Scientific Research Publishing

Advances in Alzheimer's Disease, 2023, 12, 1-16
https://www.scirp.org/journal/aad
ISSN Online: 2169-2467
ISSN Print: 2169-2459

A Systematic Review and Meta-Analysis of Randomized Control Trials to Check Role of Non-Steroidal Anti-inflammatory Drugs as Protective Factor in Alzheimer Disease Subjects

Akash Asthana[1], Shashank Tripathi[1*], Rachna Agarwal[2]

[1]Department of Statistics, University of Lucknow, Lucknow, India
[2]Department of Neurochemistry, Institute of Human Behavior and Allied Sciences, New Delhi, India
Email: akash020184@gmail.com, *tshashank70@yahoo.in, rachna1000@hotmail.com

How to cite this paper: Asthana, A., Tripathi, S. and Agarwal, R. (2023) A Systematic Review and Meta-Analysis of Randomized Control Trials to Check Role of Non-Steroidal Anti-inflammatory Drugs as Protective Factor in Alzheimer Disease Subjects. *Advances in Alzheimer's Disease*, **12**, 1-16.
https://doi.org/10.4236/aad.2023.121001

Received: December 12, 2022
Accepted: March 11, 2023
Published: March 14, 2023

Abstract

Background: Alzheimer's disease is the major neurodegenerative disease, affecting more than two third cases of dementia in the world. 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 observed by different RCTs, a systematic review and meta-analysis were conducted to develop a better understanding of the protective role of Non-steroidal anti-inflammatory drugs (NSAIDs) in AD. **Methods:** Database search was Pubmed, WebScience, and Embase. RCTs investigating the effect of NSAIDs on AD or test scores assessing cognitive function in people without AD at baseline were included. Three indicators were MMSE Score, ADAS-cog score, and CDR-sob. 10 studies were included in the present Meta-analysis. **Results:** For the ADAS-cog score, the pooled effect size was −0.31 with 95% CI −0.06 to 0.02, which was statistically significant (p = 0.03). MMSE score difference, the pooled effect size was −0.06 with 95% CI −0.22 to 0.10, which was statistically insignificant (p-value = 0.47). For the MMSE average score, the pooled effect size was −0.002 with 95% CI −0.03 to 0.07, which was statistically insignificant (p-value = 0.87). For the CDR-sob score difference, the pooled effect size calculated using the random effect model was −0.06 with 95% CI −0.39 to 0.05 which was statistically insignificant (p = 0.14). For CDR-sob average score, the pooled effect size calculated using the random effect model was 0.21 with 95% CI −0.09 to 0.51, which was statistically insignificant (p-value = 0.17). **Conclusion:** Present Meta-analysis shows that NSAIDs in general are not effective in the treatment of AD. They also have no protective effect against the development of AD on their sustained use.

Keywords

NSAIDs, Alzheimer's Disease, Meta-Analysis, Hazard Ratio

1. Background

Alzheimer's disease (AD) is the major neurodegenerative disease affecting the geriatric population, affecting more than two third cases of dementia in the world [1]. The burden of Alzheimer's disease and related dementias in 2014 was 5 million in 2015 which has been projected to be more than 13.9 million by 2060 [2]. It along with other dementias is a major global health challenge, which may lead to a high cost of health [3] [4] [5]. Multifactor-like age, environment, and genetic factors, along with the accumulation of senile plaques and neurofibrillary tangles [6] are responsible for the pathogenesis of AD. Either all factors initiate the pathogenic cascade together or one lead to disease onset and the subsequent factors are involved in disease progression [7]. As per neuroinflammatory theory proposed for the pathogenesis of AD, inflammation of the microglia appears before brain damage [8] [9]. The same has been reported in the literature based on the study of 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 [10] [11].

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 [12]. In the United States, there has been a 40% increase in over-the-counter NSAID use between 2005 and 2010 of which 26% reported using more than the recommended dose [13] [14] [15]. 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 [16]. NSAIDs inhibit COX-2, which is upregulated in neurons leading to neurodegeneration in AD [16]. In addition to it, studies show that a small number of NSAIDs like ibuprofen, sulindac acid, and indomethacin have ant-amyloidogenic activity in vivo, a function which is independent of COX inhibition [17] [18].

In literature, studies show contradictory observations. Aisen *et al.* [16] suggested that NSAIDs may be useful in the treatment of AD whereas, Reines *et al.* [8] 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.

2. Methods and Material

2.1. Design

This systematic review adhered to the Preferred Reporting Items for Systematic

Reviews and Meta-Analysis (PRISMA) and followed a prior defined but unpublished protocol [19].

2.2. Protocol Registration

Our protocol has been registered on PROSPERO. Registration number is [**CRD42022301179**].

2.3. Data Source and Literature

Two investigators (ST & AA) independently searched three databases PubMed, WebScience, and MEDLINE for the studies published between 1st January 2000 to 31st December 2021, with no language restriction. Studies published in another language than English were included if their English translation is available. Also, the authors of studies other than the English language were contacted to provide their English translations.

To evaluate the use of NSAIDs as a treatment for AD in subjects with proven or probable ADs, the effect of NSAIDs on AD or test scores assessing cognitive function in people without AD at baseline were included.

keywords used for searching kinds of literature in the above-mentioned database where "RCT", "Alzheimer's Disease", "AD", "NSAIDs", "NSAID", "ibuprofen", "Rofecoxib", "celecoxib", "Aspirin", "Naproxen", "Nimesulide", "Tarenflurbil" and "indomethacin" or more of a combination of these terms.

2.4. Indicators Used in Meta-Analysis

There is a total of three indicators used in the Meta-analysis from the RCT study design to assess the effect of NSAIDs on AD.

2.4.1. AD Assessment Scale-Cognitive Subscale (ADAS-COG)

This scale focused on AD subjects' cognition that includes 11 items to assess memory, understanding, temporal and spatial orientation, and spontaneous speech. 00 to 70 is the total score range, with higher scores indicating the worst cognitive function (10).

The above-mentioned scale was developed in the 1980s, with aim of assessing the level of cognitive dysfunction in AD. This scale is the Gold standard for assessing the efficacy of anti-dementia treatments. The ADAS-cog was developed to use in studies with dementia where there is severe cognitive impairment [20].

2.4.2. The Mini-Mental State Examination (MMSE)

This score is widely used to assess memory problems. It is defined by question and test. The maximum score is 30 points. A score between ≥27 is considered normal, a score between 10 & 26 indicates mild-to-moderate AD, and a score <10 indicates severe AD [19].

2.4.3. Clinical Dementia Rating Scale—Sum of Boxes (CDR-Sob)

CDR-sob is a useful scale to examine the AD severity with global assessment measures. This scale helps in the management, communication, and rapid selec-

tion of treatments which is approved for different stage of AD.

