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Impact of smoking on mortality and life expectancy in Japanese smokers

In this Japanese cohort, people who were born in 1920-45 and who started to smoke before age 20 and continued smoking, mortality from all causes combined was more than doubled compared with those who had never smoked, and their reduction in life expectancy was about one decade. However, much of the increase in risk was avoided by giving up smoking, and those who managed to stop by age 35 avoided nearly all of the risk in those who continued to smoke, say the authors.

WHAT OUR READERS ARE SAYING

Effect of intended intraoperative cholangiography and early detection of bile duct injury on survival after cholecystectomy

According to this study published on bmj.com on 11 October (http://www.bmj.com/content/345/bmj.e6457) using data from the national Swedish registry for gallstone surgery and endoscopic retrograde cholangiopancreatography, survival among patients with bile duct injury during cholecystectomy is significantly impaired, compared with patients without bile duct injury. Furthermore, survival after bile duct injury is impaired by the failure to detect injury intraoperatively, and the intention to use intraoperative cholangiography during cholecystectomy improves survival significantly, say the authors.

Here are some points raised by a team of UK based surgeons in a rapid response:

"The authors say that there is no international consensus on the definition of severe and less severe bile duct injury and instead use their definition relating to severity on the basis of required intervention. The Strasberg classification published in 1995 has become the gold standard of classification of bile duct injuries and allows comparison of the severity of injuries between series. To readers this change in definition compared with other studies is confusing, as injuries to the major ducts occurred in 178 cases but the authors only defined 55 (31%) of them as being severe. Furthermore in a prospectively maintained database 191/747 (25.5%) of injuries were 'not classifiable'? Surely the presence of injuries has been documented, investigated, and managed, and so the type of injury should be known to the surgeon managing the patient and hence communicated to the registry. If one in four injuries is not being accurately reported we would suggest this is a confounding factor and affecting the power of this database analysis.

"Another controversial area in our opinion is the inclusion of cystic duct and duct of Luschka leaks in the analysis relating to intraoperative cholangiography as it is unlikely to have influenced the prevalence of either lesion (unless in the presence of common duct stones).

"This study is the first to report a more than 60% reduction in mortality of patients after laparoscopic cholecystectomy if intraoperative cholangiography is undertaken—completed or performed. While there is no denying the detrimental impact on quality of life and morbidity associated with bile duct injury and all efforts to reduce this are to be encouraged, our current hospital practice continues to use intraoperative cholangiography in selective cases only and complements the critical view of safety technique in all laparoscopic cholecystectomy procedures. The findings presented in this article will fuel the debate no doubt and attract interest from the GP considering referral to a surgeon who performs routine intraoperative cholangiography or not—or, perhaps most interesting of all, the patient presenting in outpatients next month asking if they can have a intraoperative cholangiography as it would reduce mortality risk by 62%,far greater than reduction of death by motorcycle helmets (42%) and using a seatbelt to improve chance of surviving a potentially fatal crash (40-60%)."

Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis

Rajiv Chowdhury,[1] Sarah Stevens,[2] Donal Gorman,[1] An Pan,[3] Samantha Warnakula,[1] Susmita Chowdhury,[4] Heather Ward,[5] Laura Johnson,[1] Francesca Crowe,[6] Frank B Hu,[3] Oscar H Franco[1 7]

EDITORIAL by de Goede and Geleijnse

[1]Department of Public Health and Primary Care, University of Cambridge, UK
[2]Public Health Directorate, NHS Midlands and East, Fulbourn, Cambridge, UK
[3]Department of Nutrition, Harvard School of Public Health, Boston, USA
[4]Public Health Genomics Foundation, Cambridge, UK
[5]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, UK
[6]Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, UK
[7]Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands
Correspondence to: O H Franco
o.franco@erasmusmc.nl

Cite this as: *BMJ* 2012;345:e6698
doi: 10.1136/bmj.e6698

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;345:e6698

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STUDY QUESTION

What is the association between fish and long chain omega 3 fatty acids consumption and risk of cerebrovascular disease for primary and secondary prevention?

