Authors' objectives
To systematically review the evidence regarding the prevalence of valvular disease after fenfluramine exposure.

Searching
MEDLINE (from 1966 to 2000), Current Contents, the Cochrane Controlled Trials Register (from 1970 to 2000) and a pharmaceuticals database were searched with no language restrictions; some information on the search terms was provided. The indices of conference proceedings from Circulation, European Heart Journal, Journal of the American College of Cardiology and Journal of the American Society of Echocardiography were also searched from 1997 onwards. Principal authors in the field were contacted for information on unpublished work and the reference lists of selected articles were checked.

Study selection
Study designs of evaluations included in the review
Studies with a control group adequate for estimating valve disease prevalence were eligible for inclusion.

Specific interventions included in the review
Studies of fenfluramine or dexfenfluramine, either alone or in combination with phentermine, were eligible for inclusion.

Participants included in the review
Studies of both sexes and any racial group who had been exposed to the drugs of interest were eligible for inclusion. In the included studies, the participants in the intervention group were predominantly female (85%) and white (90%) with a mean age of 46 years. The weighted mean body mass index in both the exposed and unexposed groups was 36 kg/m2. The participants in the unexposed or control groups in the included studies were either: patients from the same medical setting as the exposed group; those who had been referred for echocardiogram for nonvalvular reasons; the placebo group in a clinical trial; from the general community; or from the Framingham cohort. On average, 62% were female, 85% were white and the mean age was 46 years.

Outcomes assessed in the review
Studies assessing valvular regurgitation by echocardiography as defined by Food and Drug Administration (FDA) criteria (i.e. mitral valve regurgitation of moderate or greater severity, or aortic valve regurgitation of mild or greater severity) were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The papers were assessed in relation to inclusion and exclusion criteria, choice of unexposed group, participant attrition, blinding and description of the technical approach used for the echocardiogram. The authors did not state how the papers were assessed for validity, or how many reviewers performed the assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The percentage of participants with FDA criteria and aortic and mitral valve regurgitation were extracted.
Where studies included echocardiography performed at two different times, the earliest echocardiogram was used. A correction factor (0.1) was used if data were reported for individual valves, rather than both valves concurrently.

Methods of synthesis
How were the studies combined?
Summary odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using the Mantel-Haenszel random-effects model.

Publication bias was investigated using a funnel plot together with Begg's and Egger's tests.

How were differences between studies investigated?
The studies were stratified on the basis of the mean duration of treatment (less than 90 days or more than 90 days). The statistical heterogeneity between the studies was investigated (unspecified method), and subgroup analyses were pre-specified for type of exposure (fenfluramine or dexfenfluramine) and valve (mitral or aortic). A sensitivity analysis was used to assess the influence of the method of analysis on the summary estimate.

Results of the review
Nine cross-sectional studies (n=8,778) were included.

More than 90 days duration of treatment (8 studies).
The test for statistical heterogeneity was non significant after one atypical study was removed from the analysis. The prevalence of FDA criteria valvular regurgitation was 12.0% in the group who had taken fenfluramine-derivative diet pills, compared with 5.9% in the unexposed group (OR 2.2, 95% CI: 1.7, 2.7). The findings were not substantially altered when the excluded study was re-included in the analysis (data not provided).

There was no evidence of publication bias, either graphically or based on the formal tests.

Less than 90 days duration of treatment (2 studies).
There was no evidence of statistical heterogeneity. The prevalence of FDA criteria valvular regurgitation was 6.7% in the group who had taken fenfluramine-derivative diet pills, compared with 5.8% in the unexposed group (OR 1.4, 95% CI: 0.8, 2.4). Publication bias was not assessed due to the small sample size.

Sensitivity analyses did not have a substantial effect on the results. The authors also reported data from subgroup analyses based on drug type and mitral or aortic valve disease.

Authors' conclusions
Fenfluramine-associated valvular regurgitation is less common than initially reported, but it is still present in one of 8 patients treated for more than 90 days.

CRD commentary
The review question was clear in terms of the intervention, participants, the outcomes of interest and study design. A number of relevant electronic databases were searched, unpublished data were sought, and no language restrictions were applied; this decreases the possibility of studies being missed. Where appropriate, the possibility of publication bias was investigated. The authors did not report how the study selection, data extraction and validity assessment processes were carried out. Therefore, it is unclear whether attempts were made to minimise the possibility of error and bias. Aspects of study quality were assessed and the authors highlighted areas of possible bias in this group of observational studies. Some study details were reported and appropriate measures of effect were calculated. Statistical heterogeneity was investigated. The authors' conclusions appear to follow from the evidence presented.
Implications of the review for practice and research
Practice: The authors stated that their findings support recommendations from the American College of Cardiology and American Heart Association that individuals who have taken fenfluramine or dexfenfluramine should be carefully assessed with echocardiography if they have symptoms or signs of valvular regurgitation.

Research: The authors did not state any implications for further research.

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