Compared with the Washington University Clinical Dementia Scale (CDR), CDR-sob considers more detailed quantities general index, and more information is provided in subjects with mild-to-moderate dementia. CDR-sob score combines both scores in a single score.

Memory, Orientation, Judgement, Problem-Solving, Hobbies, and Personal Care are 06 items included in the score. Each domain is rated on a 5-point scale from 0 (normal) to 3 (severe dementia) so that the final result varies from 0 to 18 [21].

2.5. Study Selection

The eligibility criteria for including the study in the present Meta-analysis were as follows:

1) Studies conducted on a population of age 55 years and above.

2) Randomized Clinical Trials, to evaluate the use of NSAIDs as a treatment for AD in subjects with Alzheimer's.

3) Studies using diagnostic criteria NINDS-AIREN for the outcome of AD describe exposure to NSAIDs.

4) Paper published in English Language only.

5) Studies published from 2000 to 2021.

Studies were excluded if:

1) They were not conducted on humans and used a non-placebo group.

2) The RCTs where mean difference or mean score was not able to calculate from a data set.

3) The studies are not published in English and also its translation is unavailable.

2.6. Data Extraction

Two investigators (ST & AA) extracted data from the articles in a standard file & third independent investigator (RA) validated data extraction. For experimental study design, data collected from each paper are shown in **Table 1** as follows: the study subjects' characteristics (number of groups and number of participants in each group); the characteristics of the subject (subject type, age, range); the experimental treatment (type of treatment, active ingredients, dose, frequency of dose and duration of treatment); the results (mainly quantitative scores of different cognitive tests expressed as mean and SD between baseline and the last follow-up assessment).

If in studies data were reported as mean and Standard Error, the Standard Error was transformed into SD using the formula $\mathrm{SD} = \mathrm{S.E.} * \sqrt{n}$.

2.7. Outcomes

The change between follow-up and baseline on a test assessing cognition (MMSE, ADAS-cog, CDR-sob) was determined for subjects without AD at baseline in

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

Study (year)	N (% of female)	Age (SD)	Treatment	Dose (mg)	Frequency (dose/day)	Duration
Aisen *et al.* (2002)	19 (47.4)	74 (8.7)	Placebo		2	84
	21 (38.1)	73 (9.1)	Nimesulide	100	2	84
Aisen *et al.* (2003)	111 (55.9)	73.8 (8.0)	Placebo		2	365
	118 (48.3)	74.1 (7.8)	Naproxen	220	2	365
	122 (54.9)	73.7 (7.2)	Rofecoxib	25	1	365
Thal *et al.* (2005)	732 (31.1)	74.8 (6.0)	Placebo		1	1460
	723 (34.3)	75.1 (6.0)	Rofecoxib	25	1	1460
Pasqualetti *et al.* (2009)	66 (65.0)	74.0 (7.8)	Placebo		2	365
	66 (61.0)	73.7 (7.3)	Ibuprofen	400	2	365
Babiloni *et al.* (2009)	17 (70.8%)	74 (6.5)	Placebo		2	365 days
	18 (78.2%)	75.6 (6.7)	Ibuprofen	400	2	
Jong *et al.* (2008)	19 (76.0)	72.2 (9)	Placebo		1	365
	19 (53.8)	72.7 (6.9)	Indomethacin	100	1	365
Green *et al.* (2009)	809 (52.5)	74.7 (8.4)	Placebo	800	2	540
	840 (49.4)	74.6 (8.5)	Tarenflurbil		2	540
Ryan *et al.* (2004)	92525 (56.4)	65 - 73 years	Placebo		1	1716
	9589 (56.4)	(median age group)	Asprin	100	1	1716
Wilcock *et al.* (2008)	46 (41.0)	75.6 (6.8)	Placebo		2	365
	48 (50.0)	75.7 (7.6)	Tarenflurbil	800	2	365
Jeannie *et al.* (2011)	722 (NR)	NR	Placebo		1	1460
	722 (NR)	NR	Naproxen	220	1	1460
	1084 (NR)	NR	Celecoxib	200	1	1460

taking NSAIDs and the control group (placebo). For the MMSE score both mean difference and mean score was used separately. Similarly, for CDR-sob both mean difference and mean score was used separately.

2.8. Data Synthesis & Statistical Analysis

All analysis was done using RStudio. A meta-analysis to estimate the overall treatment effect of AD with NSAIDs relative to placebo was performed. The Pooled Standardized mean differences across all NSAIDs (last evaluation at the end of follow-up minus baseline data) were computed using the fixed effect model and Random effect model.

When there was significant heterogeneity in effect size across all studies, Q-statistics was used to examine this heterogeneity, which follows chi-square distribution and I^2-statistics was also calculated which explains the degree of heterogeneity in effect size across all the studies [22]. Heterogeneity in Meta-analysis means effect sizes vary from study to study, therefore identifying these effect sizes and quantifying Heterogeneity is an important point to be considered. Based on these two measures of heterogeneity (Q and I^2), the appropriate model (Fixed effect Model Vs Random effect Model) is chosen to calculate a

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. The I^2 statistic is an intuitive and simple expression of the inconsistency of studies' results. Unlike Q statistics, it does not inherently depend upon the number of studies considered [22]. Therefore, the I^2 statistic must be calculated along with a 95% confidence interval while conducting any meta-analysis to explore the degree of heterogeneity in effect size across various selected studies.

Forest Plot was made to display the result of the present meta-analysis. A 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 quantitative methods (rank-correlation test) were also used to examine the association between effect size and variance.

3. Results

3.1. Characteristics of Study

A total of 1200 relevant studies were identified during the literature search on the effect of NSAIDs on the treatment of AD. Out of 490 studies, initially, 10 studies could be included for meta-analysis following inclusion criteria, and the rest of 480 studies were excluded (**Figure 1**).

NSAIDs used in 10 studies were Ibuprofen, Indomethacin, Tarenflurbil, Aspirin, Rofecoxib, Naproxen and Celecoxib. Among 10 studies, a meta-analysis was performed based on MMSE score, MMSE mean difference, ADAS-cog, CDR-sob score, and CDR-sob mean difference. The study characteristics of these studies are summarised in **Table 1**. 10 studies included in the Meta-analysis had representation from 108,436 subjects, out of which 13,370 were treated with NSAIDs and 95,066 with placebo.

