Non-steroidal anti-inflammatory drugs use in older adults decreases risk of Alzheimer's disease mortality

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Abstract

Alzheimer disease (AD) mortality risk in a large cohort of subjects treated or not with non-steroidal anti-inflammatory drugs (NSAIDs) is unknown. Our objective was to determine whether NSAIDs use is associated with decreased risk of AD mortality. In this prospective, population-based study (Neurological Disorders in Central Spain [NEDICES]) of 5,072 people without AD (aged 65 years and older), sociodemographic, comorbidity factors, and current medications were recorded at baseline. Community-dwelling older adults were followed for a median of 12.7 years, after which the death certificates of deceased participants were examined. 2,672 (52.7%) of 5,072 participants died, including 504 (18.9%) NSAIDs users and 2,168 (81.1%) non-users. Of the 2,672 deceased participants, 113 (4.2%) had AD as a cause of death (8 [1.6%] among NSAIDs users and 105 [4.8%] among non-users, chi-square = 10.70, p = 0.001). In an unadjusted Cox model, risk of AD mortality was decreased in NSAIDs users (hazard ratio [HR] for AD mortality = 0.35, 95% confidence interval [CI] 0.17–0.72, p = 0.004) when compared to non-users. After adjusting for numerous demographic factors and co-morbidities, the HR for AD mortality in NSAIDs users was 0.29, 95% CI 0.12–0.73, p = 0.009. Stratified analyses showed a significantly decreased risk of AD mortality with aspirin, whereas non-aspirin NSAIDs only showed a statistical trend toward significance in the adjusted Cox regression models. NSAIDs use was associated with 71% decreased risk of AD mortality in older adults. Our results support the hypothesis that NSAIDs use is a protective factor of developing AD.

Introduction

The development and evaluation of new therapies to slow the progression of Alzheimer's disease (AD) is a public health priority. Currently, it is an exciting time as some traditional drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), and many others in development

might have an impact in reducing the risk of AD.[1] In 1990, it was reported for the first time that patients with rheumatoid arthritis receiving NSAIDs showed a markedly reduced prevalence of AD compared to the overall population.[2] From then, different independent observational studies in humans have found that NSAIDs use is associated with a decreased risk of developing AD.[3] However, clinical trials, mostly using selective cyclooxygenase-2 inhibitors, have so far shown a null efficacy for AD treatment.[4] In fact, recently in a 2-year double-masked pharmaco-prevention trial, enrolling 195 AD family history-positive elderly, sustained treatment with naproxen sodium 220 mg twice daily did not reduce apparent progression of presymptomatic AD.[5] Notwithstanding, interest in NSAIDs has been sparked in AD research by the notion that these medications might have a mode of action beyond inflammation; specifically, their neuroprotective effects might be also mediated by alteration of oxidative phosphorylation and possibly the ribosome pathway,[6] as well as inhibition of mitochondrial Ca2+ overload.[7]. Oxidative stress has long been considered as a component of the many pathophysiological events of AD.[8]

Prospective population- or community-based based cohort studies or community-based cohort studies are preferable for studying whether NSAIDs use offer some protection against the development of AD because they decrease sources of bias and confounding.[9] To date, twelve population- or community-based studies have examined the risk of AD among those who take NSAIDs.[10] These studies have been included in a recent meta-analysis that concluded that NSAIDs use was significantly associated with reduced risk of AD compared with those who did not use NSAIDs. This association existed in studies including all NSAID types, but not in aspirin, acetaminophen or non-aspirin NSAIDs.[10] However, most these studies were not adjusted for arterial hypertension, an important variable, since this condition is associated with both NSAIDs use and AD.[10–12]

Surprisingly, AD mortality risk in a large cohort of participants treated or not with non-steroidal anti-inflammatory drugs (NSAIDs) is unknown. Another currently unexplored method to assess this potential relationship is to study NSAIDs use among deaths for which AD have been assigned as a contributory cause (here after referred to as "AD mortality").

We aimed to reevaluate the existing uncertainty regarding the effects of NSAIDs use on risk of AD by examining whether AD mortality is decreased in NSAIDs users compared to non-users. Towards this purpose, we used data from the Neurological Disorders in Central Spain (NEDICES) study, a prospective population-based study, in which participants were followed for a median of 12.7 years, after which the death certificates of deceased participants were examined. Our statistical analyses were adjusted for several confounders, including arterial hypertension. We also performed additional analyses stratified by individual NSAID type (i.e., aspirin vs non-aspirin NSAIDs).

