HHS Public Access

Author manuscript

J Am Coll Cardiol. Author manuscript; available in PMC 2022 July 06.

Published in final edited form as:

J Am Coll Cardiol. 2021 July 06; 78(1): 42–52. doi:10.1016/j.jacc.2021.04.085.

Association of Clonal Hematopoiesis with Incident Heart Failure

Bing Yu, PhD[a], **Mary B. Roberts, MS**[b], **Laura M. Raffield, PhD**[c], **Seyedeh Maryam Zekavat, BS**[d,e], **Ngoc Quynh H. Nguyen, MS**[a], **Mary Lou Biggs, PhD**[f], **Michael R. Brown, MS**[a], **Gabriel Griffin, MD**[e], **Pinkal Desai, MD**[g], **Adolfo Correa, MD**[h], **Alanna C. Morrison, PhD**[a], **Amil M. Shah, MD**[i], **Abhishek Niroula, PhD**[e,j,k], **Md Mesbah Uddin, PhD**[l], **Michael C. Honigberg, MD, MPP**[e,m,n], **Benjamin L. Ebert, MD, PhD**[j,m,o], **Bruce M. Psaty, MD, PhD**[p], **Eric A. Whitsel, MD, MPH**[q], **JoAnn E. Manson, MD, DrPH**[m,r], **Charles Kooperberg, PhD**[s], **Alexander G. Bick, MD, PhD**[t], **Christie M. Ballantyne, MD**[u], **NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium**, **Alex P. Reiner, MD**[s], **Pradeep Natarajan, MD, MMSc**[m,n,v,*], **Charles B. Eaton, MD, MS**[w,x,y,*]

[a]School of Public Health, The University of Texas Health Science Center at Houston, Houston, Texas [b]Center for Primary Care and Prevention, Brown University, Pawtucket, Rhode Island [c]Department of Genetics, University of North Carolina, Chapel Hill, North Carolina [d]Yale School of Medicine, New Haven, Connecticut [e]Broad Institute of Harvard and MIT, Cambridge, Massachusetts [f]Department of Biostatistics, University of Washington, Seattle, Washington [g]Division of Hematology and Oncology, Weill Cornell Medical College, New York, New York [h]Department of Pediatric and Medicine, University of Mississippi Medical Center, Jackson, Mississippi [i]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts [j]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts [k]Department of Laboratory Medicine, Lund University, Lund, Sweden [l]Program in Medical and Population Genetics and the Cardiovascular Disease Initiative, Broad Institute of Harvard and MIT, Cambridge, Massachusetts [m]Harvard Medical School, Boston, Massachusetts [n]Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts [o]Howard Hughes Medical Institute, Dana-Farber Cancer Institute, Boston, Massachusetts [p]Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, Washington [q]Department of Epidemiology, Gillings School of Global Public Health and Department of Medicine, School of Medicine, University of North Carolina, Chapel Hill, North Carolina [r]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts [s]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington [t]Division of Genetic Medicine, Department of Medicine, Vanderbilt University School of Medicine, Nashville,

Correspondence: Pradeep Natarajan MD, MMSc, 185 Cambridge Street, CPZN 3.184, Boston, MA 02114, Tel: 617-726-1843, Fax: 617-726-2203, pnatarajan@mgh.harvard.edu, Twitter: @pnatarajanmd, Charles B. Eaton MD, MS, 111 Brewster Street, Pawtucket, RI 02860, Tel: 978-790-0462, Fax401-729-2856, cbeaton51@gmail.com, @pnatarajanmd.

*Jointly supervised

Tweet: Presence of age-related clonal hematopoiesis was associated with a 25% increased risk of heart failure in large prospective cohort studies with up to 56,597 individuals.

Tennessee [u]Section of Cardiovascular Research, Department of Medicine, Baylor College of Medicine, Houston, Texas [v]Cardiovascular Disease Initiative of the Broad Institute of Harvard and MIT, Cambridge, Massachusetts [w]Department of Epidemiology, Brown University, Providence, Rhode Island [x]Care New England, Center for Primary Care and Prevention, Pawtucket, Rhode Island [y]Department of Family Medicine, Warren Alpert Medical School of Brown University, Providence, Rhode Island

Abstract

Background: Age-related clonal hematopoiesis of indeterminate potential (CHIP), defined as clonally expanded leukemogenic mutations (particularly in *DNMT3A*, *TET2*, *ASXL1*, *JAK2*) in asymptomatic individuals, is associated with cardiovascular events, including recurrent heart failure (HF).

Objectives: We sought to evaluate whether CHIP is associated with incident HF.

Methods: We obtained CHIP status from whole exome or genome sequencing of blood DNA in participants without prevalent HF or hematologic malignancy from five cohorts. Cox proportional hazards models were performed within each cohort, adjusting for demographic and clinical risk factors, followed by fixed-effect meta-analyses. Large CHIP clones (defined as variant allele frequency >10%), HF with or without baseline coronary heart disease (CHD), and left ventricular ejection fraction (LVEF) were evaluated in secondary analyses.

Results: Of 56,597 individuals (59% female, mean age 58 years at baseline), 3,406 (6%) had CHIP, and 4,694 developed HF (8.3%) over up to 20 years of follow up. CHIP was prospectively associated with a 25% increased risk of HF in meta-analysis (HR= 1.25, 95% CI 1.13, 1.38) with consistent associations across cohorts. *ASXL1*, *TET2*, and *JAK2* mutations were each associated with an increased risk of HF, whereas *DNMT3A* mutations were not associated with HF. Secondary analyses suggested large CHIP was associated with a greater risk of HF (HR=1.29, 95% CI 1.15, 1.44), and the associations for CHIP on HF with and without prior CHD were homogenous. *ASXL1* mutations were associated with reduced LVEF.

Conclusion: CHIP, particularly mutations in *ASXL1*, *TET2*, and *JAK2,* represents a new risk factor for HF.

Clonal hematopoiesis of indeterminate potential (CHIP) in asymptomatic individuals is associated with cardiovascular events, including recurrent heart failure (HF). We obtained CHIP status from five cohorts and evaluated whether CHIP was associated with incident HF. Of 56,597 individuals, 3,406 had CHIP, and 4,694 developed HF over 20 years of follow up. CHIP was associated with a 25% increased risk of HF. *ASXL1*, *TET2*, and *JAK2* were each associated with an increased risk of HF. Large CHIP was suggested to have a greater risk of HF. CHIP, particularly mutations in *ASXL1*, *TET2*, and *JAK2*, represents a new risk factor for HF.

Keywords

clonal hematopoiesis of indeterminate potential; heart failure; risk factor

Introduction

Heart failure (HF) is a leading cause of death in the elderly (1). Lifetime risk for HF is 1 in 5, and HF is associated with short-term mortality rates exceeding those of many cancers in western countries (2,3). Coronary heart disease (CHD), along with hypertension, atrial fibrillation, and chronic kidney disease, are all risk factors for incident HF and strongly associated with aging. Age remains the strongest independent predictor for HF, but the age-related factors promoting HF development are incompletely understood.