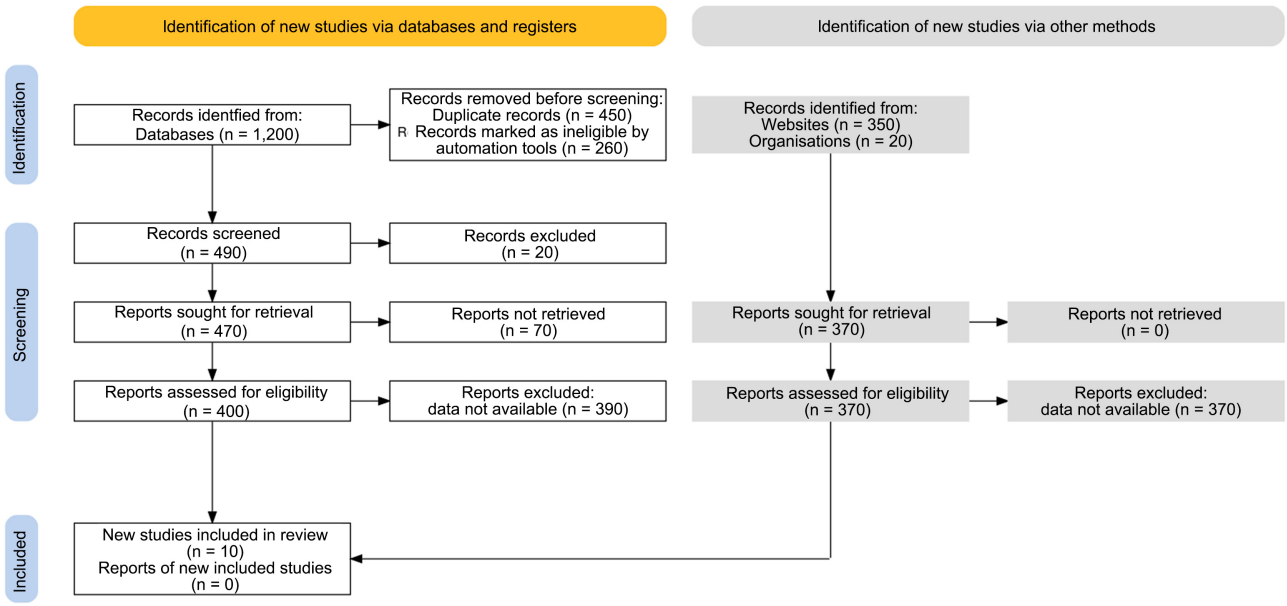

Figure 1. Flow diagram for selection of studies in systematic review and meta-analysis.

For ADAS-cog score, 01 study (Aisen 2002 [1]) used 02 drugs and 01 study (Wilcock *et al.* 2008 [23]) used 02 dosages of the drug, therefore the number of studies used for meta-analysis of ADAS-cog score was 08. For the MMSE score, 03 studies were used for meta-analysis. For MMSE score difference, 01 study (Jennie *et al.* 2012 [24]) used two drugs therefore the number of studies used for meta-analysis of MMSE score difference was 05. For the CDR-sob score, total of 02 studies were used for meta-analysis. For CDR-sob score difference, 01 study (Aisen *et al.* 2003 [16]) used 02 drugs and 01 study (Wilcock *et al.* 2008 [23]) used two dosages of the drug, therefore the total number of studies in meta-analysis becomes 07 for this particular score.

3.2. Result of Meta-Analysis

ADAS-cog Score

Meta-analysis was performed on 08 studies with 2380 observations. Heterogeneity across 08 studies in effect size was statistically significant (Q-value = 37.95, p-value< 0.0001), but the degree of heterogeneity was I^2 = 81.6% with 95% C.I 64.7% to 90.4%. Therefore, random-effect-model was used to summarize the ADAS-cog score. Forest plot to display the result of meta-analysis is shown in **Figure 2**. 02 studies (Pasqualetti *et al.* 2007 [25] and Green *et al.* 2009 [26]) shown positive SMD [0.00 (−0.34, 0.34), 0.02 (−0.08, 0.12)]. Whereas, 06 studies (Aisen *et al.* 2002 [1], Aisen *et al.* 2003 [16], Jong *et al.* 2008 [27], Wilcock *et al.* 2008 [23]) shown negative SMD −0.45 (−1.08, 0.18), −0.01 (−027, 0.25), −0.24 (−0.50, 0.02), −0.17 (−0.80, 0.47), −1.19 (1.63, −0.75), −0.66 (−1.11, −0.22). The pooled effect size was −0.31 with 95% CI −0.60 to 0.02, which was statistically significant (p-value = 0.03). Green *et al.* 2009 [26] were assigned the highest weight (15.9%), whereas Jong *et al.* 2008 [27] were assigned the lowest weight (9.1%) due to the small sample size.

The funnel plot (**Figure 3**) shows 02 studies out of the inverted funnel; therefore it indicates the presence of publication Bias. Rank-correlation test shows the statistically insignificant result of publication bias (p-value = 0.32).

MMSE average score

Meta-analysis was performed on 03 studies with 18263 numbers of subjects.

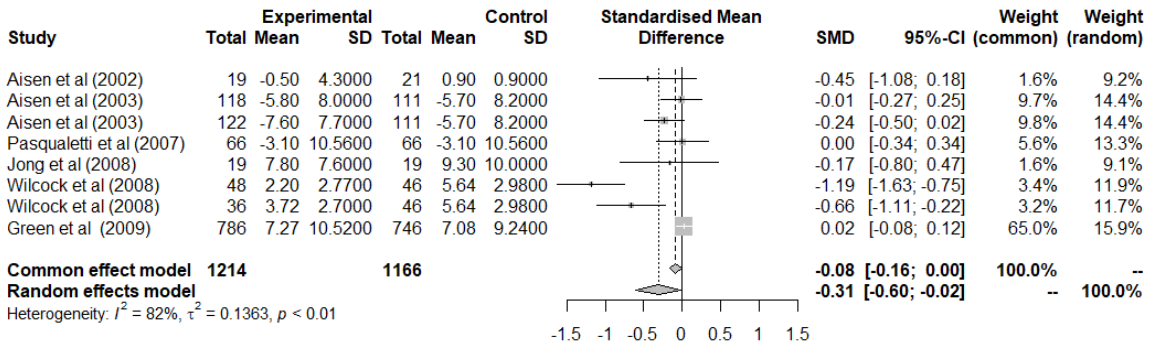

Figure 2. Forest plot showing the effects size of all studies included for meta-analysis and summary effect size of indicator ADAS-cog with their respective C.I.

