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Original Article

The relationship between nonsteroidal anti-inflammatory drug use and the risk of Alzheimer's disease: an updated meta-analysis of cohort studies

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Abstract: Aim of the study: We aimed to evaluate the potential relevance between nonsteroidal anti-inflammatory drug (NSAIDs) use and the risk of Alzheimer's disease (AD). Clinical rationale for the study: Previous studies and systematic reviews have suggested that the use of NSAIDs might be associated with a reduced incidence of AD. However, several studies do not corroborate these results. Materials and Methods: PubMed, Embase, and Cochrane library databases were searched up until May 8th, 2018. Adjusted relative risks (RRs) and 95% confidence intervals (CIs) were calculated and combined with random-effects models. Results: A total of 14 cohort studies with 81571 participants were included in the final meta-analysis. Overall, the results of this meta-analysis indicated that the use of all NSAIDs (RR = 0.88, 95% CI = 0.74-1.05) and aspirin (RR = 0.99, 95% CI = 0.82-1.20) or non-aspirin NSAIDs revealed no significant effect on AD risk. However, our study showed that aspirin might decrease the risk of dementia overall (RR = 1.22, 95% CI = 1.02-1.45); there was no significant risk of dementia observed in users of all NSAIDs (RR = 0.99, 95% CI = 0.83-1.18) or non-aspirin NSAIDs (RR = 0.97, 95% CI = 0.70-1.35). In the subgroup analyses, a significant association was observed between aspirin use and the risk of dementia during a short follow-up period (RR = 1.46, 95% CI = 1.16-1.84, P = 0.001). Conclusion: NSAIDs are not associated with the excess risk of AD incidence. But aspirin may reduce the risk of other types of dementia other than AD.

Keywords: Non-steroidal anti-inflammatory drugs, Alzheimer's disease, dementia, meta-analysis

Introduction

Dementia is a devastating disease, which is characterized by a loss of abilities related to thinking, emotions and behavior. Dementia can be classified into four major types, including Alzheimer's disease (AD), vascular dementia, Lewy body dementia, and frontotemporal dementia [1]. AD is the most common type of dementia, accounting for 60%-70% of all dementias [2]. It is indicated that AD affected about 29.8 million people worldwide in 2015 [3] and most of the patients are over 65 years old [2]. AD poses a serious threat to people's health [4].

It is reported that neuro-inflammation plays a key role in the pathogenesis of AD. Recently, substantial evidence has indicated that nonsteroidal anti-inflammatory drugs (NSAIDs) might protect against the development of AD [5]. However, other studies showed that there was no effect of NSAIDs on preventing the development of AD [6]. The reverse findings may be a result of a limited sample size [7]. Therefore, we performed this updated meta-analysis to analyze the association between AD and NSAID use. Compared with previous meta-analyses, this study included newly published papers and numerous subgroup analyses.

In this paper, we conducted an updated meta-analysis of 14 studies to reevaluate the association between NSAID use and the risk of AD. The influence of the long-term effect and populations were further analyzed.

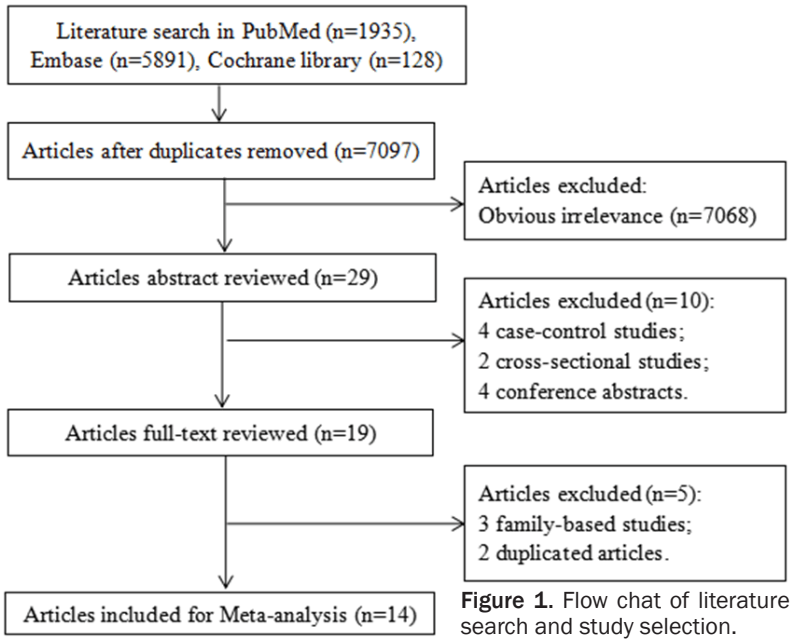

Figure 1. Flow chat of literature search and study selection.

Methods

Search strategy for included studies

This meta-analysis was conducted in accordance with PRISMA guidelines [8]. Two authors (SLJ and TF) performed an independent and extensive literature search in PubMed, EMBASE, and Cochrane library from their beginning till August 8th, 2017. The following keywords, "Alzheimer Disease", "Alzheimer*", "dement*", "Anti-Inflammatory Agents, Non-Steroidal", "NSAIDs", and "non-steroidal anti-inflammatory drug*", were used to search eligible articles. The search strategies against different libraries are shown in Table S1.

