Published in final edited form as:

Amyotroph Lateral Scler. 2012 October ; 13(6): 573–579. doi:10.3109/17482968.2012.703209.

Non-steroidal anti-inflammatory drugs and Amyotrophic Lateral Sclerosis: Results from 5 prospective cohort studies

Elinor Fondell, PhD¹, Éilis J. O'Reilly, ScD¹, Kathryn C. Fitzgerald, ScM¹, Guido J. Falcone, MD, MPH^{2,3}, Marjorie L. McCullough, ScD, RD⁴, Michael J. Thun, MD, MS⁴, Yikyung Park, ScD⁵, Laurence N. Kolonel, MD, PhD⁶, and Alberto Ascherio, MD, DrPH^{1,2,7}

¹Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts ²Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts ³Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts ⁴Epidemiology Research Program, American Cancer Society, Atlanta, Georgia ⁵Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland ⁶Epidemiology Program, Cancer Center, University of Hawaii, Honolulu, Hawaii ⁷Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

Abstract

Objective—Animal and pathological studies suggest that inflammation may contribute to amyotrophic lateral sclerosis (ALS) pathology and that non-steroidal anti-inflammatory drugs (NSAIDs) might be protective. However, there are no prospective data on the relation between NSAID use and ALS risk in humans.

Methods—The relation between NSAID use and ALS risk was explored in five large prospective cohort studies (the Nurses' Health Study, the Health Professionals Follow-up Study, the Cancer Prevention Study II Nutrition Cohort, the Multiethnic Cohort Study, and the National Institutes of Health – AARP Diet and Health Study). Detailed NSAID information was sought from 780,000 participants, 708 of whom developed ALS during follow-up. Cox proportional hazards models were used within each cohort and cohort-specific estimates were pooled with random effects models.

Results—Neither non-aspirin NSAID use, nor aspirin use was associated with ALS risk overall. The multivariable, pooled relative risk was 0.96 (95% CI 0.76-1.22) among non-aspirin NSAID users compared with non-users. Duration of NSAID use in years and frequency of NSAID use were not associated with ALS risk overall.

Conclusion—The results do not support an overall effect of NSAIDs on ALS risk, but because NSAIDs have heterogeneous effects, a role of individual compounds cannot be excluded.

Keywords

ALS; NSAID; cohort; epidemiology

Introduction

A typical characteristic of ALS is neuroinflammation (1). Neuroinflammation is promoted by cyclooxygenase-2 (COX-2) (2), and the activity of COX-2 can be inhibited by non-steroidal anti-inflammatory drugs (NSAIDs) (3, 4). NSAIDs have prolonged survival in transgenic mouse models of ALS (5, 6), but results from a clinical trial did not find a protective effect of the selective COX-2 inhibitor Celecoxib on ALS disease progression (7). It remains uncertain whether NSAID use before symptom onset can reduce risk or delay the onset of ALS. A case-control study on NSAID use and ALS (n=111 cases) yielded inconclusive results (8). No prospective cohort studies have been conducted to study the potential protective effects of NSAID use on ALS risk.

In this study, we explored the associations of use of non-aspirin NSAIDs, aspirin, acetaminophen, and ALS risk in five large prospective cohort studies including over 780,000 men and women and 708 new cases of ALS during a mean of 15 years of follow-up.

Material and Methods

Study population

The Health Professionals Follow-up Study (HPFS) consists of 51,529 male health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians), aged 40-75 at enrollment, and was established in 1986 when these men answered a mailed questionnaire about lifestyle and medical history (9).

The Nurses' Health Study (NHS) was established in 1976 and consists of 121,700 registered female nurses age 30-55 (10). For this study, we used 1980 as baseline for aspirin and acetaminophen use since that is when usage was first asked, and 1990 was used as baseline for non-aspirin NSAIDs, since use of non-aspirin NSAIDs was very uncommon in 1980 and not asked again until 1990. In HPFS and NHS, information on lifestyle factors and medical events is updated biennially by mailed questionnaires.

