What is already known on this topic

There are more men than women in India

Sex discrimination and bias in favour of male children results in selective termination of female pregnancies

Mortality is high in female infants, girls, and young women

What this study adds

There is an excess of female deaths due to easily treatable conditions

There are a large number of unexplained female deaths, which may be considered as deaths under suspicious circumstances

Could such deaths be an extension into the early neonatal period of female feticide?

The mean per capita income of families in which infants died of unexplained causes was higher than families in which infants dies from diarrhoeal diseases. Therefore it seems that any sex discrimination cannot be explained by extreme poverty. Booth et al found that fetal sex determination was more common among families with higher incomes.[13] The state of Punjab, which has one of the highest per capita income in India (19 001-22 000 rupees per year) has one of the lowest sex ratios in the country (874 females:1000 males), while poor states like Bihar and Orissa (4001-7000 rupees per capita income) have sex ratios of 921 and 972 females per 1000 males, respectively.[1]

As this was a retrospective study we could not look at the circumstances surrounding these unexplained deaths. Further community based prospective studies are needed to examine these issues. Though the 1994 act attempted to alter the adverse sex ratio by banning sex determination tests, this cannot change the attitudes of people towards female infants. Improved access to health care and education of health professionals to pay attention to girls would be beneficial.

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ELPS

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Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies

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Abstract

Objectives To quantify the risk of Alzheimer's disease in users of all non-steroidal anti-inflammatory drugs (NSAIDs) and users of aspirin and to determine any influence of duration of use.

Design Systematic review and meta-analysis of observational studies published between 1966 and October 2002 that examined the role of NSAID use in preventing Alzheimer's disease. Studies identified through Medline, Embase, International Pharmaceutical Abstracts, and the Cochrane Library.

Results Nine studies looked at all NSAIDs in adults aged >55 years. Six were cohort studies (total of 13 211 participants), and three were case-control studies (1443 participants). The pooled relative risk of Alzheimer's disease among users of NSAIDs was 0.72 (95% confidence interval 0.56 to 0.94). The risk was 0.95 (0.70 to 1.29) among short term users (<1 month) and 0.83 (0.65 to 1.06) and 0.27 (0.13 to 0.58) among intermediate term (mostly <24 months) and long term (mostly >24 months) users, respectively. The pooled relative risk in the eight studies of aspirin users was 0.87 (0.70 to 1.07).

Conclusions NSAIDs offer some protection against the development of Alzheimer's disease. The appropriate dosage and duration of drug use and the ratios of risk to benefit are still unclear.

Introduction

Pharmacological treatments of Alzheimer's disease are limited. Recent observational studies, however, have shown that use of non-steroidal anti-inflammatory drugs (NSAIDs) may protect against the development of the disease,[1 2] possibly through their anti-

Table 1 Characteristics of cohort studies evaluating role of NSAIDs and aspirin in preventing Alzheimer's disease. All were community studies

Study	No	Age (years)	Diagnosis of Alzheimer's disease	NSAID assessment	Variable adjustment	Event rate (cases/person years) with NSAIDs *v* non-NSAIDs	Adjusted relative risk or odds ratio (95% CI)	
							NSAID	Aspirin
In't Veld[1]	6989	>55	Clinical investigation	Prescription database	Age, sex, smoking, education, diabetes, antihypertensives, acid blockers	184/29 359 *v* 210/16 715	0.86 (0.66 to 1.09)	1.3 (0.97 to 1.74)
Zandi[2]	3227	>65	Interviews and clinical investigation	Patient interviews	Age, sex, APOE gene, education	79/7048 *v* 22/3017	0.67 (0.40 to 1.06)	0.82 (0.54 to 1.23)
Stewart[9]	1686	<65	Clinical investigation	Patient interviews	Age, sex, education, year of cohort entry	Only adjusted relative risks presented	0.46 (0.24 to 0.86)	0.85 (0.53 to 1.37)
Fourrier[5]	516	>65	MMSE scores†	Patient interviews	Age, education	Only adjusted relative risks presented	2.84 (0.99 to 8.10)	—
Henderson[11]	588	80*	Interviews and clinical investigation	Patient interviews	Age, sex, education, stroke, APOE gene, arthritis medication	Only adjusted relative risks presented	1.66 (0.64 to 4.32)	1.79 (0.72 to 4.45)
Breitner 1995[12]	205	NS	Interviews and autopsy	Patient interviews	Age, sex, acid blockers, insulin	Only adjusted relative risks presented	0.19 (0.02 to 1.49)	0.37 (0.17 to 0.79)

