ESC European Society of Cardiology

European Heart Journal (2024) **45**, 791–805
https://doi.org/10.1093/eurheartj/ehad670

FASTTRACK CLINICAL RESEARCH
Arrhythmias

Clonal haematopoiesis of indeterminate potential predicts incident cardiac arrhythmias

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Received 24 May 2023; revised 7 September 2023; accepted 26 September 2023; online publish-ahead-of-print 11 November 2023

See the editorial comment for this article 'Clonal haematopoiesis and cardiac arrythmias: rhythm-altering mutations', by M.A. Zuriaga *et al*., https://doi.org/10.1093/eurheartj/ehae052.

Abstract

Background and Aims Clonal haematopoiesis of indeterminate potential (CHIP), the age-related expansion of blood cells with preleukemic mutations, is associated with atherosclerotic cardiovascular disease and heart failure. This study aimed to test the association of CHIP with new-onset arrhythmias.

Methods UK Biobank participants without prevalent arrhythmias were included. Co-primary study outcomes were supraventricular arrhythmias, bradyarrhythmias, and ventricular arrhythmias. Secondary outcomes were cardiac arrest, atrial fibrillation, and any arrhythmia. Associations of any CHIP [variant allele fraction (VAF) ≥ 2%], large CHIP (VAF ≥10%), and gene-specific CHIP subtypes with incident arrhythmias were evaluated using multivariable-adjusted Cox regression. Associations of CHIP with myocardial interstitial fibrosis [T1 measured using cardiac magnetic resonance (CMR)] were also tested.

Results This study included 410 702 participants [CHIP: $n = 13\,892$ (3.4%); large CHIP: $n = 9191$ (2.2%)]. Any and large CHIP were associated with multi-variable-adjusted hazard ratios of 1.11 [95% confidence interval (CI) 1.04–1.18; $P = .001$] and 1.13 (95% CI 1.05–1.22; $P = .001$) for supraventricular arrhythmias, 1.09 (95% CI 1.01–1.19; $P = .031$) and 1.13 (95% CI 1.03–1.25; $P = .011$) for bradyarrhythmias, and 1.16 (95% CI, 1.00–1.34; $P = .049$) and 1.22 (95% CI 1.03–1.45; $P = .021$) for ventricular arrhythmias, respectively. Associations were independent of coronary artery disease and heart failure. Associations were also heterogeneous across arrhythmia subtypes and strongest for cardiac arrest. Gene-specific analyses revealed an increased risk of arrhythmias across driver genes other than *DNMT3A*. Large CHIP was associated with 1.31-fold odds (95% CI 1.07–1.59; $P = .009$) of being in the top quintile of myocardial fibrosis by CMR.

Conclusions CHIP may represent a novel risk factor for incident arrhythmias, indicating a potential target for modulation towards arrhythmia prevention and treatment.

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Structured Graphical Abstract

Key Question

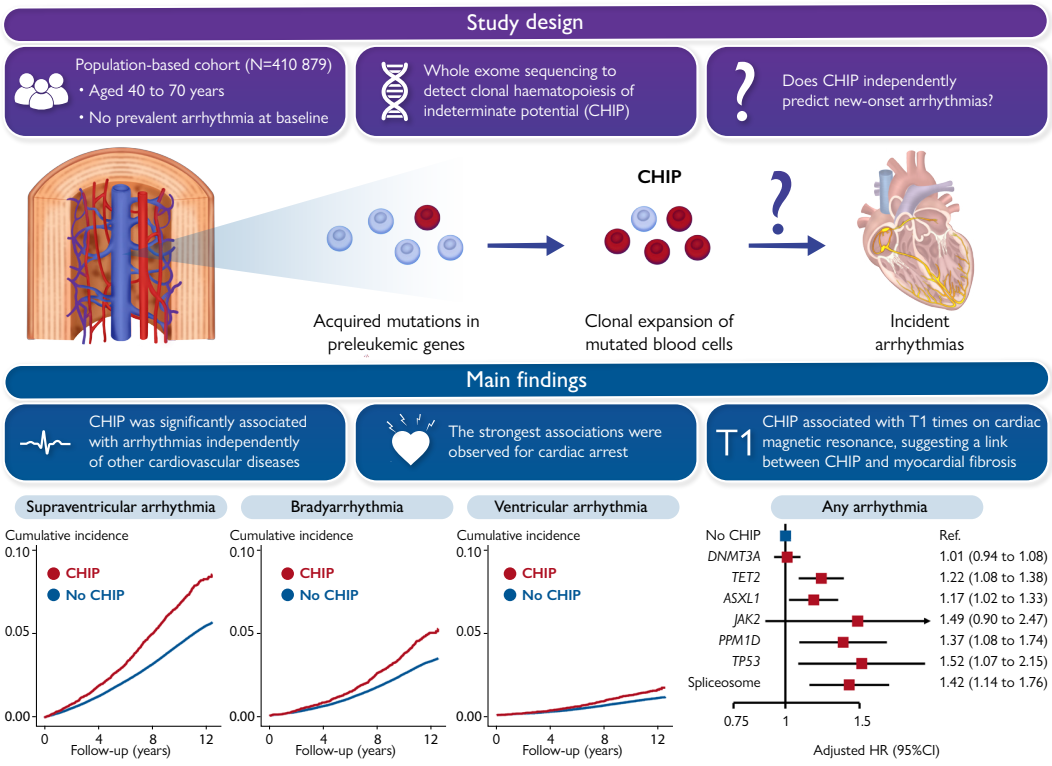
Does clonal haematopoiesis of indeterminate potential (CHIP), the age-related clonal expansion of blood cells with preleukemic mutations, independently predict new-onset arrhythmias?

Key Finding

In 410 702 middle-aged adults, CHIP was associated with arrhythmic events independent of other cardiovascular diseases. The associations differed across arrhythmia subtypes, with the highest risks observed for cardiac arrest. CHIP associated also with T1 times on cardiac magnetic resonance, suggesting a link with myocardial fibrosis.

Take Home Message

These findings suggest CHIP is a novel age-related risk factor for arrhythmias, which may ultimately have implications for precision medicine approaches in arrhythmia management.



In 410 702 middle-aged adults from the UK Biobank, clonal haematopoiesis of indeterminate potential (CHIP) was associated with incident arrhythmias independent of other cardiovascular diseases such as coronary artery disease and heart failure, with the strongest associations observed for cardiac arrest. Gene-stratified analyses revealed an increased risk of arrhythmias across driver genes other than *DNMT3A*. CI, confidence interval; HR, hazard ratio.

Keywords Arrhythmia • Aging • Atrial fibrillation • Cardiac arrest • Genomics • Prevention

Introduction

Cardiac arrhythmias impose a substantial global health burden,[1–4] leading to reduced quality of life and increased risk of stroke, heart failure, and premature mortality among affected individuals.[5–7] Recent population-based cohort studies have revealed that rhythm abnormalities affect ~1%–5% of middle-aged adults, with prevalence increasing exponentially with age.[8,9] Atrial fibrillation is the most commonly diagnosed arrhythmia and portends increased risk of stroke and mortality,[1,7,8] whereas cardiac arrest represents the most severe arrhythmic event and accounts for up to 50% of all cardiovascular deaths.[3,10,11] Despite substantial progress in the clinical management of these conditions, prevention options are limited, and the mechanisms linking aging with arrhythmias remain incompletely understood.

Large-scale genetic studies have shown that apparently healthy individuals can acquire preleukemic mutations that lead to clonal expansion of

haematopoietic cells over time.[12] The prevalence of this condition, termed clonal haematopoiesis of indeterminate potential [CHIP; traditionally defined as variant allele fraction (VAF) ≥ 2%], increases with age, affecting 10%–20% of individuals >70 years of age.[13,14] CHIP is most commonly driven by genes involved in epigenetic and transcriptional regulation (e.g. *DNMT3A*, *TET2*, *ASXL1*, *JAK2*), mRNA splicing (e.g. *SF3B1*, *SRSF2*, *U2AF1*), or DNA damage repair (*TP53* and *PPM1D*).[14,15] Emerging evidence indicates that CHIP is associated with a range of cardiovascular diseases, including coronary artery disease,[16,17] stroke,[18] and heart failure.[19] Human observations and experiments in mice with certain CHIP mutations suggest that this risk is partially driven by dysregulated inflammation[17,20,21] and cardiac fibrosis,[22–26] both of which are important contributors to the pathogenesis of cardiac rhythm abnormalities.[27–31] However, whether CHIP is associated with arrhythmic events in the general population is currently unknown.

Given the increasing availability of low-cost next-generation sequencing and the arrival of clinical trials testing CHIP-directed therapeutics,[32] identifying conditions that could be targeted with CHIP-directed prevention or intervention strategies is increasingly clinically actionable. Therefore, this study leveraged the UK Biobank to test the associations of CHIP with incident arrhythmias in a population-based cohort of over 410 000 adults. We evaluated the associations of CHIP and gene-specific CHIP subtypes with specific arrhythmia categories, including supraventricular arrhythmias, ventricular arrhythmias, and bradyarrhythmias. In addition, to explore potential mechanisms, we tested whether CHIP was linked to myocardial fibrosis in the subgroup of participants with cardiac magnetic resonance (CMR) imaging data.