All potentially relevant studies were retrieved and evaluated for study eligibility. Manual search techniques were also used to identify other potentially relevant studies. All analyses were based on previously published studies, thus no ethical approval and patient consent are required.

Study inclusion criteria

Cohort studies were included if they met the following criteria: 1) studies that compared the risk of AD or other types of dementia in patients exposed to NSAIDs (aspirin and non-aspirin NSAIDs) and those that never reviewed NSAID use; 2) studies where the enrolled subjects were adults without dementia or Alzheimer's disease; 3) studies that presented data on the adjusted HR (hazard ratio), relative risk (RR) or odds ratio (OR) and 95% confidence interval (CI).

The exclusion criteria are listed as follows: 1) studies which include family members or close relatives; 2) literatures which are reviews, comments or letters; 3) the redundant publications or multiple studies with the same data.

Data extraction and methodology quality assessment

All the pertinent articles were reviewed by two independent investigators according to the inclusion and exclusion criteria. Data extraction was performed by two investigators independently, including the first author, publication year, research region, basic information of subjects, sample size, the type of diseases and NSAID used, et al. Data were used in the meta-analysis, if there was a common consensus viewpoint. The quality of the included studies was appraised according to the Newcastle-Ottawa Scale (NOS) [9]. Three items were scored as follows: object selection (4 scores), comparability (2 scores) and exposure (3 scores).

Statistical analysis

The association between NSAID use and risk of AD was evaluated with RRs and 95% CIs. Cochran's Q statistic and I^2 test were used to test heterogeneity between studies [10]. A Q statistic $P<0.05$ and/or $I^2>50\%$ indicated heterogeneity between studies, thus we used random effect model to evaluate the pooled effect of outcomes. Otherwise, when $P\geq0.05$ and $I^2\leq50\%$, a fix-effect method was applied. Subgroup analysis was conducted based on different populations and follow-up periods. We used the method through visual inspection of the funnel plot symmetry, Egger's test and Begg's test were implemented to detect between-study publication bias, in which $P<0.05$ indicat-

Table 1. Characteristics of prospective cohort studies of nonsteroidal anti-inflammatory drug and Alzheimer's disease Risk included in a Meta-anaylsis

Authors	Type of dementia	Population origin	Follow-up, years	n, Age, years	Sex	NSAID type	Adjusted variables
Ancelin, ML 2012, France	Dementia, AD	Community	7	7234, 73.7 (5.2)	M, F	All NSAID	Gender, center, age, education, depression, ischemic pathologies, diabetes, hypercholesterolemia, caffeine, smoking, APOE 4, chronic joint or back pain, chronic bronchitis, asthma, and other chronic respiratory disorders
Arvanitakis, Z 2008, USA	AD	Older Catholic clergy	12	1019, 75	M&F	Non-aspirin NSAIDs, Aspirin	Age, sex, and education
Breitner, JC 2009, USA	Dementia, AD	Community	12	2736, 74.8	M&F	All NSAID	Age, sex, APOE status, education, underlying diseases, body mass index, and regular exercise
Chang, CW 2016, Taiwan	Dementia, AD	T2DM	5	13596, 66.9 (7.9)/64.8 (8.2)	M&F	Aspirin	Age, gender, CCI, stroke types, antidiabetic drugs, statins, and hypertensive drugs
Chang, KH 2016, Taiwan	Dementia	RA	6.7	33229, 53.9 (14.2)	M&F	All NSAID	Age, diabetes, hypertension, hyperlipidemia, coronary artery disease, head injury, stroke, COPD, congestive heart failure, and depression
Cornelius, C 2004, Sweden	Dementia, AD	Community	10	1031, ≥75	M&F	All NSAID (Aspirin, non-aspirin NSAIDs)	Age, gender, education and underlying diseases
Cote, S 2012, Canada	Dementia, AD	Community	10	5276, 75.5 (6.5)	M&F	All NSAID, non-aspirin NSAIDs	Gender, education, smoking, alcohol, antioxidant vitamin use, physical activity, arthritis, migraines, comorbidity, and vascular risk factors
Fourrier, A 1996, France	Dementia	Community	3	1252, ≥65	M&F	All NSAID	NR
Fischer, P 2008, Austria	AD	Community	2.5	479, ≥75	M&F	All NSAID	NR
Henderson, AS 1997, Australia	Dementia	Community	3.6	588, 80.3 (5.0)	M&F	Aspirin, non-aspirin NSAIDs	Age, sex, education, stroke, APOE gene, arthritis medication
In t' Veld, BA 2001, the Netherlands	AD	Community	6.8	6989, ≥55	M&F	Non-aspirin NSAIDs, Aspirin	Age, sex, education, smoking, and concomitant medication
Stewart, WF 1997, USA	AD	Volunteers	16	1686, ≥65	M&F	Aspirin, non-aspirin NSAIDs	Age, sex, education, calendar year of follow-up
Szekely, CA 2008, USA	Dementia	Community	10	3229, ≥65	M&F	Aspirin, non-aspirin NSAIDs	Age, sex, education level, presence of APOE 4, race (white or African American), and baseline 3MSE.
Zandi, PP 2002, USA	AD	Community	3	3227, ≥65	M&F	Aspirin, non-aspirin NSAIDs	Age, sex, education, APOE gene

AD = Alzheimer's disease; RA = Rheumatoid arthritis; T2DM = Type 2 diabetes mellitus; M = male; F = female; NR = not reported.