The Cancer Prevention Study II Nutrition Cohort (CPS-II Nutrition cohort) (a sub-study of the CPS-II cohort that enrolled over 1 million participants in 1982) was launched in 1992 and comprises 86,404 men and 97,786 women then aged 50-79. CPS-II participants provided updated information in 1997 and then biennially (11).

In 1993-1996, the Multiethnic Cohort Study (MEC) study was initiated and mailed questionnaires were completed by 96,937 men and 118,843 women aged 45-75 residing in Hawaii and California. The participants were mainly of African-American, Japanese-American, Latino, native Hawaiian, or white self-reported racial/ethnic heritage. Follow-up questionnaires are sent every five years (12).

The first baseline questionnaire in National Institutes of Health – AARP Diet and Health Study (NIH-AARP) was returned in 1995-1996 by 567,169 men and women. Of those participants, 327,803 completed a supplementary questionnaire in 1996-1997 on risk factors including questions about NSAID intake (13). All of the above studies have been approved by the institutional review board of the institution where the study was conducted.

Ascertainment of ALS

As previously described (14), the National Death Index was used to identify participants with ALS in all cohorts. Participants for whom the underlying or contributory cause of death was coded 335.2 (motor neuron disease, International Classification of Diseases, Ninth

Revision) were considered to have had ALS. In a validation study in CPSII, we found that ALS was the primary diagnosis in 90% of the deaths coded as 335.2. In 8.5% of the deaths we could not confirm diagnosis, and in the remaining 1.5% of the deaths coded as 335.2, a motor neuron disease other than ALS was the cause of death (15).

Incident ALS was also used in NHS and HPFS. Participants were asked to report on a specific list of medically diagnosed conditions and “any other major illness” on each biennial follow-up questionnaire. A specific question on a diagnosis of ALS was added to the list of conditions in 1992 in NHS and in 2000 in HPFS, and on the subsequent biennial questionnaires. We requested permission for release of relevant medical records for all participants who reported a diagnosis of ALS either by answering the specific question or in response to the open question on major illnesses. For those participants who died before we could send the request for release of medical records, the request was sent to the closest family member. If permission was given, we asked the treating neurologist to send a copy of the medical records, and to complete a questionnaire to confirm that the participant had ALS and the certainty of the diagnosis (definite, probable, or possible). Confirmation of the diagnosis was based on the El Escorial criteria(16) applied to information extracted from the medical records or provided by the treating neurologist. When we were unable to obtain a copy of either the medical record or the treating neurologist’s questionnaire for incident self-reported ALS, we classified the diagnosis as “possible ALS” and excluded him or her from analysis until such time as ALS was captured on the participant death certificate.

Assessment of NSAID use

In NHS, aspirin use was first assessed in 1980 (yes/no, years of use, pills/week [open questions]) and measured biennially thereafter. Use of acetaminophen and non-aspirin NSAIDs was assessed in 1990 (days/month) and biennially thereafter. Although acetaminophen is not an NSAID, it was included in this paper in a separate analysis as it is commonly used for similar clinical indications. Reasons for taking these analgesics in the NHS have been reported (17-19). The most common reasons for taking aspirin in a sub-study of 200 NHS participants in 1990 included arthritis and musculoskeletal pain (40%), headache (25%), headache and musculoskeletal pain (15%), prevention of cardiovascular disease (8%), or other reasons (11%) (18). The most common reasons for using ibuprofen and acetaminophen in a sub-study of 4238 NHS participants in 1999 were muscle/joint pain (84% and 65%, respectively); headache (5% and 24%); backache (5% and 4%); and other (6% and 8%) (17, 19).

In HPFS, the men were asked about regular use (2+ times/week) of aspirin, acetaminophen and other anti-inflammatory drugs in 1986 and biennially thereafter. Starting in 1992 details of aspirin use (days/month, pills/day [open questions]) were added.