Material and methods

Statement of ethics

All the participants included in the study gave their written informed consent after full explanation of the procedure. The study was approved by the ethical standards committee on human experimentation at the University Hospitals "12 de Octubre" (Madrid) and "La Princesa" (Madrid).

Study population

Data for these analyses were derived from the NEDICES study, a longitudinal, population-based survey of the prevalence, incidence, mortality, and determinants of major age-associated conditions of the elderly, including Parkinson's disease, essential tremor, stroke, and

dementia.[13–18] Detailed accounts of the NEDICES study population and sampling methods have been published.[19–21] The survey area consisted of three communities: (1) Margaritas (approximately 14,800 inhabitants), a working-class neighborhood in Getafe (Greater Madrid); (2) Lista (approximately 150,000 inhabitants), a professional-class neighborhood in the Salamanca district (Central Madrid), and (3) Arévalo (approximately 9,000 inhabitants), the agricultural zone of Arévalo County (125 km northwest of Madrid).

Study evaluation

Briefly, at the time of their baseline assessment (1994 to 1995), participants were interviewed face-to-face using a screening questionnaire to collect data on demographics, current medical conditions, smoking (ever vs. never), and drinker (ever/at least once per week vs. never). At this time, participants were asked to bring all medications taken in the past week to the clinic, where the interviewer recorded the name of each one. As in prior studies,[22, 23] participants were also asked to rate their current health on a 5-point scale using the question, "In general terms, how would you describe you rhealth: very good, good, fair, poor, or very poor?" A small number of participants were in extreme categories. Therefore, as suggested in several previous studies,[22, 23] we collapsed response options into 3 categories. These 3 categories were very good/good, fair, and poor/very poor.

The questionnaire included screening items for neurological disorders (dementia, cerebro-vascular disease, Parkinson disease, and essential tremor). A short form of the questionnaire was mailed to participants who refused or were unavailable for face-to-face interview. The screening questions for dementia included the Spanish adaptation of a cognitive test (a 37-item version of the Mini-Mental State Examination [37-MMSE])[17, 18, 24–27] and an 11-item version of the Pfeffer Functional Activities Questionnaire (FAQ).[28] The FAQ assesses common activities that require complex cognitive and social functioning.[28] The total score for the 11 items ranges from 0 (completely independent) to 33 (completely dependent).[28] Those participants who screened positive for dementia underwent a neurological examination at National Health Service clinics or at home. The neurological assessment was comprised of a clinical history, a general neurological examination, and a cognitive and mental state examination. The neurological examination was performed by one of eight neurologists who met at the inception of the study to establish standardized methods to perform and interpret the examination (J. B-L, F. B-P., and see https://www.ciberned.es/en/estudio-nedices.html). For participants who could not be examined, medical records were obtained from their general practitioners, from in-patient hospitalizations, and from neurological specialists (if they had visited one). In addition to these medical records, death certificate diagnoses were reviewed for each screened participant who had died prior to their neurological examination.

The diagnosis of dementia was made by consensus of two neurologists based on clinical interview. For the diagnosis of dementia, we applied the Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV criteria.[29]AD (possible or probable) was diagnosed according to NINCDS-ADRDA criteria.[30]

Follow-up data on death were collected until December 31, 2007. The date of death was obtained from the National Population Register of Spain (*Instituto Nacional de Estadística* in Spanish). In Spain, all deceased individuals receive a death certificate, completed by a physician, at the time of death. The certificate is then sent to the local authority in the municipality where the person had been living, and the information is added to the National Register. The cause of death (using the International Classification of Diseases—ICD- 9th Revision for deaths occurred prior to 1999, [http://www.cdc.gov/nchs/icd/icd9.htm], and the ICD 10th Revision [http://www.cdc.gov/nchs/icd/icd10.htm], for deaths occurring thereafter) was

revised and classified by NEDICES researchers into one of six primary categories: AD, other causes of dementia, cerebrovascular disorders, cardiovascular disorders, respiratory diseases, cancer, and other causes (infections, trauma, genitourinary or gastrointestinal disorders). In agreement with the World Health Organization, the classification of causes of death had been codified by the physicians who completed the death certificates, depending on the basic cause of death (http://www.who.int/topics/mortality/en/). This was defined as the illness or injury that started the chain of pathological events, which directly led to death (http://www.who.int/topics/mortality/en/).

