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Clonal Hematopoiesis of Indeterminate Potential and Kidney Function Decline in the General Population

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Abstract

Rationale and Objective: Clonal hematopoiesis of indeterminate potential (CHIP), defined by the age-related ontogenesis of expanded leukemogenic mutations indicative of a genetically distinct clonal leukocyte population, is associated with risk of hematologic malignancy and cardiovascular disease. In experimental models, recapitulation of CHIP promotes kidney interstitial fibrosis with direct tissue infiltration of donor macrophages. We tested the hypothesis that CHIP is associated with kidney function decline in the general population.

Study Design: Cohort Study.

Setting and Participants: 12,004 individuals from three community-based cohorts in the TOPMed Consortium.

Exposure: CHIP status from blood DNA-derived whole genome sequences.

Outcome: Risk of 30% decline in estimated glomerular filtration rate (eGFR) and percent eGFR decline per year during follow-up.

Analytical approach: Cox proportional hazards models for 30% eGFR decline endpoint and generalized estimating equations for annualized relative change in eGFR with meta-analysis. Study-specific estimates were combined using fixed-effect meta-analysis.

Results: Median baseline eGFR was 84 ml/min/1.73m^2. Prevalence of CHIP was 6.6%, 9.0% and 12.2% in persons 50–60, 60–70 and >70 years old, respectively. Over a median follow-up of 8 years, 205 kidney function decline events occurred among 1,002 CHIP carriers (2.1 events per 100-person-years), and 2,041 kidney function decline events in persons without CHIP (1.7 events per 100-person-years). In meta-analysis, CHIP was associated with kidney function decline (17% higher risk; 95%CI: 1% to 36% higher; p-value=0.036). Differences were not observed between those with baseline eGFR above or below 60 ml/min/1.73m^2, age above or below 60 years, or with or without diabetes.

Limitations: Small number of participants with moderate-to-advanced kidney disease and restricted set of CHIP driver mutations.

Conclusions: We report an association between CHIP and kidney function decline in three general population cohorts without known kidney disease. Further studies are needed to investigate this novel condition and its potential impact among individuals with overt kidney disease.

INTRODUCTION

Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related disorder among asymptomatic adults defined by the ontogenesis of leukemogenic mutations in blood DNA indicative of a genetically distinct clonal leukocyte population.[1,2] CHIP is caused by somatic mutations within a restricted set of cancer driver genes in hematopoietic stem cells (primarily *DNMT3A, TET2, ASXL1, JAK2*, and *TP53*).[1] The resulting progeny propagate through the hematopoietic system to produce a resilient clonal population with a selective survival advantage. By definition, CHIP is not overtly malignant; however, clonal leukocytes harboring CHIP mutations increase the risk of future hematologic malignancy presumably through a second genetic hit.[3] In addition to cancer, CHIP is also associated with cardiovascular diseases, including myocardial infarction, stroke, and heart failure.[4–8] In murine models, Tet2-deficient hematopoietic stem cells accelerate atherogenesis and promote cardiac and kidney interstitial fibrosis with direct tissue infiltration of donor macrophages.[4,9–11]

Kidney function declines progressively with aging. The rate of decline is variable across individuals and is associated with multiple risk factors including hypertension, diabetes, and inflammatory markers.[12,13] The pathologic hallmark of progressive chronic kidney disease (CKD) is tubulointerstitial fibrosis, which is characterized by the accumulation of inflammatory infiltrates and fibroblasts within the kidney interstitium and permanent loss of tubular epithelial cells.

Given mechanistic links connecting CHIP with both atherosclerosis and tubulointerstitial fibrosis, we hypothesized that CHIP would be associated with greater kidney function decline compared to those without CHIP in the general population. To test this hypothesis, we ascertained CHIP status of 12,004 individuals from three community-based cohort studies, and we delineated associations with the decline in the estimated glomerular filtration rate (eGFR) over follow-up.