Recent genetic analyses of large asymptomatic populations have revealed that somatic mutations (most often in *DMNT3A*, *TET2*, *ASXL1*, and *JAK2*) in hematopoietic cells leading to clonal expansion are commonly acquired during human aging (4,5). Clonally restricted hematopoiesis with cytopenias and dysplastic morphology of blood and marrow cells are associated with subsequent diagnosis of hematologic malignancies and increased risk of all-cause mortality (6). However, most individuals with clonal hematopoiesis detected in peripheral blood do not have cytopenia, dysplasia, or neoplasia, a phenomenon termed clonal hematopoiesis of indeterminate potential (CHIP) (6,7). The prevalence of CHIP increases with age; the frequency is low (<0.5%) from birth until 50 years of age after which it rises rapidly, affecting 10–20% of persons aged 70 to 80 years (4,5). There is increasing evidence that individuals with CHIP are at increased risk of incident atherosclerotic cardiovascular disease (CVD) events, including CHD, stroke and CVD-related mortality (8–13). Data from humans and experimental models relating CHIP somatic mutations to CVD have implicated altered immune cell function and pro-inflammatory cytokines (11,14–18).

Recently in a cohort of patients with HF, Dorsheimer et al found during 4.4 years of median follow-up, those with either *TET2* or *DNMT3A* mutations had increased risk of death or HF hospitalization (HR=2.1, 95% CI 1.1–4.0) (19). Murine models with hematopoietic or myeloid-specific deficiency of *Tet2* or with myeloid-specific transgenic $Jak2^{V617F}$ are more prone to cardiac dysfunction after coronary artery ligation-induced myocardial infarction or aortic constriction-induced pressure overload (20–22). Therefore, we tested the hypothesis that CHIP driver mutations are associated with incident HF in four cohorts from the NHLBI Trans-Omics for Precision Medicine (TOPMed) Program and the United Kingdom Biobank (UKBB) study.

Methods

Study Populations

Participants from five population-based cohorts, the Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study (CHS), Jackson Heart Study (JHS), UKBB, and the Women's Health Initiative (WHI) with data on HF outcomes and baseline CVD risk factors and other covariates were included the analysis. For the current analysis, we excluded participants who were not followed for HF adjudication, those who had a history of HF at enrollment, incident HF prior to blood draw, or insufficient CHIP data quality or missing covariates from each participating study. The final study population consisted of 56,597 self-identified Black, White, and Hispanic individuals. Detailed descriptions of each cohort are provided in the Supplemental Methods. The Institutional Review Board at each participating

institution approved the studies and participants from each study provided written informed consent.

Exposure

For CHS, JHS and WHI, CHIP was determined at the Broad Institute (Cambridge, MA) via whole genome sequencing (WGS) of blood DNA using the GATK MuTect2 (23) somatic variant caller through the NHLBI TOPMed project on the basis of 74 pre-specified driver mutations in genes known to promote clonal expansion of hematopoietic stem cells using a conventional variant allele frequency (VAF) of >2% as previously described (11,15). For ARIC and UKBB, CHIP was determined at the Broad Institute (Cambridge, MA) via whole exome sequencing (WES) using same calling algorithm described above as previously described (14). Detailed sequencing and variant calling are provided in the Supplemental Methods. CHIP was defined by the presence of somatic variants in genes previously implicated in hematologic cancers with a VAF >2% but without hematologic cancer or other non-neoplastic clonal disease (6). For secondary analyses, VAF >10% was used to define high-VAF CHIP.

Outcomes

All five studies used trained physician adjudicators, hospitalization records and/or International Classification of Disease (ICD) codes to verify HF events and time to event or last follow-up. Incident HF was defined as the occurrence of HF after the visit when DNA was drawn with physician adjudication and/or ICD 9 discharge or a death certificate with code 428, or ICD 10 with code I50. Details for each study are provided in the Supplementary Methods. Secondary analyses were performed to evaluate associations between CHIP and HF with or without prior CHD as defined by self-report or ICD code at baseline or incident adjudicated CHD prior to HF.

The cross-sectional association of CHIP with left ventricular ejection fraction (LVEF) from cardiac MRI data was evaluated in the UKBB in 4,122 individuals with cardiac MRI data. Only CHIP ascertained using blood sample collected at baseline visit, the same visit that LVEF was measured, were included. The UKBB performed 20-min scans using a 1.5T scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany) and used these scans to provide automated estimates of LVEF (24). LVEF extreme outliers were determined and filtered by adjusting the traditional box and whisker upper and lower bounds and accounting for skewness in the phenotypic data identified using the Robustbase package in R (setting range=3), as previously done for other phenotypes in the UKBB (25,26).

Covariates

Covariates were included at the time of blood draw. For analyses with incident HF, age at blood draw, sex, smoking status, prevalent diabetes mellitus, stroke, CHD, body mass index (BMI), systolic blood pressure (SBP), socioeconomic status, and self-reported race were adjusted for as potential confounders Cigarette smoking status was categorized as never, past, and current. In ARIC, CHS, JHS and WHI, a history of hypertension, diabetes mellitus, stroke, or CHD was either defined by self-reported history of physician diagnosis or

adjudicated outcomes prior to CHIP determination. BMI (kg/m^2) was based upon clinic exams of measured height and weight at the baseline study visit. SBP (mmHg) was measured using standard procedures during baseline clinical exams. In UKBB, history of type 2 diabetes mellitus, stroke, and CHD were identified by a combination of self-report and ICD codes as detailed in Supplemental Table 1. SBP was adjusted by adding 15 mmHg for antihypertensive medication users as previously done (26). Detailed socioeconomic status measures are provided in the Supplemental Methods.

Statistical methods

Cox proportional hazards model were fitted with adjustment for age, sex, education, diabetes mellitus, smoking status (never, past, current), stroke, coronary heart disease, SBP, antihypertensive medication use, BMI, and race (if more than one). Schoenfeld residual plots were generated to assess the proportional hazards assumption. We did not observe any pattern with time from the graphical inspection, indicating no violation of proportionality. In WHI, the subcohort was oversampled for cases of deep vein thrombosis/pulmonary embolism and stroke, therefore inverse probability weighting was used to account for selection bias. WHI, JHS and CHS were further adjusted for income categories, and UKBB was adjusted for normalized Townsend deprivation index. Using summary data from the five studies, we conducted inverse variance-weighted, fix-effects meta-analysis to obtain the effect estimates for total HF, as well as HF with and without prior CHD. In UKBB, association of CHIP status with

LVEF was performed using a linear regression model with the adjustments of age, sex, smoking status, prevalent CHD, diabetes mellitus, SBP, and self-reported race. We used forest plotted effect estimates and confidence intervals of individual study along with pooled results. All statistics were performed using SAS and R (https://www.r-project.org). Two-sided p value <0.05 was considered statistically significant.

Results

A total of 56,597 study participants were analyzed in the present study to assess the association between CHIP and incident HF. 4,694 of them developed HF with up to 20 years follow-up. The mean age of each study ranged from 54.5 to 74.6 (SD between 5.4 and 13.0) years old, 6% of the participants had CHIP, and 3.3% of the participants had high-VAF CHIP. Table 1 shows baseline characteristics for those participants with CHIP compared to those without CHIP, and Supplemental Table 2 provide HF events follow-up time. In brief, CHIP carriers were older and more likely to have comorbidities. Prevalent CHIP did not appear to be related to BMI or lipid profiles. Consistent with prior observations, the most common CHIP genes were *DNMT3A*, *TET2*, *ASXL1* and *JAK2*, as shown in Table 2. The numbers for somatic mutation carriers for each ascertained CHIP gene are provided in Supplemental Table 3.