Final selection of participants

Of the 5,278 participants evaluated at baseline, we excluded 206 with AD diagnosed or detected by NEDICES researchers at baseline evaluation (1994–1995),[17] which left 5,072 remaining participants who were included in our analyses (Fig 1).

Statistical analyses

Analyses were performed in SPSS (version 25.0). All tests were two sided, and significance was accepted at the 5% level ($\alpha = 0.05$). Using a one-sample Kolmogorov–Smirnov test, we determined that age, FAQ total score, and a comorbidity index that included diabetes mellitus, hyperlipidemia, heart disease, cancer, anemia, chronic obstructive pulmonary disease, psychiatric disorders, osteoarthritis, osteoporosis, hypoacusis, cataracts, and peripheral vascular disease, were not normally distributed, even after log-transformation. Therefore, although mean and median values were reported, differences were compared using a nonparametric (Mann–Whitney U and Kruskal Wallis tests). The chi-square or Fisher p tests were used to analyze categorical variables. Participants were divided in NSAIDs users and non-users (reference category).

We used Cox proportional-hazards models to estimate hazard ratios (HRs) for AD mortality; this also generated 95% confidence intervals (CIs). The time variable was the years from the date of the first evaluation (1994 to 1995) to the date of death. The dependent (outcome) variable was the presence of AD as a cause of death, with the remaining causes of death serving as the reference group; meanwhile the independent (exposure) variable was the NSAIDs use category at baseline (NSAIDs use vs. non-use [reference category]). We began with an unadjusted model. Then, in adjusted models, we considered baseline variables that in bivariate analyses were associated at the $p < 0.05$ level with either the exposure or the outcome ("Model 1). Finally, for completeness, we adjusted for all the potential confounders, independent of their statistical significance (i.e., even if they were not associated with either the exposure or the outcome) ("Model 2"). Age in years, sex, educational level (illiterate, can read and write, primary studies, secondary and higher studies), living area during childhood/adolescence (rural vs urban area), marital status (married or domestic partnership, single, separated or divorced, and widowed), self-rated health (good/very good, fair, and bad/very bad), smoker (ever vs never), drinker (ever vs never), FAQ total score, the comorbidity index, arterial hypertension (drug-untreated hypertension, drug-treated hypertension, and no hypertension), and cerebrovascular disease (stroke and transient ischemic attack) were assessed at baseline and considered as potential covariates.

