REVIEW

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Systematic review and meta-analysis of observational studies to check the protective role of non-steroidal anti-inflammatory drugs in Alzheimer's disease

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Alzheimer's disease (AD) is a major neurodegenerative disease, affecting more than two third cases of dementia in the world. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used anti-inflammatory analgesic agents representing 7.7% of worldwide prescriptions of which 90% are in patients over 65 years old. Based on mixed findings a systematic review and meta-analysis were conducted to develop a better understanding of the protective role of NSAIDs in AD. We used three database PubMed, Web of Science, and Embase to identify the literatures. The studies following cohort and case-control design were investigated separately to check the effect of NSAIDs on AD, by the using their fundamental indicators (relative risk and odds ratio). The fixed effect or random effects model were used to estimate the pooled relative risk and pooled odds ratio separately for both the study design, based on magnitude of heterogeneity. A total of 14 studies were selected for meta-analysis. Eight studies were following cohort study design, whereas, six studies were following case-control study design. In meta-analysis of cohort studies, the pooled relative risk was 0.67 with 95% C.I 0.39 to 1.15, which was statistically insignificant. In meta-analysis of case-control studies, the pooled odds ratio was 0.71 with 95% C.I 0.46 to 1.10, which was statistically insignificant. NSAIDs do not act as a protective factor for Alzheimer's disease. Additionally, methodologically sound randomized controlled trials are required to produce a robust result.

Key words: Alzheimer's disease, NSAIDs, meta-analysis, relative risk, odds ratio

INTRODUCTION

Alzheimer's disease (AD) is the crucial neurodegenerative malady affecting the geriatric population. Two third cases of dementia are affected due to AD across globe (Aisen et al., 2002). Five million is the burden of Alzheimer's disease and related dementias in 2014 and in 2015 it has been projected to be more than 13.9 million by 2060 (CDC Newsroom, 2016). It along with other dementias is a major global health challenge, which may lead to a high cost of health (Prince et al., 2013, 2016; Wu et al., 2017). Multi factors which are responsible for AD pathogenesis are age, environment, and genetic factors, along with the accumulation of senile plaques and neurofibrillary tangles (Miguel-Álvarez et al., 2015). The pathogenic cascade is initiated by either all factors together or one leads to disease onset and the subsequent factors are involved in disease progression (Talwar et al., 2016). As per neuroinflammatory theory proposed for the pathogenesis of AD is after the brain damage the inflammation of the microglia appears (Reines et al., 2004; Thal et al., 2005). The same has been reported in the literatures based on the brain of patients with AD. These studies have shown chronically activated microglia and increased expression of the cyclo-oxygenase-2 enzymes in neurotic plaques and tangles (Cagnin et al., 2001).

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Non-steroidal anti-inflammatory drugs (NSAIDs) are universally consumed anti-inflammatory analgesic factors representing worldwide prescriptions of 7.7%, out of which 90% are in patients over 65 years old (Veronese et al., 2017). In the United States, the NSAIDs users increased by 40% between years 2005 and 2010 of which 26% report using more than the recommended dose (Etminan et al., 2003; Scarpini et al., 2003; Zhou et al., 2014). Several epidemiological studies have reported the protective role of NSAIDs against AD on its prolonged use in low doses by slowing down cognitive decline, especially in patients with mild to moderate AD (Aisen et al., 2003). NSAIDs inhibit COX-2, which is unregulated in neurons leading to neurodegeneration in AD (McGeer et al., 1996). In addition to it, studies show that a small number of NSAIDs like ibuprofen, sulindac acid, and indomethacin have anti-amyloidogenic activity *in vivo*, a function that is independent of COX inhibition (McGeer et al., 1996; Stewart et al., 1997).

In literature, studies show contradictory observations. Veld et al. (2001) suggested that NSAIDs may be useful in the treatment of AD whereas, Wichmann et al. (2016) found no significant role of NSAIDs in the progression of AD. Hence, a systematic review and meta-analysis need to be conducted for generating promising evidence and to develop a better understanding of the protective role of NSAIDs in AD.

METHODS

Design

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews Meta-Analysis of Observational Studies in Epidemiology (Stroup et al., 2000) statements and followed a prior defined and published protocol (Asthana et al., 2023a). Our protocol has been registered on PROSPERO. The registration number is CRD42022301179.

