Title

Association of Non-Steroidal Anti-Inflammatory Drugs with Kidney Health in Ambulatory Older Adults.

Journal

Journal of the American Geriatrics Society, 69(3)

Authors

Katz, Ronit
Peralta, Carmen
Estrella, Michelle
et al.

Publication Date

2021-03-01

DOI

10.1111/jgs.16961

Peer reviewed

HHS Public Access

Author manuscript

J Am Geriatr Soc. Author manuscript; available in PMC 2021 April 06.

Published in final edited form as:

J Am Geriatr Soc. 2021 March ; 69(3): 726–734. doi:10.1111/jgs.16961.

Association of Non-steroidal Anti-inflammatory Drugs with Kidney Health in Ambulatory Older Adults

Jonathan G. Amatruda, MD[1,2], **Ronit Katz, DPhil**[3], **Carmen A. Peralta, MD, MAS**[1,2,4], **Michelle M. Estrella, MD, MHS**[2,5], **Harini Sarathy, MBBS, MHS**[1,6], **Linda F. Fried, MD, MPH**[7,8], **Anne B. Newman, MD, MPH**[7], **Chirag R. Parikh, MBBS, PhD**[9], **Joachim H. Ix, MD, MAS**[10,11], **Mark J. Sarnak, MD, MS**[12], **Michael G. Shlipak, MD, MPH**[2,13] **Health ABC Study**

[1.]Division of Nephrology, Dept. of Medicine, University of California, San Francisco, San Francisco, CA

[2.]Kidney Health Research Collaborative, San Francisco VA Medical Center & University of California, San Francisco, San Francisco, CA

[3.]Kidney Research Institute, University of Washington, Seattle, WA

[4.]Cricket Health, Inc., San Francisco, CA

[5.]Division of Nephrology, Dept. of Medicine, San Francisco VA Medical Center, San Francisco, CA

[6.]Division of Nephrology, Dept. of Medicine, Zuckerberg San Francisco General Hospital, San Francisco, CA

[7.]University of Pittsburgh School of Medicine and Graduate School of Public Health, Pittsburgh, PA

[8.]VA Pittsburgh Healthcare System and University of Pittsburgh School of Medicine, Pittsburgh, PA

[9.]Division of Nephrology, Department of Medicine, Johns Hopkins University, Baltimore, MD

[10.]Division of Nephrology-Hypertension, Department of Medicine, University of California, San Diego, CA

[11.]Nephrology Section, Veterans Affairs San Diego Healthcare System, San Diego, CA

[12.]Division of Nephrology, Dept. of Medicine, Tufts Medical Center, Boston MA

[13.]Dept. of Medicine, San Francisco VA Medical Center, San Francisco, CA

Abstract

Corresponding Author: Michael G. Shlipak, MD, Kidney Health Research Collaborative, San Francisco VA Health Care System, 4150 Clement Street, San Francisco, CA 94121, Phone: 415-750-2093, Fax: 415-379-5573, michael.shlipak@ucsf.edu.

Author's Contributions

All authors have read and approved of the submission of this manuscript. MGS, CAP, HS, and RK contributed to the study concept and design. All authors contributed to the acquisition, analysis, and interpretation of data. JGA, MGS, and MME drafted the manuscript. All authors contributed to critical revisions of the manuscript for important intellectual content. RK was responsible for statistical analysis. MGS obtained funding and provided study supervision.

Disclosures & Conflicts of Interest

Dr. Shlipak serves as a scientific advisor to TAI Diagnostics and reports equity in that venture, which falls outside of the submitted work. Dr. Peralta is Chief Medical Officer at Cricket Health. The other authors report no relevant disclosures.

Background/Objectives: Non-steroidal anti-inflammatory drugs (NSAIDs) can cause kidney injury, especially in older adults. However, previously reported associations between NSAID use and kidney health outcomes are inconsistent and limited by reliance on serum creatinine-based GFR estimates. This analysis investigated the association of NSAID use with kidney damage in older adults using multiple kidney health measures.

Design: Cross-sectional and longitudinal analyses.

Setting: Multicenter, community-based cohort.

Participants: 2,999 older adults in the Health ABC Study. A subcohort (n=500) was randomly selected for additional biomarker measurements.

Exposure: Prescription and over-the-counter NSAID use ascertained by self-report.

Measurements: Baseline eGFR by cystatin C (cysC), urine albumin-to-creatinine ratio (ACR), kidney injury molecule-1 (KIM-1), and interleukin-18 (IL-18) were measured in 2,999 participants; alpha-1 microglobulin (α1m), neutrophil gelatinase-associated lipocalin (NGAL), propeptide type III procollagen (PIIINP), and uromodulin (UMOD) were measured in 500 participants. GFR was estimated 3 times over 10 years and expressed as percent change per year.

Results: Participants had a mean age of 74 years, 51% were female, and 41% African-American. No eGFR differences were detected between NSAID users (n=655) and non-users (n=2344) at baseline (72 mL/min/1.73m^2 in both groups). Compared to non-users, NSAID users had lower adjusted odds of having ACR >30 mg/g (0.67; 95% CI: 0.51-0.89) and lower mean urine IL-18 concentration at baseline (−11%; 95% CI: −4% to −18%), but similar mean KIM-1 (5%; 95% CI: −5% to 14%). No significant differences in baseline concentrations of the remaining urine biomarkers were detected. NSAID users and non-users did not differ significantly in the rate of eGFR decline (−2.2% vs. −2.3% per year).

Conclusion: Self-reported NSAID use was not associated with kidney dysfunction or injury based on multiple measures, raising the possibility of NSAID use without kidney harm in ambulatory older adults. More research is needed to define safe patterns of NSAID consumption.