Results

The 5,072 participants had a mean duration of follow-up of 10.0 years (median = 12.7 years; range = 0.01–14.2 years). Of the 5,072 participants, 2,672 (52.7%) died over a median follow-up of 6.8 years (range 0.01–13.8 years), including 504 (18.9%) NSAIDs users and 2,168
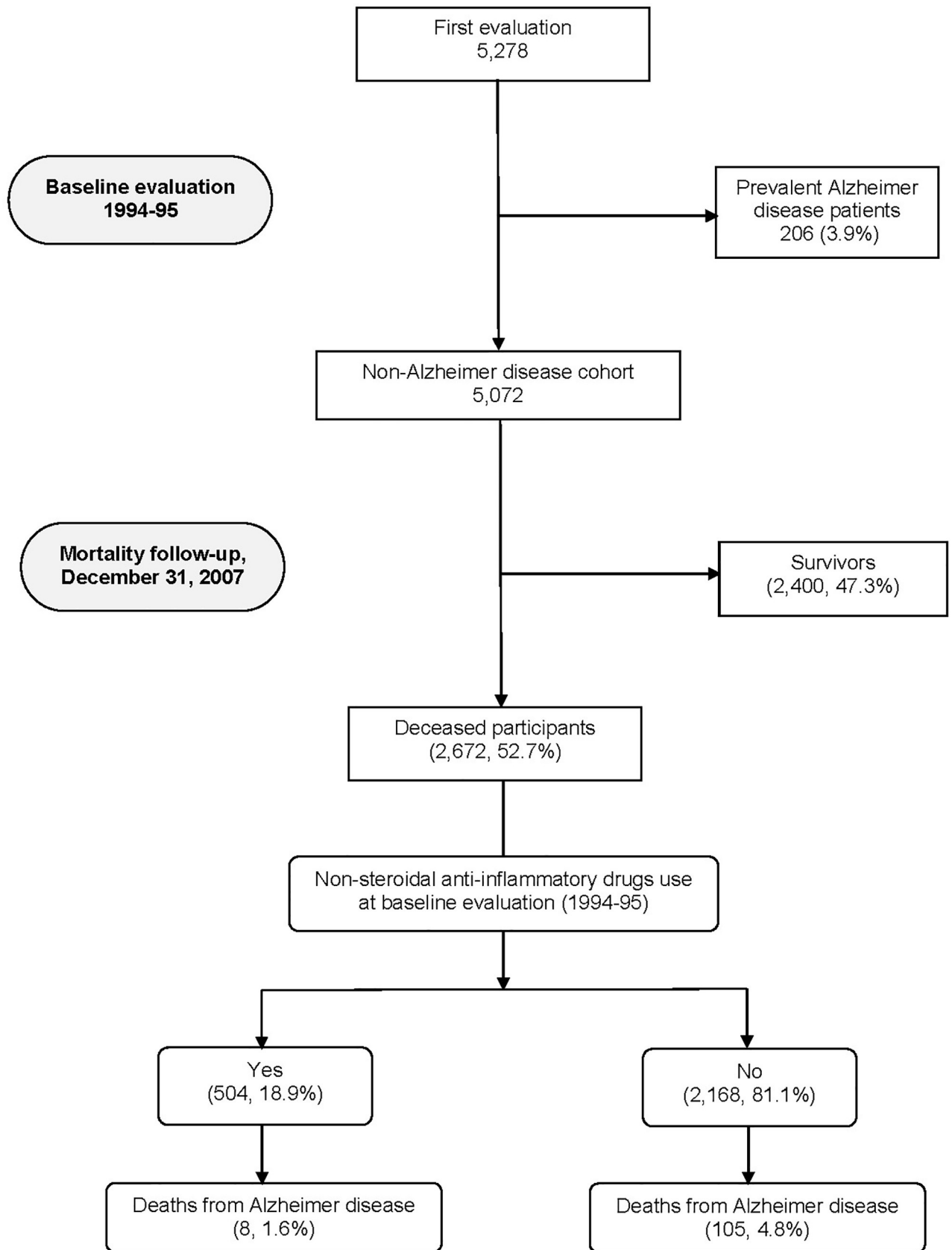
Fig 1. Flow chart of the study.

(81.1%) non-users. Of the 2,672 deceased participants, 113 (4.2%) had AD as a cause of death (8 [1.6%] among NSAIDs users and 105 [4.8%] among non-users, chi-square = 10.70, p = 0.001) (Fig 1). Table 1 shows the different NSAIDs types which were taking the 504 participants.

Baseline demographic and clinical characteristics of deceased participants who were taking NSAIDs and participants who were not are shown in Table 2. A higher proportion of NSAIDs users were more educated. In addition, NSAIDs users were more likely to have higher FAQ total scores, more drug-treated arterial hypertension, and more cerebrovascular diseases.

Baseline characteristics of the participants who died from AD vs. those who died from other causes are shown in Table 3. Those who died from AD were more likely to have been less smokers. In addition, they were more likely to have less comorbidities, but more untreated arterial hypertension.

Table 1. Non-steroidal anti-inflammatory drugs types.

Non-steroidal anti-inflammatory drugs types	Number of participants (%)
Aspirin	322 (63.9%)
Diclofenac	42 (8.3%)
Piroxicam	24 (4.8%)
Aceclofenac	20 (4.0%)
Tenoxicam	12 (2.4%)
Indomethacin	19 (3.8%)
Naproxen	9 (1.8%)
Nabumetone	7 (1.4%)
Flurbiprofen	5 (1.0%)
Ibuprofen	4 (0.8%)
Ketoprofen	4 (0.8%)
Ketorolac	3 (0.6%)
Droxicam	2 (0.4%)
Meloxicam	1 (0.2%)
Sulindac	1 (0.2%)
Niflumic acid	1 (0.2%)
Acemetacin	1 (0.2%)
Isonixin	1 (0.2%)
Aspirin and diclofenac	8 (1.6%)
Aspirin and aceclofenac	3 (0.6%)
Aspirin and indomethacin	2 (0.4%)
Aspirin and ketoprofen	2 (0.4%)
Aspirin and tenoxicam	2 (0.4%)
Aspirin and piroxicam	2 (0.4%)
Aspirin and ibuprofen	1 (0.2%)
Aspirin and nabumetone	1 (0.2%)
Aspirin and sulindac	1 (0.2%)
Aspirin and naproxen	1 (0.2%)
Aspirin and droxicam	1 (0.2%)
Aspirin and mefenamic acid	1 (0.2%)
Aspirin and isonixin	1 (0.2%)

Table 2. Baseline (1994–1995) demographic and clinical characteristics of deceased participants (N = 2,672) who were taking non-steroidal anti-inflammatory drugs and participants who were not.