Search strategy to identify studies

Two investigators (ST and AA) independently searched three databases (PubMed, Web Science, and MEDLINE) from 1st January 2000 to 31st December 2021, with no language restriction. Also, authors of studies other than the English language were contacted to provide their English translations. The keywords used for searching literature in the above-mentioned database were "cohort" OR/AND "longitudinal" OR/AND "prospective" OR/AND "case-control" OR/AND "retrospective" OR/AND "Alzheimer disease" OR/AND "AD" OR/AND "NSAIDs" OR/AND "NSAID" OR/AND "ibuprofen" OR/AND "rofecoxib" OR/AND "celecoxib" OR/AND "aspirin" OR/AND "naproxen" OR/AND "nimesulide" OR/AND "tarenflurbil" OR/AND "indomethacin" or more of a combination of these terms.

The inclusion and exclusion criteria for systematic review and meta-analysis

The eligibility criteria for including the study in the present meta-analysis followed PECO (Morgan et al., 2018) statement. P (Patients), Patients with Alzheimer's disease. E (Exposure), The patient's exposed to NSAID's. C (Comparator), The patients not exposed to NSAIDs. O (Outcome), The relative risk (RR) and odds ratio (OR) reporting relationship between NSAIDs and AD. Similarly, studies were excluded if: 1) They were not conducted in humans and used non-placebo group; 2) for cohort study design, relative risk was not given and neither the data; 3) for the case-control study design, odds ratio was not given and neither the data; 4) the studies which are not published in English and also its translation is unavailable.

Data extraction

Two investigators (ST and AA) extracted data from the articles in a standard file and third independent investigator (RA) validated data extraction. The data extraction from the selected studies for meta-analysis were as follows: 1) last name of the author; 2) year of the publication; 3) country; 4) study design; 5) total participant in study; 6) types of NSAIDs; 7) age of participants; 8) duration of study; 9) total AD patients in exposed group; 10) total AD patients in unexposed group.

If relative risk and odds ratio are not given then the reported frequency is used from the primary studies for analysis.

The relationship between the NSAIDs use and AD given by RR and OR in cohort and case-control study designs, respectively. Also, the data to estimate the RR and OR from both the respective designs were considered as an important outcome.

Quality of studies

Quality of studies included for meta-analysis was done by Newcastle-Ottawa Scale (NOS) for non-randomized studies (NEWCASTLE-OTTAWA SCALE CODING

MANUAL FOR COHORT STUDIES – Health Disparities in Quality Indicators of Healthcare Among Adults with Mental Illness – NCBI Bookshelf, n.d.). Three areas in which studies are judged by this scale are: 1) selection of study groups; 2) comparability of the group's; 3) ascertainment of either exposure or outcome of interest done by the star system.

Statistical analysis

The pooled RR and OR was estimated from cohort and case control studies selected for meta-analysis, respectively. The Q-statistic was used to examine the heterogeneity across the studies and I^2-statistic explains the degree of heterogeneity in effect size across all the studies. Based on these two measures of heterogeneity (Q and I^2), the appropriate model (fixed effect model and random effects model) is chosen to generate pooled effect size. If the degree of heterogeneity in effect size was significantly high (i.e., I^2>30%) random effect model is used; otherwise, fixed effect model is used (Asthana et al., 2023b; Cochrane Handbook for Systematic Reviews of Interventions, n.d.).

The forest plot was made to display the result of individual included studies along with their 95% confidence interval and pooled effect size with its 95% confidence interval is also displayed at the bottom of the graph. The funnel plot, the graphical method to check the publication bias of studies was also constructed. The funnel plot is a visual and informal method to examine the publication bias, but there are quantitative methods like the rank-correlation test available to examine the existence of publication bias. Both method (graphical and quantitative) will be used in the present study. All the estimates and plots were created by using "meta" package from RStudio (4.3.1.).

