Supplemental Methods:

Data sources:

We used Department of Veterans Affairs databases including inpatient and outpatient medical SAS datasets (that include utilization data related to all inpatient and outpatient encounters within the VA system) to ascertain detailed cohort participant's demographic characteristics and comorbidity information based on Current Procedural Terminology (CPT) codes, and ICD-9-CM diagnostic and procedure codes associated with inpatient and outpatient encounters. The VA Managerial Cost Accounting System Laboratory Results (a comprehensive database that includes VA-wide results for selected laboratory tests obtained in the clinical setting) provided information on outpatient serum creatinine, white blood cell count, and micro albumin/creatinine ratio. Corporate Data Warehouse (CDW) Patient Laboratory Chemistry data were used to obtain monocyte count information, and CDW Outpatient Pharmacy data provided information on angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), proton pump inhibitors (PPI), and nonsteroidal anti-inflammatory drugs (NSAID). The VA Vital Status and Beneficiary Identification Records Locator Subsystem (BIRLS) files provided demographic characteristics and death follow-up through September 30, 2013. United States Renal Data System (USRDS) data from the VA /Centers for Medicare and Medicaid Services (CMS) was used in assessing ESRD status.

Covariates:

Race/ethnicity was categorized as white, black, or other (Latino, Asian, Native American, or other racial/ethnic minority groups). eGFR was calculated using the abbreviated CKD-EPI equation(1). White blood cell count was assigned as the outpatient value closest and prior to T_0. Micro albumin/creatinine ratio (mg/g) was categorized into groups zero to less than 30, 30 to less than 300, and 300 or greater. Cohort participants were considered ACE/ARB, PPI, and NSAID users if the total days of prescription for the medication type before T_0 was greater than

or equal to 90. Covariates were treated as continuous variables where appropriate and unless otherwise specified. Comorbidities were assigned on the basis of relevant ICD-9-CM diagnostic and procedures codes and CPT codes in the VA Medical SAS datasets. ESRD for exclusion was defined as the first service date in the USRDS dataset or eGFR <15 ml/min/1.73m^2.

Spline analyses:

Cubic spline analyses -that allows for assessment of non-linear relationships of continuous monocyte count with outcomes - of the association between monocytes and renal outcomes were performed with knots placed at monocyte count quartile cutoffs and 0.4 k/cmm, the median monocyte count value of the lowest quartile, was used as the reference(2). In order to reduce the possibility of very high or very low monocyte counts influencing the spline function, those with monocyte values below the 2.5th percentile and above the 97.5th percentile were excluded from spline analyses. Cubic spline analyses were plotted with a monocyte probability distribution histogram.

Population Attributable Fraction:

Attributable fraction (AF) and Population attributable fraction (PAF) were calculated using piecewise constant hazard models for disease incidence(3). The PAF and AF for incidence of disease were obtained from the formula:

$$PAF(or\ AF)\left(T^D \le \min\left(T^M, a_J\right)\right) = 1 - \frac{\sum_{i=1}^{n}\sum_{j=1}^{J}\frac{\lambda_{ij}^{*D}}{\lambda_{ij}^{*D}+\lambda_{ij}^{*M}}\left(S_{i,j-1}^{*}-S_{ij}^{*}\right)}{\sum_{i=1}^{n}\sum_{j=1}^{J}\frac{\lambda_{ij}^{D}}{\lambda_{ij}^{D}+\lambda_{ij}^{M}}\left(S_{i,j-1}-S_{ij}\right)}$$

where D indicates disease, M mortality, n is the individuals in analysis, J the intervals, a_J the survival time, λ_{ij} the hazard of incident outcome for person i and interval j, * indicates the values

at the Theoretical Minimum Exposure Level (TMREL), and S the disease free survival from $S_{ij} = S_{ij}^{D} S_{ij}^{M} = e^{-\sum_{k=1}^{j}(\lambda_{ik}^{D}+\lambda_{ik}^{M})(a_k - a_{k-1})}$. For PAF n is the whole cohort, while for AF n is those who are exposed, in this case participants with a monocyte count in quartiles 2-4. The TMREL used was monocyte quartile 1.

Sensitivity Analyses:

We evaluated the consistency and robustness of study findings by performing a number of sensitivity analyses: a) considered chronic eGFR slope as an alternative outcome in multinomial logistic regression models; chronic eGFR slope captures longitudinal eGFR changes, and was categorized into 4 groups: positive slope, mild decline (eGFR slope 0 to -1 ml/min/1.73m^2/year); moderate decline (eGFR slope -1 to -5 ml/min/1.73m^2/year), and severe decline (eGFR slope <-5 ml/min/1.73m^2/year)(4-8); b) considered time until ESRD, dialysis, kidney transplant, or eGFR decline ≥50% as an another alternative outcome(9); c) accounted for variability in monocyte measurements by using the average monocyte count in those with more than one monocyte count measure before T_0 (n=225,228); d) assessed potential effects on the hazard ratios for monocyte count quartile by treating the censoring of ESRD, dialysis, and kidney transplant as informative(10); e) conducted bias analyses for uncontrolled confounder using the probabilistic approach through Monte-Carlo sensitivity analysis, basing bias parameters on microalbumin/creatinine ratio data for those who had measurements (n=113,596)(30-32); f) examined the association between monocyte count categorized in deciles and renal outcomes; g) examined the association between monocyte count grouped into ordinal categories of 0.1 (k/cmm) increasing values: ≤0.3, >0.3 to 0.4, >0.4 to 0.5, >0.5 to 0.6, >0.6 to 0.7, >0.7 to 0.8, and >0.8 (k/cmm) and renal outcomes; and h) additionally controlled for ACE/ARB, PPI, and NSAID use.

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