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Long-Term Exposure to Non-Steroidal Anti-Inflammatory Medication in Relation to Dementia Risk

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Keywords: dementia | neuro-inflammation | non-steroidal anti-inflammatory drugs | population-based

ABSTRACT

Background: Non-steroidal anti-inflammatory (NSAID) medication could reduce dementia risk due to anti-inflammatory and possibly amyloid-lowering properties. However, the results of observational studies and short-term randomized-controlled trials have been inconsistent, and duration and dose–response relationships are still unclear.

Methods: We included 11,745 dementia-free participants from the prospective population-based Rotterdam Study (59.5% female, mean age 66.2 years). NSAID use from 1991 was derived from pharmacy dispensing records, from which we determined cumulative duration and dose. We defined four mutually exclusive categories of cumulative use: non-use, short-term use (< 1 month), intermediate-term use (between 1 and 24 months), and long-term use (> 24 months). We determined the association with dementia risk until 2020 using Cox regression models, including NSAID use as a time-varying exposure. Models were adjusted for lifestyle factors, comorbidity, and comedication use. We repeated the analyses stratified by previously established amyloid-β lowering properties of different NSAIDs.

Results: During an average follow-up period of 14.5 years, a total of 9520 (81.1%) participants had used NSAIDs at any given time, and 2091 participants developed dementia. Use of NSAIDs was associated with lower dementia risk for long-term users (HR [95% CI]: 0.88 [0.84–0.91]), and a small increased risk with short-term use (HR [95% CI]: 1.04 [1.02–1.07]) or intermediate-term use (HR: 1.04 [1.02–1.06]). The cumulative dose of NSAIDs was not associated with decreased dementia risk (HR for ≤ 25th percentile: 1.06 [1.03–1.09], 26–50th percentile: 1.02 [0.99–1.05], 51–75th percentile: 1.03 [0.99–1.06], > 75th percentile: 0.99 [0.96–1.02]). Associations were somewhat stronger for long-term use of NSAIDs without known effects on amyloid-β than for amyloid-lowering NSAIDs (HR [95% CI]: 0.79 [0.74–0.85] versus 0.89 [0.85;0.93]).

Conclusion: Long-term NSAID use, but not cumulative dose, was associated with decreased dementia risk. This suggests that prolonged rather than intensive exposure to anti-inflammatory medication may hold potential for dementia prevention.

Summary

- Key points
  - Recent evidence demonstrates a key role of inflammation in dementia.
  - Investigating the effect of non-steroidal anti-inflammatory (NSAID) medication use on dementia risk could provide insight in possible beneficial effects of anti-inflammatory medication in the prevention of dementia.
  - In this prospective, population-based cohort study of 11,745 participants with an average follow-up of 14.5 years, we showed that long-term NSAID use, but not cumulative dose, was associated with decreased dementia risk.
- Why does this paper matter?
  - These findings provide important insight in the relationship between inflammation and dementia risk, and suggest that prolonged rather than intensive exposure to anti-inflammatory medication may hold potential for dementia prevention.

1 | Introduction

Dementia is currently one of the leading causes of disability and dependency. Prevalence is increasing, and no effective preventative treatments are available [1]. Increasing evidence from experimental studies in animals and observational studies in humans suggests a central role of inflammatory processes in various pathologies underlying dementia, including vascular brain injury and amyloid-β and tau accumulation [2, 3]. It has been postulated that important risk factors of dementia, including hypertension, cerebral hypoperfusion, atherosclerosis, and the accumulation of amyloid-β and tau, trigger chronic neuroinflammatory responses. Chronic neuroinflammation leads to amplified vascular damage and amyloid-β and tau accumulation through various processes, including blood–brain barrier breakdown and endothelial dysfunction [2, 3]. Indeed, chronic inflammation is observed in patients with vascular cognitive impairment and in areas affected by amyloid and tau pathology [4, 5] and inflammatory markers in peripheral blood are consistently associated with long-term dementia risk in cohort studies [6]. In addition, of all genetic variants that are identified to be causally implicated in Alzheimer's disease (AD), more than half are implicated in inflammatory responses; notable examples include *TREM2* and *CD33* [7]. Targeting these mechanisms could aid development of dementia therapies, and indeed approximately 20% of the treatments for AD currently in the pipeline have inflammation as their primary mechanistic target [8]. Yet, this has not led to approved medication on the market.