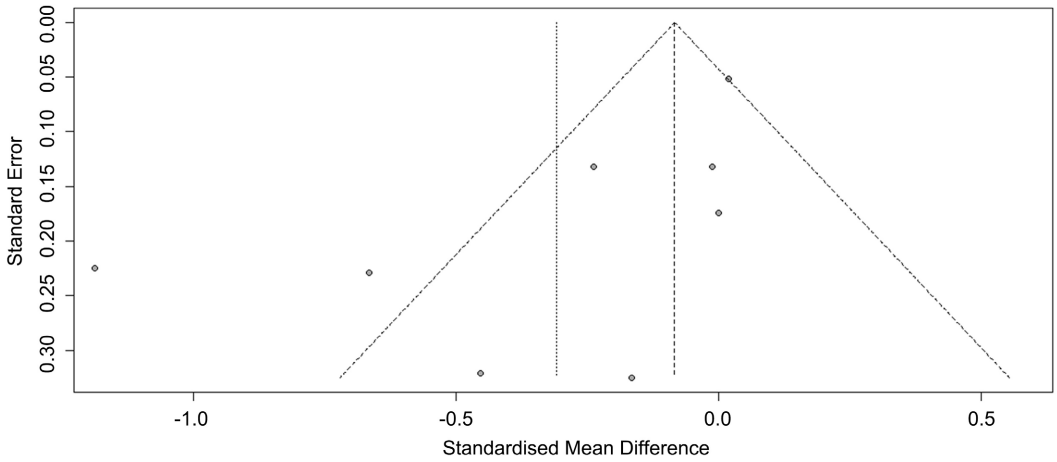

Figure 3. Funnel plot for publication bias for studies included in the meta-analysis of ADAS-cog.

Heterogeneity across 03 studies in effect size was statistically insignificant. (Q-value = 3.48, p-value = 0.17). Degree of Heterogeneity was I^2 = 42.5% with 95% CI 0.0% to 82.7%. Therefore Random-effect model was used to summarize the result of the MMSE score. Forest plot to display the result of the meta-analysis is shown in **Figure 4**. 01 study (Ryan *et al.* 2004 [28]) shows null SMD 0.0 (−1.61, 0.10), whereas 02 studies (Thal *et al.* 2005 [9], Babiloni *et al.* 2009 [29]) show negative SMD [−0.04 (−0.15, 0.07), −0.76 (1.61, 0.10)]. The pooled effect size was −0.0024 with 95% C.I. −0.03 to 0.02, which was statistically insignificant (p = 0.87). Babiloni *et al.* 2009 [29] were assigned the lowest weight (0.1%), whereas the highest weight (93.2%) was assigned to Ryan *et al.* 2020 [28].

The funnel plot (**Figure 5**) shows no study out of the inverted funnel, therefore no publication bias was present. Rank-correlation test shows statistically insignificant results of publication bias (p-value = 0.11).

MMSE score difference

Meta-analysis was performed on 05 studies with 5025 subjects. Heterogeneity across 05 studies in effect size was statistically significant (Q-value = 27.23, p-value < 0.0001). The degree of Heterogeneity was I^2 = 85.3% with 95% C.I 67.5% to 93.4%. Therefore Random effect model was used to summarize the result of the MMSE difference score. Forest plot to display the result of meta-analysis is shown in **Figure 6**. 02 studies (Jong *et al.* 2008 [27], Jennie *et al.* 2011 [24]) shows positive SMD [0.40 (−0.25, 1.04), 0.09 (0.00, 0.19)] and 03 studies (Pasqualetti *et al.* 2009 [25], Green *et al.* 2009 [26] and Jennie *et al.* 2011 [24]) shows negative SMD [−0.13 (−0.48, 0.21), −0.07 (−0.19, 0.04), −0.25 (−0.34, 0.15)]. The pooled effect size was −0.06 with 95% C.I. −0.22 to 0.10, which was statistically insignificant (p-value = 0.47).

The lowest weight (5.2%) was observed in a study by Jong *et al.* 2008 [27] and the highest weight (27.6%) was observed in the study by Jennie *et al.* 2011 [24].

The funnel plot (**Figure 7**) shows two studies out of the inverted funnel; therefore publication bias was present in the study. Rank-correlation test statistically insignificant result of publication bias (p-value = 1).

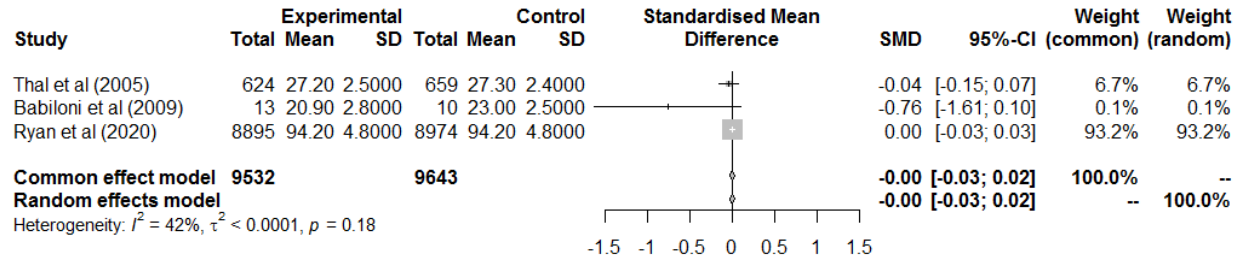

Figure 4. Forest plot showing the effects size of all studies included for meta-analysis and summary effect size for indicator MMSE average score with their respective C.I.

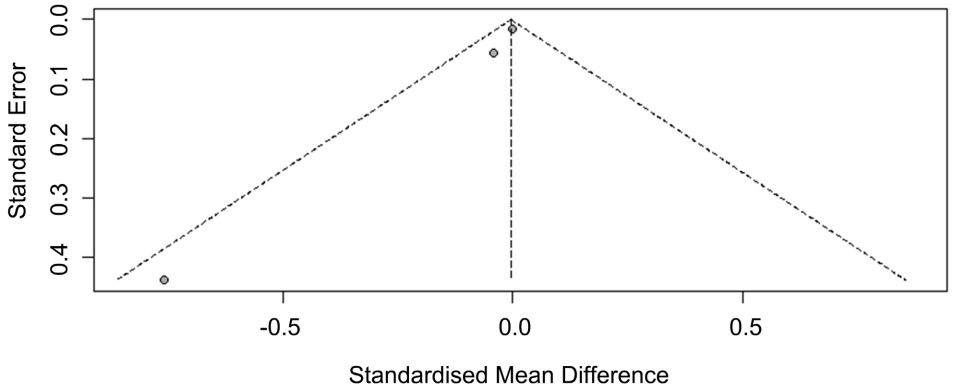

Figure 5. Funnel plot for publication bias for studies included in the meta-analysis of MMSE average score.