Keywords

chronic kidney disease; pharmacoepidemiology; nephrotoxicity; NSAID

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used, especially in older adults, and the ongoing opioid epidemic has further highlighted the utility of NSAIDs as effective, non-addictive analgesics.[1–5] However, NSAID use is limited by their potential for adverse effects including cardiovascular toxicity, peptic ulcers, and nephrotoxicity.[6–8] NSAIDs can cause acute kidney injury (AKI), which if severe or prolonged may contribute to the development of chronic kidney disease (CKD), though there is little clarity on the magnitude of these risks and their variability across populations.[9–11] Despite concerns that older adults are at especially high risk of NSAID nephrotoxicity, their risk of long-term NSAID-associated kidney damage remains uncertain.[10, 12, 13] Partially due to these concerns, the American Geriatrics Society Beers Criteria label NSAIDs as potentially

inappropriate for use in older adults.[14] Nonetheless, older adults suffer from a high burden of acute and chronic pain and might benefit if NSAIDs could be used safely in appropriate contexts.[15, 16]

Most studies of NSAID nephrotoxicity have used serum creatinine (Cr) and estimated glomerular filtration rate (eGFR) to describe kidney function, but Cr has limited sensitivity and specificity for changes in kidney function and is biased by muscle mass.[17] Conversely, serum cystatin C (cysC) is unaffected by muscle mass and more accurately detects GFR changes in older persons.[18, 19] Albuminuria, expressed clinically as the urine albumin-to-creatinine ratio (ACR), is an important measure of glomerular integrity and predicts poor outcomes for kidney and cardiovascular health as well as mortality.[20] However, Cr, cysC, and ACR may not detect damage to kidney tubules, the usual site of NSAID toxicity.[21] Therefore, to improve detection of NSAID-associated kidney injury, direct measures of kidney tubule health are also needed. Kidney tubule health broadly encompasses *damage*, representing cell injury and its physical consequences, as well as *dysfunction*, which refers to capacity for normal homeostatic mechanisms including biosynthesis, reabsorption, and secretion. Measures include biomarkers of tubule injury (kidney injury molecule-1 [KIM-1], interleukin-18 [IL-18], and neutrophil gelatinase-associated lipocalin [NGAL]); tubulointerstitial fibrosis (propeptide type III procollagen [PIIINP]); proximal tubule resorptive function (alpha-1 microglobulin [α1m]); and tubule synthetic function (uromodulin [UMOD]). These investigational biomarkers are sensitive indicators of early kidney tubule damage in the setting of medication toxicity, including NSAID nephrotoxicity, and are also associated with long-term outcomes.[22–31] Importantly, they have been applied across the age spectrum and are associated with cardiovascular disease, heart failure, and mortality in older adults.[32–34]

The Health, Aging, and Body Composition (Health ABC) study offered a unique opportunity to evaluate associations of NSAID use with multiple measures of kidney health in a cohort of community-dwelling older adults. Specifically, we explored the association of NSAID use with measures of glomerular filtration, urine albumin, and biomarkers of kidney tubule health. We compared baseline kidney function and kidney tubule biomarkers among NSAID users and non-users and evaluated the association of NSAID use with longitudinal eGFR changes. We hypothesized that NSAID use would be associated with kidney damage and dysfunction at baseline and with faster eGFR decline over time.

Methods

Study Design & Participants

This study was conducted within the Health ABC study, a large cohort designed to evaluate the risk factors for functional decline and to track changes in body composition in older adults.[35] Health ABC enrolled 3,075 men and women aged 70-79 years with preserved physical function over 1997-1998 from the vicinity of Memphis, Tennessee and Pittsburgh, Pennsylvania. Participation in Health ABC required self-reported ability to walk 0.25 miles or climb 10 steps without difficulty and to perform basic activities of daily living. Baseline evaluations were performed at recruitment, and participants underwent yearly clinic examinations over the next 6 years alternating with semi-annual telephone interviews.

Additional follow-up clinic examinations were performed at 8, 10, and 16 years after recruitment. Participants underwent informed consent, and the study protocol complied with the Declaration of Helsinki. The study was approved by the Institutional Review Boards of the University of Tennessee Health Center and the University of Pittsburgh. This analysis utilized data from an NIA-funded ancillary study to Health ABC that was led by our study team to investigate novel measures of kidney tubule health.

NSAID Use

The primary predictor was NSAID use. Current prescription and non-prescription medication use were ascertained at annual study visits through a structured interview with trained study personnel using a standardized medication inventory. Participants were instructed to bring all medications they had used in the preceding two weeks, and these were transcribed to produce medication lists, which were updated at subsequent study visits to capture changes. For cross-sectional analyses, participants were dichotomized into NSAID users versus non-users at baseline. For longitudinal analyses, NSAID use was defined as a time-dependent exposure; the last documented response was carried forward. NSAID non-users were the reference category in all analyses. Although dose and frequency were unavailable, we separately compared prescription and non-prescription NSAID users to non-users, assuming that prescription usually implies more intense exposure.

Outcomes

GFR was estimated using the serum cysC-based CKD-EPI equation, and eGFR was available at baseline, year 3, and year 10 of follow-up.[36] Creatinine was not used for eGFR calculation because the assay method changed during follow-up, precluding proper calibration. CysC was measured using a particle-enhanced immunonephelometric assay (N Latex Cystatin C) on a BNII Nephelometer (Dade Behring, Inc). Urine specimens collected at the baseline visit were stored continuously at −80°C until thawed for biomarker measurements, which were performed concurrently at the Cincinnati Children's Hospital. Urine albumin, creatinine, KIM-1, and IL-18 were measured on all participants with available urine specimens (n=2,999). We randomly selected 500 participants in whom four additional urine biomarkers (α1m, NGAL, PIIINP, UMOD) were measured concurrently. Urine albumin was measured using immunoturbidimetry with a Siemens Dimension Xpand Plus HM clinical analyzer (Siemens, Munich, Germany). Urine creatinine was measured via colorimetric enzyme assay on a Siemens Dimension Xpand Plus HM clinical analyzer (Siemens, Munich, Germany). Commercially-available enzyme-linked immunoassays (ELISA) were used to measure urine KIM-1 (R&D Systems Inc., Minneapolis, MN), IL-18 (Medical & Biological Laboratories Co. Ltd., Nagoya, Japan), NGAL (Antibody-Shop), PIIINP (ELISA USCN Life Sciences), and UMOD (MD Bioproducts, St. Paul, MN). Urine α1m was measured using the Siemens BNII nephelometer with a lower limit of detection at 0.5 mg/dL.