Methods

Study cohort

The UK Biobank is a population-based cohort study of ∼500 000 adults from the United Kingdom who were 40–70 years old at the time of recruitment between 2006 and 2010.[33] At study enrolment, participants underwent physical examination and provided information on sociodemographic characteristics, lifestyle factors, medical history, and medication use. In addition, participants underwent blood sampling for biomarker analysis, including array genotyping and whole exome sequencing (WES). Healthcare utilization was linked to national health records, allowing for the ascertainment of prevalent diseases (onset before enrolment) as well as incident events (onset after enrolment). Follow-up for incident events occurred through March 2020.

The present analysis included participants with available WES data and complete data on genetic ancestry. Individuals with any prevalent haematologic malignancy or diagnosed arrhythmia at baseline were excluded, as were those who reported the use of antiarrhythmic drugs (Vaughan Williams categories I or III) at baseline. Individuals inferred to be related (closer than third degree; kinship coefficient >.0884) were also excluded, leaving a total of 410 702 participants in the analytic cohort (see Supplementary data online, *Figure S1*).

The UK Biobank was approved by the North West Multi-centre Research Ethics Committee, and all participants provided their informed consent. UK Biobank data were accessed through application number 7089. The Mass General Brigham Institutional Review Board approved the secondary use of these data.

Exposures and covariates

CHIP and CHIP-related phenotypes were ascertained from whole blood-derived WES as recently described.[34] WES was performed using the Illumina NovaSeq 6000 platform at the Regeneron Genetics Center (Tarrytown, NY).[35] Somatic variants were identified using the Mutect2 tool from the Genome Analysis ToolKit (GATK).[36,37] CHIP mutations were called in a previously curated list of 58 genes known to drive clonal haematopoiesis and myeloid malignancies (see Supplementary data online, *Table S1*).[34] To minimize the number of false-positive CHIP calls, variants were kept for further analysis if (i) total depth of coverage was ≥20; (ii) minimum read depth for the alternate allele was ≥5; and (iii) there was variant support in both forward and reverse sequencing reads. Sequencing artefacts and germline variants were removed as described previously.[34]

The co-primary study exposures were the presence of any CHIP (i.e. VAF ≥2%)[38] and CHIP with VAF ≥10%, as prior evidence suggests that CHIP clones above this threshold are more strongly associated with clinical outcomes.[39,40] In addition, we separately examined all gene-specific CHIP subtypes that were present in >30 individuals, with a particular focus on the most common driver genes (*DNMT3A*, *TET2*, and *ASXL1*), *JAK2*, DNA damage repair genes (*PPM1D* and *TP53*), and spliceosome genes (*PRPF8*, *SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2*).[41] Given the low prevalence of driver mutations for each spliceosome gene separately, we tested spliceosome genes as a composite CHIP subtype, as done previously.[42] Additional analyses tested whether the clonal haematopoiesis risk score (CHRS)—a recently developed risk score that predicts incident myeloid malignancies in individuals with CHIP or clonal cytopenia of undetermined significance (CCUS)[43]—was associated with incident arrhythmias. Details on the CHRS can be found in the Supplementary data online, Methods and *Table S2*.

Outcomes

The co-primary study outcomes were new-onset supraventricular arrhythmia (including atrial fibrillation or flutter, premature atrial contractions, and supraventricular tachycardia), bradyarrhythmia (including atrioventricular/bundle branch block, pacemaker insertion, and sinus node dysfunction), and ventricular arrhythmia (including ventricular tachycardia, ventricular premature depolarizations, cardiac arrest, and implantable cardioverter defibrillator insertion). Incident events were defined by the occurrence of ≥1 qualifying ICD (International Classification of Diseases) code for the corresponding arrhythmia as either a primary or secondary disease diagnosis or ≥1 qualifying OPCS (Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures) code for a corresponding arrhythmia-related procedure (e.g. accessory pathway ablation for supraventricular arrhythmia).[44,45] Arrhythmia-specific definitions are listed in Supplementary data online, *Table S3*. Secondary analyses evaluated atrial fibrillation (or flutter)[8,46] and cardiac arrest separately given their clinical importance, as well as a composite of any incident arrhythmia (supraventricular, brady-, or ventricular). We also evaluated antiarrhythmic medication use during follow-up in 44.3% ($n = 182\,011$) of participants with available prescription data through linkage to primary care records (see Supplementary data online, *Table S4*).

To explore potential mechanisms underlying any associations between CHIP and incident arrhythmias, we tested the associations of CHIP and gene-specific CHIP subtypes with myocardial fibrosis (T1 measured using CMR) in the subset of UK Biobank participants who returned between 2014 and 2019 for a multi-modal imaging visit.[47,48] Details on the CMR imaging visit can be found in the Supplementary data online, Methods.

Statistical analysis

The Shapiro–Wilk test was used to evaluate whether continuous variables followed a normal distribution. Continuous participant characteristics were compared between individuals with vs. without CHIP using the Student's *t*-test for normally distributed variables or the Wilcoxon rank-sum test for skewed variables. Categorical variables were compared using the Pearson chi-squared test or Fisher exact test as appropriate.

Primary analyses tested the association of any CHIP and CHIP with VAF ≥10% with incident arrhythmia events using Cox proportional hazards models. Minimally adjusted models included age, age^2, sex, and genetic ancestry (European vs. non-European) as covariates. Fully adjusted models further included smoking status (ever vs. never), body mass index (BMI), type 2 diabetes mellitus, systolic blood pressure, antihypertensive

medication use, alcohol intake frequency, history of any cancer, and coronary artery disease as covariates (see Supplementary data online, Methods and *Table S5*). The proportional hazards assumption was tested by plotting Schoenfeld residuals against time. Follow-up started at UK Biobank enrolment, and subjects who did not experience the indicated event were censored at the end of follow-up or death. Cumulative incidence functions accounting for all-cause mortality as a competing risk were constructed using the *cmprsk* package[49] in R to visualize the incidence of arrhythmia events during follow-up. Information on covariate imputation, sensitivity analyses, recurrent event analyses, and analyses of myocardial fibrosis can be found in the Supplementary data online, Methods.

Given three co-primary outcomes, two-sided $P < .0167$ (i.e. $P < .05/3$) indicated statistical significance for the primary analyses. Findings from secondary analyses should interpreted as supportive and exploratory due to the potential for type I error. All analyses were performed in R version 4.1.3.

Results

CHIP prevalence and baseline participant characteristics

The final study sample comprised 410 702 unrelated individuals (see Supplementary data online, *Figure S1*), of whom 13 892 (3.4%) had any CHIP and 9191 (2.2%) had CHIP with VAF ≥10%, consistent with previous work in the UK Biobank.[34] CHIP prevalence increased with chronological age (see Supplementary data online, *Figure S2*). The most common CHIP driver was *DNMT3A* ($n = 8727$; 62.8% of CHIP carriers), followed by *TET2* ($n = 1972$; 14.2%), *ASXL1* ($n = 1507$; 10.8%), spliceosome genes (*PRPF8*, *SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2;* $n = 445$; 3.2%), *PPM1D* ($n = 431$; 3.1%), *TP53* ($n = 201$; 1.4%), and *JAK2* ($n = 107$; 0.8%) (see Supplementary data online, *Figure S3*). Among the 13 892 CHIP carriers, 548 (3.9%) had mutations in >1 driver gene (see Supplementary data online, *Figure S4*).

Median age at blood draw was 58 years [interquartile range (IQR), 50–63 years], and 54.5% of participants ($n = 223\,780$) were women. Participants with vs. without CHIP were older [62 (IQR, 57–66) vs. 57 (IQR, 50–63) years; $P < .001$] and more likely to have European genetic ancestry (96.1% vs. 94.6%; $P < .001$) or self-identify as White (96.0% vs. 94.4%; $P < .001$). In addition, CHIP carriers had higher BMI, blood pressure, and alcohol intake compared to those without CHIP (*Table 1*). They were also more likely to be current or former smokers and more often had pre-existing cardiovascular diseases. There were no significant differences in geographic or air pollution-related variables based on CHIP carrier status (see Supplementary data online, *Table S6*). Baseline characteristics of individuals with large (i.e. VAF ≥10%) vs. small (i.e. VAF <10%) CHIP are listed in Supplementary data online, *Table S7*.

Cumulative incidence of arrhythmic events by CHIP status

During a median follow-up of 11.1 (IQR, 10.4–11.8) years, 30 407 participants (7.4%) experienced a new arrhythmia diagnosis, yielding an incidence rate of 7.0 [95% confidence interval (CI), 6.9–7.1] events per 1000 person-years. Incidence rates for supraventricular arrhythmias, bradyarrhythmias, and ventricular arrhythmias were 4.7 (95% CI, 4.7–4.8), 2.8 (95% CI, 2.7–2.8), and 0.9 (95% CI, 0.8–0.9) per 1000 person-years, respectively. Atrial fibrillation was the most common rhythm disorder, affecting a total of 19 507 participants (4.7%) during follow-up [incidence rate, 4.4 (95% CI, 4.4–4.5) per 1000 person-years]. Cardiac arrest occurred in 1810 individuals (0.4%), yielding an incidence rate of 0.40 (95% CI, 0.39–0.42) per 1000 person-years.