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications, usually taken as analgesics. NSAIDs have anti-inflammatory effects by inhibiting the enzymatic activity of cyclooxygenase (COX)-1 and -2 [9]. Animal studies have shown that NSAID exposure also reduces the formation of amyloid-β plaques in the brains of mice; amyloid-β plaques in the brain are considered a neuropathological hallmark of AD [10]. A meta-analysis of 12 cohort studies and 4 case–control studies observed a decreased dementia risk with NSAID use when comparing ever use to never use [11]. In contrast, results from two recent meta-analyses of randomized controlled trials (RCTs) showed no effect of NSAID use on dementia risk, but out of 14 trials, 11 included participants with mild to moderate AD, in whom brain pathology might be too advanced to obtain beneficial effects [12, 13]. The duration of medication use in preventive trials was, on average, 1.5–1.8 years, which may well have been too short to observe beneficial effects. Observational studies on the long-term use of NSAIDs and dementia risk are scarce, with considerable heterogeneity across studies, stemming from variations in age, drug dosages, and adjusted variables among the studies [11]. Previous prospective cohort studies assessing the association between the duration of NSAID use and dementia risk have shown a decreased dementia risk associated with long-term use, including one previous study from the Rotterdam Study [14–17]. However, these studies were challenged by limited follow-up duration and power in the long-term exposure groups [14–17].

We therefore determined whether NSAID use is associated with the occurrence of all-cause dementia within a prospective, population-based cohort study with 30 years of data on NSAID use and dementia risk. We specifically assessed the long-term duration of use and cumulative dose, as well as the association with amyloid-lowering and non-lowering NSAIDs, in order to obtain insight into the underlying protective mechanisms of NSAIDs.

2 | Methods

2.1 | Study Population

The current study was embedded in the Rotterdam Study, an ongoing population-based cohort study in the Netherlands, details of which have been described previously [18]. Briefly, the Rotterdam Study started in 1990 with the enrollment of 7983 participants aged 55 years and older residing in the Ommoord district in the city of Rotterdam, the Netherlands. There were no prespecified exclusion criteria, meaning that all persons older than 55 years of age living in the area were invited to participate. This first cohort was extended in 2000 with a second cohort including 3011 participants who reached age 55 or moved into the study area. In 2006, an additional 3932 participants aged 45 years and over were enrolled. This resulted in the inclusion of 14,926 participants in total, who undergo follow-up examinations at a dedicated research center every 4 years. A total of 13,507 participants were dementia-free at enrollment into the Rotterdam Study and provided informed consent for follow-up through medical records. We excluded those who were censored within the first year of follow-up ($N = 82$) to allow for sufficient history on medication use. For practical reasons, within the cohort design at each date an incident case of dementia occurred, we matched on age, sex, and sub-cohort individuals who were dementia-free at that time point. Cumulative exposure to NSAIDs until dementia diagnosis in a person diagnosed with dementia was compared to exposure in age, sex, and sub-cohort matched individuals, equivalent to time-varying cox regression models. Consequently, an additional 1706 participants were

lost through lack of matching. This resulted in the inclusion of 11,745 participants in total.

2.2 | Use of NSAID Medication

Information on NSAID use was available through electronic linkage with pharmacy records, which provided detailed information on prescription date, days of use, and defined daily dose on a day-to-day basis, classified according to the anatomic therapeutic chemical (ATC) code. Pharmacy data was available from 1991 onwards for the first cohort and from 1995 onwards for the second and third cohorts. Registry data were complete for all participants. All prescriptions for oral NSAIDs filled during the entire follow-up period were used to assess NSAID use as time-dependent exposure. NSAID use was defined as the cumulative duration of use of any NSAID (ATC-code: M01). The cumulative duration of use was calculated by dividing the total number of tablets dispensed during the study period by the prescribed daily number of tablets, which resulted in the total number of days used. Additionally, we assessed cumulative defined daily dosage (DDD) as defined by the World Health Organization [19]. An overview of the overlap between cumulative duration and cumulative DDD is presented in Table S1. NSAIDs were classified as Aβ42-lowering or non-Aβ42-lowering on the basis of previously reported effects on cerebral Aβ42 levels from in vitro and mouse model studies [5]. As such, NSAIDs with Aβ42-lowering properties included Diclofenac, Ibuprofen, Piroxicam, Indometacin, Sulindac, and Flurbiprofen. Other NSAIDs were classified as non-Aβ42-lowering, including Naproxen, Rofecoxib, Nabumetone, Ketoprofen, Meloxicam, Celecoxib, Phenylbutazone, Etoricoxib, and Valdecoxib [9].