SUMMARY ANSWER

Higher fish consumption was moderately (12% reduction) but significantly associated with a reduced risk of incident cerebrovascular disease. Dietary, circulating biomarkers and long chain omega 3 fatty acid supplements were not significantly associated with cerebrovascular risk.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Evidence from observational and experimental studies on the benefits of fish consumption and long chain omega 3 fatty acids for cerebrovascular disease has been conflicting. Observational findings from this meta-analysis showed that both fish consumption and long chain omega 3 fatty acids may modestly reduce the risk of cerebrovascular diseases. Results for long chain omega 3 fatty acid supplements, based on primary and secondary prevention studies, do not support the observational evidence.

Selection criteria for studies

We carried out an electronic search through Medline, Embase, BIOSIS, and Science Citation Index, for prospective cohort studies and randomised controlled trials published before September 2012, without any language restriction. Studies were eligible for inclusion if they reported on associations of fish and long chain omega 3 fatty acids consumption, based on dietary self report, omega 3 fatty acids biomarkers or supplements, with cerebrovascular disease (any fatal or non-fatal ischaemic stroke, haemorrhagic stroke, cerebrovascular accident, or transient ischaemic attack). Both primary and secondary prevention studies (comprising participants with or without cardiovascular disease at baseline) were eligible.

Primary outcome

The main outcome measure was cerebrovascular disease.

Main results and role of chance

In cohort studies, the pooled relative risk for cerebrovascular disease, comparing categories of fish intake, for 2-4 servings/week versus ≤1 serving/week was 0.94 (95% confidence interval 0.90 to 0.98) and for ≥5 servings/week versus 1 serving/week was 0.88 (0.81 to 0.96). The relative risk for cerebrovascular disease comparing the top versus bottom thirds of baseline long chain omega 3 fatty acids was 1.04 (0.90 to 1.20) and for biomarker and dietary exposures was 0.90 (0.80 to 1.01). In the randomised controlled trials, the relative risk for cerebrovascular disease in the long chain omega 3 supplement versus control group in primary prevention studies was 0.98 (0.89 to 1.08) and in secondary prevention studies was 1.17 (0.99 to 1.38). For fish or omega 3 fatty acids the estimates for ischaemic and haemorrhagic cerebrovascular events were broadly similar.

Bias, confounding, and other reasons for caution

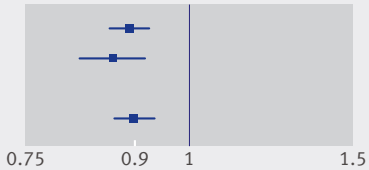
Evidence of heterogeneity and publication bias across studies or within subgroups was lacking. However, the review was limited by the moderate amount of available data on cause specific cerebrovascular outcomes. For example, only a few studies reported on more than 1000 ischaemic stroke events, whereas most involved analyses primarily on composite cerebrovascular events. Furthermore, even in aggregate fewer than 2000 cerebrovascular events were available in the randomised controlled trials and none of them were based on healthy populations.

Study funding/potential competing interests

RC is recipient of a Gates Cambridge PhD scholarship, DG and SW are supported by funding from MRC studentships, and OHF is the recipient of a grant from Pfizer Nutrition to establish a new centre on aging research focused on nutrition and lifestyle. We have no competing interests.

Association between fish consumption and risk of cerebrovascular disease in prospective cohort studies with information on intake categories and weekly increment of servings

	No of studies	No of participants	No of events	Relative risk (95% CI)
Categories of fish intake				
2-4 *v* ≤1 servings/week	18	650 210	24 612	0.94 (0.90 to 0.98)
≥5 *v* ≤1 servings/week	8	394 958	16 890	0.88 (0.81 to 0.96)
Dose-response assessment				
Increment of 2 servings/week	18	669 727	24 791	0.96 (0.93 to 0.99)



Identifying the lowest effective dose of acetazolamide for the prophylaxis of acute mountain sickness: systematic review and meta-analysis

Emma V Low,[1] Anthony J Avery,[2] Vaibhav Gupta,[2] Angela Schedlbauer,[3] Michael P W Grocott[4]

EDITORIAL by Imray

[1]School of Medicine, University of Southampton, Southampton General Hospital, Southampton, UK
[2]Division of Primary Care, School of Community Health Sciences, The Medical School, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH, UK
[3]Division of Primary Care, School of Community Health Sciences, Tower Building, University of Nottingham, UK
[4]Anaesthesia and Critical Care Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK
Correspondence to: A J Avery
anthony.avery@nottingham.ac.uk

Cite this as: *BMJ* 2012;345:e6779
doi: 10.1136/bmj.e6779

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;345:e6779

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Research: Effects of experience and commercialisation on survival in Himalayan mountaineering (*BMJ* 2012;344:e3782)

STUDY QUESTION

What is the lowest effective dose of acetazolamide for prophylaxis of acute mountain sickness for which there is evidence?