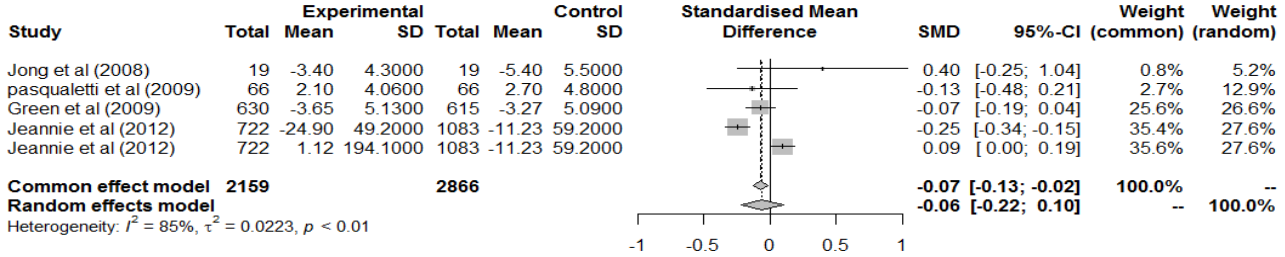

Figure 6. Forest plot showing the effects size and summary effect size of all studies included for meta-analysis using indicator MMSE score difference with their respective C.I.

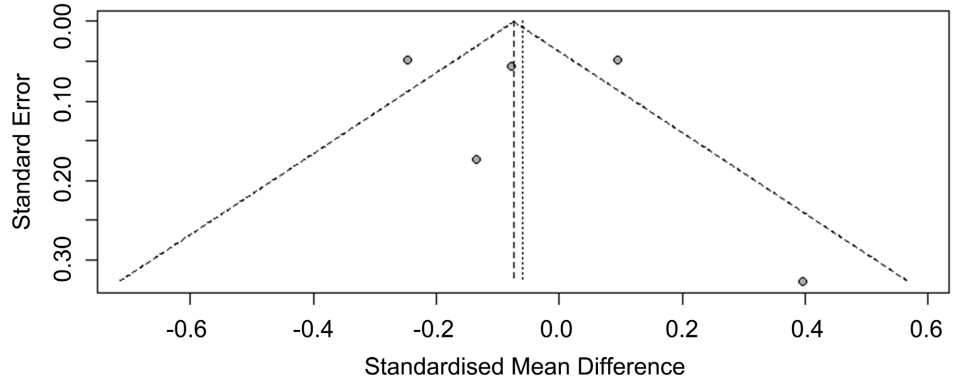

Figure 7. Funnel plot for publication bias for studies included in the meta-analysis of MMSE score difference.

CDR-sob Score difference

Meta-analysis was performed on 06 studies with 2246 subjects. Heterogeneity across 07 studies in effect size was statistically significant. (Q-value = 25.31, p-value = 0). The degree of Heterogeneity was I^2 = 76.3% with 95% C.I 50.2% to 88.7%. Therefore Random-effect-model was used to summarize the result of the CDR-sob score difference. A Forest plot to display the result of the meta-analysis is shown in **Figure 8**. 01 studies (Aisen *et al.* 2003 [16]) shown null SMD [0.00 (−0.26, 0.26)]. 01 study (Green *et al.* 2009 [26]) shown positive SMD [0.15 (0.05, 0.25)], whereas 05 studies (Aisen *et al.* 2002 [1], Aisen *et al.* 2003 [16], Wilcock *et al.* 2008 [23], Pasqualetti *et al.* 2009 [25]) shows negative SMD [−0.38 (−1.00, 0.25), −0.04 (−0.30, 0.21), −0.74 (−1.16, 0.32), −0.38 (−1.82,−0.06), −0.17 (−0.51, 0.17)]. The pooled effect size was −0.06 with 95% C.I −0.39, 0.05 which was statistically insignificant (p = 0.14). Green *et al.* 2009 [26] show the highest weight (20.3%) and Aisen *et al.* 2002 [1] show the lowest weight (8.1%).

The funnel plot (**Figure 9**) shows two studies out of the inverted funnel, so the publication bias was present. Rank-correlation shows the statistically insignificant result for publication bias (p-value = 0.0509).

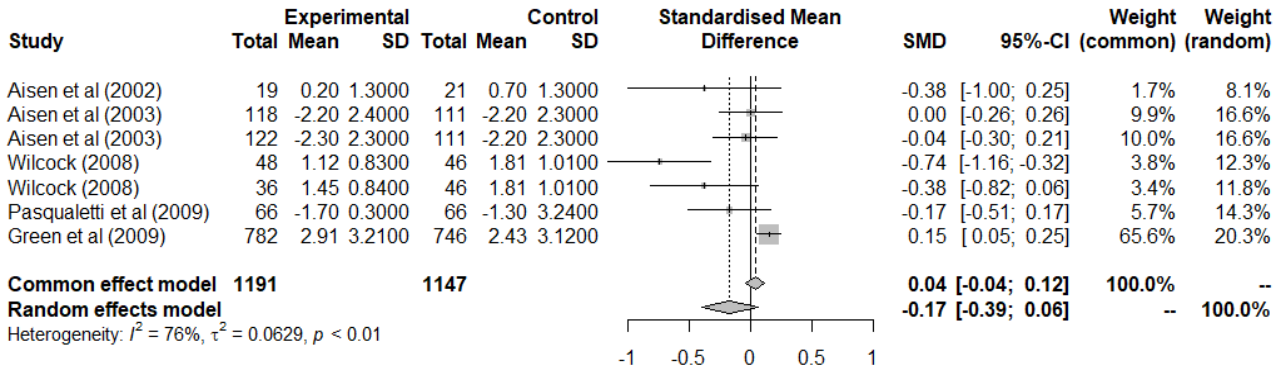

Figure 8. Forest plot showing the effects size and summary effect size of all studies included for meta-analysis using indicator MMSE score difference with their respective C.I.

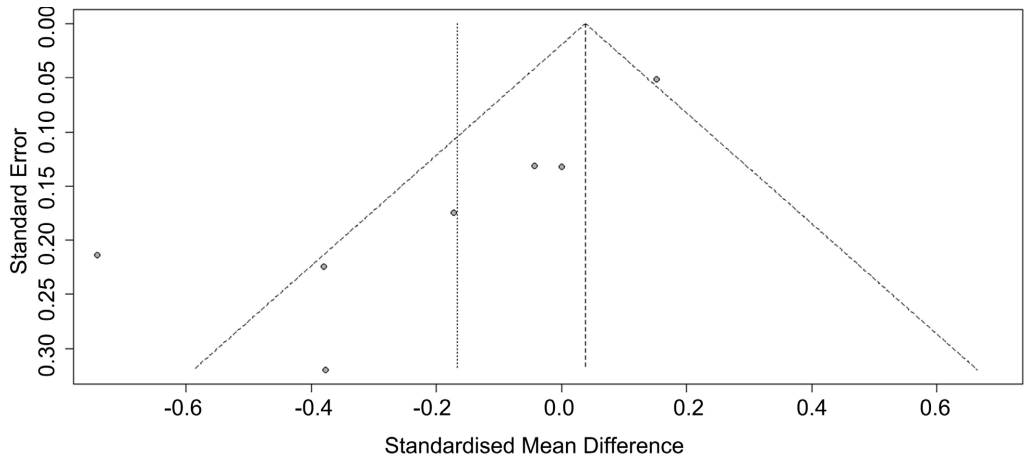

Figure 9. Funnel plot for publication bias for studies included in the meta-analysis of CDR-sob score difference.