RESULTS

Characteristics of study

The PRISMA flow chart presents the stage wise selection of studies for meta-analysis (Fig. 1). A total of 1400 relevant studies were identified during a literature search on the effect of NSAIDs for the treat-

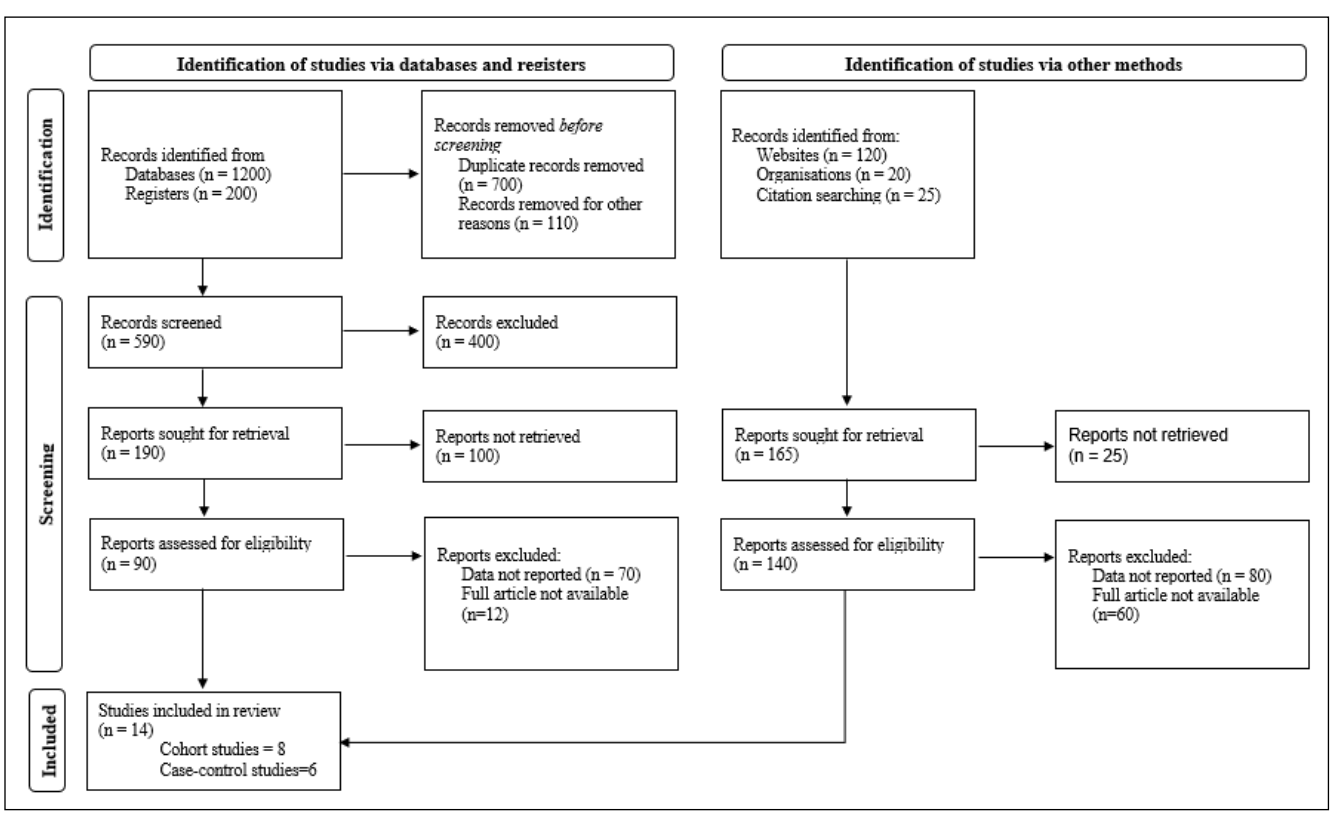

Fig. 1. PRISMA flow chart for inclusion of studies for systematic review and meta-analysis. The total of 590 articles were screened and only 90 studies were included following stringent inclusion criteria. Finally, 14 studies (8 cohort and 6 case-control studies) were included in final meta-analysis.

ment of AD. Out of 590 screened studies, initially, 14 studies could be included for meta-analysis following inclusion criteria, and the rest 580 studies were excluded. In 14 included studies, 8 were cohort studies and 6 were case-control studies. The characteristics of 14 studies included in meta-analysis is displayed in Table 1.