METHODS

Study Populations

The NHLBI Trans-Omics for Precision Medicine (TOPMed) program was designed to facilitate research in precision medicine by integrating whole-genome genetic sequencing and molecular data across established epidemiology studies.[14] For the current analysis, we studied participants from three community-based cohort studies in the freeze 8 release of TOPMed. Included studies were the Atherosclerosis Risk in Communities Study (ARIC, n=6,575)[15], the Cardiovascular Health Study (CHS, n=1,701)[16], and the Multi-Ethnic Study of Atherosclerosis (MESA, n=3,728)[17]. We selected participants who were ≥50 years old due to the rarity of CHIP in younger persons; additional inclusion criteria were valid ascertainment of CHIP status from the TOPMed genomic data and at least two longitudinal measurements of serum creatinine to assess changes in kidney function. Participants provided written consent per each study's IRB approved protocol.

Ascertainment of CHIP

We obtained CHIP genotypes from TOPMed blood DNA-derived whole genome sequences generated using GATK MuTect2, as previously described.[2,18] Several quality control steps were applied to identify and remove sequencing artifacts and germline mutations from the call set.[2] At present, a universal standard for CHIP driver variants definition does not exist. However, many groups, including ours, employ the criteria defined by Jaiswal et al in their seminal work describing CHIP.[4] Samples were assigned CHIP carriers status were identified based on the presence a leukemogenic driver mutation at variant allele frequency (VAF) > 2% in 74 pre-specified genes known to promote clonal expansion of hematopoietic stem cells (see Supplemental Table 1). For 23 of these genes, only truncating (frameshifting/nonsense/splicing) variants are permitted; for another 26, only select missense variants are permitted (mostly gain-of-function); and for the remaining 25 genes, truncating and select missense variants are permitted. These gene-specific criteria were curated to minimize the number of germline and passenger variants as well as sequencing artefacts. Median VAF for CHIP carriers was 16%. To test for associations between clonal hematopoiesis due to specific mutations and kidney disease progression, in secondary analyses we categorized CHIP driver gene mutations into those in *DNMT3A* (the most common driver gene) and those not in *DNMT3A*.

Ascertainment of kidney function decline and microalbuminuria

We estimated the eGFR at each study visit from serum creatinine concentrations, age, and sex using the 3-variable 2021 CKD-EPI equation.[19] We defined kidney function decline as a ≥30% decrease in eGFR from the baseline value.[20] This definition was selected to balance a clinically meaningful change in kidney function with sufficient numbers of events for analysis. Moreover, relative changes in eGFR are less dependent on the baseline value than absolute changes. As secondary outcomes, we assessed a ≥40% decline in eGFR, the percent eGFR decline per year over follow-up and incident eGFR <60 ml/min/1.73m^2.[21] We defined microalbuminuria by a spot urine albumin to creatinine ratio ≥30 mg/g.[22–25]

Statistical Analysis

We tabulated baseline characteristics within each study according to CHIP status. We estimated cross-sectional associations of CHIP with baseline eGFR and microalbuminuria using linear, binary, and multinomial logistic regression with age adjustment and internal standardization. We constructed Cox proportional hazards models to delineate associations of CHIP status at baseline with the first occurrence of a ≥30% decline in eGFR from the baseline value in each study cohort. Participants were censored due to death, loss to follow-up, or the end of the study data collection period, whichever came first. Regression models were adjusted for age, age-squared, sex, baseline eGFR, self-reported race, and diabetes. Models in CHS and MESA additionally adjusted for log-transformed urine albumin to creatinine ratio (uACR). Urine albumin to creatinine ratio was not measured concomitantly with CHIP in the ARIC study. Study-specific hazard ratios were combined using fixed-effect meta-analysis. For secondary analyses of annualized relative change in log(eGFR), we used a mixed effects model with random intercept with adjustment for age, age-squared, sex, self-reported race, diabetes and log-transformed uACR. We tested for multiplicative

interactions by age, baseline eGFR and baseline diabetes using a Wald test on the product term. Analyses were conducted using Stata 17 (College Station, TX).