Table 2. Summary of the results (change in type of dementia after treatment with different NSAID type in the relative risk that were included in all fourteen studies)

Study	Year	Sample size	Follow-up, years	RR (95% CI)	NSAID type
AD					
Ancelin, ML (M)	2012	2833	7	1.01 (0.49-2.09)	All NSAID
Ancelin, ML (F)	2012	4401	7	1.32 (0.86-2.03)	All NSAID
Arvanitakis, Z	2008	1019	12	0.99 (0.71-1.40)	All NSAID
Breitner, JC	2009	2736	12	1.36 (1.01-1.69)	All NSAID
Cornelius, C	2004	1031	10	1.11 (0.81-1.52)	All NSAID
Cote, S	2012	5276	10	0.73 (0.62-0.87)	All NSAID
Fischer, P	2008	479	2.5	0.40 (0.20-0.81)	All NSAID
In t' Veld, BA	2001	6989	6.8	0.88 (0.66-1.16)	All NSAID
Stewart, WF	1997	1686	16	0.64 (0.45-0.91)	All NSAID
Szekely, CA	2008	3229	10	0.76 (0.61-0.94)	All NSAID
Zandi, PP	2002	3227	3	0.75 (0.55-1.03)	All NSAID
Arvanitakis, Z	2008	1019	12	0.84 (0.63-1.11)	Aspirin
Chang, CW	2016	13596	5	1.37 (1.05-1.78)	Aspirin
Cornelius, C	2004	1031	10	1.34 (0.96-1.89)	Aspirin
In t' Veld, BA	2001	6989	6.8	0.98 (0.64-1.49)	Aspirin
Stewart, WF	1997	1686	16	0.74 (0.46-1.18)	Aspirin
Szekely, CA	2008	3229	10	0.87 (0.65-1.16)	Aspirin
Zandi, PP	2002	3227	3	0.82 (0.54-1.23)	Aspirin
Arvanitakis, Z	2008	1019	12	1.19 (0.87-1.62)	Nonaspirin NSAIDs
Cornelius, C	2004	1031	10	0.61 (0.32-1.15)	Nonaspirin NSAIDs
Cote, S	2012	5276	10	1.09 (0.79-1.49)	Nonaspirin NSAIDs
In t' Veld, BA	2001	6989	6.8	0.80 (0.55-1.18)	Nonaspirin NSAIDs
Stewart, WF	1997	1686	16	0.52 (0.30-0.91)	Nonaspirin NSAIDs
Szekely, CA	2008	3229	10	0.63 (0.45-0.88)	Nonaspirin NSAIDs
Zandi, PP	2002	3227	3	0.67 (0.40-1.06)	Nonaspirin NSAIDs
Dementia					
Ancelin, ML	2012	2833	7	0.88 (0.48-1.63)	All NSAID
Ancelin, ML	2012	4401	7	1.27 (0.88-1.83)	All NSAID
Breitner, JC	2009	2736	12	1.35 (0.93-1.97)	All NSAID
Chang, KH	2016	33229	6.7	0.76 (0.55-1.05)	All NSAID
Cornelius, C	2004	1031	10	1.03 (0.78-1.35)	All NSAID
Cote, S	2012	5276	10	0.80 (0.70-0.92)	All NSAID
Fourrier, A	1996	1252	3	0.98 (0.23-4.16)	All NSAID
Henderson, AS	1997	588	3.6	1.73 (0.89-3.34)	All NSAID
Szekely, CA	2008	3229	10	0.91 (0.65-1.27)	All NSAID
Chang, CW	2016	13596	5	1.45 (1.15-1.84)	Aspirin
Cornelius, C	2004	1031	10	1.13 (0.83-1.53)	Aspirin
Henderson, AS	1997	588	3.6	1.66 (0.64-4.32)	Aspirin
Szekely, CA	2008	3229	10	1.07 (0.88-1.32)	Aspirin
Cornelius, C	2004	1031	10	0.79 (0.49-1.29)	Nonaspirin NSAIDs
Cote, S	2012	5276	10	1.20 (0.94-1.54)	Nonaspirin NSAIDs
Henderson, AS	1997	588	3.6	1.79 (0.72-4.45)	Nonaspirin NSAIDs
Szekely, CA	2008	3229	10	0.76 (0.60-0.96)	Nonaspirin NSAIDs

CI = confidence interval; RR = relative risk.

