Hvidovre Hospital, Hvidovre, Denmark
[3]Department of Pathology, Hvidovre Hospital, Hvidovre, Denmark
Correspondence to: M Rebolj
mare@sund.ku.dk

Cite this as: *BMJ* 2011;342:d2757
doi: 10.1136/bmj.d2757

This is a summary of a paper that was published on bmj.com as *BMJ* 2011;342:d2757

STUDY QUESTION Is it possible to improve the specificity of hybrid capture 2, a commercially available human papillomavirus DNA test, and at the same time keep the test's high sensitivity for detection of high grade cervical intraepithelial neoplasia?

SUMMARY ANSWER In the range from ≥2 to ≥10 relative light units/cut-off level (rlu/co), the sensitivity of hybrid capture 2 for high grade cervical intraepithelial neoplasia would remain above 90% compared with the standard cut-off level of ≥1 rlu/co, whereas the specificity would increase significantly.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS The hybrid capture 2 test is known to have a higher sensitivity and a lower specificity than cytology in cervical cancer screening. Several countries are considering the switch to screening with human papillomavirus testing, but first the rate of false positive test results needs to be reduced. Our analysis showed that if the cut-off level of the hybrid capture 2 test was increased from the standard ≥1 rlu/co to ≥10 rlu/co, the number of positive test results without underlying high grade cervical intraepithelial neoplasia would be about halved in women aged 30 years or more without jeopardising the test's sensitivity.

Selection criteria for studies

We included in our systematic review data from four randomised controlled trials using hybrid capture 2 as a primary cervical screening test in the intervention arms. In these trials, the baseline round data on the number of women with positive test results and high grade cervical intraepithelial neoplasia lesions were reported in enough detail for further analysis. These trials were undertaken in established organised screening programmes.

Primary outcomes

From each trial and for each reported cut-off level, we calculated the relative sensitivity and the relative specificity for cervical intraepithelial neoplasia grades III or higher and II or higher compared with the standard cut-off level ≥1 rlu/co.

Main results and role of chance

By increasing the cut-off level to a range between ≥2 rlu/co and ≥10 rlu/co, the sensitivity of hybrid capture 2 for detection of cervical intraepithelial neoplasia grade III or higher remained above 90% of the detection at cut-off level ≥1 rlu/co in five of the six studied groups. The relative sensitivities for cervical intraepithelial neoplasia grade II or higher were similar. Owing to the relatively low number of cervical intraepithelial neoplasia grades III or higher and II or higher reported from most trials, the 95% confidence intervals were wide. The increase in the cut-off level led to an increase in specificity resulting in a significant reduction in the number of women with a positive hybrid capture 2 test result not associated with cervical intraepithelial neoplasia grade III or higher. At cut-off level ≥10 rlu/co only about one half of women aged 30 or more experienced such a false positive test result compared with the number at the cut-off level ≥1 rlu/co.

Bias, confounding, and other reasons for caution

The outcomes may not be generalisable to settings with opportunistic screening and settings with previously unscreened women. With longer follow-up, the data from the Finnish and Italian trials may change slightly. In the trials, women were predominantly managed according to hybrid capture 2 cut-off level ≥1 rlu/co. Owing to the slight decrease in sensitivity, an increased cut-off level may theoretically not allow the same length of the screening interval as the cut-off level ≥1 rlu/co.

Study funding/potential competing interests

This work was supported by Olga and Esper Boel's Fund; Aase and Ejnar Danielsen's Fund; Augustinus Fund; Manufacturer Mads Clausen's Fund; Family Hede Nielsen's Fund; Else and Mogens Wedell-Wedellsborg's Fund; Carl and Ellen Hertz' Grant for Danish Medical and Natural Sciences Research; and Merchant Sven Hansen and Mrs Ina Hansen's Fund. For the present paper, there has been no collaboration with, or support from any of the companies.