In cohort studies, Zandi et al. (2002), Pp et al. (2002), Wichman et al. (2016), and Aizen et al. (2005) used two drugs, whereas, Cornelius et al. (2004) used three drugs and Xue et al. (2018) used seven drugs, therefore a total number of studies becomes 19 for meta-analysis. Similarly, In the case-control study, Broe et al. (2000) used two drugs, therefore the total number of studies becomes 7 for meta-analysis.

Meta-analysis of cohort studies

Meta-analysis was performed using 19 studies with total number of 273728 participants. Heterogeneity across 19 studies in effect size was statistically significant (Q=1802.68 and $p<0.05$). The degree of heterogeneity was I^2=99.0% with 95% C.I. 98.8% to 99.2%. Therefore, random effect model was used to estimate pooled RR. Nine studies have shown RR great-

Table 1. Characteristics table for studies selected for meta-analysis.

S. No.	Author	Year	Country	Study design	Total participants	Type of NSAIDs	Age	Duration	Total AD patients in exposed/ case group	Total AD patients in unexposed/ control group
1	Aizen et al.	2005	Israel	cohort study design	49	Rofecoxib, Ibuprofen	>44 years	7 days	15	15
2	Broe et al.	2000	Australia	case-control study	647	Aspirin, NSAIDs	75 years	4 years	18	190
3	Chang et al.	2016	Taiwan	cohort study design	28321	Aspirin	>50 years	8 years	93	308
4	Cornelius et al.	2004	Sweden	cohort study design	1301	Aspirin, NSAIDs	>75 years	6 years	131	919
5	Dregan et al.	2015	UK	case-control study	20673	NSAIDs	72 years	14 years	42349	158460
6	Landi et al.	2003	Italy	case-control study	2708	NSAIDs	72.2 years	4 years	56	269
7	Linsday et al.	2002	Canada	cohort study design	4615	NSAIDs	>65 years	5 years	45	1224
8	Veld et al.	2001	Netherlands	cohort study design	6989	NSAIDs	>65 years	8 years	3	210
9	Vlad et al.	2008	USA	case-control study	246199	NSAIDs	74 years	5 years	20825	79134
10	Wichman et al.	2016	USA	cohort study design	4926	Aspirin, non-aspirin NSAIDs	>43 years	2 years	214	133
11	Wolfson et al.	2002	Canada	case-control study	599	NSAIDs	>75 years	1 years	17	327
12	Xue et al.	2019	Taiwan	cohort study design	68676	Celecoxib, etoricoxib, naproxen, diclofenac	>50 years	180 days	213	8137
13	Yip et al.	2005	USA	case-control study	691	NSAIDs	70 years	6 years	24	66
14	Zandi et al.	2002	USA	cohort study design	3227	Non-aspirin NSAIDs	>65 years	3 years	59	143

er than 1 (1.32(1.02, 1.69), 1.11(0.89,1.40), 1.78(0.76, 4.19), 1.25(0.91, 1.72), 1.13(0.85, 1.50), 1.12(0.89, 1.40), 1.03(0.80, 1.32), 1.74(0.67, 4.52), 1.01(0.70, 1.46)) and 10 studies shows RR less than 1 (0.16(0.05, 0.49), 0.66(0.41, 1.05), 0.93(0.63, 1.39), 0.64(0.51, 0.80), 0.82(0.54, 1.26), 0.56(0.24, 1.32), 0.32(0.10, 0.97), 0.77(0.37, 1.61), 0.01(0.01, 0.01), 0.97(0.47, 2.02). The pooled effect size was 0.67 with 95% C.I. 0.39 to 1.15 which was statistically insignificant (p=0.15). The lowest weight was assigned to Veld et al. (2001) and Xue et al. (2018) 4.5% and the highest weight was assigned to Linsday et al. (2002), Aizen et al. (2005), Chang et al. (2016), and Xue et al. (2018) is 5.6%. The forest plot represents the meta-analysis of cohort studies (Fig. 2). The funnel plot shows only 3 studies inside an inverted funnel (Fig. 3). A rank correlation test shows statistically significant result for publication bias (p<0.05).

