

# Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis

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## ABSTRACT

**Objective** To evaluate the effectiveness of dietary antioxidants in the primary prevention of age related macular degeneration (AMD).

**Design** Systematic review and meta-analysis.

**Data sources** Search of seven databases without limits on year or language of publication, and retrieval of references in pertinent reviews and articles.

**Methods** Two reviewers independently searched the databases and selected the studies, using standardised criteria. Randomised clinical trials and prospective cohort studies were included. Of the 4192 abstracts initially identified, 12 studies (nine prospective cohort studies and three randomised clinical trials) met the selection criteria and were included. Data extraction and study quality evaluation were independently reviewed, using standardised criteria. Results were pooled quantitatively using meta-analytic methods.

**Results** The nine prospective cohort studies included 149 203 people, with 1878 incident cases of early AMD. The antioxidants investigated differed across studies, and not all studies contributed to the meta-analysis of each antioxidant. Pooled results from prospective cohort studies indicated that vitamin A, vitamin C, vitamin E, zinc, lutein, zeaxanthin,  $\alpha$  carotene,  $\beta$  carotene,  $\beta$  cryptoxanthin, and lycopene have little or no effect in the primary prevention of early AMD. The three randomised clinical trials did not show that antioxidant supplements prevented early AMD.

**Conclusions** There is insufficient evidence to support the role of dietary antioxidants, including the use of dietary antioxidant supplements, for the primary prevention of early AMD.

## INTRODUCTION

Early age related macular degeneration (AMD) is characterised clinically by yellow deposits known as drusen and changes in pigmentation of the retina. Late AMD develops when there is an ingrowth of new blood vessels that bleed into the subretinal space or when the macula atrophies. Both conditions usually lead to severe loss of central vision. The pathogenesis of AMD is unclear<sup>1,2</sup>; older age, genetic markers,<sup>3,4</sup> and cigarette smoking are the only risk factors consistently reported.<sup>5-8</sup> Although new treatments have emerged, they are suitable only for a small proportion of people with “wet” type late AMD.<sup>9-12</sup>

Dietary antioxidants have long been suggested as useful for preventing the development and progression of AMD.<sup>13</sup> The retina, with its high oxygen content and constant exposure to light, is particularly susceptible to oxidative damage.<sup>14</sup> A large randomised clinical trial showed that patients with intermediate AMD treated with high dose antioxidant supplements had a 28% reduction in the risk of progression to advanced AMD compared with placebo.<sup>15</sup>

Evidence of the role of dietary antioxidants as a primary preventive measure for AMD remains unclear. Some studies,<sup>16 w1</sup> but not others,<sup>w2 w3</sup> indicate that diets rich in antioxidants may protect against the development of signs of early AMD.<sup>14</sup> We performed a systematic review and meta-analysis of the role of a range of dietary antioxidants in the primary prevention of AMD.

## METHODS

### Data sources

We conducted a systematic review of seven databases—PubMed, Web of Science, Embase, Medline, Cochrane library, abstracts from the Association for Research in Vision and Ophthalmology, and the National Institutes of Health clinical trial databases.<sup>17</sup>

Systematic search of these databases included the terms diet, nutrition, supplement, carotenoids, antioxidants, vitamin, zinc, selenium, iron, copper, lutein, zeaxanthin, beta carotene, and lycopene, with age related macular degeneration, retinal degeneration, drusen, and geographic atrophy. No limits were placed on the year or language of publication. References identified from pertinent articles or books were retrieved.

### Studies and participants

Randomised controlled trials and prospective cohort studies evaluating dietary antioxidants or antioxidant supplements in the primary prevention of AMD were considered for inclusion. We excluded studies in which all participants had early AMD.

For a study to be included it required a clear definition of exposure (dietary intake of vitamin A, vitamin C, vitamin E, zinc, lutein and zeaxanthin,  $\alpha$  carotene,  $\beta$  carotene,  $\beta$  cryptoxanthin, lycopene); participant follow-up for one year or longer; and statistical techniques to adjust for potential confounders.

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**Outcome measures**

The primary study outcome was early AMD (defined as soft drusen with or without retinal pigmentation changes), and late AMD was the secondary study outcome.

**Selection of studies**

Two reviewers independently searched the seven databases, finding 4192 abstracts.