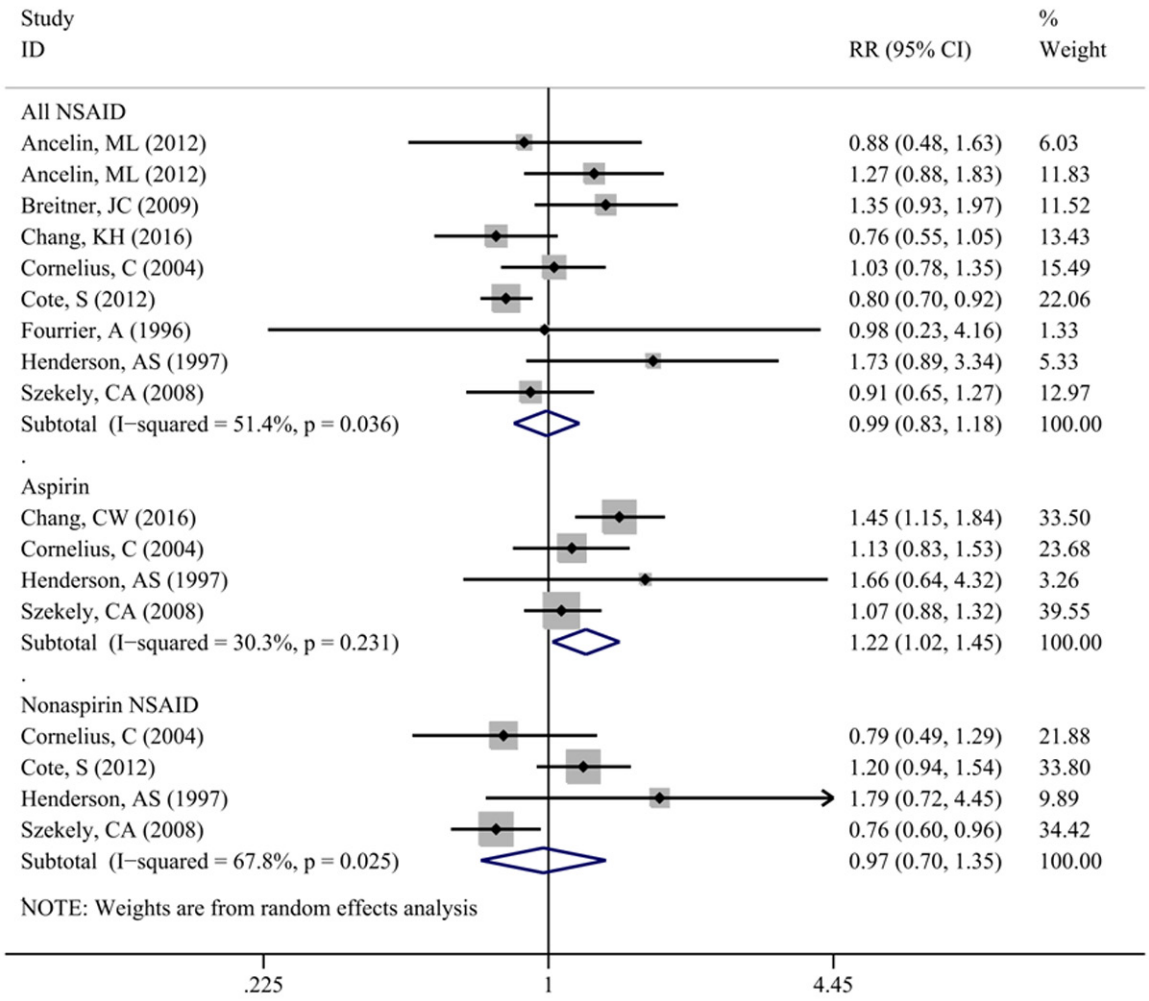

Figure 2. The correlation between the use of all NSAIDs, aspirin and non-aspirin NSAIDs with dementia.

ed a significant publication bias [11, 12]. In addition, Duval nonparametric trim-and-fill procedure was used to assess the possible influence of publication bias [13]. All the statistical analyses were performed by Stata software (version 12.0, Stata Corporation, College Station, Texas).

Results

Characteristics of included studies

The procedure of literature searching is shown in **Figure 1**, where we identified a total of 7954 studies from the literature. After removing duplicates, a total of 7097 literatures were obtained. The titles or abstracts of the literature were reviewed, and we excluded 7068 irrelevant publications. The abstract review and full-text review resulted in 10 and 5 articles exclusion, respectively. Finally, a total of 14 publications were included in the meta-analysis [5, 6, 14-25].