Covariates

Demographic and clinical factors were recorded at baseline. The following were chosen as covariates: age, gender, race, education level, osteoarthritis (ever diagnosed by a doctor), osteoporosis (ever diagnosed by a doctor), diabetes mellitus, heart failure, body mass index

(BMI), gait speed (time to walk 6 meters), grip strength (Jamar hydraulic hand dynamometer), systolic blood pressure (SBP), and use of antihypertensive medications.[35]

Statistical Analysis

Of the 3,075 total Health ABC participants, we excluded 9 with missing NSAID use values, 31 with missing cysC at baseline, 36 with missing urine biomarker measurements at baseline, leaving 2,999 participants available for analysis. We first described characteristics among users and non-users of NSAIDs at baseline. We then evaluated the cross-sectional associations of NSAID use with baseline eGFR and urine biomarker levels using separate linear regression models for each measure. All continuous outcome variables except eGFR were log-transformed to approximate normal distributions. Three nested models were used: Model 1 adjusted urine biomarkers for urine creatinine only; Model 2 additionally adjusted for age, gender, race, and education level; and Model 3 additionally adjusted for diabetes mellitus, prevalent heart failure, osteoarthritis, osteoporosis, BMI, SBP, gait speed, grip strength, and use of antihypertensive medications. Urine albumin was indexed to urine creatinine as the albumin-to-creatinine ratio (ACR). We repeated these analyses for binary CKD endpoints (eGFR <60 mL/min/1.73m^2 or ACR >30 mg/g) using multivariable logistic regression. For these CKD endpoints, we tested for interactions with heart failure, hypertension diagnosis, SBP >140 mmHg, and use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). All cross-sectional analyses were also performed separately in the subset of participants taking ACE inhibitors, ARBs, or diuretics.

For longitudinal analyses, NSAID use was time-updated using the last value carried forward, and we used linear mixed models with random intercepts and slopes to model longitudinal changes in eGFR as percent change per year during follow-up. This linear mixed model was anchored on the baseline eGFR. The same sequences of adjusted models as above were applied. We also stratified on baseline eGFR (<60 and ≥60 mL/min/1.73m^2) and repeated the longitudinal models in each subgroup. We were unable to model change in longitudinal ACR because ACR was available only at baseline. For the continuous outcome of eGFR change, we tested for interactions with heart failure, hypertension, SBP >140, and use of ACE inhibitors or ARBs. All longitudinal analyses were performed separately in the subset of participants taking ACE inhibitors, ARBs, or diuretics.

Analyses were conducted using IBM SPSS Statistics, Version 26.0 (IBM Corp., Armonk, NY, USA) and Stata version 16 (StataCorp LP, College Station, TX, USA).

Results

Baseline Characteristics

Among 2,999 participants in the study sample, 655 (22%) were categorized as NSAID users at baseline, among whom 367 (56%) used prescription NSAIDs. At baseline, average age was 74 ± 3 years, 51% were female, and 41% were African American (Table 1). The mean baseline eGFR was 72 mL/min/1.73m^2, and median ACR was 8 mg/g of creatinine (IQR: 4-20 mg/g). There were 750 (25%) participants with eGFR<60 mL/min/1.73m^2; of those, 534 (18%) had eGFR of 45-59, 169 (6%) had eGFR of 30-44, and 47 (2%) had eGFR <30

mL/min/1.73m^2. Compared to non-users, there was a higher proportion of women among NSAID users (49% vs. 59%). Osteoarthritis was more common among NSAID users than non-users (28% vs. 14%). Use of ACE inhibitors and ARBs were comparable between groups, though use of antihypertensives and diuretics was more common among NSAID users.

Cross-sectional Associations of NSAID Use with Markers of Kidney Function and Injury

There was no difference in baseline eGFR between NSAID users and non-users. The proportion of participants with eGFR <60 mL/min/1.73m^2 did not differ substantially between NSAID users and non-users (Table 2). In the fully adjusted model, the point estimate for the association of NSAID use with eGFR <60 mL/min/1.73m^2 was in the direction of lower odds of CKD (0.83; 95% confidence interval [CI]: 0.66–1.04).

The prevalence of ACR >30 mg/g was lower among NSAID users than non-users (14% vs. 19%). NSAID use was associated with lower odds of having ACR >30 mg/g (0.67; 0.52-0.87) in unadjusted analysis, and this association persisted after multivariable adjustment. NSAID users and non-users had a similar prevalence of ACR >300 mg/g (Supplementary Table S3). NSAID use was associated with 14% lower mean ACR when modeled as a continuous variable in unadjusted analysis; this estimate was modestly attenuated in the final model and no longer reached statistical significance (Table 2).

NSAID use was associated with lower adjusted odds (0.74; 0.60-0.91) of a composite CKD outcome representing either eGFR <60 mL/min/1.73m^2 *or* ACR >30 mg/g. For each of these outcomes, we found no evidence of interaction with heart failure, hypertension, SBP >140 mmHg, and ACE inhibitor or ARB use (Supplementary Table S4).

There was no significant difference between NSAID users and non-users in urine KIM-1 levels at baseline in unadjusted and adjusted analyses (Table 2). NSAID users had approximately 10% lower mean urine IL-18 levels compared with non-users; this association remained statistically significant in adjusted models. In the subcohort analyses, we observed no associations of NSAID use with concentrations of urine α1m, NGAL, PIIINP, and UMOD at baseline (Table 3).

Among participants using either ACE inhibitors, ARBs, or diuretics, these associations were directionally consistent but less precise. In this stratum, NSAID use appeared to be associated with lower odds of eGFR <60 mL/min/1.73m^2 at baseline and bordered on statistical significance through all levels of adjustment (unadjusted OR=0.71, 95% CI: 0.50-1.02; adjusted OR=0.66, 95% CI: 0.45-0.97) (Supplementary Tables S1 & S2).