2.3 | Dementia Screening and Surveillance

Participants were screened for dementia at each center visit, using the Mini-Mental State Examination (MMSE) and the Geriatric Mental Schedule (GMS). Those with MMSE <26 or GMS >0 underwent further investigation, including an informant interview and the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) [20]. In addition, the entire cohort was continuously under surveillance for dementia through electronic linkage with medical records from general practitioners and the regional institute for outpatient mental health care. All cases suspected of dementia were reviewed by a consensus panel, including a consultant neurologist, which applied Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R criteria for all-cause dementia and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for the subtype of clinical AD to come to a final diagnosis. Clinical neuroimaging was used as an aid to determine the subtype of dementia or to rule out other causes when needed. Follow-up for dementia diagnosis was completed until January 1, 2020, and complete for 96.5% of the potential person-years. Participants were censored at the date of dementia diagnosis, the date of death, the date of loss to follow-up, or January 1, 2020, whichever came first [20].

2.4 | Other Measurements

Information on age, sex, educational attainment (primary, lower, intermediate, or higher education), smoking habits (never, current, or former) and alcohol use (grams/day) was ascertained during a home interview. At the research center visit, height and weight were measured from which body mass index (BMI, kg/m^2) was computed. Blood pressure was measured in a sitting position using a random-zero sphygmomanometer. History of stroke was assessed by home interview and verified in medical records. Diabetes was defined as fasting blood glucose >7.0 mmol/L or use of antidiabetic medication. Use of antihypertensives (ATC-codes: C02, C03, C07, C08, and C09) and statins (ATC-code: C10AA/C10AB) at baseline and use of salicyclates (ATC-codes: B01AC06, B01AC08, and N02BA) until the censor date were extracted from pharmacy records. Alanine aminotransferase levels (U/L), aspartate aminotransferase levels (U/L) and gamma-glutamyltransferase levels (U/L) were assessed based on fasting blood samples using automatic enzymatic procedures (Roche Diagnostics GmbH, Mannheim, DE). Levels of serum total cholesterol and high-density lipoprotein (HDL) were assessed based on non-fasting blood samples, from which non-HDL cholesterol levels were determined.

2.5 | Statistical Analyses

Missing covariate data were imputed using fivefold imputation. The distribution of variables was similar in the imputed and non-imputed datasets. Percentages of missing data are shown in the footnote of Table 1. All covariates were at least 90% complete, except for aspartate aminotransferase (88% complete), alanine aminotransferase (88% complete), gamma-glutamyltransferase (22.0%) and alcohol consumption (71.1% complete).

For the main analysis, we assessed the association between the duration of NSAID use and the risk of all-cause dementia. NSAID use was assessed as time-dependent exposure over the entire follow-up period. Due to the right-skewed distribution of these variables, we categorized the duration of NSAID use into four mutually exclusive categories of cumulative use: never use, short-term use (<1 month), intermediate-term use (1–24 months), and long-term use (>24 months), in accordance with previous studies [14, 16]. To further assess the association with the duration of use, additional analyses were performed using an alternative categorization (no use, 1 month or less of use, 1–12 months of use, 12–24 months of use, 24–36 months of use and more than 36 months of use). We repeated the analyses for cumulative defined daily dose, categorized based on percentiles (never use; 1–25th percentile; 26–50th percentile; 51–75th percentile; and >75th percentile). Due to the time-varying design, a cohort member can contribute person-time to more than one category with increasing NSAID use.