The basic characteristics of the 14 studies are summarized in **Table 1**. A total of 81571 subjects from 14 studies were included in this meta-analysis. All the included studies were published between 1996 and 2016. Most participants were older than 55 years old. Among these included studies, 10 reported the association between aspirin, non-aspirin NSAIDs or all NSAIDs and AD incidence, and 9 specifically reported the association between aspirin, non-aspirin NSAIDs or all NSAIDs and dementia. More than 80% of participants were from Europe or North America. A quality assessment showed that the scores of the 14 studies were more than 6, which indicated good quality (Table S2). In addition, patients in the included

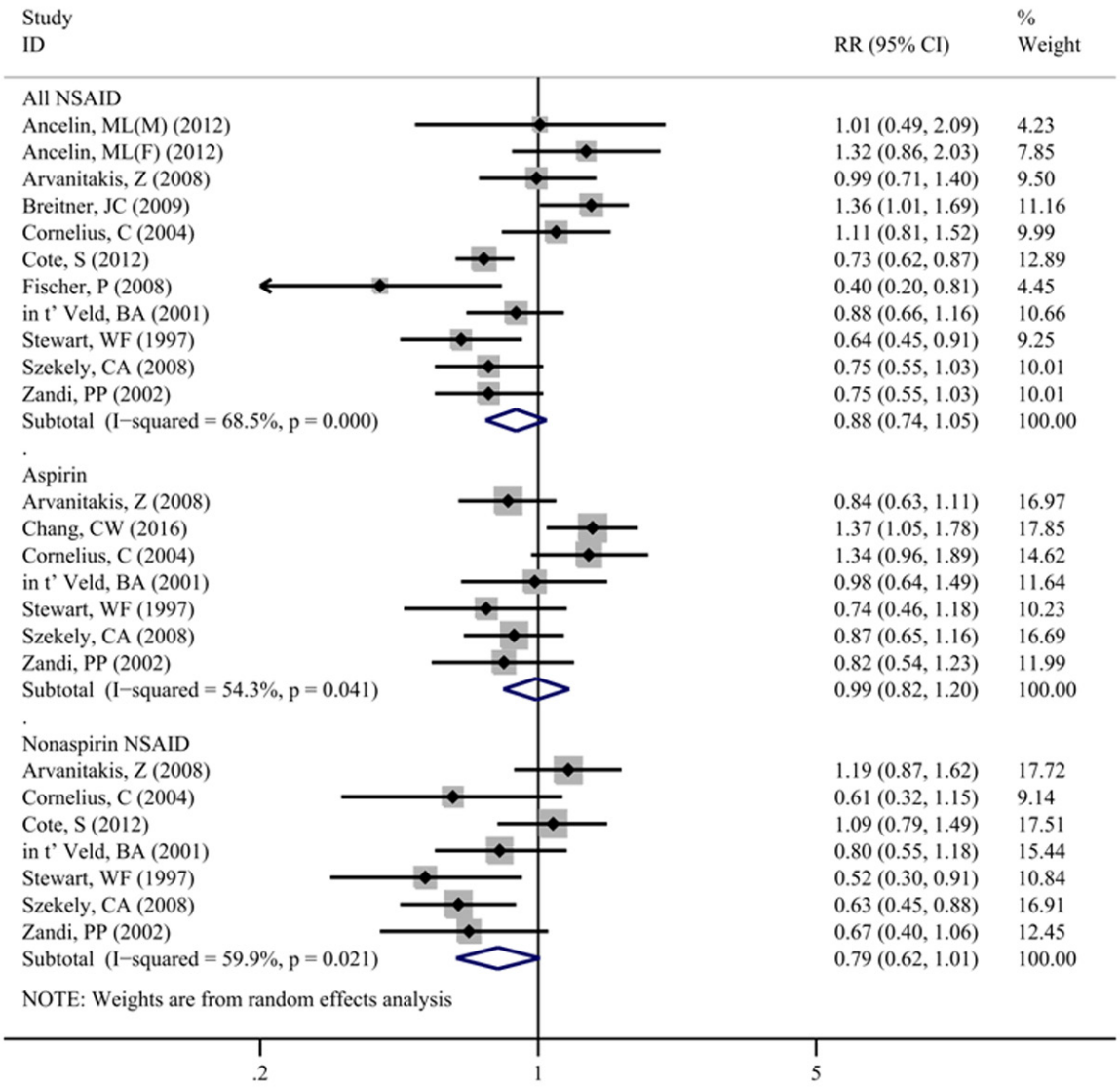

Figure 3. The correlation between the use of all NSAIDs, aspirin and non-aspirin NSAIDs with AD.

studies all had AD or other types of dementia, and the follow-up period of the 14 studies ranged from 2.5 to 16 years (**Table 2**).

Meta-analysis

The impact of NSAID use on the risk of AD or other types of dementia was analyzed separately. Significant heterogeneity of the included studies was observed, and a random-effects model was applied to evaluate the pooled effect of the outcomes. As shown in **Figure 2**, there was a significant association between aspirin use and dementia (RR = 1.22, 95% CI = 1.02-1.45; P = 0.028), while no significant risk of dementia was observed in users of all NSAIDs or non-aspirin NSAIDs (P>0.05). Data showed that there was no significant association between AD and the use of all NSAIDs, aspirin or non-aspirin NSAIDs (all P>0.05) (**Figure 3**).