Incident arrhythmias were observed in 28 892 (7.3%) without CHIP, 1515 (10.9%) with any CHIP, and 1054 (11.5%) with large CHIP. Incident supraventricular arrhythmias, bradyarrhythmias, and ventricular arrhythmias (i.e. the co-primary outcomes) were each more common in individuals with any vs. no CHIP (see Supplementary data online, *Figure S5*). When CHIP was stratified by clone size, cumulative incidence for each co-primary outcome was greater for large vs. small CHIP clones (*Figure 1*). Similarly, cumulative incidence for composite arrhythmias (including supraventricular arrhythmias, bradyarrhythmias, and ventricular arrhythmias), atrial fibrillation, and cardiac arrest were greater in individuals with large vs. small CHIP (*Figure 2*). The proportion of CHIP carriers experiencing arrhythmic events during follow-up increased with higher VAF (see Supplementary data online, *Figure S6*).

Among those with data on medication use during follow-up, CHIP carriers more often required antiarrhythmic drugs compared with those without CHIP [17.7% ($n = 1094/6172$) vs. 14.7% ($n = 25\,793/175\,839$); $P < .001$], including class II anti-arrhythmics [beta blockers; 17.0% ($n = 1051/6172$) vs. 14.2% ($n = 24\,908/175\,839$); $P < .001$], class I/III anti-arrhythmics [0.8% ($n = 49/6172$) vs. 0.5% ($n = 806/175\,839$); $P < .001$], and digoxin [0.7% ($n = 43/6172$) vs. 0.4% ($n = 625/175\,839$); $P < .001$].

Analyses incorporating information on recurrent events revealed that CHIP carriers experienced more arrhythmia events during follow-up than non-carriers, indicated by a rightward shift in the probability density distribution of the number of events experienced per participant (see Supplementary data online, *Figure S7*). The proportion of individuals experiencing more than one arrhythmic event was higher in those with vs. without CHIP (5.1% vs. 3.1%; $P < .001$), as was the proportion of individuals with events in more than one arrhythmia category (i.e. supraventricular, brady-, or ventricular arrhythmias; 2.3% vs. 1.4%; $P < .001$). Similarly, among participants who experienced at least one arrhythmia during follow-up, the cumulative incidence of arrhythmia recurrence was higher in those with vs. without CHIP (see Supplementary data online, *Figure S8*). Analyses focusing specifically on individuals who experienced cardiac arrest during follow-up revealed no major differences in underlying arrhythmias between CHIP carriers and non-carriers, except that CHIP carriers had a lower likelihood of having a prior or concomitant bradyarrhythmia diagnosis at the time of cardiac arrest [11.8% ($n = 12/102$) vs. 21.4% ($n = 366/1708$); $P = .027$; Supplementary data online, *Table S8*].

Multivariable-adjusted associations of CHIP with incident arrhythmias

The presence of any vs. no CHIP was associated with hazard ratios (HRs) of 1.11 (95% CI, 1.04–1.18; $P = .001$) for supraventricular arrhythmias, 1.09 (95% CI, 1.01–1.19; $P = .031$) for bradyarrhythmias, and 1.16 (95% CI, 1.00–1.34; $P = .049$) for ventricular arrhythmias in fully adjusted models for incident events during follow-up (*Table 2*). These associations were stronger for larger clones: CHIP with VAF ≥10% yielded multi-variable-adjusted HRs of 1.13 (95% CI, 1.05–1.22; $P = .001$), 1.13 (95% CI, 1.03–1.25; $P = .011$), and 1.22 (95% CI, 1.03–1.45; $P = .021$) for supraventricular arrhythmias, bradyarrhythmias, and ventricular arrhythmias, respectively. CHIP with VAF <10% was not significantly associated with incident arrhythmias during follow-up (see Supplementary data online, *Table S9*). Consistent with the primary analyses, participants with CHIP [HR, 1.10 (95% CI, 1.04–1.16); $P < .001$] or CHIP with VAF ≥10% [HR, 1.14 (95% CI, 1.07–1.21); $P < .001$] had a significantly increased risk of experiencing

Table 1 Baseline characteristics among included UK Biobank participants with vs. without clonal haematopoiesis of indeterminate potential

	No CHIP ($n = 396\,810$)	CHIP ($n = 13\,892$)	*P*-value
Age at enrolment, years	57 (50–63)	62 (57–66)	<.001
Female sex	216 340 (54.5%)	7440 (53.6%)	.03
Genetic ancestry	–	–	<.001
African	8063 (2.0%)	194 (1.4%)	–
American	2115 (0.5%)	51 (0.4%)	–
East Asian	2291 (0.6%)	62 (0.4%)	–
European	375 263 (94.6%)	13 353 (96.1%)	–
South Asian	9078 (2.3%)	232 (1.7%)	–
Self-reported race/ethnicity	–	–	<.001
Asian	9429 (2.4%)	241 (1.7%)	–
Black	6507 (1.6%)	148 (1.1%)	–
White	372 830 (94.4%)	13 274 (96.0%)	–
Mixed	2368 (0.6%)	66 (0.5%)	–
Other	3790 (1.0%)	98 (0.7%)	–
Smoking status	–	–	<.001
Current	41 541 (10.5%)	1729 (12.4%)	–
Former	135 175 (34.1%)	5437 (39.1%)	–
Never	220 094 (55.5%)	6726 (48.4%)	–
Alcohol intake frequency	–	–	<.001
Never	31 386 (7.9%)	1103 (8.0%)	–
On special occasions only	45 423 (11.5%)	1640 (11.8%)	–
One to three times monthly	44 103 (11.1%)	1424 (10.3%)	–
One to two times weekly	102 381 (25.9%)	3322 (24.0%)	–
Three to four times weekly	91 937 (23.2%)	3147 (22.7%)	–
Daily or almost daily	80 691 (20.4%)	3231 (23.3%)	–
$PM_{2.5}$, $\mu g/g^3$	9.93 (9.28–10.56)	9.91 (9.27–10.52)	.051
BMI, kg/m^2	26.7 (24.1–29.8)	26.9 (24.3–30.0)	.002
Systolic blood pressure, mmHg	138 (126–152)	142 (129–156)	<.001
Diastolic blood pressure, mmHg	82 (75–89)	82 (75–90)	<.001
Total cholesterol, mg/dL	219.1 (190.7–248.9)	219.0 (188.7–249.0)	.15
High-density lipoprotein cholesterol, mg/dL	54.2 (45.4–64.9)	54.3 (45.2–65.1)	.84
Low-density lipoprotein cholesterol, mg/dL	136.5 (114.5–159.6)	135.9 (113.2–159.6)	.040
Antihypertensive medication use	60 942 (15.4%)	2934 (21.1%)	<.001
Prevalent/prior diagnoses	–	–	–
Type 2 diabetes mellitus	11 777 (3.0%)	553 (4.0%)	<.001
Hypertension	112 697 (28.4%)	4820 (34.7%)	<.001
Coronary artery disease	14 877 (3.8%)	721 (5.2%)	<.001
Heart failure	1440 (0.4%)	70 (0.5%)	.009
Valvular heart disease	4235 (1.1%)	183 (1.3%)	.006

Continued

Table 1 *Continued*

	No CHIP ($n = 396\,810$)	CHIP ($n = 13\,892$)	*P*-value
History of cardiac surgery	2177 (0.5%)	118 (0.8%)	<.001
History of cancer	39 212 (9.9%)	1881 (13.5%)	<.001
IL6R p.Asp358Ala	–	–	.54
Heterozygous carrier	187 583 (47.3%)	6634 (47.8%)	–
Homozygous carrier	64 998 (16.4%)	2247 (16.2%)	–

Continuous characteristics are summarized as median (interquartile range), while categorical characteristics are summarized as number (%). Continuous participant characteristics were compared using the Wilcoxon rank-sum test (for skewed variables). Categorical characteristics were compared using the Pearson chi-squared test or Fisher exact test as appropriate. BMI, body mass index; CHIP, clonal haematopoiesis of indeterminate potential; $PM_{2.5}$, particulate matter with diameter ≤2.5 μg; VAF, variant allele fraction.

any arrhythmia during follow-up compared to those without CHIP. Furthermore, CHIP vs. no CHIP was independently associated with incident atrial fibrillation [HR, 1.11 (95% CI, 1.04–1.18), $P = .001$] and cardiac arrest [HR, 1.29 (95% CI, 1.06–1.58), $P = .012$].

Exploratory analyses found that the associations of CHIP with incident events were heterogeneous across arrhythmia subtypes, with null associations observed for incident sinus node dysfunction and ventricular premature depolarizations (see Supplementary data online, *Table S10*). Among the subset of participants with at least one arrhythmia event during follow-up ($n = 30\,407$), CHIP was also significantly associated with arrhythmia recurrence [HR, 1.10 (95% CI, 1.02–1.19); $P = .013$]. Multivariable-adjusted Poisson regression models revealed that the total event rate (including first and recurrent arrhythmias) was higher in those with vs. without CHIP, both in the full cohort [rate ratio, 1.17 (95% CI, 1.13–1.21); $P < .001$] as well as the subset of participants with at least one event during follow-up (rate ratio, 1.09 (95% CI, 1.05–1.12); $P < .001$].