	Participants taking on-steroidal anti-inflammatory drugs (N = 504)	Participants who were not taking non-steroidal anti-inflammatory drugs (N = 2,168)	p value
Age in years	76.7 (76.5) ± 6.7	76.4 (76.0) ± 7.1	0.341[a]
Sex (women)	237 (47.0%)	1,088 (50.2%)	0.201[b]
Educational level *			0.047[b]
Illiterate	63 (12.7%)	298 (13.9%)	
Can read and write	212 (42.7%)	840 (39.2%)	
Primary studies	138 (27.8%)	713 (33.2%)	
Secondary and higher studies	83 (16.7%)	294 (13.7%)	
Living area during childhood/adolescence *			0.603[b]
Rural	136 (33.5%)	514 (32.1%)	
Urban	270 (66.5%)	1,085 (67.9%)	
Marital Status *			0.169[b]
Married or domestic partnership	222 (54.1%)	947 (57.6%)	
Single	30 (7.3%)	153 (9.3%)	
Separated or divorced	7 (1.7%)	26(1.6%)	
Widowed	151 (36.8%)	518 (31.5%)	
Self-rated health *			0.113[b]
Good / very good	228 (48.2%)	1,032 (52.0%)	
Fair	155 (32.8%)	649 (32.7%)	
Bad / very bad	90 (19.0%)	304 (15.3%)	
Ever smoker (ex-smoker plus current smoker) *	168 (44.7%)	593 (39.2%)	0.052[b]
Ever drinker (ex-drinker plus current drinker) *	239 (59.0%)	935 (57.9%)	0.674[b]
FAQ total score *	4.3 (1.0) ± 6.8	3.4 (0.0) ± 6.3	0.004[a]
Comorbidity index* #	2.7 (3.0) ± 1.8	2.6 (2.0) ± 1.7	0.063[a]
Arterial hypertension *			< 0.001[b]
Drug-untreated hypertension	35 (7.2%)	160 (7.9%)	
Drug-treated hypertension	283 (58.6%)	917 (45.3%)	
No hypertension	165 (34.2%)	947 (46.8%)	
Cerebrovascular disease (stroke and transient ischemic attack)	70 (13.9%)	115 (5.3%)	< 0.001[b]

[a] Mann-Whitney test

[b] Chi-square test. Mean (median) ± standard deviation and frequency (%) are reported.

* Data on some participants were missing.

Comorbidity included 12 conditions: diabetes mellitus, hyperlipidemia, heart diseases, cancer, anemia, chronic obstructive pulmonary disease, psychiatric disorders, osteoarthritis, osteoporosis, hypoacusis, cataracts, and peripheral vascular disease. FAQ: Pfeffer Functional Activities Questionnaire.

https://doi.org/10.1371/journal.pone.0222505.t002

In an unadjusted Cox model, risk of AD mortality was decreased in NSAIDs users vs. non-users (Table 4). In a Cox model that adjusted for variables associated with either NSAIDs use or AD mortality (i.e., baseline educational level, smoker, FAQ total score, comorbidity index, arterial hypertension, and cerebrovascular disease), the risk of mortality remained decreased in NSAIDs users (Model 1, Table 4). This effect remained significant after adjusting the model for baseline age, sex, educational level, living area during childhood/adolescence, marital status, self-rated health, smoker, drinker, FAQ total score, comorbidity index, arterial hypertension, and cerebrovascular disease (i.e., all potential confounders independent of their statistical significance) (Model 2, Table 4).

Table 3. Baseline (1994–1995) demographic and clinical characteristics of participants who died from Alzheimer's disease vs other causes.