In the fixed-effect meta-analysis, we observed that any CHIP mutation aggregately was associated with a 25% increased risk of HF (HR= 1.25, 95% CI 1.13, 1.38), with consistent direction of effect in four of the five studies (Central illustration). *TET2* (HR=1.59, 95%CI 1.18, 2.14), *JAK2* (HR=2.50, 95%CI 1.35, 4.64) and *ASXL1* (HR=1.58, 95%CI 1.20, 2.08)

somatic mutations were strongly associated with an increased risk of HF, while *DNMT3A* mutations were not associated with HF (Figure 1). In secondary analyses, we observed a slightly stronger association between high-VAF CHIP and the risk of HF (HR=1.29, 95% CI 1.15, 1.44). The associations for CHIP mutations on HF without prior CHD (HR=1.21, 95%CI 1.07, 1.36) and HF with prior CHD (HR=1.26, 95% CI 0.97, 1.64, Figure 2) were homogeneous (p=0.78 for test of homogeneity,).

Follow-up analyses in UKBB were conducted to further investigate the association between CHIP and LVEF. Demographics of the 4,122 individuals in the LVEF analyses are provided in Supplemental Table 4. We found that any CHIP was not significantly associated with reduced LVEF (p = 0.07). However, *ASXL1* somatic mutations were significantly associated with reduced LVEF (beta −4.02%, 95% CI −6.97, −1.06, p=0.008). We did not observe significant associations across *DNMT3A*, *TET2*, *JAK2* specific somatic mutations (Figure 3).

Discussion

In our meta-analysis from five prospective population-based studies, CHIP (as defined by somatic mutations in leukemia-related genes in the absence of hematologic malignancy) was associated prospectively with increased risk of a first episode of hospitalized HF, independently of traditional CVD risk factors. In analyses of specific CHIP driver mutations, *TET2*, *JAK2* and *ASXL1* were most strongly associated with risk of incident HF. *ASXL1* somatic mutations were significantly associated with reduced LVEF. In secondary analyses, greater levels of clonal expansion (VAF>10%) were associated with higher risk of incident HF among individuals and there was no significant differences between those with and without prior CHD.

We included large, prospective NHLBI-sponsored cohort studies with available CHIP data, extensive baseline CVD risk factor data, and relatively long follow up on HF, as well as all available UKBB data. The large-scale study population enables us to have adequate statistical power for CHIP and HF association detection. Our findings are consistent with and extend recent observations from clinical and murine studies of CHIP and HF, as well as studies of CHIP and age-related CVD in general. CHIP has been associated with increased risk of subclinical atherosclerosis, myocardial infarction, ischemic stroke, and all-cause mortality, independently of traditional CVD risk factors (11,12,14). These associations were dependent on clone size with the greatest risk of CVD in those with VAF>10%. In a cohort of 200 patients with pre-existing ischemic HF at baseline, the presence of CHIP and magnitude of clonal expansion were prospectively associated with HF outcome severity (19). This association was confirmed in a larger cohort of 419 stable chronic HF patients with previous MI, where CHIP was associated with higher mortality independently of other risk factors (27). Moreover, individuals carrying multiple CHIP mutations had higher mortality compared to those carrying a single CHIP mutation or non-CHIP carriers (27). We analyzed HF with and without prior CHD to delineate the association in ischemic vs. non-ischemic forms of HF, and homogeneous effect of CHIP on the two forms of HF was observed. Previous animal study showed that *Tet2*, *Dnmt3a*, and transgenic *Jak2*^{V617F}

mutations in mice induced both ischemic and hypertensive models of HF (18,21,22), which supports our finding that CHIP may influence both ischemic and non-ischemic forms of HF.

While we observe an association with overall CHIP presence and incident HF, gene-based analyses demonstrate significant associations specifically for *TET2*, *JAK2*, and *ASXL1*. The protein encoded by *TET2* is an epigenetic regulatory enzyme that modulates hematopoietic stem cell self-renewal but is also involved in inflammatory pathway regulation (11). The mice experiments demonstrated that inactivation of *Tet2* and *Dnmt3* promoted Ang II-induced cardiac dysfunction and renal fibrosis (18), and in mice transplanted with *Tet2*-deficient bone marrow or conditional *Tet2* deletion in myeloid cells, there was clonal expansion of mutant cells, along with worse cardiac remodeling, hypertrophy, and fibrosis following myocardial ischemia or pressure overload (22). A recent study also showed that bone marrow transplantation of *Tet2*-deficient cells was sufficient to induce HF in otherwise unchallenged mice (28). Given the observed effect estimate, CHIP is likely an important additive risk factor for HF. Whether distinct genes yield differential risk in the context of established HF risk factors merits further study.

Similar to *TET2*, the protein encoded by *ASXL1* is an epigenetic regulator of gene expression that has been frequently mutated in myeloid malignant myeloid diseases (29–31). Somatic mutations in *ASXL1* have been associated with CHD (11), however, little is known about the effect of *ASXL1* somatic mutations and its potential role on the development of HF remains unexplored. We showed for the first time that *ASXL1* somatic mutations were associated with LVEF, which is exploratory and hypothesis-generating for future research.

The $JAK2^{V617F}$ driver mutation associated with myeloproliferative neoplasms and atherothrombotic disease is mechanistically distinct from other CHIP driver mutations. In our study population, $JAK2^{V617F}$ constitutes the majority of *JAK2* mutations. In a mouse transgenic model of myeloid-restricted expression of mutant JAK2 that more closely resembles the human CHIP phenotype, transgenic mice developed worsening HF following ischemia or pressure overload by promoting macrophage inflammation of the myocardium and cardiac remodeling and infarct size in an IFNGR1 and STAT1-dependent manner (21). The experimental data described above further support the role of inflammatory cytokine production and signaling by immune cells in the pathogenesis of HF (32). While HF in humans has diverse causes, clinical manifestations, and pathophysiologic mechanisms, inflammation represents a common mechanism involved in different HF subtypes (33). In both hematopoietically deficient *Tet2* and *Jak2* murine HF models, IL-1beta, IL-6, TNF-alpha, and CCL2 expression were increased (21,22). Thus, CHIP has diverse effects on various immune cell types and inflammatory mediators which play key roles in HF and atherosclerosis (14). These observations are also consistent with subgroup analyses from the CANTOS cohort that the IL-1beta inhibitor canakinumab was associated with a dose-dependent reduction in HF hospitalization and mortality and improvement in left ventricular function (34,35). Whether these effects for HF events are greater among individuals with CHIP as observed for MACE in a CANTOS exploratory analysis requires further study (36).

Study limitations.