In NIH-AARP, participants were asked in 1996 about regular analgesic use in the past 12 months, including use of aspirin products (yes/no, how often [in 7 categories ranging from <2/month to 2+/day]) or use of non-aspirin NSAIDs (yes/no, how often [as for aspirin]).

In the MEC study, regular use (2+ times/week) of aspirin, acetaminophen and other non-aspirin NSAIDs (yes currently, yes but not at this time, no) was assessed in the baseline questionnaire (1993-1996) as well as duration of analgesic use in years (in 5 categories ranging from ≤1 year to 11+ years).

In 1992, the CPS-II Nutrition cohort assessed use of aspirin, acetaminophen, ibuprofen and other NSAIDs (yes/no, days/month, pills/day, years of use [open questions]). Analgesic use was updated in 1997. All cohorts included baseline data on diet, smoking history, education, body mass index, and physical activity.

Data analysis

Person-time was calculated as the date of return of the questionnaire until the date of first onset of ALS symptoms (HPFS, NHS), death from ALS or any other cause, or end of follow-up. The end of follow-up was June 2006 in NHS, January 2008 in HPFS, December 2006 in CPS-IIIN, December 2005 in NIH-AARP and December 2007 in MEC. Aspirin, non-aspirin NSAID, and acetaminophen use was defined as taking two or more pills per week.

All analyses mentioned below were conducted separately within each cohort after which estimates were pooled using DerSimonian and Laird methods for random effects and heterogeneity was assessed using Q statistics (20). Because of the long duration of follow-up in NHS, we split the person-time and cases into two uncorrelated segments when analyzing acetaminophen use: 1980-1990 and 1990-2006. According to the underlying theory of survival analysis, different blocks of person-time from the same persons are asymptotically uncorrelated (21). Hence, pooling the estimates from the two periods is equivalent to using a single period, but takes advantage of the updated exposure in 1990.

Cox proportional hazards regression was used to estimate relative risks (RR) and 95% confidence intervals (CI). Age in single years was used as the time-scale. Potential confounders correlated with ALS or analgesic use were evaluated, and we adjusted for smoking status (never, past, current), education level (<high school, high school, >high school), body mass index (underweight, normal weight, overweight, obese), physical activity level (low, medium, high), use of vitamin E supplements (yes, no), pain (none-mild, moderate-severe) (in NHS only), and race (in MEC only). The association between smoking and ALS (14) and vitamin E and ALS (22) in these cohorts have been previously reported. We evaluated effect measure modification between non-aspirin NSAIDs and ALS by age (<55, ≥55 years), sex, BMI (< , or ≥ cohort specific median), physical activity (< , or ≥ cohort specific median), supplement use of vitamins C and E (yes/no) by multiplicative terms in the Cox models in each cohort.

We conducted several sensitivity analyses by: i) excluding the first four years of follow-up to minimize the possibility of including participants with ALS symptoms at the time of completing the baseline questionnaire; ii) excluding gout and rheumatoid arthritis patients since they were more likely to consume high amounts of NSAIDs, but the association with ALS is unknown; and iii) excluding participants who reported use of oral corticosteroids.

In total, 708 participants were identified who developed ALS among 9,727,583 person-years contributed by 786,274 men and women. Analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina), and STATA, version 11 (StataCorp LP, College Station, Texas).

Results

Aspirin was the most common non-prescription analgesic in both men and women; 56% of men and 48% of women reported regular aspirin use. Slightly more women than men used non-aspirin NSAIDs and acetaminophen; 42% of women and 32% of men used non-aspirin NSAIDs regularly and 39% of the women and 17% of the men reported regular acetaminophen use. Approximately 23% (91,089/(127,743 + 271,734)) of the men and 22% of the women used both aspirin and non-aspirin NSAIDs regularly. Users of non-aspirin NSAIDs, aspirin and acetaminophen were more likely to also report use of vitamin E supplements. In addition, men using acetaminophen smoked more and had lower education than men not using acetaminophen (Table 1). The results in Table 1 were similar across the cohorts.