RESULTS

The mean age was 57 ±4 years in the ARIC cohort, 72 ±5 years in CHS, and 64 ±8 years in MESA. The median baseline eGFR among all cohorts was 84 ±6 ml/min/1.73m^2; 7.3% of participants had a baseline eGFR <60 ml/min/1.73m^2. The prevalence of CHIP across all study cohorts was 6.6% in persons 50–60 years old, 9.0% in persons 60–70 years old, and 12.2% in persons greater than 70 years of age. The prevalence of CHIP was similar among men and women and in participants with and without diabetes (Table 1).

After age adjustment, the percentage of participants with a baseline eGFR <45, 45–59, and ≥60 ml/min/1.73m^2 was similar by CHIP status (Figure 1, left panel). The presence of CHIP was not associated with baseline prevalent CKD after adjustment for age and age-squared (13% higher odds, 95% CI 10% lower to 42% higher; p-value = 0.27). Age-adjusted rates of microalbuminuria were 12.5% in participants with CHIP and 10.6% in participants without CHIP (Figure 1, right panel). The presence of CHIP was associated with a 17% higher urine albumin to creatinine ratio after age-adjustment (95% CI 3% to 33% higher; p-value = 0.02).

Median follow-up was 9 years in ARIC, 7 years in CHS, and 9 years in MESA (Table 2). The median number of eGFR measurements in these studies ranged from 2–4. There were 205 kidney function decline events over follow-up in persons with CHIP (2.1 events per 100-person years), and 2,041 kidney function decline events in persons without CHIP (1.7 events per 100-person years). In meta-analysis, the presence of CHIP at baseline was associated with a 17% greater risk of kidney function decline (Table 2; 95% CI 1% to 36% greater), after adjustment for baseline age, age-squared, sex, eGFR, uACR and diabetes (Figure 1). After adjustment for the same covariates, CHIP was not associated with the outcome of a 40% decline in eGFR (Supplemental Table 2), nor with incident eGFR<60 ml/min/1.73m^2 (Supplemental Table 3). The least-squares mean slope of eGFR decline was −1.14 ml/min/1.73m^2 per year in persons with CHIP and −1.15 ml/min/1.73m^2 per year in persons without CHIP (Table 3). After adjustment, there was no significant difference in the slope of eGFR by CHIP status.

The size of the association between CHIP and kidney function decline was similar among *DNMT3A* and non-*DNMT3A* gene driver mutations (Figure 2, Supplemental Tables 4,5). Associations were also similar among participants with an eGFR<60 versus > 60 min/1.73m^2 at baseline, and those aged<60 versus >60 years at baseline (Figure 2, Supplemental Tables 6–9). These distinctions were not statistically significant (p-values for interactions > 0.5).

DISCUSSION

In this study, we assessed the association between clonal hematopoiesis and kidney function decline and found CHIP was associated with 17% higher risk of eGFR decline among adults with relatively intact kidney function. We observed non-significant results for outcomes of a 40% eGFR decline, incident eGFR<60ml/min/1.73m^2 and continuous

slope of decline. Heterogeneity in the results was seen across the studies with numerically positive associations in the ARIC and CHS cohorts and null results in MESA. Taken together, these findings provide evidence for a link between CHIP and kidney function decline in the general population. However, wide confidence limits, low CHIP prevalence, and inherent methodologic limitations of these cohorts for assessing longitudinal changes in kidney function leave residual uncertainty regarding the potential kidney consequences of CHIP and support further studies of this question. Three previous studies have examined the association of CHIP and kidney function in humans, with conflicting results. Among 190,487 participants in the UK Biobank, individuals with myeloid clonal hematopoiesis had lower eGFR – as estimated from cystatin but not from creatinine.[26] Among those with CKD, CHIP was associated with higher odds of cardiovascular events and death.[26] In a small study of patients with advanced CKD, Vlasschaert et al reported a high prevalence of CHIP (25%) and that those with the condition had a 2.2-fold greater risk of kidney failure within 5 years.[27] In contrast, a recent study of individuals with diabetic kidney disease found no association of CHIP with incident or progressive decline in kidney function.[28]