We carried out several sensitivity analyses to probe the robustness of our findings. Associations were consistent overall and became stronger for ventricular arrhythmias and cardiac arrest when individuals with pre-existing coronary artery disease, heart failure, valvular heart disease, or cardiac surgery were excluded (see Supplementary data online, *Table S11*). Moreover, associations attenuated only slightly when coronary artery disease, heart failure, valvular heart disease, and cardiac surgery were incorporated as time-varying covariates (see Supplementary data online, *Table S12*). Similarly, our findings remained unchanged when adjusting for hypertension (see Supplementary data online, *Table S13*) or cancer (see Supplementary data online, *Table S14*) as time-varying covariates. Models excluding individuals with a history of any cancer (see Supplementary data online, *Table S15*) or those with imputed covariates (see Supplementary data online, *Table S16*) also yielded similar results, as did models further adjusting for smoking pack-years (see Supplementary data online, *Table S17*) or geographic and air pollution-related variables (see Supplementary data online, *Table S18*). Additionally, when CHIP was ascertained using a more lenient minimum read depth threshold for the alternate allele (i.e. three instead of five), which increases sensitivity for detecting CHIP at the expense of decreased specificity,[34] associations with incident arrhythmias remained unchanged (see Supplementary data online, *Table S19*).

Associations of gene-specific CHIP subtypes with incident arrhythmias

Gene-specific analyses showed that *DNMT3A* CHIP, the most common CHIP subtype, was not associated with incident arrhythmias across primary (*Table 3*) or secondary (*Table 4*) outcomes. *TET2* CHIP was associated with a 1.22-fold risk of developing any arrhythmia during follow-up (95% CI, 1.08–1.38; $P = .002$), with particularly high-risk for cardiac arrest [HR, 1.81 (95% CI, 1.17–2.78); $P = .007$]. Large CHIP clones driven by mutations in *PPM1D*, *TP53*, or spliceosome genes consistently yielded the strongest associations with the co-primary outcomes. Large *PPM1D* CHIP was the highest-risk subtype for atrial fibrillation [HR, 1.80 (95% CI, 1.29–2.50); $P < .001$], whereas large *TP53* CHIP was the subtype most strongly associated with cardiac arrest [HR, 4.32 (95% CI, 1.62–11.54); $P = .003$]. The spliceosome gene *SF3B1* showed the strongest association with any arrhythmia [HR, 1.73 (95% CI, 1.17–2.56); $P = .006$] among all tested CHIP subtypes (see Supplementary data online, *Table S20*). Models excluding individuals with a history of cancer—a known risk factor for CHIP driven by *PPM1D* and *TP53*[50,51]—yielded consistent results for these genes (see Supplementary data online, *Table S21*).

Given prior research suggesting a protective effect of germline genetic interleukin (IL)-6 signalling deficiency against arrhythmias as well as CHIP-associated atherosclerosis,[39,52] we tested whether genetically proxied IL-6 signalling deficiency—proxied using a common missense variant in *IL6R* (p.Asp358Ala)—was similarly protective against arrhythmia risk in the context of CHIP or gene-specific CHIP subtypes (see Supplementary data online, *Figure S9*). Multivariable-adjusted models revealed suggestive protective associations between two p.Asp358Ala alleles vs. no p.Asp358Ala alleles and risk of composite arrhythmias in those with *PPM1D* [HR, 0.41 (95% CI, 0.15–1.09); $P = .07$] or spliceosome [HR, 0.43 (95% CI, 0.20–0.95); $P = .037$] CHIP. However, there were no statistically significant interactions between a number of protective *IL6R* alleles and *PPM1D* ($P_{interaction} = .19$) or spliceosome CHIP ($P_{interaction} = .07$) on risk for composite arrhythmias. The interaction between a number of *IL6R* alleles and *PPM1D* was nominally significant for supraventricular arrhythmias ($P_{interaction} = .048$). Consistent with murine models of *TP53* CHIP showing no effects of p53 deficiency on IL-6 or IL-1β expression,[42] genetically proxied IL-6 signalling deficiency did not appear to have a protective effect in participants with *TP53* CHIP [HR, 1.14 (95% CI, 0.35–3.65) for two vs. no p.Asp358Ala alleles; $P = .83$].

Association of CHIP and gene-specific CHIP subtypes with myocardial fibrosis

Previous research in animal models suggests that CHIP promotes myocardial fibrosis.[22–26] As profibrotic remodelling is strongly associated with incident events across arrhythmia subtypes,[27–31] we next tested

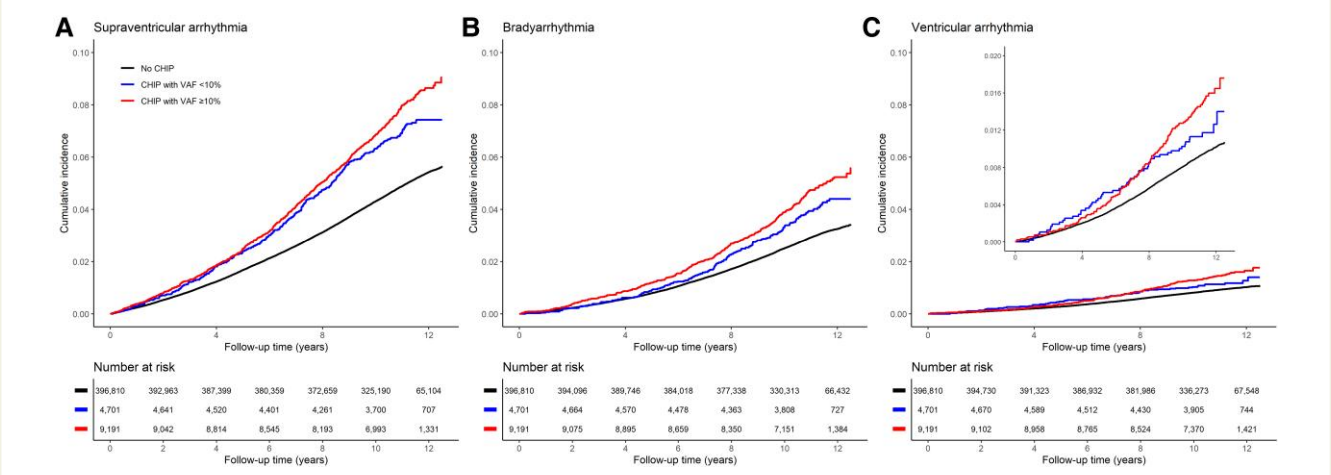


Figure 1 Cumulative incidence of (*A*) supraventricular arrhythmias, (*B*) bradyarrhythmias, and (*C*) ventricular arrhythmias during follow-up. Cumulative incidence functions were constructed using models accounting for all-cause mortality as a competing risk and represent the cumulative incidence of the co-primary study outcomes (i.e. supraventricular arrhythmia, bradyarrhythmia, and ventricular arrhythmia) during a median follow-up of 11.1 (IQR, 10.4–11.8) years. Follow-up was truncated at 12.5 years. CHIP indicates clonal haematopoiesis of indeterminate potential; VAF, variant allele frequency

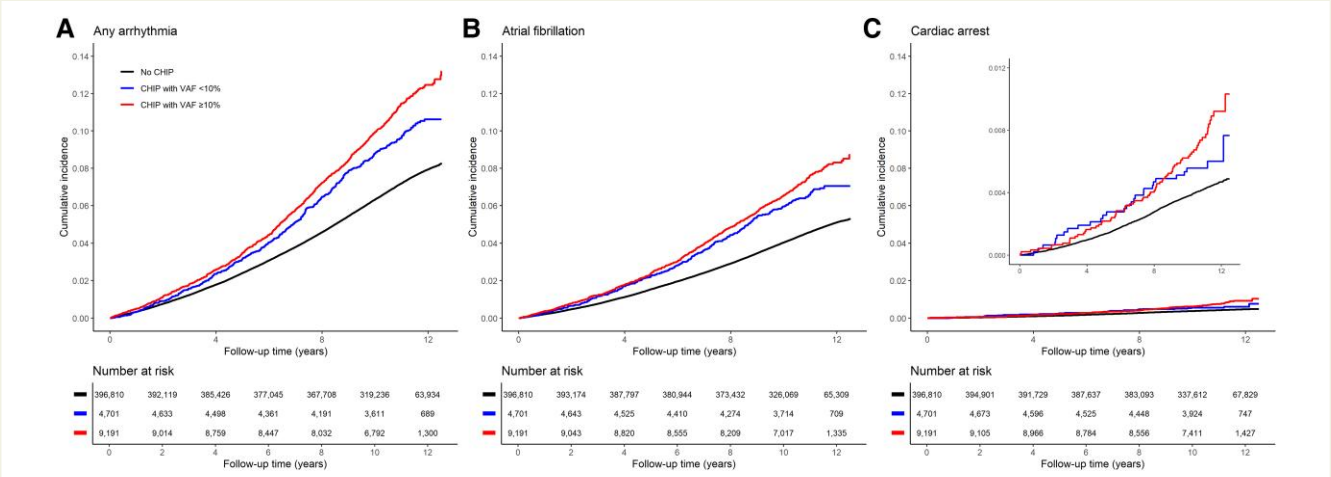


Figure 2 Cumulative incidence of (*A*) any arrhythmia, (*B*) atrial fibrillation, and (*C*) cardiac arrest during follow-up. Cumulative incidence functions were constructed using models accounting for all-cause mortality as a competing risk and represent the cumulative incidence of secondary study outcomes (i.e. any arrhythmia, atrial fibrillation, and cardiac arrest) during a median follow-up of 11.1 (IQR, 10.4–11.8) years. Follow-up was truncated at 12.5 years. CHIP indicates clonal haematopoiesis of indeterminate potential; VAF, variant allele frequency