RELATIVE SENSITIVITY AND RELATIVE SPECIFICITY FOR CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE III OR HIGHER AT CUT-OFF LEVEL ≥10 RLU/CO COMPARED WITH ≥1 RLU/CO

Trial (age range)	Relative sensitivity (95% CI)	Relative specificity (95% CI)
Italian phase 1 (25-34)	0.93 (0.68 to 1.00)	1.05 (1.04 to 1.06)
Italian phase 2 (25-34)	0.96 (0.79 to 1.00)	1.05 (1.04 to 1.05)
UK (20-64)	0.93 (0.89 to 0.95)	1.07 (1.07 to 1.07)
Italian phase 1 (35-60)	0.92 (0.79 to 0.98)	1.04 (1.04 to 1.04)
Italian phase 2 (35-60)	0.83 (0.66 to 0.93)	1.03 (1.03 to 1.03)
Finland (30-60)	0.91 (0.71 to 0.99)	1.04 (1.04 to 1.04)

Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial

Kim L Bennell,[1] Kelly-Ann Bowles,[1] Craig Payne,[2] Flavia Cicuttini,[3] Elizabeth Williamson,[3 4] Andrew Forbes,[3] Fahad Hanna,[3 5] Miranda Davies-Tuck,[3] Anthony Harris,[6] Rana S Hinman[1]

EDITORIAL by Bierma-Zeinstra

[1]Centre for Health, Exercise and Sports Medicine, Department of Physiotherapy, University of Melbourne, Parkville, 3010 VIC, Australia
[2]Department of Podiatry, School of Human Biosciences, LaTrobe University, Melbourne, Victoria, Australia
[3]Department of Epidemiology and Preventive Medicine, Alfred Hospital, Monash University, Melbourne, Victoria, Australia
[4]MEGA Epidemiology, School of Population Health, University of Melbourne, Victoria, Australia
[5]Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia
[6]Health Economics Unit, Monash University, Melbourne

Correspondence to: K L Bennell
k.bennell@unimelb.edu.au

Cite this as: *BMJ* 2011;342:d2912
doi: 10.1136/bmj.d2912

This is a summary of a paper that was published on bmj.com as *BMJ* 2011;342:d2912

STUDY QUESTION

Do lateral wedge insoles improve symptoms and slow progression of structural disease to a greater extent than flat control insoles in people with medial knee osteoarthritis?

SUMMARY ANSWER

Lateral wedge insoles worn daily for 12 months provided no symptomatic or structural benefits compared with control insoles.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Lateral wedge insoles are an inexpensive, easily available conservative treatment for medial knee osteoarthritis but their symptomatic and structural effects are unclear. This study found that lateral wedge insoles provided no additional benefits over flat control insoles and therefore the results do not support current clinical guidelines for knee osteoarthritis.

Design

This was a randomised participant and assessor blinded placebo controlled trial. Participants were stratified by disease severity (Kellgren and Lawrence grades 2 and 3) and sex and randomly allocated in permuted blocks of 6 to 12 to either a lateral wedge insole or control insole group using a computer generated table of random numbers. Full length 5 degree lateral wedged insoles or flat control insoles were worn inside the shoes daily for 12 months.

Participants and setting

Two hundred people aged 50 or more with clinical and radiographic diagnosis of mild to moderately severe medial knee osteoarthritis and neutral or varus knee alignment were recruited from the community in metropolitan Melbourne, Australia.

BASELINE AND FOLLOW-UP DATA FOR AVERAGE PAIN AND MEDIAL TIBIAL CARTILAGE VOLUME

Variables	Average pain* (0-10)	Medial tibial cartilage volume (mm^3)
Mean (SD) at baseline (week 0):		
Wedge insoles (n=103)	4.0 (2.1)	1550 (452)
Control insoles (n=97)	4.3 (1.9)	1520 (439)
Mean (SD) at follow-up (week 52):		
Wedge insoles (n=89)	3.1 (2.1)	1513 (480)
Control insoles (n=90)	3.1 (2.3)	1483 (432)
Mean (SD) within group difference (weeks 0-52):		
Wedge insoles	0.9 (2.1)	43 (45)
Control insoles	1.3 (2.4)	43 (53)
Mean (95% CI) between group difference† (wedge insole–control insole)	−0.3 (−1.0 to 0.3)	−0.4 (−15.4 to 14.6)

*Based on numerical rating scale, with higher scores indicating worse pain.
†Adjusted for baseline value of variable.