Meta-analysis of case-control studies

Meta-analysis was performed using 7 studies with total observations of 783826 and the number of events was 301735. Heterogeneity across 7 studies in effect size was statistically significant (Q=3554.89 and p<0.05). The degree of heterogeneity was I^2=99.8% with a 95% CI of 99.8% to 99.9%. Therefore, random effect model was used to estimate pooled OR. Here, 1 study shows OR greater than 1, [1.11(1.09, 1.12)] whereas 06 studies have shown an odds ratio less than 1 [0.47(0.24, 0.91), 0.28(0.12, 0.66), 0.65(0.33, 1.27), 0.77(0.57, 1.04), 0.49(0.31, 0.80), 0.87(0.86, 0.88)]. The pooled OR was 0.71 with 95% C.I 0.46 to 1.10, which was statistically insignificant (p=0.12). Two studies (Vlad et al., 2008 and Dregan et al., 2015) were given the highest weight (17.3%) and Broe et al., 2000 got the lowest weight (10.3%). The forest plot represents the meta-analysis of cohort studies (Fig. 4). The funnel plot shows 6 studies out of the inverted funnel (Fig. 5). Rank-correlation test shows a statistically insignificant result for publication bias (p=0.88).

Quality of studies

NOS score for 7 cohort studies (Veld et al., 2001, Linsday et al., 2002, Cornelius et al., 2004, Aizen et al., 2005, Wichman et al., 2004, Chang et al., 2016, and Xue et al., 2018) was above the threshold i.e., these studies came under good quality domain. Whereas, Zandi