**Data extraction and synthesis**

Data extraction and evaluation of each study's quality were done independently by two reviewers. Data were extracted using a standardised extraction form, and we assessed the methodological quality by using the

Downs and Black instrument for cohort studies,<sup>18-20</sup> The QUOROM statement checklist was used for randomised control trials.<sup>21</sup>

We used fully adjusted odds ratio or relative risk in the meta-analyses, and tested heterogeneity between studies.<sup>22</sup> Sensitivity analyses were performed where possible. We evaluated publication bias by plotting a funnel plot.<sup>23 24</sup>

**RESULTS**

Of the 4192 abstracts screened, 89 were from potentially relevant studies, of which 77 were excluded because they did not meet the inclusion criteria. The remaining 12 studies comprised nine prospective cohort studies<sup>w1-9</sup> and three randomised control trials<sup>w10-w12</sup> (see bmj.com).

**Prospective cohort studies**

The nine prospective cohort studies selected comprised seven independent studies including 149 203 people and 1878 incident cases of early AMD. All of the cohort studies recruited participants between 1980 and 1994 and were conducted in the United States or other Western countries. In most studies, participants were 49 years or older. Follow-up was 5-18 years (mean 9 years). Most studies had initial participation rates of ≥80% and follow-up rates of >75%. All but one study used validated food frequency questionnaires to evaluate intake of antioxidants.

The assessment and definition of AMD varied between studies (see bmj.com). All studies adjusted for age and smoking in their analyses.