Primary outcomes

Symptomatic outcome was overall knee pain (past week) measured on an 11 point rating scale and structural outcome was medial tibial cartilage volume from magnetic resonance imaging measured at baseline and at 12 months.

Main results and the role of chance

The differences in change in primary outcomes did not differ significantly between the groups and confidence intervals did not include minimal clinically important differences. None of the changes in secondary symptomatic outcomes of pain, function, stiffness, and health related quality of life or structural outcomes of progression of medial cartilage defects and bone marrow lesions showed differences between groups.

Harms

More participants reported problems with lateral wedge insoles (42/89, 47%) than with control insoles (21/90, 23%). Lateral wedge insoles were more likely to be associated with back and foot pain and to be difficult to fit into shoes. Lateral wedge insoles were also rated as less comfortable.

Bias, confounding, and other reasons for caution

A different magnetic resonance imaging machine was used for follow-up assessment in 54 of 171 (32%) participants. However, differences in measurements between the two machines were essentially comparable to repeated measurements from the same machine and reanalyses showed that the intervention effect did not differ between participants scanned with a single machine and those scanned with both machines. Participants were recruited from the community and may not fully reflect the patients who seek treatment from general medical practitioners. Adherence was incomplete, although the primary results did not change under a hypothetical scenario of complete adherence to treatment. A longer time frame is needed to definitively establish whether lateral wedge insoles have a modifying effect on structural disease.

Generalisability to other populations

Results cannot be generalised to lateral wedge insoles with subtalar strapping or to participants with severe medial disease or osteoarthritis predominantly in the lateral knee compartment with valgus alignment.

Study funding/potential competing interests

We have no competing interests and are independent of the funding body, the National Health and Medical Research Council.

Trial registration number

Australian New Zealand Clinical Trials Registry ACTR12605000503628 and ClinicalTrials.gov NCT00415259.

Effect of supplementation during pregnancy with L-arginine and antioxidant vitamins in medical food on pre-eclampsia in high risk population: randomised controlled trial

Felipe Vadillo-Ortega,[1] Otilia Perichart-Perera,[2] Salvador Espino,[2] Marco Antonio Avila-Vergara,[3] Isabel Ibarra,[4] Roberto Ahued,[2] Myrna Godines,[1] Samuel Parry,[5] George Macones,[5 6] Jerome F Strauss[7]

EDITORIAL
by Smeeth and Williams

[1]Department of Experimental Medicine, School of Medicine, Universidad Nacional, Autonoma de Mexico, Torre de Investigacion, 3er Piso, Ciudad Universitaria, Mexico, D F 04510
[2]Instituto Nacional de Perinatologia Isidro Espinosa de los, Reyes, Mexico
[3]Universidad Autonoma de Sinaloa, Mexico
[4]Instituto de Investigaciones Biomedicas, UNAM, Mexico
[5]Department of Obstetrics and Gynaecology, University of Pennsylvania, Philadelphia, PA, USA
[6]Department of Obstetrics and Gynaecology, Washington University, St Louis, MO, USA
[7]Department of Obstetrics and Gynaecology, Virginia Commonwealth University, Richmond, VA, USA
Correspondence to: F Vadillo-Ortega **felipe.vadillo@gmail.com**

Cite this as: *BMJ* 2011;342:d2901
doi: 10.1136/bmj.d2901

This is a summary of a paper that was published on bmj.com as *BMJ* 2011;342:d2901

STUDY QUESTION

Can supplementation with L-arginine and antioxidant vitamins in a population of women at high risk of pre-eclampsia prevent disease occurrence?

SUMMARY ANSWER

Supplementation with a medical food containing L-arginine and antioxidant vitamins significantly reduced pre-eclampsia/eclampsia.