SUMMARY ANSWER

Acetazolamide 250 mg, 500 mg, and 750 mg daily were all efficacious for preventing acute mountain sickness. Acetazolamide 250 mg was the lowest effective dose with available evidence for this indication.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

A systematic review in 2000 showed that acetazolamide 750 mg was effective in preventing acute mountain sickness, a condition commonly encountered at high altitudes. In more recent trials acetazolamide 250 mg and 500 mg daily were also effective in preventing acute mountain sickness, with 250 mg being the lowest dose for which there was evidence of effectiveness.

Selection criteria for studies

We searched Medline and Embase and three high altitude medicine journals for studies that assessed the use of acetazolamide versus placebo as a drug intervention for the prevention of acute mountain sickness. No language restrictions were applied.

Primary outcome

The primary outcome was absence of acute mountain sickness as defined by a validated scoring system such as the Lake Louise scoring system, general high altitude questionnaire, or acute mountain sickness-cerebral scoring, or by using a clear definition of acute mountain sickness predetermined by the original study authors.

Main results and role of chance

11 studies (12 intervention arms) were included. Acetazolamide was consistently more effective than placebo for the prevention of acute mountain sickness. The combined treatment effect of acetazolamide versus placebo was statistically significant at the 5% significance level (combined odds ratio 0.36, 95% confidence interval 0.28 to 0.46). The acetazolamide 250 mg, 500 mg, and 750 mg subgroups each showed statistically significant treatment effects. The 250 mg subgroup had a combined odds ratio of 0.41 (0.26 to 0.64) and number needed to treat of 6 (95% confidence interval 5 to 11). The 500 mg subgroup had a combined odds ratio of 0.37 (0.26 to 0.52) and number needed to treat of 7 (6 to 9). The 750 mg subgroup had a combined odds ratio of 0.20 (0.10 to 0.41) and number needed to treat of 3 (3 to 5). Reporting of side effects among the trials suggested that acetazolamide 750 mg is associated with a higher incidence of adverse effects (paraesthesia, polyuria, rash, and dysgeusia); however, there was no obvious dose-response increase in non-adherence to drugs.

Bias, confounding, and other reasons for caution

The methods applied by the included studies for diagnosing acute mountain sickness varied, which threatens the consistency of outcome reporting and may introduce detection bias. Studies meeting the inclusion criteria were done at relatively high altitudes.

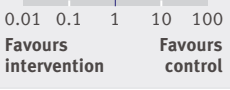
Five of the 11 included studies enrolled participants at altitudes above 4000 m, so participants may have been partially acclimatised. The mean final altitude was 4619 m (range 3800-5000 m). Data were insufficient to draw firm conclusions on the efficacy of acetazolamide at altitudes below 3800 m.

Study funding/potential competing interests

EVL and VG received funding from the University of Nottingham to complete the study. The authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years.

Efficacy of acetazolamide by dose

	No of events/total		Odds ratio Mantel-Haenszel, fixed (95% CI)	Odds ratio Mantel-Haenszel, fixed (95% CI)
	Intervention	Control		
250 mg acetazolamide				
Basnyat 2003	9/74	20/81		0.42 (0.18 to 1.00)
Basnyat 2006	14/58	13/29		0.39 (0.15 to 1.01)
Gertsch 2010	18/97	18/65		0.59 (0.28 to 1.26)
Van Patot 2008	7/22	17/22		0.14 (0.04 to 0.52)
Subtotal (95% CI)	48/251	68/197		0.41 (0.26 to 0.64)
500 mg acetazolamide				
Basnyat 2008	18/174	36/165		0.41 (0.22 to 0.76)
Basnyat 2011	10/95	13/64		0.46 (0.19 to 1.13)
Burki 1992	3/6	5/6		0.20 (0.01 to 2.91)
Chow 2005	6/20	12/20		0.29 (0.08 to 1.06)
Gertsch 2004	14/118	40/119		0.27 (0.14 to 0.52)
Hackett 1976	17/71	19/49		0.50 (0.23 to 1.10)
Subtotal (95% CI)	68/484	125/423		0.37 (0.26 to 0.52)
750 mg acetazolamide				
Basnyat 2006	14/68	14/30		0.30 (0.12 to 0.75)
Larson 1982	5/29	20/30		0.10 (0.03 to 0.36)
Subtotal (95% CI)	19/97	34/60		0.20 (0.10 to 0.41)
Total (95% CI)	135/832	227/680		0.36 (0.28 to 0.46)



Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial

Louise Lind Schierbeck,[1] Lars Rejnmark,[2] Charlotte Landbo Tofteng,[1] Lis Stilgren,[3] Pia Eiken,[4] Leif Mosekilde,[2] Lars Køber,[5] Jens-Erik Beck Jensen[1]

[1]Department of Endocrinology, Hvidovre Hospital, Kettegård alle 30, 2650 Hvidovre, Denmark
[2]Department of Medicine and Department of Endocrinology and Internal Medicine, Århus University Hospital, Århus, Denmark
[3]Department of Endocrinology, Svendborg Hospital, Svendborg, Denmark
[4]Department of Cardiology, Nephrology, and Endocrinology, Hillerød Hospital, Hillerød, Denmark
[5]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark
Correspondence to: L L Schierbeck
louise.schierbeck@gmail.com

Cite this as: *BMJ* 2012;345:e6409
doi: 10.1136/bmj.e6409

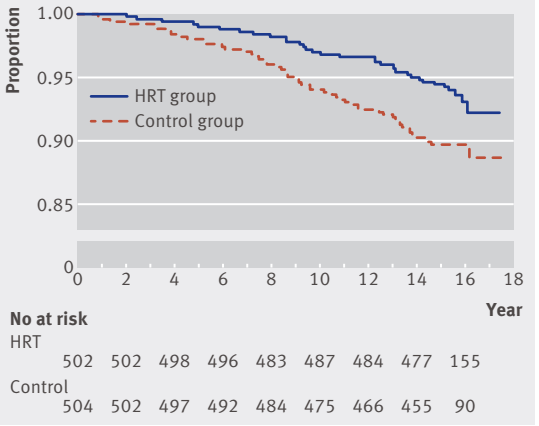
This is a summary of a paper that was published on bmj.com as *BMJ* 2012;345:e6409

STUDY QUESTION What is the long term effect of hormone replacement therapy (HRT) on cardiovascular outcomes in recently postmenopausal women?

SUMMARY ANSWER After 10 years of randomised treatment, women using HRT early after menopause had significantly reduced risks of mortality, heart failure, or myocardial infarction, without any apparent increase in cancer, venous thromboembolisms, or stroke.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Results on the benefits and safety of HRT from observational studies and randomised trials are conflicting. In this randomised controlled trial, HRT started early in postmenopause significantly reduced the risk of the combined endpoint of mortality, myocardial infarction, or heart failure.

Risk of death or admission to hospital due to heart failure or myocardial infarction over 16 years



Design

47 720 women from the general population were recruited by direct mailing to a random sample for the Danish Osteoporosis Prevention Study (DOPS), an investigator initiated multicentre trial evaluating the effect of HRT as primary prevention of osteoporotic fractures. Participants were stratified according to centre and randomly allocated to HRT or no treatment (open label) in blocks of 10, using sealed envelopes. In the HRT group (n=502), women with an intact uterus were treated with synthetic 17-β-estradiol and norethisterone acetate (Trisekvens; Novo Nordisk, Denmark). Women who had undergone hysterectomy received 2 mg 17-β-estradiol (Estrofem; Novo Nordisk).

Participants and setting

1006 women in Denmark were enrolled between 1990 and 1993 and randomly allocated to HRT or no treatment. Participants were recently postmenopausal or perimenopausal healthy white women aged 45-58.

Primary outcome(s)

In this substudy the primary endpoint was a composite of mortality, heart failure, or myocardial infarction. Intervention was stopped after about 11 years owing to adverse reports from other trials, but participants were followed for death, cardiovascular disease, and cancer for up to 16 years.