CDR-sob Average Score

Meta-analysis was performed on 02 studies with 394 subjects. Heterogeneity across 02 studies in effect size was statistically insignificant (Q-value = 1.16, p-value = 0.28). The degree of heterogeneity was I^2 = 14.0% with no C.I because only 02 studies are involved in meta-analysis. The Random-effect-model was used to summarise the result of the CDR-sob score. A Forest plot to display the result of the meta-analysis is shown in Figure 10. Both the studies (Thal *et al.* 2005 [9], Babiloni *et al.* 2009 [29]) shows positive SMD [0.15 (−0.05, 0.36), 0.63 (−0.21, 1.48)]. The pooled effect size was 0.21 with 95% CI −0.09 to 0.51, which was statistically insignificant (p-value = 0.17). The lowest weight (11.7%) was obtained by a study by Babiloni *et al.* 2009 [29] whereas, the highest weight (88.3%) was observed in the study by Thal *et al.* 2005 [9].

The funnel plot (Figure 11) shows both studies inside an inverted funnel, therefore no publication bias was present. Only 02 studies were involved, therefore no statistical test was used to check the statistical significance of publication bias.

4. Discussion

Meta-analysis performed with ADAS-cog score showed the statistically significant result in improvement of AD by use of NSAIDs, but the p-value was 0.03 which is very close to 0.05, therefore no valid conclusion could be drawn based

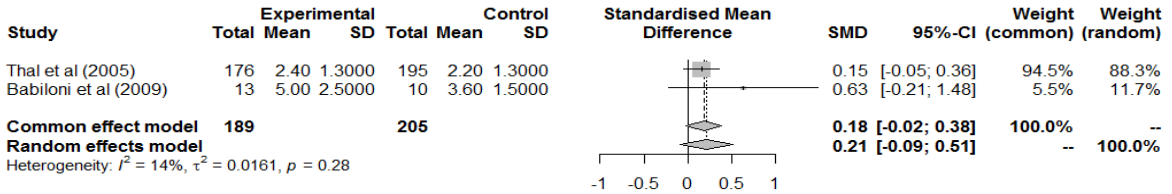

Figure 10. Forest plot showing the effects size and summary effect size of all studies included for meta-analysis using indicator CDR-sob average score with their respective C.I.

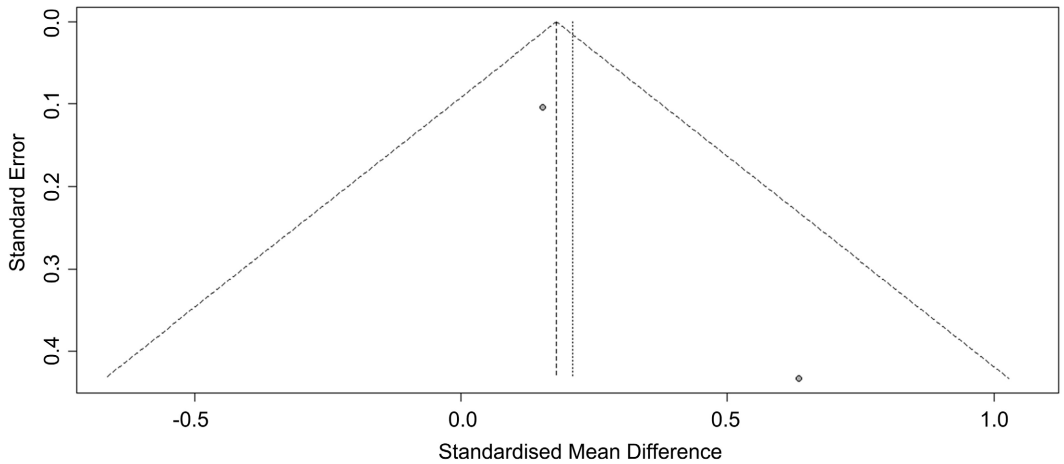

Figure 11. Funnel plot for publication bias for studies included in the meta-analysis of CDR-sob score difference.

on only this score. Meta-Analysis findings of the current study suggest that NSAID has shown no protective role in AD subjects in Standardized Mean difference of MMSE mean difference, MMSE mean score, CDR-sob mean difference and CDR-sob mean score. Therefore such findings indicate that there is no clinical improvement in subjects taking NSAIDs over subjects who are not exposed to NSAIDs.

A funnel plot created to check the publication bias has shown no publication bias present in ADAS-cog, MMSE-score, or CDR-sob, but publication bias was present in MMSE score difference and CDR-sob difference. Rank correlation test was used to check the statistical significance of publication shows the statistically insignificant result of publication bias in studies included in ADAS-cog, MMSE score, and MMSE mean difference score but statistically, a significant result was observed in CDR-sob mean difference score.

During this study, no evidence of the protective effect of NSAIDs was observed across 10 randomized control studies, when given years before the development of symptoms of AD. The use of NSAIDs as a protective factor in AD in the present study may improve our understanding of the role of NSAIDs in AD by making several conjectures like, firstly, the age of subjects taken in the present meta-analysis; all 10 studies were done in diagnosed AD cases having more than 65 years of age. AD starts to occur over 20 years before cognitive decline with pathological changes. Szekely *et al.* 2008 [30] suggested a reduced risk of AD in NSAIDs users was significant in the younger age group. Hayden *et al.* 2007 [31] also reported the use of NSAIDs before the 65 years age group had less 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 in the early stage of AD but are not effective in the later stage of AD. It suggested performing RCT to study the protective role of NSAIDs in AD after stratification of subjects by age. Secondly, the duration of exposure to NSAIDs can be taken as a secondary hypothesis, similarly, the age of subjects NSAID exposure for a long time cannot reverse the outcome. As suggested by Szekely 2008 [30] 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 developing AD. The duration of 10 studies included varies from 84 days to 1716 days. Thirdly, the dosage of NSAIDs varies from 25 mg to 800 mg per day which could be a major factor that may affect the therapeutic relevance of ϒ–the secretase modulator effect in AD subjects [32]. Fourthly, the co-morbidities in AD subjects may be taken as one of the important factors for such results, which modifies the protective effect [12]. Fifth, the scores used in current meta-analysis like MMSE (both mean score and mean difference), ADAS-cog, CDR-sob (both mean score and mean difference), and NPI are not only scores to measure the cognitive decline in an older person, there is "n" number of scores still available in the clinical market to measure the cognitive decline in older persons more than 60 years of age. Most of these scores used in the study are for the educated population and younger age group

for accurate measure. Sixth, Apo lipoprotein E in AD subjects plays a vital role in the occurrence of disease. Every individual with unique gene, therefore NSAIDs will react differently for different individuals [30]. The APOE gene may alter the association between NSAID use and the risk of developing AD. Study [30] has found a lower risk of AD only in NSAIDs users with an APOEϵ4 allele. Seventh, finally poor adherence to NSAIDs like aspirin and ibuprofen due to their severe gastrointestinal effects, leads to the loss of subjects in follow-up during these studies [12].