Our results suggesting that gene-specific driver mutations in *TET2, JAK2* and *ASXL1* may be preferentially associated with incident HF risk require confirmation in additional larger studies. While the murine experimental models of CHIP showed fairly consistent effects on inflammation-related and HF-related phenotypes across different CHIP driver genes (*TET2*, *DNMT3A*, *JAK2*), there were some differences noted in kinetics of clonal expansion and patterns of inflammatory gene expression by LPS-stimulated macrophages. In contrast to disruption of *Tet2* by gene editing, *Dntma3* deficiency did not result in clonal expansion of mutant cells, but still led to myocardial hypertrophy, fibrosis, macrophage infiltration and dysfunction in the Angiotensin II infusion model. One might hypothesize that differences in the kinetics of clonal expansion of driver mutations (which tend to be greater for *TET2* and *JAK2*) may explain the gene-specific differences in HF risk. Longitudinal studies of CHIP measured at multiple time points in humans may be needed to address this question. In addition, the recent association of multiple CHIP driver mutations with higher HF-related mortality (27) suggest that the presence of multiple CHIP driver mutations may be a surrogate measure for more extensive accumulation of DNA damage or reduced DNA repair or bone marrow-derived endothelial progenitor cell regenerative capacity (37). Another limitation of the current study was the lack of availability of HF subtype information in a substantial proportion of our overall sample, which limited our ability to explore these associations with adequate power and merits further investigation.

Conclusion

Our findings identify CHIP as a potentially important novel age-related risk factor for HF, consistent with previous findings of the role of CHIP as a risk factor for age-related atherosclerotic CVD more broadly. If confirmed, these findings ultimately may have potential implications for development or targeting of anti-inflammatory therapies such IL-1beta or NLRP3 inflammasome inhibitors in HF patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

UK Biobank analyses were conducted with application 7089.

Funding: Whole genome sequencing (WGS) for the Trans-Omics in Precision Medicine (TOPMed) program was supported by the National Heart, Lung and Blood Institute (NHLBI). WGS for “NHLBI TOPMed: The Jackson Heart Study” (phs000964) was performed at the University of Washington Northwest Genomics Center (HHSN268201100037C). WGS for “NHLBI TOPMed: Trans-Omics for Precision Medicine Whole Genome Sequencing Project: WGS for “NHLBI TOPMed: Women’s Health Initiative (WHI)” (phs001237) was performed at the Broad Institute (HHSN268201500014C). WGS for “NHLBI TOPMed: Trans-Omics for Precision Medicine (TOPMed) Whole Genome Sequencing Project: Cardiovascular Health Study” (phs001368) was performed at Baylor (HHSN268201600033I, 3U54HG003273-12S2 / HHSN268201500015C). 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 HHSN2682018000002I). 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.

The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services (contract numbers HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700004I and HHSN268201700005I). The authors thank the staff and participants of the ARIC study for their important contributions. Funding support for “Building on GWAS for NHLBI-diseases: the U.S. CHARGE consortium” was provided by the NIH through the American Recovery and Reinvestment Act of 2009 (ARRA) (5RC2HL102419). Whole exome sequencing was carried out at the Baylor College of Medicine Human Genome Sequencing Center (U54 HG003273 and R01HL086694).

The Cardiovascular Health Study (CHS) was supported by contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, 75N92021D00006, and grants U01HL080295 and U01HL130114 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The Jackson Heart Study (JHS) is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I) and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Minority Health and Health Disparities (NIMHD). The authors also wish to thank the staffs and participants of the JHS.

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C.

LMR was funded by T32 HL129982 and KL2TR00249. BY is in part supported by R01HL141824 and R01HL148050. PN is supported by grants from the National Heart, Lung, and Blood Institute (R01HL142711, R01HL148050, R01HL148565) and Fondation Leducq (TNE-18CVD04). SMZ is supported by the National Institutes of Health’s NHLBI under award number 1F30HL149180-01 and the National Institutes of Health’s Medical Scientist Training Program at the Yale School of Medicine. APR is supported by R01HL148565. MCH is supported by a grant from the National Heart, Lung, and Blood Institute (T32HL094301-07).

Disclosures: PN reports grants from Amgen, Apple, Boston Scientific, and Novartis, consulting income from Apple, Blackstone Life Sciences, Novartis, and Genentech, and spousal employment at Vertex, all unrelated to the present work. BLE has received research funding from Celgene, Deerfield, and Novartis and consulting fees from GRAIL. He serves on the scientific advisory boards and holds equity in Skyhawk Therapeutics, Exo Therapeutics, and Neomorph Therapeutics. The remaining authors have nothing to disclose.

Abbreviations list

CHIP	clonal hematopoiesis of indeterminate potential
HF	heart failure
LVEF	left ventricular ejection fraction
CVD	cardiovascular disease
CHD	coronary heart disease
SBP	systolic blood pressure
BMI	body mass index

References

1. Li H, Hastings MH, Rhee J, Trager LE, Roh JD, Rosenzweig A. Targeting Age-Related Pathways in Heart Failure. Circ Res 2020;126:533–551. [PubMed: 32078451]

2. Huffman MD, Berry JD, Ning H et al. Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. J Am Coll Cardiol 2013;61:1510–7. [PubMed: 23500287]

3. Stewart S, Ekman I, Ekman T, Oden A, Rosengren A. Population impact of heart failure and the most common forms of cancer: a study of 1 162 309 hospital cases in Sweden (1988 to 2004). Circ Cardiovasc Qual Outcomes 2010;3:573–80. [PubMed: 20923990]

4. Ayachi S, Buscarlet M, Busque L. 60 Years of clonal hematopoiesis research: From X-chromosome inactivation studies to the identification of driver mutations. Exp Hematol 2020;83:2–11. [PubMed: 32001340]

5. Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease. Science 2019;366.

6. Steensma DP, Bejar R, Jaiswal S et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood 2015;126:9–16. [PubMed: 25931582]

7. Natarajan P, Jaiswal S, Kathiresan S. Clonal Hematopoiesis: Somatic Mutations in Blood Cells and Atherosclerosis. Circ Genom Precis Med 2018;11:e001926. [PubMed: 29987111]

8. Libby P, Sidlow R, Lin AE et al. Clonal Hematopoiesis: Crossroads of Aging, Cardiovascular Disease, and Cancer: JACC Review Topic of the Week. J Am Coll Cardiol 2019;74:567–577. [PubMed: 31345432]

9. Ebert BL, Libby P. Clonal Hematopoiesis Confers Predisposition to Both Cardiovascular Disease and Cancer: A Newly Recognized Link Between Two Major Killers. Ann Intern Med 2018;169:116–117. [PubMed: 29809241]

10. Fuster JJ, Walsh K. Somatic Mutations and Clonal Hematopoiesis: Unexpected Potential New Drivers of Age-Related Cardiovascular Disease. Circ Res 2018;122:523–532. [PubMed: 29420212]

11. Jaiswal S, Natarajan P, Silver AJ et al. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. N Engl J Med 2017;377:111–121. [PubMed: 28636844]

12. Jaiswal S, Fontanillas P, Flannick J et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med 2014;371:2488–98. [PubMed: 25426837]

13. Honigberg MC, Zekavat SM, Niroula A et al. Premature Menopause, Clonal Hematopoiesis, and Coronary Artery Disease in Postmenopausal Women. Circulation 2021;143:410–423. [PubMed: 33161765]

14. Bick AG, Pirruccello JP, Griffin GK et al. Genetic Interleukin 6 Signaling Deficiency Attenuates Cardiovascular Risk in Clonal Hematopoiesis. Circulation 2020;141:124–131. [PubMed: 31707836]

15. Bick AG, Weinstock JS, Nandakumar SK et al. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. Nature 2020;586:763–768. [PubMed: 33057201]

16. Abplanalp WT, Mas-Peiro S, Cremer S, John D, Dimmeler S, Zeiher AM. Association of Clonal Hematopoiesis of Indeterminate Potential With Inflammatory Gene Expression in Patients With Severe Degenerative Aortic Valve Stenosis or Chronic Postischemic Heart Failure. JAMA Cardiol 2020.