Subgroup analysis

A subgroup analysis was performed to evaluate the difference in the anti-inflammatory effect on AD or other types of dementia. The results of the subgroup analysis based on the population and follow-up period are presented in **Table 3**. Ultimately, eleven studies containing the specific follow-up period were used to estimate the association between all NSAIDs and the risk of AD; thus, we stratified the follow-up period as shorter (<10 years) or longer (≥10 years). We

Table 3. Overall results and subgroup analyses of relative risk variation for NSAID users

Groups	N	RR (95% CI)	P_A	I^2 (%)	P_H
All NSAID and risk of AD					
Overall	11	0.88 (0.74, 1.04)	0.139	69.0	<0.001
Follow-up (years)					
<10	5	0.85 (0.63, 1.14)	0.278	57.3	0.052
≥10	6	0.90 (0.71, 1.13)	0.347	78.2	<0.001
Population					
Community	9	0.90 (0.74, 1.09)	0.283	72.3	<0.001
Other	2	0.80 (0.52, 1.22)	0.301	67.3	0.080
NSAID duration					
<2 years	2	0.81 (0.49, 1.35)	0.422	58.1	0.123
≥2 years	2	0.56 (0.31, 1.04)	0.066	0.0	0.719
Area					
Europe	5	0.94 (0.70, 1.27)	0.689	57.1	0.054
North America	6	0.84 (0.68, 1.05)	0.122	75.6	0.001
Aspirin and risk of AD					
Overall	7	0.99 (0.82, 1.20)	0.912	54.3	0.041
Follow-up (years)					
<10	3	1.07 (0.77, 1.48)	0.692	58.4	0.090
≥10	4	0.93 (0.74, 1.18)	0.568	50.6	0.108
Population					
Community	4	0.99 (0.79, 1.24)	0.920	35.3	0.200
Other	3	0.97 (0.66, 1.43)	0.890	76.0	0.015
NSAID duration					
<2 years	2	0.79 (0.60, 1.03)	0.086	0.0	0.365
≥2 years	2	0.79 (0.56, 1.10)	0.155	0.0	0.824
Area					
Europe	2	1.18 (0.87, 1.59)	0.291	22.0	0.257
North America	4	0.83 (0.70, 0.99)	0.035	0.0	0.953
Asia	1	1.37 (1.05, 1.78)	0.019	--	--
Non-aspirin NSAIDs and risk of AD					
Overall	7	0.79 (0.62, 1.01)	0.060	59.9	0.021
Follow-up (years)					
<10	2	0.75 (0.55, 1.01)	0.058	0.0	0.574
≥10	5	0.80 (0.57, 1.12)	0.195	71.2	0.008
Population					
Community	5	0.77 (0.61, 0.98)	0.032	-41.0-	-0.148
Other	2	0.81 (0.36, 1.83)	0.616	84.6	0.011
NSAID duration					
<2 years	3	0.79 (0.62, 1.01)	0.063	0.0	0.798
≥2 years	3	0.38 (0.22, 0.64)	<0.001	0.0	0.617
Area					
Europe	2	0.75 (0.54, 1.03)	0.078	0.0	0.476
North America	5	0.81 (0.59, 1.11)	0.191	71.0	0.008
All NSAID and risk of dementia					
Overall	9	0.99 (0.83, 1.18)	0.913	51.4	0.036
Follow-up (years)					
<10	5	1.05 (0.76, 1.44)	0.782	44.5	0.125
≥10	4	0.96 (0.78, 1.20)	0.749	63.2	0.043
Population					

observed no significant differences in the association of all NSAID use with AD in both subgroups, as the observed RR in the shorter follow-up subgroup was 0.85 (0.63 to 1.14, P = 0.052 for heterogeneity), while in longer follow-up subgroup the RR was 0.90 (0.71 to 1.13, P<0.001 for heterogeneity).

Next, we included four studies to evaluate the use of aspirin and the risk of dementia. The pooled relative risk of dementia was 1.22 (1.02 to 1.45, P = 0.231 for heterogeneity). There was a significant association between the use of aspirin and the risk of dementia (P = 0.028). Two of the studies were included in the shorter follow-up subgroup (<10 years), and others were included in the longer follow-up subgroup (≥10 years). It turned out that the association between aspirin use and the risk of dementia revealed a significant difference in the shorter follow-up subgroup (P = 0.001), while no notable association was found in longer follow-up subgroup.

In addition, we also conducted a subgroup analysis based on the community category. Five studies were included in the community category, and it was observed that the risk of AD for this category was 0.77 (0.61 to 0.98, P = 0.148 for heterogeneity). There was a marked correlation between the risk of AD and the use of non-aspirin NSAIDs (P = 0.032).

Publication bias

Funnel plots suggested symmetry of all the results. The Egger's test showed that there was no significant publication