Overall, use of non-aspirin NSAIDs, aspirin, or acetaminophen was not associated with ALS risk. The multivariable, pooled relative risk (RR) was 0.96 (95% CI 0.76-1.22) among non-aspirin NSAID users and RR 1.07 (95% CI 0.92-1.25) among aspirin users, compared with non-users of either drug (Fig 1a, b).

When looking at the results in individual cohorts, a potentially decreased risk of ALS was found among non-aspirin NSAID using men in the CPS-IIN study (RR 0.54, 95% CI 0.31-0.92) and in the MEC (RR 0.64, 95% CI 0.36 - 1.15). However, this potentially decreased risk of ALS among non-aspirin users was not observed among the men in NIH-AARP or in HPFS, nor was it observed among the women in any of the cohorts (Fig 1a).

Increased duration of non-aspirin NSAID use was not associated with risk of ALS in either men or women overall, nor did increased duration of non-aspirin NSAID use further decrease the risk of ALS among the men in CPS-IIN or MEC (data not shown). Details on frequency of non-aspirin NSAID intake were available in the NHS, CPS-IIN and NIH-AARP. No significant associations were found between frequency of use of non-aspirin NSAIDs and ALS risk.

Results of the association between non-aspirin NSAID use and risk of ALS remain similar in sub-analyses after adjusting for concomitant intake of aspirin or acetaminophen use (data not shown). No significant effect measure modification was found by age, use of vitamin E supplements, or physical activity. Results were similar when ALS cases with onset in the first 4 years after the report of non-aspirin NSAID use were excluded; multivariable RR of ALS among non-aspirin NSAID use compared to non-use was 0.91, (95% CI 0.73-1.13) (compare with Fig 1a). Further, to minimize potential confounding by indication, we excluded participants with chronic conditions or medications that could warrant NSAID use, such as gout, rheumatoid arthritis, or use of oral corticosteroids. Excluding these participants did not significantly change the results (data not shown).

Discussion

In this pooled analysis of five large population-based prospective cohorts, use of non-aspirin NSAID was not associated with ALS risk. Although ALS risk was lower among men using non-aspirin NSAIDs in two cohorts (CPS-IIN and MEC), the lack of consistency across studies suggests that this is a chance finding.

Among the strengths of our study are the large sample size and the prospective design, which minimizes potential recall bias and misclassifications. Further, the ALS cases included in these cohorts are likely to be representative of the whole spectrum of ALS patients, avoiding the selection bias that is often inherent when cases in case-control studies are recruited from ALS tertiary-care centers (23, 24). A limitation of this study includes the use of ALS mortality as a proxy for ALS incidence, and this precludes analyses by ALS subtype, may underestimate the number of slow-progressing cases, and may introduce some misclassification of outcome. Nevertheless, bias from this source is probably modest since death certificates have been estimated to accurately identify 70-90% of cases of ALS or motor neuron diseases (15, 25, 26) and median survival of ALS patients after diagnosis is relatively short (1.5-3 years) (27), making mortality a reasonable substitute for incidence.

Another limitation with our study is that NSAID use was self-reported. Misclassification of exposure could have diluted an existing association between NSAID use and ALS risk. However, the results of validation studies among participants in the NHS and HPFS cohorts suggest that the degree of misclassification and the resulting bias are modest (18, 19). Further, significant associations in these cohorts have been reported between NSAID use and other outcomes, such as renal cell cancer (28) and arterial hypertension (29). Another

limitation is that we did not study the NSAID dose. The number of ALS cases occurring after collection of specific information on dosage was too small for meaningful analyses. Since analgesic use was not randomized, there is potential confounding by indication. This bias is likely modest, since results remained similar after adjusting for pain or excluding chronic conditions associated with NSAID use.