17. Fuster JJ, MacLauchlan S, Zuriaga MA et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. Science 2017;355:842–847. [PubMed: 28104796]

18. Sano S, Oshima K, Wang Y, Katanasaka Y, Sano M, Walsh K. CRISPR-Mediated Gene Editing to Assess the Roles of Tet2 and Dnmt3a in Clonal Hematopoiesis and Cardiovascular Disease. Circ Res 2018;123:335–341. [PubMed: 29728415]

19. Dorsheimer L, Assmus B, Rasper T et al. Association of Mutations Contributing to Clonal Hematopoiesis With Prognosis in Chronic Ischemic Heart Failure. JAMA Cardiol 2019;4:25–33. [PubMed: 30566180]

20. Patel AP, Natarajan P. A New Murine Model of Clonal Hematopoiesis Investigates JAK2 (V617F) in Heart Failure. JACC Basic Transl Sci 2019;4:698–700. [PubMed: 31713537]

21. Sano S, Wang Y, Yura Y et al. JAK2 (V617F) -Mediated Clonal Hematopoiesis Accelerates Pathological Remodeling in Murine Heart Failure. JACC Basic Transl Sci 2019;4:684–697. [PubMed: 31709318]

22. Sano S, Oshima K, Wang Y et al. Tet2-Mediated Clonal Hematopoiesis Accelerates Heart Failure Through a Mechanism Involving the IL-1beta/NLRP3 Inflammasome. J Am Coll Cardiol 2018;71:875–886. [PubMed: 29471939]
23. Cibulskis K, Lawrence MS, Carter SL et al. Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. Nat Biotechnol 2013;31:213–9. [PubMed: 23396013]
24. Petersen SE, Matthews PM, Francis JM et al. UK Biobank's cardiovascular magnetic resonance protocol. J Cardiovasc Magn Reson 2016;18:8. [PubMed: 26830817]
25. Zekavat SM, Honigberg M, Pirruccello JP et al. Elevated Blood Pressure Increases Pneumonia Risk: Epidemiological Association and Mendelian Randomization in the UK Biobank. Med (N Y) 2020.
26. Zekavat SM, Aragam K, Emdin C et al. Genetic Association of Finger Photoplethysmography-Derived Arterial Stiffness Index With Blood Pressure and Coronary Artery Disease. Arterioscler Thromb Vasc Biol 2019;39:1253–1261. [PubMed: 31070453]
27. Cremer S, Kirschbaum K, Berkowitsch A et al. Multiple Somatic Mutations for Clonal Hematopoiesis Are Associated With Increased Mortality in Patients With Chronic Heart Failure. Circ Genom Precis Med 2020;13:e003003. [PubMed: 32598856]
28. Wang Y, Sano S, Yura Y et al. Tet2-mediated clonal hematopoiesis in nonconditioned mice accelerates age-associated cardiac dysfunction. JCI Insight 2020;5.
29. Haferlach T, Nagata Y, Grossmann V et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia 2014;28:241–7. [PubMed: 24220272]
30. Gelsi-Boyer V, Brecqueville M, Devillier R, Murati A, Mozziconacci MJ, Birnbaum D. Mutations in ASXL1 are associated with poor prognosis across the spectrum of malignant myeloid diseases. J Hematol Oncol 2012;5:12. [PubMed: 22436456]
31. Thol F, Friesen I, Damm F et al. Prognostic significance of ASXL1 mutations in patients with myelodysplastic syndromes. J Clin Oncol 2011;29:2499–506. [PubMed: 21576631]
32. Swirski FK, Nahrendorf M. Cardioimmunology: the immune system in cardiac homeostasis and disease. Nat Rev Immunol 2018;18:733–744. [PubMed: 30228378]
33. Schiattarella GG, Sequeira V, Ameri P. Distinctive patterns of inflammation across the heart failure syndrome. Heart Fail Rev 2020.
34. Everett BM, Cornel JH, Lainscak M et al. Anti-Inflammatory Therapy With Canakinumab for the Prevention of Hospitalization for Heart Failure. Circulation 2019;139:1289–1299. [PubMed: 30586730]
35. Trankle CR, Canada JM, Cei L et al. Usefulness of Canakinumab to Improve Exercise Capacity in Patients With Long-Term Systolic Heart Failure and Elevated C-Reactive Protein. Am J Cardiol 2018;122:1366–1370. [PubMed: 30244844]
36. Svensson EC, Madar A, Campbell CD et al. TET2-Driven Clonal Hematopoiesis Predicts Enhanced Response to Canakinumab in the CANTOS Trial: An Exploratory Analysis. Circulation 2018;138:A15111.
37. Djohan AH, Sia CH, Lee PS, Poh KK. Endothelial Progenitor Cells in Heart Failure: an Authentic Expectation for Potential Future Use and a Lack of Universal Definition. J Cardiovasc Transl Res 2018;11:393–402. [PubMed: 29777508]

Clinical Perspectives

Competency in Medical Knowledge:

In asymptomatic individuals, age-related clonal hematopoiesis of indeterminate potential is associated with adverse health outcomes, including heart failure.

Translational Outlook:

Further studies are warranted to determine whether clonal hematopoiesis of indeterminate potential impairs cardiac function, and if so, to explore mechanistic links.