WHAT IS ALREADY KNOWN AND WHAT THIS PAPER ADDS

Defective synthesis of nitric oxide, a potent endothelium derived vasodilator, has been documented in pre-eclampsia, and experimental data indicate that L-arginine (the substrate for nitric oxide synthase) has a beneficial effect on haemodynamics. Dietary supplementation with L-arginine and antioxidant vitamins reduced occurrence of pre-eclampsia; further study is needed to identify whether the results are due to L-arginine alone or the combination with antioxidant vitamins.

Design

We did a randomised, blinded, placebo controlled clinical trial of supplementation with medical food bars containing L-arginine plus antioxidant vitamins, antioxidant vitamins alone, or placebo during pregnancy.

Participants and setting

We studied pregnant women attending a tertiary public hospital in Mexico City from week 14-32 of gestation and followed them until delivery. We included pregnant women with a history of a previous pregnancy complicated with pre-eclampsia, or a first degree relative with pre-eclampsia, deemed to be at increased risk of recurrence of the disease.

Primary outcome(s)

The primary outcome measure was development of pre-eclampsia/eclampsia.

Main results and the role of chance

We allocated 222 women to the placebo group, 228 received L-arginine plus antioxidant vitamins, and 222 received antioxidant vitamins alone. Women had four to eight prenatal visits while receiving bars. The incidence of pre-eclampsia was 30% (n=67) in the placebo group, 13% (n=29) in the L-arginine plus antioxidant vitamins group, and 23% (n=50) in the vitamins alone group. The incidence of pre-eclampsia was significantly lower (P<0.001) in women randomised to L-arginine plus antioxidant vitamins compared with placebo (absolute risk reduction 0.17, 95% confidence interval 0.12 to 0.21). Antioxidant vitamins alone showed an observed benefit, but this effect was not statistically significant compared with placebo (P=0.052; absolute risk reduction 0.07, 0.005 to 0.15). L-arginine plus antioxidant vitamins compared with antioxidant vitamins alone resulted in a significant effect (P=0.004; absolute risk reduction 0.09, 0.05 to 0.14).

Harms

No concerning side effects of the intervention were reported.

Bias, confounding, and other reasons for caution

The study design could not determine the most appropriate time to start L-arginine plus antioxidant vitamin supplementation. The relative contributions of L-arginine and antioxidant vitamins to the observed effects of the combined treatment need to be determined.

Generalisability to other populations

Supplementation with L-arginine plus antioxidant vitamins needs to be evaluated in a population at low risk of pre-eclampsia to determine the generalisability of the protective effect, as well as in other racial/ethnic populations.

Study funding/potential competing interests

Funding was provided by the Bill and Melinda Gates Foundation, National Institutes of Health, and CONACyT.

Trial regulation number

Clinical trials NCT00469846.

RESULTS FOR PRIMARY OUTCOME

Group comparison	Absolute risk reduction (95% CI)	Relative risk (95% CI)	x^2 P value
L-arginine + vitamins *v* placebo	0.17 (0.12 to 0.21)	0.42 (0.28 to 0.62)	<0.001
Vitamins alone *v* placebo	0.07 (0.005 to 0.15)	0.74 (0.54 to 1.02)	0.052
L-arginine + vitamins *v* vitamins alone	0.09 (0.05 to 0.14)	0.56 (0.37 to 0.85)	0.004

Dietary calcium intake and risk of fracture and osteoporosis: prospective longitudinal cohort study

Eva Warensjö,[1 4] Liisa Byberg,[1 4] Håkan Melhus,[3 4] Rolf Gedeborg,[2 4] Hans Mallmin,[1] Alicja Wolk,[5] Karl Michaëlsson[1 4]

[1]Department of Surgical Sciences, Section of Orthopaedics, Uppsala University, Uppsala, Sweden
[2]Anaesthesiology and Intensive Care, Uppsala University, Uppsala, Sweden
[3]Department of Medical Sciences, Clinical Pharmacology, Uppsala University, Uppsala, Sweden
[4]Uppsala Clinical Research Centre, UCR, Uppsala University, Uppsala, Sweden
[5]Division of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Correspondence to: E Warensjö
eva.warensjo@surgsci.uu.se

Cite this as: *BMJ* 2011;342:d1473
doi: 10.1136/bmj.d1473

This is a summary of a paper that was published on bmj.com as *BMJ* 2011;342:d1473

STUDY QUESTION

What associations exist between long term dietary intake of calcium and risk of fracture of any type, hip fractures, and osteoporosis?