Our study is the first prospective study on non-aspirin NSAID use and risk of ALS. A case-control study on NSAID use and ALS (n=111 ALS patients) by Popat et al. (8) yielded inconclusive results; non-aspirin NSAID use was associated with an increased risk of ALS among men (OR 2.0, 95% CI 1.0-3.9), but not among women (OR 0.5, 95% CI 0.2-1.2) (8). Potential sources of bias in this case-control study include recall bias, and under representation of fast progressing cases. Further, it has been recently reported that pain is more frequent and more severe in ALS patients (57%) compared to age-adjusted controls (33%), and starts in early phases of ALS, often leading to the prescription of NSAIDs (38%) and non-opioid analgesics (24%) (30). Since ALS symptoms precede the diagnosis by about a year (31), and Popat et al. (8) retrospectively assessed NSAID use prior diagnosis, reverse causation cannot be ruled out. Adjusting for pain in NHS did not significantly influence our results, and the results of four-year lagged analysis did not differ from the main results in our study, suggesting that use of non-aspirin NSAIDs due to early pain among individuals with ALS did not significantly bias the results in our study.

It has recently been demonstrated in an ALS mouse model that denervation occurs before signs of inflammation, suggesting that inflammation is not the cause of ALS (32). However, it is not known whether the presence of inflammation affects ALS survival. A duality of immune function in ALS has been suggested (33, 34), where inflammation contributes to neuronal injury, but is also beneficial by clearing of debris by microglia and interacting with T cells (see (35) for a review). Treatment with the selective COX-2 inhibitor Celecoxib, has indeed been shown to increase survival in ALS mouse models (5, 36), but did not slow ALS progression in a double-blind clinical trial enrolling 300 patients (7). An observational study on 596 ALS patients found that survival was shorter in ALS patients using aspirin or other NSAIDs as compared to non-users (37), but reverse causation cannot be excluded.

In previous studies among CPS-IIN (38), HPFS and NHS participants (17), we found that use of ibuprofen, but not other NSAIDs, was associated with a reduced risk of Parkinson Disease (PD). Further, differences between NSAIDs favoring ibuprofen have also been reported in experimental and clinical studies of cognitive function (39, 40). These results raise the possibility that ibuprofen has neuroprotective effects that are not shared by other anti-inflammatory agents. In the present study, however, the number of ALS cases occurring after collection of specific information on ibuprofen use was too small for meaningful analyses.

In conclusion, in this large prospective study, we did not find convincing evidence that overall use of non-aspirin NSAIDs was associated with risk of ALS. Because of growing experimental and epidemiological evidence that some, but not all, NSAIDs may have neuroprotective effects, future investigations should focus on individual compounds.

Acknowledgments

This work was supported by a grant from the National Institute of Neurological Diseases and Stroke (R01 NS045893) and by grants P01 CA87969 and P01 CA055075 from the National Cancer Institute. E. Fondell is supported by a grant from the Blanceflor foundation, Stockholm, Sweden.

Abbreviations

ALS	amyotrophic lateral sclerosis
CPS-IIN	Cancer Prevention Study II Nutrition cohort
HPFS	Health Professionals Follow-up Study
MEC	Multiethnic Cohort Study
NHS	Nurses' Health Study
NIH	National Institutes of Health
NSAID	non-steroidal anti-inflammatory drug
RR	relative risk
CI	confidence interval