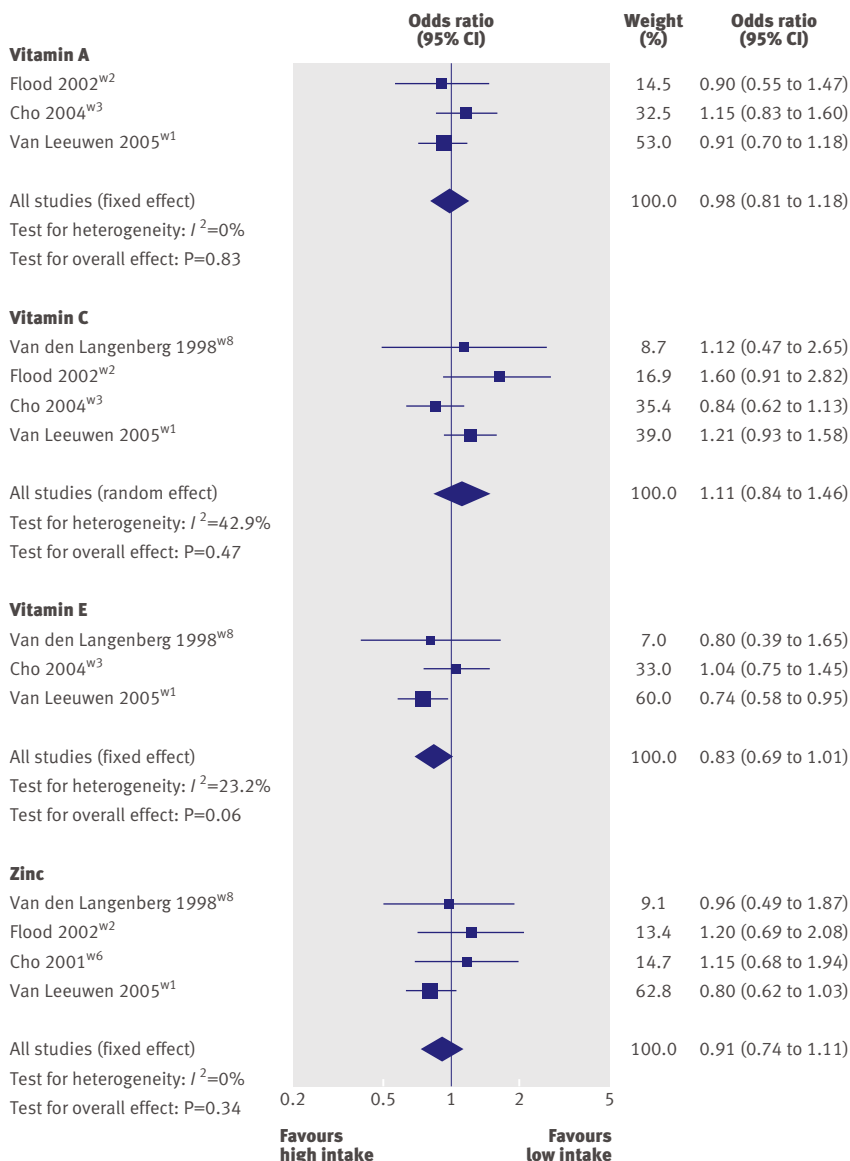
**Randomised controlled trials**

Three randomised control trials evaluated antioxidant supplementation in the primary prevention of AMD.<sup>w10-w12</sup> The vitamin E, cataract, and age related maculopathy trial (VECAT) evaluated vitamin E versus placebo supplementation in an Australian population, while the alpha tocopherol and beta carotene (ATBC) trial evaluated vitamin E or β carotene supplementation, or both, versus placebo in Finland. Neither of these trials found that antioxidant supplements were effective for primary prevention of AMD.

**Dietary antioxidants and early AMD**

The figures show the point estimates for vitamin A, vitamin C, vitamin E, zinc, lutein and zeaxanthin, α carotene, β carotene, β cryptoxanthin, and lycopene in the different studies comparing the highest versus the lowest fifth or fourth of intake for early AMD.

For vitamin A, all three cohort studies that contributed to the pooled analysis reported null associations, and the pooled odds ratio of early AMD, in a comparison of the highest to the lowest vitamin A intake category, was 0.98 (95% confidence interval 0.81 to 1.18). For vitamin C, three of the four



**Fig 1 | Pooled odds ratio for early AMD (highest v lowest dietary intake categories of vitamins and zinc)**

studies reported positive associations and one reported an inverse association. The pooled odds ratio was 1.11 (0.84 to 1.46). For vitamin E, of the

three published cohort studies that contributed to the pooled results, two reported an inverse association and one a null association (pooled odds ratio 0.83 (0.69 to 1.01). The Rotterdam eye study,<sup>w1</sup> which reported a statistically significant finding, contributed 60% weight to the pooled result. When we pooled results from the two high quality studies<sup>w1 w8</sup> the odds ratio of vitamin E was 0.75 (0.59 to 0.94).

For zinc, two of the four studies reported positive associations, one reported a null association, and one an inverse association. The pooled odds ratio of zinc for early AMD was 0.91 (0.74 to 1.11).

Six cohort studies contributed to the meta-analysis of lutein and zeaxanthin. Of these, four reported null associations, one a positive association, and one an inverse association. None of the findings in these studies was statistically significant, with little heterogeneity between studies ( $P=0.80$ ,  $I^2=0\%$ ). The pooled odds ratio for participants in the highest relative to the lowest lutein and zeaxanthin intake category was 0.98 (0.86 to 1.13). The symmetrical shape of the funnel plot indicates that publication bias is unlikely (see [bmj.com](http://bmj.com)).<sup>23 24</sup>

Four published cohort studies evaluated the associations between  $\alpha$  carotene,  $\beta$  carotene,  $\beta$  cryptoxanthin, and lycopene and early AMD (fig 2). For  $\alpha$  carotene, pooled results yielded an odds ratio of 1.05 (0.87 to 1.26). For  $\beta$  carotene, two of four studies reported null associations, one a positive association, and one an inverse association; none was significant. For  $\beta$  cryptoxanthin, the pooled odds ratio of four studies was 1.01 (0.85 to 1.22), and for lycopene it was 1.07 (0.90 to 1.28).

## DISCUSSION

Our analysis examined the role of dietary antioxidants and supplements in primary prevention of AMD and found that a range of dietary antioxidants, including vitamin A, C, and E, zinc, lutein and zeaxanthin,  $\alpha$  carotene,  $\beta$  carotene,  $\beta$  cryptoxanthin, and lycopene, have little or no effect.

### Comparison with other studies

We found few randomised clinical trials, none of which found that vitamin E and  $\beta$  carotene supplements prevented early AMD.<sup>w10-w12</sup>

For vitamin E, the borderline significant pooled odds ratio suggests that vitamin E may be associated with a reduced risk of early AMD. Results from the two randomised control trials do not support a protective effect of vitamin E supplementation, given in doses 2.5-15 times greater than the highest dietary range estimated from these cohort studies.

