


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

Jonathan G. Amatruda, MD,<sup>\*†</sup>  Ronit Katz, DPhil,<sup>‡</sup> Carmen A. Peralta, MD, MAS,<sup>\*†§</sup> Michelle M. Estrella, MD, MHS,<sup>†¶</sup> Harini Sarathy, MBBS, MHS,<sup>\*||</sup> Linda F. Fried, MD, MPH,<sup>\*\*††</sup> Anne B. Newman, MD, MPH,<sup>\*\*</sup> Chirag R. Parikh, MBBS, PhD,<sup>‡‡</sup> Joachim H. Ix, MD, MAS,<sup>§§¶¶</sup> Mark J. Sarnak, MD, MS,<sup>|||</sup> and Michael G. Shlipak, MD, MPH,<sup>†\*\*\*</sup> for the Health ABC Study

**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:** Two thousand nine hundred and ninety nine 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 estimated glomerular filtration rate (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 ( $\alpha$ 1m), neutrophil gelatinase-associated lipocalin (NGAL), propeptide type III procollagen (PIIINP), and uromodulin (UMOD) were measured in 500 participants. GFR was estimated three 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 = 2,344) at baseline (72 ml/min/1.73 m<sup>2</sup> in both groups). Compared to non-users, NSAID users had lower adjusted odds of having ACR greater than 30 mg/g (0.67; 95% confidence interval (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. *J Am Geriatr Soc* 69:726-734, 2021.

**Keywords:** chronic kidney disease; pharmacoepidemiology; nephrotoxicity; NSAID

From the \*Division of Nephrology, Department of Medicine, University of California, San Francisco, San Francisco, California; †Kidney Health Research Collaborative, San Francisco VA Medical Center & University of California, San Francisco, San Francisco, California; ‡Kidney Research Institute, University of Washington, Seattle, Washington; §Chief Medical Office, Cricket Health, Inc., San Francisco, California; ¶Division of Nephrology, Department of Medicine, San Francisco VA Medical Center, San Francisco, California; ||Division of Nephrology, Department of Medicine, Zuckerberg San Francisco General Hospital, San Francisco, California; \*\*University of Pittsburgh School of Medicine and Graduate School of Public Health, Pittsburgh, Pennsylvania; ††VA Pittsburgh Healthcare System and University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; ‡‡Division of Nephrology, Department of Medicine, Johns Hopkins University, Baltimore, Maryland; §§Division of Nephrology-Hypertension, Department of Medicine, University of California, San Diego, California; ¶¶Nephrology Section, Veterans Affairs San Diego Healthcare System, San Diego, California; |||Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, Massachusetts; and the \*\*\*Department of Medicine, San Francisco VA Medical Center, San Francisco, California.

Address correspondence to Michael G. Shlipak, MD, Kidney Health Research Collaborative, San Francisco VA Health Care System, 4150 Clement Street, San Francisco, CA 94121.  
E-mail: michael.shlipak@ucsf.edu

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## 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.<sup>1-5</sup> However, NSAID use is limited by their potential for adverse effects including cardiovascular toxicity, peptic ulcers, and nephrotoxicity.<sup>6-8</sup> 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.<sup>9-11</sup> Despite concerns that older adults are at especially high risk of NSAID nephrotoxicity, their risk of long-term NSAID-associated kidney damage remains uncertain.<sup>10,12,13</sup> Partially due to these concerns, the American Geriatrics Society Beers Criteria label NSAIDs as potentially inappropriate for use in older adults.<sup>14</sup> 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.<sup>15,16</sup>

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.<sup>17</sup> Conversely, serum cystatin C (cysC) is unaffected by muscle mass and more accurately detects GFR changes in older persons.<sup>18,19</sup> 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.<sup>20</sup> However, Cr, cysC, and ACR may not detect damage to kidney tubules, the usual site of NSAID toxicity.<sup>21</sup> 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 ( $\alpha 1m$ )); 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.<sup>22-31</sup> Importantly, they have been applied across the age spectrum and are associated with cardiovascular disease, heart failure, and mortality in older adults.<sup>32-34</sup>

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

## 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.

damage and dysfunction at baseline and with faster eGFR decline over time.

## METHODS

### Study Design and 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.<sup>35</sup> 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 2 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.<sup>36</sup> 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  $-80^{\circ}\text{C}$  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 ( $\alpha 1\text{m}$ , 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  $\alpha 1\text{m}$  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 m), grip strength (Jamar hydraulic hand dynamometer), systolic blood pressure (SBP), and use of antihypertensive medications.<sup>35</sup>

## Statistical Analysis

Of the 3,075 total Health ABC participants, we excluded nine 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/1.73 m<sup>2</sup> or ACR  $> 30$  mg/g) using multivariable logistic regression. For these CKD endpoints, we tested for interactions with heart failure, hypertension diagnosis, SBP greater than 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  $\geq 60$  ml/min/1.73 m<sup>2</sup>) 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 greater than 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) and Stata version 16 (StataCorp LP, College Station, TX).