whether CHIP was associated with T1 time (i.e. a measure of myocardial interstitial fibrosis) in the subset of human participants who underwent CMR with T1 mapping ($n = 34\,577$). Of those participants, 910 (2.6%) had any and 588 (1.7%) had large CHIP. Although participants with vs. without CHIP were older at the time of CMR imaging [69.5 (IQR, 64.4–73.4) vs. 64.7 (IQR, 58.3–70.3); $P < .001$], there was no statistically significant difference in the time between blood draw and imaging visit [9.7 (IQR, 8.1–10.9) vs. 9.6 (IQR, 8.1–10.8) years; $P = .31$]. Participant characteristics of those who underwent CMR imaging with vs. without CHIP are listed in Supplementary data online, *Table S22*.

Multivariable-adjusted models revealed that individuals with vs. without CHIP had 1.19-fold odds of being in the top 20th percentile of T1 time (95% CI, 1.01–1.41; $P = .035$; *Figure 3*). This association was stronger for CHIP with VAF ≥10% [odds ratio (OR), 1.31 (95% CI, 1.07–1.59); $P = .009$]. Among the tested CHIP driver genes, *TET2* was most strongly associated with myocardial fibrosis, yielding an OR of 1.69 (95% CI, 1.15–2.48; $P = .007$). When T1 times were tested as a continuous variable using linear regression (see Supplementary data online, *Table S23*), associations of CHIP with myocardial fibrosis were largely consistent yet slightly attenuated. The associations of CHIP with myocardial interstitial fibrosis were stronger when excluding

Table 2 Association of any and large (i.e. variant allele fraction ≥10%) clonal haematopoiesis of indeterminate potential with incident arrhythmias

	Any CHIP ($n = 13\,892$)				CHIP with VAF ≥10% ($n = 9191$)			
	Minimally adjusted model		Fully adjusted model		Minimally adjusted model		Fully adjusted model	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Primary outcomes								
Supraventricular arrhythmia	1.12 (1.06–1.20)	<.001	1.11 (1.04–1.18)	.001	1.15 (1.07–1.24)	<.001	1.13 (1.05–1.22)	.001
Bradyarrhythmia	1.11 (1.02–1.20)	.015	1.09 (1.01–1.19)	.031	1.15 (1.04–1.26)	.005	1.13 (1.03–1.25)	.011
Ventricular arrhythmia	1.18 (1.02–1.37)	.026	1.16 (1.00–1.34)	.049	1.25 (1.06–1.49)	.010	1.22 (1.03–1.45)	.021
Secondary outcomes								
Any arrhythmia	1.12 (1.06–1.18)	<.001	1.10 (1.04–1.16)	<.001	1.15 (1.08–1.23)	<.001	1.14 (1.07–1.21)	<.001
Atrial fibrillation	1.13 (1.06–1.20)	<.001	1.11 (1.04–1.18)	.001	1.16 (1.07–1.25)	<.001	1.14 (1.06–1.23)	<.001
Cardiac arrest	1.33 (1.09–1.62)	.006	1.29 (1.06–1.58)	.012	1.43 (1.13–1.81)	.003	1.39 (1.10–1.76)	.006

All models represent Cox regression models in which participants without CHIP ($n = 396\,810$) constitute the reference group. The minimally adjusted model is adjusted for age, age^2, sex, and genetic ancestry. The fully adjusted is further adjusted for smoking status, BMI, systolic blood pressure, antihypertensive medication use, alcohol intake frequency, history of any cancer, type 2 diabetes mellitus, and coronary artery disease.
CHIP, clonal haematopoiesis of indeterminate potential; CI, confidence interval; HR, hazard ratio; VAF, variant allele frequency.

individuals with prevalent coronary artery disease (see Supplementary data online, *Table S24*) at the time of CMR.

Association of clonal haematopoiesis risk score with incident arrhythmias

The CHRS is a recently developed and validated risk score that incorporates genetic and clinical parameters to predict incident myeloid malignancies in individuals with CHIP.[43] As the majority of CHIP carriers never progress to haematologic malignancies, and because previous work suggests that CHRS is associated with risk of non-malignant outcomes including ischaemic heart disease,[43] we tested whether individuals with CHRS-defined high-risk CHIP were at a heightened risk of developing incident arrhythmias. Among 13 464 CHIP carriers with available data on haematologic traits, the median CHRS was 8 (IQR, 7.5–9). The low-risk (i.e. CHRS ≤9.5), intermediate-risk (i.e. CHRS 10–12), and high-risk (i.e. CHRS ≥12.5) categories included 12,037, 1,308, and 119 individuals, respectively.

Multivariable-adjusted models indicated that CHRS was significantly associated with incident supraventricular arrhythmias [HR, 1.18 (95% CI, 1.12–1.24) per point increase; $P < .001$], bradyarrhythmias [HR, 1.11 (95% CI, 1.03–1.19) per point increase; $P = .005$], and ventricular arrhythmias [HR, 1.23 (95% CI, 1.09–1.38) per point increase; $P < .001$] among those with CHIP. Non-genetic parameters included in the CHRS, including red cell distribution width, mean corpuscular volume, and age, were independently associated with incident arrhythmias (see Supplementary data online, *Table S25*). Risk group-stratified analyses revealed a dose-response relationship between CHRS and risk of incident arrhythmias, with the highest risks observed in the high-risk CHRS category (i.e. CHRS ≥12.5) vs. those without CHIP (*Figure 4*). Consistent with these findings, the strongest associations were observed for individuals with 'progressive CHIP' (i.e. CHIP carriers who progressed to malignancy during follow-up), even though associations for those with 'stable CHIP' (i.e. CHIP carriers who did not progress to malignancy) remained materially unchanged compared with findings from the primary analyses (see Supplementary data online, *Table S26*).

Discussion

In this large cohort of middle-aged adults with next-generation sequencing, CHIP was independently associated with incident arrhythmias. We observed heterogeneity across specific arrhythmia subtypes; the strongest associations were observed for cardiac arrest, particularly in individuals with large CHIP clones. Gene-specific analyses indicated that the risk for incident arrhythmias was generally increased across gene-specific CHIP subtypes other than *DNMT3A* (**Structured Graphical Abstract**). Furthermore, CHIP carriers, especially *TET2* CHIP carriers, had higher myocardial T1 times, supporting the notion that CHIP is linked to increased myocardial fibrosis which may in turn contribute to CHIP-associated arrhythmia risk. Collectively, these findings shed light on the interplay between aging and arrhythmogenesis and highlight new potential opportunities for precision medicine in the management of arrhythmias.

First, CHIP may represent a novel, clinically relevant risk factor for arrhythmias. Previous population-based studies have established that CHIP is independently associated with increased risk of coronary artery disease,[16,17] stroke,[18] heart failure,[19] and all-cause mortality.[14] The present study extends these findings by identifying CHIP as an independent predictor of arrhythmias in the general population, independent of coronary artery disease and heart failure risk. Notably, CHIP-associated significantly with incident atrial fibrillation and cardiac arrest, both of which are important contributors to cardiovascular morbidity and mortality worldwide[1,3,4] with incompletely effective non-invasive options for prevention.[53,54] Findings from this study corroborate the notion that CHIP carriers might benefit from multi-disciplinary follow-up including cardiovascular risk factor assessment and modification. Although Mendelian randomization

Table 3 Multivariable-adjusted associations of gene-specific clonal haematopoiesis of indeterminate potential subtypes with supraventricular arrhythmias, bradyarrhythmias, and ventricular arrhythmias during follow-up