	Participants who died from Alzheimer disease (N = 113)	Participants who died from other causes (N = 2,559)	p value
Age in years	77.4 (76.0) ± 6.8	76.4 (76.0) ± 7.0	0.154[a]
Sex (women)	64 (56.6%)	1,261 (49.3%)	0.126[b]
Educational level *			0.416[b]
Illiterate	12 (10.6%)	349 (13.8%)	
Can read and write	53 (46.9%)	999 (39.5%)	
Primary studies	32 (28.3%)	819 (32.3%)	
Secondary and higher studies	16 (14.2%)	361 (14.3%)	
Living area during childhood/adolescence *			0.648[b]
Rural	25 (30.1%)	625 (32.5%)	
Urban	58 (69.9%)	1,297 (67.5%)	
Marital Status *			0.228[c]
Married or domestic partnership	44 (52.4%)	1,125 (57.1%)	
Single	4 (4.8%)	179 (9.1%)	
Separated or divorced	1 (1.2%)	32 (1.6%)	
Widowed	35 (41.7%)	634 (32.2%)	
Self-rated health *			0.320[b]
Good / very good	59 (57.8%)	1,201 (51.0%)	
Fair	31 (30.4%)	773 (32.8%)	
Bad / very bad	12 (11.8%)	382 (16.2%)	
Ever smoker (ex-smoker plus current smoker) *	25 (29.4%)	736 (40.8%)	0.036[b]
Ever drinker (ex-drinker plus current drinker) *	42 (48.8%)	1,132 (58.5%)	0.076[b]
Pfeffer Functional Activities Questionnaire total score *	2.8 (0.0) ± 5.6	3.6 (0.0) ± 6.4	0.644[a]
Comorbidity index*#	2.1 (2.0) ± 1.6	2.6 (2.0) ± 1.7	<0.001[a]
Arterial hypertension *			< 0.001[b]
Drug-untreated hypertension	18 (16.8%)	177 (7.4%)	
Drug-treated hypertension	34 (31.8%)	1,166 (48.6%)	
No hypertension	55 (51.4%)	1,057 (44.0%)	
Cerebrovascular disease (stroke and transient ischemic attack)	4 (3.5%)	181 (7.1%)	0.148[b]

[a] Mann-Whitney test

[b] Chi-square test.

[c]Fisher p test. Mean (median) ± standard deviation and frequency (%) are reported.

* Data on some participants were missing.

Comorbidity included 12 conditions: diabetes mellitus, hyperlipidemia, heart diseases, cancer, anemia, chronic obstructive pulmonary disease, psychiatric disorders, osteoarthritis, osteoporosis, hypoacusis, cataracts, and peripheral vascular disease.

https://doi.org/10.1371/journal.pone.0222505.t003

Model 1: Adjusted for baseline educational level, smoker, Pfeffer Functional Activities Questionnaire total score, comorbidity index, arterial hypertension, and cerebrovascular disease, chi-square = 21.78, p = 0.003.

Model 2: Adjusted for baseline age, sex, educational level, living area during childhood/adolescence, marital status, self-rated health, smoker, drinker, Pfeffer Functional Activities Questionnaire total score, comorbidity index, arterial hypertension, and cerebrovascular disease, chi-square = 29.10, p = 0.006.

We also conducted a sensitivity analysis in which we excluded all participants (N = 156) who were taking only non-aspirin NSAIDs. In these analyses, the HRs for AD mortality in

Table 4. Risks of Alzheimer's disease mortality in deceased participants (N = 2,672) who were taking non-steroidal anti-inflammatory drugs and participants who were not (reference group).

	Unadjusted			Model 1			Model 2		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Non-steroidal anti-inflammatory drugs users N = 504	0.35	0.17–0.72	0.004	0.29	0.12–0.72	0.008	0.29	0.12–0.73	0.009
Participants who were not taking non-steroidal anti-inflammatory drugs N = 2,168 (reference category)	1.00	–		1.00	–		1.00	–	

https://doi.org/10.1371/journal.pone.0222505.t004

aspirin users remained decreased (HR = 0.42, 95% CI = 0.18–0.95, p = 0.037, unadjusted Cox model; HR = 0.27, 95% CI = 0.10–0.90, p = 0.033, Model 1; and HR = 0.28, 95% CI = 0.10–0.90, p = 0.033, Model 2). In another analysis we excluded the 322 participants who were taking only aspirin. In these analyses, the HRs for AD mortality in non-aspirin NSAIDs users remained decreased but did not reach statistical significance in adjusted Cox models (HR = 0.30, 95% CI = 0.10–0.94, p = 0.039, unadjusted Cox model; HR = 0.26, 95% CI = 0.10–1.10, p = 0.060, Model 1; and HR = 0.25, 95% CI = 0.10–1.03, p = 0.056, Model 2).