References

- Philips T, Robberecht W. Neuroinflammation in amyotrophic lateral sclerosis: role of glial activation in motor neuron disease. *Lancet Neurol*. 2011; 10:253–63. [PubMed: 21349440]
- Kuehl FA Jr, Egan RW. Prostaglandins, arachidonic acid, and inflammation. *Science*. 1980; 210:978–84. [PubMed: 6254151]
- Klegeris A, McGeer PL. Cyclooxygenase and 5-lipoxygenase inhibitors protect against mononuclear phagocyte neurotoxicity. *Neurobiol Aging*. 2002; 23:787–94. [PubMed: 12392782]
- Carty ML, Wixey JA, Reinebrant HE, Gobe G, Colditz PB, Buller KM. Ibuprofen inhibits neuroinflammation and attenuates white matter damage following hypoxia-ischemia in the immature rodent brain. *Brain Res*. 2011; 1402:9–19. [PubMed: 21696706]
- Drachman DB, Frank K, Dykes-Hoberg M, Teismann P, Almer G, Przedborski S, et al. Cyclooxygenase 2 inhibition protects motor neurons and prolongs survival in a transgenic mouse model of ALS. *Ann Neurol*. 2002; 52:771–8. [PubMed: 12447931]
- Pompl PN, Ho L, Bianchi M, McManus T, Qin W, Pasinetti GM. A therapeutic role for cyclooxygenase-2 inhibitors in a transgenic mouse model of amyotrophic lateral sclerosis. *FASEB J*. 2003; 17:725–7. [PubMed: 12586733]
- Cudkovic ME, Shefner JM, Schoenfeld DA, Zhang H, Andreasson KI, Rothstein JD, et al. Trial of celecoxib in amyotrophic lateral sclerosis. *Ann Neurol*. 2006; 60:22–31. [PubMed: 16802291]
- Popat RA, Tanner CM, van den Eeden SK, Bernstein AL, Bloch DA, Leimpeter A, et al. Effect of non-steroidal anti-inflammatory medications on the risk of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler*. 2007; 8:157–63. [PubMed: 17538777]
- Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B, et al. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet*. 1991; 338:464–8. [PubMed: 1678444]
- Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. *J Womens Health*. 1997; 6:49–62. [PubMed: 9065374]
- Calle EE, Rodriguez C, Jacobs EJ, Almon ML, Chao A, McCullough ML, et al. The American Cancer Society Cancer Prevention Study II Nutrition Cohort: rationale, study design, and baseline characteristics. *Cancer*. 2002; 94:2490–501. [PubMed: 12015775]
- Kolonel LN, Henderson BE, Hankin JH, Nomura AM, Wilkens LR, Pike MC, et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. *Am J Epidemiol*. 2000; 151:346–57. [PubMed: 10695593]
- Leitzmann MF, Park Y, Blair A, Ballard-Barbash R, Mouw T, Hollenbeck AR, et al. Physical activity recommendations and decreased risk of mortality. *Arch Intern Med*. 2007; 167:2453–60. [PubMed: 18071167]