Community	8	1.04 (0.86, 1.26)	0.714	53.9	0.034
RA	1	0.76 (0.55, 1.05)	0.096	--	--
Area					
Europe	4	1.08 (0.88, 1.32)	0.465	0.0	0.725
North America	3	0.96 (0.71, 1.28)	0.767	70.3	0.035
Asia	1	0.76 (0.55, 1.05)	0.096	--	--
Australia	1	1.73 (0.89, 3.35)	0.104	--	--
Aspirin and risk of dementia					
Overall	4	1.22 (1.02, 1.45)	0.028	30.3	0.231
Follow-up (years)					
<10	2	1.46 (1.16, 1.84)	0.001	0.0	0.787
≥10	2	1.09 (0.92, 1.29)	0.328	0.0	0.771
Population					
Community	3	1.10 (0.93, 1.30)	0.252	0.0	0.666
T2DM	1	1.45 (1.15, 1.83)	0.002	--	--
Area					
Europe	1	1.13 (0.83, 1.53)	0.433	--	--
North America	1	1.07 (0.87, 1.31)	0.513	--	--
Asia	1	1.45 (1.15, 1.83)	0.002	--	--
Australia	1	1.66 (0.64, 4.31)	0.298	--	--
Non-aspirin NSAIDs and risk of dementia					
Overall	4	0.97 (0.70, 1.35)	0.873	67.8	0.025
Follow-up (years)					
<10	1	1.79 (0.72, 4.45)	0.210	--	--
≥10	3	0.91 (0.65, 1.27)	0.585	72.8	0.025
Population					
Community	4	0.97 (0.70, 1.35)	0.873	67.8	0.025
Area					
Europe	1	0.79 (0.49, 1.28)	0.340	--	--
North America	2	0.95 (0.61, 1.49)	0.835	85.5	0.009
Australia	1	1.79 (0.72, 4.45)	0.210	--	--

PA = *P* value for test of the association; PH = *P* value for between-study heterogeneity.

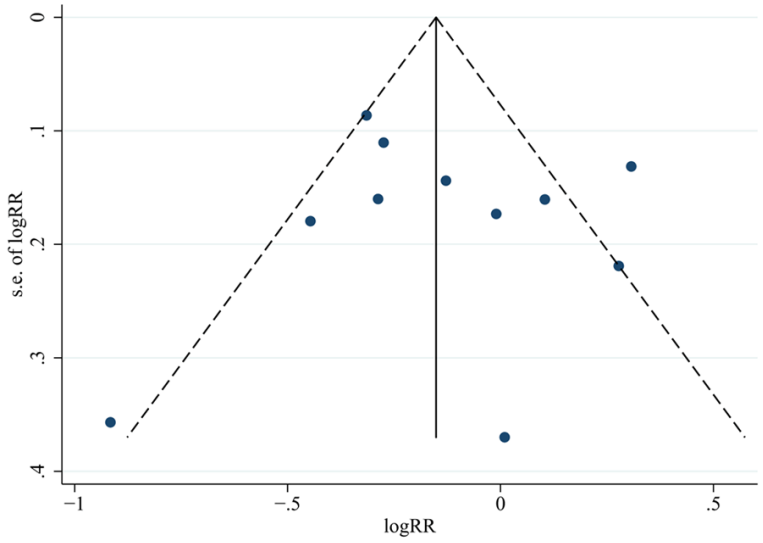

Figure 4. Funnel plot of studies of NSAID use and Alzheimer's disease.

bias in the effect of all NSAIDs on risk of AD (P = 0.729, **Figure 4**), indicating a stable result.

Discussion

The present study was designed to explore the association between the use of NSAIDs and AD, based on previously published data from cohort studies. The meta-analysis included a large number of subjects from 14 cohort studies according to the inclusion criterion. Although there were 14 cohort studies included in meta-analysis, the number of studies was not enough. The results were heterogeneous in nature, and a random-effects model was used to adjust for the pooled effect. Family members and close relatives were excluded from our study, which prevented evaluation of the effect of hereditary factors on the development of AD. In addition, the quality assessment analysis showed a relatively high score for all the included studies, indicated the reliability of the results of meta-analysis.

Our data analysis showed that there was no significant association between the use of all NSAIDs, aspirin or non-aspirin NSAIDs and the incidence of AD in participants. These results were consistent with the previous cohort study [6]. Fourrier et al. suggested that the incidence of AD in NSAID users was comparable to that in nonusers, and there was no favorable variation in the mini-mental status examination score in terms of age and educational status [1]. The previous study was limited by a small number of samples (53 NSAID users and 1199 nonusers). Our meta-analysis includ-

ed a total of 81571 participators, which may avoid the effect of a small number of samples.

It has been reported that AD as a neurodegenerative disorder is associated with neuro-inflammation induced by a defective neuronal insulin signaling pathway [26, 27]. Preclinical studies have also shown that inflammatory cytokines are overexpressed in AD, and play an important role in the development of AD [27]. In addition, previous prospective studies have reported a protective effect of NSAIDs against the development of AD in patients with arthritis. The self-reported presence of arthritis might increase considerable errors and affect the reliability of findings. Beyond that, there was no further evidence for the role of neuro-inflammation in the development and progression of AD.

Our data also showed that the use of aspirin was significantly associated with dementia (RR = 1.22, 95% CI = 1.02-1.45), while there was no significant association between the risk of dementia and the use of all NSAIDs and non-aspirin NSAIDs. The subgroup analysis also suggested a protective effect of aspirin against dementia. This means that aspirin might reduce the risk of other types of dementia other than AD. However, aspirin alone revealed a remarkable association with dementia during short-term follow-up (<10 years), conforming that the long-term effects of aspirin for the treatment of AD should be further analyzed. Besides, only two studies were included in the short-term follow-up subgroup, which might have led to considerable errors in evaluating the overall effect. Similarly, in the present study, aspirin showed a protective effect against AD and other types of dementia in an Asian population. Nevertheless, the current evidence is insufficient.