Evidence from animal models also suggests that clonal hematopoiesis could plausibly contribute to kidney function decline. In hypercholesterolemic mice, transplantation of hematopoietic stem cells genetically deficient for *Tet2*, one of the most commonly altered genes in CHIP, leads to accelerated age-related glomerulosclerosis.[4] Transplantation of *Tet2*-deficient hematopoietic stem cells results in rapid infiltration of Tet2-deficient donor cells into the kidney interstitium, replacement of resident macrophages, and accelerated interstitial fibrosis.[11] Moreover, transplantation of *Tet2*-deficient hematopoietic stem cells leads to the expansion of atherosclerotic plaque size and stimulation of pro-inflammatory cytokines; these experimental results are corroborated by associations of CHIP with incident cardiovascular events in human populations.[4,5]

It is possible that CHIP accelerates kidney function decline in persons with established kidney disease but has smaller effects on kidney function in the absence of pre-existing disease or injury. We did not detect significant differences in the size of the association between CHIP and eGFR decline among participants with a baseline eGFR <60 versus ≥60 ml/min/1.73m^2.

However, the number of participants with CKD, particularly moderate-advanced disease, was too small to reliably address this question, motivating future studies in kidney disease populations.

It is also possible that the study lacked sensitivity for detecting a true association between CHIP and kidney function decline. The included cohorts included relatively few serum creatinine measurements over time, reducing precision and increasing the possibility for differential censoring. Most serum creatinine measurements were within the normal range, in which GFR estimating equations are least precise. The number of participants with CHIP who experienced a 30% decline in eGFR was relatively small, contributing to the wide confidence limits. Larger declines in eGFR are clinically meaningful and used as outcomes in randomized trials; however, such declines were rare in this study population.

In summary, we detected an association between CHIP and kidney function decline in three general population cohorts without known kidney disease. Further studies are needed to investigate this novel condition and its potential impact on kidney disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Support:

Whole genome sequencing (WGS) for the Trans-Omics in Precision Medicine (TOPMed) program was supported by the National Heart, Lung and Blood Institute (NHLBI). Genome sequencing for “NHLBI TOPMed: Whole Genome Sequencing and Related Phenotypes in the Framingham Heart Study” (phs000974.v1.p1) was performed at the Broad Institute Genomics Platform (3R01HL092577-06S1, 3U54HG003067-12S2). Genome sequencing for “NHLBI TOPMed: the Atherosclerosis Risk in Communities Study” (phs001211.v1.p1) was performed at the Broad Institute Genomics Platform (3U54HG003273-12S2, HHSN268201500015C, 3R01HL092577-06S1). Genome sequencing for “NHLBI TOPMed: the Multi-Ethnic Study of Atherosclerosis” (phs001416.v1.p1) was performed at the Broad Institute Genomics Platform (HHSN268201600034I, 3U54HG003067-13S1). Genome sequencing for “NHLBI TOPMed: the Cardiovascular Health Study” (phs001368.v1.p1) was performed at the Broad Institute Genomics Platform (HHSN268201600034I) and Baylor College of Medicine Human Genome Sequencing Center (HHSN268201600033I). Centralized read mapping and genotype calling, along with variant quality metrics and filtering were provided by the TOPMed Informatics Research Center (3R01HL-117626-02S1; contract HHSN268201800002I). Phenotype harmonization, data management, sample-identity QC, and general study coordination were provided by the TOPMed Data Coordinating Center (3R01HL-120393-02S1; contract HHSN268201800001I). We gratefully acknowledge the studies and participants who provided biological samples and data for TOPMed. PN is supported by grants from the National, Heart, Lung, and Blood Institute (R01HL142711, R01HL148050, R01HL151283, R01HL148565, R01HL135242, R01HL151152), National Institute of Diabetes and Digestive and Kidney Diseases (R01DK125782), Fondation Leducq (TNE-18CVD04), and Massachusetts General Hospital (Paul and Phyllis Fireman Endowed Chair in Vascular Medicine).