14. Wang H, O'Reilly EJ, Weisskopf MG, Logroscino G, McCullough ML, Thun MJ, et al. Smoking and risk of amyotrophic lateral sclerosis: a pooled analysis of 5 prospective cohorts. *Arch Neurol*. 2011; 68:207–13. [PubMed: 21320987]
15. Weisskopf MG, McCullough ML, Calle EE, Thun MJ, Cudkowicz M, Ascherio A. Prospective study of cigarette smoking and amyotrophic lateral sclerosis. *Am J Epidemiol*. 2004; 160:26–33. [PubMed: 15229114]
16. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2000; 1:293–9. [PubMed: 11464847]
17. Gao X, Chen H, Schwarzschild MA, Ascherio A. Use of ibuprofen and risk of Parkinson disease. *Neurology*. 2011; 76:863–9. [PubMed: 21368281]
18. Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B, Speizer FE, et al. A prospective study of aspirin use and primary prevention of cardiovascular disease in women. *JAMA*. 1991; 266:521–7. [PubMed: 2061978]
19. Curhan GC, Knight EL, Rosner B, Hankinson SE, Stampfer MJ. Lifetime nonnarcotic analgesic use and decline in renal function in women. *Arch Intern Med*. 2004; 164:1519–24. [PubMed: 15277282]
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; 7:177–88. [PubMed: 3802833]
21. Rothman, KJ.; Greenland, S.; Lash, TL. *Modern epidemiology*. 3rd ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; Philadelphia: 2008.
22. Wang H, O'Reilly EJ, Weisskopf MG, Logroscino G, McCullough ML, Schatzkin A, et al. Vitamin E intake and risk of amyotrophic lateral sclerosis: a pooled analysis of data from 5 prospective cohort studies. *Am J Epidemiol*. 2011; 173:595–602. [PubMed: 21335424]
23. Logroscino G, Traynor BJ, Hardiman O, Chio A, Couratier P, Mitchell JD, et al. Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. *J Neurol Neurosurg Psychiatry*. 2008; 79:6–11. [PubMed: 18079297]
24. Armon C. An evidence-based medicine approach to the evaluation of the role of exogenous risk factors in sporadic amyotrophic lateral sclerosis. *Neuroepidemiology*. 2003; 22:217–28. [PubMed: 12792141]
25. Hoffman PM, Brody JA. The reliability of death certificate reporting for amyotrophic lateral sclerosis. *J Chronic Dis*. 1971; 24:5–8. [PubMed: 5568745]
26. Chio A. Risk factors in the early diagnosis of ALS: European epidemiological studies. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2000; 1(Suppl 1):S13–8. [PubMed: 11464920]
27. del Aguila MA, Longstreth WT Jr, McGuire V, Koepsell TD, van Belle G. Prognosis in amyotrophic lateral sclerosis: a population-based study. *Neurology*. 2003; 60:813–9. [PubMed: 12629239]
28. Cho E, Curhan G, Hankinson SE, Kantoff P, Atkins MB, Stampfer M, et al. Prospective evaluation of analgesic use and risk of renal cell cancer. *Arch Intern Med*. 2011; 171:1487–93. [PubMed: 21911634]
29. Forman JP, Rimm EB, Curhan GC. Frequency of analgesic use and risk of hypertension among men. *Arch Intern Med*. 2007; 167:394–9. [PubMed: 17325302]
30. Chio A, Canosa A, Gallo S, Moglia C, Ilardi A, Cammarosano S, et al. Pain in amyotrophic lateral sclerosis: a population-based controlled study. *Eur J Neurol*. 2011
31. Cellura E, Spataro R, Taiello AC, La Bella V. Factors affecting the diagnostic delay in amyotrophic lateral sclerosis. *Clin Neurol Neurosurg*. 2011
32. Kano O, Beers DR, Henkel JS, Appel SH. Peripheral nerve inflammation in ALS mice: cause or consequence. *Neurology*. 2012; 78:833–5. [PubMed: 22377817]
33. Moisse K, Strong MJ. Innate immunity in amyotrophic lateral sclerosis. *Biochim Biophys Acta*. 2006; 1762:1083–93. [PubMed: 16624536]
34. Schwartz M, Shechter R. Systemic inflammatory cells fight off neurodegenerative disease. *Nat Rev Neurol*. 2010; 6:405–10. [PubMed: 20531383]
35. McCombe PA, Henderson RD. The Role of immune and inflammatory mechanisms in ALS. *Curr Mol Med*. 2011; 11:246–54. [PubMed: 21375489]