Neither prescription nor non-prescription NSAID users had significantly different baseline eGFR compared to non-users (Supplementary Table S8). Prescription NSAID users had lower urine IL-18 levels and were less likely to have ACR >30 compared to NSAID non-users, but there were no other statistically significant associations (Supplementary Tables S8 & S9).

Longitudinal Associations of NSAID Use and Kidney Function

Median follow-up was 784 days for NSAID users versus 783 days for non-users. The mean rate of eGFR decline was similar among NSAID users (−2.21%; −2.49% to −1.92% per year) and NSAID non-users (−2.31%: −2.47% to −2.16% per year). In absolute units of eGFR, NSAID users experienced an average decline of 1.86 (standard deviation=5.12) mL/min/1.73m^2 per year compared with 1.81 (standard deviation=4.75) mL/min/1.73m^2 per year among non-users. No adjusted association between NSAID use and eGFR decline was observed (Table 4). Prescription NSAID users, non-prescription NSAID users, and non-users were not significantly different in rates of eGFR decline in crude or adjusted analyses (Supplementary Table S10). When participants were stratified by baseline eGFR, 21% of those with eGFR <60 mL/min/1.73m^2 and 22% of participants with eGFR ≥60 mL/min/1.73m^2 were NSAID users at baseline. Time-varying NSAID use was not significantly associated with eGFR decline in either stratum of baseline eGFR and by use of ACE inhibitors, ARBs, or diuretics (Supplementary Table S5). There was evidence for an interaction between NSAID use and hypertension, whereby NSAID use appeared to be modestly associated with slower eGFR decline in participants without hypertension and to have no association with eGFR decline among participants with hypertension (Supplementary Tables S6 & S7).

Discussion

Safe and effective pain control in older adults remains challenging and demands reassessment of analgesic options for this population. Our analyses demonstrated no associations between NSAID use and kidney damage or dysfunction in a large cohort of ambulatory older adults. Cross-sectional analyses revealed no differences between NSAID users and non-users for six measures of kidney function and injury, but NSAID use was associated with slightly lower urine albumin and IL-18 concentrations. We detected no difference between NSAID users and non-users in the rate of eGFR decline, even when stratified by baseline eGFR or use of RAAS inhibitors and diuretics. These findings were the same among prescription NSAID users, despite presumed exposure to higher doses and frequencies compared to other participants. In summary, no findings supported our *a priori* hypothesis that NSAID use would be associated with kidney injury and would accelerate kidney function decline as measured by multiple, sensitive indicators of kidney health. These results encourage additional study and reappraisal of the connection between NSAID exposure and long-term kidney damage.

Though NSAIDs can certainly cause AKI, associations between NSAID use and CKD lack consistency, even among older adults. The PRECISION trial randomized participants (mean age 63) with osteoarthritis or rheumatoid arthritis to celecoxib, naproxen, or ibuprofen and demonstrated relatively low rates of renal events (see supplement for definitions) over a mean follow-up of 34 months.[6] Longer term outcomes such as GFR decline derive from observational studies, of which only a few focused on middle-aged and older adults. A foundational study in older adults by Field, *et al.* showed that chronic NSAID users had significantly higher serum creatinine compared to non-users.[37] Notably, this study analyzed only prevalent users based on medication review and did not include dosage or duration of

NSAID use. In a cohort of 10,184 Canadians at least 66 years old, NSAID users with the highest cumulative NSAID exposure had 26% higher odds of rapid GFR decline compared to NSAID non-users.[38] Conversely, the Nurses' Health Study of 1,697 participants aged 30-55 years-old at baseline showed no association between lifetime NSAID use and eGFR decline over 11 years of follow up.[39] Two separate analyses of the Physicians' Health Study participants also found no association between NSAID use and kidney dysfunction over 14 years.[40, 41]

Most NSAID-associated kidney injury results from intrarenal hemodynamic dysregulation causing decreased GFR and nephron ischemia. High-dose or prolonged NSAID exposure as well as volume depletion, renal vasoconstriction, and impaired autoregulation increase risk of injury.[11, 42] Owing to a high prevalence of CKD and frequent co-administration of diuretics, ACE inhibitors, ARBs, and other renin-angiotensin-aldosterone system (RAAS) inhibitors, older persons are presumed to be more susceptible to NSAID-associated kidney injury. However, findings from a large CKD cohort suggested that opioids are more strongly associated with adverse kidney outcomes than NSAIDs.[43] Likewise, we observed no association of NSAID use with an array of kidney damage markers in Health ABC participants despite their median baseline age of 74 years, 36% prevalence of CKD, as defined by eGFR<60 mL/min/1.73m^2 or ACR >30 mg/g, and common use of RAAS inhibitors and diuretics.

Our study benefitted from multiple measures of kidney function and injury. GFR was estimated using cysC, a better marker of kidney filtration function in older adults. We measured urine albumin, an indicator of glomerular damage that is highly prognostic for kidney function decline and mortality.[20] We also evaluated multiple measures of kidney tubule injury (KIM-1, NGAL, IL-18), fibrosis (PIIINP), and dysfunction (α1m, UMOD). These biomarkers are more sensitive and specific for kidney tubule damage than current clinical measures.[21] Likewise, they have proven useful in evaluating medication nephrotoxicity. Several kidney tubule biomarkers are used by the U.S. Food and Drug Administration for drug safety evaluation in early phase studies, and many of these markers have been leveraged to characterize nephrotoxicity associated with tenofovir and antihypertensive therapy.[29, 30, 44, 45] Studies of children and adults undergoing NSAID therapy showed that even with brief high-intensity NSAID use, tubule injury biomarkers rise before and independently of serum creatinine.[31, 46] However, we observed no evidence of kidney tubule injury or dysfunction among NSAID users in the Health ABC cohort despite the use of an array of biomarkers capturing multiple dimensions of kidney health in a large sample of at-risk individuals.