	Any CHIP ($n = 13\,892$)				CHIP with VAF ≥10% ($n = 9191$)			
	Minimally adjusted model		Fully adjusted model		Minimally adjusted model		Fully adjusted model	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Supraventricular arrhythmia								
DNMT3A	1.03 (0.95–1.12)	.5	1.03 (0.95–1.12)	.48	1.02 (0.92–1.13)	.74	1.02 (0.92–1.14)	.68
TET2	1.13 (0.97–1.31)	.13	1.12 (0.96–1.31)	.15	1.16 (0.98–1.38)	.09	1.15 (0.97–1.37)	.10
ASXL1	1.24 (1.06–1.46)	.007	1.15 (0.98–1.35)	.08	1.29 (1.08–1.55)	.006	1.19 (0.99–1.43)	.06
JAK2	1.83 (1.06–3.16)	.029	1.86 (1.08–3.21)	.025	1.83 (1.06–3.16)	.029	1.86 (1.08–3.21)	.025
PPM1D	1.51 (1.14–2.00)	.004	1.42 (1.07–1.88)	.014	1.79 (1.29–2.50)	<.001	1.72 (1.24–2.40)	.001
TP53	1.91 (1.30–2.81)	<.001	1.79 (1.22–2.63)	.003	1.86 (1.18–2.91)	.007	1.77 (1.13–2.78)	.012
Spliceosome genes	1.53 (1.18–1.97)	.001	1.47 (1.14–1.90)	.003	1.68 (1.29–2.19)	<.001	1.61 (1.24–2.09)	<.001
Bradyarrhythmia								
DNMT3A	0.98 (0.88–1.10)	.73	0.98 (0.88–1.10)	.79	1.01 (0.88–1.16)	.88	1.02 (0.88–1.17)	.83
TET2	1.24 (1.02–1.50)	.028	1.25 (1.04–1.52)	.019	1.18 (0.95–1.47)	.14	1.19 (0.96–1.48)	.12
ASXL1	1.35 (1.11–1.65)	.003	1.25 (1.02–1.52)	.028	1.40 (1.12–1.76)	.003	1.29 (1.03–1.61)	.028
JAK2	1.16 (0.48–2.79)	.74	1.13 (0.47–2.70)	.79	1.16 (0.48–2.79)	.74	1.13 (0.47–2.70)	.79
PPM1D	1.42 (0.98–2.05)	.07	1.34 (0.92–1.94)	.12	1.60 (1.02–2.52)	.039	1.55 (0.99–2.43)	.06
TP53	1.62 (0.94–2.79)	.08	1.53 (0.89–2.63)	.13	1.32 (0.66–2.63)	.44	1.26 (0.63–2.51)	.52
Spliceosome genes	1.46 (1.04–2.03)	.027	1.43 (1.02–1.99)	.036	1.64 (1.17–2.31)	.005	1.61 (1.14–2.27)	.006
Ventricular arrhythmia								
DNMT3A	0.99 (0.80–1.21)	.89	0.99 (0.81–1.21)	.9	1.06 (0.82–1.36)	.66	1.06 (0.82–1.36)	.66
TET2	1.28 (0.90–1.81)	.17	1.32 (0.93–1.87)	.12	1.12 (0.74–1.70)	.59	1.15 (0.76–1.75)	.51
ASXL1	1.26 (0.86–1.84)	.24	1.11 (0.76–1.63)	.58	1.15 (0.72–1.82)	.56	1.00 (0.63–1.59)	1
JAK2	1.56 (0.39–6.24)	.53	1.52 (0.38–6.10)	.55	1.56 (0.39–6.24)	.53	1.52 (0.38–6.10)	.55
PPM1D	1.40 (0.70–2.81)	.34	1.29 (0.65–2.59)	.47	2.02 (0.96–4.25)	.06	1.90 (0.90–3.98)	.09
TP53	2.50 (1.12–5.57)	.025	2.29 (1.03–5.11)	.042	2.75 (1.14–6.61)	.024	2.57 (1.07–6.18)	.035
Spliceosome genes	2.05 (1.21–3.46)	.008	1.94 (1.15–3.29)	.013	2.26 (1.31–3.90)	.003	2.16 (1.25–3.72)	.006

All models represent Cox regression models in which participants without CHIP ($n = 396\,810$) constitute the reference group, adjusted for age, age^2, sex, genetic ancestry, smoking status, BMI, systolic blood pressure, antihypertensive medication use, alcohol intake frequency, history of any cancer, type 2 diabetes mellitus, and coronary artery disease. Spliceosome genes include *PRPF8*, *SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2*.
CHIP, clonal haematopoiesis of indeterminate potential; CI, confidence interval; HR, hazard ratio; VAF, variant allele frequency.

analyses support a causal role for CHIP in the development of atrial fibrillation,[55] additional mechanistic research is needed to understand specific causal mediators and prioritize targets for therapeutic development. Future clinical trials should test whether CHIP-guided precision therapeutics[32] can effectively reduce arrhythmia risk.

Second, myocardial interstitial fibrosis may contribute mechanistically to the associations of CHIP with cardiovascular diseases. Cardiac arrhythmias encompass a diverse group of diseases with distinct aetiologies, pathophysiological mechanisms, and clinical consequences.[56] However, shared pathways associated with aging may contribute to different arrhythmia subtypes.[27] Studies in both humans and animals have shown that fibrotic changes in the heart can disrupt electrical impulse propagation and generate re-entry circuits, thereby predisposing individuals to rhythm disorders such as atrial fibrillation and cardiac arrest.[29,57] Mice with cardiomyocytes that overexpress the NLRP3 inflammasome—which acts upstream of inflammatory mediators IL-1β and IL-6—exhibit increased atrial fibrosis and susceptibility to atrial fibrillation, implicating inflammation in the association of fibrotic remodelling with arrhythmogenesis.[58] A recent study of 104 patients undergoing aortic valve replacement revealed that the presence of CHIP was associated with an increased risk of developing atrial fibrillation within 7 days after surgery.[59] Patients with vs. without CHIP had higher counts of activated circulating monocytes and myocardial macrophages, which resulted in a more pronounced perioperative

Table 4 Multivariable-adjusted associations of gene-specific clonal haematopoiesis of indeterminate potential subtypes with any arrhythmia, atrial fibrillation, and cardiac arrest during follow-up

	Any CHIP ($n = 13\,892$)				CHIP with VAF ≥10% ($n = 9191$)			
	Minimally adjusted model		Fully adjusted model		Minimally adjusted model		Fully adjusted model	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Any arrhythmia								
DNMT3A	1.01 (0.94–1.08)	.84	1.01 (0.94–1.08)	.83	1.02 (0.94–1.12)	.61	1.03 (0.94–1.12)	.56
TET2	1.22 (1.07–1.38)	.002	1.22 (1.08–1.38)	.002	1.21 (1.05–1.39)	.009	1.21 (1.05–1.39)	.009
ASXL1	1.26 (1.10–1.44)	<.001	1.17 (1.02–1.33)	.023	1.31 (1.12–1.52)	<.001	1.20 (1.03–1.40)	.017
JAK2	1.47 (0.88–2.43)	.14	1.49 (0.90–2.47)	.13	1.47 (0.88–2.43)	.14	1.49 (0.90–2.47)	.13
PPM1D	1.45 (1.14–1.85)	.002	1.37 (1.08–1.74)	.01	1.73 (1.30–2.29)	<.001	1.68 (1.27–2.23)	<.001
TP53	1.62 (1.15–2.30)	.006	1.52 (1.07–2.15)	.018	1.55 (1.03–2.33)	.037	1.48 (0.98–2.23)	.06
Spliceosome genes	1.46 (1.17–1.81)	<.001	1.42 (1.14–1.76)	.002	1.61 (1.28–2.01)	<.001	1.55 (1.24–1.94)	<.001
Atrial fibrillation								
DNMT3A	1.03 (0.95–1.13)	.45	1.03 (0.95–1.13)	.44	1.03 (0.93–1.15)	.54	1.04 (0.93–1.16)	.49
TET2	1.15 (0.99–1.35)	.07	1.15 (0.98–1.34)	.09	1.19 (1.00–1.41)	.051	1.18 (0.99–1.40)	.06
ASXL1	1.23 (1.05–1.45)	.012	1.14 (0.97–1.34)	.12	1.27 (1.06–1.54)	.012	1.17 (0.97–1.41)	.1
JAK2	1.77 (1.01–3.13)	.047	1.81 (1.03–3.18)	.041	1.77 (1.01–3.13)	.047	1.81 (1.03–3.18)	.041
PPM1D	1.58 (1.20–2.10)	.001	1.48 (1.12–1.96)	.006	1.87 (1.35–2.61)	<.001	1.80 (1.29–2.50)	<.001
TP53	1.93 (1.30–2.85)	.001	1.79 (1.21–2.65)	.004	1.84 (1.16–2.92)	.01	1.76 (1.11–2.79)	.017
Spliceosome genes	1.50 (1.15–1.94)	.002	1.44 (1.11–1.87)	.006	1.64 (1.25–2.15)	<.001	1.57 (1.20–2.06)	.001
Cardiac arrest								
DNMT3A	0.99 (0.74–1.33)	.96	0.99 (0.73–1.33)	.94	1.18 (0.83–1.67)	.36	1.17 (0.83–1.66)	.37
TET2	1.77 (1.15–2.73)	.009	1.81 (1.17–2.78)	.007	1.50 (0.89–2.54)	.13	1.53 (0.90–2.59)	.11
ASXL1	1.57 (0.96–2.57)	.07	1.38 (0.84–2.26)	.2	1.48 (0.82–2.68)	.2	1.28 (0.71–2.32)	.42
JAK2	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
PPM1D	2.23 (1.00–4.97)	.05	2.06 (0.92–4.59)	.08	3.05 (1.27–7.35)	.013	2.87 (1.19–6.90)	.019
TP53	3.54 (1.33–9.43)	.012	3.21 (1.20–8.56)	.02	4.66 (1.75–12.42)	.002	4.32 (1.62–11.54)	.003
Spliceosome genes	2.13 (1.01–4.49)	.046	2.00 (0.95–4.20)	.07	2.18 (0.98–4.87)	.06	2.05 (0.92–4.57)	.08

All models represent Cox regression models in which participants without CHIP ($n = 396\,810$) constitute the reference group, adjusted for age, age^2, sex, genetic ancestry, smoking status, BMI, systolic blood pressure, antihypertensive medication use, alcohol intake frequency, history of any cancer, type 2 diabetes mellitus, and coronary artery disease. Spliceosome genes include *PRPF8*, *SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2*.