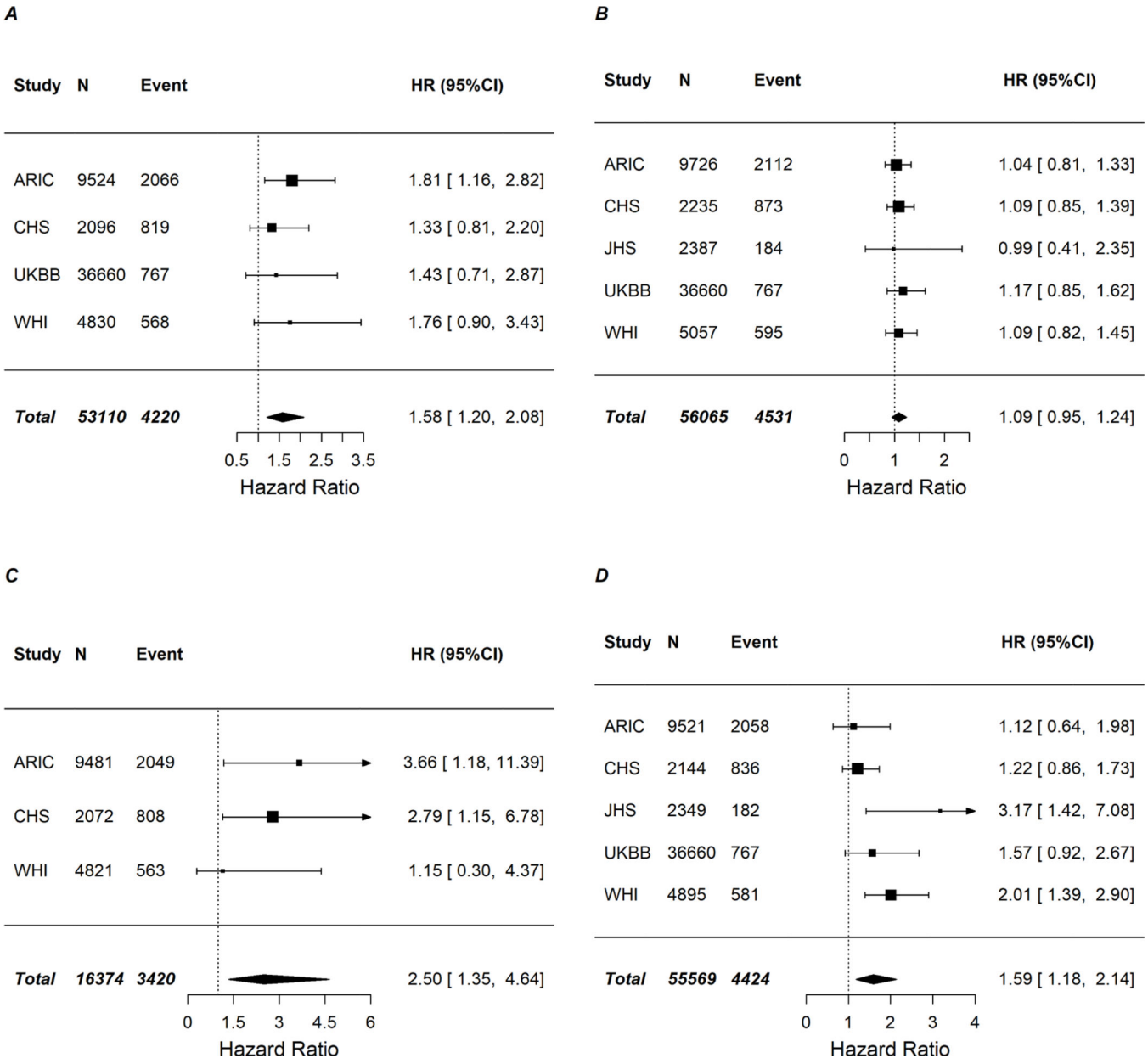


Figure 1. Clonal hematopoiesis in individual genes and incident heart failure.

Individual genes analyzed include a) *ASXL1*, b) *DNMT3A*, c) *JAK2* and d) *TET2.* Event represents the number of incident heart failure cases. For each gene, multivariable adjusted hazard ratios and 95% CIs were calculated separately in each study adjusting for age, sex, education, diabetes mellitus, smoking status, stroke, coronary heart disease, systolic blood pressure, hypertension medication use, body mass index, and race (if more than one) and combined using a fixed-effect meta-analysis. Abbreviations as in Central Illustration.

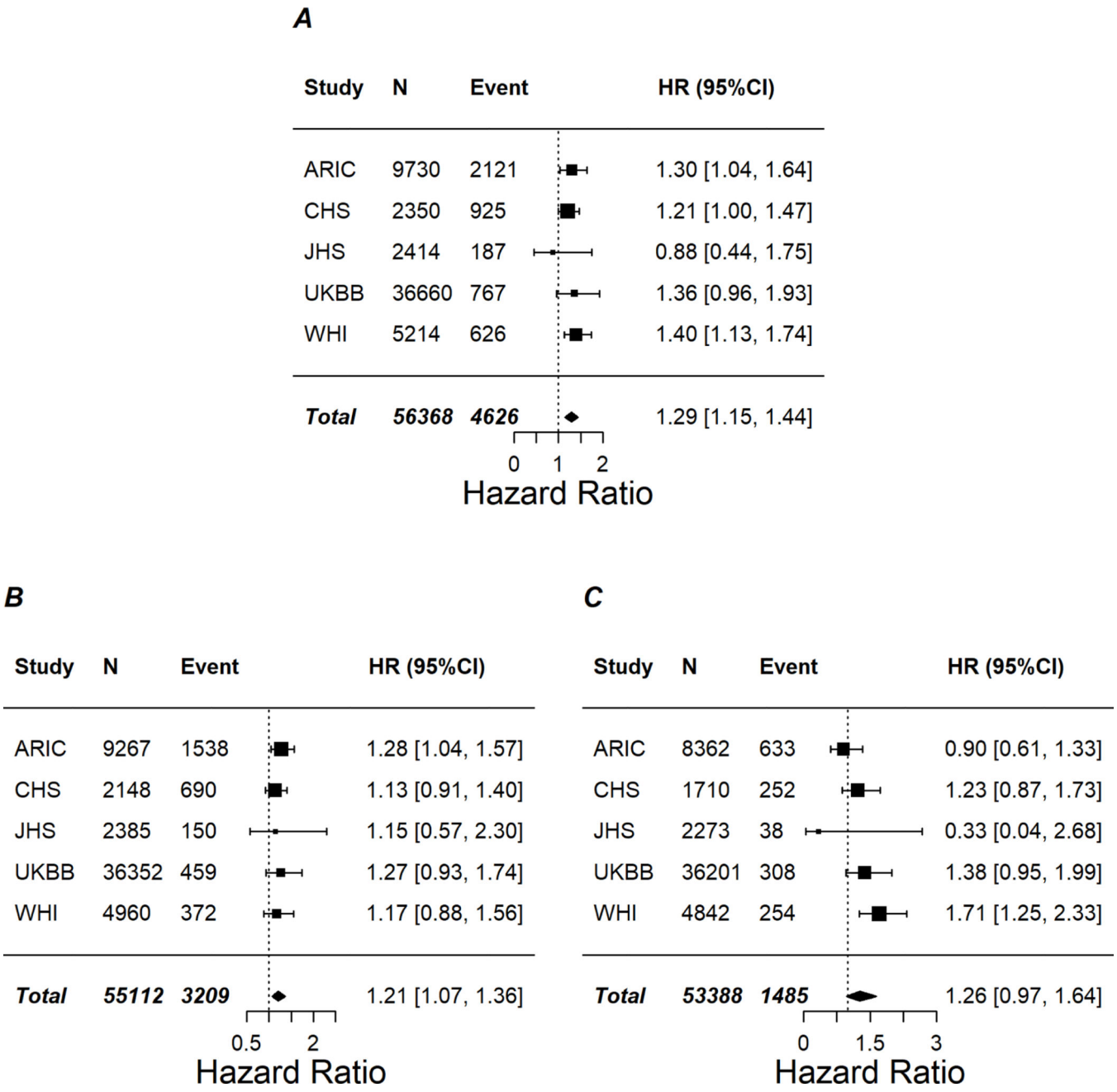


Figure 2. Associations for somatic mutation and heart failure subgroups.

a) clonal hematopoiesis of indeterminate potential with variant allele frequency > 10% and incident heart failure, b) clonal hematopoiesis of indeterminate potential and incident heart failure without prior coronary heart disease, and c) clonal hematopoiesis of indeterminate potential and incident heart failure with prior coronary heart disease. Event represents the number of incident heart failure cases. For each model, multivariable adjusted hazard ratios and 95% CIs were calculated separately in each study adjusting for age, sex, education, diabetes mellitus, smoking status, stroke, coronary heart disease, systolic blood pressure, hypertension medication use, body mass index, and race (if more than one) and combined

using a fixed-effect meta-analysis. Coronary heart disease status was not adjusted in the associations of heart failure with or without prior coronary heart disease. Abbreviations as in Central Illustration.