Subjects recruited in the selected studies already have pathogenesis set in after microglia activation or they have recent NSAID exposure as shown by Rotterdam and Cache County observational studies [33] [34]. These studies show no protection with NSAIDs used 2 years before the onset of dementia. Subjects with healthier brains (*i.e.* for those subjects in which onset of AD would be some years later in the future) exposed to NSAIDs may explain the weak but non-significant protective effect of NSAIDs for AD as the effect of NSAIDs exposure vary depending on the stage of brain disease progression [32].

The present meta-analysis neither shows that NSAID treatment decreases the progression of cognitive decline in AD nor any protective effect against the development of AD on its sustained use.

Any study is incomplete without its limitations. Therefore limitation of the present study was as follows, the number of RCTs taken for meta-analysis is few, dosage in each included study varies by a huge margin, and 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, no study included in the present meta-analysis, assessed the effect of genetic factors like APOE genotype with on association of NSAID use and AD risk and Meta-regression and sub-group analysis is not advisable as a number of studies were less than 10.

The strength of the study was, that the literature search strategy was rigorous, the research question was supported by clear eligibility criteria, each step in the review was done by multiple reviewers to ensure accuracy, and preferred reporting items of a systematic review and meta Analysis during the preparation of manuscript is followed and meta-analysis was conducted adhering guidelines Cochrane handbook of systematic review and meta-analysis.

It is suggested to perform studies after stratification of subjects by age and gender, to check the role of NSAIDs as a protective factor in AD subjects, duration of exposure should also be considered, and the uniform dosage of NSAIDs should be taken, so that the robust results can be generated, variation in dosage of NSAIDs disturbs the outcome. All studies should be also adjusted for APOE genotyping before conducting the study so that robust results can be obtained. The study which assessed the effect of genetic factors like APOE genotype with an association between NSAID use and AD risk must be included. The NSAIDs in a present meta-analysis must be divided into subgroups based on their chemical structure and mechanism of action, appropriate techniques should be taken

into consideration for subjects who are lost in the follow-up of the study, and more number of studies adhering to a standard pre-defined protocol must be conducted to get a more clear scenario of the situation and the meta-regression with a large number of selected studies, may also be conducted for better understanding the role of the use of NSAID's in AD.

5. Conclusions

As 03 scores were used to check the protective role of NSAIDs in AD subjects followed by 05 meta-analysis, only one score has shown a significant protective role of NSAIDs, but because its p-value was very close to 0.05, hence solid conclusion should not be drawn based only on this score. However, more randomized control trials with sound methodology are required on the current topic.

So we concluded from the present study is NSAIDs do not act as a protective factor in AD subjects.

Declaration

Ethics Approval and Consent to Participate Are

Not applicable because this paper is a Systematic Review and Meta-Analysis based on already published studies.

Availability of Data and Materials

Data from this study is extracted from already published studies.

Conflicts of Interest

The authors declare that they have no competing interests.

Author s' Contribution

AK, ST, and RA contributed to designing the study protocol equally.

References

[1] Aisen, P.S., Schmeidler, J. and Pasinetti, G.M. (2002) Randomized Pilot Study of Nimesulide Treatment in Alzheimer's Disease. *Neurology*, **58**, 1050-1054. https://doi.org/10.1212/WNL.58.7.1050

[2] CDC (2016) CDC Newsroom. https://www.cdc.gov/media/releases/2018/p0920-alzheimers-burden-double-2060.html

[3] Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W. and Ferri, C.P. (2013) The Global Prevalence of Dementia: A Systematic Review and Metaanalysis. *Alzheimer's Association*, **9**, 63-75.e2. https://doi.org/10.1016/j.jalz.2012.11.007

[4] Prince, M.J., Wimo, A., Guerchet, M.M., Ali, G.C., Wu, Y.T. and Prina, M. (2015) World Alzheimer Report 2015—The Global Impact of Dementia. An Analysis of Prevalence, Incidence, Cost and Trends. Alzheimer's Disease International, London.

[5] Wu, Y.T., Beiser, A.S., Breteler, M.M.B., Langa, K.M., *et al.* (2017) The Changing Prevalence and Incidence of Dementia over Time—Current Evidence. *Nature Reviews Neurology*, **13**, 327-339. https://doi.org/10.1038/nrneurol.2017.63

[6] Miguel-Álvarez, M., *et al.* (2015) Non-Steroidal Anti-Inflammatory Drugs as a Treatment for Alzheimer's Disease: A Systematic Review and Meta-Analysis of Treatment Effect. *Drugs Aging*, **32**, 139-147. https://doi.org/10.1007/s40266-015-0239-z

[7] Talwar, P., *et al.* (2016) Dissecting Complex and Multifactorial Nature of Alzheimer's Disease Pathogenesis: A Clinical, Genomic, and Systems Biology Perspective. *Molecular Neurobiology*, **53**, 4833-4864. https://doi.org/10.1007/s12035-015-9390-0

[8] Reines, S.A., Block, G.A., Morris, J.C., Liu, G., Nessly, M.L., Lines, C.R., Norman, B.A. and Baranak, *C.C.* (2004) Rofecoxib: No Effect on Alzheimer's Disease in a 1-Year, Randomized, Blinded, Controlled Study. *Neurology*, **62**, 66-71. https://doi.org/10.1212/WNL.62.1.66

[9] Thal, L.J., *et al.* (2005) A Randomized, Double-Blind, Study of Rofecoxib in Patients with Mild Cognitive Impairment. *Neuropsychopharmacology*, **30**, 1204-1215. https://doi.org/10.1038/sj.npp.1300690

[10] Williams, C.S., Mann, M. and DuBois, R.N. (1999) The Role of Cyclooxygenases in Inflammation, Cancer, and Development. *Oncogene*, **18**, 7908-7916.