## 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  $74 \pm 3$  years, 51% were female, and 41% were African American (Table 1). The mean baseline eGFR was 72 ml/min/1.73 m<sup>2</sup>, and median ACR was 8 mg/g of creatinine (IQR = 4–20 mg/g). There were 750 (25%) participants with eGFR less than 60 ml/min/1.73 m<sup>2</sup>; of those, 534 (18%) had eGFR of 45–59, 169 (6%) had eGFR of 30–44, and 47 (2%) had eGFR less than 30 ml/min/1.73 m<sup>2</sup>. 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 less than 60 ml/min/1.73 m<sup>2</sup> did not differ substantially between NSAID users and non-users (Table 2). In the

**Table 1. Baseline Characteristics of Health Aging, Body, and Composition Study Participants by Baseline Self-Reported NSAID Use**

	NSAID use	
	No (N = 2,344)	Yes (N = 655)
Age (SD)	74 (3)	74 (3)
Females (%)	1,150 (49)	387 (59)
African Americans (%)	965 (41)	274 (42)
Site (%)		
Memphis	1,150 (49)	349 (53)
Pittsburgh	1,194 (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	1,016 (43)	293 (45)
Former	1,080 (46)	301 (46)
Current	248 (11)	61 (9)
Body mass index, kg/m <sup>2</sup> (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 6 m, sec (SD)	5.3 (1.1)	5.5 (1.3)
Comorbidities (%)		
Hypertension	1,174 (51)	350 (54)
Diabetes mellitus	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/1.73 m <sup>2</sup>	591 (25)	159 (24)
Medications (%)		
Any antihypertensive medication	1,249 (53)	393 (60)
Diuretics	559 (24)	210 (32)
ACEi/ARB use	405 (17)	122 (19)

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

Abbreviations: ACEi/ARB, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers; MI, body mass index; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drugs; SD, standard deviation.

fully adjusted model, the point estimate for the association of NSAID use with eGFR less than 60 ml/min/1.73 m<sup>2</sup> was in the direction of lower odds of CKD (0.83; 95% confidence interval (CI) = 0.66–1.04).

The prevalence of ACR greater than 30 mg/g was lower among NSAID users than non-users (14% vs 19%). NSAID use was associated with lower odds of having ACR greater than 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 greater than 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 less than 60 ml/min/1.73 m<sup>2</sup> or ACR greater than 30 mg/g. For each of these outcomes, we found no evidence of interaction with heart failure, hypertension, SBP greater than 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  $\alpha$ 1m, 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 less than 60 ml/min/1.73 m<sup>2</sup> at baseline and bordered on statistical significance through all levels of adjustment (unadjusted odds ratios (OR) = 0.71, 95% CI = 0.50–1.02; adjusted OR = 0.66, 95% CI = 0.45–0.97) (Supplementary Table S1 and Supplementary Table 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 greater than 30 compared to NSAID non-users, but there were no other statistically significant associations (Supplementary Table S8 and Supplementary Table 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/1.73 m<sup>2</sup> per year compared with 1.81 (standard deviation = 4.75) ml/min/1.73 m<sup>2</sup> 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 less than 60 ml/min/1.73 m<sup>2</sup> and 22% of participants with eGFR 60 ml/min/1.73 m<sup>2</sup> or more 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

**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 $\beta$ (95% CI)	Model 2 $\beta$ (95% CI)	Model 3 $\beta$ (95% CI)
	No (N = 2,344) Mean (SD)	Yes (N = 655) Mean (SD)			
eGFR <sup>a</sup>	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)
	NSAID use		Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
	No (N = 2,344) N (%)	Yes (N = 655) N (%)			
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 <sup>b</sup> > 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 <sup>b</sup>	9.2 (5.2)	7.6 (4.76)	-14% (-26% to -1%)	-13% (-25% to 0%)	-12% (-24% to 1%)
KIM-1 <sup>c</sup>	731 (3)	739 (3)	2% (-7% to 12%)	5% (-4% to 15%)	5% (-5% to 14%)
IL-18 <sup>d</sup>	32.9 (2.4)	30.3 (2.3)	-9% (-16% to -2%)	-11% (-18% to -4%)	-11% (-18% to -4%)

Note: 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 body mass index, osteoarthritis, osteoporosis, diabetes mellitus, SBP, antihypertensive medications, prevalent heart failure, gait speed, and grip strength.