First, we determined the association between the duration of NSAID use and the risk of all-cause dementia using Cox proportional hazards regression models with calendar time in days as the time axis, and including NSAID use as a time-varying exposure. During follow-up, each time an event

occurred, cumulative exposure to NSAIDs was determined. The exposure in the case developing at that time point was compared to exposure until then in age, sex, and sub-cohort matched individuals who were dementia-free at the time of the event. Matching on sub-cohort occurred to adjust for the differences in exposure time between cohorts. All models included adjustment for education (Model 1), and additionally, in a second model, for smoking habits, alcohol consumption, serum levels of non-HDL cholesterol, ASAT, ALAT, and GAMMA-GT, history of diabetes, history of stroke, and use of antihypertensive medication and statins (Model 2). Since salicylates are pharmacologically related to NSAIDs but are mostly used in low doses as a platelet-inhibiting agent, we repeated the analyses including acetylsalicylic acid as a time-varying covariate in an additional model (Model 3).

In sensitivity analyses, we excluded 2 years in potential NSAID exposure immediately prior to dementia diagnosis. In this way, we assessed the effect of protopathic bias that might occur due to changes in NSAID use in the prodromal phase of dementia. Furthermore, we assessed the association between NSAID use and clinical AD separately. Additionally, we assessed the association with Aβ42-lowering and non-Aβ42-lowering NSAIDs, and we stratified based on presence of at least one *APOE*-ε4 allele. Last, we assessed the association with salicylates. We compared hazard ratio's between models based on 83.4% confidence intervals to achieve a type 1 error probability of 0.05, as described in previous research [21]. All analyses were done using SPSS version 28.

2.6 | Ethical Approval and Consent to Participate

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare, and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

3 | Results

Table 1 shows baseline characteristics of the study population. At baseline, the mean age was 66.2 years, and 59.5% were female. During follow-up, 9553 (81.3%) participants used NSAIDs, representing a total of 93,859 cumulative months of use, with a median defined daily dose of 1.1. Overall use was similar in males and females, but long-term use was more common in females than in males. Moreover, compared to short-term users, long-term users had higher average BMI and more frequent diabetes but were less often smokers (Table S2). Of all users, 3508 (29.9%) used only NSAIDs with Aβ42-lowering properties, 682 (5.8%) used only non-Aβ42-lowering NSAIDs, and 5352 (45.6%) used both.

TABLE 1 | Baseline characteristics of the study population.

Characteristics	Total study population ($N = 11,745$)
Mean follow-up duration (years)	14.5 (±6.9)
Age (years)	66.2 (±9.0)
Females	6991 (59.5%)
Education	
Primary	2057 (17.5%)
Lower/intermediate or lower vocational	4811 (41.0%)
Intermediate vocational or higher	3132 (26.7%)
Higher vocational or university	1564 (13.3%)
Smoking	
Never	4837 (41.2%)
Former	4553 (38.8%)
Current	2164 (18.4%)
Alcohol (grams/day)	4.0 (0.26–14.1)
Body mass index (kg/m^2)	26.9 (±4.0)
Systolic blood pressure (mmHg)	139.2 (±21.7)
Diastolic blood pressure (mmHg)	76.8 (±11.8)
Non-HDL cholesterol (mmol/L)	4.9 (±1.2)
Aspartate aminostransferase (U/L)	22.7 (±11.6)
Alanine aminotransferase (U/L)	22.1 (±13.8)
Gamma-glutamyltransferase (U/L)	32.6 (±38.7)
Prevalence of Type II diabetes	647 (5.5%)
Prevalence of stroke	303 (2.6%)
Statin use	785 (6.7%)
Antihypertensive use	2870 (24.4%)
Acetylsalicylic acid use	5576 (47.5%)

Note: Data are presented as frequency (%) for categorical, mean ± standard deviation for normally distributed continuous variables and median ± quartiles for non-normally distributed continuous variables. Covariates with missing data in total study population: education (1.5%), smoking (1.6%), alcohol (28.8%), body mass index (6.2%), systolic blood pressure (5.8%), diastolic blood pressure (5.8%), non-HDL cholesterol (6.8%), aspartate aminotransferase (22.0%), alanine aminotransferase (22.0%), gamma-glutamyltransferase (22.0%), stroke (< 0.01%).