[11] Cagnin, A., Brooks, D.J., Myers, R., *et al.* (2001) *In-Vivo* Measurement of Activated Microglia in Dementia. *The Lancet*, **358**, 461-467. https://doi.org/10.1016/S0140-6736(01)05625-2

[12] Veronese, N., *et al.* (2017) Low-Dose Aspirin Use and Cognitive Function in Older Age: A Systematic Review and Meta-analysis. *Journal of the American Geriatrics Society*, **65**, 1763-1768. https://doi.org/10.1111/jgs.14883

[13] Scarpini, E., Scheltens, P. and Feldman, H. (2003) Treatment of Alzheimer's Disease; Current Status and New Perspectives. The *Lancet Neurolgy*, **2**, 539-547. https://doi.org/10.1016/S1474-4422(03)00502-7

[14] Etminan, M., Gill, S. and Samii, A. (2003) Effect of Non-Steroidal Anti-Inflammatory Drugs on Risk of Alzheimer's Disease: Systematic Review and Meta-Analysis of Observational Studies. *BMJ*, **327**, Article 128. https://doi.org/10.1136/bmj.327.7407.128

[15] Zhou, Y., Boudreau, D.M. and Freedman, A.N. (2014) Trends in the Use of Aspirin and Nonsteroidal Anti-Inflammatory Drugs in the General U.S. Population. *Pharmacoepidemiology and Drug Safety*, **23**, 43-50. https://doi.org/10.1002/pds.3463

[16] Aisen, P.S., *et al.* (2003) Effects of Rofecoxib or Naproxen Vs Placebo on Alzheimer Disease Progression: A Randomized Controlled Trial. *JAMA*, **289**, 2819-2826. https://doi.org/10.1001/jama.289.21.2819

[17] McGeer, P.L., Schulzer, M. and McGeer, E.G. (1996) Arthritis and anti-Inflammatory Agents as Possible Protective Factors for Alzheimer's Disease: A Review of 17 Epidemiologic Studies. *Neurology*, **47**, 425-432. https://doi.org/10.1212/WNL.47.2.425

[18] Stewart, W.F., Kawas, C., Corrada, M. and Metter, E.J. (1997) Risk of Alzheimer's Disease and Duration of NSAID Use. *Neurology*, **48**, 626-632. https://doi.org/10.1212/WNL.48.3.626

[19] Hamrick, I., Hafiz, R. and Cummings, D.M., (2013) Use of Days of the Week in a Modified Mini-Mental State Exam (M-MMSE) for Detecting Geriatric Cognitive Impairment. *JABFM*, **26**, 429-435. https://doi.org/10.3122/jabfm.2013.04.120300

[20] Kolibas, E., Korinkova, V., Novotny, V., Vajdickova, K. and Hunakova, D. (2000) ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive Subscale)—Validation of the Slovak Version. *Bratislavske Lekarske Listy*, **101**, 598-602.

[21] O'Bryant, S.E., Waring, S.C., DVM, Cullum, M., *et al.* (2008) Staging Dementia Using Clinical Dementia Rating Scale Sum of Boxes Scores. *Archives of Neurology*, **65**, 1091-1095. https://doi.org/10.1001/archneur.65.8.1091

[22] Borenstein, M., Hedges, L.V., Higgins, J.P.T. and Rothstein, H.R. (2009) Introduction to Meta-Analysis. John Wiley & Sons, Ltd., Hoboken. https://onlinelibrary.wiley.com/doi/book/10.1002/9780470743386

[23] Wilcock, G.K., *et al.* (2008) Efficacy and Safety of Tarenflurbil in Mild to Moderate Alzheimer's Disease: A Randomised Phase II Trial. The *Lancet Neurology*, **7**, 483-493. https://doi.org/10.1016/S1474-4422(08)70090-5

[24] Leoutsakos, J.M.S., Muthen, B.O., Breitner, J.C.S., Lyketsos, C.G. and ADAPT Research Team (2012) Effects of Non-Steroidal Anti-Inflammatory Drug Treatments on Cognitive Decline Vary by Phase of Pre-Clinical Alzheimer Disease: Findings from the Randomized Controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial. *International Journal of Geriatric Psychiatry*, **27**, 364-374. https://doi.org/10.1002/gps.2723

[25] Pasqualetti, P., *et al.* (2009) A Randomized Controlled Study on Effects of Ibuprofen on Cognitive Progression of Alzheimer's Disease. *Aging Clinical and Experimental Research*, **21**, 102-110. https://doi.org/10.1007/BF03325217

[26] Green, R.C., *et al.* (2009) Effect of Tarenflurbil on Cognitive Decline and Activities of Daily Living in Patients with Mild Alzheimer Disease: A Randomized Controlled Trial. *JAMA*, **302**, 2557-2564. https://doi.org/10.1001/jama.2009.1866

[27] de Jong, D., *et al.* (2008) No Effect of One-Year Treatment with Indomethacin on Alzheimer's Disease Progression: A Randomized Controlled Trial. *PLOS ONE*, **3**, e1475. https://doi.org/10.1371/journal.pone.0001475

[28] Ryan, J., *et al.* (2020) Randomized Placebo-Controlled Trial of the Effects of Aspirin on Dementia and Cognitive Decline. *Neurology*, **95**, e320-e331. https://doi.org/10.1212/WNL.0000000000009277

[29] Babiloni, C., *et al.* (2009) Ibuprofen Treatment Modifies Cortical Sources of EEG Rhythms in Mild Alzheimer's Disease. *Clinical Neurophysiology*, **120**, 709-718. https://doi.org/10.1016/j.clinph.2009.02.005

[30] Szekely, C.A., *et al.* (2008) NSAID Use and Dementia Risk in the Cardiovascular Health Study: Role of APOE and NSAID Type. *Neurology*, **70**, 17-24. https://doi.org/10.1212/01.wnl.0000284596.95156.48

[31] Hayden, K.M., *et al.* (2007) Does NSAID Use Modify Cognitive Trajectories in the Elderly? The Cache County study. *Neurology*, **69**, 275-282. https://doi.org/10.1212/01.wnl.0000265223.25679.2a

[32] ADAPT Research Group *et al.* (2007) Naproxen and Celecoxib Do Not Prevent AD in Early Results from a Randomized Controlled Trial. *Neurology*, **68**, 1800-1808. https://doi.org/10.1212/01.wnl.0000260269.93245.d2

[33] In't Veld, B.A., *et al.* (2001) Nonsteroidal Antiinflammatory Drugs and the Risk of Alzheimer's Disease. *The New England Journal of Medicine,* **345**, 1515-1521. https://doi.org/10.1056/NEJMoa010178

[34] Szekely, C.A., Zandi, P.P., Ek, M., Breitner, J.C.S., Goodman S.N., Thorne, J.E. and Messias, E. (2004) Nonsteroidal Anti-Inflammatory Drugs for the Prevention of Alzheimer's Disease: A Systematic Review. *Neuroepidemiology*, **23**, 159-169. https://doi.org/10.1159/000078501