Abbreviations: CI, confidential interval; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio; SD, standard deviation.

<sup>a</sup>eGFR reported as ml/min/1.73 m<sup>2</sup>.

<sup>b</sup>ACR reported as mg/g.

<sup>c</sup>KIM-1 reported as pg/ml.

<sup>d</sup>IL-18 reported as pg/ml.

evidence for an interaction between NSAID use and hypertension, whereby NSAID use seemed 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 Table S6 and Supplementary Table 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

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

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

Abbreviations:  $\alpha$ 1m, alpha-1 microglobulin; NGAL, neutrophil gelatinase-associated lipocalin; PIIINP, propeptide type III procollagen; UMOD, uromodulin.

<sup>a</sup> $\alpha$ 1m reported as mg/dl.

<sup>b</sup>NGAL reported as ng/ml.

<sup>c</sup>PIIINP reported as  $\mu$ g/L.

<sup>d</sup>UMOD reported as  $\mu$ g/ml.

**Table 4. Association of Non-Steroidal Anti-Inflammatory Drugs (NSAID) Use With Annualized Change in eGFR: Overall and Stratified by Baseline Kidney Function**

All Participants (N = 2,999)	Mean eGFR Change in % per year (95% CI)	Model 1 $\beta$ (95% CI)	Model 2 $\beta$ (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 = 2,344)	-2.31 (-2.47 to -2.16)	0 (reference)	0 (reference)
eGFR $\geq$ 60 ml/min/1.73 m <sup>2</sup> (N = 2,249)			
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 <sup>2</sup> (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)

Note: Model 1: adjusted for age, gender, race, education. Model 2: further adjusted for body mass index, osteoarthritis, osteoporosis, diabetes mellitus, SBP, antihypertensive medications, prevalent heart failure, gait speed, and grip strength.

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.<sup>6</sup> 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.<sup>37</sup> 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.<sup>38</sup> 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.<sup>39</sup> Two separate analyses of the Physicians' Health Study participants also found no association between NSAID use and kidney dysfunction over 14 years.<sup>40,41</sup>

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.<sup>11,42</sup> 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.<sup>43</sup> 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 less than 60 ml/min/1.73 m<sup>2</sup> or ACR greater than 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.<sup>20</sup> We also evaluated multiple measures of kidney tubule injury (KIM-1, NGAL, IL-18), fibrosis (PIINP), and dysfunction ( $\alpha$ 1m, UMOD). These biomarkers are more sensitive and specific for kidney tubule damage than current clinical measures.<sup>21</sup> 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.<sup>29,30,44,45</sup> 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.<sup>31,46</sup> 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.<sup>47</sup> 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.<sup>45</sup> 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 greater than 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.<sup>48,49</sup> 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.<sup>50</sup> However, we found no significant differences in kidney health between users of prescription versus over-the-counter NSAIDs. We were unable to exclude 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.<sup>31,46</sup>

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.

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**Author 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.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

**Supplementary Data S1: Supplementary Table S1.** Association of baseline NSAID use with markers of kidney function in cross-sectional analyses in 789 Health ABC participants who were users of ACE inhibitors, angiotensin receptor blockers, or diuretics.



**Supplementary Table S2.** Association of baseline NSAID use with additional kidney tubule biomarkers in cross-sectional analyses in subcohort of 122 health ABC participants who were users of ACE inhibitors, angiotensin receptor blockers, or diuretics.

**Supplementary Table S3.** Association of baseline NSAID use with baseline kidney function and albuminuria.

**Supplementary Table S4.** Test for interactions of NSAID use with heart failure, hypertension diagnosis, SBP greater than 140 mmHg, and ACE inhibitor or ARB use.

**Supplementary Table S5.** Association of NSAID use with annualized change in eGFR among 789 participants who were users of ACE inhibitors, angiotensin receptor blockers, or diuretics: overall and stratified by baseline kidney function.

**Supplementary Table S6.** Association of NSAID use with annualized change in eGFR: overall and stratified by hypertension diagnosis and systolic blood pressure.

**Supplementary Table S7.** Test for interactions of NSAID use with heart failure, hypertension, SBP greater than 140, and ACEi/ARB use.

**Supplementary Table S8.** Association of baseline prescription (Rx) and over-the-counter (OTC) NSAID use with markers of kidney function in cross-sectional analyses in 2,999 health ABC participants.

**Supplementary Table S9.** Association of baseline prescription (Rx) and over-the-counter (OTC) NSAID use with additional kidney tubule biomarkers in cross-sectional analyses in subcohort of 500 health ABC participants.

**Supplementary Table S10.** Association of prescription (Rx) and over-the-counter (OTC) NSAID use with annualized change in eGFR: overall and stratified by baseline kidney function.