Data Sharing:

Individual whole-genome sequence data for TOPMed whole genomes, individual-level harmonized phenotypes, harmonized germline variant call sets, the CHIP somatic variant call sets, RNA-Seq and peripheral blood methylation data used in this analysis are available through restricted access via the dbGaP.

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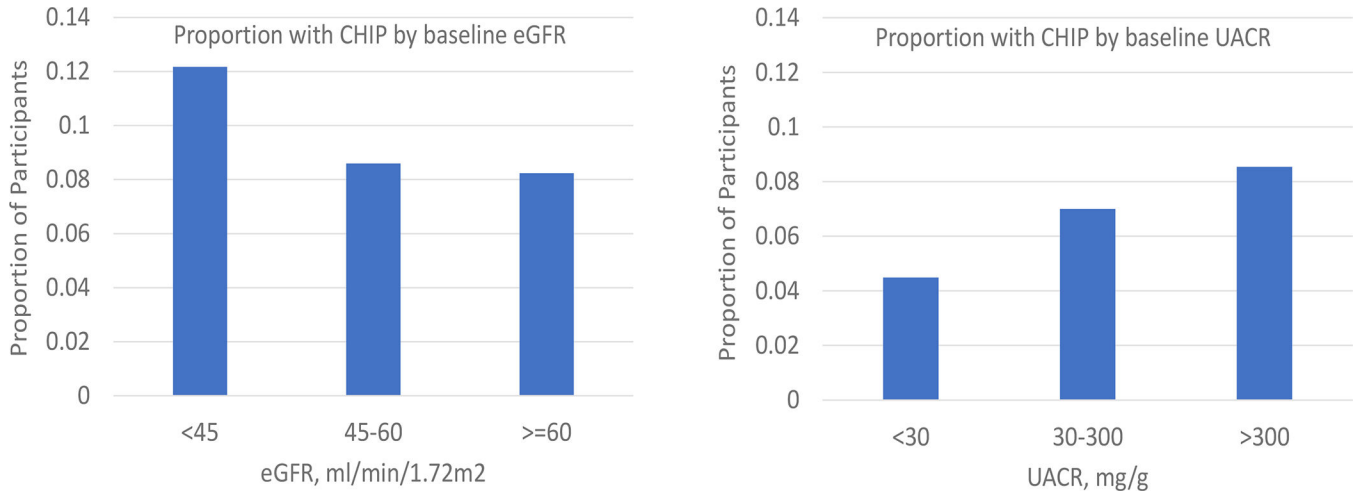

Figure 1. Age-adjusted associations of CHIP with baseline eGFR and microalbuminuria categories.

Y-axis depicts the age-adjusted (age and age-squared) proportions of participants with CHIP within each category of baseline eGFR <45, 45–59, and ≥60 ml/min/1.73m^2 and within each category of baseline albumin-to-creatinine ratio <30, 30–300 and >300mg/g. Urine albumin-to-creatinine ratio was not concomitantly measured with CHIP in the ARIC Study and was not included in the estimates. Age-adjusted estimates were determined using Poisson regression. CHIP = Clonal hematopoiesis of Indeterminate Potential, eGFR = estimated glomerular filtration rate, uACR = urine albumin-to-creatinine ratio.