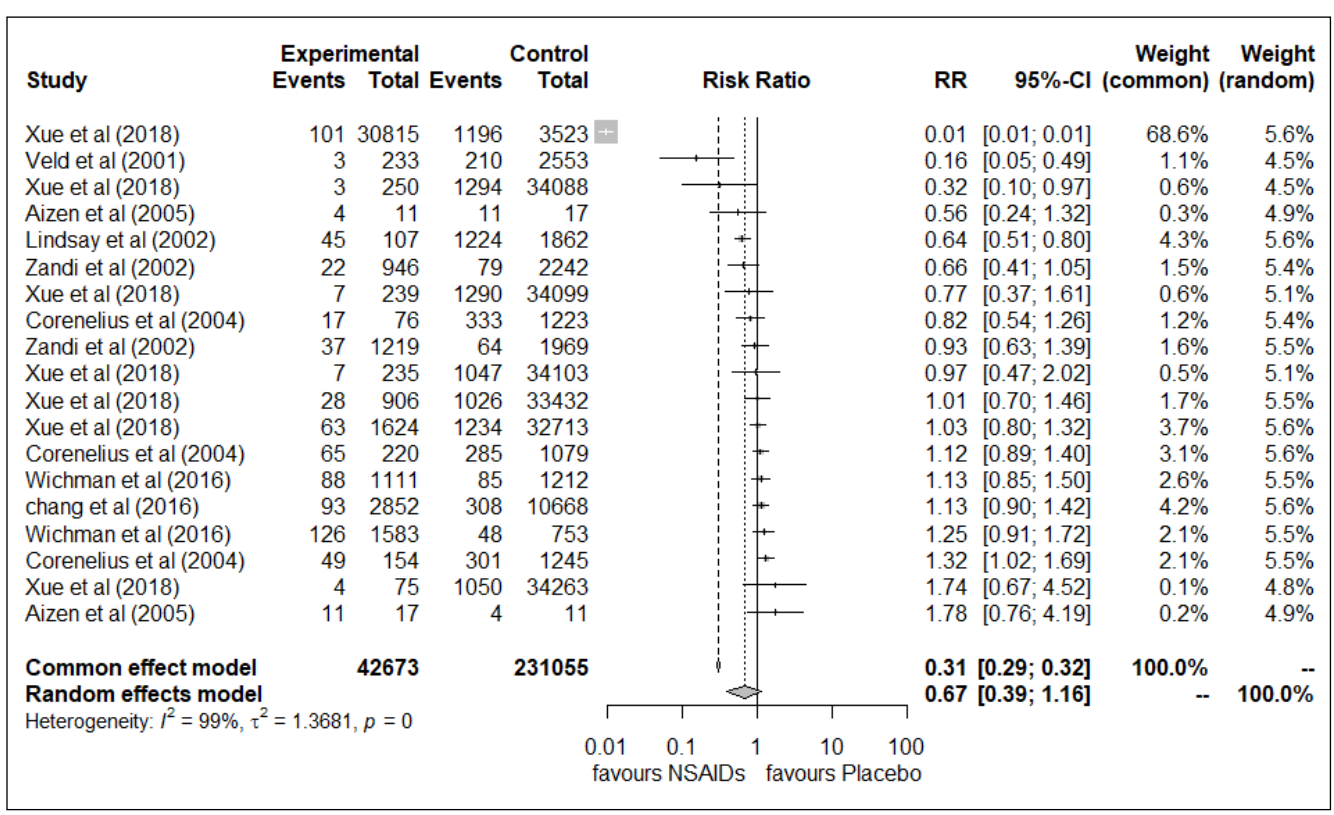

Fig. 2. Graphical display of results of individual studies and summary effect size with 95% C.I for meta-analysis of relative risk. In meta-analysis of 19 cohort studies, the I^2 statistics was 99%. Hence, the pooled RR using random-effects model was 0.67 with 95% CI 0.39 to 1.16.

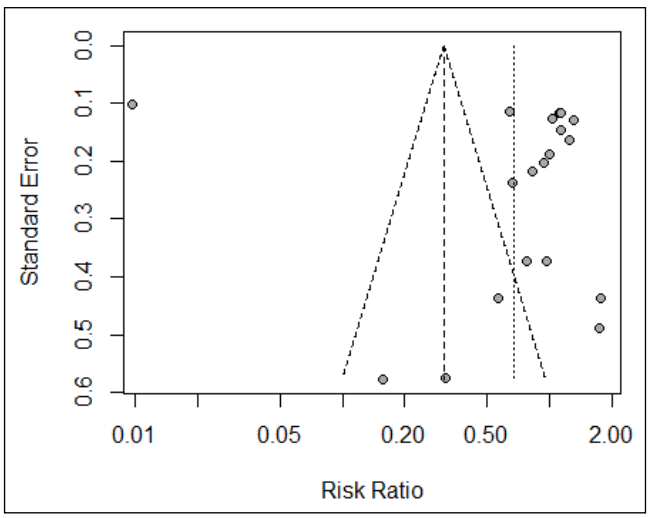

Fig. 3. Funnel plot to check publication bias of studies following cohort study design. Only three studies were present inside the inverted funnel created for case-control studies. Hence publication bias was present.

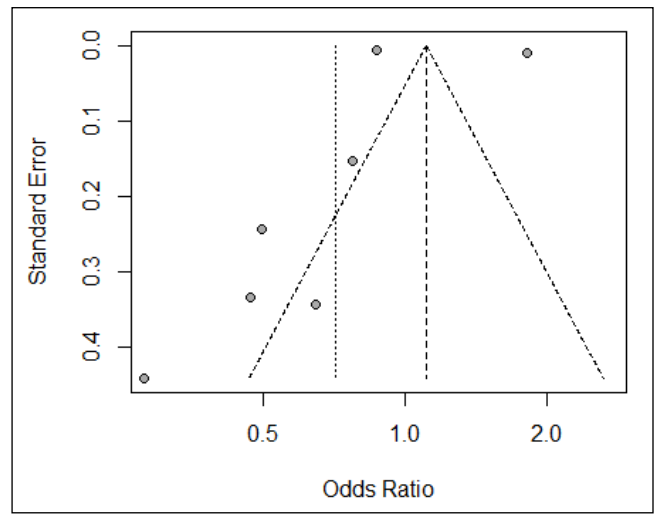

Fig. 5. Funnel plot to check publication bias of studies following case-control study design. Only one study was present inside the inverted funnel created for case-control studies. Hence publication bias was present.

et al. (2002) came under fair quality domain. The NOS results for cohort studies are displayed in Table 2. For case-control studies, all the studies were in good quality domain i.e., NOS score ranges from 8 to 9. The NOS results for case-control studies are displayed in Table 3.