Main results and the role of chance

The primary endpoint occurred in 49 women (33 controls *v* 16 treated women; hazard ratio 0.48, 95% confidence interval 0.26 to 0.87; P=0.015). During the intervention period 41 women died (26 controls *v* 15 treated women; 0.57, 0.30 to 1.08; P=0.084). After an additional six years of non-randomised follow-up the primary endpoint occurred in 86 women (53 controls *v* 33 treated women; 0.61, 0.39 to 0.94; P=0.02). During the 16 years 40 women in the control group and 27 in the treated group died (0.66, 0.41 to 1.08; P=0.10).

Harms

Stroke rates did not differ between randomised groups (14 controls *v* 11 treated women; 0.77, 0.35 to 1.70; P=0.70). The rate of venous thromboembolism was low and did not differ significantly between groups. Three women had confirmed deep vein thrombosis (2.01, 0.18 to 22.16) and only one woman (control) was admitted to hospital with pulmonary embolism. The occurrence of any cancer did not differ significantly between groups (39 controls *v* 36 treated women; 0.92, 0.58 to 1.45; P=0.71) or breast cancer (17 controls *v* 10 treated women; 0.58, 0.27 to 1.27; P=0.17), and no significant difference in the occurrence of other cancers (25 controls *v* 26 treated women; 1.04, 0.60 to 1.80; P=0.88). The composite endpoint mortality or breast cancer occurred in 40 women in the control group and 22 in the treated group (0.54, 0.32 to 0.91; P=0.02). After additional six years of non-randomised treatment, the risk of cancer, stroke, or venous thrombo-embolisms was still not increased.

Bias, confounding, and other reasons for caution

The study was an open label design with no placebo or blinding. Endpoints were determined without knowledge of treatment allocation, using a prospectively, randomised, open with blinded endpoint evaluation design.

Study funding/potential competing interests

The study was supported by the Karen Elise Jensen Foundation and the Danish Health Research Council. Novo Nordisk, Novartis, and Leo Pharma Denmark provided the study drug free of charge. The funders had no influence on the study design or interpretation of data.

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"It is unfortunate that the absolute risks and cancer event numbers are not clearly stated in this report. While the cardiovascular findings are reassuring, the study does not appear to be powered to exonerate hormone therapy as a risk factor for breast cancer."
Bo Abrahamsen, professor, Gentofte Hospital, Copenhagen, Denmark.
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Neglected tropical diseases: survey and geometry of randomised evidence

Shanthi Kappagoda,[1] John P A Ioannidis[2]

[1]Center for Primary Care and Outcomes Research and Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford, CA, USA

[2]Stanford Prevention Research Center, Department of Medicine and Department of Health Research and Policy, Stanford University School of Medicine, and Department of Statistics, Stanford University School of Humanities and Sciences, Stanford

Correspondence to: J P A Ioannidis, Stanford Prevention Research Center, 1265 Welch Road, MSOB X306, Stanford, CA 94305-5411, USA **jioannid@stanford.edu**

Cite this as: *BMJ* 2012;345:e6512
doi: 10.1136/bmj.e6512

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;345:e6512

bmj.com
Editorial: Fighting neglected tropical diseases in the southern United States (*BMJ* 2012;345:e6112)

STUDY QUESTION What is the amount, distribution, and geometry of the evidence from randomised controlled trials for treatment of 16 major neglected tropical diseases?

SUMMARY ANSWER The 971 published randomised trials were distributed unevenly among the 16 diseases. Leishmaniasis was the most studied (184 trials) and Buruli ulcer the least studied (five trials). Evidence for a recommended treatment often came from single or small trials, and many first and second line treatments lacked head to head comparisons.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Diseases described as "neglected" have historically not been targeted for research and drug development, despite carrying a high cumulative global burden of disease.
This study showed that the distribution of randomised evidence across neglected tropical diseases is uneven. Even in diseases with substantial overall evidence, such as leishmaniasis and geohelminth infections, some recommended treatments have limited supporting data and a lack of head to head comparisons.

Selection criteria for studies
We searched PubMed and Cochrane Central Register of Controlled Trials for randomised controlled trials in humans examining treatment of 16 neglected tropical diseases: American trypanosomiasis, Buruli ulcer, cysticercosis, dengue, dracunculiasis, echinococcosis, foodborne trematode infections, geohelminth infections, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, rabies, schistosomiasis, and trachoma.