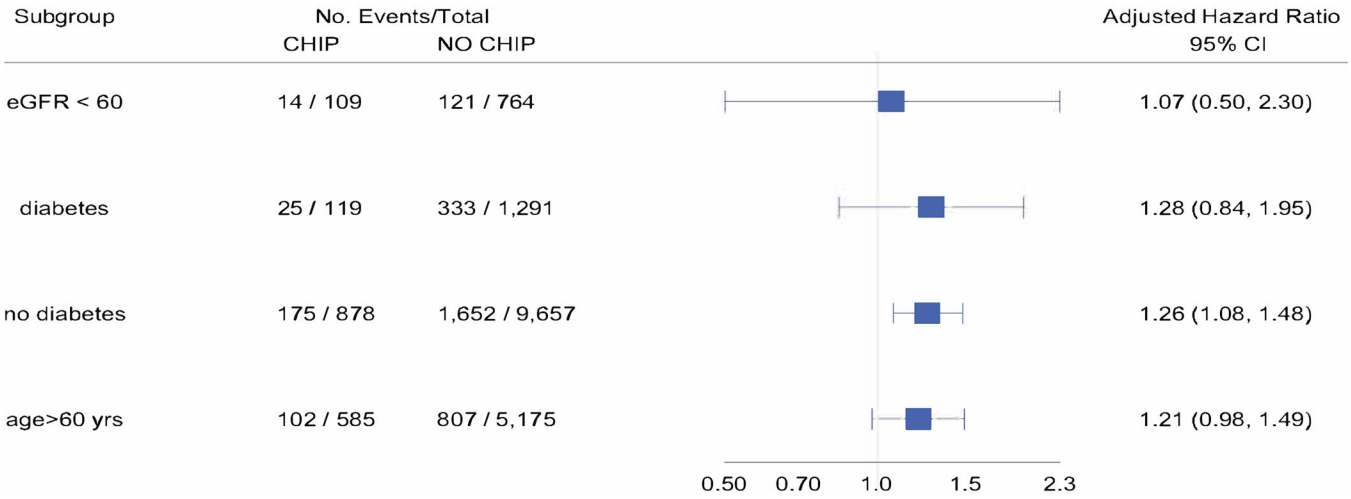

Figure 2. Associations of CHIP with 30% decline in eGFR among subgroups of interest.

Forest plot of adjusted hazard ratio for association of CHIP with 30% decline in eGFR (meta-analysis of ARIC, CHS and MESA) among 1) individuals with eGFR<60ml/min/1.73m^2 at baseline, 2) diabetes at baseline, 3) no diabetes at baseline and age >60 years at baseline. Adjusted for age, age-squared, sex, baseline eGFR, diabetes, and log-urine albumin to creatinine ratio (where available at baseline).CHIP = Clonal hematopoiesis of Indeterminate Potential, eGFR = estimated glomerular filtration rate.

Table 1.

Baseline Characteristics of Study Populations

	Atherosclerosis Risk in Communities Study (n=6,575)		Cardiovascular Health Study (n=1,701)		Multi-Ethnic Study of Atherosclerosis (n=3,728)	
CHIP status	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
N	584	5,991	240	1,461	178	3550
Age, years	58 (4)	58 (4)	74 (5)	73 (5)	68 (8)	64 (8)
Male Sex, n(%)	295 (50)	2,789 (46)	113 (47)	626 (43)	83 (46)	1728 (48)
Race/ethnicity, n(%)						
White	489 (84)	4,895 (82)	205 (85)	1,223 (84)	85 (48)	1462 (42)
Black	95 (16)	1095 (19)	35 (15)	238 (16)	44 (24)	851 (24)
Chinese	-	-	-	-	14 (8)	473 (14)
Hispanic	-	-	-	-	35 (20)	764 (22)
Diabetes, n(%)	64 (10)	650 (11)	33 (14)	222 (15)	22 (12)	428 (12)
BMI, kg/m^2	28 (6)	28 (6)	26 (4)	26 (4)	28 (6)	28 (6)
eGFR, $ml/min/1.73m^2$	98 (14)	100 (12)	69 (16)	71 (16)	76 (14)	80 (14)
Urine albumin-to-creatinine ratio, mg/g	-	-	9 (6, 24)	9 (5, 21)	6 (3, 12)	6 (3, 12)
Microalbuminuria, n(%)	49 (10)	437 (8)	35 (15)	223 (15)	27 (16)	293 (8)

Table 2.

Associations of Clonal Hematopoiesis of Indeterminate Potential with 30% Decline in eGFR.