Results from the alpha tocopherol and beta carotene trial and the physicians' health study are consistent with data from prospective cohort studies. The pooled odds ratio of dietary  $\beta$  carotene intake for early AMD was 1.04 (0.85 to 1.27), comparing

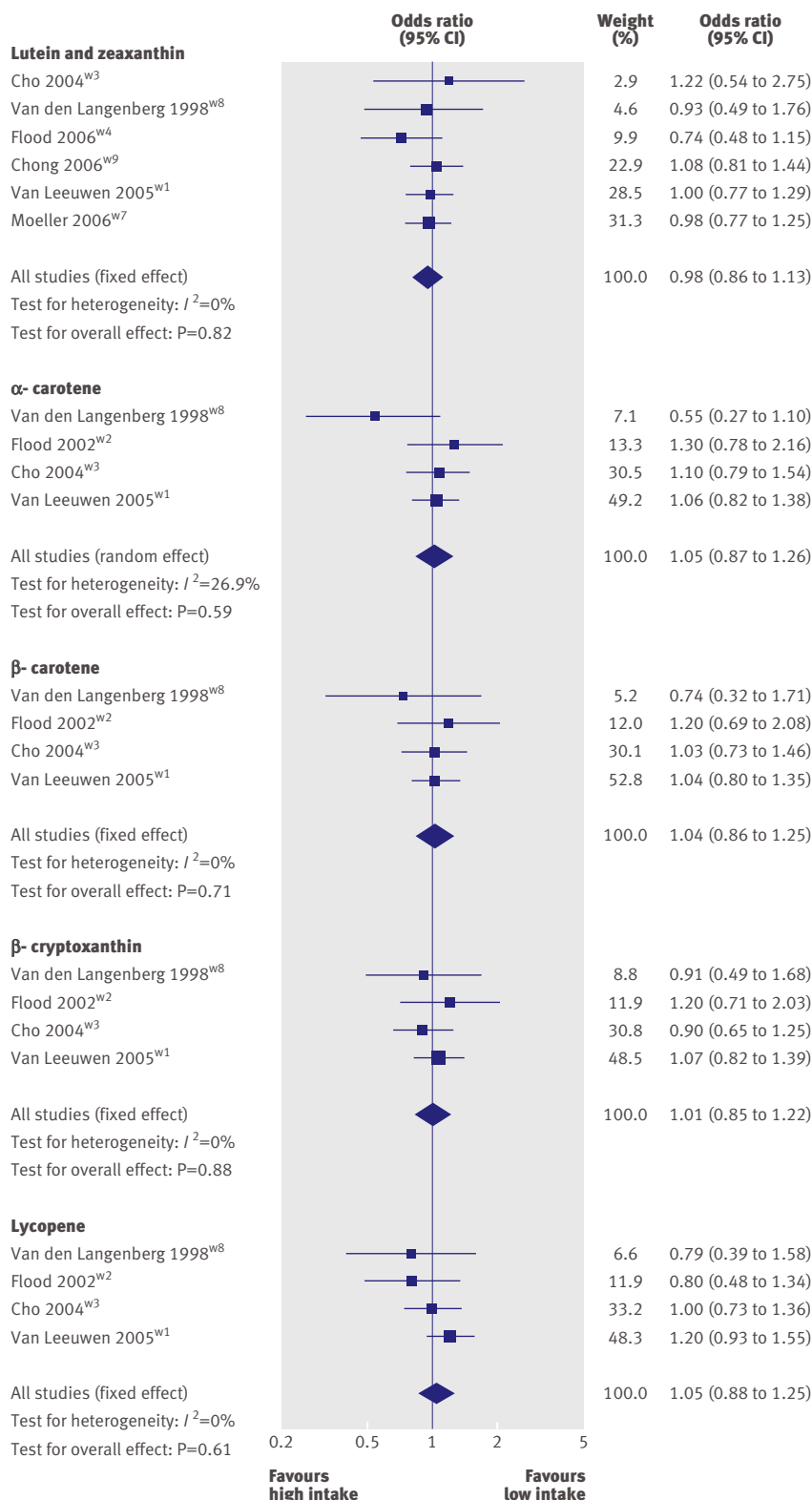


Fig 2 | Pooled odds ratio for early AMD (highest v lowest dietary intake categories of carotenoids)

**WHAT IS ALREADY KNOWN ABOUT THIS TOPIC**

Age related macular degeneration (AMD) is the leading cause of visual loss in older people

Antioxidants have been hypothesised to reduce oxidative damage to the retina, but the effectiveness of dietary antioxidants in the primary prevention of AMD is unclear

**WHAT THIS STUDY ADDS**

Dietary antioxidants had little or no effect in the primary prevention of early AMD in well nourished Western populations

Cigarette smoking remains the only widely accepted modifiable risk factor for the primary prevention of AMD

the highest to the lowest category of dietary  $\beta$  carotene.