Although a moderate number of studies were included to evaluate the efficacy of anti-inflammatory medicine to protect against the development of AD, the studies included in one category were limited. It might have affected the reliability of the results. A large number of studies with high quality should be included to verify the stability of results.

Conclusion

In summary, based on our meta-analysis of 14 cohort studies, we cannot draw a qualitative conclusion that the use of NSAIDs can be association with the incidence of AD. But we speculate that aspirin might reduce the risk of other types of dementia other than AD during short-term follow-up. These results may be limited by the sample size, study quality and the classification of dementia. Further analysis including different dementias and larger sample size studies are warranted.

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Disclosure of conflict of interest

None.

Abbreviations

CI, confidence intervals; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; NOS, Newcastle-Ottawa Scale; OR, odds ratio; AD, Alzheimer's disease; RR, relative risk.

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Table S1. Search strategy for PubMed, EMBASE and Cochrane Library

A. PubMed (Publication date to 2017/08/07)

1. "Alzheimer Disease" [Mesh]

2. (Alzheimer* [Title/Abstract]) OR dement* [Title/Abstract]

3. 1 OR 2

4. "Anti-Inflammatory Agents, Non-Steroidal" [Mesh]

5. (NSAIDs) [Title/Abstract] OR (NSAID) [Title/Abstract]

6. (non-steroidal anti-inflammatory drug*) [Title/Abstract]

7. (ampyrone OR antipyrine OR apazone OR aspirin OR bufexamac OR clofazimine OR clonixin OR curcumin OR dapsone OR diclofenac OR diflunisal OR dipyrone OR epirizole OR etodolac OR fenoprofen OR flurbiprofen OR glycyrrhizic acid OR ibuprofen OR indomethacin OR ketoprofen OR ketorolac OR ketorolac tromethamine OR meclofenamic acid OR mefenamic acid OR mesalamine) [Title/Abstract]

8. 4 OR 5 OR 6 OR 7

9. 3 AND 8

B. EMBASE (Publication date to 2017/08/08)

1. 'Alzheimer disease'/exp

2. (Alzheimer* OR dement*):ab,ti

3. 1 OR 2

4. 'nonsteroid anti-inflammatory agent'/exp

5. (NSAIDs OR NSAID OR ampyrone OR antipyrine OR apazone OR aspirin OR bufexamac OR clofazimine OR clonixin OR curcumin OR dapsone OR diclofenac OR diflunisal OR dipyrone OR epirizole OR etodolac OR fenoprofen OR flurbiprofen OR 'glycyrrhizic acid' OR ibuprofen OR indomethacin OR ketoprofen OR ketorolac OR 'ketorolac tromethamine' OR 'meclofenamic acid' OR mefenamic acid OR mesalamine):ab,ti

6. 4 OR 5

7. 3 AND 6

C. Cochrane Library Central Register of Controlled Trials (Publication date to 2017/08/08)

1. MeSH descriptor: [Alzheimer Disease] explode all trees

2. (Alzheimer* or dement*):ti,ab,kw (Word variations have been searched)

3. 1 OR 2

4. MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees

5. (NSAIDs or NSAID or ampyrone or antipyrine or apazone or aspirin or bufexamac or clofazimine or clonixin or curcumin or dapsone or diclofenac or diflunisal or dipyrone or epirizole or etodolac or fenoprofen or flurbiprofen or 'glycyrrhizic acid' or ibuprofen or indomethacin or ketoprofen or ketorolac or 'ketorolac tromethamine' or 'meclofenamic acid' or mefenamic acid or mesalamine):ti,ab,kw (Word variations have been searched)

6. 4 OR 5

7. 3 AND 6

8. 7 AND trials

Table S2. Quality assessment of the included studies with Newcastle-Ottawa quality assessment scale

Study	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factors or additional factors	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality scores
Ancelin, ML	☆	☆	☆	☆	☆☆	☆	–	☆	8
Arvanitakis, Z	–	☆	☆	☆	☆	☆	☆	☆	7
Breitner, JC	☆	☆	–	☆	☆☆	☆	☆	☆	8
Chang, CW	–	☆	☆	☆	☆☆	☆	–	☆	7
Chang, KH	–	☆	–	☆	☆☆	☆	–	☆	6
Cornelius, C	☆	☆	☆	☆	☆	☆	☆	☆	8
Cote, S	☆	☆	–	☆	☆☆	☆	☆	☆	8
Fourrier, A	☆	☆	–	☆	☆	☆	–	☆	6
Fischer, P	☆	☆	–	☆	☆	☆	–	☆	6
Henderson, AS	☆	☆	–	☆	☆☆	☆	–	☆	7
Stewart, WF	–	☆	–	☆	☆	☆	☆	☆	6
Szekely, CA	☆	☆	–	☆	☆☆	☆	☆	☆	8
In t' Veld, BA	☆	☆	☆	☆	☆☆	☆	–	☆	8
Zandi, PP	☆	☆	☆	☆	☆	☆	–	☆	7