	CHIP	Number of participants	Number of eGFRs (IQR)	Median follow-up time, years (IQR)	Number of events	Incidence per 100 person-years	Unadjusted HR (95% CI)	Adjusted* HR (95%CI)
ARIC	Yes	584	3 (3,4)	9 (8,22)	143	2.20	1.23 (1.04,1.46)	1.20 (1.01, 1.43)
	No	5,991	3 (3,4)	9 (8,23)	1,392	1.94	*reference*	*reference*
CHS	Yes	240	3 (2,3)	7 (3,7)	40	2.14	1.48 (1.02, 2.13)	1.38 (0.92, 2.06)
	No	1,461	3 (2,3)	7 (4,7)	216	1.53	*reference*	*reference*
MESA	Yes	178	4 (4, 4)	9 (9, 10)	22	1.44	0.99 (0.64, 1.52)	0.85 (0.55, 1.30)
	No	3,550	4 (4, 4)	9 (9, 10)	433	1.39	*reference*	*reference*
Meta-Analysis	Yes	1,002	3 (3,4)	8 (7, 14)	205	2.05	1.24 (1.07, 1.43)	1.17 (1.01, 1.36)
	No	11,002	3 (3,4)	8 (7, 15)	2,041	1.71	*reference*	*reference*
							p = 0.004	p = 0.036

ARIC = Atherosclerosis Risk in Communities Study; CHS = Cardiovascular Health Study; MESA = Multi-Ethnic Study of Atherosclerosis; CHIP = Clonal hematopoiesis of indeterminate potential; eGFR = estimated glomerular filtration rate.

*Adjusted for age, age-squared, sex, baseline eGFR, diabetes, and log-urine albumin to creatinine ratio (where available at baseline).

Table 3.

Associations of Clonal Hematopoiesis of Indeterminate Potential with Longitudinal Change in eGFR.

Cohort	CHIP	Number of participants	Number of eGFRs	Follow up time, years median (IQR)	Percent eGFR decline per year	Adjusted* difference (95% CI), %/year	Absolute eGFR decline per year	Adjusted* difference (95% CI), ml/min/ 1.73m^2/year
ARIC	Yes	584	3 (3,4)	9 (8,22)	−2.30 (3.08)	−0.25 (−0.51, 0.01)	−1.87 (2.30)	−0.17 (−0.34, −0.01)
	No	5,991	3 (3,4)	9 (8,23)	−2.02 (2.80)	*reference*	−1.69 (2.06)	*reference*
CHS	Yes	240	3 (2,3)	7 (3,7)	−0.98 (4.60)	−0.13 (−0.60, 0.35)	−0.57 (2.67)	−0.09 (−0.39, 0.20)
	No	1,461	3 (2,3)	7 (4,8)	−0.85 (3.89)	*reference*	−0.47 (2.29)	*reference*
MESA	Yes	178	4 (4, 4)	9 (9, 10)	−1.60 (2.60)	0.36 (−0.01, 0.74)	−1.03 (1.44)	0.22 (0.01, 0.44)
	No	3,550	4 (4, 4)	9 (9, 10)	−1.71 (2.44)	*reference*	−1.16 (1.49)	*reference*
Meta-Analysis	Yes	1,002	3 (3,4)	9 (7, 16)	−1.75 (1.82)	−0.02 (−0.40, 0.36)	−1.14 (1.11)	−0.02 (−0.26, 0.23)
	No	11,002	3 (3,4)	9 (8, 17)	−1.66 (1.66)	*reference*	−1.15 (1.07)	*reference*
						p = 0.934		p = 0.906

ARIC = Atherosclerosis Risk in Communities Study; CHS = Cardiovascular Health Study; MESA = Multi-Ethnic Study of Atherosclerosis; CHIP = Clonal hematopoiesis of indeterminate potential; eGFR = estimated glomerular filtration rate.

*Adjusted for age, age-squared, sex, baseline eGFR, diabetes, and log-urine albumin to creatinine ratio (where available at baseline).

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