In a final analysis, we analyzed the risk of AD mortality in those taking acetaminophen (N = 153) vs. those who were not. In these analyses, the risk of AD mortality in acetaminophen users was not significant (HR = 1.05, 95% CI = 0.46–2.38, p = 0.916, unadjusted Cox model; HR = 0.83, 95% CI = 0.30–2.30, p = 0.722, Model 1; and HR = 0.73, 95% CI = 0.22–2.34, p = 0.593, Model 2).

Discussion

The results of the current study suggest that non-AD older adults taking NSAIDs are at decreased risk of AD mortality. Relative to non-users, the HR for AD as underlying cause of death was 71% lower in NSAIDs users. The association persisted even after controlling for a variety of combinations of covariates in adjusted models. Stratified analyses by individual NSAID type showed a significantly decreased risk of AD mortality with aspirin, whereas non-aspirin NSAIDs only showed a statistical trend toward significance in the adjusted Cox regression models. The fact that the non-aspirin NSAID-AD mortality association was not statistically significant may be due to small numbers, rather than to the lack of a real association.

It remains to be established how the relation between NSAIDs, particularly with aspirin, and AD mortality is mediated. We can speculate on possible explanations for this association. First, the inhibition of the cyclooxygenase isoenzymes (1 and 2) by NSAIDs reduces the levels of substances that are known to be related with AD pathogenesis, such as prostaglandins, prostacyclin, and thromboxanes,[31–33] Second, aspirin is an irreversible inhibitor of both cyclooxygenase-1 and cyclooxygenase-2, which is known to reduce oxidative stress and protect against oxidative damage.[34] In transgenic AD mice, selective cyclooxygenase-1 inhibition has been demonstrated to reduce neuroinflammation, amyloid pathology, and improvement of cognitive function.[35] Third, biomarker studies have shown that amyloid-β protein deposits in brain precedes AD onset more than a decade before cognitive deficits appear.[36, 37] It has been hypothesized that NSAIDs use may be beneficial only in the normal brain by inhibiting the production of amyloid-β protein.[38] Once the abnormal deposition process of amyloid-β protein has started, NSAIDs are no longer effective and may even be detrimental because of their inhibiting activity on activated microglia of the AD brain, which mediates amyloid-β protein clearance and activates compensatory hippocampal neurogenesis.[38] This

would explain, on one hand, why epidemiological studies suggest that NSAIDs can ameliorate this neurodegeneration process if they are started before clinical signs develop and, on the other, the disappointing results of clinical trials in AD patients.[39]

Our study has limitations. First, we did not consider the dose and frequency of NSAIDs use, so we were not able to evaluate whether higher current dose or cumulative dose of these medications was associated with lower risk of AD mortality. Second, data on NSAIDs exposure were available at baseline, but not for any intermediate time intervals between baseline and follow-up. Such data would have been of value in terms of assessing variation in drug exposure over time. Third, we based the diagnoses of AD on the revision of death certificates. AD may be omitted as a cause of death from the death certificates of patients with known AD in life. [40] Such omissions, however, are equally likely for NSAID users and non-users. Fourth, the residual confounding distortion by unmeasured factors is possible, but a large range of covariates were considered for Cox proportional hazards analyses. Finally, competing mortality is a potential issue in this type of studies. Indeed, there could be a potential for survival bias, considering that a small proportion of individuals may have died from AD at younger ages. However, AD is an ageing-related disease and competing mortality could have a null or limited influence on our findings.

Despite these limitations, the study was population-based, allowing us to assess a group of participants who were unselected for treatment considerations. In addition, NSAIDs users were compared to a large sample size of several hundred NSAIDs non-users. Finally, we could adjust for the potential confounding effects of several crucial factors.

In NEDICES, we demonstrated that NSAIDs use was associated with decreased risk of AD mortality, even after controlling for confounders. Our results support the hypothesis that NSAIDs use is a protective factor of developing AD.

Author Contributions

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Investigation: Julián Benito-León, Saturio Vega, Félix Bermejo-Pareja.

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Software: Julián Benito-León, Saturio Vega, Félix Bermejo-Pareja.

Supervision: Julián Benito-León, Saturio Vega, Félix Bermejo-Pareja.

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Writing – review & editing: Julián Benito-León, Israel Contador, Saturio Vega, Alberto Villarejo-Galende, Félix Bermejo-Pareja.

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