During a total of 169,976 person-years of follow-up (mean: 14.5 years, range: 0.5–29.8 years), 2091 (17.8%) participants had a diagnosis of dementia. Of these, 1534 (73.4%) were diagnosed with clinical AD. Compared to never use, short-term and intermediate-term use of NSAIDs were associated with a small increased risk of all-cause dementia (hazard ratio [95% confidence interval] for short term use: 1.04 [1.02–1.07], intermediate use: 1.04 [1.02–1.06], Figure 1). Long-term use (> 24 months) of NSAIDs was associated with a lower dementia risk (HR [95% CI] for long term use: 0.88 [0.84–0.91]; Figure 1). The cumulative dose of NSAIDs was not associated with dementia risk (HR

[95% CI] for < 25th percentile: 1.06 [1.03–1.09], > 25th percentile ≤ median: 1.02 [0.99–1.05], > median ≤ 75th percentile: 1.03 [1.00–1.06], > 75th percentile: 0.99 [0.96–1.02]).

3.1 | Sensitivity Analyses

Using a more extensive categorization of duration of use showed similar patterns of results with decreased dementia risk in > 24 months of use (Table S3). Between 12 and 24 months of use was associated with a somewhat increased risk of dementia (Table S3). Including a 2-year lag time prior to dementia diagnosis did not alter the results (HR [95% CI] for short-term use: 1.04 [1.02–1.07], intermediate term use: 1.05 [1.03–1.08] and long-term use: 0.91 [0.88–0.95]). The association with long-term NSAID use was more pronounced in clinical AD than in all-cause dementia (HR [95% CI]: 0.79 [0.76–0.83], Figure 1). Long-term use of non-Aβ42-lowering NSAIDs was associated with stronger reductions in all-cause dementia risk compared to Aβ42-lowering NSAIDs (HR [95% CI] for long-term use of Aβ42-lowering NSAIDs: 0.89 [0.85–0.93] and non-Aβ42-lowering NSAIDs: 0.79 [0.74–0.85]; Table 2). Similar results were observed in clinical AD (HR [95% CI] for long-term use of Aβ42-lowering NSAIDs: 0.81 [0.76–0.85] and non-Aβ42-lowering NSAIDs: 0.64 [0.59–0.70]). Long-term use of NSAIDs was associated with lower all-cause dementia risk in those without APOE-ε4 allele present, but not in those with APOE-ε4 allele present (HR [95% CI] for long-term use in APOE-ε4 positive participants: 1.02 [0.95–1.11], and APOE-ε4 negative participants: 0.86 [0.82–0.90]; Table 3). Long-term use of acetylsalicylic acid showed no association with dementia risk (HR [95% CI] for short term use (< 1 month): 0.85 [0.81–0.89], intermediate use (1–24 months): 1.00 [0.98–1.03] and long-term use (> 24 months): 1.02 [1.00–1.04]).

4 | Discussion

In this prospective population-based cohort study, we observed a lower risk of dementia with long-term use of NSAIDs, but not with short-term use. This association appeared dependent on the duration of use, rather than the cumulative dose, and could not be explained by the amyloid-lowering properties of specific NSAIDs.

Our results suggest that prolonged use of anti-inflammatory medication may reduce dementia risk. Short-term (≤ 1 month)