Primary outcome
Amount and description (interventions, trial size, and funding sources) of evidence from randomised controlled trials for each disease relative to its global burden of disease and currently recommended treatment guidelines.

Main results and role of chance
We identified 971 eligible randomised trials. Leishmaniasis (184 trials, 23 039 participants) and the geohelminth infections (160 trials, 46 887 participants) were the most studied diseases, while dracunculiasis (nine trials, 798 participants) and Buruli ulcer (five trials, 337 participants) were least studied. Relative to its global burden of disease, lymphatic filariasis had the fewest trials and participants. Within each disease, the number of trials conducted over time has changed. For six diseases—Buruli ulcer, cysticercosis, dengue, echinococcosis, human African trypanosomiasis, and leishmaniasis—there were more randomised controlled trials published in the past 12 years than in the preceding 50. Only 11% of trials were industry funded. The randomised evidence for a first or second line treatment for Buruli ulcer, human African trypanosomiasis, American trypanosomiasis, cysticercosis, rabies, echinococcosis, New World cutaneous leishmaniasis, and each of the foodborne trematode infections came from either a single trial or a total of fewer than 100 participants. For several diseases evidence on pivotal head to head comparisons did not exist or was limited. Among the 10 disease categories with more than 40 trials, five (New World leishmaniasis, visceral leishmaniasis, trichiuriasis, ascariasis, hookworm infection) lacked sufficient head to head comparisons between first or second line treatments.

The distribution of randomised evidence across neglected tropical diseases is uneven. Even in diseases with substantial overall evidence, such as leishmaniasis and geohelminth infections, some recommended treatments have limited supporting data and a lack of head to head comparisons.

Bias, confounding, and other reasons for caution
Exclusion of unpublished trials and trials published only in abstracts underestimates the amount of randomised evidence. The correlations between the estimates of global burden of disease based on disability adjusted life years (DALYs) and the amount of data from randomised controlled trials should be interpreted with caution.

Study funding/potential competing interests
SK was supported in part by the US Agency for Healthcare Research and Quality.

Number of trials, total sample size, and annual global burden of disease for each disease

	No of trials*	Total sample size†	Annual global burden of disease in 1000s of DALYs
Leishmaniasis	184	23 039	2090
Geohelminth infections	160	46 887	3796
Schistosomiasis	142	35 026	1702
Leprosy	120	14 772	198
Lymphatic filariasis	73	9996	5777
Onchocerciasis	62	25 182	484
Trachoma	54	10 420	2329
Rabies	45	6756	1780
Cysticercosis	32	2872	—
Dengue	24	2374	616
American trypanosomiasis	22	1772	667
Echinococcosis	15	1064	666
Foodborne trematode infections	14	1306	665
Human African trypanosomiasis‡	10	2840	1525
Dracunculiasis	9	798	—
Buruli ulcer	5	337	—

*Includes both primary disease and its complications.
†Calculated with "units of randomisation" in each trial, including number of clusters in cluster randomised trials and number of randomised units in trials in which unit of randomisation was not individual (for example, skin lesions in leishmaniasis or eyes in trachoma). It slightly underestimates number of individual participants.
‡Early and late stage *Trypanosoma brucei gambiense*.

Use of 3×2 tables with an intention to diagnose approach to assess clinical performance of diagnostic tests: meta-analytical evaluation of coronary CT angiography studies

Georg M Schuetz,[1] Peter Schlattmann,[2] Marc Dewey[1]

[1]The Charité-Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, Freie Universität Berlin, Department of Radiology, 10117 Berlin, Germany

[2]The Department of Medical Statistics, Informatics and Documentation, University Hospital of Friedrich Schiller University Jena, Jena, Germany

Correspondence to: M Dewey
dewey@charite.de

Cite this as: *BMJ* 2012;345:e6717
doi: 10.1136/bmj.e6717

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;345:e6717

STUDY QUESTION

How can different approaches of dealing with non-evaluable test results affect the outcome of diagnostic accuracy studies?

SUMMARY ANSWER

A 3×2 table with an intention to diagnose approach, rather than a 2×2 table, provides a more realistic picture of the clinical potential of diagnostic tests.