NS=not stated, all older adults.
APOE=apolipoprotein E.
*Mean age.
†Folstein mini-mental state examination.

inflammatory properties.[3] Though one previous systematic review showed a beneficial effect, it included only three studies of NSAIDs.[4]

There remain some unanswered questions. For example, we do not know whether the benefit is a class effect or whether it is restricted to specific agents; the role of aspirin in particular has been examined.[5] We therefore carried out an updated meta-analysis to quantify the risk of Alzheimer's disease in NSAID users and specifically in aspirin users and to discuss the influence of the duration of use on the potential prevention of Alzheimer's disease.

Methods

Study selection—We systematically searched Medline (1966 to October 2002), Embase (1974 to October 2002), International Pharmaceutical Abstracts (a database extending back to 1975), and the Cochrane Library (issue 2, 2002) for all relevant English language articles (see bmj.com).

Data extraction—We included a study if it had clearly stated diagnostic criteria for the outcome of Alzheimer's disease or dementia and explicitly described exposure to NSAIDs. We excluded studies that examined exposure to other analgesics, studies in which vascular dementia was the primary outcome as the biology of this condition differs from that of Alzheimer's disease,[6] and those that might have results duplicated elsewhere. We defined use of NSAIDs as any use any time during the study period. All studies were reviewed by two of the authors, and discrepancies were resolved by consensus with the third author.

Analysis—We carried out three separate analyses. Firstly, we selected studies that explored the risk of Alzheimer's disease in users of all NSAIDs. Secondly, we looked at the risk of Alzheimer's disease specifically among aspirin users. Thirdly, we looked at the risk of Alzheimer's disease according to duration of use of NSAIDs. We used the random effects model to calculate pooled relative risks and 95% confidence intervals. Odds ratios were considered an approximation of relative risks. Publication bias was assessed with a funnel plot.

Results

We identified 15 potential studies. Details of the inclusion and exclusion criteria can be found on bmj.com. We included nine studies in the analysis of use of any NSAID.[1 2 5 7–12] Six were cohort studies (13 211 participants, table 1)[1 2 5 9 11 12] and three were case-control studies (1443 participants, table 2).[7 8 10] We included eight studies for the analysis of aspirin users,[1 2 8–12 13] of which five were cohort studies[1 2 9 11 12] and three were case-control studies.[8 10 13]

The pooled relative risk of Alzheimer's disease was 0.84 (0.54 to 1.05) among users of NSAIDs in the cohort studies, 0.62 (0.45 to 0.82) among users of NSAIDs in the case-control studies, and 0.72 (0.56 to

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Table 2 Characteristics of case-control studies evaluating role of NSAIDs and aspirin in preventing Alzheimer's disease

Study (setting)	No	Age	Diagnosis of Alzheimer's disease	NSAID assessment	Variable adjustment	Cases	Controls	Adjusted relative risk or odds ratio (95% CI)	
								NSAID	Aspirin
Breitner 1994[10] (WW II twins)	46	75*	Telephone interview	Questionnaire	None	Only crude OR presented		0.50 (0.10 to 2.23)	0.56 (0.16 to 1.81)
Lindsay[13] (community)†	4915	>70	Clinical investigation	Questionnaire	Age, sex, education	45/152	1224/3086	—	0.85 (0.55 to 1.31)
CSHA[7] (community and institution)‡	793	>65	Clinical investigation	Questionnaire	Age, sex, education, community or hospital status	61/224	205/529	0.55 (0.37 to 0.82)	—
Beard[8] (community)	604	>65	Medical records	Medical records	Age and sex matched	9/155	18/157	0.79 (0.20 to 1.38)	0.90 (0.51 to 1.59)

WW II=second world war.
*Mean age.
†Only data on aspirin used from this study.
‡ Canadian study of health and ageing.