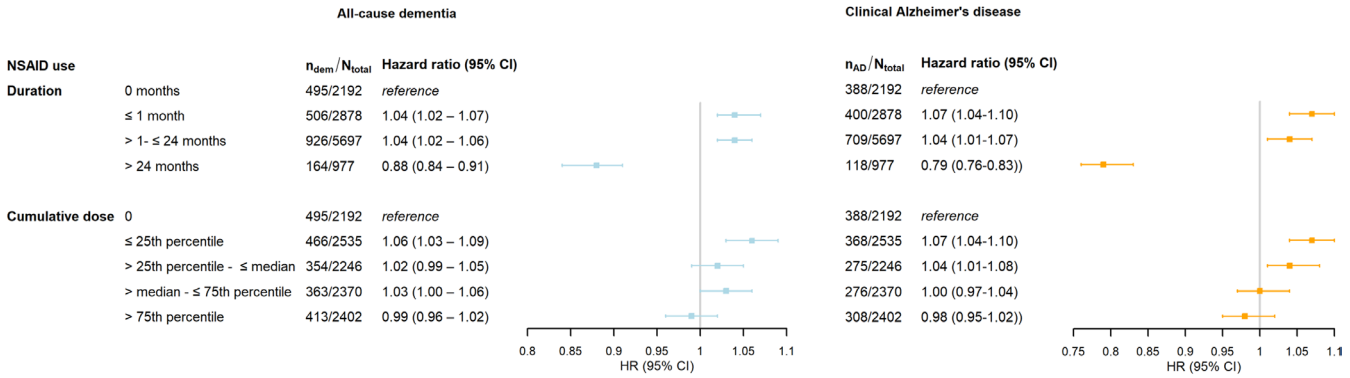

FIGURE 1 | NSAID medication use and risk of all-cause dementia and clinical Alzheimer's disease. Estimates shown are adjusted for age, sex, education, cohort, smoking behavior, alcohol use, non-HDL cholesterol levels, body mass index, systolic blood pressure, diastolic blood pressure, levels of aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyltranspeptidase, prevalence of diabetes, prevalence of stroke, and use of antihypertensive medication, statins, and acetylsalicylic acid. The twenty-fifth percentile cumulative dose was 30.0 defined daily dose (DDD), the median was 86.0 DDD, and the 75th percentile was 250.0 DDD. CI = confidence interval, N_{dem} = number of dementia cases, NSAID = non-steroidal anti-inflammatory drugs, N_{total} = total number of participants in the group. N_{AD} = number of cases with clinical Alzheimer's disease.

TABLE 2 | NSAID medication use and risk of all-cause dementia, by amyloid-lowering property.

	Amyloid lowering		Non-amyloid lowering	
NSAID use	n_{dem}/N_{total}	**Hazard ratio (95% CI)**	N_{dem}/N_{total}	**Hazard ratio (95% CI)**
Duration				
0 months	632/2885	*Reference*	1125/5715	*Reference*
≤ 1month	563/3456	1.00 (0.98–1.03)	448/2910	1.07 (1.04–1.09)
> 1–≤ 24 months	792/4808	1.00 (0.98–1.03)	463/2774	1.07 (1.04–1.09)
> 24months	104/596	0.89 (0.85–0.93)	55/346	0.79 (0.74–0.85)

Note: Estimates shown are adjusted for age, sex, education, cohort, smoking behavior, alcohol use, non-HDL cholesterol levels, body mass index, systolic blood pressure, diastolic blood pressure, levels of aspartate aminotransferase, alanine aminotransferase and gamma-glutamyltranspeptidase, prevalence of diabetes, prevalence of stroke, and use of antihypertensive medication, statins and acetylsalicylic acid.
Abbreviations: CI = confidence interval, N_{dem} = number of dementia cases, NSAID = non-steroidal anti-inflammatory drugs, N_{total} = total number of participants in group.

TABLE 3 | Duration of NSAID use and risk of all-cause dementia stratified by *APOE*-ε4 genotype.

	APOE-ε4 negative		APOE-ε4 positive	
NSAID use	n_{dem}/N_{total}	**Hazard ratio (95% CI)**	N_{dem}/N_{total}	**Hazard ratio (95% CI)**
Duration				
0 months	251/1373	*Reference*	166/543	*Reference*
≤1 month	255/1806	1.06 (1.03–1.10)	162/709	1.00 (0.95–1.05)
>1–≤24 months	517/3790	1.08 (1.05–1.12)	284/1268	1.05 (1.02–1.10)
>24 months	95/673	0.86 (0.82–0.90)	49/201	1.02 (0.95–1.11)

Note: Estimates shown are adjusted for age, sex, education, cohort, smoking behavior, alcohol use, non-HDL cholesterol levels, body mass index, systolic blood pressure, diastolic blood pressure, levels of aspartate aminotransferase, alanine aminotransferase and gamma-glutamyltranspeptidase, prevalence of diabetes, prevalence of stroke, and use of antihypertensive medication, statins and acetylsalicylic acid.
Abbreviations: CI = confidence interval, N_{dem} = number of dementia cases, NSAID = non-steroidal anti-inflammatory drugs, N_{total} = total number of participants in group.