Our cross-sectional analysis demonstrated two statistically significant differences between NSAID users and non-users: ACR and urine IL-18 were lower among NSAID users at baseline, both of which suggest better kidney health. Although rarely NSAIDs have been implicated in causing nephrotic syndrome, NSAIDs can reduce albuminuria by decreasing glomerular capillary pressures, and our results might reflect this effect.[47] However, if NSAID effects on kidney hemodynamics reduced ACR, we might have expected to observe a complementary increase in serum creatinine, as noted in the intensive blood pressure control arm of the SPRINT study.[45] Alternatively, albuminuria may have been confounded

by antihypertensive use, though we observed no interactions between NSAID use and ACE inhibitor or ARB use for the prevalence of ACR >30 mg/g. The explanation for NSAID users having lower urine IL-18 is uncertain, as IL-18 levels rise with kidney tubule cell injury. Reduced interleukin levels could reflect the anti-inflammatory or hemodynamic effects of NSAIDs. The ACCORD and SPRINT trials demonstrated lower urine IL-18 levels with intensive blood pressure control, perhaps signaling reduced risk of kidney tubule injury in the setting of decreased intrarenal capillary pressures.[48, 49] However, these explanations are speculative and underscore the need to investigate further the unique urine biomarker patterns associated with NSAID use.

These analyses are limited by the potential for residual confounding. The cross-sectional design precluded analysis of biomarker changes after NSAID initiation or discontinuation. Though the medication data were reviewed for generic and brand name NSAIDs, as listed in the supplement, we acknowledge that some less commonly used NSAID preparations may have escaped ascertainment. Participants were categorized as users irrespective of dose and frequency of NSAID use, though these factors are important determinants of risk for NSAID nephrotoxicity.[50] However, we found no significant differences in kidney health between users of prescription versus over-the-counter NSAIDs. We were unable to rule out confounding by contraindication, whereby participants with the highest risks avoid NSAIDs. Nonetheless, NSAID users and non-users in our study had comparable baseline kidney function by eGFR. In addition, the rate of eGFR decline in this cohort was slower than among cohorts of persons with advanced CKD, and NSAID use may be riskier in individuals with more rapidly progressive CKD. Finally, our set of biomarkers may have been unable to capture NSAID-specific toxicity; however, prior studies have demonstrated that NSAID exposure can cause increases in kidney tubule injury biomarkers.[31, 46]

In summary, we found no evidence for associations of NSAID use with kidney dysfunction or damage in this cohort of well-functioning older persons. We believe that these unexpected null findings warrant further study to define which patterns of NSAID use cause kidney injury in this population. Although we might speculate that NSAID use in the Health ABC cohort was predominantly sporadic and at low doses, the lack of association between NSAID use and kidney damage or dysfunction across several measures suggests that there is a pattern of NSAID use that does not harm the kidney in older adults. These findings, along with investigations focused on high-dose NSAID users, will contribute to a better characterization of the safe range of NSAID use, which can empower more effective pain management. However, we also recognize the potential for other NSAID-related adverse events in older adults, including GI bleeding, atherosclerotic events and heart failure, and we emphasize that kidney safety is only part of the risk-benefit calculation. To determine how these medications could be administered safely in older adults who bear a high burden of pain, future studies should strive to obtain more detailed measurements of NSAID exposure and utilize multidimensional assessments of kidney health while monitoring for extra-renal adverse effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the Health ABC Study sponsors for facilitating this ancillary study through the provision of samples and approval of the study design and analysis plan. This work has not been previously published and is not being considered for publication elsewhere, in whole or in part, in any language, except as an abstract.

Funding & Sponsor's Role

This work was supported by a grant from the National Institute on Aging (grant # 2R01AG027002). The National Institute on Aging had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Dr. Amatruda is also supported by the T32 Ruth L. Kirschstein National Research Service Award (5T32DK007219-43).

References:

1. Davis JS, Lee HY, Kim J, et al. Use of non-steroidal anti-inflammatory drugs in US adults: changes over time and by demographic. Open Heart. 2017;4(1):e000550. doi:10.1136/openhrt-2016-000550 [PubMed: 28674622]
2. Pathan SA, Mitra B, Cameron PA. A Systematic Review and Meta-analysis Comparing the Efficacy of Nonsteroidal Anti-inflammatory Drugs, Opioids, and Paracetamol in the Treatment of Acute Renal Colic. European Urology. 2018//04/ 2018;73(4):583–595. doi:10.1016/j.eururo.2017.11.001 [PubMed: 29174580]
3. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. JAMA. 2018//12/18 2018;320(23):2448–2460. doi:10.1001/jama.2018.18472 [PubMed: 30561481]
4. Gross JL, Perate AR, Elkassabany NM. Pain Management in Trauma in the Age of the Opioid Crisis. Anesthesiol Clin. 3 2019;37(1):79–91. doi:10.1016/j.anclin.2018.09.010 [PubMed: 30711235]
5. Wick EC, Grant MC, Wu CL. Postoperative Multimodal Analgesia Pain Management With Nonopioid Analgesics and Techniques: A Review. JAMA surgery. 2017//07/01 2017;152(7):691–697. doi:10.1001/jamasurg.2017.0898 [PubMed: 28564673]
6. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. New England Journal of Medicine. 2016/12/29/ 2016;375(26):2519–2529. doi:10.1056/NEJMoa1611593
7. Singh G, Lanes S, Triadafilopoulos G. Risk of serious upper gastrointestinal and cardiovascular thromboembolic complications with meloxicam. Am J Med. 7 15 2004;117(2):100–6. doi:10.1016/j.amjmed.2004.03.012 [PubMed: 15234645]
8. Lucas GNC, Leitão ACC, Alencar RL, Xavier RMF, Daher EDF, Silva GBd Junior. Pathophysiological aspects of nephropathy caused by non-steroidal anti-inflammatory drugs. Brazilian Journal of Nephrology. 2018/09/21/ 2018;41(1):124–130. doi:10.1590/2175-8239-jbn-2018-0107 [PubMed: 30281062]
9. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. JAMA. 10 1 2019;322(13):1294–1304. doi:10.1001/jama.2019.14745 [PubMed: 31573641]
10. Nash DM, Markle-Reid M, Brimble KS, et al. Nonsteroidal anti-inflammatory drug use and risk of acute kidney injury and hyperkalemia in older adults: a population-based study. Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association. 2019/07/01/ 2019;34(7):1145–1154. doi:10.1093/ndt/gfz062
11. Baker M, Perazella MA. NSAIDs in CKD: Are They Safe? Am J Kidney Dis. 5 29 2020;doi:10.1053/j.ajkd.2020.03.023
12. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in The Elderly. Aging and Disease. 2018 2018;9(1):143. doi:10.14336/AD.2017.0306 [PubMed: 29392089]
13. Anderson S, Eldadah B, Halter JB, et al. Acute kidney injury in older adults. J Am Soc Nephrol. 1 2011;22(1):28–38. doi:10.1681/ASN.2010090934 [PubMed: 21209252]