CHIP, clonal haematopoiesis of indeterminate potential; CI, confidence interval; HR, hazard ratio; VAF, variant allele frequency.

[a]Cox regression models were not run when no incident events occurred in the indicated gene-specific CHIP subgroup.

inflammatory response and potentially increased risk of arrhythmogenesis.[59] These results further support the notion that dysregulated inflammation and inflammation-related fibrosis may contribute to arrhythmia risk in individuals carrying somatic mutations such as those defining CHIP. Furthermore, the present study found that CHIP was significantly associated with T1 times in a population-based cohort of middle-aged adults, extending recent findings of more severe liver fibrosis in humans with vs. without CHIP and mice modelled for *TET2* CHIP.[60] As both myocardial interstitial fibrosis and CHIP predict new-onset heart failure[19,61] as well as adverse outcomes in individuals with valvular heart disease[62,63] or established heart failure,[64–66] myocardial fibrosis may contribute to CHIP-associated cardiovascular risk in these contexts as well.

Third, the effects of CHIP on arrhythmia risk may vary depending on the specific driver mutation. Gene-specific analyses revealed an increased risk for incident arrhythmias across driver genes other than *DNMT3A*, which is consistent with epidemiologic studies indicating weaker associations of *DNMT3A* CHIP with heart failure[19] and atherosclerotic cardiovascular disease,[40,42] as well as recent work suggesting biologic differences between CHIP driven by *DNMT3A* vs. other driver genes.[67–69] Although our findings suggest that the associations of other gene-specific CHIP subtypes with arrhythmias are independent of

	Participants with fibrosis data	Participants in the top 20% of fibrosis	Adjusted OR (95% CI)	P-value
No CHIP	33,667	6,714	Ref.	
Any CHIP	910	201	1.19 (1.01 to 1.41)	0.035
Large CHIP (VAF ≥10%)	588	138	1.31 (1.07 to 1.59)	0.009
Any CHIP				
DNMT3A	584	124	1.10 (0.90 to 1.36)	0.35
TET2	138	39	1.69 (1.15 to 2.48)	0.007
ASXL1	75	16	1.36 (0.77 to 2.41)	0.29
Large CHIP				
DNMT3A	338	78	1.23 (0.95 to 1.60)	0.12
TET2	107	27	1.45 (0.92 to 2.27)	0.11
ASXL1	52	12	1.48 (0.76 to 2.88)	0.25

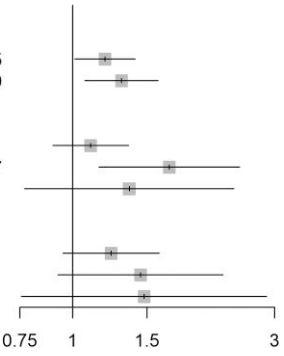


Figure 3 Multivariable-adjusted associations of CHIP and gene-specific CHIP subtypes with myocardial fibrosis. All models represent logistic regression models in which participants without CHIP ($n = 33\,671$) constitute the reference group, adjusted for age, age^2, sex, age × sex, time between blood draw and imaging visit, genetic ancestry, smoking status, BMI, systolic blood pressure, antihypertensive medication use, alcohol intake frequency, history of any cancer, type 2 diabetes mellitus, and coronary artery disease at baseline. Myocardial fibrosis was evaluated using rank-based inverse-normal-transformed T1 times, modelled as a binary variable in which the top 20th percentile of T1 time serves as the outcome of interest (i.e. '1'). CHIP indicates clonal haematopoiesis of indeterminate potential; CI, confidence interval; OR, odds ratio; VAF, variant allele frequency

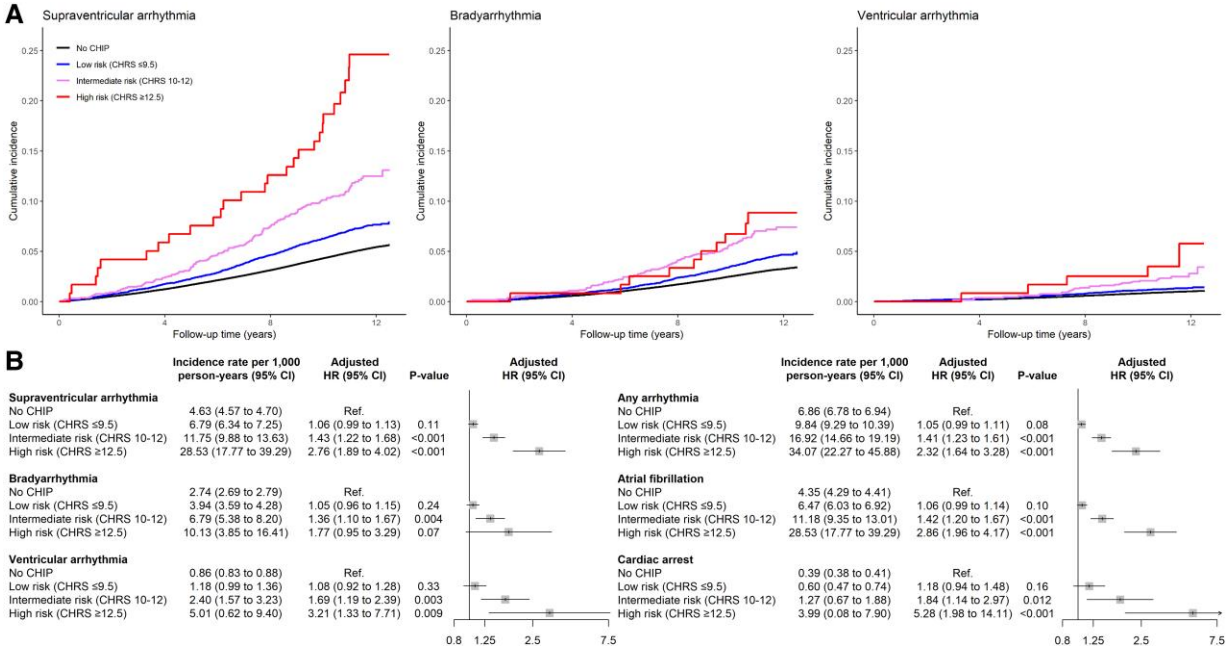


Figure 4 (*A*) Cumulative incidence of incident arrhythmias across CHRS categories and (*B*) multi-variable-adjusted associations of CHRS categories with incident arrhythmias. (*A*) Cumulative incidence functions were constructed using models accounting for all-cause mortality as a competing risk and represent the cumulative incidence of the co-primary study outcomes (i.e. supraventricular arrhythmia, bradyarrhythmia, and ventricular arrhythmia) during a median follow-up of 11.1 (IQR, 10.4–11.8) years. Follow-up for cumulative incidence functions was truncated at 12.5 years. (*B*) Forest plots represent Cox regression models in which participants without CHIP ($n = 396\,810$) constitute the reference group, adjusted for age, age^2, sex, genetic ancestry, smoking status, BMI, systolic blood pressure, antihypertensive medication use, alcohol intake frequency, history of any cancer, type 2 diabetes mellitus, and coronary artery disease. CHIP indicates clonal haematopoiesis of indeterminate potential; CHRS, clonal haematopoiesis risk score; CI, confidence interval; HR, hazard ratio; VAF, variant allele frequency

cardiovascular diseases such as coronary artery disease and heart failure, there may be overlapping pathways linking different CHIP driver genes with arrhythmogenesis. For instance, mice that were engineered to mimic *TET2* or *ASXL1* CHIP and subsequently exposed to myocardial ischaemia or cardiac loading conditions exhibited overproduction of IL-6 and IL-1β, as well as increased myocardial fibrosis.[22,23,26] *PPM1D* CHIP may similarly induce a proinflammatory state with increased IL-6 and IL-1β levels,[25] but mechanistic data on *TP53* are less

conclusive.[42,70] A recently developed atherosclerotic mouse model of *TP53* CHIP did not suggest involvement of IL-6 or IL-1β,[42] whereas another line of evidence suggests that *TP53* CHIP has detrimental effects on doxorubicin-induced cardiotoxicity through increased neutrophil infiltration in the myocardium.[70] Myocardial neutrophil infiltration has recently been shown to induce ventricular arrhythmias and cardiac arrest,[71] which supports the strong associations of *TP53* with these arrhythmias. CHIP driven by spliceosome mutations has not been extensively investigated in experimental models of cardiovascular disease. However, some preclinical evidence suggests increased IL-6 mRNA in myeloid cell lines and patients with mutations in spliceosome genes *SF3B1*, *SRSF2*, or *U2AF1*.[72] Further research is needed to elucidate pathways driving arrhythmia risk in individuals with CHIP, particularly those with driver mutations in DNA damage repair or spliceosome genes.