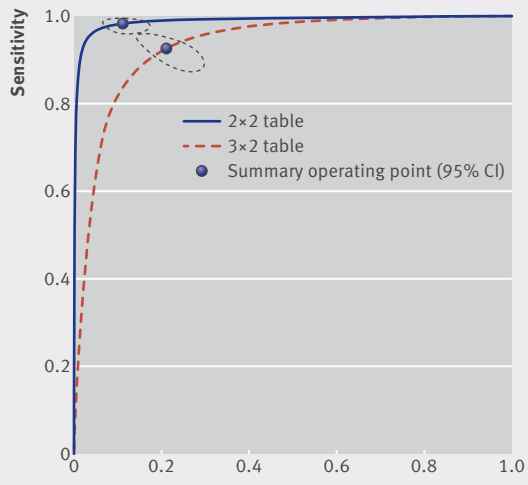
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Diagnostic accuracy studies and meta-analyses of pooled results constitute an important step in evaluating diagnostic tests, yet there is no consensus on how diagnostic accuracy studies should handle non-evaluable results. Our meta-analytical examination of a pool of studies in non-invasive coronary computed tomography (CT) angiography shows that common approaches of dealing with non-evaluable results lead to significant differences that could be avoided.

Selection criteria for studies

We searched Medline (via PubMed), Embase (via Ovid), and ISI Web of Science electronic databases for prospective English or German language studies comparing coronary CT with conventional coronary angiography in all patients and providing sufficient data for patient level analysis.

Summary receiver operating characteristics curves when using classic 2x2 table or 3x2 table calculations based on results from 26 studies with sufficient data



	2×2 table	3×2 table
Sensitivity (95% CI)	0.98 (0.97 to 0.99)	0.93 (0.89 to 0.95)
Specificity (95% CI)	0.89 (0.84 to 0.93)	0.79 (0.73 to 0.84)
AUC (95% CI)	0.99 (0.98 to 1.00)	0.93 (0.91 to 0.95)

Primary outcomes

Diagnostic accuracy of coronary CT angiography when non-evaluable test results were excluded (that is, using the "classic" 2×2 table), compared with the intention to diagnose approach of including non-evaluable results as either false positives or false negatives, depending on the results of the reference standard (that is, using a 3×2 table).

Main results and role of chance

We analysed full texts of 120 eligible studies varying greatly in handling non-evaluable findings. We found 26 studies (2298 patients) that allowed us to calculate alternative 3×2 tables. Using a bivariate random effects calculation, we compared results from the 2×2 table with those from the 3×2 table. The figure shows summary receiver operating characteristics (SROC) curves using pairs of sensitivity and specificity of the 26 studies; curves include a summary operating point for sensitivity and specificity on the curve and a 95% confidence contour ellipsoid. We found significant differences (P<0.05) between the 2×2 and 3×2 table calculations for pooled sensitivity, area under the curve (AUC), positive likelihood ratio (9.1 (6.2 to13.3) *v* 4.4 (3.3 to 6.0)), and negative likelihood ratio (0.02 (0.01 to 0.04) *v* 0.09 (0.06 to 0.15)). Further common approaches, categorically declaring non-evaluable results as either positive or negative, overestimated either sensitivity (98.3 (96.9 to 99.0)) or specificity (90.5 (86.8 to 93.2)).

Bias, confounding, and other reasons for caution

This meta-analytical evaluation uses coronary CT angiography as an example of a diagnostic test, and these results might not apply to all types of diagnostic tests.

Study funding/potential competing interests

PS and MD have received grant support for meta-analyses from the German Federal Ministry of Education and Research (BMBF) and the German Science Foundation (DFG); PS has received lecture fees from Bayer-Schering; MD has received grant support from Heisenberg Program of the DFG for a professorship, European Regional Development Fund, German Heart Foundation/German Foundation of Heart Research, GE Healthcare, Bracco, Guerbet, and Toshiba Medical Systems; MD has received lecture fees from Toshiba Medical Systems, Guerbet, Cardiac MR Academy Berlin, and Bayer (Schering-Berlex); MD is a consultant to Guerbet and one of the principal investigators of multicentre studies on coronary CT angiography sponsored by Toshiba Medical Systems; MD is the editor of *Coronary CT Angiography* and *Cardiac CT*, published by Springer, and offers hands-on workshops on cardiovascular imaging; institutional master research agreements for MD exist with Siemens Medical Solutions, Philips Medical Systems, and Toshiba Medical Systems. Full details of funding and competing interests are in the main paper.