and intermediate-term (1–24 months) use showed statistically significant associations with a small increased risk of all-cause dementia; however, effect estimates were too small to obtain clinical relevance. Between 12 and 24 months of use was associated with a somewhat increased risk of dementia; this was not supported by any clinically relevant harmful effects in any of the other categories, nor in cumulative dose, clinical AD, and for both Aβ42-lowering and non-Aβ42-lowering NSAIDs. Recent randomized-controlled trials comparing NSAIDs with placebo showed no effect of NSAID use on cognitive decline and dementia risk [12, 13]. The discrepancy might be attributed to variation in study population and duration. Twelve out of fourteen performed RCTs included participants with MCI, AD or probable AD, in whom Alzheimer's pathology might be too advanced to obtain beneficial effects of anti-inflammatory medication. In prevention trials, the median duration of medication use was 1.5–1.8 years, which might have been too short to observe beneficial effects. Since RCTs are typically limited in follow-up duration due to feasibility and cost constraints, long-term observational data are needed to establish the long-term effect of NSAIDs on dementia risk. Our results are in line with the results of a previous study on NSAID use and dementia risk in the Rotterdam Study and provided increased follow-up duration and substantially more power in the exposure groups [14].

Currently, no preventative disease-modifying treatments for dementia are available. Our results show reduced risk with the use of both amyloid-lowering and non-lowering NSAIDs, suggesting that the potential beneficial effects of NSAID use go beyond the lowering of amyloid deposition. Additionally, we did not observe an association in ApoE4-positive individuals. NSAID use might exert effects on different pathological pathways than ApoE4, resulting in positive results in ApoE4-negative individuals and absence of an association in ApoE4-positive individuals. Alternatively, it is possible that the harmful effects of ApoE4 might outweigh the potential beneficial effects of NSAID use. Furthermore, we observed stronger effect estimates in clinical AD compared to all-cause dementia. All-cause dementia includes various subtypes of dementia; each of these subtypes has distinct pathways that may not be affected by NSAID use. Including these subtypes in the analysis could result in weaker effect estimates. NSAIDs can reduce dementia risk through inhibiting the enzymatic activity of COX-1 and COX-2, hereby reducing chronic neuroinflammation and associated harmful effects, such as vascular damage and accumulation of amyloid-beta and tau [2]. Previous RCTs were halted due to severe side effects of NSAID use, cautioning against prolonged use [22]. Despite this, our results offer valuable insights for future development of preventative therapeutics against dementia. Our results suggest that long-term inhibition of detrimental inflammatory processes, rather than exposure to a high cumulative dose, is more effective in the prevention of dementia.

The current study is strengthened by its detailed, long-term information on NSAID use as well as incident dementia. There are also limitations to consider. First, in the Netherlands, NSAIDs are available on prescription as well as over the counter (OTC) without a prescription. In the current study, we were not able to include OTC use. In the case of over the counter NSAID use, exposed participants might have been misclassified as unexposed, which most likely has led to attenuated results. Second, we were not able to include biomarkers in the diagnosis for clinical AD, which might have led to misclassification in the diagnosis of AD. Third, our results might be influenced by the healthy adherer effect. Long-term users who tolerated NSAIDs well might have been healthier compared to short-term users and therefore less at risk to develop dementia. However, long-term users showed no consistent healthier profile compared to short-term users. Last, this study was performed in a predominantly White population, potentially hampering generalizability.

5 | Conclusions

Long-term NSAID use, but not cumulative dose, was associated with decreased dementia risk. This suggests that prolonged rather than intensive exposure to anti-inflammatory medication may hold potential for dementia prevention. Sustained suppression of harmful inflammatory processes might be more beneficial in the prevention of dementia rather than short-term intensive suppression. Although our results are an indication of the important role of inflammation in the treatment of dementia, they do not justify the recommendation of long-term treatment with NSAIDs for the prevention of dementia, given its potential adverse effects. NSAIDs are currently listed as potentially

inappropriate medications in older adults according to the Beers criteria [23]. Our results warrant further investigation on the potential of anti-inflammatory medication in the prevention of dementia.

Author Contributions

Study design: I.H., B.H.S., M.A.I., F.J.W.; Data collection: I.H., B.H.S., M.K.I.; Data analysis and writing: I.H., F.J.W.; Data interpretation: I.H., B.H.S., M.A.I., F.J.W.; Critical Review: B.H.S., M.K.I., M.A.I., F.J.W. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data from The Rotterdam Study can be made available to interested researchers upon request. Requests can be directed to the secretariat of the department of Epidemiology (secretariat.epi@erasmusmc.nl), or visit the following website for more information: http://www.ergo-onderzoek.nl/wp/contact.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.