While our study benefits from large sample size and the use of next-generation sequencing methods to ascertain CHIP, findings should be interpreted in the context of limitations. First, this study utilized population-scale WES, which has greater sensitivity to detect mutations in candidate genes and can more accurately identify CHIP carriers than whole genome sequencing;[73] however, in comparison with deeper targeted sequencing, WES may have reduced sensitivity for detection of clonal haematopoiesis at VAF <5%[73] and result in an underestimation of overall CHIP prevalence. We also used a stringent filtering protocol that may misclassify the proportion of individuals carrying CHIP clones with VAF <10%. However, this approach also minimizes the number of false-positive CHIP calls, resulting in a high-fidelity CHIP call set.[34,52] Although sensitivity analyses using more lenient filtering strategies supported our primary analyses, future studies are needed to identify optimal VAF thresholds for arrhythmia prediction using targeted deep sequencing methods. Second, outcome ascertainment relied primarily on ICD and procedure codes, which might introduce misclassification. However, previous studies using the same outcome definitions revealed high-definition accuracies in an external validation cohort (with positive predictive values ≥80% across arrhythmia categories)[8] and successfully replicated well-known Mendelian gene-trait associations for these diseases in the UK Biobank.[45] Additionally, self-report, which was used together with ICD and procedure codes to ascertain prevalent but not incident diseases, is associated with high accuracies for traits such as type 2 diabetes in the UK Biobank.[74] Third, the majority of study participants had European ancestry or self-reported as White, precluding adequately powered subgroup analyses in participants from other races/ethnicities. Future studies should examine whether relationships generalize to other ancestry groups, who generally have lower CHIP prevalence than European ancestry individuals. Four, CHIP was only ascertained at baseline in the UK Biobank. As such, were unable to test whether associations of CHIP or gene-specific CHIP subtypes with incident arrhythmias differed by rate of clonal expansion. Some participants without CHIP at baseline may also have developed CHIP during follow-up, potentially introducing misclassification of the study exposure. However, any such misclassification is expected to bias results towards the null. Fifth, although we identified CHIP as an independent risk factor for arrhythmias, the association of CHIP with incident arrhythmias did not reach statistical significance in the subset (~8%) of participants with CMR data, precluding formal mediation analysis to test the role of myocardial fibrosis in the CHIP-arrhythmia association. In addition, the CMR subset included individuals that were healthier than the rest of the UK Biobank cohort,[75,76] likely indicating survival bias and leading to an underestimation of the association between CHIP and arrhythmias in this subgroup. Finally, we lacked the power to examine less common CHIP drivers in the CMR sub-cohort.

Conclusions

In this study, CHIP was independently associated with certain arrhythmias spanning supraventricular, brady- and ventricular arrhythmias. Individuals carrying CHIP also had higher T1 times, supporting the notion that myocardial fibrosis may contribute to CHIP-associated arrhythmia risk. Future research should delineate mechanisms driving the observed associations and define the role of CHIP as potential target for modulation towards arrhythmia prevention and treatment.

Acknowledgements

The authors thank the participants of the UK Biobank.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

Dr. Nauffal reports travel grants from Biotronik (unrelated to this work). Dr. Klarqvist reports grants from Bayer AG and IBM (all unrelated to this work). Dr. Weeks reports consulting fees from Abbvie (unrelated to this work). Dr. Lin reports consulting fees from employment by TenSixteen Bio (unrelated to this work). Dr. Lubitz reports employment by Novartis Institutes for Biomedical Research; research support from Bristol Myers Squibb, Pfizer, Bayer AG, Boehringer Ingelheim, and IBM; previous consultancy for Bristol Myers Squibb, Pfizer, Bayer AG, Blackstone Life Sciences, and Invitae; a patent application for 'interactive subgroup discovery' (application number: 17/4797852); executive board membership for AF-Screen; advisory board membership for CAPCat; safety monitoring board membership for Pulsewatch; and stock ownership for Novartis (all unrelated to this work). Dr. Ballantyne reports consulting fees from TenSixteen Bio (unrelated to this work). Dr. Jaiswal reports consulting fees from TenSixteen Bio, Bitterroot Bio, and AstraZeneca; payment or honoraria from GSK; stock ownership for Bitterroot Bio and TenSixteen Bio; and is a co-founder of TenSixteen Bio (all unrelated to this work). Dr. Libby reports unpaid consultancy to, or clinical trial involvement for Amgen, AstraZeneca, Baim Institute, Beren Therapeutics, Esperion Therapeutics, Genentech, Kancera, Kowa Pharmaceuticals, Medimmune, Merck, Moderna, Novo Nordisk, Novartis, Pfizer, and Sanofi-Regeneron; scientific advisory board membership for Amgen, Caristo Diagnostics, Cartesian Therapeutics, CSL Behring, DalCor Pharmaceuticals, Dewpoint Therapeutics, Eulicid Bioimaging, Kancera, Kowa Pharmaceuticals, Olatec Therapeutics, Medimmune, Novartis, PlaqueTec, TenSixteen Bio, Soley Therapeutics, and XBiotech, Inc.; research funding in the last 2 years from Novartis, Novo Nordisk, and Genentech; Board of Directors membership of XBiotech, Inc.; financial interests in Xbiotech, TenSixteen Bio, and Soley Therapeutics (all unrelated to the present work). Dr. Ebert reports research funding from Deerfield, Novartis, and Calico; consulting fees from and stock ownership for Neomorph Inc., TenSixteen Bio, Skyhawk Therapeutics, and Exo Therapeutics (all unrelated to the present work). Dr. Bick reports consulting fees from and stock ownership for TenSixteen Bio (unrelated to this work). Dr. Ellinor reports research support from Bayer AG, IBM, Bristol Myers Squibb, and Pfizer (unrelated to this work). Dr. Natarajan reports research grants from Allelica, Apple, Amgen,

Boston Scientific, Genentech/Roche, and Novartis; personal fees from Allelica, Apple, AstraZeneca, Blackstone Life Sciences, Foresite Labs, Genentech / Roche, GV, HeartFlow, Magnet Biomedicine, and Novartis; scientific advisory board membership of Esperion Therapeutics, Preciseli, and TenSixteen Bio; equity in Preciseli and TenSixteen Bio; spousal employment at Vertex Pharmaceuticals; and is a scientific co-founder of TenSixteen Bio (all unrelated to this work). Dr. Honigberg reports consulting fees from CRISPR Therapeutics; advisory board service for Miga Health; and grant support from Genentech (all unrelated to this work).

Data Availability

UK Biobank data are available to approved investigators by application (https://www.ukbiobank.ac.uk/).

Funding

Mr Schuermans is supported by the Belgian American Educational Foundation. Dr Cho is supported by the Korea Health Industry Development Institute (HI19C1330). Dr Nakao is supported by an Overseas Fellowship from the Japan Society for the Promotion of Science and the National Heart, Lung, and Blood Institute (NHLBI; 1K99HL165024). Dr Lin is supported by the John S. LaDue Memorial Fellowship from Harvard Medical School, a Research Training Award from the American Society of Hematology for Fellows, and a Merck Research Fellowship from the American College of Cardiology Foundation in Cardiovascular Disease and the Metabolic Syndrome. Dr Lubitz is supported by the National Institutes of Health (NIH; R01HL139731, R01HL157635) and the American Heart Association (18SFRN34250007). Dr Ballantyne is supported by the NIH (R01HL148050). Dr Jaiswal is supported by Fondation Leducq; the Ludwig Institute for Cancer Research; the Knight Foundation; the Leukemia and Lymphoma Society; and the NIH (DP2-HL157540). Dr Libby is supported by the NHLBI (1R01HL134892 and 1R01HL163099-01); the McCormick Foundation; and the Simard Fund. Dr Ellinor is supported by the NIH (2R01HL092577), the American Heart Association (18SFRN34110082), and the European Union's Horizon 2020. Dr Natarajan is supported by a Hassenfeld Scholar Award and the Paul & Phyllis Fireman Endowed Chair in Vascular Medicine from the Massachusetts General Hospital; the NHLBI (R01HL142711, R01HL148565 and R01HL148050); the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK125782); and Fondation Leducq (TNE-18CVD04). Dr Honigberg is supported by the NHLBI (K08HL166687) and American Heart Association (940166, 979465).

Ethical Approval

The UK Biobank was approved by the North West Multi-centre Research Ethics Committee, and all participants provided their informed consent. UK Biobank data were accessed through application number 7089. The Mass General Brigham Institutional Review Board approved the secondary use of these data.

Pre-registered Clinical Trial Number

Not applicable.

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