DISCUSSION

The meta-analysis performed on the cohort study design shows the insignificant result for use of NSAIDs in AD. The graphical method and mathematical method shown the presence of publication bias. Similarly, the meta-analysis performed on the case-control study design shows the insignificant result for use of NSAIDs in AD. The publication bias was present by use of the graphical method, but not by mathematical method.

During the study, no evidence of the protective effect of NSAIDs was observed across 8 cohorts and 6 case-control studies, when exposed to years before the development of symptoms of AD. We can improve our understanding on relationship between NSAIDs and AD by making several conjectures. First, the age of subjects taken in the present meta-analysis, out of 15 studies, 11 studies were done in diagnosed AD cases having more than 65 years of age. AD starts to occur

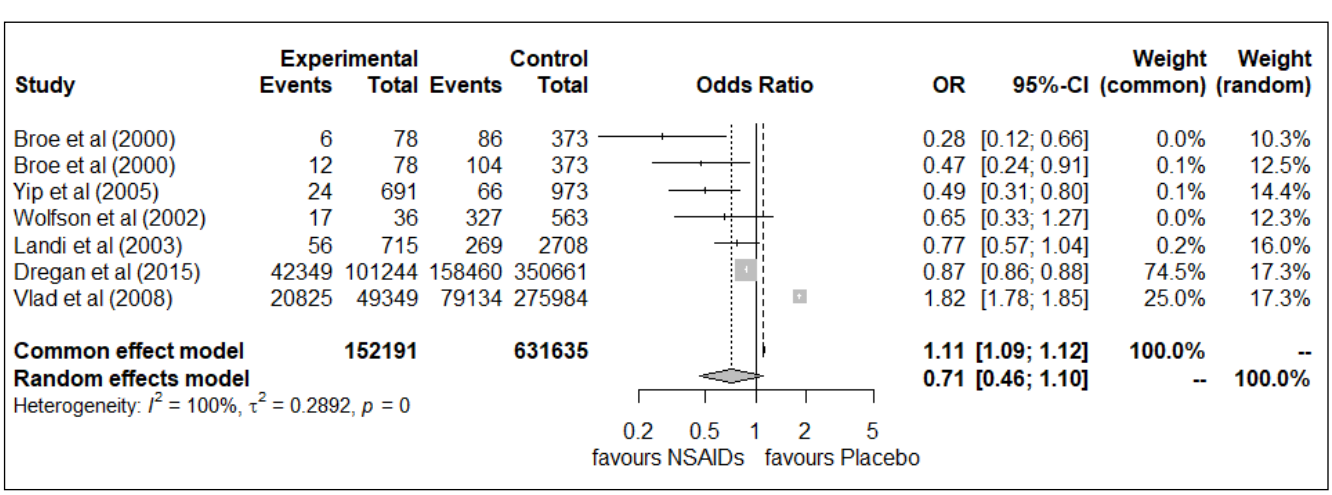

Fig. 4. Graphical display of results of individual studies and summary effect size with 95% C.I for meta-analysis of odds ratio in Alzheimer's disease. In meta-analysis of 07 case-control studies, the I^2 statistics was 100%. Hence, the pooled OR using random-effects model was 0.71 with 95% CI 0.46 to 1.10.

Table 2. Newcastle-Ottawa scale result for cohort studies included in the meta-analysis.

Study (year)	Selection				Comparability	Outcome			Score
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	The outcome of interest is not present at the start of the study	Comparability of the cohort on basis of design or analysis	Assessment of outcome	Sufficient follow-up time	Adequacy of follow-up	
Veld et al. (2001)	*	*	*	*	**	*	*	*	9/9
Zandi et al. (2002)	*	*			*	*		*	5/9
Linsday et al. (2002)	*	*	*		*	*	*	*	7/9
Cornelius et al. (2004)	*	*	*		*	*	*	*	7/9
Aizen et al. (2005)	*	*	*	*	**	*		*	8/9
Wichman et al. (2016)	*	*	*	*	**	*	*	*	9/9
Chang et al. (2016)	*	*		*	*	*	*	*	7/9
Xue et al. (2018)	*	*	*		*	*	*	*	7/9

Table 3. Newcastle-Ottawa scale result for case-control studies included in the meta-analysis.