SUMMARY ANSWER

Gradual increases in dietary calcium intake above the first quintile of our female population were not associated with a further reduction in the risk of fractures or osteoporosis.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Meta-analyses of previous studies have not established a reduction in fracture or osteoporosis risk with increasing calcium intake. We found that dietary calcium intakes below approximately 700 mg per day in women were associated with increased risk of hip fracture, any fracture, and osteoporosis.

Participants and setting

A population based cohort in Sweden established in 1987.

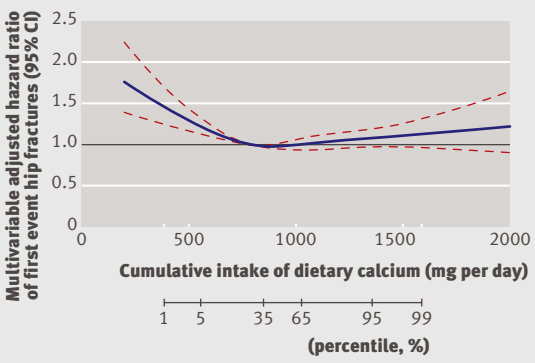
Design, size, and duration

61 433 women (born between 1914 and 1948) were followed up for 19 years. During follow-up 14 738 women (24%) experienced a first fracture of any type and among them 3871 (6%) a first hip fracture. In a subcohort of 5022 women, 1012 (20%) were measured as osteoporotic by dual energy x ray absorptiometry. Diet was assessed by repeated food frequency questionnaires.

Main results and the role of chance

The risk patterns with dietary calcium were non-linear. The crude rate of a first fracture of any type was 17.2/1000 person years at risk in the lowest quintile of calcium intake (<751 mg/day) and 14.0/1000 person years at risk in the third quintile, corresponding to a multivariable adjusted hazard ratio of 1.18 (95% confidence interval 1.12 to 1.25). Hazard ratio for a first hip fracture was 1.29 (1.17 to 1.43) and the odds ratio for osteoporosis was 1.47 (1.09 to 2.00). With a low vitamin D intake, the rate of fracture in the first calcium quintile was more pronounced. The highest quintile of calcium intake did not further reduce the risk of fractures of any type or of osteoporosis, but was associated with a higher rate of hip fracture, hazard ratio 1.19 (1.06 to 1.32).

SPLINE CURVE SHOWING ASSOCIATION BETWEEN DIETARY CALCIUM INTAKE AND FIRST HIP FRACTURE RATE



Bias, confounding and other reasons for caution

The observational study design precludes conclusions regarding causality.

Generalisability to other populations

Our results might not apply to women of other ethnicities or men.

Study funding/potential competing interests

Supported by the Swedish Research Council, grant numbers 2008-2202 and 2009-6281. The funding source was not involved in the design, conduct, or interpretation of the study, or in the writing of the submitted work. All authors have declared no competing interests relevant to the submitted work.

Trial regulation number

This is a summary of a paper that was published on bmj.com as *BMJ* 2011;342:d1473

BMJ pico: advice to authors

The full text of all accepted *BMJ* research articles is published online in full, with open access and no word limit, on bmj.com as soon as it is ready. In the print *BMJ* each research article is abridged, as a one page BMJ pico, with the aim of making research more inviting and useful to readers. Since August 2009, authors have written their own BMJ picos.

We have designed BMJ pico with evidence based medicine experts to succinctly present the key evidence from each study, to help minimise delay between online and print publication, and to enable us to publish more research in each week's print *BMJ*. For more details, see http://tinyurl.com/kp5c7o/.

There is no need for authors to prepare a BMJ pico to submit along with the full research article. Authors produce their own BMJ pico, using a template from us, only after the full article has been accepted.

Because publication of research on bmj.com is definitive, rather than interim "epublication ahead of print," authors who do not wish to abridge their articles using BMJ pico will be able to opt for online only publication.