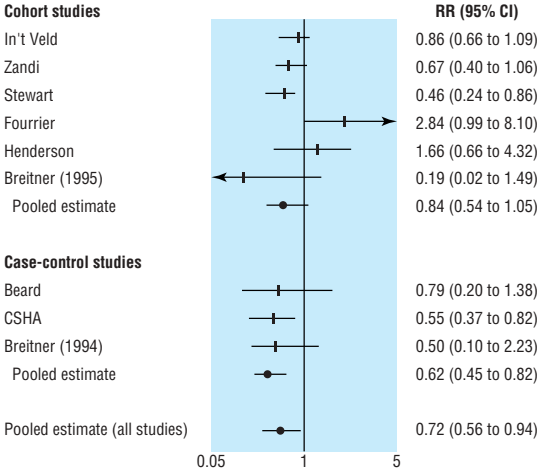
0.94) in both (figure). The pooled relative risk for aspirin users was 0.87 (0.70 to 1.07, P=0.79 for heterogeneity). For intermediate and long term NSAID users the relative risks were 0.83 (0.65 to 1.06, P=0.34 for heterogeneity) and 0.27 (0.13 to 0.58, P=0.06 for heterogeneity).

The results from cohort studies and case-control studies were generally similar for both analyses, with little statistical heterogeneity (see bmj.com). We did, however, find slight heterogeneity among the cohort studies for any NSAID use. The source of this heterogeneity was the study by Fourrier et al,[5] possibly because they diagnosed dementia using the Folstein mini-mental state exam. This has limited accuracy in distinguishing between early Alzheimer's disease and normal cognition.[14] Despite the relatively small number of studies, funnel plot analysis did not indicate significant publication bias (see bmj.com).

Discussion

Our results, based on analysis of a large number of patients, show that use of an NSAID lowers the risk of developing Alzheimer's disease. The magnitude of this benefit is consistent with that found in a recent large study with long follow up data.[1] Our results also show a greater benefit with long term rather than intermediate term use. This may be one explanation for the lack of benefit seen in two of the studies included in this review in which participants were followed up for a relatively short period and therefore may not have had enough time to benefit from the protective effects of NSAIDs.[5 11] An editorial suggested that there may be an association between duration and response for NSAIDs in preventing Alzheimer's disease, with at least two years of exposure necessary to obtain full benefit.[3]

The meta-analysis also indicates that aspirin has a protective effect, although this result was not significant, probably because of the small number of studies that specifically evaluated the effects of aspirin. There are theoretical reasons why aspirin may differ from other NSAIDs in terms of effectiveness.[15 16] At present, however, there are insufficient data on which to base any comparisons between aspirin and other NSAIDs in the prevention of dementia.



Relative risks (95% confidence intervals) from studies of NSAID use and effect on Alzheimer's disease

What is already known on this topic

Few treatments exist for people with Alzheimer's disease, and recent efforts have focused on preventive measures

Observational studies have suggested that non-steroidal anti-inflammatory drugs (NSAIDS) protect against Alzheimer's disease, but results have been inconsistent

What this study adds

Use of NSAIDs seems to lower the risk of developing Alzheimer's disease in adults aged >55 years