Study (year)	Selection				Comparability	Outcome			Score
	Adequate case definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and control on basis of design or analysis	Ascertainment of exposure	Same method for ascertainment of case and control	Non-response rate	
Broe et al. (2000)	*	*	*	*	*	*	*	*	8/9
Wolfson et al. (2002)	*	*	*	*	*	*	*	*	8/9
Landi et al. (2003)	*	*	*	*	*	*	*	*	8/9
Yip et al. (2005)	*	*	*	*	**	*	*	*	9/9
Vlad et al. (2008)	*	*	*	*	**	*	*	*	9/9
Dregan et al. (2015)	*	*	*	*	**	*	*	*	9/9

over 20 years before cognitive decline with pathological changes. Szekely et al. (2008a) suggested a reduced risk of AD in NSAID users was significant in the younger age group. Hayden et al. (2007) also reported use of NSAIDs before 65 years age group had lower cognitive decline as compared to individuals more than 65 years of age group. Therefore, it can be inferred that NSAIDs might show a protective effect at an early stage of AD but not effective in the later stage of AD. It suggested performing RCT to study NSAID's role as a protective effect in AD after stratification of subjects by age. Second, the duration of exposure to NSAIDs can be taken as the second hypothesis similar to the age of subjects, NSAIDs exposure for a long period cannot reverse the outcome. As suggested by Szekely et al. (2008b) subjects with less age have less risk of AD, therefore it can be inferred that subjects who were exposed to NSAIDs for a longer period have less risk of development of AD. Third, the duration in the 15 studies included varies from 7 days to 14 years, and the dosage of NSAIDs varies from 12.5 mg to 1000 mg per day which could be a major factor that may affect the therapeutic relevance of ϒ–secretase modulator effect in AD subjects (Szekely et al., 2004). Fourth, co-morbidities in AD subjects may be taken as one of the important factors for such results, which modifies the protective effect (Veronese et al., 2017). Fifth, apolipoprotein E in AD subjects plays a vital role in the occurrence of the disease (Szekely et al., 2008b). Every individual have a unique gene, therefore NSAIDs will react differently for different individuals. APOE gene may alter the association between NSAID use and the risk of developing AD. Study Szekely et al. (2008) has found a lower risk of AD only in NSAIDs users with an APOE∈4 allele. Finally, poor adherence to NSAIDs like aspirin and ibuprofen due to its severe gastrointestinal effects leads to loss of subjects in follow-up during these studies (Veronese et al., 2017).

Subjects recruited in studies already have pathogenesis set after microglia activation or they have recent NSAID exposure as shown by Rotterdam and Cache County observational studies (Veld et al., 2001; Szekely et al., 2004). These studies show no protection with NSAIDs used 2 years before the onset of dementia. Subjects with the healthier brain (i.e., those subjects whose onset of AD would be some years in the future) exposed to NSAIDs may explain the weak but non-significant protective effect of NSAIDs for AD, as effect of NSAIDs exposure vary depending on the stage of brain disease progression (ADAPT Research Group et al., 2007). Asthana et al. (2023b), used the different study design (randomized control trials), shown insignificant result of NSAIDs as protective effect on AD.

Any study is incomplete without its limitations, similar to the current investigation had the following limitations. First, studies included for meta-analysis are few in number. Second, the dosage in each included study varies by a huge margin. Third, for inclusion of more studies, more studies are suggested to be done on subjects with less than 65 years age and are in long term use of NSAIDs. Fourth, no included study has assessed the effect of genetic factors (like APOE genotype) association with NSAID use and AD risk.

Also, there are few strengths of our study. First, the literature search strategy was rigorous. Second, the research question was supported by clear eligibility criteria. Third, each step in the review was done by multiple reviewers to ensure accuracy. Fourth, preferred reporting items of a systematic review and meta-analysis during the preparation of manuscript was followed. Lastly, meta-analysis was conducted adhering guidelines Cochrane handbook of systematic review and meta-analysis.

CONCLUSION

After conducting meta-analysis on observational studies (cohort and case-control study design) there was no evidence found to support that non-steroidal anti-inflammatory drug act as a protective factor in AD. Further, methodologically sound randomized controlled trials are required to produce a robust result.

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