36. Klivenyi P, Kiaei M, Gardian G, Calingasan NY, Beal MF. Additive neuroprotective effects of creatine and cyclooxygenase 2 inhibitors in a transgenic mouse model of amyotrophic lateral sclerosis. *J Neurochem.* 2004; 88:576–82. [PubMed: 14720207]
37. Qureshi M, Shui A, Dibernardo AB, Brown RH Jr, Schoenfeld DA, Cudkowicz ME. Medications and laboratory parameters as prognostic factors in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler.* 2008; 9:369–74. [PubMed: 18608098]
38. Chen H, Zhang SM, Hernan MA, Schwarzschild MA, Willett WC, Colditz GA, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. *Arch Neurol.* 2003; 60:1059–64. [PubMed: 12925360]
39. Pasqualetti P, Bonomini C, Dal Forno G, Paulon L, Sinforiani E, Marra C, et al. A randomized controlled study on effects of ibuprofen on cognitive progression of Alzheimer's disease. *Aging Clin Exp Res.* 2009; 21:102–10. [PubMed: 19448381]
40. McKee AC, Carreras I, Hossain L, Ryu H, Klein WL, Oddo S, et al. Ibuprofen reduces A β , hyperphosphorylated tau and memory deficits in Alzheimer mice. *Brain Res.* 2008; 1207:225–36. [PubMed: 18374906]

A. Regular use of non-aspirin NSAIDs and risk of ALS

B. Regular use of aspirin and risk of ALS

C. Regular use of acetaminophen and risk of ALS

Figure 1.

Study specific and pooled relative risk of amyotrophic lateral sclerosis (ALS) among users of non-aspirin NSAIDs (**A**), aspirin (**B**), and acetaminophen (**C**), compared to non-users of either drug. The relative risks are adjusted for age, sex, smoking status, physical activity, body mass index, education level, race (in MEC), pain (in NHS) and vitamin E supplement use. The gray squares represent the study weights and the diamond represents the pooled relative risk and 95% confidence interval.

Table 1

Age-adjusted characteristics of study participants at baseline (baseline year in parenthesis) according to use of non-aspirin NSAIDs, aspirin, or acetaminophen in HPFS (1986), NHS (1990), CPS-IIN (1992), NIH-AARP (1996), and MEC (1993-1997).

	Use of non-aspirin NSAIDs		Use of aspirin		Use of acetaminophen [†]	
	Yes	No	Yes	No	Yes	No
Men						
No. of participants	127,743	271,734	220,512	174,801	33,107	157,010
No of ALS cases [*]	105	331	236	192	20	193
Person-years [*]	1,387,948	3,435,435	2,494,625	2,291,285	415,089	2,256,994
Age, mean (SD) [*]	61 (7)	61 (8)	62 (7)	60 (9)	60 (9)	60 (9)
BMI, mean (SD)	27 (4)	26 (4)	27 (4)	26 (4)	26 (4)	26 (4)
Current smokers, %	12	12	12	12	17	13
Education > high school, %	76	76	77	74	60	75
Vitamin E supplement use, %	57	44	53	41	48	38
No of aspirin users [*]	91,089	122,225	-	-	-	-
No of acetaminophen users ^{†*}	13,974	17,755	19,038	12,909	-	-
Women						
No. of participants	160,797	226,000	185,668	204,219	87,878	139,740
No. of ALS cases [*]	112	160	138	142	65	97
Person-years [*]	2,009,568	2,894,632	2,330,713	2,618,577	1,252,562	1,926,626
Age, mean (SD)	60 (7)	61 (8)	61 (7)	60 (8)	59 (9)	60 (8)
BMI, mean (SD)	27 (6)	26 (5)	26 (5)	26 (5)	27 (6)	25 (5)
Current smokers, %	14	13	14	12	15	12
Education > high school, %	70	68	70	67	68	68
Vitamin E supplement use, %	61	53	60	52	52	49
No of aspirin users [*]	84,282	84,808	-	-	-	-
No of acetaminophen users ^{†*}	40,559	38,302	37,324	40,392	-	-

Abbreviations: HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; CPS-IIN, Cancer Prevention Study II Nutrition Cohort; MEC, Multiethnic Cohort study; NIH, National Institutes of Health; ALS, amyotrophic lateral sclerosis; BMI, Body Mass Index.

* Values are not age-adjusted.

[†]Based on CSP-IIN, MEC, HPFS, and NHS