Benefits may be greater the longer NSAIDs are used

The evidence behind the potential preventive use of aspirin is not robust

Although a few small randomised controlled trials have shown some beneficial effects on cognition with use of NSAIDs in patients with established Alzheimer's disease,[17 18] no randomised controlled trial to date has looked at the prevention. Currently the relative benefit of COX 2 selective inhibitors over traditional NSAIDs is purely speculative. However, studies are now underway to determine the role of COX 2 selective inhibitors in the prevention of Alzheimer's disease.[19 20]

Limitations of study

Although publication bias does not seem to be a problem in this analysis we cannot exclude it as the funnel plot may not detect publication bias when the number of studies is small. Secondly, the possibility of confounding and bias may be more significant in meta-analyses of observational studies than in meta-analyses of randomised trials, and statistical adjustment for confounding variables in observational studies may not entirely resolve these problems. Case-control studies are particularly at risk of biased patient selection that may unduly weight the outcome in favour of the exposure under evaluation. In our review, the case-control studies all tended to support NSAIDs having a protective effect, while the cohort studies had more variable results (figure). Another relevant bias is recall bias as in some of the studies information on NSAID use was obtained by interviewing patients.

There were important differences in study design, including the assessment of exposure and adjustments for confounding factors (see tables 1 and 2). Adjustments were not always made for important risk factors for Alzheimer's disease such as family history and apolipoprotein E status. These differences in study design may give rise to clinical heterogeneity, which may not be fully reflected in the results of our statistical tests of heterogeneity. Finally, the restriction of our systematic review to English language studies may have resulted in language bias with potentially relevant studies published in other languages being missed.[21]

Conclusion

In light of the growing evidence from observational studies and the current absence of evidence from ran-

domised controlled trials, our systematic review lends support to the hypothesis that NSAIDs may protect against the development of Alzheimer's disease. The appropriate dose, duration, and ratios of risk to benefit are still unclear.

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Prevalence of five common clinical abnormalities in very elderly people: population based cross sectional study

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As the prevalence of disease rises with age, the number of people with unidentified abnormalities is also likely to increase. We assessed the number of previously known and newly identified patients with anaemia, diabetes mellitus, thyroid dysfunction, atrial fibrillation, and hypertension in a population based sample of 85 year old people.

Participants, methods, and results

The study design and baseline characteristics of the 599 participants in the Leiden 85 plus study have been published elsewhere.[1] All participants gave informed consent. We used standard laboratory techniques to identify anaemia, diabetes mellitus, and thyroid dysfunction. Atrial fibrillation, including flutter, was identified on an electrocardiogram. Hypertension was identified by averaging two standardised blood pressure readings measured with a sphygmomanometer at two separate visits. For 40 people a blood sample, electrocardiogram, or blood pressure measurement was not available. Furthermore, we excluded all 31 residents of nursing homes because they do not voluntarily consult a general practitioner but are continuously monitored by a nursing home physician.

We obtained the medical history of the 528 remaining people from their general practitioner. By including a local general practitioner (JG) in our research team, we managed to get all 60 general practitioners in Leiden to cooperate with us. Moreover, all pharmacies in Leiden provided detailed information on prescribed drugs for all patients. All drugs were encoded according to the WHO Anatomical Therapeutic Chemical (ATC) classification.[2]

Abnormalities were considered known when a positive medical history was present or when patients were currently using one of the following ATC coded drugs: B03 for anaemia, A10 for diabetes mellitus, H03 for thyroid dysfunction, B01AA04/B01AA07 combined with C01AA05 for atrial fibrillation, or C02, C03, C07, C08, or C09 for hypertension.

The definitions for newly identified clinical abnormalities were: haemoglobin <130 g/l (<8.1 mmol/l) in men or <120 g/l (<7.5 mmol/l) in women for anaemia[3]; non-fasting serum glucose concentrations >11.0 mmol/l for diabetes mellitus; serum thyroid stimulating hormone <0.3 mU/l and serum free thyroxin >24 pmol/l (hyperthyroidism) or thyroid stimulating hormone >4.8 mU/l and free thyroxin <10 pmol/l (hypothyroidism) for thyroid dysfunction; Min-

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