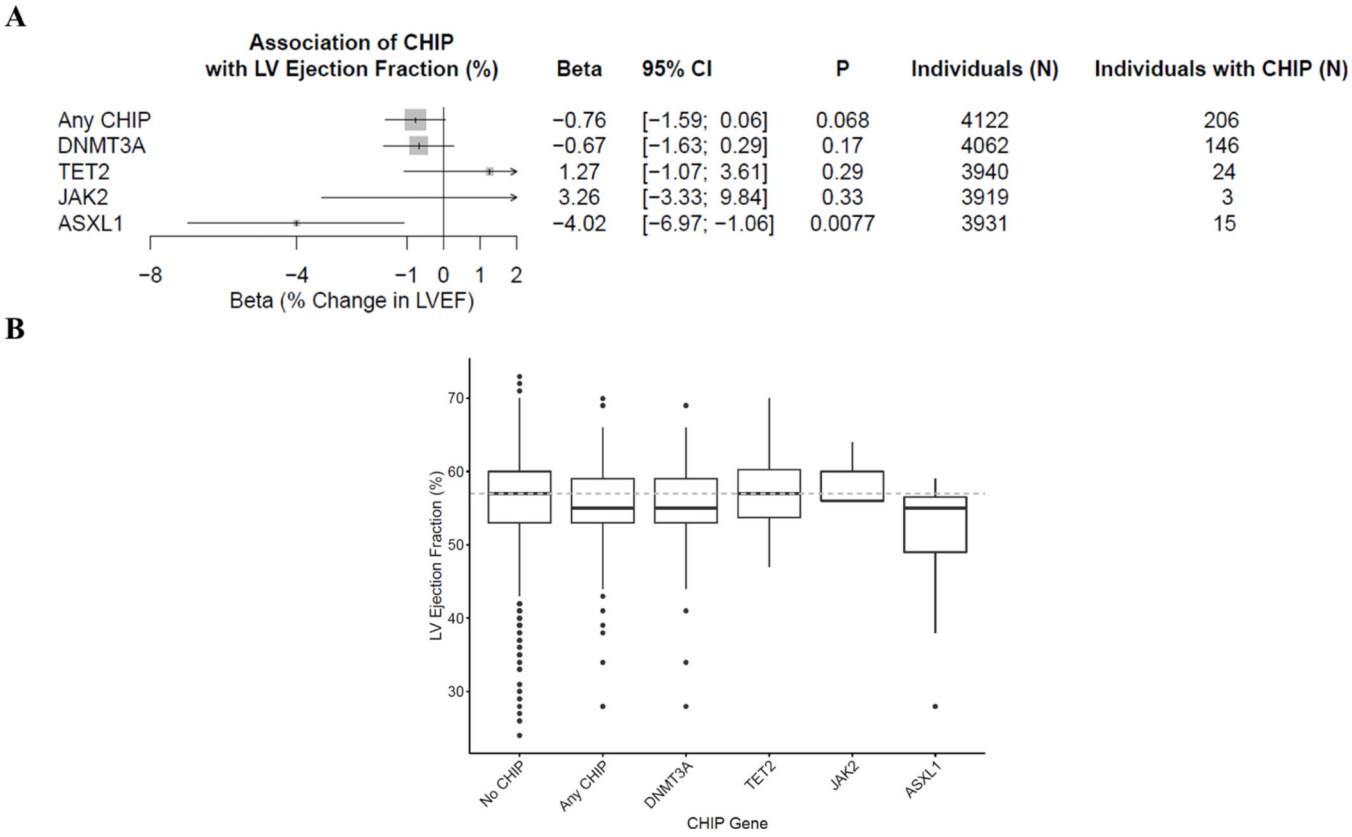
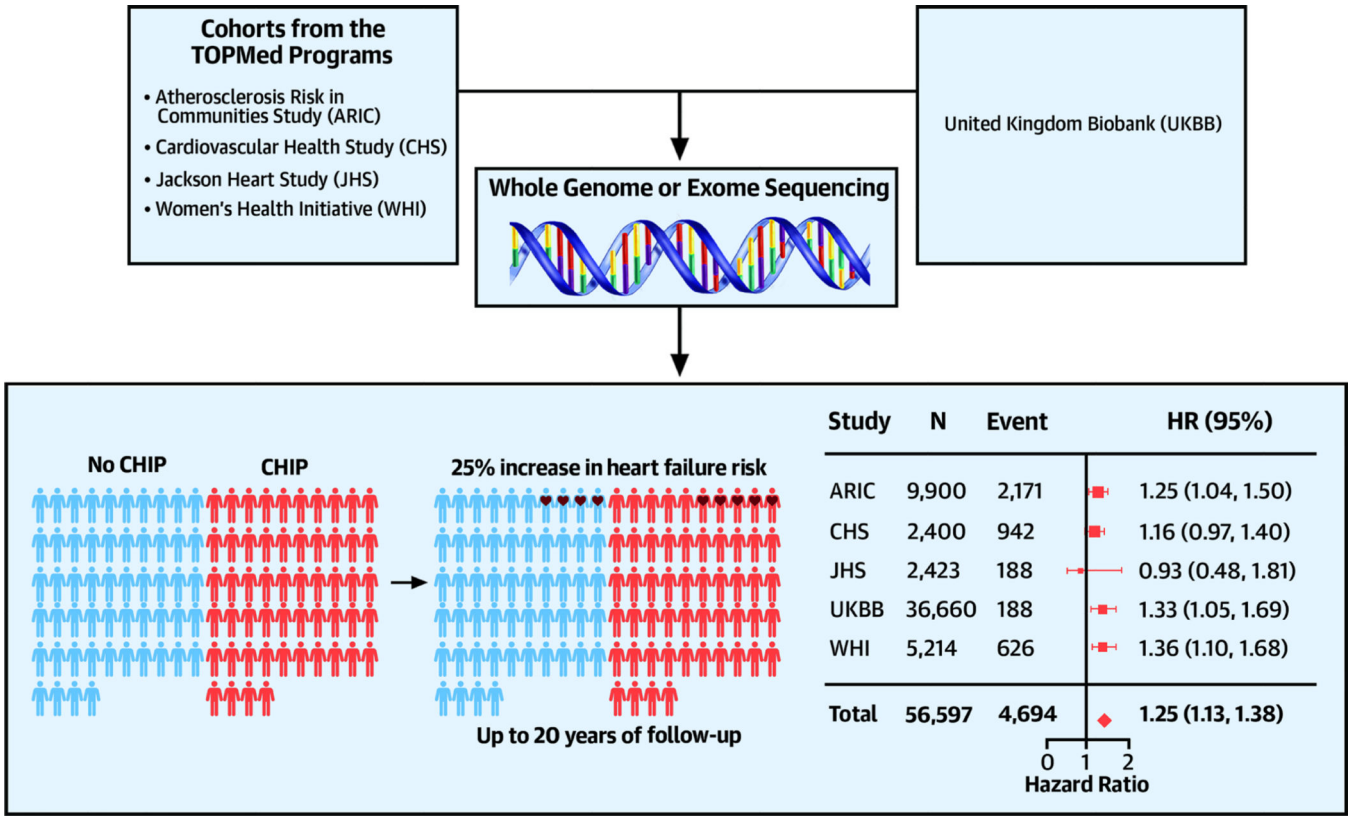


Figure 3. Clonal hematopoiesis and left ventricular ejection fraction in UK Biobank.