14. American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 11 2015;63(11):2227–46. doi:10.1111/jgs.13702 [PubMed: 26446832]
15. Sawyer P, Bodner EV, Ritchie CS, Allman RM. Pain and pain medication use in community-dwelling older adults. Am J Geriatr Pharmacother. 12 2006;4(4):316–24. doi:10.1016/j.amjopharm.2006.12.005 [PubMed: 17296537]
16. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older P. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 8 2009;57(8):1331–46. doi:10.1111/j.1532-5415.2009.02376.x [PubMed: 19573219]
17. Molitoris BA. Beyond Biomarkers: Machine Learning in Diagnosing Acute Kidney Injury. Mayo Clinic Proceedings. 2019/05// 2019;94(5):748–750. doi:10.1016/j.mayocp.2019.03.017 [PubMed: 31054601]
18. O'Riordan SE, Webb MC, Stowe HJ, et al. Cystatin C improves the detection of mild renal dysfunction in older patients. Ann Clin Biochem. 11 2003;40(Pt 6):648–55. doi:10.1258/000456303770367243 [PubMed: 14629803]
19. Shlipak MG, Katz R, Sarnak MJ, et al. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. Ann Intern Med. 8 15 2006;145(4):237–46. doi:10.7326/0003-4819-145-4-200608150-00003 [PubMed: 16908914]
20. Nitsch D, Grams M, Sang Y, et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. BMJ. 1 29 2013;346:f324. doi:10.1136/bmj.f324 [PubMed: 23360717]
21. Moledina DG, Hall IE, Thiessen-Philbrook H, et al. Performance of Serum Creatinine and Kidney Injury Biomarkers for Diagnosing Histologic Acute Tubular Injury. Am J Kidney Dis. 12 2017;70(6):807–816. doi:10.1053/j.ajkd.2017.06.031 [PubMed: 28844586]
22. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int. 7 2002;62(1):237–44. doi:10.1046/j.1523-1755.2002.00433.x [PubMed: 12081583]
23. Parikh CR, Jani A, Melnikov VY, Faubel S, Edelstein CL. Urinary interleukin-18 is a marker of human acute tubular necrosis. Am J Kidney Dis. 3 2004;43(3):405–14. doi:10.1053/j.ajkd.2003.10.040 [PubMed: 14981598]
24. Bolignano D, Donato V, Coppolino G, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a marker of kidney damage. Am J Kidney Dis. 9 2008;52(3):595–605. doi:10.1053/j.ajkd.2008.01.020 [PubMed: 18725016]
25. Ix JH, Katz R, Bansal N, et al. Urine Fibrosis Markers and Risk of Allograft Failure in Kidney Transplant Recipients: A Case-Cohort Ancillary Study of the FAVORIT Trial. Am J Kidney Dis. 3 2017;69(3):410–419. doi:10.1053/j.ajkd.2016.10.019 [PubMed: 28024930]
26. Ix JH, Biggs ML, Mukamal K, et al. Urine Collagen Fragments and CKD Progression-The Cardiovascular Health Study. J Am Soc Nephrol. 10 2015;26(10):2494–503. doi:10.1681/ASN.2014070696 [PubMed: 25655067]
27. Weber MH, Verwiebe R. Alpha 1-microglobulin (protein HC): features of a promising indicator of proximal tubular dysfunction. European Journal of Clinical Chemistry and Clinical Biochemistry: Journal of the Forum of European Clinical Chemistry Societies. 1992/10// 1992;30(10):683–691.
28. Garimella PS, Biggs ML, Katz R, et al. Urinary uromodulin, kidney function, and cardiovascular disease in elderly adults. Kidney Int. 11 2015;88(5):1126–34. doi:10.1038/ki.2015.192 [PubMed: 26154925]
29. Ascher SB, Scherzer R, Estrella MM, et al. Association of Urinary Biomarkers of Kidney Injury with Estimated GFR Decline in HIV-Infected Individuals following Tenofovir Disoproxil Fumarate Initiation. Clinical journal of the American Society of Nephrology: CJASN. 2018//09/07 2018;13(9):1321–1329. doi:10.2215/CJN.01700218 [PubMed: 30154221]
30. Zhang WR, Scherzer R, Estrella MM, et al. Tenofovir disoproxil fumarate initiation and changes in urinary biomarker concentrations among HIV-infected men and women. AIDS (London, England). 2019/03/15/ 2019;33(4):723–733. doi:10.1097/QAD.0000000000002114