Carotenoids have been shown to be good filters of harmful blue light, and their antioxidant properties have been demonstrated *in vitro*.<sup>25</sup> However, results from our review suggest that high antioxidant levels in the healthy retina do little to prevent the development of early AMD. A Cochrane review showed that antioxidant supplements may have a role in delaying the progression of early to late AMD.<sup>26</sup> These contrasting results could imply that uncontrolled oxidative chain reactions of reactive oxygen species may have begun in eyes with AMD at early or intermediate stage, and thus high antioxidant levels at this stage of the disease process may be effective in slowing progression of AMD.

**Strengths and weaknesses of the study**

We performed an extensive search through seven databases and did not limit our searches by language or time.<sup>27,28</sup> The funnel plot shows that publication bias was unlikely.<sup>23,24</sup> We had specified the inclusion criteria for the studies. Studies that were included had adequate follow-up, had sound methods, and were of good quality. All studies had risk estimates adjusted for age, cigarette smoking, and energy intake. There was little heterogeneity between studies.

**Limitations in published studies**

Our review identified important limitations in the current literature. We found few randomised controlled trials. Of the primary prevention trials, the two published randomised controlled trials evaluated only two potential antioxidants. Hence, prospective cohort studies currently provide the best available evidence regarding dietary antioxidants in the primary prevention of AMD. Meta-analysis of observational data is known to have more biases than meta-analysis of randomised controlled trials.<sup>29</sup>

Participants in some of the studies (healthcare professionals, for example) may not be representative of the wider community. Moreover, all studies were conducted in relatively well nourished

populations in developed Western countries, and results may not be generalisable to other countries.

The assessment and definition of AMD varied between studies. Definitions ranged from those based on photographs to those that included visual acuity criteria.

Finally, most studies used food frequency questionnaires to assess dietary intakes of antioxidants, and these questionnaires were administered only once at study baseline.

**Conclusion**

Dietary intake of nine antioxidants evaluated in this systematic review had little or no effect in the primary prevention of early AMD in well nourished Western populations. There is insufficient evidence that antioxidants or supplements prevent the onset of AMD.

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**Competing Interests:** None declared.

**Ethical approval:** Not required.

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- 1 Arroyo JG. A 76-year-old man with macular degeneration. *JAMA* 2006;295:2394-406.
- 2 Chakravarthy U. Age related macular degeneration. *BMJ* 2006;333:869-70.
- 3 Haines JL, Hauser MA, Schmidt S, Scott WK, Olson LM, Gallins P, et al. Complement factor H variant increases the risk of age-related macular degeneration. *Science* 2005;308:419-21.
- 4 Baird PN, Richardson AJ, Robman LD, Dimitrov PN, Tikellis G, McCarty CA, et al. Apolipoprotein (APOE) gene is associated with progression of age-related macular degeneration (AMD). *Hum Mutat* 2006;27:337-42.
- 5 Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP. Smoking and age-related macular degeneration: a review of association. *Eye* 2005;19:935-44.
- 6 Christen WG, Glynn RJ, Manson JE, Ajani UA, Buring JE. A prospective study of cigarette smoking and risk of age-related macular degeneration in men. *JAMA* 1996;276:1147-51.
- 7 Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. *JAMA* 1996;276:1141-6.
- 8 Kelly SP, Thornton J, Lyrtzopoulos G, Edwards R, Mitchell P. Smoking and blindness. *BMJ* 2004;328:537-8.
- 9 Eter N, Krohne TU, Holz FG. New pharmacologic approaches to therapy for age-related macular degeneration. *BioDrugs* 2006;20:167-79.
- 10 Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004;351:2805-16.
- 11 Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419-31.
- 12 Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432-44.
- 13 Jampol LM, Ferris FL 3rd. Antioxidants and zinc to prevent progression of age-related macular degeneration. *JAMA* 2001;286:2466-8.
- 14 Seddon JM, Hennekens CH. Vitamins, minerals, and macular degeneration: promising but unproven hypotheses. *Arch Ophthalmol* 1994;112:176-9.
- 15 Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular

- degeneration and vision loss: AREDS report No 8. *Arch Ophthalmol* 2001;119:1417-36.
- 16 Seddon JM, Ajani UA, Sperduto RD, Hiller R, Blair N, Burton TC, et al. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. *JAMA* 1994;272:1413-20.
  - 17 National Institutes of Health. Clinical Trials Database. <http://clinicaltrials.gov> (accessed November 2006)
  - 18 Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52:377-84.
  - 19 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.
  - 20 Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakaravitch C, Song F, et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7:iii-x, 1-173.
  - 21 Clarke M. The QUORUM statement. *Lancet* 2000;355:756-7.
  - 22 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
  - 23 Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001;54:1046-55.
  - 24 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
  - 25 Britton G. Structure and properties of carotenoids in relation to function. *Faseb J* 1995;9:1551-8.
  - 26 Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. *Cochrane Database Syst Rev* 2006;(4):CD000254.
  - 27 Egger M, Zellweger-Zahner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet* 1997;350:326-9.
  - 28 Moher D, Fortin P, Jadad AR, Juni P, Klassen T, Le Lorier J, et al. Completeness of reporting of trials published in languages other than English: implications for conduct and reporting of systematic reviews. *Lancet* 1996;347:363-6.
  - 29 Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. *BMJ* 1998;316:140-4.

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## Comparison of hospital episode statistics and central cardiac audit database in public reporting of congenital heart surgery mortality

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### ABSTRACT

**Objective** To verify or refute the value of hospital episode statistics (HES) in determining 30 day mortality after open congenital cardiac surgery in infants nationally in comparison with central cardiac audit database (CCAD) information.

**Design** External review of paediatric cardiac surgical outcomes in England (HES) and all UK units (CCAD), as derived from each database.

**Setting** Congenital heart surgery centres in the United Kingdom.

**Data sources** HES for congenital heart surgery and corresponding information from CCAD for the period 1 April 2000 to 31 March 2002. HES was restricted to the 11 English centres; CCAD covered all 13 UK centres.

**Main outcome measure** Mortality within 30 days of open heart surgery in infants aged under 12 months.

**Results** In a direct comparison for the years when data from the 11 English centres were available from both databases, HES omitted between 5% and 38% of infants operated on in each centre. A median 40% (range 0-73%) shortfall occurred in identification of deaths by HES. As a result, mean 30 day mortality was underestimated at 4% by HES as compared with 8% for CCAD. In CCAD, between 1% and 23% of outcomes were missing in nine of 11 English centres used in the comparison (predominantly those for overseas patients). Accordingly, CCAD mortality could also be underestimated. Oxford provided the most complete dataset to HES, including all deaths recorded by CCAD. From three years of CCAD, Oxford's infant mortality from open cardiac surgery (10%) was not statistically

different from the mean for all 13 UK centres (8%), in marked contrast to the conclusions drawn from HES for two of those years.

**Conclusions** Hospital episode statistics are unsatisfactory for the assessment of activity and outcomes in congenital heart surgery. The central cardiac audit database is more accurate and complete, but further work is needed to achieve fully comprehensive risk stratified mortality data. Given unresolved limitations in data quality, commercial organisations should reconsider placing centre specific or surgeon specific mortality data in the public domain.

### INTRODUCTION

The inquiry into congenital heart surgery deaths in Bristol was widely publicised, became a political issue, and has had a profound effect on surgical practice in the United Kingdom.<sup>1</sup> Irrespective of the intense controversy generated by public reporting of mortality statistics in the American healthcare system, the Department of Health has insisted on a similar policy for cardiac surgical outcomes in the UK.<sup>2,3</sup>

The Bristol inquiry used hospital episode statistics (HES) to compare outcomes with those of other congenital cardiac surgical units in the UK.<sup>1</sup> In 2004 the *BMJ* published a paper from the "Dr Foster" Unit at Imperial College, London, which described HES for mortality in congenital heart surgery.<sup>4</sup> The paper suggested that one unit, Oxford, had significantly higher mortality than the national average for open operations in infants.