Association of clonal hematopoiesis of indeterminate potential status with left ventricular ejection fraction was performed using a linear regression with the adjustments of age, sex, smoking status, prevalent coronary heart disease, diabetes, systolic blood pressure, and self-reported race in the UK Biobank participants. Unadjusted first quartile, median, and third quartile of left ventricular ejection fraction were presented in the boxplots, and outliers were presented as dots. LVEF = left ventricular ejection fraction; other abbreviations as in Central Illustration.



Central Illustration. Clonal hematopoiesis of indeterminate potential mutation and incident heart failure.

Clonal hematopoiesis of indeterminate potential, determined by whole exome or genome sequencing, was significantly associated with an increased risk of heart failure in five prospective studies including 56,597 African, European and Hispanic populations with up to 20 years follow-up. Multivariable adjusted hazard ratios and 95% CIs were calculated separately in each study adjusting for age, sex, education, diabetes mellitus, smoking status, stroke, coronary heart disease, systolic blood pressure, hypertension medication use, body mass index, and race (if more than one) and combined using a fixed-effect meta-analysis. CHIP = clonal hematopoiesis of indeterminate potential; ARIC = Atherosclerosis Risk in Communities Study; CHS = Cardiovascular Health Study; JHS = Jackson Heart Study; UKBB = United Kingdom Biobank; WHI = Women's Health Initiative.

Table 1.

Characteristics by clonal hematopoiesis of indeterminate potential status.

	ARIC		CHS		JHS		UKBB		WHI		All studies	
Category	**CHIP**	**No CHIP**	**CHIP**	**No CHIP**	**CHIP**	**No CHIP**	**CHIP**	**No CHIP**	**CHIP**	**No CHIP**	**CHIP**	**No CHIP**
N	427	9473	337	2063	91	2332	2143	34517	408	4806	3406	53191
Age (years)	60 (5.9)	57.4 (6.1)	74.6 (5.6)	73.4 (5.4)	65.6 (9.0)	54.5 (13.0)	60.6 (6.6)	56.8 (7.8)	67.4 (6.6)	65.2 (6.9)	62.9 (7.9)	58.2 (8.6)
Female	239 (56)	5325 (56)	173 (51)	1161 (56)	55 (60)	1464 (63)	1131 (53)	18593 (54)	408 (100)	4806 (100)	2006 (58.9)	31349 (58.9)
Race												
White	290 (68)	6884 (73)	285 (85)	1673 (81)	0 (0)	0 (0)	2143 (100)	34517 (100)	288 (71)	3147 (66)	3006 (88.3)	46221 (86.9)
Black	137 (32)	2589 (27)	52 (15)	390 (19)	91 (100)	2332 (100)	0 (0)	0 (0)	93 (23)	1296 (27)	373 (11)	6607 (12.4)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	25 (6)	354 (7)	25 (0.7)	354 (0.7)
DM	67 (16)	1337 (14)	62 (18)	336 (16)	26 (28)	527 (23)	63 (3)	885 (3)	22 (5)	364 (8)	240 (7)	3449 (6.5)
HTN	174 (41)	3296 (35)	159 (47)	991 (48)	65 (71)	1183 (51)	761 (36)	10277 (30)	169 (41)	2082 (43)	1328 (39)	17829 (33.5)
CHD	22 (5)	484 (5)	35 (10)	212 (10)	5 (5)	69 (3)	155 (7)	1846 (5)	13 (3)	186 (4)	230 (6.8)	2797 (5.3)
Stroke	16 (4)	164 (2)	16 (5)	78 (4)	2 (2)	83 (4)	31 (1)	459 (1)	3 (1)	64 (1)	68 (2)	848 (1.6)
Current smoker	117 (27)	2040 (22)	35 (10)	249 (12)	10 (11)	290 (12)	213 (10)	2913 (9)	27 (7)	474 (10)	402 (11.8)	5966 (11.2)
BMI (kg/m^2)	27.5 (5.4)	28.1 (5.4)	26.9 (4.6)	26.8 (4.7)	31.0 (6.6)	31.8 (7.4)	27.5 (4.5)	27.4 (4.7)	29.8 (6.2)	29.7 (6.2)	27.8 (5)	27.9 (5.2)
SBP (mmHg)	125.2 (19.4)	121.9 (18.3)	135.2 (20.4)	136.9 (21.7)	133.9 (16.7)	126.9 (16.2)	145.3 (20.8)	141.4 (20.6)	132 (17.4)	131 (17.8)	139.9 (21.5)	136.2 (21.3)
HF events	125	2046	139	803	11	177	75	695	64	562	414	4283
Follow-up years	17.7 (8.5)	20.0 (7.8)	10.5 (6.4)	11.8 (6.7)	8.4 (3.3)	9.7 (2.5)	10.1 (1.3)	10.2 (1.5)	14.7 (6.2)	15.7 (6.2)	11.6 (5.2)	12.5 (5.7)

Frequencies and percentages are displayed for categorical variables. Mean and SD are displayed for continuous variables. CHIP, clonal hematopoiesis of indeterminate potential; DM, prevalent diabetes mellitus; HTN, prevalent hypertension; CHD, prevalent coronary heart disease; BMI, body mass index; SBP, systolic blood pressure.

Table 2.

Most frequent genes with somatic mutations by each study.

Somatic Mutations	ARIC N (%)	CHS N (%)	JHS N (%)	UKBB N (%)	WHI N (%)	All Studies N (%)
ASXL1	51 (0.5)	33 (1.4)	3 (0.1)	148 (0.4)	24 (0.5)	259 (0.5)
DNMT3A	253 (2.6)	172 (7.2)	55 (2.3)	1370 (3.7)	251 (4.8)	2101 (3.7)
JAK2	8 (0.1)	9 (0.4)	2 (0.1)	21 (0.05)	15 (0.3)	55 (0.1)
TET2	48 (0.5)	81 (3.4)	17 (0.7)	334 (0.9)	89 (1.7)	569 (1.0)
Any mutation	427 (4.3)	337 (14.0)	91 (3.8)	2143 (5.8)	408 (7.8)	3406 (6.0)
Large CHIP	257 (2.6)	287 (12)	82 (3.4)	879 (2.4)	342 (6.6)	1847 (3.3)

Frequencies and percentages are displayed