31. Nehus E, Kaddourah A, Bennett M, Pyles O, Devarajan P. Subclinical Kidney Injury in Children Receiving Nonsteroidal Anti-Inflammatory Drugs After Cardiac Surgery. The Journal of Pediatrics. 2017//10/ 2017;189:175–180. doi:10.1016/j.jpeds.2017.06.045 [PubMed: 28712521]
32. Jotwani V, Katz R, Ix JH, et al. Urinary Biomarkers of Kidney Tubular Damage and Risk of Cardiovascular Disease and Mortality in Elders. Am J Kidney Dis. 8 2018;72(2):205–213. doi:10.1053/j.ajkd.2017.12.013 [PubMed: 29602632]
33. Driver TH, Katz R, Ix JH, et al. Urinary kidney injury molecule 1 (KIM-1) and interleukin 18 (IL-18) as risk markers for heart failure in older adults: the Health, Aging, and Body Composition (Health ABC) Study. Am J Kidney Dis. 7 2014;64(1):49–56. doi:10.1053/j.ajkd.2014.01.432 [PubMed: 24656453]
34. Sarnak MJ, Katz R, Newman A, et al. Association of urinary injury biomarkers with mortality and cardiovascular events. J Am Soc Nephrol. 7 2014;25(7):1545–53. doi:10.1681/ASN.2013070713 [PubMed: 24511130]
35. National Institute on Aging. Introducing the Health ABC Study: The Dynamics of Health, Aging, and Body Composition. Accessed 6 April, 2020. https://healthabc.nia.nih.gov/
36. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 7 5 2012;367(1):20–9. doi:10.1056/NEJMoa1114248 [PubMed: 22762315]
37. Field TS, Gurwitz JH, Glynn RJ, et al. The renal effects of nonsteroidal anti-inflammatory drugs in older people: findings from the Established Populations for Epidemiologic Studies of the Elderly. J Am Geriatr Soc. 5 1999;47(5):507–11. doi:10.1111/j.1532-5415.1999.tb02561.x [PubMed: 10323640]
38. Gooch K, Culleton BF, Manns BJ, et al. NSAID use and progression of chronic kidney disease. The American Journal of Medicine. 2007/03// 2007;120(3):280.e1–7. doi:10.1016/j.amjmed.2006.02.015
39. Curhan GC, Knight EL, Rosner B, Hankinson SE, Stampfer MJ. Lifetime nonnarcotic analgesic use and decline in renal function in women. Arch Intern Med. 7 26 2004;164(14):1519–24. doi:10.1001/archinte.164.14.1519 [PubMed: 15277282]
40. Rexrode KM, Buring JE, Glynn RJ, Stampfer MJ, Youngman LD, Gaziano JM. Analgesic use and renal function in men. JAMA. 7 18 2001;286(3):315–21. doi:10.1001/jama.286.3.315 [PubMed: 11466097]
41. Kurth T, Glynn RJ, Walker AM, et al. Analgesic use and change in kidney function in apparently healthy men. Am J Kidney Dis. 8 2003;42(2):234–44. doi:10.1016/s0272-6386(03)00647-4 [PubMed: 12900803]
42. Hörl WH. Nonsteroidal Anti-Inflammatory Drugs and the Kidney. Pharmaceuticals. 2010/07/21/ 2010;3(7):2291–2321. doi:10.3390/ph3072291 [PubMed: 27713354]
43. Zhan M, Doerfler RM, Xie D, et al. Association of Opioids and Nonsteroidal Anti-inflammatory Drugs With Outcomes in CKD: Findings From the CRIC (Chronic Renal Insufficiency Cohort) Study. Am J Kidney Dis. 4 18 2020;doi:10.1053/j.ajkd.2019.12.010
44. United States Food and Drug Administration. List of Qualified Biomarkers. Updated April 14, 2020. Accessed October 3, 2020, https://www.fda.gov/drugs/cder-biomarker-qualification-program/list-qualified-biomarkers
45. Malhotra R, Craven T, Ambrosius WT, et al. Effects of Intensive Blood Pressure Lowering on Kidney Tubule Injury in CKD: A Longitudinal Subgroup Analysis in SPRINT. American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation. 2019/01// 2019;73(1):21–30. doi:10.1053/j.ajkd.2018.07.015 [PubMed: 30291012]
46. Shukla A, Rai MK, Prasad N, Agarwal V. Short-Term Non-Steroid Anti-Inflammatory Drug Use in Spondyloarthritis Patients Induces Subclinical Acute Kidney Injury: Biomarkers Study. Nephron. 2017 2017;135(4):277–286. doi:10.1159/000455167 [PubMed: 28171854]
47. Sriperumbuduri S, Hiremath S. The case for cautious consumption: NSAIDs in chronic kidney disease. Curr Opin Nephrol Hypertens. 3 2019;28(2):163–170. doi:10.1097/MNH.0000000000000473 [PubMed: 30531470]

48. Nadkarni GN, Chauhan K, Rao V, et al. Effect of Intensive Blood Pressure Lowering on Kidney Tubule Injury: Findings From the ACCORD Trial Study Participants. Am J Kidney Dis. 1 2019;73(1):31–38. doi:10.1053/j.ajkd.2018.07.016 [PubMed: 30291011]

49. Zhang WR, Craven TE, Malhotra R, et al. Kidney Damage Biomarkers and Incident Chronic Kidney Disease During Blood Pressure Reduction: A Case-Control Study. Ann Intern Med. 11 6 2018;169(9):610–618. doi:10.7326/M18-1037 [PubMed: 30357395]

50. Nderitu P, Doos L, Jones PW, Davies SJ, Kadam UT. Non-steroidal anti-inflammatory drugs and chronic kidney disease progression: a systematic review. Family Practice. 2013/06/01/ 2013;30(3):247–255. doi:10.1093/fampra/cms086 [PubMed: 23302818]

Key Points

- Among ambulatory older adults, self-reported NSAID use was not associated with glomerular or tubular damage.
- NSAID users and non-users had comparable rates of kidney function decline over 10 years.

Why Does this Paper Matter?

NSAID use may not be inevitably associated with kidney injury and dysfunction among older adults.

Table 1:

Baseline characteristics of Health Aging, Body, and Composition Study participants by baseline self-reported NSAID use

	NSAID use	
	No (N = 2344)	**Yes (N = 655)**
Age (SD)	74 (3)	74 (3)
Females (%)	1150 (49)	387 (59)
African Americans (%)	965 (41)	274 (42)
Site (%)		
Memphis	1150 (49)	349 (53)
Pittsburgh	1194 (51)	306 (47)
Education (%)		
Less than high school	561 (24)	190 (29)
High school education	788 (34)	190 (29)
Postsecondary education	987 (42)	275 (42)
Smoking status (%)		
Never	1016 (43)	293 (45)
Former	1080 (46)	301 (46)
Current	248 (11)	61 (9)
BMI, kg/m^2 (SD)	27.2 (4.7)	28.3 (5.1)
Systolic blood pressure, mmHg (SD)	136 (21)	135 (21)
Diastolic blood pressure, mmHg (SD)	71 (12)	71 (11)
Markers of physical function		
Grip strength, kg (SD)		
Right arm	31.2 (10.6)	28.9 (10.3)
Left Arm	29.5 (10.3)	27.3 (10.1)
Time to walk 6m, sec (SD)	5.3 (1.1)	5.5 (1.3)
Comorbidities (%)		
Hypertension	1174 (51)	350 (54)
Diabetes	449 (19)	109 (17)
Heart failure	78 (3)	15 (2)
CVD	657 (29)	158 (25)
Osteoarthritis	320 (14)	182 (28)
Osteoporosis	198 (8)	98 (15)
Any cancer	412 (18)	100 (15)
eGFR <60 mL/min/1.73m^2	591 (25)	159 (24)
Medications (%)		
Any antihypertensive medication	1249 (53)	393 (60)
Diuretics	559 (24)	210 (32)
ACEi/ARB use	405 (17)	122 (19)

Data presented as mean (SD) or numbers (%).

Table 2.

Association of baseline NSAID use with markers of kidney function in cross-sectional analyses in 2,999 Health ABC participants

	NSAID use		Model 1	Model 2	Model 3
	No (N=2344)	Yes (N=655)			
	Mean (SD)	Mean (SD)	β (95% CI)	β (95% CI)	β (95% CI)
eGFR[a]	72 (19)	72 (18)	−0.47 (−2.14 to 1.21)	−0.45 (−2.09 to 1.19)	0.63 (−0.97 to 2.24)
	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
eGFR <60	591 (25)	159 (24)	0.92 (0.74 to 1.14)	0.91 (0.73 to 1.13)	0.83 (0.66 to 1.04)
ACR[b] **>30**	451 (19)	92 (14)	0.67 (0.52 to 0.87)	0.70 (0.54 to 0.90)	0.67 (0.51 to 0.89)
eGFR <60 or ACR >30	869 (37)	212 (32)	0.81 (0.66, 0.98)	0.81 (0.66, 0.98)	0.74 (0.60, 0.91)
	Geometric mean (SD)	Geometric mean (SD)	Percent change (95% CI)	Percent change (95% CI)	Percent change (95% CI)
ACR[b]	9.2 (5.2)	7.6 (4.76)	−14% (−26% to −1%)	−13% (−25% to 0%)	−12% (−24% to 1%)
KIM-1[c]	731 (3)	739 (3)	2% (−7% to 12%)	5% (−4% to 15%)	5% (−5% to 14%)
IL-18[d]	32.9 (2.4)	30.3 (2.3)	−9% (−16% to −2%)	−11% (−18% to −4%)	−11% (−18% to −4%)

Model 1: adjusted only for urine creatinine for KIM-1 and IL-18 (eGFR and ACR unadjusted); Model 2: adjusted for age, gender, race, education; Model 3: further adjusted for BMI, osteoarthritis, osteoporosis, diabetes, SBP, antihypertensive medications, prevalent heart failure, gait speed, and grip strength.

[a] eGFR reported as mL/min/1.73m^2.

[b] ACR reported as mg/g.

[c] KIM-1 reported as pg/mL.

[d] IL-18 reported as pg/mL.

Table 3.

Association of baseline NSAID use with additional kidney tubule biomarkers in cross-sectional analyses in subcohort of 500 Health ABC participants

	NSAID use		Model 1	Model 2	Model 3
	No (N=392)	Yes (N=108)			
	Geometric mean (SD)	Geometric mean (SD)	Percent change (95% CI)	Percent change (95% CI)	Percent change (95% CI)
α1m[a]	0.95 (1.98)	0.93 (2.05)	−1% (−15% to 15%)	4% (−10% to 21%)	4% (−11% to 20%)
NGAL[b]	30.1 (7.4)	29.4 (6.2)	1% (−37% to 53%)	1% (−37% to 53%)	−1% (−38% to 51%)
PIIINP[c]	2.03 (3.26)	2.45 (3.19)	0% (−24% to 30%)	9% (−17% to 40%)	8% (−17% to 39%)
UMOD[d]	23.6 (2.31)	25.6 (2.07)	6% (−12% to 26%)	8% (−10% to 29%)	14% (−5% to 36%)

Model 1: adjusted only for urine creatinine; Model 2: adjusted for age, gender, race, education; Model 3: further adjusted for BMI, osteoarthritis, osteoporosis, diabetes, SBP, antihypertensive medications, prevalent heart failure, gait speed, and grip strength.

[a] α1m reported as mg/dL.

[b] NGAL reported as ng/mL.

[c] PIIINP reported as μg/L.

[d] UMOD reported as μg/mL.

Table 4.

Association of NSAID use with annualized change in eGFR: Overall and Stratified by baseline kidney function

All participants (N=2999)	**Mean eGFR change in % per year (95% CI)**	**Model 1 β (95% CI)**	**Model 2 β (95% CI)**
NSAID users (N=655)	−2.21 (−2.49 to −1.92)	−0.11 (−0.45 to 0.22)	−0.06 (−0.39 to 0.28)
NSAID non-users (N=2344)	−2.31 (−2.47 to −2.16)	0 (reference)	0 (reference)
eGFR ≥60 mL/min/1.73m^2 (N=2249)			
NSAID users (N=496)	−2.36 (−2.62 to −2.11)	−0.06 (−0.36 to 0.23)	−0.001 (−0.31 to 0.31)
NSAID non-users (N=1753)	−2.42 (−2.56 to −2.29)	0 (reference)	0 (reference)
eGFR <60 mL/min/1.73m^2 (N=750)			
NSAID users (N=159)	−1.74 (−2.52 to −0.96)	−0.27 (−1.16 to 0.62)	−0.29 (−1.19 to 0.61)
NSAID non-users (N=591)	−2.00 (−2.41 to −1.59)	0 (reference)	0 (reference)

Model 1: adjusted for age, gender, race, education.

Model 2: further adjusted for BMI, osteoarthritis, osteoporosis, diabetes, SBP, antihypertensive medications, prevalent heart failure, gait speed, and grip strength.